VIAVI Solutions

Application Note

Real-time monitoring of powder flow in tablet presses by NIR spectroscopy

Tableting is one of the final steps in pharmaceutical, nutraceutical and other solid forms manufacturing. Monitoring moisture, particle size and blend uniformity throughout the process is essential to avoid out of specification of intermediate mixtures, but problems may still arise at the very last – tableting – step.

Introduction

Sticking, one of the major defects associated with tablet manufacturing, can be due to the inaccurate addition of excipients or errors in the granulation process. Lamination, another typical tableting issue, can be created by fines, excess of trapped air between particles, or inadequate moisture in the powder blend. Although physical defects are easy to detect, often by visual inspection of the finished tablets, identifying the source of the problem requires laboratory analyses, after which corrective action can only be taken on future production. The defective batch must be scrapped, which results in material waste and lost time. In absence of tablet physical defects, out-of-specification tablets would be detected only after laboratory analysis and may lead to risk management corrective actions, including product recalls. The implementation of NIR sensing in a tablet press enables the detection of anomalies in the formulation before the compression stage and allows real-time root cause analysis of the problem and immediate corrective action.

In summary, the disadvantages of post-tableting quality control are:

- Time consuming and expensive root-cause analysis of physical defects
- Possible waste of material, lost time, and inconsistent production yield
- Late detection of out-of-specification tablets with potential risk of product recall

Installing an NIR sensor directly on-line can be an effective solution to avoid all of these drawbacks. Specifically, the MicroNIR™ PAT-U miniature process spectrometer allows continuous monitoring of powder mixtures before the compression stage, in real-time. In the pharmaceutical industry, the direct monitoring approach based on PAT (Process Analytical Technology) enables the implementation of QbD (Quality by Design), which is now advocated by the FDA (see, e.g., the Guidance for Industry PAT - A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance). In other industries, the direct monitoring of the process represents a valuable advancement toward LEAN manufacturing.

Real time powder flow monitoring before tablet compression is a fundamental step in the transition from process validation to continuous process verification, in which every step of every batch is controlled during the production phase.

This document describes how the MicroNIR PAT-U can be integrated into commercial manufacturing equipment for the purpose of identifying sources of tableting defects and out-of-specification formulations, directly on-line in real time.

System Configuration

Setting up the MicroNIR PAT-U to monitor powder mixtures in a tablet press is a quick and easy procedure. The system setup steps are:

- Mounting the MicroNIR instrument on the press equipped with a standard quick release clamp
- Connecting the instrument to the computer via a USB cable
- Adjusting the acquisition time interval to fit the dynamics of the powder flow

With some minor additional software settings, the system is ready to display the consistency of the powder blend feeding the press, allowing a direct and non-invasive monitoring of the dynamics occurring in the feed frame, or chute.

The MicroNIR PAT-U is completely isolated from the blend by a sapphire window, which allows non-contact operation. When the tableting process is complete, CIP (Cleaning in Place) and SIP (Sterilization in Place, if needed) can be accomplished without disassembling the system. In case of mechanical/space constraints due to the press equipment design, an optional extended probe allows the installation of the instrument on the feed frame with additional flexibility, with no impact on the instrument performance. The HazLoc version of the instrument – the MicroNIR PAT-Ux – is safe in the presence of flammable gases, vapors, and dust, and enables the above capabilities in hazardous locations.

From Real-Time Data to Executable Information

Unlike most NIR applications, real-time powder blend uniformity can be monitored with no need for data modeling. The typical time-consuming acquisition of reference standards, as well as the development of regression PLS modeling, are not required. Principal Component Analysis (PCA) is a powerful mathematical tool for tracking changes in the spectral “fingerprint” of the blend over time. PCA is an “unsupervised” data processing algorithm that does not require pre-calibration and explains the variance of a data set with no need for additional information. The PCA algorithm transforms information embodied in the spectra into new variables, called Principal Components (PCs), that correspond to specific spectral absorptions. The uniformity of the pre-blended material is monitored throughout the feeding cycle by plotting the trajectories of PCs over time. In the ideal case where the composition, moisture, particle size, and other critical parameters remain constant, the trajectory of the principal component(s) over time remains flat or stationary within set limits of variation. Any anomaly in the PCA plot pattern, including slopes or steps, indicates either a continuous variation in the blend, or one or multiple undesirable variations over time.

Moving Block Standard Deviation (MBSD) is another unsupervised method to monitor product uniformity in real time. While MBSD can be used for the same purpose, PCA has the advantage of providing potentially useful information to explain the nature of an anomaly. The interpretation of an anomaly is possible by jointly interpreting the PCs trajectory and the loadings profile, which is a dedicated graph that represent the contribution of each absorption band to the new variables (PCs).

Let's call the first principal component PC-1 and the second principal component PC-2. Each of these PCs explains some fraction of the observed variance in the product, with PC-1 explaining the largest part, PC-2 the next largest, etc. By examining the loadings, if the PC-1 loadings profile has a high contribution (absolute value) in the typical region of water absorptions, for example, it is possible that the process variation is due to an increase or decrease in the concentration of moisture. Once the PCA trajectory of a specific process is confirmed by multiple repetitions, the user can define thresholds, enable triggers to stop the equipment and avoid the production of out-of-specification tablets.

Figure 1. MicroNIR PAT-U and optional extended probe

Case-study

In order to demonstrate the capability of the MicroNIR PAT-U to detect changes in the powder mix flow, a tablet press was fitted with an instrument[1] and sequentially loaded with blends of the same ingredients (lactose, talc, and magnesium stearate) in different ratios as reported in Table 1. Data processing procedure included both PCA and MBSD methods.

Table 1: Powder blends composition

Ingredients	Blend 1	Blend 2	Blend 3
Lactose synchronization	98%	93%	94%
Talc	1%	3%	5%
Mg Stearate	1%	1%	1%

The absence of moving parts in the MicroNIR line of spectrometers allows rapid data acquisition and averaging of 100 spectra in one second, delivering excellent signal to noise data and the collection speed required for continuous monitoring. The MicroNIR PAT-U acquisition parameters used to collect data are reported in Table 2.

Table 2: Acquisition parameters

Acquisition Mode	Diffuse Reflectance
Integration Time (ms)	8.9
Scan Count	100
Delay Time (ms)	600

[1] In this experiment the MicroNIR PAT-U was mounted on the press chute. However, since the feed frame is the final stage before compression, installing the sensor on the feed frame might be preferred. The chute installation may require longer acquisition time to average the dynamics of the powder and air flow and the resulting irregular instrument response as material ebbs and flows around the sensor window. Ultimately, the choice of instrument location depends on the process and the characteristics of the equipment in use.

Results and Discussion

The acquired spectra were preprocessed using Standard Normal Variate (SNV) and first derivative (1der) transforms. The preprocessed NIR absorbance spectra for the duration of the entire experiment are shown in Figure 2. At a first glance, the spectra appear very similar, except mainly in the 1354–1550 nm region where slight variations are observed. Those slight variations represent significance in the data.

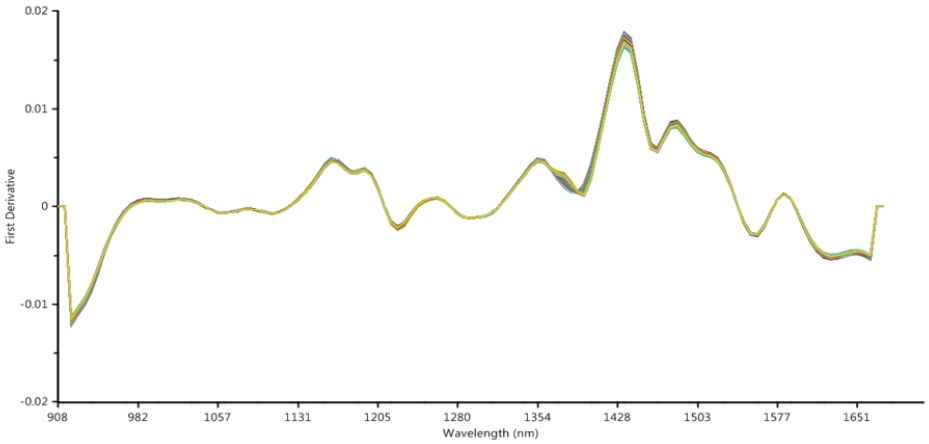

Figure 2. SNV and first derivative processed spectra of the entire experiment.

Variations in the process are reflected by structured variations in the PCA and MBSD analyses of the time-series data. With reference to Figure 3, both the MBSD profile (3a) and the trajectory of the first PC (PC-1) (3b) indicate three distinct steps or stages of the process.

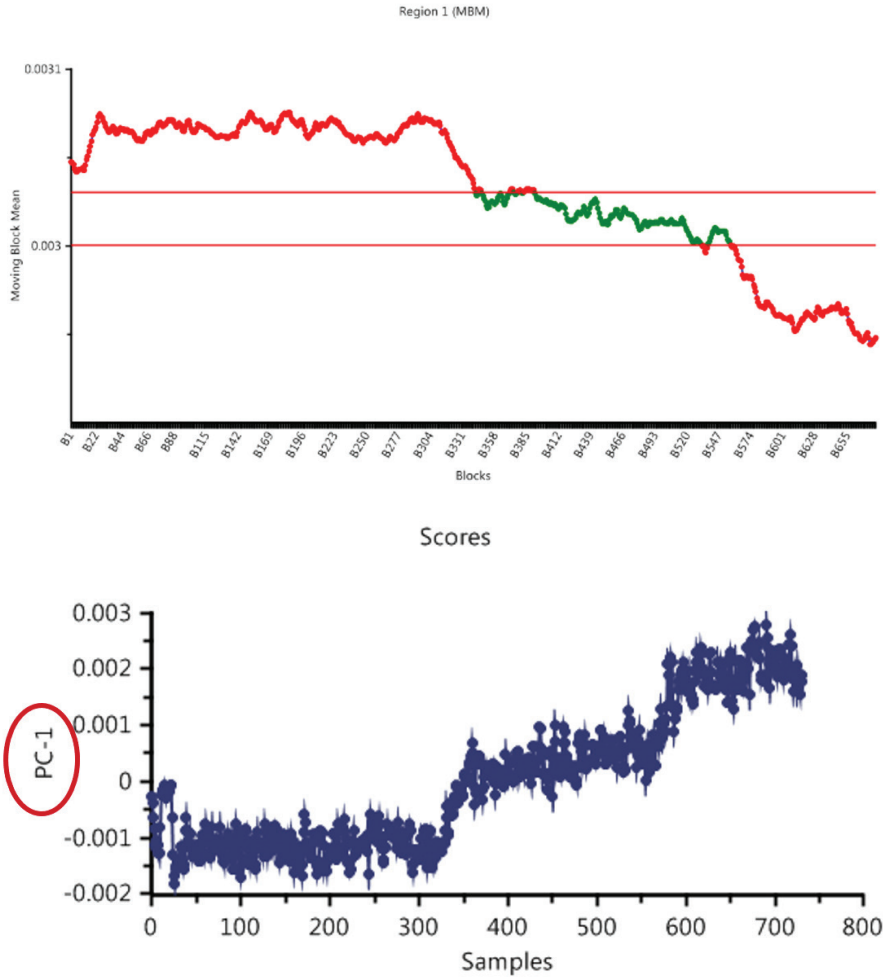

Figure 3. top) Moving block standard deviation (mean); bottom) PCA PC-1 trajectory

A closer examination of the PCA results shows that PC-1 is accounting for almost the entire variability of the system (Figure 4a) and it is mainly ascribable to variations in the talc absorption band, highlighted in Figure 4b. Thanks to PCA it was possible to demonstrate that, despite its low value (that varies by a factor of 5), the variations in talc concentration are detectable in real time by means of NIR spectroscopy.

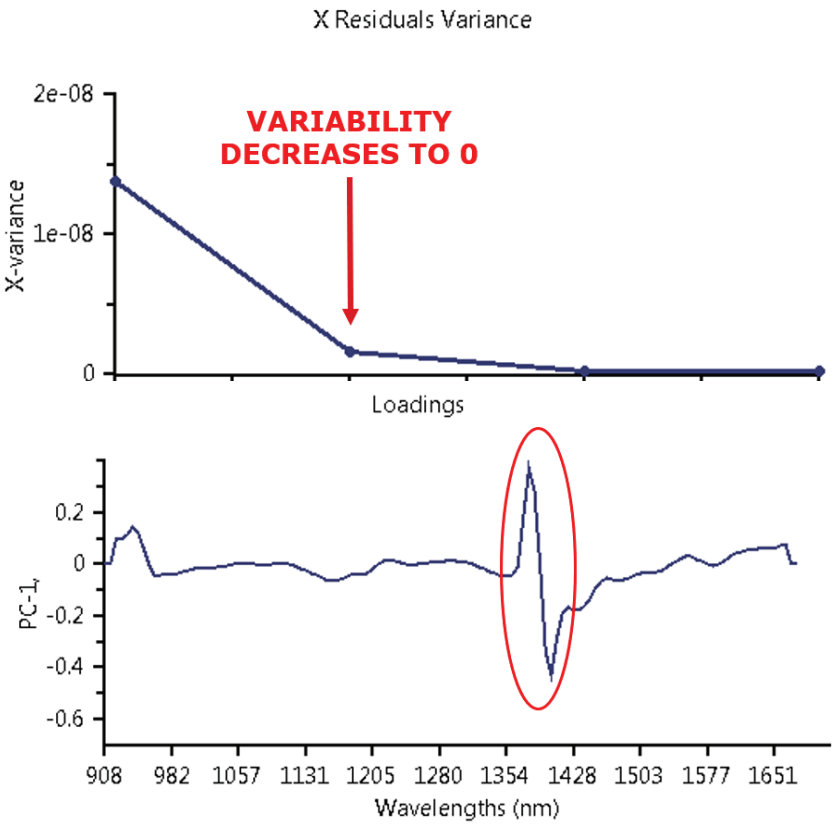

Figure 4. top) PCA explained variance; bottom) PC-1 loading plot

Further insight can be gained by examining the score plot in which PC-1 and PC-2 define a new orthogonal space. On this plot, the spectra are represented as points in a scatter chart. The score plot in Figure 5 shows three distinct trajectories and two intermediate trajectories. This graph represents the powder flow dynamics, from blend 1 with 1% talc concentration to blend 3 with 5%, and the two transitions between as the process changes from one blend to the next. The goal of process development should be a uniform and consistent flow, which would be represented in a PC-2 vs. PC-1 plot as a single cluster of scores, without separations or outliers.

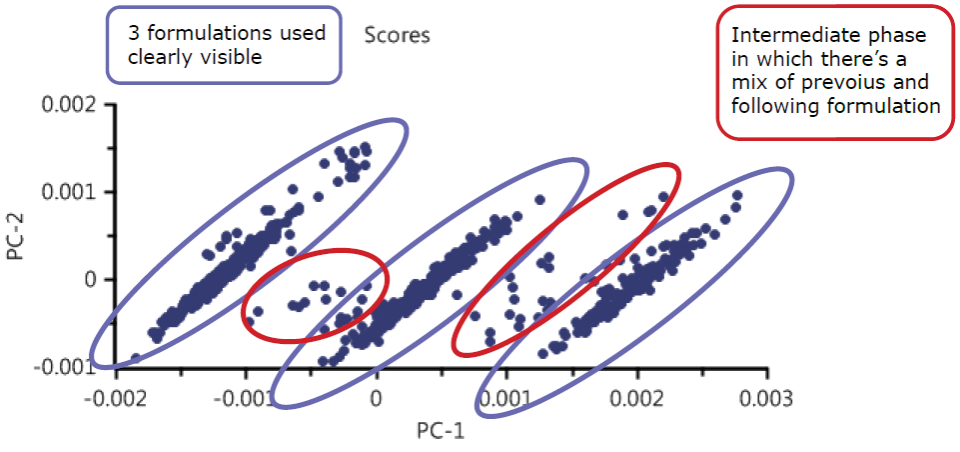

Figure 5. PC-1 and PC-2 score plot.

Conclusions

Powder flow continuous monitoring in a tablet press by means of the MicroNIR PAT-U and PCA analysis can yield a deeper understanding of your process, a critical step toward the realization of QbD in pharmaceutical manufacturing. This statement applies equally to LEAN manufacturing in any industry compressing tablets or employing analogous manufacturing processes. The PAT-U and can be successfully used to:

- Enable process monitoring, from laboratory to production, through a scalable path
- Acquire actionable insight on variations in the process
- Minimize time and material waste by improving yield
- Minimize out-of-specification and potential product recall risks

The MicroNIR PAT-U can also be used to enhance process understanding on other manufacturing equipment including High Shear Mixers (HSMs) and Fluid Bed Dryer (FBDs), and ribbon blenders. The MicroNIR line of compact process and handheld instruments is IP65/67 rated and supported by a GMP-compliant software suite and optional OPC process control interfaces. MicroNIR instruments can help simplify and accelerate the entire journey from pilot laboratory experiments through manufacturing process development, process optimization, and all the way up to full-scale mass production.

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