Pharma

# In-line inspection of powder blends in the tablet press by means of NIR Spatially Resolved Spectroscopy

## Introduction

Solid dosage forms such as tablets represent the majority of the pharmaceutical formulations on the market. This has been the case for many years, because of their easy handling, compact format, excellent stability and their simple, low-cost production processes.

In the last few years, however, continuous manufacturing and the introduction of PAT (Process Analytical Technology) tools have led to a change in mentality for quality control of these formulations.

Always concerned to improve patient safety, the regulating authorities encourage the use of in-line inspection tools to guarantee product quality directly during production rather than testing it subsequently in the laboratory.

This was the driving force behind this study of the integration of near-infrared sensors in tablet presses.

Measure up

## ▪ Objective

The goal of the study was to assess the effectiveness of the SAM-SPEC (Spatially Advanced Measurement by Spectroscopy) technology in the near-infrared for high-speed quality control of a powder blend.

With this method, it is possible to predict in real time the API concentration directly in the feedframe of the tablet press, in the context of the development of solid dosage forms with real-time release.

## ▪ Materials and methods

In the study presented here, INDATECH's SAM-SPEC solution was integrated in the feedframe of a rotary tablet press. A Hy-Ternity acquisition unit was used to collect the near-infrared spectra in the 900 to 1650 nm spectral range in real time. Using optical fibers, the SAM-SPEC probe with 12 collection points (Figure 1) was incorporated into the feedframe by means of an immersion fitting. Ten powder blends of a model formulation comprising 5 components were thus analyzed dynamically at high speed, using an integration time of only 0.6 ms for simultaneous acquisition of the 12 measurement points. INDATECH's 'SRS Ready' software was used for data acquisition. This software is 21 CFR part 11 compliant and can also be controlled via OPC-UA or TCP/IP. The data were then analyzed using PLS_Toolbox (Eigenvector Research) running in the MATLAB (MathWorks) environment.

A support specially designed by INDATECH was used to take the white reference ($I_0$) on Spectralon (NIST-certified 99% reflectance standard). This method makes it possible to perform reproducible and repeatable measurements without having to remove the immersion fitting from the tablet press. By taking a reference, it is then possible to convert the raw data acquired on the powder blends into absorbance units by means of the formula $A = -\mathrm{Log}\left(\frac{I}{I_0}\right)$.

A variability caused by the wave pattern due to the movement of the paddles under the probe was observed in the spectral data. Because of the very short acquisition time, several spectra were collected during the passage of each paddle blade, capturing the wave pattern with high resolution. The spectra collected near to and during the crest had a larger absorbance than the data acquired during the trough of the wave pattern. The increase in absorbance is due to the change in apparent density when the powder is pressed against the probe while the paddles pass.

Consequently, a filtering algorithm was applied in the software in order to select only the spectra with high absorbance values obtained near to and during the peak for chemical interpretation.


Figure 1: configuration of the SAM-Spec probe for physical and chemical measurement

# ▪ Results and discussion

Near-infrared spectra were collected at three distances (3, 4 and 5) from the light source. So three different optical trajectories of 1, 1.4 and 1.7 mm, respectively, were studied. By calculating $\mathrm{Log}\left(\frac{\text{I position 4}}{\text{I position 5}}\right)$, an SRS ratio is determined and it can then be analyzed in a similar way to a traditional near-infrared spectrum.

It directly provides a level of absorbance independent of the fluctuations of the light source, thus ensuring robust data acquisitions for the measurements in production over a whole day.

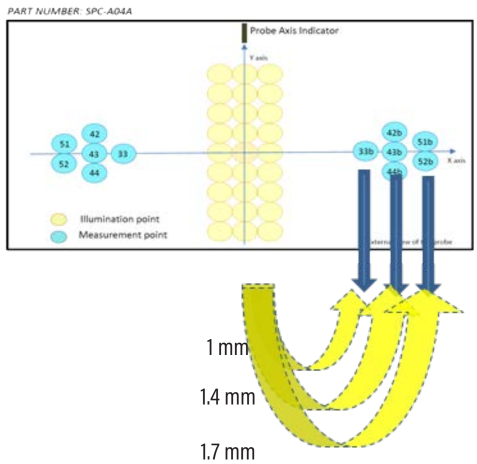
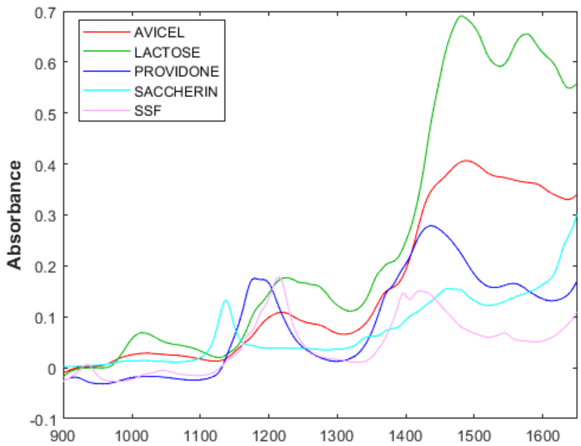
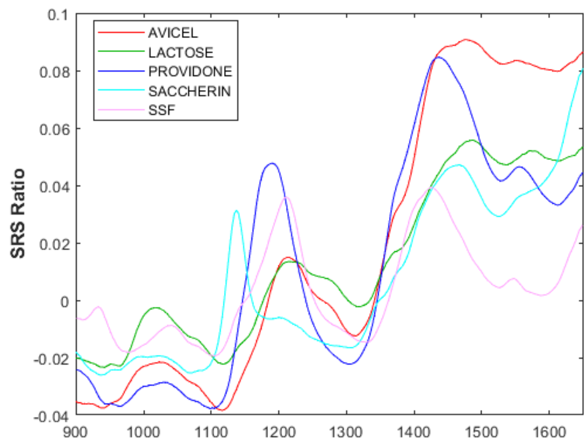



Figure 2: the three positions used and their corresponding distances from the light source




Calculation of the absorbance spectra of the pure compounds by means of $A = -\mathrm{Log}\left(\frac{I}{I_0}\right)$



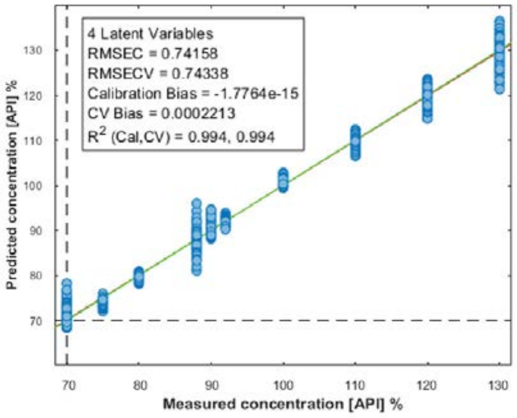

Calculation of the SRS ratio of the pure compounds by means of $\mathrm{Log}\left(\frac{\text{I position 4}}{\text{I position 5}}\right)$

Figure 3: Spectra of pure compounds

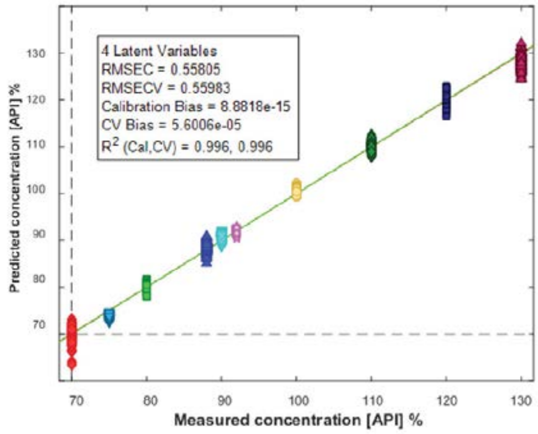
Figure 3 shows that similar results are obtained using the SRS ratio as with a classic absorbance calculation approach with a reference $I_0$ taken on Spectralon.

Two PLS (Partial Least Squares) regression models were then constructed from a database comprising 4,097 absorbance spectra with 10 concentration levels. The first PLS model was obtained by using the absorbance spectra from a single measurement point (position 52b was chosen because it yielded the best results) calculated with the traditional approach $A = -\mathrm{Log}\left(\frac{I}{I_0}\right)$.

For the second PLS model, an SRS approach based on calculation of an intensity ratio with the formula $\mathrm{Log}\left(\frac{\text{I position 4}}{\text{I position 5}}\right)$ was used.




Classic approach using $I_0$ with a single measurement point (position 52b)




SRS approach

Figure 4: PLS API prediction models using the traditional approach with $I_0$ versus the SRS approach

## ▪ Advantages of Indatech's SAM-SPEC technology

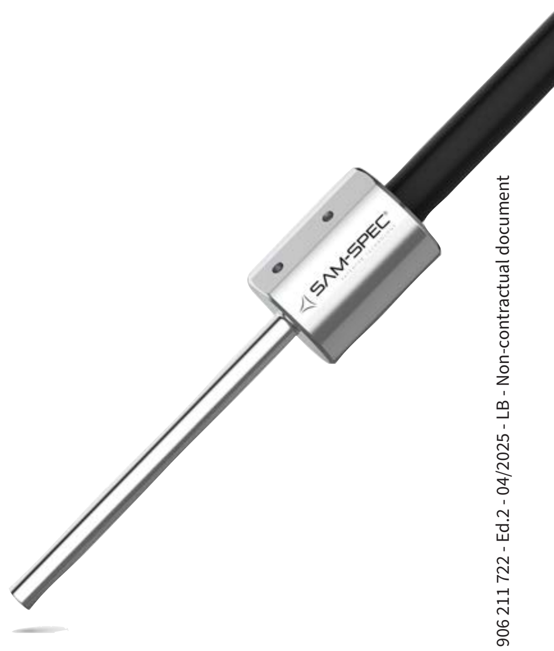
The model obtained using Indatech's hardware and software technology beat the performance of the classic approach, with slightly lower RMSEP (Root Mean Square Error of Prediction) values. Moreover, the model developed by the signal ratio approach proved more resistant to the variations in the process, which was confirmed by reduced dispersion of the samples on the calibration curve.

Use of the ratio calculation technique offers several advantages. First of all, it frees users from constrictive use of the $I_0$ reference, which may be an advantage in a continuous production line. In addition, the ratio offers the advantage of making it possible, in real time, to correct and normalize any drift in the process, such as changes in the temperature, measuring distance or line speed. This approach can be used to measure a reference for every acquisition, thus solving the problem of determining when and how to take a reference when a batch is released.

## ▪ Conclusion

Using spatially resolved spectroscopy, a high-quality predictive model was developed to quantify the level of API in powder blends directly in-line at high speed. This predictive model is both robust and accurate, speeding up development of the processes by facilitating the phase for determining the production parameters.

In the case of continuous production, this model can be used to implement real-time inspection before the validation of each product, while anticipating critical drift on the production equipment.

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