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Use of diffuse reflectance Fourier transform near-infrared spectroscopy to confirm blend uniformity

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Abstract

Diffuse reflectance Fourier transform near-infrared (FT-NIR) spectroscopy was investigated as a tool to monitor the integrity of production blending processes. Laboratory blends were used to produce calibration samples for two different products. The calibration models derived from these blends were then used to predict the contents of real production samples for the respective products. The results of this study demonstrate that FT-NIR is a good approach for in-process confirmation of blending. The excellent sample interrogation provided by FT-NIR was deemed critical for this application.

Introduction

For pharmaceutical manufacturers who produce solid dosage forms, mixing or blending processes are critical. It is the blending step that assures the resulting dosage forms will be uniform.

Blending validation has been a critical issue for many years. This is the procedure by which a given mixing process is tested to make sure it is suitable for its intended purpose – the production of a uniform blend. Both incomplete blending (blending time cut short) and over-blending (blending time prolonged) can be detrimental to the final product. The Food and Drug Administration requires that these validation experiments be performed. Many companies are, however, going beyond this requirement by implementing routine procedures to monitor blending. Such procedures ensure that the process proceeds correctly every time it is performed. Such a step can help to control production processes, thereby avoiding problematic issues with products before they occur.

Fourier transform near-infrared (FT-NIR) spectroscopy is a useful means of in-process monitoring that offers many advantages. It is easy to use and requires no sample preparation. Therefore, it can be used at-line away from the laboratory by production personnel, and it allows practitioners to avoid the use and disposal of hazardous chemicals. It also provides rapid sample testing via faster feedback of process data. This allows more timely decisions and optimizes production time and equipment usage.

The applicability of the FT-NIR technique for monitoring the blending of proprietary products is described in this paper. The work is based on a quantitative calibration with laboratory mixtures. The predictions were made on real production samples.

Figure 1: Antaris FT-NIR method development sampling system.

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Experimental

Samples: The raw materials were supplied by a proprietary source and were used as received to produce calibration samples. Production samples representing two distinct products were received from this same source. A second set of production samples (Product 2 only) were received for testing four weeks after initial method development. These latter samples were analyzed to test the intermediate precision and stability of the method.

Instrumentation: The FT-NIR measurements were performed on a Thermo Scientific Antaris™ FT-NIR analyzer (Figure 1)using the integrating sphere module.

Sample Preparation and Measurement: The calibration samples were prepared by weighing the appropriate amounts of materials on a five-place balance and transferring them into 2-dram vials to achieve the weight percentages listed in the Tables 1 and 2. The sample compositions ranged from 40% to 60% for each major component. The admixtures were then shaken thoroughly using the aid of a mechanical mixer for about 10 seconds. They were further mixed by hand-tumbling. The production samples and samples of the raw materials were transferred to individual 2-dram glass vials. All of the samples were then analyzed without further preparation by placing each of the vials directly on the integrating sphere and measuring through the bottoms of the vessels. Each calibration sample was analyzed in triplicate.

Sample #	% Component 1	% Component 2
1	64.13	35.87
2	59.44	40.56
3	51.69	48.31
4	47.87	52.13
5	42.73	57.27
6	35.26	64.74

Table 1. Composition of calibration samples for Product #1.

Sample #	% Component 1	% Component 2	% Component 3
2-1	63.85	35.17	0.98
2-2	58.01	41.09	0.90
2-3	51.96	47.08	0.96
2-4	47.14	51.78	1.07
2-5	40.44	57.98	1.58
2-6	35.15	64.01	0.84

Table 2. Composition of calibration samples for Product #2.

Product #1 contained two components. The calibration samples were prepared according to Table 1. Product #2 contained three components. Calibration samples for this product were prepared according to the information in Table 2. Component #2 is the same for both product mixtures.

Spectroscopic Parameters: The parameters used for data collection are tabulated below.

Spectroscopic Range: 10000 to 4000 cm^{-1}

Resolution: 8 cm^{-1}

Number of Co-averaged Scans: 32
(24 second collection time)

All data were collected with the cGMP-compliant Thermo Scientific RESULT™ software. The instrument performance was qualified prior to use with the Thermo Scientific ValPro™ system qualification software. This software utilizes an internal validation wheel with NISTtraceable standards to assure consistency in the photometric response of the equipment. Also in the wheel is a NISTtraceable polystyrene standard to confirm band position accuracy. ValPro also measures noise, energy ratios and short and long term stability. An internal gold flag was used for background collection. This approach is advantageous because 1) the background medium is protected for long term stability and 2) unlike Spectralon®, which is commonly used for FT-NIR background measurements, gold has no discernible spectral features in the NIR region.

Chemometric Processing: The chemometric processing was performed using the Thermo Scientific TQ Analyst™ chemometric software package. All of the data were mean-centered and then converted to their respective second-derivative spectra prior to the development of calibration models. This was accomplished using a Norris derivative with a 9-point segment and no gap. Derivatization is one option typically used to remove multiplicative scattering phenomena common in NIR measurements. Scattering generally does not contribute relevant information to the measurement of interest. The first derivative normalizes the spectral offset while the second derivative normalizes the baseline slope. After derivatization of the data, calibrations were constructed using Stepwise Multiple Linear Regression (SMLR) and Partial Least Squares (PLS) regression models.

Results and discussion

Product #1: Figure 2 shows the spectra for the calibration samples for Product #1 prior to derivatization. Figure 3 shows the spectra following the derivative processing. Also shown with the second-derivative spectra are the spectra for the raw materials. It should be noted that absorbance maxima become minima with secondderivative transformation.
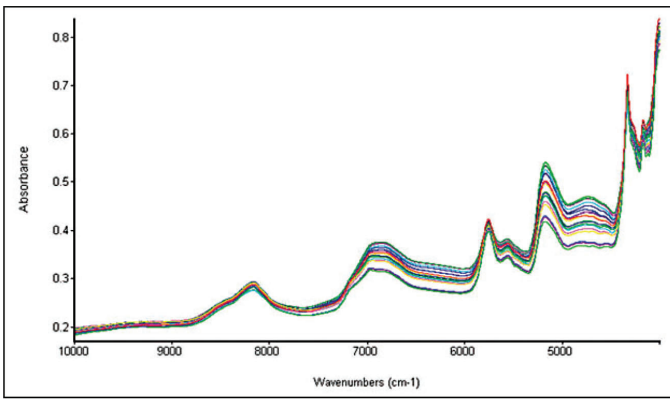
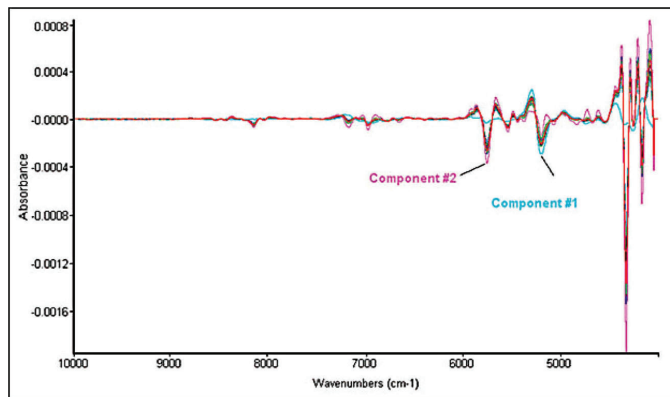Figure 2. Unprocessed spectra for Product #1 calibration samples.

Figure 3. Second-derivative spectra of Product #1 samples and raw materials.

For this product, SMLR calibration equations for thecontents of both components were found to be adequate.The use of simple SMLR models in a feasibility study isgenerally desirable because few calibration samples are typically available. In this case, the fact that the matrix issimple also makes SMLR an attractive choice. A simple modelthat yields good correlation and good predictive ability normally portends success for these types of applications.

Single data points were used to construct the models for the contents of both components. The region used for the calibrations is shown in Figure 4. In this case, since there were only two components, one data point (5438 cm^{-1}) was adequate for producing calibration models for both. This is a
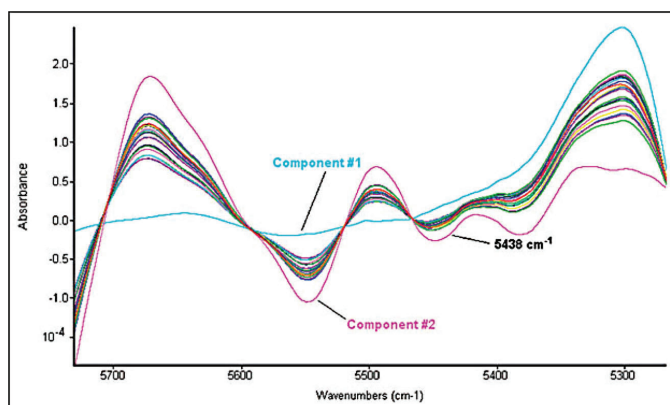

Figure 4. Region of interest for Component #2 calibration.

reasonable approach because the absence of one component indicates the presence of the other. The correlation coefficient for both models was 0.9918 and the Root Mean Square Error of Calibration (RMSEC) was 1.24. This statistic is comparable to one standard deviation across the entire calibration range. Figure 5 shows the calibration plot.
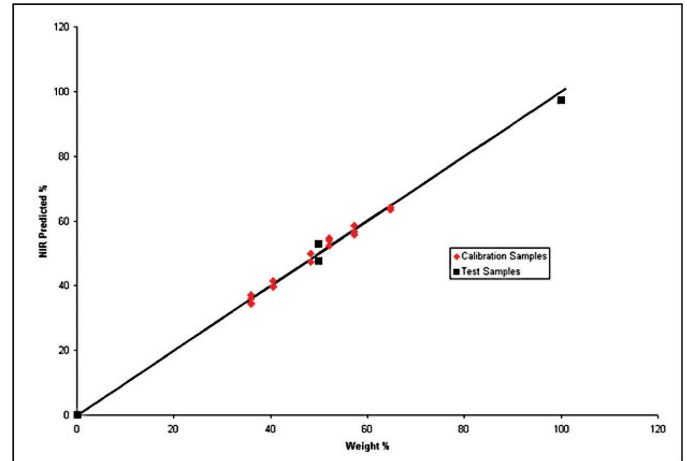

Figure 5. Calibration plot for the Product #1 data.

Predictions of two production samples are represented on the plot in Figure 5 ("Validation" samples found in the middle of the plot). The model predicted that the two samples represented on the plot contained an average of 49.7% component #1 and 50.3% component #2. This agrees well with the theoretical contents of 50% for each component. Also shown are predictions of the extreme samples of 100% component #1 and 100% component #2 (noted as "Validation" samples at the extremes of the plot). The fact that these samples are predicted well with the component #2 equation (-0.154% and 97.1%, respectively) indicates that the method is linear over a large range. This suggests that the calibration can account for cases in which unexpectedly large deviations in the sample content might occur. This also gives further confidence that a calibration model constructed for this application will be rugged.

Method precision and sample precision were the aspects of greatest interest. The precision of the instrument was determined by measuring one of the production samples six times without moving it between analyses. The average of these measurements was 46.0% component #2 with a relative standard deviation (RSD) of 0.67%. The sample precision was then determined by measuring a different production sample twelve times. The sample was shaken between each measurement to re-orient the contents of the vial. The average of these measurements was 52.8% component #2 and the RSD was 6.9%. The range of these measurements was 48.7 to 56.6% content for component #2.
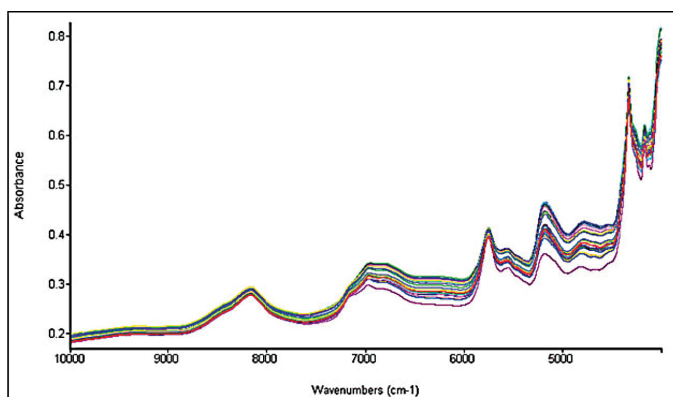
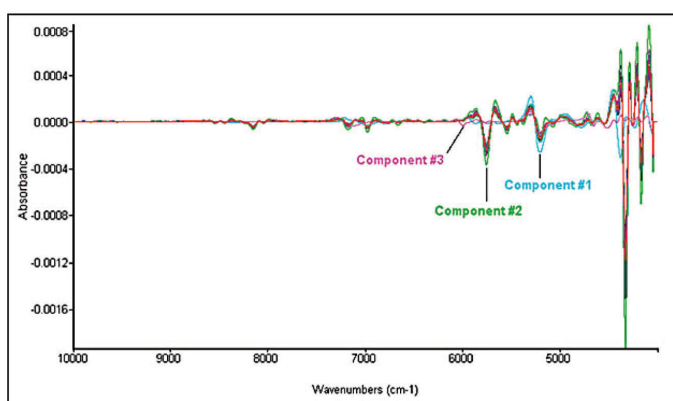Figure 6. Uncorrected spectra for the Product #2 calibration samples.

Figure 7. Second-derivative spectra of Product #2 calibration samples and raw materials.

The data indicate that the predictions for the production samples using the model for component #2 gave the results that were anticipated. The instrument precision was very good, however, the discrepancy between the instrument precision and the sample precision suggests that there is ten times the variability in the sample relative to the measurement variability. This indicates that Product #1 exhibited significant variability within the sampling area with each FT-NIR determination. The non-destructive nature of FT-NIR provides an excellent opportunity to measure the lot-to-lot consistency of a product as the RSD from one production event to the next should be constant. This could be used as a primary criterion for the determination of blend uniformity. As an in-process check, an RSD criterion could be used to indicate that the end-point has been reached. Failure to reach a specified RSD might suggest a problem.

Product #2: Figure 6 shows the spectra for the calibration samples for Product #2 prior to derivatization. Figure 7 shows the second-derivative plots for the calibration samples and the raw materials.

For Product #2, a PLS method was needed to produce adequate results. This was probably due to the additional complexity of this blend compared to Product #1. The region from 5200 to 6500 cm-1 was used to generate both calibrations. While good SMLR calibration models could be produced for component #2, an SMLR approach was not particularly good for the calibration of component #1. The PLS models for the two components each required four factors. Component #3 was essentially constant and, therefore, no calibration was constructed for this material. The number of factors is high considering the number of calibration samples but the predictions for the production samples using these models appeared good. Another indication of the validity of using four factors for this calibration is the good predictive ability for the samples with extreme component content (100% component #1 and 100% component #2).

For the component #1 calibration, the correlation coefficient was 0.9990 and the RMSEC was 0.434. The correlation coefficient for the component #2 calibration was 0.9993 and the RMSEC was 0.377. For the measurement of component #1, the instrument precision for six replicate determinations was 0.089% and for component #2 it was found to be 0.072%.

One set of production samples was measured to test the calibrations at the time they were developed. Another set of production samples was received about four weeks after the development of the method to test the intermediate precision and stability of the calibrations. The latter sample set was received in two portions (part a and part b). The predictions of the production samples are shown in Table 3. The samples were taken from different points (top, middle and bottom) in the blending vessels for these production lots. The data reported are the results of duplicate measurements. The reasonable results obtained for the samples of the component raw materials indicate good predictive linearity for these calibration models. This suggests that extrapolation is possible, which in turn, indicates good method ruggedness.

Sample ID	% Component #1 prediction	% Component #2 prediction
Sample 1 Top	47.6	51.2
Sample 1 Middle	47.9	51.0
Sample 1Bottom	48.0	50.8
Sample 2a Top	53.4	45.5
Sample 2a Middle	49.2	49.6
Sample 2a Bottom	53.7	45.2
Sample 2b Top	52.3	46.6
Sample 2b Middle	48.8	50.2
Sample 2b Bottom	50.6	48.3

Table 3. Prediction results for calibrations made for Product #2.

The predictions listed in Table 3 indicate that the predicted values for components #1 and #2 consistently add up to 98.8 to 99.0% based on the use of independent calibrations. This is consistent with the fact that these two components make up about 99% of the mixture while component #3 composes about 1% of the blend.
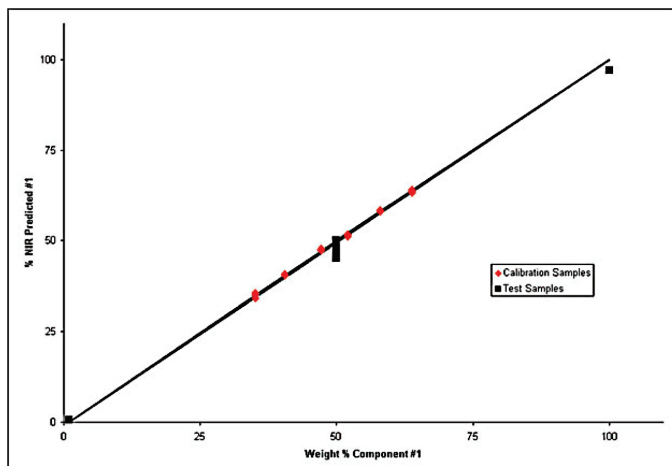
Figure 8: Calibration plot for Component #1 in Product #2.
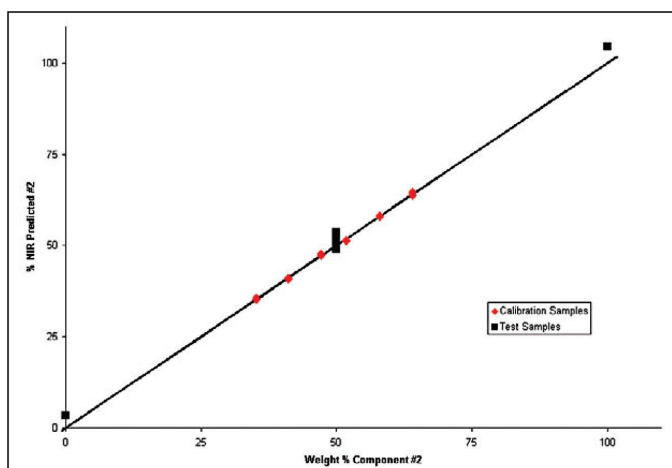

Figure 9: Calibration plot for Component #2 in Product #2.

Figures 8 and 9 show the calibration plots for the two components, respectively. The samples used for the precision test are represented as "Validation" samples. Also represented on the plot are predictions for the raw material samples.

The calibrations for Product #2 yielded accurate and precise results. The predictions for the production samples were in the expected range. The instrument precision was excellent (less than 0.1%), indicating there was significant variation in the sample data relative to the instrument precision. Just as with the first product formulation, the data indicate that FT-NIR can be used to monitor the content variance in Product #2. In-process monitoring can be done at-line if rapid feedback is needed.

Conclusions

The Thermo Scientific Antaris FT-NIR analyzer is an excellent tool to measure the progress of blending processes. The models presented in this study yield predictions that are precise and give accurate representations of true batch variability. Because the Antaris FT-NIR analyzer allows representative sampling, it is a good tool for fast and accurate blend uniformity confirmation in a process environment. This work suggests that calibration samples can be prepared from laboratory blends for these two products, which is not possible with many products.

The data were collected using an older model instrument Antaris FT-NIR. Currently, Thermo Scientific offers an improved model, the Antaris II FT-NIR, which offers superior speed and performance over its predecessor model.

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