COMBINED FEEDFORWARD/FEEDBACK CONTROL OF AN INTEGRATED CONTINUOUS GRANULATION PROCESS

By

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ABSTRACT OF THE THESIS

Combined Feedforward/Feedback Control of an Integrated Continuous Granulation Process

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Continuous pharmaceutical manufacturing (CPM) offers shorter processing times and increased product quality assurance, among several other advantages which makes it an ever growing interest among pharmaceutical companies. A suitable efficient control system is however desired for CPM to achieve a consistent predefined end product quality. The feedforward controller measures and takes corrective actions for disturbances proactively before they affect the process and thereby product quality. The feedback controller considers the real time deviation of control variable from pre-specified set point and keeps it at a minimum possible value. The deviation of a control variable from the set point could be because of both measurable and unmeasurable disturbances. In order to control product quality more accurately, the effects of input disturbances need to be proactively mitigated. Therefore, it is desired that a combined feedforward/feedback

control system integrated with suitable Process Analytical Technology (PAT) be implemented over a traditional feedback-only control system. In this work, an advanced combined control strategy has been developed for a continuous twin screw wet granulation (WG) process. A pre-blend of the active pharmaceutical ingredient (API) and intragranular components is fed into the continuous twin screw granulator (TSG), together with second stream containing excipient. Lack of homogeneity of the active ingredient in the pre-blend stream is a major source of variability in the process. Negligible back mixing within the granulator ensures that the input variability exits the granulator unfiltered and is manifested as content non-uniformity in the granules. An integrated flowsheet was developed and simulated in order to evaluate the effect of control loops on critical quality attributes (CQAs). Different strategies of manipulation have been evaluated and the best strategy was identified. *In silico* study on the combined feedforward/feedback control strategy and feedback-only control strategy demonstrates that the combined loop results in diminished variability of the CQAs. Different control algorithms were then evaluated and the best control algorithm was successfully implemented in the pilot plant.

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Chapter 1: Introduction

1.1. Literature Review

Continuous manufacturing has been in use for a long time in the petrochemical, metal casting and bulk chemical industry. However, it has recently been of growing interest in the pharmaceutical sector because it offers substantial economic benefits along with increased product quality assurance among several other advantages (Schaber, Gergiorgis et. al. 2011). In 2002, the FDA launched an initiative that supports a risk-based approach towards modernizing pharmaceutical manufacturing (FDA 2004a). In December 2015, the agency also published a draft guidance which encourages the industry to move towards continuous manufacturing aligned with quality-by-design (QbD) (FDA 2004a; FDA 2015). In the past decade, extensive work has been carried out to study the benefits of continuous pharmaceutical manufacturing over batch-wise manufacturing (Leuenberger 2001; Lee, O'Connor et. al. 2015). Studies have also been carried out as to how academia, industry and regulatory bodies can work together to promote development of continuous manufacturing in small-molecule pharmaceutical sector (Myerson, Krumme et. al. 2014).

Product quality in pharmaceutical drug manufacturing, one of the most strictly regulated manufacturing practices, is of utmost importance. Variations in the properties of raw materials and process disturbances affect the quality of the product. These variations are a result of factors such as noise from the various unit operations, process conditions and variations in raw materials. A major approach towards complying with the stringent quality criteria imposed by regulatory authorities is the development of an advanced control strategy.

Since the initiative by the FDA on continuous manufacturing came into existence, great amount of research has been carried out to study the role of control systems in pharmaceutical drug manufacturing. Muteki et al. suggested a feedforward control strategy for a dry granulation process using a partial least squares model to compensate for the effect of variability in raw materials on the final tablet properties (Muteki, Swaminathan et. al. 2012). A detailed study has been carried out in developing control strategies for different continuous granulators such as high shear granulator and fluid bed granulator (Bardin, Knight et. al. 2004; Burggraeve, Silva et. al. 2012; Sanders, Hounslow et. al. 2009). Singh et al. have designed and implemented an advanced hybrid model predictive control (MPC) system and a simple proportional integral derivative (PID) control system on a pilot-scale direct compaction continuous tablet manufacturing process (Singh, Velazquez et. al. 2016). A combined feedforward/feedback control system for an integrated continuous direct compaction tablet manufacturing process has been also developed (Singh, Muzzio et. al. 2015). A feedback control system for a twin screw granulator (TSG) with focus on controlling granule properties has been also proposed (Singh, Barrasso et. al. 2014).

Traditional feedback controllers are essential in a control loop to ensure product quality. However, these controllers take action only after the disturbance has propagated through the system and affected the product quality. On the other hand, a feedforward only controller takes action before the disturbance propagates. However, it does not take into account the real time measurement of control variables and cannot assure product quality. Therefore, it is desired that a combined feedforward/feedback control system integrated with suitable Process Analytical Technology (PAT) be implemented over a traditional

feedback control system. The feedforward controller measures and takes corrective actions for disturbances before they affect the process while the feedback controller considers the effect of process parameters and ensures the consistency of the output.

As mentioned above, since the FDA's initiative in 2002 for modernizing pharmaceutical manufacturing, efforts have been made towards continuous manufacturing and implementation of control systems with suitable PAT. A guidance for industry PAT was published by the FDA in 2004 to encourage industry to improve the production process (FDA 2004b). For continuous manufacturing, it is necessary to analyze data continuously in real-time, to take specific control actions in order to ensure product quality. This is where the bridge between PAT and control systems is established. The most favored PAT technique in the pharmaceutical industry used to analyze different critical quality attributes (CQAs) is the near infrared (NIR) spectroscopy. Vanarase et al. applied NIR for monitoring drug concentration to a continuous mixing process (Vanarase, Alcalà et. al. 2010). Singh et al. implemented a hybrid MPC-PID control for continuous tablet manufacturing with real-time monitoring of API composition using NIR at the outlet of a continuous blender (Singh, Sahay et. al. 2014). A method for real time monitoring of powder bulk density needed for combined feedforward/feedback control of a continuous direct compaction manufacturing process has also been developed (Singh, Román-Ospino et. al. 2015).

1.2. Objectives

This study was carried out with an objective of understanding the different control schemes and how they control the critical quality attribute for continuous feeder and granulation process. Prior to this work, no attempt has been made to design an advanced feedforward/feedback control system for an integrated continuous tablet manufacturing

process via wet granulation that can enable drug concentration control. In this work, an advanced control system has been designed for an integrated continuous pharmaceutical tablet manufacturing process via wet granulation. The considered process consists of two feeders and one twin screw granulator. The main objectives of this work are:

1. To analyze the process and determine the CPPs and CQAs
2. To develop an integrated flowsheet model of the process.
3. To identify control loops.
4. To identify suitable actuator for control of drug concentration in granules.
5. To develop a feedback control strategy and a combined feedforward/feedback control strategy and evaluate their performance.
6. To develop a Model Predictive control (MPC) system for drug concentration in granules.
7. To implement an advanced control strategy on the pilot plant.

Chapter 2: Background

2.1. Wet Granulation

There are three tablet manufacturing routes, wet granulation (WG), dry granulation (DG/RC) and direct compaction (DC). Granulation is known as a size enlargement process where small particles aggregate together into comparatively permanent large particles and where the original particles can still be distinguished (Ennis and Litster 1997). Granulation can be of two types depending on the manufacturing route, dry granulation and wet granulation. Dry granulation method is normally used for water sensitive materials. Wet granulation is one of the most common and important routes of manufacturing solid oral dosage forms. This process involves the addition of a liquid binder to a powder bed where it undergoes wetting, nucleation, consolidation, growth, breakage and attrition simultaneously. This size enlargement has numerous advantages in the pharmaceutical manufacturing process such as improved flow and handling, improved homogeneity of the downstream blend, increased bulk density and improved compression characteristics. There are a number of unit operations involved in the continuous pharmaceutical tablet manufacturing process via wet granulation as shown in Figure 1. It is to be noted that, Figure 1 is one type of integrated set up for the continuous tablet manufacturing process via wet granulation and can be modified according to need, number of ingredients involved and availability of space and equipment. As seen, granulation is the third unit operation in the entire flowsheet and thus controlling the quality of product at this step can avoid variations downstream in the process.

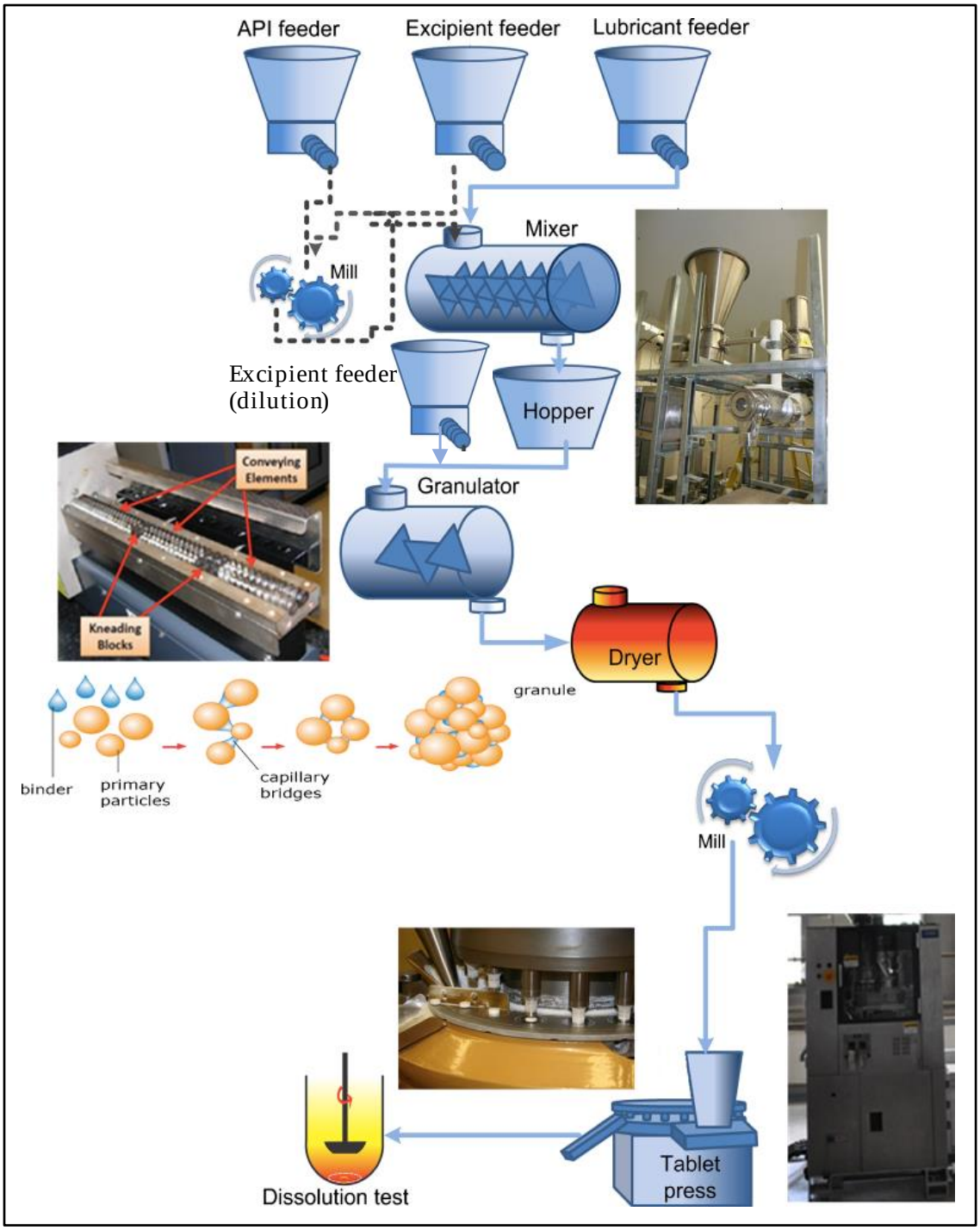

Figure 1: Continuous tablet manufacturing process via wet granulation (Singh et al., 2014)

2.1.1. Continuous wet granulation

Both, batch and continuous granulators are commercially available to be used in batch and continuous pharmaceutical tablet manufacturing processes. In batch manufacturing, the

materials are fed into the equipment at the start of the process and discharged at the end of the process. The discharged material at the end of the process then goes into the next unit operation. In continuous manufacturing material is fed in and discharged continuously from the equipment. Since pharmaceutical manufacturing has traditionally been a batch manufacturing process, the challenge for continuous manufacturing lies in the availability of its technology. Equipment manufacturers like GEA, Glatt, Bohle and Loedige are examples of some who provide the equipment for integrated continuous wet granulation that contributes towards the continuous pharmaceutical manufacturing technology (Parikh 2016). Different forms and techniques that could be implemented for continuous granulation process has been previously discussed and these include fluid bed agglomeration, spray drying, extrusion, high speed mixer/granulator, roller compaction and semi-continuous granulation (Vervaet and Remon 2005). There are several advantages of moving towards continuous granulation. Scale-up of the process is not as difficult which results in shorter development time and manufacturing continuously leads to running the production line continuously (Keleb, Vermeire et. al. 2004). Continuous granulation gives higher throughput in comparison to batch granulation and also reduces equipment footprint when higher throughput is desired (Dhenge, Fyles et. al. 2010).

2.1.2. Twin Screw Granulation

Granulation by a twin screw extruder was first reported few decades ago for production of paracetamol (Gamlen and Eardley 1986). However, twin screw extrusion for granulation has recently gained tremendous popularity as a continuous granulation technique in the pharmaceutical industry. Thermo Fisher Scientific offers a range of twin screw extruders for continuous granulation based on the barrel diameter and correspondingly the

throughput (Thermo Fisher Scientifc). The twin screw granulator consists of two co-rotating screws enclosed in a barrel that are made up of a number of different elements. The twin screw granulator with the help of these elements, conveys the material along the length of the screw while simultaneously providing the mechanical energy required for liquid distribution and granulation in the mixing zones (Seem, Rowson et. al. 2015). In comparison to batch granulation, the granulation process of nucleation, growth and breakage happen simultaneously but are physically separated and happen one after the other along the length of the screw (Seem, Rowson et. al. 2015). Extensive research has been carried out lately to determine the factors that affect the quality of granules. An important advantage of the twin screw granulator is that it is suitable for continuous processing. This has been shown in the study conducted by Keleb et. al. where twin screw granulation was used for the continuous granulation of lactose (Keleb, Vermeire et. al. 2002). The screws of the twin screw granulator are intermeshed thus allowing self-cleaning that minimizes accumulation. As mentioned before, it allows for continuous processing and since it has minimal hold up, material losses at start up and shut down are considerably low. To summarize, the twin screw granulation process is flexible with minimal labor making it economical and helps in providing a complete automated production line for implementation in pharmaceutical industry.

2.2. Integrated Process Overview

The process section considered for this study is shown in Figure 2. This section, is part of an integrated continuous pharmaceutical tablet manufacturing process via wet granulation route. In this wet granulation process, two gravimetric feeders have been integrated with a continuous twin screw granulator. The process involves a batch pre-blending step where

the API and intragranular components are mixed, and subsequently fed into feeder 1. The blend consists of 12 % API and 88 % excipient. The other feeder, feeder 2 is for pure excipient only. The gravimetric feeders are the loss-in-weight feeders. They consist of a hopper and a twin screw that conveys dry bulk material out of the feeder at a constant weight per unit time and adjusts the screw speed to control flow rate.

The TSG is integrated after the two feeder hoppers where the streams are mixed and passed with a specific liquid to solid (L/S) ratio to form granules. The feed from the two streams enters the TSG in the transport zone. The liquid binder used for the granulation process is water which is added before the first kneading block. The powder then passes into the mixing zone where it is wetted and forms granules that are conveyed further down by the twin screws. The comingling of the two feeder streams leads to an overall low concentration of API at the granulator outlet. The granule product is then dried, milled, and batch blended with superdisintegrants and extragranular excipients (to further dilute API to ~1%), and then compressed and coated.

A potential source of product variability is the lack of homogeneity of the stream entering the extruder. The noise propagated by the screws of the feeder to the powder being fed also causes a change in the concentration of API. Pre-blends discharged by a tumbling blender are known to fluctuate fairly significantly in composition and due to limited back mixing in the TSG, these fluctuations are propagated to the granulator exit, affecting the content uniformity of API in the granules. In turn, such variability can affect both product content uniformity (CU) and product dissolution characteristics. Fortunately, since the composition of the stream discharged by the feeder can be assayed instantaneously using PAT methods, it is conceptually possible to adjust the ratio of the API-bearing stream and the excipient-

only stream, and their flow rates, to compensate for composition fluctuations entering, and therefore exiting, the extruder.

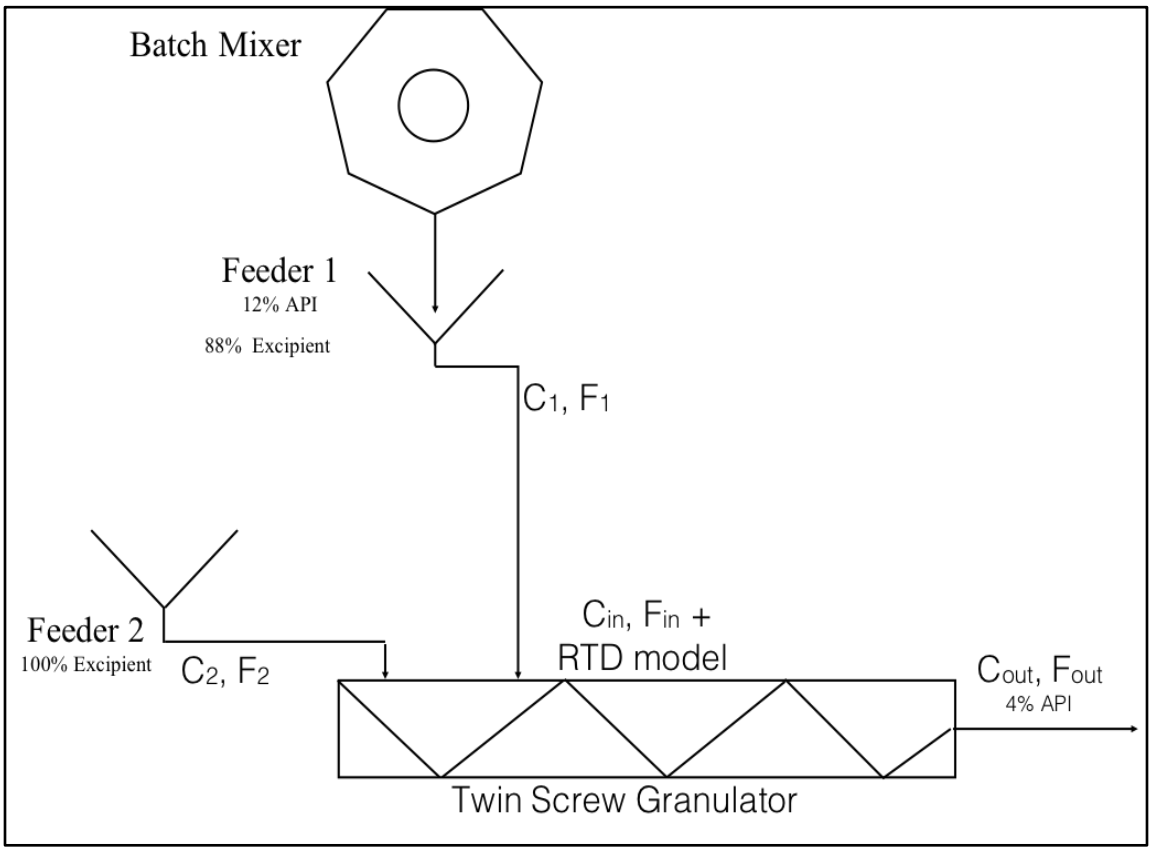

Figure 2. Integrated Continuous Wet Granulation Process Flowsheet without control loops

2.3. Feedback Control

The paradigm shift by pharmaceutical industries from batch to continuous manufacturing has provided opportunity to control the process in real time. Closed-loop control enables for a rather Quality by Design (QbD) approach than the traditional Quality by Testing (QbT) approach. One of the popular forms of process control implemented in various industries is the feedback controller. The feedback controller algorithm predominantly is of two types, proportional-integral-derivative (PID) control and on-off control. However, PID controllers are more widely used than on-off controllers since they are more flexible

and efficient (Seborg, Edgar et. al. 2011). Figure 3 shows the block diagram of a feedback controller. The control objective is to maintain the process output such as concentration or flow rate constant by manipulating suitable actuator within the process. The output from the process is measured by a sensor and sends this measurement as a signal to the comparator that compares the measured value against the set point (desired value) and generates an error. The feedback controller following the PID control algorithm takes this error as an input and calculates the corresponding output value. The calculated output is then sent as a signal to the process.

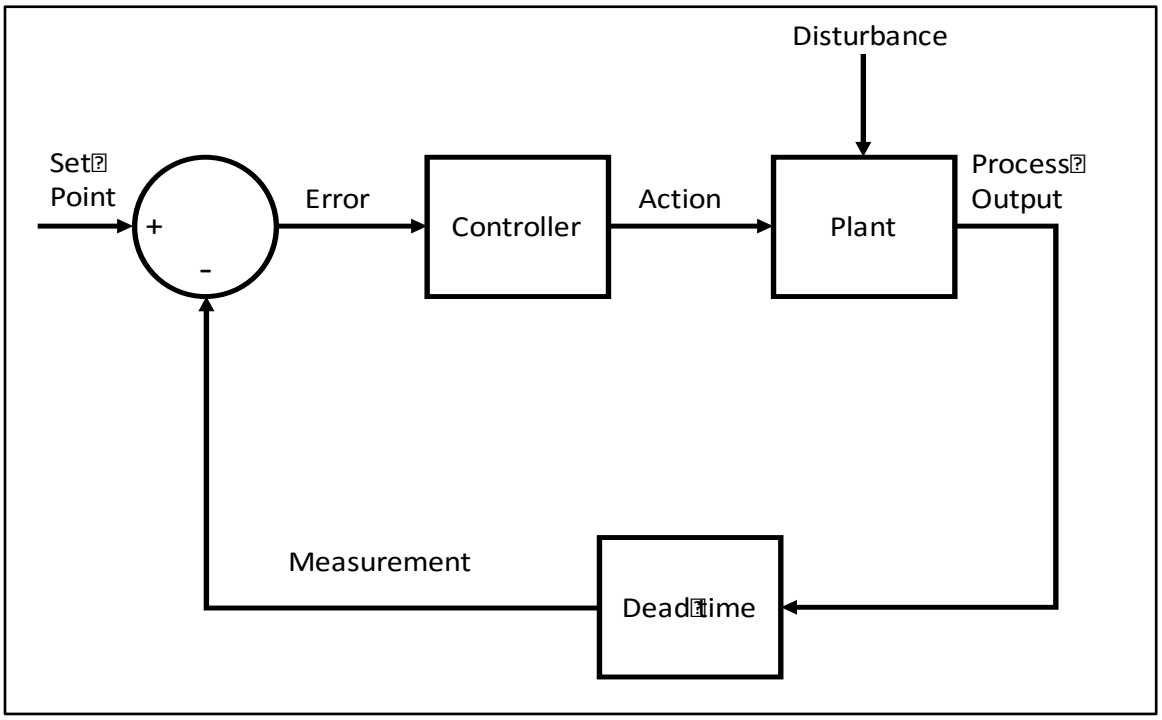

Figure 3: Block diagram of Feedback control

Various studies have been conducted on design and implementation of feedback control in pharmaceutical manufacturing. A fuzzy logic based feedback control strategy was developed to control granule growth in high shear granulation of pharmaceutical powders (Watano, Numa et. al. 2001). Singh et. al. have designed an in-silico closed-loop PID based feedback control strategy for a continuous wet granulation pharmaceutical manufacturing

process (Singh, Barrasso et. al. 2014). A Raman-based feedback control strategy (PID) has been implemented for a continuous twin screw blending and tableting process (Nagy, Farkas et. al. 2017). Feedback controllers have numerous advantages and some of them are:

1. It is flexible to different process conditions which would require a small amount of re tuning but satisfactory results can be achieved.
2. A control action is undertaken when the controller detects the error or the deviation of the controlled variable from the set point.

From the second bullet point, we know that feedback control takes the necessary control action only after the disturbance has passed through the process. It doesn't take any predictive action over measured disturbances. Thus in cases where feedback only control is not satisfactory, adding a feedforward control to it could make the performance better.

2.4. Feedforward control and Combined control scheme

In comparison to the feedback controller discussed in section 2.3., the feedforward controller measures the disturbance and takes corrective action before the disturbance passes through and upsets the process. A simplified block diagram of feedforward control in order to compare with the block diagram for feedback control is demonstrated in Figure 4. As seen in the figure, for a particular process, inlet disturbance can be measured by a sensor. This sensor then sends the measured signal to the feedforward controller and the feedforward controller accordingly changes the process variable to maintain the process output constant. Feedforward controllers require an online/inline measurement of the disturbance and thus takes action only on the measured disturbance and not unmeasured

disturbances. Thus, in practical applications, feedforward control is generally used as a combination with feedback control. Thus on combining Figure 3 and Figure 4, we get the combined control block diagram as shown in Figure 5.

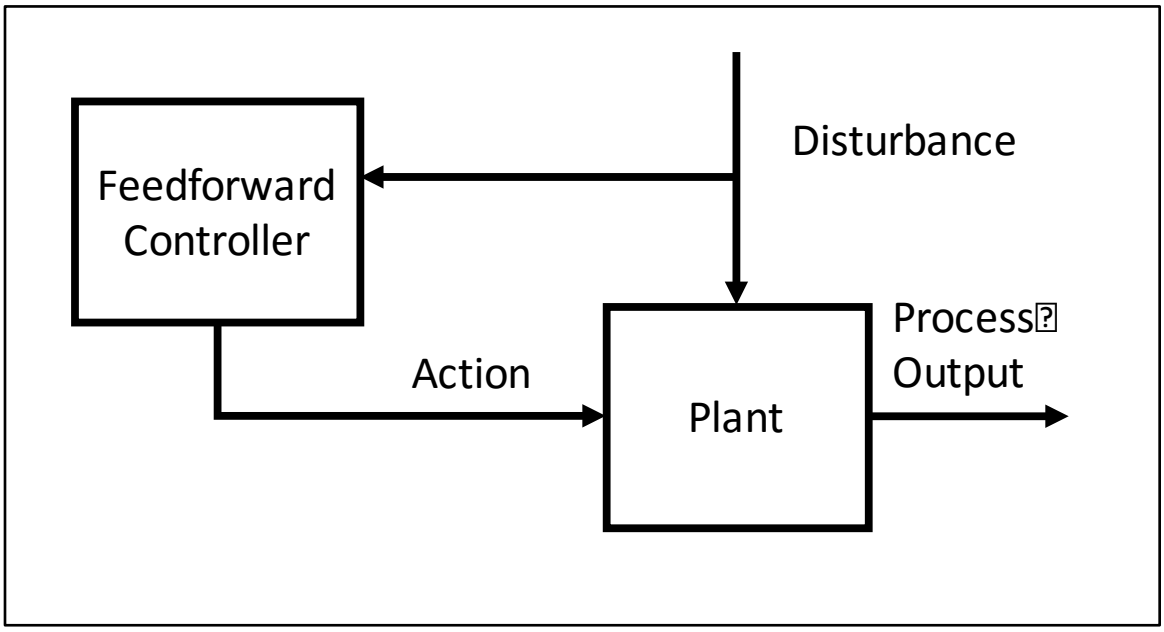

Figure 4: Block diagram of feedforward control

In the combined feedforward/feedback control, the feedforward controller reduces the effect proactively caused by measured disturbances on the controlled variable while the feedback controller reduces the effect caused by unmeasured process disturbances. Recently, studies have been carried out to determine the efficiency of combined feedforward/feedback control over traditional feedback controller in pharmaceutical manufacturing. Singh et. al. developed a combined feedforward/feedback control with cascading to control the tablet hardness for a direct compaction continuous tablet manufacturing process (Singh, Muzzio et. al. 2015). A combined feedforward/feedback control strategy was also demonstrated for control of concentration in a continuous pharmaceutical pilot plant from API crystallization to end product being tablets (Lakerveld, Benyahia et. al. 2014).

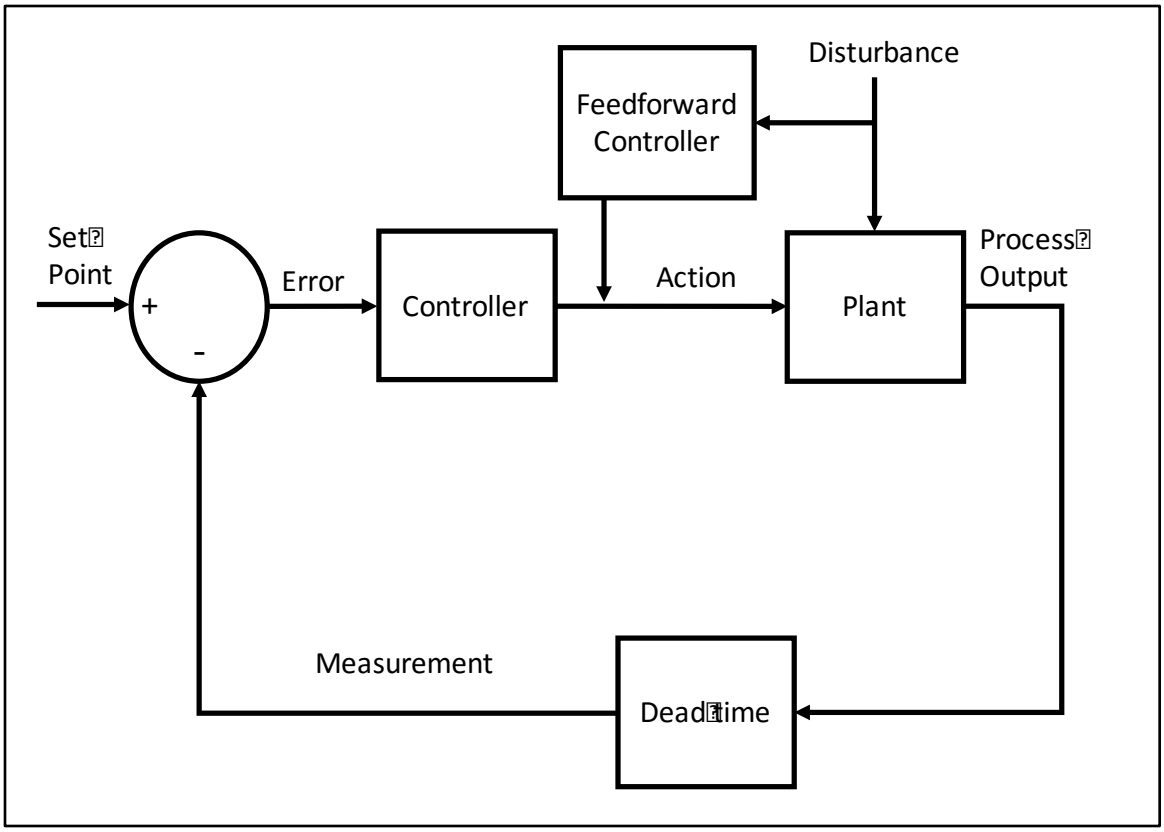

Figure 5: Block diagram of combined feedforward/feedback control

2.5. Model Predictive Control (MPC)

MPC was originally developed to meet the specialized control needs of power plants and petroleum refineries. With process control just recently dawning into the pharmaceutical industry, this field is an open area of research with challenges on deciding the type of control strategy to be implemented and the integration of control hardware and software. MPC has several advantages over traditional PID control but it is more expensive and complex to implement. Studies have been carried out for design and implementation of MPC for a tablet compaction process (Bhaskar, Barros et. al. 2017; Haas, Ierapetritou et. al. 2017; Singh, Sahay et. al. 2014). When compared with PID controllers, MPC has an option to start adjusting the control signal ahead of reference changes with substantially less control error, while PID cannot start before. Smoother control signal with MPC (lesser

propagation of noise through MPC than PID) is accomplished. MPC is better in compare to PID for dead time dominant processes, and highly interactive multi input multi output (MIMO) processes.

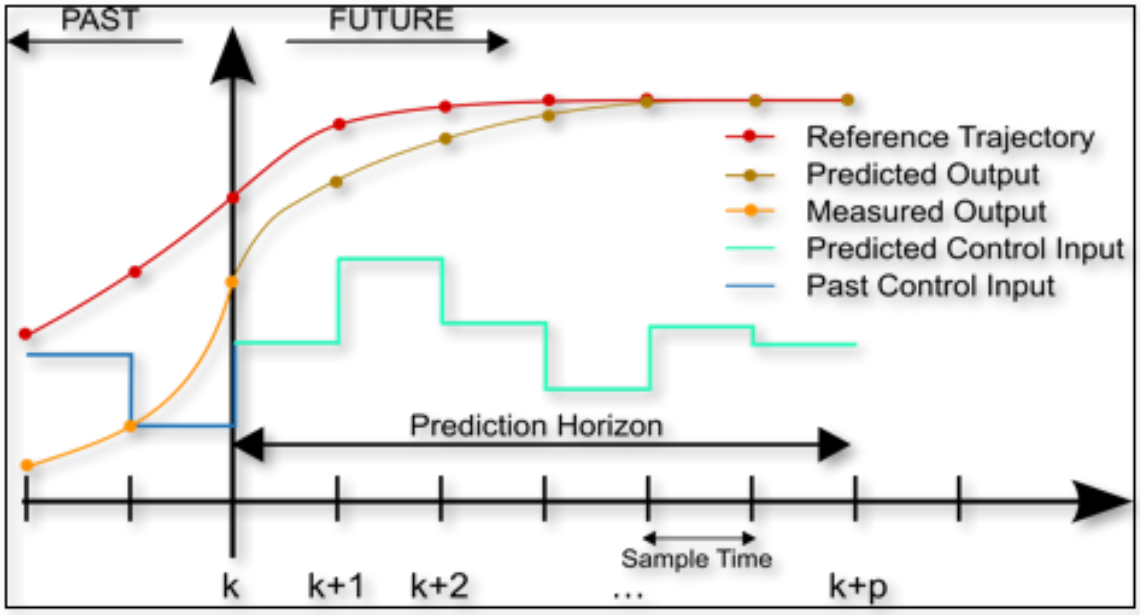

Figure 6: Principle of Model Predictive Control (adapted from Singh et al., 2013)

Figure 6 depicts the principle of MPC. MPC is actually a repeated function of a finite horizon open-loop optimal control problem subject to the system dynamics. Based on the values obtained at time *t*, the dynamic behavior of the system is predicted by the controller for a sample time space. The algorithm utilizes a dynamic process model to predict the effect of future control actions by using the current state of the plant as the initial state; the optimization method yields an optimal control sequence and the first control in this sequence is applied to the plant. During the repeated process of optimization at each sampling period, the information is always updated. This prediction capability allows solving optimal control problems on line, where tracking error, namely the difference between the predicted output and the desired reference, is minimized over a future horizon, possibly subject to constraints on the manipulated inputs and outputs.

Chapter 3: Control Method Development

3.1. Integrated Process Flowsheet

In order to implement continuous manufacturing, various models have been built for the different unit operations involved in the continuous tablet manufacturing process via wet granulation to enhance *in-silico* study. These models have been developed in the gPROMS library to facilitate integrated flowsheet modeling. The procedure for dynamic flowsheet modeling of continuous pharmaceutical manufacturing using individual models and integrating them together has been previously reported (Boukouvala, Ramachandhran et. al. 2011; Boukouvala, Niotis et. al. 2012; Boukouvala, Chaudhary et. al. 2013).

3.1.1. Feeder

The feeders are used to provide the stream containing the pre-blend of API and excipient and the stream containing only excipients to the process. The process model used for this integrated flowsheet simulation and control has been previously developed as described in (Escotet-Espinoza, Rogers et. al. 2014). This model is based on the Heckel model that relates powder density to its pressure thus effectively developing the feed factor model for the feeder.

3.1.2. Continuous Granulation (TSG)

While performing granulation experiments, it is observed that some material deposits on the walls of the barrel, and on the screws. Thus a Residence Time Distribution (RTD) model has been used for this integrated flowsheet. This model has been adapted from Muddu et. al. where the granulator has been modeled akin to a reactor system as the

material flows through the granulator like a plug flow. However, to account for the back-mixing provided by the mixing and kneading elements, the model developed consists of continuously stirred tank reactor (CSTR) elements too. Lastly, the material that remains in the granulator has been incorporated as dead volume fraction.

3.1.3. Integration of the unit operations model

The feeder model and the granulator model discussed in section 3.1.1 and 3.1.2 were then integrated to facilitate integrated flowsheet modelling in gPROMS. Figure 7 displays this integration. Each of the feeders has a built-in PID controller that controls the outlet flow rate of the feeder. Built-in PID tool provided by gPROMS has been used for this purpose. Outlet from the feeders (flow rate and concentration) is passed on to the granulator as two different streams. Stream 1 connects the API feeder to the granulator. Concentration of API in this stream is ideally fixed. Stream 2 connects excipient feeder to the granulator. There should be no API in this stream. The built-in PID controller maintains the flow rate of the feeder at the desired set point. The measured variable for these PID controllers is the flow rate coming out of the feeder and the manipulated variable is the screw rotational speed. The variables important for the design of the control system have been discussed in detail in the **Results and Discussion** section.

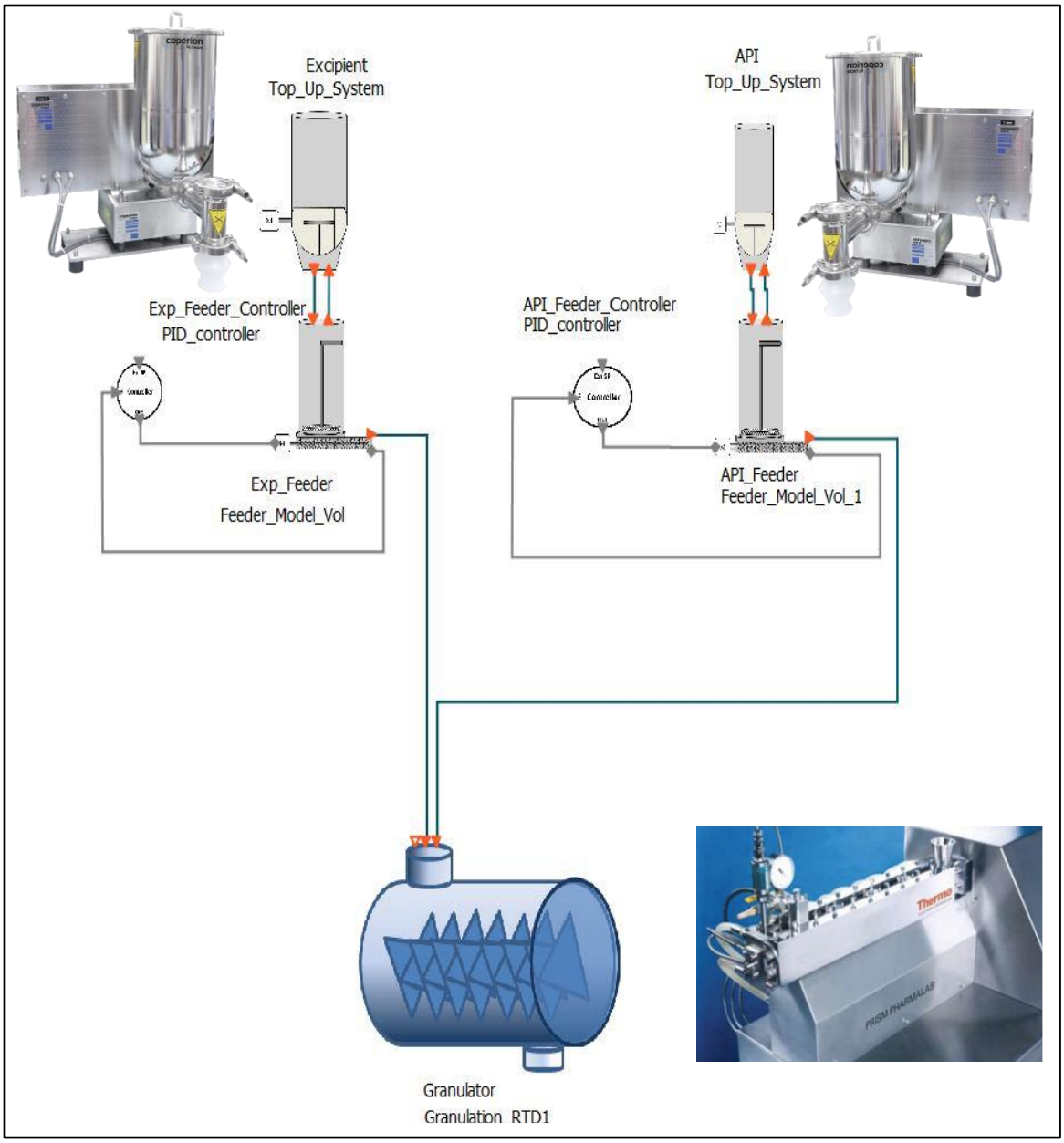

Figure 7: Integrated Flowsheet Model (open loop)

3.2. Identification of control loops

There are different options to control the concentration of API in granules. Based on the variable to be actuated the two different options to control composition of API are listed in

Table ***1***. As seen in the table there are two possible actuators to control the composition of API in granules. The first actuator is the flow rate of the excipient feeder. In this option, keeping the flow rate of API feeder constant, the flow rate of the excipient feeder can be manipulated. The second option is that of actuating the API Ratio. The API Ratio is a ratio that results from the material balance given in Equation 1 and is represented in Equation 2. Actuating the API Ratio leads to manipulating the API Ratio to maintain the API composition constant. However, in this case the total flow rate is kept constant which is the summation of flow rates of the two feeders. Thus from Equation 2, the set point for flow rate of the API feeder is calculated and this flow rate when deducted from the total flow rate gives the set point for the excipient feeder flow rate. Thus actuating the API Ratio then actuates the flow rates of the two feeders. A comparison between the two actuators for a feedback controller has been discussed in the **Results and Discussions** section. Actuating the API Ratio, changes the API Ratio and thus $C_{granulator,inlet}$ varies linearly with respect to the actuator. However, actuating only the flow rate set point of the excipient feeder, changes the flow rate of the excipient feeder only which makes $C_{granulator,inlet}$ vary nonlinearly with respect to the actuator.

Table 1: Different control options based on actuator

Type of Actuation	Actuator	Controlled variable	Advantages	Disadvantages
Non linear	Flow Rate set point of excipient feeder	API composition in granules	Input disturbances in API composition are less in comparison	Only API composition in granules is controlled. Nonlinear actuator has restrictions with implementing MPC since a nonlinear MPC would have to be developed.
Linear	API Ratio set point	API composition in granules	Production rate is controlled along with API composition in granules. Easier to implement a MPC controller for a linear actuator.	Input disturbances in API composition are introduced due to changes in API feeder flow rate

$$C_{granulator,inlet} = \frac{C_{API\ Feeder} F_{API\ Feeder}}{F_{API\ Feeder} + F_{Excipient\ Feeder}} \quad (1)$$

$$API\ Ratio = \frac{C_{granulator,inlet}}{C_{API\ Feeder}} = \frac{F_{API\ Feeder,SP}}{F_{API\ Feeder,SP} + F_{Excipient\ Feeder,SP}} \quad (2)$$

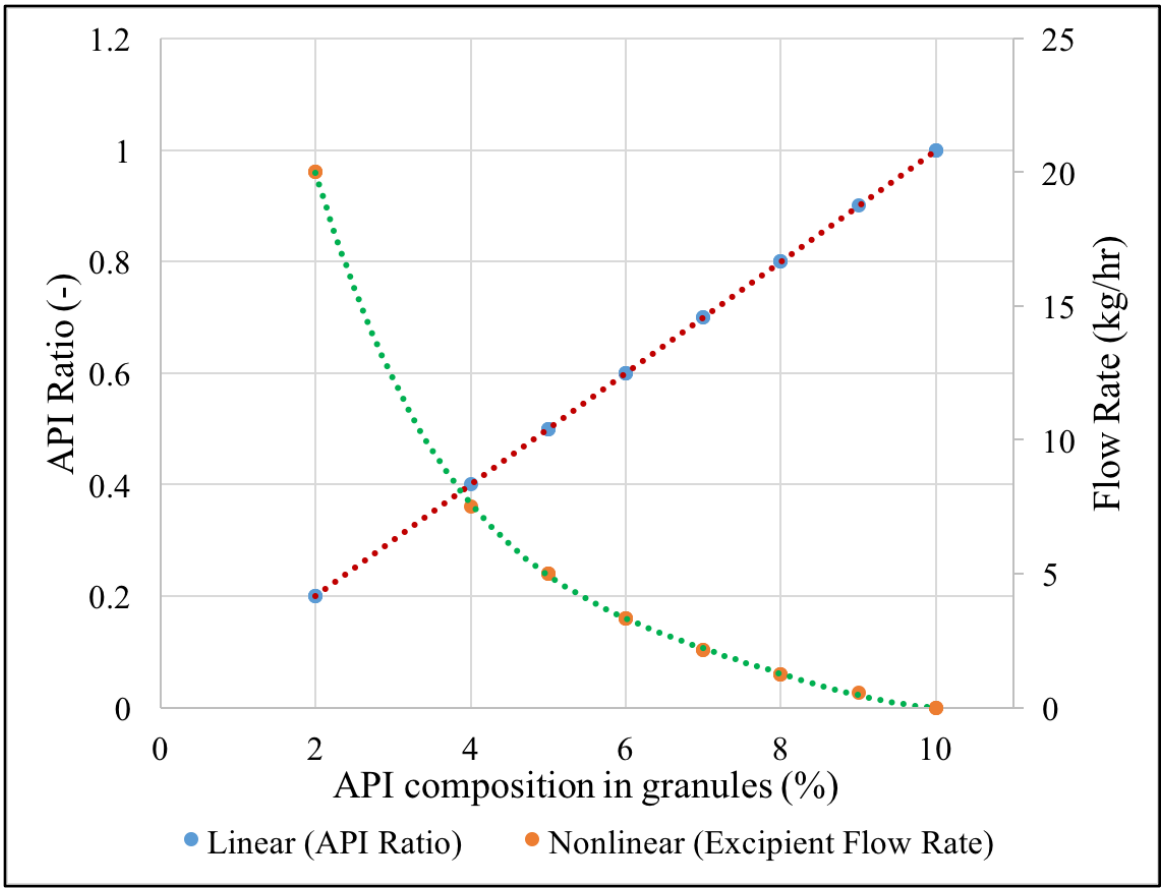

Figure 8: Actuator Vs API Composition in granules for the two actuator candidates

3.3. Control relevant transfer function model

The model for the feedforward controller can be given as $(-G_d/G_p)$ which is found by equating the characteristic equation to zero (Marlin, 2000). In order to develop this transfer function model for the feedforward controller, a transfer function model for disturbance was developed which would relate the disturbance to the control variable. Next, process models for the two feeders and the granulator was developed. These models were developed in System Identification Toolbox (Matlab, Mathworks, Natic, MA, USA) using step change data. The input and output variables for each process model are as given in Table 2.

Table 2: Process Transfer Function Model

Transfer Functions	Inputs	Outputs	Models
$G_{p1}(s)$	Screw rotational speed	API + excipient flow rate	$\frac{0.0247}{25s^2 + 0.5s + 1}$
$G_{p2}(s)$	Screw rotational speed	Excipient flow rate	$\frac{0.0247}{25s^2 + 0.5s + 1}$
$G_{p3}(s)$	API composition at granulator inlet	API composition at granulator outlet	$\frac{0.7379s + 0.03702}{s + 0.03613} e^{-20s}$
$G_d(s)$	API composition at feeder 1 outlet	API composition at Granulator outlet	$\frac{1}{s^2 + 0.4204s + 0.1501} e^{-25s}$

The feeder transfer functions (G_{p1} and G_{p2}) relate the feeder screw rotational speed to the outlet flow rate through a second order transfer function with no zero and two poles. Both feeders are assumed to be exactly same. The feeders dead time is too less and therefore it has been assumed to be negligible. The pole-zero map and the bode diagram are as shown in Figure 9. The map shows that the two poles are imaginary and the feeder process is stable but oscillatory. The bode diagram gives information about the gain margin and the phase margin. Typical design specification requires that the gain margin be greater than 1.7 dB and the phase margin be greater than 30° (Seborg, Edgar et. al. 2011). For the feeder transfer function, both the phase margin and the gain margin are infinity. The granulator transfer function (G_{p3}) relates the inlet API composition to the outlet API composition

through a first order transfer function with one zero and one pole. The pole-zero map and the bode plots for it are shown in Figure 10 and it can be seen that the system is stable and non-oscillatory. The gain margin and phase margin for this system are both infinity. Similarly, the disturbance transfer function model relates the API composition at feeder 1 outlet to the API composition at the outlet of the granulator. The model is based on a step change in concentration. The transfer function model is a second order transfer function model with two imaginary poles. The pole-zero map is shown in Figure 11 where it can be observed that the system is stable but oscillatory. The gain margin for the disturbance transfer function is infinity while the phase margin is 17.5464°.

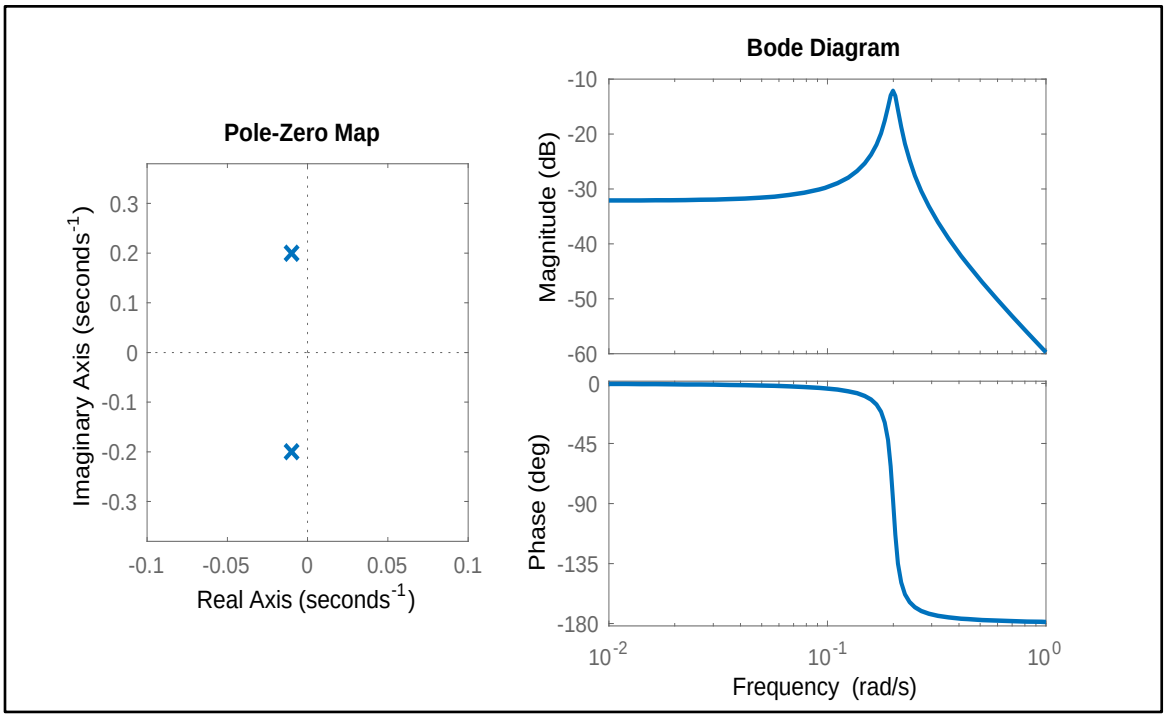

Figure 9. Pole-zero map and bode plot for feeder transfer function

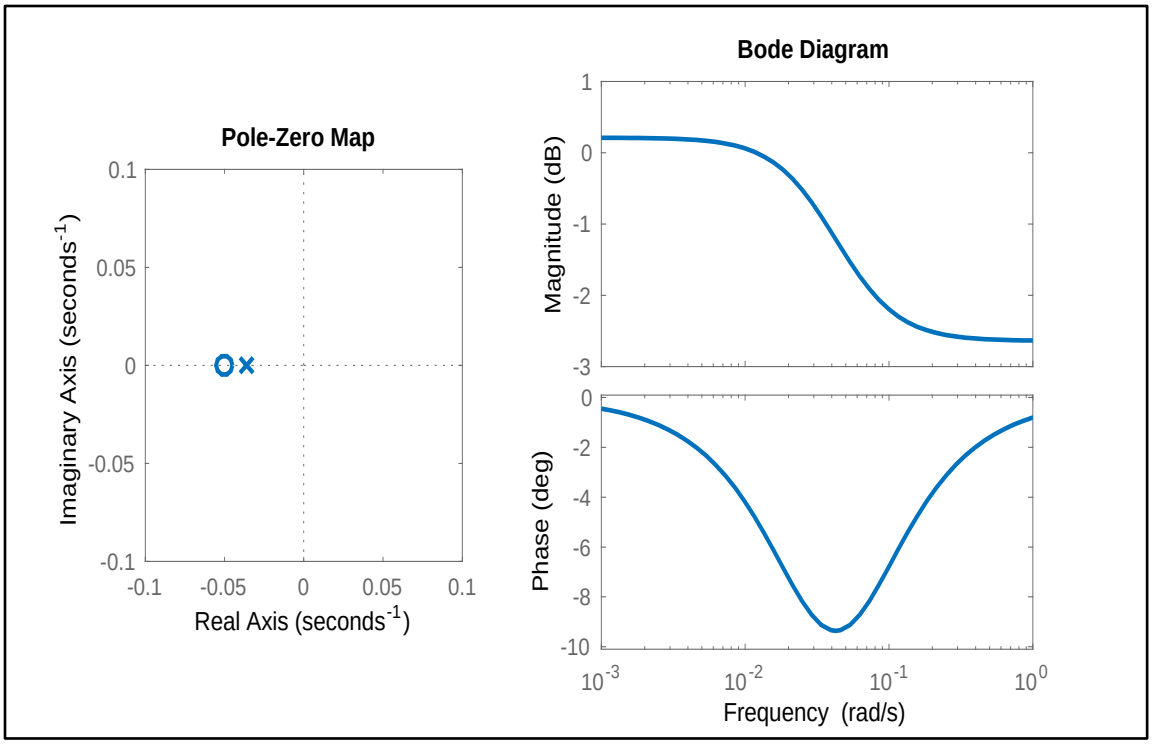

Figure 10. Pole-zero map and bode plot for granulator transfer function

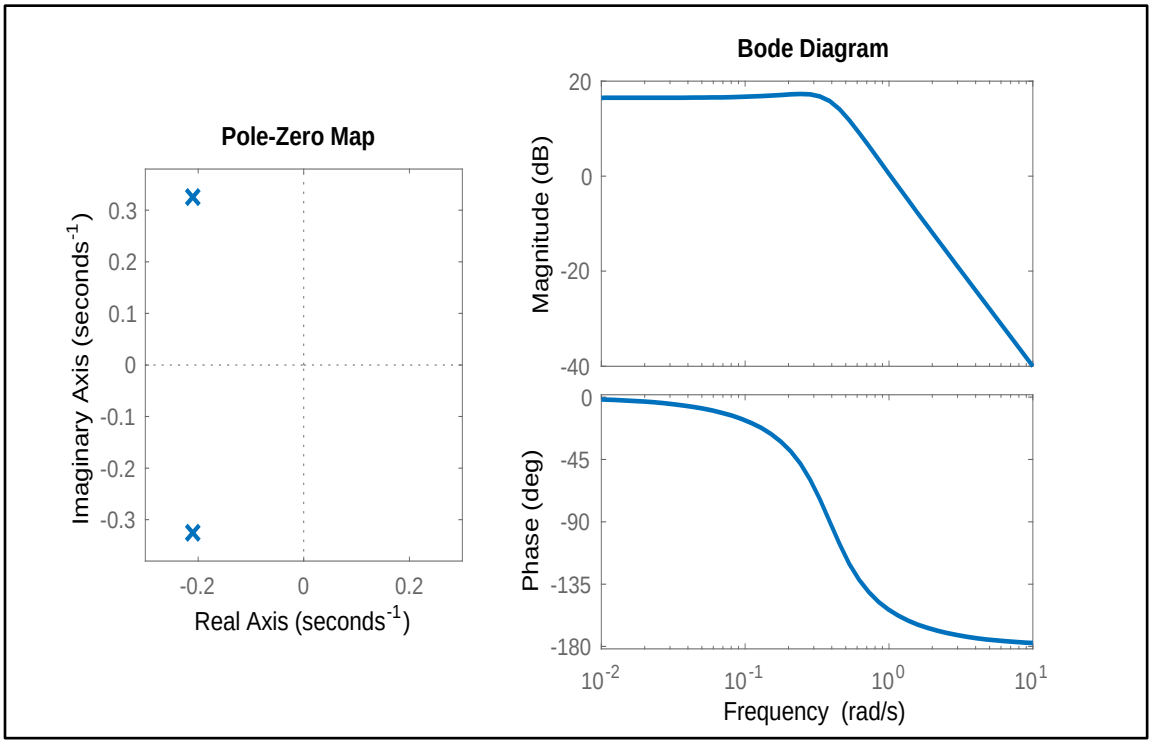

Figure 11. Pole-zero map and bode plot for disturbance transfer function

3.4. Design of control system

As discussed earlier, a combined feedforward/feedback control loop helps to achieve the desired controlled response. In this section, the feedforward controller model has been developed for a continuous twin screen granulation process. The control variable for the respective control strategy is the concentration of API at the outlet of the granulator C_{out}. A pre-blend of API and excipient is the feed through one feeder and pure excipient is the feed through the second feeder. Feeders and a twin screw granulator are the two unit operations around which the control loops have been built. This feedforward controller model is specific to a particular formulation since it depends on the concentration of API in the pre-blend. Control loops with NIR sensing have been added to the open loop process flowsheet shown in Figure 2 which gives us the closed loop process flowsheet shown in Figure 12. An NIR sensor is mounted at the exit of feeder 1, which measures the concentration of API exiting feeder 1 and sends the measured value to the feedforward controller. NIR sensor mounted at the exit of the granulator sends the measured value of API concentration in granules to the feedback PID controller. Together the feedback controller and the feedforward controller manipulate the flow rate of the excipient feeder (feeder 2). The excipient feeder flow rate is then controlled by manipulating the screw rotational speed. An advanced process control system i.e. combined feedforward/feedback control for continuous tablet manufacturing process via wet granulation has been designed in accordance with that described in Singh et al. (Singh, Muzzio et. al. 2015).

3.4.1. Combined feedforward/feedback control system architecture

The proposed control architecture is as shown in Figure 13 and consists of four control loops. Loops 1 and 2 are the built-in feedback control loops for the two feeders. Loop 3 is the master feedback controller and loop 4 is the feedforward controller. The controlled variables, inputs and outputs for the controller structure have been listed in Table 3.

Control loop 1 is the built-in feedback loop for feeder 1 and works on the loss-in-weight feeder concept. The feedback loop is the classical PID based controller. The built-in PID controller model in gPROMS was used. This loop controls the output flow rate of API and excipient blend from feeder 1 by manipulating the screw rotational speed of the feeder through the PID controller. As given in Table 3, the deviation of the flow rate from the set point that would be predetermined is the input to the PID controller and the screw rotational speed is the output.

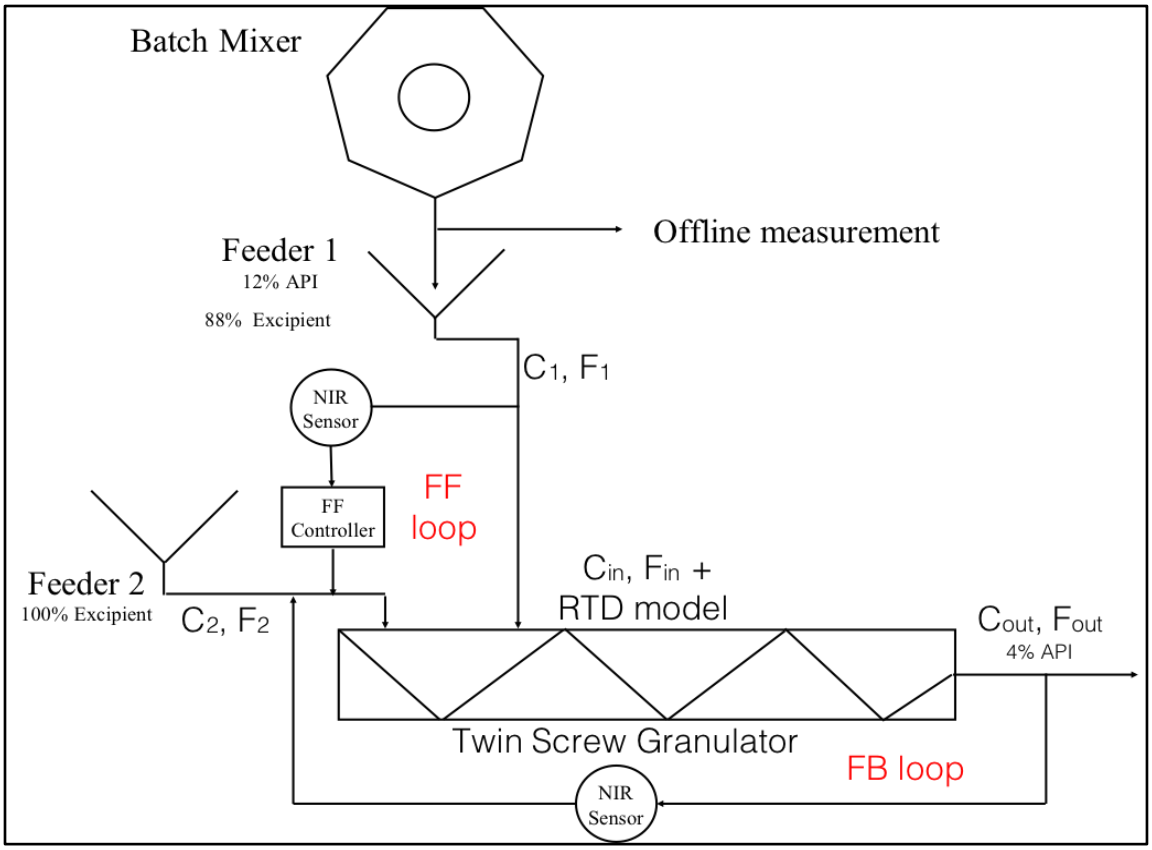

Figure 12. Integrated Continuous Wet Granulation Process Flowsheet with control loops. FF: Feedforward, FB: Feedback

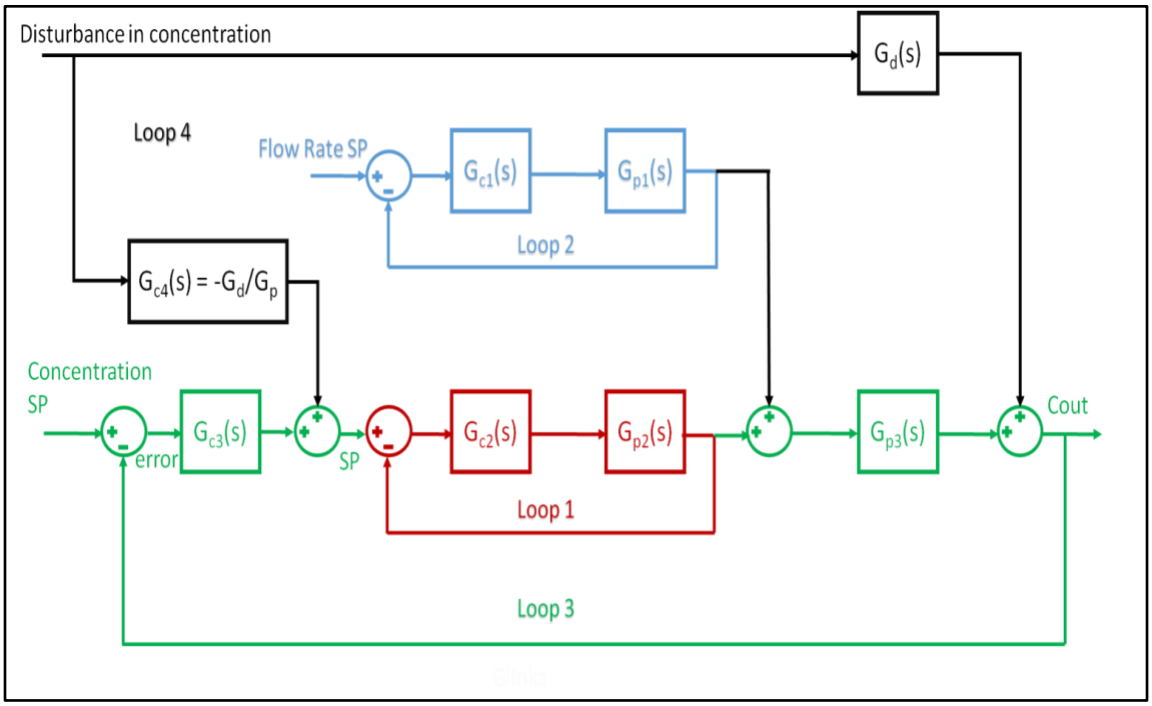

Figure 13. Architecture of the combined feedforward/feedback control

Control loop 2 is also the built-in feedback loop for feeder 2 and works on the same concept as control loop 1. This loop controls the output flow rate of excipient from feeder 2 by manipulating the screw rotational speed of the feeder. The input to the PID is the deviation of flow rate from set point that is given by the outputs of the master feedback controller and the feedforward controller.

Control loop 3 is the master feedback controller which is also the classical PID based controller. NIR spectrometer mounted at the exit of the granulator measures the concentration of API in the granules. The input to the PID is this measured concentration and the output is the set point it provides to control loop 2 (feeder 2 flow rate set point) along with the feedforward controller.

Loop 4 is a feedforward control loop. The feedforward controller measures real-time the concentration of API in the outlet of feeder 1. The real-time measurement of concentration is done by the NIR sensor mounted at the exit of the feeder. The model for the feedforward controller is developed using transfer function model in Matlab (Mathworks, Natic, MA, USA). The input to this controller is the real-time measurement of drug concentration exiting feeder 1 and the output is the set point to control loop 2 along with the master feedback controller. Note that, the feeder 2 flowrate set point is the summation of outputs of both feedforward and feedback controllers. There are two actuator candidates for supervisory feed forward/feedback control as discussed in Section 3.2.

Table 3: Controller Configuration

Controller loops	Controller	Controlled variables	Inputs	Outputs
1. Feedback	$G_{c1}(s)$	API + excipient flow rate	Deviation of API + excipient flow rate from set point	Screw rotational speed
2. Feedback	$G_{c2}(s)$	Excipient flow rate	Deviation of excipient flow rate from set point	Screw rotational speed
3. Feedback	$G_{c3}(s)$	API concentration	Deviation of API concentration from set point	Excipient flow rate set point or Ratio*
4. Feedforward	$G_{c4}(s)$	-	API concentration	Excipient flow rate set point or Ratio*

*Two actuator candidates are possible: Excipient feeder flows rate set point and Ratio

3.4.2. Controller parameters tuning

It can be noted from Table 3 that three PID controllers have been used. Tuning the controller is essential to achieve the desired performance. There are several methods and rules to achieve controller tuning, it could be either heuristic method or it could be defined as an optimization problem (Coughanowr, LeBlanc 2009). The PID controller has three tuning parameters, proportional gain (P), integral time constant (I) and derivative time constant (D). Heuristic tuning methods or the rule-based methods of tuning have limitations

based on the plant model. However, Simulink provides an inbuilt methodology for the tuning of these three parameters. This methodology follows an optimization problem where the objectives include closed loop stability, adequate performance and adequate robustness. For a single-input/single-output system, the PID tuner achieves the above objectives by balancing between the controller performance and robustness. The PID tuner considers all the blocks in the control loop except itself and computes a linear model of the plant. Based on the open loop frequency response of this linear model, it computes an initial set of parameters. Changing the response time, bandwidth, transient behavior or phase margin in time domain or frequency domain computes a new set of PID parameters. This automatic tuning selects a design that balances between set point tracking and disturbance rejection. Preference can be given to either of the performance measures on the PID Tuner interface. The PID parameter for the three feedback control loops are given in Table 4. Plugging the three parameters in Equation 3, gives the controller transfer function.

$$G_c(s) = P + I\frac{1}{s} + D\frac{N}{1+N\frac{1}{s}} \tag{3}$$

In the combined feedforward/feedback control system, either the feedback controller or the feedforward controller can be tuned first. The feedback control system can be tuned once the process transfer function G_p is identified which in our case is given by Equation 4. Once, the feedback controller is tuned, the disturbance transfer function model can be identified through experiments as given in Table 2. Thus, the feedforward controller model is arrived upon as discussed in section 3.3. We have assumed our plant and disturbance model to be accurate and hence the feedforward controller doesn't require any tuning. However, the feedforward controller can be tested by simulating only feedforward control loop. If there is an offset in the response variable, it indicates an error in the feedforward

gain K_{ff}. The dynamic tuning parameters i.e. the lead and lag time is determined by removing feedback control action and using tuning parameters for feedforward control described in literature (Coughanowr, LeBlanc 2009). It should also be noted that the feedforward controller model changes with any change in the process or the material and hence is specific to a given process and formulation.

$$G_p = \left(G_{p1} + G_{p2}\right) \times G_{p3} \quad (4)$$

Table 4: PID controller tuning parameters

Controllers	Proportional gain (P)	Integral time constant (I)	Derivative time constant (D)	Filter coefficient (N)
G_{c1}	200.27 revolutions/kg	80.11 s	1800.17 s	104.65
G_{c2}	200.27 revolutions/kg	80.11 s	1800.17 s	104.65
G_{c3}	18.033 kg/hr (-)	0.891 s	-160.572 s	0.084

Chapter 4: Implementation of control strategy into pilot plant

4.1. Pilot plant

The experiments were conducted on the integrated twin screw granulation pilot-plant. The pilot plant consists of two powder feeders at a height above the granulator which allows for gravitational material flow (Singh, Sahay et. al. 2014). There are two feeders of which one is a K-Tron feeder which consists of a hopper and twin screw that conveys powder with consistent flow rate depending on the weight detected by the load cell. This feeder feeds the API Pre Blend which is a blend of API and excipients. The second feeder is a Brabender feeder that consists of a flexible trapezoidal hopper that is agitated by paddles for consistent mass flow and this feeder is utilized to feed the excipient blend (All the excipients in the API preblend other than the API). The powder collectively is fed to the granulator using a conical hopper at the solid input port. A liquid feeder provides water for granulation at the liquid input port. The solid and the liquid enter in the transport zone and are then conveyed into the mixing zone by the conveying elements where the powder is wetted and further kneaded by the kneading blocks and thus form granules.

4.2. Materials and Methods

As mentioned in section 4.1. there are two blends, one that consists of API and excipients and the other that consists of excipients only. For the experiments performed, the API preblend consisted of 12% of API, and 88% Excipients. The excipients consist of 5 ingredients. The excipient blend consisted of all the excipients mentioned in the API pre blend other than the API. The blends were prepared in a V Blender before they were transferred to their respective feeders. The blender was operated at 25 revolutions per

minute for 20 minutes and the materials were fed in a layered order into the blender from both the arms up to 60% volume of the blender to ensure efficient blending. 2 kg of blends were prepared and hence multiple batches were prepared for the entire experiment.

All the experiments were performed using a loss-in weight twin screw feeder (K-Tron) that feeds the API Pre blend, a loss-in weight single screw feeder (Brabender) that feeds the excipient blend and a co-rotating twin screw granulator (Eurolab 16 TSG, Thermo Fisher Scientific) which was used for wet granulation purpose. The feeders consists of a hopper, conveying screw, impeller (for the K-Tron feeder) and load cell for gravimetric control. The barrel of the twin screw granulator was maintained at 30ºC and the screw speed was maintained at 500 rpm. A constant screw configuration was used throughout all the experiments for this study. Deionized (DI) water was used as the water for granulation using a peristaltic pump. The barrel at the outlet of the K-Tron feeder is a modified barrel that consists a MATRIX-F NIR spectrometer (Bruker Optics) that measures the API concentration at the outlet of the K-Tron feeder. OPUS (Version 7) software was used to operate the spectrometer and collect spectra. At the outlet of the granulator, the granules are conveyed on to a DR100 vibratory feeder (Retsch) which provide a surface in 1-D approach for NIR spectral acquisition. At the outlet of the granulator, NIR spectrometer (Wavelength Stable Back-Thinned 2D FFT CCD Array from Control Development Inc. Sound Bend, IN, USA) measures the concentration of API in granules.

4.3. Integration of control hardware and software

In order to implement the control system, control hardware and software are integrated with the plant. First, the process, the two feeders and the granulator are completely integrated under the Thermo Fisher programmable logic controller (PLC) platform. The

PLC communicates the process data to a remote computer for data analysis. The remote computer is equipped with PharmaMV control platform that reads the process data from the PLC via OPC (OLE for process control). This established connection reads process variables and communicates actuator signals back to the plant as input. Second, NIR sensors have been integrated with the control platform and plant for real-time monitoring of API composition. The sensor operating software collects the spectra and sends the measured spectra to the PharmaMV Real Time System via spectral file polling. The Real Time System consists of the spectral device, spectral range and the calibration model previously developed in the "PharmaMV Development System" and which is used for the real time prediction of API composition. After the integration of process data and PAT sensors, the control-loops are added for advanced process control. The controller connects the actuator variables with the controlled variables. The input to the controller is the plant output which is the controlled variable while the output from the controller, calculated using a control algorithm is the plant input which is the actuator variable. The control hardware and software integration is as shown in Figure 14. As seen in the figure, the API composition in granules and at the feeder outlet are measured by NIR spectrometers. The spectrometers are operated by their individual software which collects the spectra in an SPC file and transfers these files to the PharmaMV platform via spectral polling. The PharmaMV platform uses a calibration model previously built in the development mode to give real time predictions. These real time predictions of API composition are used as an input to the controller and an output is calculated based on the control algorithm in place. The output is the API Ratio which goes through a calculation block that calculates the respective flow rates of the two feeders by maintaining the production rate constant.

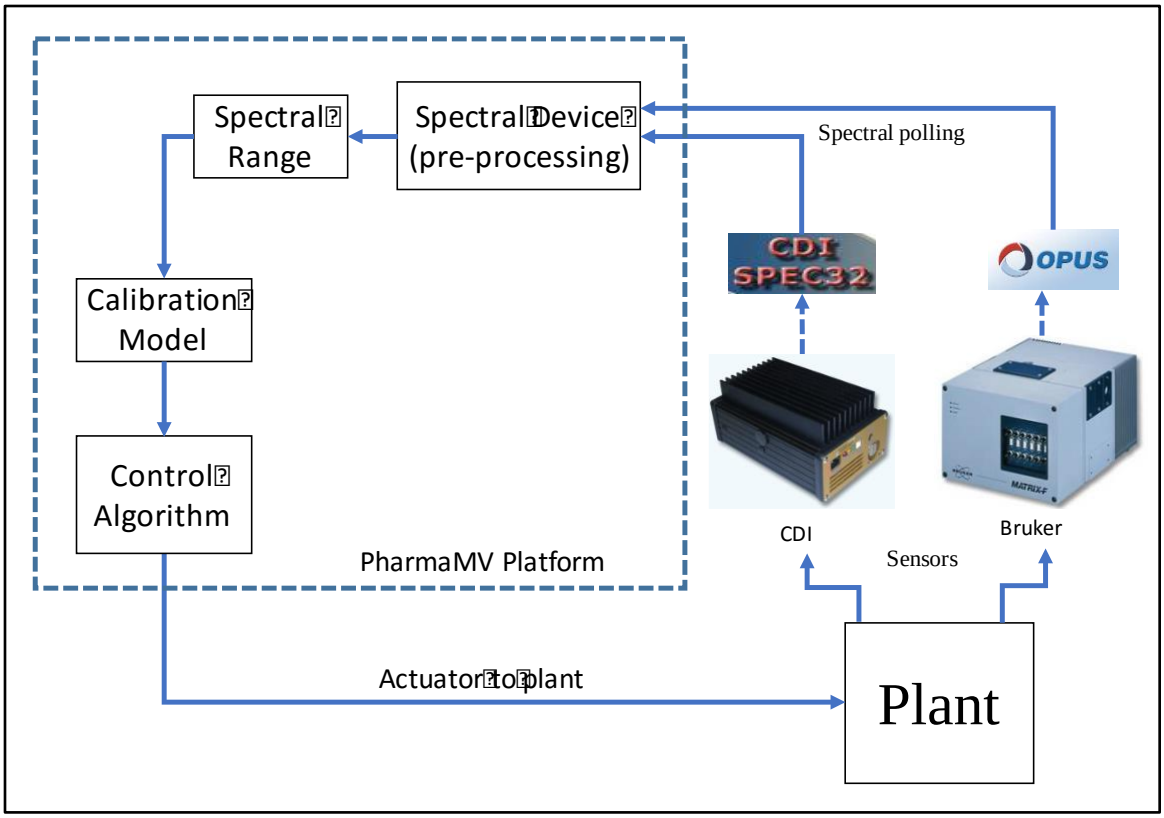

Figure 14: Integration of control hardware and software

4.4. Real-time measurement of API composition

API composition in granules is monitored in real-time by Near Infrared Spectroscopy (NIRS) in diffuse reflectance mode. The NIR source was placed over a vibratory feeder (Retsch DR100) that is used to convey the granules. The reflected radiation was collected via fiber optic connected to the NIR spectrometer (Wavelength Stable Back-Thinned 2D FFT CCD Array from Control Development Inc. Sound Bend, IN, USA) in the spectral range of 1105-2197nm. The spectrometer is operated by SPEC32 software. Each spectrum is the average of 54 spectra for a total acquisition time of approximately 1s. The collected spectrum is then transferred to PharmaMV Real Time platform where API composition is predicted in real time using a PLS calibration model.

For real time measurements, the PLS calibration model was previously developed by in-line measurements on the granulator. Blends of API composition 75.0%, 87.5%, 100%, 112.5% and 125% were prepared. The spectra were then transferred to SIMCA 14.1 (Sartorious, Umeå, Sweden) for further analysis. Spectral range for API selectivity was selected by analysis of the pure components spectra that was acquired off-line.

As the blend consists of multiple components, a number of factors contribute to the variation in the spectra collected. The variation could be due to the different components in the blend (chemical variation), different powder density and flow rates (physical variables). Therefore highlighting the chemical variation associated to changes in API composition is necessary through data pretreatments. To minimize differences in particle sizes that produces baseline shifts and slope variations, first derivative was used. This data preprocessing, removes baseline differences and thus, highlights variation according to the API composition. A portion of 67% of the spectra was used for calibration purpose while 33% of the spectra was used for test purpose. The spectra was preprocessed using Savitzky Golay first derivative with 9 smoothing points in the spectral range 1670-1885 nm . Orthogonal PLS scores plot is as shown in Figure 15 where each data point represents a spectrum colored according to the API concentration in granules. It can be seen that the first principal component is the API concentration explaining 78% of the total variation. Figure 16 describes the predicted values of the test set by the PLS calibration model. 4 PLS factors was selected after an evaluation was made from 1-5 PLS factors for the test set. It should also be noted that during spectral acquisition three L/S ratios were also included within the experiment. The PLS calibration model has been evaluated with 4 PLS factors for the test set of spectra which is given in Table 5. For 6% of API composition in granules,

the root mean square error of prediction (RMSEP) is 0.14, the relative standard error of prediction (RSEP) is 2.27 and the bias is 0.05. This same configuration of the calibration model construction was replicated at the PharmaMV development platform which then predicts API composition in real time.

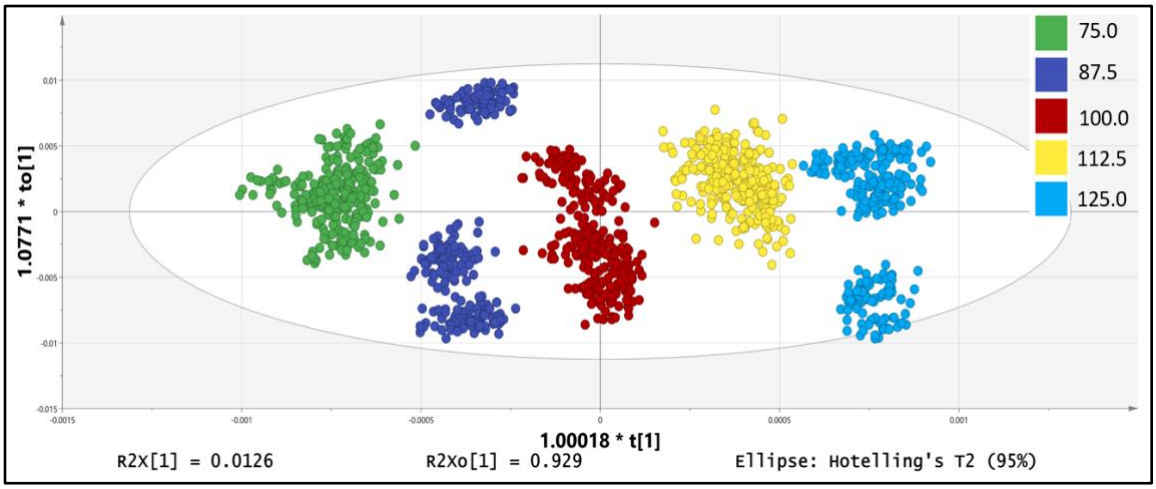

Figure 15: Scores plot of test set (33% of the spectra) colored according to API concentration in granules.

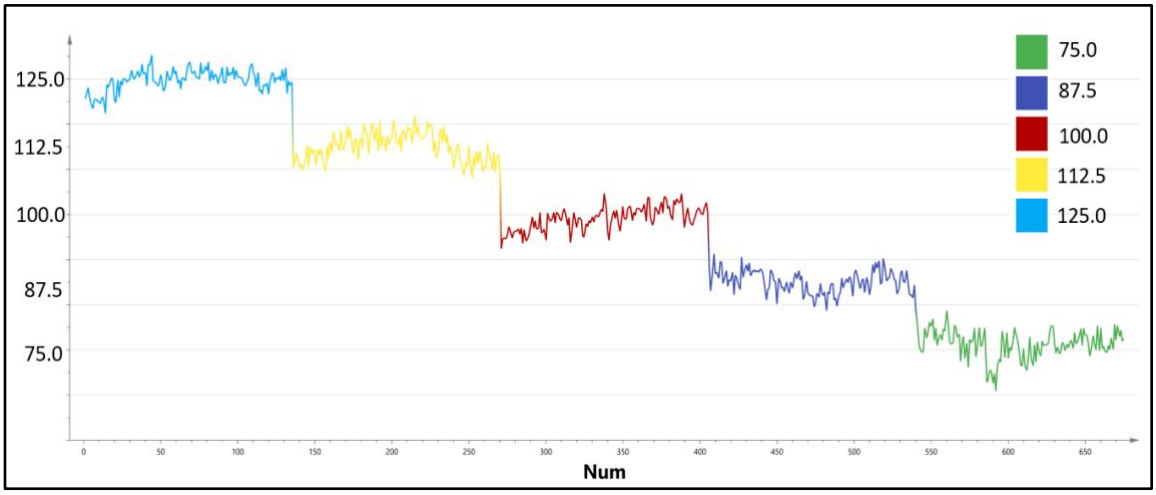

Figure 16: Predicted values of test set (33% of the spectra) colored according API concentration in granules.

Table 5: Evaluation of API granules calibration model by using 100% w/w as center point.

% of API	N of Spectra	Average	StDev	RSD	RMSEP	RSEP	Bias
125.00	135	124.78	1.95	1.56	0.12	1.56	0.01
112.50	135	112.48	2.64	2.35	0.16	2.34	0.00
100.00	135	99.24	2.15	2.17	0.14	2.27	0.05
87.50	135	87.55	2.14	2.44	0.13	2.44	0.00
75.00	135	76.04	2.59	3.41	0.17	3.71	-0.06

4.5. MPC model identification, controller generation and MPC parameter tuning

The process model for MPC was generated in PharmaMV. For MPC specifically, incremental changes in process inputs were introduced and depending on the effect seen in the process outputs, a process model was generated. For the process model generation, a pseudo random binary sequence (PRBS) was introduced in the input variable, actuator which is the API ratio. The nominal value for it was 57.5 and the amplitude was 20. Thus, the random step changes varied between 47.5 and 67.5. The PRBS interval is selected such that it is approximately 20% of the settling time of the response. The shortest interval for PRBS was set to 12 seconds. Thus changes in API ratio changed the flow rates of the two feeders. The total throughput was maintained at 4 kg/hr and thus at 47.5% API Ratio, the flow rate of the excipient feeder was 2.1 kg/hr and the flow rate of the API feeder was 1.9 kg/hr. Similarly at 67.5% API Ratio, the flow rate of the excipient feeder was 1.3 kg/hr and

the flow rate of the API feeder was 2.7 kg/hr. After specifying the mean, amplitude and PRBS interval, the actuation signals in PharmaMV have to be enabled. The PRBS testing is conducted for a minimum of 10 steps. The change in API composition in granules to the PRBS in API Ratio is measured in real time by NIR spectrometer as discussed in section 4.4. Figure 17 represents the PRBS signal introduced into API Ratio. As discussed, it can be seen from the figure that the step change varies between 57.5 and 67.5. The measured API composition is as shown in Figure 18 and consists of the unfiltered and filtered signal. A moving average of 8 seconds was considered to smooth the signal. The response shows process delay and fluctuations in measurement. A single input single output (SISO) system was considered and the input and output data was then used to build a process model.

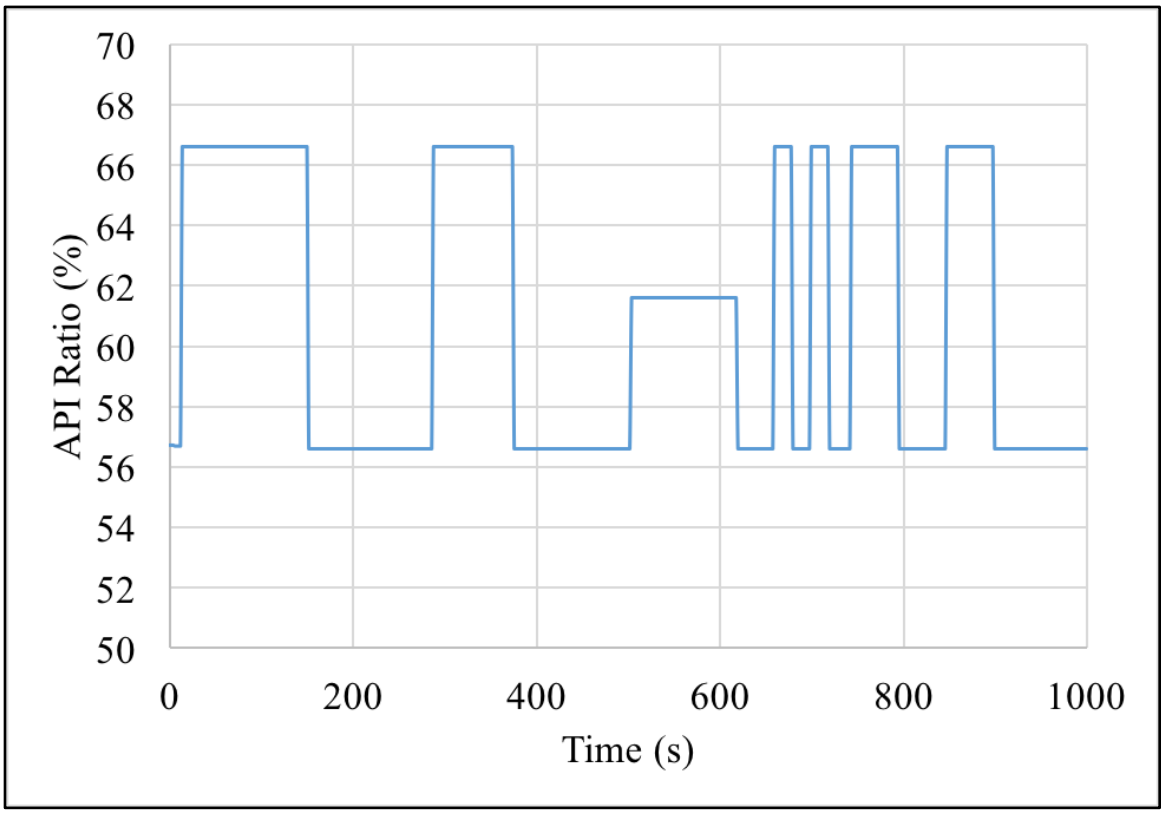

Figure 17: PRBS sequence introduced for the actuator

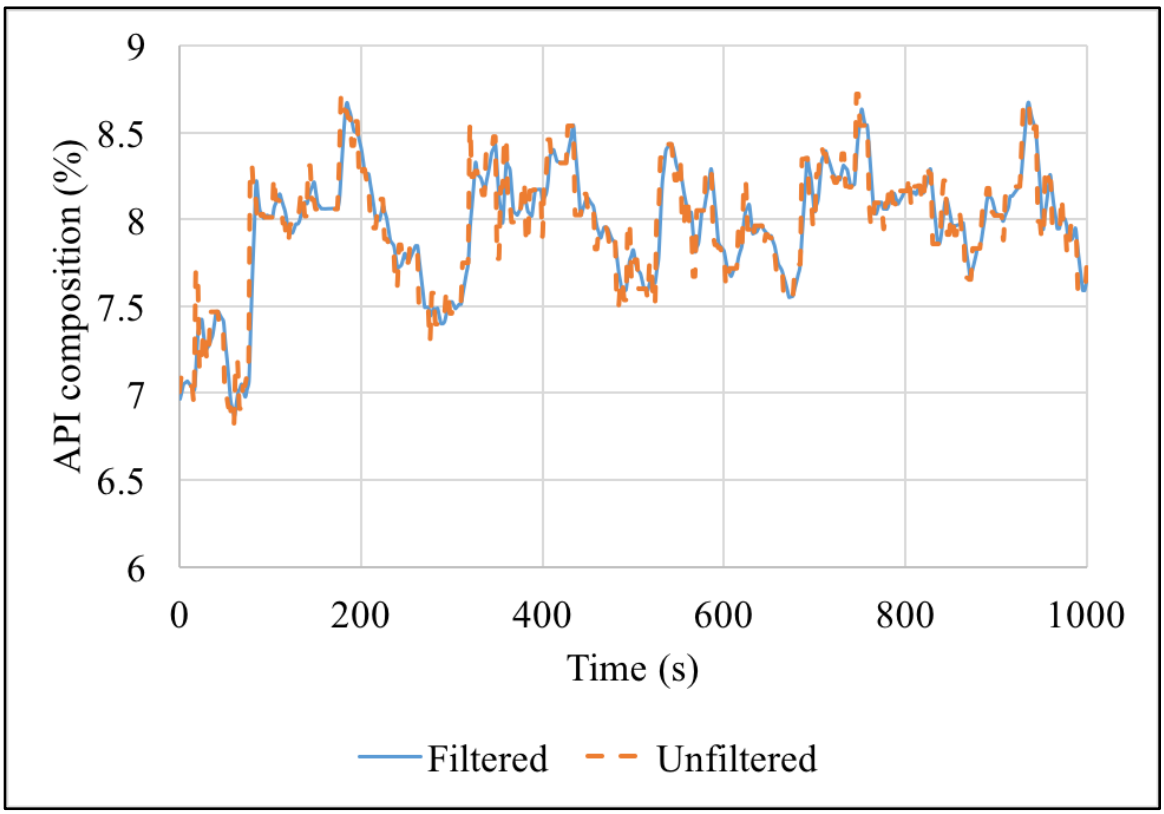

Figure 18: Response in API composition to PRBS

The input and output data generated from the PRBS test was loaded into the PharmaMV development platform. As mentioned before, for MPC incremental changes in process output due to incremental changes in process input is to be modeled, and thus an incremental model was selected. A first order Auto Regressive with eXogenous Inputs (ARX) model was developed. It is difficult to obtain a perfect match between the model predictions and the plant response. However, it is also desired that the model predicts the behavior accurately and hence some kind of tuning is required for the linear model. When the linear model is developed, the coefficients of the model can be viewed and sometimes, the coefficients towards the very end on the right are zero. This signifies that the model uses more coefficients than necessary and decreasing the number of coefficients could improve the accuracy of the model. This is achieved by reducing the total delay while

specifying the model. It should also be noted that too few coefficients also reduce the model efficiency and thus an optimum value for the coefficients can be reached at by monitoring the RMSE value.

Once, the process model has been developed, the MPC controller can be developed by importing the model in the PharmaMV Real-Time system. Once the model is imported and the update interval is specified, the MPC controller is established from the process model. There are three horizon parameters which are constrained horizon, compressed horizon and compression width. The constrained horizon is basically the control horizon over which the controller executes control moves. The constrained horizon is typically set as the response settling time. The other horizons are maintained at the default value. After adding constraints to the variables, the MPC controller was activated and the controller was tested. Once the controller is tested against simulated data, it was tuned to increase the efficiency. There are three tuning parameters, set point weight, move weight and target weight. The effect of the three parameters were observed and then the simulation was saved to test in real time.

Chapter 5: Results and Discussions

Modeling and simulation is gaining increasing importance in pharmaceutical industry. The use of process models in pharmaceutical manufacturing will help reduce cost and enhance quality of products (Kremer, Hancock 2006). This section focusses on evaluating the performance of the combined feedforward/feedback control through process simulation before implementing it on the pilot plant. The primary focus is on set-point tracking and disturbance rejection. For set point tracking, a step change in concentration was introduced and the ability of the controller to track the change was observed. For disturbance rejection, random noise was passed through the system and the ability of the controller to reject the disturbance was evaluated. In order to measure the quality of controlled response, measures such as ITAE, RMSE, ISE, IAE, T2P, D2R and M2P have been discussed.

5.1. Evaluation of closed loop control

5.1.1. Set Point Tracking

As discussed in section 3.1 the unit operation models were developed and simulated in gPROMS and open loop response of the integrated flowsheet model was analyzed. Variables important for the control of API concentration at the exit of the granulator have been systematically studied. In order to highlight the importance of automatic control system for continuous wet granulation process, the open loop response has been first compared with feedback-only closed loop response. As shown in Figure 19, the feedback-only control tracks the predefined set point which is not possible in open loop operation. Set point tracking is essential for our process to provide for bump-less transfer from one

set point to another set point. This also makes the process robust to a range of concentrations.

In Figure 20, we have described four important variables that are affected or manipulated by changing the set point in the feedback control loop. Figure 20 (a) shows the response of manipulated variable (the set point for the excipient feeder flow rate) as a function of time. The feedback controller provides the necessary set point to the PID controller of the excipient feeder. As can be seen, the manipulated variable also follows the set point. When the concentration is increased, the set point for the excipient feeder is lowered indicating that the excipient must flow at a lower flow rate thus increasing the concentration. Figure 20 (b) shows the response of screw speed of the excipient feeder (in revolutions per minute) as a function of time and it behaves similarly to the excipient feeder flow rate set point. Figure 20 (c) shows the response of total inlet flow rate to the granulator. As the excipient flow rate is decreased at 500 s to account for the increase in concentration, the total inlet flow rate also decreases because the flow rate from the API feeder is held constant. Figure 20 (d) shows the total inlet concentration of API entering the granulator as a function of time. As the excipient flow rate is reduced, the concentration of API entering the feeder also increases according to Equation 1.

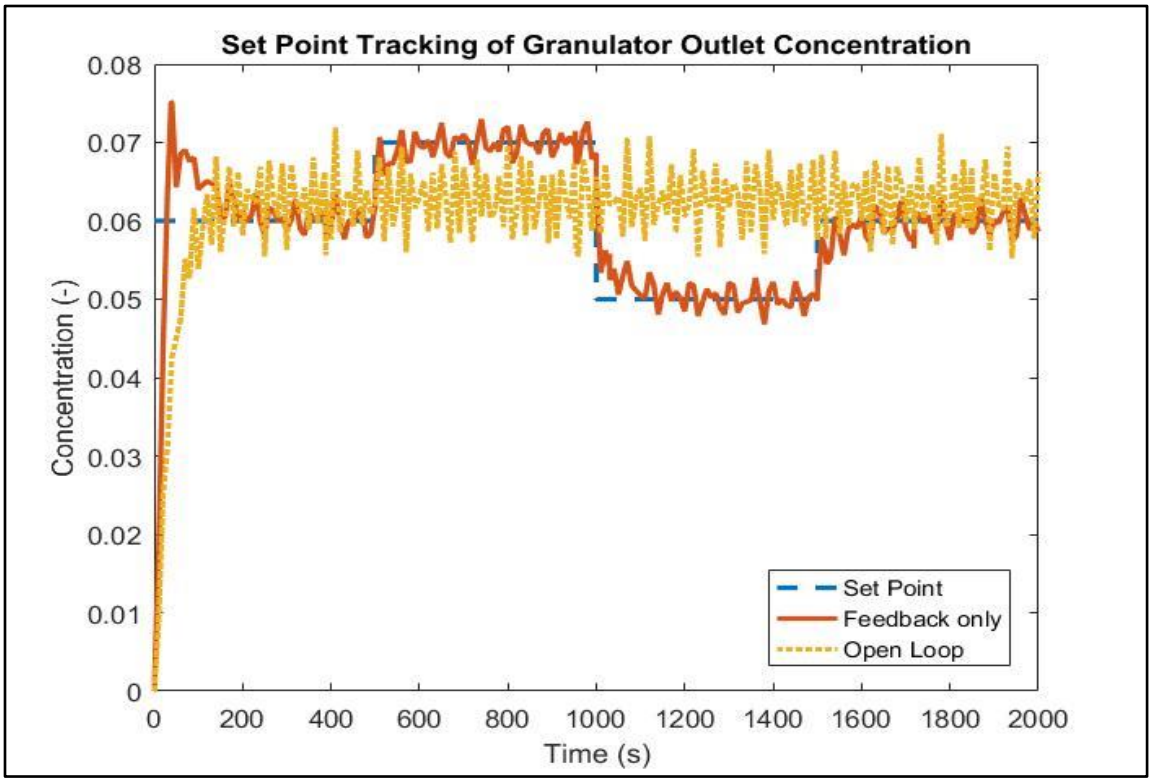

Figure 19: Comparison of Open Loop and Closed Loop response (Set Point Tracking)

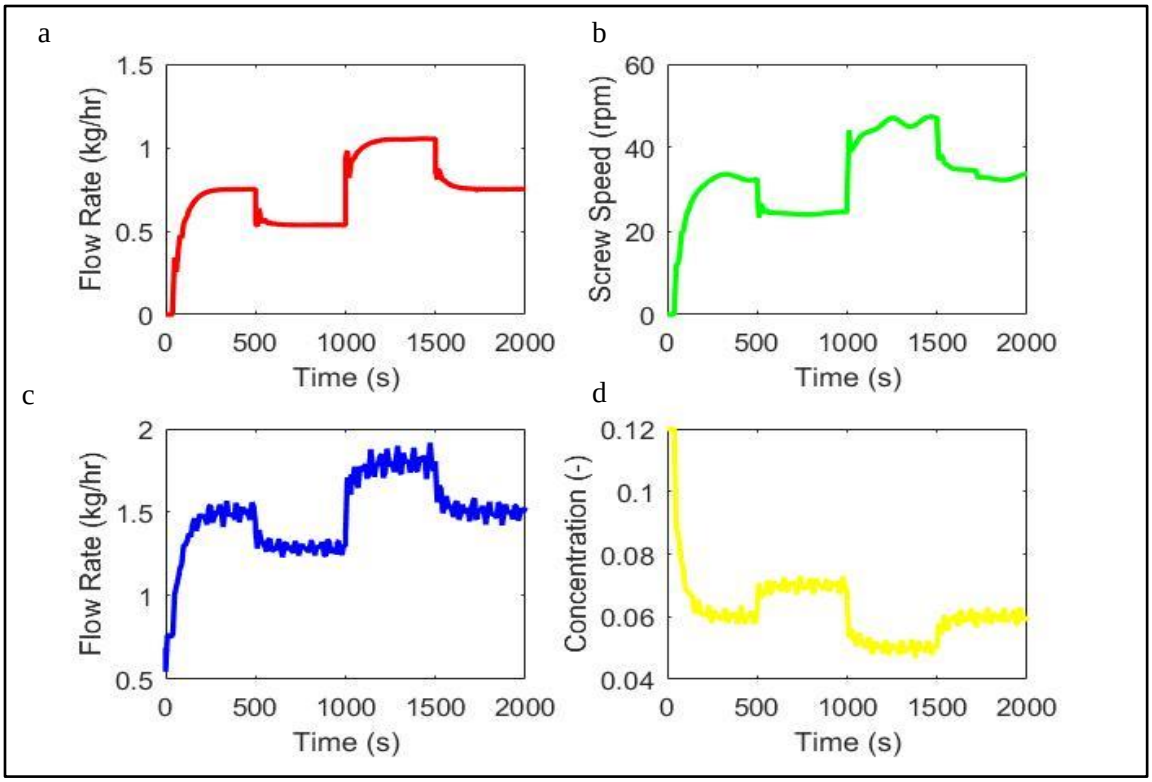

Figure 20: (a) Manipulated variable i.e. Set Point for excipient feeder Flow Rate. **(b)** Screw Speed of excipient feeder. **(c)** Total inlet flow rate to Granulator. **(d)** Total inlet concentration to Granulator

5.1.2. Disturbance rejection

One of the primary reasons to use the control system is to reject the effect of known and unknown disturbances on CPP's and CQA's in real time. Therefore, the disturbance rejection ability of the control system has been evaluated in this section. In the considered process, there can be a disturbance in the concentration exiting the feeder due to non-uniformity in the pre-blend fed to the API feeder. There could also be disturbance in the flow rate of the API feeder and that could affect the concentration of the granules exiting the granulator. The controller's ability to reject the effect of these two types of disturbances is discussed in the following sections.

Step Disturbance Rejection (in Concentration)

The first disturbance rejection considered is a step change in concentration. The set point for the granulator outlet concentration was maintained at 6%. A disturbance was then introduced at 1000 s where the concentration from the outlet of the API feeder was changed from 12% to 15%. This type of disturbance could be observed in practical manufacturing scenario as well. In Figure 21, the open loop response shows an increase in the granulator outlet concentration after 1000 s. This is in accordance to how the process would operate in the absence of control. However, the feedback control loop has a sudden increase of concentration at 1000 s and then settles very quickly back to the set point of 6%. Thus, it is shown that feedback control can rejects this disturbance. However, for a short interval, the product need to be rejected where the API composition in granule got deviated.

Figure 22 describes the different variables that were manipulated or affected by the step disturbance. Figure 22 (a) shows the step disturbance in API concentration at the outlet of

the API feeder as a function of time. Figure 22 (b) plots the manipulated variable (set point for the excipient feeder flow rate) as a function of time. It can be seen that when the API concentration increases at 1000 s, the set point for the excipient feeder flow rate also increases as it was needed to maintain consistent API concentration at granulator outlet. This response is due to the action of the feedback controller. Figure 22 (c) describes the total inlet flow rate to the granulator as a function of time. An increase in the total inlet flow rate can be seen after 1000 s due to the increase in the excipient feeder flow rate. In accordance with Equation 1, the two flow rates increase which causes the inlet API concentration to remain approximately constant as seen in Figure 22 (d). Therefore, the API concentration at the outlet of the granulator is also constant.

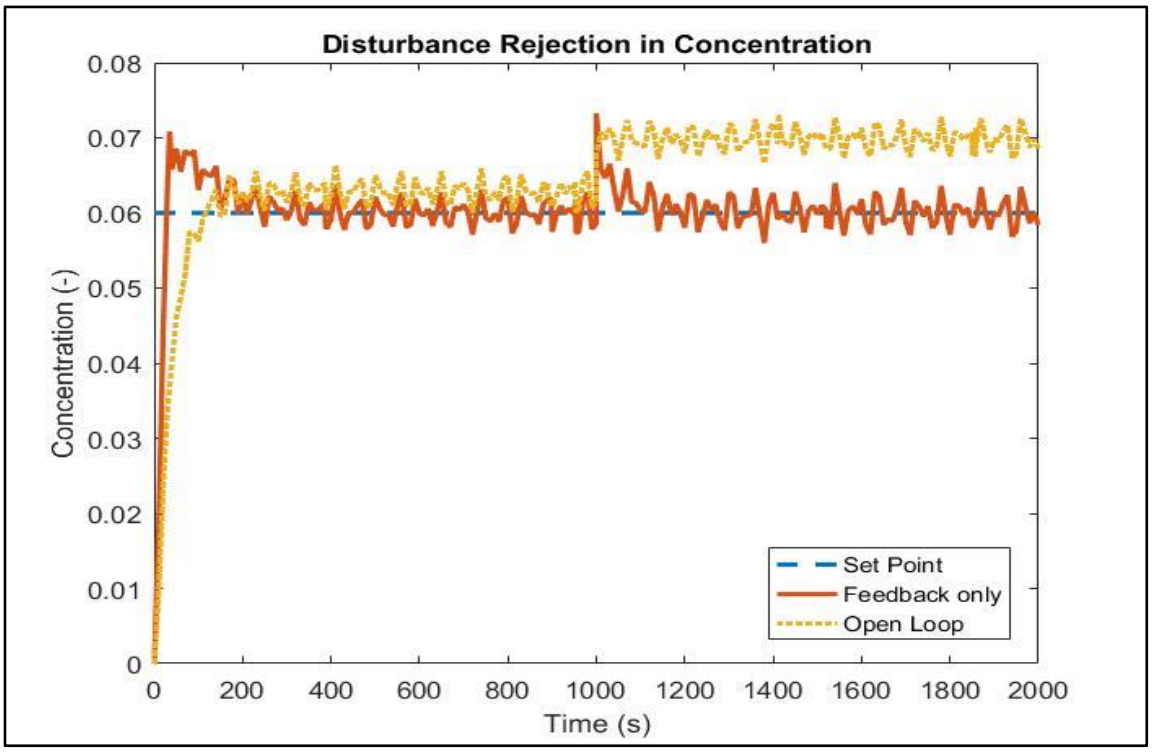

Figure 21: Comparison of Open Loop and Closed Loop (Disturbance Rejection – Step Disturbance in Concentration)

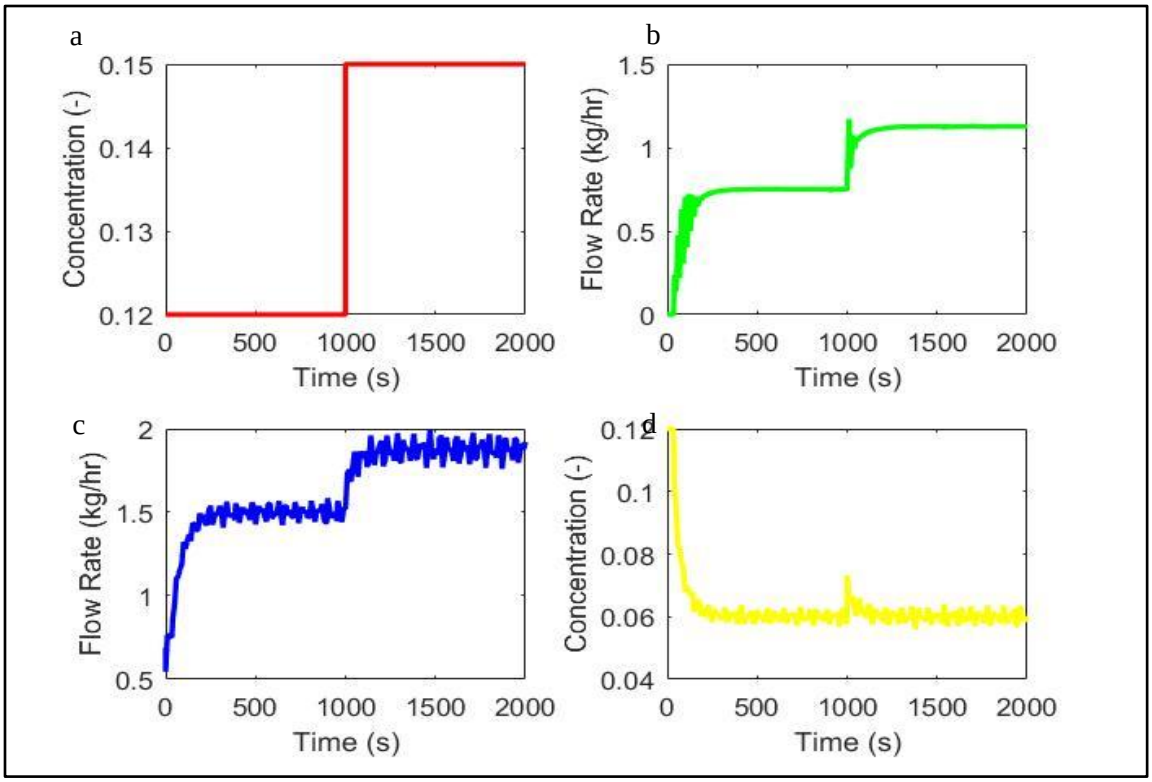

Figure 22: (a) Step Disturbance in Concentration. **(b)** Manipulated variable i.e. Set Point for excipient feeder flow rate. **(c)** Total inlet flow rate to Granulator. **(d)** Total inlet concentration to Granulator.

Operational Disturbance Rejection (API Feeder Flow Rate)

The second disturbance rejection considered is an operational disturbance. It is a step disturbance in the flow rate of the API feeder. This disturbance accounts for any changes made in the throughput of the process. In this analysis, the disturbance was introduced at 1000 s by changing the API feeder flow rate from 0.75 kg/hr to 0.85 kg/hr. Figure 23 shows the effect of this disturbance on the outlet concentration for open loop and feedback-only loop as a function of time. The open loop responds to the increase in the API flow rate by increasing the outlet concentration after 1000 s. This follows Equation 1, since the granulator inlet API concentration increases when the API flow rate increases. However,

the feedback control loop maintains the concentration at the set point after the disturbance has been introduced.

Figure 24 (a) shows a step disturbance in the API feeder flow rate as a function of time. The variable manipulated by the feedback controller to maintain the concentration is the set point of the excipient feeder given by Figure 24 (b). As the API feeder flow rate increases after 1000 s, the excipient feeder flow rate also increases to maintain the inlet concentration to the granulator given in Figure 24 (d) and thereby controlling the outlet concentration. Thus, the total feed flow rate entering the granulator increases and this is depicted by Figure 24 (c).

The above two analyses confirm that feedback controller rejects most of the disturbances, however as seen in the two figures, there are some random disturbances propagated through the granulator. Therefore, a feedback controller alone is not sufficient to reject these disturbances. Thus, it was proposed that a combined feedforward/feedback controller be implemented for this particular process. In section 5.2, we discuss and evaluate the performance of the combined feedforward/feedback control strategy.

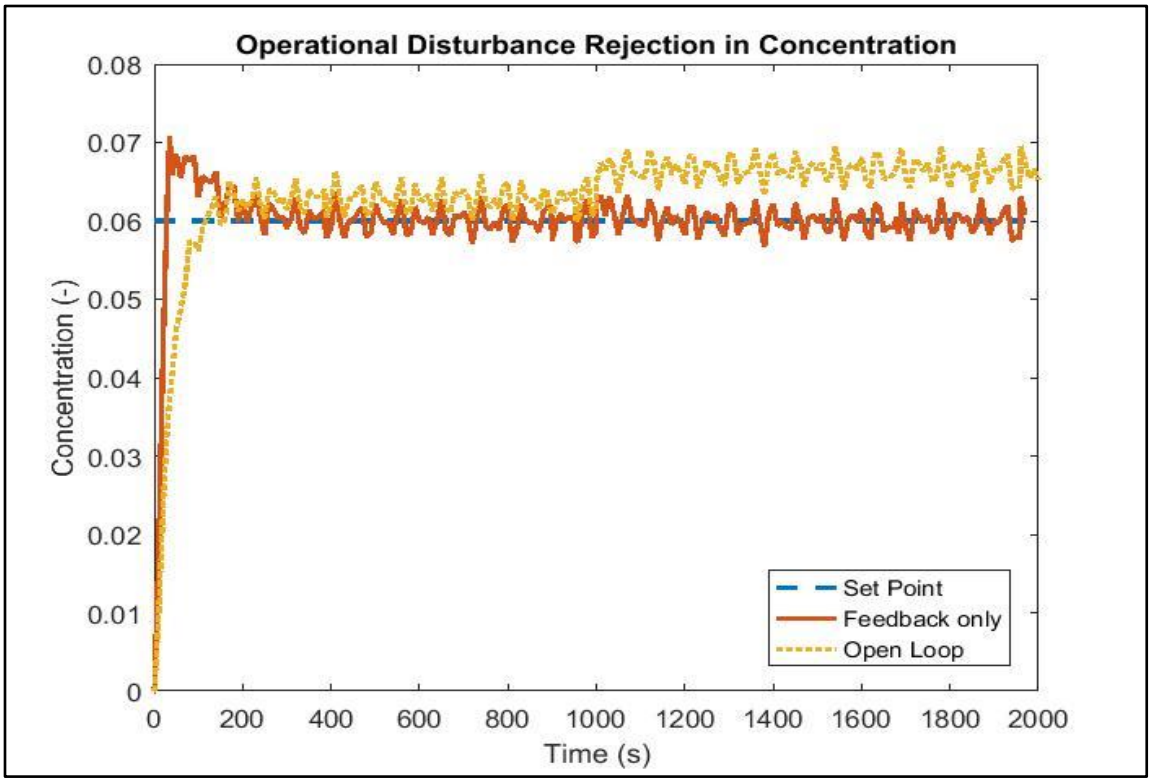

Figure 23: Comparison of Open Loop and Closed Loop (Disturbance Rejection – Step Disturbance in API Flow Rate)

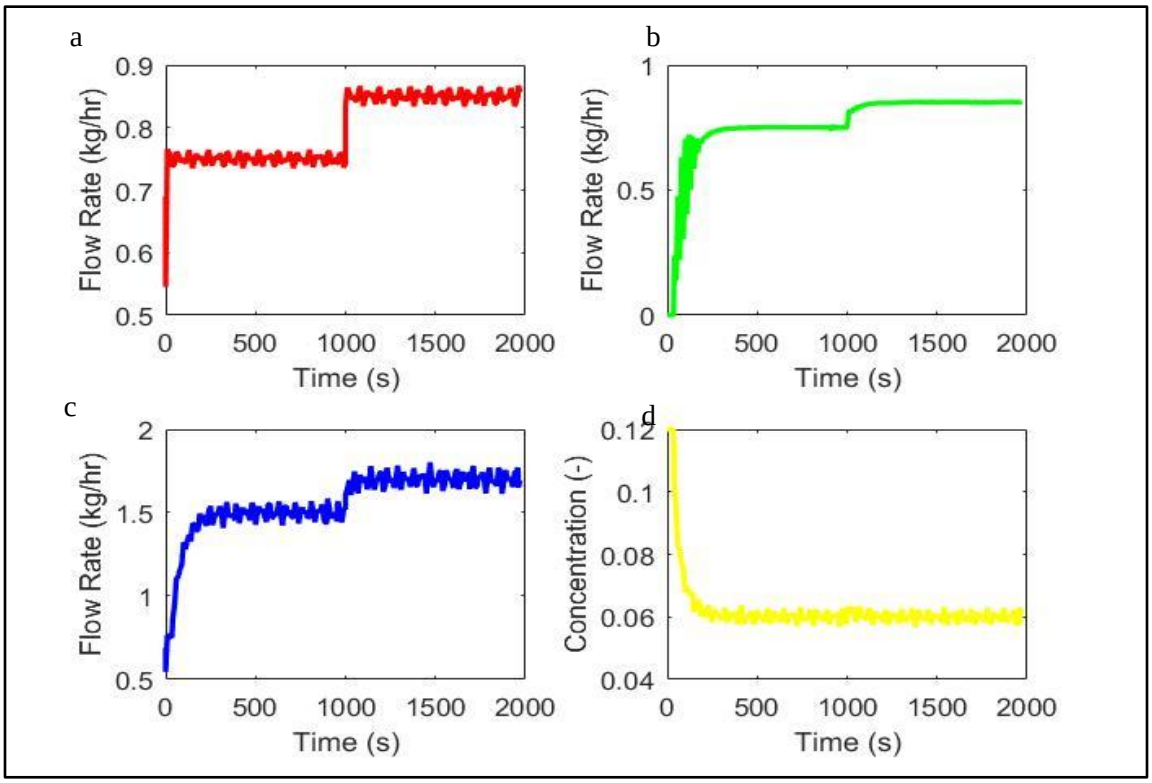

Figure 24: **(a)**. Step Disturbance in API Flow Rate. **(b)**. Manipulated variable i.e. Set Point for excipient feeder flow rate. **(c)**. Total inlet flow rate to Granulator. **(d)**. Total inlet concentration to Granulator.

5.2. Comparison of linear and nonlinear actuators

In order to evaluate combined feedforward/feedback control strategy and MPC control strategy, simulation was performed using Simulink (Mathworks) because the gPROMS simulation platform currently does not have the capability to add feedforward controllers or MPC controller. Thus, the gPROMS flowsheet model was transferred into Simulink. The relevant transfer function models for the various unit operations have been described in section 3.3 These transfer function models were fit to the data generated by the gPROMS model so that the two integrated flowsheet models were similar. Open loop analysis was also carried out on the integrated Simulink model to ensure that the model responded accurately. Before discussing the two control options, a comparison was conducted between the two actuators.

Figure 25 compares the response of a basic feedback (PID) control when a linear actuator (API ratio) is used versus when a nonlinear actuator (Flow rate set point of excipient feeder) is used. As can be seen from the figure, when the linear actuator is used, the control response is similar to that of a first order response with no overshoot. However, when a nonlinear actuator is used, the response is similar to that of a second order response with some overshoot. The rise time for the linear actuator is 95 seconds which is slightly higher than the rise time for the nonlinear actuator which is 60 second. However, the settling time for the linear actuator is 140 seconds while the settling time for the nonlinear actuator is 336 seconds.

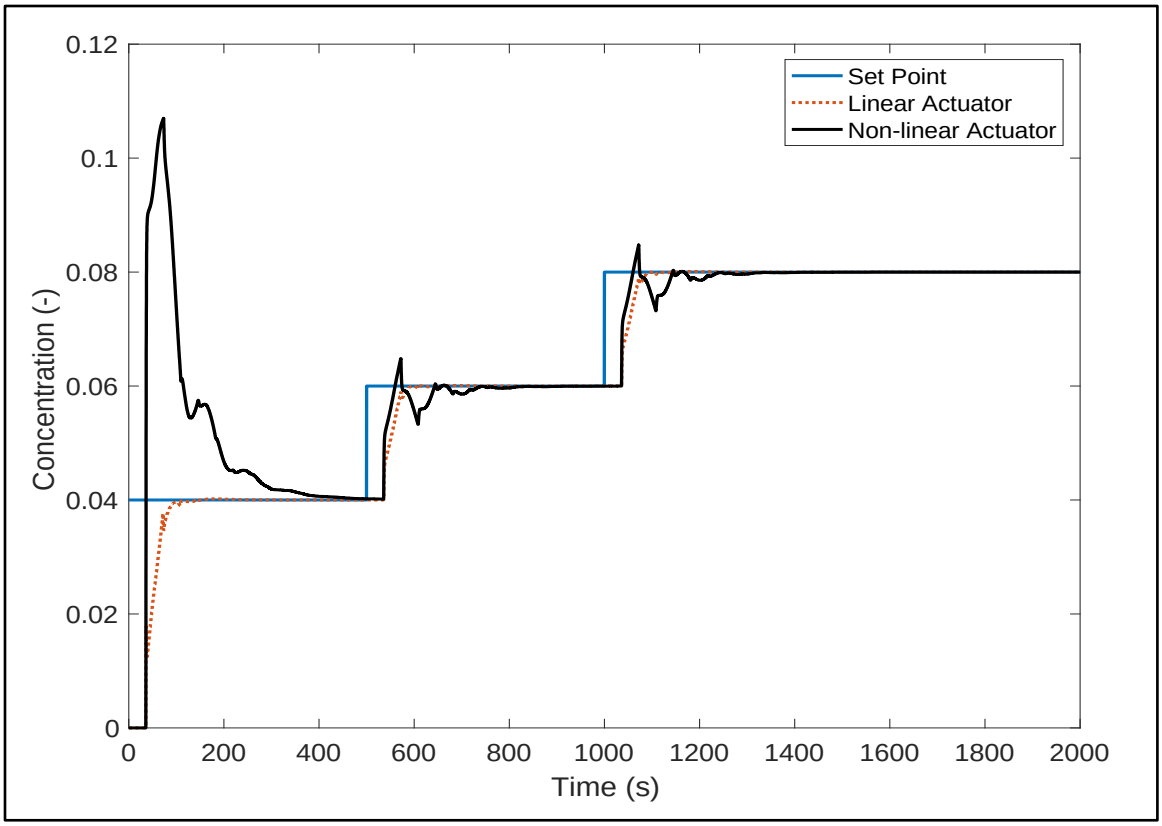

Figure 25: Comparison of the feedback control response for API composition in granules for the two actuator candidates

Figure 26 shows the response of API feeder flow rate for the two control options. It can be seen that the flow rate of API feeder remains constant for the non-linear actuator however the flow rate of API feeder changes with each step change for the linear actuator. Thus in case of nonlinear actuator, the input disturbance in API concentration would be minimal in comparison since the flow rate of the API feeder remains constant.

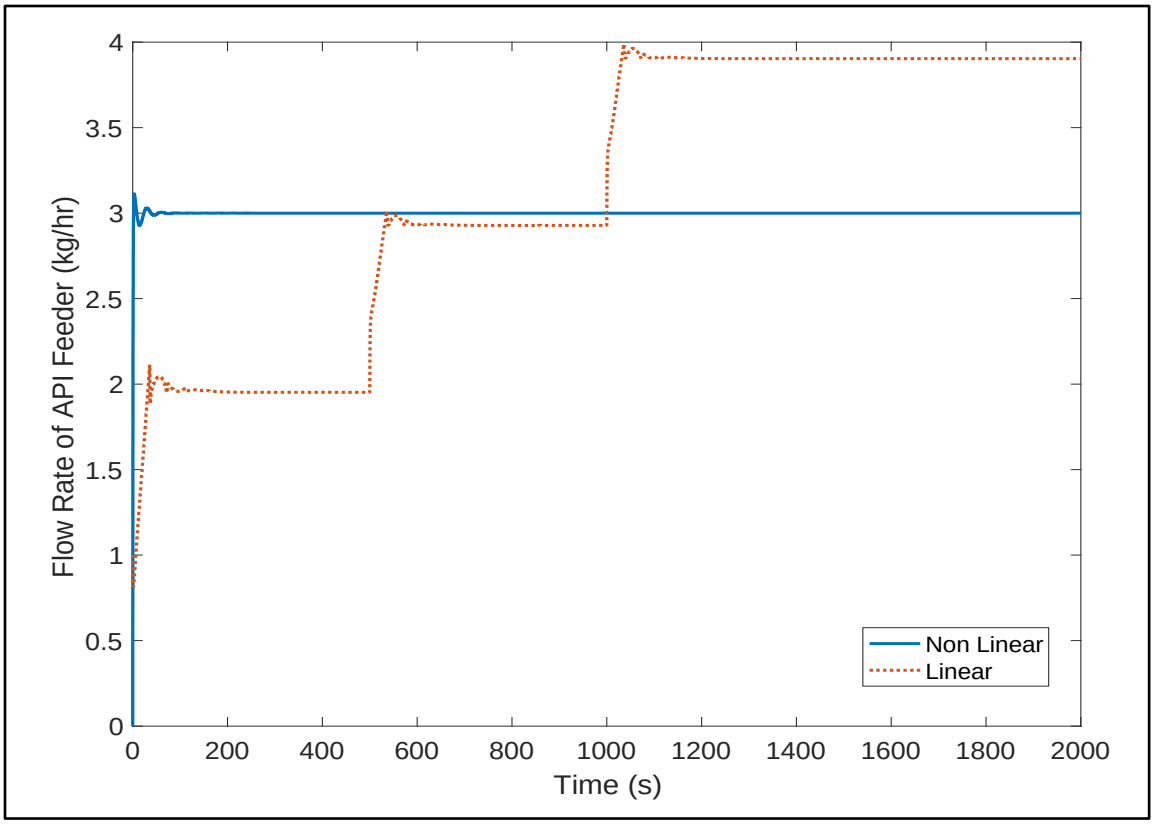

Figure 26: Flow Rate of API feeder for the two actuators

Figure 27 describes the flow rate of excipient feeder for the two control options. In this case, for both the control options, the flow rate changes based on the step change. However, for linear actuator, the production rate as shown in Figure 28 remains constant whereas the production rate for nonlinear actuator varies. Thus, in case of linear actuator, the composition of API as well as the production rate are controlled while in case of nonlinear actuator only the composition of API is controlled. The production rate for the two cases is different before 500 seconds because as can be seen in case of nonlinear actuator, the API composition in granules is quite high and it takes a long time for the response to settle. Thus the controller in the case of nonlinear actuator doesn't actuate the excipient feeder high enough and thus the total production rate before 500 seconds is less in the case of nonlinear actuator than in the case of linear actuator.

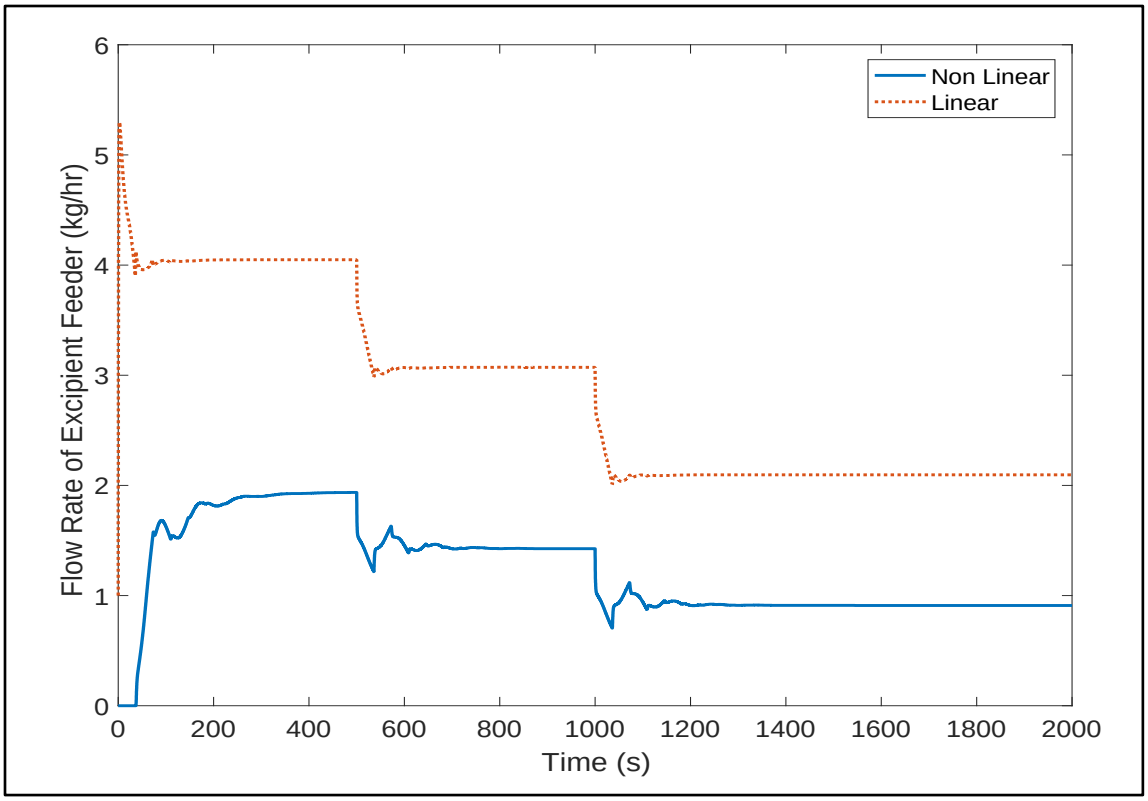

Figure 27: Flow Rate of excipient feeder for the two actuators

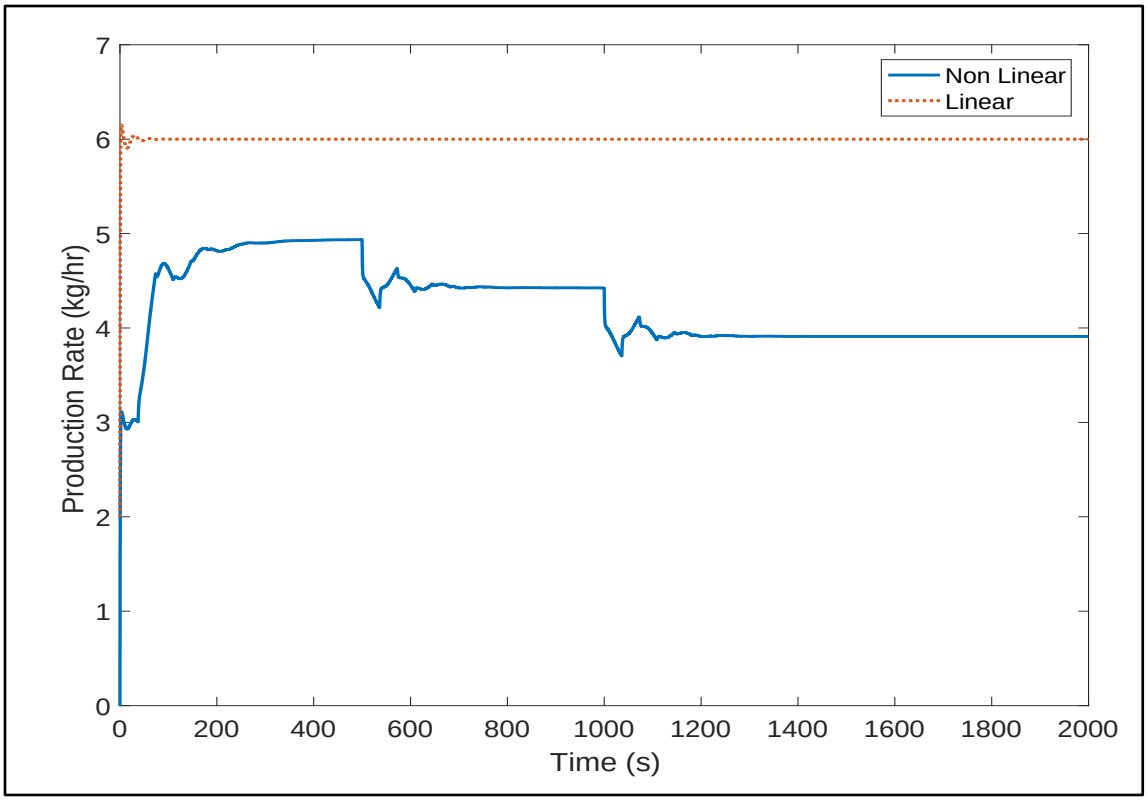

Figure 28: Total production rate for the two actuators

5.3. Evaluation of combined feedforward/feedback control (Nonlinear actuator)

In order to implement a feedforward controller on this process, the flowsheet was simplified and is described in Appendix A. This was done because during implementation a combined transfer function model for the plant would be required and it also brings the model a step closer to implementation in the pilot plant. The simplified model was then simulated for feedback-only control strategy and for combined feedforward/feedback control strategy to compare the two responses.

5.3.1. Random Disturbance Rejection

A random disturbance was introduced in the API concentration at the outlet of the API feeder. Figure 29 shows the response for outlet concentration under the feedback-only control strategy and the combined feedforward/feedback control strategy. As can be seen in the figure, the combined control strategy rejects the disturbance effectively while the feedback-only control strategy propagates the disturbance through the process. There is a comparatively high overshoot at startup for the feedback controller, however there is a slight undershoot for the combined control strategy. The rise time and settling time are less for both the controllers as is desired. Figure 30 (a) shows the disturbance introduced to the process as a function of time. Figure 30 (b) plots the actuator response (set point for the excipient feeder flow rate) as a function of time for the two control strategies. From this figure, it can be noted that the combined feedforward/feedback control reacts faster to the disturbance than feedback-only control. There are also higher magnitude oscillations in the

actuator response for combined control, since it manipulates the actuator to a higher degree to maintain a constant concentration.

In Table 6, the time integral performance criteria are given. The root means square error (RMSE) gives the standard deviation of the residuals and determines the average deviation of the response from the set point. As seen in Table 6, a lower value of RMSE is obtained for the combined control strategy which is favorable. Integral time-weighted absolute error (ITAE) integrates the product of time and absolute error over time. When the ITAE tuning is applied, a quick settling response with smaller oscillations is obtained. However, the initial response is sluggish. The integral squared error (ISE) integrates the square of the error over time. Since the error is being squared, the ISE tuning will eliminate large errors quickly but will tolerate small errors. This will lead to a faster response having small consistent oscillations. Integral absolute error (IAE) integrates the absolute error over time. The IAE tuning results in slower response than the ISE but with fewer oscillations. Numerical values for these are given in Table 6 for random disturbance rejection. These values are smaller for the combined control strategy over the feedback-only strategy which indicates that the combined control strategy performs better and rejects disturbances more effectively.

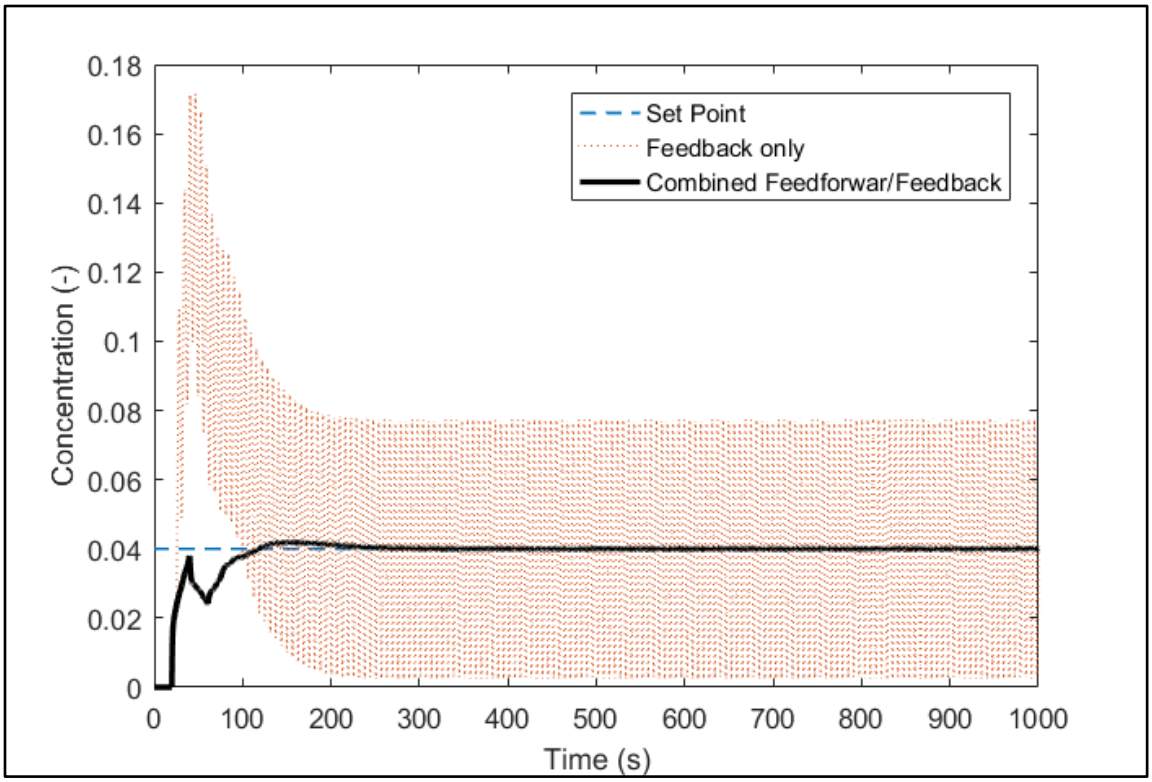

Figure 29: Comparison of Combined feedforward/feedback control with feedback-only control (Random Disturbance).

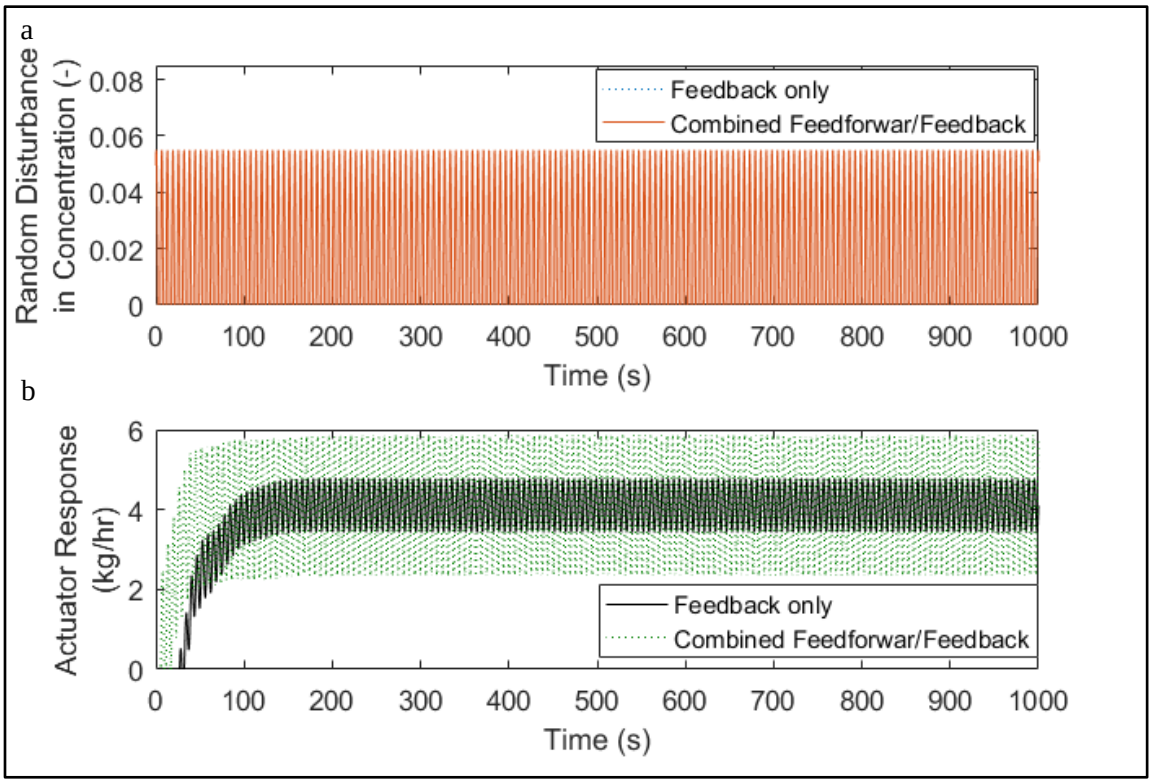

Figure 30: (a). Disturbance (Random) in Concentration. **(b)**. Actuator Response i.e. Set Point of excipient feeder flow rate (kg/hr).

Table 6 Performance Evaluation of Combined feedforward/feedback control vs. feedback-only control (Random Disturbance in Concentration)

Controller	RMSE (-)	ITAE (-) s^2	ISE $(-)^2$ s	IAE (-) s
Combined feedforward/feedback	0.006	1410.157	0.257	14.417
Feedback-only	0.032	120816.07	10.184	265.834

* (-) indicate no unit of error

5.3.2. Step Disturbance Rejection

A step disturbance was introduced in API concentration at the outlet of the API feeder. A step change of magnitude 10% was introduced to the concentration at 500 s. Figure 31 shows the response of the outlet concentration to the step disturbance as a function of time for the combined feedforward/feedback control strategy and the feedback-only control strategy. As seen in the figure, when the disturbance is introduced at 500 s, the feedback controller overshoots, however the combined control strategy rejects this step disturbance and maintains the concentration approximately constant. Figure 32 (a) shows the step change in the API concentration as a function of time. Figure 32 (b) shows the actuator response to the step disturbance as a function of time for both the control strategies. The feedback-only control shows a delay in the actuator response when the disturbance was passed. However, the combined control strategy reacts faster to the disturbance by manipulating the set point for the excipient feeder flow rate.

Table 7 discusses the time integral performance criteria and some qualitative indicators for control performance of the two control strategies. The RMSE value for feedback-only

control is about 5 times that for combined feedforward/feedback control which shows that the combined control strategy controls the concentration at the desired set point more effectively. The ITAE, ISE and IAE values are also smaller for combined feedforward/feedback control in comparison to feedback-only control. Qualitative performance criteria have also been discussed for this disturbance rejection and these are time to product (T2P), duration to reject (D2R) and magnitude to product (M2P) (Haas, Ierapetritou et. al. 2017). T2P determines the time taken for the disturbance to affect the product from the time it first entered the process. From the values mentioned in Table 7, it takes longer for the disturbance to affect the product in the case of combined feedforward/feedback control. D2R gives the time taken for the disturbance to be rejected from when it first affected the product. This value is lower for the combined control strategy and thus it signifies that combined feedforward/feedback control rejects disturbances faster in comparison. M2P gives the maximum deviation from the set point after the disturbance has affected the product. For the combined feedforward/feedback controller there is a slight undershoot. However, for the feedback controller, the value is positive and shows a higher deviation in comparison to combined control strategy. Thus, from the two disturbance rejection analyses, it can be seen that under combined control strategy, the concentration of API is better controlled with no sustained oscillations.

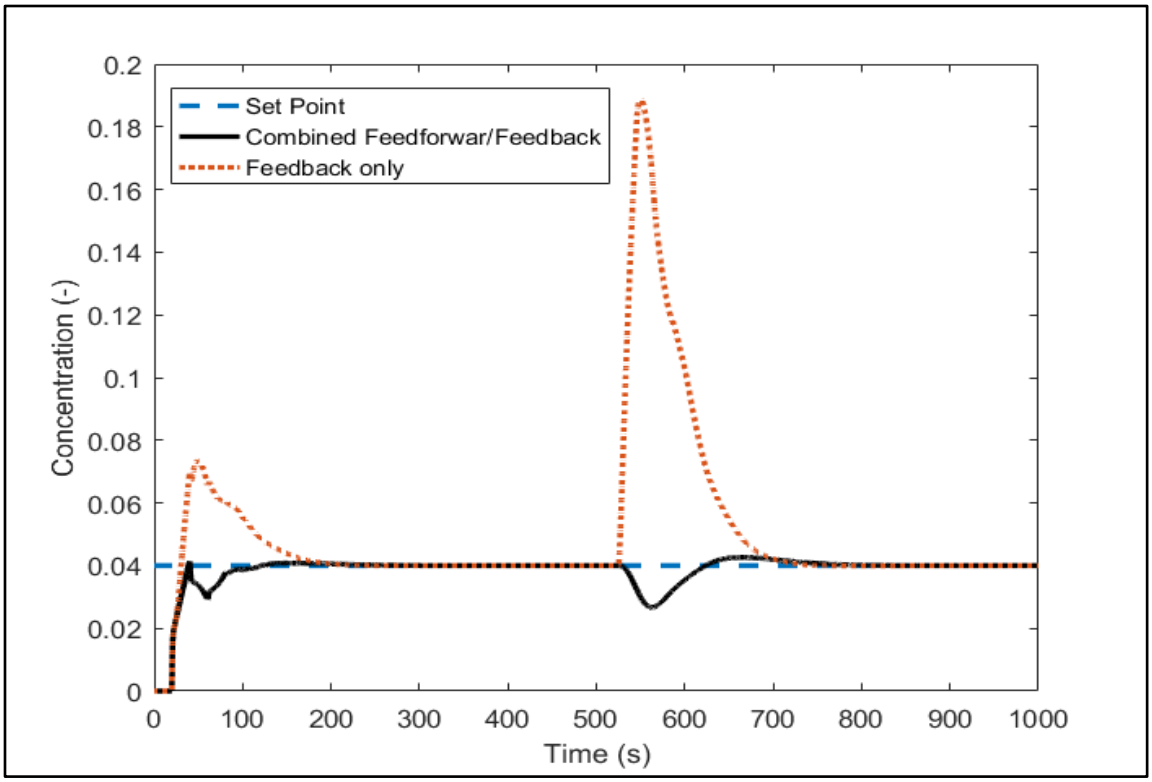

Figure 31: Comparison of Combined feedforward/feedback control with feedback-only control (Step Disturbance).

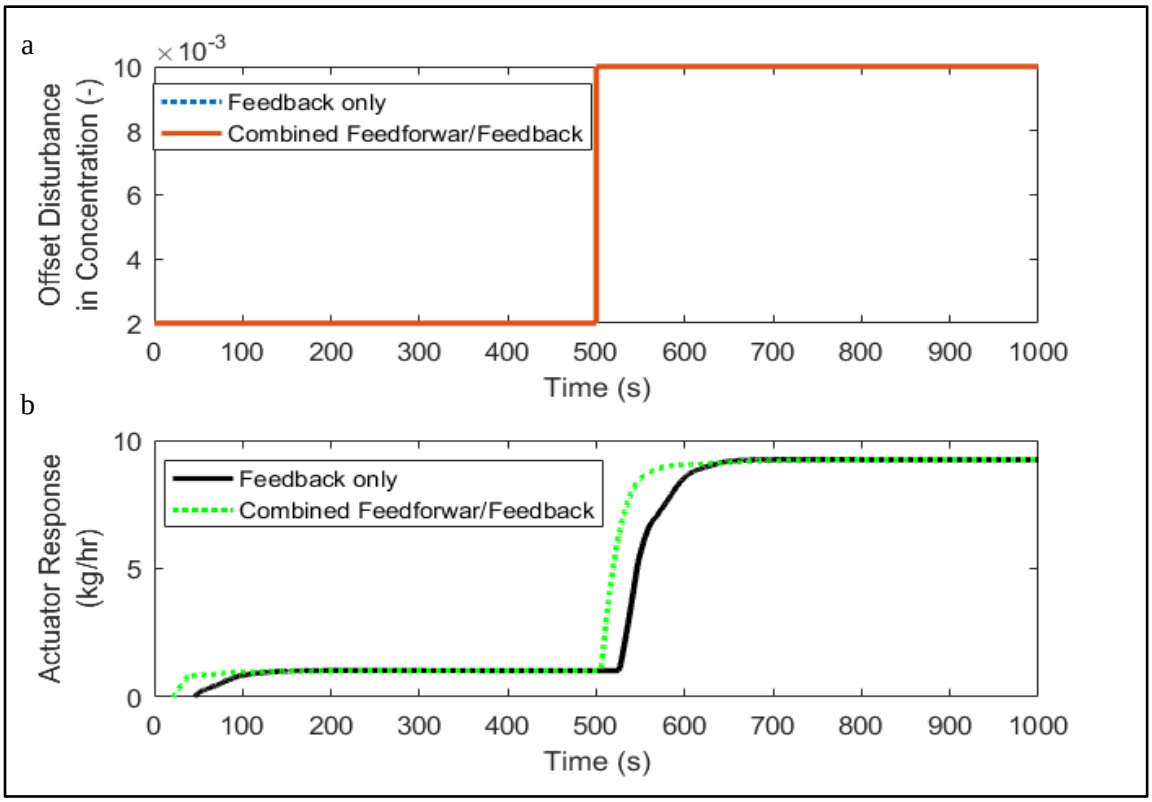

Figure 32: (a). Disturbance (Step) in Concentration. **(b)**. Actuator Response i.e. Set Point of excipient feeder flow rate (kg/hr)

Table 7 Performance Evaluation of Combined feedforward/feedback control vs. feedback-only control (Offset Disturbance in Concentration)

Controller	RMSE (-)	ITAE (-) s^2	ISE $(-)^2$ s	IAE (-) s	T2P (s)	D2R (s)	M2P (-)
Combined feedforward /feedback	0.0067	5863.755	0.284	19.046	31.4	163.7	-0.013
Feedback-only	0.031	55054.884	9.183	119.053	25.4	175.8	0.149

5.4. Evaluation of combined feedforward/feedback control (Linear actuator)

Section 5.3 discusses the combined feedforward/feedback control strategy for the nonlinear actuator. This section focusses on evaluating the combined feedforward/feedback control strategy for the linear actuator. Offset kind of disturbances were introduced in the concentration of API exiting the feeder since due to lack of blend uniformity, certain regions of the powder show either a higher concentration or a lower concentration. Figure 33 describes the disturbance introduced which are step changes every 250 seconds. The response of API composition in granules for feedback only control and for combined feedforward/feedback control is described in Figure 34. From the figure it can be seen that every 250 seconds, when the disturbance is introduced, the feedback control has an overshoot or undershoot depending on the disturbance. However, in comparison to feedback only, combined feedforward/feedback control has lesser overshoot and settles comparatively faster.

Table 8 discusses the performance evaluation criteria and some qualitative indicators of the two control strategies for the linear actuator. The RMSE value for the combined control strategy is less than that for the feedback only control strategy which shows that the combined control strategy controls the composition of API in granules more efficiently when an input disturbance affects the process. From the table we also see that the ITAE, ISE and IAE values are smaller for the combined control strategy in comparison to the feedback only control strategy. The T2P value for both the control strategies is the same which indicates that disturbance takes the same time to affect the product in both cases. The D2R value is smaller for combined control strategy than for feedback only which indicates that it rejects disturbances faster than feedback only controller. The M2P value for feedback only control is more than that for combined control as can also be seen in Figure 34.

Table 8 Performance Evaluation of Combined feedforward/feedback control vs. feedback-only control (Linear Actuator)

Controller	RMSE (-)	ITAE (-) s^2	ISE $(-)^2$ s	IAE (-) s	T2P (s)	D2R (s)	M2P (-)
Combined feedforward /feedback	0.0086	11895	1.1344	36.253	31.2	219.2	0.0013
Feedback-only	0.0093	43032	1.3672	63.389	31.2	292.6	0.0046

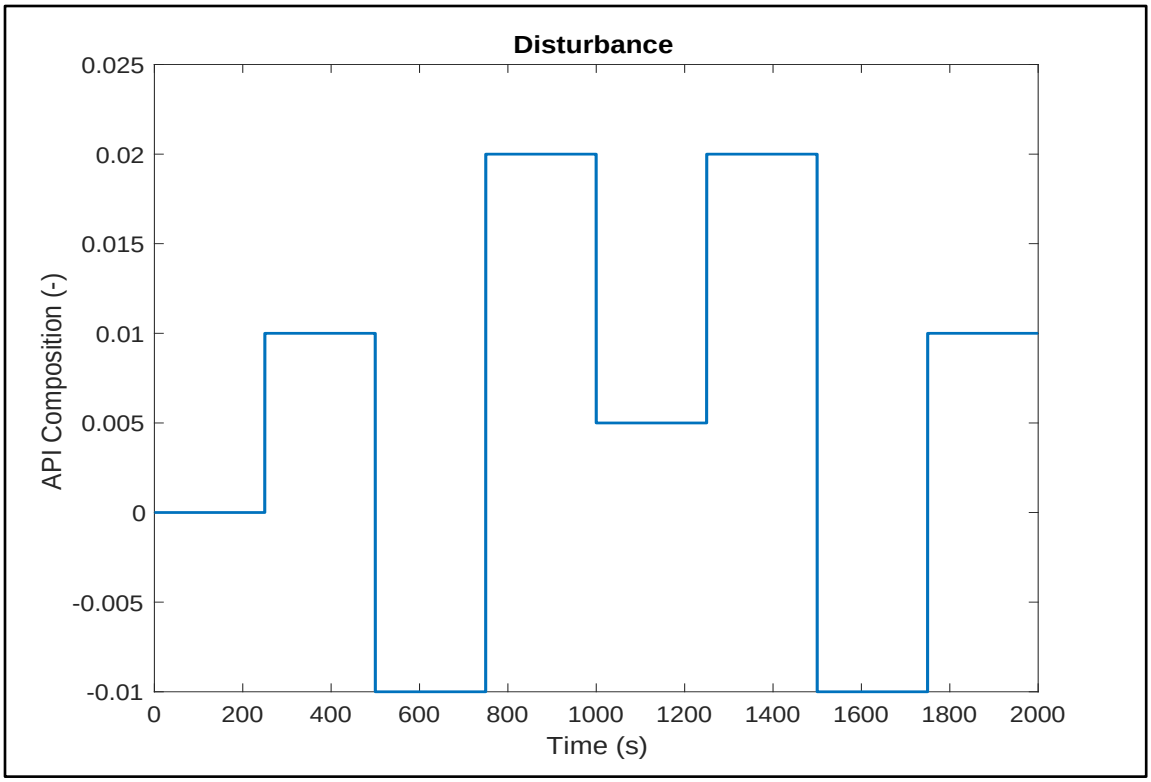

Figure 33: Disturbance introduced (Step changes in concentration)

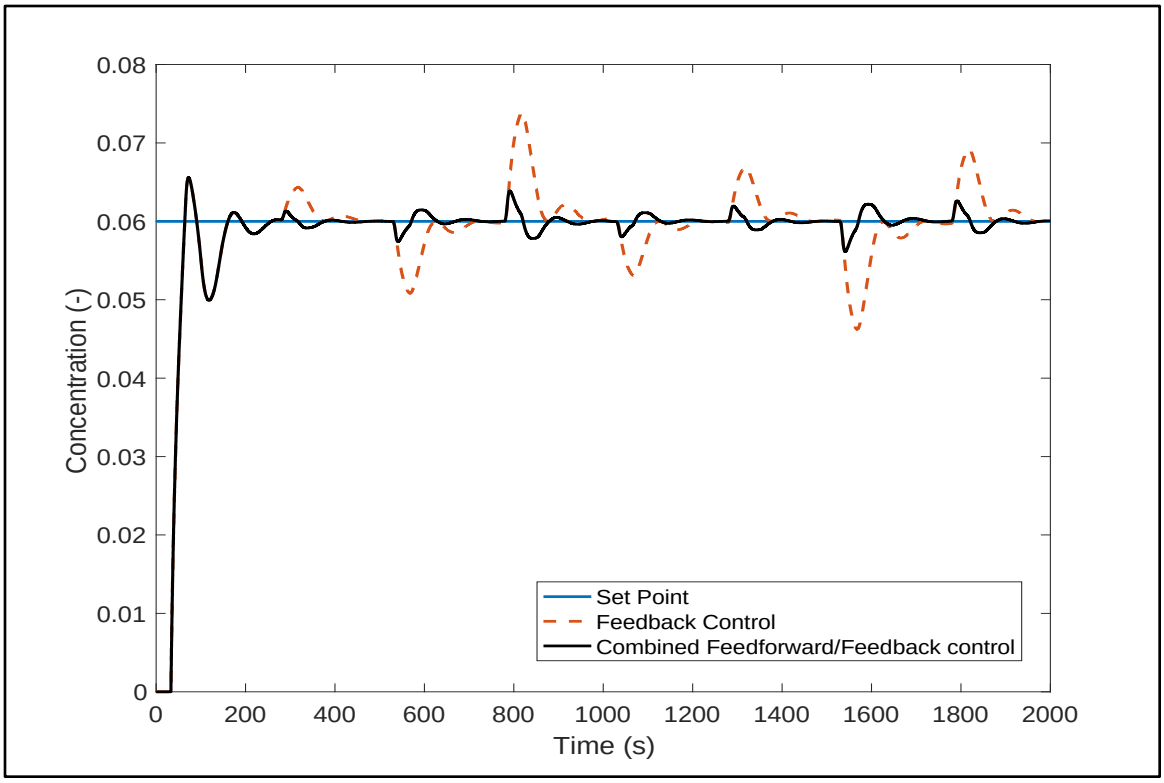

Figure 34: Comparison of combined feedforward/feedback with feedback only for linear actuator

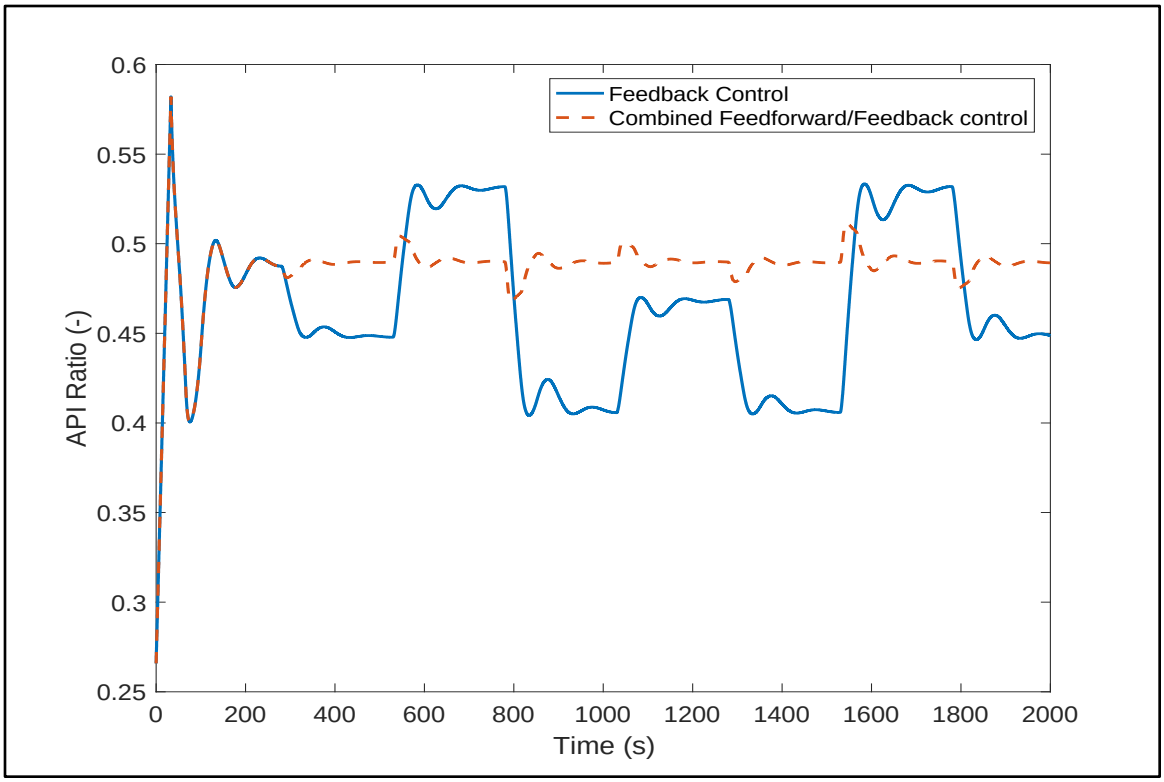

Figure 35: Actuator response i.e. API Ratio

5.5. Evaluation of MPC over PID control (Linear actuator)

In section 5.3 a combined feedforward/feedback control was evaluated for the nonlinear actuator as one of the control options. In this section, the linear actuator based transfer function model has been used for PID control as well as Model Predictive control. The two control strategies have been evaluated with a random disturbance in measurement as observed experimentally.

Figure 36 is a comparison of the response for composition of API in granules for MPC as well as PID control. A random disturbance was added in the measured signal which is similar to that observed experimentally. The response for composition of API in granules for MPC is indicated in red dotted line while the response for composition of API in granules for PID control is indicated in black solid line. As can be seen, the rise time for

MPC which is 54 seconds is less than that for PID control which is 65 seconds. It can also be clearly noted that MPC rejects the disturbance observed in the measured signal whereas PID controller does not reject it efficiently.

Figure 37 represents the actuator response to the disturbance in measured signal. The blue solid line indicates the actuator response for MPC control while the red dotted line indicates the actuator response for PID control. As can be seen, MPC doesn't actuate the API ratio as much as the PID controller does, since it accounts for the disturbance as the disturbance in measured signal and not process disturbance.

Table 9 gives the performance evaluation for MPC over PID control in case of linear actuator. The RMSE value for MPC is less in comparison to feedback only control which indicates that it controls the API composition in granules more efficiently and which can also be noticed in Figure 36.

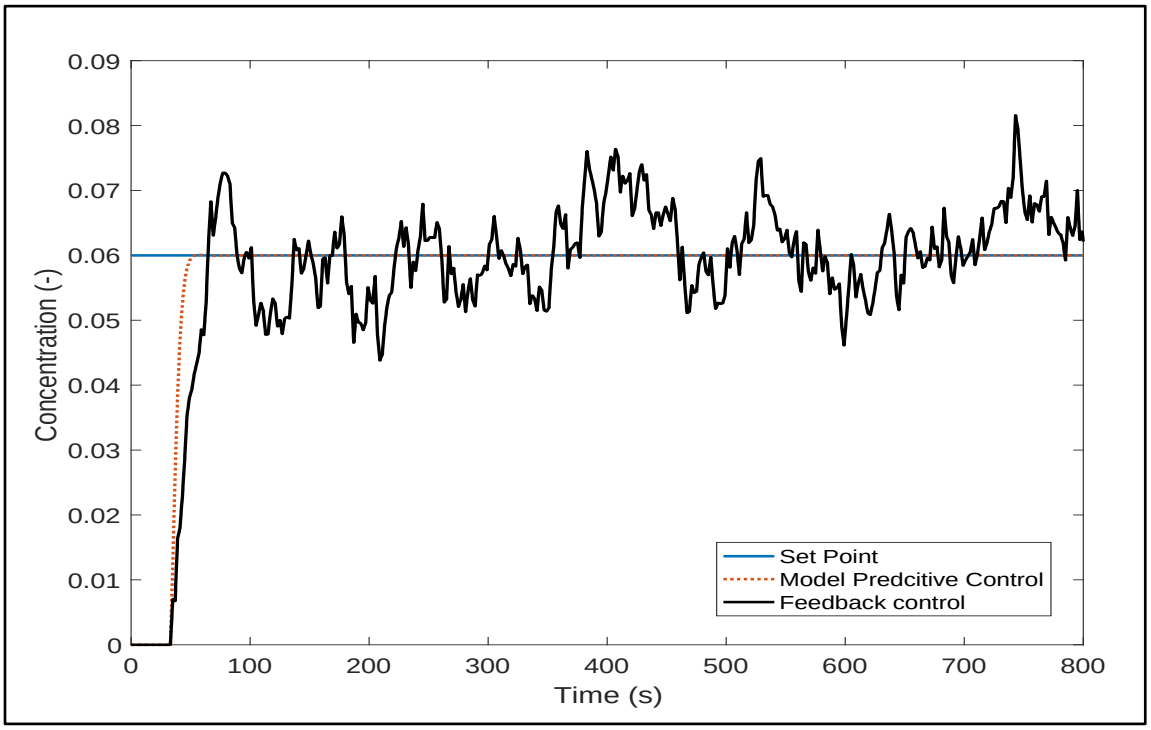

Figure 36: Comparison of MPC with PID control for disturbance in measured signal

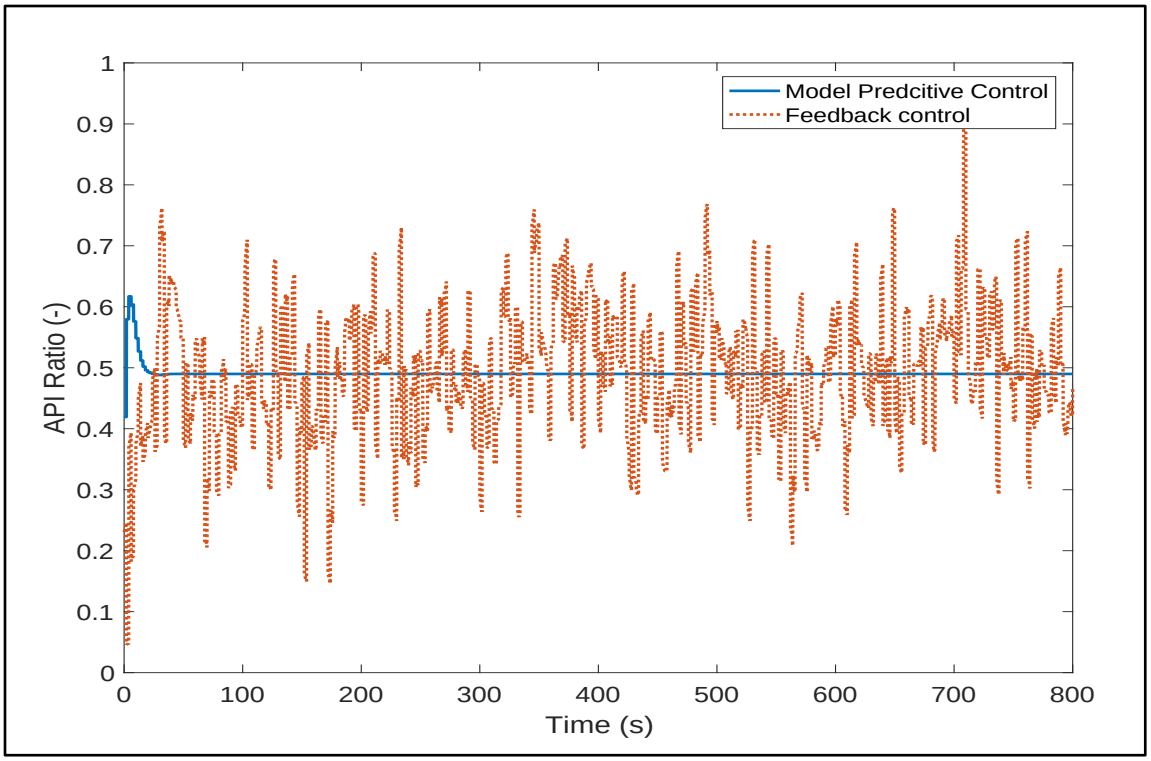

Figure 37: Actuator response of MPC and PID control to disturbance in measured signal

Table 9: Performance evaluation of MPC over PID control

Controller	RMSE (-)	ITAE (-) s^2	ISE $(-)^2$ s	IAE (-) s
Model Predictive Control	0.0127	418.6453	0.9482	17.0913
PID	0.0151	16830	1.4689	60.9941

5.6. Implementation of advanced control in pilot plant

The control system was first evaluated in simulation mode before implementing it on the pilot plant. From the *in silico* study carried out in the previous sections, we see that model predictive control algorithm gives better performance and hence this control scheme was

selected to be implemented on the pilot plant. The control platform integrated with the plant also provides for a model predictive controller. The developed MPC was then executed in real-time in closed loop to test its efficiency. Two feeders were connected to the TSG, one consisting of API Pre Blend and one consisting of excipient blend. A CDI NIR spectrometer (Wavelength Stable Back-Thinned 2D FFT CCD Array from Control Development Inc. Sound Bend, IN, USA) is used to measure the composition of API in granules at the outlet of the granulator. The developed PLS model is used to give real time predictions for API composition in PharmaMV Real-Time system. These predictions are then used by the linear model generated for MPC which calculates the actuator following an algorithm and generates an actuator signal. The actuator signal is the API Ratio which is sent to a Ratio calculation block which calculates the flow rate set point of the two feeders.

Figure 38 shows the performance of the feedback based MPC controller in the pilot plant. Figure 38 (a) describes the mode in which the control platform is running. The control platform was initially running in HMI mode which corresponds to a value of 1 where the controller is deactivated. At 96 seconds, the mode was changed to APC (Advanced Process Control) corresponding to a value of 2 where the controller was activated. Again at 326 seconds, the mode was changed back to HMI. Figure 38 (b) shows the API composition in granules as measured by NIR. It should be noted that this is the filtered measurement where a moving average of 8 seconds was taken. During the time when the controller is active, the composition of API is controlled fairly efficiently to around 6% as can be seen from the figure. When the controller is not active, the composition of API is either below 6% (before 96 seconds) or above 6% (after 326 seconds). It can also be noticed after 326

seconds, when the controller is turned off the API composition hasn't shifted much since the two feeders are operating at the flow rate last set by the controller. Figure 38 (c) shows the API Ratio which is the manipulated variable. As seen in the figure, the manipulated variable changes when the controller is activated in order to control the composition of API in granules. From the API Ratio, the flow rate set point for the two feeders are calculated. Figure 38 (d) shows the production rate throughout the process. It can be seen that the production rate is held constant at 6 kg/hr throughout the entire process. Figure 38 (e) and (f) show the flow rates for the API blend feeder and the excipient feeder respectively. Before 96 seconds, it can be seen that both the feeders operate at 3 kg/hr. When the controller is activated, the flow rates change based on the change in API Ratio. At 326 seconds, when the controller is turned off, the flow rate of the two feeders are at the value last set by the control action. The controller performance in comparison to when the process runs in open loop was evaluated with performance evaluation parameters discussed earlier. The RMSE value for when the controller is active is 0.31 while for open loop it is 0.54. ITAE value is 3950, IAE is 30.9264 and ISE is 10.5197 for closed loop control while the respective values for open loop are 50897, 180.622 and 114.8573. Thus, a feedback based MPC controller was successfully implemented with satisfactory control.

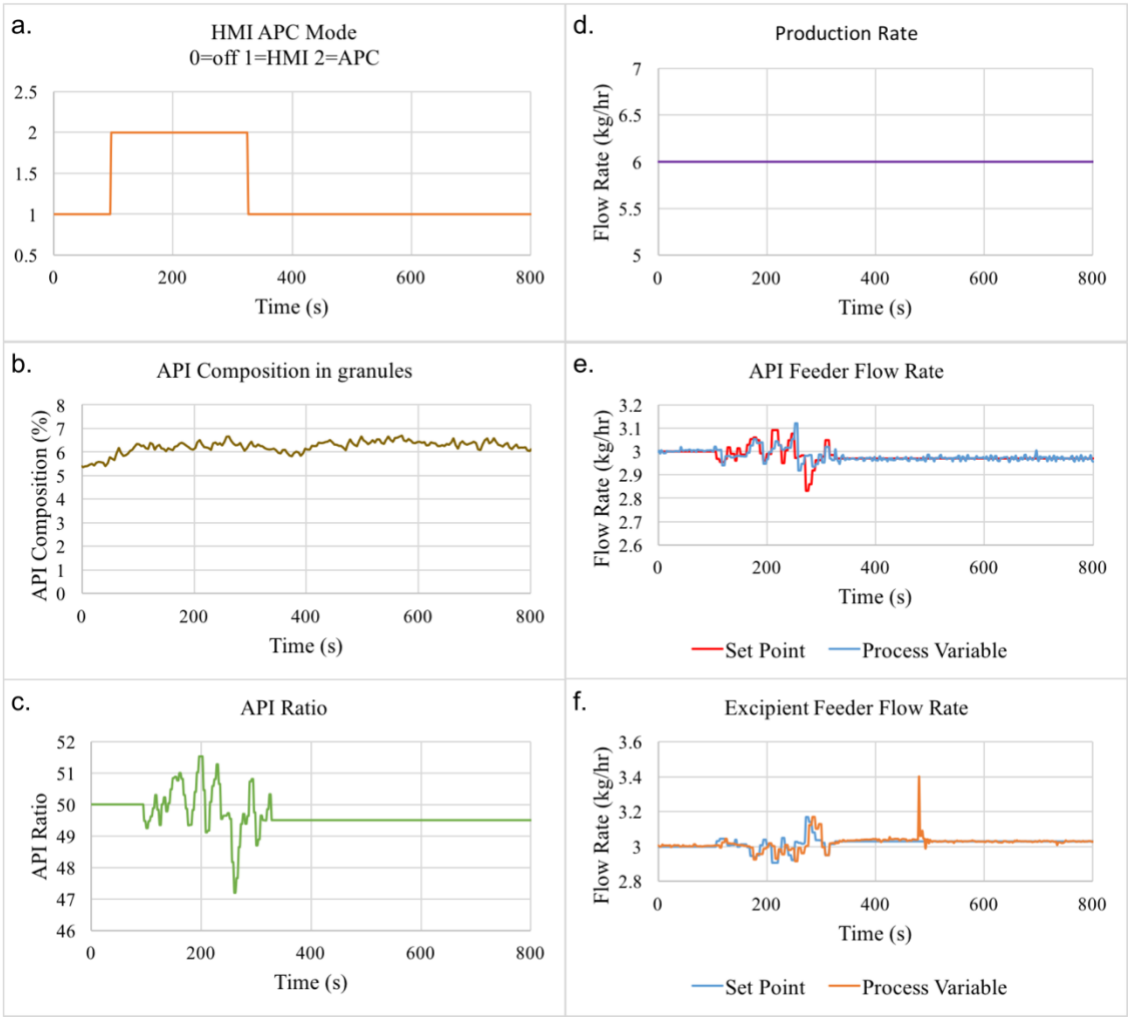

Figure 38: Implementation of feedback based MPC controller in pilot plant

Chapter 6: Conclusions and Future prospects

6.1. Conclusions

In this work, an advanced control strategy has been developed for an integrated continuous granulation process and *in silico* study has been performed. It is crucial to have pharmaceutical products of the right composition and thus it is important to develop control strategies around these unit operations. The unit operations considered in this process are the feeders and a continuous twin screw granulator. Two control options were identified based on the variable to be manipulated. The first control option was to manipulate the flow rate of excipient feeder while keeping the flow rate of API feeder constant and the second control option was to manipulate the API ratio thus manipulating both the feeder flow rates. Control option 1 avoids the input disturbances in API concentration that could be generated as a result of manipulating the feeder flow rate. Control option 2 provides for control over production rate along with control over API composition, however it could induce additional disturbances due to changing the flow rate of the feeder.

Control loops have been designed around these two unit operations where the feeders consist of an inbuilt PID controller with the main control architecture being compared for feedback only and combined feedforward/feedback control with the two actuators. The feedback controller considered is a PID and the feedforward controller has been developed from the characteristic equation. The controllers were tested for set point tracking and disturbance rejection abilities for different types of disturbances. The results show that the combined control strategy performs better in comparison to feedback-only control strategy. The feedforward controller rejects the disturbance before it affects the product while the

feedback controller corrects process disturbances. It should be noted that the process model has been considered to be perfect and thus the controller model is ideal. A feedforward controller is specific to a particular process and material and thus it needs to be adapted whenever there is a change in the process or the material. A PID based control algorithm and a MPC based control algorithm were also compared and the MPC control algorithm controlled the concentration of API more efficiently. Hence, the first step towards implementing a control strategy was to implement a MPC based feedback controller which was successfully executed. For the manufacture of tablets, the process consists of other unit operations downstream from the granulator. Proposing a control strategy at this stage in the process is important since major disturbances are generated after the feeder unit operation. Thus, controlling at this stage avoids propagation of these disturbances further downstream.

6.2. Future Prospects

This thesis discussed the different control options *in silico* for the integrated continuous twin screw granulation process. The findings were tested by implementing one of the control strategies on the pilot plant. An MPC feedback controller was developed and it controlled the composition of API satisfactorily. However, we know that blending is the upstream unit operation from which the feeder receives the API blend and there could be blending issues which could impact the blend uniformity. Thus there could be disturbances in the inlet composition of API and as discussed in section 5, a combined feedforward/feedback control typically helps in eliminating these input disturbances over a feedback only control. Thus, one opportunity with respect to extension of this project would be to implement a combined feedforward/feedback based MPC controller to control

the composition of API in granules. However, there are certain challenges that were identified in implementing this control strategy. In order to develop a feedforward controller, a step change analysis has to be conducted in the API concentration measured at the exit of the feeder. Due to mixing within the feeder, layering of different blends within the feeder or loading the feeder with blends of different composition one after the other restricts in getting a sharp step change which is required to build the feedforward controller. Hence, work is being carried out to determine the best possible way of achieving a step change in API composition in the feeder. Figure 39 indicates the control strategy that has been implemented in (a) and the control strategy to be implemented as part of future work.

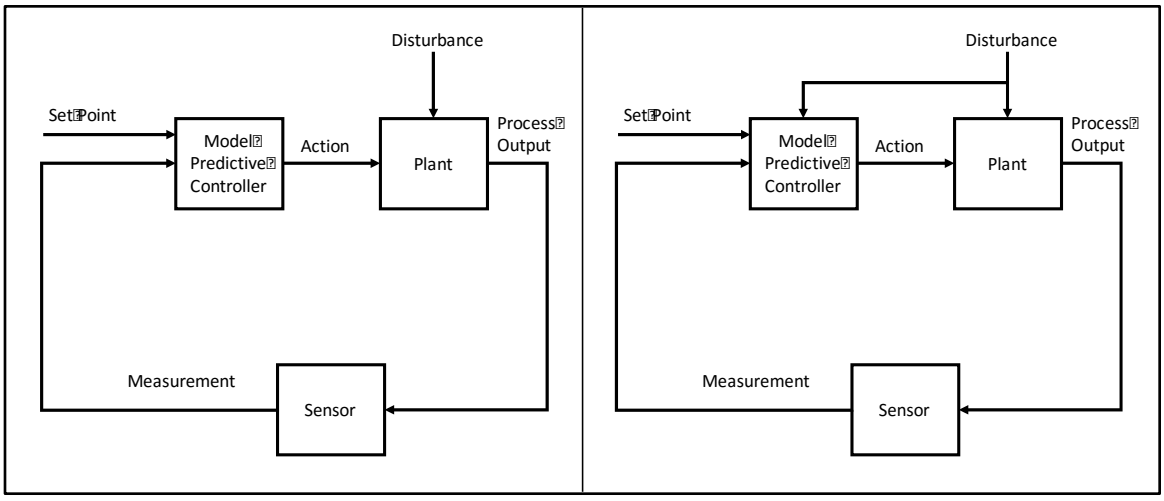

Figure 39: (a) Implemented MPC based feedback control strategy (b) MPC based combined feedforward/feedback control strategy for future work

Appendix

Appendix A

Feedforward Model

The feedforward controller model was developed in Matlab workspace and Simulink. The integrated flowsheet model developed in gPROMS was converted to an integrated flowsheet Model in Simulink. Transfer function models were developed from data generated by the gPROMS model. These models were developed in System Identification Toolbox and the best fit model was selected. The pole-zero plot and bode diagrams for these transfer functions were also developed to ensure that the transfer functions were stable. These transfer function models describe the various unit operations in the flowsheet. The flowsheet transfer function model is described in Figure 40.

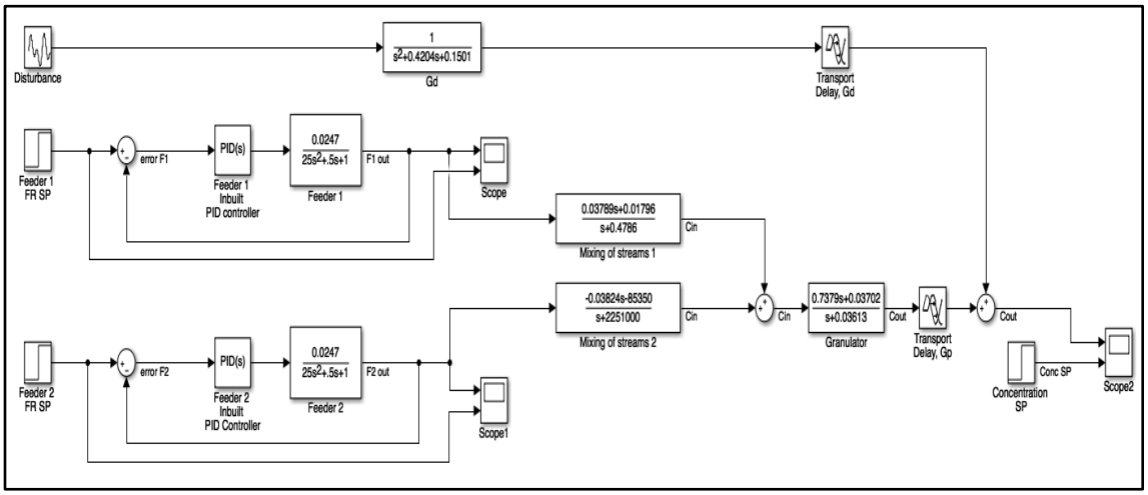

Figure 40: Integrated flowsheet model simulated in Simulink (open loop).

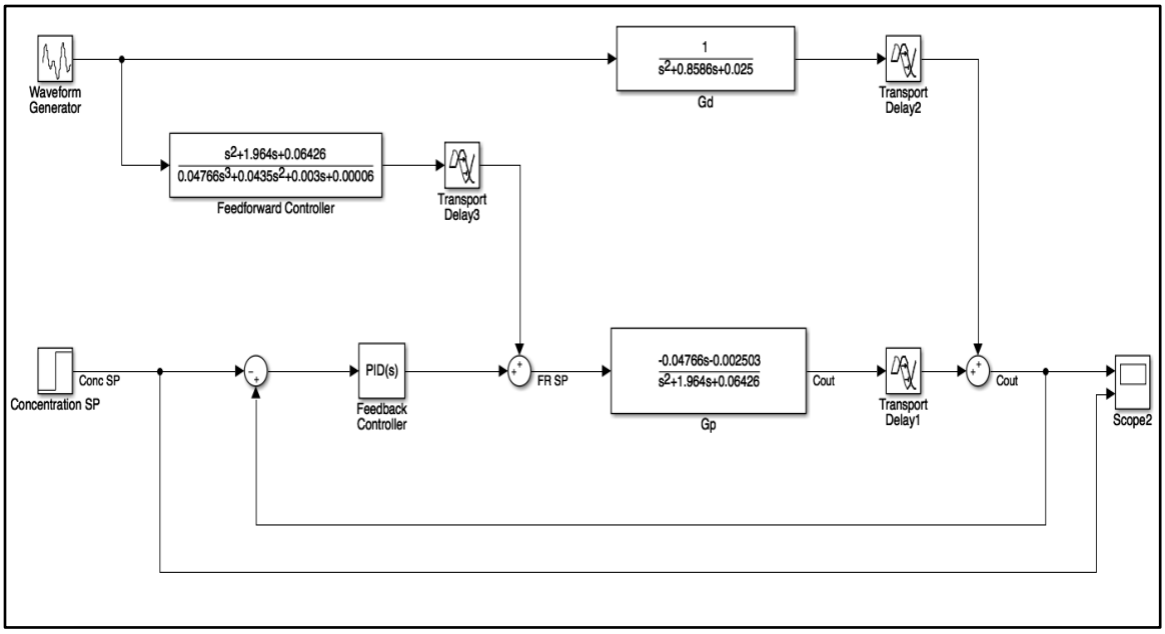

Figure 41: Integrated flowsheet with combined feedforward/feedback control in Simulink.

The above transfer function model was simplified because during implementation a simplified model for the entire process would be required. The simplified process model which also represents the ideal case was developed using the data generated by the Simulink model described in Figure 40. The feedforward controller was then developed using the Disturbance model and the process model given in Figure 41. The feedforward controller transfer function is achieved by equating the characteristic equation to zero. The general form of that is given in Equation 5. Both the disturbance transfer function (G_d) and process transfer function (G_p) are specific to a particular process and material and would change if any changes are made to the process or the materials.

$$G_{FF} = -\frac{G_d}{G_p} \tag{5}$$

Appendix B: Nomenclature

Abbreviations

API	Active Pharmaceutical Ingredient
CPM	Continuous Pharmaceutical Manufacturing
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
CSTR	Continuously Stirred Tank Reactor
CU	Content Uniformity
D2R	Duration to Reject
IAE	Integral of Absolute Error
ISE	Integral of Square of Error
ITAE	Integral of Time Absolute Error
L/S	Liquid to Solid
M2P	Magnitude to Product
MPC	Model Predictive Control
MRT	Mean Residence Time
MSC	Multiplicative Scattering Correction
NIR	Near Infrared
PAT	Process Analytical Technology
PFR	Plug Flow Reactor
PID	Proportional Integral Derivative
PLS	Partial Least Squares
QbD	Quality by Design

RMSE	Root Mean Square Error
RMSEP	Root Mean Square Error of Prediction
RSEP	Relative Standard Error of Prediction
RSD	Relative Standard Deviation
RTD	Residence Time Distribution
SP	Set point
SSE	Sum of Squared Errors
T2P	Time to Product
TSG	Twin Screw Granulator
WG	Wet Granulation
Symbol	**Variable**
$G_d(s)$	Disturbance transfer function model
$G_p(s)$	Process transfer function model
G_c	Controller transfer function model
P	Proportional gain
I	Integral time constant
D	Derivative time constant
Subscript	**Description**
d	disturbance
p	process
c	controller
1,2,3,4	Process or controller numbers

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