

The PAT Front End Using FT-NIR

Move beyond raw material ID and into manufacturability and control **BY SCOT ELLIS AND BRIAN DAVIES**

The pharmaceutical industry is beginning to deal with the meaning, possibilities and risks of implementing Process Analytical Technology (PAT). As industry leaders, regulators, consultants and technology vendors discuss approaches and solutions, attention has been focused on the largely physical processes that make up solid dosage form manufacturing. These processes are not completely understood and are deserving of the application of analytical technology for their characterization, understanding and control.

NIR SPECTROSCOPY

The definition of PAT encompasses the testing of raw input materials where the output of raw material testing is used to restrict or control the manufacturing process. The discussion of PAT in relation to raw materials testing has been less forthcoming than those surrounding real-time analytical approaches for blending, granulation and drying. Because of the regulatory approval process in drug manufacturing, these processes are validated and subsequently fixed.

PAT moves us to an era where these processes can be adjusted for variable input to produce consistent output. While fixed processes are indeed at the heart of the problem, a root cause analysis of variable medicine product quality will often point back to variable inputs.

This article discusses a phased approach that starts with better control over inputs, and opens up the potential for forward-fed data for process control. At the heart of the matter is getting to know your raw materials better.

Risk- and Regulation-driven

Testing of raw materials has historically been risk-based and driven by regulatory guidance. The main risk is generally considered to be chemical identity and purity. In recent years, much of the burden of this screening or “pre-qualification” of raw materials has been shifted to the suppliers of solid dosage form excipients through certification programs intended to guarantee purity and consistency. The next generation of raw materials inspection programs will be a shift from chemical suitability, already determined by the supplier, to the manufacturability of materials.

Near infrared (NIR) is one of the most widely pursued analytical techniques for pharmaceutical PAT, due to its ability to analyze materials quickly and in-situ. NIR use is on the rise for raw material testing because of the ability to quickly screen raw materials at or near point-of-use, while offering improved efficiency and precision over HPLC and other test methods. Although complete lab testing is rarely completely replaced, NIR reduces the risk of pushing processes forward while waiting for quarantine release.

NIR spectroscopy is a technique which must be calibrated or programmed to be useful for real world applications. It is a molecular vibrational spectroscopy technique, particularly sensitive to diffractive scattering due to the proximity of NIR wavelengths and the particle sizes of material used for tablet manufacture. NIR spectra are made up of a myriad of “interactions and overlaps” of fundamental vibrational information located in the mid-infrared spectral region. These come together to create a spectroscopic bonus—the technique can be calibrated to predict physical information as well as chemical.

If a chemometric technique can model a relationship between spectral variation and reference numbers for these physical properties, the trait can be predicted (or indirectly measured) by NIR spectroscopy. The relationships between material characteristics such as particle size and their NIR spectra have been studied both in pharmaceuticals¹ and other industries². The prediction of traits goes further than this. Because many properties of materials are related to basic physical parameters such as par-

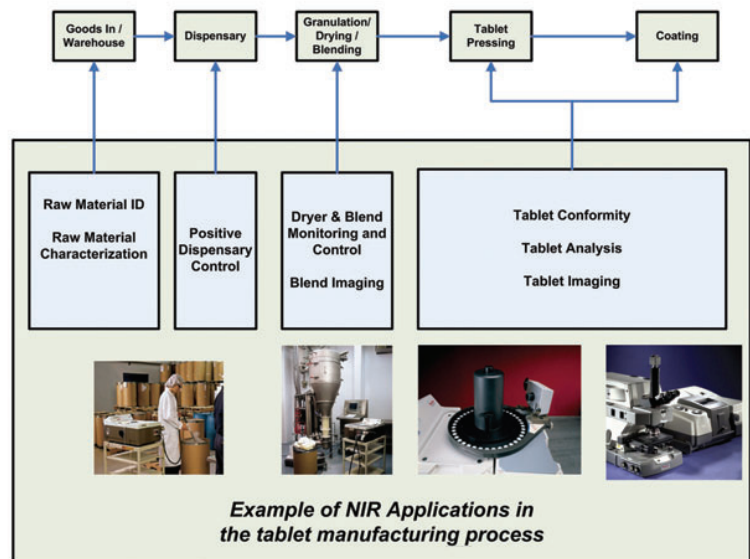


Fig. 1: Potential NIR Applicability to PAT

ticule size and crystalline morphology, traits with a degree of separation can be predicted by NIR. With calibration, a quick NIR scan could tell you a number of things about the “manufacturability” of a material in question.

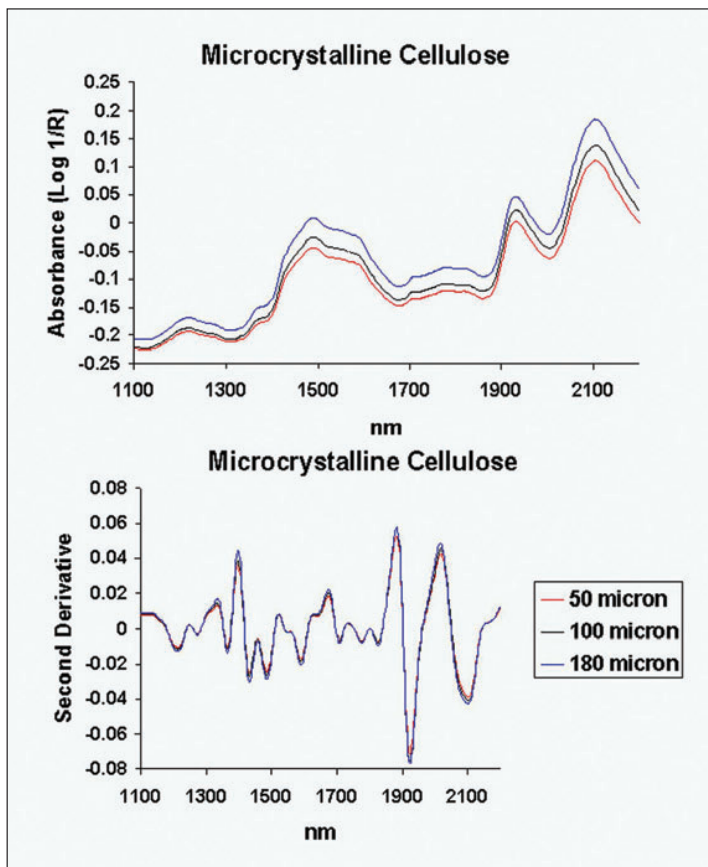


Fig. 2: Infrared signatures emphasizing differences in particle size (top) and chemical ID information (bottom) based on data format and treatment

What can be Gained?

Commercial tablet making processes consist of many physical operations strung together; these operations are recipe-based and are defined in product development and scale-up. Once the chemical identity of the materials in these processes is no longer in question, the success of those processes mainly depends on the morphology of the chemicals used, and primarily those of excipients that make up the bulk of the mass of tablets.

Better understanding of the relationship between excipient morphology and tablet quality might be a good first step for process control. Setting raw material specifications around both purity and a new understanding of the optimal particle size, hydration or crystallinity for a desired end product can have a major impact when it comes to consistent quality. Putting an NIR analyzer in a receiving or dispensary area may not have the excitement of an on-line monitoring sys-

tem, but is much more straightforward.

Stories of newly discovered relationships with raw material properties, such as correlation between certificate of acceptance data and product output, are becoming more common as PAT knowledge contributes to new levels of understanding. In many cases, the actual combination of excipient properties leads to the difference between a good and bad

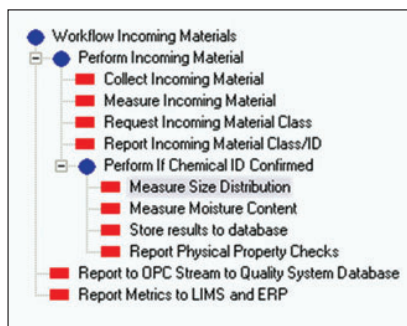


Fig. 3: A single NIR scan can be set up in an automated workflow to replace many tests, and do so quickly at point-of-use

SETTING RAW MATERIAL SPECIFICATIONS AROUND BOTH PURITY AND A NEW UNDERSTANDING OF THE OPTIMAL PARTICLE SIZE, HYDRATION OR CRYSTALLINITY FOR A DESIRED END PRODUCT CAN HAVE A MAJOR IMPACT WHEN IT COMES TO CONSISTENT QUALITY.

tablet batch. But if an NIR material signature can consistently be correlated to tablet performance, a fundamental question is raised—how necessary is scientific causal understanding if product quality can suddenly be made consistent?

One might ask if a specification can be set based on an NIR signature of a material. While an NIR spectrum and model only provides secondary (calibrated) access to attributes, a specification based on NIR can be validated; near infrared can be as accurate and often more precise. And NIR's ability to predict many traits in a single measurement enables efficient screening for both chemical purity and physical traits that together largely define tablet output for a truly fixed process. In keeping with the spirit of alleviating the workload by pushing some responsibility to suppliers, could NIR specifications based on PAT understanding be a prerequisite for suppliers and a fundamental piece of data on a material certificate?

The traditional approach to testing all of these traits is prohibitive of true screening, and NIR makes it possible to check all materials, even at point of use. Even if data is not fed forward, timely point-of-use analytical screening based on improved process understanding that results in a controlled output, falls under the definition of PAT. Raw material screening based on NIR spectroscopic signatures can further be extended to the dispensary and integrated as an automatic control tool in the process.

The 0th Order

Implementation of NIR raw material screening can be used for process control in varying levels of complexity. The simplest level of NIR for pharmaceuti-

cal raw materials—which we will call the “0th order” of NIR raw material control—provides the highest value for the required investment and provides the most valuable and low-risk entry into the world of PAT.

As you ascend the levels of control, based on NIR raw material, the complexity increases and the size of the benefit may become smaller, depending on the goals of the plant and the overall integration of PAT for a production line. Value and benefit are realized through reduction of scrap and other costs associated with poor quality, better and more consistent medicines, and potential extensibility to other operations. The costs are those of time, materials and capital required to investigate, develop and implement a functioning PAT system.

The 0th order involves getting to know your raw materials better. As with all manufacturing process parameters, there is a statistical variation between batches. For example, particles tumbling in a bin blender represent, on a particulate level, an extremely complex process.

However, using technologies like FT-NIR and chemometrics, not only can the behavior of the particle population be predicted, this can be verified using empirical measurements. Understanding the variability inherent in huge non-linear mechanical systems is the domain of on-line analyzers that identify process signatures.

For raw material screening, we attempt to eliminate the variability going into that process, and therefore, treat those processes as fixed—so far as they are controlled today, they are run the same every time. If processes are fixed and variable inputs causes variable outputs, two things are certain: One, significant reduction of variability will reduce the inherent variability in the process itself, and two, shrinking and tuning the “error bars” of acceptance to those known to result in very good quality will improve the process output and repeatability.

PAT as an Integrated Active Control Mechanism

For those who think of PAT as an integrated, active control mechanism, this

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basic level of NIR control can be used in just such a way. An NIR analyzer can be implemented at the dispensary and using a communication protocol such as OPC or a PLC communication system, the analyzer can prevent out-of-range material from being put into the system. This way, the analyzer even eliminates the variable of human error. The FDA has strengthened its message of such process control in recent months.

The statement that 0th order raw material control is relatively simple cannot go without caution. The knowledge base required to predict outputs based strictly on inputs is both a living document and not without its own initial cost. Establishing the connections between raw material NIR signatures and tablet outcomes takes time and investment.

The PAT era is one in which continuous improvement is encouraged so you can start small and improve over time. Additionally, the construction of knowledge in pharmaceutical processes will be a lengthy and careful process at every point. Putting NIR at the front of the process is an extension of the lab testing that’s done today, but can now be integrated with PAT. The investment and risk are both minimal compared to that needed to enter the exciting world of on-line sensors, analyzers and control systems.

The construction of the knowledge base of input-output relationships might be done by formulation development groups, in collaboration with development and pilot engineering, and perhaps, commercial operations. Fortunately, the benefits of the process extend back from manufacturing to product development. The development of manufacturable and functional formulations in the future can become more streamlined through effective tapping of data on material parameters and their interactions as they are

related to tablet quality. One can envision expert systems that minimize trial and error, and proof statements that get stronger as the knowledge base grows. Assumptions that must be made today to make a project manageable in a short timeline become justifiable and confidence in formulation strategies goes up.

Building Relationships

The next level of feeding information forward enables a broader optimization of operations and improves plant efficiency. By understanding input-output relationships and the differences between several product processes, materials can be matched to processes and mapped accordingly. First order feed-forward moves NIR raw material into the realm of integrated economic benefit.

If we can get as far as tightening specifications on materials to a fixed process, the new raw material PAT protocols can be tied back into the more exciting parts of PAT. The processes are fixed; this really means that they are run using the same parameters each time.

If PAT allows for continuous improvement and real-time control, then raw material specifications can not only be tightened significantly, but variability within an expected range can conceivably be compensated by small adjustments to the process. While current thinking on blending and drying is centered on determining the true endpoint based on inline analytics, why not apply input information to the equation?

In other words, if an input material is on one edge of a specification, an additional piece of information is known before the process starts. This information is valuable for understanding and controlling the process. Theoretically, variability can be closed down even further than is possible by material screening and endpoint monitoring. This is a second order of feed-forward for NIR raw material information.

NIR screening and control for raw materials can be made a transparent part of a robust process. Typical use of NIR or other techniques for raw material testing involves manual data processes. Manufacturing execution systems and other

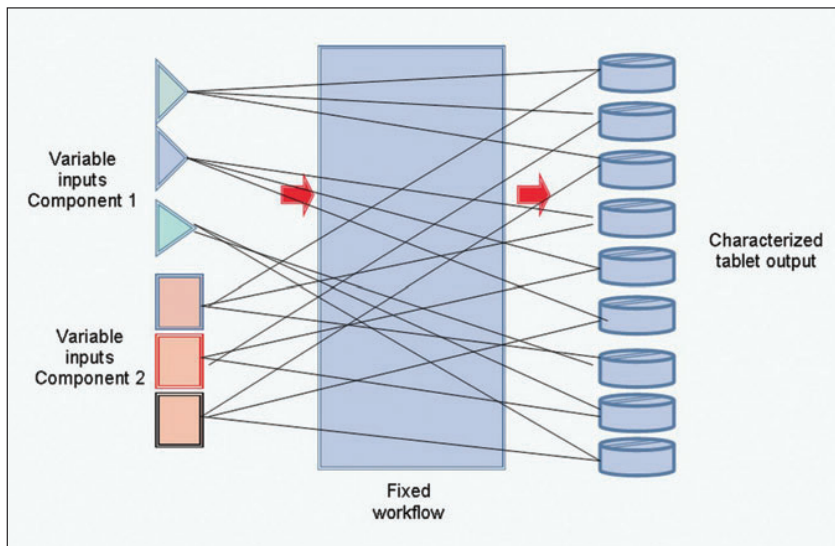


Figure 4: Representation of relationship building; variable inputs obtained from real processes or product development batches run through fixed processes are correlated to process outputs

control software, ERP systems such as SAP, quality management systems, and LIMS all track and use information about materials as they enter the tablet manufacturing value chain. It is conceivable, through the use of barcode and RFID systems, tex-

tual and other connectivity to various information systems, that the disposition and tracking process can be integrated electronically to eliminate manual data entry, human error and delays.

Furthermore, electronic linking of material property criteria with lots and batches will allow feed-forward information to be automatically interpreted by control systems, and processes automatically adjusted as necessary.

The inputs into tablet making processes are a perfectly valid point to implement PAT. Fur-

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thermore, focusing on raw materials provides an ideal entry point to deeper understanding of process, and with a potentially fast economic return. By understanding raw materials better and using a fast technology like NIR, the manufacturability of those materials can be used for process control. The technique can be easily integrated with process points both physically and through data communications in a way that is consistent with current procedures and workflows. Better raw material understanding should be a fundamental part of any PAT program and NIR spectroscopy provides a powerful partner for both understanding and control. ■

References:

- (1) O'Neal, Jee, and Moffat, *Analyst*. 123, 2297-2302 (1998)
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Scot Ellis is product manager for FT-IR and FT-NIR Analyzers, Thermo Electron Corp. **Brian Davies** is director of Process Analytical Technology at Thermo Electron Corp. (Madison, Wis.) and can be reached at 608-276-6100 or brian.davies@thermo.com.

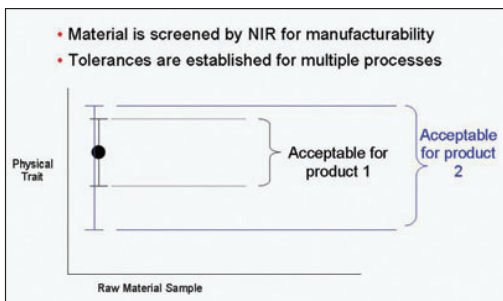


Figure 5: First order of feed-forward for NIR raw material screening allows for optimization of operations by understanding a larger product base and mapping materials according to processes that they match

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Thermo

ELECTRON CORPORATION

Thermo Electron Corporation

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

Part Number: AR51035_E 11/05M