Implementation of an Advanced Control Strategy into a Continuous Direct Compaction Pharmaceutical Tablet Manufacturing Process

by

APARAJITH BHASKAR

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

Completed under the direction of

Ravendra Singh

And Approved by

_____

_____

_____

New Brunswick, New Jersey

October, 2018

Abstract of the Thesis

Implementation of an Advanced Control strategy into a Continuous Direct Compaction Pharmaceutical tablet manufacturing process

By APARAJITH BHASKAR

Thesis Director:

Ravendra Singh

In the context of the pharmaceutical manufacturing, a recent momentum has developed in using continuous manufacturing lines as opposed to conventional batch manufacturing systems. Processes that are continuous in nature traditionally have been adapting process systems engineering (PSE) tools to assist in their quality management process. The pharmaceutical industry, which has been newly initiated into the domain of continuous manufacturing, presents new and challenging problems within the PSE domain. The primary reason for these challenges is the particulate nature of the raw materials. The design, development and implementation of control systems in such an environment lacks a comprehensive literature base. This work attempts to fill in this void through an exploration of control schemes that can be implemented into a Direct Compaction (DC) continuous manufacturing line. Focus was given to model predictive control (MPC) systems due to their expected augmented performance in comparison to the classical Proportional Integral Derivative (PID) controller. Multiple control strategies were developed in the domain of tablet compaction. A key result was the development and implementation of a multi input multi output (MIMO) MPC that was capable of controlling tablet weight and compression force simultaneously under the assumption that real time tablet weight data was available.

Building upon this Model Predictive Control scheme, an optimization algorithm that was adapted from a previous simulation based study was modified for implementation into the DC manufacturing line. The methodology for its implementation along with some key experimental results is presented here. Here, the demand was a user input to the optimization. The output of this calculation was the production rate set point which was relayed to the MPC. The actual value of the production rate is treated as a disturbance variable. Main compression force was monitored and controlled during various demand scenarios to give an indication of tablet quality.

Finally, a Residence Time Distribution (RTD) based control system was implemented *insilico* for proof of concept. The RTD of a system can be used to predict outlet parameters if input parameters are known. This was used to predict the concentration of the active pharmaceutical ingredient (API) in tablets at the outlet of the compaction process. This information was used to develop a rejection system that would divert tablets that violate specified tolerance limits.

Acknowledgements

I would like to thank Dr. Ravendra Singh for giving me the opportunity to work in his research group. I thank him for his constant guidance and support through the course of my Master's program. His guidance was truly valuable and his patience was one that kept us all on the ground without panicking. I would also like to thank my thesis defense committee members Dr. Rohit Ramachandran and Dr. Shishir Chundawat.

I would also like to thank the FDA and Rutgers research council for their financial support in the work done in this thesis. I would like to acknowledge the Engineering Research Center for Structured Organic Particulate Systems (C-SOPS), Department of Chemical and Biochemical Engineering, Rutgers University, NJ, USA, for providing support and giving me a hands on experience on the various pharmaceutical unit operations and software mentioned in my thesis.

I would like to give thanks to Fernando Nunes De Barros with whom I have spent a significant amount of time working on projects. I do believe this work was made possible with his contributions. It was great collaborating with Matthew Billups, Rahul Ramakrishnan, Yash Malkeri, Atul Rewari and Disha Patel who are all part of the research group.

Lastly, but definitely not the least, I would like to thank my parents, my friends and everyone else around that provided support. Being in the US and working in a research program like this has been a privilege and I'm indebted to all the people that made this happen.

Table of Contents

Abstract of the Thesis ..... **ii**

Acknowledgements ..... **iv**

List of Figures ..... **vii**

List of Tables ..... **ix**

Chapter 1 Introduction **1**

1.1 Literature Review **1**

1.2 Objectives **5**

1.3 Overview of thesis **5**

Chapter 2 Background **7**

2.1 Continuous Direct Compaction solid oral dosage manufacturing process **7**

2.2 Feedback Control **11**

2.3 Model Predictive Control **13**

Chapter 3: Implementation of a model predictive control system into continuous tablet compaction process **16**

3.1 Direct compaction continuous manufacturing process **16**

3.2 Materials and methods **17**

3.3 Hardware and software integration **17**

3.4 Real Time tablet weight measurement: **19**

3.5 Open loop response analysis and identification of control loops **21**

3.6 Step response analysis **22**

3.7 Sensitivity Analysis **23**

3.8 Overview of developed flexible control system **24**

3.9 Advanced model predictive cascade MIMO control system **25**

3.10 Implementation of advanced model predictive control system into continuous pharmaceutical manufacturing pilot-plant **26**

3.11 Development and tuning of advanced model predictive controller (MPC) **28**

3.12 Development, implementation and tuning of PID controller **35**

3.13 Closed loop performance evaluation **37**

3.14 Results and discussions **38**

Chapter 4 Residence time distribution (RTD) based diversion system for continuous pharmaceutical manufacturing process **46**

4.1 Drug concentration based real time diversion strategy **46**

4.2 Residence Time Distribution (RTD) model **48**

4.3 Strategies for real time assurance of tablet drug concentration **50**

4.4 Systematic framework for design, evaluation and implementation of RTD based diversion system 55

4.5 *Insilico* design of RTD based diversion system 58

4.6 Results and discussion 61

Chapter 5: Integrated scheduled optimization and model predictive control implementation into continuous direct compaction line 79

5.1 Materials and methods 79

5.2 Hardware and software integration 79

5.3 Integrated Moving horizon based optimization and model predictive controller implementation 81

5.4 Results and discussion 85

Chapter 6: Conclusions and Future perspectives 101

References 105

List of Figures

Figure 2.1. Schematic of continuous direct compaction (DC) tablet manufacturing process situated at Rutgers University, NJ, USA 11

Figure 2.2. Graphical representation of Model Predictive control (Singh et *al*. 2013) 15

Figure 3.1. Integration of control hardware and software for tablet press automation and control (Bhaskar et al., 2017). 18

Figure 3.2. Implementation of a developed systematic methodology for real-time monitoring of tablet weight (Bhaskar et al., 2017). 20

Figure 3.3. Feedback superstructure for tablet press control (Bhaskar et al., 2017). 22

Figure 3. 4. Open loop response of tablet compaction process (MCH: Main compression height) (Bhaskar et al., 2017). 23

Figure 3.5. Sensitivity analysis for main compression force (Bhaskar et al., 2017). 24

Figure 3.6. Advanced multi input multi output model predictive control strategy (Bhaskar et al., 2017). 26

Figure 3. 7. Implementation of an advanced model predictive control system into continuous pharmaceutical manufacturing pilot-plant (MPC: model predictive controller, AI: analog input, AO: analog output, SCLR: scale-up/down, BKCAL: back-calculation, PCF: pre compression force, MCF: main compression force, FD: fill depth, MCH: main compression height) (Bhaskar et al., 2017). 27

Figure 3.8. Main compression force open loop response for MPC model development (Bhaskar et al., 2017). 29

Figure 3.9. Pre compression force open loop response for MPC model development (Bhaskar et al., 2017). 31

Figure 3.10. Multi inputs multi outputs MPC Model Generation (Bhaskar et al., 2017). 32

Figure 3.11. Model verification (control mode 2) (Bhaskar et al., 2017). 34

Figure 3. 12. PID controller tuning for main compression force control (control mode 1) (Bhaskar et al., 2017). 36

Figure 3. 13. Closed loop response of main compression force (MCF). (a) inbuilt control strategy, (b) external PID controller, (c) advanced model predictive controller (MPC). (Bhaskar et al., 2017). 38

Figure 3. 14. MCF closed loop response analysis (control mode 1) (Bhaskar et al., 2017). 40

Figure 3. 15. PCF controller closed loop response (control mode 2) (Bhaskar et al., 2017). 41

Figure 3. 16. Open loop response of pre and main compression force. MCH: Main compression height (Bhaskar et al., 2017). 42

Figure 3. 17. Closed loop response of pre and main compression forces (2x2 MPC closed loop response) (Bhaskar et al., 2017). 43

Figure 3. 18. Real-time table weight measurements (Bhaskar et al., 2017). 44

Figure 3. 19. Closed loop response of tablet weight supervisory control loop (Bhaskar et al., 2017). 45

Figure 4.1. Overview of drug concentration based real time diversion strategy. G: Good tablet, B: Bad tablet 48

Figure 4.2. Real time diversion of pharmaceutical tablets. 0: Accept, 1: Reject 51

Figure 4.3. Fixed window based tablet diversion system 53

Figure 4.4. RTD based tablet diversion system 55

Figure 4.5. Framework for implementation of RTD based control 58

Figure 4.6. Comparison of FIR response and convolution integral 60
Figure 4.7. Fluctuation in API concentration (a) High magnitude (b) Low magnitude 64
Figure 4.8. Negative pulse disturbance (a) High magnitude (b) Low magnitude 66
Figure 4.9. Step disturbance (a) Step up (b) Step down 69
Figure 4.10. Short positive offset in concentration (a) High magnitude (b) Low magnitude 72
Figure 4.11. Short negative offset in concentration (a) High magnitude (b) Low magnitude 74
Figure 4.12. RTD based control simulated for a noisy input concentration data. 75
Figure 4.13. Performance assessment of RTD based control with different RTD models. 77
Figure 5. 1. Hardware and software integration 81
Figure 5.2. Schematic representation of Model predictive control strategy with disturbance handling capacity and supervisory optimization. 84
Figure 5.3. Real time optimization of demand. 87
Figure 5.4. Real time optimization of direct compaction line without a controller and rejection considerations. 88
Figure 5.5. Real time optimization of direct compaction line with rejection considerations and without a controller. 90
Figure 5.6. Main compression force open loop response for MPC model development with step changes in production rate and fill depth. 92
Figure 5.7. Closed loop response for MPC to control main compression force using fill depth. 93
Figure 5.8. Main compression force open loop response for MPC model development with step changes in production rate and main compression height. (CF-Compression Force, MCH – Main Compression Height, PR – Production rate) 95
Figure 5.9. Main compression force MPC implementation. 96
Figure 5.10. Closed loop response for MPC to control main compression force using main compression height. 97
Figure 5. 11. Real time optimization of direct compaction line with MPC. 99
Figure 5.12. Performance evaluation of real time optimization and MPC controller**.** 100

List of Tables

Table 3.1. Key tablet press parameters..... 17
Table 3. 2 Different options to control the tablet press. A feasible pairing is denoted by 'X'..... 21
Table 3.3. Summary of control modes. 25
Table 3.4. MPC model parameters (Bhaskar et *al*., 2017). 30
Table 3.5. MPC tuning parameters..... 35
Table 3.6. MCF control algorithms analysis**.** 40
Table 4.1. Manufacturing efficiencies of Case studies 1-5 77
Table 5.1. Rejection fraction 89
Table 5.2. Performance metrics for MCH based MCF controller 97

Chapter 1 Introduction

1.1 Literature Review

Traditionally, pharmaceutical products involving solid dosages forms have been manufactured through batch processes. The varied levels of complexity arising from material handling, product quality, process understanding etc. inhibited the fast adoption of new technologies in the pharmaceutical industry and therefore, continuous manufacturing which was adapted by other industries, took a back seat here. But in recent times, a significant amount of momentum has accumulated that is thrusting forward the continuous manufacturing paradigm (Leuenberger 2001; Lee et *al*. 2015). An effort in facilitating this has been undertaken in terms of the research required to develop an understanding of the challenges and possible solutions to the variety of new research problems in manufacturing. A big facet to this is the development of process systems engineering (PSE) methods and tools, which includes modelling, control and optimization of the manufacturing plant. This work focuses on the control and optimization aspects of process systems engineering in continuous pharmaceutical manufacturing.

The direct compaction (DC) route is the simplest and most economical manufacturing process (Meeus 2011). The wet granulation (WG) process is preferred when granulation of materials is needed before compaction. The roller compaction (RC) route, also known as the dry granulation process, is used when granulation of water sensitive material is needed. Among these manufacturing options, the DC route is becoming more popular for continuous pharmaceutical manufacturing. Due to the embryonic state of work in the area of control, the DC route was chosen to test the developed control schemes. A manufacturing plant of this kind is available at Rutgers University, USA that is integrated and connected to multiple control platforms. The

details of this are given in the Background section [2.1] of the thesis. Critical quality attributes that are of importance in this process are the tablet weight, potency and tensile strength or breaking force. These parameters directly influence the characteristics of the tablets dissolution properties and thus, warrant a control system that can constrain them in the case of an offset in the parameters beyond a predefined threshold.

The development and implementation of control methodologies in pharmaceutical industries, especially in solid oral dosage forms, is still a developing field. This makes it an exciting research area (Muzzio et *al*. 2013). Extensive work has been done to design and develop the control system for continuous pharmaceutical manufacturing process in last decade using *insilico studies*. There has been some limited demonstration of model predictive control methods for granulation systems (Gatzke et *al.* 2001). Model based control schemes that systematically address problems arising from product quality specifications are addressed in Pottmann et al. 2000. Studies have been done on developing enhanced process design and control of a multiple-input multiple-output (MIMO) granulation process (Ramachandran et *al.* 2012). There has been some prior work on modelling the granulation process which provides insight into improved control and design including measurement selection (Sanders et *al*. 2009) . An efficient plant-wide control strategy for an integrated continuous pharmaceutical tablet manufacturing process via roller compaction has been designed in silico (Singh et *al*. 2012). A control system for wet granulation process has been also developed (Singh et *al*. 2014**).** There have been studies showing comparisons between PID and MPC control schemes, illustrating potential of a hybrid control scheme in improving pharmaceutical manufacturing operations (Singh et *al*. 2013). A validated model and multi input multi output (MIMO) control system has been developed for tablet press (Nunes de Barros et *al*. 2017). A combined feed forward/feedback control strategy

using both PID and MPC control algorithms has been also developed for direct compaction tablet manufacturing process (Singh et *al*. 2015; Haas et *al*. 2017)**.**

Some efforts have been also made for implementation of the control strategy into continuous pharmaceutical tablet manufacturing pilot-plant. A systematic framework for the onsite design and implementation of the control system in continuous tablet manufacturing process has been developed (Singh et *al*. 2014). An advanced hybrid MPC–PID control architecture coupled with real time inline/online monitoring tools and principal components analysis (PCA) based additional supervisory control layer has been implemented into a continuous direct compaction tablet manufacturing process with focus on drug concentration assurance (Singh et *al*. 2014). The real time monitoring and control of powder level in transfer pipe (chute) has been practically demonstrated using advanced model predictive control system (Singh 2017). Advanced model predictive control system has been also implemented into the tablet press unit operation of continuous pharmaceutical manufacturing process (Bhaskar et *al*. 2017). End-to-end continuous pharmaceutical manufacturing was investigated taking in considerations for model predictive control that can implemented for control of critical quality attributes (Mesbah et *al*. 2017). The theory on model predictive control itself has been extended greatly and reviewed extensively in the literature (Mayne 2014). There has been a significant advancements in both nonlinear and linear commercially available controllers (Qin et *al.* 2003). In this thesis, model predictive control (MPC) strategy as well as PID have been implemented into a tablet press unit operation of direct compaction tablet manufacturing pilot-plant. The performance of MPC and PID have been evaluated and compared(Bhaskar et *al*. 2017).

Post development of a control system, in some circumstances due to varying market demand there may be a lower requirement or higher requirement of product. This fluctuation can result in

a need for modified operating regimes of a continuous line. Typically, these operating regimes are determined by an optimization algorithm that maximizes a metric through modifications in the process. This thesis undertakes the problem of optimizing the production rate to meet market demand while supervising any model predictive controller that has been implemented in the direct compaction line. Prior literature on this includes the investigation of an optimal dynamic operation of a continuous process for the production of a pharmaceutical product (Shoham et *al.* 2017). Some case studies are presented to demonstrate the effectiveness of the proposed approach (Sahlodin et *al.* 2015). The most significant theme running through the implementation hurdles encountered though was the lack of information available to the model (Powell et *al*. 2002). At Rutgers, a moving horizon-based real-time optimization (MH-RTO) which was integrated with a hybrid model predictive control (MPC) system for a continuous tablet manufacturing process for quality by design (QbD)-based efficient continuous manufacturing was developed (Singh et *al*. 2015). This work has been adapted and further developed upon in this thesis with focus on its implementation into the direct compaction continuous pharmaceutical tablet manufacturing process.

Still, there are circumstances where batch manufacturing persists. In this situation product is tested in between unit operations and if it is out of spec then entire batches maybe discarded. To prevent this, an open loop continuous manufacturing strategy with essential diversion strategies maybe installed. Ideally, a diversion strategy would simply divert product if it were out of spec and allow material to flow through if it were within spec. This determination/prediction of whether a material can be qualified for further processing is another challenging area of work. This is a topic still that is still being explored and being debated within the research and

industrial communities. There is not much prior work done in this area some of the details of this are given in the background section.

1.2 Objectives

This study was carried out with an objective of developing an understanding of the challenges involved in implementing advanced control strategies in the direct compaction continuous manufacturing system. There has been no attempt made in the past to improve upon existing control strategies inbuilt in the traditional tablet presses to the best of the author's knowledge. This work attempts to contribute to this space. Importance has been given to developing a holistic control system in a theoretical manner, and implementing sections of this control system. This work made used of the continuous direct compaction line available in ERC-SOPS, Rutgers, USA. The main objectives can be listed as follows:

1. In depth study of challenges involved in implementing control strategies into the pharmaceutical manufacturing system.
2. Implementation of a model predictive control (MPC) system into the tablet press unit operation of continuous tablet manufacturing pilot-plant.
3. *Insilico* design and development of a pharmaceutical tablet diversion system that can assure drug concentration under control mode failures.
4. Implementation of an optimization algorithm into the continuous direct compaction line to produce tablets efficiently under varying demand changes.

1.3 Overview of thesis

A brief overview of the rest of chapters is provided here to assist the reader.

Chapter 2 provides a brief background to all the various aspects of the pharmaceutical industry that are covered in this thesis. Focus has been given to the continuous direct compaction tablet manufacturing route. Brief reviews on feedback control and model predictive control has also been provided that directs readers appropriately for more information regarding these.

In Chapter 3, an in-depth documentation of the work done in implementation of a control strategy that uses the Model predictive control algorithm is presented. The details of all experiments have been elaborated on. This chapter also presents the novel methodology for model development that was used along with a new method for real time weight measurement. An attempt was made to accomplish objectives 1 and 2 in this chapter.

Chapter 4 develops the theory through *insilico* studies with regards to the implementation of Residence Time Based control. This work is focused on the implementation for a tablet compaction unit in the direct compaction route. Objective 3 has been accomplished in this chapter.

In lieu of the objective that requires the implementation of an optimizations strategy (objective 4), chapter 5 adapts previously published work to develop a ground for implementation of a real time optimization strategy for the direct compaction manufacturing line. Finally, the concluding remarks from all the works done and a way forward into the future work in given in chapter 6.

Chapter 2 Background

2.1 Continuous Direct Compaction solid oral dosage manufacturing process

The shift in manufacturing from batch to continuous that has been initiated is guided by the regulatory constraints imposed by the FDA. This was done to encourage early adaptation of new technological advances, facilitate industry application of model quality management techniques, implementation of risk based approaches, ensure regulatory policies are based on state-of-the-art science, and enhance the consistency and coordination of drug quality regulatory policies. The International Conference on Harmonization (ICH) implemented a trio of quality guidance: Q8 (R2), Q9, and Q10 (FDA 2009a; FDA 2009b) which introduced valuable concepts such as Quality by Design (QbD), Quality by Control (QbC) and Real Time Release Testing (RTRT). There is a need to contribute to the literature to expand knowledge so as to facilitate implementation of such new regulatory ideas through efficient manufacturing strategies. This thesis focuses on contributing to this space through research centered on tablets produced via the direct compaction route.

Before getting into the details of direct compaction itself it may be important to note that tablet production can take place in three different ways: wet granulation, dry granulation and direct compaction. In each of these processes the intermediate product- mixed powder or granules, is compacted through a rotary tablet press to produce a finished uncoated tablet. Direct compaction is deemed the simplest and the most economical of the three for a variety of reasons. The simplest reason is that it contains the fewest process stages- weighing, blending and compaction, leading to a shorter process cycle and faster production times (Augsburger et *al.* 2002).

In some cases, an additional coating can be applied to the finished tablets and capsules, but this is an option not a necessity. In most cases, the direct compaction process consists of a feeding element, followed by milling. The product from these unit operations is continuously fed into a blender which in turn supplies the tablet press with powder. The finished compacted powder is then sent for coating which to the best of the author's knowledge is still being done in a batch or semi-batch processes across the industry.

Prior work has been done in developing control strategies for the direct compaction process but this thesis revisits some of these strategies from a more mechanistic perspective. The focus has been given to the tablet compaction process itself.

Tablet compaction takes place through a systematic series of steps. At the start of this process, the powder is fed into a rotary tablet press through a mechanical chute. The material then enters a feed frame where rotating blades fill powder into the dies one by one. An increase or decrease in the feed frame speed can change the instantaneous density through consolidation or can decrease the instantaneous density by fluidization depending on the speed and material properties. Another important parameter is the filling depth. This defines the total volume of powder that will be filled at this stage through an adjustable height. An increase in this parameter is essentially an increase in the depth to which powder can be filled thus, increasing the volume of powder that is filled and subsequently the weight. The powder, once filled in the dies has the excess removed by a scraper. Thus, at this stage the weight of the tablet is defined, assuming that there are no defects in the tablet.

After this, the powder goes through two compression stages, the pre compression stage and the main compression stage. With respect to both stages, the mechanics of this is such that two rotating drums on the top and bottom can be adjusted in terms of the spacing between them. The drum at the bottom can be moved vertically in order to change the spacing, while the upper drum is kept stationary. At their respective stations, the spacing between the two drums determines the final height that the powder will be compacted to. The two parameters that can be adjusted are the pre compression height and the main compression height. When the dies come in contact with the drums during rotation the top die presses down towards the bottom one thus, generating a compaction. The force the upper die experiences during this process is essentially the compression force data that can be extracted from the press and used for control. The pre compression force station is necessary as it reduces phenomena such as capping, increases the dwell time and also causes de-aeration of the powder. The main compression force station is where the actual compaction takes place. For a certain fill depth, a decrease in main and pre compression height increases the force the upper drum experiences. Subsequently, this also increases the breaking force and density of the tablets. Further details of the tablet compression process can be found in Järvinen et *al*. (2013) and Augsburger et *al.* (2002).

2.1.1 Continuous Tablet Manufacturing Process and Pilot Plant at Rutgers University

The experiments that are referred to in this thesis were conducted in the continuous direct compaction tablet manufacturing pilot-plant that has been installed at ERC-SOPS, Rutgers University, USA. The schematic of the continuous direct compaction pharmaceutical manufacturing process is shown in Figure 2.1. The construction of the plant uses three levels to take advantage of gravity for material flow purposes. The top level is designated to powder

feeding and storage, while the middle layer is assigned to the task of de-lumping and blending, the bottom floor is used for compaction. Each level spans an area of 10 × 10 feet. The equipment present in the lab includes three gravimetric feeders with the capability of expansion. Following the feeders, a co-mill is integrated for de-lumping the powders as mentioned before and creating contact between the components. The lubricant feeder is added after the co-mill in order to prevent over lubrication of the formulation in the co-mill. All these streams are then connected to a continuous blender to create a homogeneous mixture of all ingredients. The exit stream from the blender is fed to the tablet press via a rotary feed frame. The powder blend fills a die, which is subsequently compressed in order to create a tablet. This plant is modular in nature, thus, enabling the use of equipment in different combinations specific to the required experiments.

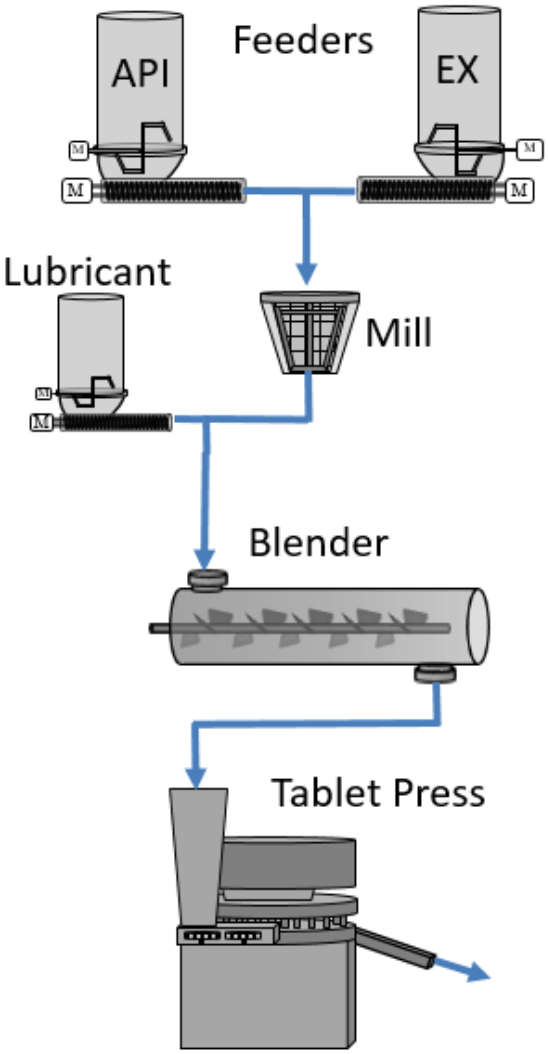


Figure 2.1. Schematic of continuous direct compaction (DC) tablet manufacturing process situated at Rutgers University, NJ, USA

The DC process has been intensively studied and schematic has been previouly reported in several scientific literatures by C-SOPS researcher (e.g. Boukouvala et al. 2012)

2.2 Feedback Control

In recent years, the performance requirements for process plants have become increasingly difficult to satisfy. Stronger competition, tougher environmental and safety regulations, and

rapidly changing economic conditions have been key factors in tightening product quality specifications. A further complication is that model plants have become more difficult to operate because of the trend toward complex and highly integrated processes. For such plants, it is difficult to prevent disturbances from propagating from one unit to other interconnected units.

In view of increased emphasis placed on safe, efficient plant operating, it is only natural that the subject of process control has become increasingly important in recent years. This increase in interest in the domain of control is even more recent in the pharmaceutical industry since its shift from batch to continuous manufacturing.

Feedback control essentially involves three things; sensing of data from controlled variables in the plant, a correlation between these parameters and their respective manipulated variable and a controller that efficiently manages this information. Historically, Proportional (P), Integral (I) and Derivative (D) controllers were used to constrain variables in manufacturing plants. A combination of these controllers in one is called a PID controller. Due to this combinatorial nature, PID controllers have large amounts of flexibility and are far more efficient in comparison with their individual entities.

A PID controller is relatively simple to implement and tune. These controllers are computationally inexpensive, based on the difference between the set point values and actual values of the controlled variables. A PID controller is inherently unconstrained and restricted to single input and single output systems. In the case that there are multiple variables that require manipulation, multiple PID controllers are required to be applied.

This thesis uses a PID control to compare its performance with a Model Predictive Controller (MPC) for the tablet press unit operation in the continuous direct compaction pharmaceutical tablet manufacturing process.

2.3 Model Predictive Control

Since the early 70s, various techniques have been developed for the design of model based control systems for robust multivariable control of industrial unit processes. Predictive control was pioneered simultaneously by Richalet et *al*. (1976) and Cutler et *al*. (1979). The first implemented algorithms and successful application were reported in the references papers. Since then, Model predictive control technology has evolved from a basic multivariable process control technology that enables operation of processes within well-defined operating constraints. The main reasons for acceptance of MPC technology by the process industry since 1985 are- MPC is a model based controller design procedure, which can easily handle processes with large time-delays, non-minimum phases, process interaction, multivariable systems and unstable processes. Currently, the increasing interest in process systems engineering in the pharmaceutical industry raises questions about applicability of this advanced control strategy. A lack of extensive research in this area makes it an exciting and challenging area to work in.

Model predictive control is essentially an optimization based controller. It also consists of the manipulated variable and the controlled variable like the PID. Additionally, to this, it is also possible to feed into the model predictive controller the disturbances in the process if they are measured or if they have been externally modelled. These variables are called disturbances variables. The controller uses a model of the process in the process of optimization. The development of this model is an important step in using model predictive control and is part of

the tuning procedure. Industrial model predictive controllers normally have within them toolboxes that perform step changes on the plant to use the acquired data to develop empirical models. The structure of these models can change if the systems dynamics are accurately captured.

Once a model is in place, the current state of the manipulated variables is fed to this model as an input. The outputs of the model are the current and future states of the controlled variables. The predicted output trajectory is compared with the required set points. The difference between these two trajectories is minimized through calculation of a new trajectory for the manipulated variables (predicted control input) in each time instant. The first value of this calculated trajectory is sent into the plant. This process of predicting the controlled variable trajectory, optimization of the difference between the set point and current values is repeated at each time step. Figure 2.2 gives a brief graphical illustration of these trajectories where the measured output gives the current state of the controlled variable. The requirement to run such an optimization in each time step creates a layer of complexity that is dependent on the type of model used. A nonlinear model may not be easily optimized. This point raises concerns in the industry due to difficulties that may arise in actual application. All models used in this thesis are however, linear and time invariant.

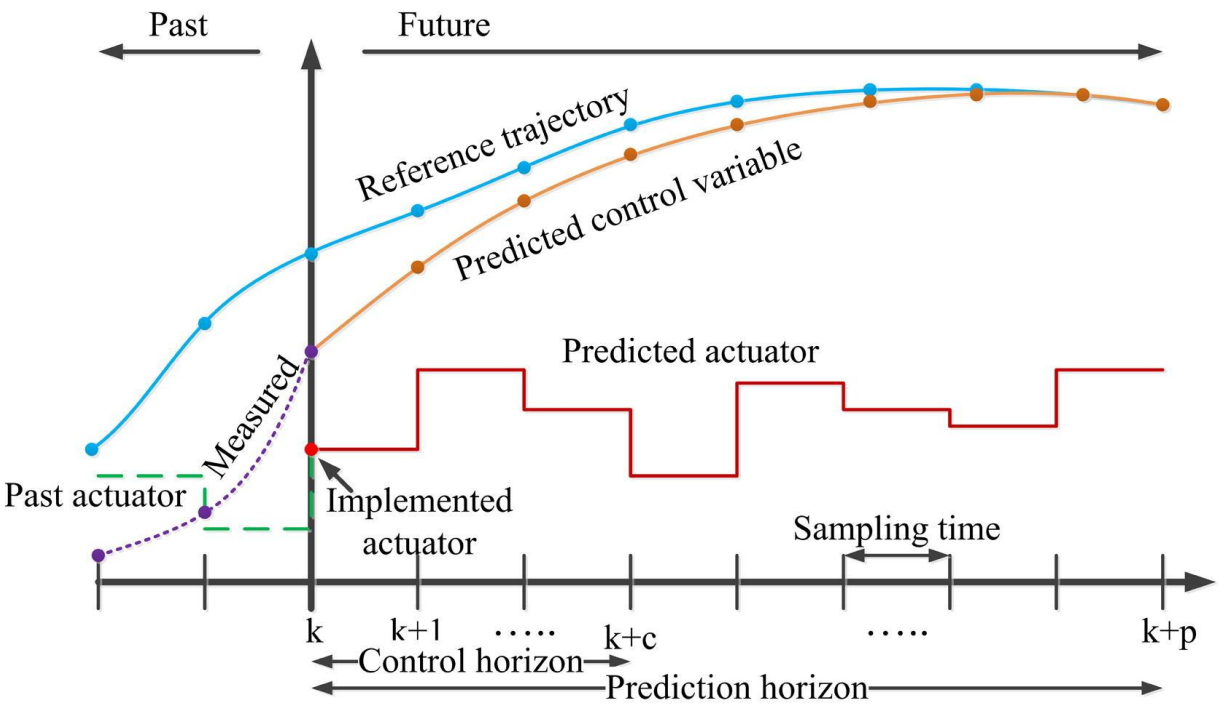


Figure 2.2. Graphical representation of Model Predictive control (Singh et *al*. 2013)

Reprinted with permission from Singh, R., et al. (2013). System-wide hybrid MPC–PID control of a continuous pharmaceutical tablet manufacturing process via direct compaction. Eur J Pharm Biopharm. 85:1164–1182. Copyright Elsevier.

Additionally, this thesis makes uses of a Model predictive controller on a variety of strategies. Work has been done to show the relevance of its advantages in the pharmaceutical industry and the improved efficiency it provides. In Chapter 3, the focus is primarily on developing the reasons for use of MPC in a pharmaceutical manufacturing line. This idea is furthered and developed upon in Chapter 5 where it is applied in an augmented capacity and supervised by an optimization that was externally run.

Chapter 3: Implementation of a model predictive control system into continuous tablet compaction process

Acknowledgements:

This chapter is based on following published manuscript and all authors/co-authors are acknowledged. The author led the work in terms of the experimental work and writing:

Bhaskar A, Barros FN, Singh R*. 2017. Development and implementation of an advanced model predictive control system into continuous pharmaceutical tablet compaction process. Int J Pharm. 534:159–178. doi:10.1016/j.ijpharm.2017.10.003

This work is supported by the Rutgers Research Council, through grant 202342 RC-17-Singh R, the US Food and Drug Administration (FDA), through grant 5U01FD005535, and National Science Foundation Engineering Research Center on Structured Organic Particulate Systems, through Grant NSF-ECC 0540855.

*Corresponding author (Email: ravendra.singh@rutgers.edu)

3.1 Direct compaction continuous manufacturing process

A brief description of the continuous pharmaceutical tablet manufacturing pilot-plant has been given in Section 2.1.1. This work is focused around tablet compaction unit operation. A detailed explanation of the compaction process has been provided in Section 2.1. For the compaction experiments in this chapter, API, excipient and lubricant were pre-blended using a batch blender before being manually fed into the tablet press hopper. The single sided rotary tablet press has been used in the experiments. Tablet press parameters were monitored and controlled in DeltaV (Emerson) through OPC connection. The key parameters are highlighted in Table 3.1. Circular tablet punches with a diameter of 12 mm were used. Tablets were collected in a container placed on a catch scale in order to monitor the tablet weight in real-time.

Table 3.1. Key tablet press parameters.

Parameter	Availability	Value
Production rate	Set point & actual	8000–20,000 tablets/h
Turret speed	Actual	Dependent on production rate
Feed frame speed	Set point & actual	30 rpm
Main compression force	Set point & actual	Controlled
Pre compression force	Actual	Controlled
Main compression height	Set point & actual	Manipulated
Pre compression height	Set point & actual	4.05 mm
Fill depth	Set point & actual	Manipulated

3.2 Materials and methods

All the experiments were conducted using a blend with a composition of 89% lactose monohydrate (excipient), 9% acetaminophen (API) and 1% magnesium stearate (lubricant). The blend was prepared in a Glatt batch blender run at 25 revolutions per minute (rpm) for 30 min with a layered loading order to ensure that thorough mixing is achieved. The maximum capacity of each batch was of 7 kg, so multiple batches had to be prepared throughout the experiments. Most tablet press parameters were kept constant throughout the experiments unless otherwise needed as part of study. The parameters and their values are presented in Table 3.1 (Bhaskar et *al.* 2017).

3.3 Hardware and software integration

The communication between the control platform and the tablet press unit takes place in a local area network through OPC protocol. In order for the connection to be completed there must be an OPC server installed on each end (tablet press and control platform) and an OPC client to interface the communication between servers. Process variables are commonly referred as tags in OPC servers and clients. Advanced link tags must be configured in the OPC client in order to establish data flow between tags located in different servers.

A diagram of the control platform and the tablet press unit integration is schematically presented in Figure 3.1. Initially, the data from the tablet press is stored in the internal tablet press OPC server. The OPC client then reads the data from the tablet press OPC server and writes it to the DeltaV OPC. From DeltaV OPC server, the data can be accessed by the controller, which applies the desired control algorithms and determines the control action to be taken. The information about the control action then follows the reverse path to the tablet press where the manipulated variables actuated on, leading to changes in the process and closing the control loop (Bhaskar et *al.* 2017).

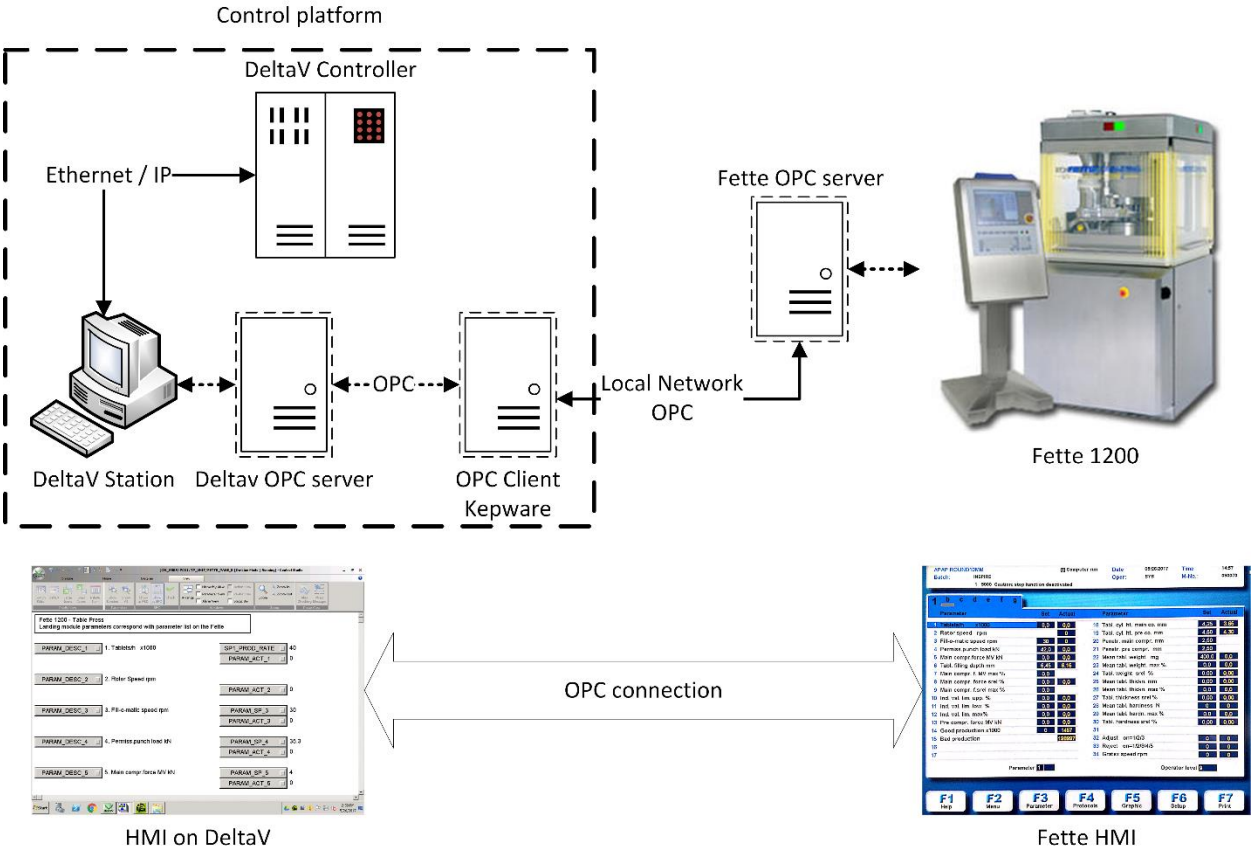


Figure 3.1. Integration of control hardware and software for tablet press automation and control (Bhaskar et *al*. 2017).

Once the variables are accessible in DeltaV, a landing module is created in order to monitor and manipulate each process parameter. The landing module consists of a series of input and output blocks configured as external references that point the address of each tag in the OPC server. Set points are configured as output blocks while actual readings are configured as input blocks.

Blocks with the description of each parameter are also added to the landing module. The landing module replicates every parameter available in the tablet press HMI (human machine interface). Control modules created in DeltaV point to the tablet press landing module.

3.4 Real Time tablet weight measurement:

The critical process parameters (e.g. main compression force) of tablet press are measured using inbuilt sensors. However, there are no commercial tools available that can measure the critical quality attributes (CQAs) (e.g. tablet weight, tablet hardness) in real-time. The commercially available inline tool for tablet weight and hardness measurements (e.g. Check master (FETTE)) is slow, can measure only a portion of the tablets produced, and is based on a destructive method. The real-time measurement of the CQAs are needed for real-time feedback/feedforward control. A toolbox is being developed at C-SOPS (Rutgers) that can measure the tablet CQAs in real-time specifically suitable for real-time feedforward/feedback control and real-time release (RTR) and is subject of future publication.

A novel method for measurement of tablet weight in real-time is reported in Bhaskar et *al.* (2017). The method is based on 'gain in weight' concept and consists of a catch scale, which collects the tablets and measures the weight of all tablets produced in real-time. The average mass of the tablets is calculated based on the production rate and the change of mass on the load scale during a specified duration. A schematic of the weight measurement implementation is shown in Figure 3.2 and the equation used in the calculation block is given below (Bhaskar et *al.* 2017).

$$\bar{m}(t) = \frac{(m_T(t) - m_T(t - \Delta t))}{P * 3600 * \Delta t} \quad (1)$$

Where $\bar{m}$ is the average tablet weight, m_T is the total mass on the catch scale, P is the tablet production rate in tablets per hour, and Δt is the time difference between measurements. The value of Δt is set by changing the value of the time delay block.

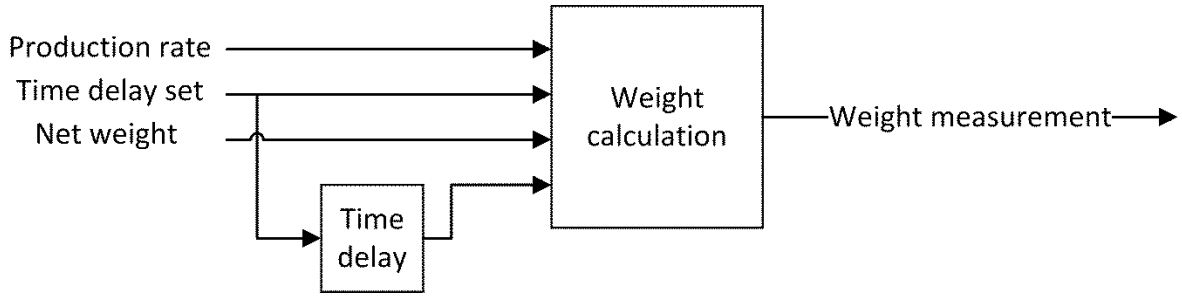


Figure 3.2. Implementation of a developed systematic methodology for real-time monitoring of tablet weight (Bhaskar et *al*. 2017).

The time delay should be determined according to the process and the production rate used. An ideal value of dead time should be large enough to avoid the oscillations caused by the tablets dropping on the catch scale, but still be small enough not compromise the performance of the control system. Smaller values for time delay can be used as production rate increases (Bhaskar et *al.* 2017).

The method for real-time tablet weight measurement is implemented in DeltaV (Emerson) control platform as shown in Figure 3.2 and described in Bhaskar et *al.* (2017). A feeder (K-Tron) has been used as a catch scale in which the tablets are collected in real-time. This catch scale is just employed for proof of concept of the method and using (or building) more precise catch scale can improve the measurement quality significantly. The catch scale is first connected with the DeltaV control panel via Profibus connection, and then the signal from the Profibus is transmitted to the DeltaV controller. From DeltaV controller block, the signal goes to the DeltaV control platform (operating computer) via Ethernet cable where the weight measurement method has been implemented.

Table 3. 2 Different options to control the tablet press. A feasible pairing is denoted by 'X'.

	Final control variables	**Weight**		**Tablet breaking force**
	Intermediate control variables	**PCF**	**MCF**	**MCF**
Actuators	Fill depth	X	X	X
	Main compression height			X

PCF – Pre Compression Force, MCF – Main Compression Force

3.5 Open loop response analysis and identification of control loops

Different options to control the tablet press are given in Table 3.2 (Bhaskar et *al.* 2017). Tablet weight and breaking force are the main control variables that can be controlled via a supervisory control system. The critical process parameters that can be measured in real-time are the pre compression force and the main compression force. Therefore, it is a good strategy to utilize these measurements for tablet weight and breaking force control. The tablet weight can be controlled either via pre compression force or main compression force. Tablet breaking force can be controlled via main compression force. Fill depth and main compression thickness are two actuator candidates. Fill depth affects both CPPs (pre and main compression forces) and both CQAs (weight and tablet breaking force). The main compression thickness only affects the main compression force and tablet breaking force. The tablet weight and breaking force can be controlled through cascade control arrangements where the slave controllers control CPPs and master controller controls CQAs. The master controllers provide the set points for slave controllers. There could be also possibility to control the tablet weight and breaking force through a single loop arrangement where these CQAs are controlled directly by manipulating the actuators. Some intermediate option such as controlling one CQA through cascade system and another through a single loop system could be also feasible. Similarly, from Table 3.2, several other control options can be generated. Two control options are feasible for main compression force control, one for pre compression force control, four options for tablet breaking force control and three for tablet weight. There are twelve feasible options to control tablet weight and breaking force simultaneously and this is diagrammatically represented in Figure3.3. Therefore,

the design of an optimal control system is a challenging task and is still an open area of research (Bhaskar et *al.* 2017).

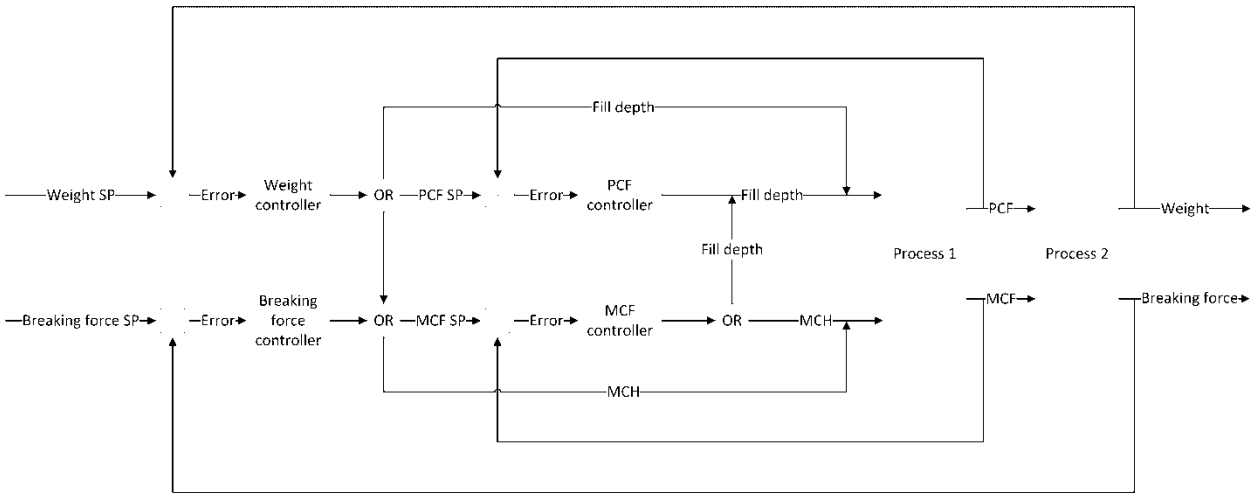


Figure 3.3. Feedback superstructure for tablet press control (Bhaskar et *al*. 2017).

3.6 Step response analysis

This section analyses the effect that the manipulated variables have on the controlled variables in an open loop configuration. This analysis is important to understand the process dynamics and thereby to design, pair, and tune the controller. Figure 3.4 shows the step changes made to the fill depth and main compression height. The PCF and MCF responses to these manipulations are shown subsequently. When a change in fill depth is made, both pre compression and main compression forces change, but these changes vary in magnitude. This is because the pre compression height is higher and thus the sensor reads a lower force value. When a step change is made in the main compression height, a response is observed only in the main compression force and not in the pre compression force as it was expected. This is due to the fact that the change, in terms of the process hierarchy, happens after the pre compression phase. Therefore, there is no correlation between the main compression height and the pre compression force. Similarly, the step response analysis has been performed for other process variables (results are not reported here) (Bhaskar et *al.* 2017).

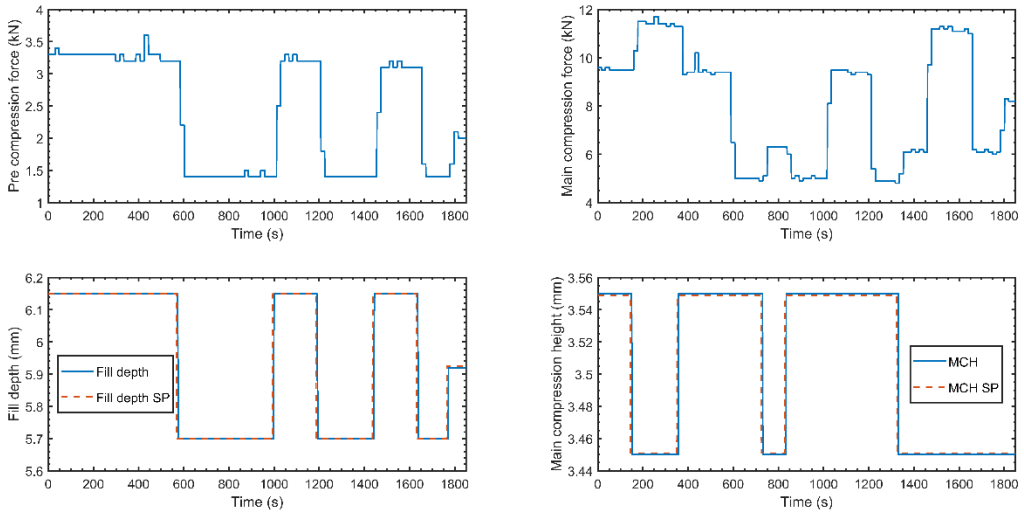


Figure 3. 4. Open loop response of tablet compaction process (MCH: Main compression height) (Bhaskar et *al*. 2017).

3.7 Sensitivity Analysis

The sensitivity analysis is important to understand the effect of process inputs on CPPs and CQAs. A fundamental understanding of the tablet press drives the pairing of actuators and controlled variables. It is well known from the open loop experiments that the fill depth affects both the main compression force and pre compression force (see Figure 3.4). In keeping with the goal of trying to control both variables separately, an alternate actuator is required to control the main compression force. Among the available options, the Main Compression Height (MCH) is chosen. In order for MCH to be used as the actuator, it would have to be more sensitive as compared to the fill depth. Only small changes in the main compression height would be permissible in order to stay within the constraints set by regulatory bodies. Therefore, the actuator candidates for MCF are the fill depth and the main compression height. Data from the open loop experiments was used to analyze the sensitivity of the variables. The change in control variable is calculated as follows (Singh et *al*. 2009):

$$Absolute\ \%\ change\ in\ controlled\ variable = 100\left|\frac{Y_0^j(t) - Y_i^j(t)}{Y_0^j(t)}\right| \qquad (2)$$

Where $Y_i^j(t)$ is the value of the controlled variable in the ith perturbation of the jth actuator candidate and $Y_0^j(t)$ is the base value of the jth actuator candidate (Singh et *al.* 2012).

The sensitivity analysis for main compression force is shown in Figure 3.5. As can be seen in figure, the main compression height induces a higher change in the MCF with a relatively lesser change in its own magnitude when compared to fill depth. This is especially the case when the step changes are made in the upward direction. This makes it the ideal choice for usage in feedback control. It should be noted that this study of sensitivity and quantification of interactions can be done post generation of a relative gain array method as well (Singh et al. 2013).

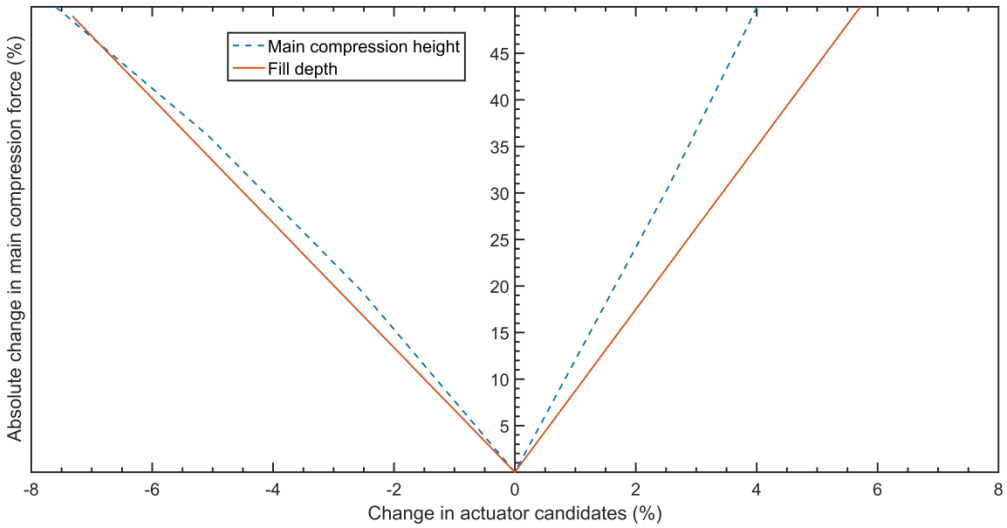


Figure 3.5. Sensitivity analysis for main compression force (Bhaskar et *al.* 2017).

3.8 Overview of developed flexible control system

Multiple control systems were developed that represent the different 'modes of closed loop operation' (Bhaskar et *al.* 2017). It provides flexibility for the user (plant operator) in terms of closed loop operation mode selection based on need. Furthermore, within a selected control mode, the user has flexibility to select a specific control algorithm. Different levels of control are needed for different formulations and manufacturing scenarios and therefore, the flexible nature

of the control system is very useful for continuous pharmaceutical manufacturing. In order to facilitate readability, a number was assigned to each mode of closed loop operation. All the control modes of operation along with its designated control variables and actuators are listed in Table 3.3. These control modes have been described in detail in Bhaskar et *al.* (2017).

Table 3.3. Summary of control modes.

Control mode	CNTRL1	CNTRL2	MNLPT1	MNLPT2
1	Main compression force	-	Fill Depth	-
2	Pre compression force	-	Fill Depth	-
3	Pre compression force	Main compression force	Fill Depth	MCH
4	Tablet weight	-	PCF SP	-
5	Tablet weight	Tablet hardness	PCF SP	MCF SP

PCF: Pre compression force, MCF: Main compression force, MCH: Main compression height, SP: Set point

3.9 Advanced model predictive cascade MIMO control system

The advanced MPC strategy aims to control both tablet weight and breaking force independently. Having control over both variables independently allows an accurate tailoring of the tablet dissolution profile in order to match regulatory requirements. Control is achieved by decoupling the weight and tablet breaking force in a strategy that consists of two model predictive controllers, with two inputs and two outputs each, placed in a cascade arrangement (see Figure 3.6). The slave controller is in charge of maintaining both the main and pre compression forces at the remotely defined set points via manipulation of main compression height (tablet thickness) and fill depth respectively. The master controller, based on the error (deviation from set point) in weight and breaking force values, determines the set points for PCF and MCF. Changes in weight are handled by varying PCF set point while changes in tablet breaking force are achieved

by varying MCF set point. A schematic representation of the control strategy is shown in Figure 3.6. As shown in the figure the master controller is in charge of defining the remote set point for the pre and main compression forces controller. This in turn actuates on the fill depth and main compression height respectively. This strategy represents control mode 5 described in Section 3.7 (Bhaskar et *al.* 2017).

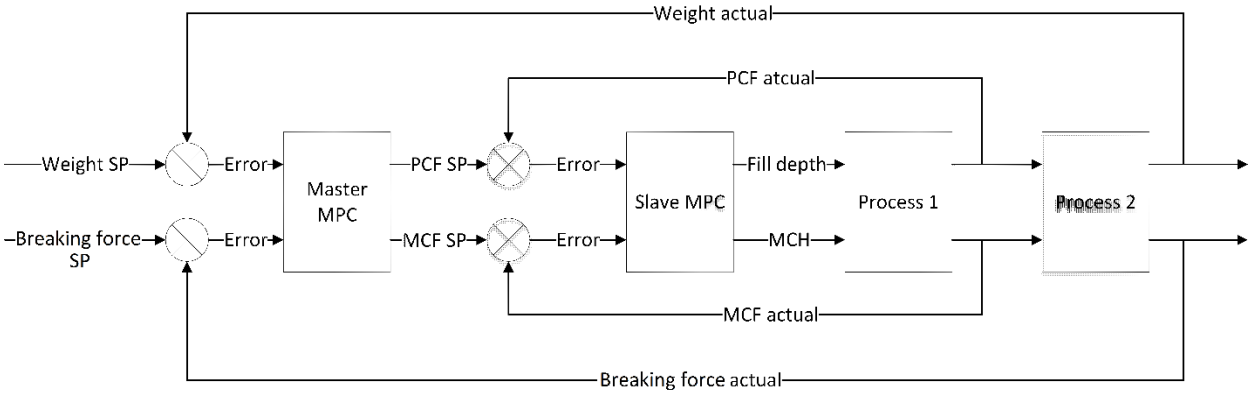


Figure 3.6. Advanced multi input multi output model predictive control strategy (Bhaskar et *al.* 2017).

3.10 Implementation of advanced model predictive control system into continuous pharmaceutical manufacturing pilot-plant

A control strategy for tablet weight (control mode 4) has been considered to demonstrate the control loop implementation. This strategy was implemented in DeltaV using the Control Studio feature. A diagram representing the implementation in DeltaV is shown in Figure 3.7. An input block containing an internal reference to the tablet weight landing module receives the weight reading and directs it to a scalar block where the value is scaled in range of 0%–100%. The scaled weight is then received by the master Single Input Single Output (SISO) MPC block as the controlled variable. It is important to properly scale all the controlled variables received by MPC blocks so that even small changes in their values can be perceived by the controller. This is specifically important in the case of pre compression force control since the variation in measured signal is expected to be very small during normal operation. The scaling strategy proposed in this manuscript can make the control of those variables, which the variations in

measured signal are expected to be very small, feasible. The output of the master controller then goes through an analog output block (AO) and is connected as the PCF set point of the slave controller. The MCF set point, which is related to tablet breaking force, is defined by the operator. The slave controller receives scaled PCF (controlled variable 1) and MCF (controlled variable 2) values from input blocks. Values for the manipulated variables (fill depth and MCH) are calculated by the slave MIMO MPC and go through AO blocks followed by scalar blocks in order to rescale them to their original ranges. The rescaled values are finally sent back to the plant by means of output blocks with reference to the tablet press landing module. It is important to note that each AO block also generates a back-calculation value that must be fed back as a back-calculation input in their respective MPC blocks in order to ensure proper function of the control module. Note that, currently the real-time measurement of tablet breaking force is not possible and therefore the supervisory tablet breaking force control loop, which should ideally provide the set point of main compression force, has not been integrated. It has been assumed that a consistent MCF can lead to consistent tablet breaking force.

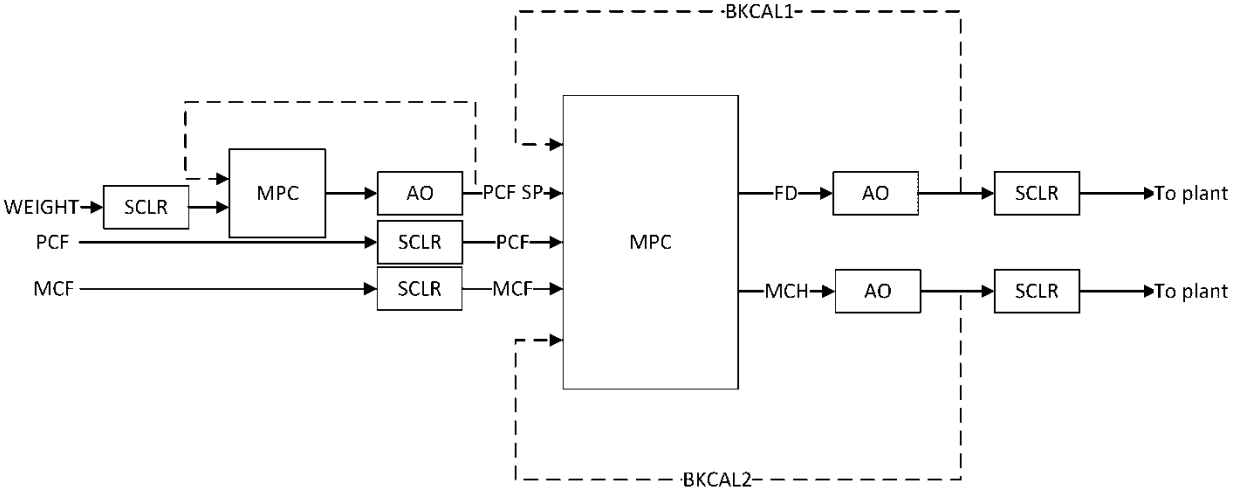


Figure 3. 7. Implementation of an advanced model predictive control system into continuous pharmaceutical manufacturing pilot-plant (MPC: model predictive controller, AI: analog input, AO: analog output, SCLR: scale-up/down, BKCAL: back-calculation, PCF: pre compression force, MCF: main compression force, FD: fill depth, MCH: main compression height) (Bhaskar et *al*. 2017).

3.11 Development and tuning of advanced model predictive controller (MPC)

3.11.1 MPC model generation

The models for the MPC controllers were generated using DeltaV Predict "auto-generate" feature. This feature creates a process model based on open loop data. For the SISO (single input single output) model the process was initially tested using a tool built into the software, but the results were not satisfactory. The tool applied a pseudo-random binary sequence test (PRBS), which consists of a series of bump tests that are equal in magnitude with random duration. Some of the applied bumps had duration smaller than 20 s, causing no response from the system, since the values for the compression forces are only updated every 20 s due to limitations in the tablet press data acquisition system.

With this limitation in mind, all the process tests for MPC model generation were done based on manually determined step changes. For a SISO system, the open loop tests can be easily done by applying a series of regular step changes to the manipulated variable. The MPC model generation for main compression force that was used to develop 'control mode 1' is shown in Figure 3.8. As shown in the figure, the step changes in fill depth have been introduced and consequently the main compression force response was measured. The generated MPC model is given in Table 3.4 (see control mode 1) (Bhaskar et *al.* 2017).

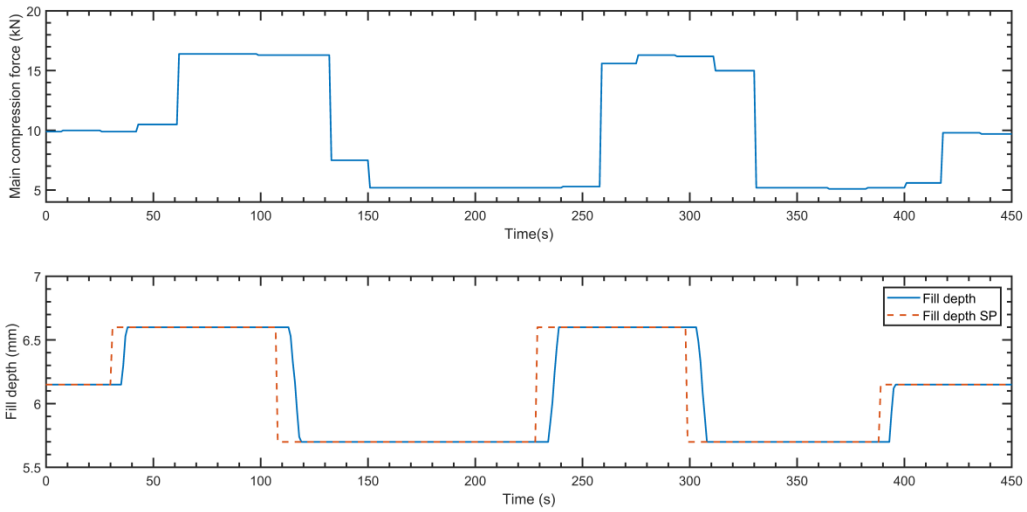


Figure 3.8. Main compression force open loop response for MPC model development (Bhaskar et *al*. 2017).

Table 3. 4. MPC model parameters (Bhaskar et *al*. 2017).

Control mode	Model	Dead time (s)	Gain	FO time constant (s)	SO time constant (s)	Lead time constant (s)
1	MCF – FD	25	0.537713 (kN/mm)	3.84615	3.84615	0
2	PCF – FD	17	0.300986 (kN/mm)	10.9694	1.33824	0
3	PCF – FD	25	1.12937 (kN/mm)	5.38462	0	0
	PCF – MCH	0	0 (kN/mm)	0	0	0
	MCF – FD	27	2.15 (kN/mm)	4.61538	0	0
	MCF – MCH	23	−1.14998 (kN/mm)	5.19639	0.188222	0
	PCF – FD	15	0.307 (kN/mm)	3.84615	0	0
	PCF – MCH	0	0 (kN/mm)	0	0	0
4	MCF – FD	13	0.65 (kN/mm)	5.38462	0	0
	MCF – MCH	10	−0.144755 (kN/mm)	4.61538	0	0
	TW – PCF	51	3.63841 (mg/kN)	10	0	0

*FO: First order. SO: Second order.

Similarly, the MPC model has been generated for pre compression force control in order to develop ‘control mode 2’. The step response data which was used to generate this controller is shown in Figure 3.9. The generated MPC model is given in Table 3.4 (see control mode 2).

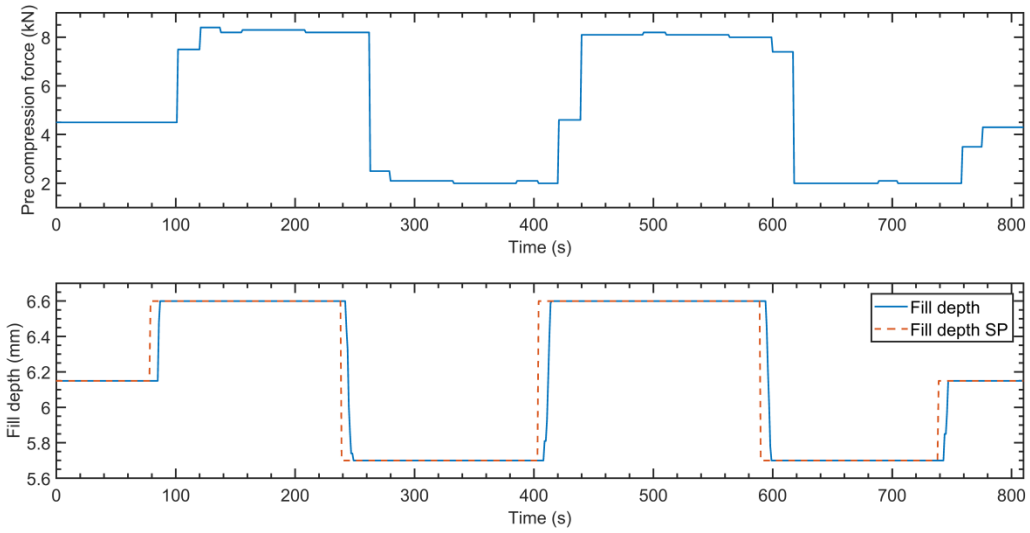


Figure 3.9. Pre compression force open loop response for MPC model development (Bhaskar et *al*. 2017).

For a MIMO (multi input multi output) system with two manipulated and two controlled variables the complexity is slightly increased. As shown in Figure 3.10, step changes were first applied to main compression height, leading to variations only in main compression force. Then, the fill depth is decreased to 5.7 mm and step changes are again applied to the main compression height. This decrease in fill depth causes a decrease in both main and pre compression forces. The main compression height is then increased to 3.55 mm and step changes are made in fill depth. The increase in main compression height leads to a decrease only in main compression force, while the change in fill depth causes variations in both forces. Finally, the main compression height is decreased, which leads to an increase in main compression force, and step changes are again applied to the fill depth. Figure 3.10 shows the control variables response with respect to actuators set point. The developed MPC model relates the actuators set point with the control variables. The achieved actuator signals are the intermediate responses that affect control

variables. Understanding the dynamics between actuators set point and achieved signals as well as the dynamics between achieved actuator signals and control variables are important to implement the control system. Combining these two dynamics generates the overall dynamics of a control loop and therefore it affects the overall performance of the control system. Similarly, the MPC mode for 'control mode 4' has been generated as given in Table 3.4. The MPC model for 'control mode 5' has not been generated because currently no sensor is available to measure the tablet breaking force in real-time according to the best knowledge of authors.

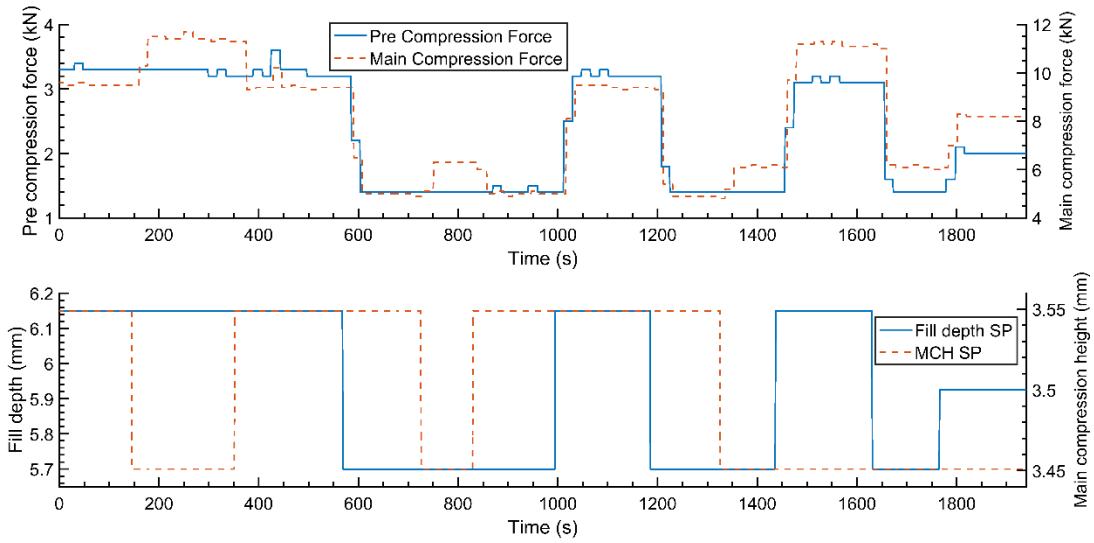


Figure 3.10. Multi inputs multi outputs MPC Model Generation (Bhaskar et *al*. 2017).

The overall model for a MIMO MPC consists of a matrix of models where each individual represents the relation between a controlled and manipulated variable pair. The model parameters for the different models generated are given in Table 3.4. The models generated in control platform (DeltaV) are described by dead time, gain, first order constant, second order constant and lead time constant. In the tablet press, a modification of the fill depth will modify the amount of powder filled into the dies. This has a direct impact on the force experienced by the sensors. Therefore, a change in the fill depth impacts a change in the pre compression force and the main compression force. This interaction essentially means that model, during control, has to counter this interaction if these variables are not directly paired. It is for this reason that

in Table 3.4, under control mode 3, the MCF-FD variable pair displays nonzero model parameters. A major difference can be seen in the shorter dead times of control mode 4 as compared to control mode 3. This change can be attributed to the fact that the process was run at a higher production rate during control mode 4 model generation and operation. The production rate was increased to ensure that the tablets flowed evenly into the catch scale. This also reduced the weight variability in the data that was obtained since the weight is being averaged over a larger number of tablets. It is important to note that the model parameters are optimized by "DeltaV Predict" based on the open loop response tests. Given that each open loop test was performed independently, a slight variation in model parameters is expected and observed. Fine tuning can be achieved based on thorough knowledge of the process.

3.11.2 Model response and validation

Within DeltaV using the Predict feature, it is possible to verify and display the accuracy of a model once it has been generated. To elaborate on this, one example has been displayed in Figure. 11. This example is from ‘control mode 2’ that has been used to control the pre compression force. In the image we can see the graph of actual and predicted vs sample. The blue line depicts the actual values of the controlled variable as obtained from the open loop experiments. The output of model that the software subsequently generates is plotted in green and serves as a comparison between the actual and the predicted values to evaluate the accuracy of the model. In this case, the model displayed matched very well with the predicted values. This is reflected in the R-squared value (0.956462). Given that this is the case for the pre compression force; the data availability is limited to 20 s intervals. This creates room for error which is also quantified in the Squared Error panel. The MPC algorithm can handle small errors in model prediction and therefore, it has been the most successful control algorithm in commercial manufacturing where an ideal model with zero prediction error is practically difficult to achieve. It may also be noted that the models were verified for all control modes but the model verification graphs have not been shown for the sake of brevity.

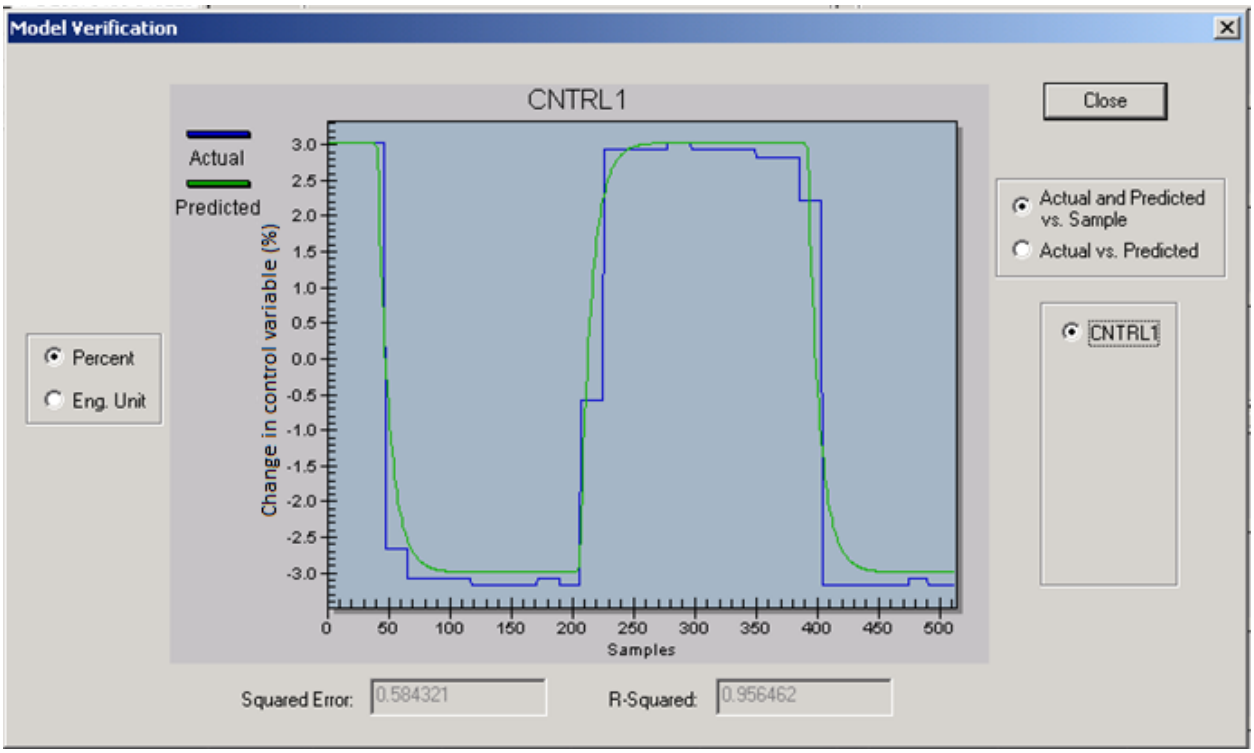


Figure 3.11. Model verification (control mode 2) (Bhaskar et *al*. 2017).

3.11.3 MPC controller tuning

The MPC controller parameters were then tuned based on the generated models. The parameters available in DeltaV are: control horizon, penalty on move (PM) and penalty on error (PE). Control horizon represents the number of predicted control moves. Higher values for control horizon make the controller more aggressive at the price of increasing the computational requirements. Penalty on move defines how much a controller is penalized for changes in a specific manipulated variable (Singh et *al*. 2014) . Low PM values result in a fast controller with a narrow stability margin, while controllers with a high PM value have a wide stability margin with sluggish response. PM values most affects the controller when there is a mismatch between the model and the process (Wojsznis et *al*. 2003). PM is analogous to the input or rate weight terms commonly used in the control language. PE weights the output variables according to their importance, with the most important variable to be controlled having the highest value (Seborg et *al*. 2004) . PE is commonly referred as output weight. The penalty on move was adjusted in order

to ensure that changes made to the pre compression force set point had the least effect on main compression force. The values for MPC parameters are presented in Table 3.5 (Bhaskar et *al.*, 2017).

Table 3.5. MPC tuning parameters.

Control mode	Controlled variable	Control horizon	Penalty on Error	Penalty on Move
1	Main compression force	5	1	8
2	Pre compression force	5	1	8
3	Pre compression force	5	1	1.5
4	Main compression force	5	1	12
	Pre compression force	9	1	6
	Main compression force		1	3
	Tablet weight	5	1	24.5

3.12 Development, implementation and tuning of PID controller

The main compression force (mode 1) has been considered here as an example to demonstrate the development, implementation and tuning of a PID controller. The PID controller for MCF was tuned using DeltaV InSight on-demand tuning tool. First, the tool applies a series of step changes with the same magnitude and duration to the manipulated variable according to the user input. Based on the dynamic response of the system, the software calculates values for the process dead time, gain and time constant, as well as the controller ultimate gain and period. The

user then selects the desired tuning method and response speed, which generates values for the control parameters. The generated values can then be fine-tuned by the user if necessary.

The controller tuning was done based on a process response test with a step size of 19%, using the "Typical – PI" (Ziegler et *al.* 1993) method, which is built into DeltaV, with fast desired response speed. The step response generated for the PID controller tuning is shown in Figure 3.12. As shown in the figure, the multiple step changes have been introduced in the fill depth set point. The achieved fill depth response is also shown in the figure. As shown in the figure, there is a lag time between the fill depth set point and actual fill depth of approximately 6 s. Corresponding changes in the main compression force is also shown in the figure. The main compression force follows the profile of fill depth but with some lag time. The generated data has been used to tune the controller. Fine tuning was done by the authors. The PI controller used in the experiments was tuned with a gain of 0.78 kN/mm and a reset of 31.2 s.

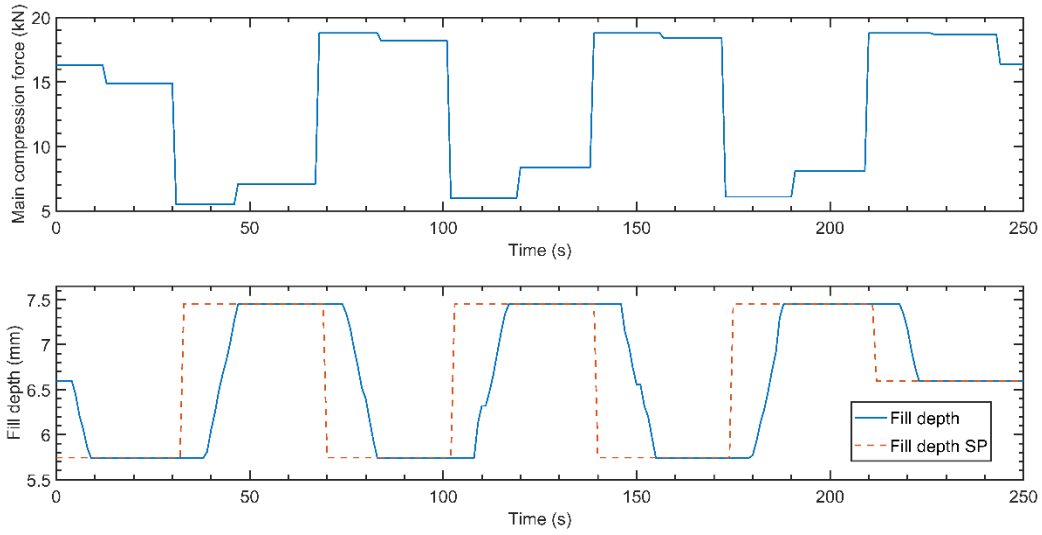


Figure 3. 12. PID controller tuning for main compression force control (control mode 1) (Bhaskar et *al*. 2017).

3.13 Closed loop performance evaluation

All the controllers were evaluated based on closed loop performance metrics. Three metrics were used, integral of absolute error (IAE), integral of square error (ISE) and integral of time absolute error (ITAE). The equations for ITAE (3), IAE (4) and ISE (5) are presented below:

$$ITAE = \int_0^{t_f} t\left|y_{act}(t) - y_{sp}(t)\right| dt \tag{3}$$

$$IAE = \int_0^{t_f} \left|y_{act}(t) - y_{sp}(t)\right| dt \tag{4}$$

$$ISE = \int_0^{t_f} \left(y_{act}(t) - y_{sp}(t)\right)^2 dt \tag{5}$$

Where t_f is the duration of the experiment, $y_{act}(t)$ and $y_{sp}(t)$ are the actual and setpoint values of the controlled variable i respectively, and n is the number of controlled variables.

The integral of absolute error weights all the error equally. Systems optimized using IAE tend to present a slower response with less sustained oscillations when compared to the other metrics. Integral of the square error tends to penalize large error more than small errors, creating systems the eliminated large errors quickly but tend to have sustained small amplitude oscillation. ITAE emphasizes errors that occurs after a long time rather than errors at the beginning of the process. This generates controllers that settle quicker than the other methods but have a sluggish initial response.

Steady state error (offset), rise time, settling time and percent overshoot were also calculated. The steady state error is the relative difference between set point and actual values. Rise time is the time needed for the control variable to first reach 80% of the desired to the set point. Settling time is the time required for the process output to reach and remain inside a +−5% range around the set point (Seborg et *al*. 2004).

3.14 Results and discussions

3.14.1 Evaluation of control algorithms (using control mode 1)

In order to determine the most adequate control algorithm to be applied, three different controllers were evaluated namely inbuilt controller, developed external PID controller and developed external advanced model predictive controller (MPC). The control variable, main compression force (MCF) has been considered here as a demonstrative example. The closed loop responses of main compression force along with the actuator signals are shown in Figure 3.13.

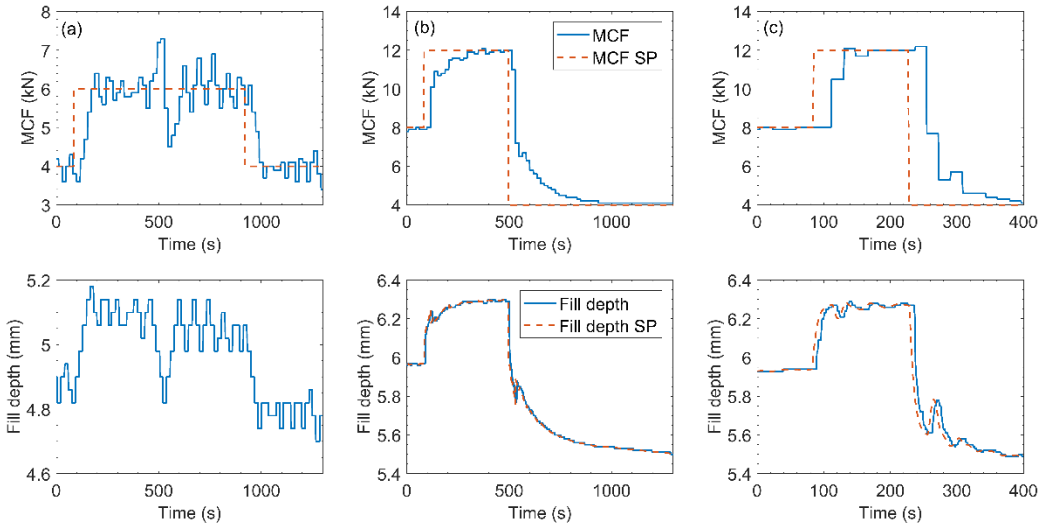


Figure 3. 13. Closed loop response of main compression force (MCF). (a) inbuilt control strategy, (b) external PID controller, (c) advanced model predictive controller (MPC). (Bhaskar et *al*., 2017).

First, the tablet press was run under inbuilt control scheme of main compression force. This experiment was started by letting MCF stabilize at 4 kN. The MCF set point value was then changed to 6 kN and the closed loop response of the system was observed. Once constant oscillations were achieved, the MCF set point was again stepped down to 4 kN. The experiment was ended when constant oscillations around 4 kN were observed. A pulse on MCF can be noticed at around 520 s into the experiment. This disturbance can be caused the readjustment of the powder in the chute by the operator, which led to a slight change in the powder bulk density.

The closed loop response is shown in Figure 3.13a. The experiments for the PID controller were conducted after setting up an appropriate connection and building the loop on DeltaV. The tuning for the PID was done based on the methodology described in Section 3.11. Post this, the tablet press was run in open loop to achieve a steady state before the closed loop experiment was started. The initial MCF value was set to 8 kN. This value was chosen based on previous experiments that showed that the tablet breaking force was adequate (results of this not displayed here). The MCF was increased by 50% from the initial value to a value of 12 kN and then reduced by 100% from the initial value to a value of 4 kN to analyze its performance. The experiments for the MPC were conducted in the exact same manner as for PID with the exception that the tuning of the MPC block was done through the strategy explained in Section 3.10. The step changes were made from the same base value of 8 kN.

A comparison of the response of the three strategies (Figure 3.13) shows that the MPC has a faster response than PID. The step changes applied to the PID and MPC were kept the same for the sake of consistency. A look into the actuator graphs show that the MPC response is much faster in achieving proximity to the set point.

The closed loop responses of main compression force under above mentioned three control algorithms are shown in Figure 3.14. The closed loop response under inbuilt control strategy is shown in right y axis while the responses under external PID and MPC are shown in left y axis. This is because, the starting set point in first case was different in comparison to other two cases. However, the magnitude of step size was the same in all three cases and therefore, the closed loop performance can be directly compared. As shown in Figure 3.14, the MPC has a better response in comparison to the PID and inbuilt controller. It reaches the new set point faster and also has lesser settling time. Table 3.6 summarizes the performance metrics along with closed loop statistics for the three different control loops. The performance metrics were calculated for a single normalized step change and the period considered for the calculations was of 160 s. The faster response along with the performance metrics led to a conclusion that the MPC is superior to PID in this specific process. The reason for this superior performance is that the process has a considerable dead time and the value for compression forces is only updated every 20 s. Another major advantage of using MPC is that it allows a flexible implementation of MIMO controllers

using a single block in DeltaV. Given that this was the case, all the control modules built in the proceeding experiments are MPC based (Bhaskar et *al.* 2017).

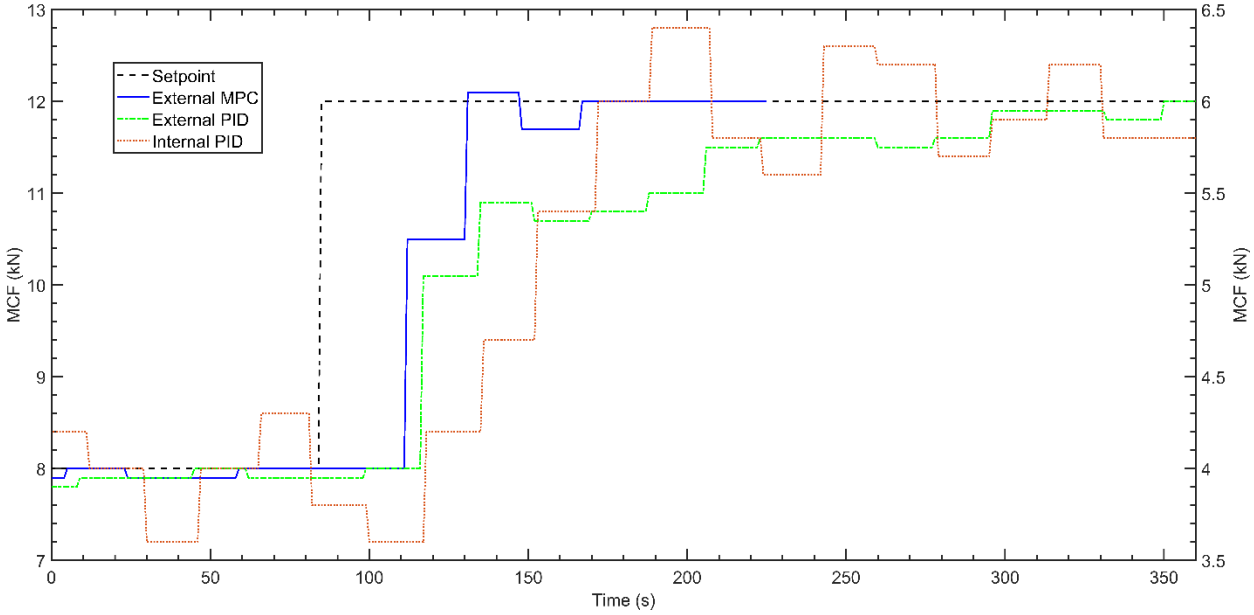


Figure 3. 14. MCF closed loop response analysis (control mode 1) (Bhaskar et *al*. 2017).

Table 3.6. MCF control algorithms analysis**.**

Strategy	**IAE (kN.s)**	**ITAE (kN.s)**	**ISE (kN.s)**	**Rise time (s)**	**Settling time (s)**	**Overshoot (%)**
Inbuilt	80.08	3646	68.67	87	>280	1.2
External PID	65.19	3173	42.67	121	211	0
External MPC	46.25	1589	35.34	46	153	0

3.14.2 Investigation of pre compression force controllability (control mode 2)

It has been normally assumed that the pre compression force cannot be controlled in real-time and therefore, most commercially available tablet press units do not have an inbuilt controller for pre compression force. A control system for pre compression force has been developed (Bhaskar et *al.* 2017). The pre compression force experiments were conducted using a MPC block on DeltaV. The actuator for this controlled variable was decided to be the fill depth in accordance with the overall hypothesis. The development and tuning of the MPC was done as explained in Section 3.10. The step changes were made to evaluate the set point tracking capability of the controller. The first step up in pre compression force set point was made from 5 kN to the 7 kN. As can be seen in the figure, after a system imposed dead time of 25 s, the controller brings the signal back to the set point. The rise time is 43 s. A small overshoot of 1.5% can be seen in the response of control variable. However, this overshoot is acceptable. The existence of overshoot is very common in closed loop response. The achieved settling time 115 s, which is acceptable. Figure 3.15 shows that after an initial small overshoot, a perfect ideal control with no oscillation has been achieved. It was concluded from this experiment that the pre compression force can be properly controlled through manipulations in the fill depth using a MPC (Bhaskar et *al.* 2017).

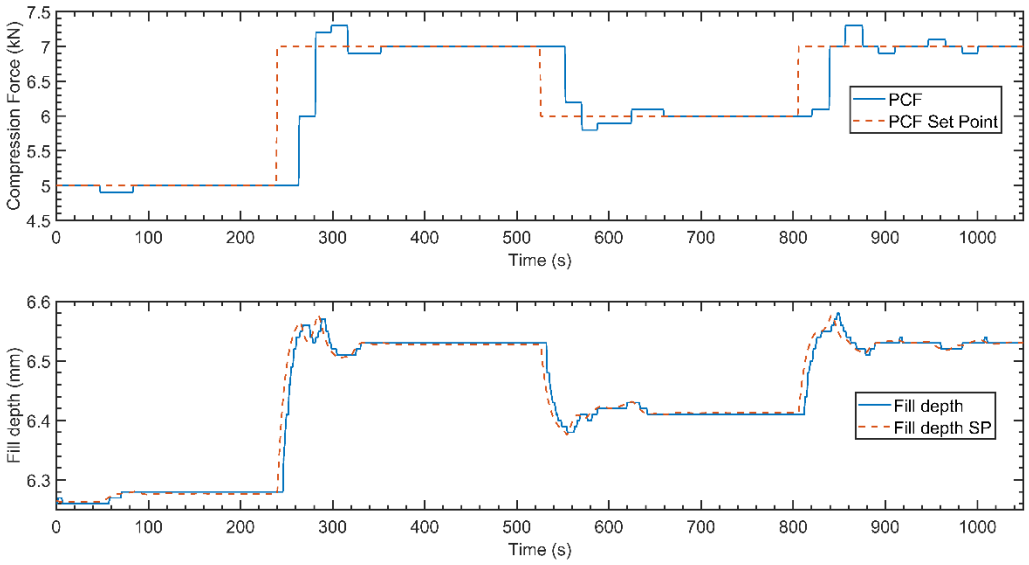


Figure 3. 15. PCF controller closed loop response (control mode 2) (Bhaskar et *al*. 2017).

3.14.3 Simultaneous control of main and pre compression forces (control mode 3)

The performance of a MIMO MPC with two controlled variables and two manipulated variables was evaluated. Because of interactions between two control loops, the MIMO system is more difficult to control. The controller was developed and tuned according to the procedure described in Sections 3.10. Both control loops are interactive since fill depth affects both control variables. The interaction of these control loops is shown in Figure 3.16 via an open loop response. The pre compression force control loop affects the main compression force control loop while the main compression force control loop does not have an effect on pre compression force control loop. The goal of implementation of this 2×2 MPC is to be able to manipulate main and pre compression forces independently to control tablet breaking force and weight respectively. The experiment was divided in two parts (Bhaskar et *al.* 2017).

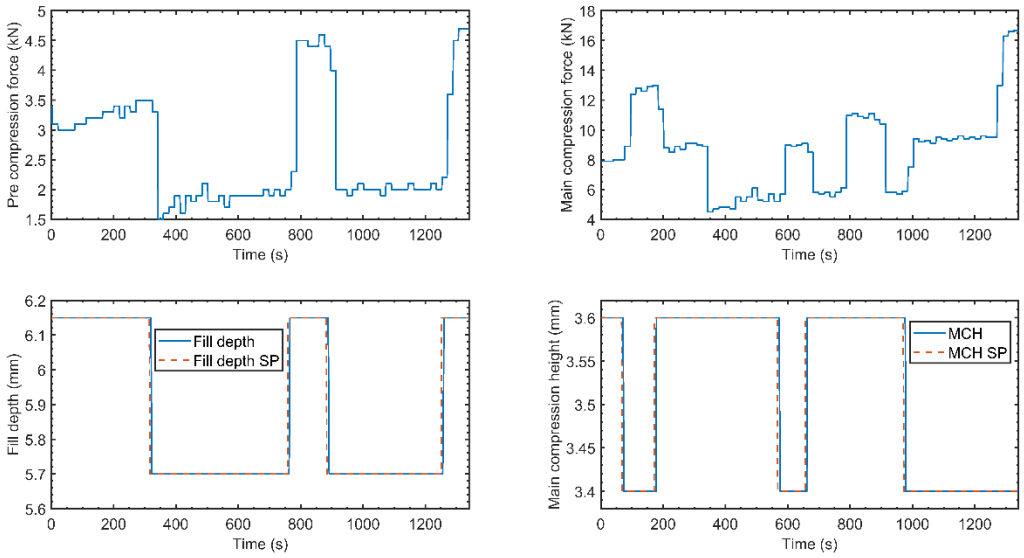


Figure 3. 16. Open loop response of pre and main compression force. MCH: Main compression height (Bhaskar et *al.* 2017).

In order to test the controller and each input-output set in isolation, step changes were made in MCF while keeping PCF at a constant set point. The system reacted as expected, with changes only in the actuator for MCF. For the second part of the experiment, set point changes were made in PCF while maintaining MCF constant. It can be seen from the dynamic response of the system that PCF properly tracked the set point changes. Small oscillations in MCF values can be seen after the changes in PCF set point. These oscillations occur because changes in fill depth (PCF actuator) lead to variations in both compression forces. As expected, the controller promptly takes action to mitigate the variations in MCF caused by changes in fill depth. This result also serves as a disturbance rejection for the MCF controller. Accurate process models and optimal tuning of the MPC should minimize the magnitude of these variations (Bhaskar et *al.* 2017). The responses of the system are presented in Figure 3.17.

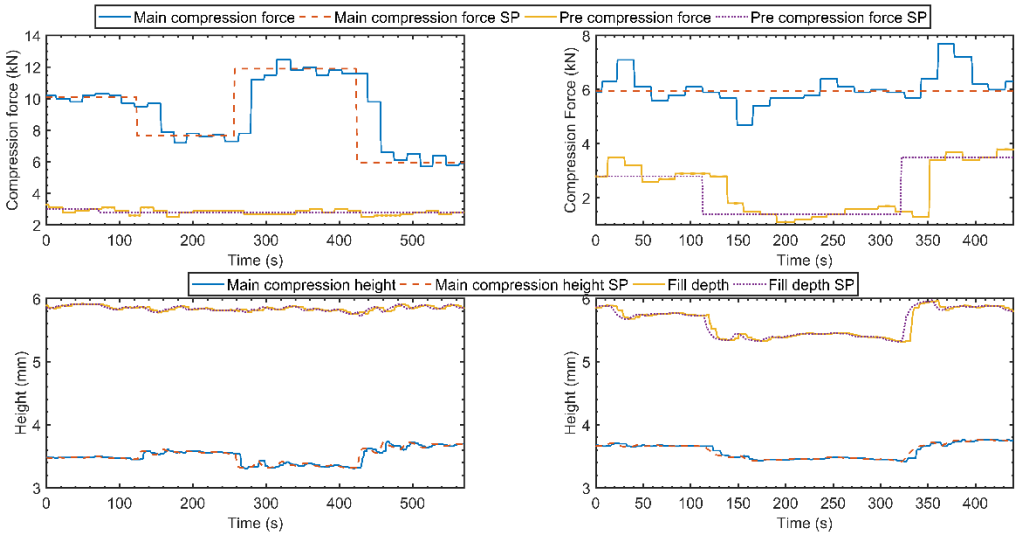


Figure 3. 17. Closed loop response of pre and main compression forces (2x2 MPC closed loop response) (Bhaskar et *al*. 2017).

3.14.4 Real-time tablet weight measurement validation and feedback control

The developed methodology for tablet weight measurement was evaluated as a proof of concept (Bhaskar et *al.* 2017). Changes in fill depth were applied to the system and the effect on tablet weight was observed. The system response with no signal processing applied is shown in Figure

3.18. As expected, the measured tablet weight is directly proportional to fill depth and the magnitude of the weight variations is the same as the fill depth variation. A considerable oscillation in tablet weight, which was likely caused by an irregular inflow of tablet in the catch scale, can be noticed at around 160 s.

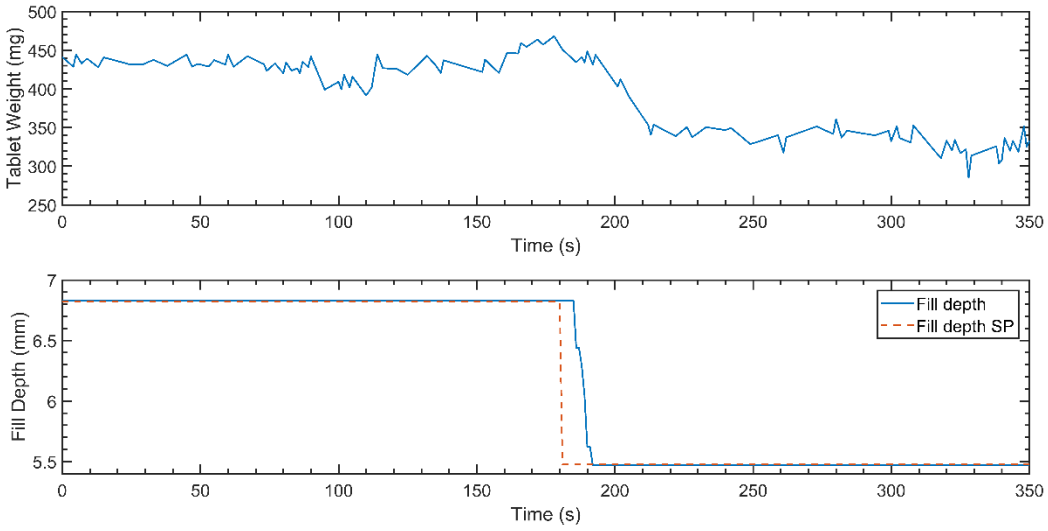


Figure 3. 18. Real-time table weight measurements (Bhaskar et *al*. 2017).

The available weight measurement technique was then used for the implementation of a supervisory tablet weight controller. The goal of this experiment was to prove that simultaneous control of tablet weight and main compression force, which is directly related to tablet breaking force, is possible, even though a fully established real-time tablet weight measurement method is not available at the moment. The controller was tuned according to the methodology described in Section 3.10. The closed loop response of the controller is shown in Figure 3.19. As shown in the figure, the predefined consistent tablet weight has been achieved. The controller was able to maintain the tablet weight at the set point. A consistent main compression force has been also achieved. The objective of this study was to perform a proof of concept experiment for real-time tablet weight control and it has been achieved successfully (Bhaskar et *al.* 2017). However, there is a significant scope for improving the closed loop performance. Augmenting the weight

measurement system by developing a commercial sensor could improve the measured signal and thereby the performance of the control system.

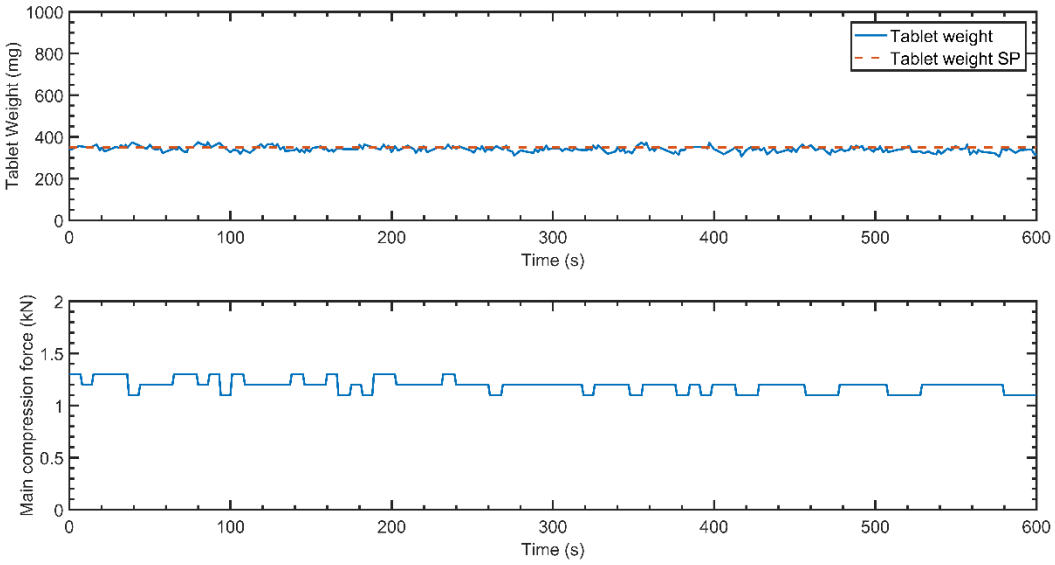


Figure 3. 19. Closed loop response of tablet weight supervisory control loop (Bhaskar et *al*. 2017).

Chapter 4 Residence time distribution (RTD) based diversion system for continuous pharmaceutical manufacturing process

Acknowledgements:

This chapter is based on the following manuscript submitted for publication and all authors/co-authors are acknowledged:

Bhaskar A, Singh R*. 2018. Residence time distribution (RTD) based diversion system for continuous pharmaceutical manufacturing process. Under review.

This work is supported by the Rutgers Research Council through grant 202342 RC-17-Singh R, the US Food and Drug Administration (FDA) through grant 11695471, Glaxo Smith Kline (GSK), and National Science Foundation Engineering Research Center on Structured Organic Particulate Systems.

*Corresponding author (Email: ravendra.singh@rutgers.edu)

4.1 Drug concentration based real time diversion strategy

A drug concentration based diversion system is an intrinsic requirement for continuous pharmaceutical manufacturing. Conventional pharmaceutical manufacturing was based on batch processes and therefore such a system was not needed before. In a batch process, as seen in Figure 4.1 (a), individual raw materials are mixed in a blender. The output from this is transferred into drums and is subsequently tested for content uniformity offline. If the product does not meet specifications, then entire batches maybe disposed. Product that meets regulatory constraints is then stored and transported to the next unit operation. In the case of solid dosage forms for direct compression, the product is then feed through a feeder into a tablet press. The compacted tablets are then transferred to coating and packaging process.

On the other hand, for the continuous manufacturing process, an upstream disturbance could propagate downstream if it has not been controlled locally or if the local control is not efficient causing overshoots. Depending on the performance of downstream unit operations, this disturbance could amplify or diminish. Nonetheless, due to this disturbance propagation, there is a need to control or be able to mitigate situations that have the capacity to deteriorate end product quality. It's steady state operation of a continuous manufacturing process allows for the development of control systems as mentioned before. Drug concentration control as described in the following sections, although not traditional in the sense of control is a strategy that is necessary as it eliminates the need for offline testing post the compaction stage. It facilitates Real Time Release Testing (RTRT) as the tablets can then be seamlessly transported to the coating and packaging processes.

In Figure 4.1 (b), such a "drug concentration based diversion system" has been schematically illustrated. As shown in the figure, the blender is connected to the tablet press via a shoot that is designed to house Process Analytical Technology (PAT) devices. A spectroscopic device (NIR) is integrated here and data from this is collected and used for real time monitoring of drug concentration. This creates a real time availability of the inlet drug concentration data at the entry of the tablet press. The drug concentration based control strategy developed in this work then uses this inlet concentration to determine a signal for the diversion strategy that can accurately be used to reject tablets that are out of tolerance limits at the outlet of the tablet press.

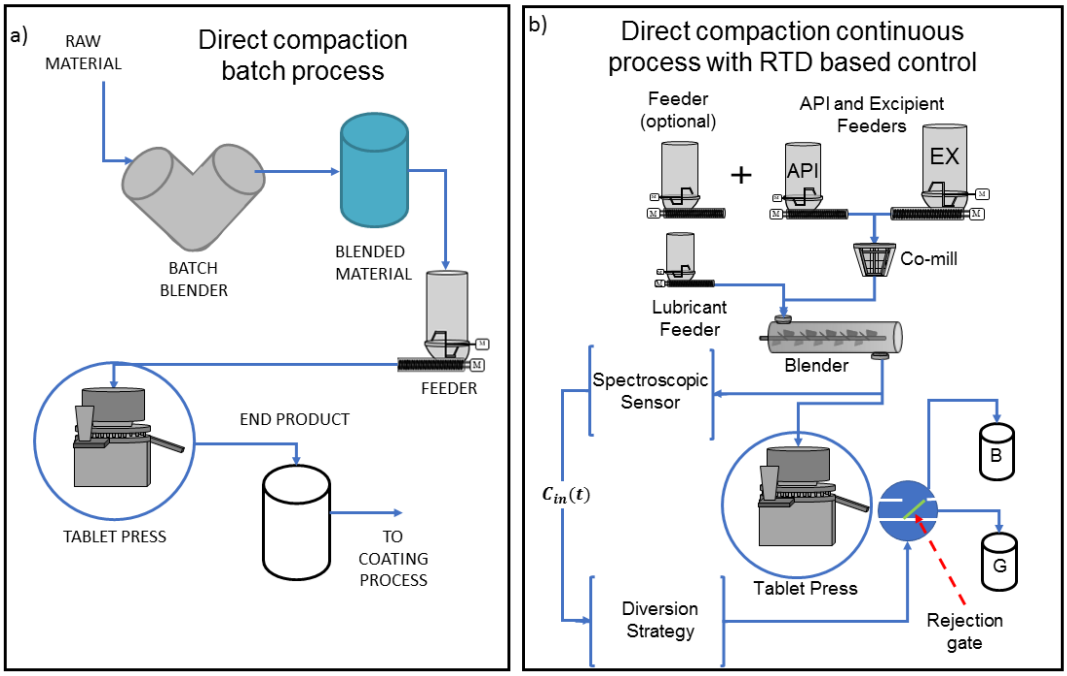


Figure 4. 1. Overview of drug concentration based real time diversion strategy. G: Good tablet, B: Bad tablet

4.2 Residence Time Distribution (RTD) model

An RTD based strategy is proposed to be applied for real time tablet diversion. Prior to elaborating on the details of the soft sensor, the fundamentals of RTD have been introduced in this section.

RTD is the probability distribution of time that solid or fluid materials stay inside one or more unit operations in a continuous flow system. For a manufacturing plant or equipment, the RTD is a characteristic of the mixing occurs inside it (Fogler 2006). Typical chemical engineering jargon differentiates the RTD at the definitional stage using a Continuous Stirred Tank Reactor (CSTR) and Plugged Flow Reactor (PFR) where the former exhibits a thorough mixing while the latter introduces a time delay.

For a system, the RTD may be derived by conducting tracer experiments. For a pulse experiment, once the inlet and the outlet concentration data is collected, the RTD function can be calculated as follows,

$$\boldsymbol{E_{exp}(t) = \frac{c_{out}(t)}{\int_0^\infty c_{out}(t)dt}} \qquad (1)$$

Where $E_{exp}(t)$ is the experimentally obtained RTD and $c_{out}(t)$ is the outlet concentration with respect to time. This can be converted into the Cumulative Distribution Function (CDF) ($F_{exp}(t)$) using the following relation,

$$\boldsymbol{F_{exp}(t) = \int_0^t E_{exp}(t)dt} \qquad (2)$$

On the other hand, for a step change based experiment, the following equation maybe used to calculate the Cumulative Distribution Function (CDF),

$$\boldsymbol{F_{exp}(t) = \frac{C(t)-C_0}{C_f-C_0}} \qquad (3)$$

Where, C_0 is the inlet concentration before the step change, C_f is the inlet concentration after the step change and $C(t)$ is the outlet concentration at time t. This can be converted into the RTD function using the following relation.

$$\boldsymbol{E_{exp}(t) = \frac{dF_{exp}(t)}{dt}} \qquad (4)$$

Additionally, from experimental data the RTD can be characterized using the calculated mean residence time and variance. These can be determined using the following equations,

$$\boldsymbol{\tau = \int_0^\infty tE(t)dt} \qquad (5)$$

$$\sigma^2 = \int_0^\infty (t-\tau)^2 E(t)dt \qquad (6)$$

The increased involvement of RTD in the chemical engineering field has also led to the development of a myriad of models. The work has made use of the tank in series (T-I-S) model. The generalized model for tanks in series is given by the following equation,

$$E(t) = \frac{t^{n-1}}{(n-1)!\left(\frac{\tau}{n}\right)^n} e^{\left(\frac{-nt}{\tau}\right)} \qquad (7)$$

Where τ, is the mean residence time and n is the number of Continuous Stirred Tank Reactors (CSTRs). The experimental data can be used to fit into this equation by determining the number of tanks and mean residence time using a least squares technique.

4.3 Strategies for real time assurance of tablet drug concentration

The real time diversion of tablets based on drug concentration is challenging because there is currently no sensor available that can measure the tablet potency and mean drug concentration of tablet in real time. However, the drug concentration of blend can be measured in real time using well stablished PAT techniques and tools (Singh et *al*. 2014). Therefore, the sorting method relies on the real time measurement of blend uniformity and model predicting tablet potency and residence time from sensor location and tablet press outlet (diversion gate). A systematic tablet sorting procedure is shown in Figure 4.2. As shown in the Figure 4.2, two approaches can be considered for tablet sorting based on drug concentration: a fixed window of diversion approach and a Residence time distribution (RTD) based approach. The first approach is simpler to implement but may lead to lower production efficiency. The second approach is based on more advanced technique and will ensure more efficiency but is relatively complex to implement. Both strategy need prior experimentations to identify the parameters needed for control methodology

developed in this work. However, the second approach may need relatively complex experiments to be conducted in compare to the first approach.

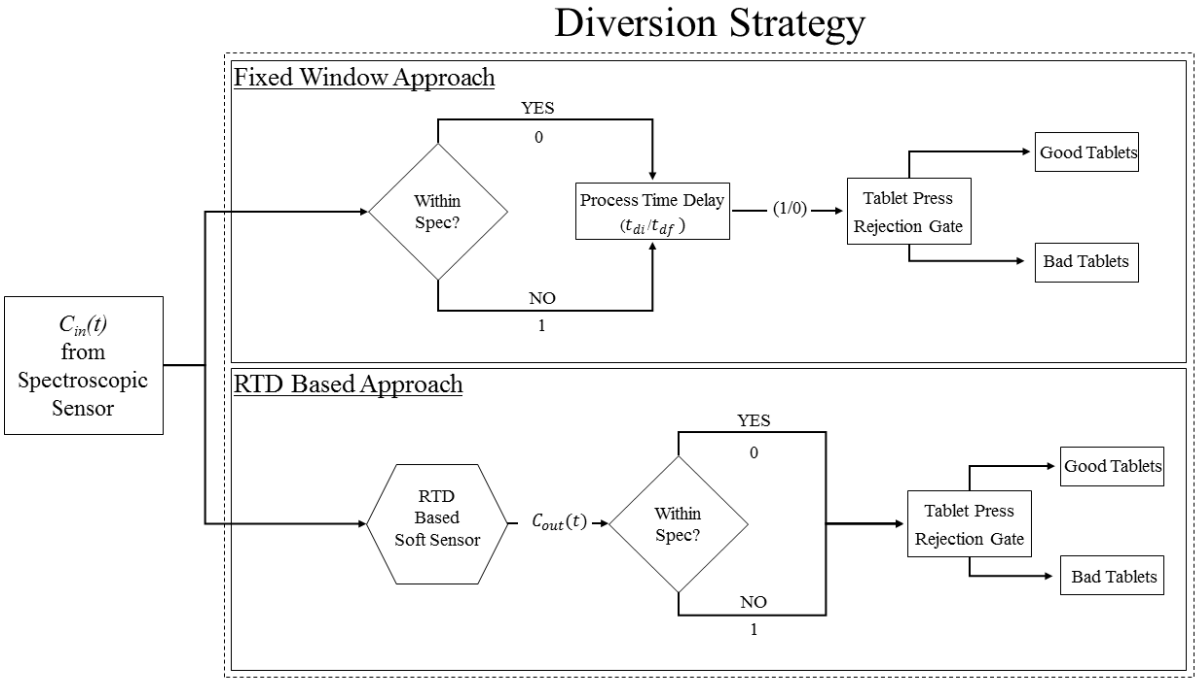


Figure 4. 2. Real time diversion of pharmaceutical tablets. 0: Accept, 1: Reject

4.3.1 Fixed window approach

Tablet diversion is facilitated using this approach through knowledge of Time delays from the point of detection (chute or feed frame) to the point of the affect (tablet press outlet gate) in the system. The sensor that detects the concentration is connected to a comparator block which decides if the said concentration is within the specifications. If it is not within specification, the experimentally derived time delay is applied and post this the diversion begins. The diversion stops when a concentration within spec is detected and the another time delay is applied. These protocols can be represented using Equation (8) and Equation (9). The time to start diversion can be calculated as follows.

$$t_r = t_{offspec} + t_{di} - \Delta t \qquad (8)2$$

Where t_r is the time at which diversion should start, $t_{offspec}$ is the time at which the drug concentration of the blend goes out of its specifications, t_{di} is the time delay that the system requires to realize the change in concentration at the outlet and Δt is the safety margin to guarantee that no off spec tablets will be sorted in good tablet lot. $t_{offspec}$ can be obtained using real time PAT sensor for blend uniformity measurement. $t_{di}$is predetermined using offline experimentations and it depends on both formulation and plant characteristics. It must be re-estimated if there are any changes in formulation &/or process conditions. Δt is chosen by the operator based on experience working with the system

The time to stop diversion can be calculated as follows:

$$t_a = t_{spec} + t_{df} + \Delta t \qquad (9)$$

Where t_a is the time at which diversion should stop, t_{spec} is the time at which the drug concentration returns to an acceptable range, t_{df} is the time delay that the system requires to wash out the previous off spec materials and like in Equation 8, Δt is the safety margin to guarantee that no off spec tablets will be sorted in good tablet lot. t_{df} is similar to t_{di} and in most cases it is likely to be the same. Nonetheless to avoid any assumptions these are treated differently and it may be predetermined using offline experiments. Another reason to treat these values differently is that the system may behave differently for fluctuations in formulation &/or process conditions.

This concept is further illustrated in Figure 4.3. In the Fixed Window approach, for a pulse disturbance of unit magnitude from nine to ten, the diversion according to Equation (8) will

begin at tr and goes on until ta. The diversion begins after the initial time delay, t_{di} has been applied and then last for the duration of the pulse disturbance. It then lasts another extended period of time governed by the value of t_{df}.

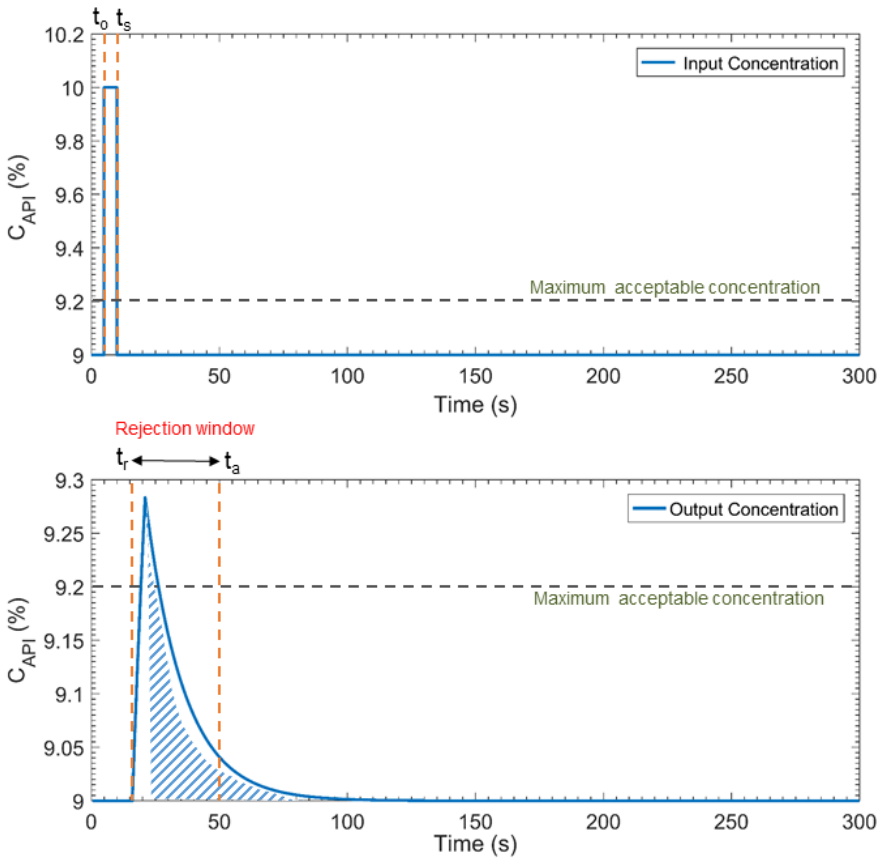


Figure 4. 3. Fixed window based tablet diversion system

4.3.2 RTD based approach

In this methodology, the RTD of the system is estimated through tracer experiments. This estimated RTD can be used to predict the outlet concentration from the inlet concentration. The details of the implementation of the RTD based diversion on Simulink is further illustrated in a

later section in the paper. The outlet concentration can be calculated using the convolution integral as follows:

$$\boldsymbol{C_{out}(t) = C_{in}(t) * E(t)} \qquad (10)$$

Where $C_{out}(t)$is the outlet concentration, $C_{in}(t)$ is the inlet concentration and $E(t)$is the RTD of the system.

Using this relation, the outlet concentration can be predicted in real time and this signal can be used to initiate the diversion. One scenario is explored in Figure 4.4, where a pulse disturbance is introduced in the system. The response in the system as predicted using the RTD shows a period where the concentration is out of specification. The diversion system which is dependent on the predicted signal rejects tablets only when the outlet concentration is out of specification. At this point a comparison can be made between the fixed window approach and the RTD based approach. It is clear that the RTD based approach sees a more accurate diversion of tablets. The improvement that the RTD based approach provides is further explored in this paper.

An important consideration at this point is to note that the mean API concentration of the tablet is used to determine the diversion window as opposed to the Potency. The reason for this lies in the dependency of potency on the tablet weight which at this point does not have many reliable real time measurement methodologies. A constant value of weight can be used for the calculation of Potency but this would not result in any new information as it would simply amplify the disturbances in the predicted outlet concentration.

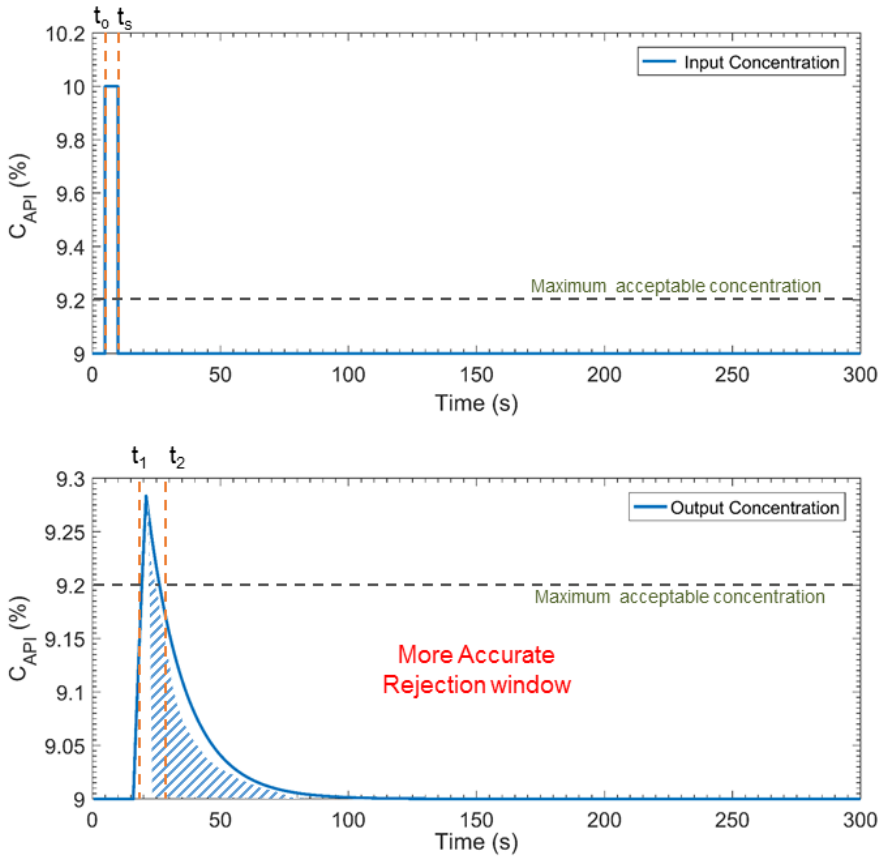


Figure 4. 4. RTD based tablet diversion system

4.4 Systematic framework for design, evaluation and implementation of RTD based diversion system

Figure 4.5 shows a sequential framework that can be followed for the development and implementation of RTD based diversion system. Given that the Residence Time Distribution characterizes the mixing within a unit operation under certain operation conditions and the quanta of time a fraction of material spends inside said operation, a change in the spatial characteristics; example change in reactor size for a reactor or fill depth in the case of tablet compaction, the RTD would be modified due to the change in time that a material spends in the process. The formulation characteristics can drastically change the flow behavior within the

process. This too can modify the RTD of the system. From this, the reader may glean that the process parameters and the formulation must be kept constant for a system. Therefore, in the development of the RTD based diversion strategy, a first step would be to accurately define the product, process and plant configurations. The process should be run under operating conditions to be used in final manufacturing. At this point, the RTD can be determined as mentioned in Section 4.4.

Post RTD determination, the implementation of this methodology is developed. For a linear system, a pulse or step response of a system at any time will behave and spread through the system just like a pulse of equal magnitude (Engisch and Muzzio 2016). A measured input stream could be represented with a string of discrete values representing the fluctuations in the stream. Using the convolution integral for mixing, the final drug concentration can then be estimated. Using the Equation 8, it is possible to predict the outlet of a unit operation as long as the concentration of the inlet stream, $C_{in}(t)$, and the RTD, $E(t)$, are both known. The implementation of this equation in real time system can be used to develop a soft sensor where the inlet concentration of a blend is measured and the outlet concentration in a unit operation is predicted.

This convolution integral methodology can be implemented *insilico* with available process models. Various scenarios can be simulated and tested to analyze the control system. This manuscript, illustrates this step in detail as can be seen in the Section 4.8 (results). The *insilico* analyses provides a tool for the implementation and development of a control strategy. This step is essential since it optimizes the use of expensive raw material in the developmental stages. The performance of the strategy can also be tested to check for the accurateness of the RTD model.

Additionally, performance metrics can also be developed and tested *insilico*. An example of such a metric that can be used and is used in this work is the manufacturing efficiency as defined by Equation 11.

$$Manufacturing\ Efficiency\ (\varepsilon) = 100 * \frac{Good\ Production(t)}{Total\ Production\ (t)} \qquad \textbf{(11)}$$

A real time analysis of the manufacturing efficiency can also be used to determine alarms in the control system. A production efficiency lower than a certain threshold can give process operators an indication of whether the production needs to be stopped to rectify any process faults.

Post the *insilico* design and performance assessment, the RTD model can be used in the plant for real time tablet diversion based on mean API concentration. The implementation step essentially requires the integration of the plant with the diversion system and resolving all hardware and software connectivity issues. Validated PAT models must also be developed for real time drug concentration measurement. At this point, the system maybe run to test the diversion capability of the developed system. Performance issues with the RTD soft sensor based control system, at this stage can be attributed to inaccurate RTD model identification and concentration detection methods. An iterative re-estimation of existing data can be used to arrive at accurate models.

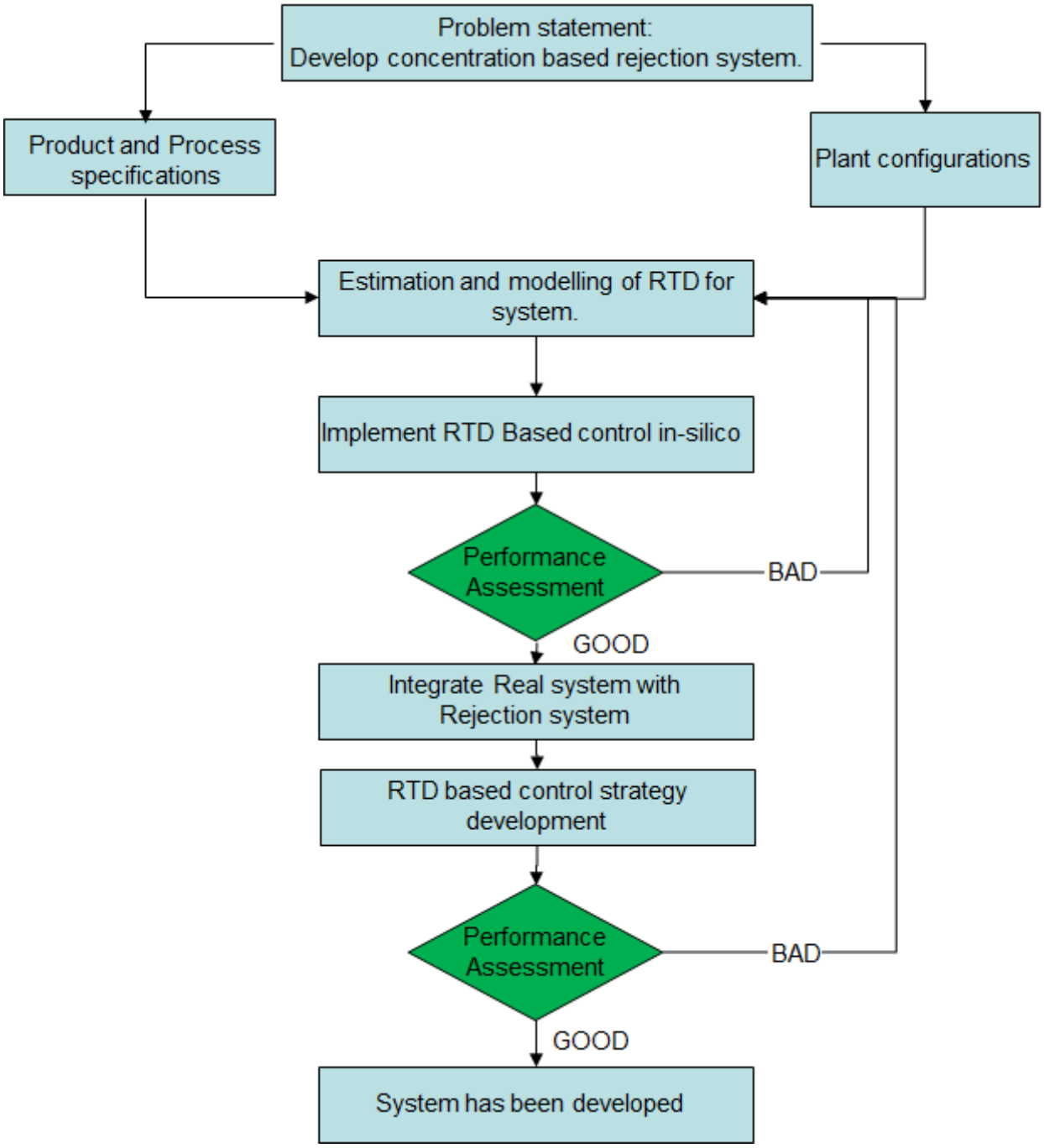


Figure 4.5. Framework for implementation of RTD based diversion

4.5 *Insilico* design of RTD based diversion system

The RTD based diversion system was developed and implemented using a combination of Matlab and Simulink. The details of the implementation are elaborated on in this section.

4.5.1 Implementation of RTD model for prediction of mean API composition of tablets

The Cumulative Distribution Function of a unit operation from Equation 2 and 3 when normalized maybe plotted on an X and Y axis where the maximum value on the Y axis is one and the minimum value is zero. The X axis maybe extended as per the necessity to incorporate the full RTD function. Such a plot is shown in Figure 4.6. The RTD model was implemented by entering a vector containing all the values from the Y axis into the Finite Impulse Response Block in terms of their increments for a certain sampling time.

It was observed that the convolution integral from Equation (10) could be calculated in real time by simply feeding the inlet concentration to the FIR block where the output signal is the convoluted outlet concentration. Figure 4.6 gives an illustration of this for a unit step response. A comparison of the output from the convolution integral and the output of the FIR block has been shown. As can be seen, the only difference lies in the step like structure of the FIR response. This step like structure can be attributed to the sample time which in this case is one second. It can be smoothened by using a smaller sample time. All the scenarios in this paper were generated using the FIR block as the RTD based soft sensor.

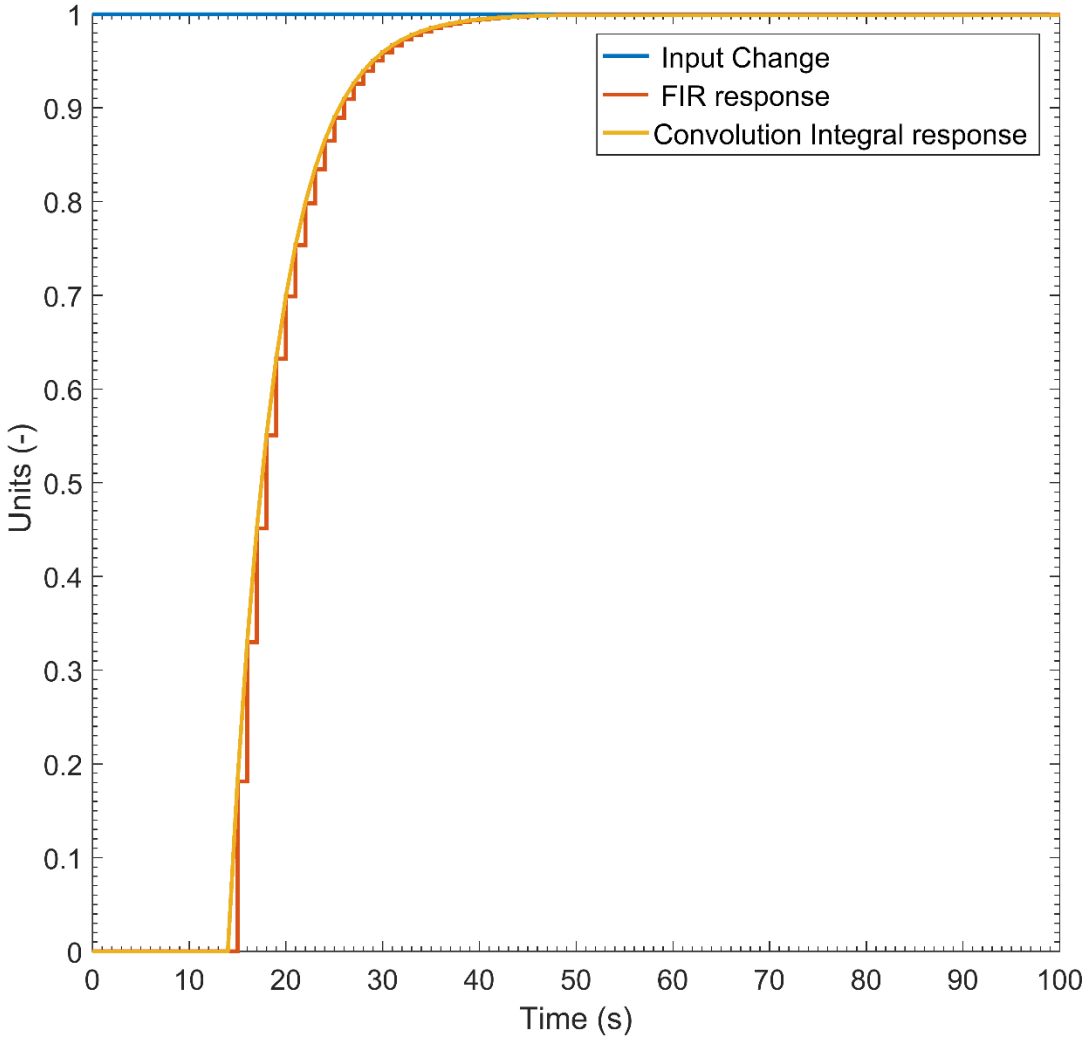


Figure 4. 6. Comparison of FIR response and convolution integral

4.5.2 Tablet potency prediction

Although, the proposed diversion system is based on mean API composition of the tablet, the potency has also been analyzed to demonstrate that it is also controlled using this control strategy. The potency calculation assumes that there is continuous real time data for tablet weight. The potency is then calculated using the expression:

$$Potency = T(t) * C_{out}(t) \quad \textbf{(12)}$$

Where $T(t)$ is the continuous tablet weight and $C_{out}(t)$ is the RTD based prediction of the outlet concentration.

A methodology for real time tablet weight measurement has been previously reported (4). To simulate a signal similar to this a band limited white noise block was used with following parameters: Noise power = 0.0000000001, sample time = 2 and seed = 23341. This signal is summed with a constant value of 0.4 g to simulate the real time tablet weight $T(t)$ from the Equation 12 .

4.5.3 Tablet diversion system

The signal generated from the RTD soft sensor (represented by the FIR block), that is, the predicted outlet concentration is fed to the diversion system. The diversion system is based on the difference between the reference mean API composition of tablet and the actual concentration (Cout(t)). The absolute value of this difference is compared with an allowed tolerance via a relay which produces a binary output. This output is used to calculate the period of good production and the period of diversion.

4.6 Results and discussion

In this section, scenarios were generated with both the RTD and Fixed window based diversion system. Both methodologies were compared in each scenario and its production efficiency was analyzed. These scenarios were generated based on potential manufacturing problems during

production. In each case, the disturbance has been introduced before entry into the tablet press and the affect is seen post compaction.

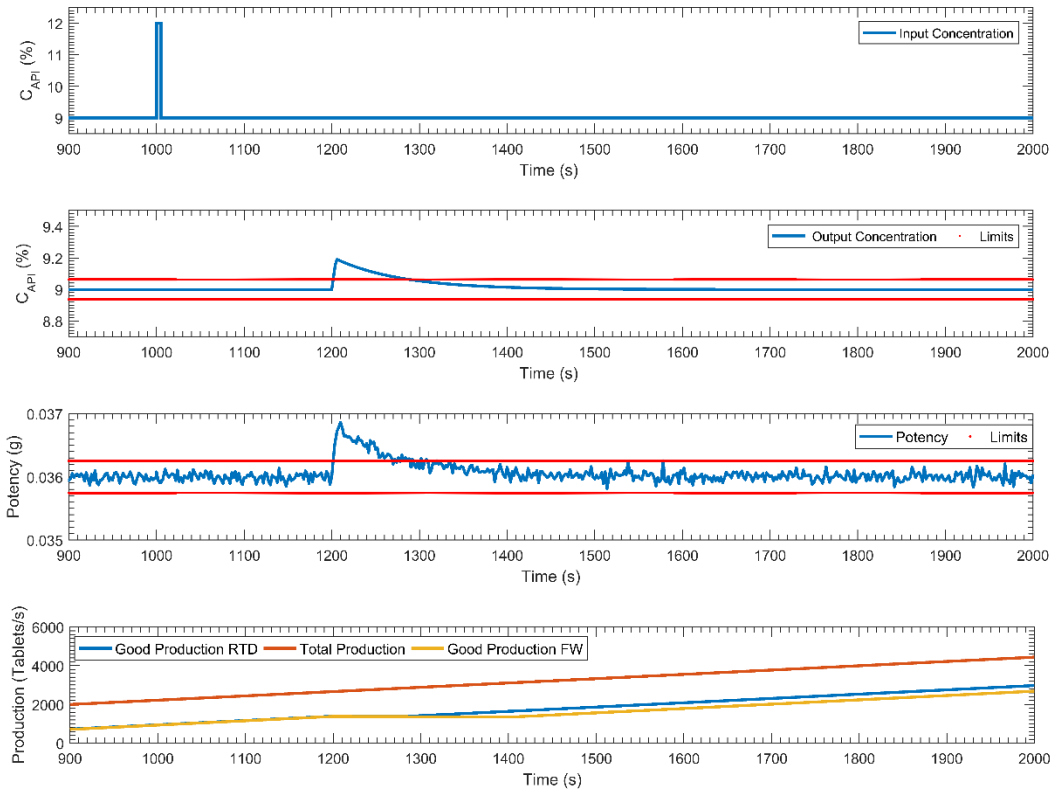
4.6.1 Evaluation of RTD based diversion system for rejecting pulse disturbances

The API, which contains small particles with a tight size distribution, in some cases may agglomerate to larger granules. When the blending is not very efficient, agglomerated particles can cause sudden changes in the API concentration. Other reasons for such fluctuations can be if the feeder stops working for a short duration, a lump of API is introduced into the tablet press, API feeder control overshoot, API feeder response time is faster or slower than the excipient feeder. Nonetheless, such an occurrence can be treated as a disturbance and has been simulated in the form of a pulse disturbance. Two cases have been considered, one with a positive higher low magnitude and another with a negative high and low magnitude. as can be seen in Figure 4.7 and 4.8. In both cases, the disturbance is introduced at the hundredth second. It should also be noted that the initial 80s have been allotted to startup of the simulation.

4.6.1.1 Case study 1: Diversion of more potent tablets caused by positive pulse disturbances

In Figure 4.7 (a), the output concentration spreads after a certain time delay and subsequently exceeds the acceptable range of both concentration and potency. The concentration and potency eventually return to the acceptable range once the effect of the disturbance has ceded. During this time period a plot analyzing the production has been plotted. The RTD based approach rejects tablets for a lesser time period and only when the actual predicted tablet concentration is out of range. In the case of the Fixed window approach the tablets are rejected for a slightly longer time duration.

Similarly, in Figure 4.7 (b) the output concentration spreads and rises as an effect of the input pulse disturbance but does not exceed the boundaries at any time. The potency does not exceed the boundaries at any point. Therefore, the RTD based diversion approach does not reject any tablets after the disturbance has been affected. According to the Fixed Window approach though, since it is dependent on the input concentration there is a definite diversion period that follows the disturbance.



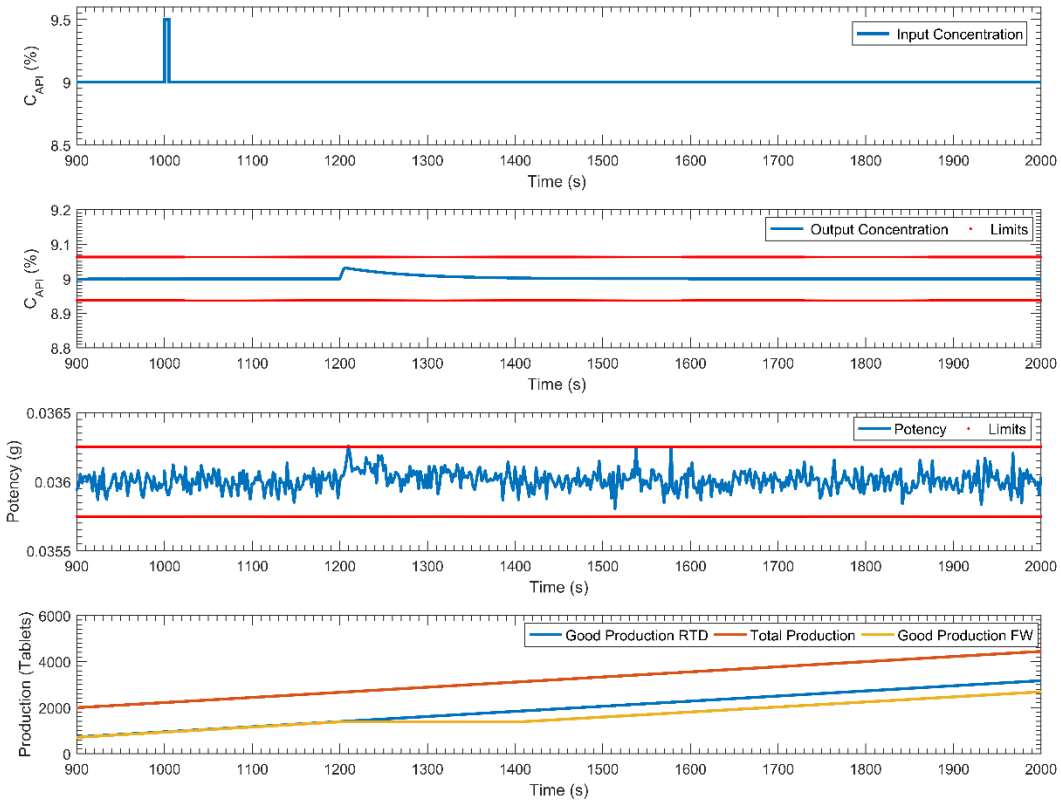
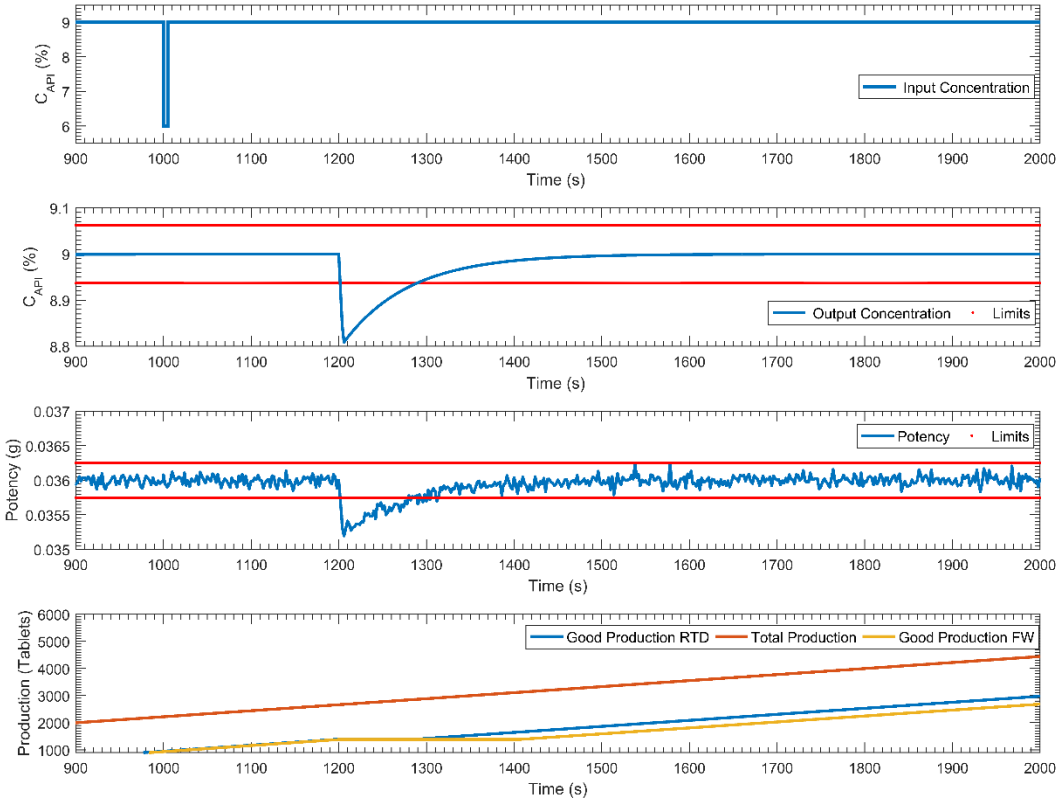


Figure 4. 7. Fluctuation in API concentration (a) High magnitude (b) Low magnitude

4.6.1.2 Case study 2: Diversion of less potent tablets caused by negative pulse disturbances

In Figure 4.8 (a), the variation in the inlet concentration causes a change in the outlet concentration. A spread after a certain time delay exceeds the acceptable range of both concentration and potency. The concentration and potency eventually return to the acceptable range once the effect of the disturbance has ceded. The production plot shows that the RTD based approach rejects the tablets for a lesser time period and only when the actual predicted tablet concentration is out of range. On the other hand, in the case of the Fixed window approach, tablets are rejected for a slightly longer time duration.

In Figure 4.8 (b), the output concentration spreads and rises as an effect of the input pulse disturbance but does not exceed the boundaries at any time. The potency does not exceed the boundaries at any point. According the RTD based diversion approach there is no diversion post the eightieth second since the outlet concentration is within the boundaries. According to the Fixed Window approach, since it is dependent on the input concentration there is a definite diversion period that follows the disturbance..



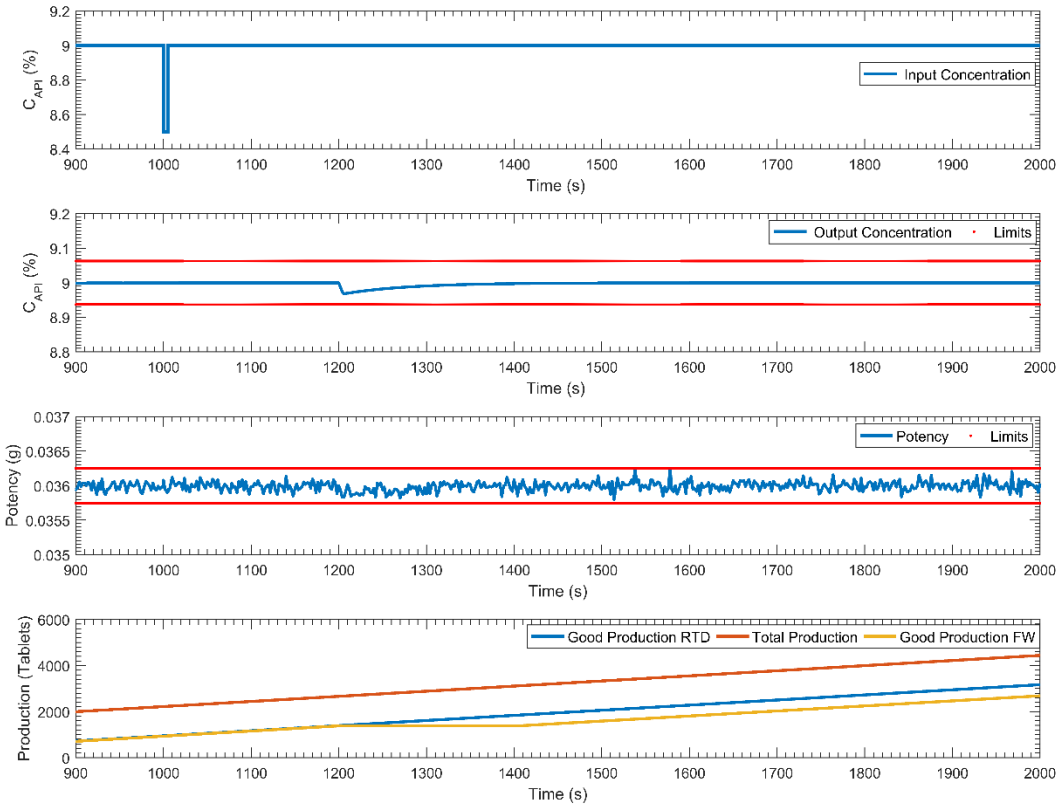


Figure 4.8. Negative pulse disturbance (a) High magnitude (b) Low magnitude

4.6.2 Evaluation of RTD based diversion system for rejecting step disturbances

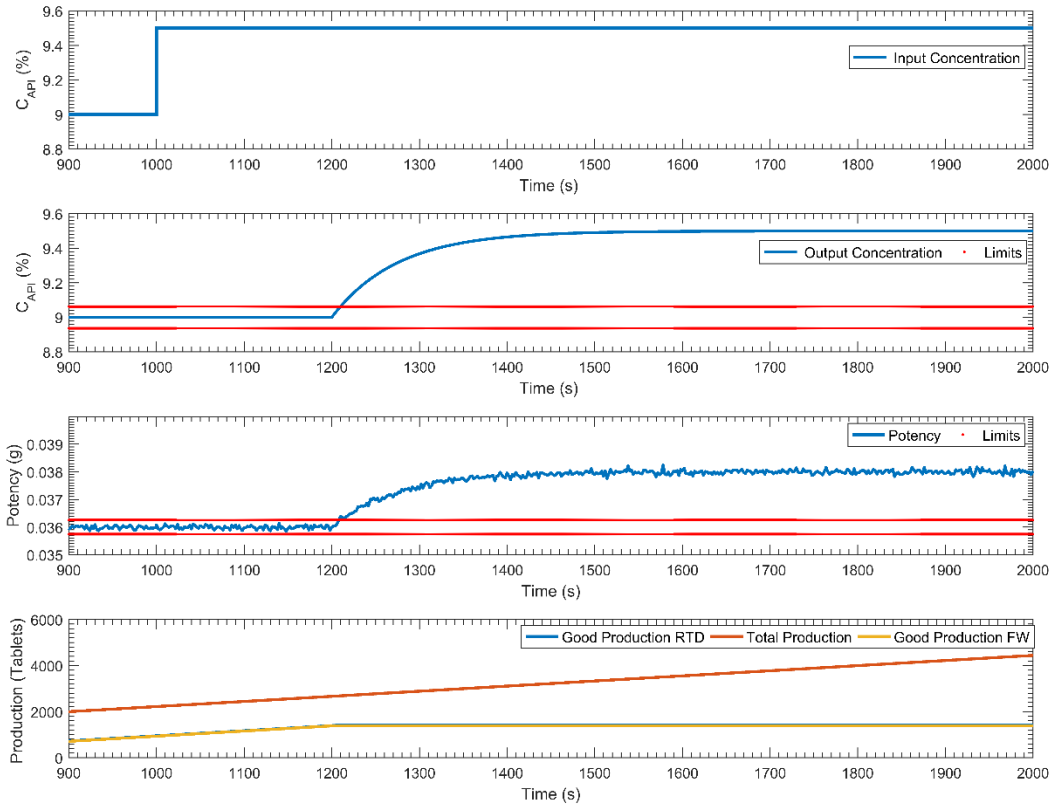
In some situations, a feeder might start feeding more or less and this may go undetected. If the process monitoring system does not detect this, then another fail safe measure would be to make use of the real time diversion system at the tablet press outlet. This scenario has been simulated by a step change disturbance.

4.6.2.1 Case study 3: Diversion of more potent tablets caused by step disturbances

In Figure 4.9 (a) a step change disturbance has been simulated in the concentration to represent an excipient feeder that is feeding less. The resulting increase in the API concentration causes the potency to increase as well. The dynamics exhibited by this increase is derived from the RTD of the system. In both, the RTD based approach and the fixed window approach the diversion begins at around the same time and since the concentration does not return to the desired range and therefore, there is no need to stop the diversion during this time. On observing the graphs, it can be seen that there is little difference in the RTD based approach and the Fixed Window approach. The RTD based approach is 1% percent better.

4.6.2.2 Case study 4: Diversion of less potent tablets caused by step disturbances

In Figure 4.9 (b), similarly a step down has been simulated in the concentration to represent an excipient feeder that is feeding more. The resulting decrease in the API concentration causes the potency to decrease as well. As is apparent from the graphs, this case is a mirror image of the case of the step up disturbance. The step down magnitude is exactly the same as the step up magnitude.


Input Concentration
C_{API} (%)
Time (s)
Output Concentration
Limits
C_{API} (%)
Time (s)
Potency
Limits
Potency (g)
Time (s)
Good Production RTD
Total Production
Good Production FW
Production (Tablets)
Time (s)

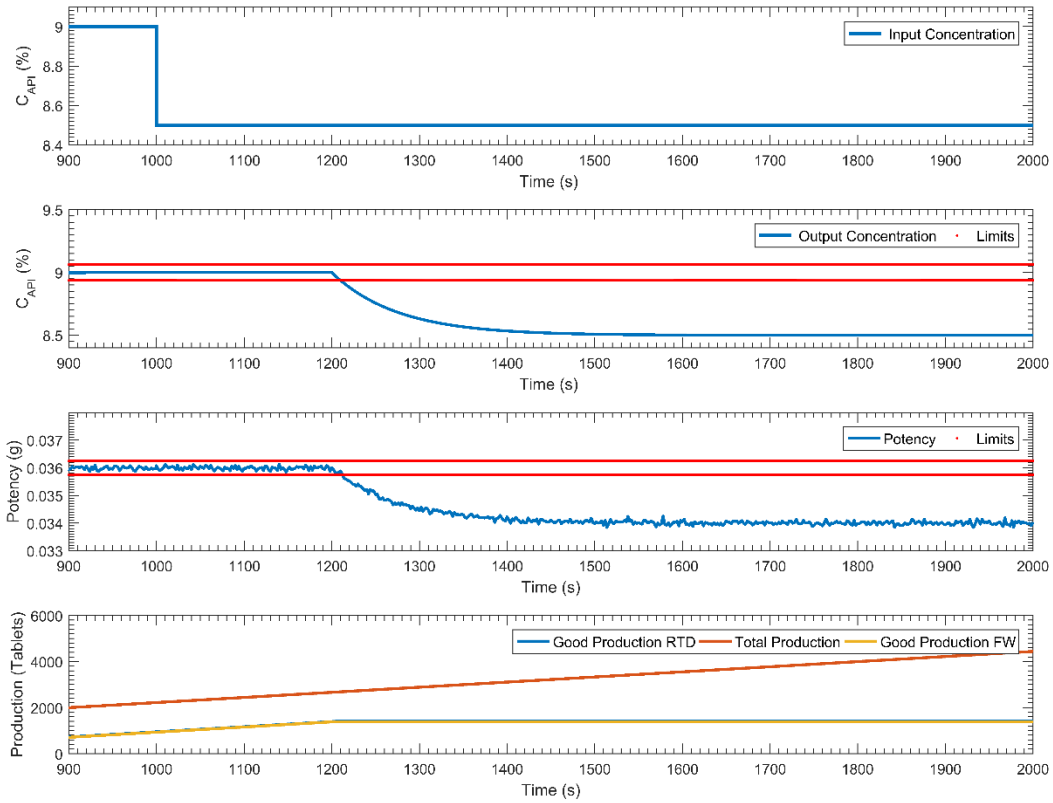


Figure 4.9. Step disturbance (a) Step up (b) Step down

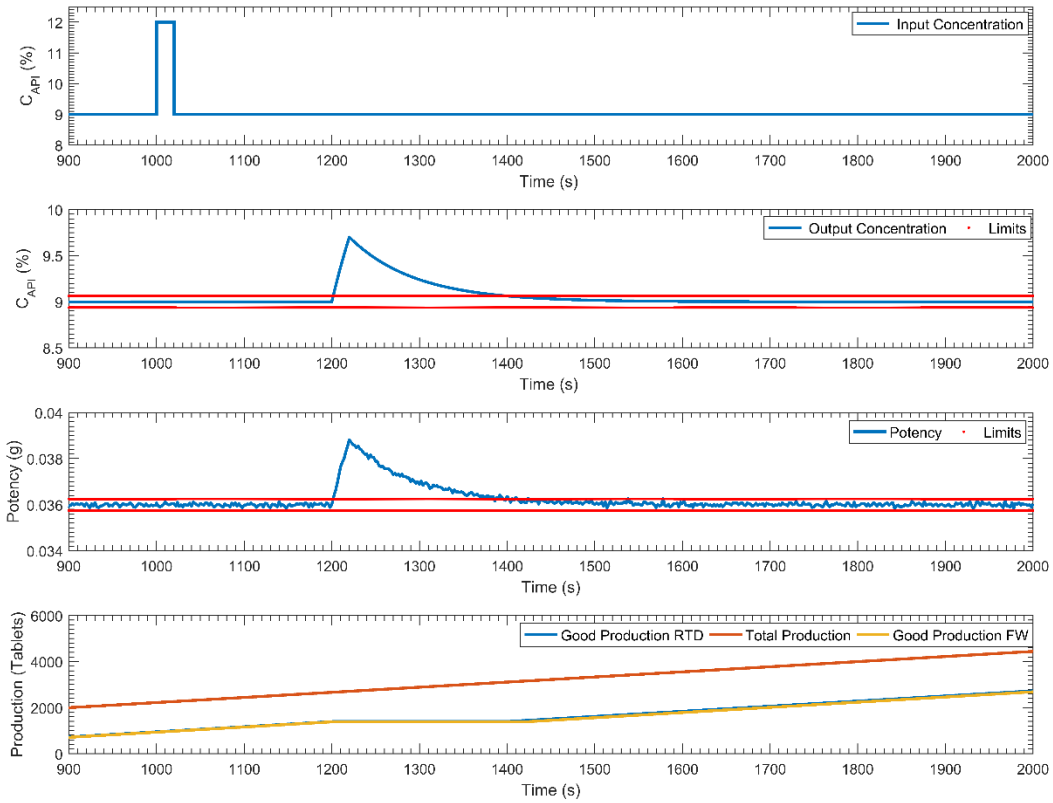
4.6.3 Evaluation of RTD based diversion system for rejecting short step change disturbances

In some situations, compacted and badly mixed API can result in disturbances that may last more than a few seconds and subside once the material passes. This has been simulated in Figure 4.10 with two magnitudes. The degree to which powder is compacted can result in a high or low magnitude disturbance.

4.6.3.1 Case study 5: Diversion of more potent tablets caused by short positive step disturbances

In Figure 4.10 (a), the disturbance is of a higher magnitude and lasts twenty seconds. The output concentration response and potency as predicted is shown and this exceed the tolerance. The result of this is a diversion as seen in the plot. The Fixed window approach and the RTD based approach provide very similar results in this case but the latter provides a one percent improvement.

In Figure 4.10 (b), the disturbance lasts for twenty seconds as well but the magnitude is much lesser. The concentration and potency exceed the toleration limits and the subsequently the diversion begins in both the RTD based approach and the Fixed window based approach. In this case the decreased magnitude of the disturbance results in the improved performance of the RTD based approach.


Input Concentration
C_{API} (%)
Time (s)
Output Concentration
Limits
C_{API} (%)
Time (s)
Potency
Limits
Potency (g)
Time (s)
Good Production RTD
Total Production
Good Production FW
Production (Tablets)
Time (s)

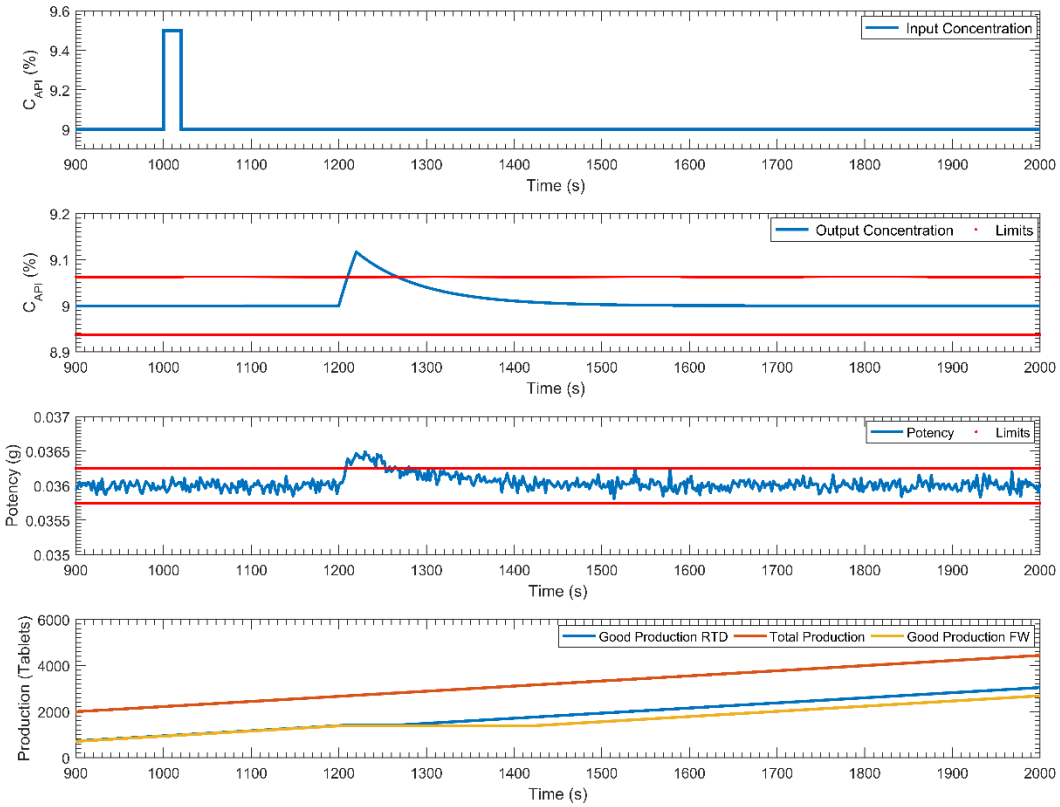
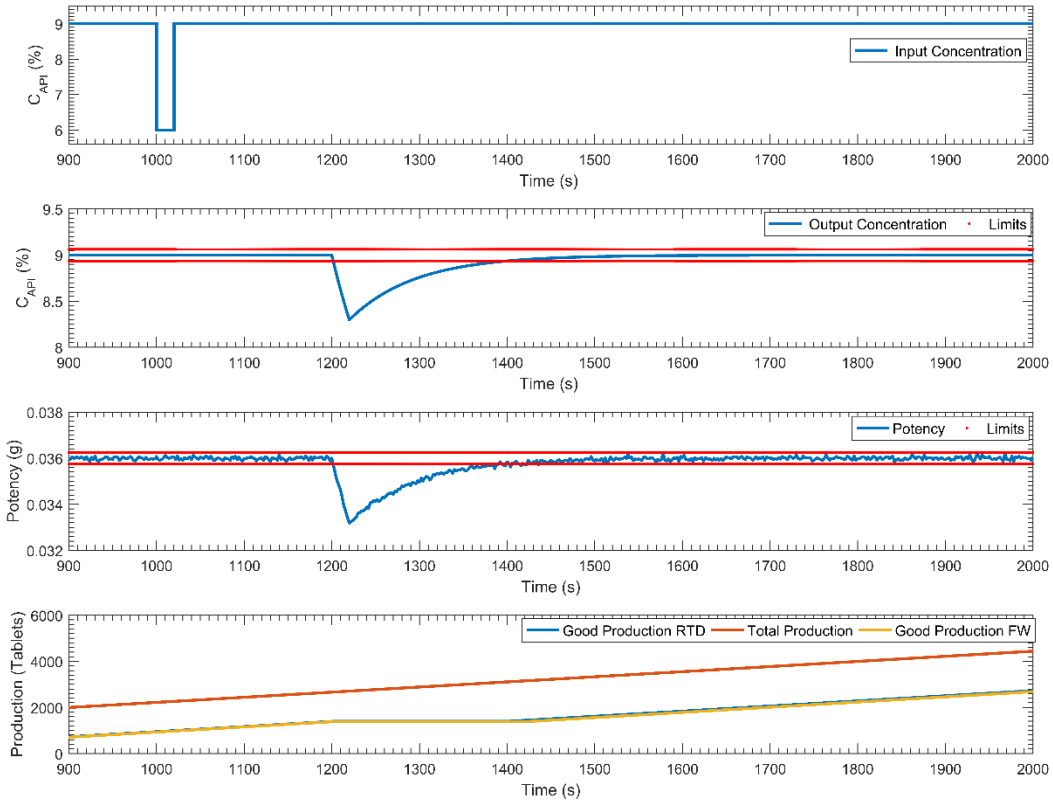


Figure 4.10. Short positive offset in concentration (a) High magnitude (b) Low magnitude

4.6.3.2 Case study 5: Diversion of less potent tablets caused by short negative step disturbances

In Figure 4.11 (a), the disturbance is in the negative direction and lasts twenty seconds. The output concentration response and potency as predicted is shown and this exceeds the tolerance. The result of this is a diversion as seen in the plot. The Fixed window approach and the RTD based approach provide very similar results in this case but the latter provides a one percent improvement.

In Figure 4.11 (b), the negative disturbance is of a smaller magnitude but lasts for twenty seconds as well. The concentration and potency exceed the toleration limits and the subsequently the diversion begins in both the RTD based approach and the Fixed window based approach. In this case the decreased magnitude of the disturbance results in the improved performance of the RTD based approach.



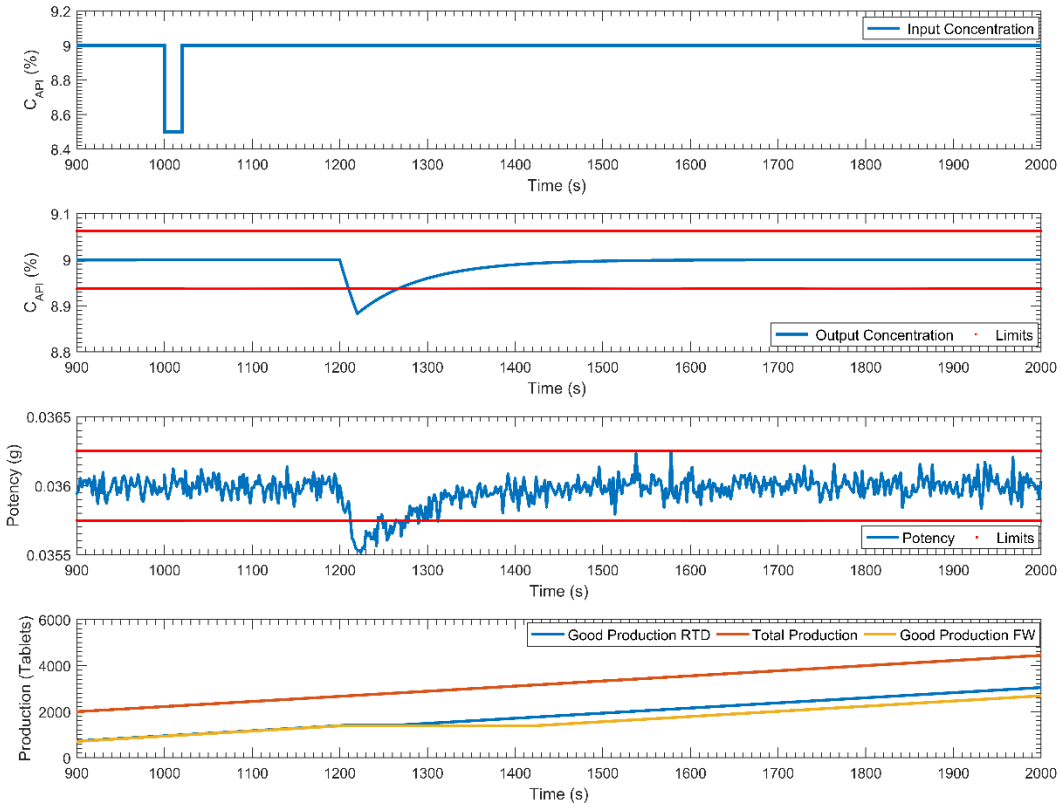


Figure 4.11. Short negative offset in concentration (a) High magnitude (b) Low magnitude

4.6.4 Evaluation of RTD based diversion for rejecting random disturbances

In the pharmaceutical industry, real time concentration is measured using NIR, RAMAN and other spectroscopic devices. These devices rely on the collection of spectra inline and PAT models for their concentration prediction. It is possible that for short periods of time there is a high fluctuation in the inlet concentration. Even if the powder is uniformly mixed it is possible that the concentration varies continuously in magnitude around a certain mean. Such a signal has been simulated in Figure 4.12. Here the input concentration fluctuates constantly and violates the boundaries. In such a situation, since the fixed window approach is dependent on the input signal

it would initiate diversion. Since there is a violation of the boundaries at multiple time points there would subsequently be more diversions initiated. This would detrimentally effect manufacturing efficiency since all tablets rejected during this period as seen from the calculated output concentration are within the allowed limits almost throughout the entire timespan of simulation except at the one hundred and sixtieth second. This means that there would be unnecessary diversion by the Fixed Window strategy. On the other hand, the RTD based diversion strategy would reject tablets only during the brief period that there is a violation.

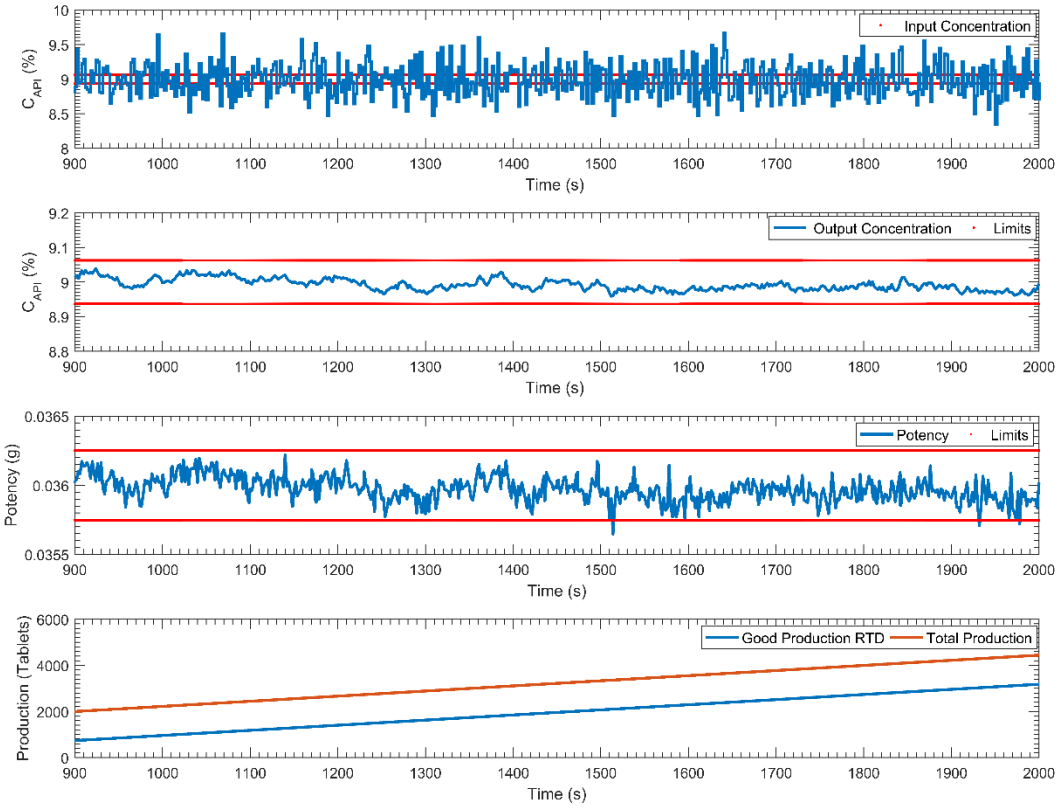


Figure 4. 12. RTD based diversion simulated for a noisy input concentration data.

4.6.5 Performance assessment of RTD based diversion for different processes

The proposed RTD based diversion system is process dependent and must be re-tuned for different processes. In this section, the RTD based diversion strategy has been evaluated for different processes. The different processes have been simulated via varying number of tanks in the tank in series model with a plug flow reactor to simulate the delay in the response. The justification for this consideration is to show that the prediction of the outlet concentration can be drastically different in different systems and the performance may vary based on the system. In Figure 4.13, the outlet concentration has been plotted for 1,5,10 and 15 tanks. With an increase in the number of tanks the spread of the response widens and the effect of the disturbance persists in the system for much longer. Subsequently, the diversion times increase with the number of tanks.

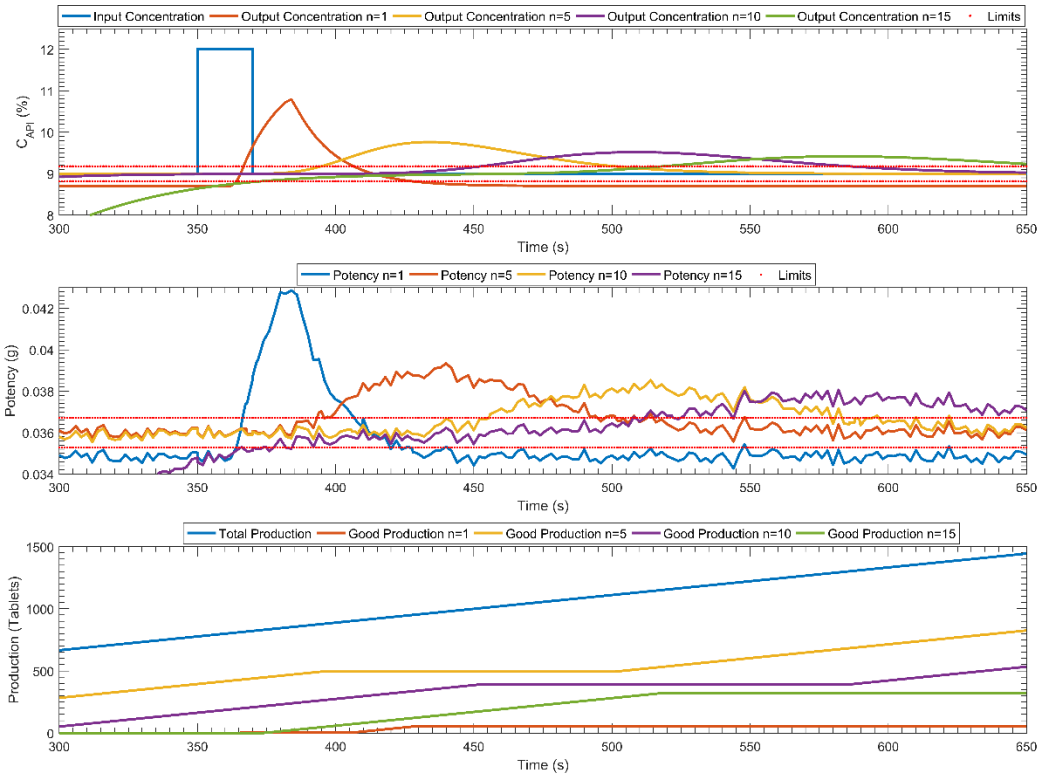


Figure 4. 13. Performance assessment of RTD based diversion with different RTD models.

Table 4.1. Manufacturing efficiencies of Case studies 1-5

Scenario		Magnitude	Manufacturing Efficiency, ε (%)	
			RTD	**Fixed Window**
Pulse Disturbances	Case Study 1	High	94.6667	87.1667
		Low	100	87.1667
	Case Study 2	High	94.6667	87.1667
		Low	100	87.1667
Step Disturbances	Case Study 3	NA	71	69
	Case Study 4	NA	71	69
Short Step disturbances	Case Study 5	High	72	71
		Low	79	71
	Case Study 6	High	72	71
		Low	79	71

4.6.6 Discussions:

In this work an RTD based diversion system was designed, developed and implemented in silico. This methodology was compared to an alternative fixed window methodology. In the fixed window methodology, process time delays are applied to determine diversion periods while in the RTD based strategy the predicted outlet concentration determines the diversion window. From the results, it was observed that the RTD based approach is always better than the fixed window approach. This is reinforced by the manufacturing efficiency in Table 1, which was used as a metric to quantify the improvement. The magnitude of improvement changes depending on factors such as the magnitude and type of disturbance. If the system exhibits long step like disturbances, then either the Fixed Window approach or the RTD based approach can be used. From Table 4.1, one could also draw the conclusion that the RTD based diversion system performs best when the disturbance is a short pulse. In this work, the developed system's application is directed mainly towards continuous pharmaceutical manufacturing processes where it can facilitate more efficiency in production. This however, does not restrict its use to a Direct Compaction Continuous Pharmaceutical line. It can be adapted and used in any continuous processes.

Chapter 5: Integrated scheduled optimization and model predictive control implementation into continuous direct compaction line

Acknowledgements:

This chapter is based on the work done in collaboration with Rahul Ramakrishnan, the MS student from same research group of Dr. Singh*, Department of Chemical and Biochemical Engineering, Rutgers University, NJ, USA. The work has been built upon the previous research, optimization methods and tools developed by Singh et al. (2015). The contribution and supports of Rahul and Dr. Singh are acknowledged.

*Correspondence (Email: ravendra.singh@rutgers.edu)

5.1 Materials and methods

The pilot plant has been described in Section 2.1.1 of the background. The compaction process is described in detail in Section 2.1. The moving horizon based real time optimization (MH-RTO) method for continuous pharmaceutical manufacturing processes has been taken from Singh, Sen, et al. (2015). The experiments were conducted using a blend of 90% lactose 310 (excipient), 9% acetaminophen (API) and 1% magnesium stearate (lubricant). The API, excipient, and lubricant were pre-blended using a batch v blender for 30 minutes at 25 RPM. A rotary tablet press (Fette 1200) was used for the compaction process. Tablet press parameters were monitored and controlled using DeltaV (Emerson) in combination with Matlab through OPC connection. The punches used in the tablet press were 12 mm and circular in shape.

5.2 Hardware and software integration

Communication was established between Matlab, the control platform and the actual tablet press. This was achieved through the local area network through OPC protocol. The connection between the tablet press and DeltaV has been explained in detail in Chapter 3 under Section 3.3.

The connection between DeltaV, Matlab and the tablet press that was used for the optimization has been explained further in this section.

There are essentially three units involved in this integration – the matlab work station, the Delta V work station and the tablet press. Each of these houses an OPC server. Communication between these units is facilitated by the local area network and further managed by an OPC client [Kepware]. Figure 3.1 can further illustrate this. On each of the servers, it is possible to setup tags on kepware that project data outgoing from an OPC enabled software into the server. DeltaV and Matlab are both OPC enabled software and kepware is used to setup these tags. On one of the work stations, an advanced tag is setup to tube the tags together. Essentially, the tags on the OPC servers are interconnected to enable desired communication. In this case, the advanced tags are setup on the DeltaV work station. This integration has been schematically represented in Figure 5.1. It is further assisted by Figure 3.1.

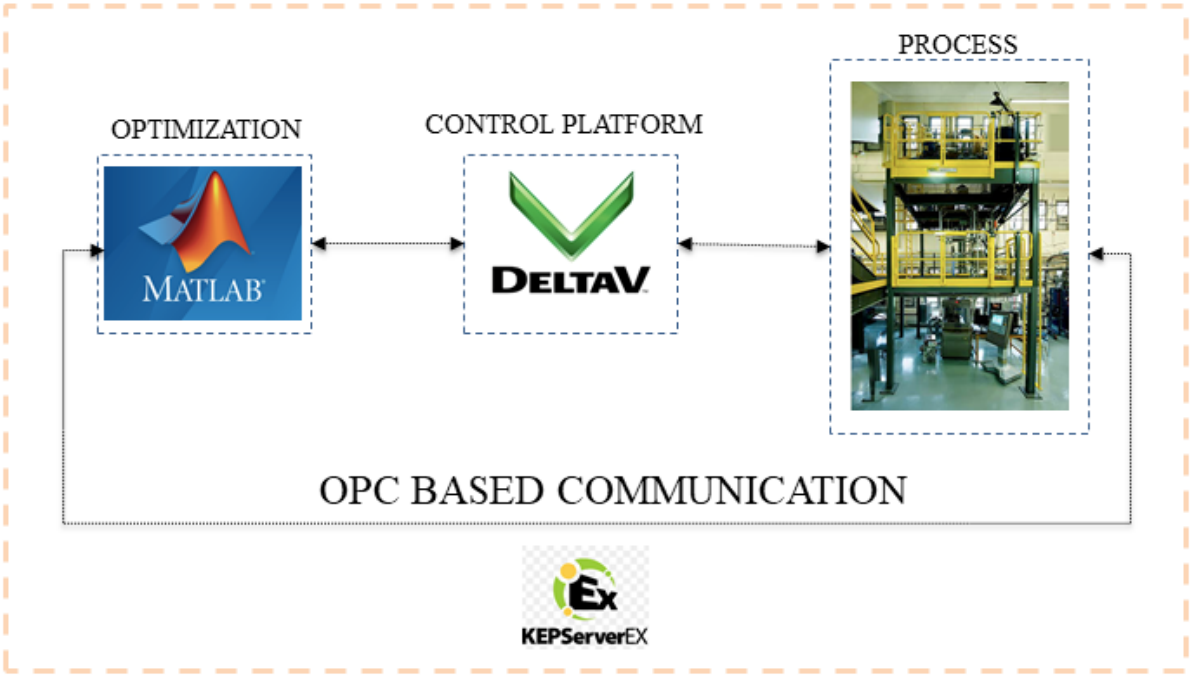


Figure 5. 1. Hardware and software integration

5.3 Integrated Moving horizon based optimization and model predictive controller implementation.

An ideal moving horizon based optimization consists of an optimization algorithm that uses process information along with external inputs to maximize profit through a set of calculations. (Singh et *al*., 2015). It would ideally receive two inputs, the current and past production rates as a trajectory and demand for the product. Based on this, with the motivation of maximizing profit, the optimization predicts a trajectory for the production rate for a predefined future interval. The first point from this is applied to the plant. It is assumed that control for the plant has already been developed and is being supervised by model predictive control. The controller receives updated set points for the production rate and based on this keeps the process parameters in check for optimal tablet production.

The implementation of the optimization in this case does not involve a prediction of future trajectories or take into account past data. It seeks to investigate potential challenges that may arise in using such a strategy from the perspective of the continuous direct compaction manufacturing line. Following assumptions and considerations have been made for the implementation:

1. It is assumed that the demand changes periodically and this change in demand update takes into account prior deficiencies or excesses.
2. The control of main compression force is a reflection of the control of tablet breaking force.
3. Only slave control loop was enable while running in optimization mode.
4. Tablet concentration control at the feeder level is assumed to be efficient based on ratio control.
5. It is assumed that the controller performs optimally within a given production rate range such that the production under control meets demand. Although this assumption is made, this point is further investigated and potential advantages and disadvantages of this assumption are explored.

This simplified optimization algorithm that was developed based on these assumptions has been termed scheduled optimization. The implementation strategy has been elaborated in the next section.

5.3.1 Scheduled Optimization

An optimization algorithm was adapted from a previous paper (Singh et *al*. 2015). This was simplified for implementation into the direct compaction tablet manufacturing pilot plant. Following were the main modifications to the previously published work:

1. The inputs to the objective function are the demand which is a user input and the rejection fraction which can be a variable that is derived from the tablet press or operator provided based on the method of implementation.
2. The demand is provided per optimization run in another file that calls the optimization. The optimization runs the Matlab inbuilt 'Fminbnd' on the objective function to output a production rate (Forsythe et *al*. 1977). The production rate is written to DeltaV before which it is relayed to the tablet press.

5.3.2 Disturbance handling main compression force model predictive controller

A model predictive controller was developed with the motivation of keeping process parameters constrained during the optimization. This has been schematically shown in Figure 5.2.

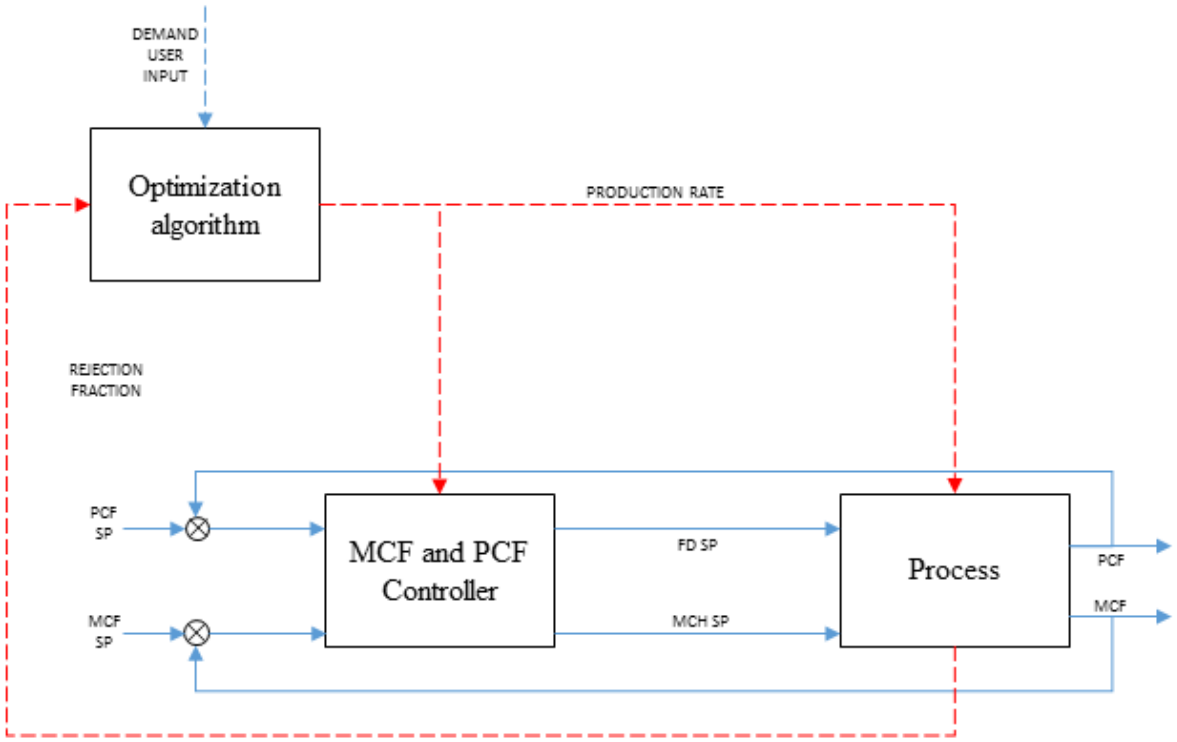


Figure 5.2. Schematic representation of Model predictive control strategy with disturbance handling capacity and supervisory optimization.

As can be seen, the manipulated variables are the main compression height (MCH) and the fill depth (FD). This pairing was chosen based on the Sensitivity analysis presented in Section 3.7 of Chapter 3. Although, schematically presented, only the main compression force controller was implemented for the sake of simplicity. As seen in the Figure 5.2, the production rate was fed to the MPC as a disturbance. The set point of the production rate is set by the optimization; the actual value of the production rate is used as a disturbance variable in the MPC. This was done to take into account the effect the production rate has on the correlation between main compression force and main compression height.

5.4 Results and discussion

This results and discussion section has been generated based on the implementation of a series of scenarios. The first of these scenarios was the implementation of the optimization without a controller and rejection considerations. In this case, there was no controller that would control the critical process parameters and it was assumed that all production was good. This was done to expose the potential gains of having a controller in place and also some open loop characteristics of the compaction process.

The second of these scenarios was the implementation of the optimization with an approximated methodology for taking into account rejection in real time. This methodology is further elaborated in the section 5.4.2. This scenario is justified as one could make the argument that a switch type control can be put in place to reject material as and when it is out of spec. This further seeks to make evident the need for a complex control system.

Post this, the controller is developed and run in combination with the optimization. Two actuator candidates are evident for the SISO MPC. One is the filling depth and the other is the main compression height. From the understanding of the mechanical working of the tablet press, one can make the statement that for a change in production rate, the rate at which the powder is filled into the dies would be affected. To mitigate this, one would need to feedback information about the die filling efficiency and manipulate fill depth accordingly. But in the situation that the die is filled inefficiently, both hardness and the weight would be impacted. Therefore, this would reflect on the main compression force. So it can be justified that maintaining the main compression force through manipulation of the fill depth can possibly control both hardness and weight. Considering this, it was a scenario that was implemented.

Another more tested possibility is that the main compression force can be controlled through manipulations in main compression height. This assures tablet breaking force control. It however, don't control the weight of the tablet. To control the weight, the MPC would have to be expanded to the 2x2 strategy with disturbance as presented in Figure 5.2. The implementation of this presents complexities in developing the model that is required to run the MPC strategy. For simplicity sake, this work has not been pursued. This would however be a future direction to pursue so as to build on this work. In this work, the MPC controlling hardness through manipulations of main compression height is however implemented.

Following are the scenarios as described above.

5.4.1 Scheduled optimization without controller and rejection considerations

The product demand was varied from 8,000 tablets/h to 15,000 tablets/h and from 15,000 tablets/h to 25,000 tablets/h and so on as shown in Figure 5.3. Step changes were introduced in the demand. At each step change, the optimization was run, and this produced new set point values for the production rate. This set point was sent to DeltaV and then to the tablet press. Four such optimization cycles are observed as shown in Figure 5.3.

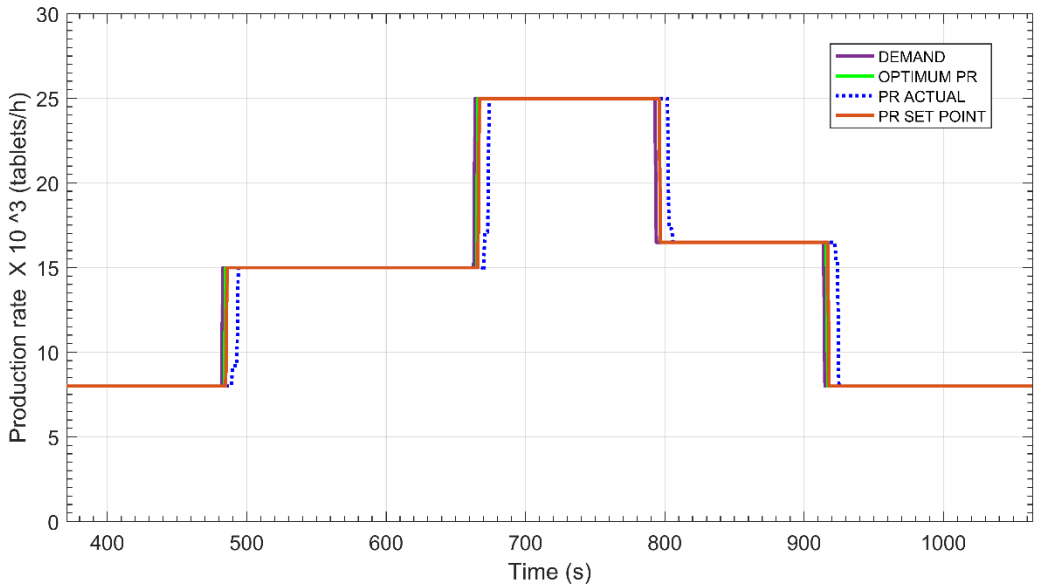


Figure 5. 3. Real time optimization of demand.

Due to operation within the optimizer limits, an assumed lack of rejection in product, the optimized production rate follows the path of the demand. As the production rate increased the main compression force (MCF) and the pre-compression force (PCF) decreased. This is seen in Figure 5.4. The MCF which was the variable of importance has a set point of 2.7 which was decided from previous experiments. A 10 % tolerance limit is provided. It can be seen that post the changes in production rate, the main compression force and pre compression force follow a similar decreasing trend. This can be attributed to bad die fill efficiency due to faster turret rotation and same feed frame speed a lower dwell time because the lower compression time.

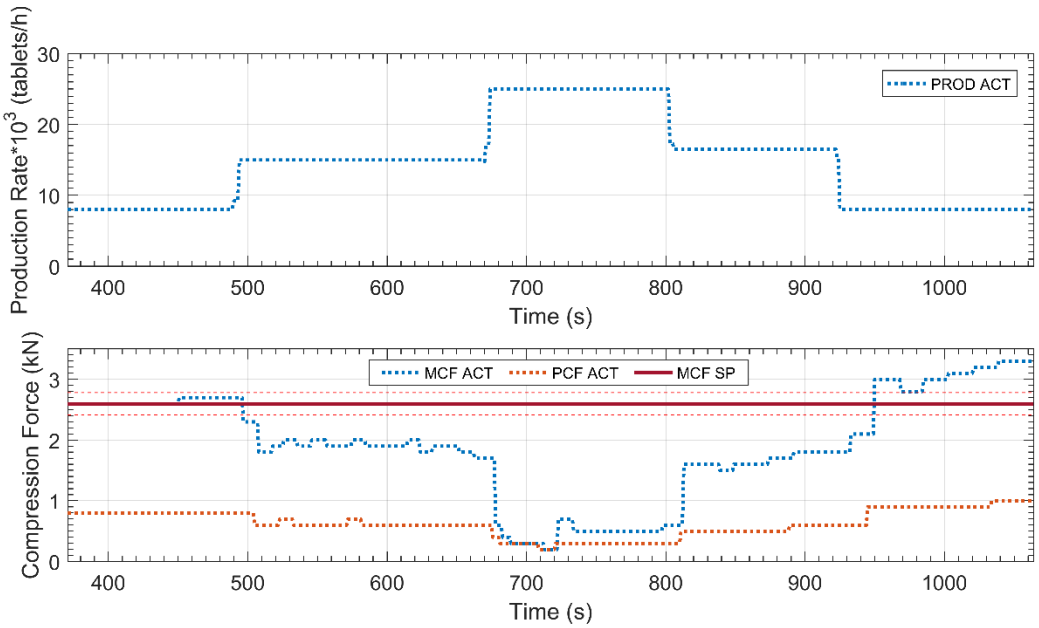


Figure 5.4. Real time optimization of direct compaction line without a controller and rejection considerations.

5.4.2 Scheduled optimization without control and approximated rejection considerations

The rejection fraction in this scenario has been defined based on the main compression force values that are received from the tablet press. There is currently no data available to build a model that relates main compression force to a metric that determines rejection fraction. In this work, a DeltaV calculation block allotted a rejection fraction based on the current value of main compression force. The main compression force range and assumed rejection fraction is given in Table 5.1

Table 5.1. Rejection fraction

Main Compression force (kN) Range	Rejection fraction (units)
MCF>3.2	0.01
2=>MCF=>3.2	0.1
1=>MCF=>2	0.3
MCF<1	0.6

As seen in Figure 5.5, the demand was changed from an initial 8000 tablets per hour to 15000 tablets per hour. The main compression force during this run remains above 3.2 kN and therefore does not cause a change in the rejection fraction. The demand is then further increased from 15,000 to 17,500 tablets per hour. The MCF decreases further and now is lesser than 3.2 causing the rejection fraction to rise 0.11. A feedback of this into the optimization and a rerun generates an increased production rate of 17,700 tablets/h. Due to the increase in production rate again, there is a further decrease in MCF resulting in the increase in rejection fraction to 0.3. This causes the production rate to rise and the take the value of 19,700 tablets/h. Due to further increase in production rate, the MCF decreased and the rejection fraction increased to 0.6 and caused the production rate to jump to 25,000 tablets/h. At this stage, from visual inspection the tablet press was not producing tablets but shooting out uncompressed powder.

At this stage the demand is reduced to 8,000 tablets/h. Due to this, the production rate decreases from 25,000 to 20,000 tablets per hour. An increase in MCF causes a lowering of the rejection fraction to 0.3 resulting in a lower value of production rate (11,400 tablets per hour). A further lowering of the rejection fraction (0.3 to 0.01) is caused due to the increase in the main compression force. One can see from this that in an open loop state, the system with rejection

consideration enters a region of instability at higher demand values. Due to the manually run methodology used here, the system was brought back to stable operating conditions. A continuous real time system however would have led to high production rates and very low MCF values. At this juncture the need for an MCF controller is evident. Thus it has to be fixed which can be done by controlling the MCF.

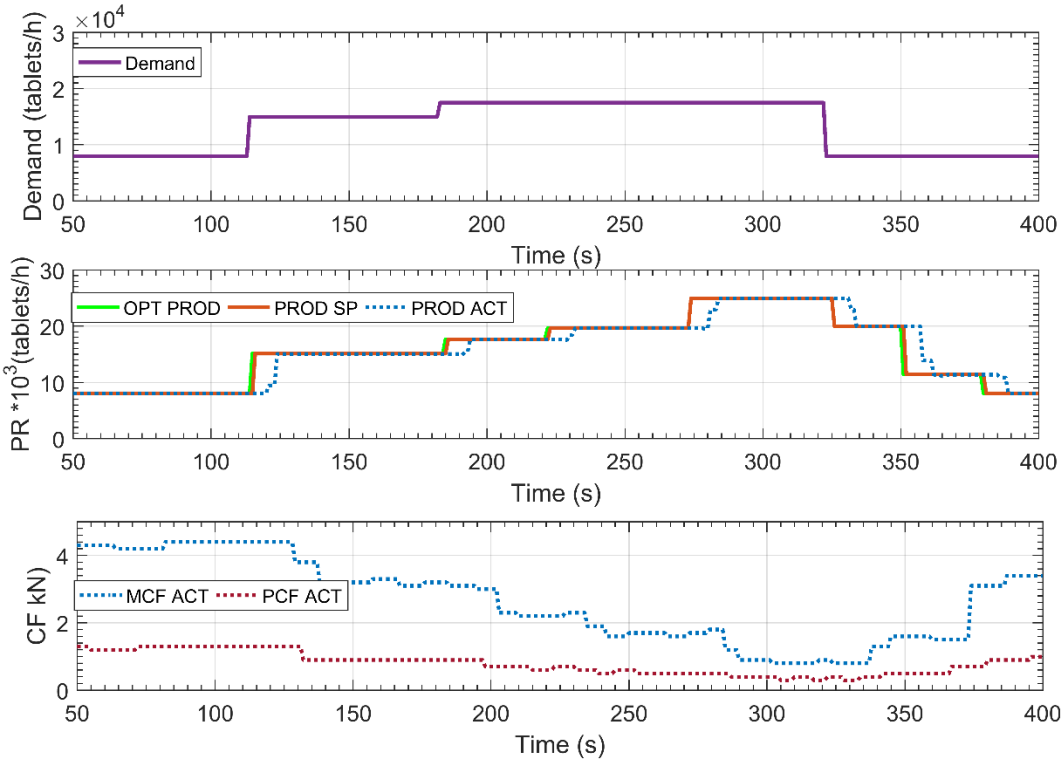


Figure 5.5. Real time optimization of direct compaction line with rejection considerations and without a controller.

5.4.3 Closed loop performance of disturbance handling MPC

5.4.3.1 Fill Depth actuator based controller performance

The development of an MPC follows the same procedure as followed in Chapter 3. Step changes are applied to develop an MPC model. This model is then used in building a controller.

Figure 5.6 shows the open loop step changes that were made. The production rate is varied along with the fill depth and the changes in MCF are observed. The production rate set point was first changed from 8,000 to 25,000 tablets per hour. The actual production rate followed the path of the set point. It is noticed here that the optimization was not considered during this experiment. A decrease in the MCF is noted. Next, the fill depth set point was changed from 5.5 mm to 6.5 mm and the actual fill depth value followed the set point. This change in fill depth caused an increase in MCF. Following this, production rate set point was reduced back to 8,000 tablets per hour which increased the MCF to 13.3 mm. Then the fill depth set point was changed to 4.5 mm. Further step changes were introduced. From these step changes, a model for the model predictive controller (MPC) was developed.

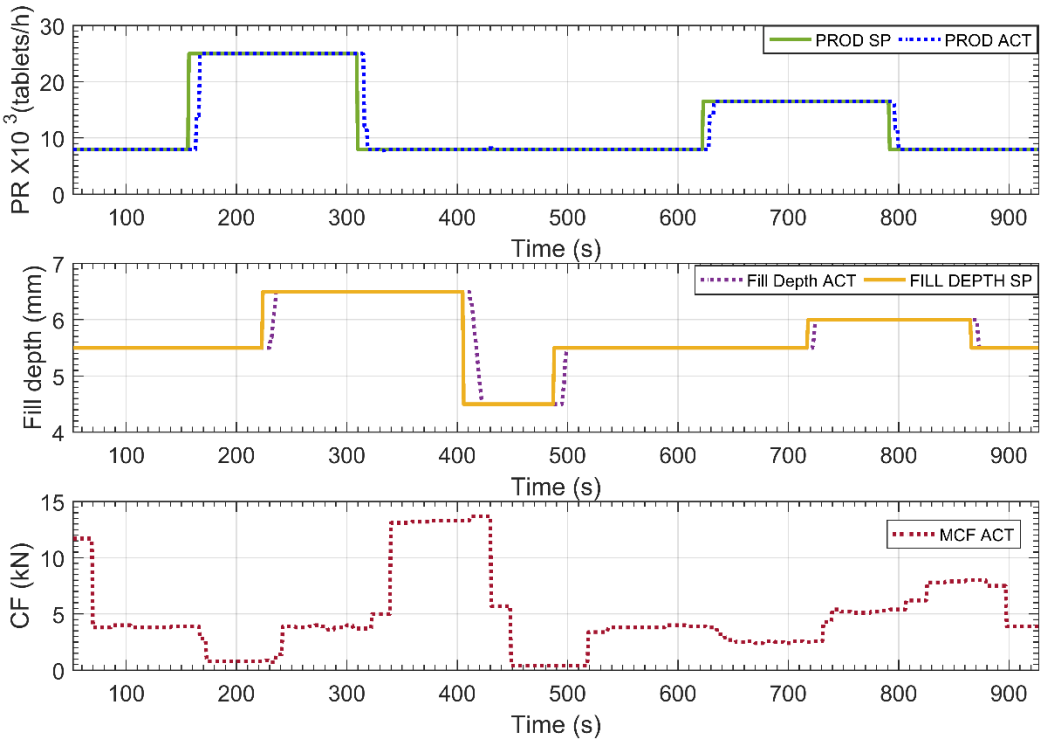


Figure 5.6. Main compression force open loop response for MPC model development with step changes in production rate and fill depth.

Post controller development, two tests were conducted. A set point tracking test and a disturbance rejection test.

In the case of set point tracking the set point for MCF was changed from 3.6 mm to 4.8 mm. As seen in Figure 5.7, manipulations in the fill depth bring the MCF to its set point. Some oscillations are observed. The set point was then changed back to 3.6 mm. The fill depth was further manipulated accordingly to achieve the MCF set point.

The disturbance rejection test was conducted in the same run. For this the production rate set point was changed from 8,000 to 16,500 tablets per hour, which caused the MCF to drop. It is

seen from figure 5.7 that the MPC increased the fill depth set point to control the MCF but oscillations started to appear. The oscillations increased with time and thus the production rate set point was brought back to 8,000 tablets/h. This was done to prevent the tablet press from breaking down to high values of MCF. Post the return to 8000 tablets per hour the main compression force stabilizes. This result shows that the controller is unstable at higher production rates. This can be attributed to high sensitivity of changes in the fill depth to the main compression force at higher production rates, inability for the model to capture the dynamics correctly and a lack of further process understanding at this operating regime.

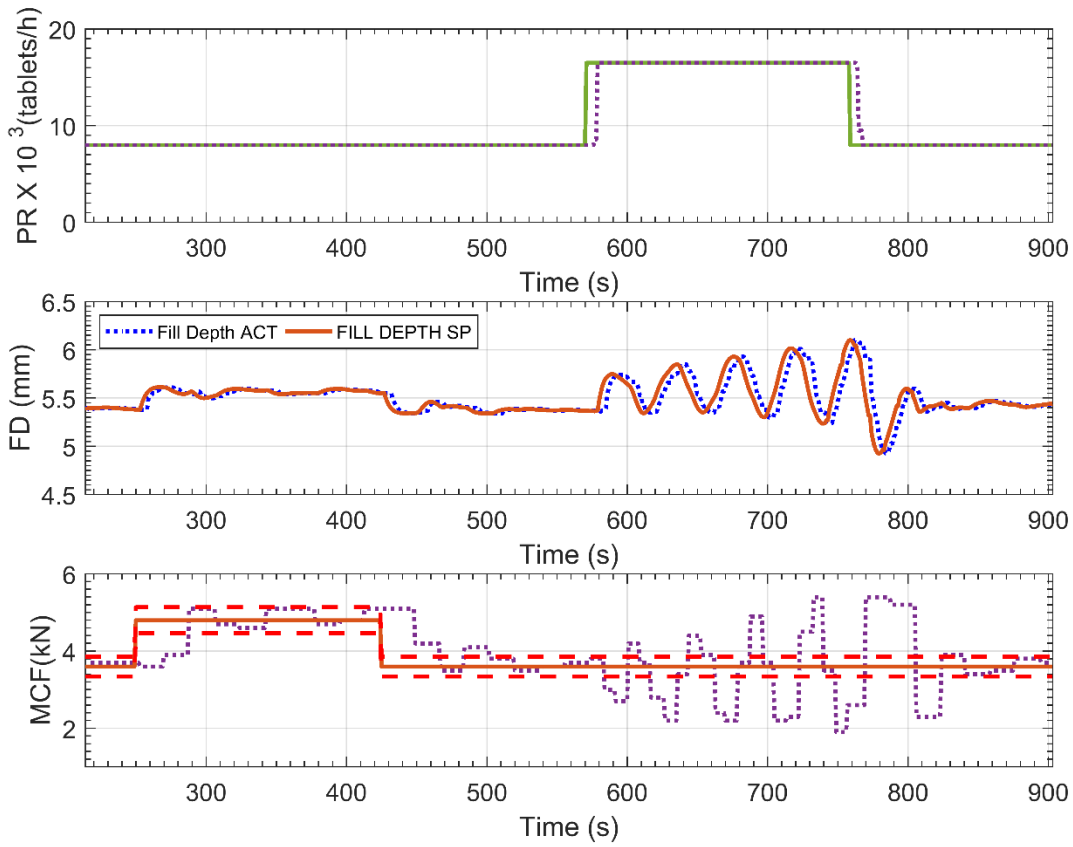


Figure 5.7. *Closed loop response for MPC to control main compression force using fill depth.*

5.4.3.2 Main Compression height based controller performance

The controller with main compression height as the actuator is the second of the two alternatives that was tested. Like before, the model is developed and tested.

For the open loop step test, the MCH set point was first changed from 3 mm to 3.25 mm. this caused the MCF to decrease. Following this, the production rate was changed from 8,000 to 25,000 tablets per hour. The MCF is observed to decrease to 0.9 kN. The MCH was changed to 2.9 mm and then to 3.25. The production rate was then increased to 16,500 tablets per hour. The MCF changes were noted. Later, the MCH set point was brought down to 2.5 mm and then to 3.4 mm and back to 3.25 mm. After which the production rate set point was changed back to 8,000 tablets/h. Here its seen that the main compression force (control variable) is inversely proportional to main compression height (actuator) as well as production rate (measurable disturbance to the control loop). This data was used for the controller model development.

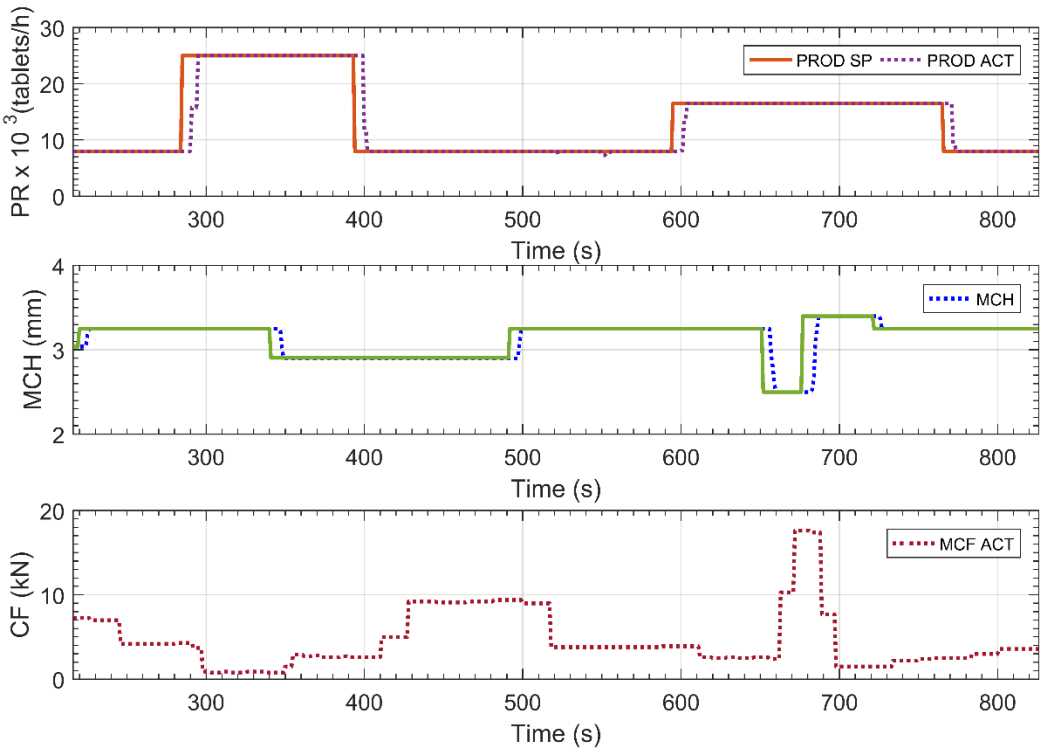


Figure 5.8. Main compression force open loop response for MPC model development with step changes in production rate and main compression height. (CF-Compression Force, MCH – Main Compression Height, PR – Production rate)

The developed model is used to implement closed loop MPC based control as shown in Figure 5.9. Set point tracking and disturbance rejection tests were conducted to test efficiency of the controller.

For set point tracking, the MCF set point was changed from 3.6 mm to 4.4 mm. As seen in Figure 5.10, MCH is manipulated accordingly to bring the set point of MCF to its target. The MCF set point, post stable operation, was then brought back to 3.6 mm. The MCH was manipulated efficiently to bring the MCF back to target.

For the disturbance rejection, the production rate was changed from 8,000 to 16,500 tablets per hour post set point tracking stable operation. The increase in production rate as seen in Figure 5.8 causes the MCF to decrease. The MPC rejects this disturbance through appropriate manipulations in MCH. Post this; the production rate was increased to 25,000 tablets per hour. The set point of MCF is maintained post a short spike in its value. This was also observed when the production rate set point was changed back to 8,000 tablets/h where the MPC increased the MCH set point so that the MCF can follow is set point. Thus, the MCF was controlled with the MCH set as manipulating variable and production rate as the disturbance. Some performance metrics for this were calculated and have been presented in Table 5.2

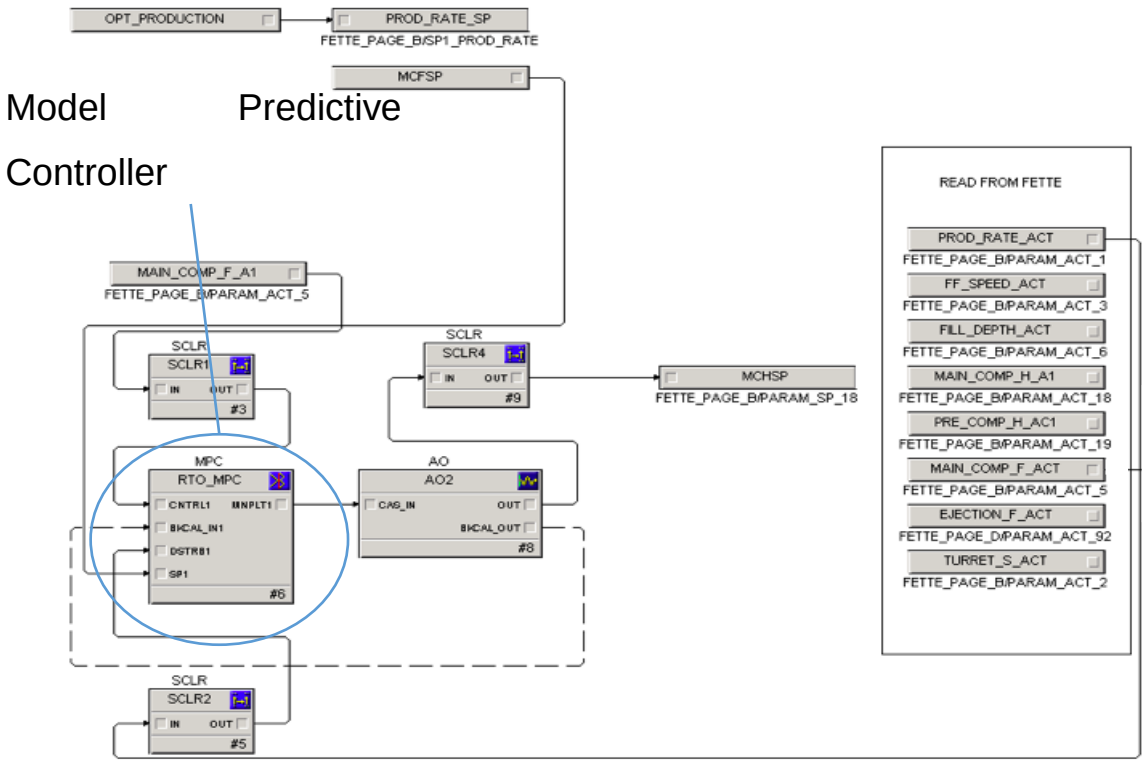


Figure 5.9. Main compression force MPC implementation.

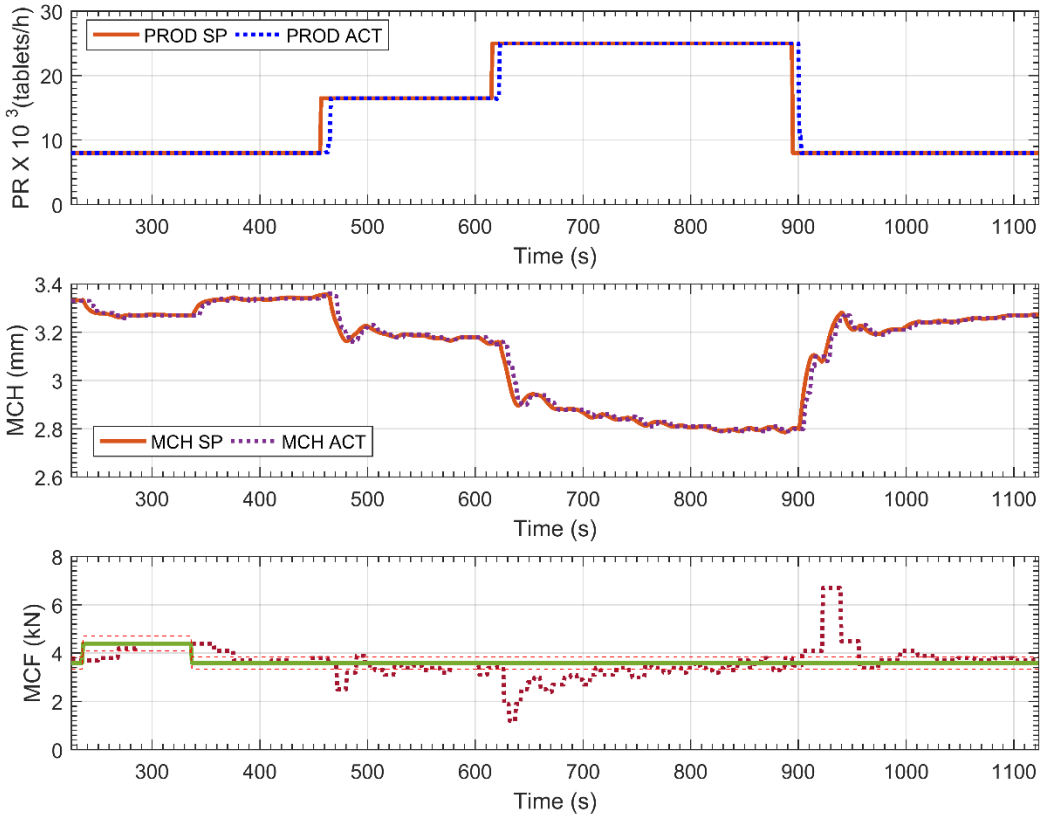


Figure 5.10. Closed loop response for MPC to control main compression force using main compression height.

Table 5.2. Performance metrics for MCH based MCF controller

ITAE	IAE	ISE	Rise time	Settling time	Over shoot
6893.65	87.65	75.205	99	120	1.75

5.4.3.3 Time to steady-state based rejection

Given that to some extent main compression force is controllable within the defined production rate, an observation from the closed loop tests revels a consistent two minutes time to steady post appearance of a production rate disturbance. Traditionally, main compression force violations are

used to reject tablets. If time to steady state is considered to be consistent within the optimization range, then tablets should be rejected for the time period that the process is unsteady. Therefore, this time period can be used to fractionalize the rejection per run if the total run time is known. It was predefined that the demand would be varied every seven minutes. Therefore, if there is rejection during the first two minutes, then the rejection fraction for that time period is 2/7. This numeric value is used in further experimentation to account for rejection.

5.4.4 Integrated Scheduled optimization and MPC implementation

Having developed controllers, the optimization is now retested with the system in closed loop. The demand was provided every seven minutes. Subsequently, the optimization was run every time the demand was changed. The rejection fraction is now a numerical value in the optimization. The demand of 5,750 tablets per hour was initially provided in Matlab, the optimization ran to give a production rate set point of 8,100 tablets per hour. Then the demand was changed to 10,000 tablets per hour and the optimization was run to give a production rate set point of 14,000 tablets per hour to DeltaV. The production rate changed with respect to its set point. This caused the MCF to change and hence the MPC controlled the MCF through manipulations in MCH. Then the demand was changed to 15,000 tablets/h and the optimization gave 21,000 tablets/h. Similarly, the demand was changed to 8,000 tablets/h then to 5,000 tablets/h and then to 20,000 tablets/h with a 7 min gap between each other. Thus, caused the production rate to change 11,200 tablets/h then to 18,430 tablets/h and then to 25,000 tablets/h respectively. Form the figure 13, its seen that the MPC controlled the MCF for all these step changes. Thus the real time optimization with MPC was implemented.

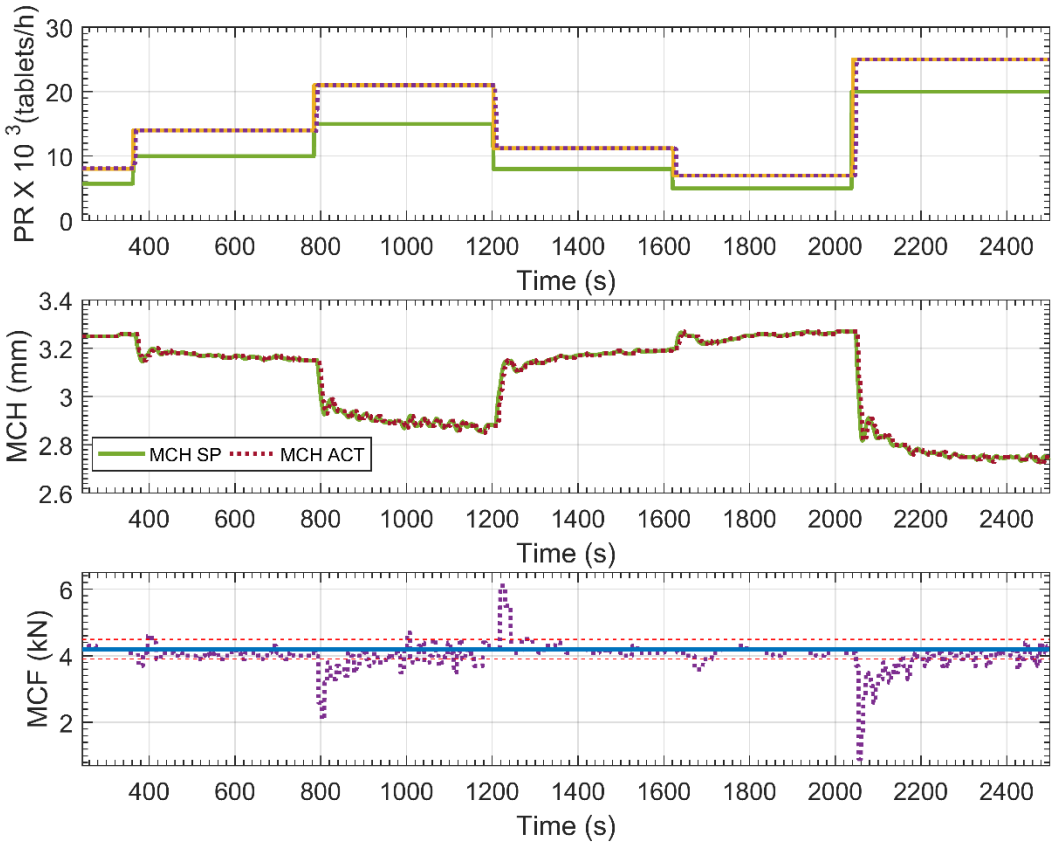


Figure 5. 11. Real time optimization of direct compaction line with MPC.

Figure 14 show demand vs production vs good tablets for the demand changes made above. The upper bound considered here for production rate was 25,000 tablets/h and so the good tablets didn't meet the demand for the final case.

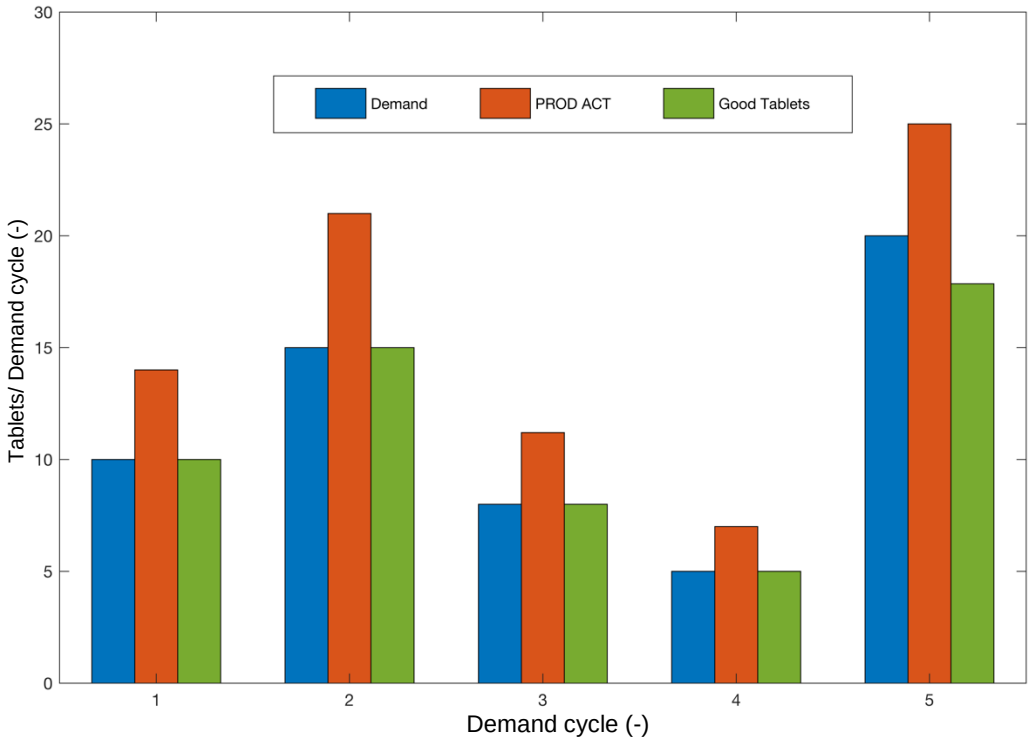


Figure 5.12. Performance evaluation of real time optimization and MPC controller**.**

Chapter 6: Conclusions and Future perspectives

This chapter has been written in accordance with the objectives for the thesis. Each objective has been concluded and a future path has been set. The scientific literature review to identify the gaps in the state of arts along with the background required has been systematically presented as seen in Chapters 1-2.

As seen in Chapter 3, multiple control strategies were presented for the direct/indirect control of tablet weight and hardness. A MIMO cascade MPC based strategy was proposed for tablet press. A 2X2 MPC was implemented for simultaneous control of pre and main compression forces and thereby indirect control of tablet weight and hardness. A master loop has been also implemented using a novel real time tablet weight measurement method for direct control of tablet weight. Results show that tablet weight was controlled in real time and a cascade controller as elaborated on can be considered as a potential CQA controlling methodology. It is important to note that the master hardness control loop is currently not possible to implement because of unavailability of real time measurement sensor of tablet hardness and it could be a direction of future investigation. Also, drift in the density or the composition would not be taken into account. This segueways into an important aspect of this that has not been explored in this thesis, that is, the control of composition along with tablet weight and hardness. Numerous strategies have been postulated as seen in the introduction section but none have been implemented with an MPC in the system in real time and that could be a future research direction.

As presented in Chapter 4, an RTD based control system was designed, developed and implemented *Insilico*. This methodology was compared to an alternative fixed window methodology. In the fixed window methodology, process time delays are applied to determine diversion periods while in the RTD based strategy the predicted outlet concentration determines

the diversion window. From the results, it was observed that the RTD based approach is always better than the fixed window approach. In this work, the developed system's application is directed mainly towards continuous pharmaceutical manufacturing processes where it can facilitate more efficiency in production. This however, does not restrict its use to a Direct Compaction Continuous Pharmaceutical line. It can be adapted and used in any continuous processes. The future work includes the implementation of RTD based control strategy into our pilot-plant facility.

As described in Chapter 5, the implementation of an optimization algorithm in the continuous direct manufacturing line to produce tablets efficiently under varying demand changes was achieved with control over the main compression force that indirectly control tablet hardness. Some assumptions were made about this. This can be considered as a stepping stone in achieving a holistic control system with supervisory optimization. The author acknowledges the simplicity of the current solution. Future steps can take into account more variables from the Direct Compaction manufacturing process and expand the optimization space.

Nomenclature

Abbreviations	Variables
API	Active pharmaceutical ingredient
CSTR	Continuous stirred tank reactor
CQA	Critical quality attributes
NIR	Near infrared reflectance
PFR	Plugged flow reactor
PAT	Process analytical technology
RTRT	Real time release testing
RTD	Residence time distribution
AI	Analog Input
AO	Analog Output
API	Active Pharmaceutical Ingredient
CNTRL	Controlled Variable
CPP	Critical Process Parameter
IAE	Integral of Absolute Error
ISE	Integral of Square of Error
ITAE	Integral of Time Absolute Error
MgSt	Magnesium Stearate
MCF	Main Compression Force
MCH	Main Compression Height
MNPLT	Manipulated Variable
MPC	Model Predictive Control
OPC	OLE (Object linked and embedding) for process control)
PCF	Pre Compression Force
PCH	Pre Compression Height
PE	Penalty on Error
PID	Proportional Integral Derivative
PM	Penalty on Move
QbD	Quality by Design
QbT	Quality by Testing
SCLR	Scalar
SP	Set point
CF	Compression Force

Symbol	Variable	Units
C	Concentration	g/m^3
C(t)	Concentration at time t	(%)

E(t)	Residence time distribution function	s^{-1}
F(t)	Cumulative distribution function	(-)
N	Number of tanks	(-)
T	Time	s
E	Manufacturing efficiency	%
Σ	Variance	s
T	Mean residence time	s

Subscript	**Variable**
A	Accept
Di	Initial delay
Df	Final delay
Exp	Experimental
F	Concentration after step change
In	Input stream
O	Off-specification
Out	Output stream
S	Specification
R	Reject

References

Augsburger L, Zellhofer N. 2002. Tablet formulation. Swarbrick J, Boylan JC, Ed Encycl Pharm Technol 2nd ed New York Marcel Decket Inc, 2705-2707.

Bhaskar A, Barros FN, Singh R. 2017. Development and implementation of an advanced model predictive control system into continuous pharmaceutical tablet compaction process. Int J Pharm. 534:159–178. doi:10.1016/j.ijpharm.2017.10.003.

Cutler CR, Ramaker BL. 1979. Dynamic matric control - a computer control algorithm. AICHE Natl Meet Houston, TX.

Engisch W, Muzzio F. 2016. Using Residence Time Distributions (RTDs) to Address the Traceability of Raw Materials in Continuous Pharmaceutical Manufacturing. J Pharm Innov. 11:64–81. doi:10.1007/s12247-015-9238-1.

FDA. 2009a. ICH. Guidance for Industry: Q8 (R2) Pharmaceutical Development. Food Drug Adm.

FDA. 2009b. Guidance for Industry: ICH Q10 Pharmaceutical Quality System. Food Drug Adm.

Fogler H. 2006. Elements of Chemical Reaction Engineering.

Forsythe GE, Malcolm MA, Moler CB. 1977. Computer Methods for Mathematical Computations. J Appl Math Mech. 59:141–142.

Gatzke EP, Doyle FJ. 2001. Model predictive control of a granulation system using soft output constraints and prioritized control objectives. Powder Technol. 121:149–158. doi:https://doi.org/10.1016/S0032-5910(01)00334-5.

Haas NT, Ierapetritou M, Singh R. 2017. Advanced Model Predictive Feedforward/Feedback Control of a Tablet Press. J Pharm Innov. 12:110–123. doi:10.1007/s12247-017-9276-y.

Järvinen MA, Paaso J, Paavola M, Leiviskä K, Juuti M, Muzzio F, Järvinen K. 2013. Continuous direct tablet compression: effects of impeller rotation rate, total feed rate and drug content on the tablet properties and drug release. Drug Dev Ind Pharm. 39:1802–1808. doi:10.3109/03639045.2012.738681.

Lee SL, O'Connor TF, Yang X, Cruz CN, Chatterjee S, Madurawe RD, Moore CM V, Yu LX, Woodcock J. 2015. Modernizing Pharmaceutical Manufacturing: from Batch to Continuous Production. J Pharm Innov. 10:191–199. doi:10.1007/s12247-015-9215-8.

Leuenberger H. 2001. New trends in the production of pharmaceutical granules: batch versus continuous processing. Eur J Pharm Biopharm. 52:289–296. doi:https://doi.org/10.1016/S0939-6411(01)00199-0.

Mayne DQ. 2014. Model predictive control: Recent developments and future promise. Automatica. 50:2967–2986. doi:https://doi.org/10.1016/j.automatica.2014.10.128.

Meeus L. 2011. Direct Compression Versus Granulation. Pharm Technol Eur. 23.

Mesbah A, Paulson JA, Lakerveld R, Braatz RD. 2017. Model Predictive Control of an Integrated Continuous Pharmaceutical Manufacturing Pilot Plant. Org Process Res Dev. 21:844–854. doi:10.1021/acs.oprd.7b00058.

Muzzio F, Singh R, Chaudhury A, Rogers A, Ramachandran R, Ierapetritou M. 2013. Model-predictive design, control, and optimization: Applying model-predictive methods and a continuous process-control framework to continuous tablet-manufacturing processes.

Nunes de Barros F, Bhaskar A, Singh R. 2017. A Validated Model for Design and Evaluation of Control

Architectures for a Continuous Tablet Compaction Process. Process . 5. doi:10.3390/pr5040076.

Pharma D. Direct compression.

Pottmann M, Ogunnaike BA, Adetayo AA, Ennis BJ. 2000. Model-based control of a granulation system. Powder Technol. 108:192–201. doi:https://doi.org/10.1016/S0032-5910(99)00220-X.

Powell WB, Marar A, Gelfand J, Bowers S. 2002. Implementing real-time optimization models: A case application from the motor carrier industry. Oper Res. 50:571–581.

Qin SJ, Badgwell TA. 2003. A survey of industrial model predictive control technology. Control Eng Pract. 11:733–764. doi:https://doi.org/10.1016/S0967-0661(02)00186-7.

Ramachandran R, Chaudhury A. 2012. Model-based design and control of a continuous drum granulation process. Chem Eng Res Des. 90:1063–1073. doi:https://doi.org/10.1016/j.cherd.2011.10.022.

Richalet J, Rault A, Testud JL, Papon J. 1976. Algorithmic control of industrial processes.

Sahlodin AM, Barton PI. 2015. Optimal Campaign Continuous Manufacturing. Ind Eng Chem Res. 54:11344–11359. doi:10.1021/acs.iecr.5b01376.

Sanders CFW, Hounslow MJ, Doyle FJ. 2009. Identification of models for control of wet granulation. Powder Technol. 188:255–263. doi:https://doi.org/10.1016/j.powtec.2008.05.005.

Seborg DE, Mellichamp DA, Edgar TF. 2004. Process Dynamics and Control, 3rd Edition.

Shoham Patrascu M, Barton PI. 2017. Dynamic Optimization of Continuous Manufacturing of Pharmaceuticals. In: Espuña A, Graells M, Puigjaner LBT-CACE, editors. 27 European Symposium on Computer Aided Process Engineering. Vol. 40. Elsevier. p. 2803–2808.

Singh R. 2017. A Novel Continuous Pharmaceutical Manufacturing Pilot-Plant. Pharma Focus Asia.:3–5.

Singh R, Barrasso D, Chaudhury A, Sen M, Ierapetritou M, Ramachandran R. 2014. Closed-Loop Feedback Control of a Continuous Pharmaceutical Tablet Manufacturing Process via Wet Granulation. J Pharm Innov. 9:16–37. doi:10.1007/s12247-014-9170-9.

Singh R, Boukouvala F, Jayjock E, Ramachandran R, Ierapetritou M, Muzzio F. 2012. Flexible Multipurpose Continuous Processing of Pharmaceutical tablet Manufacturing Process. PharmPro Mag Pharm Process.:22–25.

Singh R, Gernaey K V, Gani R. 2009. Model-based computer-aided framework for design of process monitoring and analysis systems. Comput Chem Eng. 33:22–42. doi:https://doi.org/10.1016/j.compchemeng.2008.06.002.

Singh R, Ierapetritou M, Ramachandran R. 2012. An engineering study on the enhanced control and operation of continuous manufacturing of pharmaceutical tablets via roller compaction. Int J Pharm. 438:307–326. doi:https://doi.org/10.1016/j.ijpharm.2012.09.009.

Singh R, Ierapetritou M, Ramachandran R. 2013. System-wide hybrid MPC–PID control of a continuous pharmaceutical tablet manufacturing process via direct compaction. Eur J Pharm Biopharm. 85:1164–1182. doi:https://doi.org/10.1016/j.ejpb.2013.02.019.

Singh R, Muzzio JF, Ierapetritou M, Ramachandran R. 2015. A Combined Feed-Forward/Feed-Back Control System for a QbD-Based Continuous Tablet Manufacturing Process. Process . 3. doi:10.3390/pr3020339.

Singh R, Sahay A, Karry KM, Muzzio F, Ierapetritou M, Ramachandran R. 2014. Implementation of an

advanced hybrid MPC–PID control system using PAT tools into a direct compaction continuous pharmaceutical tablet manufacturing pilot plant. Int J Pharm. 473:38–54. doi:https://doi.org/10.1016/j.ijpharm.2014.06.045.

Singh R, Sahay A, Muzzio F, Ierapetritou M, Ramachandran R. 2014. A systematic framework for onsite design and implementation of a control system in a continuous tablet manufacturing process. Comput Chem Eng. 66:186–200. doi:https://doi.org/10.1016/j.compchemeng.2014.02.029.

Singh R, Sen M, Ierapetritou M, Ramachandran R. 2015. Integrated Moving Horizon-Based Dynamic Real-Time Optimization and Hybrid MPC-PID Control of a Direct Compaction Continuous Tablet Manufacturing Process. J Pharm Innov. 10:233–253. doi:10.1007/s12247-015-9221-x.

Wojsznis W, Gudaz J, Blevins T, Mehta A. 2003. Practical approach to tuning MPC**Based on Practical Approach to Tuning MPC by Wojsznis, Gudaz, Mehta, and Blevins, published in the Proceedings of the ISA 2001 Conference, September 10-13, 2001, Houston, TX [11]. ISA Trans. 42:149–162. doi:https://doi.org/10.1016/S0019-0578(07)60121-9.

Ziegler JG, Nichols NB. 1993. Optimum Settings for Automatic Controllers. J Dyn Syst Meas Control. 115:220–222.