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A systematic framework for onsite design and implementation of a control system in a continuous tablet manufacturing process

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ABSTRACT

A novel manufacturing strategy based on continuous processing integrated with online/inline monitoring tools coupled with an advanced control system is highly desired for efficient Quality by Design (QbD)-based pharmaceutical manufacturing. A control system ensures the predefined end product quality, satisfies the high regulatory constraints, facilitates real time release of the product, and optimizes the resources. In this work, a systematic framework for the onsite design and implementation of the control system in continuous tablet manufacturing process has been developed. The framework includes a generic methodology and supporting tools through which the control system can be designed at the manufacturing site and can be implemented for closed-loop operation. The control framework has different novel features such as the option to run the plant in closed-loop (MPC/PID), open-loop and simulation mode. NIR sensor, an online prediction tool, a PAT data management tool, and a control platform have been used to close the control loop.

1. Introduction

Currently, there is a high level of interest in the pharmaceutical industry in continuous-manufacturing strategies, integrated with online/inline monitoring tools, and efficient control systems. These strategies can accelerate the full implementation of the QbD paradigm for the next generation of pharmaceutical products (FDA, 2004; PhRMA, 2012; Singh, Godfrey, et al., 2013; Singh, Ierapetritou, & Ramachandran, 2012a). In addition to its flexibility and time and cost-saving features, continuous manufacturing is intrinsically steady and therefore easily amenable to model predictive design, optimization, and control methods (Cervera-Padrell, Skovby, Kiil, Gani, & Gernaey, 2012; Singh et al., 2012c; Kumar, Gernaey, Beer, & Nopens, 2013; Muzzio et al., 2013). Excitingly, in the pharmaceutical industry, the application of a control system is in its infancy, and is an open area of research for academics and technology providers (Muzzio et al., 2013).

Many solid processes (e.g. pharmaceuticals) reach no more than 60% of their design capacity and often require ten times as much time to start-up as compared to fluid processes. This is primarily attributed to the lack of development and implementation of advanced control strategies and closed-loop control. The main barriers to implement the control system are described as follows: (1) integration of control hardware, software and sensors with process equipment is a challenging task due to lack of pharmaceutical equipment standardization for control perspectives. (2) Difficulties in real-time online/inline monitoring of the process variables that need to be controlled are another barrier that prevents the implementation of control systems. Spectroscopic sensors (e.g. NIR, Raman), though not new to the pharmaceutical industry, have not been yet applied for feedback control. (3) The most suitable control strategies (PID, PI, MPC, feed forward controller, feedback controller) for tablet manufacturing processes is still unknown. (4) There is no standard control package commercially available that can be employed to implement a control system in the pharmaceutical plant. If pharmaceutical companies need to shift from an open-loop process to a closed-loop process, a novel system must be developed, which is resource intensive and involves many uncertainties. Therefore, a systematic framework, as proposed in this manuscript, is needed, through which a control system can be easily designed onsite and implemented to the plant with less time and resources.

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The specific aims of the proposed systematic framework is two-fold: first, to provide stepwise guidelines for integration of advanced control strategies, control hardware/software and sensing technologies (PAT tools), and second, to support the design and implementation of the control strategies. It includes the installation of the advanced sensors (e.g. NIR) within the plant to monitor process variables (e.g. composition) in real time. The application of spectroscopic sensors for feedback control remains a challenging task since the measured spectrum needs to communicate to the multi-variable analysis (MVA) model performing PCA/PLS in real time. A control signal can then be sent to the process automation system (PAS) through an OLE process control (OPC) communication protocol. Through the framework, the advanced control strategy (hybrid MPC-PID) can be developed and implemented using the process automation system (e.g. Emerson's DeltaV PAS), and the control hardware can be integrated within the plant to allow closed-loop manipulation of the physical process. The control system utilizes a PAT-based multi-variable data management platform (e.g. synTQ) to integrate the control platform (e.g. DeltaV) with an NIR analyzer and MVA model. The proposed systematic framework will enable the creation of a platform technology in the pharmaceutical industry that supports both present and future pharmaceutical process development. Through the commercial implementation of advanced control strategies and the integration of these strategies with control hardware and sensing technologies, this platform technology will lead to more efficient manufacturing operations, alleviating labor and cost-intensive experimentation and also facilitating QbD in the pharmaceutical industry.

Four essential steps to move from open-loop operation to closed-loop operation are: process understanding, control system design, control hardware/software and sensor integration, and control system implementation. For an understanding of the continuous tablet manufacturing process, extensive model-based (Barrasso & Ramachandran, 2012; Barrasso, Walia, & Ramachandran, 2013; Boukouvala, Niotis, Ramachandran, Muzzio, & Ierapetritou, 2012; Boukouvala, Ramachandran, Vanarase, Muzzio, & Ierapetritou, 2011; Sen, Dubey, Singh, & Ramachandran, 2013; Sen & Ramachandran, 2012; Sen, Singh, Vanarase, John, & Ramachandran, 2012; to name a few) as well as experimental (Portillo et al., 2010; Vanarase, Alcala, Rozo, Muzzio, & Romanach, 2010; Vanarase, Gao, Muzzio, & Ierapetritou, 2011; Vanarase & Muzzio, 2011, to name a few) studies have been done. Few attempts have been also made toward the design of a control system for the tablet manufacturing process. Singh, Gernaey, and Gani (2010) have suggested a monitoring and control system for a batch tablet manufacturing process. (Hsu et al. (2010a, 2010b) have suggested a control system for a roller compactor, an important unit operation used for a dry granulated continuous tablet manufacturing process. Ramachandran & Chaudhury (2012) have proposed a control system for a continuous drum granulation process. A detailed review on the control of a fluid bed granulation process has been performed by Burggraeve et al. (2012), and discussion has been provided by Bardin, Knight, and Seville (2004) on the control aspects for efficient operation of a high shear mixer. Sanders, Hounslow, and Doyle (2009) have performed extensive control studies using proportional integral derivative (PID) and model predictive control (MPC) methods on an experimentally validated fluidized bed granulation model. An MPC strategy has been proposed for a wet drum granulation process (Gatzke & Doyle, 2001; Long, Polisetty, & Gatzke, 2007; Pottmann, Ogunnaike, Adetayo, & Ennis, 2000). Ramachandran, Arjunan, Chaudhury, and Ierapetritou (2012) have designed a regulatory control system for a continuous direct compaction process with emphasis on blending and tableting process. Singh et al. (2013b) have developed an advanced model predictive control system (MPC) for direct compaction continuous tablet manufacturing process. Singh, Ierapetritou, et al. (2012a; 2014) have designed a control system for the roller compaction and wet granulation routes of the continuous tablet manufacturing process. However, no attempts have been made to integrate the control hardware/software and sensors with a continuous tablet manufacturing process and therefore to implement the control system into an actual pilot-plant process.

In this manuscript, a systematic framework for the onsite design and implementation of an advanced and regulatory control strategy has been proposed. The application of the framework has been demonstrated through a continuous tablet manufacturing process. An efficient continuous tablet manufacturing process integrated with online/inline monitoring tools and coupled with an advanced hybrid MPC-PID control system is described. A process flowsheet model is introduced that performs virtual experimentation and optimizes the design of the process, including its control architecture. For the first time, the closed-loop operation of the tablet manufacturing plant using NIR sensor has been demonstrated in this manuscript, which is a significant advancement in pharmaceutical manufacturing as endorsed by the Food and Drug Administration (FDA) and other regulatory authorities as part of the Quality by Design (QbD) paradigm.

2. Systematic framework for onsite design and implementation of the control system

A systematic methodology for the onsite design and implementation of the control system is shown in Fig. 1. The methodology consists of seven hierarchical steps through which a control system can be designed onsite and implemented at the manufacturing plant using a real control platform. The problem is defined in terms of plant specifications and the desired product quality specifications which are inputs to the methodology. The first step is to design the control system for a given process at manufacturing site using the real control platform to be used for the implementation of the control system. The final control variables, actuators, control strategies and controller parameters are identified in this step (Singh, Gernaey, & Gani, 2009; Singh, Ierapetritou, et al., 2012). The monitoring tools (sensors) (Singh, Gernaey, & Gani, 2010b), control hardware and software required for implementation of the control system are identified in step 2. In this step, the online/inline monitoring tools for all control variables, the appropriate control platform in which the control strategy can be implemented, the control hardware needed to communicate data with the plant and the software tools needed to close the loop are selected. In step 3, the sensors are integrated with the plant to facilitate real time online/inline monitoring. This step integrates sensors with the plant through a suitable sampling interface and with the computer through operating software. The measured signal is then sent to the control platform in step 4. For spectroscopic sensors (commonly used in pharmaceutical process), this step includes the development of a calibration model (Vanarase et al., 2010), the integration of the sensor operating software with the real time online prediction tools, the integration of the online prediction tools with the PAT data management tool and the integration of the PAT data management tool with the control platform via the OPC communication protocol. Through this step, the measured signal and any other signals (e.g. alarms, warnings, etc.) can be sent to the control platform to be recorded in the historian, and any data from the control platform can be sent back to the PAT data management tool for data storage, inspection and auditing purposes. This step is very simple for a non-spectroscopic sensor. The plant is then integrated with the control platform in step 5. In this step, the plant hardware/unit operations are connected with the control platform so that they can be operated through the control interface. Standard industrial communication protocols such as Fieldbus or EtherNet/IP

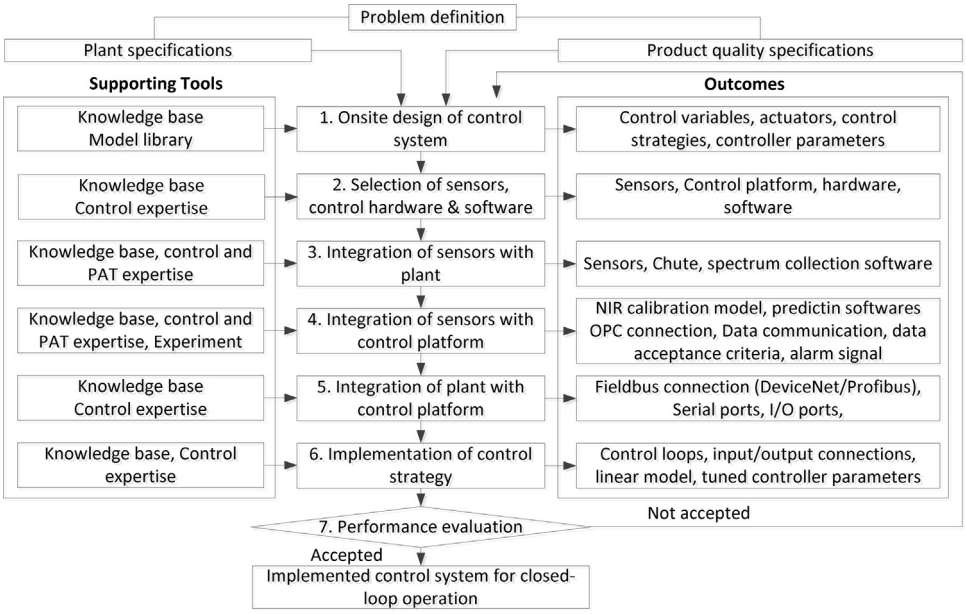

Fig. 1. Systematic framework for onsite design and implementation of the control system.

can be used to make these connections (Blevins, Wojsznis, & Nixon, 2013). Through this connection, the actuator signals can be sent to the plant as an input. To connect the plant input (actuators) with the plant output (control variable), the control strategy is implemented in step 6. The input for the controller comes from the sensors and the output from the controller goes to the plant. Finally, the performance of the control system is evaluated in step 7 through closed-loop operation. If the performance is satisfactory, then the implemented control system can be considered as the final control system for closed-loop manufacturing. Otherwise steps 1–6 need to be repeated until satisfactory performance is obtained.

3. Case study: direct compaction continuous tablet manufacturing process

3.1. Process description

A direct compaction continuous tablet manufacturing process is shown in Fig. 2. As shown in the figure, there are three gravimetric feeders to provide the necessary lubricant, API and excipient. The feeders contain a hopper that can hold a certain amount of material and a rotating screw to change the flow rate. These feeds are then supplied to a blender to generate a homogeneous mixer. Before the blending process, a milling step can be used for delumping purposes if required. After the blender, the blended powder is sent directly to the tablet press through a feed frame. The final compacted tablets are obtained from the tablet press, and among them, some tablets are sent for dissolution testing. This process flowsheet has been simulated using the simulation software gPROMS (Process Systems Enterprise, http://www.psenterprise.com/). The process conceptually represents a pilot plant situated at the Engineering Research Center for Structured Organic Particulate Systems (ERC-SOPS), Rutgers University.

3.2. Process model

The integrated flowsheet model for direct compaction continuous tablet manufacturing process that has been used for onsite design of the control system has been previously reported (Boukouvala et al., 2012; Singh, Ierapetritou, & Ramachandran, 2013b). The detailed developments of these models are reported elsewhere as summarized here. The mathematical model for powder blending, an important but complex unit operation, has been previously developed (Sen & Ramachandran, 2012; Sen et al., 2012, 2013). The model for the tablet compression process is previously reported in Singh et al. (2010a). This model is based on the Kawakita powder compression model (Kawakita & Ludde, 1971) and tablet hardness model described in Kuentz and Leuenberger (2000). The dissolution model was adapted from Kimber, Kazarian, and Stepánek (2011). The models for the different unit operations have been developed and included in gPROMS library to facilitate the integrated flowsheet modeling. The development of the integrated process flowsheet using individual unit operation models has been previously demonstrated (Boukouvala et al., 2012, 2013).

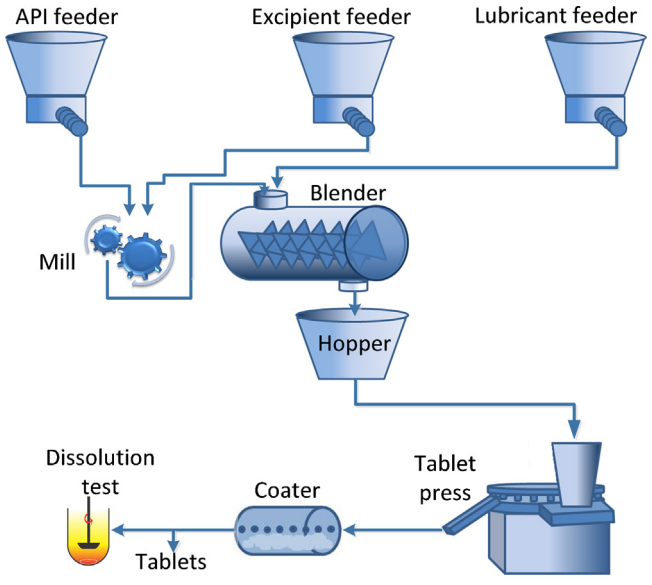

Fig. 2. Direct compaction continuous tablet manufacturing process.

Fig. 3. Direct compaction tablet manufacturing pilot plant (adapted from Singh et al., 2012b) (whole plant is not shown): (a) feeders, (b) blender, (c) tablet press.

3.3. Pilot plant

A continuous direct compaction tablet manufacturing pilot plant has been developed, situated at ERC-SOPS, Rutgers University. The snapshot of the pilot plant is shown in Fig. 3 (whole plant is not shown). The pilot plant is built in three levels at different heights to take advantages of gravitational material flow. The top level is used for feeder placement and powder storage, the middle level is used for delumping and blending, and the bottom level is used for compaction. Each level consists of 10 × 10 square feet working area. There are three gravimetric feeders (K-Tron)-with the capability of adding more- that feed the various formulation components (API, excipient etc.). A mill (Glatt) is also integrated after the feeder hopper primarily for de-lumping the powders and creating contact between components. The lubricant feeder is added after the mill to prevent over lubrication of the formulation in the mill. These feed streams are then connected to a continuous blender (Glatt) within which a homogeneous powder mixture of all the ingredients is generated. Subsequently, the outlet from the blender is fed to the tablet press (Fig. 3).

4. Onsite design and implementation of a control system

The systematic methodology as shown in Fig. 1 has been applied for onsite design and implementation of the control system for direct compaction continuous tablet manufacturing process.

4.1. Onsite design of control system (step 1)

A designed control system consists of the control variables, corresponding actuators, control strategies, controller parameters and sensors. The systematic methodology for offsite design of the control system has been previously developed (Singh et al., 2009, 2012a). This methodology has been extended to facilitate onsite design of the control system. In onsite design of the control system, the control loops are implemented in a real control platform (e.g. DeltaV (Emerson), PCS7 (Siemens)) and the input and output of each control loop is connected with the process model simulated in a simulation tool. Some of the advantages of onsite design of the control system are that the scenario is more similar to the real plant, control loops do not need to be rebuilt, identified linear models for MPC and controller parameters can be directly used for closed-loop plant operation, controller can be easily retuned, and the input and output of the control loops can be easily switched with the input and output of the plant for closed-loop operation. The design and implementation of the control system is an iterative procedure. Therefore, onsite design of the control system can save time and resources. For onsite design, the process model needs to be integrated with the control platform. Commercially available control platforms can be easily connected with the simulation tools via either MS Excel or via any intermediate tool that has the OPC feature. If the control platform and the simulation tool both have the OPC feature (e.g. MATLAB) then they can be directly connected without any intermediate software tool. Most of the simulation tools (e.g. gPROMS (PSE), ICAS-MoT (CAPEC) (Sales-Cruz, 2006; Singh et al., 2010a)) can be easily connected with MS Excel and therefore with the control platform. The connection of one simulation tool (gPROMS) with a control platform (DeltaV) is shown in Fig. 4. However, this connecting methodology is generic and can be applied to any simulation tool and control platform. As shown in Fig. 4, the flowsheet model has been integrated with DeltaV using the gORUN feature of gPROMS, MS Excel and I/GEAR connecting software. The model is simulated in gPROMS simulation software and the control strategy has been implemented in DeltaV control studio. The gORUN feature of gPROMS is used to connect gPROMS with MS Excel, and I/Gear is used to connect MS Excel with DeltaV.

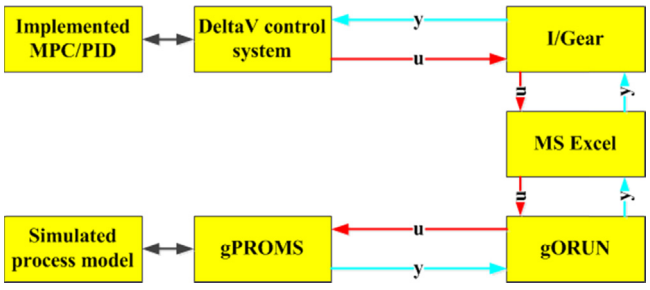

Fig. 4. Integration of flowsheet model with control platform (DeltaV).

The signal of the control variable generated from the model simulation is sent to DeltaV and acts as the input to the controller that generates the actuator. The controller output (actuator) is sent to the process model and acts as the input to calculate the new signal of the control variable. This flowsheet model can also be integrated with the control platform via MATLAB OPC toolbox. The integration of the flowsheet model with MATLAB has been previously demonstrated (Singh, Ierapetritou, et al., 2013b). The flowsheet model (simulated in gPROMS) is therefore OPC compliant, and can be integrated with any actual operating and control platform to facilitate onsite control system design. This facilitates tuning of controller parameters and identification of the linear model for MPC, as well as performance evaluation of the control system before running the actual plant to reduce cost and improve performance.

The Ziegler and Nichols (1942) method or any optimization-based method (e.g. integral of time absolute error (ITAE) (Seborg et al., 2004) can be used for tuning the PID controller parameters. Tuning of MPC parameters and objective function formulation has been described in scientific literatures (Singh, Ierapetritou, et al., 2013b; Wojsznis, Gudaz, Blevins, & Mehta, 2003).

A control system for the direct compaction continuous tablet manufacturing process has been designed online using the methodology shown in Fig. 4. The process model is simulated in gPROMS while the control strategies are implemented in the DeltaV control platform. A combination of model predictive control (MPC) and the more commonly used proportional integral derivative (PID) is used for the control strategy since MPC is better at handling process delay and process variable interactions and can be tuned easily. An NIR sensor is placed at the blender outlet for blend composition measurement. This is the input for the master controller, which generates the feeder ratio set point. Based on this ratio set point and the total powder flow rate, the individual flow rate set points for API, excipients and lubricant feeders are calculated and then controlled by manipulating the respective feeder RPMs using built-in feeder controllers. The total flow rate set point comes from another controller that is specially designed to achieve a consistent hopper level, irrespective of variations in turret speed and/or feed frame speed. The change in the total flow rate due to the feeder level control is usually small and therefore does not lead to a violation of the blender operational constraints (required powder holdup, and residence time). In the tablet press, the tablet weight and hardness are controlled through a cascade control arrangement using two master loops and one slave loop. Master loops are used to control the weight and hardness and provide the set point for the slave controller, which controls the main compression force by manipulating the fill depth. They share a common slave controller, meaning that only one master controller is activated at a time. The tablet weight is measured and controlled more frequently. Note that the hardness control loop is activated only when the measured hardness deviates by a certain percentage (e.g. 2% of set point) from the desired set point.

4.2. Selection of sensors, control hardware and software (step 2)

Implementation of the control system requires integration of different sensors, control software and hardware. The type of sensors, control software and hardware required depends on the type of process variable to be controlled. Many pharmaceutical processes require the implementation of spectroscopic techniques to monitor different process variables, which makes the implementation of the control system a challenging task. Fig. 5 shows the software and hardware required for a pharmaceutical process to close the control loop. The first step is to select the sensing technique and corresponding sensing tool (step 2.1). To monitor one variable there may be many techniques and tools available. The selection of the sensor mainly depends on its performance for the process variable. Different performance criteria (e.g. accuracy, precision, operating range, response time, resolution, sensitivity, drift) and cost need to be considered before selecting a sensor (Singh et al., 2010b). For a spectroscopic sensor, the next step is to select multivariate analysis tool and real time online prediction tool (step 2.2). A multivariate analysis tool is needed for principal component analysis (PCA) and partial least square (PLS) and thereby to develop a calibration model required for prediction of desired variable from the acquired spectrum from the spectroscopic tool selected in step 2.1. An online prediction tool is also needed for real time prediction of the control variable. The selection of the multivariate data analysis tool and prediction tool mainly depends on its performance, availability, cost, GMP compliance, regulatory validation, and its suitability to integrate with the sensor and data management and OPC tool. The third step is to select a PAT data management tool (step 2.3). The PAT data management tool should have an OPC feature so that the data can be communicated with the control platform. This tool has many advantages. For example, here, the data can be stored, plotted, and protected, and alarms can be created. It also provides the auditing feature required by regulatory authorities to validate the process operations. The selection of the PAT data management tool mainly depends on its ability to integrate the required sensors, online prediction tool and control platform together with its data management capability, as well as its cost. The last step is to select the control platform (2.4). Presently, there are a limited number of control platforms commercially available and their selection mainly depends on the user needs.

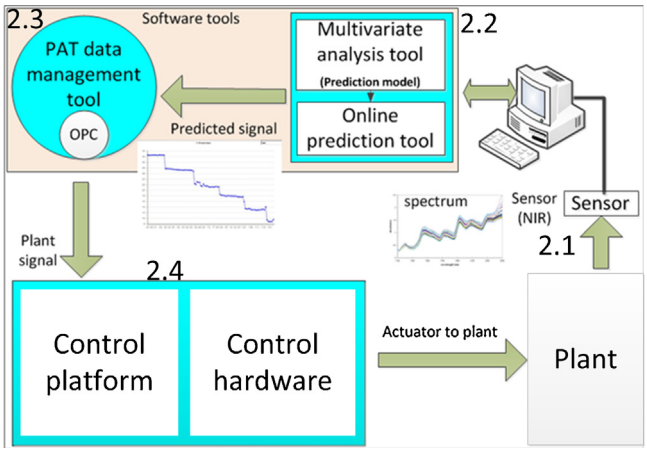

Fig. 5. Software and hardware required for implementation of control system.

Spectroscopic techniques are the preferred option for the monitoring of the pharmaceutical tablet manufacturing processes because of their non-destructive nature. They can be used to monitor different process variables, such as the API composition of a powder blend, blend uniformity and API tablet potency (total API content of a tablet). The most commonly used techniques in the pharmaceutical industry are NIR and Raman. NIR is used for this study.

In the continuous manufacturing line, a number of variables are monitored in real time, namely the API concentration of the powder blend, the moisture content of the disintegrant, the content uniformity of the tablets, the level in the tablet press hopper and the tablet weight and hardness. Reflectance based NIR spectroscopy for continuous monitoring of API composition has been implemented. A Bruker Matrix and JDSU micro-NIR have been utilized for this purpose. Both instruments are connected to the tablet press using an instrumented hopper where the blended formulation is presented for sampling using a sapphire window. One of the challenges lies in the design of the sampling interfaces as there can be problems with powder sticking and clogging the sampling

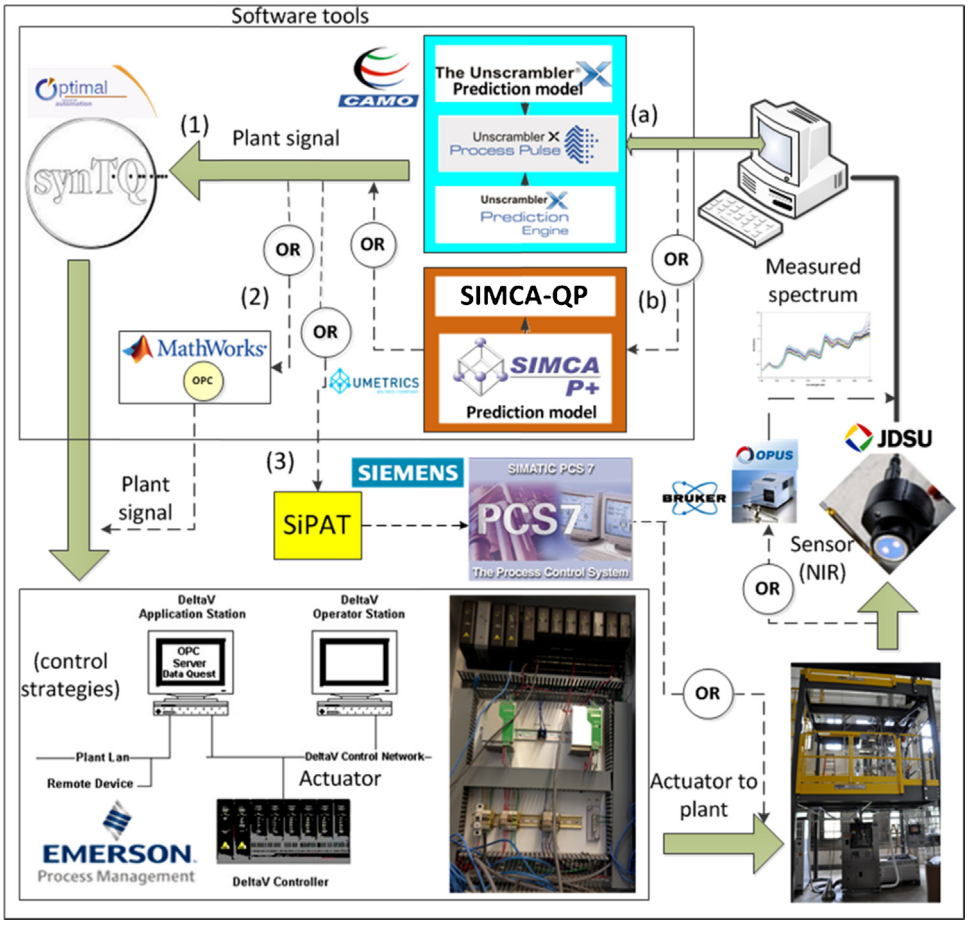

Fig. 6. Selection of control hardware and software.

window. For the tablet content uniformity measurement, a Bruker MPA transmission NIR can be used atline. Some tablets exiting the press can be transported to a sampling wheel and the spectra can be acquired in approximately 1 min. An ultrasonic level sensor or webcam based sensor can be used to measure the powder level in the hopper above the tablet press. In the tablet press itself, compression forces are measured by strain gauge; tablet weight and hardness are measured by the Checkmaster (Fette). The Checkmaster is a tablet tester with an internal feeder chute, a round collector with 12 glasses and a waste glass for testing tablets, oblongs, coated tablets and capsules. Tablets, oblongs and coated tablets can be tested for all four parameters: weight, thickness, hardness and diameter. Some of the monitoring tools are also available in the scientific literatures (Blanco and Alcalá, 2006; Huang, Wang, & Li, 2002; Prats-Montalbán, Jerez-Rozo, Romañach, & Ferrer, 2012; Roggo, Jent, Edmond, Chalus, & Ulmschneider, 2005; Singh et al., 2010a, 2010b).

The blending process has been considered as a demonstrative example considering API composition as a control variable. Monitoring tools, control hardware and software are shown in Fig. 6. The figure is illustrative and therefore is not comprehensive. For the API composition measurement, two options have been explored: the micro NIR (JDSU) and the Matrix (Bruker). For NIR prediction, two tools have been considered: via CAMO, and via UMETRICS. Using CAMO, 'Unscrambler X' is used to develop the prediction model. The Unscrambler prediction engine (OLUPX) is used to make the real time online prediction, and Unscrambler Process Pulse is used to provide the user interface and to communicate the data with MATLAB OPC. Note that the Unscrambler Process Pulse is needed only for the MATLAB OPC route and is not necessary for the SynTQ route. Similarly, using UMETRICS the prediction model can be developed in SIMCA P+ and SIMICA QP can be used for online prediction. As shown in Fig. 6, there are three options to close the control loops depending on the preferred platform the industry would like to use. (1) via DeltaV (Emerson) and SynTQ (Optimal), (2) via DeltaV and MATLAB OPC, and (3) via PCS7 and SIPAT (Siemens). In all the options, the actuator signal is sent back to the plant.

4.3. Integration of online/inline sensors with the plant (step 3)

The systematic methodology to integrate the spectroscopic sensors with the plant is shown in Fig. 7. As shown in the figure, first a control variable needs to be selected (from the list generated in step 1), then a corresponding sensor (generated in step 2) to be integrated into the plant is selected. Based on the equipment structure with which the sensors need to be integrated, a sampling point can then be selected. For continuous manufacturing involving a solid dosage form, the sampling point is normally at the outlet of each unit operation. The sampling point also depends on whether the control mode is feedback or feed forward. The control mode (feedback/feed forward) is identified in step 1 of the methodology. An interface (chute) is needed to integrate the inline measuring probe. The design of the chute depends on several factors, including the type of sensor considered, the variables that need to be monitored and the process equipment. For example, if the objective of the NIR sensor is to measure the characteristics of the flowing powder, then a powder layer always needs to be presented in front of the probe, and therefore, the sampling interface should be specifically designed to provide an area where the new powder layer can be formed by displacing the old powder layers continuously.

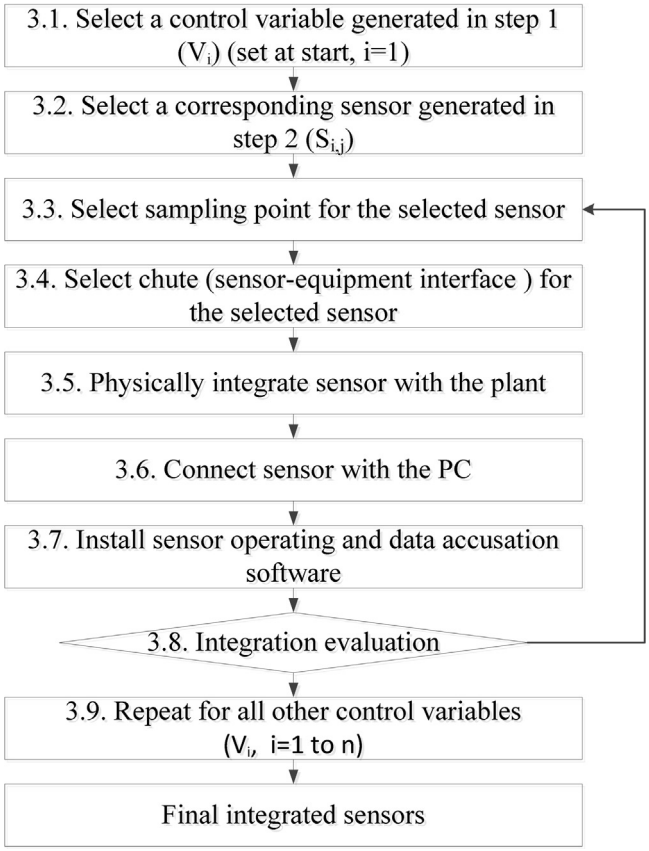

Fig. 7. Integration of online/inline sensors with the plant.

After placing the interface (chute) in place, the sensor must be integrated with the chute and the operating computer. The sensor, operating, and data accusation software (provided by the sensor manufacturer) can then be installed in operating computer. Finally, the integration should be evaluated by running the sensor and identifying if the data is acquired in real time. If the integration is successful, then steps 3.1–3.8 can be repeated for each control variable.

The methodology shown in Fig. 7 has been applied to integrate the sensors to the plant for online/inline measurement. The blending process where NIR has been integrated for the API composition measurement has been considered here as a demonstrative example. The sampling point is located at the outlet of continuous blender. An instrumented hopper (chute) has been used to interface the NIR with the continuous blender. The chute is specifically designed to provide an interface where the new powder layer can form by displacing the old powder layers. The integration of the chute with the blender and sensor is shown in Fig. 8. As shown in the figure, the chute is placed beneath the blender and the powder from blender enters the chute from the top. The circular interface point in the middle is used to attach the sensor. The outlet of the chute is then connected with the tablet press. The sensor connects with the computer with a USB interface.

The software user interface for the JDSU micro NIR is shown in Fig. 9. As shown in figure, the integration time (40,000) and the number of samples (50) has been provided, then the NIR is calibrated. For calibration at 0%, the lamp is turned off, and for calibration at 100%, the lamp is turn on, and the NIR is pointed toward a spectralon (100% absorbance). A directory where the measured spectrum is saved is then provided. From this folder, the spectrum is accessed by the NIR prediction software. As shown in Fig. 9, the different options are selected as needed for dynamic spectrum collection (without prompting) and online prediction (Row-major csv file). An example of the collected spectrum is also shown in Fig. 9.

4.4. Integration of sensors with control platform (step 4)

In this step, the sensors have been integrated with a centralized control platform for real time online/inline monitoring and control of the process variables. The spectroscopic sensors are widely used for pharmaceutical manufacturing involving solid dosage form, but are also more complex to integrate with the control platform because of the needs of additional PAT tools. A systematic methodology to integrate the spectroscopic sensors with the control platform is shown in Fig. 10. As shown in the figure, the first step is the selection of a sensor integrated with the plant and a corresponding operating and data accusation software. The software tool to develop the calibration model is selected in step 2. The calibration model must be built in the software environment with which the prediction engine is compatible. In order to develop the calibration model, the design of experiment (DOE) must first be performed to collect spectrums from samples of known compositions. The powder flow rate and changes in the properties of the powder during operation affect the performance of the prediction model. Therefore, these variations need to be taken into consideration in the DOE (Martinez, Peinado, Liesum, & Betz, 2013; Vanarase et al., 2010). The different powder samples must be prepared and pre-blended using a batch blender. Then the pre-blended sample is passed through the continuous plant and the resulting spectrum is collected using the integrated sensor. The collected spectrums are exported into the model development software and PCA and exploratory data analysis (EDA) are performed. EDA is an approach to analyzing data sets to summarize their main characteristics. The calibration model can be developed using the PLS regression method. PLS is a quantitative regression method that looks for correlation between spectral data (X-matrices) and the independent variable of interest (Y-vector). After developing the calibration model, it must be integrated with the online prediction tool. The sensor operating and data acquisition software must then be integrated with the prediction tool. Subsequently, the online prediction tool must be integrated with the PAT data management tool. The PAT data management tool (e.g. synTQ (Optimum), SiPAT (Siemens)) provides a systematic data collection and storage system. It is required for systematic GMP-based production and to ensure that the pharmaceutical product is manufactured as per the imposed regulations by the regulatory authority (e.g.

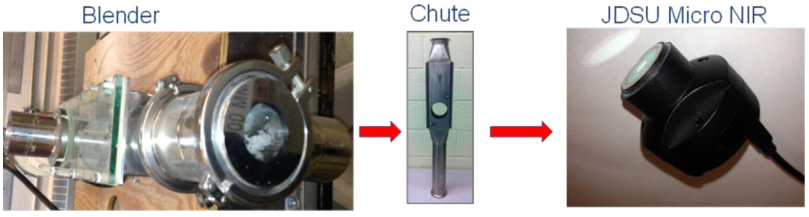

Fig. 8. Integration of the NIR sensor with the plant.

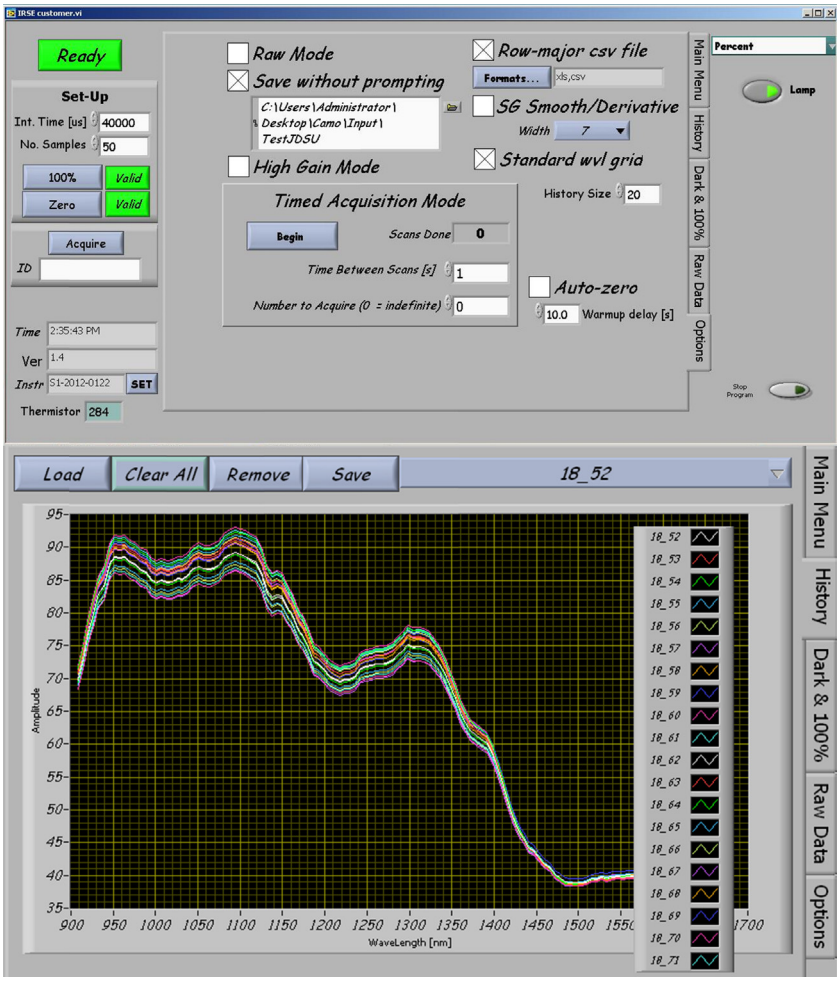

Fig. 9. Dynamic NIR spectrum collection.

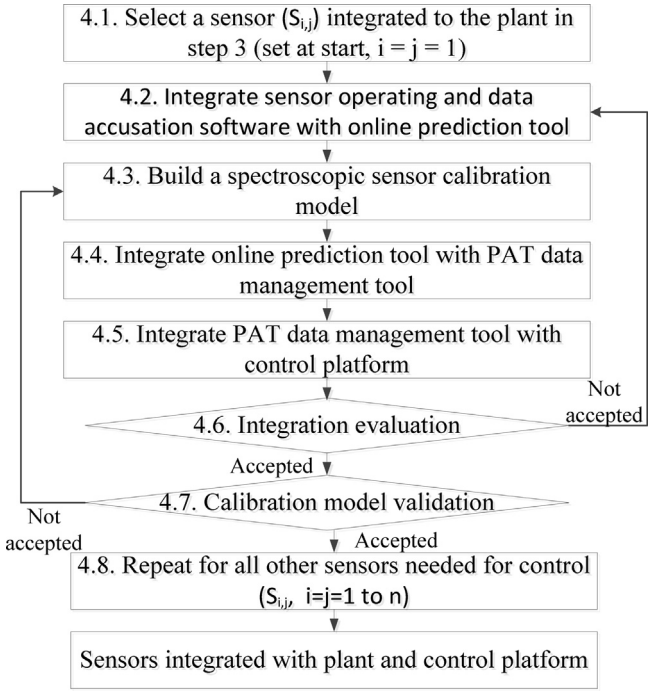

Fig. 10. Integration of online/inline sensors with the control platform.

FDA). Moreover, the PAT data management tool also has an OPC communication protocol. Therefore, it can communicate with the control platform that also has OPC features. The PAT data management tool is then integrated with the control platform using the OPC communication protocol. After completing the integration described in this step, the sensor can be operated and all connections should be evaluated. If the real-time plant signal is obtained at the control platform, then all the integrations are working correctly. Finally, the calibration model must be validated through experimentation. After obtaining an acceptable model, steps 4.1–4.7 need to be repeated for all other sensors.

4.4.1. Integration of continuous tablet manufacturing process sensors with control platform

The integration of the NIR sensor for monitoring of the API composition has been considered here as a demonstrative example (step 4.1). A microNIR (JDSU), has been integrated with it's operating interface (IRSE) and the IRSE has been integrated with real time online prediction tools, Process Pulse and OLUPX (CAMO)) (step 4.2). A NIR calibration model has been developed in Unscrambler X (CAMO)) for measurement of API composition (step 4.3). The spectral data is analyzed through principle component analysis (PCA) and exploratory data analysis (EDA). The model is developed using the partial least square (PLS) regression method. The developed model has been then integrated with the online prediction tool (Unscrambler Process Pulse) as shown in Fig. 11.

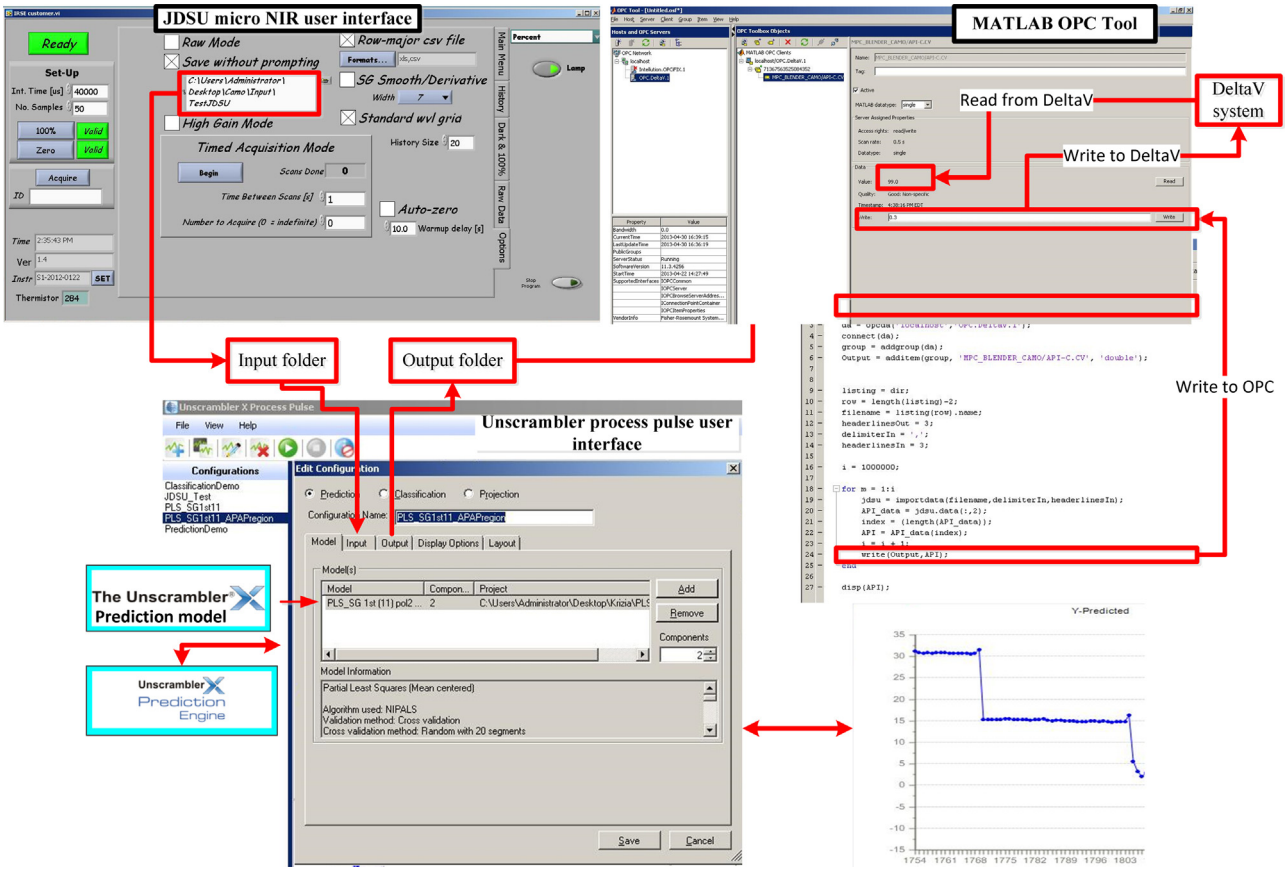

Fig. 11. Illustration of the sensor integration and data communication through OPC communication protocol (via MATLAB).

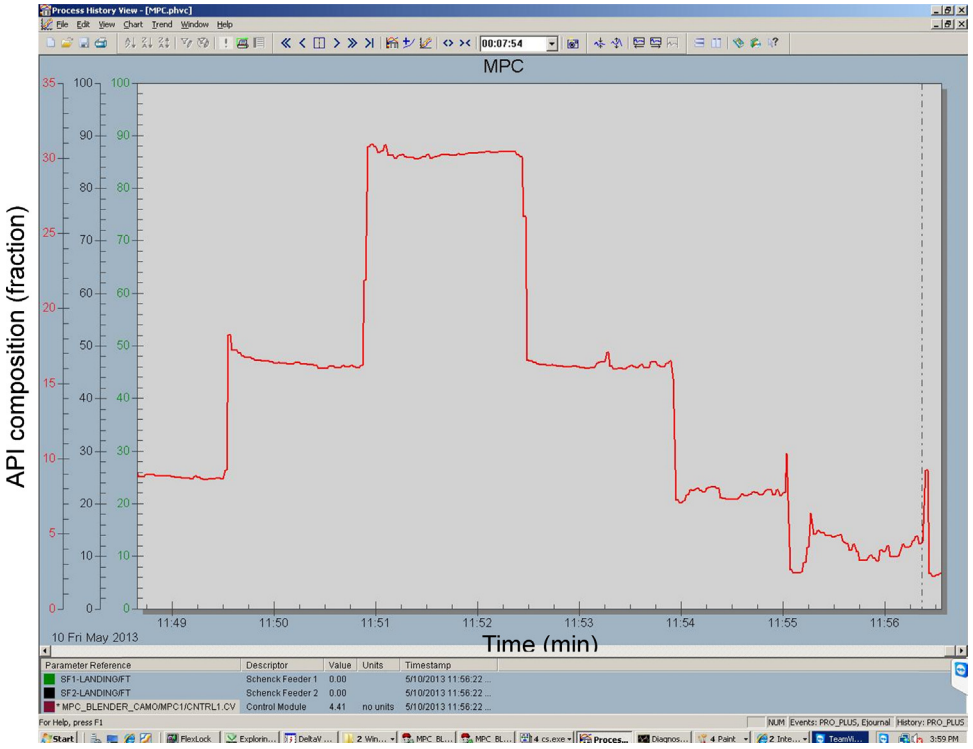

Fig. 12. Measured data communication to DeltaV through OPC communication protocol (screenshot from DeltaV historian). The result shows that NIR sensor is well connected with the real time prediction tool and control platform.

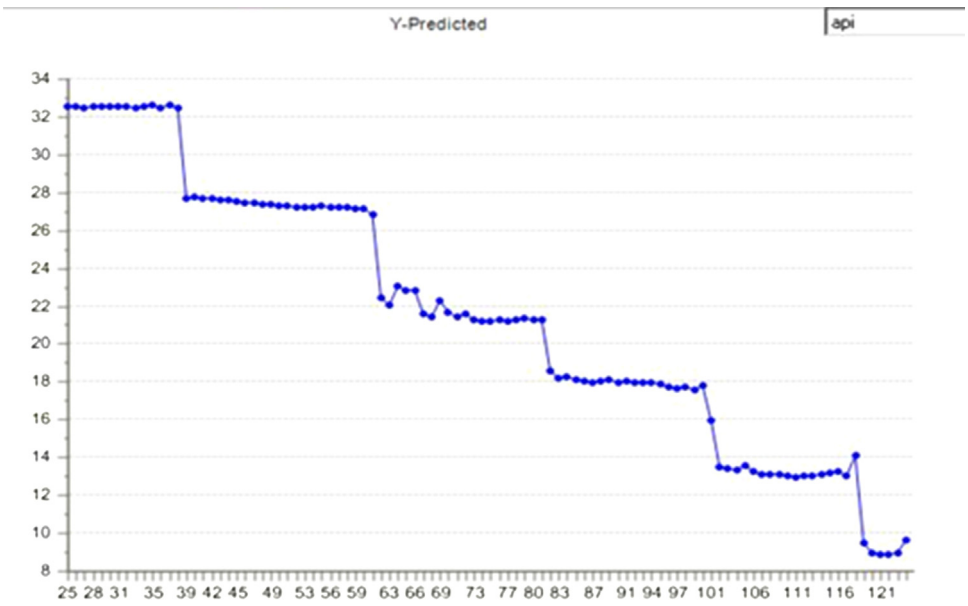

Fig. 13. Validation of NIR prediction model (screenshot from Unscrambler Process Pulse).

4.4.1.1. Integration of PAT tools and data communication to the control platform (steps 4.4–4.8). There are different methods to communicate the data to the control platform and all the methods rely on the OPC communication protocol. A demonstrative example for sensor integration and data communication to the DeltaV control platform through an OPC communication protocol is shown in Fig. 11 (via MATLAB). As shown in the figure, the spectrum collected through NIR is saved in an input folder which is accessed by Process Pulse. Process Pulse uses the prediction model and generates the API composition and saves it in an output folder. This output folder is assessed by a MATLAB program that links this folder with the MATLAB OPC toolbox. Finally, via OPC the data is sent to the DeltaV control platform. An example of communicated data to DeltaV (using the OPC) is shown in Fig. 12. As shown in the figure, the step change in the measurement has been introduced and the response can be seen in the DeltaV historian that indicates that the integration is working properly. Similarly, from DeltaV, the variable (e.g. actuator) can also be imported to MATLAB via OPC. Alternatively, any PAT tool (e.g. synTQ, SiPAT) can be used in place of MATLAB and any other control platform (e.g. PCS7) in place of DeltaV. The NIR prediction model has been validated against new samples as shown in Fig. 13, where the API composition changes from 30% to 15%.

4.5. Integration of plant with control platform (step 5)

The plant needs to be integrated with a control platform so that it can be operated through a centralized user interface and receive actuator signal. At a minimum, all the actuators need to be integrated with the plant and control platform. A systematic methodology to integrate the plant with the control platform is shown in Fig. 14. As shown in the figure, first an actuator (generated in step 1) is considered, and the analog signal corresponding to this actuator that needs to be manipulated to create an action in the plant is identified. In the next step, the process equipment is connected to the control platform (standard industrial communication protocol). Subsequently, the control hardware (controller) is connected to the operating computer in which the control software is already installed. The required drivers are added to the control platform, if needed, so that the plant equipment can be accessed through the control platform. The control software communicates with the control hardware, which communicates with the plant via fieldbus/serial ports. Finally, the connection needs to be checked to determine if the signal from the control platform can be sent to the plant. Steps 5.1–5.6 need to be repeated for all remaining actuators.

The API composition control at blender outlet is considered as the demonstrative example. The feeders screw rotational speed is the final actuator to control the API composition at blender outlet. The corresponding analog signal is the current intensity. A demonstrative example of the connection of the plant with the control platform is shown in Fig. 15. As shown in the figure, feeders are connected with the control hardware through DeviceNet and control hardware is connected with the control platform. A model predictive control (MPC) strategy is implemented in the control studio of the DeltaV system. The inputs for the control loop

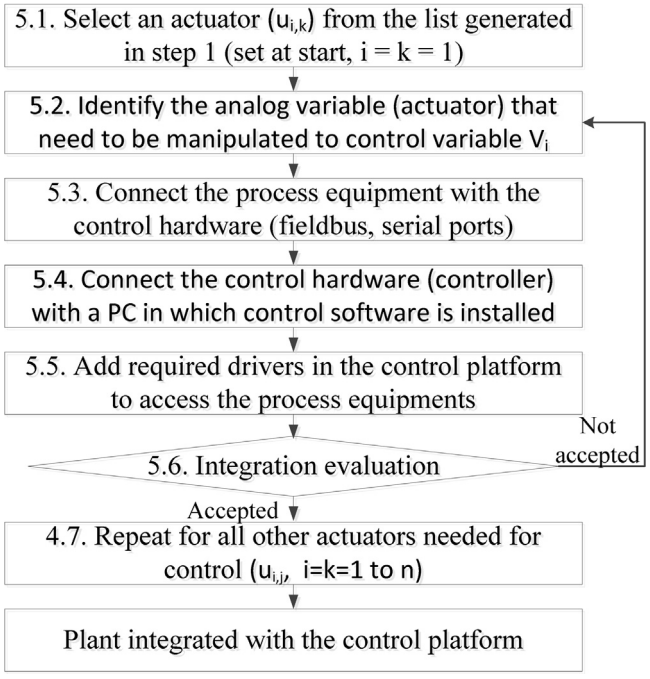

Fig. 14. Integration of pharmaceutical plant with the control platform.

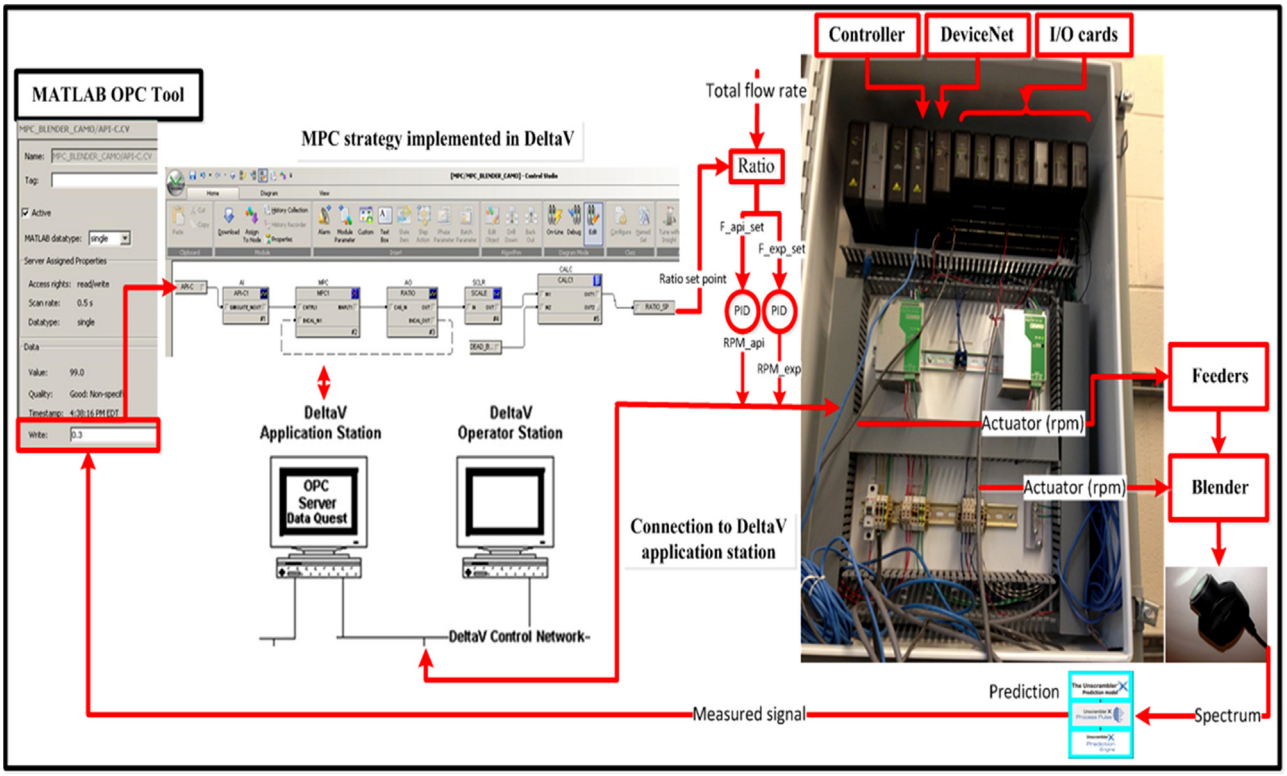

Fig. 15. Connection of the plant with DeltaV control platform and implementation of model predictive controller (MPC).

(controlled variable: API composition) come from the MATLAB OPC tool. The output of the MPC (ratio set point) is the input of the ratio controller that generates the flow rate set points of API and excipient feeders. The powder flow rate from API and excipient feeders are controlled through slave PID controllers (inbuilt in feeders). The actuators generated from the slave PID controllers are then sent to the plant through a DeviceNet card. The signals of blender RPM can be also directly send to the blender through a serial port as shown in Fig. 15.

4.6. Implementation of control strategy (step 6)

The systematic methodology to implement the control strategy is shown in Fig. 16. As shown in the figure, the first step of this methodology is to select a control variable, corresponding actuator and control strategy from the list generated in step 1 to be considered for implementation. Then, the control studio (toolbox) of the control platform should be employed to add the controller. Subsequently, the controller input is connected to the measured signal (control variable) and the control output with the actuator which needs to be sent to the plant. If the model predictive controller (MPC) has been used, the linear model needed for MPC must be identified. To identify the linear model, either the first-principles process model (as described in step 1) or plant can be used. In either case, step changes in the actuator (input) need to be introduced and a linear model needs to be generated based on the output (control variable) response. The parameters for PID and MPC have been identified in step 1. However, these parameters may need to be fine-tuned in this step. Finally, the integration needs to be evaluated through closed-loop operation. Steps 6.1–6.6 need to be repeated for all remaining control variables.

The systematic methodology, as shown in Fig. 16, has been employed to implement the control strategy. The control variable, "API composition" and corresponding actuator (ratio set point) has been considered for the demonstration of control loop implementation. The control strategy has been implemented in DeltaV using its control studio feature. Three control schemes namely PID, PID with Smith predictor and hybrid MPC-PID have been implemented and connected with a switch button so that the user can select one control scheme at a time. The different schemes are used only for the master controller while the slave PID

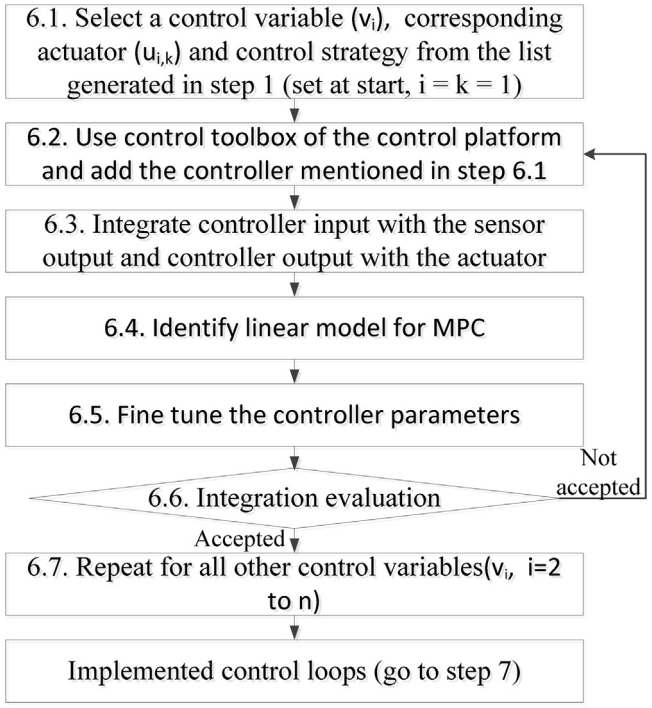

Fig. 16. Integration of pharmaceutical plant with the control platform.

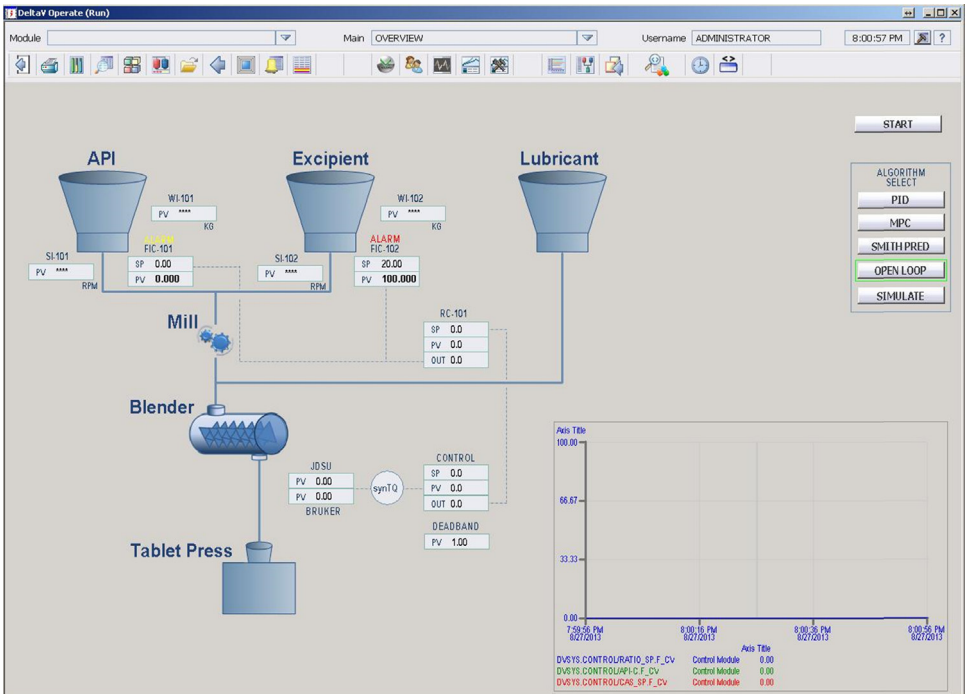

Fig. 17. Systematic framework for onsite design and evaluation of the control system (graphical user interface).

controllers built into the feeders are always same (not shown here). The implemented MPC scheme to control the API composition at blender is shown in Fig. 15. The ratio set point (CAS_SP) and the measured composition (API-C) are the inputs to the MPC that generate the actuator which goes to a selector block (used to select control strategies). After the selector block, this input will enter a calculator block where the dead band has been integrated. The dead band is used to ensure that the controller output lies within a range. After this block, the output goes to the ratio controller.

4.7. Performance evaluation (step 7)

After completing all integration and implementing all control loops, the performance of the control system needs to be evaluated. For performance evaluation, the set point tracking ability and disturbance rejection ability of the control system can be analyzed. If the implemented control system is able to track the step change in the set point and able to reject the disturbances, then the control system can be considered as the final control system. In the case of an unsatisfactory response, steps 1–6 need to be repeated.

5. Results and discussion

Through steps 1–6, a systematic framework for the onsite design and implementation of a control system has been developed. The developed graphical user interface for closed-loop operation of the direct compaction continuous tablet manufacturing process is shown in Fig. 17. In the graphical user interface, three feeders (for the API, excipient and lubricant), a mill, a blender and a tablet press have been included. Each unit can be also operated individually. As shown in the figure (see right hand corner), the user has the option to run the plant in a closed-loop or an open-loop scenario. In the closed-loop scenario, there are three options for the control strategy. These options are PID, MPC and PID with Smith predictor. There is also an option to run the control strategy in simulation mode. In simulation mode, the input and output signals of the controller are linked with the process model instead of the plant. This option is useful for control system design, tuning of controller parameters, development of a linear model for MPC and training purposes. The response of the control variable can also be seen directly at the user interface.

The developed framework (see Fig. 17) has been used to evaluate the performance of the control system. The control of the API composition through MPC has been considered here as a demonstrative example. There is a cascade control arrangement where the master controller is MPC and the slave controllers are PID. The input signal for MPC is the API composition (control variable) and the output signal from MPC is the ratio set point. The ratio set point acts as the input for a ratio controller. The ratio controller provides the flow rate set points for the slave PID controllers built into the feeders to control the API, excipient and lubricant flow rates. The final actuators are the rotational speeds of the feeders. First simulation mode has been used to evaluate the performance of control system and to demonstrate the concept. Simulation mode has been selected in the user interface (see Fig. 17, SIMULATE). In simulation mode, the controller input comes from a process model simulated in gPROMS then MPC calculates the actuator using a linear model in DeltaV and sends the actuator back to the process model. The closed-loop response is shown in Fig. 18. As shown in the figure, the step change in the set point has been introduced and the model predictive controller (MPC) tracks the set point. The figure shows that the controller tracks the set point very well. Similarly, the performance of the other control-loops has been evaluated.

Finally, the plant has been run in closed-loop scenario to validate the different integrations and proposed control framework. In one feeder API (APAP (acetyl-para-aminophenol)) is filled and in second feeder Excipient (Silicified Microcrystalline Cellulose (SMCC)) mixed with 1% magnesium stearate is filled. JDSU micro NIR sensor has been used to measure the API composition at blender outlet. A PLS model developed in Unscrambler X is used for NIR prediction. Unscrambler Process Pulse and a prediction engine (OLUPX) are used for real time NIR prediction. The API composition is then sent to DeltaV using MATLAB OPC communication protocol. Option for MPC mode from the user interface (see Fig. 17, MPC) has been selected. MPC uses a linear model to calculate the actuator (ratio set

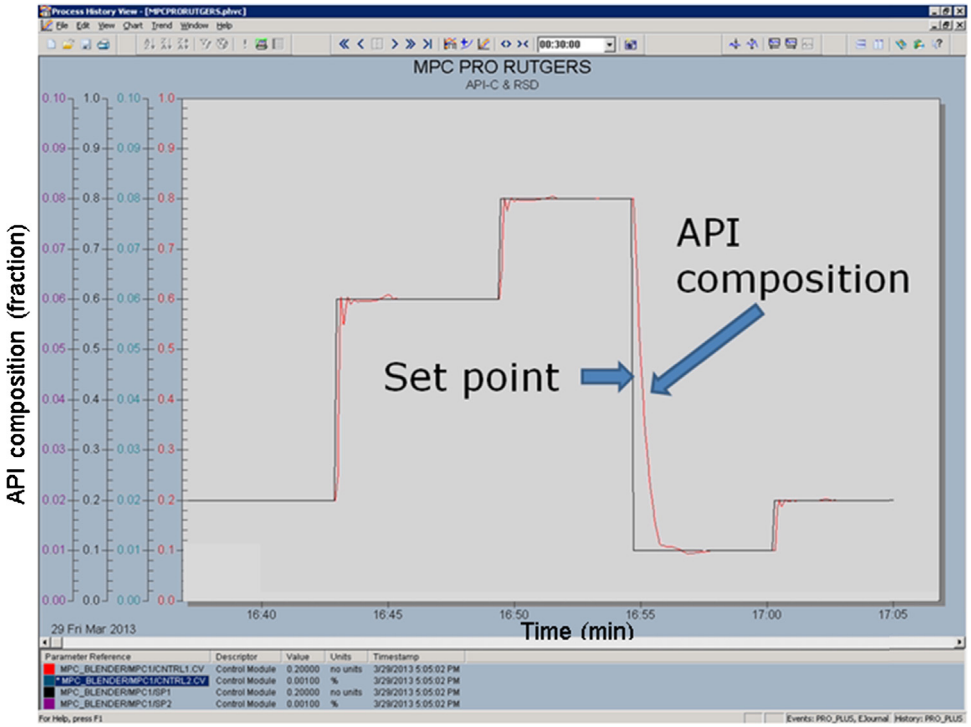

Fig. 18. Closed-loop response for API composition control (model-based performance evaluation of control system).

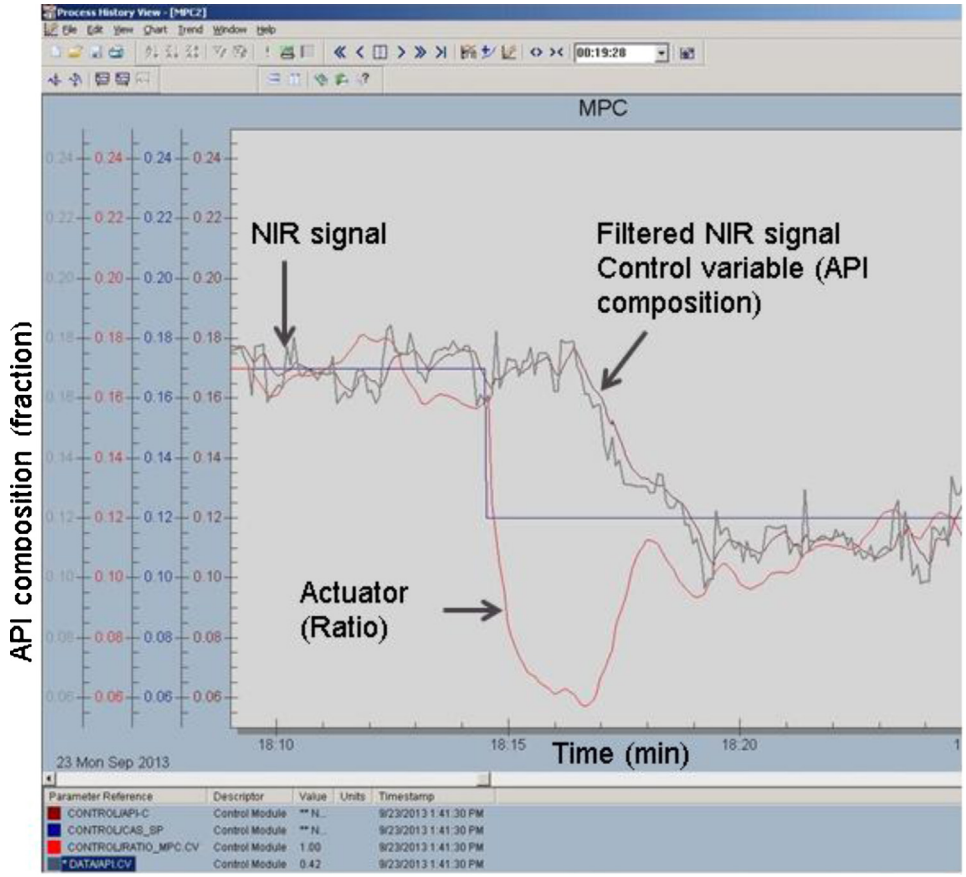

Fig. 19. Experimental validation of the sensor, control software and hardware integration and the proposed framework (closed-loop response for API composition control).

point) which is then sent to a ratio controller as the input. The ratio controller then calculates the flow rate set point of API and Excipient feeders. API and Excipients are then controlled by manipulating the rotational speed of respective feeders. The blender speed is kept at 30% of the maximum speed. The different variables for example, the set point provided by the user, signals obtained from the sensors, and signals sent to the plant are then plotted in the historian of DeltaV. The closed-loop response of API composition control loop is shown in Fig. 19. The figure shows the API composition set point, API composition measured by NIR, filtered API composition signal and the actuator response. Filtered API composition signal is the input for model predictive controller. As shown in the figure, the API composition is controlled at 0.17 set point then a step change is introduced from 0.17 to 0.12. The figure shows that the controller is able to track the step change in set point. The actuator response is also reasonable. The results presented here validate that the NIR sensor has been integrated with the plant. The sensor output has been successfully communicated with the control platform (DeltaV) via OPC communication protocol. Real time online prediction of NIR signal has been made. The controller output has been communicated with the plant.

6. Conclusions

A systematic framework for onsite design and implementation of the control system has been developed. The framework includes a generic methodology and supporting tools through which the control system can be designed at a manufacturing site and can be implemented for closed-loop operation. The framework has been used for onsite design and implementation of a control system into a continuous tablet manufacturing pilot plant using PAT tools. The developed control framework for continuous tablet manufacturing processes has different novel features, such as the option to run the plant in an open-loop or a closed-loop scenario. Furthermore, within the closed-loop scenario, options for a simpler PID, a dead time compensator (Smith predictor) and an advanced model predictive controller have been included. The feature to run the control strategy in simulation mode has been also added in the control platform that facilitates quick onsite control system design and performance evaluation. The proposed systematic control framework supports the paradigm shift of pharmaceutical tablet manufacturing from conventional QbT-based batch-wise, open-loop production to QbD-based continuous, closed-loop production. The proposed framework is generic and should have a broad application range in the pharmaceutical, food, agriculture, chemical and biochemical industries. Future work includes performance evaluation of the different implemented control loops based on closed-loop operation of the continuous tablet manufacturing process. The performance of the PID and MPC strategies will be also compared.

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