Self-Guided Control of a Fluid Bed Granulation Process

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Figure 1: SmartX System

Introduction

Globally there is an increasing trend towards the use of Industry 4.0 principles and with the Industrial Internet of Things (IIoT) being a key component, regulators are actively encouraging pharmaceutical companies to modernise their approaches to drug manufacturing. The world's patient population is experiencing 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. 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).

Many of these issues can be resolved by embracing the Industrial 4.0 revolution and incorporating technologies and tools such as process analytical technology (PAT), big data analytics, manufacturing intelligence, in-process control and cloud architecture into everyday pharmaceutical product development and commercial manufacturing. 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).

This paper presents an example of an advanced, controller-based, approach to Fluid Bed Granulation, incorporating Industry 4.0 principals. The controller development and process execution outlined here was facilitated by SmartX, an Advanced Manufacturing Platform developed by Innopharma Technology Ltd. Incorporating Process Analytical Technology (PAT), the controller uses real-time particle size and moisture content data as well as Fluid Bed Granulation process data to make real-time process control decisions. Particle size was measured in real time by the Eyecon$_2$ particle analyser, while real-time moisture content was measured by the Multieye$_2$ NIR Spectrophotometer. This automated approach resulted 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.

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 through 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 Avicel microcrystalline cellulose (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 – Eyecon$_2$

The Eyecon$_2$, a non-product contact direct imaging particle size 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 vertically integrated, advanced development and manufacturing platform for Fluid Bed Systems to enable rapid process development and a more robust approach to process automation and control. The platform is comprised of a modular technology suite made up of the Fluid Bed System, PAT analysers; Myltieye$_2$ and Eyecon$_2$, data analytics tools, cloud-storage and manufacturing intelligence (see Figure 3).

Process automation is facilitated through an Advanced Dynamic Process Control (ADPC) module while a data integration engine enables simultaneous communication between the various modular components.

Throughout the process, the cloud platform enables continuous collection of real-time data from PAT analysers and process sensors within the Fluid Bed System. The data generated is processed by a suite of advanced data analytics enabling Manufacturing Intelligence through the real-time interpretation of CQAs & CPPs. This Manufacturing Intelligence is a key component of the Industry 4.0 concept. The system has the ability to use this information to self-adjust critical process parameters in response to deviations in process performance, resulting in a more stable and reproducible process.

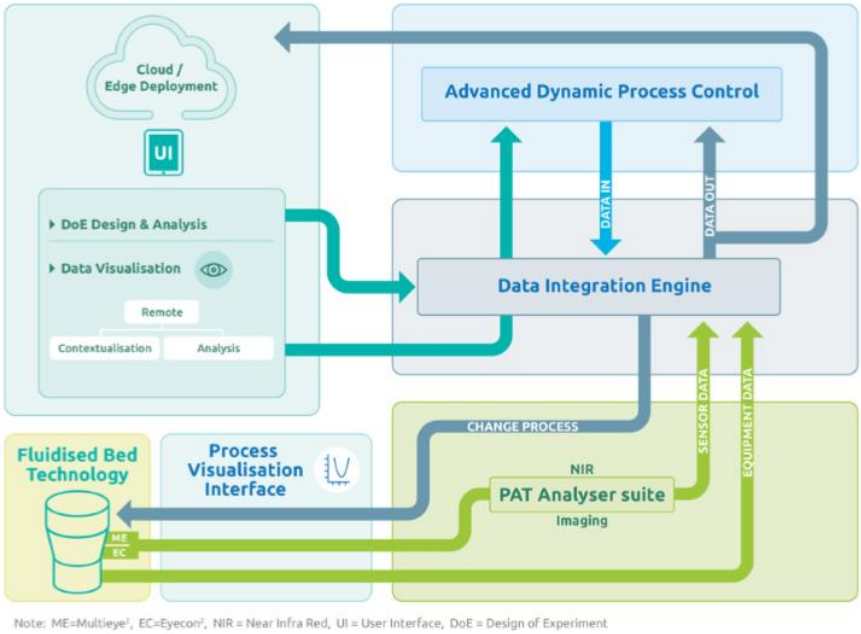

Figure 3: SmartX System Structure

A customisable Process Visualiser (see Figure 4) provides a single point of interaction with the system and displays CQA, CPP and Fluid Bed System data which allows for greater process insight and real-time monitoring. Aggregated and time aligned data can be viewed from any time point in the process via a secure online dashboard. The ADPC controlled processes presented here were executed using the SmartX system located in Innopharma Technology's Process Development Laboratory.

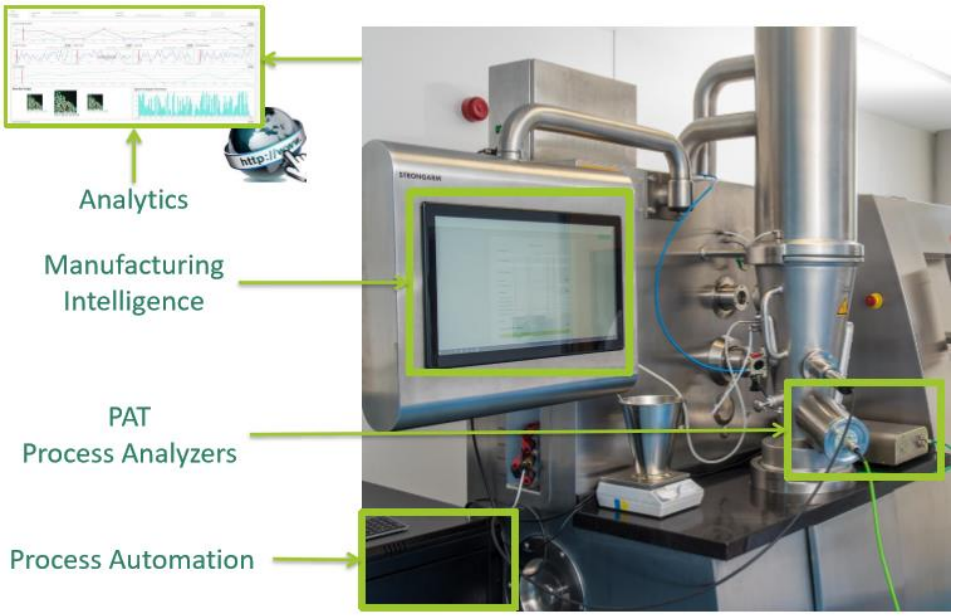

Figure 4: Overview of SmartX

Advanced Dynamic Process Control and 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 manufacturing of numerous Fluid Bed Granulation batches.

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 configured, this flexible control logic is then implemented and executed via a process centric scripting environment within SmartX's integrated Advanced Dynamic Process Control (ADPC) module.

Throughout the process, real-time PAT data and process sensor data from the Fluid Bed System provide a continual input feed to the controller. The controller uses this information to make scenario-based decisions on how to respond to process deviations as well as required process changes including phase changes and endpoint detection.

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.

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.

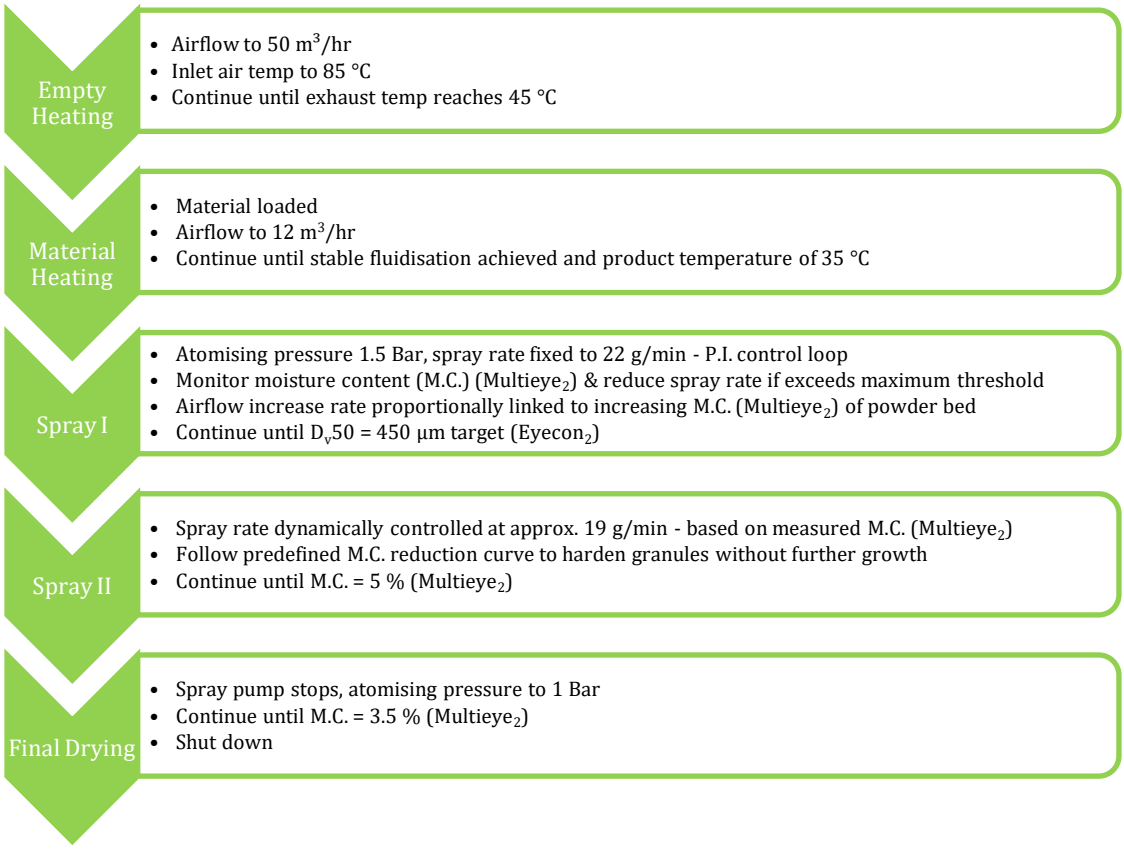

Figure 5: Flow diagram demonstrating key set points and endpoint criteria for each of the phases within the controller.

Results & Discussion

Process Stability

Two sets of results are presented for this study, from two iterations of the ADPC controller.

ADPC Controller i

The following series of CQA and CPP profiles represent the evolution of a Fluid Bed Granulation process using an earlier iteration of the ADPC controller, 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. Controller phases are indicated as follows; EH – Empty Heating, MH – Material Heating, Spray I, Spray II and FD – Final Drying (see Figure 6 to Figure 10). The key dynamic control relationships are examined in closer detail in subsequent sections.

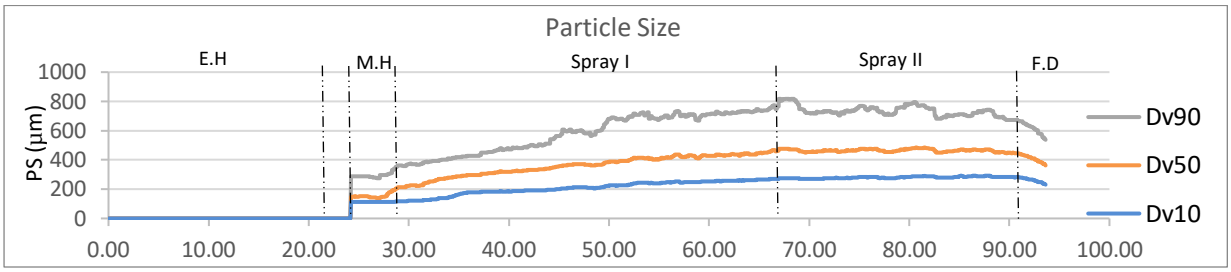

Figure 6: D_v10, D_v50, D_v90 values as measured by the Eyecon$_2$; ADPC Controller i.

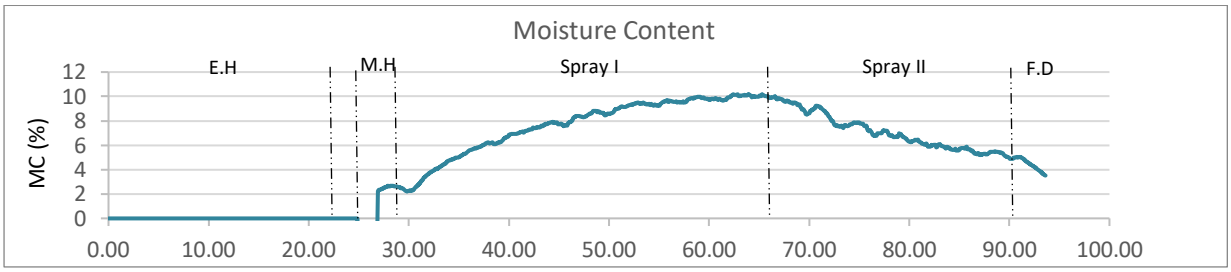

Figure 7: Moisture Content profile as measured by the Multieye$_2$; ADPC Controller i.

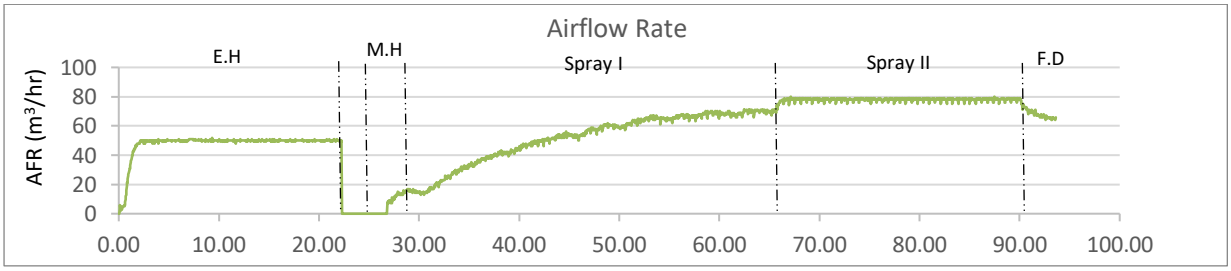

Figure 8: Airflow Rate Profile; ADPC Controller i.

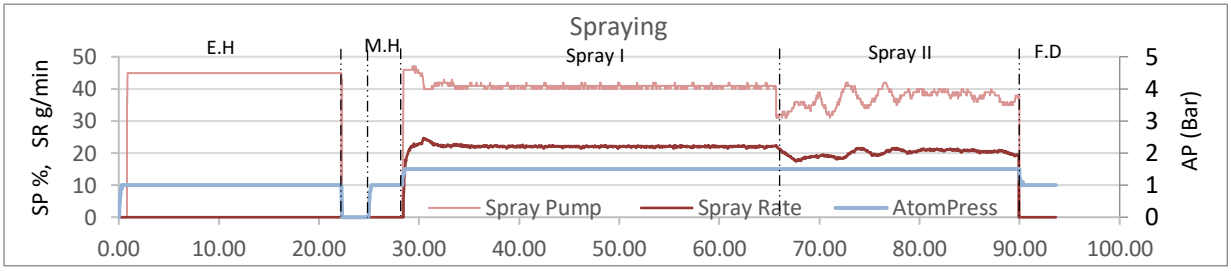

Figure 9: Spray Pump, Spray Rate, Atomising Pressure; ADPC Controller i.

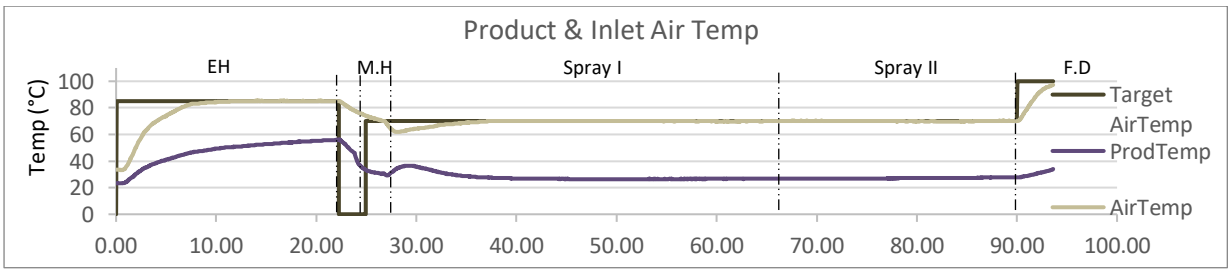

Figure 10: Product Temperature, Inlet Air and Target Inlet Air Temperature profile; ADPC Controller i.

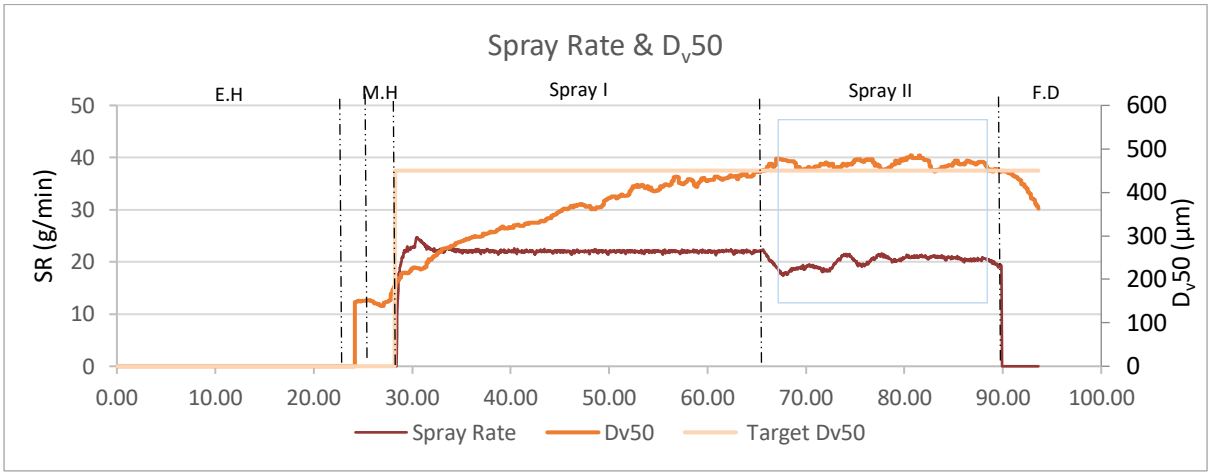

Figure 11: Relationship bewteen Spray Rate and D_v50 partilel size; ADPC Controller i.

Figure 11 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.

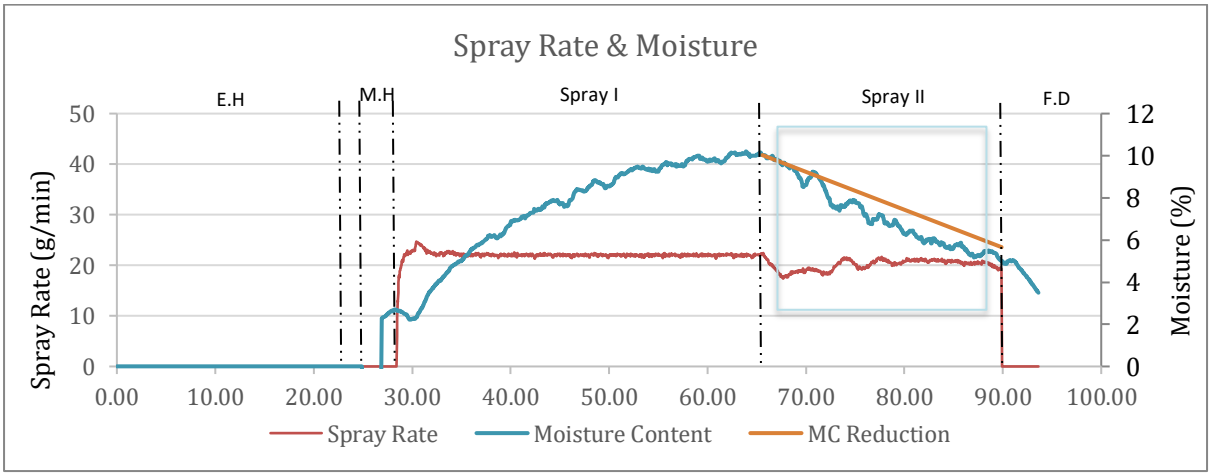

Figure 12: Relationship between Spray Rate and Moisture Content; ADPC Controller i.

Figure 12 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 12, 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 19.

Figure 13 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.

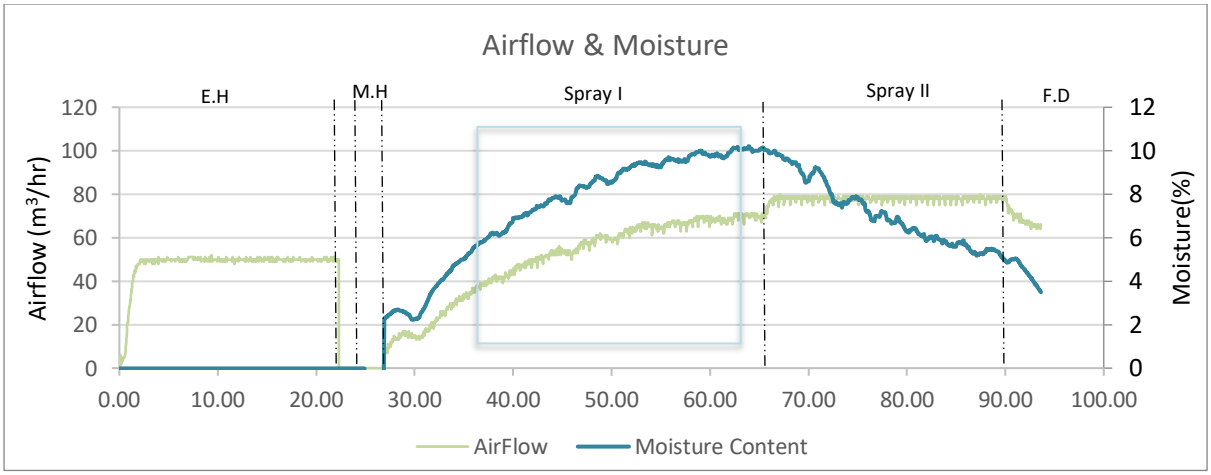

Figure 13: Dynamic relationship between Airflow rate and Moisture Content; ADPC Controller i.

ADPC Controller ii

The next series of CQA and process parameter profiles 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.

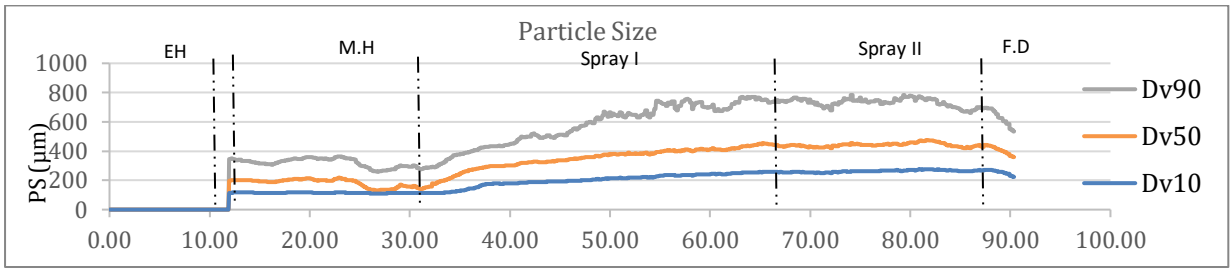

Figure 14: D_v10, D_v50 D_v90 values as measured by the Eyecon$_2$; ADPC Controller ii.

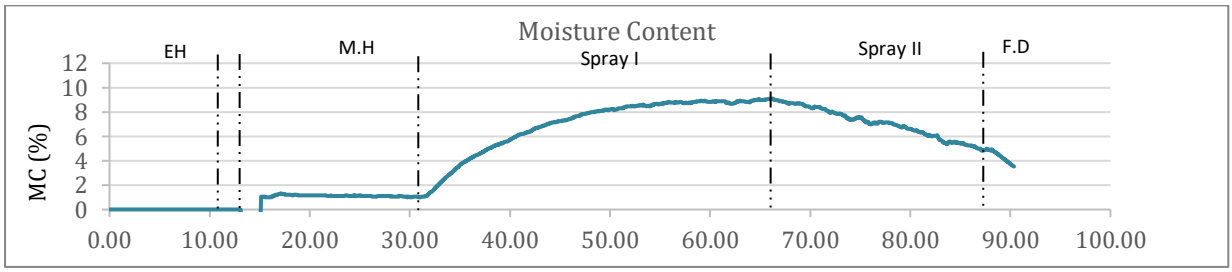

Figure 15: Moisture content profile as measured by Mulitieye$_2$; ADPC Contoller ii.

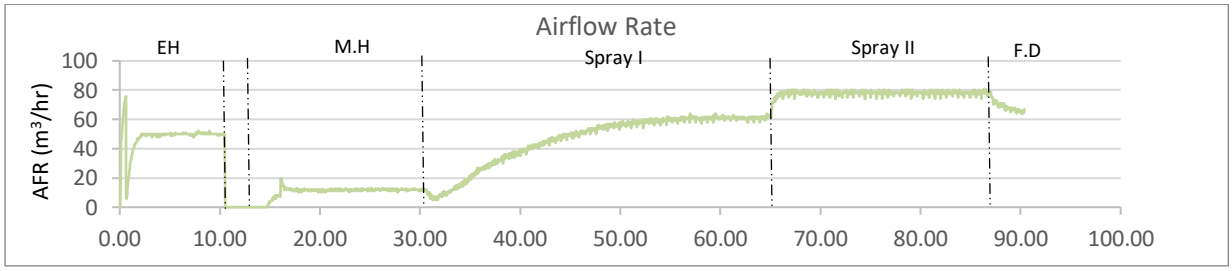

Figure 16: Airflow Rate profile; ADPC Controller ii.

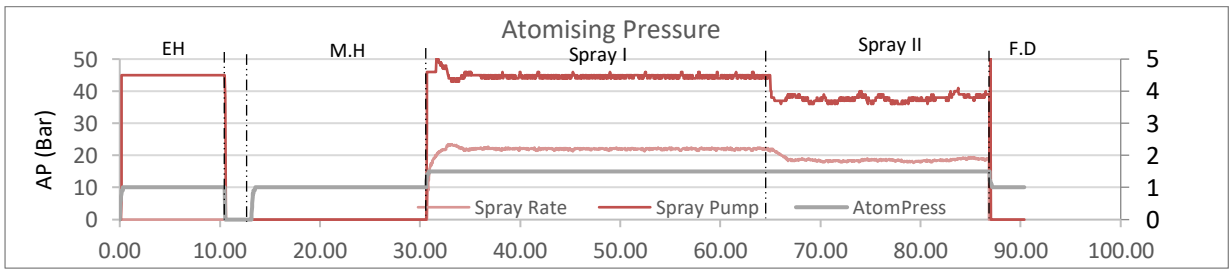

Figure 17: Spray Pump Speed, Spray Rate, Atomising Pressure; ADPC Controller ii.

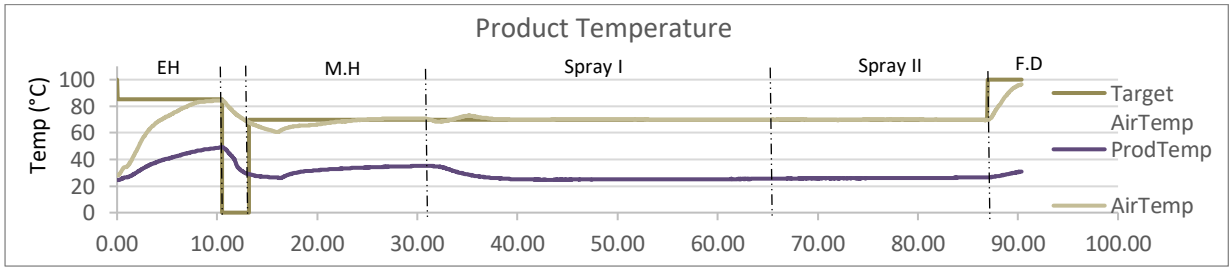

Figure 18: Product Temperature, Inlet Air and Target Inlet Air Temperature profile; ADPC Controller ii

Figure 19 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.

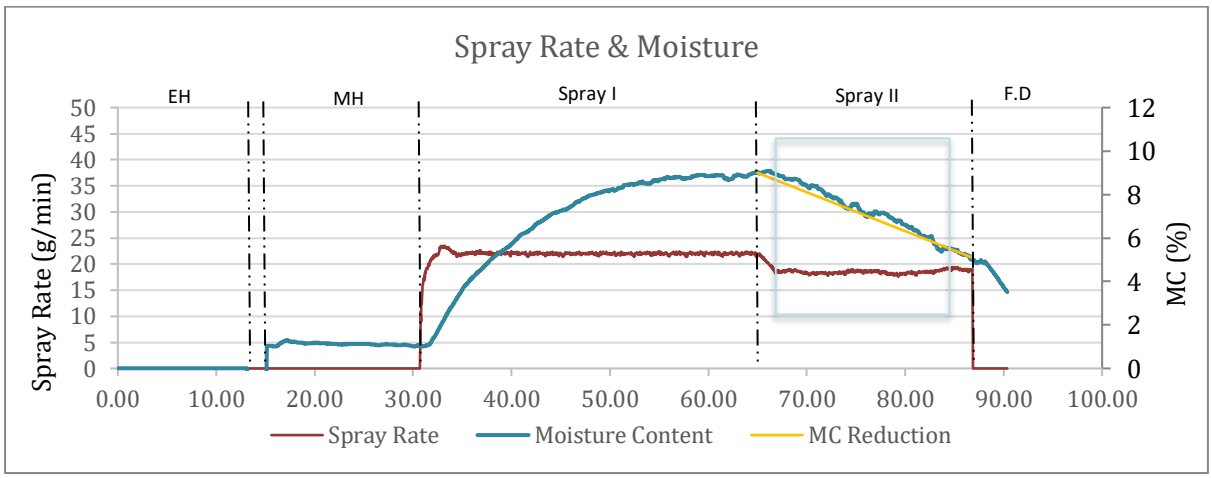

Figure 19: Dynamic relationship between spray rate & moisture content; ADPC Controller ii.

End Product Quality

Endpoint D_v50 particle size values from a number of granulation batches manufactured with the ADPC controller were compared to the endpoint D_v50 particle size values from earlier batches manufactured using a non-ADPC controlled, recipe driven approach. Although the two processes methodologies varied with regards to some parameter settings, a significant difference in endpoint product consistency is apparent between the two approaches.

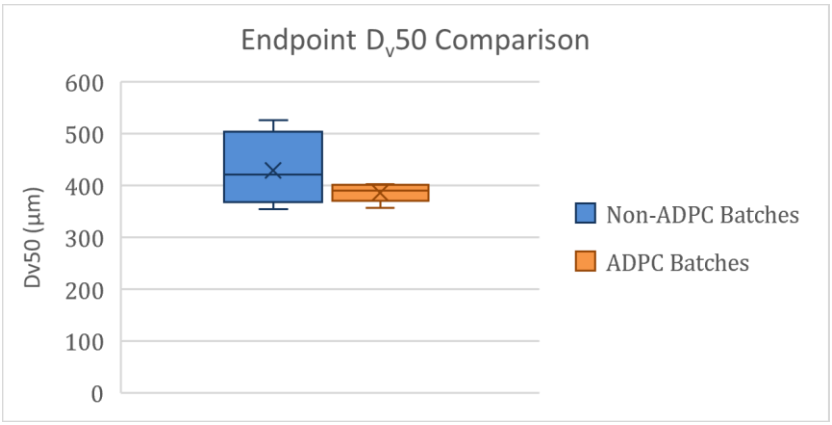

Figure 20: Endpoint D_v50 particle size values from non-ADPC controlled and ADPC controlled batches

Figure 20 illustrates a significantly wider distribution of endpoint D_v50 particle sizes for earlier batches manufactured via the non-ADPC controlled approach, with 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 to the above, 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 approaches, primarily due to the non-ADPC controlled approaches using product temperature as an indication of endpoint rather than in-line moisture measurement.

Figure 21 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.

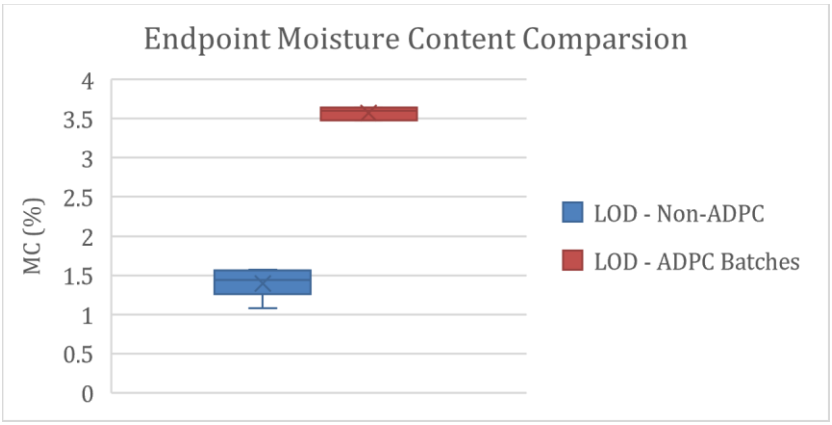

Figure 21: Endpoint Moisture Content values for non-ADPC controlled and ADPC controlled batches

Endpoint moisture content of the Fluid Bed Granulation process is critical to final product quality and performance and must be tightly controlled to avoid issues with product stability as well as dissolution and absorption rates in the body. Implementing such a control approach can significantly reduce batch to batch variation and greatly improve batch repeatability.

Conclusions

- The ADPC controlled approach to Fluid Bed Granulation was shown to produce significantly more consistently sized granules with less batch to batch variation when compared to granules produced from a non-ADPC controlled process.
- 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 non-ADPC controlled approach.
- Innopharma Technology's Eyecon$_2$ enabled real-time in-line measurements of particle size during processing while the Mulieye$_2$ enabled real-time in-line measurements of moisture content.
- 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 allowed the ADPC controller to effectively determine phase-end criteria.
- 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.
- Innopharma Technology's SmartX Advanced Manufacturing System demonstrated consistent process repeatability and reproducibility through the successful manufacture of multiple automated Fluid Bed Granulation batch processes.

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