Application note

Raw materials qualification within a workflow: FT-NIR analysis using the Antaris II Analyzer

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Keywords

Antaris II, FT-NIR, PAT, raw materials

Abstract

In this case study, we demonstrate the incorporation of the Thermo Scientific™ Antaris™ II FT-NIR (Fourier transform near-infrared) Analyzer into a raw material analysis program that examines both the physical and chemical properties of supplied materials. This study is representative of a model for a front-end Process Analytical Technology (PAT) application where analytical information about materials is collected and analyzed throughout the product manufacturing process.

Introduction

Raw material analysis is the front end of any successful PAT implementation. Supplied materials such as API, bulking agents, lubricants, and solvents are all qualified at the point of entry into the factory to ensure finished product integrity. Analysis of these materials includes not only chemical analysis, which can differentiate compounds, but also physical analysis that can discriminate properties like density, particle size, crystallinity, flow, compressibility, and morphology.

Chemical component determination is of great importance in this type of analysis, i.e., the chemical nature of the raw material must be identified before it goes into the process. Vibrational techniques like FT-NIR spectroscopy are well-suited for this type of analysis because they are sensitive to molecular vibrations that occur at specific frequencies for specific compounds. This allows chemicals with almost any functional group important in organic pharmaceutical synthesis—alkyl, amino, thio, hydroxyl, acid, ester, etc.—to be identified unambiguously within seconds, whereas laboratory-based identification is limited by the inefficiency of traditional techniques such as titration or HPLC. In addition, FT-NIR spectroscopy is non-destructive, so the sample that is analyzed can be put into process as opposed to being discarded.

Physical properties have an equal importance in raw material qualification due to their ability to affect how materials will react to different processing conditions. Particle size is probably the most-cited example of a physical property impinging on material processability. With smaller particles, reaction rate increases which will drastically affect reaction conditions *in-situ* like batch reaction time or required heat input. Flowability, tablet compressibility, and hardness may also be affected by particle size. Morphology has a direct impact on processability because different polymorphs may have completely different solubilities and or stabilities.

In the current case study, several branches of a raw material analysis protocol are examined within the framework of an automated workflow. Material discrimination and particle size analysis are accomplished in sequence without the need for specialized operator training. At the heart of this analytical program are the Antaris II FT-NIR Analyzer (Figure 1) and Thermo Scientific™ RESULT™ Software. The Antaris II is a rapid, non-destructive analyzer that is capable of discriminating hundreds of classes of compounds without removing them from their respective packaging. RESULT Software allows for seamless integration of near-infrared spectroscopy into highly-regulated process environments without the need for any spectroscopy experience.

Figure 1: Antaris II FT-NIR Analyzer.

The workflow

RESULT Software is based on the idea of a workflow, a pre-programmed, customizable macro that allows maximum flexibility to accomplish analytical tasks in both the lab and the warehouse. The basic unit in the workflow is an event. Events can be as simple as a delay or a spectral collection or more complex like events that incorporate logic to automate decision-making. The raw material analysis in the current study uses a moderate-scale workflow to do several tasks, all of which are critical to the integration of analytical technology into a pharmaceutical or chemical manufacturing process.

The initial event in this raw material analysis is an information input, as shown in the workflow in Figure 2. This information can be culled from several sources using the Request event in RESULT:

1. An operator typing input into a computer—usually a simple sample ID number entered directly before the material is to be analyzed
2. Bar code input usually contains multiple fields of information like material identity, manufacturer, material class, and lot number.
3. Text files can provide multiple inputs to a workflow. This is especially useful when doing several analyses in a short timeframe. One example of this is using an autosampler to identify and classify raw materials without any operator interaction.
4. Process control systems like DCS or SCADA or even inventory control systems may supply some information that is necessary to the analysis automatically without input from the user.

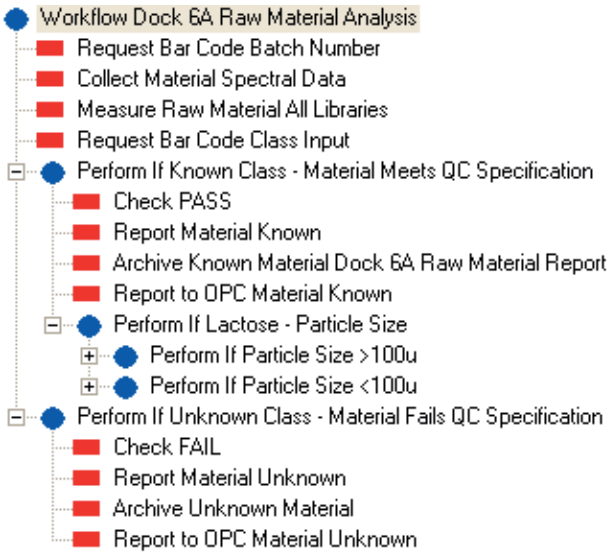

Figure 2: Raw Material ID workflow.

In the above workflow, the batch number and expected class of the material are part of a prompt that is answered using a cordless bar code reader. The bar code reader automatically incorporates the data strings into the proper spot in the Request event, and the parsed information follows the data gathered for each sample.

After the necessary information is entered, the instrument automatically begins spectral data acquisition using, in this case, a Thermo Scientific™ SabIR™ fiber bundle attached to the Antaris II. Fiber probes are excellent tools for raw material ID and purity analysis because they allow the user to bring the sampling to the sample. The SabIR probe uses diffuse reflection to sample raw materials non-destructively through the drum liner. Information about both the lining and the material contained inside is read by the instrument. For example, a polyethylene liner will have major absorptions at 4251 cm^{-1}, 4322 cm^{-1}, 5663 cm^{-1}, and 5775 cm^{-1}, but other resonances in the spectrum will be from the sample inside the liner. It is the remaining peaks that will contribute to the automatic identification of the unknown sample using the Measure event. Using an appropriate chemometric model and algorithm (see below), these polymer peaks can be effectively ignored in the analysis freeing the user from any concerns regarding the effects from the container matrix.

In the Measure event, a pre-determined algorithm compares the spectrum from an unknown sample to a set of known samples called a “Training Set.” The “Training Set” can also be referred to as the “Library.” In this raw material workflow, we are using several different libraries and quantifying the unknown spectrum against all libraries simultaneously. This provides freedom from making one singular method for all raw materials. This makes use of the “Classify Multiple” option in a Measure event in RESULT (listed in the workflow as “Measure Raw Materials All Libraries”).

Several chemometric tools are available for the analysis of near-infrared data using RESULT and Thermo Scientific™ TQ Analyst™ Software, our chemometric analysis package. There are four main qualitative algorithms useful in Near IR:

- QC Compare, Similarity Match, Distance Match, and Discriminant Analysis. These techniques provide flexibility in the type of analysis that can be used.
- The Similarity Match algorithm allows an unknown to be given a Match Value for how closely it resembles one specific class of material. If the goods-in area is receiving only starch samples, this type of analysis is excellent not only for determining whether the sample under investigation is starch but how similar to and consistent with good batches of starch it is. This allows the user to design an experiment where they can rate the purity of incoming materials in addition to simply identifying them.
- QC Compare allows the user to create an extensive library of materials using only a few standards to represent many different classes of materials.
- Distance Match works very well for materials that contain varying amounts of the same materials. A common usage for this algorithm is in identifying tablets with differing amounts of API.
- Discriminant Analysis is a principal component technique that differentiates between very similar compounds, which may also have their own internal variability. The output from this algorithm is a Mahalanobis Distance which is a vector sum of principal components that shows how close an unknown is to a class of samples.

In this application, we have chosen to do a “Classify Multiple” libraries using the Discriminant Analysis algorithm. This gives the latitude of having hundreds of different material classes spread among several different methods. The spectral variation between all the classes of different materials can readily be seen when plotting a second derivative of the raw spectral data (Figure 3). In addition, in this case, a Multiplicative Scattering Correction was applied to the data as well as a smoothing factor due to the tendency of derivatives to add noise to the data. After the principal component scores were calculated, a discriminant analysis method yielded a Scores plot showing how the different materials can be discriminated from one another (Figure 4).

Once the Measure step has been executed, the workflow uses a “Perform If” event to make a decision based on that data. If the best class match to the analyzed material is contained in the library, then RESULT will issue a PASS result. If a PASS is issued, then RESULT will continue on to archive and report this outcome to the operator as well as to the DCS using an OPC protocol.

In addition, the workflow, in this case, has been set to do a particle size analysis if the identified class happens to be lactose. This may happen in a situation where several types of lactose can enter a factory for different purposes. All lactose samples will be identified as a spectroscopic match for lactose, but particle size, a physical characteristic, manifests itself differently in the data. Oftentimes, for a particle size analysis, spectral offsets result from scattering effects that come from particle size differences. This can be readily seen by simply looking at all the relevant spectral data on a common absorbance scale (Figure 5). In addition, the data shows spectral differences from sample to sample in the second derivative mode (Figure 6).

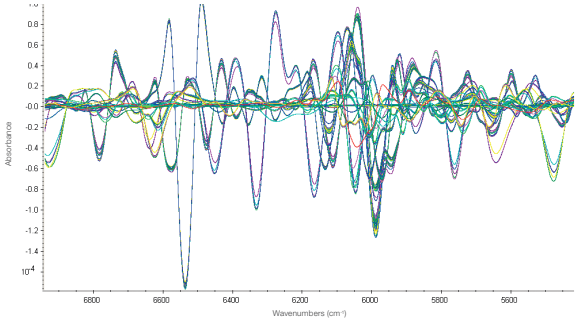

Figure 3: Classes of raw materials in second derivative mode.

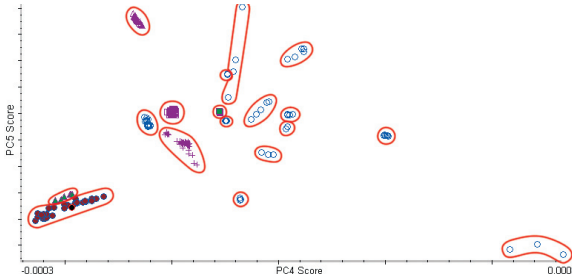

Figure 4: Scores plot (PC4 vs 5) of material classes.

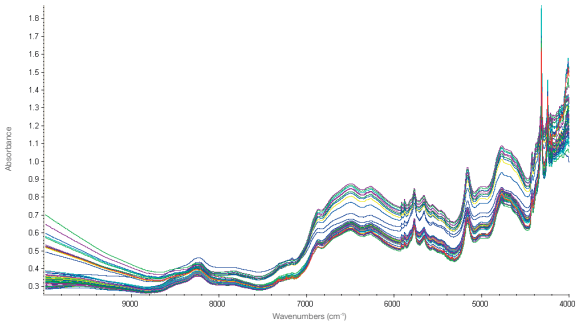

Figure 5: Different particle size samples of lactose showing offsets.

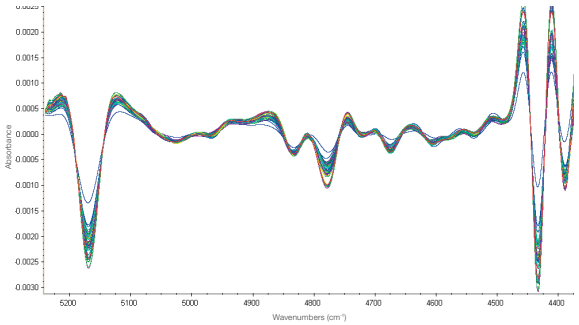

Figure 6: Lactose particle size samples with offsets removed.

Two methods were developed for particle size analysis. The first used untreated spectral data with a Discriminant Analysis algorithm with TQ Analyst's SIMCA option. This option creates a class distribution that is unique to each class. This technique usually requires at least 5 standards per class but can provide exceptional discrimination. The second method used a second derivative pretreatment and a Norris Smoothing filter with a segment length of 9 and a gap of 3. The polyethylene resonances, which occur from approximately 4200 cm^{-1} to 4350 cm^{-1} and from 5650 cm^{-1} to 5800 cm^{-1}, have been removed from both methods. The particle size analysis in this study was done using samples of Pharmatose from DVM International with mesh sizes of 50*µ*, 80*µ*, 90*µ*, 100*µ*, 110*µ*, and 125*µ*.

Particle size analysis is only completed if the workflow shows the identity of the raw material to be lactose. If the raw material is not identified as being within any of the libraries, then RESULT will label the material as a FAIL. In addition, the spectral data, in this case, will be archived in a separate file location and will notify a LIMS or inventory control system that a failure has been found at Loading Dock 6A and to transport the sample to quarantine and to notify the supplier.

Conclusion

The Antaris II FT-NIR Analyzer and RESULT Software have been shown in this raw material application to be very effective tools for integrating FT-NIR analytics into the front end of a process analytical protocol. Bar code input, decision-making capability, powerful chemometric algorithms, and OPC process systems integration are all essential parts of an effective strategy for raw materials analysis in challenging locations.

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