Model-based analysis and dynamic optimization of feeder refill strategy

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ABSTRACT OF THE THESIS

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Traditionally, the pharmaceutical industries have been using batch processes for their ease of production of a broad range of products using the same equipment. But due to the increased challenges faced by the pharmaceutical industry and limitations of batch process manufacturing of pharmaceutical products such as controllability and scale-up issues, the pharmaceutical industries have led to come up with more efficient manufacturing techniques and transitioning to the continuous production of pharmaceutical products. To facilitate the speed of transition, the importance of process engineering and optimization through modeling has surfaced. Robust modeling of different unit operations and integration of them create numerous applications. These include analysis of the effect of variation in critical process parameters on the product quality attributes and leads into a

reduction in the wastage of time and material via dynamic optimization of a process in comparison to a traditional heuristic experimental based method.

In this work, a model-based method has been proposed to investigate, analyze, and identify the feeder refill strategy. A systematic framework was developed for the dynamic optimization of a unit operation, which was exemplified through the optimization of the refill strategy. The effect of process parameters and material properties on the refill parameters was also investigated.

Acknowledgments

Thank you, Dr. Ravendra Singh, for the opportunity to work with you and your research group and for the guidance and support provided towards the completion of my thesis. His mentorship facilitated me through different challenges encountered over the course, and lessons learned through these experiences are the ones I will take with me for the rest of my life. I would also like to thank defense committee members Dr. Rohit Ramachandran and Dr. Alberto Cuitino for their valuable time and consideration in reviewing this thesis

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Chapter 1: Introduction

1.1. Literature Review

Conventionally, pharmaceutical industries have been using the batch processes for the manufacturing of solid dosage forms because of its flexibility to produce a range of different products with the same equipment, and a well-defined quality batch of product. But due to the limitations of the batch processes such as larger footprint, higher operation cost, and poorer controllability and scale-up issues, recently, significant momentum has been accumulated in the direction of continuous manufacturing of pharmaceutical products (Singh, Ierapetritou, & Ramachandran, 2012). Controllability of the process can be improved by shifting from the batch mode of operation to continuous, making the process more robust and reliable with fewer scale-up issues and with the advantage of achieving steady-state quickly in a few minutes (Bhaskar, Barros, & Singh, 2017). Moreover, a reduction in equipment and operation costs and time is achieved by manufacturing continuously for an extended period of time.

Although pharmaceutical industries have always been very innovative and thriving in the field of new drug discovery and development (Boukouvala, Niotis, Ramachandran, Muzzio, & Ierapetritou, 2012), only recently, an effort has been undertaken in terms of research in the development of process systems engineering (PSE) methods and tools. PSE includes modeling, control, and optimization of the manufacturing plant. It needed for understanding and facilitating the fast adoption of the continuous manufacturing of pharmaceutical drug products. Hence, the desire for such paradigm shift requires describing of each unit operation mathematically and integrating them to develop a predictive flowsheet model describing the process accurately (Dubey, Boukouvala, Keyvan, & et. al., 2012; Parka, Galbraitha, Liu, & et al., 2018). The modeling is helpful to improve the product quality, to reduce the consumption of raw materials, to improve experimental effectiveness, and to reduce time to market as well as to minimize the risk of failure by enabling design, analysis, optimization, and robust process development (Boukouvala, Niotis, Ramachandran, Muzzio, & Ierapetritou, 2012; Hakemeyer, et al., 2016; Lee, O'Connor, Yang, & et al., 2015; Rogers, Inamdar, & Ierapetritou, 2013; Simon, Pataki, Marosi, Meemken, & et al., 2015; Singh, Sahay, Muzzio, Ierapetritou, & Ramachandran, 2014). Therefore, the modeling approach for process optimization is highly desired.

Being the first step to regulate the composition of the final product by controlling the addition rate of each ingredient in continuous manufacturing, the feeder plays a vital role among other unit operations. The material properties and the refilling of the feeder also affect the feeder flow rate variability. Therefore, a robust refill strategy, which includes feeder weight when the refill needs to be initiated, refill size, and refill rate (feeder screw RPM during refill), is essential to obtain to minimize the feeder flow rate variability during refill. (Yadava, Holman, E., Tahir, & et. al., 2019). Engisch and Muzzio have demonstrated the effect of periodic refilling of the hopper of feeders on the quality of products (Engisch & Muzzio, 2015). Traditionally, these parameters have been identified through intensive experimentation, but this approach leads to inefficient usage of time and material, which in turn reflects on production/utility cost. Therefore, it is essential to come up with a solution based on model-based optimization, which would reduce the time, materials, and resources. Moreover, during the early stage of product development, enough materials to carry out the experiments are often not available. However, no attempt has been made to develop the systematic methods and tools for dynamic optimization of the feeder refill strategy.

1.2. Objectives

The objectives of this thesis are to optimize the feeder refill strategy through a model-based approach and to understand the effects of the feeder's operational parameters and material properties on the feeder refill strategy. To the author's best knowledge, no attempts have been made in the past to obtain the optimum refilling parameters using dynamic optimization through a model-based approach.

The main objectives are as follows:

1 To understand the impact of varying feeder refill parameters on the composition of granules at the end of the granulation process.

2 To present a model-based systematic framework for dynamic optimization of feeder refill strategy.

3 To demonstrate the effect of process parameters and material properties on the feeder refill strategy.

1.3. Thesis Overview

A brief overview of the remaining chapters is provided for the reader’s convenience.

In chapter 2 of this thesis, the key concepts required for the full understanding of the work done are described. A description of different routes of tablet manufacturing and the importance of refill strategies for feeders are presented in this chapter.

In chapter 3, the impact of varying feeder refill parameters on the composition of granules at the end of the granulation process was studied.

The framework for the dynamic optimization of the feeder refill strategy through a model-based approach is presented in Chapter 4, followed by the study of the impact of process and material properties on the feeder refill parameters.

Finally, Chapter 5 elaborates on the conclusions of this work and future perspectives on the presented topics.

Chapter 2: Background

2.1. Pharmaceutical tablet manufacturing process

There are different routes of continuous tablet manufacturing, such as direct compaction (DC), dry granulation (DG), and wet granulation (WG). Direct compaction being the preferred method for tablet manufacturing due to its simplicity. It basically involves the feeding, blending of different kinds of powders together and then compacting to obtain tablets (Li, et al., 2019). Direct compaction is suitable for good flowing, less segregating, and easily compactable materials.

Granulation process, in general, improves the flowability and reduces segregation (Michrafy, Zavaliangos, & Cunningham, 2017). In dry granulation, granulation is achieved using a dry binder and high mechanical force to enable agglomeration, and two widely used agglomeration techniques in pharmaceutical industries are slugging and roller compaction followed by milling and sieving to form granules that are then compacted in the form of tablets (Xingyou, et al., 2019).

The wet granulation process is similar to dry granulation in a sense, and it is used to produce 70% of the worldwide industry's granules. (Xingyou, et al., 2019). In the wet granulation (WG) process, the overall powder particle size is enlarged by the addition of a liquid phase binder, allowing agglomeration (De Simone, Caccavo, Lamberti, d'Amore, & Barba, 2018; Hapgood, Litster, & Smith, 2003; Iveson & Litster, 1998). The WG process not only increases the particle size but also has better control of drug uniformity, improved flowability, increased bulk density, and porosity (Faure, York, & Rowe, 2001; Thapa, Tripathi, & Jeong, 2019). Moreover, the WG technique is also suitable for low-dose drugs

(Mahours, Shaaban, Shazly, & Auda, 2017)

2.2. Process model

The pharmaceutical tablet manufacturing process via wet granulation has several unit operations. However, this work is focused on only the process needed to produce granules. The models involved in this study are briefly discussed below:

2.2.1. Summary of available feeder modeling approaches

The density of the powder that is fed varies during the process, which makes it difficult to calculate the mass flow rate of the discharge powder and thereby to make it challenging to model the feeder. In the past, the feeder has been modeled through different approaches (Boukouvala, Muzzio, & Ierapetritou, 2010). Boukoulava et al. and Roger et al. described the dynamic behavior of the loss in weight feeder by employing a first-order delay differential equation (Boukouvala, Niotis, Ramachandran, Muzzio, & Ierapetritou, 2012; Rogers, Inamdar, & Ierapetritou, 2013). A semi-empirical model for a feeder to simulate the feeder by introducing a concept of feed factor has also been developed (Escotet-Espinoza, et al., 2015; Wang, Escotet-Espinoza, & Ierapetritou, 2017). A complete model to calculate the mass flow rate of the discharging powder by introducing a concept of channel fill fraction, which compensated for variation of density of the material in the process through several differential equations and iterations, has also been developed. The model of the feeder hopper has been developed by Janssen, 1973. The Jannsen model is further expanded to develop the feeder model based on the prediction of channel fill fraction (Don Clancy, 2016, AIChE). Table (1) summarizes the types of feeder modeling approaches available.

Table 1: Types of feeder modeling approaches

Types of the feeder modeling approach	References
First-order delay differential equation-based model	Boukoulava et al. (Boukouvala, Niotis, Ramachandran, Muzzio, & Ierapetritou, 2012) and Roger et al. (Rogers, Inamdar, & Ierapetritou, 2013)
Semi-empirical model introducing a concept of feed factor	Escotet-Espinoza, et. al. and Wang et. al, (Escotet-Espinoza, et al., 2015; Wang, Escotet-Espinoza, & Ierapetritou, 2017)
Empirical feeder hopper model to predict the density at the bottom of the hopper	Janssen, 1972
Extended Jannsen's model to predict the flow rate of powder from feeder based on the prediction of channel fill fraction	Don Clancy, 2016, AIChE

2.2.2. Twin-screw granulator model

There are different modeling approaches available for twin-screw granulator (TSG). The population balance model (PBM), provide a more fundamental framework for tracking particle properties over time (Barrasso & Ramachandra, 2012). The residence time distribution (RTD) based modeling is especially suitable for the prediction of drug concentration in granules. The RTD model has been used for this work.

Chapter 3: Analysis of critical process parameters through flowsheet modeling

Several unit operations are involved in the manufacturing of pharmaceutical tablets, including feeders, blender, granulators, dryer, co-mill, tablet press. Among these unit operations, feeder affects the continuous manufacturing of the tablets the most since the composition of the tablets mainly depends on the feed rate of each feeder involved in the production of the tablets. Thus, it becomes essential to optimize the operation of the feeder to minimize the variation in the quality attributes of the tablets. The flow rate of the feeder is dictated by different process parameters (refill strategy and operating parameters) and material properties. The impact of these parameters and properties has been traditionally evaluated through intensive experimentation, which leads to inefficient usage of material and time. Therefore, it is essential to utilize the modeling approach to study the effect of process parameters, which is demonstrated in this chapter through a case study of the wet granulation process.

In this chapter, scenario analysis and refill analysis was carried out *Insilco* to study the effect of feeder refill parameters (refill start mass, refill end mass, and screw speed during the refilling) on the product quality. The flowsheet model for the process of wet granulation considered consists of two feeders containing API and excipient flowing at a specific flow rate to the twin-screw granulator to produce granules.

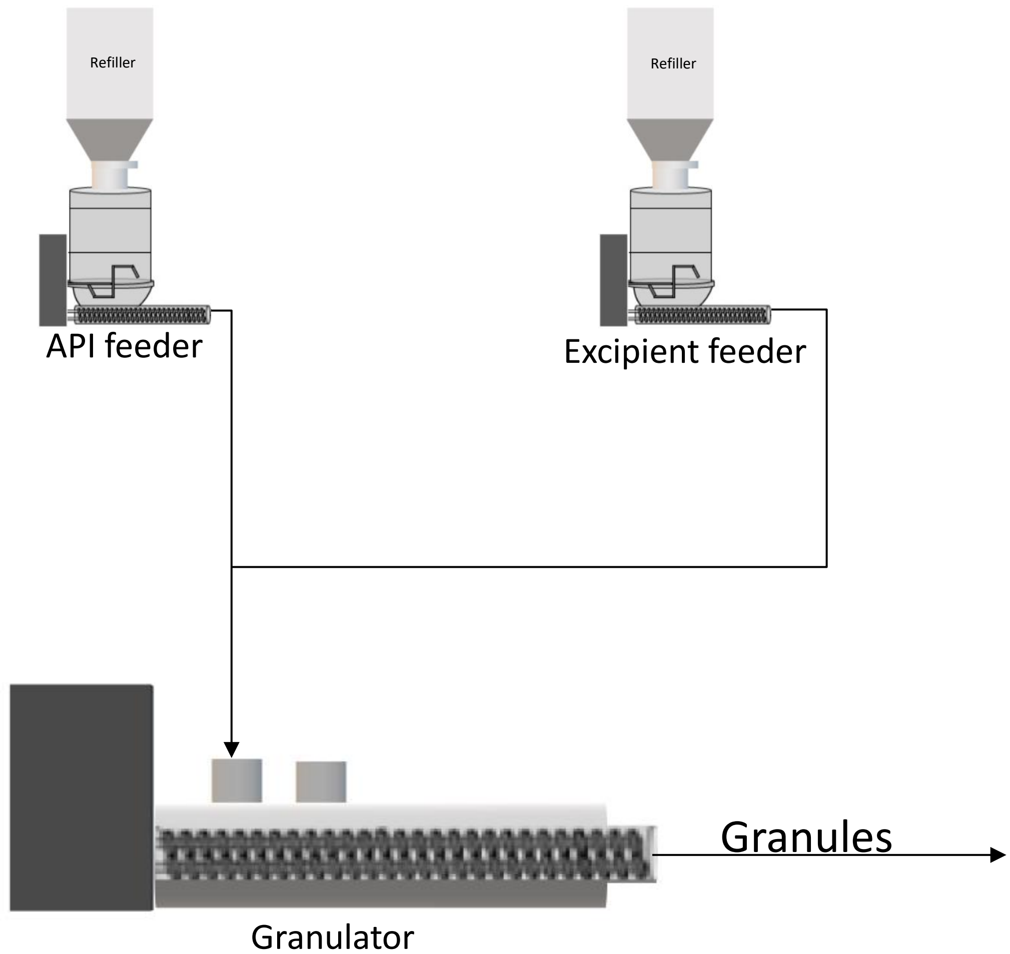

Figure 1: Flowsheet model of the wet granulation process

3.1. Scenario analysis

Batch to batch variability is essential to investigate to ensures the quality of batches. The product quality could be affected by the variation in the pre-blend concentration fed into the feeder during a refill.

For this analysis, a step change was made in API refill pre-blend to find the effect of disturbance in the product keys. During refill, different pre-blend concentration (8%,10%,12%,14%,16%, where 12% is the targeted pre-blend concentration) considered for the analysis.

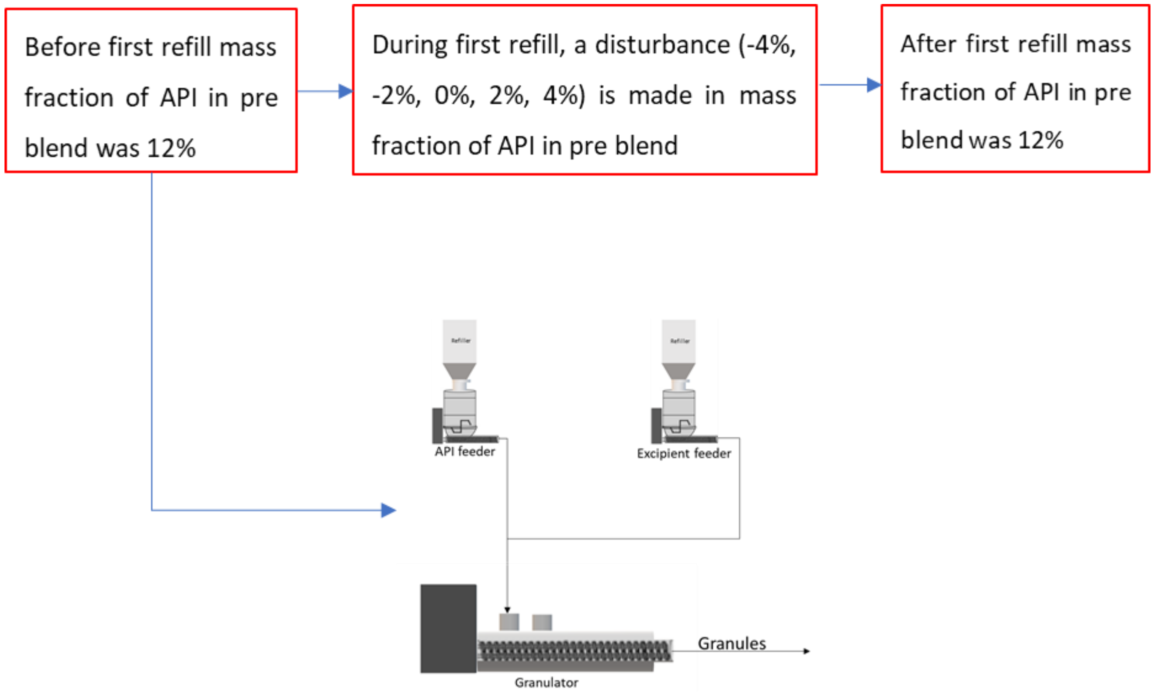

Figure 2: Batch to batch variability analysis

Figure 3 demonstrates that the property of product keys may fluctuate if the process and feeder refill strategy are not properly optimized. This fluctuation is due to the impact of a change in the mass flowrate of API feeder during refill. Hence, the refill strategy must be optimized to have minimal impact of change in mass flowrate of feeders during the gravimetric and volumetric mode. An approach to dynamically optimize the refill strategy is explained in chapter 4.

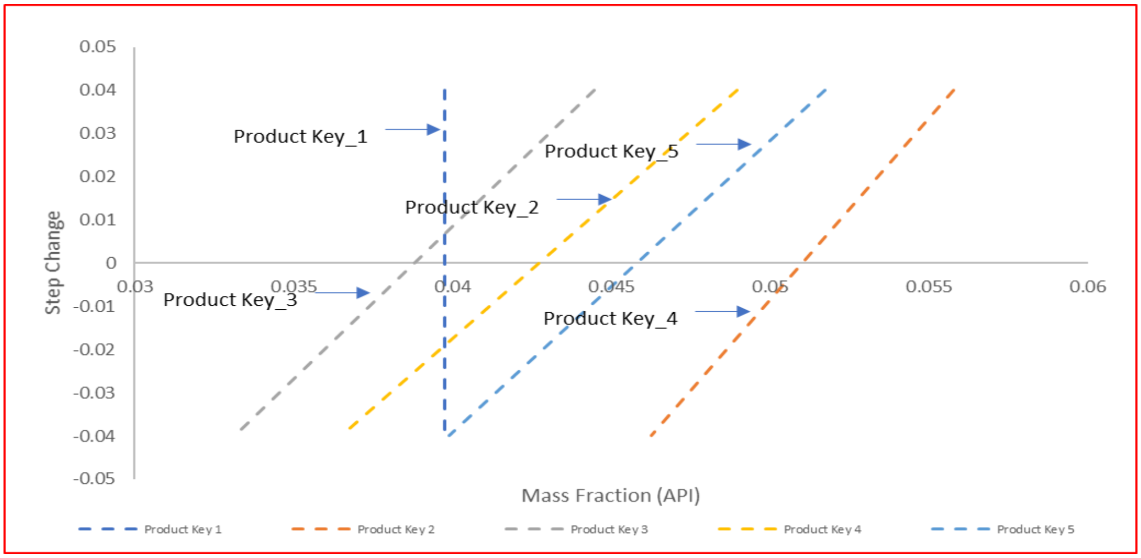

Figure 3: Batch to Batch variability in case of non-optimal process

3.2. Feeder refill analysis

During refill, the significant difference in the screw speed (RPM) (when the feeder switches from the gravimetric mode to volumetric mode) affects the composition of the product. Therefore, an analysis was carried to demonstrate the effects of refill size and refill time on the composition of the product.

A step-change in refill time for API feeder was made indirectly by changing the outlet mass flow rate of powder of the refill unit. Refill time range would depend upon the refill size and mass flow rate, thereby making refill time different for different refill size. The refill start mass has been changed while the refill end mass has been kept constant. Higher the refill start mass, lower the refill size. Figure 4 shows the relation between refill time, refill start mass, and mass flow rate. As shown in the figure, for a given refill size, the refill time decreases on increasing the refill flow rate. The refill time also decreases with a decrease in the refill size (or increasing the refill start mass). This result establishes a relationship among the refill time, refill size and refill rate.

The mass flow rate was varied from 2 kg/min to 20 kg/min, resulting in the refill time varying from 3 seconds to 135 seconds. For instance, with the refill start mass of 6kg and refill mass flow rate of 6 kg/min, the refill time, as inferred from figure 4, is roughly 30 secs.

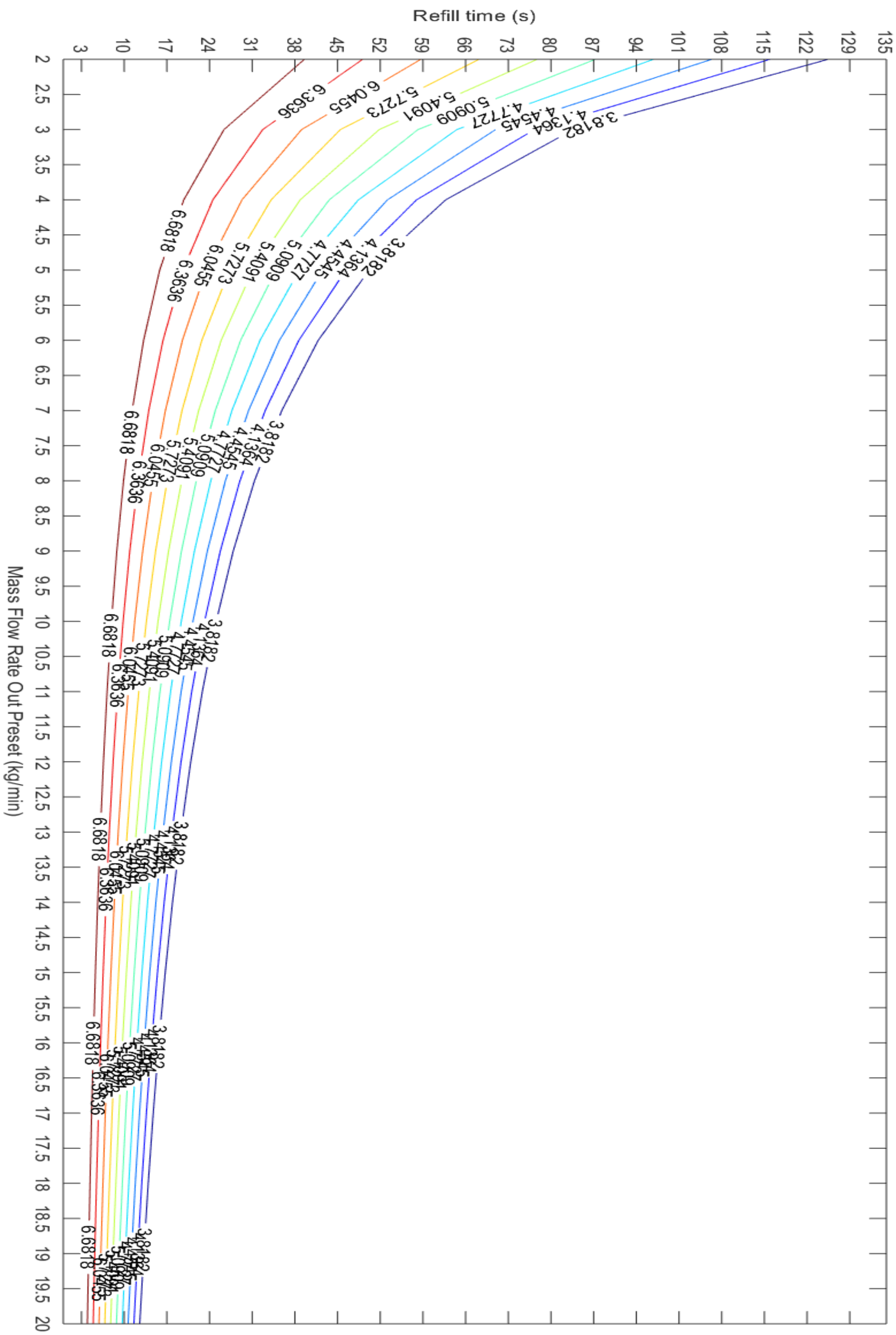

Figure 4: Relation between refill time and outlet mass flow rate of the refill unit.

3.2.1. Refill time analysis

In this analysis, the refill size was kept constant, but the refill time was varied via changing the outlet flow rate of the refill unit. The effects of variation of refill time were observed in the mass fraction of 3 different product keys. The mass flow rate setpoint of API feeder was set to 0.32641 kg/min while the excipient feeder was set to 0.67359 kg/min to obtain the API mass fraction of 0.04.

Three cases were considered for the analysis, refilling mass flowrate out being equal to 2, 4, and 20 kg/min with a refill duration of 112.616s, 47.413s, and 8.619s, respectively.

With an increase in the refilling mass flowrate out, the refill duration is decreased and correspondingly affects the product keys. The product key 2 is affected to a large extent as compared to product key 1 and product key 3, as given in Table 2. A decrease in refill duration reduces the time of operation of feeder in volumetric mode and thus reduces the impact of variation in the composition of product keys. The refill duration of 8.619 seconds has a minimum effect on the variation in the product composition, among others.

Table 2: Effect of refill duration

Cases		Mass Fraction		
		Product Key 1	Product Key 2	Product Key 3
A	Refill duration – 112.616s	0.04000258	0.051565196	0.039863985
B	Refill duration – 47.413s	0.04000258	0.04710128	0.04009614
C	Refill duration – 8.619s	0.04000258	0.044378925	0.040687088

3.2.2. Refill size analysis

Like refill time analysis, here a step-change in refill start mass for API feeder was made, thereby changing the size of the refill while keeping the refill end mass constant. The refill start mass was varied from 3.5 kg to 7 kg, and the end mass was set to 8 kg, while the initial mass in the feeder was considered to be 2 kg more than the refill start mass considered in each case. The composition of three product keys was considered as the response variable for the analysis. The mass fraction of 0.04 of API in product key was obtained by setting a mass flowrate setpoint of API feeder to 0.32641 kg/min.

Three cases were considered for the analysis, refill start mass being 3.5 kg, 5.2 kg, and 7 kg.

With an increase in refill start mass and decrease in refill size, the time of operation of feeder in volumetric mode decreases, and thus the impact of variation on the product composition decreases, hence the effect of refill can be decreased as seen in product key 2 as given in Table 3.

Table 3: Effect of refill start mass

Cases		Mass Fraction		
		Product Key 1	Product Key 2	Product Key 3
D	Start mass – 3.5	0.040001944	0.049088195	0.040097564
E	Start mass – 5.2	0.04000258	0.04710128	0.04009614
F	Start mass – 7	0.039996624	0.044705305	0.04164774

3.3. Global sensitivity analysis of feeder refill strategy

Global sensitivity analysis was carried out for the above refill analysis to generate a graphical representation of the effect of refill time over a range of 2kg/min to 20 kg/min, refill start mass over the range of 3.5 kg to 7 kg on the mass fraction of API in the product key. Percentage deviation plot was generated for each of the product keys. The entire analysis was carried by setting RPM of feeder during volumetric mode at 357.

3.3.1. Analysis of first product key

As seen in figure 5, product key 1 is not affected by refill since there is some processing delay involve in-between refill unit and granulator outlet. The first product key has been collected before the refill disturbance has propagated to the product key. The refilling occurs during the production of the second product key. Therefore, the impact of the refill is seen in the composition of the second and third product key.

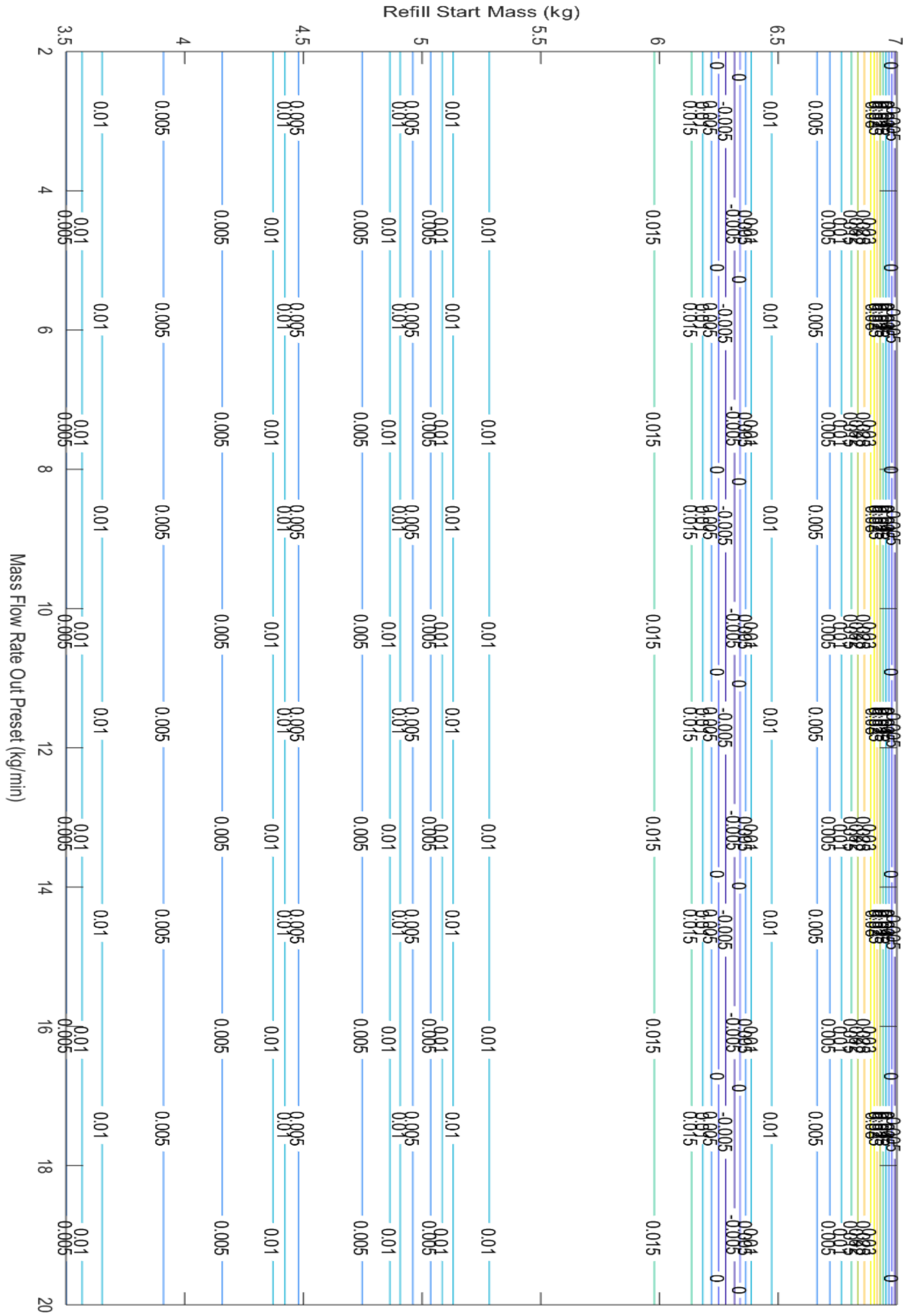

Figure 5: First product key: % deviation contour plot

3.3.2. Analysis of second product key

It can be concluded from figure 6 that there is a relationship between the second product key and the refill strategy. As shown in the figure, with the increase in the refill start mass (kg) and refill mass flow rate (kg/min) for constant refill end mass, the deviation in the granule composition of the product key 2 decreases as the impact of the refilling decreases with smaller refill size and faster refill rate. For example, with refill start mass of 5 kg and refill mass flow rate of 6 kg/min (refill time of roughly 30 seconds, as graphically inferred from figure 4), the deviation in the product key composition is between 13.6716 to 14.8027 % which is reasonably high, while with refill start mass of 6.5 kg and refill mass flow rate of 20 kg/min (refill time of 19.5 seconds, from figure 4), the deviation in the composition of the granulation is roughly 8.0158% which is less than the previous deviation described but still considerably high for deviations in product keys.

Therefore, it is essential to optimize the refill strategy to reduce the deviation in the product quality and increase the uniformity in the granule composition.

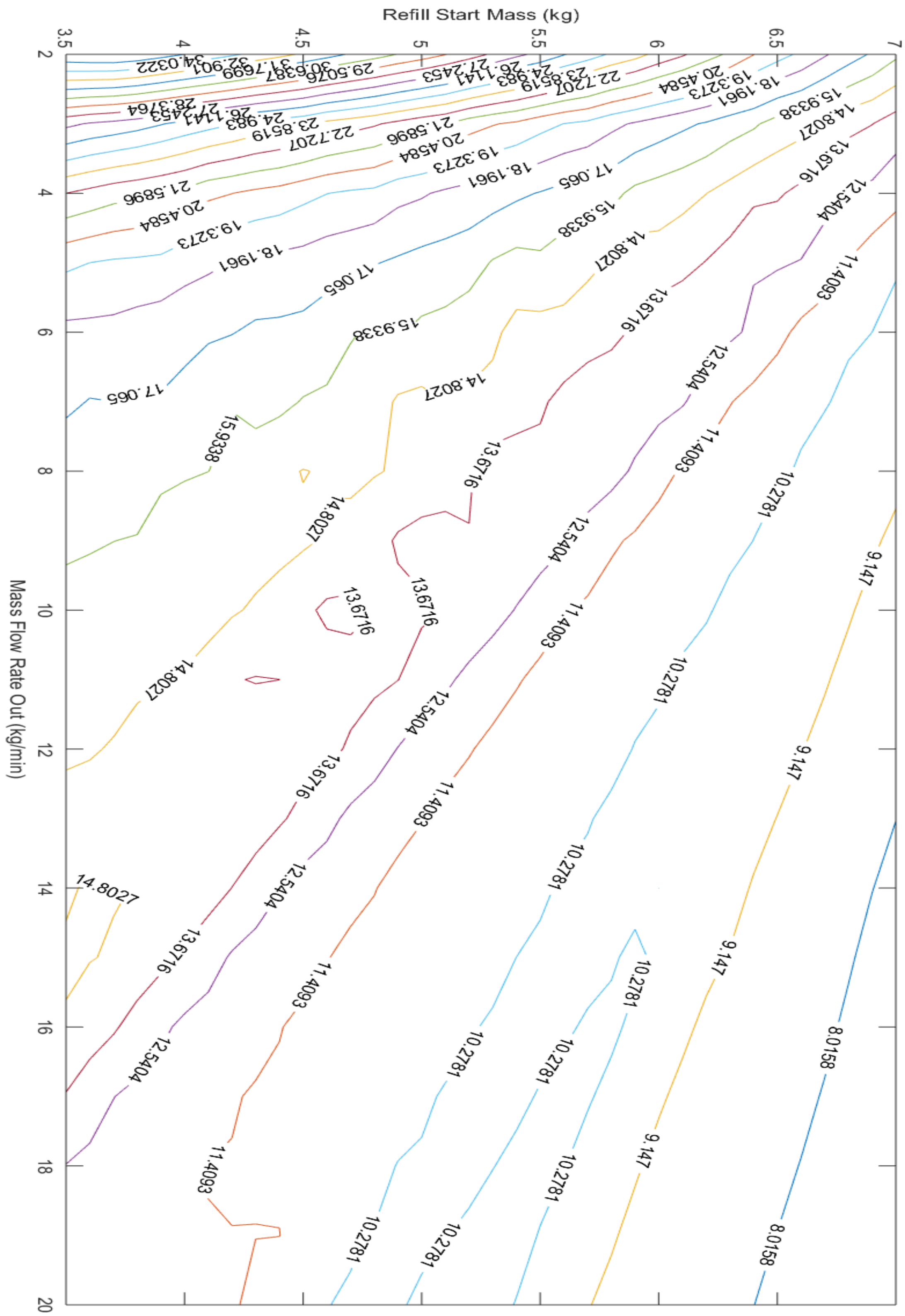

Figure 6: Second product key: % deviation contour plot.

3.3.3. Analysis of third product key

The impact of the refilling can be seen in the composition of the product key 3, as shown in figure 7. From figure 7, to achieve 0% deviation in the composition of the granules in product key 3, the range of refill start mass should be between 3.5 to 6.5 kg and refill mass flow rate should be between 2 to 6 kg/min (refill time between 65 seconds to 105 seconds, from figure 4) or else the refilling should be short and frequent (refill start mass of more than 7 kg, refill mass flow rate of more than 19 kg/min, and refill time less than 22 seconds (as inferred from figure 4) with refill end mass at 8 kg).

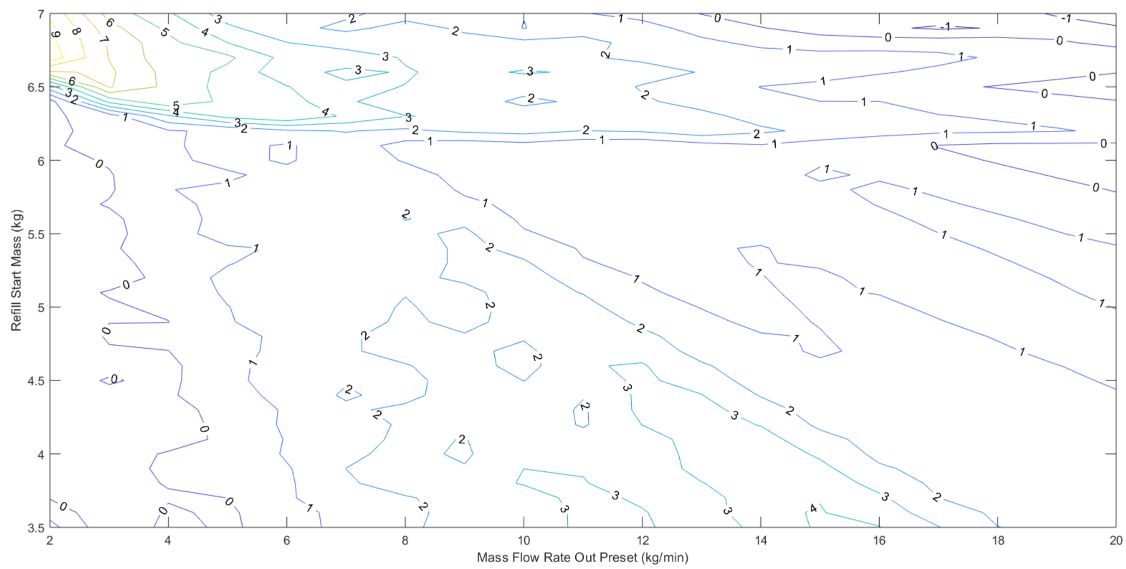

Figure 7: Third product key: % deviation contour plot

The entire above analysis was carried out again with the volumetric RPM at 244 (last recorded RPM when refilling starts) instead of 357. Due to the increase in the density of the powder bed at the bottom of the feeder hopper during refilling, the switch from volumetric mode to gravimetric mode at the end of refilling creates a drastic drop in the screw speed to maintain the flow rate at the set point. Hence, reduction in RPM of volumetric mode reduces the impact of the drop in the rotation speed after refilling when switches back to gravimetric mode to a large extent. Therefore, the deviation in the product key 2 and 3 is seen less when RPM is set to 244 instead of 357, as seen when figures 6 and figure 9 are compared for the deviation in product key 2 and when figures 7 and figure 10 are compared for product key 3 respectively. This result indicates that the feeder RPM during refill may also impact the product key and therefore need to be considered as one of the important parameters during dynamic optimization.

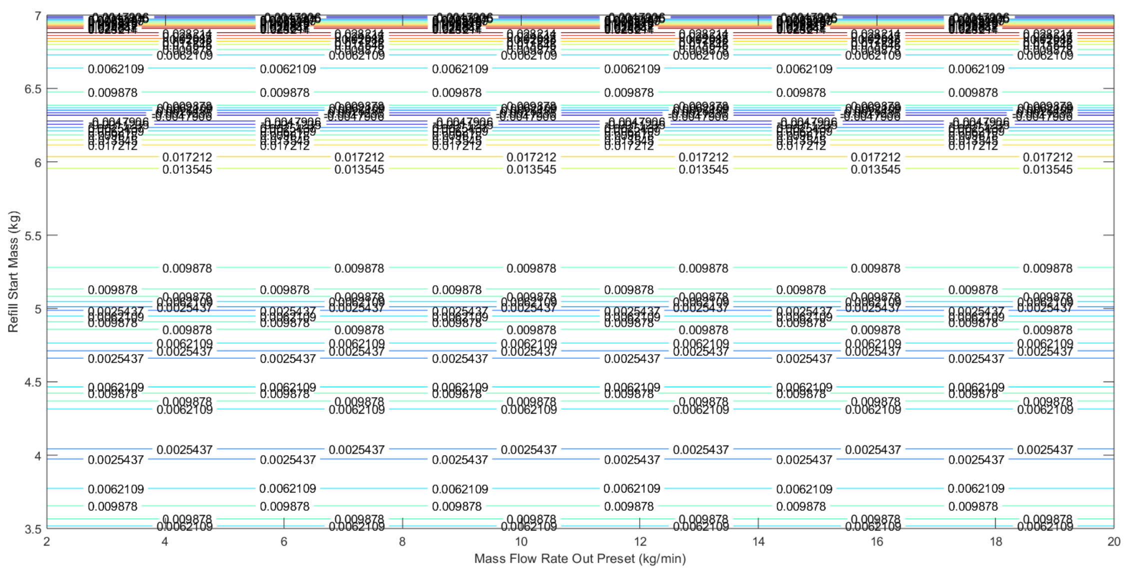

Figure 8: First product key: % deviation contour plot

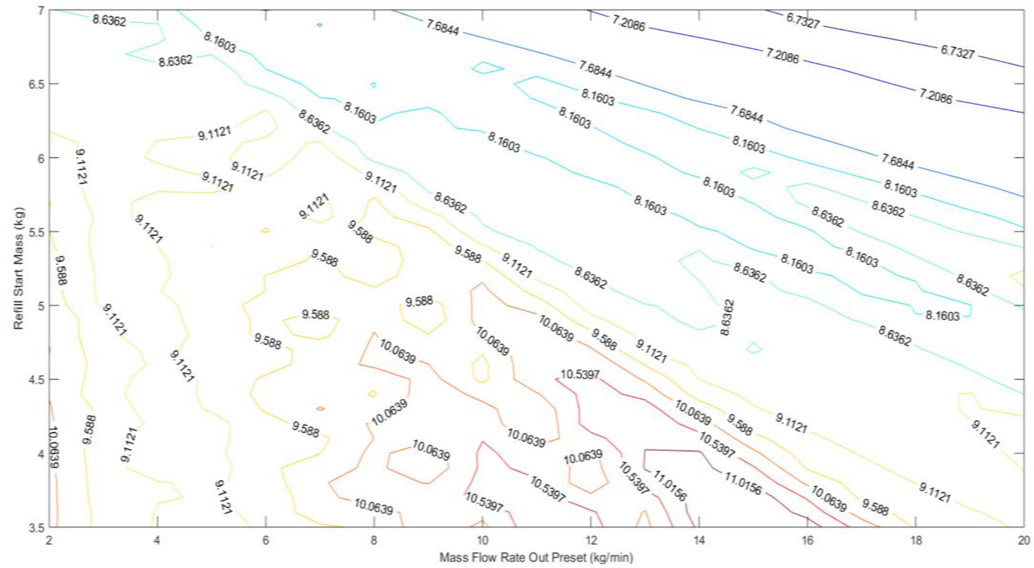

Figure 9: Second product key: % deviation contour plot

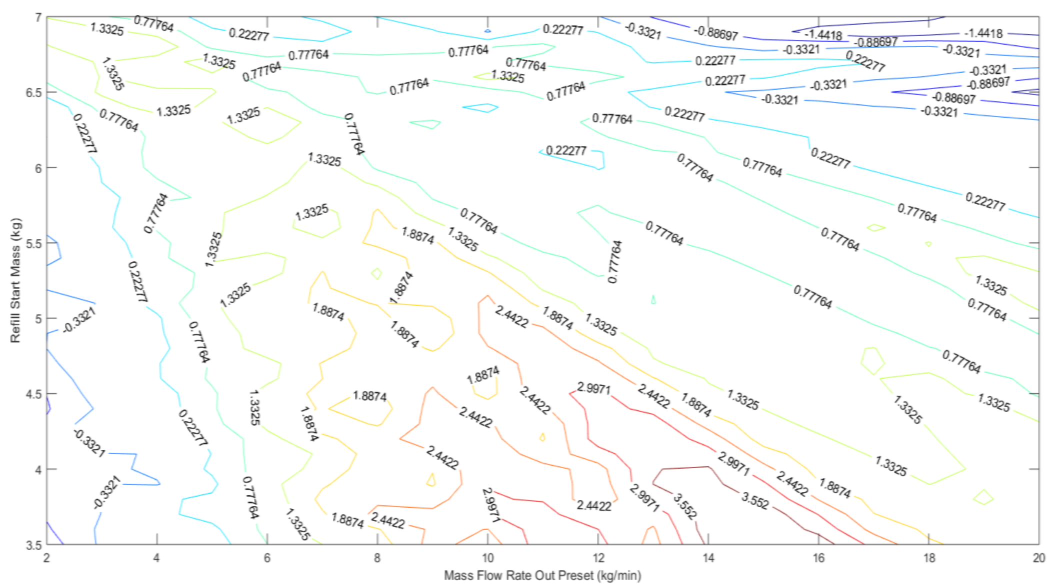

Figure 10: Third product key: % deviation contour plot

Chapter 4: Dynamic Optimization Of Feeder Integrated With Continuous Pharmaceutical Manufacturing

The previous chapter clearly demonstrates the complexities involved in feeder refill strategy identification and thereby the need for employing the dynamic optimization approach to get the refill parameters with fewer materials, time, and resources. This chapter focuses on the optimization of the refill strategy for the feeder through dynamic optimization.

4.1. Process description

The feeder considered in this study is shown in Figure 11. The feeder itself comprises several parts, namely hopper, screws, impeller pitch, and an in-built controller. In the hopper, powders are dumped and later used for feeding to the system. They are of different dimensions depending upon the amount of powder that needs to be fed. Screws are rotated at a particular revolution per minute to maintain the flow rate of the powders from the feeder. There are different types of screws (e.g., Course, Auger) available that have different pitches and screw designs. The selection of the screw depends upon the material properties to be fed. The agitator in the feeders is used to ensure proper mixing of the powder in the feeder.

An in-built controller is another essential part of the feeder to ensure the consistent mass flow rate of powder flowing out of the feeder. The feeder operation without the control is known as the volumetric mode (constant screw speed) of the operation, while the feeder operation under control is known as the gravimetric mode (consistent mass flow rate). In volumetric mode, the flow of powder of the feeder depends on the speed of rotating screws. The speed of the screws is set to a specific value (RPM), with no controller involved, to maintain the mass flow rate. Since the in-built controller is not engaged, the variation of the material density is not compensated. Also, the flow rate of materials is sensitive to the material build-up or other factors affecting the calibration of the feeder. While on the other hand, in gravimetric mode, the feeder adds a weight system and a control scheme to otherwise regular volumetric mode. Because of this control system, direct measurement and control of the discharge rate are possible. Unlike volumetric run, gravimetric run compensates for variation of material densities, and it is insensitive to the material build-up.

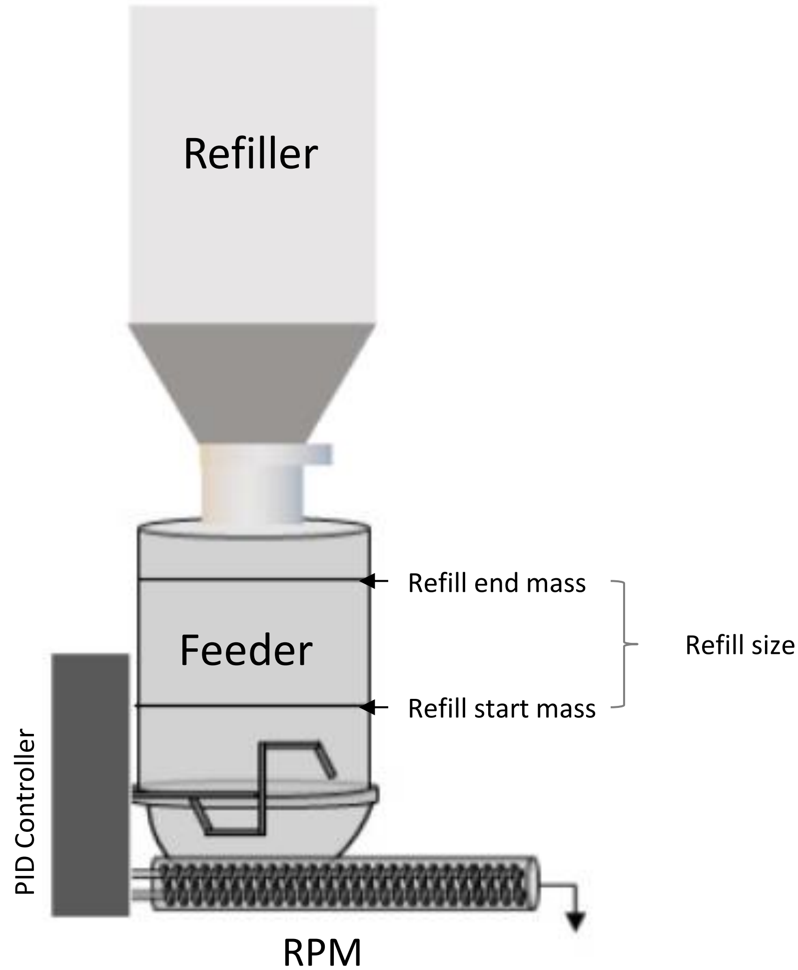

Figure 11: Feeder with Refilling unit

4.2. Feeder refill strategy

Developing a robust refill strategy is essential and important to minimize the variation in the flow rate of the feeder during a refill when the mode of operation switches from gravimetric to volumetric. This, in turn, has an effect on the performance of the feeder

(Yadava, Holman, E., Tahir, & et. al., 2019). Periodic refilling of the hopper of feeders also affects the quality of the product as it can lead to inconsistency and poor feeding performance (Muzzio & Engisch, 2015). Engisch and Muzzio have demonstrated the use of a refill strategy that replenishes the feeder hopper at a slower and more controlled rate of refill has better results in the performance and consistency of feeder than the higher rate of refill (Muzzio & Engisch, 2015). They have also confirmed that the fill level of the hopper is an essential factor that can reduce the deviation effects due to refill (Muzzio & Engisch, 2015). Operating parameters of refill strategy such as start mass (feeder weight when the refill need to be initiated), refill size, and volumetric speed of the screws (RPM) at which feeder run during the refill are also critical parameters which affect the quality attributes of the product to a great extent.

There have been several attempts to minimize the deviations in quality attributes of the products, as described by Muzzio (Muzzio & Engisch, 2015). These attempts include the usage of stored values during the emptying of feed hopper to control screw speed during refill, the use of entirely different feeders while the main one is in the process of refilling, and the use of redundant replenishment hoppers instrumented with load cells. These techniques may work to reduce or eliminate the issues, but do not always eliminate the problem or involves purchasing the additional instruments.

Currently, industries operate feeder by employing the refill parameters obtained through a heuristic approach involving multiple experimental runs leading to inefficient usage of material, time, and resources. This chapter will be discussing the systematic approach to reduce the deviations in the product quality through a model-based dynamic-optimization approach.

4.3. A systematic framework for feeder refill optimization

A systematic framework for feeder refill optimization is shown in Figure 12, which involves several hierarchical steps. Through these steps, when followed sequentially, a refill strategy can be optimized.

The first step of systematic optimization is to specify the process for which the optimization needs to be carried out. Process specification mainly encompasses different unit operations and order of the unit operations. It also involves the listing of the process parameters that need to be optimized. For example, manufacturing tablets through direct compaction process would involve feeding, blending, co milling, and tablet pressing in that order. The process parameters for the feeder that has to be optimized may include the deviation from the setpoint for the flow rate of the feeder. The product specifications mainly include critical quality attributes (CQA’s).

The next step is to develop models for each unit operations necessary for the manufacturing of pharmaceutical products, incorporating known processes and product specifications. Models thus developed can be data-driven models, first principles-based, or a semi-empirical model. These developed models, representing each essential unit operation, can be integrated together to replicates the real processes in the plant. For instance, for the direct compaction process of tablet manufacturing, models for feeding, blending, co-milling, and tablet pressing was developed, validated, and integrated to reproduce the real process manufacturing and product quality based on the processes and product specifications.

The integration of different platforms is the subsequent step, after development models for different unit operations, to ensure that the optimization of the process can be successfully executed. The optimization of process parameters involves multiple simulations to minimize the optimization function. These multiple simulations by a single click may or may not be possible using the current process modeling platform, depending on whether the simulation platform has the optimization feature or not. More ever, it needs to have a global optimization tool rather than a local optimization tool. Hence, these optimization limitations can be overcome by integrating the modeling platform with other platforms that enable the same. In case studies described in this manuscript, the process model was developed in gPROMS, and optimization program was developed in MATLAB in which the optimization can be performed using in-build Fminsearchbnd function.

Once, the successful execution of dynamic optimization is ensured, the next step is to define the objective function. The minimization of the error in the objective function leads to the optimization of the process parameters. The objective function, which depends on the inputted values of process parameters, must be defined in such a manner that a reduction in its value would eventually lead to the optimization of unit operation. Here in the case studies described below, the objective considered for feeder process optimization is SSE (sum of squared errors). This SSE function considers error between expected and actual outlet flow rate of material from a feeder. Examples of other objective functions could include MAPE (mean absolute percentage error), SD (standard deviation), and variance.

Objective function considered for case studies discussed below is given as:

$$\text{SSE} = \int_0^t (Feeder\ mass\ flowrate\ out\ - Controller\ set\ point)^2 dt \qquad \textbf{4.3.}$$

Another vital aspect to be considered in dynamic optimization is the boundaries for the process parameters. Within these limits, the process must be operated to ensure the accurate working of the model; also, these boundaries serve as an operating range within which optimization of process parameters must be carried out. For example, the limits considered for case studies for this work are given in table 4.

The next step after building the process model, defining the objective function, and boundaries of process parameters is running the optimization simulation to obtain a minimum value of the objective function.

The optimized values of process parameters should be within the boundary conditions specified at the start of the process. The connectivity of the modeling and optimization platforms needs to be verified before performing the optimization to ensure that the dynamic optimization process produces actual results instead of giving unexpected results. These optimized parameters can then be implemented in the actual system to verify experimentally and subsequently used in the continuous manufacturing of pharmaceutical tablets. If the results of experimental verifications do not reciprocate, then the accuracy of the integrated flowsheet model, integration of the modeling platform, and optimization platform need to be verified or rerun the dynamic optimization process.

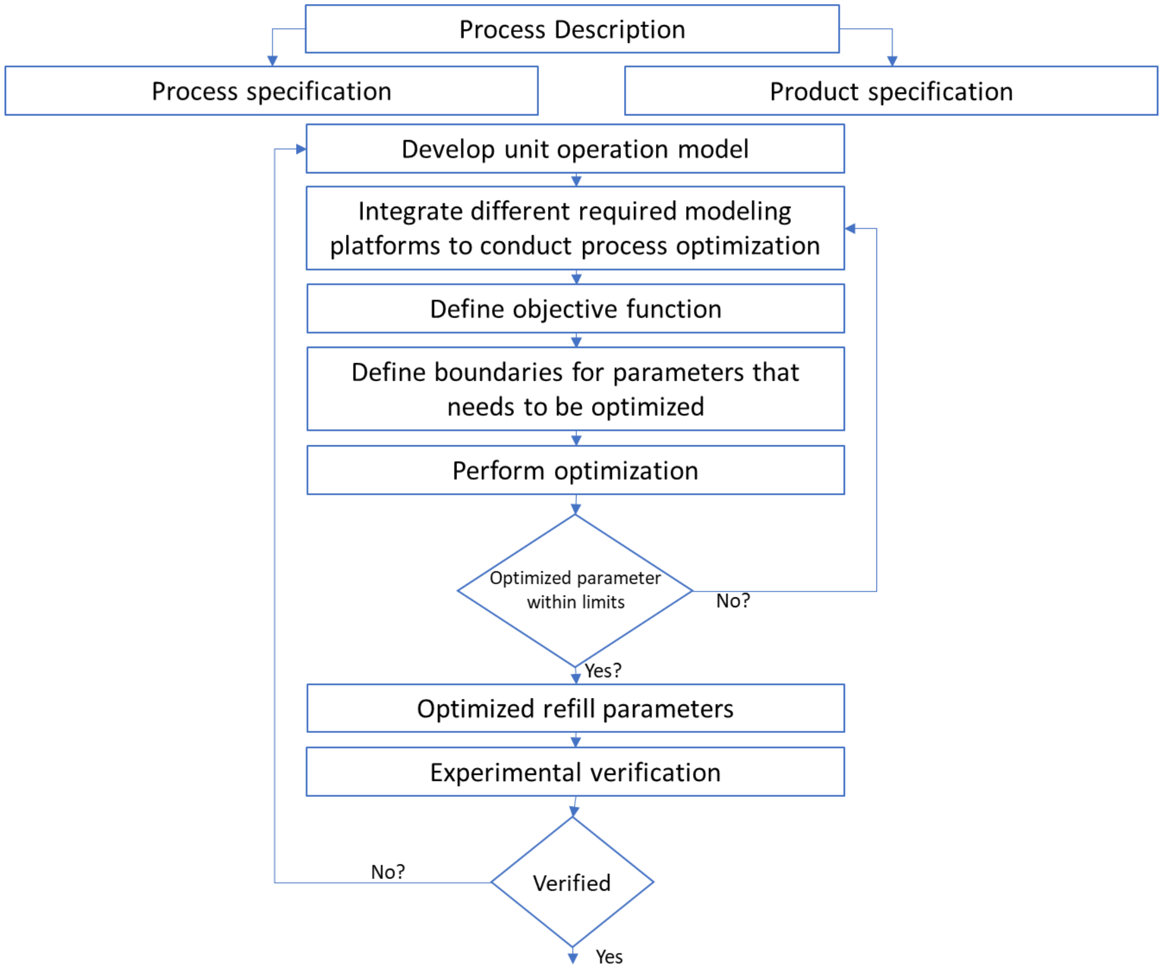

Figure 12: A systematic methodology for feeder refill optimization

Table 4: Boundary Conditions for process parameters for optimization

Process parameters	Boundary conditions
Refill start mass (kg)	2.5 – 6
Refill Size (kg)	0.5 - 4
Feeder screw rotational speed (RPM)	100- 500

4.4. Demonstrative case study – I: Optimization of feeder refill strategy

Case study - I is focused on the optimization of the feeder's refill strategy involved in continuous pharmaceutical manufacturing via wet granulation. The system consists of two feeders (one for API and another for pre-blend of API and excipient mixture), and a twin-screw granulator, as shown in figure 13. The product is collected at the granulator outlet. Feeders discharge the powder at a different flow rate to granulator, where powders are being granulated into granules. The composition of granules depends on the discharge rate of each feeder, which is, in turn, dependent on the refill strategy of each feeder. After granulation, the granules are then stored in product keys.

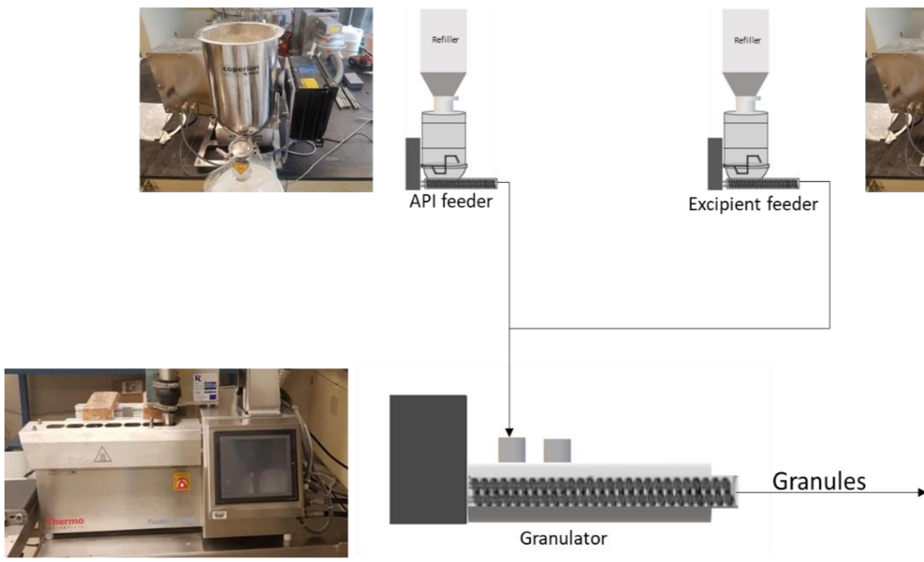

Figure 13: Pictorial representation of continuous wet granulation process (all unit operations are not shown)

The process flowsheet model was developed in gPROMS' FormulatedProducts software. It consists of the properties model, two refill models, two feeders, a PID controller, a twin-screw granulator, and a product key. The PID controllers are necessary for the gravimetric run to maintain the mass flow rate of the powder discharging through the feeder. After the granulation process, the granules are emptied in a product key, collecting a specified amount of granules per product key. The layout of the process is shown below. The entire process is complex and includes a large number of equations for calculation of mass fraction in the product. Real-time operation time of the process (i.e., from feeder till the end of the twin-screw granulator) is 3 minutes implying the production rate of granules in actual is 1kg/min.

Refill strategy for each feeder, which includes rotational speeds of the feeder screws, starting and ending point of refilling, can affect the overall concentration of API in the product key as RPM of the screws vary during refilling and non-refilling conditions. During refill, the feeder runs in volumetric mode (constant screw speeds); else, it runs in gravimetric mode (varying the speed of the screws according to the properties of the powder). Due to this variation in the rotation speed of screws, the overall mass flow rate of the feeder varies, which in turn causes deviation in the expected composition of the granules. In (Muzzio & Engisch, 2015) , Muzzio et. Al. demonstrated the impact of refill start mass and refill size, as the incoming powder compresses the bed of powder in the hopper, producing an increase in the density and thus amplifying the deviations in the flow rate of a feeder. Hence, it was necessary to investigate the impact of different refill strategies on the concentration of API in the product key, to obtain an optimized plan that has minimum effect on the composition of granules entering the dryer at the end of the granulation process. Conventionally, the feeder refill strategy is optimized through a heuristic approach. A conceptual example of a refill strategy is given below:

Table 5: Heuristically determined refill strategy for feeders of Case study -I

Process parameters	Excipient feeder	API feeder
Start mass (kg)	5.2	4.2
Refill size (kg)	2.8	2.8
Feeder screw rotational speed (RPM)	357	365

Fminsearchbnd, an in-built function of MATLAB, which finds a minimum of a constrained multivariate function using a derivative-free method, is utilized to find the minimum of the objective function defined in the process model developing software (gPROMS FormulatedProducts). Here, in this case, the objective function is SSE, sum of squared errors of prediction between the outlet mass flow of the feeders and targeted flow rates (refer to equation 4.3.) and the process parameters for a feeder that needs to be optimized are refill start mass, refill end mass and volumetric mode RPM. An additional toolbox of gO:MATLAB was necessary for the integration of MATLAB and gPROMS. gO:MATLAB is a powerful tool among other gPROMS objects, which enables control engineers to solve complex gPROMS advanced models using well known and widely-used Mathworks' MATLAB environment. Usage of gO:MATLAB tool allows the user to enter an array of input variables to complicated gPROMS advanced control designs and obtain corresponding results in a well-organized manner.

The refill optimization process was carried out by ensuring the connections between gPROMS and MATLAB were established to enable gO:MATLAB tool to run. The overall communication between MATLAB and gPROMS is shown in figures 14 and 15.

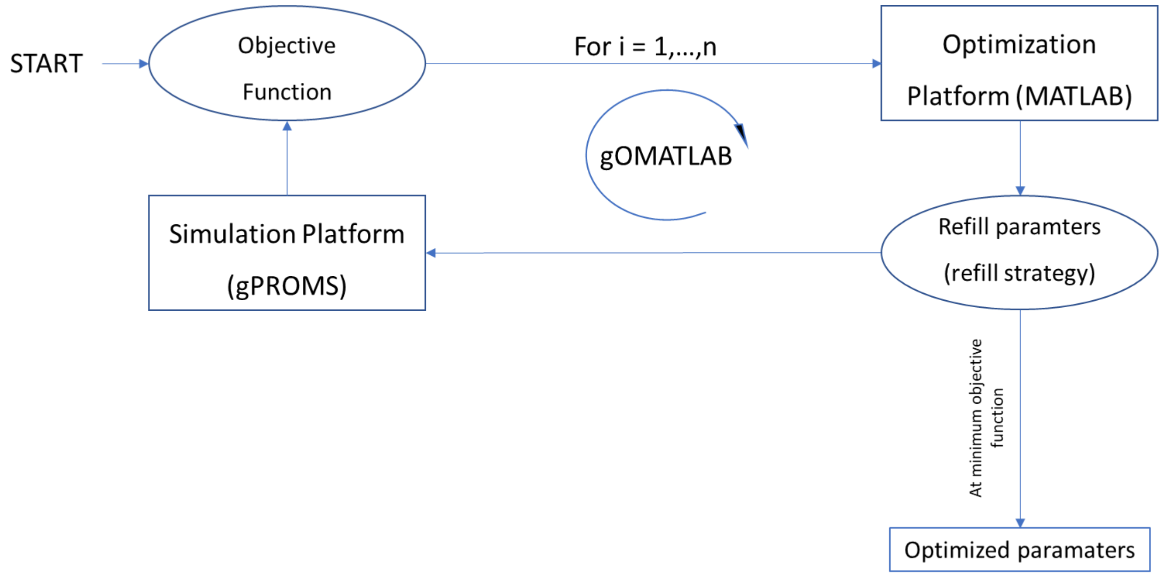

Figure 14: Flow diagram for the overall process of interaction between MATLAB and gPROMS

Through the ensured connection between modeling and optimization platforms, values of the objective function from gPROMS FormulatedProducts and inputs from MATLAB are being communicated to each other. The data from MATLAB through gO:MATLAB is being transmitted to gPROMS modeling software, which calculates the objective function through numerous equations. This calculated value of the objective function is then communicated back to MATLAB for evaluation of the minimum value of the objective function. The inputs from MATLAB at which the minimum value of the objective function is achieved are optimized parameters of the process.

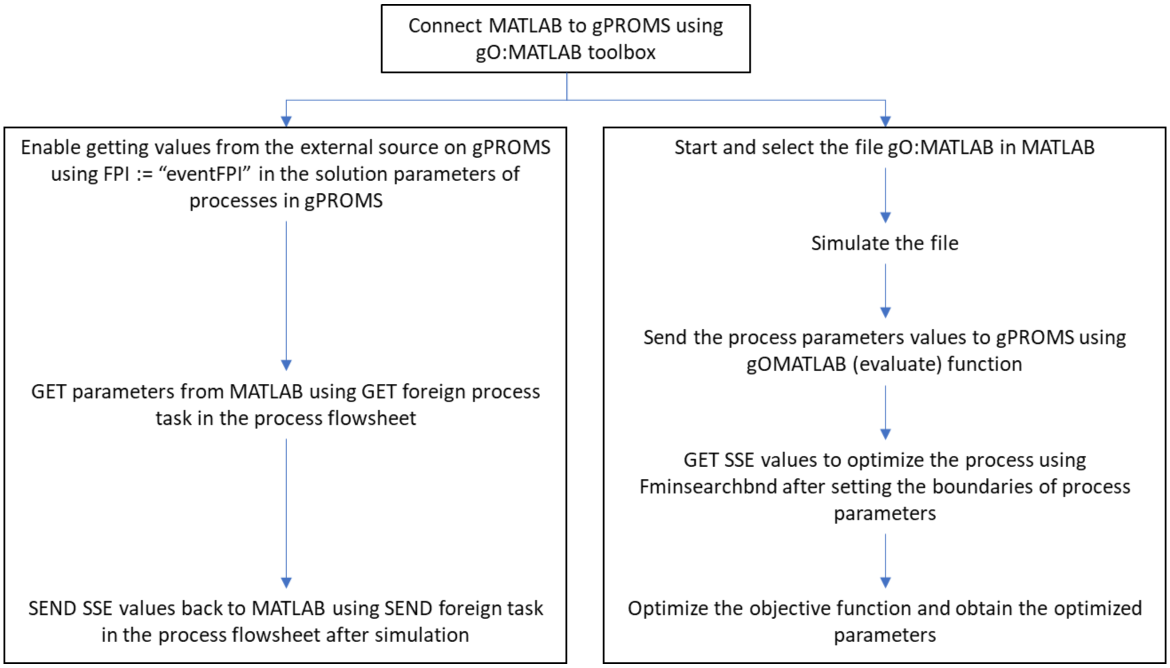

Figure 15: Flow diagram for the process of communication between MATLAB and gPROMS

After a thorough evaluation of the connectivity between the two software, the optimization process was carried out for one feeder at a time (process parameters were optimized for API feeder first then for the excipient feeder). Five product keys were considered for the accurate evaluation of the impact of refill on the composition of product keys.

4.5. Demonstrative case study – II: Effect of process parameters on feeder refill strategy

In this case study, the impact of different mass flow rate setpoints of the same material on the refill process parameters was studied. This analysis was carried out by considering four values of the mass flow rate setpoints for the Avicel PH105, from 0.345 kg/min to 0.54 kg/min. Four different mass flow rate setpoints, 30.345 kg/min, 0.41

kg/min, 0.475 kg/min and 0.54 kg/min. The refill strategy for each of the mass flow rate setpoints was optimized.

Similar to the previous case study, gPROMS is the modeling platform, and optimization of the process parameters was carried out using the Fminsearchbnd toolbox of MATLAB, and the objective function is also the same as that of Case study -I, refer to equation 4.3.

The boundary conditions for the optimization of process parameters are similar to the case study – I, refer to table 5. Simulations for optimization were carried out in a similar manner to that of case study – I, one mass flow rate at a time, and five product keys (simulated for a total of 1080 seconds) were considered to evaluate the impact of refill on the variation in the discharge rate of each mass flow rate.

4.6. Demonstrative case study – III: Effect of material properties on feeder refill strategy

This case study focuses on the analysis of the effect of material properties with similar mass flow rate set points on the refill process parameters. Avicel PH 105 (Excipient 1, Bulk density 343.05 kg/m3) and lactose 200M (Excipient 2, 570.20 kg/m3) were considered for the study due to the difference in their densities. The material properties of both materials were measured using Brookfield Powder Flow Pro V1.3 Build 23.

The mass flow rate for the two feeders for Excipient 1 and 2 was set at the same mass flow rate of 345 grams per minute, and the dynamic refill optimization was executed in a similar way as that of the Case study – I and II and compared. The objective function is the same as that of Case Study – I and II, refer to equation 4.3.

4.7. Results and discussions

The refill optimization was carried out for all the above cases.

4.7.1. Demonstrative Case Study – I: Optimization of feeder refill strategy

The below graphs illustrate both mass flow rate and screw speeds of the API feeder in both scenarios (original and optimized). The screw's speed of the feeder changes continuously, maintaining the flow rate over the entire operation of the feeder to compensate for the variation of density of powder. During the gravimetric run (during no refill), because of the decrease in the amount of powder in the hopper, the density at the bottom of the hopper decreases and thereby triggering the screw’s speed (RPM) to increases with the decrease in the amount of powder in the hopper. While, during refilling (volumetric mode), the screw’s speed required to maintain the same flow rate reduces as the density of powder at the bottom of the hopper to shoots up because of the incoming material.

As seen in figure 16, for the first 100 seconds, the feeder operates in gravimetric mode (no refilling), and the amount of powder in the hopper decreases from 5 kg to 4.2 kg causing a decrease the density of powder at the bottom of the hopper and subsequently increasing the screw’s speed (RPM). The feeder switches to volumetric mode once the amount of powder in the hopper reaches 4.2 kg, during which it operates at constant screw speed. Because of the increase in the density at the bottom of the hopper during refilling, as the incoming material compresses the powder bed present in the hopper, the switch from the volumetric to gravimetric mode after completion of refilling produces an acute drop in the screw speed required to maintain the mass flow rate at the setpoint which induces deviation in the mass flow rate. Therefore, instead of volumetric screw speed being set to last set value of gravimetric speed (365 rpm) when feeder switches from gravimetric mode to volumetric mode while refilling for non-optimized refill strategy, the volumetric speed is set lower (360 rpm) so that the impact of drop in the rotation speed when feeder switches back to gravimetric mode is reduced to a greater extent.

The optimized refill strategy has a higher number of refill due to lower values of refill start mass and refill size, as seen in figure 16, compared to the non-optimized refill strategy. This frequent refilling of small batches of powders reduces the variation of density at the bottom of the hopper and thereby decreases the variation of the mass flow rate to a greater extent. This reduction in the deviation of the flow rate can be seen through the SSE value, as it decreased from 1.311 (the non-optimized refill strategy) to 1.267 (the optimized refill strategy).

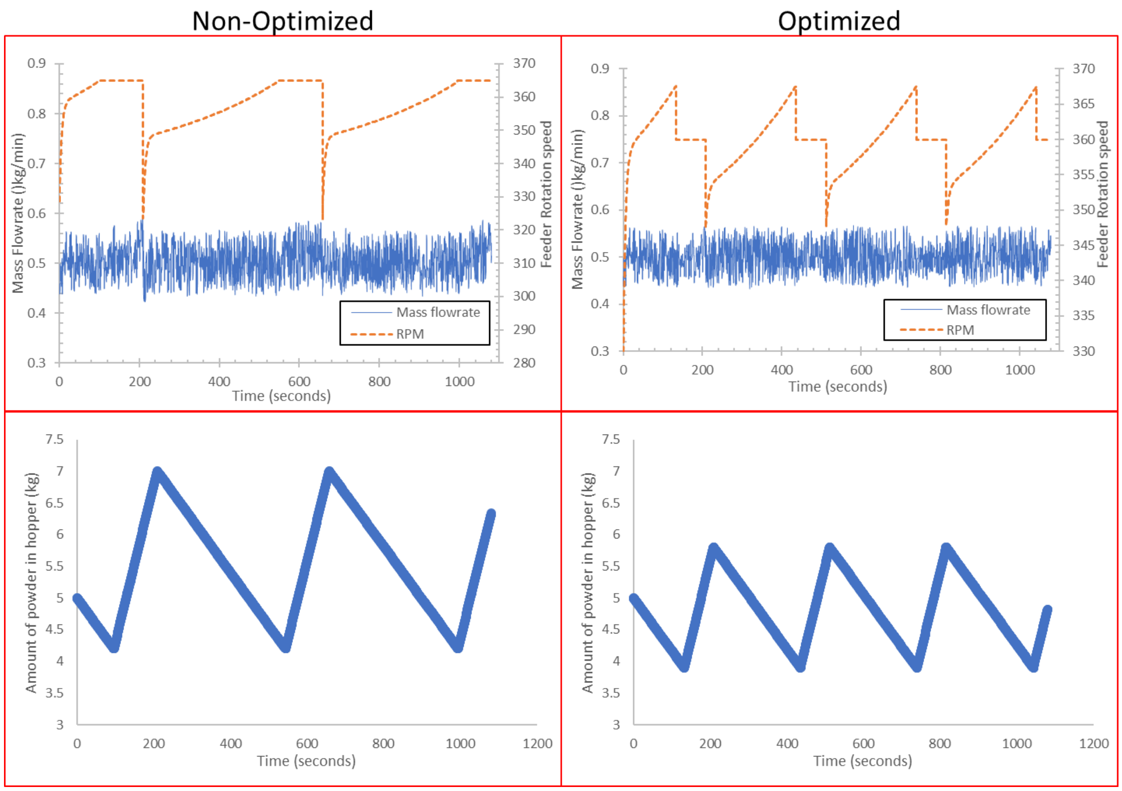

Figure 16: Comparison of refill strategy for API feeder. Mass flow rate and RPM comparison and amount of powder in the hopper in the feeder for Case study –I

A similar procedure was carried out for the excipient feeder. The variation in the flow rate of excipient feeder is reduced by frequent refilling of small batches of powder, as seen in figure 17, compared to a non-optimized refill strategy. Also, similar to the API feeder, the variation in the flow rate of powder is decreased by reducing the value of volumetric screw speed to 355 rpm from 357 rpm of non-optimized refill strategy, leading to a decrease in SSE value from 1.310 (non-optimized refill strategy) to 1.268 (optimized refill strategy).

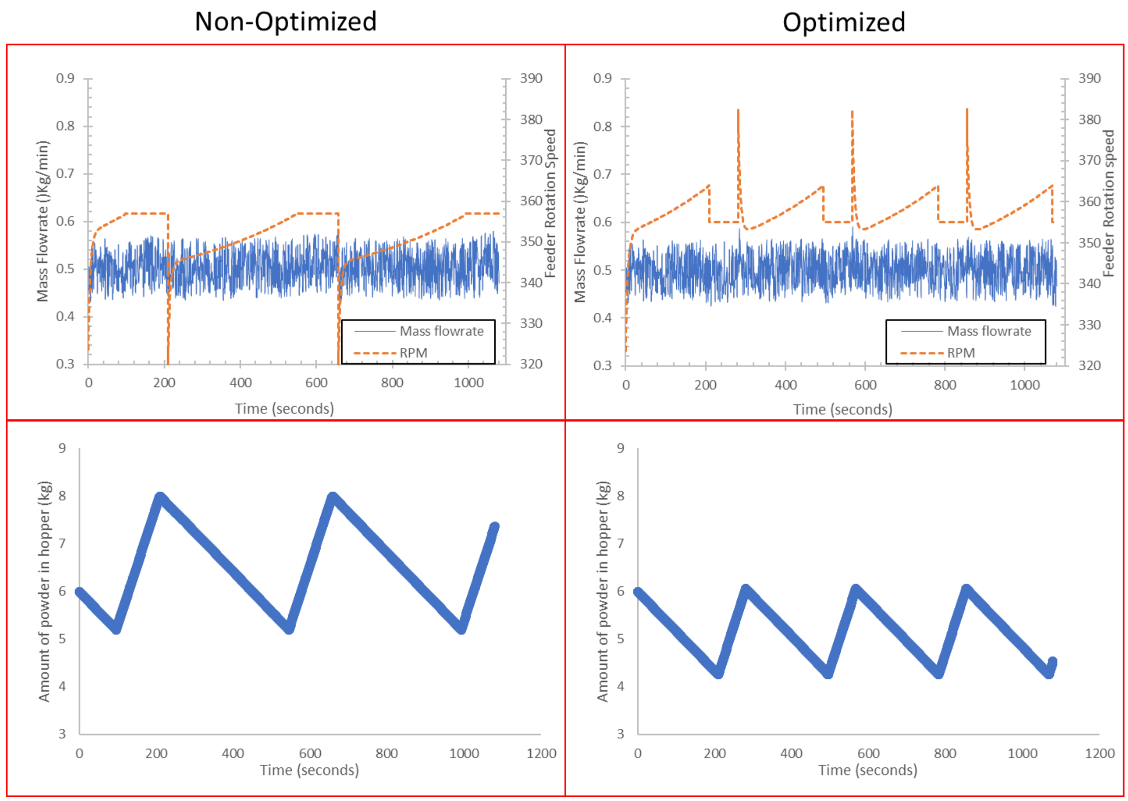

Figure 17: Comparison of refill strategy for Excipient feeder. Mass flow rate and screw speed comparison, and amount of powder in the feeder for Case study -I

The overall result from the above simulation experiment is given in table (6). The overall SSE for both the feeder is less for the optimized refill strategy than for the original refill strategy.

Table 6: Overall result table for Case study - I

Process Parameters	Non-Optimized		Optimized	
	Excipient feeder	API feeder	Excipient feeder	API feeder
Start mass (kg)	5.2	4.2	4.26	3.9
Refill size (kg)	2.8	2.8	1.8	1.9
Feeder Rotation Speed	357	365	355	360
SSE	1.274	1.313	1.241	1.2205

4.7.2. Demonstrative Case Study – II: Effect of process parameters on feeder refill strategy

The dynamic refill optimization was executed for different set points of mass flow rates. Four mass flow rate setpoints, 0.345 kg/min, 0.41 kg/min, 0.475 kg/min, and 0.54 kg/min, were considered for the analysis. Figure 18 demonstrates an increase in screw speed with an increase in the mass flow rate setpoint.

With the increase in mass flow rate setpoint, the overall rate of change of density and pressure in the hopper increases during the gravimetric run, thus the value of density at the end of the gravimetric run is lower for higher mass flow rate setpoint. During refill, due to the incoming flow of powder, a larger refill size would increase the density of the bed to a great extent and decreasing the screw speed by a considerable amount and thereby reducing the impact of the change of screw speed (RPM) when the feeder switches the mode of operation from volumetric to gravimetric. This reduces the deviation in the mass flow rate, which is ideal for low mass flow rate setpoint. While on the other hand, smaller refill size increases the density of the powder to a less extent, thus decreasing the screw speed by a small amount, reducing the impact of the change of RPM when the feeder switches from volumetric to gravimetric mode, making it the best fit for higher mass flow rate setpoint.

For higher mass flow rate setpoints, the lower refill start mass is expected, as the drop in the density during the gravimetric run would be higher. Therefore, at the beginning and the end of the refill, the variation in density will be less in comparison with other flow rates , and screw speed will be high, making it suitable for a higher mass flow rate setpoint. Contrarily, for lower mass flow rate setpoints, the higher refill start mass is the best fit, as the drop in the density will be less. Consequently, density will be more and screw speed being less at the beginning and end of refill; thus, there will be a minimum deviation in mass flow rate. Figure 18 demonstrates the decrease in values for both refills start mass and refill sizes with an increase in mass flow rate.

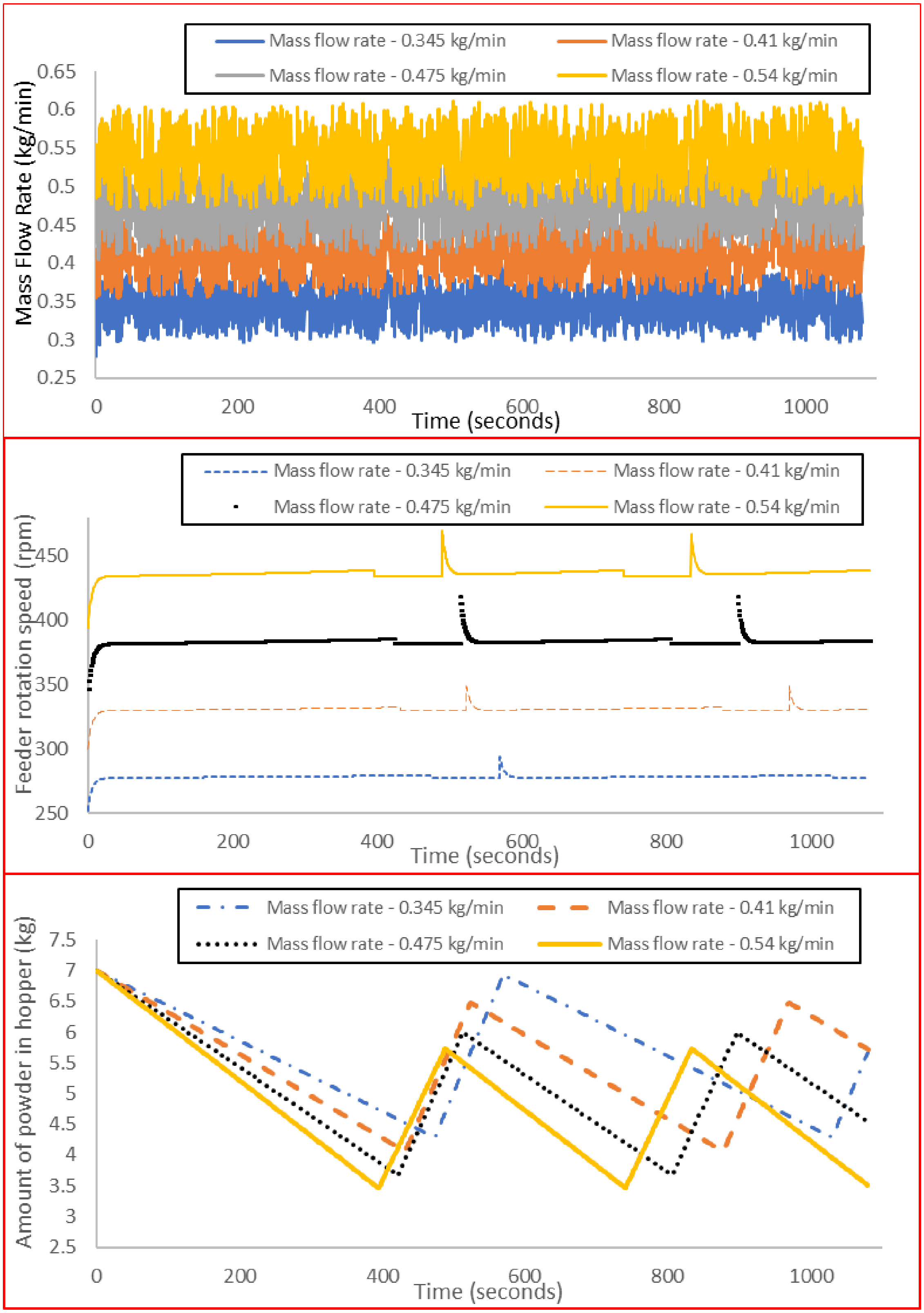

Figure 18: Comparison of Mass flow rate, volumetric feeder rotational speed, amount of

powder in the hopper for different mass flow rate setpoints of a feeder containing Avicel PH 105

Refill optimized parameters for all flow rates were plotted together, as shown in figure 19. Also, figure 19 indicates that the increase in the mass flow rate (indirectly increase in screw speed of feeder) leads to a decrease in refill process parameters (refill start mass and refill size). Both refill start mass (R^2 = 0.996) and refill size (R^2 = 0.9084) demonstrates direct linear relationship while screw speed (R^2 = 1) shows indirect linear relationship with mass flow rates.

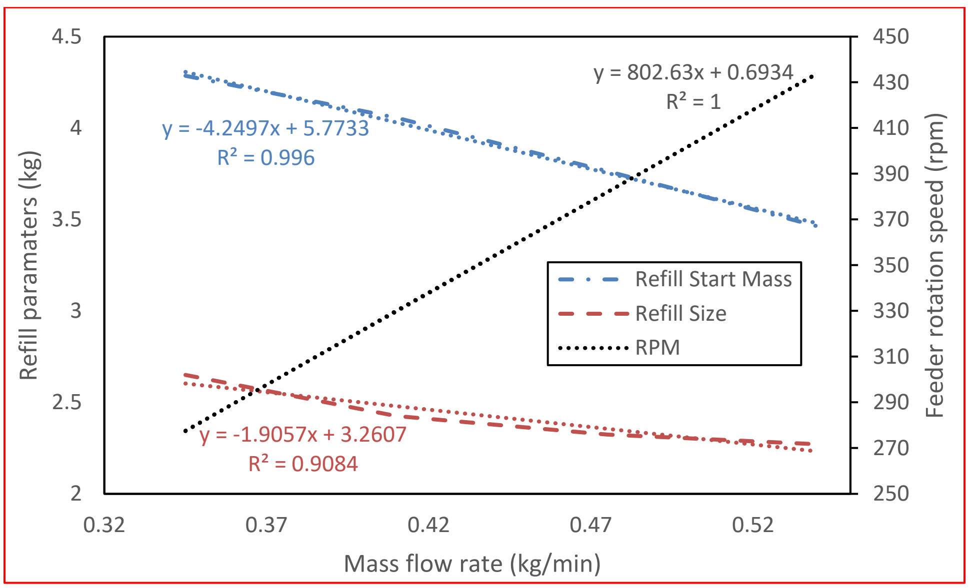

Figure 19: Relation of refill process parameters with different mass flow rate setpoints of a feeder containing Avicel PH 105

The overall result for each of the dynamic refill optimization is given in table 7.

Table 7: Comparison of refill process parameters for different mass flow rate setpoints of a feeder containing Avicel PH 105

Process parameters	**Avicel PH 105**			
	Mass flow rate – 0.345 kg/min	**Mass flow rate – 0.41 kg/min**	**Mass flow rate – 0.475 kg/min**	**Mass flow rate – 0.54 kg/min**
Start mass (kg)	4.2859	4.0572	3.7657	3.4623
Refill size (kg)	2.6502	2.425	2.3236	2.2711
Feeder Rotation speed	277.43	330	382	434
SSE	0.6049	0.8085	1.03406	1.31312

4.7.3. Demonstrative Case Study – III: Effect of material properties on feeder refill strategy

Similar to case study – II, the dynamic refill optimization for both feeders containing Avicel PH 105 and Lactose 200M (operating at the same mass flow rate of 345 grams/min) was carried out to evaluate the effect of density on the refill parameters. Figure 20 demonstrates the mass flow rate data for each of the feeders.

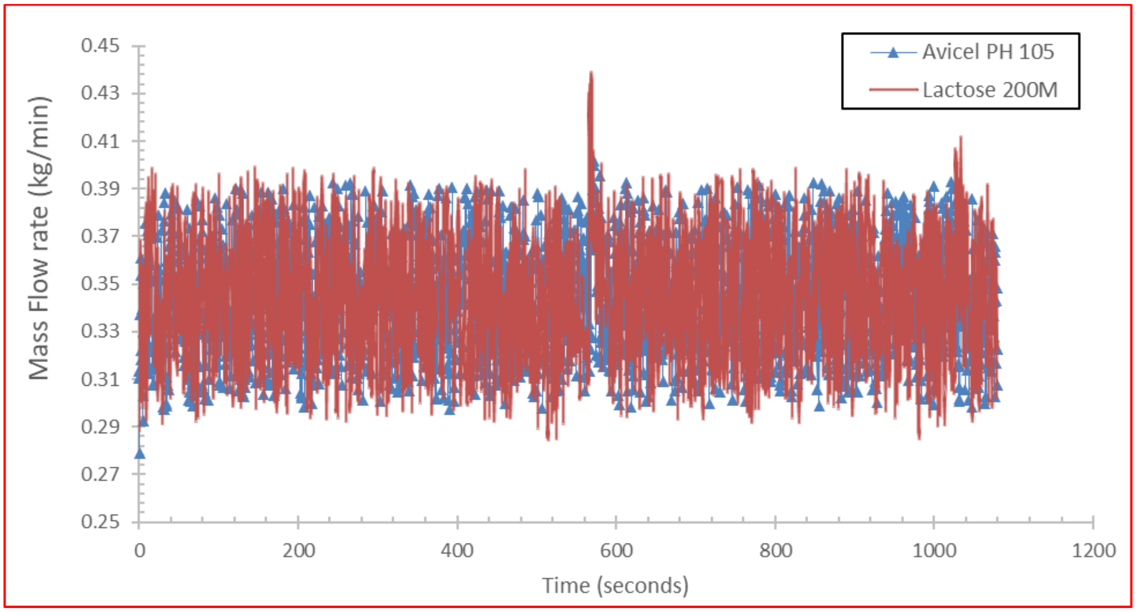

Figure 20: Mass flow rate comparison for feeders with Avicel PH 105 and Lactose 200M

Lactose 200M being denser than the Avicel PH 105, it is expected for the latter to have a higher screw speed (both volumetric and gravimetric mode of operation) than the former to maintain the flow rate at same set point, which is established in figure 21 below. With the increase in density, the screw speed required to maintain a particular value of mass flow rate decreases, thereby having an effect on the refill strategy.

Similar to case study – II, less dense material can have a higher start mass, as the drop in the density will be less, thereby screw speed would be lower at the beginning and the end of refill than the denser material. This reduces the deviation in the flow rate. Also, less dense material can have a larger refill size as the rate of variation in the density will be lower; thus, more refill time could be more. From figure 21 and the table 8, it can be inferred that Avicel being less dense than Lactose, the start of the refilling of Avicel with more amount of powder is present in the hopper, and larger refill size has a lesser impact on the flow rate than Lactose.

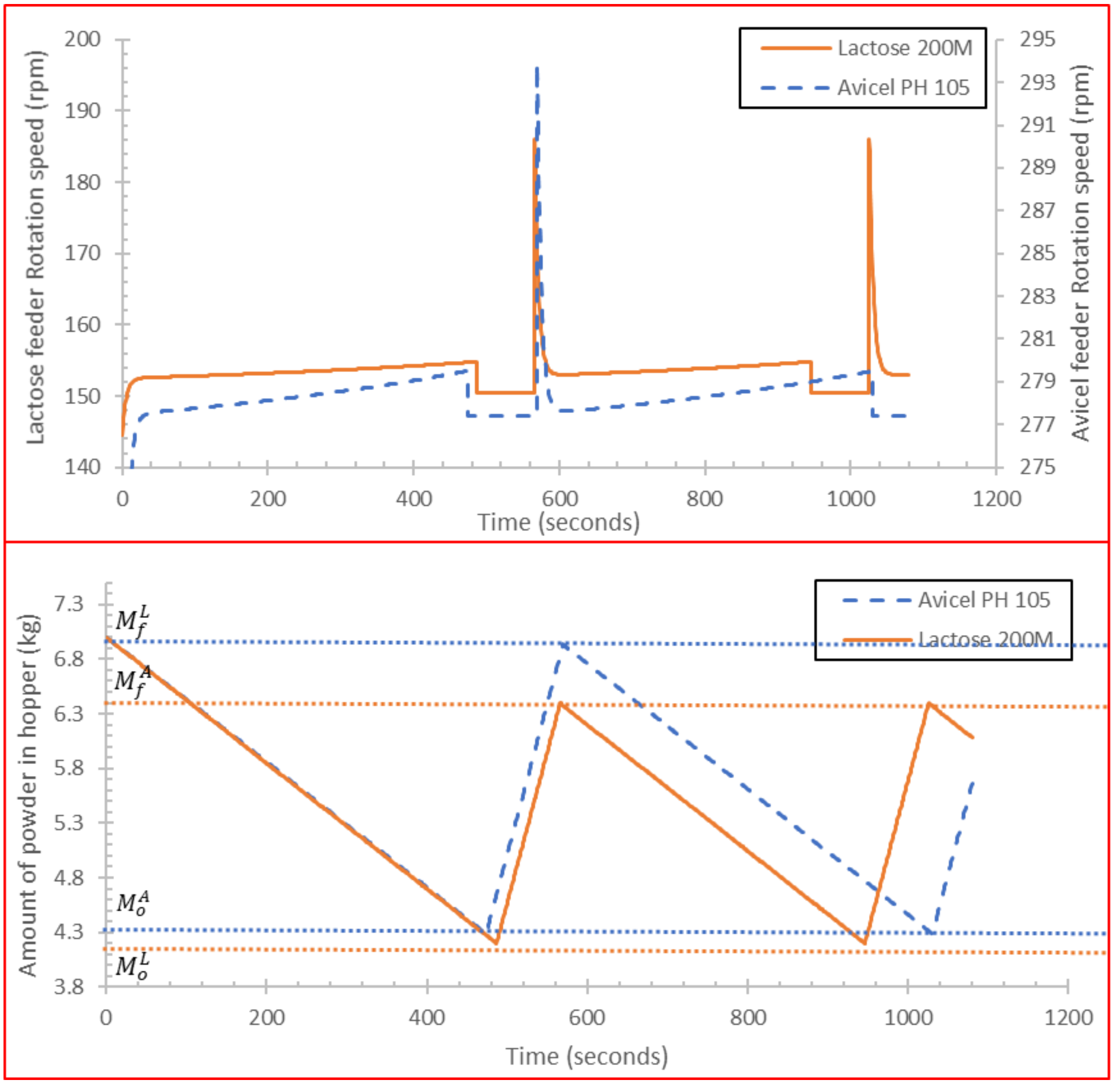

Figure 21: Feeder rotation speed comparison for Avicel and lactose feeder running at the same mass flow rate.

The optimized values of the refill strategy for feeders containing Avicel and Lactose are given in table 8.

Table 8: Result for comparison of refill process parameters for case study - III

Process parameters	**Excipient 1 (Avicel PH 105)**	**Excipient 2 (Lactose 200M)**
Start mass (kg)	4.2859	4.2
Refill size (kg)	2.6502	2.2006
Feeder Rotation speed	277.43	150.3745
SSE	0.6049	0.84966

Chapter 5: Conclusions and Future Perspectives

5.1. Conclusions

Advancements were made in the field of process system engineering. The impact of the refilling of the feeder was studied thoroughly and quantitatively analyzed.

In this work, the flowsheet model was utilized to demonstrate the applications of modeling approaches in the field of process engineering and optimization. Challenges such as acceptability of product due to batch to batch variability and impact of variation of refill size and refilling time on the product composition were tackled. The essentiality of the optimization of the refill strategy for the feeder was demonstrated to improve the content uniformity and blend uniformity.

The addition rate of each feeder in continuous manufacturing regulates the product composition, thus plays an important role. This flow rate of the feeder may be greatly dependent on the material properties and refilling strategy of the feeder. In looking at the challenges involved in the optimization of the refill strategy, a systematic framework for dynamic optimization was proposed. Thus, utilization of the modeling approach for the optimization of the refill strategy will reduce the consumption of materials and time. The application of the framework has been demonstrated through the refill optimization of a feeder and to study the impact of process parameters and material properties on the refill strategy.

5.2. Future Perspectives

With increasing complexities in the manufacturing of pharmaceutical drug products, it is essential to develop models of other unit operations and optimize the process through modeling approaches to increase efficient production. Although the refill strategy for the material used in feeder optimized using the framework developed provided better results than the heuristically developed refill strategy, it is crucial to validate the results through experimentations.

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Appendix A: Nomenclature

Symbols	Description
M_0^A	Refill start mass for Avicel feeder
M_f^A	Refill end mass for Avicel feeder
M_o^L	Refill start mass for Lactose feeder
M_f^L	Refill end mass for Lactose feeder
E(t)	Residence time distribution
Eexp(t)	Experimental residence time distribution
Emodel(t)	Fitted residence time distribution
f	A fraction of the tracer component

Abbreviations	Description
API	Active Pharmaceutical Ingredients
PID	proportional–integral–derivative controller
RPM	Revolution per minute
SSE	Sum of squared errors of prediction
MAPE	mean absolute percentage error
SD	standard deviation
TIS	Tank in series
PFR	Plug flow reactor
MRT	Mean residence time

Superscript	Description
A	Avicel PH 105
L	Lactose 200M

Abbreviations	Description
M_o	Refill start mass
M_f	Refill stop mass