Modeling, Control and Material Traceability in Continuous Pharmaceutical Manufacturing

By

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A thesis submitted to the

School of Graduate Studies

Rutgers, the State University of New Jersey

In partial fulfillment of the requirements

For the degree of

Master of Science

Graduate program in Chemical and Biochemical Engineering

Written under the direction of

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And approved by

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New Brunswick, New Jersey

October, 2018

ABSTRACT OF THE THESIS

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The priority in pharmaceutical industry is the manufacturing of high quality drug products that meet predefined specifications mandated by regulator. With the advances in continuous manufacturing for solid drug products, there are technical challenges and regulatory requirements that must be investigated and solutions that must be satisfied. Powder feeding is a critical first step in the continuous direct compression of tablets. The ability to model feeding performance will allow for better process understanding and control of the initial unit operations in the line.

With continuous manufacturing strategy growing in use, there is also a need for all regulatory requirements to be met to maximize benefits of continuous manufacturing. One area that needs attention is material traceability for continuous manufacturing. For patient safety and regulatory compliance, the history of each drug product should be known and traceable. It requires the current guidelines to be applied to a continuous manufacturing line, through the application of residence time distribution (RTD) of each component in the formulation. This allows for raw material batch numbers to be traced to the outlet and

documented appropriately for release. Continuous manufacturing in the pharmaceutical industry currently lacks the implementation framework and software to utilize material traceability in its novel solid dose continuous manufacturing processes. A systematic framework is necessary for material traceability to ensure that this methodology is implemented properly. Because material traceability is not able to be verified during production, there must be certainty that all considerations and factors that influence the accuracy and implementation are understood.

The goal of this work is two-fold. First, to develop a control relevant model for powder feeding of K-Tron feeder and implement and investigate the control system performance. Second, to develop and implement a systematic material traceability framework for the continuous pharmaceutical tablet manufacturing process. We were able to achieve an accurate model to explore and simulate realistic disturbances and evaluate feeder control performance in these scenarios. And with a focus on regulation, we successfully designed and deployed prototype software for material traceability in the continuous line.

Acknowledgments

Thank you Dr. Ravendra Singh for the opportunity to work with you and your research group and advising this thesis. Lessons learned through these experiences are ones I will take with me the rest of my life. I would also like to thank committee members Dr. Rohit Ramachandran and Dr. Gerardo Callegari for their time and consideration.

I am grateful for all members of ERC-SOPS whose open collaboration and communication allowed for progress and success of the past couple of years. Specifically, Fernando Nunes de Barros and Aparajith Bhaskar for their unwavering encouragement, help, and friendship. To Andrés Román-Ospino, James Scicolone, and Tianyi Li, your support allowed me to learn so much and accomplish this work.

Finally, my parents and family for their constant moral support and love.

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Chapter 1: Introduction

Pharmaceutical manufacturing is an area with high regulation and precise quality control of drug products. There are initiatives in place for advanced manufacturing technologies to be utilized in the pharmaceutical industry (Subcommitte for Advanced Manufacgturing of the National Science and Technology Council 2016). This requires the regulatory constraints to be applied in new ways to these manufacturing practices. Primary focus is on advancement of continuous pharmaceutical manufacturing. Advancement in this area would allow for lower equipment costs due to smaller footprint and hold up of equipment, as well as provide opportunities to apply advanced process control on the drug products to impact quality in real-time (Yu 2008). It would also decrease the amount of material inventory due to manufacturing unit operations being connected and allowing transfer of material to downstream processes continuously (Plumb 2005).

Powder feeding is a critical step in the continuous manufacturing process for pharmaceutical solid products. It is the first step in ensuring that the product meets concentration requirements at the outlet. Feeding performance can be affected by many factors of the process. Building a control relevant model requires an understanding of all the feeding parameters. A design and implementation of a control strategy for this model were also developed, to better simulate feeding performance.

For patient safety and regulatory perspectives, the history of each pharmaceutical product should be known and traceable so that the products can be recalled if needed. This is

straightforward for batch pharmaceutical manufacturing since each batch of raw materials produces a corresponding batch of final product. However, in continuous pharmaceutical manufacturing, establishing a historical relationship between the raw materials and finished product is a challenging task and thereby the product recalls are currently difficult.

1.1. Literature Review

1.1.1. Modeling and Control of Powder Feeding

There are at least three approaches for studying particulate material flow. The earliest being the study of bulk material flow in vertical silos, suited for agricultural and mining applications. Beginning with Janssen, who derived the Janssen equations which were the basis of studying bulk materials in 1895. Later on, Walters studied the static and dynamics stresses during and after filling of vertical silos (Walters 1973). Recently, Artoni and colleagues expanded on Walters work by theoretically studying the stress profiles in large hoppers containing dense metallic granules and then performing experimental validation of the theory (Artoni et al. 2009; Artoni et al. 2011).

The second area has been with the use of discrete element method (DEM) modeling to study material flow. Shimizu and Cundall first introduced this area to DEM for modeling screw conveyors. While their work is the basis for studying screw conveyors by DEM, they started with narrow range of equipment configurations and particle properties, but made advances in creating the 3D objects required for these DEM simulations (Shimizu and Cundall 2001). Owen and Cleary analyzed horizonal and inclined screw conveyors for agricultural applications. However, the screw rotation speeds studied were much higher than anything used in loss-in-weight (LIW) feeders for pharmaceutical applications. They found that particle size plays a critical role in their simulation results, something that varies

between pharmaceutical products, limiting the scope of the work (Owen and Cleary 2009). Kretz and Callau-Monje have recently applied DEM to study design considerations of screw tooling to feed bulk material. This work used various screw shapes and one type of material to experimentally validate DEM results and their work provided experimental and simulated results illustrating mass flow fluctuations commonly scene in bulk material handling in screw conveyors, a critical observation (Kretz et al. 2016).

The third area in material feeding focuses on specific applications for the pharmaceutical industry. Engisch and Muzzio focused their work on exploring behavior of continuous powder feeding. First, they developed methods for characterizing and evaluating feeder performance (Engisch and Muzzio 2012). Then, they explored refill instances and ways to mitigate mass flow disturbances (Engisch and Muzzio 2015). And finally, demonstrated case studies utilizing this previous work to demonstrate its applicability with pharmaceutical products (Engisch and Muzzio 2014). Boukouvala et al. have developed a feeder model based on first order delayed differential equations (Boukouvala et al. 2012). Escotet-Espinoza et al. built upon this knowledgebase and presented a strategy for modeling powder feeder performance, based on a "feed-factor profile," which relates mass of material in hopper to the weight of material displaced per screw revolution (Escotet-Espinoza et al. 2015). The modeling work, however, was focused on GEA compact feeder. Wang et al. worked to predict feeder performance through studying the effect of material properties on the relative standard deviation (RSD) of mass flow (Y. Wang et al. 2017). Moghtadernejad and colleagues provided valuable insight to practical considerations when operating continuous powder feeding and analyzing proceed data post operation (Moghtadernejad et al. 2018). However, much less attention has been paid to developing

the control relevant feeder model and to investigate the control strategy. Moreover, with the best of the author's knowledge, no attempt has been made to develop a validated model for K-Tron feeder.

1.1.2. Material Traceability

Thus far, there has been a focus on part production and batch production. Traceability in these processes is easier to accomplish in comparison to continuous processes. There is a lack of scientific literature on traceability in continuous processes, especially in application of pharmaceutical manufacturing. The literature present addresses challenges in the diary, food, mining, and pulp industries. Lundqvist & Kubulnieks focuses on traceability applied to the chemical pulp mill operation, creating a system with operator interaction and feedback and prediction of process performance to improve operator's modifications (Lundqvist and Kubulnieks 1995). While this would be a useful and applicable strategy in the pharmaceutical industry, there is less flexibility with operator making changes to the process. Quality is of utmost importance in pharmaceutical manufacturing, and tolerances much smaller as compared to pulp mill operations. Therefore, operator modifications to the process are much less frequent. In pulp processing, the residence time distribution (RTD) is on scale of days, not minutes or seconds, therefore the accuracy and experimental considerations of RTD are not addressed in this work, which would be required for applications in the pharmaceutical industry. Moe introduced the advantages of internal traceability within manufacturing step in the supply chain, such as improved process control, correlation or process data to raw materials, and the cause and effect indications for non-conforming product (Moe 1998). However, the details of implementing such a strategy are not discussed, especially the method of RTD for internal traceability, which is

of utmost importance for applications of traceability in continuous pharmaceutical manufacturing. Mousavi et al. focuses on the standardization and automation strategies essential for supply chain tracking in animal products (Mousavi et al. 2002). This system however, fails to utilize traceability within manufacturing steps and the use of RTD. Jansen-Vullers et al. describes the accurate managing of traceability information through a systematic framework (Jansen-Vullers et al. 2003). However, implementation of RTD methodology for in-process traceability of raw materials, an essential piece for material traceability in the pharmaceutical industry, is not addressed. Folinas et al. describes data management framework for food supply chain operation using conventional technologies such as internet, email, and cell-phones (Folinas et al. 2006). However, this framework does not address use of RTD in traceability framework, which is necessary for implementation for continuous manufacturing traceability. Finally, Kvarnström & Oghazi discusses traceability in continuous processes and the use of RTD (Kvarnström and Oghazi 2008). However, this work describes the various methods and does not present a framework in which RTD can be used for traceability. There is no discussion on what information is extracted from RTD or how that information is used for material traceability. Engisch and Muzzio introduced using RTD for material traceability in manufacturing of continuous solid dose manufacturing (Engisch and Muzzio 2016). While they addressed some of the specific challenges, more work needed to be done for the implementation of material traceability. Therefore, a systematic material traceability framework is needed that can be efficiently applied to continuous pharmaceutical manufacturing process. The work presented in this manuscript provides a solution for implementation of material traceability

in continuous manufacturing, specifically for the solid-dosage pharmaceutical products industry.

1.2. **Objectives**

The objectives of this thesis are to explore the experimental factors that influence feed factor, develop control relevant powder feeding model, and implement material traceability strategy for continuous solids pharmaceutical manufacturing. Prior to this work, modeling the control of powder feeding had not been studied. In addition, a framework and software prototype for implementation of material traceability for continuous pharmaceutical manufacturing had not been accomplished. Therefore, the main objectives of this work are:

1. *Investigate experimental factors of feed factor profile.*
2. *Develop and validate control relevant open-loop feeder model using MATLAB and Simulink simulation platform.*
3. *Implement and evaluate control strategy in the closed-loop model.*
4. *Design framework for implementation of material traceability in continuous manufacturing.*
5. *Design and implement software prototype for material traceability.*

Chapter 2: Background

2.1. Continuous manufacturing

The continuous manufacturing process and pilot-plant considered for this study is situated at C-SOPS, Rutgers University. Figure 1 illustrates the flowsheet for the continuous direct compaction tablet manufacturing process. Three gravimetric feeders provide the necessary API, excipient, and lubricant to the system. The feeders manufactured by K-Tron contain a hopper that holds a specific amount of material and rotating screws below the hopper to feed the powder out of the barrel at specific rates. These feeds flow into a continuous blender manufactured by Glatt to create a more homogenous mixture of raw materials. The blended powder flows into the tablet press (Fette). Powder enters the feed frame within the tablet press and is finally compacted into tablets.

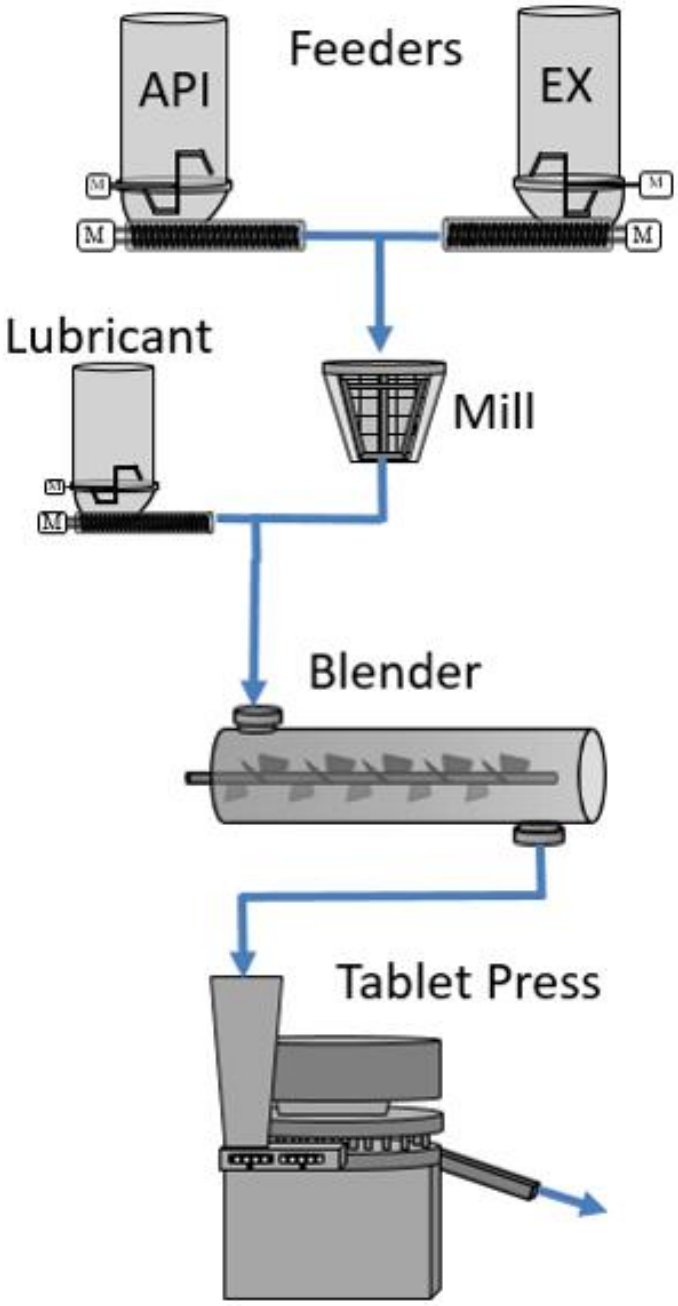

Figure 1. Configuration of unit operations used for demonstration of continuous direct compression tablet manufacturing process

2.2. Modeling and Control of Powder Feeders

Powder feeders consist of a hopper, agitator bar and feeding screws, all situated on a load cell. The material to be fed is added to the hopper, then when running, the horizonal screws rotate, carrying material out of the hopper to outlet of feeder. There are many different equipment manufacturers of powder feeders, and many configurable options. The screw pitch and depth are customizable, as well as the general thread shape. There are spirals, augers, and concave screws, all of which feed material differently (Engisch and Muzzio 2014). There are also different height hoppers, which can hold more material without requiring a refill. It is important to note that changes in feeder tooling, will impact the feeding performance.

One of the challenges with powder feeding is the variability in particulate systems. Many factors can cause this, specifically the tendency for pharmaceutical bulk material to clump together. As the screws rotate, and material is pushed out in pulses due to the orientation of the thread at the end of the screw, whether it is on the top or bottom of its cycle. This behavior was verified by Kretz and Callau-Monje, experimentally and through DEM simulations (Kretz et al. 2016). The clumping can be intrinsic to cohesive materials, as well as influenced by moisture and compressibility of the material All of these could lead to deviations in feeding performance and lack of consistency.

There are two ways to operate powder feeder. The first is volumetric feeding, where speed of the screw rotation is fixed. The density of material is a function of the static pressure above the material entering the feedings screws. That pressure decreases with less material in the hopper, altering density of material over time of operation. So the mass flow rate

from the feeder will fluctuate based on this pressure realized by the material (Engisch and Muzzio 2015). Another mode is called “gravimetric,” which attempts to control the mass flow rate out of the feeder by manipulating the speed of the feeding screws. An inbuilt controller compares user-defined set point to the mass flow out of the feeder calculates screw speed to correct deviation from SP.

For the control relevant feeder model, the model must be set up to accommodate a feedback loop. Closed-loop control allows the error between the target setpoint and the process control variable to be minimized by making actions in the manipulated variable. For powder feeders, the control variable is the mass flow rate of material leaving the feeder and the manipulated variable is the screw speed. By adjusting screw speed, the error between mass flow setpoint and the actual mass flow can be minimized during operation.

2.3. **Material traceability**

There have been recent developments in real-time PAT and process modeling to monitor the continuous manufacturing process. To assure the CQAs in real time, advanced control strategies have been implemented into continuous pharmaceutical tablet manufacturing process (Singh et al. 2013; Singh et al. 2014; Singh et al. 2015) . Further understanding of particulate systems is also being developed for applications about continuous powder feeding, which is required for robustness of continuous manufacturing process (Engisch and Muzzio 2012). Another challenge which must be addressed for continuous processes is the traceability of raw materials in the final products. As per regulatory guidelines, “the failure of a batch of any of its components to meet any specifications shall be thoroughly investigated, whether or not the batch has been already distributed” (FDA 2015). This

means that each component in the formulation should have associated batch number from manufacturer. Every tablet lot and batch should have an associated record of each components' specific batch information to maintain material traceability should any component fail to meet any specification and an investigation finds recall is required. If recall is required, knowing which tablet batches, and lots within the batch, contain the affected component would allow exact affected tablets to be recalled, no more and no less.

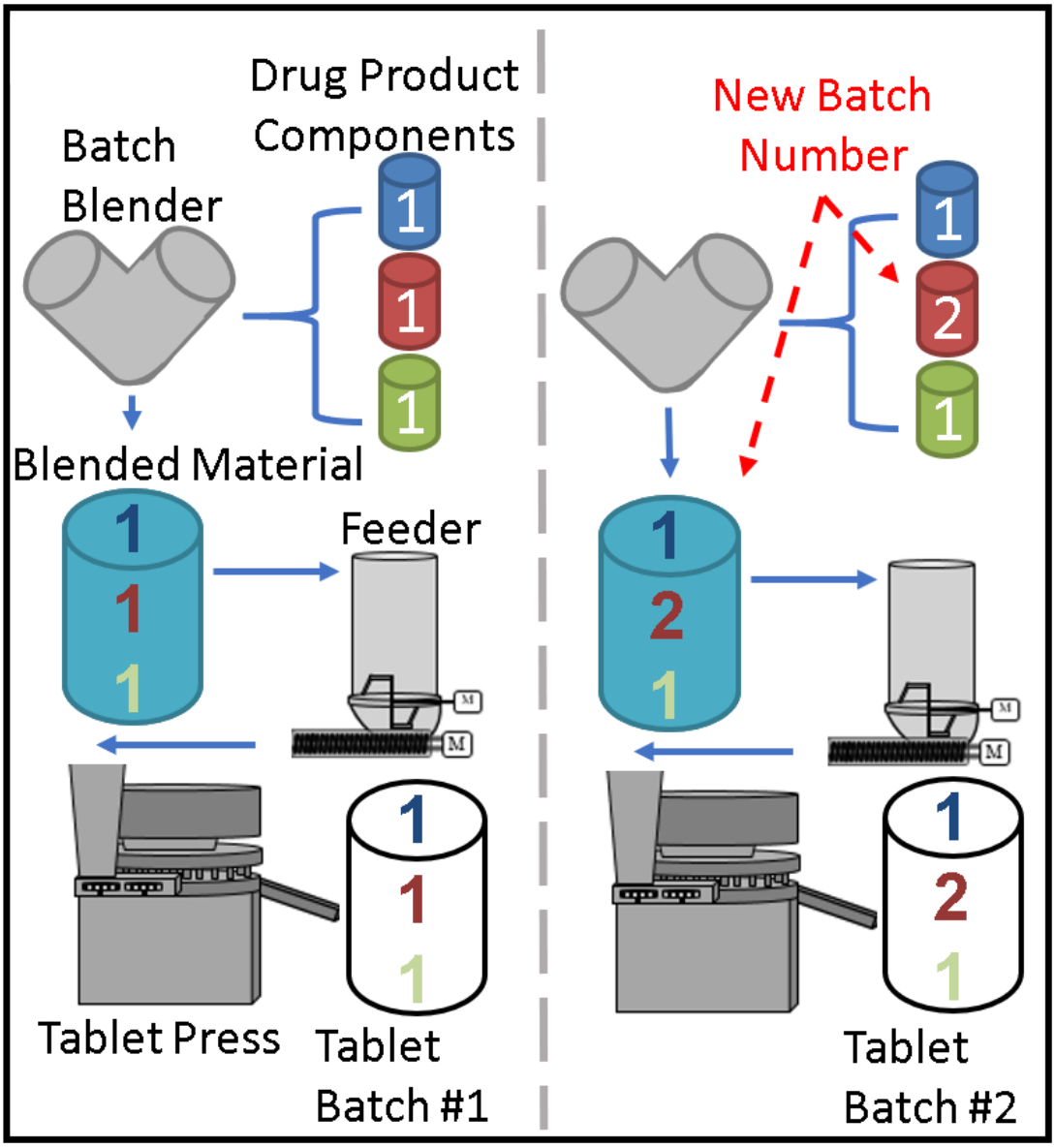

Figure 2. Illustration of material traceability in batch pharmaceutical tablet manufacturing. The red component is used up such that a new batch must be used to meet manufacturing demand(Billups and Singh 2018).

One strategy for material tracing in a process is using the residence time distribution (RTD), which describes how material moves through continuous unit operations (Kvarnström and Oghazi 2008; Engisch and Muzzio 2016). By conducting tracer experiments using a pulse or step change of detectable material at the inlet, the response of

the tracer at the outlet can be measured (Williams and Rahman 1972). The amount of time it takes for tracer to first be detected at the outlet, as well as the time it takes for clearance of the tracer material provide valuable information for material traceability. RTD is a well-established technique and extensively has been used to characterize the manufacturing processes. However, much less attention has been paid to employing the RTD concept for material traceability in continuous pharmaceutical manufacturing applications.

The process considered for development of the material traceability implementation framework is a continuous direct compaction tablet manufacturing pilot plant situated at Engineering Research Center for Structured Organic Particulate Systems at Rutgers University in New Brunswick, NJ. Specifics of the plant have been previously described (Singh et al. 2013). Extensive experimentation has been performed on the performance of this continuous line (Vanarase et al. 2010; Gao et al. 2011; Vanarase and Muzzio 2011). To add, recent advances in flowsheet modeling for process analysis and optimization have added valuable insight to the operation of this line (Boukouvala et al. 2012; Z. Wang et al. 2017).

Chapter 3: Feeder Experimental Characterization

3.1. Materials and methods

The powder of interest was lactose monohydrate from Foremost Farms USA (product number 310) with regular grind specification. The feeder used to conduct these experiments was manufactured by K-Tron. The specific model for this feeder was the twin screw KT-35. The tooling used was the 14.5:1 gearbox reduction with fine pitch concave screws. To gather all relevant data and control the feeder during experimentation, a Profibus adapter was used to connect KCM to the DeltaV control system. The DeltaV system has a continuous historian saving process values on a 1 second interval.

3.2. Feeder Data Interpretation and Calculations

When analyzing feeder data, we were able to extract certain values directly from the K-Tron, as summarized in Table 1. Other signals were calculated from feeder data after experiments were conducted, as given in Table 2.

Table 1. List of critical feeding parameters to be received from fieldbus device.

Parameter	**[units] description**
Net weight (NW)	[kg] weight of material in hopper
Motorspeed	[rpm] speed of motor

Table 2. List of derivable feeding values useful for analysis, calibration, and process understanding.

Parameter	**[units] description**
Mass Flow rate (MF)	[kg/hr] mass flow rate from feeder
Screw speed (SS)	[rpm] revolutions of screws per minute
Feed factor (FF)	[g/revolution] mass lost per revolution

$$MF = \frac{NW(t-1) - NW(t)}{\Delta t} * unit\ conversion\ factor \qquad [Equation\ 1]$$

$$SS = \frac{Motorspeed}{gearbox\ reduction} \qquad [Equation\ 2]$$

$$FF = \frac{MF}{SS} * unit\ conversion\ factor \qquad [Equation\ 3]$$

To smooth out MF, a 5 second trailing moving mean was applied to the signal to decrease noise. This strategy has been utilized in feeding applications prior (Falk et al. 2015). The reason trailing moving mean was used as opposed to centered moving mean was so that during simulation and future implementation, the calculation could be conducted in real-time.

3.3. Results and discussion

Analyzing continuous feeder performance using feed factor is a new area that continues to be explored. There are many factors that may impact feed factor profile, besides the tooling and material composition, which have been addressed prior. With powder being compressible, and the density changing based on the handling history, this opens the

question to the impact of refill size and RPM on the profile. To answer this, we performed a series of experiments, as described in Table 3. The experiment consisted of filling the hopper with the correct refill size as specified in the plan, then setting the set point of the feeder to the correct value such that the desired screw speed was used. Then the feeder was turned on and run until empty.

Table 3. Design of experiments for feed factor characterization

Run Number	Refill Size (kg)	Screw Speed (rpm)
1	2	118
2	2	118
3	2	118
4	2	59
5	4	118
6	4	59
7	4	59
8	4	118
9	2	59
10	4	118
11	4	59
12	4	59
13	4	118

3.3.1. Impact of refill size on feed factor

All the experiments were run, resulting in relationships between the feed factor and the net weight of material in the hopper for each run. This data was then sorted based on size of refill for that experiment, to see if there is any distinction between the data sets which

started at 2 kg hopper mass, and those that started with 4 kg in the hopper. These results are shown in Figure 3.

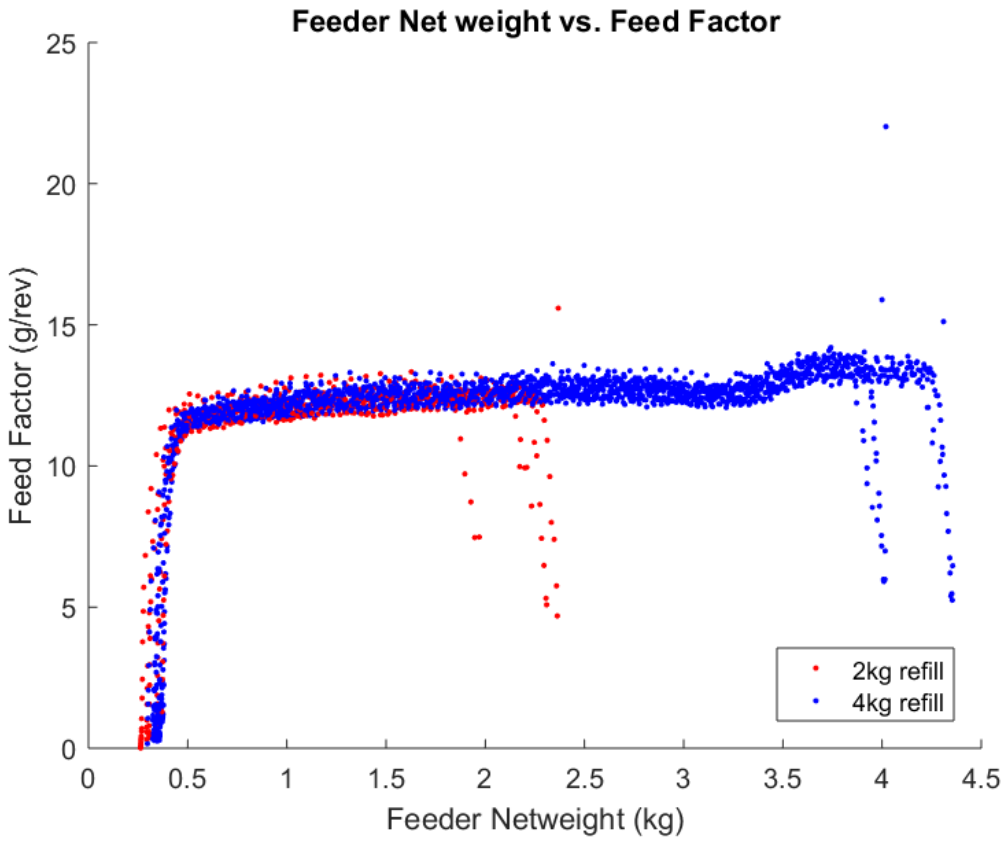

Figure 3. Feed factor profile data comparing 2 kg refill in red and 4 kg refill in blue.

We can see that there is no distinction between the feed factor profiles. This result was surprising given the understanding that powder handling history has an impact on the power properties. However, this difference in filling of the hopper did not impact these feed factor profiles. Therefore, no limitation or distinction must be made as to how the material was filled into the feeder hopper.

3.3.2. Impact of screw speed on feed factor

The impact of screw speed on the feed factor profile was another question that had not been addressed. To answer this, we grouped the results based on the screw speed of the experiment, as shown in Figure 4.

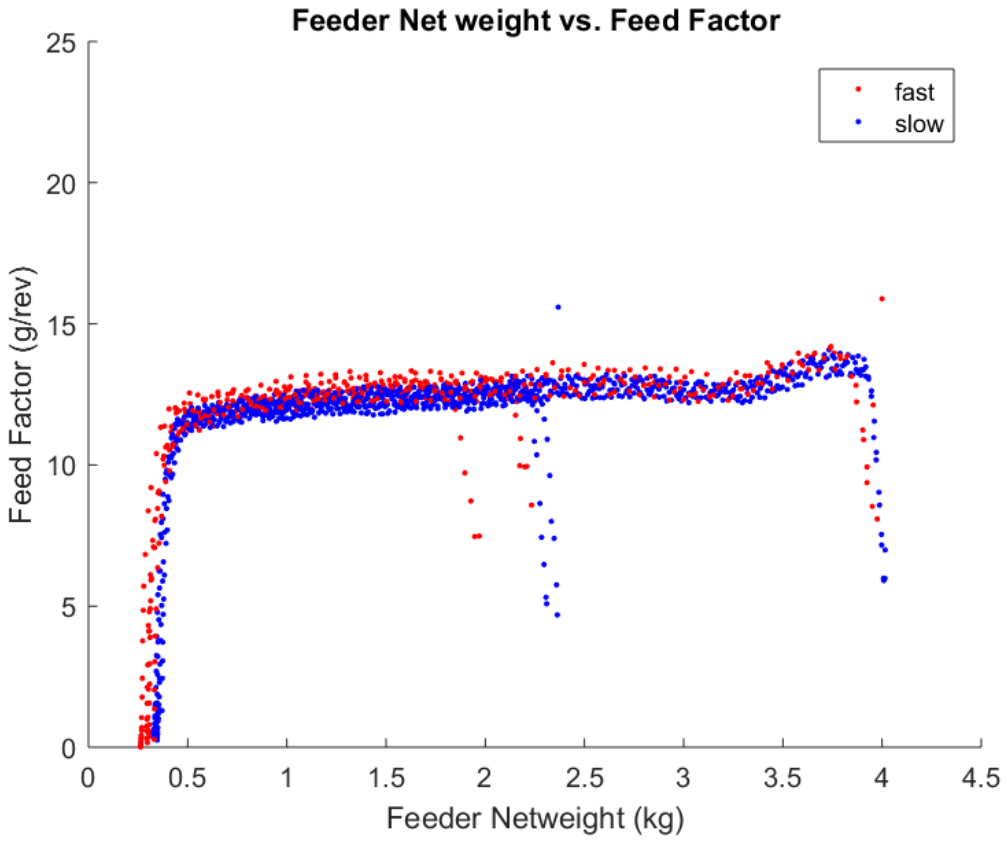

Figure 4. Feed factor profile data comparing screw speed.

We can see here that there is a slight difference between the fast and slow experiments. It appears that the red data (fast) is slightly higher feed factor than the blue data (slow). However, statistical methods were used to conclude that there is no relevant difference between the two data sets. Therefore, we concluded that screw speed did not impact the feed factor profile.

Chapter 4: Control Relevant Feeder Modeling

This chapter is focused on development of control relevant feeder model. The model has been developed and validated for the K-Tron feeder (KT35 with fine pitch concave screws).

4.1. System Identification and Model Development

4.1.1. Overall Control Relevant Model Development

To control the powder feeding unit operation within a pharmaceutical manufacturing plant, a basic control framework must be implemented, as illustrated in Figure 5. First a set point (F_{sp}) must be compared to the actual controlled variable (F_{act}). Then, the difference in these signals is defined as the error, which enters the controller. The output of the controller is the manipulated variable. This variable is adjusted to make changes to screw speed of the feeder. In this specific application, the manufacturer calls this signal set point (SP). This signal then enters the overall process model (GP_{TOT}), which will predict the actual mass flow rate from the powder feeder given certain conditions of the feeder.

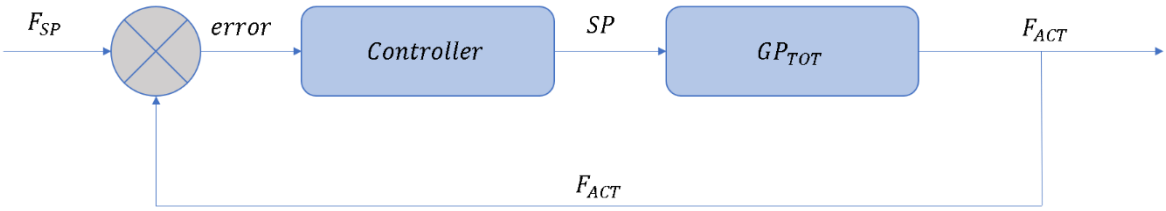

Figure 5. Overall modeling and controls strategy for continuous feeding.

4.1.2. Control Relevant Unit Operation Model

The process model, (GP_{TOT}), predicts outlet mass flow rate from feeder. Figure 6 illustrates the framework for this model for volumetric operation, with Table 4 describing abbreviations in this schematic. As mentioned in previous section, the parameter which

adjusts the feeder speed is referred to as "SP". The CPU within the feeder converts the value of this parameter to a screw speed set point, (SS_{SP}). Then, there is a transfer function model for the dynamics of the screw speed actuation,(G_A). This results in a signal for actual screw speed of the feeder (SS_{ACT}). Then, this value is multiplied by the predicted feed factor (FF) and a unit conversion factor to yield the actual mass flow rate out of the feeder (F_{ACT}). By integrating this signal over time, we can calculate the change in net weight (NW) of powder still in the hopper above the screws. These equations are discussed in detail in the following sections.

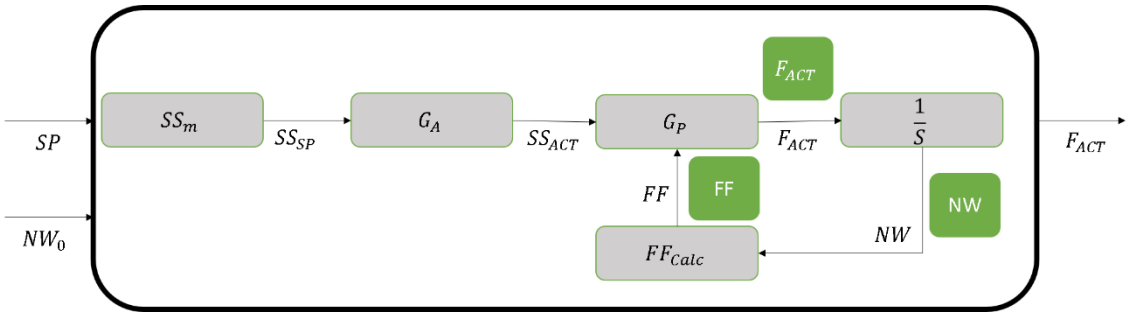

Figure 6. Continuous feeder mechanistic process model.

Table 4: Description of abbreviations used in ***Figure 6****.*

Symbol	Type	Description
$\boldsymbol{SP}$	Signal	Set point value
$\boldsymbol{NW_0}$	Value	Initial net weight of material in the feeder (kg)
$\boldsymbol{SS_m}$	Block/model	Screw speed model, which contains equation of relationship between SP and the Screw speed set point
$\boldsymbol{SS_{SP}}$	Signal	Screw speed set point (RPM)
$\boldsymbol{G_A}$	Block/model	Transfer function model of screw actuator
$\boldsymbol{SS_{ACT}}$	Signal	Actual screw speed (RPM)

G_P	Block/model	Process model, which calculates mass flow rate
F_{ACT}	Signal	Mass flow rate (kg/hr)
$\frac{1}{S}$	Block	Integrates the flow rate signal, to get a change in net weight of material in feeder hopper (kg)
NW	Signal	Mass of material in the feeder hopper (kg)
FF_{Calc}	Block/model	Predicts feed factor from NW
FF	Signal	Feed factor value used for calculation of mass flow (g/rev)

4.1.3. Feed Factor Model

The feed factor is defined as the amount of material lost from the feeder per revolution of the screw. Many experimental factors can affect this feeding parameter. The powder composition and the grade of material will certainly impact feed factor. Also, the tooling configurations such as screw pitch and shape will also impact feed factor.

The basis for this model was first proposed in (Escotet-Espinoza et al. 2015) for GEA compact feeders and was implemented in gPROMS software (PSE) for process optimization using flow sheet modeling (Z. Wang et al. 2017). This model has an exponential form similar to that of the Heckel model, however applies to processes with much lower pressure than applications of the Heckel equations.

The empirical model takes the form of Equation 4, where a, b, and c are fitted parameters from experimental data. NW is the net weight of material in the hopper in kilograms, FF is the feed factor of material in grams per revolution of screws.

$$FF = a - exp(-b * NW) * (a - c) \qquad \text{[Equation 4]}$$

4.2. Experimental Design

4.2.1. Design of Experiments

In order to study powder feeding performance, a series of experiments must be run to provide data for each of the models in GP_{TOT}. For efficiency, the experiments conducted would have to provide data for all the model fitting and process analysis. The experiments defined in Figure 7 were conducted in triplicate, making step changes of various sizes at high and low regions within feeder operating range to characterize feed factor. One goal was to understand the effect of screw speed on mass flow rate from the feeder. This characterizes the overall feeding performance. Also, the step changes enabled us to determine actuator dynamics of the screws. Finally, these experiments provided data on the relation between feed factor and net weight required to fit the feed factor model. These experiments provided all the relevant data to validate open-loop performance of process model over the design space. Experimental condition specifics can be seen in Table 5. Using experiment (1) as a sample description, the screw speed was set to 59 RPM. Then after 500g had been fed, a step was performed to 62 RPM (+3). Then after another 500g, a step was performed to 56 RPM (-3). This pattern was continued until all material fed. This design gave data for various step sizes at different NW values in feeder.

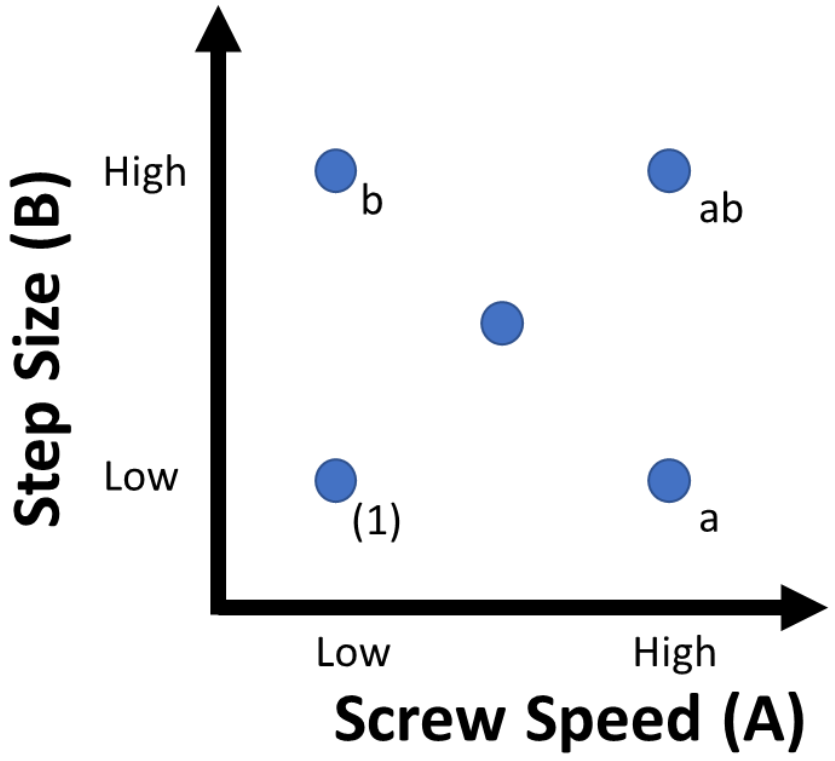

Figure 7. Illustrates the various feeding conditions that were run experimentally.

Table 5. Describes experimental conditions for this DOE.

Experiment	**Screw Speed (RPM)**	**Step Size (RPM)**
(1)	Low (59)	Low (± 3)
A	High (118)	Low (± 6)
B	Low (59)	High (± 9)
Ab	High (118)	High (± 18)
	Middle (88)	Middle (± 10)

To collect this volumetric feeding data, 4 kg of lactose was added to the hopper. The set point was set to reflect the desired screw speed. Then every 500 g of material fed, a step would be made from the initial set point. This stepping pattern was done until the hopper was empty. This design gave us a wide variety of information regarding feed factor at varying screw speeds and at varying net weight values in the hopper.

4.3. Model Calibration

4.3.1. Screw Speed Set point model

Due to system limitations in operation of K-Tron feeder, screw speed set point cannot be directly set. However, a parameter called "set point" (SP) is used to adjust the screw speed. When the feeder is run in volumetric mode, as all these experiments were, SP can be related to the screw speed set point (SS_{SP}) by a linear relation. Another parameter within the feeder, initial feed factor (IFF), is set at 117 kg/hr for these experiments and remains unchanged throughout all experiments. The SS_{SP} is affected by both SP and IFF, and by keeping IFF constant, we can determine a relation for SS_{SP} as a function of SP. By performing the DOE described above, we gathered data to fit this model.

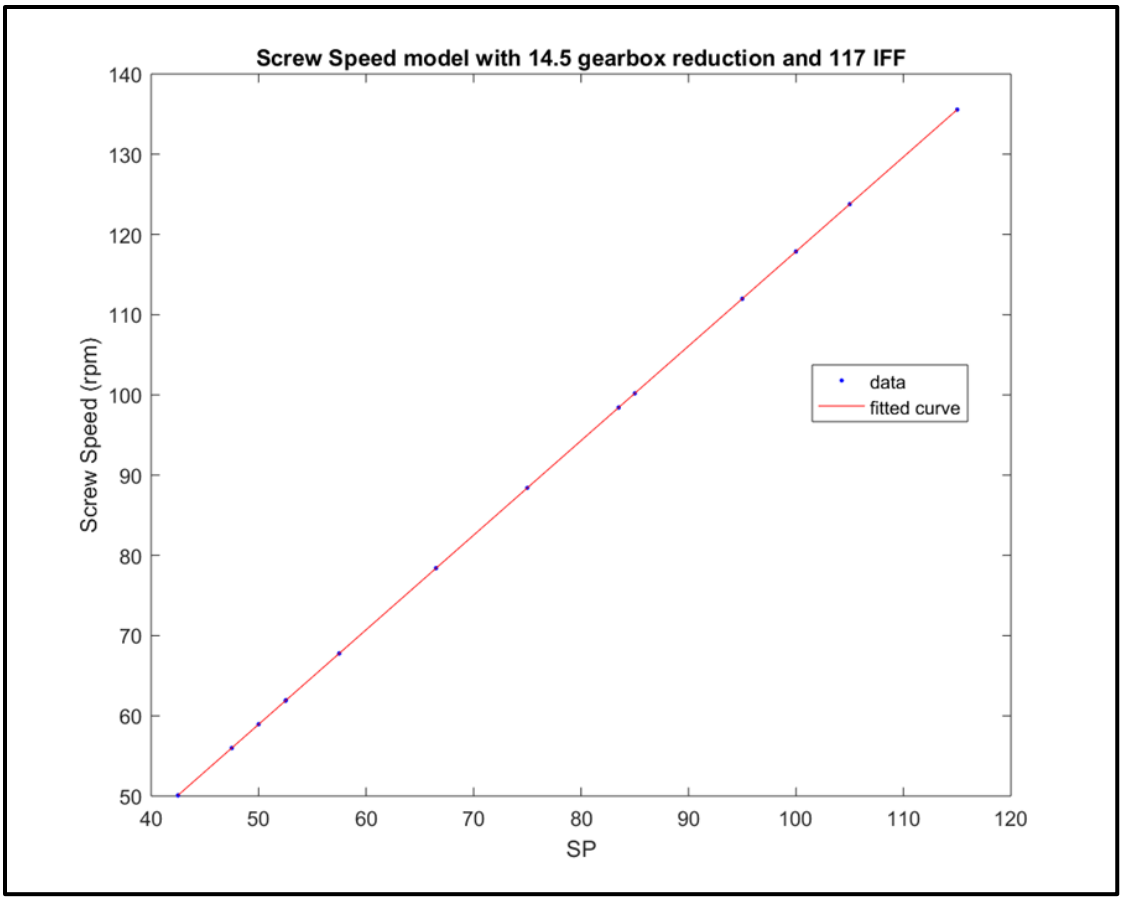

Figure 8. Illustrates experimental relationship between SP and screw speed within K-Tron feeder with Initial feed factor of 117 kg/hr.

From this data, we can see that it fits a linear function and is described by Equation 5 where $r^2 = 1.000$.

$$Screw\ Speed = 1.179 * SP \qquad [Equation\ 5]$$

4.3.2. Actuator model

It was hypothesized that the system dynamics of screw speed reaching setpoint from internal motor controller could be significant to the dynamics of the overall process. To incorporate this into the model, the dynamics of the screw actuator must be modeled. From the experiments run, we collected data on over 70 steps, at many starting points and values. Every step was normalized such that they step up from 0 to 1. Then all the step responses were averaged which was used to fit a first order transfer function. Figure 9 illustrates the normalized step input, the average experimental response of the screw speed, and the fitted first order transfer function.

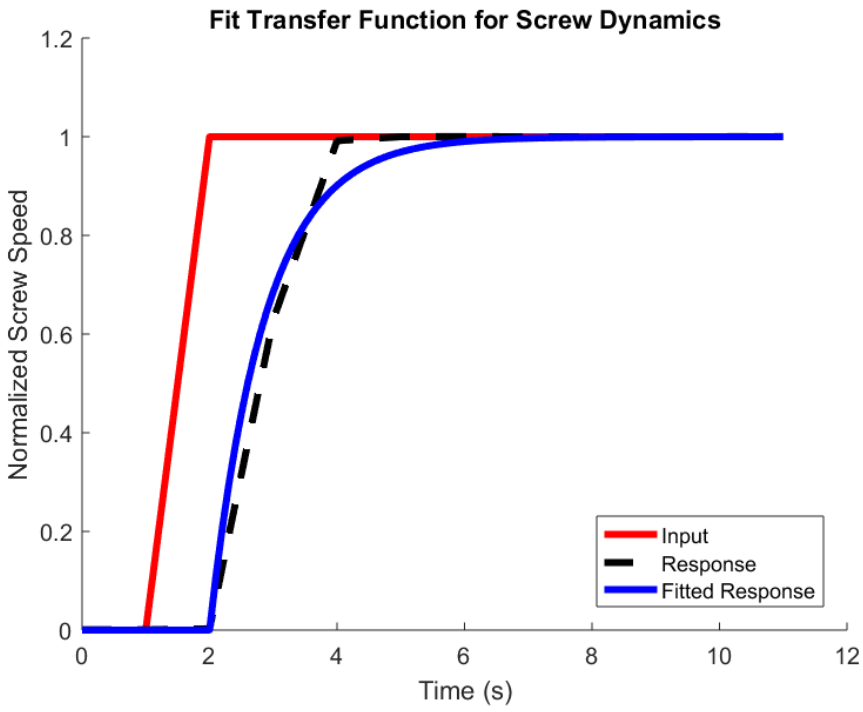

Figure 9: Experimental input and response to screw speed changes. The fitted, first-order transfer function response is illustrated by the blue line.

The first order transfer function takes the form of Equation 6. For a system with no offset, the ratio of $\frac{n}{d_2}$ equals 1. Therefore, n and d_2 were set to 1 and d_1 was the fitted parameter.

$$u(s) = \frac{n}{d_1 * s + d_2} \qquad [Equation\ 6]$$

Table 6: First-order transfer function parameters for screw actuator.

Parameter	Value
n	1
d_1	0.8634
d_2	1

4.3.3. Feed factor model

Using the data from the experiments summarized in Table 5, we were able to develop an empirical data set for K-Tron feeder to investigate and fit the feed factor model parameters, as seen in Figure 10. We chose to fit the model between the range of 0.1 kg and 2.5 kg net weight. When used in manufacturing, the feeder will likely be refilled prior to 0.1 kg left in the hopper. With the steep decrease in feed factor, it would be suggested to operate feeder above this region, therefore the lower limit of the design space was determined. The upper limit of the design space was determined because of the behavior of feed factor above 2.5 kg. We can see that the model would not describe the experimental data in this region. One theory for this shift in feed factor can be attributed to the internal mixing of powder in the hopper. When 4kg of material is added to the hopper, there is a portion above the agitator. When powder is being fed and there is a region above the agitator, that "static powder bed" exerts pressure of the lower region, causing an increased feed factor. Over time, that "static powder bed" decreases in size since level in the hopper is decreasing. Once all the powder in the hopper is being mixed by the agitator, there is no static powder

bed region exerting pressure on the mixed region and the feed factor decreases. The experimental feed factor is well characterized by the feed factor model within this region. Therefore, model fitting parameters from this design space are seen in Table 7.

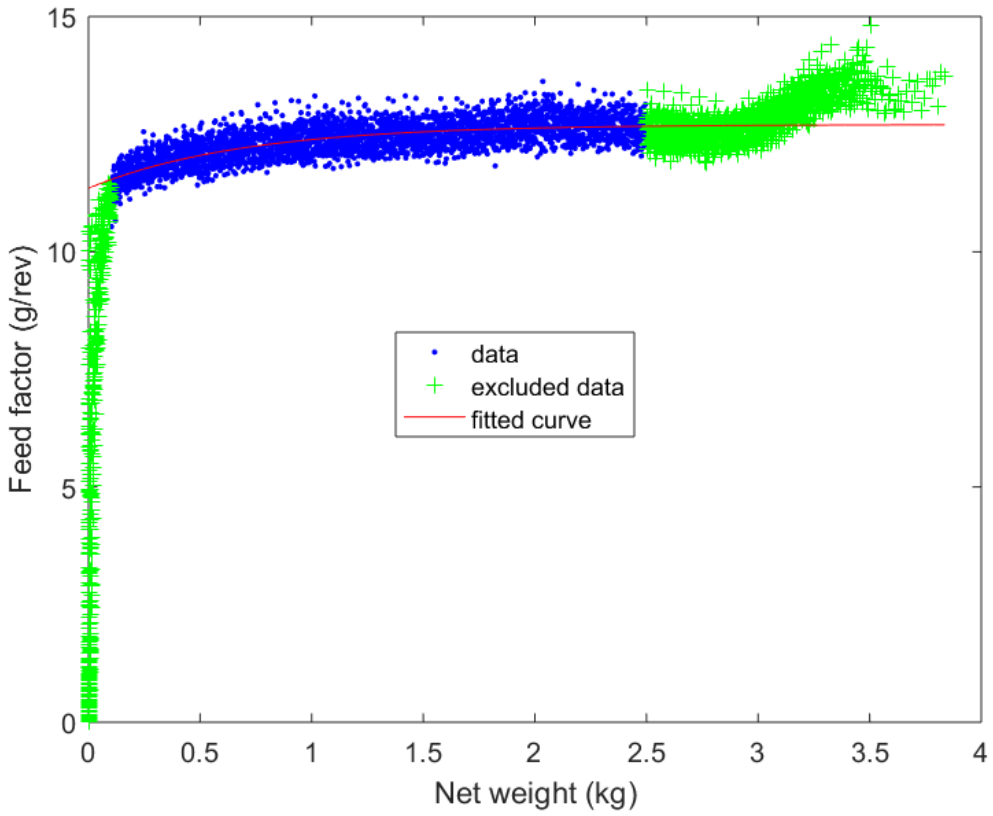

Figure 10. Fit of feed factor equation using experimental data from selected region.

Table 7. Fitted feed factor model parameters and 95% uncertainty ranges.

Parameter	**Parameter Value**	**95% certainty range**
A	12.71	± 0.30
B	1.362	± 0.12
C	11.37	± 0.05

4.4. **Model validation**

To validate the control relevant process model, the SP data from experimental runs was input to the developed process simulation. The experimental and simulated results for mass flow rate, net weight, screw speed and feed factor were then compared. The practical implementation of the control relevant process model was created in MATLAB Simulink (Mathworks), as shown in Figure 11. This model input is SP. The "SSspModel" block calculates the appropriate screw speed set point according to the screw speed set point model calibration above. The actuator transfer function block was created based on calibration above. Then the "GpModel" block calculates mass flow. To calculate the net weight of the feeder, the mass flow rate was integrated over a time step, to calculate how much material left the feeder. This requires the mass flow signal in kg/hr to be in the same units as the simulation time scale which is seconds. Therefore, the gain block was added to convert the units of mass flow rate to kg/s and make it negative, since net weight must decrease over time. The noise was characterized as the difference between the actual feed factor and the feed factor prediction based on the model. This noise signal was added to the predicted feed factor, to provide similar frequency of noise. Illustration of model performance and accuracy is illustrated in the following results section. These validate the open loop process response to changes in screw speed set point and how that affects primary feeding performance attributes.

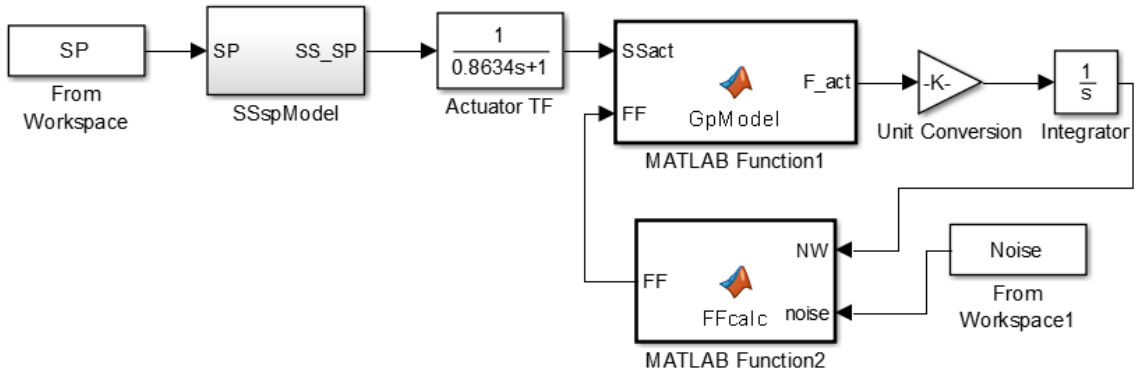

Figure 11. Simulink model for open loop feeder process simulations.

4.5. Applications of model for control system design and tuning

The model is an important tool to taste and tune the controller and thereby to improve the controller performance. The controller re-tuning is recommended for different formulations and/or operating conditions to achieve enhanced performance. Since the process model is validated, we can implement control strategies to maintain the mass flow rate using the model. Because of the simplicity of the process dynamics and faster response, the classical PID controller has been selected here for demonstration of the application of the model. Note that, the same model can be used for many other applications such as sensitivity and scenario analysis but the focus of this work is to demonstrate the applications of the model for control purposes.

4.5.1. Implementation of controller into the model for closed-loop simulation

A PI controller was first implemented for mass flow control, as seen in Figure 12. As shown in figure, a PID controller has been added into the process model. The feeder flow rate is

predicted through simulation. The predicted signal is sent back to a comparator block where it has been compared with desired set point. The deviation signal (error) is then sent to controller that provides actuator signal. Finally, the actuator is sent to the process. In real manufacturing scenario, the model will be replaced with actual equipment. The controller involves 3 tuning parameters that need to be tuned properly.

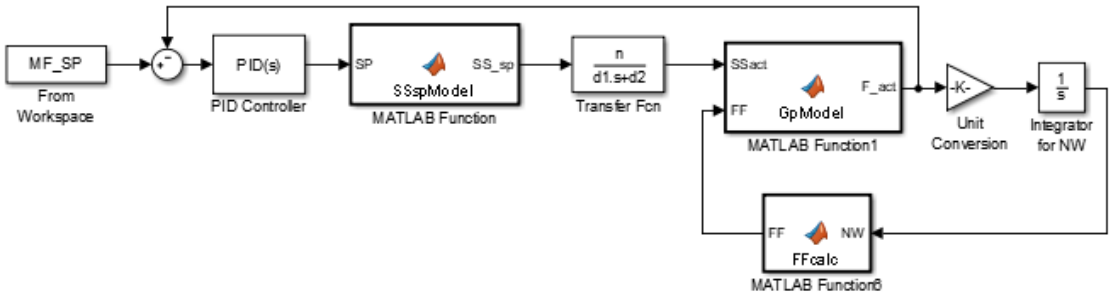

Figure 12. Schematic of PID control strategy implemented in feeder simulation using SIMULINK.

4.5.2. Strategy for tuning of controller parameters

The controller parameters were tuned by minimizing the integral absolute error (IAE). The reason optimization-based tuning was used as opposed to a typical heuristic-based controller tuning algorithm like Zeigler-Nichols or other methods was because we tuned controller performance to accommodate the actual noise in the process, as well as the changing feed factor. If Zeigler-Nichols were performed for only one step, at a certain time in the simulation, it would only be optimal for this situation. Therefore, the optimization algorithm was applied to achieve optimal performance. Details of this tuning algorithm are described in the following section.

This feeding model is a time variant, non-linear process, due to the feed factor model's non-linear correlation to net weight. Therefore, to tune this controller, a unique optimization strategy was implemented to find the best parameters. This was done by running the feeding simulation and increasing the mass flow set point by 5 kg/hr, every 25 seconds, until the net weight of the feeder reached zero. The IAE was calculated for that simulation. Then the simulation was reset and run again decreasing mass flow by 5 kg/hr, every 25 seconds, until the net weight of the feeder reached zero. The IAE was calculated for this simulation. Then the IAE for the step up simulation and step down simulation were combined. This summed IAE was used for minimization and the optimal tuning parameters for the non-linear system over the operating range were found. The results for this are summarized in Table 8.

Table 8. Results from tuning PID controller using different optimization metrics.

Minimized Metric	**P value**	**I value**
IAE	0.8132	1.1886

4.5.3. Closed-loop performance evaluation

The performance of control system is normally evaluated using multiple metrices such as integral of absolute error (IAE) and integral of time weighted absolute error (ITAE). Another metric which can be used to measure how the mass flow tracked the set point, is the mean percentage error (MPE), presented in Equation 7. n is the number of samples, or the time points for the simulation, a_t is the actual mass flow signal, sp_t is the mass flow set point.

$$MPE = \frac{100\%}{n} * \sum_{t=1}^{n} \frac{a_t - sp_t}{a_t} \qquad [Equation\ 7]$$

For this simulation, the MPE is quite small for a system with this much noise. The controller was able to handle this scenario without becoming unstable, an essential performance criterion.

Another metric which can be used to see how much noise was present in the signal is the mean absolute percentage error (MAPE), presented in Equation 8. This is almost the same as MPE, however fluctuations above and below the setpoint no longer cancel out, making this metric able to tell how much noise was present during simulation.

$$MPE = \frac{100\%}{n} * \sum_{t=1}^{n} \left|\frac{a_t - sp_t}{a_t}\right| \qquad [Equation\ 8]$$

4.6. Results and discussions

4.6.1. Model performance evaluation

The model has been validated against a separate set of experimental data. The results are shown in Figure 13 and Figure 14. It can be seen that the model simulates these scenarios closely to the experimental results collected. One important note for the mass flow plots in the upper right quadrant of and , is that the simulated mass flow is quicker to respond than experimental mass flow. It was determined that this less steep transition in experimental mass flow was an analytical artifact due to a 5 second trailing moving average applied to the experimental data for signal smoothing. When our simulation mass flow has the same

averaging method applied, the experimental results and simulation match well. This also helps us to conclude that there is no added dynamics in the process response to changes in screw speed, that the observed dynamics can be attributed to the signal smoothing technique applied. This leads us to believe that this simulation accurately predicts the feeding process behavior and performance for this tooling configuration and material, providing us a validated control relevant process model for the feeder.

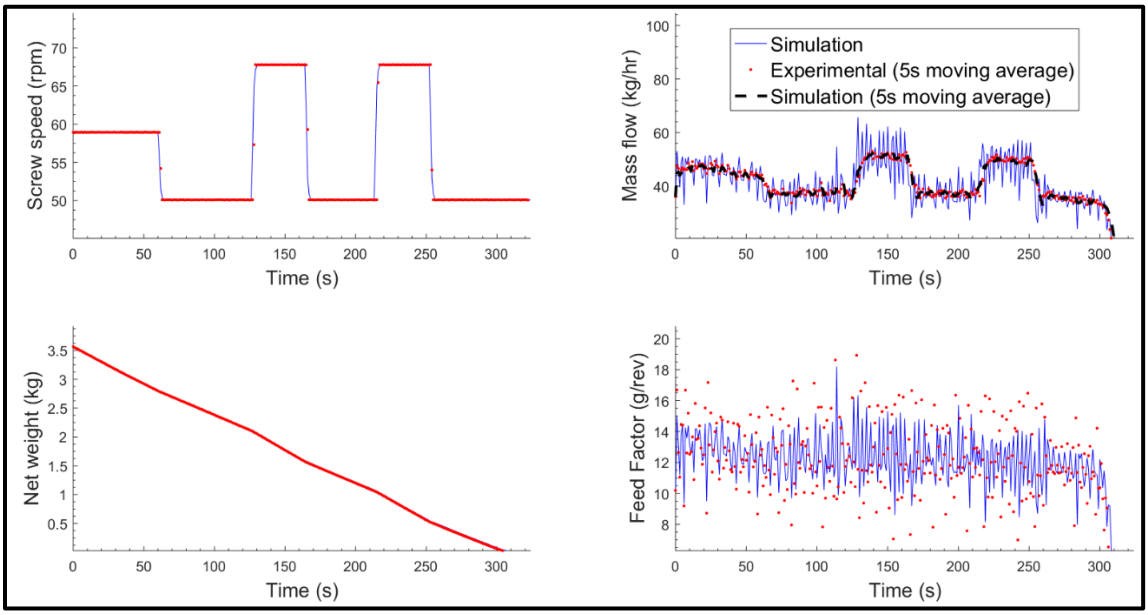

Figure 13. Illustrates simulation performance in the range of 68 rpm.

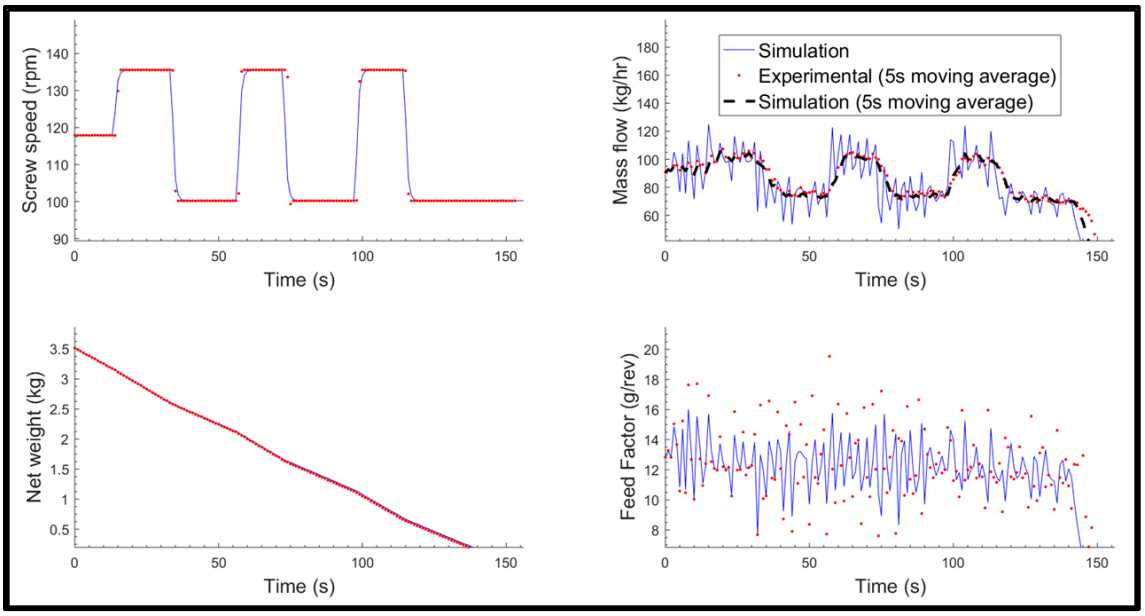

Figure 14: Illustrates simulation performance in range of 118 rpm.

4.6.2. Performance evaluation for closed-loop operation

In many pharmaceutical applications, maintaining set point is the primary role of feeder control. As we have seen, the feed factor changes as a function of net weight, therefore screw speed actuates to maintain mass flow set point. Figure 15 illustrates the performance of the PID control strategy presented in this work. We can see from the results of controller performance presented in *Table 9.*

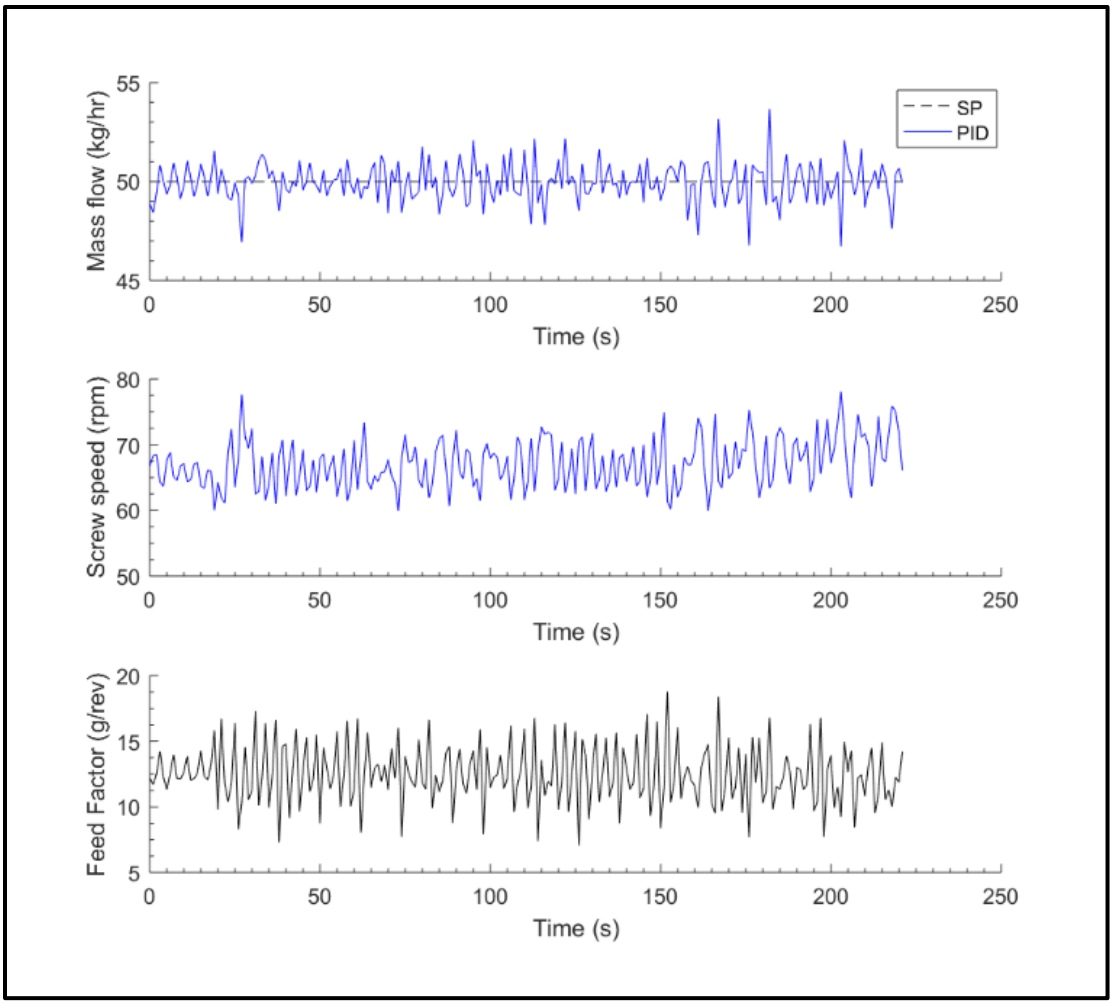

Figure 15. Controller performance for maintaining constant set point during feeder operation.

Table 9. Controller performance for maintaining constant set point using IAE optimized tuning parameters.

	IAE [kg/hr]	ITAE [kg/hr]	MPE [%]	MAPE [%]
PID	1499	170,210	-3.24	14.60

4.6.3. Set point tracking

To test the set point tracking performance of the controllers, over the operating range of this non-linear model, a stair pattern was used, as shown in Figure 16. This was done to

determine controller performance of steps at instances where the process gain is varying, specifically at different values of net weight. Those results are presented in Table 10.

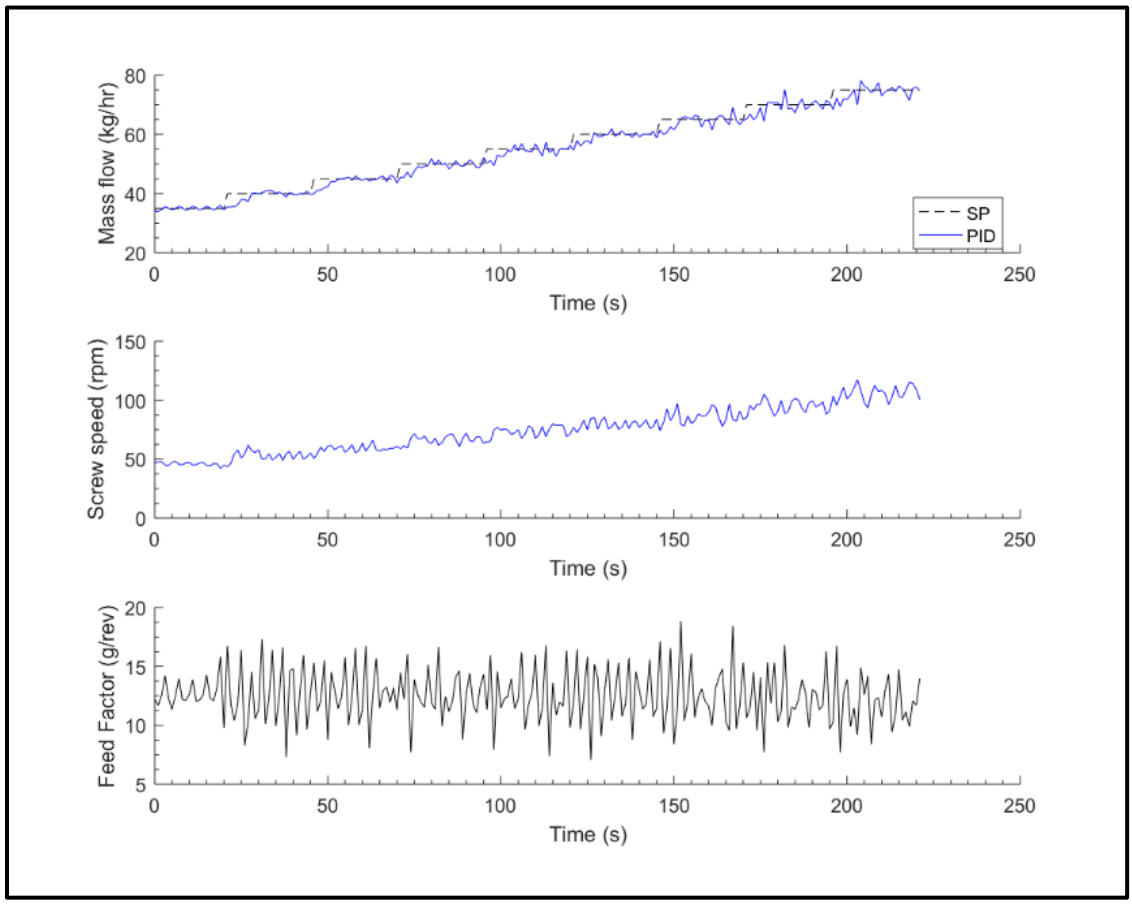

Figure 16. Controller performance for setpoint tracking during feeder operation.

Table 10. Controller performance for setpoint tracking using IAE optimized tuning parameters.

	IAE [kg/hr]	**ITAE [kg/hr]**	**MPE [%]**	**MAPE [%]**
PID	1680	213990	-3.76	14.68

We can see for this system with increasing set points, as well as realistically noisy feed factor, the controller was able to maintain set point and control process.

4.6.4. Process disturbance rejection

While we have shown that the controller is suitable for set point changes as well as maintaining constant set point, we can further investigate how the controller will handle certain disturbances that could occur in the plant. The first scenario simulated is a disturbance in the feed factor. This could be caused by a release of dense powder from screws or hopper caused by continuous use or could be the affect if the feeder was disrupted during feeding. During operation, there is some compaction of powder in certain place in the feeding system, such as in the hopper near the agitator bar or near the feeding screws. These accumulations could release themselves at unpredictable instances, introducing a disturbance in feed factor. It is also possible at lower flowrates for a clump of material to fall from the feeder barrel, increasing the amount of material released per revolution of the screws.

This simulation makes a step up in feed factor by 5 grams per revolution, for 2 consecutive seconds, shown in Figure 17 in the bottom subplot, to simulate dense agglomerate being released in the feeder. As shown in the top subplot, mass flow does get disrupted slightly by this disturbance, but the controller is able to stabilize in a reasonable amount of time. The performance of the controller for this scenario is summarized in Table 11.

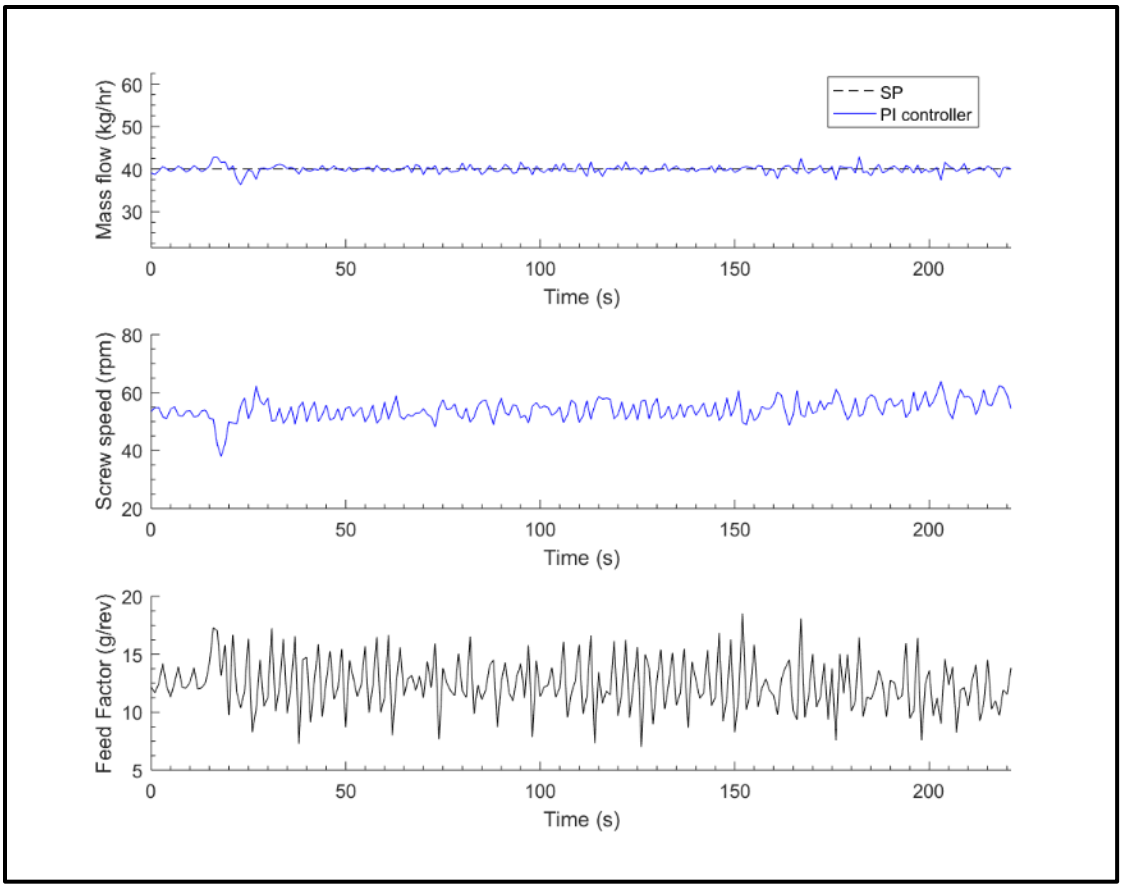

Figure 17. Illustrates controller performance for process disturbance in feed factor.

Table 11. Performance criteria for PID control during process disturbance.

	IAE [kg/hr]	ITAE [kg/hr]	MPE [%]	MAPE [%]
PID	1216.1	136,710	-3.31	14.81

Chapter 5: Systematic Framework for Material Traceability

Acknowledgements

This work has been previously published and authors/co-authors are acknowledged.

1. Billups, M., Singh, R. **(2018)**. Material Traceability in Continuous Pharmaceutical Tablet Manufacturing. Pharmaceutical Technology 42 (2), 32-35, 59.
2. Billups, M., Singh, R. **(2018)**. Systematic framework for implementation of material traceability into continuous pharmaceutical tablet manufacturing process. Journal of Pharmaceutical Innovation. Review submitted.

5.1. Batch and lot definition

The following definitions are defined according to the Code of Federal Regulations Title 21 (FDA 2015).

- **Batch:** "specific quantity of drug or other material that is intended to have uniform character and quality, within specified limits, and is **produced according to a single manufacturing order** during the same cycle of manufacture."
- **Lot:** "batch, or a **specific identified portion of a batch**, having uniform character and quality within specified limits; or, in the case of a drug product produced by continuous process, it is a specific identified amount produced in a unit of time or quantity in a manner that **assures its having uniform character and quality** within specified limits."

- **Lot number:** "means any distinctive combination of letters, numbers, or symbols, or any combination of them, from which the **complete history of the manufacture**, processing, packing, holding, and distribution of a batch or lot of drug product or other material can be determined."

In order to comply with the guidelines, set by the FDA with regards to defining "batch" and "lot" there is a specific way continuous manufacturing pharmaceutical drug product batches and lots can be defined. For commercial applications, where regulatory guidelines are mandatory, it is required to follow a manufacturing protocol (FDA 2015). This protocol defines validated operating conditions for the unit operations involved in manufacturing. This holds true for continuous manufacturing as well as the traditional batch processes. Each unit operation in the line would have a set of parameter ranges which the parameter must operate within, and usually there is a set point for each parameter to follow during production. If a production order follows this group of set points, as well as stays within the parameter ranges, then the product should have "uniform character and quality, within specified limits" due to reproducibility of the process at the same conditions. In continuous manufacturing, this can also be the case. If no change is made to operating conditions and the process is not interrupted, then the length of time which this is true would follow the definition of a "batch".

In the case that one component of the formulation changes batch number, theoretically, the tablet quality should not change given that the process conditions are unchanged. However, for material traceability purposes, the tablets containing raw material from one batch and

another need to be distinguished. This raw material batch change occurs during a single manufacturing order and with no changes to the process conditions, therefore is still the same batch. However, we can assign these tablets containing new raw material batch to a separate “lot”, within the current tablet batch. This would be a “specific identified portion of a batch” in which the tablets contain material from a raw material batch different from the previous lot. The idea is that, when tablets are released, with a specific batch number and lot number, it exactly traces to what raw material batches may be present in the tablet. By changing the lot based on raw material batch composition in the tablets, it can be certain, if recall was required for specific raw material batch, which lot of tablets must be recalled as well, without recalling the entire batch, many of which tablets contain none of the recalled raw material batch.

If there was a change in raw material batch, the tablet lot number would increment once that new batch is predicted to reach the tablet. Tablets would be collected, knowing that raw material from both the old and new batch can be present in the tablet. Once it is predicted that all the old material has cleared from the line and none will be present in the tablets, a new lot number would be assigned to the tablets and collected separately from the other lots. That way, lots of tablets containing different raw material batch compositions will be known and their raw material make up will be logged. This is visualized in Figure 18.

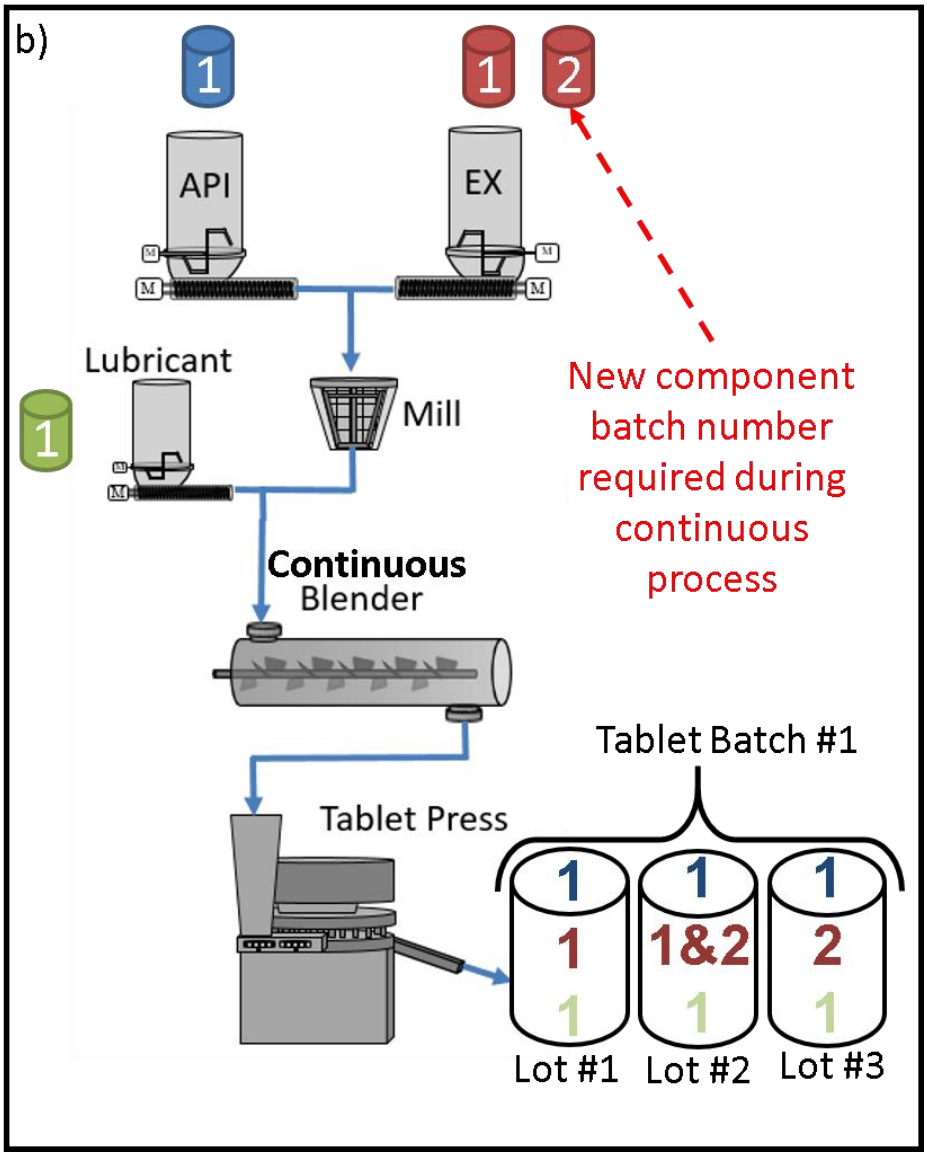

Figure 18. Illustrates continuous manufacturing material traceability where red component is used up during the production run and a new batch is used.

As shown in Figure 19, at t = 0, the new batch of one component (e.g. excipient) is added to the feeder. According to residence time experiments, we can predict that at t = T1, the new batch will begin to be present in the tablets. That defines the start of a new tablet lot, lot number 2, where both previous and new batches of excipient are present in the tablets. Then at t = T2, the previous batch of excipient has been entirely cleared from line and no

longer present in tablets. Therefore, tablet lot is defined as lot number 3. The same concept will apply for the other components of formulation. The correlation between tablet lot number and batch number is given in Table 12.

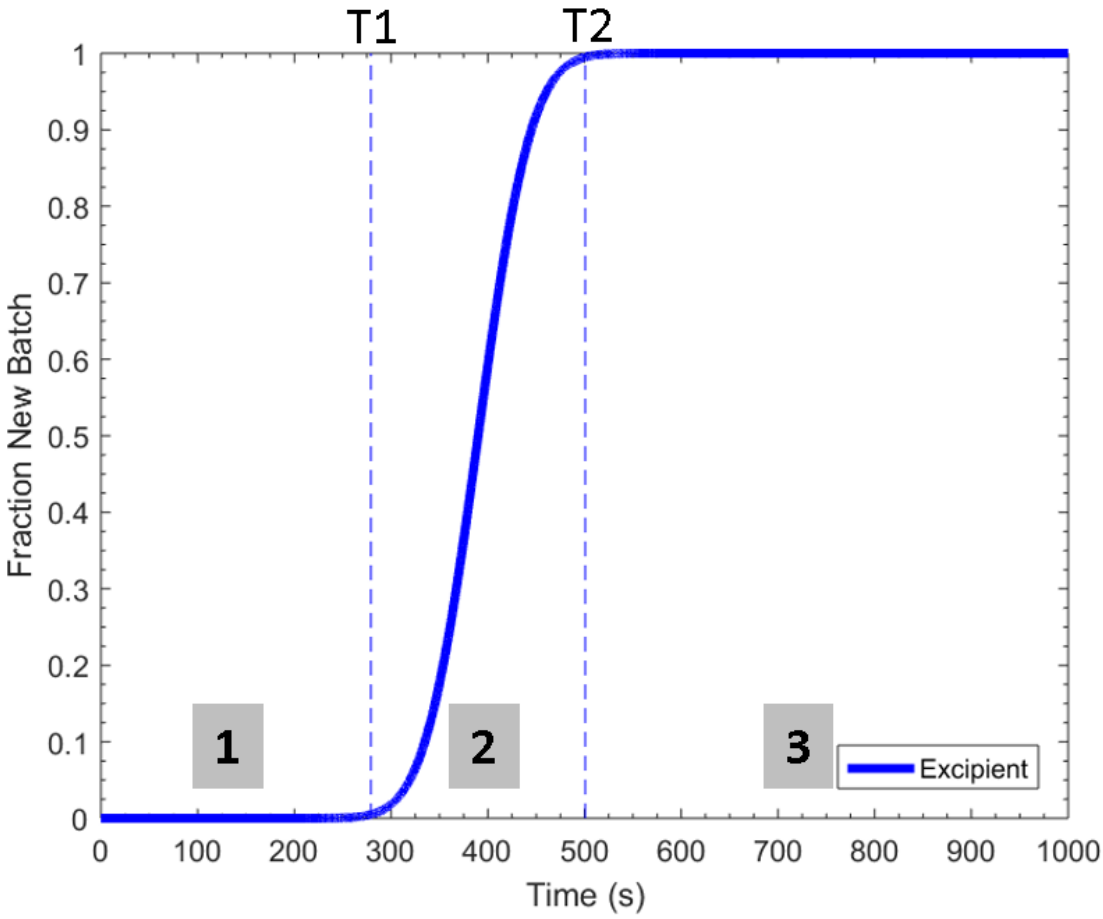

Figure 19. Demonstration of concentration of new component (e.g. excipient) batch changes at the outlet of the system. At t=0, the new batch of excipient is added to the feeder. 1, 2, 3: Tablets lots. T1, T2: Time to initiate new lots.

Table 12. Defines correlation between tablet lot number and batch number as illustrated in Figure 19.

Time	Tablet Lot Number	Component Batch
0	1	Excipient_Batch 1
T1	2	Excipient_Batch 1 & Batch 2
T2	3	Excipient_Batch 2

This strategy can be also applied to systems where multiple components are transitioning from previous batches to new batches as illustrated in Figure 20. As shown in the figure, the excipient (e.g. Lactose) refill occurs at t = 0 seconds. Then at t = 120 seconds, the API (e.g. acetaminophen) component refill occurs. At t = T1, the new batch of excipient is predicted to be present in the tablets, as well as the previous batch. At t = T2, the new batch of API is predicted to be present in the tablets, as well as the previous batch. At t = T3, the excipient previous batch is cleared from the continuous line, leaving tablets to contain only new batch. And at t = T4, the API previous batch is cleared from the continuous line, leavings tablets to contain only the new batch. Based on the time at which these events occur dictates when new tablet lots should be defined. The tablet lot definitions and compositions are described in Table 13. Similarly, the concept can be applied for multi-component formulations. The complexities in material traceability will increase as the number of components will increase. The change in batches can occurs in any order depending on formulation composition and feeder capacity. Therefore, a systematic software tool is needed to manage the complexities.

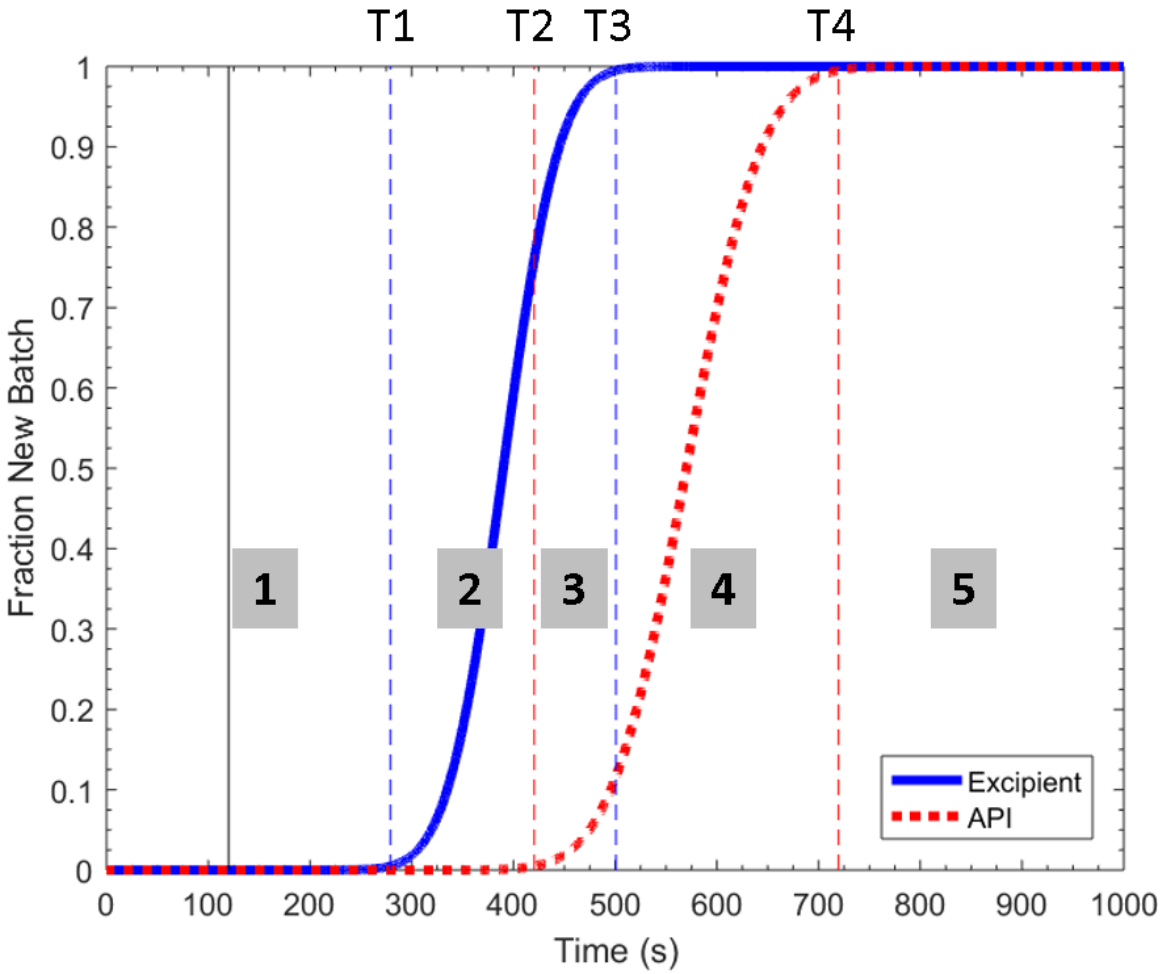

Figure 20.Illustrates tablet lot assignment based on concentration of new component batch. Excipient is transitioning from Excipient_Batch 1 to Excipient_Batch 2 and API is transitioning from API_Batch 1 to API_Batch 2. Excipient batch change initiated at t = 0. API batch change initiated at t=120.

Table 13. Defines correlation between tablet lot number and lactose and acetaminophen batch numbers as illustrated in Figure 20.

Time	Tablet Lot Number	Excipient Batch	API Batch
0	1	Excipient_Batch 1	API_Batch 1
T1	2	Excipient_Batch 1 & 2	API_Batch 1
T2	3	Excipient_Batch 1 & 2	API_Batch 1 & 2
T3	4	Excipient_Batch 2	API_Batch 1 & 2
T4	5	Excipient_Batch 2	API_Batch 2

If there was a change in process set points outside of the range defined in the validated protocol, if a new manufacturing protocol was to begin to be followed, or if the production line stopped for any reason, that would signify a different batch of tablets. When raw material batches change, the lot would increment within the new batch of tablets. For the records, this naming system would allow batch records to still contain all process condition set points and ranges for that batch, and actual process variables can be compared to the protocol to ensure no deviation outside of the ranges.

5.2. Systematic framework for material traceability

Many specific steps must be taken to integrate material traceability, as outlined in Figure 21. There are three initial steps which must be completed in parallel. The first requirement is plant automation and communication between control hardware and software. This

allows for process data storage, as well as communication between control software and material traceability tool. Another step is the creation of the feeder refill protocol to be followed during continuous operation of the feeders. This must be determined early in the framework since both RTD experiment and the process operation require reproducible refill results. Final step is finalization of formulation specifics, which includes what materials are used, the grade and type of each component, as changes in this could affect RTD and material traceability.

The next step is to configure the continuous manufacturing line by determining each unit operation, specify the tooling to be in each piece of equipment and assemble the continuous line. This is critical because changes in any of these specifications will change the RTD for the process, leading to inaccurate traceability. Then, experiments are conducted to determine RTD of each component from moment of refill to outlet of process. The information extracted from the RTD is stored in a model library. Now all the information and process decisions have been made to implement the material traceability methodology. And in executing this methodology, a log file is created defining the raw material batch numbers for each tablet lot.

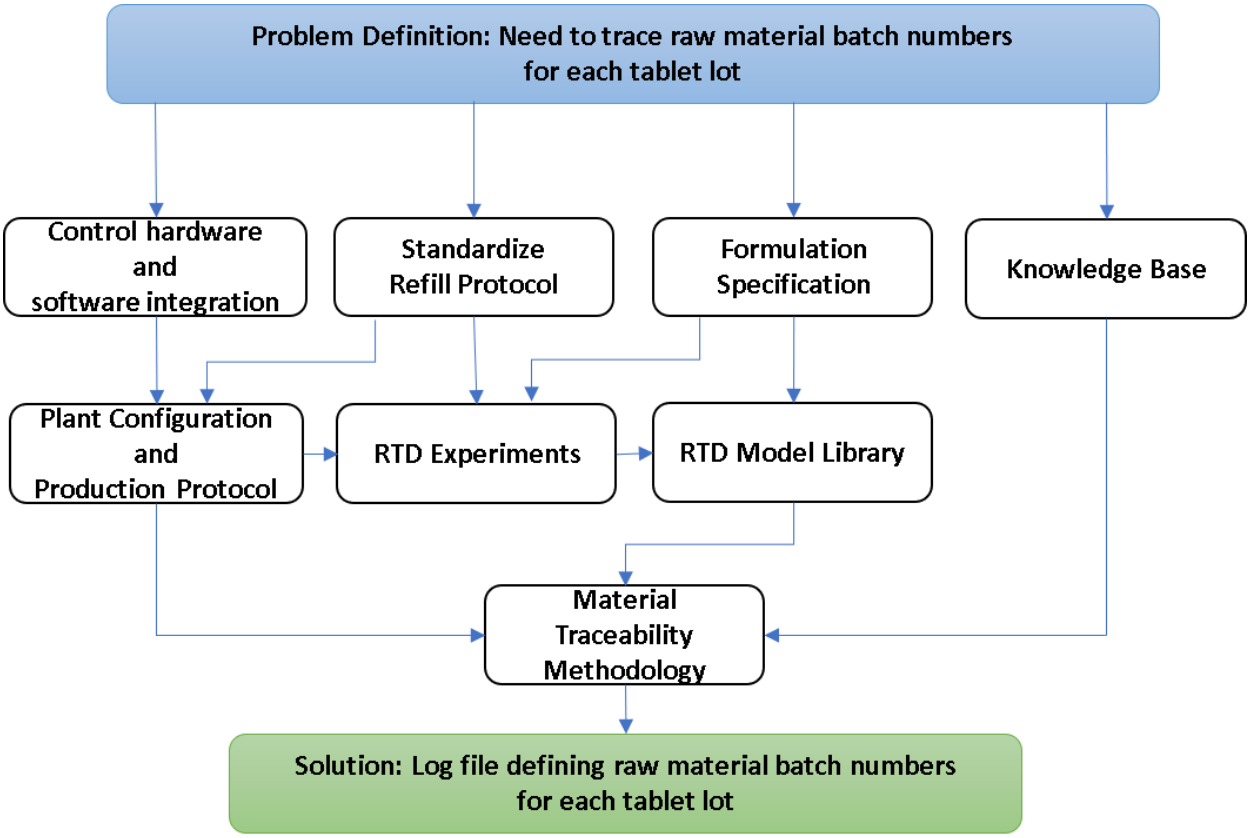

Figure 21. Overview of proposed systematic framework for material traceability.

In order to implement this framework for material traceability, there are a few conditions which must be met prior to operation during production. The first condition is that a protocol must be written detailing the feeder refill procedures. The accuracy and repeatability of this procedure is essential for creating consistent RTD models, as well as increasing accuracy of the RTD models' parameters to the continuous production campaign where the models' parameters will be implemented. The refill procedure must specify the size of feeder hopper on each feeder, as well as the point in which refill occurs. This information must be defined and standardized, so that RTD models accurately replicate conditions during continuous manufacturing process. In order to define the specific process attributes we are looking to get out of the model, the minimum residence time and

maximum residence time, the RTD models must also be developed in a specific and consistent manner.

The goal of these RTD tracer experiments is to determine from the moment that a new batch is used to refill each feeder, how long it takes for that new material batch to make it into the tablet as well as how long it takes for the old material batch to be cleared from the process. RTD models can be built by doing tracer experiments with a pulse of NIR detectable material which has similar flow properties. Since the model will be applied to a "step" change of new batch of material, rather than a pulse, we propose that the RTD tracer experiments be performed with a step change. This will provide cumulative change data, rather than a RTD, but will better simulate the raw material batch change experienced during production. Using the empirical data for the tracer concentration over time, we will be able to determine the duration of time after refill occurs that the tracer is detected (minimum residence time), in addition to the time duration after which only tracer is present and all initial material has cleared (maximum residence time).

To conduct these RTD tracer experiments most effectively, there are a few specific details that must be understood and applied. First point to note is that each component in the formulation will have different residence time in the continuous line. Because different components having different flow properties, their hold up in their respective feeder will be different. In addition, some materials will be added to the process further downstream, therefore decreasing their residence time in the system. For example, lubricant is normally added after milling operation. Therefore, a tracer experiment must be performed for each component independently. Second point to note is that these RTD tracer experiments are

formulation specific and depend on composition of the blend as it moves down the line. This means that each tracer experiment must be performed with the intended powder formulation used in production. Powder substitutes, or surrogates, should only be used during RTD experiments when they have been proven to behave like the component they are replacing. Third point to note is that these RTD experiments determine residence time attributes of the entire line. To validate the results from convolution of individual RTDs, an entire line experimental RTD must be conducted to prove that the models accurately predict behavior of the entire process. However, for the applications in material traceability, the minimum and maximum residence time values are the primary information extracted from RTD experiments. Such values can be gathered directly from an RTD experiment of the entire line and RTD models of the individual unit operations are not required. It also decreases the number of tracer experiments that need to be performed for each formulation. For example, with a continuous direct compression manufacturing line, as seen in Figure 1, that has 6 unit operations- 3 feeders (one for each raw material), one co-mill, one continuous blender, and one tablet press- the number of experiments is greatly reduced from 11 individual unit operation tracer experiments down to 3 entire line tracer experiments. RTD for each unit operation, and every component within each operation, requires one RTD experiment per feeder, two experiments for the mill, three experiments for the blender and tablet press, resulting in 11 RTD experiments to describe three components in this line. RTD of the entire line requires just three experiments, one per component.

This methodology stores the tablet lot number in the control platform. Therefore, prior to running the production batch, the lot number signal must be configured to communicate between the material traceability tool and the control platform. This configuration can be done in a number of ways. One common communication protocol to send information between different pieces of software is through OLE process control (OPC) servers. The OPC server management software must be configured to pass the desired information through the network to the desired location.

Once these processes are completed offline prior to the production run, a material traceability tool can be utilized to trace composition of each tablet lot created during a production batch. This tool must be capable of logging the raw material batches for each tablet lot, as well as send the lot number via OPC to the control system at the correct time based on the residence time attributes. To accomplish these tasks, the program must allow the user to specify the residence time attributes for each component, as well as the number of raw material this specific formulation contains. It must also allow user to specify the batch number of the initial raw material drums. Then, it must allow for seamless changes of batches, creating new tablet lot and logging what material is present in each of the lots and send that information in real-time through OPC to the control system for data logging. The program for sending lot changes to the control system must be able to handle multiple changes in rapid succession, where multiple raw material components are “transitioning” between batches. And finally, it must provide the log to the user in an easy-to-read manner so that the material lot information can be included in the master batch record for that batch of tablets.

5.2.1. Residence time Distribution Model Library

For the RTD models to accurately predict the appearance of the new raw material batch in the tablet, as well as the time delay for clearance of the previous raw material batch, models must be built for each formulation, and component within that formulation. Depending on the current design of the continuous tablet manufacturing line and the specific unit operations, the time delay values must be determined. When determining RTD models, the tooling of each unit operation should be exactly the same as to be used in production. Any change that could affect the flow properties of the powder blend will impact the RTD model. If there is a change in tooling of a continuous blender for example, or if a different type of blender is added, RTD determinations must be re-tested to determine the time delays of the entire line associated with the new equipment or tooling of existing equipment. Also, if there is a formulation with same components but different strength, new RTD models must be determined due to changes in feeding ratios. This could affect the RTD of each component, therefore a new set of model parameters would be used and stored in the model library. Also if the formulation is the same, but there is a change in tablet production rate, that would also affect the RTD parameters. So for each combination of formulation and production rate present, specific RTD parameters must be determined.

There are many methods for determining the minimum and maximum residence time experimentally. One possible method would be to monitor tracer composition in tablet using PAT. Spectroscopy calibration model development for this formulation would be required to allow for real-time detection of tracer in tablets. This PAT instrument could be NIR, Raman, or microNIR, depending on the formulation and tracer. The limitation of this

strategy is the limit of detection for low concentrations of tracer in the tablet. To avoid this limitation, it is also possible to analytically determine tracer concentration in tablets. An HPLC method could be developed to detect much lower concentrations of tracer, increasing accuracy of minimum and maximum residence time attributes.

The steps involved in applying the RTD model for material traceability is systematically shown in Figure 22. First, the refill protocol must be developed and followed for the experiments. Then according to the manufacturing order, the production rate and formulation specifics must be applied. This means that each feeder must run at the correct production rate, and the specific components must all be used. The tracer is needed to perform an RTD experiment. Since each component has different properties, a tracer must be selected to match those properties and demonstrate the same flow behavior of each component. The continuous process is started, and then the tracer is added to the feeder according to the refill protocol as a step change. The minimum and maximum residence times for that component are then determined by detection of outlet tracer concentration. Then the line is reset and the process is repeated until residence time attributes for every component have been determined. These values are then added to the model library, which will be used by the material traceability tool.

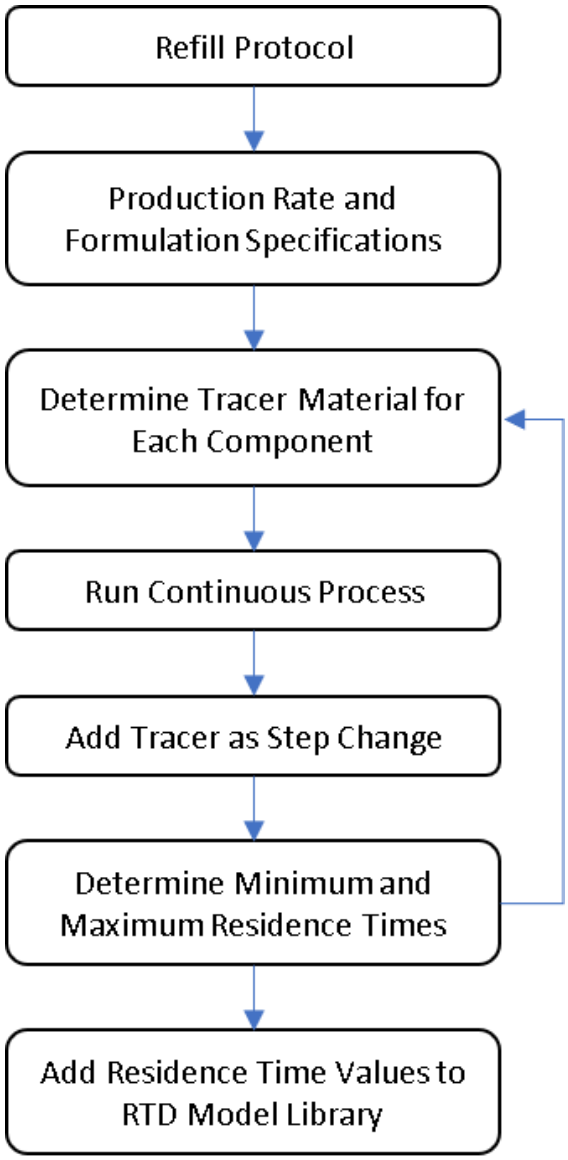

Figure 22. Application of RTD model for material traceability.

5.2.2. Supporting Software Tools

In order to implement real-time material traceability into continuous pharmaceutical tablet manufacturing, a suite of different software tools is required as shown in Figure 23. The first is the utilization of a traditional programming language to interface with the user. This

will allow user to enter the tablet batch name, the select RTD model parameters and make raw material batch changes during run time. This could be MATLAB, python, Java, or any other language to design the user interface.

What is also needed is a plant automation system and control software. To track the tablet lot number, this value could be sent to the control software and stored like other plant process variables. That way, comparisons and trends could be observed in real-time as the tablet lots change based on the raw material batches they contain. This could be very useful if certain critical quality attributes change in connection with a raw material batch change. For example, if fill depth in the tablet press is actuating more dramatically to control main compression force after a lot change, then we may be able to understand how that new raw material batch impacts the tablets when compared to the previous raw material batch.

Also required is OPC server management software. This allows signals to be communicated from one OPC server to another, namely the machine that is running the material traceability program and the server in the control system. This is extremely useful when communicating signals over a network between different devices. A client computer near the feeders could be running the material traceability program, and initiating raw material batch changes. Then the lot number signal can be sent via OPC to the computer that contains the controls software. This OPC server management software allows user to customize the OPC tags and addresses to allow this seamless communication to occur in real-time, accurately incrementing lot number changes as they are predicted to occur.

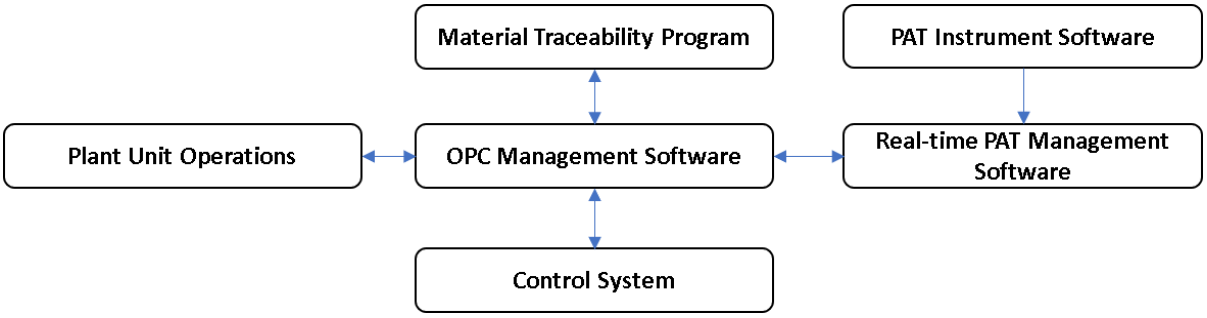

Figure 23. Hardware and software integration for material traceability.

5.2.3. Systematic algorithm for material traceability

A systematic algorithm for material traceability is shown in Figure 24. As shown in the figure, the first step is to scan initial drums and select model from RTD model library. Then operation of the continuous line begins start-up phase, where all unit operations reach desired operating conditions. Then the start-up phase is completed and tablets are to be collected. The material traceability software tool is then started, and tablet lot number is initialized. When refill of one of component feeders occurs using a new batch, lot number is incremented according to residence time values for that feeder. This is continued until batch is complete, successfully tracing material batch number for each tablet lot.

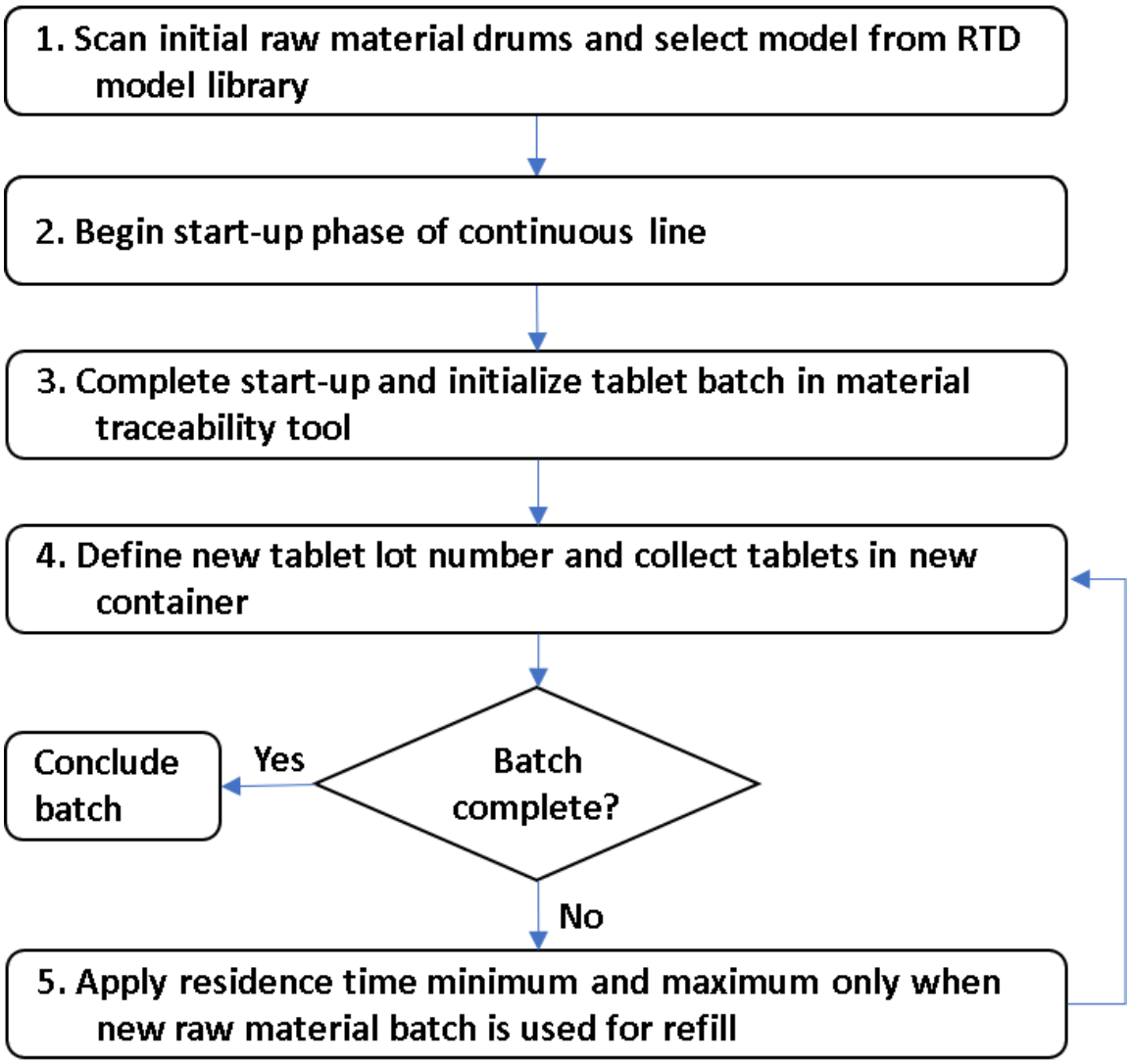

Figure 24. Systematic algorithm for material traceability.

5.2.4. Expandable features/ Future add-ons

5.2.4.1. Formulation Library

In a commercial setting, where many continuous batches of the same formulation are being run, it could be possible to create a formulation library, containing the material names and residence time minimum and maximum for each component at a certain production rate. That would ensure that material component names are correct and there is no operator error

when entering residence time values. Once residence time maximum and minimum are validated for a certain plant for a certain formulation, the values could be added to the library.

5.2.4.2. Scanning of raw material drums and final tablet drums

To improve upon the efficiency of the system and limit the need for manual entry of new batch numbers into the program, raw material drums could contain radio frequency identification sensors (RFID) to transmit information to a materials database (Want 2006). By scanning the passive tag with an RFID reader, batch information could be sent to the material batch queue. This would allow much more information about each raw material batch to be passed into the program, such as manufacturer name, location of manufacture, as well as flowability properties, like particle size, moisture content and density measurements. And when it is time for the component's new batch, operator could select from a list of scanned drums already put into the queue.

Once drums begin to be filled with tablets, the RFID tag on each drum could contain batch and lot information. The RFID reader is capable of writing information to the RFID tag, which would allow the tablet lot number and batch number written to a tag on a drum. As the RFID technology continues to improve, more information can be stored in the tag, besides just identification numbers (Want 2006).

5.2.4.3. Automation of batch refill

Another way to automate raw material tracing would be to initiate batch change when refill is detected. Because the control software is connected to the feeder in real-time, the

software can read the signal of the net weight of the feeder. Prior to detection of a positive change in net weight, the operator would only need to specify which drum in the queue is soon to be refilled, and incrementation of the lot can initiate automatically.

5.2.4.4. Automation of tablet lots collection

In the tablet press, the outlet chute can actuate a flap and change where the tablets are collected. This feature is often used for acceptance and rejection of tablets based on real-time measured CPPs and CQAs. This technology could also be utilized when a new tablet lot is defined, as predicted by the material traceability tool. The control software could simply detect a change in tablet lot number, and actuate the chute to put tablets into the next container designated for the next lot. The design for this could manifest itself by using two flaps in series. Traditional tablet rejection and acceptance criteria control the first flap. Then the path for accepted tablets will have a second flap to direct tablets to appropriate lot container. The proposed system would have three tablet collection locations, one for rejections, one for current lot, and one for handling the previous lot and preparing for the next one. This would remove operator's responsibility of switching the tablet container exactly when the new lot is defined, which would introduce a source of human error. This would greatly improve the operation of the line, especially with formulations with many different components refilling at different intervals over a longer production time.

Taking this concept further for automation of tablet collection, the drums could be arranged on a system of conveyor belts, moving the drums into position when appropriate and removing drums when they either are full or lot number has incremented. This would be most useful for production orders with many components and a high production rate.

5.2.5. Further examination of residence time

The current method of determining residence time is dependent on the formulation and specific production rate. If there is a component change, or change in production rate, the residence time experiments will need to be revalidated. Experimentation to better understanding of how production rate and component flowability properties affect the residence time values would decrease the amount of experimentation required for changes in formulation or production rate. If demand for product was increased, a prediction of the new residence time values would allow for increase in production rate to meet such a demand, without the need to experimentally determine residence time minimum and maximum values.

5.3. Results and discussions

The proposed framework has been automated and a software prototype has been developed. The detail of software development along with case studies demonstrating the applications of the framework and corresponding software prototype is given in Chapter 6.

Chapter 6: Material Traceability Software Tool Development

Acknowledgements

This work has been previously published and authors/co-authors are acknowledged.

1. Billups, M., Singh, R. **(2018)**. Material Traceability in Continuous Pharmaceutical Tablet Manufacturing. Pharmaceutical Technology 42 (2), 32-35, 59.
2. Billups, M., Singh, R. **(2018)**. Systematic framework for implementation of material traceability into continuous pharmaceutical tablet manufacturing process. Journal of Pharmaceutical Innovation. Review submitted.

6.1. Software development

A prototype software has been developed for material traceability based on the framework presented in Chapter 5. The primary responsibility of the software is to handle information required for material traceability. The functionality of the software can be sorted into two areas, the initial configuration prior to production and run-time operation of the program. For initial configuration, each feeder must be assigned to a specific material. The residence time attributes associated with each feeder must be stored. The raw material batch number for each feeder must initially be stored. During run-time, the program must send lot number to the control system. The program must also increment lot number based on residence time attributes for the correct feeder. Also, it is responsible for maintaining the tablet lot log in real-time.

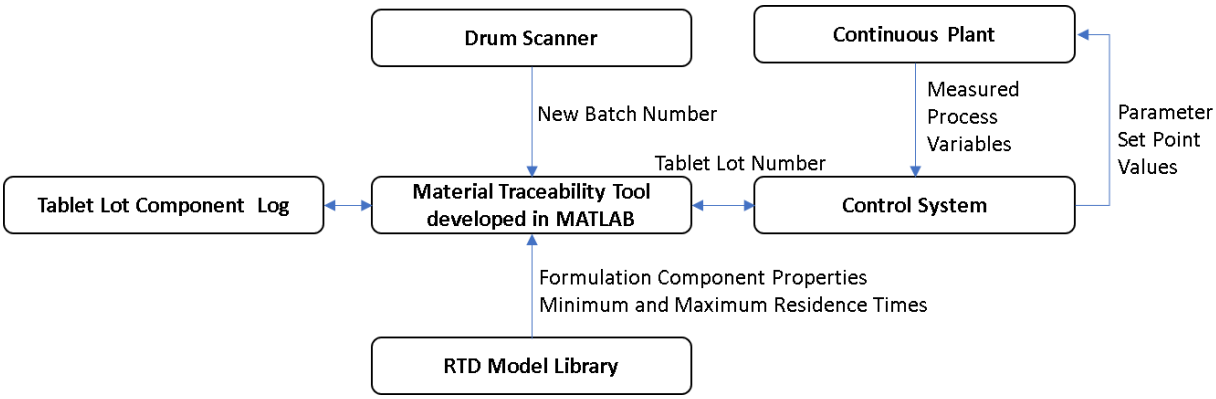

Figure 25. Dataflow for material traceability software program.

6.1.1. Residence Time Attributes

As described previously, each feeder has its own specific minimum and maximum residence time values due to varying powder properties and flow rates. The minimum and maximum times are retrievable based on the name feeder which is going through the batch change. The residence time values contained in this data structure represent the duration of time the impact of that refill is predicted to reach the outlet of the process.

6.1.2. Batch Number Organization

Each feeder is designated to a specific raw material during a production order. Initially, each feeder hopper is filled prior to the start of the continuous production. Therefore, each feeder contains material with its unique batch number. The batch number for raw material within each feeder is stored with that feeder. Tablets created during this time contain material from the specified batches. Upon refill of a hopper in which a new batch number is present, the feeder and new batch number must be specified. There will be a period of time, specified by the residence time values, in which tablets will contain material from both batch numbers.

6.1.3. Tablet Lot Log

This is the data structure of tablet lot numbers, and the corresponding batch numbers for each component in the tablet lot. After refill of material with a new batch number, transitional lot will be designated in which the component in transition will have both batch numbers recorded, to indicate the possible composition of tablets. Every time refill occurs with new batch of material, tablet lots will increment, specifying composition of each tablet lot as the batch numbers of the components comprising the tablets within that lot. This data structure must be accessible by the main program to append new lots to the table.

6.1.4. Refill Instances

In preparation for a refill, the feeder must be specified and the batch number for new material must be stored. Once refill of a feeder is initiated, the minimum and maximum residence times are used to delay the simultaneous incrementation of lot number and update of tablet lot log to reflect outlet composition of tablets within the new lot. It is possible for refills of different feeders to occur in rapid succession, therefore multiple components in tablet to be undergoing transitions. The tablet lot log must be appended upon reaching the respective minimum and maximum residence times for each feeder's component, such as described in Figure 20.

6.2. Software prototype

The developed software prototype has two primary windows: the configuration window and the runtime window.

6.2.1. Initialization and Configuration Window

This window allows the user to input the values required for material traceability. Specifically, the component names, minimum and maximum residence time values for

each component and the initial batch number for each component. This information will be used for creation of a material traceability log, which contains the tablet lot number, and the batch numbers for each component present in that lot. Before the production run begins, the log is initialized with lot number 1, and the batch number for each component is the initial batch numbers.

In this window, we are also able to select whether or not we want to run in “TEST” mode or “RUN” mode. By selecting these, we specify if an OPC connection should be established between program and server for control system. Once all information is supplied, a button is pressed which initializes the material traceability system and the runtime window appears.

6.2.2. Runtime Window

The runtime window appears when tablet batch is running and provides user with operations that are useful during runtime. One side provides a material traceability log updated in real-time. The other side is the refill queue. This queue allows users to input future refill information. This allows easier operation when it is time to refill a component feeder with a new raw material batch. The component names provided in the configuration window appear in a drop-down menu, where the user selects the appropriate name and inputs the new batch number. That information is then added to the que, which is visible to the user.

Entries in the queue can be selected to either be removed from que or used in refill. When a queue item is selected for refill, the residence time attributes associated with that component are applied to timers. The timers delay the incrementation of lot and the update

of the material traceability log. When refill is performed, two timers begin: one delaying a function callback to define component batch number as both old batch number and new batch number, and one for defining component batch number as solely the new batch number. This timer will delay the callback function until the elapsed time has passed as specified by the timer. So whatever the status of the log is when the timer ends, the log and lot number will be updated accordingly. This allows multiple components to change at varying intervals. A change for one component does not affect a change in different component. So when one component is transitioning between old and new batches, a different component can also be transitioning without interruption.

Depending on whether the status of the program is in "TEST" or "RUN" mode will determine whether it sends the lot number value to the OPC server on the PC running the control system. The callback function at timer completion looks for the "run mode" to determine whether or not to run the function to send lot number value through OPC.

6.2.3. Completion of batch

When production has ended, a file is created to store the residence time values used during the program's operation, as well as the material traceability tablet lot log. This allows for accountability and recordability when analyzing the batch post-production.

6.3. Case study

To demonstrate the application of the developed framework and corresponding software prototype in a continuous direct compaction tablet manufacturing pilot-plant, we defined a few process conditions to meet. First, the sample formulation used in this case study is 25%

acetaminophen (API), 74% lactose (excipient), and 1% magnesium stearate (lubricant). To create these tablets, our plant must be arranged such that the top level of the plant has the API and excipient feeders, feeding into the co-mill. Then on the middle level, the lubricant feeder adds to the powder stream and it enters the continuous blender. From there, the powder blend enters tablet press on the lower level. To create tablets with 325 mg active ingredient, this defines that total tablet weight is 1.3 g. If we define the production rate of our process to be 16,000 tablets per hour, that means we will be feeding 20.8 kg per hour of powder formulation blend into the tablet press. And given our formulation, the feed rates defined in Table 14 are required for each component in the line.

Table 14. Feed rate for tablet components.

Material	**Feed Rate (kg/h)**
Excipient (Lactose)	15.392
API (APAP)	5.200
Lubricant (MgSt)	0.208

In this work, assumed values for the minimum and maximum residence times are used for demonstration of the application of the framework. To demonstrate the concept and implement the framework, these values can be approximated based on process understanding. For example, because the composition of lactose is almost triple that of acetaminophen in this formulation, we can conclude that the minimum and maximum

residence time for lactose will be shorter due to it's increased feed rate.. And since magnesium stearate has a very low feed rate relative to acetaminophen, we would expect it to have the highest maximum residence time. The values given in the Table 15 may be hypothetical, but successfully illustrate the point that each component will have specific residence time values and could be determined experimentally to accurately predict minimum and maximum residence times of an actual system. This is also visualized in Figure 26.

Table 15. Hypothetical minimum and maximum residence time of components based on formulation ratios and feeder positions.

Material	**Minimum Residence Time (s)**	**Maximum Residence Time (s)**
Excipient (Lactose)	280	500
API (APAP)	300	600
Lubricant (MgSt)	270	700

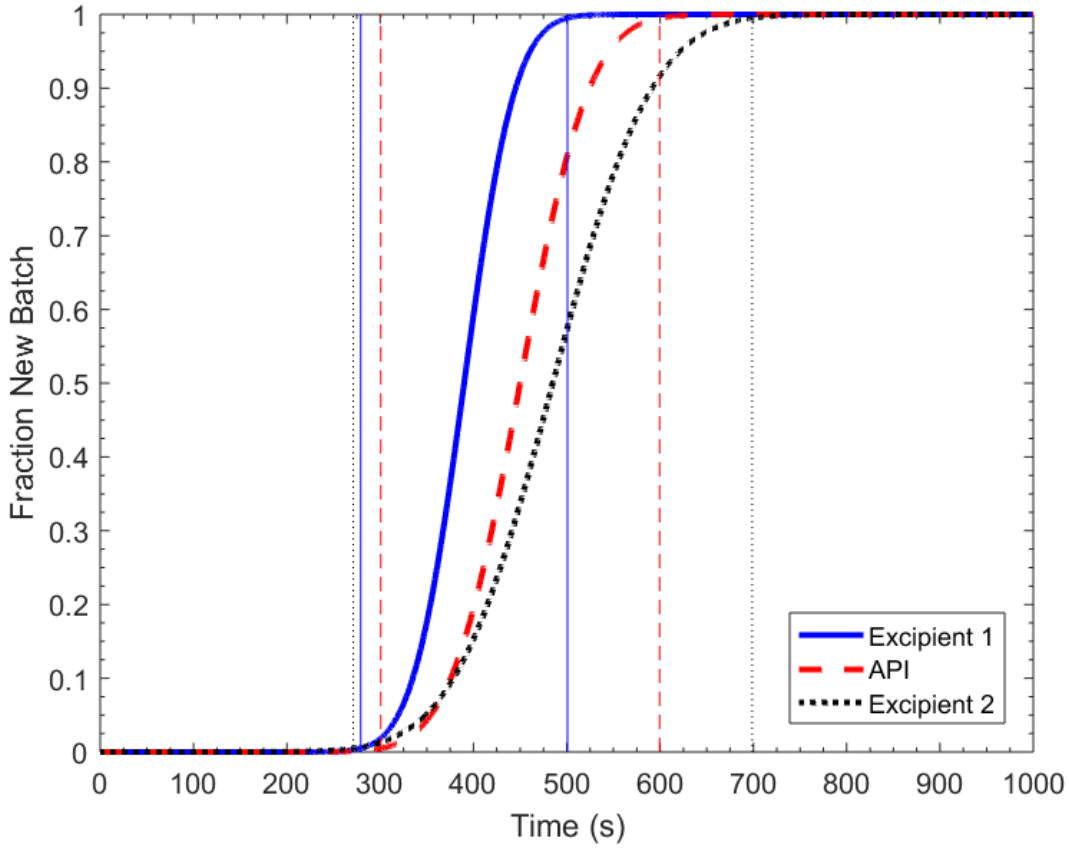

Figure 26. Graphical illustration of the minimum and maximum residence times of each component and how they could differ based on feeder location and formulation ratios

This case study has been used to demonstrate the applications of the developed systematic framework and software prototype as discussed in results and discussion section.

6.4. Results and discussions

6.4.1. Demonstration of the application of developed framework and software prototype

To implement the framework in our continuous pilot plant, we must perform or simulate the off-line determinations. Above, we have determined the hypothetical formulation we want to manufacture, as well as the minimum and maximum residence time attributes for the system running at 16,000 tablets per hour.

The next step was to build a user interface to input batch information for material traceability. This program was built using MATLAB and contains features relevant to the implementation of material traceability in our bespoke plant. This first screen (see Figure 27) allows the user to input the material information, initial raw material batch number, and minimum and maximum residence times for that component. It also allows user to operate in either demonstration mode, which does not connect through OPC servers to the control software, or in OPC connection mode, which does send lot number signal in real-time to the control software.

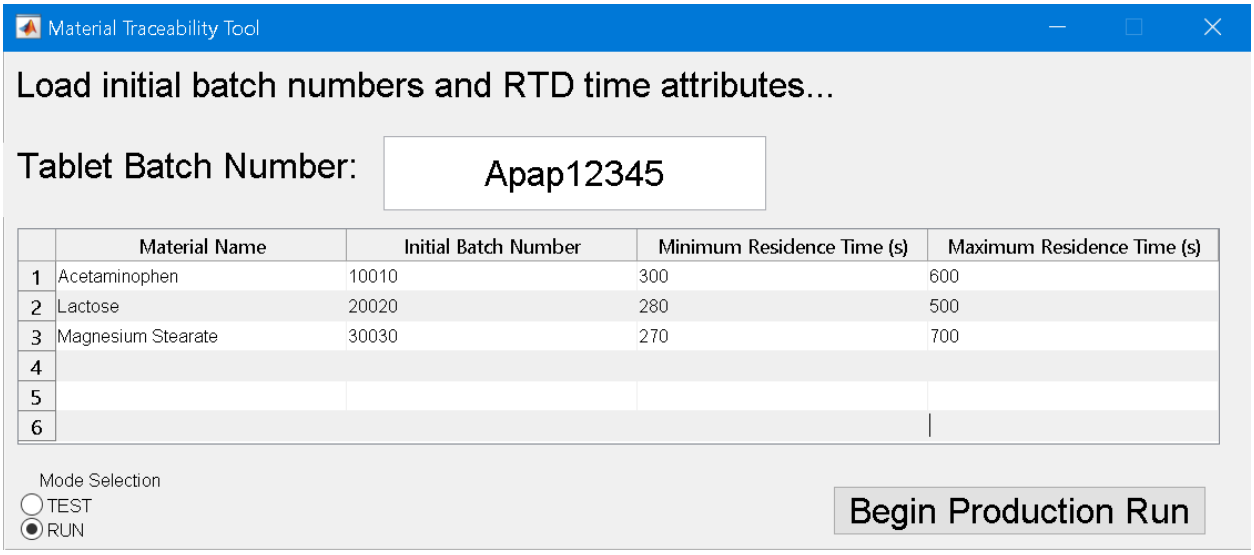

Figure 27. Initial window where material name, initial batch number of each component, and the minimum and maximum residence times of each component in the process.

After configuration, the production run is initiated and the runtime screen is displayed as shown in Figure 28. There are two panels, the batch change queue, and the tablet lot composition log. The queue allows user to input the future batch changes for the different

materials. The log allows user to see the batch number of each component in that lot of tablets.

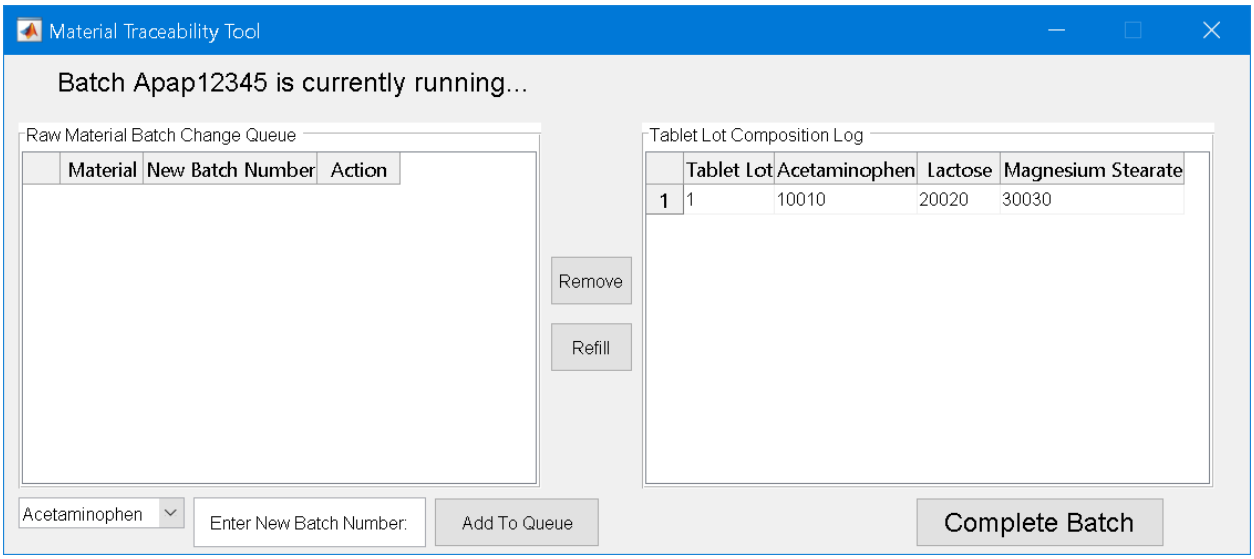

Figure 28. Run time screen where the tablet lot number is sent to control system and batch numbers for the components can be added to the queue.

As seen in Figure 29, once batches have been added to the queue, they can either be applied by selecting that entry and pressing refill button upon refill or can be removed from queue if user error. Once refill is pressed, any entry that is selected is initiated. The minimum and maximum residence times for that component are applied to accurately increment the tablet lot number and update composition when impact reaches the process outlet. Every time a minimum or maximum residence time is reached, the lot is incremented and that lot number signal is sent through OPC to the control software.

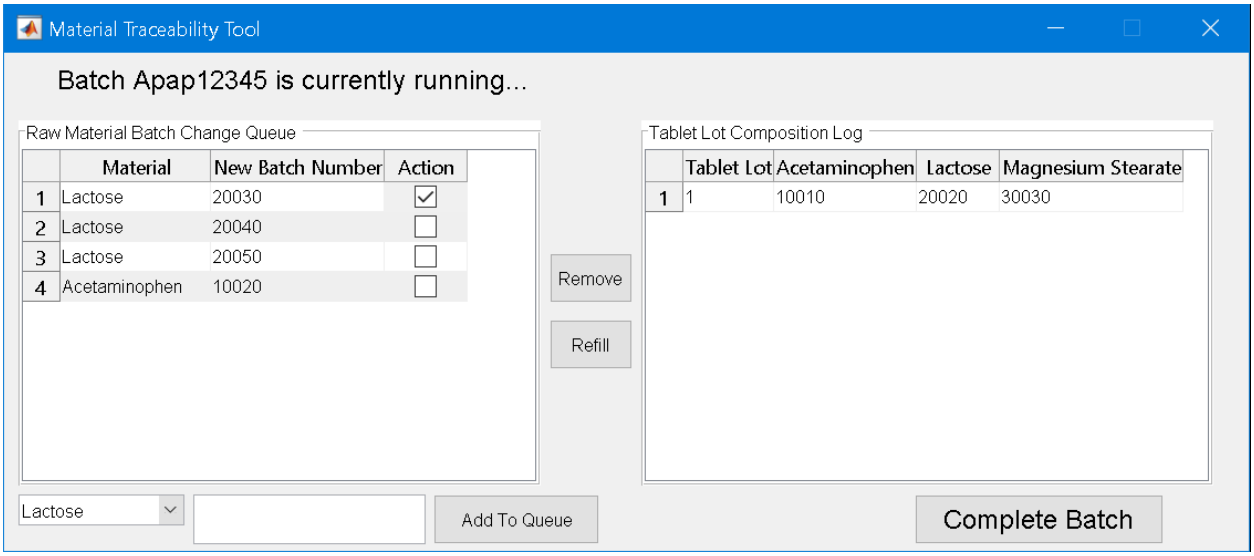

Figure 29. Demonstrates addition of new batches to batch change queue.

In this example, lactose batches change much more quickly than the other two components. As demonstrated in Figure 30, lactose was changed from batch number 20020 to 20030 to 20040 during production. Then when lactose was changing from 20040 to 20050, acetaminophen was changing from 10010 to 10020. The tablet lots incremented following the strategy proposed in Figure 20. When the batch is complete, the “Complete Batch” button can be pressed and information is saved into separate file to be included in master batch records, as seen in Figure 31.

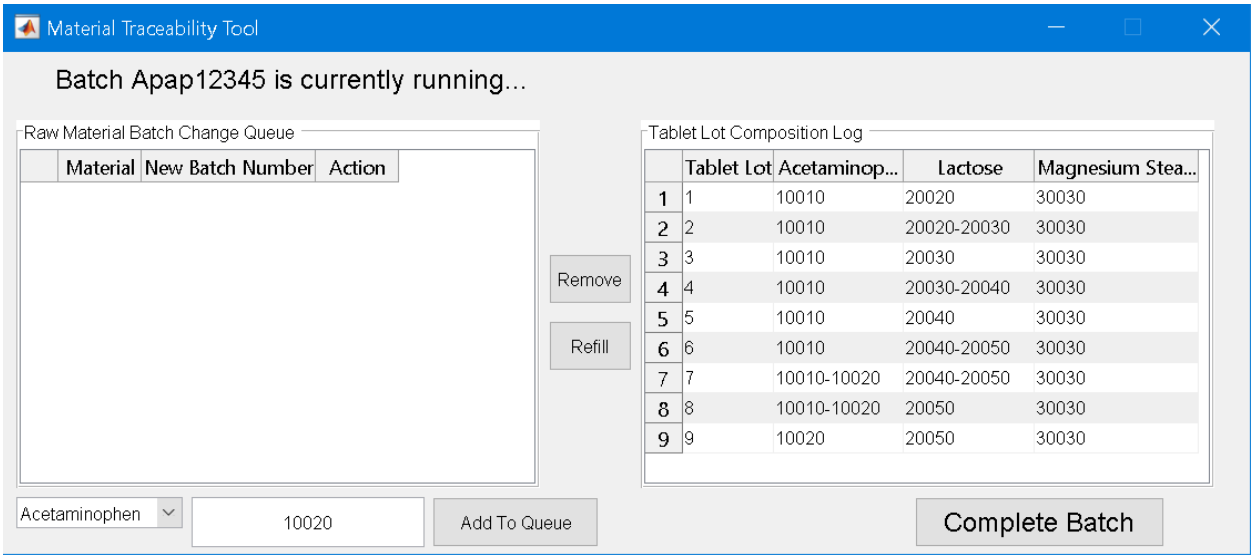

Figure 30. Illustrates tablet lot composition log when raw material batch changes have occurred.

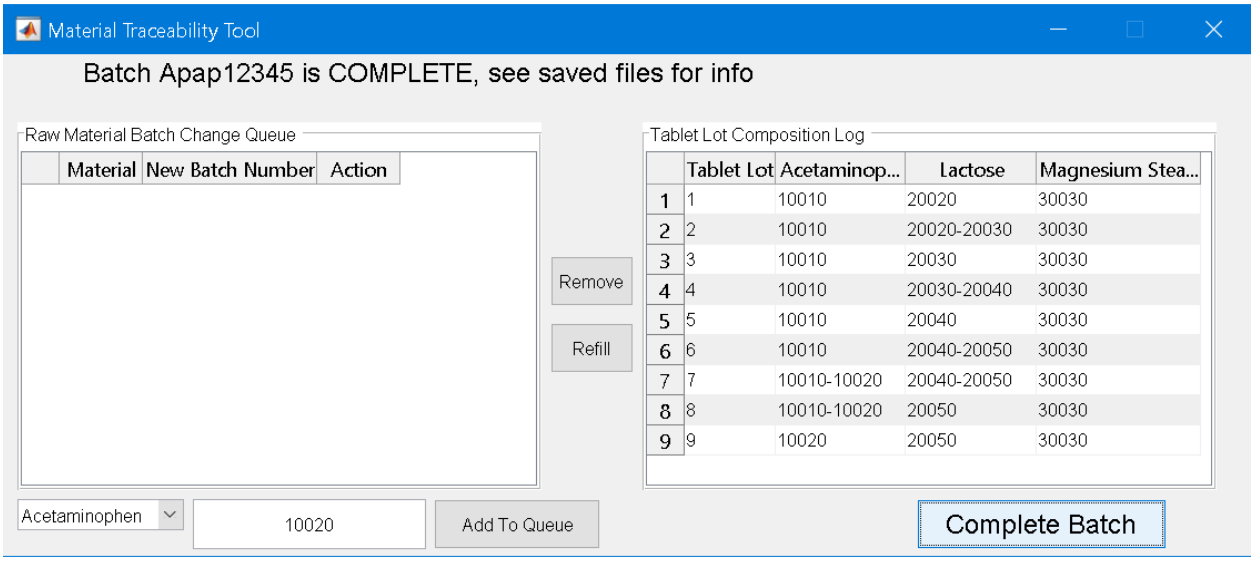

Figure 31. Completion of tablet batch.

6.4.2. Demonstration of material tracing in 5-component formulation

The developed software prototype is also capable of handling formulations with many more components. Figure 32 demonstrates the prototype handling material traceability for a 5-component formulation. Here we can see components “A” through “E” change batch

numbers during operation. In this example, component B changes first. And before batch 1 for component B is fully cleared from the line, component D changes. Then after D completes the transition, component A changes. Then component B changes again.

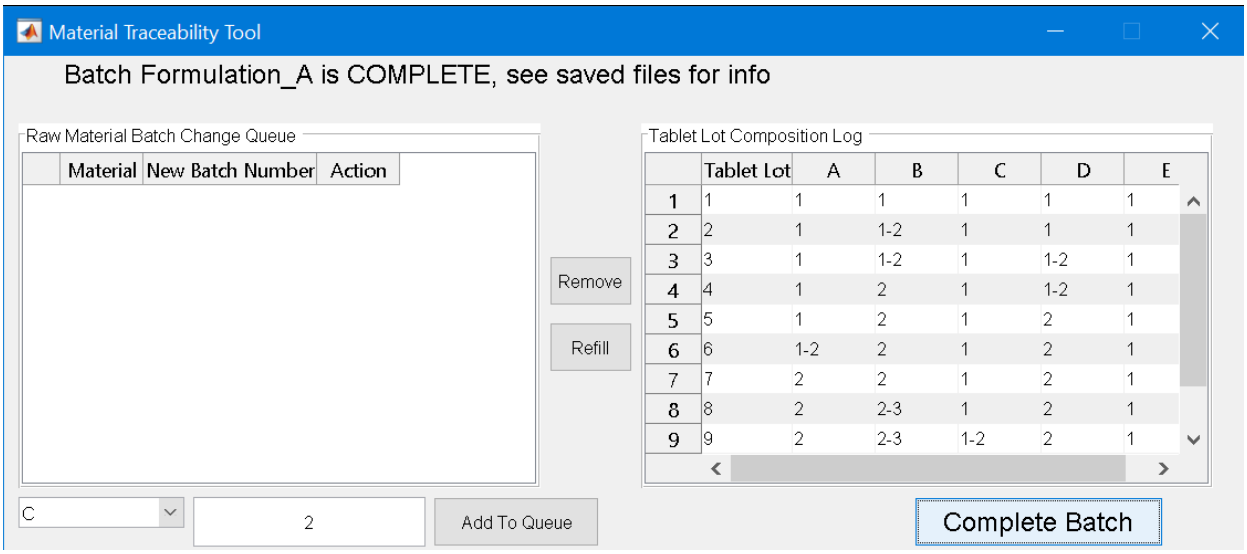

Figure 32. Material traceability program for 5-component formulation. Component names "A" through "E" represent 5 different components in a potential formulation.

Chapter 7: Conclusions and Final Remarks

In this work, advancements were made in the modeling of K-Tron powder feeding and the design of a framework for implementation of a material traceability system in the continuous pharmaceutical manufacturing space. In the area of feeder modeling, it was shown that a process model can be built and validated for a given material and feeder tooling. This model was then built upon to implement control strategies for mass flow rate using the feed factor model as a basis for calculating mass flow rate from the feeder. A PID controller was implemented with optimization based tuning strategy, which performed very well for a non-linear system with noise. With a control model in place, further disturbances were explored such as simulating realistic deviations that could happen in the plant. Simulating process disturbances like a feed factor pulse due to a density variation was analyzed. The more scenarios that this model is applied to, the more useful it will be at predicting process response.

In looking at the challenge of material traceability in continuous pharmaceutical manufacturing, a framework for implementation was proposed. A systematic framework has been developed for implementing material traceability in continuous pharmaceutical manufacturing process. Also included is a framework for software development, which details the responsibilities and dataflow of the software. A corresponding software prototype has been also developed to automate the procedure. The application of the framework has been demonstrated through the direct compaction tablet manufacturing

process case study, and can be applied to any continuous manufacturing process where the residence time distribution is able to be measured.

There are many impacts this tool can provide with respect to direct compression continuous tablet manufacturing in industry when operating at commercial scale. The first being automatic logging of tablet lot number and associated raw material batch information. This feature allows this information to be accurately stored in master batch record, specifying the raw material batch information for each tablet lot. By having the tablet lot number stored with the process variables, as well as raw material batch properties associated with that specific tablet lot, this data can be used for process monitoring and troubleshooting. Multivariate analysis techniques can be applied to the process data to determine correlations between the different parameters. After all, it is possible that a change in raw materials could affect a CPP for tablet production, and that would be easily seen if raw material batch information is included with process data, which this framework allows for.

This accurate material traceability also allows transitional lots to be tested and released, not immediately discarded because of uncertainty in composition. In principle, changing batch of raw material should not impact tablet quality. This material traceability tool would run in parallel with any other process monitoring technologies to determine acceptance and rejection.

And finally, this framework for integration could be used to incorporate material traceability into the control software. So instead of developing a stand-alone tool to meet the process requirements, this tool could be built directly into the software as another

feature. This would make data management easier, as well as integration of this feature into the process monitoring dashboard. That way, all process monitoring could be done from one programmed dashboard, containing material traceability user interface, PAT results, CPPs, and real-time CQAs displayed for operators and engineers.

Chapter 8: Future Perspectives

To expand further in the feeder modeling area, more study on developing an effective tuning strategy are necessary to implement gain scheduled PID control. Various other real-plant disturbances can be tested on the simulation. Also, increasing the understanding of the feed factor model by increasing the design space and range for which the model is valid. As well as analyzing other materials to see how their feed factor behaves during feeding. Another area of future work would be understanding and modeling refill scenarios of the feeder, an area that needs improved control.

The gain scheduled PID (GS) controller may be interesting to investigate due to the time-variant, non-linear process being modeled, as shown in . This strategy is one of the most popular approaches to non-linear control problems (Vesely and Ilka 2013). To implement this controller, we can create a look-up tables of the tuning parameters for the scheduled variable. In this case, the non-linear model is feed factor, therefore that is our scheduled variable.

To tune the look up tables, the scheduled variable need to be set constant, which will linearize the process model. Future work could be done to properly tune this type of control strategy to improve feeding performance over a wider range of feed factors, applicable for different materials.

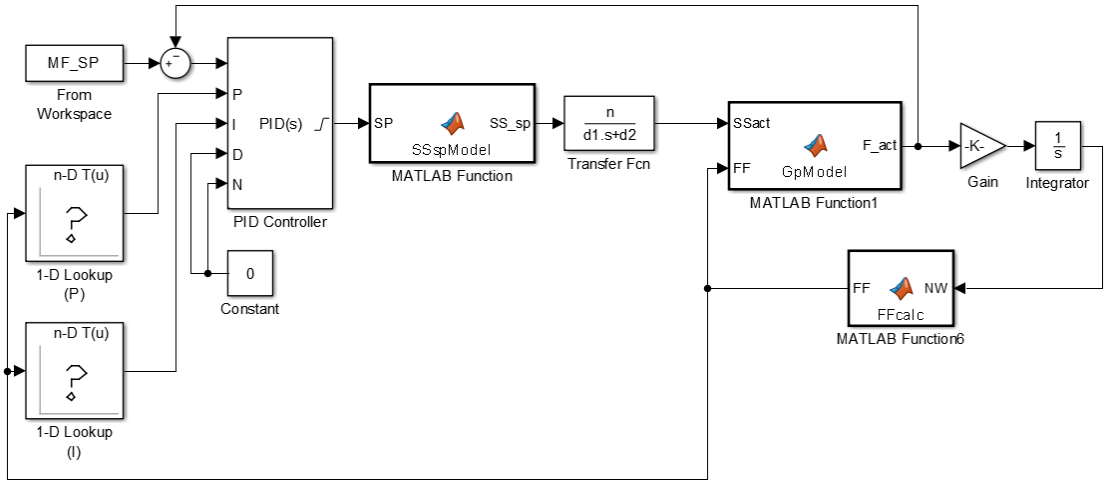

Figure 33. Schematic of Gain Scheduling control strategy implemented in feeder simulation using SIMULINK.

The developed material traceability framework is generic and therefore can be applied in any continuous manufacturing process. This framework takes evolving fields in pharmaceutical engineering such as experimental determination of residence time, predictive models for residence time of individual unit operations based on material properties, improved unit operations for continuous application, as well as advancing the understanding of these processes, and utilizes them to accomplish this necessary goal of material traceability. The newest and best ways being developed in these evolving fields will only strengthen and make more efficient this framework for material traceability in continuous pharmaceutical manufacturing. The developed framework is complementary to the existing control platform and thus could have a broad application in continuous pharmaceutical industries. The future work includes the practical demonstration of the

developed systematic framework and corresponding software tool for material traceability in continuous direct compression pharmaceutical tablet manufacturing pilot-plant.

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