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Case studies

Industry 4.0 in Action: Digitalisation of a Continuous Process Manufacturing for Formulated Products

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A B S T R A C T

The pharmaceutical industry is going through a significant change to adopt smart manufacturing for more integrated supply chains and improved sustainability. Today's competitive market demands have put pressure on healthcare systems to take a comprehensive assessment of the drug life cycle, its environmental effect, industrial use of energy and resources, supply chain, and impact on end-users. The exploitation of emerging Industry 4.0 technologies will allow a sustainable process design and personalised health care system through the realisation of digital twins, which could transform the pharmaceutical sector to be more flexible, robust, adaptive, and smart. A significant level of research and development has been applied to pharmaceutical manufacturing especially in existing, outdated design and scale-up paradigms in isolated unit operations. However, addressing the key challenges in pharmaceutical manufacturing requires whole systems approaches to incorporate Industry 4.0 concepts.

This paper aims to share the latest development of an advanced digital twin of a continuous wet granulation and tableting process at The University of Sheffield. These include the delivery of a digital platform consisting of an Advanced Process Control system (APC), mechanistic model platform and industrial IoT platform for data analytics and visualisation. The combined solution aligns with the concepts of Industry 4.0 by providing a digital twin, cloud integration, sophisticated statistical, as well as hybrid and mechanistic models. The models are in turn, used for soft-sensors, Model Predictive Control and Optimisation algorithms to predict and control product Quality Attributes. The potential application of digital twins in the pharmaceutical industry will also be explored.

Introduction

Great research and development are undergoing in engineering concepts, methods, and tools for smart process manufacturing. In particular, the pharmaceutical industry is embracing the general digitalisation trend with the help of academic institutions, solution providers and regulatory agencies. However, despite the strong desire to move towards digitalised continuous manufacturing, this trend seems to be less well advanced compared to the oil and petrol industries (Ding, 2018; Lee et al., 2015; Litster & Bogle, 2019). Pharmaceutical manufacturing technologies continue to advance as Pharma 4.0 begins to challenge the traditional batch approaches and old business models for the manufacture of pharmaceuticals. This is especially highlighted during the COVID-19 pandemic, where the need for manufacturing technologies that are flexible, more responsive to changing demand and less dependent on human interventions during production became paramount. For example, with lockdowns preventing people from being in factories, the use of automation and control in industry rose. The pandemic has shown that digital technologies can be used to enable remote working. In addition, there has been a shift in specialities firms to continuous operations. The transformation has been fostered by regulatory entities as well as driven by cost reduction and shorter development cycles (Batch Manufacturing | Batch to Continuous | Control Global, 2021). The Quality by Design guidelines has promoted the comprehensive generation of necessary product and process understanding required to execute a continuous and systematic operation for process operation and product quality control. This includes determining essential quality characteristics, process parameters, and control techniques.

In recent years, comprehensive methodologies for the design and implementation of control strategies for continuous drug product manufac-

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turing, particularly the incorporation of Process Analytical Technologies sensors into the control system, have been implemented and gradually improved (Su et al., 2019). For example, a simulated plant-wide model predictive control for an end-to-end continuous production line has been presented at the Novartis-MIT centre (Su et al., 2019). Global sensitivity analysis methodologies allow systematically identifying key process parameters that affect critical product attributes (Metta et al., 2019). Continuous manufacture of formulated products necessitates the use of PAT for quality control (Stegemann, 2016 ; Rehrl et al., 2018). However, often commercially available unit operations lack a comprehensive online assessment unit; as a result, the adoption of PAT devices requires monetary investment.

With the growing need for patient-centeredness in medicine, consumer-focused manufacturers of formulated products are acutely aware of the need to move towards smart and continuous manufacturing. However, at this stage, they are uncertain about the adoption of digital technologies due to the lack of industrial-scale demonstrators compliant with the regulations such as 21 CFR Part 11 for industrial research (Manzano & Langer, 2018; Chen et al., 2020; Schneider et al., 2010; Nematollahi et al., 2017). In particular, the pharmaceutical industry operates under tight regulations from governing bodies, e.g. the US Food and Drug Administration (FDA). The exploitation of emerging Industry 4.0 technologies such as closed-loop control, online quality monitoring of continuous processes, real-time data processing and soft sensors will allow a sustainable process design and personalised health care system while reducing environmental footprints (Bengtsson-Palme et al., 2018; Gernaey et al., 2012; Stegemann, 2016).

The competitive edge of Industry 4.0 does not lie in having an integrated production line; but also in embedding digital systems in the production which can independently generate data to make and inform correct decisions. There is a demand for the deployment of more sophisticated model-based tools to demonstrate the benefit of digital twins' application in the pharmaceutical sector. As the pharmaceutical sector prepares to introduce quality by design, integrated unit operation processes and product models and the use of advanced control platforms to maintain desirable product quality is paramount. Progress on product and process models for customer demand and improved integration with model-based design optimization will fuel a service-oriented business model in the formulated product sector. An integrated digital twin will enable manufacturers to be more attentive to their consumers' needs to provide timely products of consistently excellent quality.

The Challenge

Industry 4.0 delivers many benefits to process industries; however some barriers impede digital transformation. These include costs associated with model development and revalidation of existing systems, regulatory costs to make the change; lack of expertise in digital technologies; knowledge gap in digital design and mathematical process models (Litster & Bogle, 2019). According to Ślusarczyk et al's survey, the most important challenge to implementing Industry 4.0 is a lack of digital culture and training, which is indicated by half of the respondents (Ślusarczyk, 2018). A lack of support from managers, ambiguous economic advantages from investments in digital technology, cyber-physical security and significant financial investment needs are all major considerations. From Ślusarczyk's survey, the least frequently indicated barrier is the fear of losing control over the intellectual property of the company (Ślusarczyk, 2018). Large data sets, including critical and possibly secret information, are shared, necessitating safe connection and processing across all platforms.

Many large pharmaceutical companies have not embraced the new digital ecosystem, and many of their pharmaceutical manufacturing processes utilize legacy automation systems with no IoT capabilities (Amini et al., 2020). Research shows that 70% of all pharmaceutical manufacturing data is not collected and therefore goes to waste (Manzano & Langer, 2018). Lengthy, capital-intensive development timelines and legacy processes have made it difficult to exploit the full potential of emerging digital technologies (Huang et al., 2021; Kopalle et al., 2020; Leclerc and Smith, 2018). And therefore, the pharmaceutical industry still heavily relies on batch production of products as there are certain manual procedures within the process such as laboratory testing and in-process control checks for drug quality (Chen et al., 2020).

Pharmaceutical manufacturing has been confronted with the need for flexibility due to changing markets and the need for a more customer-centric approach. However, due to insufficient sensors and intelligent devices for interactions and co-operations between machines and operators, it is very challenging to meet these demands (Gunes et al., 2014). Different modelling methods for both upstream and downstream unit activities in pharmaceutical production have been developed. However, there is no vigorous model that captures Critical Process Parameters (CPPs) and Critical Quality Attributes (CQAs) for all the unit operations in the integrated process (Chen et al., 2020). Work in a holistic or systems thinking approach that goes beyond the physical infrastructure of the manufacturing plant and its digitisation could enable the successful integration of Industry 4.0 technologies. However, due to high computational costs, implementing all these methods within the digital space is challenging (Chen et al., 2020). Industry 4.0 digital technologies such as cloud and edge computing have prompted the pharmaceutical manufacturing industry to adopt cutting-edge solutions such as Advanced Process Control (APC) and continuous production. An Advanced Process Control across the entire process operation will enable coordinated control of CPPs to reduce the variability of CQAs, improving product quality and process robustness (Huang et al., 2021). Pharmaceutical industries follow strict regulatory laws; therefore, accepting new technologies, such as an advanced model-based control system that can be used for process fault detection (process monitoring) or to control the process (APC), usually takes a longer time than other process industries (Huang et al., 2021; Gunes et al., 2014). For example, the pharmaceutical industry can learn from aerospace's implementation of digital technologies in swift adoption of predictive maintenance of aero engines. Incompatible platforms, models and systems remain a barrier to achieving integration. Heterogeneity in equipment program is an issue that may be overcome by developing a standardised interface or file format that allows seamless integration (Chen et al., 2020).

This paper aims to provide a detailed description of the present status of the digital architecture of the University of Sheffield's Diamond Pilot Plant (DiPP), its benefits and application in industry. In the first instance, the project sought out an advanced digital control at the granulator and tabletting components of the DiPP and has later evolved to include smart manufacturing technologies across the entire tablet manufacturing process. These technologies include soft sensing, cloud technology and data visualization platforms.

The remainder of the paper is structured as follows. Firstly, a description of DiPP's key powder processes such as crystallisation, wet granulation and tablet press is provided. Secondly, a detailed description of the critical components of the DiPP's digital twin architecture and evaluation of the performance of these components are given. These include the advanced control system, moisture content soft sensor and the MindSphere cloud integration. After discussing the status of digital architecture, the limitations connected with the development and application of the Digital Twin will be discussed, followed by future directions and conclusions.

Process Description

The University of Sheffield commissioned DiPP within the Faculty of Engineering in 2018. DiPP includes large scale equipment representing several industries but mainly the pharmaceutical industry. These include a continuous crystallisation unit, a filter dryer and an industrial-scale GEA Consigma 25 powder to tablet line, representing an example of a continuous process in the pharmaceutical industry. The continuous os-

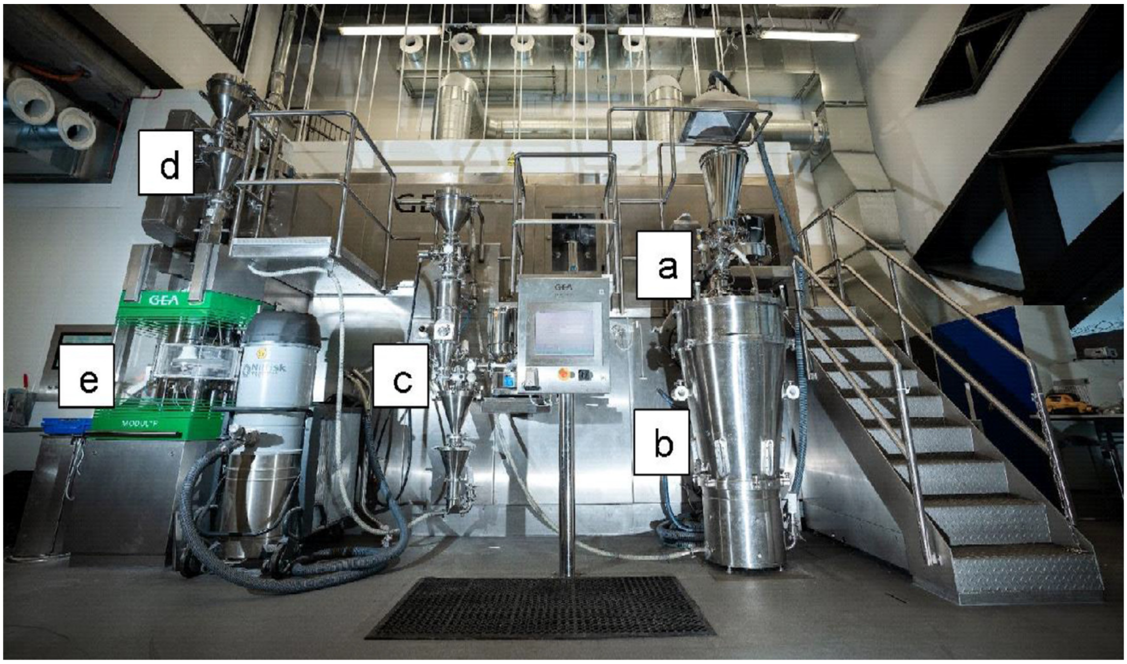

Figure 1. The Consigma 25 line at Diamond Pilot Plant (DiPP) (a) Twin screw granulator (b) Segmented fluidized bed dryer (c) Cone mill (d) Blender (e) Tablet press.

cillatory baffled crystallizer (COBC) and the continuous filter dryer are both used to produce high purity crystals/ drug substances which can act as active materials for the preparation of drug products. As shown in Figure 1, the Consigma 25 line includes a series of unit operations. The plant starts with a hopper and a loss-in-weight feeder, which deliver pre-blended powder to the twin-screw granulator (TSG), where granules are produced after mixing with the appropriate binder. The mixing in the granulator occurs via two screws which come with kneading and conveying elements to provide different stress based on the configuration. The wet granules are then transported gravimetrically to the fluidized bed dryer (FBD), this is a six segmented dryer in which granules are dried at pre-set drying conditions. The dried granules are then transported pneumatically to the granules conditioning unit where the moisture content is monitored using a NIR technology and then granules are milled down using a cone mill. The NIR probe acts as a Process Analytical Technology (PAT) tool to monitor the product quality, namely the moisture content and it sends feedback to the system on whether to keep the product or divert it to waste. Following the milling, process granules are passed through an additional two blending units where an extra material can be added as well as lubricants before going to the last unit which is the rotary tablet press.

The new continuous powder processing in the DiPP emphasises the importance of complex particulate products and formulated products more broadly in modern chemical engineering and the University of Sheffield is reflecting this in their new curriculum in chemical engineering. DiPP key features include a dedicated industrial control room that accommodates an advanced control system and a digital twin of the whole plant. The University of Sheffield, Perceptive Engineering and Siemens collaborated forces to develop an innovative solution to digitalise the whole continuous drug manufacturing process from crystallisation to tablet press and convert it into the world's leading Industry 4.0 demonstrator. The main objective of the project was to adopt a data-centric approach and automation as well as demonstrate facilities to test and validate potential IoT applications in the real world.

The challenges in digitalisation of the continuous tablet manufacturing process included a low detailed process maturity; in other words, the process was not IoT enabled. Each system and process unit represented its own isolated data islands, therefore, data had to be locally saved in separate locations and then brought together manually for offline analysis. Also, existing knowledge from technical personnel could not be fully leveraged when controlling the process, ultimately making the operation of the pilot plan highly manual resulting in considerable workload on operators. The University of Sheffield wanted to develop a solution that could improve the system operations and overcome these challenges. The main goals of the research were to coordinate all data from the different systems in a centralised location, develop dashboards for monitoring the systems locally and remotely, a solution that could use all the data in real-time and can use machine learning techniques to model, predict and ultimately control critical process variables. Also, to implement a solution that can upload in real-time all data to the cloud, such as Siemens MindSphere so the data can be used across the university for data science research activities.

Results and Discussion

Development of an Advanced Process Control System

The first step in the development of the control system for the pilot plant was to set up the digital architecture, summarised in Figure 2. Perceptive Engineering's PharmaMV software platform was employed for the fusion of all data from the process, digital twin and Siemens MindSphere platform. This facilitated access to all data from a single interface. This digital architecture enables synergy between the statistical and nonlinear models providing a complete set of tools for monitoring advanced process control and machine learning, seamless integration to the process units and PAT instruments and enabling data fusion and alignment across the platform.

PharmaMV software collects and aligns to all process data from all process units at the DiPP and was set up as a single point repository for all the data in real-time. Then, an Optimised Experimental Design Platform (OEDP) template was configured for all the equipment to enable control, monitoring and data-driven predictions in real-time. The OEDP is a commercial solution built upon PharmaMV software developed by Perceptive Engineers and provides the workflow and tools for

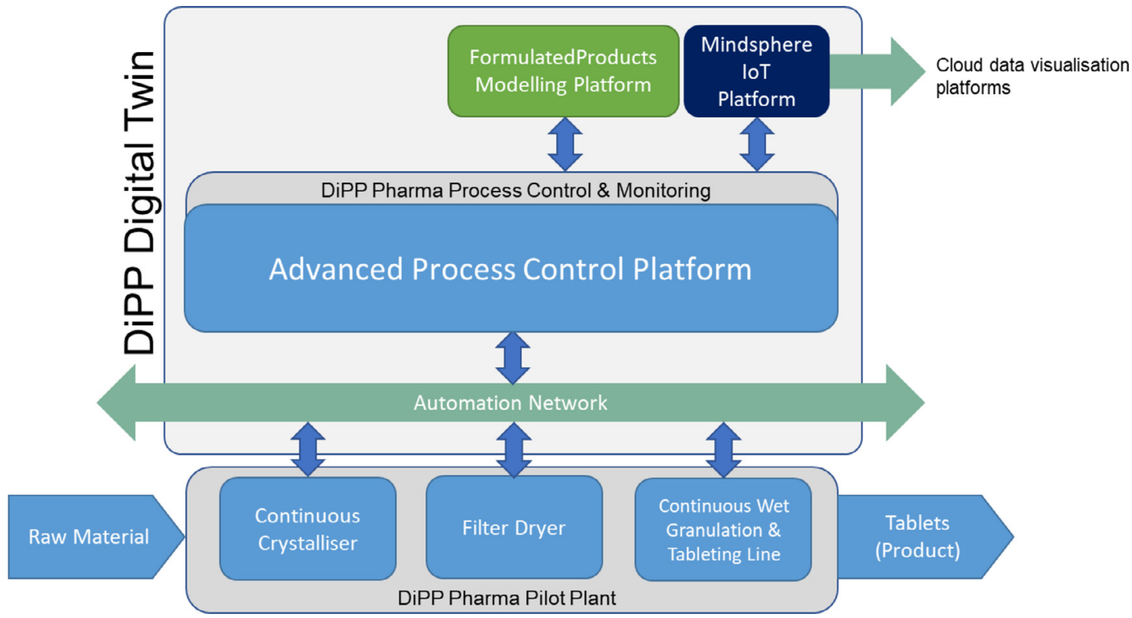

Figure 2. Integrated Digital Architecture of the DIPP's Digital twin. The architecture's key parts include an Advanced Process Control platform (PharmaMV), MindSphere clouds platform, and real-time endpoint prediction software, gPROMS Formulated Products. The architecture's structure and data flow network are set up to allow all process-relevant data to be collected, aligned and centrally stored, the use of intuitive and accessible process dashboards, an Advanced Process Control of product-relevant data capable of controlling measured or inferred quantities and cloud connectivity of all process units.

rapid process development using optimised experimental design techniques. These techniques include the automated design of experiments, machine learning for self-optimisation and automated model adaption, response testing and integration with mechanistic digital twins for the development and deployment of advanced process control. OEDP Solution has been employed in other projects in a different research centre, e.g., Digitalisation and APC for a fed-batch reactor for mammalian cell growth (Craven et all.,2014). OEDP solution is provided in PharmaMV and can be modified by scientists/engineers. The OEDP includes pre-configured tools and embedded documentation to reduce overall configuration and development effort. All these tools can be accessed via interactive dashboards shown in Figures 3, so operators can navigate across all the process units drill down to a specific part of the system and activate any of the digital tools using such interactive dashboards. The platform also supports user authentication with different levels of access; for example, limiting user's access to only allow process monitoring. OEDP enables smart process development for the crystalliser filter dryer and the Consigma continuous tablet line. The APC was equipped with a mechanistic modelling platform, gPROMS FormulatedProducts, via a Foreign Process Interface for the exchange of control variables and model predictions of CQA's, which is included within the standard package. gPROMS FormulatedProducts has been selected in this project because it brings the added value of utilising mechanistic models to serve as digital twins for the process. The standard package includes available model library to describe all unit operations and transformations involved in each case to the required fidelity. The required unit operations and the required fidelity of model with respect to phenomena considered and ability to predict the effect of process parameters Critical Quality Attributes (CQA's) has not been available in other modelling packages. And finally, the platform's ability to communicate with the rest of the DiPP's digital twin platforms, including PharmaMV and MindSphere has been another advantage.

Statistically rich data from modelling torque dynamics can be generated using the OEDPs response test tool. Then, through machine learning techniques, the platform is able to identify the model automatically and adapt the model to new operating conditions if needed. Figure 4 shows how a model can be identified to predict the torque of the twin-screw wet granulator. An example of an automated step test is displayed on the right-hand side of the dashboard, displayed in Figure 4. Real-time torque measurements are displayed in green on the top trend. The other trends shown in red are the steps applied by PharmaMV, and in blue, readbacks from the process variables. These data are used in real-time to adapt the model and after a predefined time has elapsed or when a model accuracy level is reached, the automated modelling stops, and the new model is integrated within a Model Prediction Control (MPC) architecture to control torque to the setpoint. The MPC package was developed by Perceptive Engineering and is part of the PharmaMV tools. The MPC is based on the following function:

$$J = \sum_{i=0}^{N} \left[e_{i+1} P e_{i+1}^{T} + \Delta u_i Q \Delta u_i^{T} + f_i R f_i^{T} \right]$$

where e is set-point error, P is set-point weight (configured by the user), Δu is actuation move, Q is move weight (configured by the user), f is manipulated variable target and R is manipulated variable target weight (configured by the user). Operators can activate and configure the automated model adaptation via the panel at the left-hand side of the dashboard. The platform will continuously monitor the quality of the data and will notify operators of any interface communication errors. The platform will stop any response test if such communication errors are detected. Data from any automated response test is uploaded to MindSphere in real-time to allow the users access to the data for analysis and research activities.

A data driven moisture soft sensor was developed for CQA prediction and subsequent control for monitoring and real-time control of end-point moisture by manipulated the drying time in real-time as the campaign runs. Data for modelling were obtained by executing an automated Design of Experiments (DoEs) on the fluidised bed dryer. This data was then analysed offline to develop the below moisture soft-sensor model:

$$Final\ moisture = (Drying\ Time\ PV - Filling\ Time) \times Gradient + Bias$$

where, the *Gradient* and the *Bias* are computed based on available data from normal operation. The *Bias* can be modified online based on the current liquid-to-solid ratio and the product key (PK) weight:

$$Bias = Liquid\ to\ Solid\ ratio/2 \times 100 \times PK\ weight$$

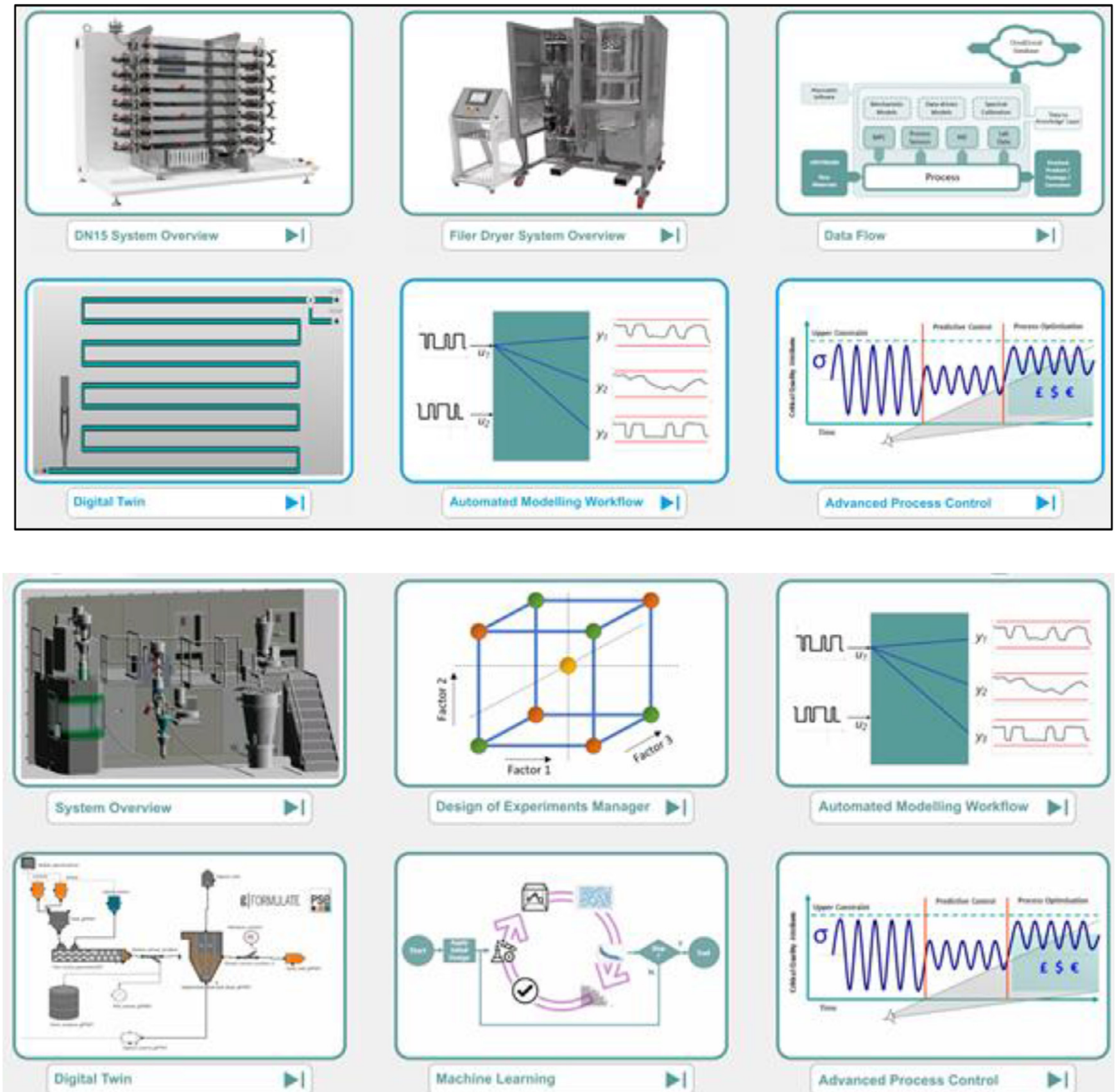

Figure 3. Overview screen of PharmaMV User Interface for (top) Continuous oscillatory baffled crystallizer and Filter-Dryer system and (bottom) DiPP Continuous Wet granulation and Tableting process. Operators can navigate between dashboards using the embedded buttons and monitor specific unit operations and access configurable tools i.e automated DoE, step testing, APC and online model adaption to monitor and control unit operations.

The soft sensor accuracy to estimate moisture continuously can be observed on the top trend in Figure 5, in which the blue line shows moisture measurements in real-time using NIR spectrometer equipped with a fiber-optic Lighthouse Probe^{TM} (LHP, GEA Pharma Systems) and the green line corresponds to the soft sensor predictions. The advantages of the data-driven approach for development of moisture soft-sensor compared to hybrid approaches used in other woks (Rehrl et al. 2020) are that in this approach deep knowledge of the system dynamics is not required, easier to identify, more robust for extrapolation which makes them good candidates for implementation in model predictive control approaches, provided that the operation conditions do not change. However, it should be noted that a model re-identification is needed when the operating conditions change.

The tableting line has a single moisture sensor located after the dryer. This sensor can be relocated to monitor a single chamber out of six in the dryer. With this new soft sensor, it is now possible to monitor moisture across the six chambers in real-time while using the single NIR Moisture sensor to measure moisture at the endpoint before feeding the granules to the tablet press. The trends at the bottom of Figure 5 can be used to compare the soft sensor endpoint moisture predictions versus the actual measurement taken with the LHP after the dryer. The predictions and real-time measurements are close to each other after the soft sensor was validated. And it is now in use for online control of the drying time to reduce moisture viability.

The APC system developed for the DiPP allows to monitor, interact and optimise the tableting line using pre-configured dashboards. Figure 6 shows the dashboard employed by operators to activate and monitor the APC for the tableting line. The trends displayed in Figure 6 show the results of implemented a Model Predictive Control (MPC) to control torque. For the torque MPC control, step testing was implemented to generate statistically rich data to identify the model for MPC. Then the linear model identified for the MPC was employed in simulation to perform the initial tuning of the controller and determine: the prediction horizon (set to be time to steady state for the slowest response from an input step change), the control horizon (set to match the prediction horizon), the set-point weight for torque, the move weights, and the move limits for the manipulated variables. Set-points high and low limits, as well as manipulated variable high and low limits were set by operators of the tableting line and they are linked to the process safe operation limits. Noise was added to the simulation for tuning the

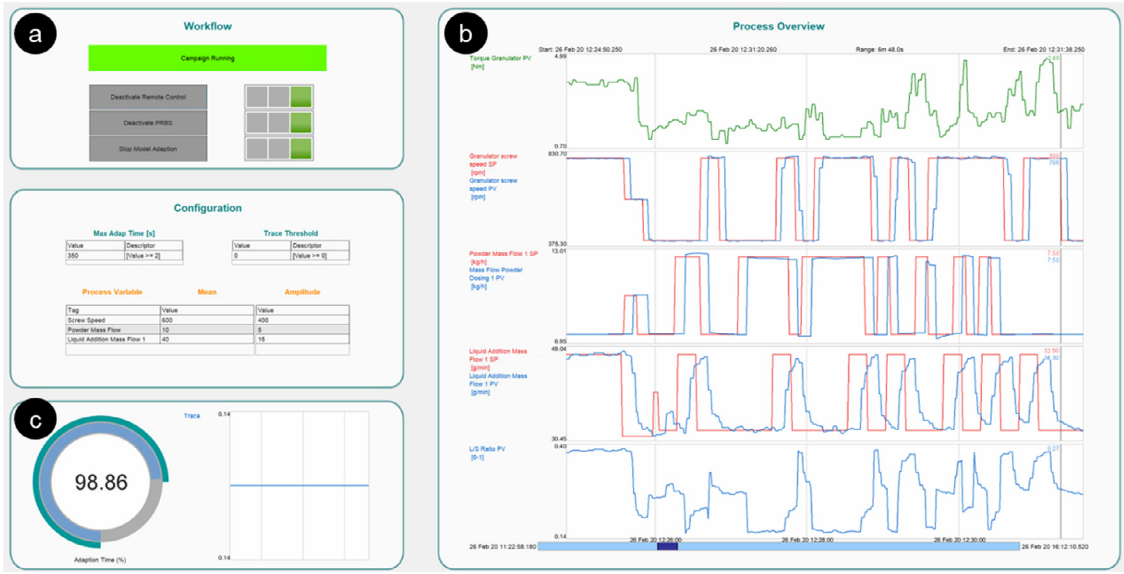

Figure 4. Interactive dashboard for activation and monitoring of automated modelling adaptation of the twin-screw wet granulator torque. (a). Data quality monitor (DQM) to stop adoption if communication errors are detected (b). Time-series trends to observe how the twin screw wet granulator torque changes with liquid to solid ratio. (c). Dial to provide further warning information on the model adaption time.

MPC where the signal-to-noise ratio used in the simulation was approximately equal to what was observed on the real system. After the MPC was tuned in simulation, it was deployed in real-time to control the real system, at which point a fine-tuning was carried out. The MPC can make the necessary adjustments to manipulated variables to follow different setpoint values. The benefits of the MPC system were observed during test fronts. For example, the MPC controller reduced the standard deviation by up to 43% and demonstrated that it is possible to minimise the impact of process disturbances, including changes in raw material properties. Another significant improvement is the implementation of a moisture endpoint control for the fluidised bed dryer. During the early test runs, the moisture soft sensor showed an endpoint prediction error of less than 0.5%.

Cloud Integration and Data Visualisation

One of the main goals of the project was to connect physical assets and upload data to the cloud to manage the data in real-time. Two Siemens nano boxes were interfaced to PharmaMV to enable the possibility of pushing data from all process units to the University of Sheffield's MindSphere account. MindSphere is Siemens industrial IoT as a service solution which allows collecting, monitoring, and analysing data in real-time. In addition, it enables the development of apps and solutions for different applications. Figure 7 shows an example of how data from the physical process collected by PharmaMV is uploaded into the cloud in real-time. The data can be accessed by users both online and offline at the University of Sheffield for further data processing.

The importance of big data visualisation as a tool for Industry 4.0 is widespread and well documented (Allen et al., 2021). An example of the benefits of this project is the integration of web-based data analytics/visualisation tools to enable real time collection, monitoring and analysis of the data. Here, we integrated Wiz with DiPP through MindSphere (Balzer et al., 2020). Wiz provides state-of-the-art data visualisation and analytics solutions to give both industry and academia access to the data generated in DiPP. Development of new products would be greatly accelerated if we develop better understanding of their key material and process properties. Identification of such properties can take years as it requires time-consuming calculations or experiments. Clearly, creation of data-driven insights and product-process relationships are essential to narrow down the design space and guide manufacturing efforts towards quality products. Recently, high-throughput practices have allowed us to study hundreds of processes/products to optimise their performance. Given the enormous amount of data generated via such strategies, it is important to develop data analytics tools that are able to establish relationships between different parameters and extract values from multidimensional datasets. These relationships reveal critical components of manufacturing performance and guide experiments to generate quality products. Figure 8 shows a number of prototypical plots produced in the Wiz application. By integrating Wiz in MindSphere, real-time data from process equipment can be analysed through user-friendly platforms lowering the barrier for understanding large datasets and providing valuable insights into troubleshooting or optimizing manufacturing processes.

Future work

Fusing three digital platforms, PharmaMV, gPROMS FormulatedProducts and MindSphere, provides a fast and cost-effective hybrid strategy for in silco development of a closed-loop controller. The current approaches for controller development are data-driven and require step response testing and plant to be operational. However, a digital design-based control leverages in silco modelling and simulation to reduce experimental effort during development of the APC control strategy. Using gPROMS FormulatedProducts, the Diamond Pilot Plant unit operation will be modelled using high fidelity mechanistic models. The software's advanced statistical analysis method will be used to estimate kinetic parameters with high precision. It also its built-in global analysis will be employed to carry out sensitivity analysis to choose key parameters and to design appropriate experiments. Several methods and tools will be used to interpret the results of the parameter estimation including Goodness of Fit Test, Bias Test and Lack of Fit tests. The correlation matrix will reveal the relationships between the unknown parameters. Covariance between unknown parameters can increase the uncertainty in their values as many combinations can result in a similar solution. Furthermore, additional information about the solid products, such as dissolution rates, will be incorporated into the simulation to determine the best process setup and parameters for a specified product specification. This also allows the integrated flowsheet to take a holistic view of the drug cycles. The modelling of the process will also allow the digital

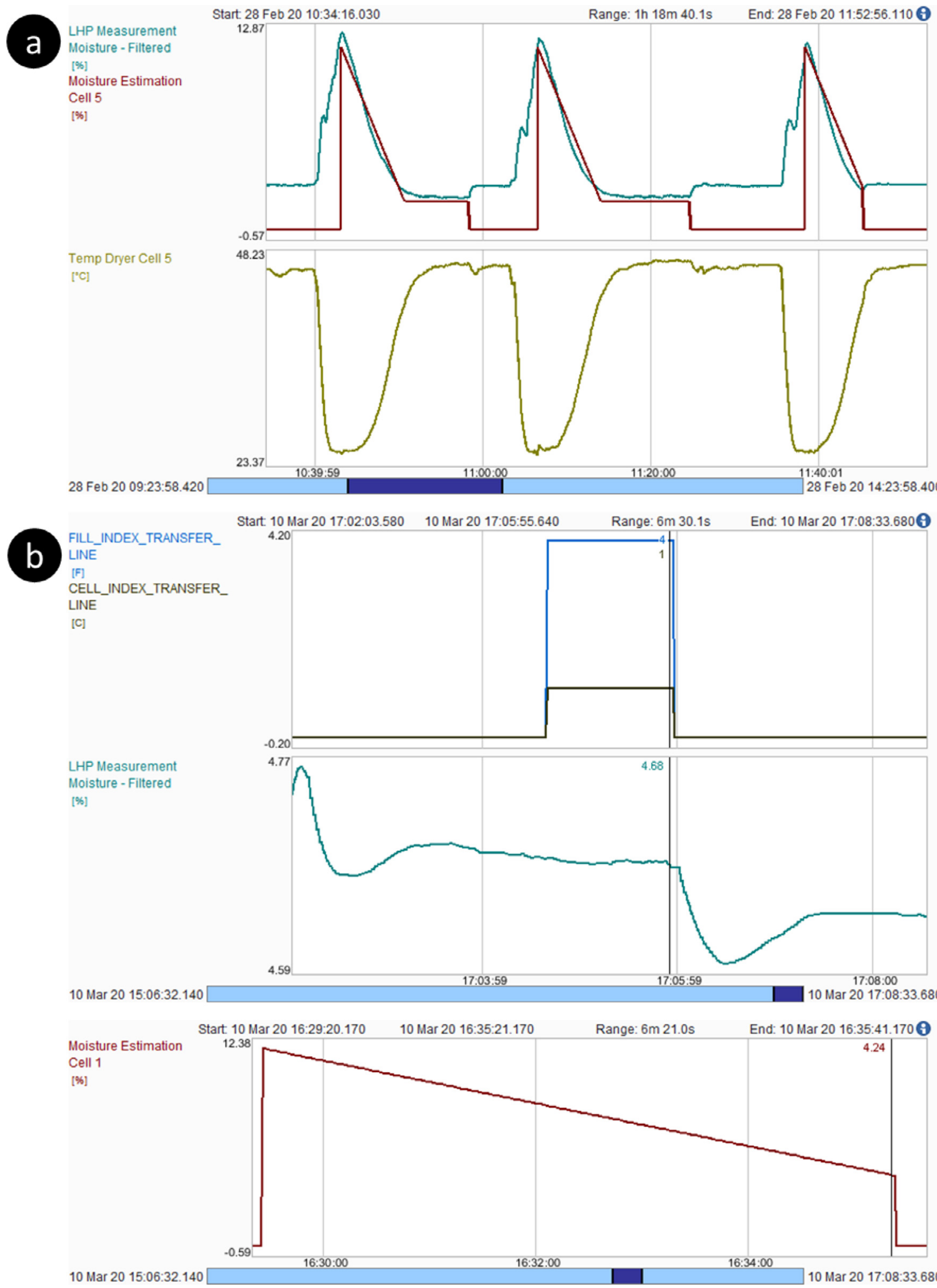

Figure 5. Comparison of the moisture soft sensor performance with PAT sensor. (a) continuous real-time actual measurement vs prediction data and (b) actual moisture End-Point Measurement and Moisture Prediction in Consigma 25.

twin to take advantage of the Digital Model Prediction Control (MPC) shown in Figure 9. The controller output (actuator) in PharmaMV can be transmitted to the process model and act as the input used to compute the new control variable signal. Digital Model Prediction Control will allow for controller parameter adjustment, model identification for MPC, and assessment of the data-driven control system. The benefit of this digital model predictive control is a reduced waste of material as the control strategy can be designed without relying on PAT data from the process, less operational downtime, and reduced experimentation (Reynolds, 2019; Singh et al., 2014).

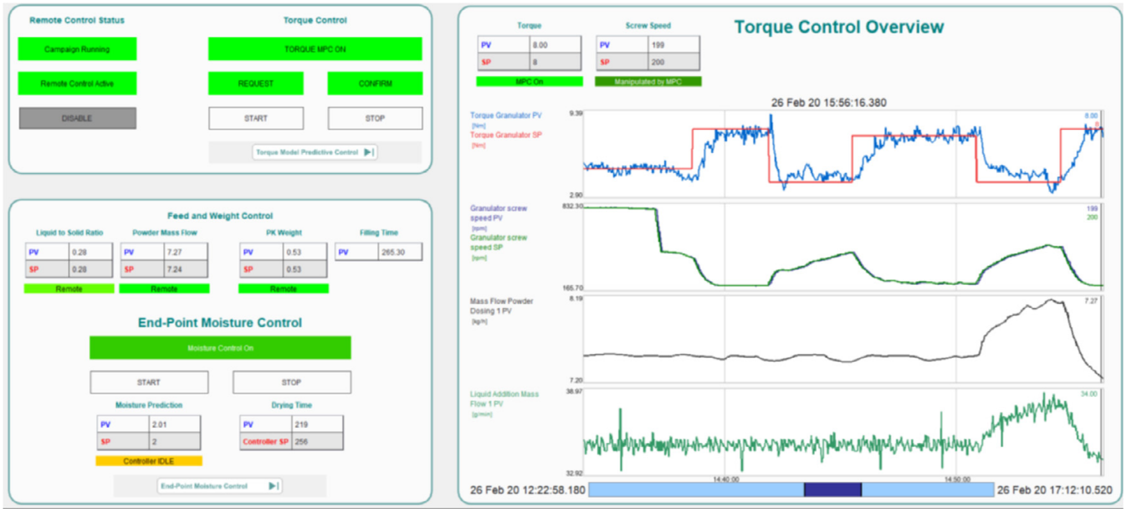

Figure 6. Pre-configured PharmaMV Advanced Process Control (APC) dashboard developed for the twin-screw wet granulator torque control. Operators can now monitor, interact and optimise the unit operations. On the left-hand side panels, there are indicators and activation buttons for the APC. The panel includes a faceplate to display the setpoint and actual values of the control variable which include endpoint moisture, PK weight, liquid to solid ratio and torque. On the right-hand side, there are real-time measurements trends relevant to torque MPC control.

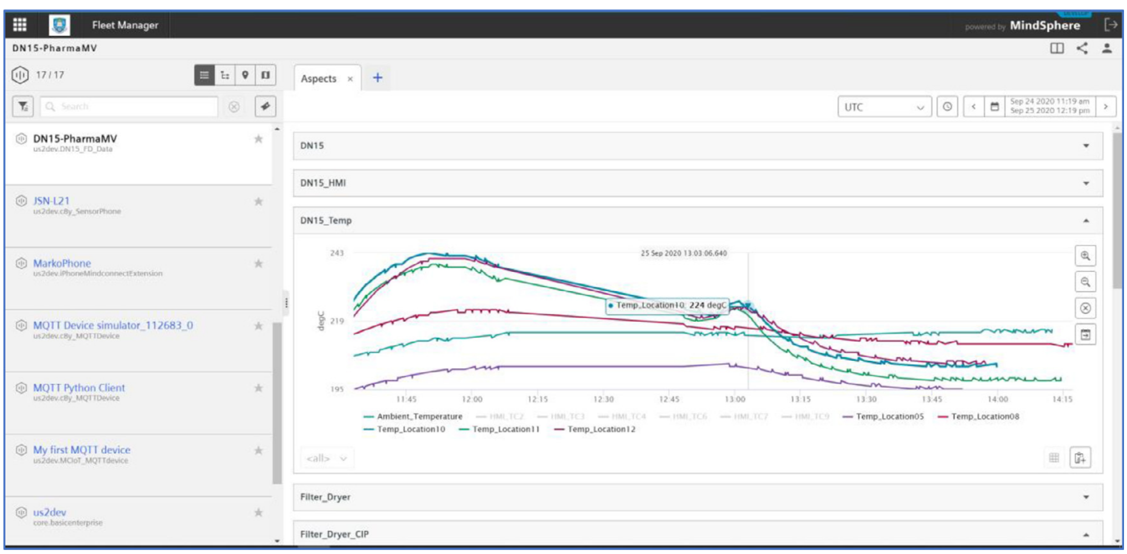

Figure 7. Example of real-time temperature readings at different locations of the DiPP's MindSphere.

Conclusions

This case study summarises the present state of the digital twin at the University of Sheffield, offering insights and emphasising the obstacles and benefits of deploying a fully integrated digital twin in the pharmaceutical sector. In addition to the summarised opportunities and benefits, further research direction of the development of digital model control using mechanistic models has been explored. An advanced digital architecture platform for the control and optimisation of complex dynamic particulate processes has been presented. The control system was developed on PharmaMV platform, which provides a full suite of analytical modelling and APC tools for rapid process development and optimization. It allows fusion and visualisation of processing analytical data in real-time. For the DiPP, PharmaMV enables the prediction of Critical Quality Attributes using data-driven and mechanistic models. It also enables the implementation of Model Predictive Control for CQAs and can be interfaced with IoT platforms such as MindSphere to transfer data in real-time to the cloud.

The digital architecture platform is highly flexible, customisable and scalable from one process unit to an entire line. The project has also demonstrated the transmission of the DiPP production line data to cloud technology and the deployment of an interactive dashboard in MindSphere for multivariate data analysis. It has been shown how implementing APC in the line can reduce process variability and increase process stability; for example, it has been demonstrated that the implementation of an MPC controller reduced the standard deviation of torque by 43%. Similarly, it has been shown that data-driven models identified using machine learning algorithms can provide accurate predictions, and such predictions can be used to monitor difficult-to-measure process variables, and ultimately allowing the use of these predictions to further control the system automatically; the example in this work is the moisture soft sensor that was developed and implemented in real-time. This sensor allows continuous and end-point moisture estimation for all the six chambers of the segmented fluidized bed dryer; the sensor showed an endpoint prediction error of less than 0.5%. This level of prediction accuracy allowed the implementation of automatic end-

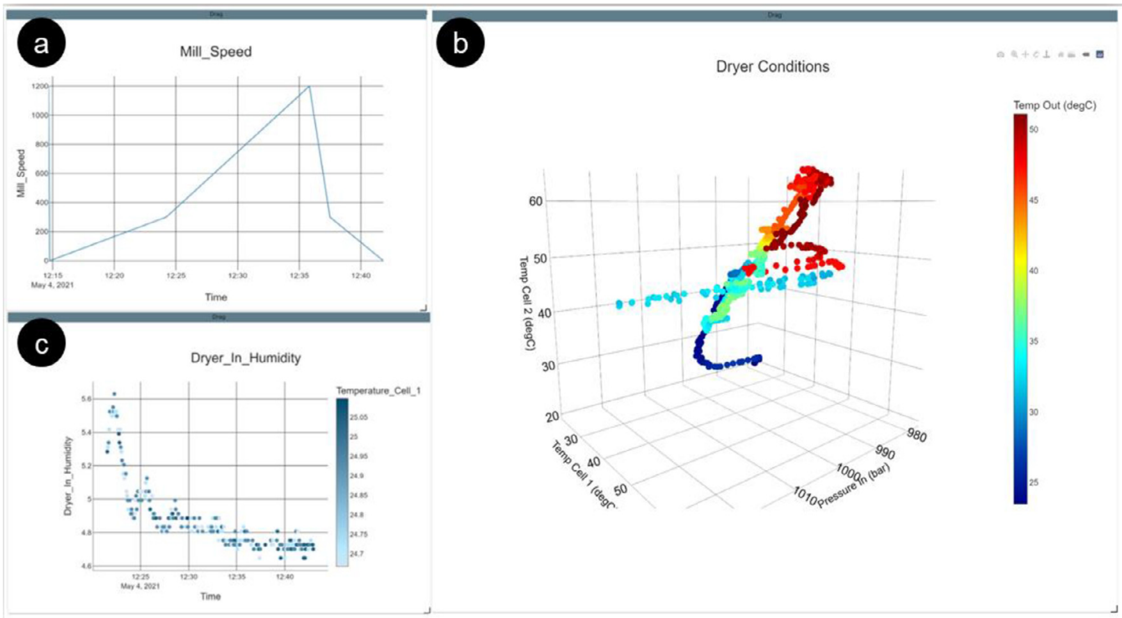

Figure 8. Wiz interactive dashboard in Siemens' MindSphere (a) Real-time mill speed time-series trends from DiPP (b) Real-time dryer humidity scatter data and (c) Four-dimensional visualisation of different temperatures vs pressure in the dryer unit.

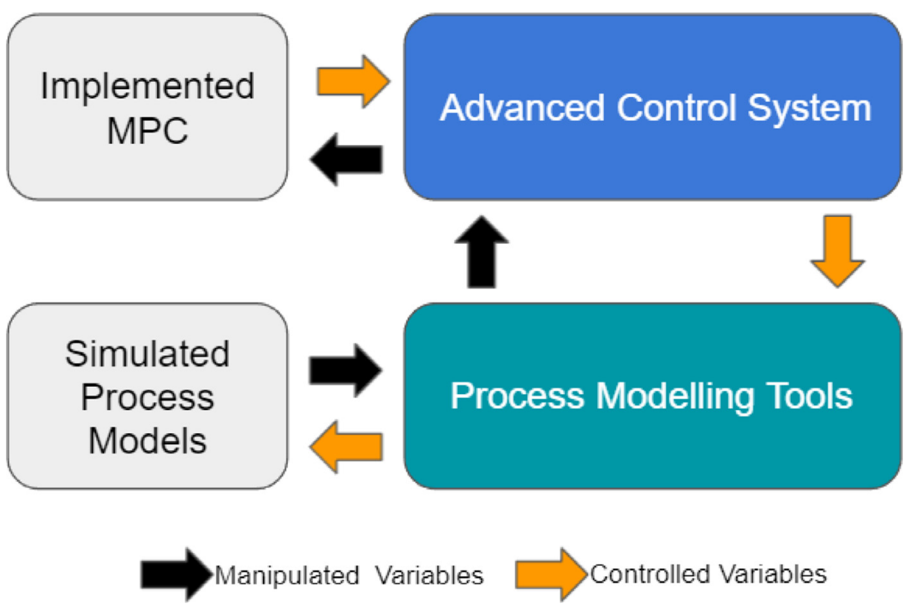

Figure 9. Integration of the flowsheet model and control platform. The synchronisation of the two platforms will allow data flow (manipulated and control variable data) between flowsheet model and control platform for digital model prediction control (MPC) and real time simulation.

point moisture control that can be activated by the operators using the interactive dashboards.

The adoption of Industry 4.0 has had an impact on how to approach pharmaceutical manufacturing at the DiPP. The benefit of the digital pharmaceutical manufacturing solution developed for the diamond pilot plant includes a digital control system that allows adopting a data-centric approach and automation. Data also from the DiPP is continuously collected and used to predict Critical Quality Attributes (CQAs) through data-driven models and Digital Twin forecasts. It allows for cost-effective testing with production-class operating equipment without the costly downtime and output reductions that would be required if done on actual production units. It enables access to and optimization of low-level control systems in a non-competitive context, as well as the establishment of a client-oriented business model. The digital architecture also allows an experience created by the engagement of in-use information within a DiPP's digital ecosystem through data visualisation and virtual reality. It is expected that the data-calibrated approach outlined in the future work section using process model will reduce experimental effort in developing control strategies, reduce waste of the API materials, minimizes interruptions in the process production time for step-testing and reduce process variability by accurately controlling CQA through APC. This hypothesis will be examined in future works.

The project team has successfully collaborated to upgrade the University of Sheffield's industrial continuous wet granulation and tableting with the latest Industry 4.0 and APC enabled automation technology. The upgrades provide a hands-on demonstrator for research and training. Data fusion and visualisation including multivariate trends, charts, and interactive dashboards, as well as automated execution of DoEs and process response testing reduces experimental workload and streamlines data generation for design space exploration and process modelling and simulation. The use of machine learning techniques such as online model adaption enables the evaluation and deployment of process condition monitoring, MPC optimization, and soft sensing approaches. The MindSphere platform allows process units to connect to the cloud to support research and development across all data science activities. DiPP's Industry 4.0 demonstrator will be utilised to explore and exhibit the full potential and benefits of digital technologies for the pharmaceutical industry.

Declaration of Competing Interest

None.

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