NIR Spectroscopy for Real-Time, In-Line Measurement of Moisture Content for Improved Process Understanding in Fluid Bed Granulation

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Abstract

Figure 1: Multieye, an NIR spectrophotometer, used to improve process understanding of how Critical Process Parameters (Atomisation Pressure, Inlet Air Temperature and Spray Rate) of a Fluid Bed Granulation system influence the moisture content, a critical quality attribute.

Multieye, a near infrared spectroscopy process analytical technology sensor, was implemented to track the moisture content of powder during Fluid Bed Granulation in a Glatt GPCG2. The critical process parameters were varied in a full factorial $2^3 + 1$ Design of Experiment to investigate the effect of changes on moisture content, a critical quality attribute of the product.

Introduction

Granulation in Oral Solid Dose Pharmaceuticals
To prepare pharmaceuticals for oral solid dosing, it is often necessary to blend active pharmaceutical ingredients (APIs) with excipients, and to form granules from the blend. This is usually necessary to ensure that the powder mixture has suitable properties (such as flowability and/or improved...
compaction properties) for further processing. Granulation also allows greater control over the end-product properties such as dissolution.\(^1\)

Figure 2: Formation and growth of granules for Oral Solid Dose Pharmaceuticals. (Adapted from Iveson, 2001)\(^2\)

Granulation begins with nucleation, by wetting a powder or blend with a binder solution. On further wetting, granulate nuclei can consolidate and coalesce into larger granules (see Figure 2).

In Fluid Bed Granulation, pressurised air is forced up from beneath the powder mixture in a granulation bowl. This fluidises the mixture, keeping the powder in constant motion and circulating throughout the chamber. In top-spray granulation, a binder solution is sprayed from above onto the fluidised bed of powder during a wetting phase (see Figure 3), then the solvent is evaporated during the drying phase when spraying stops and the inlet air temperature is typically increased.

Figure 3: The Fluid Bed Granulation process (adapted from Glatt, 2019)\(^3\)

Care must be taken not to over-dry the granules, which would lead to increased friability and product fracture, and significantly increases the proportion of fines.\(^4\) By contrast, it is also necessary to ensure that the moisture content of granules is sufficiently low to prevent the product from sticking to processing equipment, which could lead to bed-stalling and fouling, resulting in loss of yield, increased man-hours for cleaning, and even in stoppages.
For this reason, moisture content is a critical quality attribute (CQA) of Fluid Bed Granulation, and the critical process parameters, i.e. those used to control the process evolution and ultimately the properties of the end-products, include spray rate, atomisation pressure (during the wetting phase) and inlet air temperature.\(^5\)

Especially where the aim is automated control, understanding the influence of process parameters on the process and product is essential. Therefore, it is necessary to continuously monitor the process’s CQAs, such as particle size and moisture content. NIR spectroscopy can be used for in-line moisture content measurement and show real-time trends which indicate the stability, progress and reliability of the process.

Because the Multieye\(_2\) can be used in-line for real-time analysis, the need for sampling for off-line analysis is eliminated or substantially minimised. Furthermore, because process measurements are recorded in situ, process data can be instantly accessed, allowing rapid decision making during both product development and manufacture.

Control decisions can be made based not just on a process recipe but also on the true CQAs of the material at that point in time. This allows for more dynamic process control, compensating for variabilities such as raw material variations or mechanical wear in processing components. It also supports compliance with newer QA initiatives such as continuous verification. So real-time process information allows faster development of process control methods and facilitates smart manufacturing.

The trend toward Industry 4.0 is actively being encouraged by regulators, with detailed specifications in the European Pharmacopeia and United States Pharmacopeia. Indeed, the FDA’s Process Analytical Technology Framework includes descriptions of the necessary tools such as multivariate analysis and PAT sensors in process control and continuous improvement.\(^6\)

**Experimental Plan**

The objective of this study was to improve process understanding through the use of the Multieye\(_2\) by monitoring the changes in moisture content of a placebo formulation in response to altering Fluid Bed Granulation process parameters.

<table>
<thead>
<tr>
<th>Critical Process Parameter</th>
<th>Low State</th>
<th>Medium State</th>
<th>High State</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atomising Pressure (bar)</td>
<td>1</td>
<td>1.5</td>
<td>2</td>
</tr>
<tr>
<td>Inlet Air Temperature (°)</td>
<td>50</td>
<td>60</td>
<td>70</td>
</tr>
<tr>
<td>Spray Rate (g/min)</td>
<td>12</td>
<td>20</td>
<td>28</td>
</tr>
</tbody>
</table>

A full factorial \(2^3 + 1\) Design of Experiment (DoE) was devised from three critical process parameters (see Figure 4): atomising air pressure (AP), inlet air temperature (IT) and spray rate (SR). For each parameter, the phase space was perturbed from a starting set of AP, IT and SR values which were known to yield granules suitable for compaction.
Figure 4: Design of Experiment with three critical process parameters – inlet air temperature, spray rate and atomisation pressure

The moisture content was measured using a non-contact fibre optic probe, mounted to a viewing port in a GPCG2 granulation bowl (see Figure 5).

Figure 5: Multieye2 with non-contact probe positioned on sight window on a GPCG2 Granulation bowl

Materials & Equipment

Materials
Lactose (Pharmatose 200M, 800 g) was mixed 2:1 with microcrystalline cellulose (Avicel, 400 g). The powder mixture was added to the bowl, then pre-heated before beginning the spraying phase of Fluid Bed Granulation. The inlet air temperature was set to 50°, 60° or 70°. An aqueous solution of polyvinylpyrrolidone (PVP90, 1L, 5% w/v) was sprayed onto the fluidised bed at atomising pressure 1, 1.5 or 2 bar at spray rate of 12 g/min, 20 g/min or 28 g/min.
Fluid Bed Granulation
Granulation was allowed to progress until spraying had completed (the full 1L solution of PVP90 had finished spraying). The bed was then dried until the bed temperature reached 42°C.

Analytical Instrument – Multieye₂
Multieye₂ is a multipoint near-infrared (NIR) spectrophotometer designed for real-time in-line process monitoring. A single sensor with up to four discrete channels allows measurements from four probes located within a process eliminating any complex time-consuming aligning procedures and channel-to-channel variation commonly found with multiple single point systems. Multieye₂ is the ideal tool for use in advanced development and manufacturing to aid rapid identification, monitoring and control of critical quality attributes and critical process parameters as part of a process control strategy.

Figure 6: Multieye₂ - Multipoint NIR Spectrophotometer

In this instance the Multieye₂ was used to monitor moisture content but the technology can also be implemented in applications where blend uniformity, API concentration or ribbon density are of interest. Spectra were acquired in-line using Innopharma Technology’s Quanta software.

Innopharma Technology’s Eyecon₂ was also used for end-point particle size analysis.

Chemometric Model Development
In-line spectral data were compared to off-line Loss-On-Drying measurements as the reference method. A two-component moisture analysis chemometric model was prepared using Partial Least Squares Regression as previously described with Innopharma Technology’s Quanta Model Developer (see spectral pre-treatment parameters of the optimised PLS model, Table 2).

Table 2: Parameters of the optimised PLS model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Period</td>
<td>5</td>
</tr>
<tr>
<td>Derivative</td>
<td>Enabled</td>
</tr>
<tr>
<td>Derivative Order</td>
<td>1</td>
</tr>
<tr>
<td>Savitzky-Golay filtering</td>
<td>Enabled</td>
</tr>
<tr>
<td>Polynomial order</td>
<td>1</td>
</tr>
<tr>
<td>Window size</td>
<td>3</td>
</tr>
</tbody>
</table>
The results of optimisation and the effects of pre-treating the data are shown below, with the untreated data compared to the pre-treated data (see Figure 7 for the calibration dataset and see Figure 8 for the validation dataset).

The known CQA values (moisture content %) were also plotted against the predicted CQA values, as were the corresponding residuals, to understand the linearity and accuracy of the optimised model. The root-mean-square error was reported for each dataset: RMSECV is the error of cross validation for the calibration dataset, where Leave-One-Out cross validation was applied (see Figure 9). The R-squared value represents the coefficients of determination of the data: how much of the variance in the data is accounted for by the model.
The known CQA values (moisture content %) were also plotted against the predicted CQA values for the validation dataset, as were the corresponding residuals (see Figure 10). RMSEP is the error of prediction of the validation dataset.

In this case, the model is linear (no trends are observed in the residuals), approximately 98% of the variance in the data is explained by the model and the RMSEP is approximately 0.8% (i.e. if the model predicts 10%, the reference method is expected to report 10±0.8%).
Results & Discussion

Applying the known “good” values for the three critical process parameters (the Medium State values reported in Table 1), the moisture content prediction tracked very well with the reference method (LOD) throughout the process (see Figure 11). The moisture content was 1.6% at the start of the process, increased smoothly to a peak at 20% after 40 minutes of spraying, and fell to 1.3% after 40 minutes of drying.

When the atomising pressure (AP) and spray rate (SR) were increased and the inlet air temperature (IT) was decreased, there are two significant effects on the process: first, the increased spray rate
reduces the duration of the spraying phase; second, the droplet size decreases, which results in larger granules and, hence, higher maximum moisture content (see Figure 12). However, these effects compete: although the spraying rate is faster, the larger granules trap moisture for longer, resulting in a longer drying process. With respect to total process duration, there is minimal change.

Figure 13: Changes in moisture during Fluid Bed Granulation with elevated Atomising Pressure and reduced Spray Rate and Inlet Air Temperature. The dashed vertical line indicates the beginning of the drying phase. End-point size fractions (D_{10}, D_{50} and D_{90}) are also reported.

With elevated atomising pressure and decreased spray rate and inlet air temperature, the process duration increased significantly, as expected (see Figure 13). Interestingly, the maximum moisture content was not significantly higher than when the starting “good” values were applied.

Figure 14: Changes in moisture during Fluid Bed Granulation with reduced Atomising Pressure, Spray Rate and Inlet Air Temperature. The dashed vertical line indicates the beginning of the drying phase. End-point size fractions (D_{10}, D_{50} and D_{90}) are also reported.
The NIR prediction tracked the LOD measurements closely until the start of the drying phase. Build-up of powder on the inside of the process window (fouling) was observed after the spraying had stopped (see Figure 14). Powder stopped moving past the sensor, resulting in the probe seeing the same material until it dried out and was dislodged from the window: un-fluidised powder stuck to the process window dries more slowly, leading to the NIR prediction of moisture lagging behind the LOD-reported values. Once the powder build-up dislodged, the Multieye continued to accurately predict the moisture content.

![Figure 15: Changes in moisture during Fluid Bed Granulation with reduced Atomising Pressure and elevated Spray Rate and Inlet Air Temperature. The dashed vertical line indicates the beginning of the drying phase. End-point size fractions (D_{10}, D_{50} and D_{90}) are also reported.](image)

As mentioned previously, over-drying leads to smaller endpoint particle size because granules become friable and break down. However, the endpoint was determined by measuring product temperature throughout the process, and, because multiple parameters were changed between each experimental run, it is not justified to draw conclusions relating the duration of drying to changes in particle size. Indeed, with low atomising pressure, high spray rate, but with high inlet air temperature, the product reached temperature at the same time the powder dried (see Figure 15).
Figure 16: Changes in moisture during Fluid Bed Granulation with reduced Atomising Pressure and Inlet Air Temperature but elevated Spray Rate. The dashed vertical line indicates the beginning of the drying phase. End-point size fractions ($D_{10}$, $D_{50}$, and $D_{90}$) are also reported.

By contrast, decreased inlet air temperature, resulted in a much longer time to reach the end point product temperature (see Figure 16), yet the granule size was significantly larger. This indicates that it is not only the duration of the drying time that causes the granules to break down, but the temperature of the system.

Figure 17: Changes in moisture during Fluid Bed Granulation with elevated Atomising Pressure, Spray Rate and Inlet Air Temperature. The dashed vertical line indicates the beginning of the drying phase. End-point size fractions ($D_{10}$, $D_{50}$, and $D_{90}$) are also reported.

Can a process simply be accelerated by increasing the atomising pressure, spray rate and inlet air temperature? Shorter duration experimental runs were achieved, but the resulting granule size was the smallest observed across the DoE (see Figure 17).
Reduced spray rate and elevated inlet air temperature caused lag during drying: the finer mist of sprayed binder is thought to dampen more fine particles (see Figure 18). These fines readily stick to the process window and initially result in a cataract effect. They very quickly act as seeds for the attachment of larger granules. Smaller granules that are stuck to the process window dry out more quickly than the larger particles, resulting in the LOD measurements lagging behind the NIR prediction. Notwithstanding this, as the drying phase progressed the process window became clear of fouled particles and the NIR prediction indicated good correlation with LOD towards the endpoint of the process.

Figure 18: Changes in moisture during Fluid Bed Granulation with elevated Atomising Pressure and Inlet Air Temperature and reduced Spray Rate. The dashed vertical line indicates the beginning of the drying phase. End-point size fractions (D_{10}, D_{50} and D_{90}) are also reported.

Figure 19: Changes in moisture during Fluid Bed Granulation with reduced Atomising Pressure and Spray Rate and elevated Inlet Air Temperature. The dashed vertical line indicates the beginning of the drying phase. End-point size fractions (D_{10}, D_{50} and D_{90}) are also reported.
Even during the spraying phase, with elevated inlet air temperature but reduced atomising air pressure and spray rate, small droplets are heated as they are being sprayed onto the product. This means that the product temperature increases during the spraying phase to such an extent that the product begins to dry before spraying has completed (see Figure 19).

![Drying Time, Maximum Moisture vs CPP](image)

**Figure 20:** Drying time and maximum moisture content for each of the experiments. **Above,** schematic of the process parameters. **Below,** drying time and maximum moisture content.

While some causal links are evident (lowering the atomising pressure and spray rate but increasing the inlet air temperature will reduce the maximum moisture content and the drying time, for example), overall, the relationship between the process parameters and the process end-points is complex (see Figure 20).

Because there are interactions between the droplet size, granule size and moisture content, which in turn all influence the final particle size and flowability, inline NIR is essential to understanding the process interactions, since it can be used to monitor the evolution of the process in real-time.

PAT such as the MultiEye2 is therefore vital to understanding a process and can help in creating a systematic approach to development.

**Conclusions**

**MultiEye2 NIR Spectrophotometer was used effectively to monitor moisture content.**

- The technology was shown to be able to measure from 0 to 27 ± 0.8%.
- Real-time acquisition of spectra and chemometric interpretation was achieved using Quanta.
- Chemometric models were developed with Quanta Model Developer.
- Real-time determination of moisture content with MultiEye2.
- For some process settings evidence for fouling was observed during the initial drying phase however its effect on predicted NIR measurement was short-lived and strong correlation between NIR and LOD at endpoint was determined for all process runs.
**Multieye\textsuperscript{TM} NIR Spectrophotometer can be successfully used to improve process understanding.**

- Interaction between the three process parameters is complex
  - Both the process evolution and the end material characteristics were affected
- A combination of moisture content and particle size analysis was crucial to understanding the process parameters’ effects on the process

**References:**


Innopharma Technology Ltd., PAT Sensors – Multieye\textsuperscript{TM}, Available from: [https://www.innopharmalabs.com/tech/products/multieye2tm](https://www.innopharmalabs.com/tech/products/multieye2tm)

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