APPLICATION NOTE

FT-NIR Spectroscopy

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Verification of Pharmaceutical Raw Materials Using the Spectrum Two N FT-NIR Spectrometer

Introduction

Near-infrared (NIR) spectroscopy is an important technique for materials checking at various stages of the manufacturing process, but is particularly useful at the raw materials inspection stage. Raw materials come in a variety of physical forms including liquids, gels, and solids, requiring a versatile instrument with convenient, interchangeable sampling modules to cater to the entire range of raw materials encountered.

Rapid identification of a material by its NIR spectrum can be achieved by comparison against a series of reference spectra for that specific material, requiring the material to be both identified and discriminated from similar materials.

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This application note describes how the Spectrum Two N™ FT-NIR spectrometer can be deployed using a workflow approach, suitable for a regulated environment, to overcome a range of different challenges in raw material identification while also meeting the stringent requirements of 21 CFR Part 11 compliance. NIR spectroscopy is a good technique for raw material identification of solids, allowing faster and easier sample measurements than other analytical techniques such as Raman. No sample preparation or dilution is required, and the measurements can be performed directly through glass vials or Petri dishes using a Near Infrared Reflectance accessory, such as the NIR Reflectance Module (NIRM) on the Spectrum Two N, shown in Figure 1.

Figure 1. Spectrum Two N with NIR Reflectance Module.

The NIRM has significant performance advantages over alternative integrating sphere accessories:

- Mirror-based collection gives tight control of optical geometry, high collection efficiency, large depth of field, and can be manufactured very consistently, improving method transferability to other instruments
- Illumination beam optics provide excellent spectral uniformity across the beam
- Tighter control of (and thus lower) stray light from window and sample containers
- Stable and protected internal reference material
- Stray light and reference correction to ensure that the spectrum obtained contains only spectral features from the sample

The NIR spectral bands of materials are due to the combination and overtone bands derived from the fundamental vibrations in the mid-infrared region of the spectrum, and are still unique fingerprints for that material. Spectra of three of the raw materials are shown in Figure 2. These fingerprints allow for identification of the material by comparison against a series of reference spectra using an appropriate algorithm.

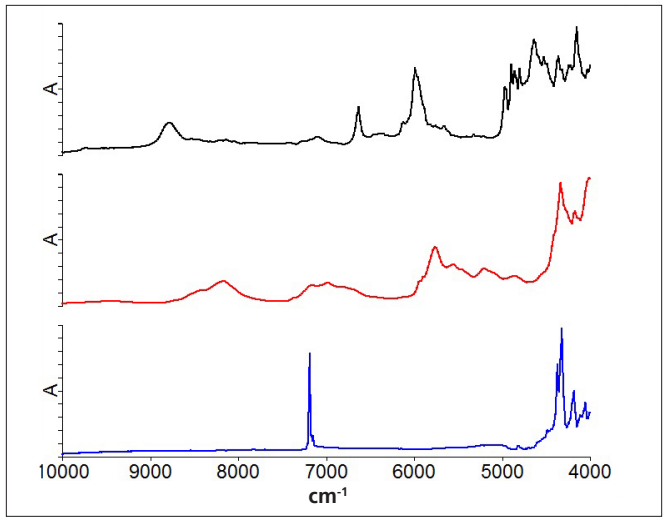

Figure 2. Example NIR spectra of raw materials. Top to bottom: diclofenac (black), poloxamer (red), talc (blue).

The Spectrum software has a range of algorithms that can be deployed, the decision typically based on the complexity of the analysis. Most standard raw material identification methods use the Compare™ algorithm. Compare will measure the correlation of an unknown spectrum against a series of reference spectra and report the closest material to the unknown (a score of one is a perfect match, a score of 0 shows no correlation between the sample and reference spectra). When analyzing materials, it is important that the analysis is focussing on the spectral features of the materials. Problems arise when calculating the similarity of spectra due to:

- Reproducibility of sampling, e.g. sample repack errors with solid sampling
- Varying baselines
- Non-uniform noise distribution

These effects can be decreased by using a number of mathematical filters that reduce the contribution where the information tends to be unreliable. The net result of these filters is to enhance material-specific spectral features while minimizing spectral contributions related to instrument, sampling, and atmospheric conditions.

Compare allows Pass/Fail thresholds based on both correlation with the reference materials and discrimination from the second-best matches in the reference materials, ensuring the correct material is identified and no false positives are obtained from other reference materials.

Soft Independent Modeling Class Analogies (SIMCA) is a chemometric approach which models the variation within the collection of reference spectra for a given material, as well as the difference between spectra of different materials. This allows SIMCA to be sensitive to small spectral differences, for example impurities, even in the presence of normal batch-to-batch or sampling variations.

For ease of implementation, either of these algorithms can be deployed using a workflow approach, an example shown in Figure 3.

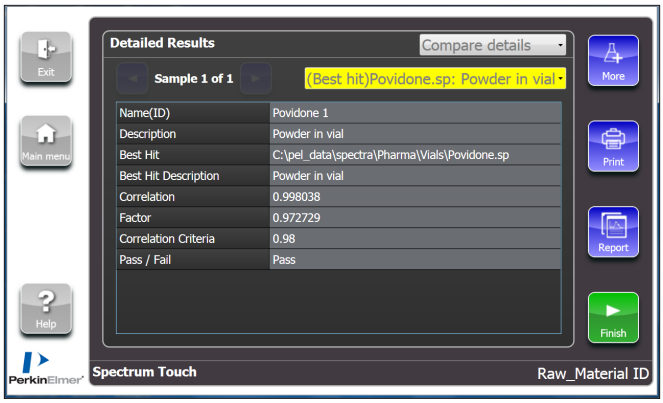

Figure 3. Example Raw Material ID result from a Spectrum Touch ES method.

The Spectrum Touch™ ES software mimics existing QA workflows, with the AssureID component guiding users through method development, validation and trending, and analysis of results. Expertise is built into the software to provide fast data modelling, troubleshooting, and method validation without prior knowledge of chemometrics. Spectrum Touch ES also meets the stringent requirements of 21 CFR Part 11 compliance.

Experiments

A range of experiments were performed representing the typical challenges encountered in raw material identification measurements. Each of these challenges will require a different algorithmic approach to the data analysis.

1. NIR Spectra of 34 chemically different solid raw materials were measured, the raw material "library" containing a small number of active ingredients (AI), the remainder being excipients. Since these materials are chemically different, their NIR spectra should be sufficiently different to allow easy identification of the material using the Compare algorithm.
2. Spectra of seven different grades of Avicel®, a microcrystalline cellulose, were measured. Since all of these materials are chemically the same, but vary in physical properties, a more powerful algorithm, SIMCA, is required to discriminate the materials.
3. Identification of an unexpected failure material. In cases where a material fails the raw material identification, further investigative analysis is required. Library searching against commercial spectral libraries is often capable of identifying

Table 1. Sample Measurements.

Parameter	Value
Instrument	Spectrum Two N FT-NIR
Sample Measurement	NIR Reflectance Module, samples in disposable vials
Spectral Resolution	8 cm^{-1}
Scan Time	40 seconds
Corrections	AVI, Atmospheric Correction, Stray Light, Reference Correction

Experiment 1. Raw Material Identification Using Compare

NIR reflectance spectra were collected for a series of 34 different powdered raw materials to be used as reference spectra library for the raw material identification method using the Compare algorithm. A series of nine independent validation spectra were collected consisting of three samples of povidone from different batches, three samples of Avicel® from different batches, and one sample of the following materials: calcium ascorbate, hydroxypropyl methyl cellulose, and magnesium stearate. These validation samples were obtained from different suppliers to the original reference set. Spectra of these five different material types are shown in Figure 4. The Pass/Fail criteria were set to a correlation value of 0.98 and a discrimination value of 0.05.

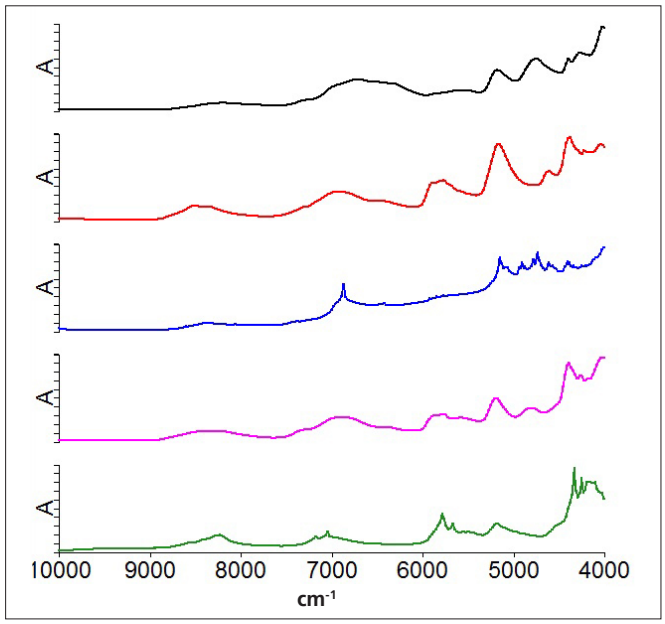

Figure 4. Spectra of validation materials. Top to bottom: Avicel®, povidone, calcium ascorbate, HPMC, magnesium stearate.

Table 2. Compare results for validation materials.

Sample Name	Identified Material	Correlation	Discrimination	Pass/Fail
Avicel V1	Avicel	0.9993	0.0922	Pass
Avicel V2	Avicel	0.9993	0.0952	Pass
Avicel V3	Avicel	0.9991	0.0948	Pass
Povidone V1	Povidone	0.9967	0.0804	Pass
Povidone V2	Povidone	0.9980	0.0723	Pass
Povidone V3	Povidone	0.9955	0.0698	Pass
Calcium Ascorbate V1	Calcium Ascorbate	0.9980	0.5913	Pass
HPMC V1	Hydroxypropyl Methyl Cellulose	0.9811	0.1534	Pass
Magnesium Stearate V1	Magnesium Stearate	0.9965	0.0842	Pass

Table 3. Compare results for repeat runs of Avicel.

SAMPLE	Avicel 1	Avicel 2	Avicel 3	Avicel 4	Avicel 5	Avicel 6	Avicel 7	Avicel 8	Avicel 9	MEAN	STD DEV
Correlation	0.99837	0.99843	0.99826	0.99836	0.99825	0.99826	0.99817	0.99819	0.99837	0.99829	9.1206E-05

All of the materials exceeded the correlation and discrimination thresholds and were therefore classed as Pass materials. Since the raw materials are chemically different, their NIR spectra and Compare are easily capable of identifying the materials.

Further method validation was performed for the material Avicel® using three batches of the same grade of Avicel® PH103. A sample from each batch was placed in a glass vial. Each glass vial was then measured in triplicate shaking the sample in the vial and replacing it on the NIRM. This represents a total of nine measurements with the results shown in Table 3.

The results show excellent repeatability with minimal variation in the results.

Experiment 2. Discrimination of Closely Related Materials

Avicel® PH is a microcrystalline cellulose product with the PH designating that it is suitable for pharmaceutical use. It has excellent compressibility and is used for tablet compression and also for wet granulation. There are several different grades of Avicel® PH – for example PH101, PH102, PH103, PH301, PH302 – that differ mainly in particle size and moisture content. Correct choice of the right grade is essential to achieve the compressibility required for tabletting or low moisture content for use with moisture-sensitive active ingredients. Since the Avicel® materials are all of the same chemical nature, their NIR spectra are almost identical making it difficult to easily discriminate the different grades. However, NIR spectra are affected by particle size and spectral features due to moisture observed.

The NIR spectra of a series of samples with different Avicel® PH grades were used to develop a SIMCA model to allow confirmation of the grade of Avicel® raw materials. Three samples were taken for each of the following grades of Avicel®: PH101, PH102, PH103, PH105, PH113, PH301, and PH302. For each of the three samples, triplicate measurements were made on the NIRM, representing nine spectra per grade and a total of 63 spectra total for the seven grades. The spectra of all of the samples are shown as Figure 5.

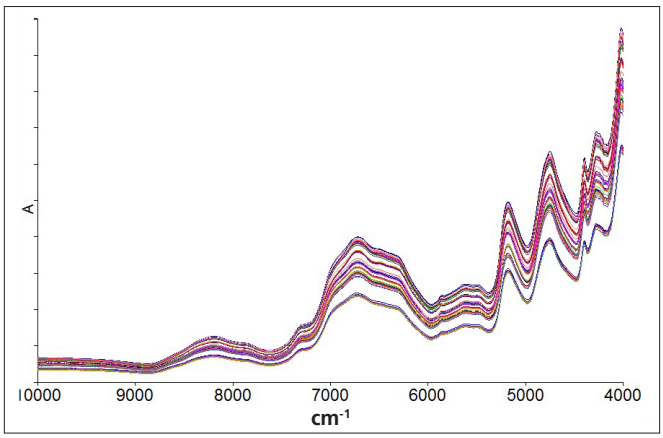

Figure 5. Spectra of Avicel® samples.

The Compare algorithm correctly identified all of the materials as Avicel®. However, it was not able to discriminate between the different grades with all grades exceeding the Pass/Fail correlation limit. SIMCA uses a chemometric approach to spectral modelling and is capable of accounting not only for the differences between different materials, but also for the variability within the same material due to batch differences. The 63 spectra of the Avicel® samples were input into a SIMCA method to try to separate out the different grades of materials, the resultant score plot shown in Figure 6.

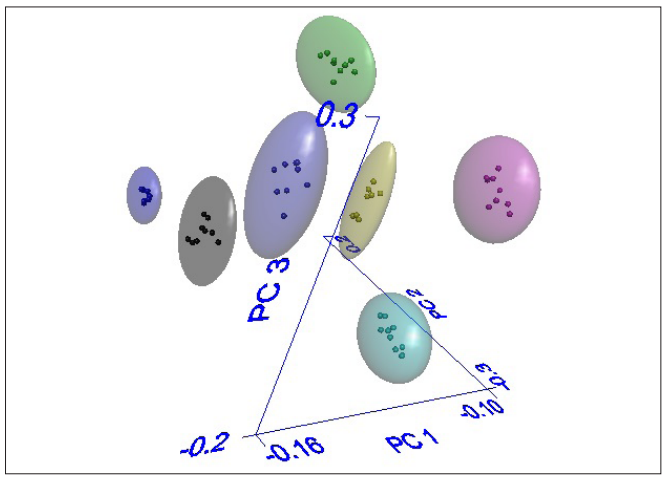

Figure 6. Principal Component scores plot showing separation of Avicel® grades.

Each of the spheres in the plot represents the data from each of the Avicel® grades; the further apart the spheres (larger intermaterial distance), the better the chance of discrimination. A Coomans plot, as shown in Figure 7, shows the model distances between two classes of material – in this case, Avicel® PH101 and PH102 exhibit clear separation. In this model, there are no overlaps between the grades, meaning there is less chance of misclassification.

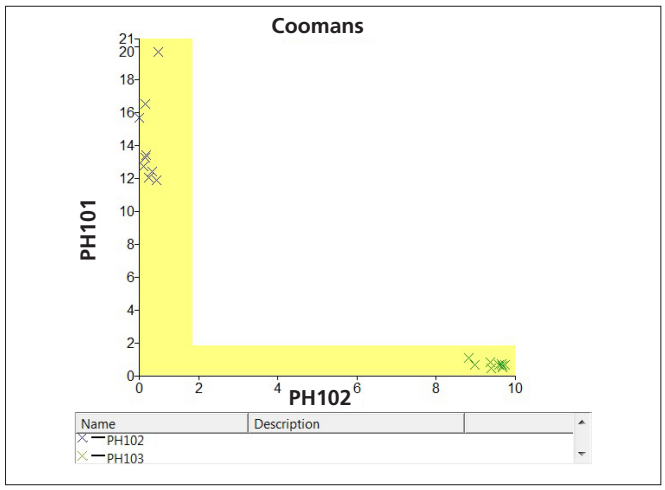

Figure 7. Coomans plot showing separation of classes of materials.

This experiment demonstrates the power of the SIMCA algorithm, which is capable of distinguishing between chemically identical substances having different physical properties. In this example, SIMCA successfully separated seven different grades of Avicel® in which the grades differed only in particle size and moisture content. The Compare algorithm was capable of correctly identifying the samples as Avicel® but was unsuccessful at distinguishing between the different grades.

Experiment 3. Identification of an Unexpected Failure Material

Occasionally, an NIR raw material analysis can result in a failure requiring further investigation. This can occur, for example, when a new supplier is selected for a particular raw material or, in extreme cases, where the wrong material has been supplied. Thankfully, this is a rare occurrence, but requires further investigation and correct identification of the suspect material. Commercially available pharmaceutical NIR spectral libraries are available containing over 1300 spectra of pharmaceutical excipients, drugs or active substances, and other supporting chemicals used in the pharma industry. Using these spectral libraries with a library search algorithm allows for identification of unknown materials.

An unlabeled powder material was tested in a glass vial using the NIR Reflectance Module. The NIR spectrum collected was tested using the Compare set of 34 reference standards described earlier in this application note. The sample failed the Compare analysis with the best hit being dextrose with a Compare score of approximately 0.48, well below the acceptance threshold of 0.98 as shown in Figure 8.

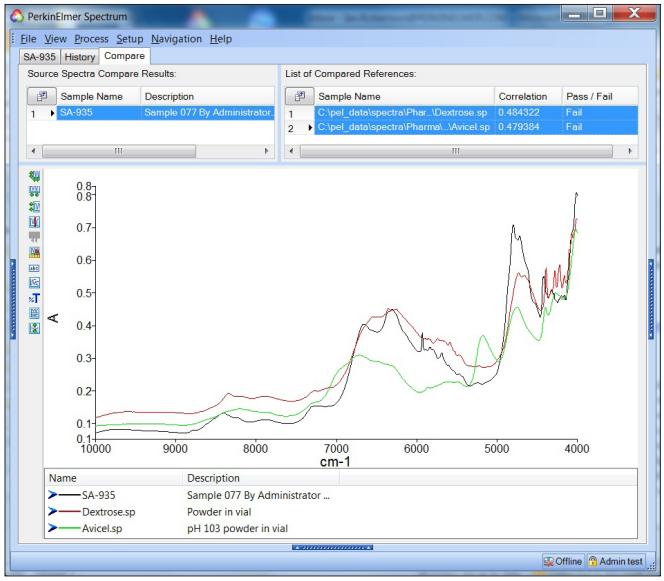

Figure 8. Compare results from suspect sample.

The same spectrum was then analyzed using the Search algorithm comparing the unknown against the NIR Pharma database from ST Japan, containing 1340 spectra. Using the Search algorithm, the material has been correctly identified as mannitol with a Search score of 0.99 as shown in Figure 9.

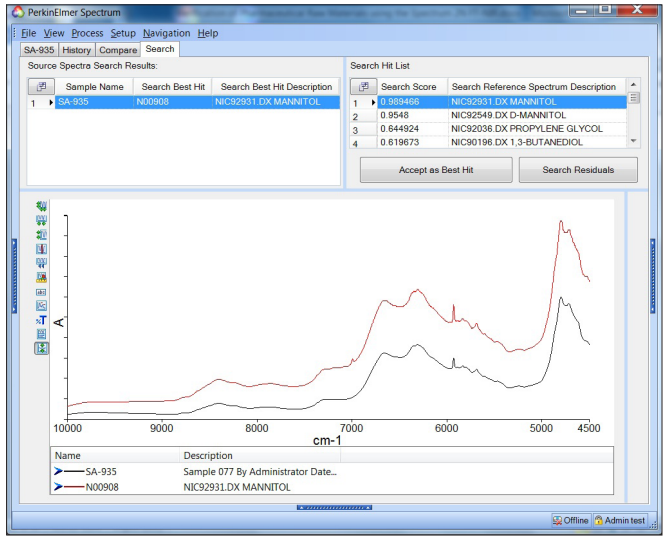

Figure 9. Search result identifying the material as mannitol.

Conclusion

NIR spectroscopy has shown to be a fast and easy technique in the pharmaceutical industry for raw material identification. Materials can be measured within seconds using sampling techniques, such as NIR reflectance in glass vials, which require no sample preparation. NIR spectra are specific to the material being analyzed, allowing samples to be tested against databases of standard reference spectra. A choice of algorithms allows for the analysis to be applied to routine identification of chemically different materials, advanced analysis of very similar materials, and identification of unknown materials. All of these approaches are available using a workflow approach to method building and running using Enhanced Security™ (ES) versions of the software to facilitate 21 CFR Part 11 compliance.

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