Enhancing the Capabilities of Fluid Bed Granulation through Process Automation and Digitalisation

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Figure 1: SmartX-equipped fluid bed system at the University of Limerick

Abstract

This paper describes a PAT-enabled, digitalised, and automated fluid bed granulation system. A multichannel Near-Infrared (NIR) spectrophotometer and a direct imaging particle size and shape analyser are in constant dialogue with the SmartX no-code/low-code platform, providing a ground-breaking process automation toolset now located at the Bernal Institute in the University of Limerick. Two sets of results are presented for this study, from two iterations of the Advance Dynamic Process Control (ADPC) controller application. The results demonstrate the direct measurement and control of the product's critical quality attributes through digitality enabled feedback control of processing setpoints and parameters. The platform controlled the particle size more tightly compared to non-automated control and a more accurate measurement-driven process endpoint for moisture content was achieved. Implementing a digitally enabled control approach can significantly reduce batch to batch variation and greatly improve process performance and product consistency.

Introduction

Globally, there is an unprecedented technological transformation taking place, propelled by the Fourth Industrial Revolution, and accelerated by the Covid-19 pandemic where rolling lockdowns have served as a catalyst in transforming the ways in which we work (World Economic Forum, 2020). Manufacturers are now implementing advanced technologies, automating and digitizing processes, as well as introducing advanced data analytics to streamline their operations (Dukart, et al., 2020).
With this increasing trend towards adoption of Industry 4.0 principals, with the internet of things being a key component, Regulators such as the FDA, are actively encouraging pharmaceutical companies to modernize their approaches to drug manufacturing, while also working to decrease regulatory uncertainty around adoption of new emerging technologies (Hahn & Rom, 2021), (Markarian, 2018). And now the new arrival of Industry 5.0, a concept which aims to compliment Industry 4.0 by using new emerging technologies to better serve in the green and digital transition to a more human-centric, sustainable, and resilient industrial future (European Commission , 2021).

The world's patient population continues to experience a rapidly increasing frequency of drug shortages whereby patients cannot get access to the medicines they critically need. According to the FDA, drug shortages are caused by many factors, including raw materials (27%), manufacturing problems (37%), Quality; delays/capacity (27%), as well as many other disturbances within the supply chain. The industry has issues with batches being rejected and in the worst case being recalled from the marketplace contributing to these drug shortages. The Covid-19 pandemic has also exacerbated the supply chain crisis, driving global demand for critical medicines to unprecedented levels. There has been a real recognition by countries of the need for a restructuring of supply chains and the onshoring of strategic manufacturing capabilities to prevent bottle necks in future 'unforeseen events' (Nathalie Moll, 2021). This supply chain 'sustainability' and 'resilience' are two of the three key pillars of Industry 5.0 born out of the EU policy paper, and are likely to be key areas of policy focus in the near future made possible by harnessing the productivity gains of Industry 4.0 and the digital transformation (European Commission , 2021).

Many of these issues described previously can be resolved by embracing advanced technologies and tools such as process analytical technology (PAT), advanced data analytics, manufacturing intelligence, in-process control and automation, digitalization as well as cloud architecture into everyday pharmaceutical product development, right throughout the manufacturing lifecycle. Adoption of these technologies would also dramatically improve productivity while maintaining competitive advantage and reducing costs for the manufacturer (Dedeurwaerder, et al., 2018), (Gaertner, 2016).

Better process understanding, drug product development and manufacturing throughout the commercial lifecycle of drug products will lead to faster to market products and a more reliable, predictable supply chain (Kiernan, 2019)

One major roadblock faced by manufacturers with regard to introduction of these automation and data driven technologies, is the lack of specific skill sets needed for their implementation e.g. Developers, Data Scientists and Data Engineers (Dukart, et al., 2020). Drug manufacturing processes are complex, requiring extensive process / product knowledge by the process experts, however they typically do not possess the expert programming skills required to implement automation solutions. Low code / no code development technologies are now helping to address this skills gap.

Innopharma Technology Ltd. have developed SmartX - a powerful process automation and digitalization platform which enables implementation of flexible process automation through a low code / no code interface, removing the need for programming skills by the end-user, thereby placing control back in the hands of the process expert.

This paper presents an example of an advanced controller-based approach to a Fluid Bed Granulation Process, incorporating Industry 4.0 principals. The controller development and process execution outlined here was facilitated by SmartX, onsite at Innopharma Technology's Process Development Laboratory in Sandyford, Dublin. Developed as a process agnostic platform SmartX has so far been deployed on Fluid Bed Coating and Granulation, Twinscrew Extrusion and Crystallization processes. A recent installation of SmartX on a GLATT Multilab System at the Bernal Institute in the University of Limerick represents a significant opportunity for industrial and academic collaboration on advanced fluid bed process control techniques, and research into modernisation of manufacturing for legacy or problematic products.

Incorporating real-time data from Process Analytical Technology (PAT), the controller uses particle size and moisture content data as well as Fluid Bed system data to make real-time process control decisions. Particle size is measured in real time by the Eyecon$_2$™ particle analyser, while real-time moisture content is measured by the Multieye$_2$ NIR Spectrophotometer. An extensive powder characterisation suite is available at the Bernal Institute in the University of Limerick to support the development of process control solutions.

This automated approach results in greater in-process control and repeatability as well as less batch to batch variation. The controller design presented here is intended as a novel example to highlight the flexibility and potential when developing such an automated control driven approach and to highlight the usability of the SmartX Platform for such process automation tasks.

The Granulation Process

Many oral solid dose formulations require a wet granulation step to ensure more suitable powder properties such as better flowability and compactability. Wet granulation involves agglomerating a mix of dry primary powder particles (Active Pharmaceutical Ingredients or APIs and excipients) by the addition of a granulating solution in a Fluid Bed Granulator (Parikh, 2005). After the addition of a predefined quantity of granulation solution, the granules are dried to the desired moisture level.

The drying phase is critical, as over-drying the granules can lead to increased attrition and fracture of the product while insufficient drying can result in bed stalling, poor flow and product stability issues (Mattes, et al., 2005). The relationship between particle size variation and product performance is also significant, greatly impacting flow and compaction properties which can lead to issues with content uniformity, dissolution and absorptions rates.

As a result, the critical or key quality attributes of a Fluid Bed Granulation process which are further identified throughout this paper as CQAs, are moisture content and particle size. Critical process parameters (CPP's) include inlet air flow, inlet air temperature, spray rate and atomising pressure. Careful monitoring and control of the CQAs and CPPs within predefined optimum limits is essential to ensure consistent process performance and product quality.

The traditional control approach is typically recipe driven and largely operator dependent where the operator must constantly monitor process and material performance making the necessary manual adjustments to process parameters during the manufacturing process. At-line analysis of samples taken throughout the process are required for process insight, but this delay results in a time lag between results and current process conditions. This recipe driven approach does not account for variabilities such as raw material variations or seasonal changes in inlet air humidity levels which are known to effect drying capacity, leading to variations in final granule properties (Lipsanen et al., 2008).

Incorporating Industry 4.0 principles enabled by the development of an automated smart controller approach can reduce risks associated with traditional approaches, ensuring greater process stability and reproducibility.

Materials and Equipment

Formulation

A placebo formulation was used for all batches. This consisted of a mixture of Pharmatose 200M Lactose (1 kg) and Microcrystalline cellulose PH-101 (0.5 kg). The liquid binder was an aqueous solution of Polyvinylpyrrolidone (PVP) K90 (1 L, 5.8% w/v). Materials were supplied by IMCD Ireland.

Process Equipment

Fluid Bed Granulation was carried out in a Glatt GPCG2 Fluid Bed System. The product bowl used allows for the attachment of PAT technologies such as the Mulieye$_2$ and Eyecon$_2$™ to existing process windows.

Figure 2: The PAT product bowl with integrated PAT & wiper

Process Analytical Technology – Multieye$_2$

The Multieye$_2$ is a multichannel Near-Infrared (NIR) spectrophotometer designed for rapid real-time in-line monitoring of CQAs and CPPs making it an ideal tool for use in Advanced Manufacturing. For this study, a single NIR probe was externally mounted to a process window located within the down bed (see Figure 2) and moisture content was measured using an LOD-based predictive model.

Process Analytical Technology – Eyecon₂™

The Eyecon$_2$™ , a non-product contact direct imaging particle size and shape analyser, was used for in-line particle size measurements. The Eyecon$_2$™ was positioned on the outside of a process window, located within the down bed in order to capture representative data (see Figure 2). To mitigate window fouling, a mechanical wiper/scraper prototype was installed and configured to periodically clear the inside of the window.

SmartX Platform

SmartX is a flexible process digitalisation and automation platform which can be deployed to control a range of complex pharmaceutical processing operations such as crystallisation, extrusion, or in this case fluid bed granulation. It enables rapid data-driven process development, with integral gold-standard quality by design, as well as a ground-breaking process automation toolset detailed below. The platform is comprised of a modular technology suite made up of the processing hardware, PAT analysers; Myltieye$_2$ and Eyecon$_2$™ , data analytics tools, cloud-storage and manufacturing intelligence (see Figure 3). The flexible, and fully in-house developed data integration engine module enables simultaneous communication between the various modular components.

During processing, the cloud platform provides continuous collection of real-time data from PAT analysers and the fluid bed system or other processing platforms, as well as any other sensors, connected via a wide range of supported protocols. This data may be reviewed after processing, analysed against previous batches for trend detection, and exported if required for further analysis. The SmartX cloud also supports advanced live analytics such as real-time validation of CPPs and CQAs against a process model to determine adherence within specified limits.

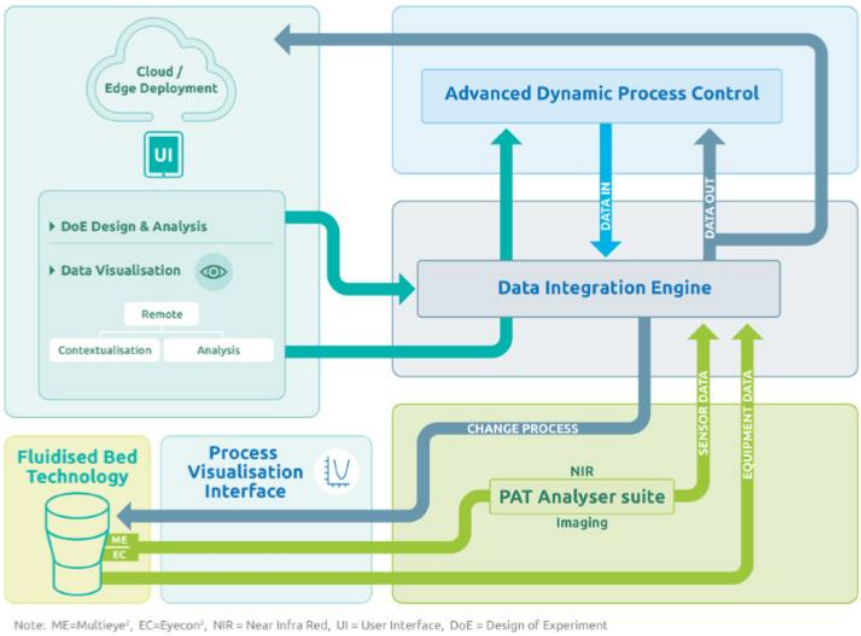

Figure 3: SmartX for fluid bed system structure

A customisable Human Machine Interface (HMI) provides a single point of interaction for the process operator. At an advanced user level multiple dashboards can be configured to ensure that the data of greatest importance to the current process is always on display, supporting greater real-time process insights. Dashboards are configured via a simple graphical user flow supporting use by those with the relevant process expertise, without the need for additional specialised skillsets.

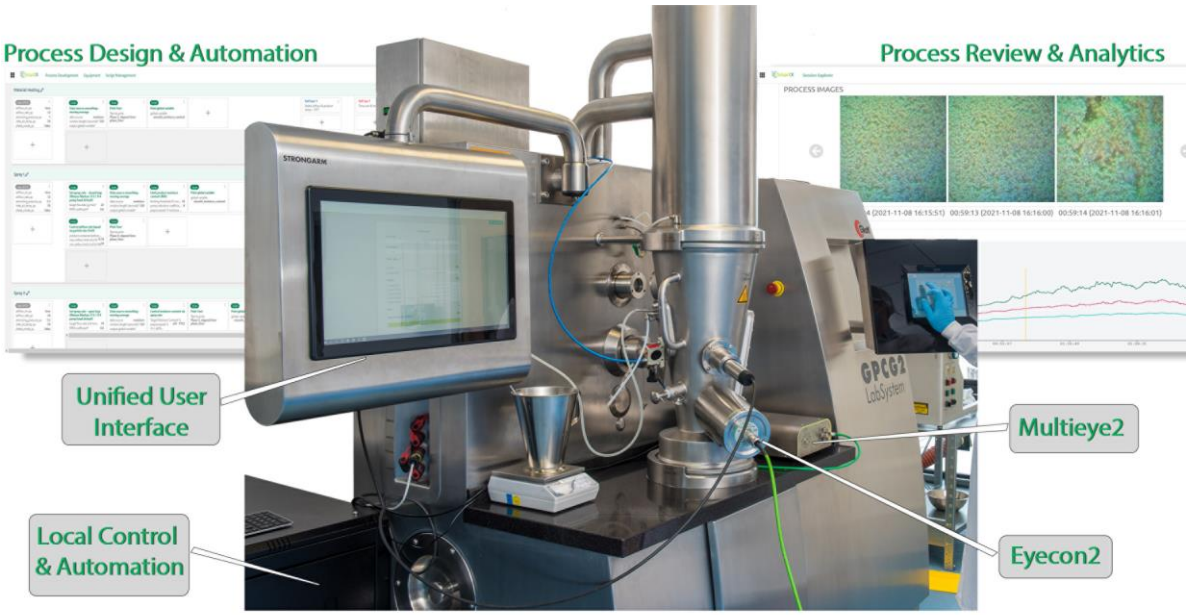

Figure 4: Overview of SmartX

Accessible Process Automation to Bridge the Skills Gap

Powerful process automation is delivered by means of the Advanced Dynamic Process Control (ADPC) module. ADPC delivers uniquely user-friendly and accessible process automation through a low-code/no-code interface embedded in the SmartX cloud. This provides a toolset with minimal learning curve which requires no programming / coding skills, bridging the gap between those with process expertise, and existing automation-expert-orientated software tools, generally requiring significant projects and cross-functional teams to implement effectively. SmartX's ADPC system takes a truly user-centric approach, enabling those with the essential process expertise to implement extensive automated control of their processes, without the need for additional skillset support.

This accessible automation is achieved through a fully graphical, browser-based process configuration interface in which the process expert can create phases to govern each step of the process requiring different control logic. Separate sections within each phase then offer context-specific control elements to manage aspects like initialisation, recursive control, and phase endpoint definition. All changes naturally require user authentication and generate audit trail entries per 21 CFR part 11 requirements. See Figure 5 below.

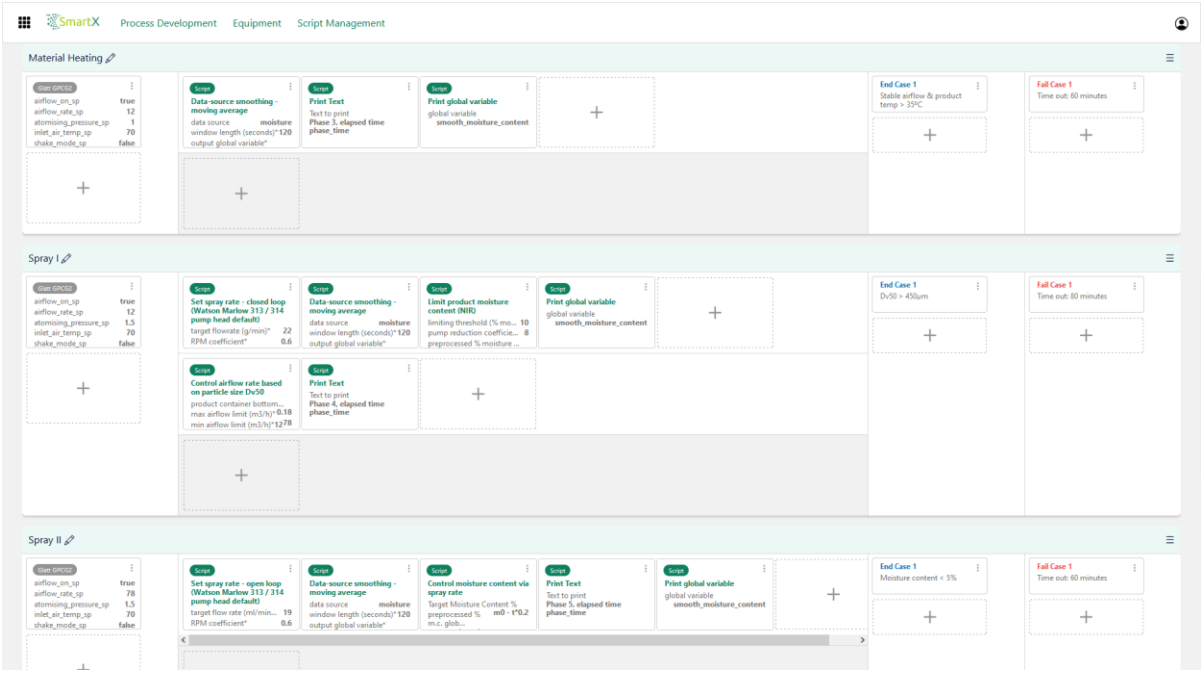

Figure 5: SmartX low-code/no-code process automation interface

The control elements provided in this process configuration interface can be chosen from the SmartX system's extensive library of process-type-specific functions. These functions may be mixed and

matched, running either in parallel or sequentially during phases, to deliver advanced combination control logic as required. In the event that a complex or application-specific piece of logic is required which cannot be achieved by means of the functions in the library, additional functions can be created through a low-code Python scripting interface, where all complex timing and device-level communications are managed by SmartX. These scripts may be written either by an in-house individual with the appropriate skillset and user permissions, or as a service offered by Innopharma Technology. This interface again provides full 21 CFR part 11 compliance with version control, audit trail and user access controls. Figure 6 below.

The ADPC controlled processes presented in this article were executed using the SmartX system located in Innopharma Technology's Process Development Laboratory.

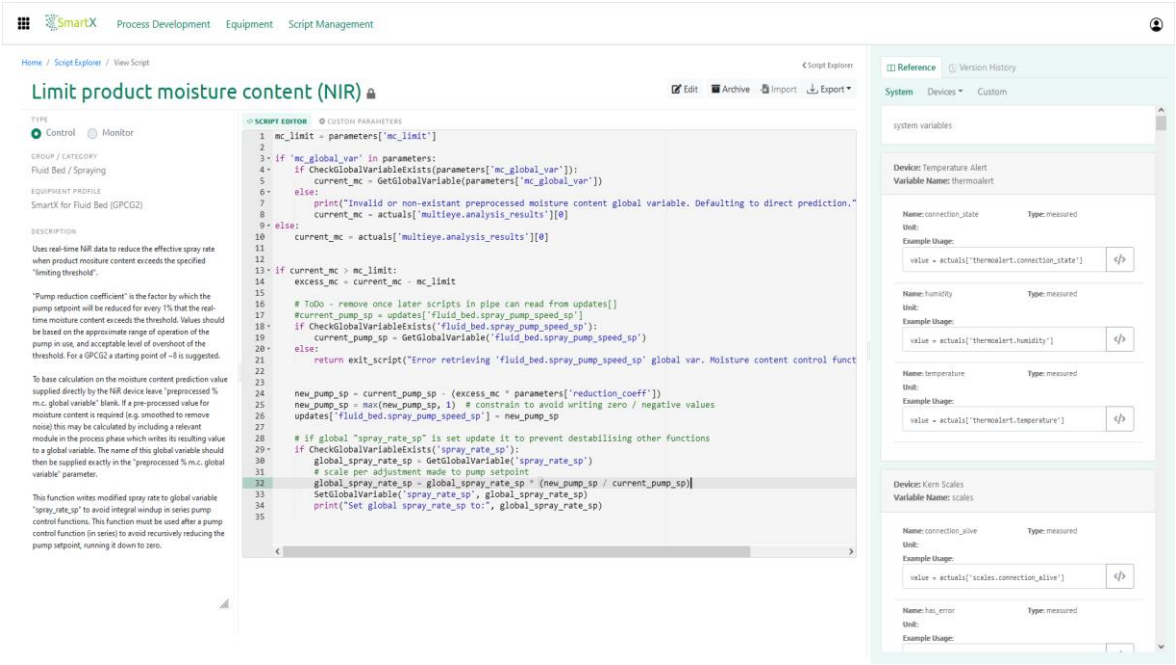

Figure 6: SmartX custom functionality Python scripting interface for advanced users

Advanced Dynamic Process Controller Development

Controller development is complex and requires a thorough understanding of the process, including CPPs, CQAs and the quality target product profile (QTPP). In this case, the knowledge was acquired through detailed experimentation and retrospective studies involving the manufacturing of numerous Fluid Bed Granulation batches. Historical data generated through earlier manual and automated process runs was used to inform elements of the controller development for this particular process.

The first step is to clearly define the control logic for each process phase. This includes identification of key dynamic control relationships, establishing fixed setpoints as well as phase and process endpoint criteria. Once these requirements were defined, they could be easily configured through the SmartX cloud process configuration interface.

For the advanced controller example presented in this paper, five process phases were defined: Empty Heating, Material Heating, Spraying I, Spraying II and Final Drying. The key control parameters and criteria for these phases are outlined in Figure 7 below.

Spraying is divided into two phases to demonstrate how various PAT measurements may be implemented to achieve in-process control. Additionally, the two phases are designed with the intention to help mitigate against product attrition as typically observed during final drying, thus delivering more consistent endpoint particle size with less variation. Spraying I is defined by rapid wetting and maximum growth, while Spraying II is defined by further hardening of the granules through reduced binder addition rate and increased moisture removal to mitigate against product fracture during the drying phase.

Maintaining a specific moisture content reduction rate was empirically determined to result in a quasi-stable D_v50 particle size while allowing for faster control reaction and therefor minimised process deviations as compared to controlling directly based on particle size.

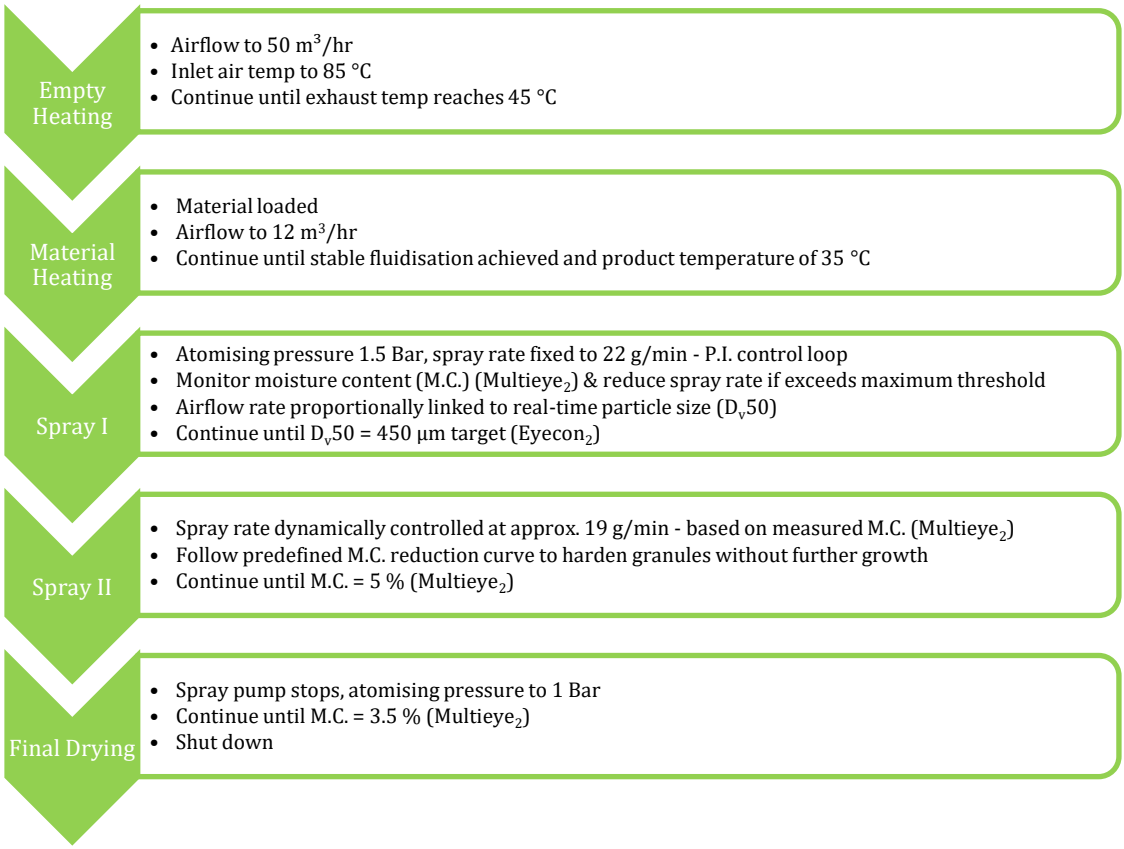

Figure 7: Flow diagram demonstrating key set points and endpoint criteria for each of the phases within the controller

Results & Discussion

Process Stability

Two sets of results are presented for this study, from two iterations of the ADPC controller referred to as ADPC controller i and ADPC controller ii

ADPC Controller i

Figure 8 presents a time-aligned series of CQA and CPP profiles representing the evolution of a Fluid Bed Granulation process using an earlier iteration of the ADPC controller i.e. ADPC controller i, and give an example of more dramatic process deviations and subsequent control responses. This earlier controller exhibits less stability with regards to feedback control elements, when compared to the final controller iteration described later. This earlier iteration also uses a moisture-based airflow rate control approach during Spray I, rather than the later particle-size-based approach.

Controller phases are indicated as follows; EH / Empty Heating, MH / Material Heating, Spray I, Spray II and FD / Final Drying. The key dynamic control relationships are examined in closer detail in subsequent sections (see Figure 9 to Figure 11).

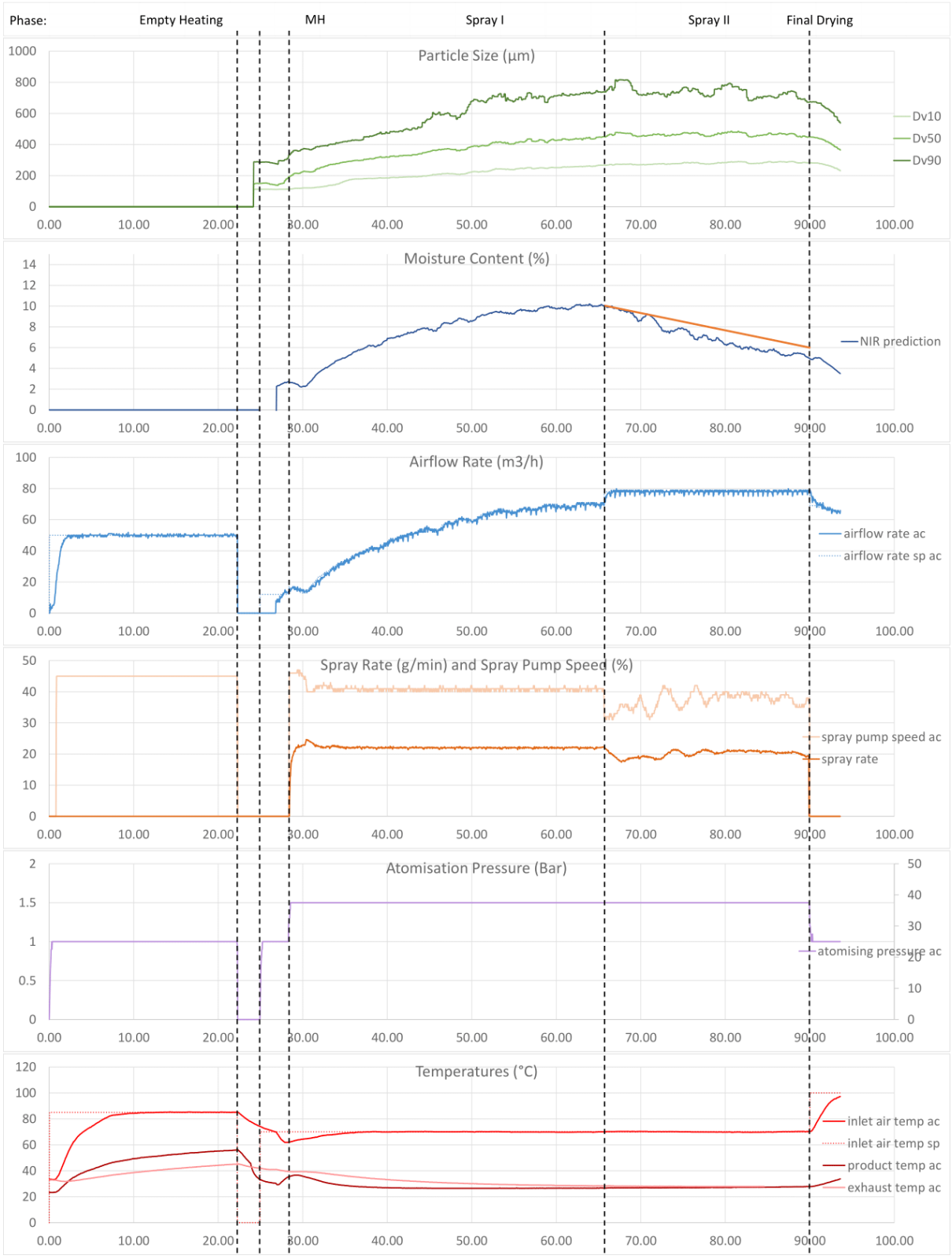

Figure 8: Key process parameters & quality attributes; ADPC Controller i

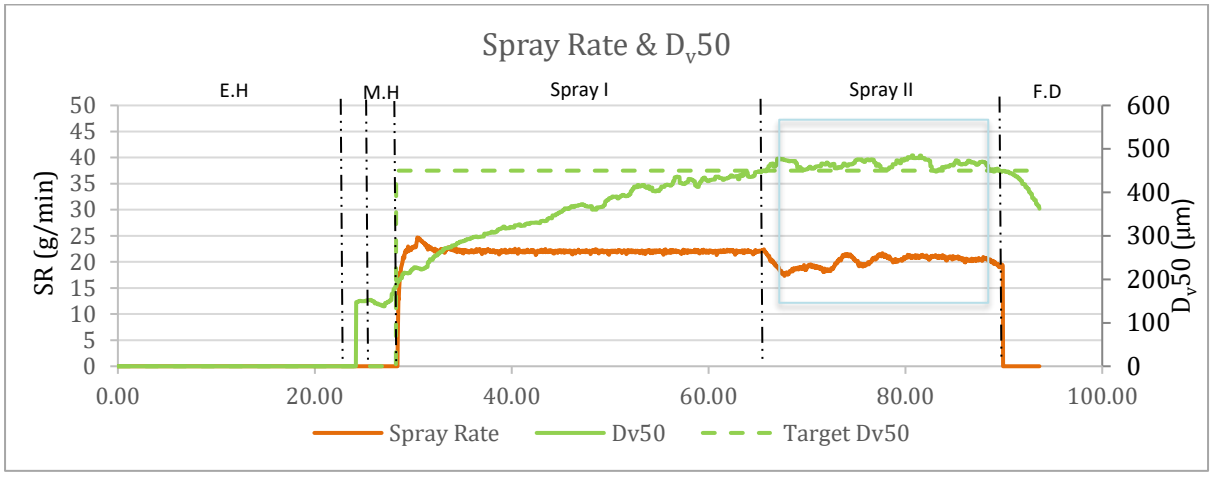

Figure 9: Relationship bewteen spray rate and D_v50 particle size; ADPC Controller i

Figure 9 illustrates the key relationship between spray rate and target D_v50 particle growth. The controller sets the D_v50 particle size target of 450 µm for the duration of spraying and uses real-time particle size data, as measured by the Eyecon$_2$™ , to monitor the growth profile. During Spray I, a fixed spray rate is maintained for rapid moisture addition and growth until the target particle size is reached. On entering Spray II, the target particle size is maintained by following a target moisture content reduction profile as demonstrated below.

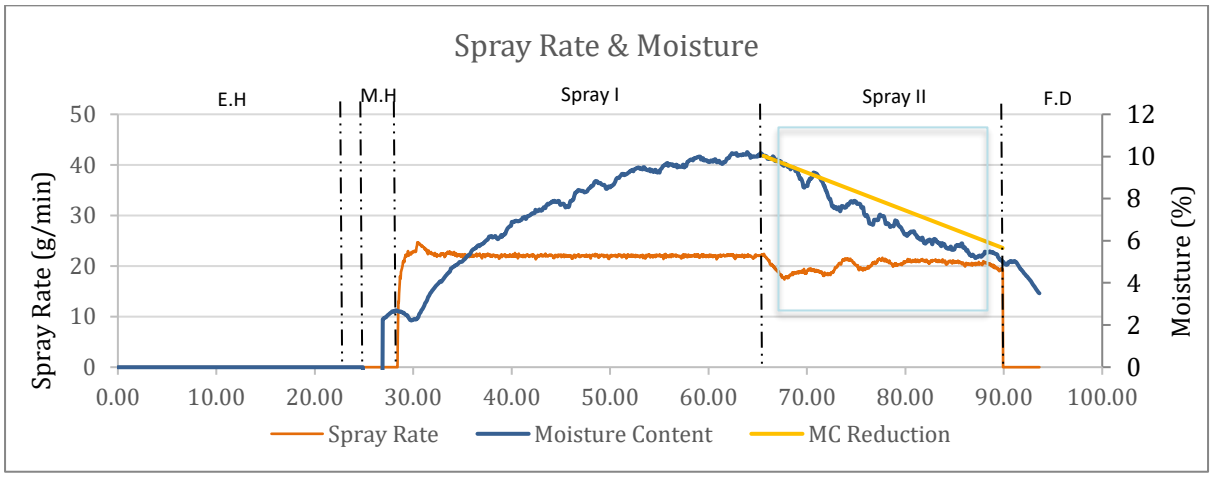

Figure 10: Relationship between spray rate and moisture content; ADPC Controller i

Figure 10 illustrates the key relationship between spray rate and moisture content. Moisture content rapidly increases during Spray I, as the binder solution is added at the fixed spray rate. In Spray II the controller continually adjusts spray rate to maintain moisture content within the target moisture content reduction profile indicated in Figure 10, where the granulate is slowly dried to 5% moisture content. In this example, as the spray rate is lowered to approximately 19 g/min, the moisture content begins to fall too rapidly and overshoots the target profile. The controller begins to respond

immediately by increasing the spray rate proportionately to restore the moisture content to the target. In this instance while the controller continually adjusts spray rate, it never quite succeeds in returning to the target profile before hitting the 5% moisture content endpoint target. Later changes to the controller resulted in an optimised relationship between spray rate and the moisture control as shown in Figure 13.

Figure 11 depicts the dynamic relationship between airflow increase rate and real-time moisture content of the product bed during Spray I and represents another novel aspect of this controller design. Maintaining sufficient fluidisation throughout rapid moisture addition is critical to prevent bed stalling as the bed becomes heavier and more cohesive due to increased liquid addition. By linking airflow increase rate directly to bed moisture content the controller can counteract changes in the product bed. While reasonably effective, this approach was altered in the later version of this controller, to a particle-size based airflow rate control approach which was determined to be less formulation-dependant. (Godek, 2013).

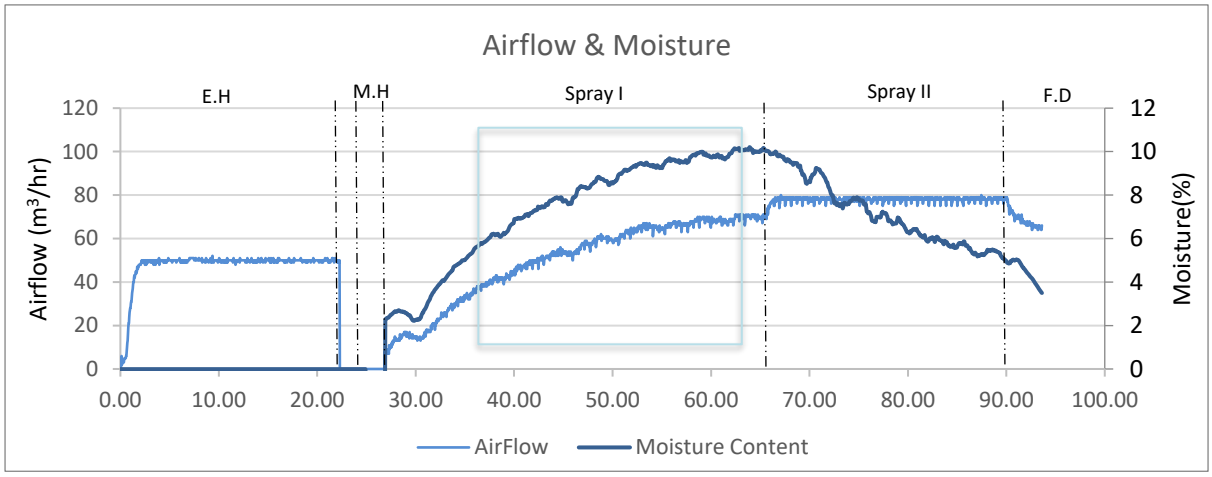

Figure 11: Dynamic relationship between airflow rate and moisture content; ADPC Controller i.

ADPC Controller ii

The next series of CQA and process parameter profiles presented in Figure 12 represent a Fluid Bed Granulation process carried out using the final iteration of the controller which had undergone further fine tuning and demonstrates its capabilities in maintaining good process stability, at all times.

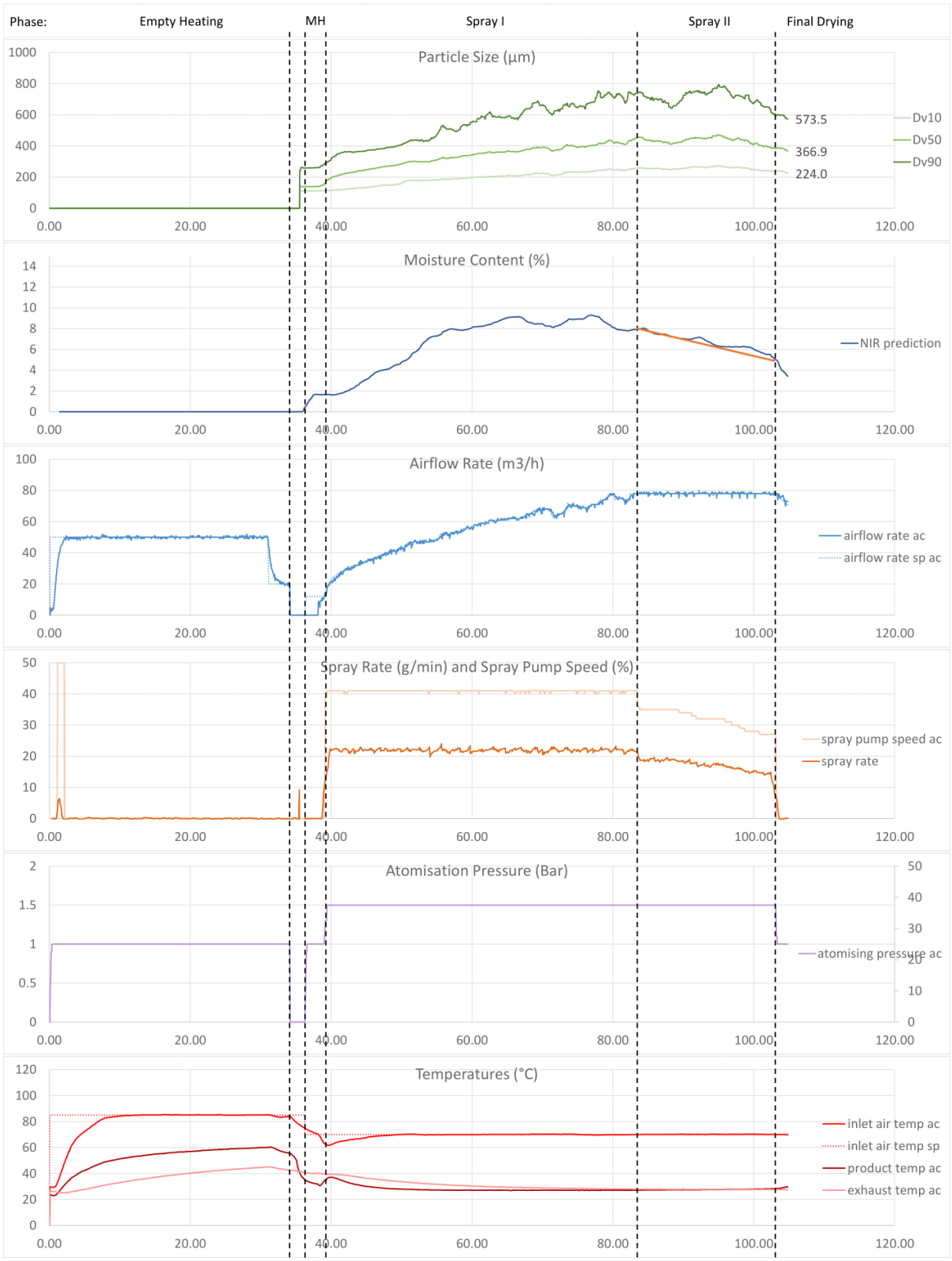

Figure 12: Key process parameters & quality attributes; ADPC Controller ii

Figure 13 illustrates the dynamic relationship between spray rate and moisture content and demonstrates the precision of the controller, post-optimisation. Improvements to the long-term error correction component of the Spray II moisture content control relationship within the controller prevents the spray rate oscillating too far beyond the ideal moisture reduction curve. It is clear the true moisture content tracks the target moisture content reduction profile very well when compared to the earlier controller.

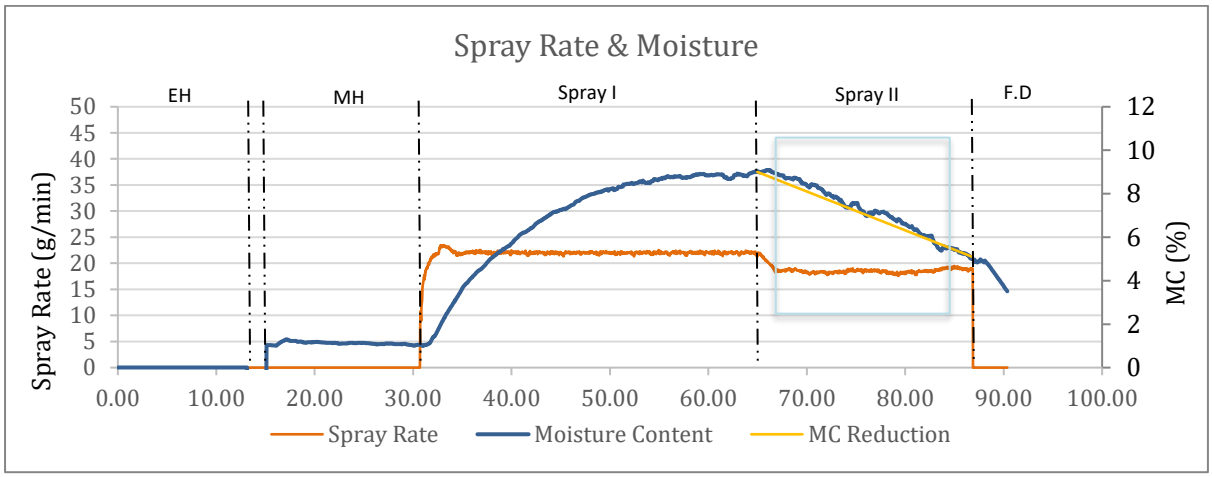

Figure 13: Dynamic relationship between spray rate & moisture content; ADPC Controller ii.

End Product Quality

To assess end product quality, endpoint D_v50 particle size values from a number of granulation batches manufactured with the ADPC controller were compared to endpoint D_v50 particle size values from a number of previous batches manufactured using a more traditional recipe driven approach (referred to as non-ADPC batches), produced prior to the development of the ADPC controller, . Although the two process methodologies varied with regards to some parameter settings, a significant difference in endpoint product consistency is apparent between the two approaches.

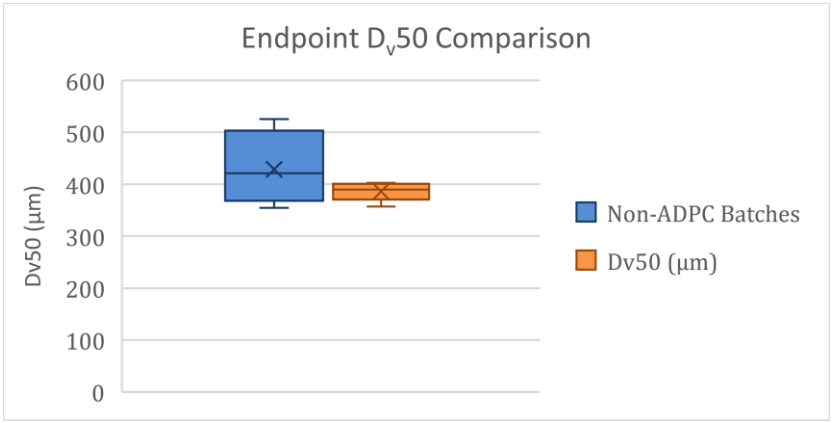

Figure 14: Endpoint D_v50 particle size values from non-ADPC controlled and ADPC controlled batches

Figure 14 illustrates a significantly wider distribution of endpoint D_v50 particle sizes for previous batches manufactured via the more traditional recipe driven, non-ADPC controlled approach with a variation of 171 µm from the smallest to largest D_v50 value. Compared to batches manufactured with the ADPC controller, a tighter distribution in endpoint D_v50 particle size values is evident, with variation of only 46 µm reported from smallest to largest D_v50 value. These results demonstrate the consistency in batch to batch particle size which can be achieved by implementing such a control approach within a Fluid Bed Granulation process. The ability to achieve greater particle size control via the ADPC controller approach leads to more consistent endpoint particle size and less variation between batches, therefor less out of spec batches ensuring patients get access to the medicines they critically need.

In addition, endpoint moisture content values analysed using the at-line Loss on Drying (LOD) methodology were compared for both manufacturing approaches. There is a significant difference in the endpoint LOD values for both of these control methods, primarily due to the more traditional recipe driven, non-ADPC controlled approaches using product temperature as an indication of endpoint rather than in-line moisture measurement as was the case in the more traditional batches.

Figure 15 clearly demonstrates this variation with a much wider distribution of final LOD values evident for the earlier recipe driven, non-ADPC controlled manufactured batches. The total spread of moisture content values is 0.48% for these batches, compared to only 0.16% for the ADPC controlled batches.

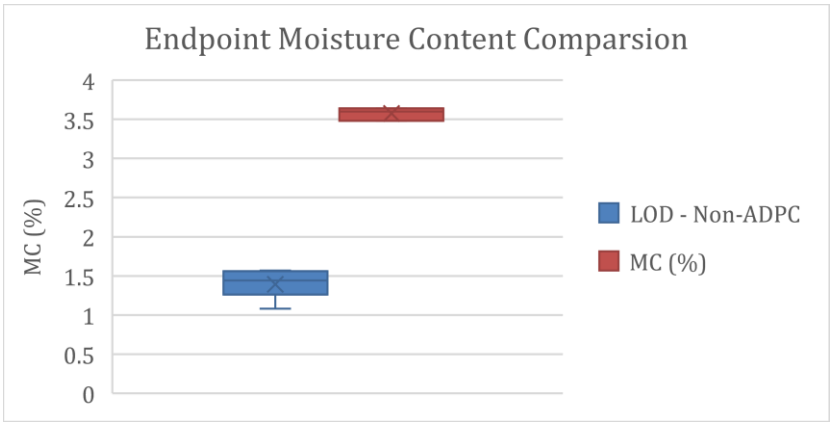

Figure 15: Endpoint moisture content values for non-ADPC controlled and ADPC controlled batches

Endpoint moisture content of the Fluid Bed Granulation process is critical for downstream processing steps such as tablet compression, as well as the stability of the final drug product (Lipsanen et al., 2008). As a result endpoint moisture content must be tightly controlled to mitigate these issues.

Implementing such a control approach can significantly reduce batch to batch variation and greatly improve batch repeatability.

Conclusions

- SmartX – Innopharma Technology's flexible automation and digitalization platform was used to implement advanced dynamic process control of a Fluid Bed Granulation process, using default library functions in the low code / no code interface.
- SmartX can play a pivotal role in addressing the current skills gap, by enabling process experts to implement flexible automation and control solutions through the low code / no code interface, removing the need for extensive coding expertise. This interface also enables the user to custom-configure their HMI and data dashboard for a given process.
- SmartX supports dynamic 'on the fly' process development, allowing the process expert to manually adjust process variables during an automated process for rapid optimisation during development. SmartX enables real-time dynamic process model validation, where a process can be driven or tracked against a model facilitating cross verification in real time.
- The ADPC controlled Fluid Bed Granulation process examples presented here were shown to produce significantly more consistently sized granules, with less batch to batch variation when compared to granules produced from the more traditional recipe driven non-ADPC controlled processes.
- Endpoint LOD analysis for the ADPC controlled approach to Fluid Bed Granulation showed significantly less variation and greater batch to batch consistency, compared to endpoint LOD analysis for the recipe driven non-ADPC controlled approach.
- Real-time moisture content data enabled the controller to dynamically manage spray rate ensuring a pre-determined moisture content profile was followed, as well as accurately determining phase and process end points
- Real-time particle size data provided by the Eyecon$_2$™ allowed the ADPC controller to effectively determine phase-end criteria. In addition, real-time particle size data was used for dynamic control of the fluidising airflow rate during the spraying phase.
- The need for at-line sampling associated with more traditional granulation approaches is greatly reduced as well as the risks associated with operator dependent processes.
- Finally, the SmartX automation and digitalisation platform enabled the rapid development of a robust and reproducible process with a low code / no code automation strategy, that could respond in real-time to material and process variabilities, delivering a final product consistently within specification.

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