APPLICATION NOTE

FT-NIR Spectroscopy

Whole Tablet Measurements Using the Frontier Tablet Autosampler System

Introduction

Recent advances in NIR technology have changed the ways in which both the pharmaceutical industry and the regulators view the current approaches to tablet testing in manufacturing.

In 2001, among the FDA's top 10 reasons for product recall were problems with sub-potency and tablet dissolution. In addition, recent cases of cGMP violations have highlighted issues in tablet manufacturing. One area where the industry is seeking to improve its processes is in the blending area. After tablet pressing, measurement of uniformity of content usually involves taking a sample (typically 10 tablets) from the batch and performing individual assays by HPLC. The standard deviation of assay is intended to provide an idea of the uniformity of the blend. This measurement is required before batch release and can cause serious bottlenecks, especially if out-of-specification results are generated. The HPLC technique used is slow, requires skilled analysts, provides little or no information on the matrix and destroys the sample. Analysts are actively seeking faster, non-destructive methods which can provide more information on the sample and are capable of being used by less experienced operators.

NIR now offers the possibility of performing non-destructive, whole tablet testing at much higher speeds and also provides more sample matrix information. It is also readily automated thus providing the potential for more and/or faster tablet testing using less specialized operators. More efficient, more informative measurement in this area is a key factor in delivering more process understanding; an objective pursued by industry and regulators alike.

This note describes an example showing the application of NIR tablet transmission measurements to determine the active content of whole tablets.

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Method

The aim of the study was to present whole, coated tablets to the analyser to determine active level, then to perform a series of analyses on a batch of tablets to provide information on the uniformity of the batch. Using the system described below, the samples are presented horizontally to the spectrometer and a masked beam illuminates each sample with a spot diameter of 6 mm. The power of the beam at the sample position is relatively low (ca 200 mW) in order to avoid unwanted heating problems in the tablet, which could interfere with results.

The tablets to be tested were 350 mg in weight, ca 12 mm in length and ca. 5-mm thick. Using the NIR transmission approach, it is important to present the sample to the instrument in such a way as to minimize stray radiation from the instrument passing around the side of the sample and going onto the detector. To overcome this potential problem, special custom tablet holders may be fabricated to ensure a tight fit between tablet holder and tablet. An illustration of the sample holders is shown in Figure 1.

The Spectrum™ One NTS FT-NIR spectrometer was equipped with the Tablet Autosampler sampling system. The system includes detectors for both transmission and reflectance measurement, and an automated sample wheel for batch measurements (Figure 2). Dedicated detectors allow for optimized operation for this potentially demanding measurement. The method development and system integration software (AssureID™ version 2) provides simple construction of methods which can be easily readied for effective push-button operation in the plant (Figure 3). Given the method is generally used by users in a production environment numerous system design features in both software and hardware are oriented towards more robust methods – from sample presentation to the software workflows designed to minimize the likelihood of operational errors.

Figure 1: Tablet holder for NIR transmission measurements.

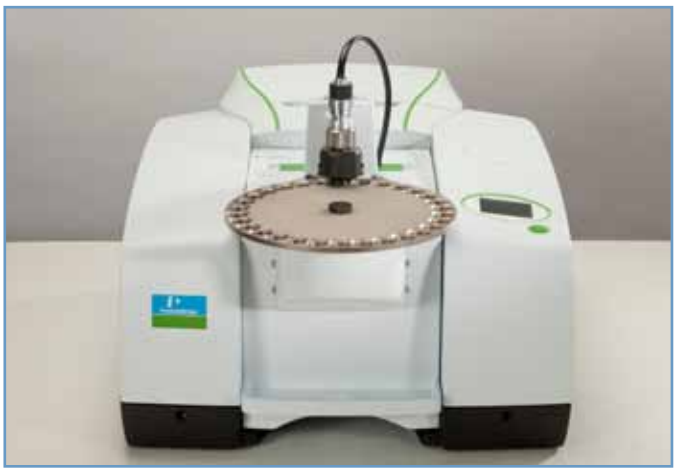

Figure 2: Frontier NTS tablet autosampler system.

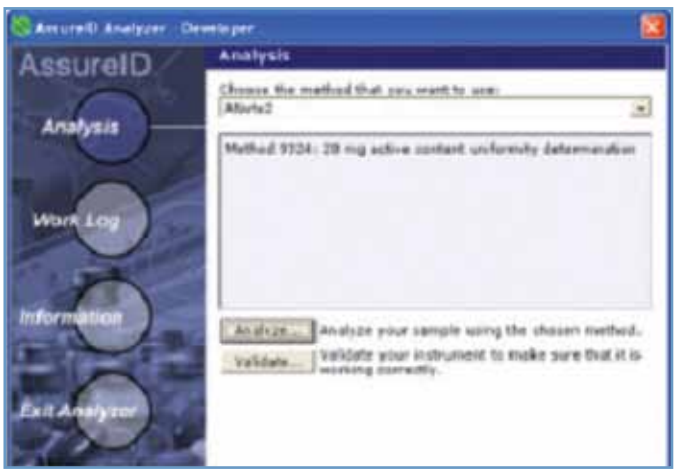

Figure 3: AssureID software for tablet analysis automation.

Calibration

When setting up the system for analysis, it is necessary to calibrate the system using a training set of samples which span the target assay value – usually 80-120% of target value is chosen. This can sometimes be the slowest part of the system implementation as it can be difficult to obtain samples which are so "off-spec," especially for mature processes. Hence it is often most effective to implement this technology earlier in the product lifecycle in the formulation development or scale-up stages when a wider range of calibration tablets is more likely to be at hand.

The target concentration for this product was 20 mg per 350-mg tablet. To generate the calibration, samples ranging from 16-mg content to 24-mg content were scanned and the Quant+ quantitative software application used to generate the calibration equation relating the spectral changes to the concentration values. The Quant+ software offers a full suite of diagnostics to help optimise the calibration before incorporating the model into the analysis workflow. For this study, it was found adequate to use a sample training set, a calibration set of 20 samples and to test the model with 68 independent samples, spanning the same concentration range (validation set) were used. Calibration details are shown in Table 1.

When the primary property of interest is chemical composition such as active content, there are some steps that can be taken to improve the robustness of the method to operator and/or sampling variability. For example, the choice of using derivative spectra for the analysis can considerably improve the robustness of the calibration with respect to sampling variations such as tablet height position and for this method it was found that a smoothed second derivative approach worked well. It is a very simple operation in Quant+ to switch-on various forms of data pre-treatment and to view the effects on the calibration performance. The calibration model used and certain sampling precautions are key factors in determining the ultimate robustness of the method in everyday use and, as a rule, extra care taken at this stage is easily paid back in terms of the reliability of the final method.

Relevant instrument data collection parameters for optimum results for this sample set are shown in Table 2. For the batch calculations, 10 tablets were placed into the tablet holders which in turn were mounted onto the wheel. It is also advisable to generate a tablet presentation SOP to ensure correct positioning of the tablets into the autosampler between different operators. The AssureID software allows users to display their own SOP prior to analysis. This can contain product-specific information which is linked to that particular method.

Number of calibration samples	20
Number of validation samples	68
Calibration algorithm	Partial least squares (PLS1)
Data pre-processing	2nd derivative, 25 point smooth width
Number of PLS factors	2
Standard error of calibration (20 samples)/mg	0.8
Standard error of prediction (60 samples)/mg	0.9

Table 1: Quantitative calibration details.

Scan range/cm^{-1}	12000-8500
Resolution/cm^{-1}	16
Scan time/per sample	60 sec
Scan time per batch	10 min
Apodization	Strong
Background reference	Open beam

Table 2: Instrument details for tablet assay measurement.

Results and Discussion

For this analysis, batches of 10 samples were analysed using the PLS1 method outlined above and simple batch statistics including the mean assay value, standard deviation, and minimum and maximum batch values were calculated and output to the reports and secure database. The database may be queried within the AssureID application to show result trends, revealing important information about the process. An example plot is shown in Figure 4. A typical output from a query is shown in the figure below. Individual records may also be examined, tracing calculated results to associated instrument conditions, spectra and system check results, Figure 5.

This kind of display provides useful information on a number of important process issues, assisting the overall understanding of the process:

- Potency drift during the run of the tablet press
- Potency variability between runs on a tablet press
- Potency variability between tablet presses
- Potency variability with differing blending conditions
- Direct comparison with HPLC assay values. In general due to the much faster and more representative NIR analysis it is possible to obtain trend plots with far more data points than the corresponding HPLC trend plots.

This kind of information is beneficial not only from the point of view of improved understanding of the blending/pressing from the point of view of potency, but can be extended to provide similar information on other ingredients, and in favourable cases some physical properties such as coating thickness and hardness – with no significant impact of on batch analysis time.

Next, it is envisaged tablet analysis will be extended to the following:

- Other matrix components.
- Physical properties such as hardness and/or coating thickness.
- Powder blends before tablet pressing. This will be possible by extracting sample from the blender using a sample thief and pressing the blend into wafers prior to NIR transmission analysis.
- Other uncoated tablets where moisture will be measured in addition to active. Moisture will be measured by reflectance and active content by transmission.

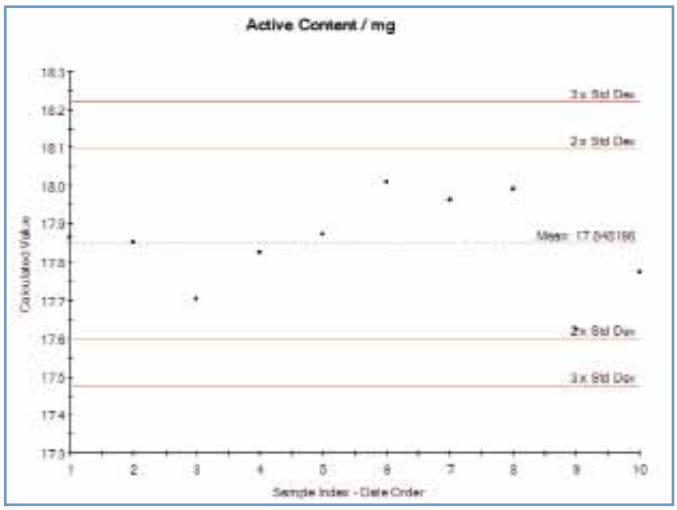

Figure 4: Trend display showing variation of potency within a batch.

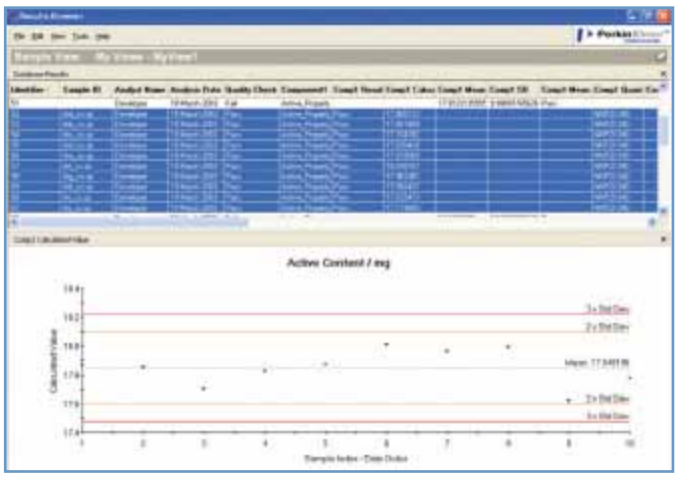

Figure 5: Tablet analysis database display.

As the technique becomes more accepted by the industry, it is expected that more "calibration-free" approaches will be adopted in tablet analysis. Such methods skip the step of developing a model relating the spectral changes to properties of interest for a pre-analysed training set of samples and applying the model to predict properties for the samples. In this case changes in the spectra are related directly to some variability in the process. For example, the standard deviation of an isolated active peak height may be related directly to uniformity of a batch thereby eliminating the need to calibrate using samples which are already beyond the bounds of normal process variability. This approach may be easier for some products, where the active absorption in the spectrum is very clearly differentiated from the other ingredients in the spectrum. For other products, however, the distinction is less clear making it necessary to introduce more sophisticated data analysis techniques. Figure 6 shows the NIR transmission spectra of two different products. In Figure 6a, the active band is not overlapped with those of the other ingredients and simple band height measurements can be correlated directly with the potency. In Figure 6b, the active band is overlapped with the absorption of the other ingredients and for this particular product, a chemometricsbased approach worked better. The method can be run in parallel with the conventional HPLC method during the validation stage.

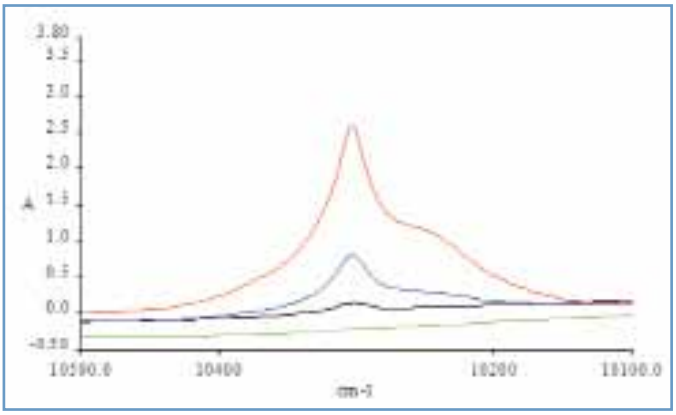

Figure 6a: NIR transmission spectra where active absorption is separated from other components in the matrix. Spectra from 0-, 10-, 50-, 200-mg strength tablets.

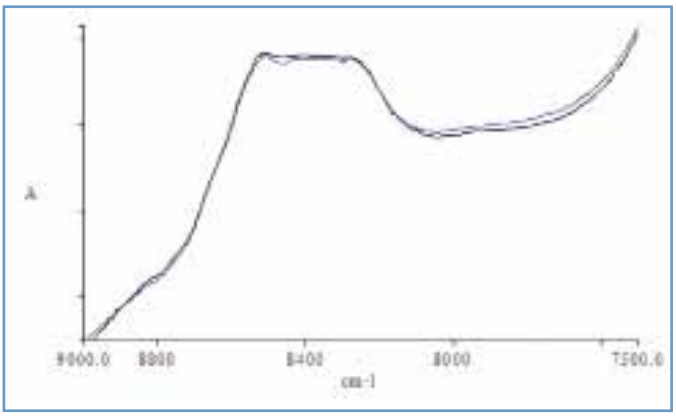

Figure 6b: NIR transmission spectra where active absorption is overlapped with other ingredients. The two traces show spectra from tablets of two strengths, ca 5 and 10% active, where the absorption due to the active indicated.

Conclusion

The use of NIR transmission for whole tablet analysis can effectively improve the efficiency of the tablet pressing step by allowing faster feedback into the process than the conventional HPLC method. NIR can be an order of magnitude faster. More analytical information per sample and more tablet analyses in a given time greatly increases process understanding.

Increasing scrutiny from the regulators and the drive for improved process understanding will ensure the technique will become more widespread. The anticipated development of official guidelines for setting up and testing NIR transmission methods in a similar manner to the NIR reflectance methods will be another factor in the growth of this exciting development.

As the pharmaceutical industry begins to realize the benefits of the new technologies for NIR testing, it will then be just a matter of time before NIR becomes established as a standard method used as commonly as mid-IR in pharmacopeial methods.

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006832A_02 Printed in United Kingdom