NIR Spectroscopy for Real-Time, In-Line Measurement of API Concentration in a Continuous Blending Process

Authors: Emmet Hogan[A], Gareth Clarke[A], Ossi Korhonen[B], Tuomas Ervasti[B], Anssi-Pekka Karttunen[B]
[A]Innopharma Technology, Dublin, Ireland
[B]University of Eastern Finland, School of Pharmacy, Kuopio, Finland

Introduction

A fundamental requirement of continuous processing is continuous monitoring of the process' critical quality attributes (CQAs) to gain a sufficient understanding to devise a data driven control strategy. A suitable in-line Process Analytical Technology (PAT) sensor enables real-time measurements of the CQA and provides a real-time trend of the stability of the process. The FDA's PAT Framework includes tools such as multivariate analysis, PAT sensors, process control and continuous improvement in a risk-based approach to pharmaceutical development. PAT sensors are used to measure certain quality attributes of product within the manufacturing process, eliminating or substantially minimising the need for sampling for off-line analysis. This approach has several key advantages over traditional off-line analysis methods and includes process measurements in situ with instant access to data which facilitates rapid decision making during both product development and manufacture. This is particularly important when developing a process within a continuous manufacturing system. While the time between sampling and off-line results may range from minutes to days depending on the test being performed and the analytical structures in place, many PAT systems are capable of real-time measurement results, enabling control decisions to 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 a more dynamic process control, compensating for variabilities such as raw material variations or mechanical wear in processing components, and supports compliance with newer QA initiatives such as continuous verification. Additionally, the potential to develop an automated control with real-time release could minimise operator time when compared to testing samples at-line or off-line and manually adjusting the process within the specification.

Active pharmaceutical ingredient (API) concentration measurement is the tracking of the key component(s) in a powder blend; this is carried out to ensure that the correct amount of drug substance is being introduced into the material during the blending process. Measurement of the concentration of the API in a continuous blending process is critical to ensure the quality of end-product material.

Multieye$_2$, an NIR spectroscopy PAT sensor, was implemented to track the API concentration of the powder being outputted from a continuous blender in the University of Eastern Finland continuous processing lab in the School of Pharmacy, Kuopio. The concentration of API was varied to investigate the sensitivity of the instrument to process changes. Both step and impulse changes of the API concentration were introduced to the system.

Experimental Plan

The objective of this study was to examine the ability of the Multieye$_2$ to accurately monitor the concentration of API being added to the product by the continuous blending system.

A test protocol was devised, Figure 1, consisting of varying concentrations of the active ingredient being produced in step changes from 10% to 5% to 15% to 20% and back to 10%, w/w. This was then followed by impulses of 2.5 g, 5 g, 10 g and 15 g API being introduced into a blend of 10% w/w API.

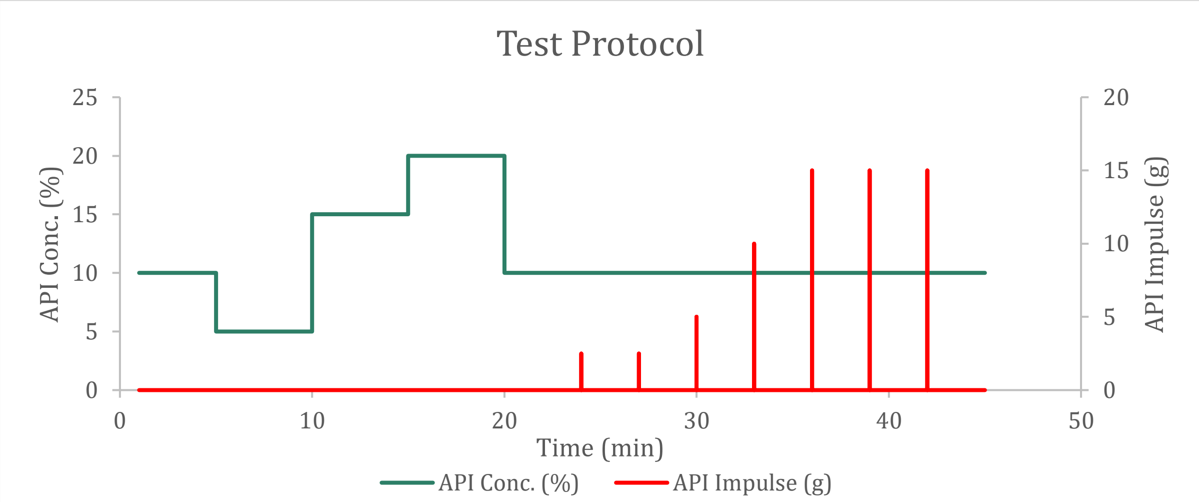

Figure 1: Experiment Test Protocol

The API concentration was measured at two positions using two different probe types. The first position was directly after the outlet of the blender using an NIR integrating sphere probe and the second was a non-product contact probe analysing the material as it progressed down along a transfer chute. See Figure 2.

Figure 2: Continuous Blender, NIR Integrating Sphere & Chute

Materials & Equipment

Materials

There was two ingredients in the powder blend; the excipient, Prosolv EasyTab SP and, the API that was being monitored, Paracetamol. The powders were fed from separate feeders into the blender and the concentration of paracetamol was changed throughout the experiment.

Continuous Blender

The blending equipment used was a Modulomix by Hosokawa Micron B.V. The Modulomix is a continuous modular mixer based on cyclomix batch mixing technology ([1]Hosokawa Micron B.V.). There is only one parameter setting, impeller speed, and it was set to 900 rpm. The total feed rate was 10 kg/hr.

Analytical Instrument – Multieye$_2$

Multieye$_2$ is a multipoint near-infrared (NIR) spectrometer 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. Multieye$_2$ 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. ([2]Innopharma Technology Ltd.).

Figure 3: Multieye$_2$ - Multipoint NIR Spectrometer

Figure 4: Multieye$_2$ - Real-Time Spectral Acquisition

In this instance the Multieye$_2$ was used to monitor API/component concentration but the technology can also be implemented in applications where blend uniformity, moisture content and ribbon density are of interest. The Multieye$_2$ was set up with its own standard non-contact reflectance probe attached to the view-port in the base of the material transfer chute. This probe analyses the powder through the view-port as it flows down the chute, utilising the Multieye$_2$ internal light source. The Multieye$_2$ was also attached to the NIR-integrating sphere. The sample powder flows down through an optical cuvette inside the integrating sphere and is flooded by light supplied by an external light source, the response is collected and returned by a 6-1 fibre bundle to the Multieye$_2$.

Results & Discussion

Two sets of results were generated from this study; from the analysis performed using the NIR integrating sphere and from the analysis performed using the non-contact probe on the chute. As this study was an initial feasibility investigation, no chemometric model had been developed for the process. The spectral response from each probe was taken and loaded in Camo Analytics Unscrambler for processing. Standard Normal Variate (SNV) pre-treatment was applied to the two data sets and Principal Component Analysis was carried out, outputting the following results.

NIR Integrating Sphere

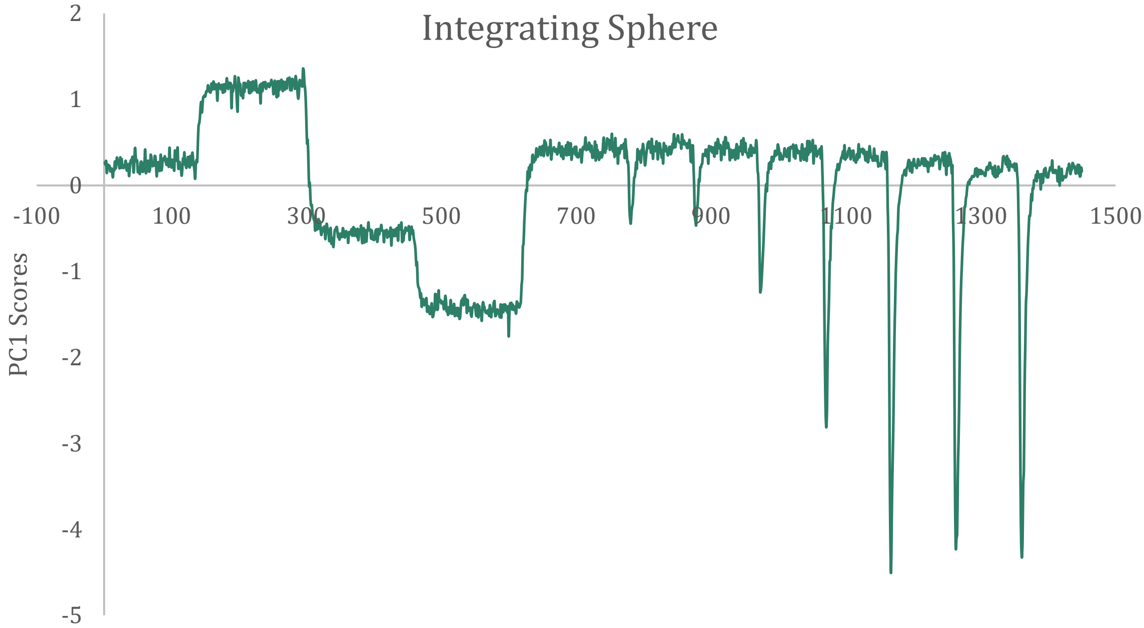

Figure 5: Pre-Treated Response from NIR Integrating Sphere

Upon application of the SNV pre-treatment, an immediate and obvious response to the changes in API concentration was observed. Both step and impulse changes were observed very clearly. Each of the step changes and impulses resulted in a proportionate and timely response. A small amount of noise was observed in the measurements, this could be improved upon through further development of a chemometric model.

Non-Product Contact Probe

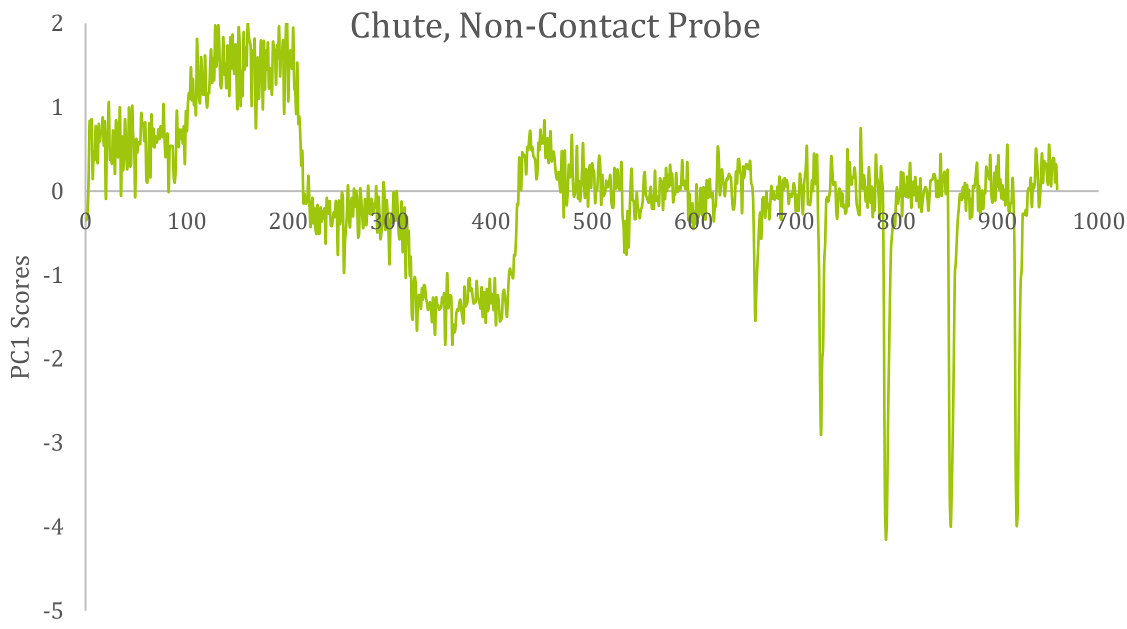

Figure 6: Pre-Treated Response from Non-Contact Probe

Again, with the non-contact probe a response to the changes in API concentration was clearly observed upon application of the SNV pre-treatment. Both step and impulse changes were observed in the response. In comparison to the integrating sphere, the response of the non-contact probe was not as precise. There was an increased level of noise in the output which was most evident in the second 2.5 g impulse where the response was indistinguishable from the noise. The noise in the response was most likely attributable to residual powder remaining on the view-port. Such powder build-up could be reduced through implementation of anti-static material in the view-port, use of window heating or an air-purge. It is possible that the noise in the response was introduced from other sources, such as consistency of the powder flow over the window. This requires further investigation and, where possible, elimination through apparatus optimisation or within a chemometric model.

Conclusions

Multieye$_2$ NIR Spectrometer can be successfully used for monitoring of continuous blending operations.

- The technology was shown to be able to measure different levels (5%, 10%, 15% and 20%) of paracetamol concentration, as may be required for varying product SKUs.
- The technology was shown to be able to detect spikes of varying magnitude (2.5 g, 5 g, 10 g and 15 g) of paracetamol coming from the blender, allowing for real-time detection of changes in the process.
- Chute view-port fouling needs to be further investigated and eliminated to remove signal noise.

References:

[1] Hosokawa Micron B.V., Continuous Modular Mixer, Available from: https://www.hosokawa-micron-bv.com/technologies/mixing-equipment/continuous-mixing-solutions/modulomix-continuous-modular-mixer.html

[2] Innopharma Technology Ltd., PAT Sensors – Multieye$_2$, Available from: https://www.innopharmalabs.com/tech/products/multieye2tm

For More Information on Multieye$_2$™ Please Contact:

Innopharma Technology Ltd.
info@innopharmalabs.com
www.innopharmalabs.com/technology