# Using Near-IR Spectroscopy to better understand Tablet uniformity and properties.

## 1 The significance of Tablet Uniformity

Among the FDA's top 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 industry is seeking to improve its processes is in the blending area.

One of the key measurements of product quality is the standard active content uniformity test. This provides a measure of uniformity of the blend from the assay of a number of tablets (typically 10) taken from the tablet press. The test usually involves dissolving the tablet for HPLC and only the active content is measured. However, the tablet comprises a number of other ingredients and it is known that these ingredients can impact important product properties such as dissolution, stability, bioavailability and various process-quality parameters such as hardness.

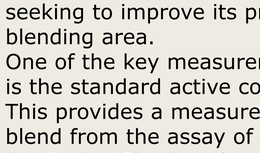
## 2 Advantages of Near-IR Measurements

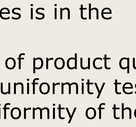
The HPLC technique used, while well established in the industry is slow, requires skilled analysts, provides little or no information on the matrix and destroys the sample.

Near-IR (NIR) now offers the possibility of performing non-destructive, whole tablet testing at much higher speed and provide more sample matrix information. It is also readily automated thus providing the potential for more and/or faster tablet testing.

NIR offers the analyst the opportunity to measure both the macro chemical properties (such as active concentration) of the tablet and also the micro structure (such as distribution of the components). Both of these properties are important in determining the behaviour and consistency of the product.

## 3 Macro NIR Analyses





Individual Tablet Holder for Transmission measurement

**Figure 1 Spectrum 100N with Tablet AutoSampler**

The Spectrum 100N with tablet autosampler measures transmission spectra through the whole tablet and can be calibrated to provide quantitative values for the active (API) concentration within each tablet.

## 4 Uniformity of API in Tablet Batch

Using the system shown in Figure 1, a series of reference tablets were analysed to develop a suitable calibration for the measurements of the API concentration. The concentration range of these standards covered 80-120% of the target value. The tablets to be tested were 350mg in weight, 12mm in length and 5mm thick. The wavelength range was 12,000-8500cm$^{-1}$ with a resolution of 16cm$^{-1}$. Each tablet was analysed for 30 seconds. The calibration and subsequent analysis of the batch tablets was carried out using AssureID Software.

Ten samples from a typical batch were analysed using the method outlined above and simple batch statistics including the mean assay value, standard deviation, minimum and maximum batch value were calculated and output to the reports and secure database.

The database may be queried within the AssureID application to show results trending, to reveal important information about the process, an example plot is shown in Figure 2.

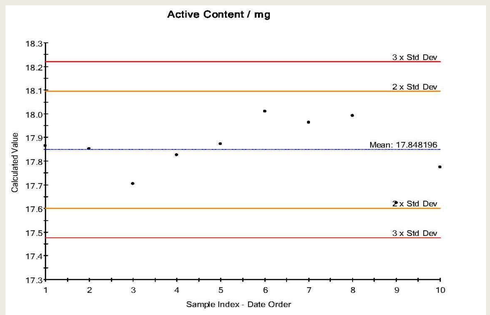



**Figure 2 Trend display showing variation of potency within a batch**

This kind of display provides useful information on a number of important process issues.:

Potency variability

- during the run of the tablet press
- between runs on a tablet press
- between tablet presses
- with different blending conditions
- correlation with variation in physical properties such as solubility and stability.

The information can also be used in direct comparison with HPLC data but since the NIR data can be collected much faster and easier it is possible to obtain trend plots with much more data points.

## 5 The Microscopic structure of tablets

The properties of a tablet are not only determined by the overall composition of the ingredients but also on the size and distribution of both the actives and the excipients. Until recently little has been known about the distribution of ingredients in tablets and yet a better understanding of this parameter is paramount to a greater understanding of the properties and potency of these products.

NIR microscopy and imaging offers the analyst the opportunity to study the microscopic distribution of the various ingredients in a tablet and relate this information to tablet properties such as dissolution.

The Spotlight 400 Imaging system (Figure 3) allows data to be obtained from areas measuring 6.25x6.25 or 25x25 or 50x50 microns across the surface of the tablet and displayed as a NIR image. From these images it is possible to calculate and display the relative distribution of the various ingredients.

**Figure 3 Spotlight 400 NIR Imaging System**

Tablets were placed on a glass microscope slide and a flat surface was analysed by simple diffuse reflectance. A typical area of 5x5 mm was analysed at a pixel resolution (spatial resolution) of 25x25 microns. The wavelength range was 7500-3600cm$^{-1}$ at a spectral resolution of 16cm$^{-1}$. The total analysis time was 15 minutes. A Total NIR reflectance image is shown in Figure 4a. Each 25x25 pixel has an associated spectrum (Figure 4b) and there are ~ 37,000 spectra in each image.

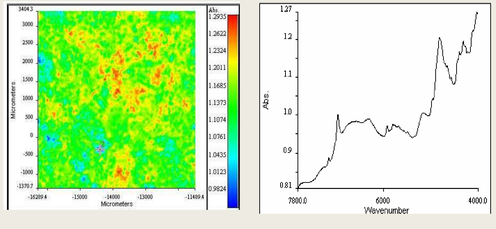



**Figure 4 NIR Reflectance Image and typical reflectance spectrum**

## 6 Uniformity and aggregate size at a micro scale

Using the NIR imaging technique it is possible to compare component distribution in good and poorly blended tablets. Figure 5 shows distribution of active (red colour) in a series of tablets. The top row shows tablets with good blending whereas the bottom row shows poor blending.

It is also interesting to note that the original particle size of the active was ~11 microns whereas even in the well blended tablets the average aggregate size is ~ 200 microns. In the poorly blended sample the aggregate sizes go up to ~ 400 microns.

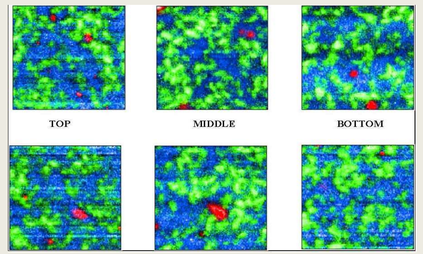



**Figure 5 Chemical images of active distribution**
**Top row shows good blend distribution**
**Bottom row shows poor blend distribution**

## 7 Macro and micro NIR Tablet analysis

To get a full understanding of the uniformity and ingredient distribution of a tablet it is possible to configure the NIR Spotlight system to have both the macro sampling capabilities using the automated tablet analyser and also micro sampling using the imager.

The analyses in this poster are discussed in more detail in the following application notes available from PerkinElmer:

- Whole Tablet Analysis
- Analysis of Solid Dosage Forms

## 8 Conclusion

NIR Spectroscopy is an ideal spectroscopic technique for the study of tablet uniformity and microscopic ingredient distribution. It is a faster and easier technique than HPLC and can give vital information about the concentration, the domain size and the distribution of the constituents.

This information can be related to physical properties of the tablets such as dissolution and stability and help in improving process-quality parameters.

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