Near-infrared (NIR) spectroscopy has been used for qualitative and quantitative measurements in the agricultural, food, and chemical industries for several decades. It has also been effectively used in numerous pharmaceutical applications, from the inspection of incoming raw materials to the final testing of manufactured products. Improving product quality and lowering cost are drivers in decision making for many industries. Ensuring product quality throughout the manufacturing process can be time-consuming, with materials and product quarantined until test results are generated. Rapid testing by NIR spectroscopy, at all stages of the manufacturing process, can reduce manufacturing time and provide rapid analysis tool because samples can be analyzed directly, without preparation, in less than a minute. The NIR spectral region carries chemical information, with the strongest absorbances being those related to CH, OH, and NH functional groups. This allows for quantitative measurement of chemical concentration in a matrix, and qualitative analysis to discriminate one material from another (1, 2). From a single spectrum, numerous components within a matrix can be simultaneously quantified once calibration models have been developed.

NIR spectroscopy, combined with chemometric tools, can be used for the development of calibration models for qualitative and quantitative analysis of materials measured in transmission or reflectance. It has been used widely for applications ranging

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**Near-Infrared Spectroscopy as a Process Analytical Tool**

**Part I: Laboratory Applications**

Katherine A. Bakeev

Hello again, gentle readers. You didn’t think I could allow just one column on near-infrared (NIR) spectroscopy, did you? Aside from my personal interests in NIR, it is, after all, the most mature of the (molecular) spectroscopic methods available for process analytical technologies (PAT). There are, in fact, so many places that NIR is used, there will be two articles on it. The first, on lab applications (known as off-line) will show how a rapid measurement near the process line may speed up the actual process. The second installment will be devoted to at-line and on-line applications, and the implementation of NIR for such analyses.

I asked Katherine A. Bakeev to do the honors for NIR. She is as good a writer as she is a speaker, so you should enjoy and learn from these two articles.

— Emil W. Ciurczak, Column Editor
from rapid identification testing of materials (8–10) to assay of intact tablets (11) to process monitoring (12–14). Figure 1 illustrates NIR applications throughout the manufacturing process.

**Process Analytical Chemistry**

Process analytical chemistry refers to measurements that are made to provide analytical information to increase process control. The measurements may be made in a laboratory, in a materials dispensary, or directly in the process stream. Analysis that is done with a direct interface of the analyzer to the process is called in-line, while on-line analysis entails use of a recirculation loop or sample transport system which removes sample automatically from the process and brings it to the analyzer. Analyses that are done on samples removed from the process may be off-line, in a remote or centralized laboratory, or at-line when an analyzer is located in close proximity to the process (15, 16).

NIR spectroscopy is one of many tools used to help ensure product quality by measurement throughout a process, from incoming raw materials to final product. It is important that process analytical projects be problem-driven and not technology-driven, in order that the tool that provides the needed data and information is used. The analysis must be made in such a
way that the data provide information that can be used to control the process. The analyzer must be able to detect changes in the process over the time scale at which they occur.

Process analytical applications of NIR can be used to follow trends in quantitative analysis for determination of end points and control of specification limits. It can also be used as a qualitative tool or to determine if a process is following a reaction trend similar to previous runs. Qualitative analysis allows identification/qualification of raw materials, and ensures that final product spectra compare well with previous “acceptable” batches. By using NIR as a process analytical tool, information about the process can be generated in near–real time.

Overview of Laboratory-Based NIR Applications

Raw materials identification. The application of NIR spectroscopy as an identification method provides a rapid means of testing materials without the need for sample preparation. It can be used to distinguish between different materials such as excipients (Figure 2) or materials that vary in their state of hydration (17). Methods for identification of incoming raw materials by NIR in the pharmaceutical industry have been validated (10) and used for testing large volumes of material without the need for lengthy testing by wet chemical or chromatographic techniques. An NIR raw material library is developed by scanning numerous lots of raw materials. Discriminate analysis is then used to develop a qualitative identification method for the materials. As a routine test procedure, the spectrum of a new sample is scanned and its spectrum compared to the mean spectrum of each product in the library to get a rapid identification. Qualification (determination of accept/reject) can be determined using tolerances from spectra of previously qualified “acceptable” materials.

Moisture measurement. Water is a very strong absorber in the NIR region, making it a good candidate for quantitative analysis by NIR (Figure 3). The strong combination OH band at about 1930 nm and first overtone OH stretching at approximately 1450 nm can be used for measuring moisture. Determination of moisture in agricultural products was one of the earliest applications of NIR, dating to 1965 (18). Moisture is an important measurement in the pharmaceutical industry. One can see how the NIR spectrum of the product changes with changes in the moisture level (Figure 4). The moisture level can be determined when calibration models have been developed against a reference method such as Karl Fischer titration.

NIR has been used to monitor moisture in lyophilized products without removing samples from their lyophilization vials (19). NIR has also been used to measure the total water, as well as the surface and bound water, in drug substances in drying processes (20). Moisture has also been measured by NIR in wet granulation operations to determine the end point of a granulation process (3).

Polymorph determination. Identifying the polymorphic form of a pharmaceutical compound is important because of the differences in the efficacy of various polymorphs and their behavior in processing. NIR is sensitive to different polymorphs because of the different arrangement of molecules and the concomitant change in hydrogen bonding.
Figure 5 shows the NIR spectra of two different polymorphs of a substance. It can be seen that polymorphism can lead to substantial differences in the spectrum. Rapid and sensitive methods for determining polymorphic quality using NIR and pattern recognition methods have been developed (5). Qualitative analysis was used to discriminate between the desired polymorph and other polymorphic forms. Low levels of polymorphs in binary mixtures have been quantified using reflectance NIR spectroscopy (6).

Testing of solid dosage forms. Final product testing of intact tablets can be performed using NIR in transmission or reflection mode (11, 21). The use of NIR on solid tablets maintains sample integrity, so the samples can be used for additional testing or retained for future uses. NIR spectra of tablets have been used to develop quantitative identification methods for tablets, as well as quantitative methods to measure dosage strength. Because the NIR reflectance measurement can penetrate several millimeters into the sample (depending on the coating and the density of the sample), dosage can be measured in the reflection mode.

Particle size analysis. Samples of varying particle size show different scattering effects when measured in diffuse reflectance spectroscopy. These effects cause changes in the baseline of the spectrum, and can be used to measure the mean particle size of powders (22). The NIR data can be correlated to mean particle size using a multilinear regression of one or two wavelengths.

Implementation Strategies

In seeking to apply NIR as a process analytical tool, careful consideration must be given to what to monitor, and where that monitoring is best done. Using NIR for laboratory measurements of moisture or dosage forms can result in substantial time savings compared to chromatographic or titrimetric techniques for these measurements. If the measurements can be moved to a location closer to the production site, the turnaround time for analysis can be further reduced. Additionally, with such a rapid analysis technique, the possibility exists to make more frequent tests, ensuring stability of a process. Identification by NIR enables the testing of more containers of raw material, giving greater assurance as to the identity of more samples.

Conclusions

NIR is an excellent tool for use throughout the manufacturing process. It has been widely used for raw materials testing and for quantitative measurements, both off-line and on-line. Examples of applications of laboratory NIR measurements from the pharmaceutical industry have been presented. In the next installment of “Molecular Spectroscopy Workbench,” on-line applications will be discussed, along with important aspects of implementing NIR for process analysis.

References