

## Near-Infrared Spectroscopy as a Process Analytical Tool

### Part II: At-line and On-line Applications and Implementation Strategies

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*Greetings, once again, dear readers. I am happy to present the second half of Katherine A. Bakeev's presentation on near-infrared spectroscopy in process analytical technologies (PAT). As I attend many meetings around the country (FACSS and AAPS, for example), I am struck by the growing number of sessions devoted to PAT. Having been on the validation section of the PAT subcommittee to FDA, I am aware of the input of some extremely talented pharmaceutical analysts from around the world. As more companies see the benefits of process control, I think this initiative will be the biggest thing since sliced bread. So, stay tuned for future installments in this series. — Emil W. Ciurczak, Column Editor*

In the first article of this pair (1), a general introduction to near-infrared (NIR) spectroscopy was presented. Additionally, laboratory applications of this technique in the pharmaceutical industry were discussed. This installment will explore NIR applications performed at-line and on-line. Some of the same types of measurements as those made in the laboratory can also be performed at-line and on-

line — for example, moisture and particle-size measurements, or polymorph determinations. Other on-line applications include monitoring of reactions and powder blend uniformity. This article will also discuss some points to be considered in implementing NIR as a process analytical tool.

#### NIR Spectroscopy

NIR spectroscopy, combined with chemometric tools, can be used for qualitative and quantitative analysis of organic compounds in a variety of applications. In the pharmaceutical laboratory, NIR is used for moisture measurement, raw material identification, and for quantitation of the polymorphic content or present crystallinity of a material, as was discussed in the first article of this series for laboratory analysis. These

measurements can also be made during material processing. NIR can be used for process monitoring (2–9), with a wide variety of analyses performed at-line or on-line. Such analyses allow for near-real-time measurement of a process, reducing deviations from specification during the manufacturing process, and decreasing dependence on lengthy laboratory testing.

#### Process Analytical Chemistry

Process analytical chemistry has been used for many decades in the petrochemical, food, and chemical industries, with NIR being just one of the tools that can be applied for on-line analyses. The measurements are made in a laboratory, on the manufacturing floor, or directly in the process stream to give rapid information about a process (5–8). The adoption of NIR should be based on its feasibility to make the required measurement for a given situation. The analysis must be made in such a manner that the data provide information that can be used to control the process. The analyzer must detect changes in the process over the time scale at which they occur or can be adjusted.

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Process analytical applications of NIR can be used to follow trends in quantitative analysis for monitoring reaction progress, determining end-points, controlling specification limits, and determining if a process is following a reaction trend similar to previous runs of the same process. Qualitative analysis enables comparison of product spectra, ensuring that they are similar to previous batches. By using NIR as a process analytical tool, information about the process and product can be generated in near-real time.

### Overview of NIR Applications

**Reaction monitoring.** On-line application of NIR allows one to follow the progress of a chemical reaction as the reaction proceeds. It provides a window on the process, with information on the concentration of reactants, formation of by-products, and the end-point of a reaction. Multiple measurements can be made simultaneously within a reaction

from each spectrum that is recorded. By directly interfacing the analyzer to the reactor, one reduces safety hazards that may arise from the need to sample from a reactor. NIR has been used to determine the end-point of a hydrogenation reaction (3), to monitor fermentation reactions (9), and for process analysis of fluidized bed granulation (10, 11), to name just a few examples.

**Moisture measurement.** Moisture determination is perhaps one of the most widely made NIR measurements, covering industries as varied as agriculture, forestry, textiles, chemical, and pharmaceutical. At-line measurements are made for lyophilized products and for tablet analyses. On-line applications in the pharmaceutical industry are often made for active substances. NIR is used to measure the amount of moisture during granulation, drying, and purification stages of solids and liquids. In a recent study (12), NIR was

used to measure moisture during the process optimization of a cytotoxic compound.

**Polymorph determination.** NIR has been used for the identification of the polymorphic form of a pharmaceutical compound in both laboratory and process settings (13–15). Due to substantial differences in the NIR spectrum arising from changes in polymorphs, NIR is a sensitive and rapid method for quantifying polymorphs, and measurements can be made much more rapidly than can crystallographic measurements by x-ray. NIR has also been used to monitor the interconversion of crystalline products during a batch reaction process (16).

**Testing of solid dosage forms.** Testing of intact tablets for active concentration and content uniformity may be performed using NIR in either transmission or reflection mode (17, 18). At-line measurements are often run in the tablet manufacturing area, eliminating

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## Project team view of process analytical implementation plan.

- Define Opportunity
- Investigate Payback/Future Returns
- Preliminary Justification
- Define Project
- Define Team/Meeting
- Define Proofs
- Finalize Justification
- Test Management
- Evaluate Vendors
- Site Survey/Analyzer
  - Location
- Determine Analyzer Outputs
- Project Time-Line for Implementation
  - Engineering Involvement
  - System Selection
  - Revise Justification
  - Submit to Management
  - Purchase Asset
  - Installation Requirements
  - Operator Training
  - Schedule Installation
  - Install System
  - Method Development
  - Method Validation
  - Process Interface
  - Service Training
  - Process Routine Testing
  - Process Optimization
  - Realize Return on Investment/
    - Gain Future Returns.

the need to take samples to a remote laboratory, and allowing for immediate product release.

**Particle-size measurement during processing.** Particle-size measurements can be made by NIR and are often performed during granulation and blending processes. NIR has been used to measure the particle size of nanoparticles in high-solids dispersion (19). It was found to be effective for controlling the end-point of the particle production, with an accuracy of 2.4 nm. The spectrum of the dispersion changes with particle size and, even in the second derivative spectrum, there are significant signal changes related to the

change in effective pathlength of the NIR light as the particle size is varied.

**Powder blending.** The measurement of blend homogeneity is complicated by the sample thief that is used for extracting samples from the blend. Direct on-line measurement during the blending process removes the problems associated with sample thieves and allows for a measure of all the components in the blend simultaneously. On-line monitoring of blending processes by NIR has been accomplished using qualitative analysis tools, and by comparing the standard deviation of successively scanned spectra (20–23).

**Solvent monitoring.** Monitoring of the mixture of solvents in a solvent recovery process is important in the purification and reuse of the solvents. By using transmission NIR, the solvent mixtures can be quantitatively measured. This application finds use in many manufacturing processes and can reduce waste as well as increase cycle time. NIR calibrations have been developed to monitor the switching of solvents from one alcohol to another and to determine distillation end-points (24).

### Implementation Strategies

In seeking to apply NIR as a process analytical tool, careful consideration must be given to what is to be monitored, and where that monitoring is best done to provide information that can be acted on. The motivations for choosing the process include improving product quality, reducing product variability, reducing cycle-time and manufacturing costs, and reducing hazards including the potential dangers to operators who currently need to sample a process. The use of process analyzers can also reduce or eliminate difficult and costly laboratory measurements.

The implementation of a process analyzer requires a multifunctional team, especially if the project will involve technology transfer from the R&D organization to a manufacturing site. The successful team may consist of a strong leader with support from senior management, an analytical chemist, a chemometrician, a process development chemist, a control engineer, a production engineer, and someone to

oversee documentation and validation. The scope must be well defined and consideration must be given to all the steps involved in implementation as given the sidebar. Some organizations have a process analytical group with the responsibility for all analyzers throughout the company. With such a group, the collective experience of working with different plants and analyzers and working with a project through the entire process aids in implementation.

Once a process has been identified for NIR analysis, the choice becomes whether to make a reflectance or transmission measurement. For solids and highly scattering slurries, reflectance measurements can be made with a fiber-optic probe directly interfaced to the process or through a sampling window. For liquid systems, transmission or transfection measurements can be used. The optimal pathlength for the measurement must be determined, and the best sample interface determined. For batch reactions, measurement can be made on-line using a pair of transmission probes inserted directly into the reactor (one for sample illumination, and the other for collection of transmitted light), or in-line with a transfection-type probe. For in-line measurement, the probe pair can be interfaced to a recirculation loop or a flow cell can be used.

One of the biggest challenges of on-line and in-line analysis is the sampling system (5, 8, 25). It is best if a probe can be interfaced directly to a process, but if this is not possible there are several considerations. The sample that is being measured must be representative of the process being measured. One must also determine how the sample will be presented to the analyzer. The placement of the analyzer, probes, and computer must be determined based on site and measurement requirements. The interfacing of the probes to the sample must be determined: will the measurement be on-line with a side stream or conditioned sample slipstream, or will the measurement be in-line? Care should be taken to minimize the necessity of in-



terface cleaning and interrupting the process other than during planned routine maintenance.

The analyzer will need to be calibrated for the desired measurements. It is necessary to collect representative samples to develop a calibration equation. This may take some time if the process is run with little variation. By collecting spectra during process start-up and during upsets, one can obtain more variation. There must be defined acceptance criteria for the calibrations. A process of testing the calibration must also be established and performed, ensuring that the calibration produces accurate predictions. Guidelines covering quantitative multivariate analysis of spectrometers have been published (8, 26). There are also guidelines available pertaining to the validation of process spectrometers (27). Development of robust calibration models that cover the expected variation of a process will reduce the necessity of making updates to the calibration over the long run.

It is also important that the lab analysis be representative of the sample that the NIR scans. Often, this means collecting samples during the NIR scan, or as near to that time as possible, and also in close proximity to where the NIR scans are conducted.

## Conclusions

NIR is an excellent tool for use throughout the manufacturing process. It has been widely used for qualitative and quantitative measurements both off-line and on-line. Examples of applications of NIR from the pharmaceutical industry — from incoming raw material testing, throughout the process, to final product — have been shown. Some important aspects of implementing NIR for process analysis have also been discussed.

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