

Pharmaceutical Industry Embraces NIR Technology

Hallie Forcinio

Near-infrared spectroscopy moves into warehouses to check incoming drug substances, excipients, and packaging materials, and onto the production floor to monitor characteristics such as blend uniformity, moisture content, and dissolution rate.



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Near-infrared (NIR) spectroscopy is capturing the imaginations of pharmaceutical manufacturers as a quicker, potentially more accurate, and less expensive way to perform some of the quality checks required in a current good manufacturing practices (cGMPs) setting. Equipment innovations are making it easier to operate and validate NIR devices and are opening doors for use beyond the lab. As a result, NIR is moving into the warehouse to check incoming drug substances, excipients, and packaging materials, and onto the production floor to monitor characteristics such as blend uniformity, moisture content, and dissolution rate.

“A lot of companies are looking for QC [quality control] methods to replace ones that take longer and/or require dissolution or reagents,” said Scot Ellis, NIR product manager at Thermo Electron (Madison, WI), which developed its Antaris line of NIR units especially for pharmaceutical applications.

Because NIR can nondestructively analyze multiple constituents on any matrix, it can confirm that the right dose goes in

the right package in real time (1). Mounting NIR equipment on blister packaging machines not only catches any stray incorrect tablets, but also is especially useful to check the sequence of regimens where the dosages vary and for clinical trials, which typically include pills that look the same but have different chemical compositions. In addition, NIR can detect counterfeit drugs and confirm the structure and weight of packaging materials.

The long wavelength of NIR, which ranges from 700 to 2500 nm, makes it possible to sample drug substances, excipients, and finished products through packaging materials. This nondestructive examination opens the door to production line usage, minimizes the need for destructive testing with its attendant loss of salable product, and eliminates the lag time associated with waiting for lab results. In many cases, quarantine time can be eliminated.

NIR also can reduce inventory requirements, boost throughput, and increase product quality and consistency.

Encouraging use of NIR is FDA's process analytical technologies (PAT) initiative, which seeks to improve product quality and consistency through the adoption of at/on/in-line measurement of performance attributes and real-time or rapid feedback controls. “PAT provides support for companies to increase their understanding of their process through online measurements,” said Bernard Olsen, research advisor for Lilly Research Laboratories, Eli Lilly and Co. (Lafayette, IN). “NIR is one technique that is useful for doing that.”

Another positive influence is *USP Chapter 1119*, published by the U.S. Pharmacopeia (Rockville, MD). The general chapter “Near Infrared Spectrophotometry, 2nd Supplement” provides guidance on how to use and qual-

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ify the technology. Other guidance documents related to calibration, validation, and maintenance of NIR devices in a pharmaceutical setting have been published by the European Agency for the Evaluation of Medicinal Products (EMA, London, United Kingdom), the European Directorate for the Quality of Medicines, European Pharmacopeia (EDQM, Strasbourg, France), and a United Kingdom-based industry forum called the Pharmaceutical Analytical Sciences Group (PASG).

How NIR Works

NIR identification is based on the principle that a material absorbs NIR energy and transmits or reflects it in a unique manner according to its chemical composition and physical characteristics. This makes it possible to use NIR for both qualitative and quantitative purposes (2).

Successful analysis depends on identifying the optimal spectral region for the target material. This requires considering the sampling parameters, the physical properties of the sample, and the analytical performance needed. Some mathematical manipulation also may be necessary to pinpoint the desired spectral data (3).

Qualitative analysis requires building a library with which samples are compared. This is done by collecting spectral data from known good material from multiple lots, determining an average, and examining variability to decide what constitutes a significant difference.

Quantitative analysis depends on assembling a calibration, or training, set of samples that shows the expected range of variation for the target material (4).

NIR Applications

AstraZeneca UK (Macclesfield, United Kingdom) has used NIR technology since 1996. Initially deployed in the warehouse, it checks incoming materials to support the company's vendor assurance program and provide the identity check required by GMPs to confirm that the contents of the container match what the label says is inside.

"We were looking for a technique that could identify many different materials and accommodate both solids



NICOLET ANTARIS METHOD DEVELOPMENT SAMPLING SYSTEM

and liquids," said Steve Holland, senior scientist in research development, who served as work project manager in the QA environment during AstraZeneca's early exploration of NIR technology. "The equipment also had to be operated by a nonchemist in a nonlab environment."

Previously, samples from incoming shipments would be sent to the laboratory to undergo a classical testing regimen, a relatively time-consuming and costly process. "Our goal was a rapid materials flow," Holland said. "We wanted to get the material fully authorized [on receipt] so it could move through the system quickly."

The NIR system for checking incoming materials is now validated. "The first library was done in a couple months," Holland said. But building a complete database of all incoming drug substances, excipients, and packaging materials took several years because the team relied on incoming deliveries to collect the NIR data needed. To ensure benefits would be realized quickly, the first libraries focused on key raw materials and excipients.

When a shipment arrives, an NIR probe is inserted into the container or a sample is presented in a vial. A reading is taken and compared with the library to confirm the identity of the contents. If correct, the material is cleared for immediate usage. If a problem is detected, the shipment can be rejected.

The benefits of near-instantaneous test results and simple operation have prompted AstraZeneca to consider other uses for NIR, including monitoring moisture levels in a fluid bed dryer. "The first stage is to measure the final drying result," Holland said. "Ultimately, we would like to control moisture levels on a

batch-to-batch basis. The whole idea is to get better reproducibility on moisture content in the final granules. The existing technique, an off-line IR dryer balance, involves stopping the process and taking a sample. With NIR, we hope to do this in real time."



NICOLET ANTARIS FT-NIR MULTIPLEXER

Other studies at AstraZeneca use NIR to test content uniformity and as an investigative tool to troubleshoot process, scale-up, and production anomalies.

"There's a big advantage in being able to test tablets without destroying the matrix," Holland said. "There's a lot of information in how the tablet holds together."

In yet another study, AstraZeneca has installed NIR at the point of dispensing in a zoned hazardous area. In this application, 30-m fiber-optic cables link NIR probes to a multiplex unit positioned in a safe zone. The probes are inserted into drums or double-bagged bulk products being handled under laminar hoods to confirm the identity of every ingredient charged into the process. "The idea is to eliminate the warehouse test," Holland said.

Eli Lilly also is looking at online applications of NIR technology and has researched its potential for counterfeit detection (5).

"NIR is portable enough that instruments could be used in the field [to detect counterfeits]," Olsen said, although "there would have to be appropriate controls to make sure you're getting valid results."

Selecting NIR Systems

Today's NIR systems for the pharmaceutical industry are designed to be rugged, reliable, and easy to use. Reference standards and protocols may be built in and a push of a button yields a pass/fail response. As a result, equipment operation doesn't require a technician skilled in spectroscopy.

State-of-the-art NIR systems improve on two features generally absent in earlier models — transferability and networkability — and also comply with

the requirements of *21 CFR Part 11* regarding electronic records and signatures. Transferability means units are designed and built so a library or calibration set that works in one will perform exactly the same way in another. Transferability is particularly useful for organizations with multiple lines or multiple facilities. Without it, libraries and calibration sets have to be created for each NIR unit and rebuilt after any maintenance or repair. Deployments with multiple NIR devices also benefit from networkability because it permits operation, monitoring, and diagnostics from a single, potentially remote, location via an Internet connection.

Adoption of NIR technology requires a capital investment of \$50,000–\$150,000 per unit and a serious commitment. In fact, AstraZeneca's Holland recommends dedicating resources to the development of NIR methods.

It's also essential to understand the problems associated with any sampling technique. "We spent quite a lot of time

making sure we were using the best method of presenting the sample," Holland said. "Good use of experimental design in the early stages of method development is extremely important. It's essential to have a good knowledge of multivariate analysis, rather than just pressing a button and trusting the data that comes out."

Finally, potential NIR users shouldn't underestimate the amount of validation required because "There's a fair amount of work involved in large libraries," Holland warns.

When it comes to selecting hardware, "Look at who has the most experience and installed base in pharmaceutical," said Phil Irving, president of Foss NIRSystems (Silver Spring, MD). Then match the machine to the application. Foss's XDS series of NIR spectrometers, for example, includes a range of models, each oriented toward specific tasks. The decision-making process should consider sensitivity, speed, transferability, and networkability in relation to the

application. For some applications, sensitivity is most critical, while the priority for others might be speed, transferability, or networkability.

For example, in an application with a single plant and one process, transferability and networkability may not be essential features. If product is made in multiple locations, transferability and networkability can save time, money, and effort. Otherwise, transfer of libraries and calibration sets to other units can be challenging, if not impossible.

Finally, NIR technology is not a panacea. "It's important to target the right applications and not simply try to use NIR to solve every problem," Holland said.

References

1. H. Forcinio, *Pharmaceutical Technology* 25(10), 28–32 (2001).
2. Foss NIRSystems, *A Guide to Near-Infrared Spectroscopic Analysis of Industrial*

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Short Courses

Analysis by plasma spectrochemistry. Topics include trace analysis of biomedical materials; analysis of foods and food products; solving multidisciplinary analytical problems; analytical and process chemistry in semiconductor devices fabrication; spectrochemical analysis of long-lived radionuclides; determination of inorganic arsenic, selenium, and chromium species in environmental and industrial samples; geoanalysis mass spectrometry; petroleum analysis with plasma spectrometry; water quality applications and environmental chemistry; spectroscopic techniques and applications in a pharmaceutical laboratory; trace and ultratrace analysis of high-purity materials; spectrochemical applications of reference materials; determination of plutonium by ICP-MS; and understanding and implementing ICP-AES methods 200.7 and 6010B.

Instrumentation. Topics include: calibration and data evaluation in atomic spectrometry; method validation and measurement uncertainty; advanced concepts in analytical quality assurance; high-resolution ICP-MS; glow discharge atomic emission and mass spectrometry; time-of-flight MS for elemental analysis; ICP-MS I: introduction; ICP-MS II: advanced topics; laboratory accreditation for plasma spectrochemistry; field flow fractionation ICP-MS; selecting an ICP-AES system; selecting an ICP-MS system; evaluation and control of ICP-AES and ICP-MS systems; and theory and operation of reaction cells for ICP-MS.

Sample introduction techniques. Topics include: micro and nano samples by ICP spectroscopy; electrothermal vaporization for atomic and mass spectrometry; flow injection analysis techniques and applications; micronebulizer diagnostics and analytical and fundamental characteristics; laser ablation atomic and mass spectrometry I; laser ablation atomic and mass spectrometry II, advanced; nebulizer characteristics, design, and routine operation for ICP-AES and ICP-MS; plasma spectroscopic detection in chromatography; sample introduction for ICP-AES and ICP-MS; and solid sample introduction techniques and instrumentation.

Plasma spectrochemical techniques. Topics include: advanced sample preparation for plasma spectrometry; applications of isotope dilution and isotopic measurements; plasma on a chip; element preconcentration in trace analysis; glow discharge modeling; typical errors in ICP analyses and how to avoid them; microwave sample preparation for inorganic analysis; clean microwave digestions for ultratrace analysis; plasma analysis quality control and assessment procedures; plasma diagnostics: fundamentals, measurements, applications; trace element speciation; preparing your laboratory for ICP-MS; contamination issues in trace elemental analysis; analysis of biological samples by high-resolution ICP-MS; who wants to be a millionaire? – bring your new technology to market; stable isotopes for metabolic studies; wet digestion for trace element analysis; elemental speciation for biological samples; U-Th-Pb dating of geological samples by laser ablation ICP-MS; improving laboratory productivity and data quality; solid phase microextraction for trace element speciation; achieving reliable trace elemental measurements; and becoming an expert witness.

ganization, its purpose is to promote, foster, advance, and improve study, research, teaching, and dissemination of knowledge regarding plasma spectrochemistry, analytical chemistry, science education, and related areas.

Conference travel, registration, and newsletter subscription grants are offered to students to support their atten-

dance and participation at the Winter Conference and in the spectroscopic scientific community. During the past several Winter Conferences, a significant number of student travel grants were awarded and funded by contributions from manufacturers and other plasma supporters. Travel support is also available for scientists and stu-

dents. Training and research grants are also available to both students and professional analytical chemists. Grants range from \$100 to \$3000 for international scientists, and as many people are supported as funds will allow. Information about these grants is published in the *ICP Information Newsletter*; it can also be obtained by contacting Ramon Barnes (see final paragraph).

The above charitable, educational, and scientific purposes are achieved, in part, by fund-raising. To this end, the organizers of the Winter Conference are looking for industrial, manufacturer or individual sponsors to make tax-free contributions to these grant funds. In return for their support, sponsors can have high-profile symposia named after their companies or take advantage of special discounts. Interested parties can contact Ramon Barnes directly to make the necessary arrangements.

Social activities held during the Winter Conference enhance the conference experience not only by affording a chance to relax, but also to meet new faces and make valuable contacts. The Conference holds daily social mixers as well as a conference dinner event.

The location for the 2004 Winter Conference will be the Wyndham Resort and Spa (www.wyndham.com/bonaventure) in Fort Lauderdale, Florida (www.sunny.org). For program, registration, hotel, and transportation details, contact Ramon Barnes, ICP Information Newsletter, Inc., P.O. Box 666, Hadley, MA 01003-0666, (413) 256-8942, fax: (413) 256-3746, e-mail: wc2004@chem.umass.edu, or visit the web site at www.unix.oit.umass.edu/~wc2004/WinterConf2004.htm. ■

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- Manufacturing Processes 2* (undated).
3. Foss NIRSystems, *A Guide to Near-Infrared Spectroscopic Analysis of Industrial Manufacturing Processes 4* (undated).
4. Foss NIRSystems, *A Guide to Near-Infrared Spectroscopic Analysis of Industrial Manufacturing Processes 6* (undated).
5. B.A. Olsen, M.W. Borer, F.M. Perry, and R.A. Forbes, *Pharmaceutical Technology* 26(6), 62–71, 95 (2002). ■