

Post-Tableting NIR Analysis: A Look at PAT Applicability to the Output of Solid Dosage Forms

A majority of current discussion about NIR's applicability to pharmaceutical manufacturing is focused on preparative processes such as granulation, drying, and blending. The author examines different considerations for NIR for the output of the manufacturing line – finished tablet analysis.

Scot Ellis

Process Analytical Technology (PAT) goes far beyond process analyzers and chemical analysis techniques. Indeed, PAT embodies a holistic approach to analytics to develop an understanding of the inputs and outputs of a process, and everything in between. However, much of the discussion about PAT centers on a particular analytical technique: near-infrared (NIR) spectroscopy. A majority of current discussion with NIR's applicability to pharmaceutical manufacturing is focused on such preparative processes as granulation, drying, and blending. Here, we take a look at different considerations for NIR for the output of the manufacturing line: finished tablet analysis.

Near infrared's great promise for PAT largely lies in advantages afforded by the characteristics of light in the NIR portion of the electromagnetic spectrum. This range features long sample path lengths and relative insensitivity to glass, allowing sampling of materials through containers or windows in their natural form, without sample preparation. It is therefore non-destructive and allows tested material to still be used for other purposes. It can be coupled very efficiently with fiber optics, allowing sampling to be done remotely from instruments. Measurements take seconds, allowing real-time process monitoring. Once set up for a process, a robust

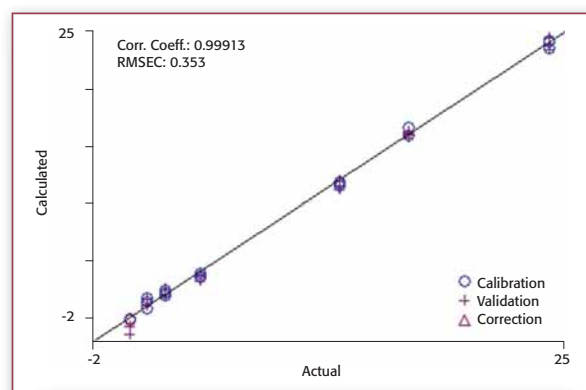


Figure 1. Tablet transmission analysis can be extremely effective to verify dosages. This plot shows concentration values for a proprietary active pharmaceutical ingredient from a study meant to test sensitivity limits. Concentrations down to .5% by weight were predicted easily. Mahalanobis analysis also shows that the different dosages could be discriminated qualitatively.

calibration is extremely repeatable and can be migrated from instrument to instrument with little or no maintenance on the right platform. Furthermore, the NIR spectral range's

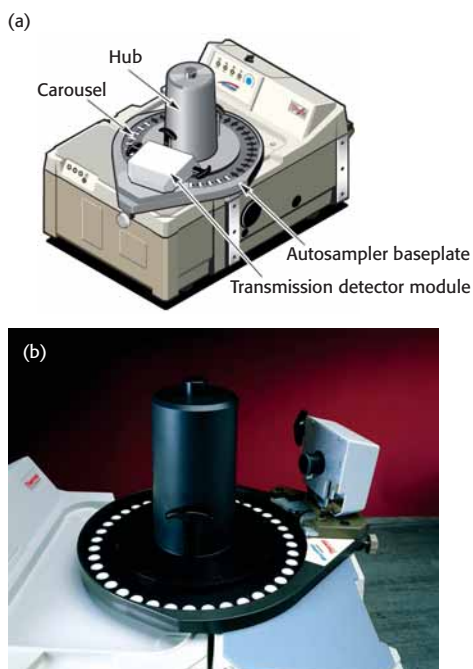


Figure 2. Example of a tablet autosampling system that can be migrated between lab and plant use.

sensitivity to the optical properties of typical pharmaceutical samples (for example, scattering characteristics due in large part to the relationship between wavelength and particle size or spacing) means that NIR spectra contain information about physical properties as well as chemical. While the use of chemometric algorithms are required to model the relationships between spectral characteristics and material information, the resulting predictive engine can run rapid analysis of multiple properties that traditionally have been investigated in the lab.

PAT Tablet Analysis in Analytical R&D

As is being pointed out with increasing frequency at conferences and in the literature, while the ultimate goals of PAT are manufacturing processes with quality designed in, the analytics being applied to generate the prerequisite process understanding don't have to be on- or in-line. While the mantra of PAT might be quality designed in rather than tested in, there is

this experiment might include granulation, drying, or blending relationships, but almost certainly it means looking at the end products. How do the tablets turn out? For this reason, PAT should be coordinated with analytical R&D.

PAT activities in the laboratory are common for at least two types of activities. The first is the use of analytical expertise to generate bodies of information that can be mined and explored for the relationships between process parameters and output for existing products, as in scenarios such as that described briefly above. This is a cautious approach to PAT for incoming products, and makes perfect sense because it seeks understanding of relationships with minimal impact on operations. The second is the development of analytical understanding of dosage forms at the formulation development level. While FDA has stated that one should not expect lab methodologies to transfer to the tableting line, there is a great deal to be said about beginning the analytical understanding

great opportunity to use PAT to better understand processes that already have been designed. How do we get there? Before we rush to insert probes and sensors into existing processes, acquiring a certain set of base knowledge is in order. Experiments are needed that coordinate recorded process parameters, lab-based primary analytical results, and analytical views from a potential future on-line analyzer technique such as NIR. Designing

long before pilot manufacture is undertaken, and even before lab-scale manufacture. Whether the methodology transfers or not, an ideal approach would allow work on an analytical approach, chemometric modeling, tool validation, and even tool use and documentation to be built upon from the lab usage to reduce efforts in manufacturing that can otherwise dilute an effective PAT project. An approach to PAT development in the lab that facilitates migration to plant is advisable if it is feasible. This is applicable particularly to tablet analysis, because until PAT programs and real-time release are a reality, tablets will come full circle back to an analytical QC lab before batch release. It makes little sense to duplicate efforts in analytics between like environments, and if the same approach to tablet analysis can occur at the tablet line, the system can become self-validating until the QC lab might not be necessary at all.

Considerations for Tablet Analysis by NIR

The benefits of NIR for PAT discussed previously extend well to tablet analysis. Chemical and physical properties can be extracted from spectra, and depending upon the tablet, the analyzer, and the chemometric approach, predictions of identity, API content, tablet hardness, and dissolution sometimes can be made. The application of broadest interest is active content, and down to sub-percentage levels NIR can be an excellent tool. The long pathlength characteristics combined with today's sensitive detectors allow cross-sectional assay of many tablets, capsules, and softgels. There often is a choice to be made, because content can be predicted accurately in tablets simply using surface reflection techniques.

Fourier transform NIR (FT-NIR) has gained ground as the preferred NIR technology for tablet analysis. Higher spectral resolution generally means greater sample specificity and leads to robust calibrations with significantly fewer calibration standards

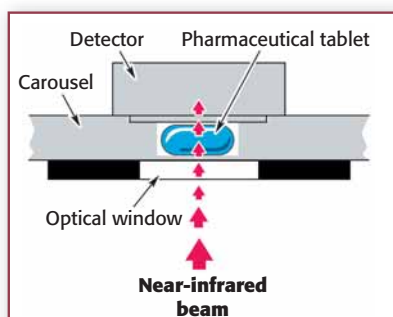


Figure 3. An arrangement for maximum sample energy and elimination of stray light in at- or on-line tablet analysis. An automated motorized system positions the detector at the tablet and moves it prior to sample movement.

than historically needed with older NIR technology. Its broad spectral range allows access to information in the combination, first, second, and third overtone vibrational regions. The information contained in high-resolution NIR spectra (generally considered 8 cm^{-1} or higher across the entire spectral range) allow most tablet analyses to be modeled from between the NIR boundary and the second overtone region (approximately $4000\text{--}7500\text{ cm}^{-1}$, or $2500\text{--}1350\text{ nm}$). The continuous internal calibration of a Fourier transform analyzer via a helium-neon laser helps to make it one of the most stable and repeatable types of NIR available.

Near-infrared sampling is done by reflection or transmission of radiation from or through an analyte. For tablet analysis, these techniques can yield complementary information particularly if coatings are of analytical interest. However, there are cases where one technique simply is better suited to the analysis. Reflection sampling calibrations can yield beautiful correlations at higher concentrations, but can fall apart when a concentration range falls below a percent or two. In these cases, transmission analysis, which provides an interrogation of much more of the tablet, can

provide the needed accuracy.

A key consideration for tablet transmission analysis, sensitivity determines how small of a chemical presence can be detected for sample prediction or discrimination. Because solid-tablet transmission really is diffuse transmission, a design that maximizes signal from the tablet is highly desirable. The closer the detector system can be to the tablet surface the greater the signal acceptance and stray light rejection will be. Placing the detector too far away rejects much signal, which falls off as roughly $1/d^2$ where d is the distance from the tablet because of the diffusion within the tablet. Stray light gives spectral contribution that is unrelated to the sample and will reduce both method accuracy and sampling repeatability.

The physical shape and dimensions of a tablet tend to magnify the effects of NIR's sensitivity to a sample's optical properties. The importance of sample positioning in tablet analysis, especially in transmission mode, are discussed in the literature (1). When developing a tablet method, particular care must be given to understanding the effects of sample placement and orientation relative to focus and detector positions. Changes in these positions can result in baseline shifts and other changes. A rule of thumb in NIR is to model any anticipated variation in to the calibration, but this is not always feasible. For PAT, this is an issue if the ultimate goal is integrated, on-line tablet testing. Fortunately, some validatable spectral pre-treatments can help compensate for sample positioning variation. Remembering, however, that we are looking to design quality into

a process, the tools for analytics should be no different. Eliminating or controlling positional variability as much as possible is highly desirable.

Risk due to sample positioning also can be mitigated through tablet handling apparatus design. Tight mechanical tolerances for autosampler positioning, and carousels specifically fitted to tablet types can help on-line tablet analysis be repeatable. In fact, this approach is designed into an autosampler model that can be used in the plant at-line, adopted to online use, and in the lab as well. Figure 2 shows an autosampler that facilitates repeatable autosampling in transmission and reflection mode on a Nicolet Antaris FT-NIR Analyzer (Thermo Electron Corp., Waltham, MA). This system allows fast swapping of tablet carousels that are custom-built for particular tablet specifications.

The goal for NIR as a quality control tool always has been the ability to transfer methods and their calibrations from analyzer to analyzer. We have seen that there are sources of variability in tablet analysis that can be reduced by careful design of sample handling and chemometric modeling. Another source of variability that must be considered in PAT is the variability of analyzer design itself. Analyzer differences mean that calibration transfer requires the collection of new spectral data for calibration adjustment. Using a Fourier-transform instrument can reduce the variability from analyzer to analyzer to make transfer easier. Using a single analyzer platform with tight optical tolerances in both the method development lab and at the tablet press

Table I. User Requirements for R&D and Manufacturing

R&D Equipment and Software Requirements	Manufacturing Equipment and Software Requirements
Powerful development tools	Rugged Industrial Design
High Performance	High Sample Throughput
Flexibility	SOP and Record Control
GLP level compliance	Repeatability
	High MTBF/low CoO
	Minimal Operator Training and Skill
	cGMP Validation and Compliance

can further reduce or eliminate variability due to differences in instrument performance caused by optical and component variation.

Once NIR does make it to the tablet line, if that is the goal, it is important to have reasonable expectations and well-defined goals. In-line, 100% inspection of tablets in real-time is not realistic with today's technology, nor does it make sense statistically. Even if the analyzer could handle the volume, there is no data system that could process the data in a useful manner. At-line analysis of tablets often is a significant improvement over waiting for laboratory results — it meets the criteria of timely information. But on-line transmission analysis running at rates of one tablet per minute could go a long way toward real-time, statistically significant sampling of an entire tablet run.

Standardizing and Automating

We have touched on the case for making an analytical connection between R&D and operations, or viewed another way, between the lab and the plant, earlier in the discus-

sion of current PAT developments. Some aspects of PAT can be simplified by standardizing on a platform that meets both the development and process requirements of the R&D and manufacturing groups, respectively. This is not simple, because the user requirements are very different for the two groups (see Table I).

The issues listed in the table can be eliminated largely and company PAT gains improved dramatically by implementing a common platform that meets the requirements of both environments, and has been developed with the following design criteria from the ground up:

- Method transfer
- Calibration transfer
- Simple deployment
- Common platform
- Laboratory and manufacturing environment requirements

We have discussed very briefly some basic concepts of NIR for tablet analysis and some considerations for making a connection between the R&D area and solid

dosage form operations. The ideal of real-time release has implications for the elimination of post manufacturing sampling and QC testing.

Placing automated tablet testing by NIR in the final stage of the tablet creation process goes a long way toward that elimination. But until then, tablet testing at the line and in the lab, in conjunction with analytics further up the line at steps such as drying and blending, provides a self-validation loop that ultimately will help provide the justification to achieve PAT's ideals. The body of cross-correlated data will go a long way toward justifying the easier acceptance of change and making continuous process improvement a regulatory and practical reality.

Reference

1. J. Hirsch and R. De Maesschalck, *Method Transfer of Solid Dosage Forms. European Pharmaceutical Review*, Issue 1 (2004). ■

Scot Ellis is product manager for FT-IR and FT-NIR analyzers, Thermo Fisher Scientific. E-mail: analyze@thermo.com.

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Thermo Fisher Scientific
5225 Verona Road
Madison, WI 53711
Tel: (608) 276-6100, (800) 532-4752
Fax: (608) 273-5046
Email: analyze@thermo.com
Web: www.thermo.com/nir

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