

---

# Molecular Spectroscopy Workbench

# Near-infrared Chemical Imaging and the PAT Initiative

**NIR-CI adds a completely new dimension to conventional NIR spectroscopy.**

**E. Neil Lewis, Joe Schoppelrei, and Eunah Lee**

---

*Dear and gentle readers, this month I present an important tool in the process analytical technologies (PAT) initiative: Near-infrared chemical imaging (NIR-CI). You might wonder why I am seemingly concentrating on IR and NIR. The answer is quite simple: I need all the heat I can get, here in New York. Seriously, E. Neil Lewis, Joe Schoppelrei, and Eunah Lee of Spectral Dimensions (Olney, MD) have put together an excellent explanation of what NIR-CI is and what its part in PAT is and will be. For those of you who do not know Neil Lewis, he is one of the pioneers in IR and NIR imaging. He has won numerous awards for his research at the National Institutes of Health (NIH) and subsequent accomplishments. It is truly exciting to have this paper in my humble column and I know you will find it informative and entertaining.*

**T**he US Food and Drug Administration (FDA) recently released a new guideline strongly advocating the use and development of new measurement technologies in pharmaceutical manufacturing (1). The process analytical technology (PAT) initiative, as it is known, promotes the use of techniques that enable the monitoring of critical process parameters during pharmaceutical manufacturing. The goal is to not only enable process measurement but, more importantly, to enable process understanding and ultimately process optimization. Although FDA historically has focused on purity and potency as its yardstick of product quality, in the future more time will be spent trying to address issues dealing with physical processes. For example, what effects, if any, do small changes in the blending, drying, pressing, coating, or

other manufacturing steps have on the final dosage form? To encourage the PAT initiative FDA is streamlining the mechanism for adopting new technologies in pharmaceutical manufacturing.

## **The Role of Near-infrared Chemical Imaging (NIR-CI)**

A typical tablet is not just a pressed block of a single material, but rather a complex matrix containing one or more active pharmaceutical ingredients (APIs), fillers, binders, disintegrants, lubricants, and other materials. A basic problem in pharmaceutical manufacturing is that a relatively simple formulation with identical ingredients can produce widely varying therapeutic performance depending upon how the ingredients are distributed in the final matrix. More potent APIs can be formulated at dosages of 5 mg or less, but the finished tablet still must be large enough for convenient handling. In this case, maintaining content uniformity is even more crucial. Pharmaceutical makers also are developing advanced tablets for drug dosage management, which can provide longer, flatter, or sometimes complex bloodstream profiles. Approaches include the use of barrier layers, cored tablets, selective-release microspheres, and even osmotic pumps. These tablets essentially are highly engineered drug delivery systems in which the physical structure is as critical as the chemical composition.

Existing analytical techniques such as high performance liquid chromatography (HPLC) and mass spectrometry (MS) often are used to accurately determine the gross composition of a dosage form, but they provide no information about the distribution of the individual components. The manner and duration of component release is examined through dissolution testing. However, this provides no insight into the cause of the profiles obtained. All of these techniques require destruction of the sample, making it difficult or impossible to trace the sources of failures or anomalies.

Spectroscopic techniques enable rapid, nondestructive analysis of samples and can be employed at a number of points in the pharmaceutical development and manufacturing process. In particular, NIR spectroscopy quickly is becoming a workhorse technique for the industry due to its high in-



### **Emil W. Ciurczak**

works as a consultant with Integrated Technical Solutions, 77 Park Road, Goldens Bridge, NY 10526. He can be reached via e-mail at: [emil@ciurczak.com](mailto:emil@ciurczak.com).

formation content and flexibility of implementation. It is used widely for the characterization of raw materials, and also has been used in applications such as blend homogeneity, moisture measurement, and the analysis of intact tablets (2–4).

NIR-CI adds a completely new dimension (pun intended) to conventional NIR spectroscopy. It offers the ability to obtain high fidelity, spatially resolved pictures of the chemistry of the sample. Elucidation of compositional heterogeneity and structure is invaluable for both the development and manufacture of solid dosage forms (5, 6). NIR images can be used to determine content uniformity, particle sizes, and distributions of all the sample components, polymorph distributions, moisture content and location, contaminants, coating and layer thickness, and a host of other structural details (7–9). Through the development phases of preformulation and scale-up, NIR-CI can be used to identify precisely the elusive critical control parameters that will affect the performance of the finished product. The technique is fast and non-destructive and can be used independently or in concert with other techniques, such as dissolution analysis, to rapidly diagnose potential production problems. NIR-CI instrumentation also is rugged and flexible, suitable for both the laboratory and the manufacturing environment. Therefore, analysis methods developed in the laboratory often can be tailored for implementation near-line or at-line. NIR-CI also is massively parallel NIR spectroscopy, making the technique well-suited for high throughput at-line and even on-line applications.

Imaging also can represent significant economic benefits to the pharmaceutical manufacturer. “Blind” manufacturing processes produce products that can be tested only after the fact. Traditional analytical techniques usually are, in many cases, unable to pinpoint the sources of defects and failures in a timely fashion leading to costly delays. NIR-CI provides chemical and physical information at return rates that are faster than those of any other existing technique, improving testing turn-

around, and reducing time-to-market.

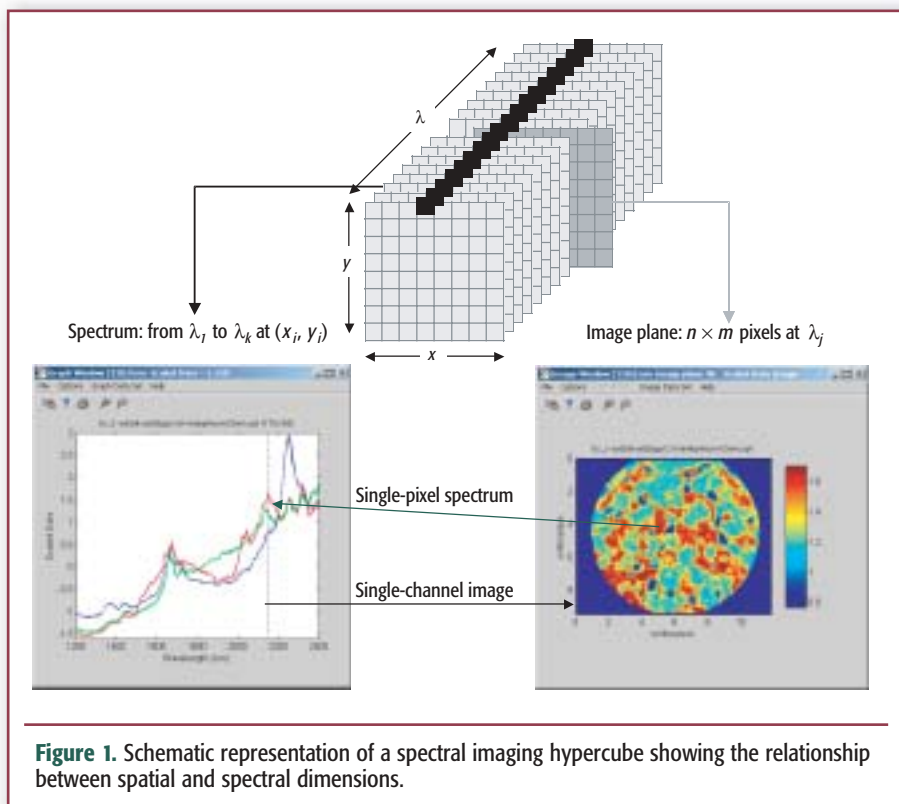
### Chemical Imaging Principles

Conventional digital imaging is the process of reproducing the spatial information of a scene onto a two-dimensional optical detector. The typical image recorded with a standard digital camera or web-cam is collected across a broad range of optical wavelengths, usually in the visible region, to produce a grayscale image. Placing relatively broadband color filters in front of the same detector produces a conventional color image. On the other hand, a single spectral image usually is collected across a narrow wavelength range (very often in the IR or NIR spectral region). It can be used to reveal the chemical composition of the sample through absorption by one or more chemical species within the sample of that particular diagnostic wavelength. The result is a spatially resolved chemical map of the sample. Chemical, or hyperspectral, imaging is the acquisition of images across a larger, usually contiguous series of narrow spectral bands comparable to traditional (single-point) spectroscopic techniques, thus integrating the complete spatial and chemical information of the

sample. This is the fundamental concept of chemical imaging: a rapid analytical method that simultaneously delivers spatial, chemical, structural, and functional information.

**The hypercube.** Spectral images are visualized as a three-dimensional block of data spanning one wavelength and two spatial dimensions called a hypercube (Figure 1). The hypercube can be treated as a series of spatially resolved spectra (called pixels) or, alternatively, as a series of spectrally resolved images (called image planes or channels). Selecting a single pixel will yield the spectrum recorded at that particular spatial location in the sample. Similarly, selecting a single image plane will show the intensity response (typically scaled to color) of the scene at that one particular wavelength.

**Data analysis.** The ultimate goal of the experiment is to generate highly specific chemical contrast in an image to visualize and identify the compositional heterogeneity within the sample. Analysis of the hypercube to produce this contrast can be accomplished at several different levels. In some cases simply selecting the image plane at a wavelength of a characteristic band from a species



**Figure 1.** Schematic representation of a spectral imaging hypercube showing the relationship between spatial and spectral dimensions.

of interest will readily indicate the spatial distribution and abundance of that material. However, this univariate approach of data interrogating is quite wasteful of the total information content of the complete hypercube.

Most chemical images comprise many thousands of pixels and each pixel represents a full spectrum. Therefore, these data are well suited for multivariate (chemometric) analysis techniques such as principal component analysis (PCA), principal component regression (PCR) and partial least squares (PLS) modeling (10, 11). These methods use the full spectral range and can distinguish subtle, but real, chemical variations, even for complex samples. Consequently, data analysis and software are the key components in producing a successful experiment or method. Ideally, the analysis tools must be designed specifically to handle large hyperspectral data sets, and should incorporate a complete set of image and spectral processing options, as well as chemometric analysis procedures and image visualization options. Several software options are available (12).

Although the prospect of using chemometric analysis techniques for routine processing of hyperspectral data might, at first blush, seem daunting, in fact the ability to work with large sample sets can improve the statistical reliability of the results significantly. In addition, with the correct choice of sampling arrangement and magnification it also can significantly reduce the tedious sampling requirements associated with single-point collection methods. For example, if the size scale (magnification) of the imaging experiment is set such that individual pixels represent relatively pure chemical components analysis methods can be used that simply classify the chemical identity of each element. The resulting classification images provide high-contrast pictures of chemical distributions in the sample. Qualitative and quantitative information often can be derived through pixel-counting or by analysis of the statistical distributions of the classification results. While this approach is quick and simple to implement, chemical imaging data obviously also are amenable to the

application of conventional multivariate quantitative methods in which individual pixel spectra are analyzed using calibration data sets and techniques such as PLS. Again, access to the right software tools that provide a variety of options is important when attempting to implement the best processing scheme for a given experiment or sample.

## The Dawn of Infrared Chemical Imaging

### Spatially resolved spectroscopy – mapping.

The concept of spectral imaging can be applied to almost any optical spectroscopic technique. IR, Raman, fluorescence, UV/Vis, and NIR spectral imaging instruments currently are available. However, chemical imaging has been generally, but not exclusively, coined to refer to vibrational spectroscopic imaging approaches (IR, NIR, and Raman) which offer the high chemical selectivity necessary to distinguish a wide range of materials. Historically, the first spatially resolved IR spectra appeared in *Nature* in 1949, which described the use of a microscope coupled with an IR spectrometer (13). However, this was not an imaging instrument because it was limited to the collection of single-point IR

spectra. In 1988, Harthcock and Atkin (14) published the first chemical maps collected with an Fourier-transform IR (FT-IR) microscope fitted with a moving stage, demonstrating the concept of spatially localizing chemical species using infrared spectroscopy.

During the past 15 years, great improvements in optical designs and computer and automation technology have occurred; thus, IR and Raman mapping instruments have become almost commonplace in most well equipped research laboratories. However, many of these instruments still utilize a moving sample stage and the step-and-acquire acquisition mode. IR mapping instruments are limited to this method by their detectors' configurations, which are capable of collecting data from only a single point. They are, by design, unable to capture an image the same a manner as a camera.

**The infrared focal-plane array.** Unlike mapping, infrared chemical imaging relies on the use of a two-dimensional detector array. By way of contrast, the typical visible spectral range digital camera uses a two-dimensional charge-coupled device (CCD) or complementary metal oxide semiconductor (CMOS) array. At

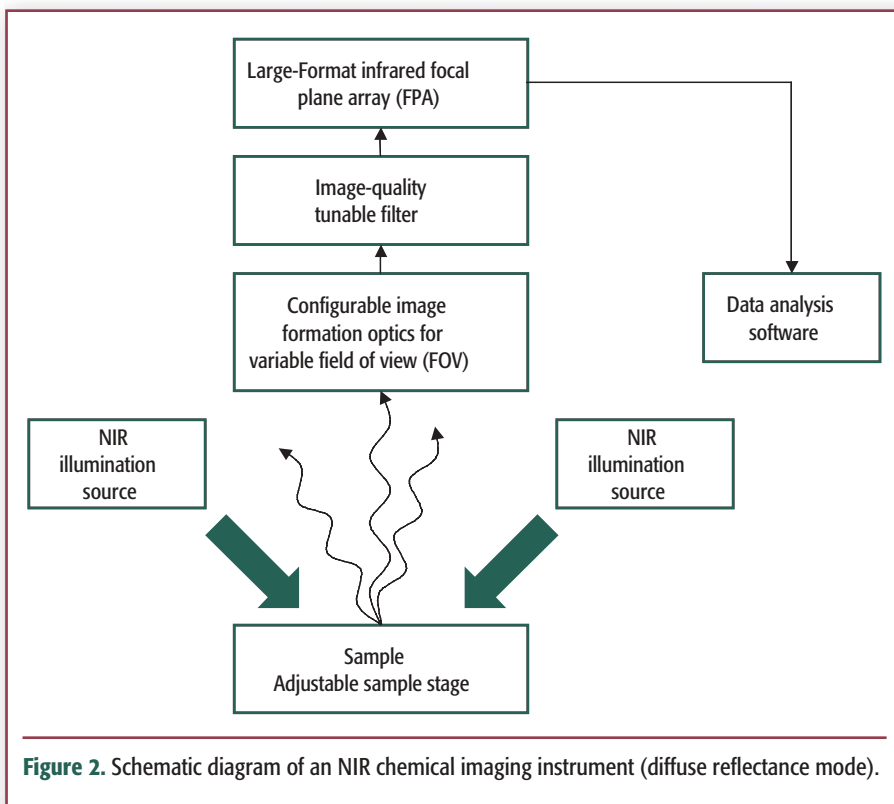


Figure 2. Schematic diagram of an NIR chemical imaging instrument (diffuse reflectance mode).

the high-end of the price range, these detectors are used for sensitive low-light level applications in science and astronomy; at the other end, they are used as a camera embedded in a cell phone. The long-wavelength analogs of these detectors are IR focal-plane array detectors that originally were developed for military applications such as missile detection, targeting, and night-vision devices. It is only within the last decade or so that they have been used by the general IR spectroscopy community (15).

Originally, only small format arrays ( $64 \times 64$  pixels) were available and these arrays were constructed from material such as indium antimonide (InSb) or mercury–cadmium–telluride (MCT). They were prone to mechanical failure, required cryogenic cooling, and were quite expensive ( $> \$10/\text{pixel}$ ). More recently, as the technology has begun to shift from military applications to higher volume commercial uses, more economical, large format ( $320 \times 256$  pixels) focal-plane arrays made from InSb, MCT, or indium–gallium–arsenide (InGaAs) have entered the market ( $< \$1/\text{pixel}$ ). Many of these cameras operate uncooled or incorporate solid-state thermoelectric cooling, exhibiting much improved operability and durability. More recently, the IR camera market has seen the emergence of the uncooled microbolometer array using low-cost CMOS technologies (16). These arrays promise to set whole new price performance levels for infrared focal plane arrays.

**Wavelength selection.** As described earlier, the chemical imaging experiment is an exercise in collecting data from a sample along three dimensions: two spatial and one spectral. While the use of an infrared focal-plane array provides the two spatial dimensions, several approaches for coupling it to a wavelength selection device have been described in the literature (7, 15, 17) and, in some cases, subsequently implemented by instrument manufacturers.

Each technology has its own benefits and limitations, but it is beyond the scope of this article to explore these in detail. Mid-IR and some NIR imaging instruments utilize the Fourier-transform scheme and as a result, function in

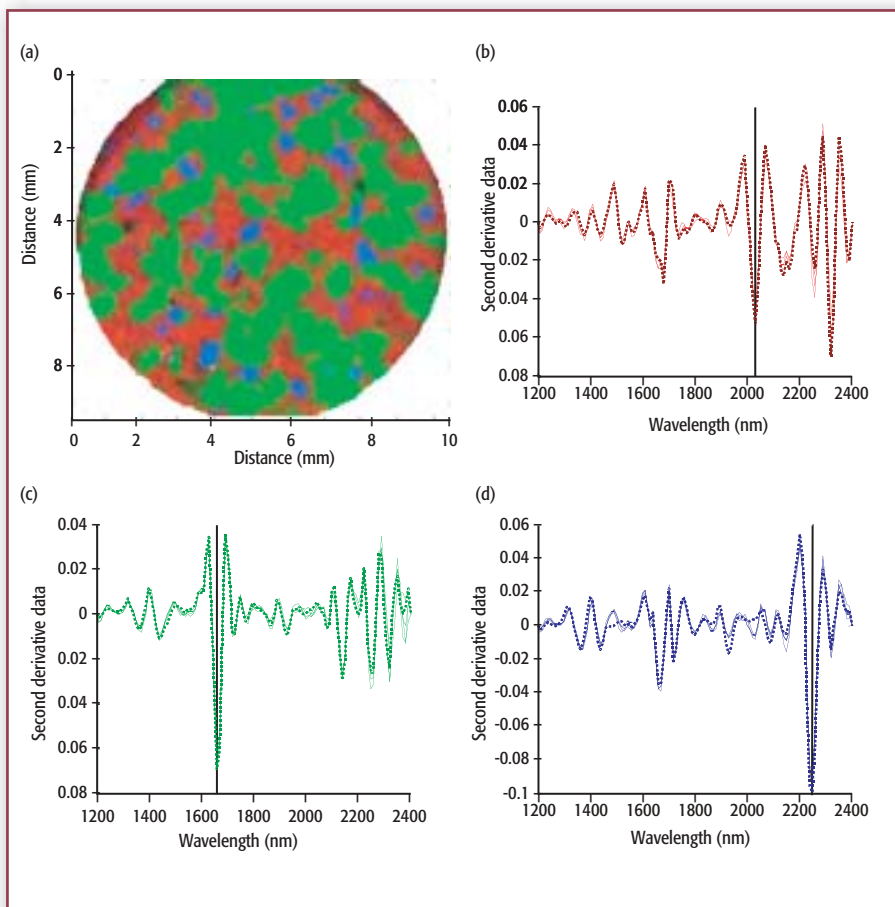
much the same way as traditional FT-IR mapping systems, obviating the need for a moving stage. NIR and Raman imaging instruments have been constructed using solid-state tunable filter technologies, which offer several distinct advantages for industrial applications, including mechanical simplicity and flexibility for industrial applications.

### NIR Imaging Instrumentation

NIR spectroscopy has been shown to be an excellent tool applied to the solution of a wide range of pharmaceutical applications (2–4). It provides high-information content along with ease and flexibility in sampling. Compared with many other spectroscopic approaches

the majority of samples can be analyzed noninvasively in diffuse-reflection with little or no preparation and as a result, it has been employed in numerous pharmaceutical process applications. NIR-CI enjoys these same advantages. While the focus of this article is to illustrate how NIR-CI fits into the pharmaceutical PAT initiative, the instrumentation used for NIR imaging also must fit. It should be flexible, robust and amenable to the manufacturing environment.

Figure 2 shows a generalized schematic of a NIR imaging instrument using a tunable filter for wavelength discrimination. The simple optical design and compact size allows these instruments to be deployed in a wide range of



**Figure 3.** Visualizing the tablet composition of an over-the-counter pain medication. Shown are (a) an RGB image, where the red channel is a single-channel image at 2030 nm representing acetaminophen, the green channel is a single-channel image at 1660 nm representing aspirin, and the blue channel is a single channel image at 2250 nm representing caffeine; (b) A single-pixel microspectrum from a  $40 \times 40 \mu\text{m}$  spot from the red region, overlaid with a pure bulk acetaminophen spectrum; (c) a single-pixel microspectrum from a  $40 \times 40 \mu\text{m}$  area from the green region, overlaid with a pure bulk aspirin spectrum; and (d) a single-pixel microspectrum from a  $40 \times 40 \mu\text{m}$  area of the blue region, overlaid with a pure bulk caffeine spectrum.

situations. They have no moving parts and, with the exception of power, require no external utilities. Thus, instruments also can be mounted in side-looking or inverted orientations. Laboratory instruments normally are mounted in a downward looking orientation, on a stand fitted with the illumination source and a sampling stage.

A great benefit of these instruments is their “staring” configuration coupled with a variable field of view. Working in the NIR permits the use of refractive optics and the simple optical design allows the user to adjust the magnification of the instrument simply by exchanging the image formation lens. A standard laboratory system can be configured for microscopic applications ( $<10\ \mu\text{m}/\text{pixel}$ ) or macroscopic applications ( $\sim 500\ \mu\text{m}/\text{pixel}$ ). The result is a chemical image data set comprising tens of thousands of spectra of a single pharmaceutical granule or an entire blister pack collected rapidly from the same in-

finished process applications might only require collection over a narrow spectral range or even just a few analytically relevant wavelengths. The ability of the tunable filter to access these wavelengths randomly can be used to reduce the time needed to collect the data dramatically. Well-defined methods can be optimized and bundled such that collection and analysis is integrated and accomplished in real time with little or no operator intervention.

### **Application Examples and Possibilities**

**Component distribution visualization.** Figure 3 depicts the results of imaging analysis of an over-the-counter pain medication. The tablet was imaged with the Sapphire (Spectral Dimensions, Inc., Olney, MD) NIR-CI system in diffuse reflectance with a single-pixel magnification of  $40 \times 40\ \mu\text{m}$ . The chosen spectral range for this particular data set was 1200–2400 nm, with 10-nm

like most tablets, this sample is not blended homogeneously even when visualized at fairly modest magnifications but is composed of a matrix of localized domains, or particles, of each of the component materials.

Casual inspection of the image readily indicates that the caffeine component has the smallest mean particle size and has the lowest relative abundance of the three APIs (fewer red domains). The acetaminophen particles also are quite distinct and are somewhat larger than those of caffeine while the aspirin appears to form the continuous matrix in which the relatively large domains of the other two components sit. The high-contrast image also can be used to provide more quantitative information quickly. By simply measuring the area of coverage of each of the domains a quick estimation of the composition of this tablet can be determined without the need for first deriving a calibration curve.

Clearly, one also could derive a stan-

## **THE FDA-SUPPORTED PAT INITIATIVE APPEARS TO HAVE GATHERED SIGNIFICANT PACE AND MOMENTUM DURING THE PAST YEAR AND WILL HAVE A MAJOR IMPACT UPON THE WAY PHARMACEUTICAL MANUFACTURING IS CONDUCTED IN THE FUTURE.**

strument. Instruments which image even larger areas can be purpose-built for process, high throughput, or other specialized applications. The optical configuration supports relatively large depths-of-field so curved or uneven sample surfaces do not pose significant problems, making it possibly the most rugged and robust chemical imaging technique available.

The tunable-filter technology also has other distinct PAT advantages. As stated above, these devices have no moving parts, and their small size allows them to be combined with a focal-plane array into a unified wavelength-selectable chemical imaging engine. Discrete wavelengths can be selected rapidly, through software control, and a full-spectrum/hypercube comprising approximately 80,000 spectra collected in less than 5 min. For most research and problem analysis experiments it is useful to collect data over the entire spectral range of the instrument. However,

data spacing. The total time to collect all 81,920 spectra was approximately 5 min. The data were transformed using a second-derivative calculation to highlight the chemical differences and to minimize contributions from sample topology and scattering. Initial interrogation of the hypercube suggested that three distinct spectral types were present, each having uniquely characteristic absorption bands.

The intensity images at 2030, 2250, and 1660 nm each were assigned a color (red, blue, and green, respectively) and overlaid to form the RGB image shown in Figure 3a. Individual pixel spectra from the contrasting domains were compared with reference bulk spectra (Figures 3b–d) and revealed that this product primarily is composed of three active ingredients, acetaminophen (red), acetylsalicylic acid (green), and caffeine (blue). The composite image shows the distribution of each of the components in the finished product. It shows that,

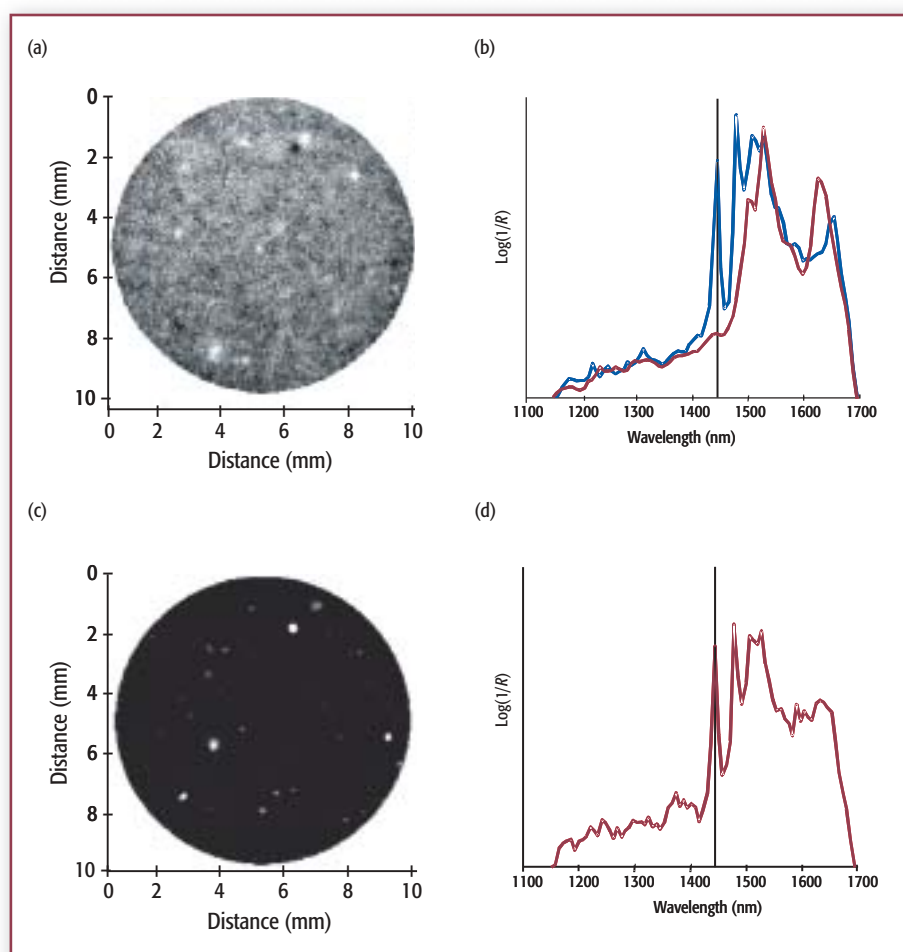
dard NIR calibration curve from a series of mixture spectra and apply conventional multivariate methods such as PLS to each pixel individually. Although this approach works universally and typically provides an improved result, the binary approach, when applicable, is quicker, simpler and only requires access to a single tablet. Further, by using the binary chemical images for each of the three APIs separately, automated software tools can be applied to derive quantitative data based on particle statistics. These tools can assess the size and shape of individual particles as well as determine average values and component distribution information for the sample as a whole.

While much of the emphasis in the past for determining pharmaceutical quality has relied on determining purity and potency it now is clear that the component distribution and particle sizes of both the active ingredient and excipients can impact a product's man-

ufacturability, stability, and dissolution characteristics. NIR-CI is a very useful tool for identifying the root causes of such defects and failures. The ability to visualize and quantify uniformity, component distributions, and particle sizes and shapes within blends or finished solid dosage forms can provide insight into the physical forces that influence the manufacturing process. Imaging analysis incorporated into the preformulation and scale-up phases can be used to positively ascertain the influence of each of the unit operations such as granulating, milling, drying, and blending allowing optimization of the process and preventing failures in the first place.

**Contaminant-trace analysis.** Figure 4 represents the NIR-CI analysis of a tablet that contains a single API component in a mixture of excipients. In this study a library of pure-component spectral data was used to construct a PLS model to derive the contribution and distribution of the individual materials. When the model is applied to a sample hypercube, each spectrum (pixel) is assigned a score denoting the relative abundance of the modeled component at that particular location. The PLS score image for furosemide (the API) is shown in Figure 4a and indicates that the distribution is much more homogeneous than in the previous example. However, furosemide has been shown to break down under certain conditions, possibly resulting in the presence of a contaminant in the finished product. The NIR spectra of the API and the degradation product are overlaid in Figure 4b. The later exhibits a prominent spectral feature at 1444 nm, allowing it to be distinguished readily from both the API and excipient materials.

Because impurities are expected to occur at very low concentrations, the spectral contribution from the drug material was enhanced in the image through a scaled subtraction of the spectrum of the bulk (excipient) material from each pixel in the original hypercube. The single-channel image at 1444 nm of the residual data clearly shows several small areas of increased intensity distributed across the sample



**Figure 4.** Trace contaminant analysis of a furosemide (API) sample. Shown are (a) a PLS score image highlighting a furosemide-rich area; (b) spectra of the pure API (red) and the degradation product (blue); (c) a single-channel image at 1444 nm highlighting the impurity rich areas – the impurity concentration derived from sample statistics is  $\sim 0.61\%$ ; and (d) a residual microspectrum (red) observed at the center of one of the bright spots after subtracting the variance due to the predominant chemical component (an excipient) from the entire data set – compare this spectrum with the impurity spectrum in (b).

area (Figure 4c). Single-pixel residual spectra from these regions closely resemble the known spectrum of the degradation product (Figure 4d) and verify its presence in the sample tablet. The overall abundance of the impurity in the sample was again calculated through pixel-counting statistics and estimated to be approximately 0.61% of total tablet volume.

This analysis pinpoints another advantage of chemical imaging over single-point spectroscopic analysis techniques. Low-concentration or weakly absorbing species often are difficult or impossible to detect in the mean spectrum obtained through bulk, macro-scale spectroscopy. The distinguishing

spectral features simply are lost in the average of the stronger signals obtained from the rest of the sample. Microscopic approaches can provide highly localized spectra, effectively increasing the relative concentration (and thus, the detectivity) of a scarce component in the sampled area. However, traditional microspectroscopy requires the selection of the correct location for detection. Therefore, one either must have prior knowledge of the location of the impurity, or it must be found by time-consuming mapping techniques. NIR-CI collects spatially organized microspectra from large area of the sample in a single experiment.

The full area of a typical 1-cm di-

---

ameter tablet sample can be interrogated with a spatial resolution of about  $40 \times 40 \mu\text{m}$  in only a few minutes, providing both enhanced sensitivity, and location information. Even if a rogue material is detected but is unidentifiable by its NIR spectrum alone, the location information of the imaging experiment greatly assists in the rapid analysis of the suspect region by other analytical methods. In other experiments, we also have used this approach with some success to determine the existence and localization of low levels of different polymorphic forms within finished products. The NIR-CI analysis of an extended-release dosage form is shown in Figure 5. This product is a capsule filled with small microspheres containing the therapeutic agent and extended release mechanism. A sample of the filling was removed from a capsule and imaged with the Sapphire NIR-CI system. The single-channel image at 2130 nm (Figure 5a) indicates that there are two types of spheres present in the sample, each producing

distinctly different spectra (Figure 5b). Quantitative information about the dosage form was obtained from the image simply by setting the appropriate intensity level so as to define each of the observed spheres as a discrete particle (Figure 5c). Automated image analysis of the result indicated that there are twice as many bright — 91 — as dark — 45 — spheres in this particular field of view, and that the bright spheres are, on average, approximately 5% larger in diameter.

The mechanism of the form was elucidated through the further analysis of the individual sphere types. One of each type of sphere was cut in half and the cut faces were analyzed at higher magnification. The resulting image (Figure 5d) reveals that the dark sphere is relatively homogeneous while the bright sphere is made up of a coating surrounding a core composed of the same material found in the dark spheres. This coating presumably comprises the extended release mechanism.

It is readily apparent that the spatial

information provided by NIR-CI is invaluable in both the development and manufacture of complex delivery systems such as this product. Note the relatively uneven nature of the coating observed in the image of the bright sphere in Figure 5d. It ranges in thickness from approximately 150 to 250  $\mu\text{m}$ . Imaging analysis during the development and scale-up of a process which produces the coated spheres would provide a clear picture of this component and allow the critical control parameters to be quickly identified, thus improving quality and reducing the risk of costly performance failures. During manufacturing, chemical imaging could be applied to monitor the uniformity of coating thickness, mean diameter, and relative composition of mixtures of different types of microspheres enabling the desired composition to be maintained.

**High-throughput applications.** Figure 6 demonstrates how NIR-CI can be configured as a high-throughput technology for use in the pharmaceutical manufacturing process. In these

applications, the highly flexible field of view and robust imaging capability of the technique are used to great value to spatially analyze a larger array of samples, simultaneously. In this example a sealed blister pack containing 10 visually identical white tablets, approximately  $7 \times 11$  cm in size, was analyzed. Before the experiment one of the tablets was removed and replaced with an identical form containing a different API. Figure 6a is a visible image of the adulterated package.

The NIR spectral image of the complete sample was collected without disturbing the samples or the packaging. The PCA score image of the arrangement in Figure 6b clearly identifies the rogue tablet containing the different active form. Although the result of this measurement is an image, the data also can be considered as simply a series of NIR spectra taken in parallel. With this thought in mind we can interpret the data as a quality control measurement performed on all 10 tablets simultaneously. Furthermore, it is obvious that

the number of objects that can be addressed simultaneously in this manner is only limited by magnification and the number of pixels on the infrared array. For instance, the data in Figure 5 also can be considered in the same manner. In this case 136 objects were examined simultaneously.

There are numerous applications for such a system in which it simply replaces single-point or multiplexed NIR spectrometers, providing significant advantages in sample throughput and handling. Furthermore, these advantages can operate over a range of size scales and sample shapes that are difficult or impossible for current single-point instrumentation to address. One such example is the validation of the filling of clinical trial blister packs in which a series of variable dosage or placebo dosage forms are handled and packaged in predefined geometric arrangements. Clearly, the intent of such an exercise is to provide a predefined dosage regimen to individuals, in a manner that is blind to the patient and

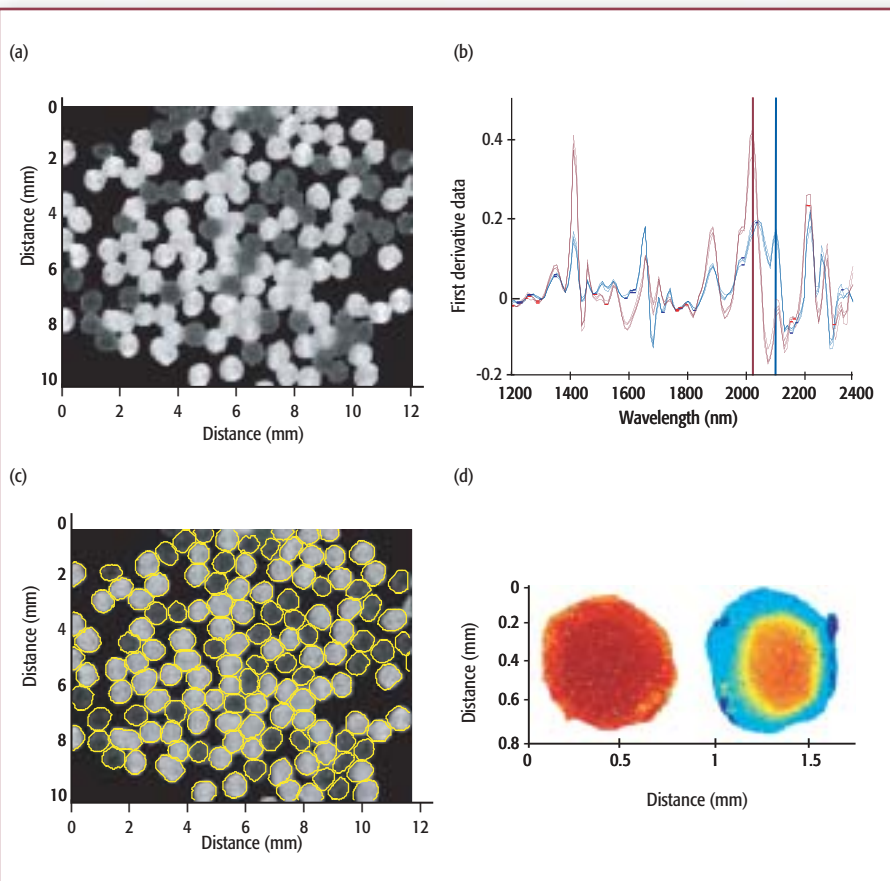
also, in the case of double-blind trials, the dispensing physician. For this to be feasible, the physical size and shape of all types of dosage forms must be indistinguishable. The ability to rapidly verify the efficacy of this complex packaging process after the product is sealed offers significant benefit.

Errors can void a clinical trial, imposing significant costs in both immediate resources and lost time to market for a new drug. In many cases this array-based approach can be optimized so that only a few carefully selected wavelengths are needed for the identification, yielding an inspection time on the order of seconds, which is critical if 100% inspection is the goal. In addition, the large, flexible field of view of an array-based approach enables a variety of package shapes and orientations to be analyzed with little or no reconfiguration.

### Final Thoughts

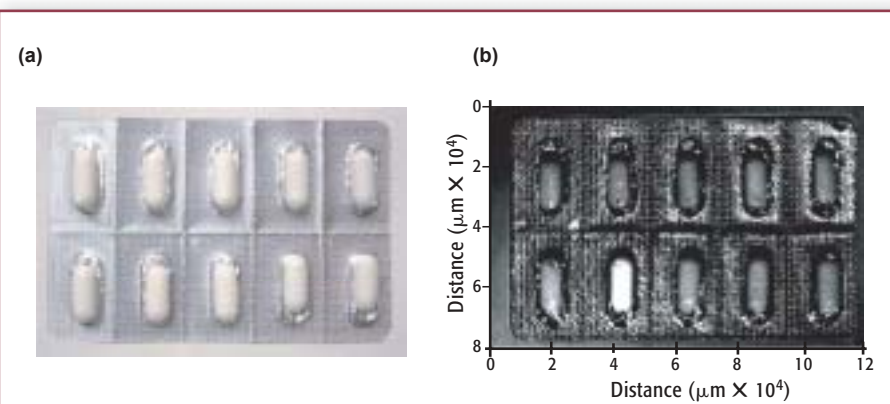
The FDA-supported PAT initiative appears to have gathered significant pace





**Figure 5.** Whole microbeads from an extended-release dosage at low magnification showing two distinct types. Shown are (a) a single-channel image at 2130 nm; (b) single-pixel microspectra of the two bead types; (c) an image obtained after performing particle-contour statistics; and (d) high-magnification chemical images showing spatial differences in the composition of the two types of beads identified in (a) – the left and right hand beads correspond to the dark and bright beads from (a).

For Client Review Only. All Rights Reserved. Advanstar Con



**Figure 6.** An adulterated pharmaceutical blister pack containing a single rogue tablet. Shown are (a) a visible image and (b) an NIR PCA score image.

and momentum during the past year or so, and undoubtedly will have a major impact upon the way pharmaceutical manufacturing is conducted in the future. The basic message is not just the implementation of more in-process measurements to shorten existing quality assurance–quality control times but to embrace the concept of process understanding, ultimately leading to process optimization. In order to accomplish this, the industry will need to look toward new technologies that can provide true insight into the component relationships and physical forces that drive and determine the quality and performance of pharmaceutical products. NIR-CI is such a tool.

### Acknowledgments

The authors would like to acknowledge the support of Dr. Robbe Lyon and Dr. Ajaz Hussain of the USFDA for providing the contaminant sample and pure component materials reported in this work.

### References

1. <http://www.fda.gov/cder/OPS/PAT.htm>
2. K.A. Bakeev, *Spectroscopy* **18**(11), 32 (2003).
3. C.T. Rhodes and K. Morissau, in *Encyclopedia Pharmaceutical Technology*, 2nd ed., J. Swarbrick and J.C. Boylan, Eds. (Marcel Dekker, New York, 2002) pp. 2689–2700.
4. *Pharmaceutical and Medical Applications of Near-Infrared Spectroscopy*, E.W. Ciurczak and J.K. Drennen III, Eds. (Marcel Dekker, New York, 2002).
5. S.V. Hammond, *European Pharmaceutical Review* **3**(4), 47 (1988).
6. F.C. Clarke, R.D. Jee, A.C. Moffat, and S.V. Hammond, *J. Pharm. Pharmacol.* **52**, 66 (2000).
7. E.N. Lewis, J.E. Carroll, and F.C. Clarke, *NIR News* **12**(3) 16 (2001).
8. R.C. Lyon, E.H. Jefferson, C.D. Ellison, L.F. Buhse, J.A. Spencer, M.M. Nasr, and A.S. Hussain, *Amer. Pharma. Rev.* **6**(3), 62 (2003).
9. R.C. Lyon, D.S. Lester, E.N. Lewis, E. Lee, L.X. Yu, E.H. Jefferson, A.S. Hussain, *AAPS PharmSciTech.* **3**(3), article 17 (2002).
10. H. Mark, *Anal. Chem. Acta.* **223**, 75 (1989).
11. P. Geladi and H. Grahn, *Multivariate Image Analysis* (John Wiley & Sons, United Kingdom, 1996).
12. [http://www.spectraldimensions.com/ps\\_isys.php](http://www.spectraldimensions.com/ps_isys.php).
13. R. Barer, A.R.H. Cole, and H.W. Thompson, *Nature* **163**, 198 (1949).
14. M.A. Harthcock and S.C. Atkin, *Appl. Spectrosc.* **42**, 3 (1988).
15. P.J. Treado, I.W. Levin, and E.N. Lewis, *App. Spectrosc.* **46**, 553 (1992).
16. D.S. Tezcan, S. Eminoglu, and T. Akin, *IEEE Trans. Electron. Devices* **50**(2), 494 (2003).
17. E.N. Lewis, P.J. Treado, R.C. Reeder, G.M. Story, A.E. Dowrey, C. Marcott, and I.W. Levin, *Anal. Chem.* **67**, 3377 (1995). ■

**E. Neil Lewis** is chief executive officer of Spectral Dimensions, Inc. (Olney, MD). **Joe Schoppelrei** and **Eunah Lee** are applications scientists for Spectral Dimensions. Please address correspondence to: [nlewis@spectraldimensions.com](mailto:nlewis@spectraldimensions.com).