Self-Guided Control of a Fluid Bed Granulation Process

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Advanced dynamic process control using PAT data improves product quality.

Globally, there is an increasing trend toward the use of Industry 4.0 principles, with the Industrial Internet of Things (IIoT) being a key component, while regulators are actively encouraging pharmaceutical companies to modernize their approaches to drug development and manufacturing to deliver higher quality products. Better process understanding, drug product development, and manufacturing throughout the commercial lifecycle of drug products will lead to faster time-to-market and a more reliable, predictable supply chain (1).

Adopting several of the tools and technologies which are part of the current Industry 4.0 revolution (e.g., process analytical technology [PAT], big data analytics, manufacturing intelligence, in-process control, and cloud architecture) into everyday pharmaceutical product development and commercial manufacturing may provide an effective solution to many manufacturing quality challenges. Adoption of these technologies would also dramatically improve productivity while maintaining competitive advantage and reducing costs for the manufacturer (2,3).

This article presents a practical application of Industry 4.0 architecture with commercially available technology solutions and demonstrates how the system can be implemented to reduce risks associated with traditional fluid-bed granulation manufacturing processes.

Fluid-bed wet granulation involves agglomerating a mix of dry primary powder particles (APIs and excipients) by the addition of a granulating solution in a fluid-bed granulator. In the subsequent drying phase, control is crucial because over-drying can lead to increased attrition and fracture of the product, while insufficient drying can result in bed stalling, poor flow, and product stability issues (4). The traditional control approach is recipe driven and largely operator dependent, with minimal provisions for the impacts of raw material or atmospheric variations, both of which are known to affect final granule properties (5).

The automated approach described in this article 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 this type of automated, control-driven approach.

Materials and equipment

Formulation. A placebo formulation was used for all batches. It consisted of a mixture of lactose (1 kg Pharmatose 200M, DFE Pharma) and microcrystalline cellulose (0.5 kg AvicelPH-101 NF, DuPont). The liquid binder was an aqueous solution of polyvinylpyrrolidone (1 L, 5.8% w/w, Plasdone K-90, Ashland). Materials were supplied by IMCD Ireland.

Process equipment. Fluid bed granulation was performed in a granulator (Glatt GPCG2) equipped with a particle analyzer (Eyecon$_2$, Innopharma Technology) and near infrared (NIR) spectrophotometer (Multieye$_2$, Innopharma Technology) measuring particle size distribution and product moisture content, respectively. The equipment is shown in **Figure 1**. The automated process control platform

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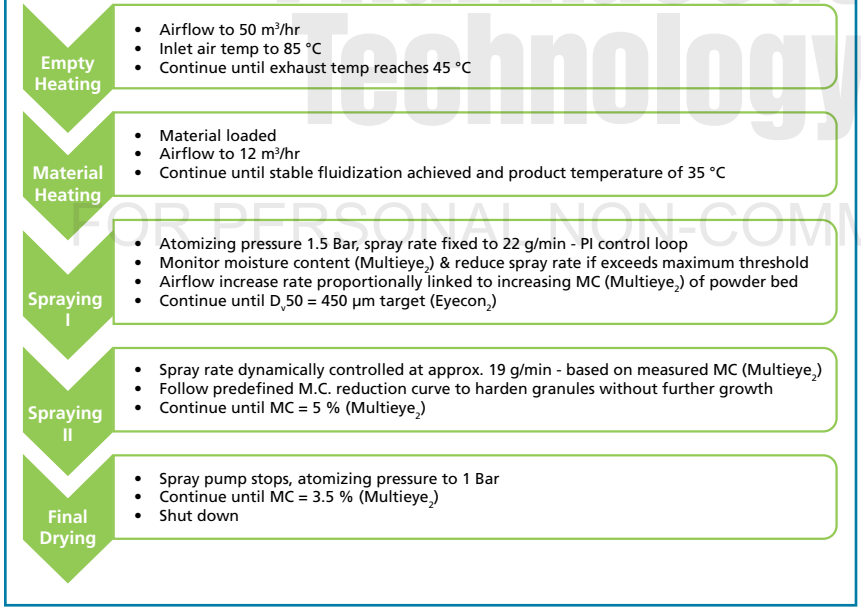
Figure 1. Fluid-bed granulator (Glatt GPCG2) equipped with a particle analyzer (Eyecon2, Innopharma Technology) and near infrared spectrophotometer (Multieye2, Innopharma Technology) with a system user interface (SmartX, Innopharma Technology).

Figure 2. Flow diagram demonstrating key set points and endpoint criteria for each of the phases within the controller. PI is proportional integral control; MC is moisture content.



(SmartX, Innopharma Technology) provided time-aligned data aggregation of process parameter data, PAT data, and environmental sensor data.

Controller development

Controller development is complex and requires a thorough understanding of the process, including critical process parameters (CPPs), their impact on critical quality attributes (CQAs), and the required process specifications. In this case, information on the process design space and optimum control was derived from retrospective analysis of more than 160 batches run on the test-bed system (SmartX Innopharma Technology), while further detailed experimentation was performed to quantify the differences in end-product quality between the results of this advanced dynamic process control (ADPC) approach and the results using a traditional control approach.

The first step in the development was to clearly define the control logic for each process phase. This included identification of key dynamic control relationships, establishing fixed set-points as well as phase and process endpoint criteria. Once configured, this flexible control logic was then implemented and executed via a process-centric scripting environment within the integrated ADPC module.

Throughout the process, real-time PAT data and process sensor data from the fluid-bed system and environmental systems provided a continual input feed to the controller. The controller used 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.

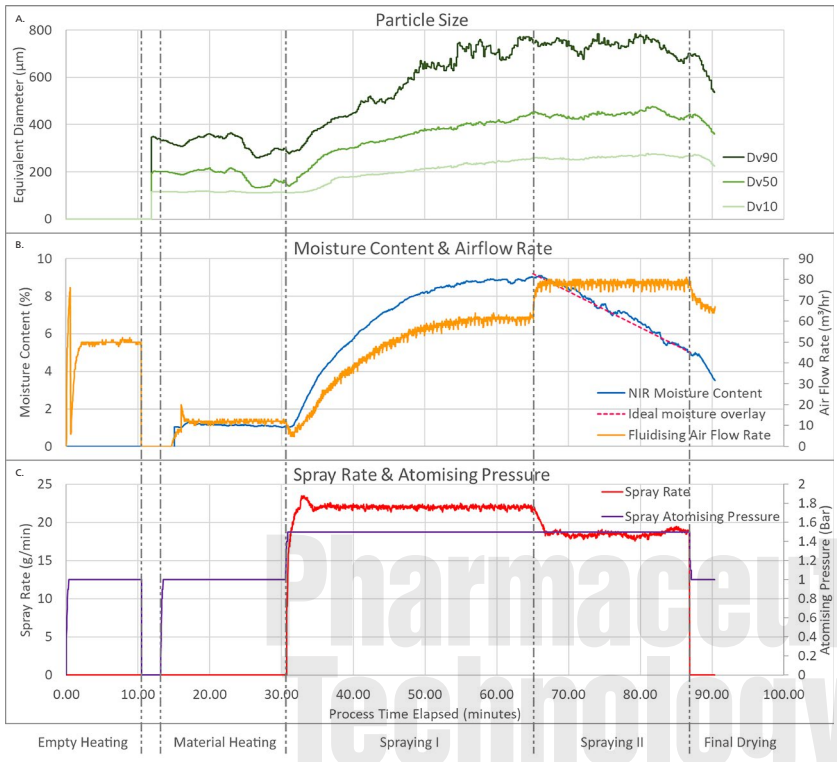
For the ADPC example presented in this article, five process phases were defined: empty heating, material heating, spraying I, spraying II, and final drying. **Figure 2** describes the five process phases and their corresponding key set-points and endpoint criteria.

Spraying is divided into two phases to demonstrate how 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 batch-to-batch variation. Spraying I is defined by rapid wetting and maximum growth, while Spraying II is defined by further hardening of the granules through reduced spray rate and increased moisture removal to mitigate against product attrition during the drying phase.

A specific moisture-content reduction rate was empirically determined to achieve a quasi-stable median volume distribution (D_v50) particle size while allowing for faster control reaction and, therefore, minimized process deviations as compared to controlling directly based on particle size.

ALL FIGURES COURTESY OF THE AUTHOR.

Figure 3. Advanced dynamic process control controller process profiles. NIR is near infrared spectrophotometer; D_v10, D_v50, and D_v90 are volume-based particle-size distributions containing 10, 50, and 90%, respectively.



Results and discussion

ADPC controller. The series of CQA and CPP profiles shown in **Figure 3** are taken from one of the fluid-bed granulation processes executed by the ADPC controller that was developed; these profiles demonstrate the control method's capabilities.

Dynamic control relationships. The key relationship between spray rate and D_v50 particle size can be observed between **Figure 3a** and **3c**. The controller sets the D_v50 particle size target to 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 Spraying I, a fixed spray rate is maintained for rapid moisture addition and growth until the target particle size is reached. On entering Spraying II, the target particle size is maintained by following the empirical target moisture-content profile.

This profile is maintained by dynamic control of the spray rate based on real-time moisture content data. Comparing **Figure 3b** and **3c**, modulation of the spray rate after a brief delay can be observed in response to small deviations of the moisture content trend either above or below the target moisture content profile (see **Figure 3b**, dashed line labeled ideal moisture overlay). This process slowly dries the granulate to 5%, which is the trigger to transition to the final drying phase.

Another novel aspect of this control approach can be observed in **Figure 3b**, where the effect of linking air flow rate to moisture content during the Spraying I phase can be seen. This approach allows optimum fluidization to be maintained while the bed becomes heavier and more cohesive, avoiding both the attrition and efficiency impacts of over-fluidizing, and the under-fluidizing risk of bed-stalling.

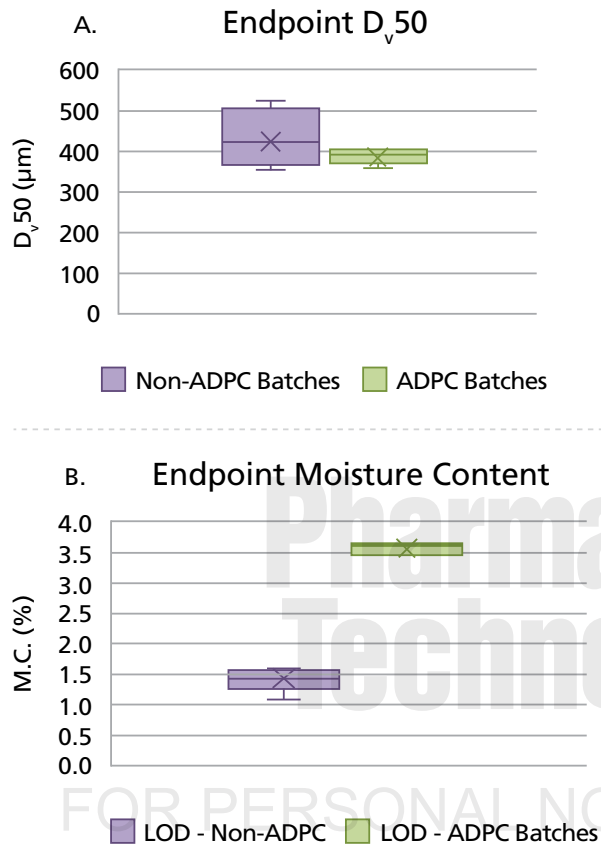
End-product quality. Endpoint D_v50 particle size values from a number of granulation batches manufactured with the ADPC controller were compared to the endpoint D_v50 particle size values from earlier batches manufactured using a non-ADPC controlled, recipe-driven approach. A significant difference in endpoint product consistency is apparent between the two approaches.

Figure 4a illustrates a significantly wider distribution of endpoint Dv50 particle sizes for batches manufactured via the non-ADPC controlled approach, with variation of 171 µm from the smallest to largest Dv50 value. Comparing batches manufactured with the ADPC controller, a tighter distribution in endpoint Dv50 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 that 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.

Endpoint moisture content values analyzed using the at-line loss-on-drying (LOD) methodology were compared for both control 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. The resulting over-drying of the non-ADPC batches is a source of energy waste and possible attrition of the end-product material. Additionally, the ability to reliably fall within, but at the upper end, of a moisture specification helps to improve overall product yield.

Figure 4b clearly demonstrates this variation with a much wider distribution of final LOD values evident for the non-ADPC controlled batches. The total spread of moisture content values is 0.48% for these batches, compared to only 0.16% for the ADPC-controlled batches, which demonstrate much tighter control. These results

Figure 4. Endpoint material comparisons of (a) median particle size volume distribution (D_v50) for batches made with advanced dynamic process control (ADPC) and with conventional control and (b) moisture content; LOD is loss on drying.



demonstrate the benefit of the in-line NIR moisture-content endpoint detection method.

Endpoint moisture content of the fluid bed granulation process is critical to final product quality and process performance and must be tightly controlled to avoid issues with downstream processing, product dissolution, and stability as well as drug absorption rates in the body. Implementing an ADPC approach can reduce batch-to-batch variation and improve batch repeatability and quality.

Conclusion

The ADPC-controlled approach to fluid bed granulation was shown to produce more consistently sized granules with less batch-to-batch variation when compared to granules produced from a non-ADPC controlled process. In addition, endpoint LOD analysis for the ADPC batches showed significantly less variation and greater consistency. Overall, high process repeatability and reproducibility were demonstrated across multiple, successfully manufactured fluid-bed granulation batches.

The real-time measurements of particle size and moisture content allowed the ADPC controller to effectively determine phase-end criteria. It was further shown to be possible to dynamically manage spray rate, thus ensuring a predetermined moisture content profile was followed by leveraging the NIR moisture-content data.

Finally, the addition of PAT and its integration into the process control strategy dramatically reduces the need for at-line sampling and testing associated with more traditional granulation approaches, as well as reducing the risks associated with human error.

References

1. L. Kiernan, "The Role of Smart Manufacturing in Enabling QRM and KM to Realize Safer and More Affordable Products for Patients in the 21st Century," in *An Audience with Pharmaceutical Regulators, Academia and Industry* (TU Dublin Academic Press, Dublin, 2019), pp. 65–74.
2. T. Dedeurwaerder, et al., "How Data is Changing the Pharma Operations World," *Mckinsey.com*, August 2018.
3. R. Gaertner, "Pharma 4.0—Time to Rethink Manufacturing and Quality," *Manufacturingchemist.com*, January 13, 2016.
4. R. Mattes et al., "In-line Process Analysis of Residual Moisture in a Fluid Bed Granulator-Dryer Using NIR Spectroscopy," *Pharmaceuticalonline.com*, Jan. 2005.
5. T. Lipsanen, et al., *Int. J. Pharm.*, 357 (1-2) 37-43 (2008). **PT**