analysis

Applications of NIR spectroscopy in assessing raw materials and solid dosage forms

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This article summarizes the principals of near-infrared (NIR) analysis and discusses how it has been applied to evaluate raw materials and finished products, including correlating NIR and dissolution testing results.

NIR spectroscopy has established itself in the pharmaceutical industry as a core analytical tool for quantitative and qualitative analysis of raw materials, finished products, and in-process samples. The power of NIR lies in its non-invasive and non-destructive methodology and its ability to extract product-specific information relatively quickly.

There are three spectroscopic methods used to observe molecular vibrations: Mid-range infrared, near infrared, and Raman. Mid-range infrared, more commonly called Fourier transform infrared (FTIR) is widely used to identify materials. It looks at fundamental molecular vibrations and the transition that occurs from the vibrational ground state to an excited state. There is inherent selectivity with FTIR because the fundamental vibrations give rise to strong absorbance. Preparing a sample for FTIR spectroscopy involves diluting it and combining it with a pellet of potassium bromide (KBr) or a mull of Nujol, which is a heavy mineral oil with an uncomplicated IR spectrum. Both compounds are ionic and will typically not generate peaks in the FTIR range, whose fundamental frequency vibrations lie between 400 and 4,000 reciprocal centimeters (cm^{-1}).

NIR spectroscopy looks at the higher energy states of vibrations—known as overtones—and at combination bands of the fundamental vibrations that are observed in the mid-range IR region. These overtones occur between 4,000 and 12,500 cm^{-1}, which is roughly two to three times the frequency of the fundamental vibrations. The stretching of nitrogen-hydrogen (N-H), carbon-hydrogen (C-H), and oxygen-hydrogen (O-H) bonds produces absorption bands in the NIR region; the absorption intensity decreases and the band broadens as the overtones increase.

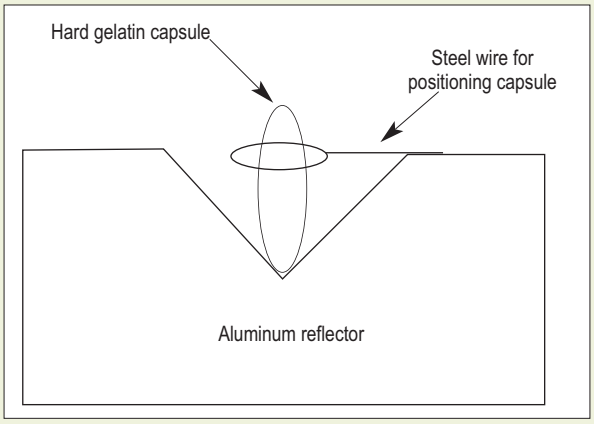
It is the lower intensity of absorption that allows direct NIR analysis of samples, eliminating the dilution step that FTIR requires. In fact, modern NIR analyzers incorporate Fourier transform, which enables them to give superior resolution over the earlier dispersive NIR instruments.

Raman spectroscopy differs from FTIR and NIR. It measures the light scattered from the sample, not the light it absorbs. Raman instruments can use visible or NIR laser light as their source, and Raman technology is complementary to mid-range and near infrared because it is sensitive to compounds that exhibit weak absorption (e.g., inorganic compounds and symmetric linkages such as C=C, C≡C, S-S, and C=N).

NIR analysis occurs through one of three primary modes: diffuse reflectance, transmittance, or fiber optic systems. When diffuse reflectance is used, the sample rests in an integrating sphere or reflector cone (Figure 1). Samples placed directly on a conical reflector have incident NIR light that is reflected—both directly and diffusely—and absorbed. The diffusely reflected light is collected and sent to a detector. In contrast, transmittance analysis involves incident light that is collected by the detector after it passes through the sample. With fiber optics, a cable carries the NIR source light to a probe sampling window, and after it has interacted with the sample (via reflectance or transmittance) the light returns to the NIR analyzer.

FIGURE 1

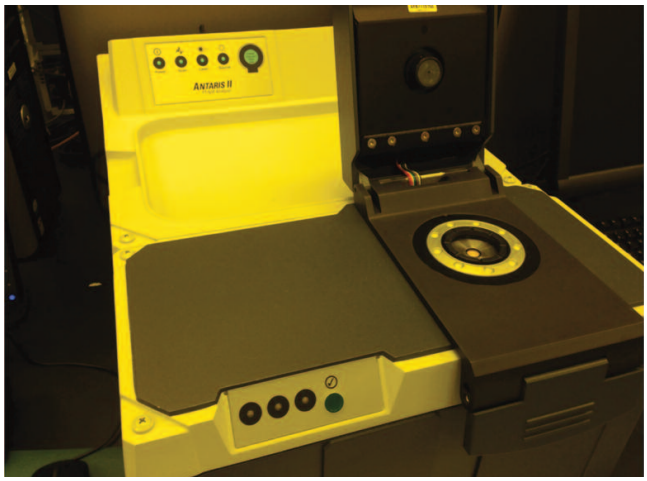
Diagram of a conical (90-degree) reflector used to scan hard gelatin capsules within an NIR spectrophotometer



NIR spectroscopy has been used in a number of pharmaceutical applications, including raw-material identification, in-process quantitative analysis, and finished-product assessment. Most materials lend themselves to NIR analysis, but those that do not (e.g., calcium phosphate and sodium chloride) are almost exclusively used as raw materials and can be analyzed by other spectroscopic techniques (e.g., Raman) or other technologies, including inductively coupled plasma (ICP) and ICP-mass spectroscopy.

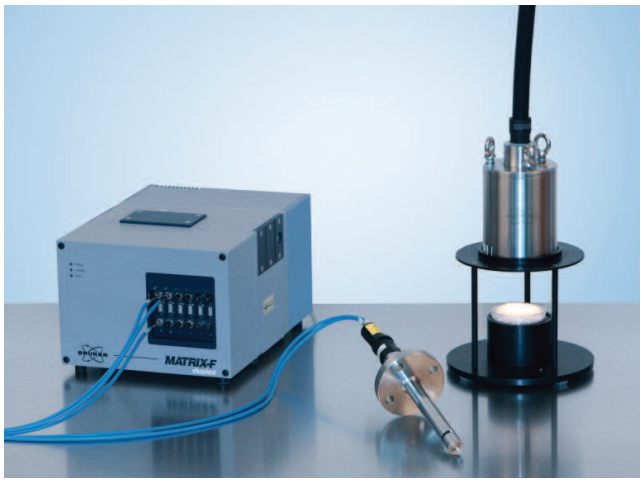
Raw-materials testing

NIR unambiguously identifies most raw materials by comparing a sample spectrum of each lot to a reference spectrum held in a "library." One of the greatest advantages of NIR instruments is their ability to scan materials through glass bottles, plastic bags and, in some cases, plastic drum-liners. This method of analysis is nondestructive and eliminates sampling.



An FT NIR analyzer (Antaris II, Thermo Fisher)

Several companies offer both hand-held and benchtop NIR analyzers. The photo above shows a benchtop analyzer that can provide just-in-time analysis of pharmaceutical raw materials. Other instruments, such as the one shown below, can measure materials with or without contacting them, which adds flexibility. Another advantage of NIR is the ability to analyze raw materials in both solid and liquid form.



FT-NIR spectrometer with a fiber optic coupling for use with flow cells and conventional probes that are suitable for solids and liquids (Matrix-F, Bruker Optics)

One key hurdle, or drawback, to using NIR for testing raw materials is the need to assemble a spectral reference library. Such libraries must often be custom-made because different companies or sites may use different grades of the same chemical. Microcrystalline cellulose, for example, comes in a variety of particle-size grades, and each would present different reference spectra, possibly complicating sample identification. This could be especially problematic at contract research organizations (CROs), which can test and release hundreds of different raw materials, including various grades of the same material. Assembling a library of reference spectra requires a large investment of time.

Once the library is ready and the NIR analyzer has collected the data, a multivariate analysis tool, such as principal component regression (PCR) is used to process the data. PCR reduces the dimensionality of a data set—

which includes a large number of uncorrelated variables—by linear transformation into a new set of uncorrelated variables called principal components (PCs).

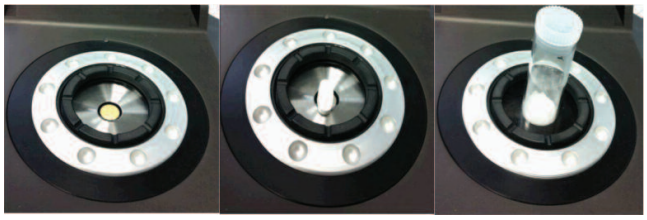
The PCs are structured so that the first few retain most of the spectral variation contained in all the original variables [1]. PCR is required in order to properly distinguish between subtle physical differences of raw materials. In general chapter <1119> "Near Infrared Spectrophotometry," USP 37 discusses method validation using NIR with respect to qualitative aspects, such as raw material identification. Specifically, it requires presenting both positive and negative challenges to the identification method to demonstrate specificity. A positive challenge entails the analysis of material that was independently received (e.g., the same material from three different lots) but that was not used to create the spectral library itself. Subsequently, this material must pass the test for identification. A negative challenge can also involve materials received on site that are similar to the library compounds in chemical structure, but not identical. These challenge materials should fail the identification test [2].

In-process testing

NIR has been used to determine percentage assay of drug in core (uncoated) tablets and in the powder blends used to make drug products. While penetration depths of 2 to 4 millimeters are possible with NIR (depending on the wavelength), methods typically use the diffuse reflectance mode for tablets and blends contained in glass vials. As with indentifying raw materials, NIR requires calibration standards, which are specially prepared tablets or blends that contain the exact amounts of drug or analyte. For example, three calibration standards for an assay method of cores might include drug concentrations of 90 percent, 100 percent, and 105 percent of the label claim. These three standards would be used for determining system suitability before the actual core tablets or blend samples were analyzed.

To generate a chemometric model, which is used to correlate the NIR spectral response with the amount of drug in tablet cores and blend samples, more extensive reference or "training" sets are required. For example, 10 reference standard blends spanning a range of 70 percent to 115 percent of the target drug concentration might be prepared, and a portion might be compressed into tablets. Ideally the tablets used in this calibration set would be compressed at the same hardness. Next, partial least squares or principal component analyses algorithms would be applied to the calibration set, and a mathematical model would be created that relates the NIR spectra to the concentration of drug in either the tablets or the blends.

For core tablets, the sample is typically set directly on the instrument's sapphire window, and at least one replicate is performed on each side (left and center photos in next column). Powder blends are placed in a glass vial in an amount sufficient to cover the bottom in a layer of at least 4 to 5 millimeters. Replicates are obtained by shaking or spinning the vial between readings. In a more subtle use of NIR spectroscopy, Cogdill et al. [3] correlated tablet hardness to changes in NIR spectra. Their study is important because it reinforces the need to establish the training or calibration sets discussed above using carefully controlled physical parameters.



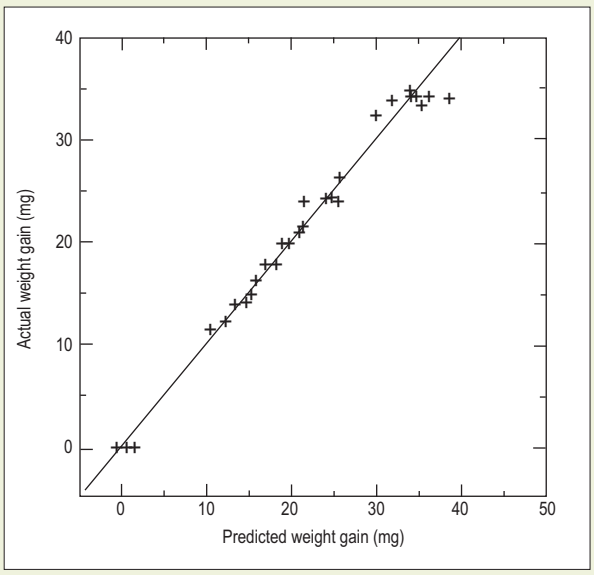
The diffuse reflectance sample window of an FT NIR analyzer (Antaris II). From left to right: Open cell; tablet placed directly on window; and vial with formulation blend covering the window.

Finished-product testing

Moisture uptake of capsules. NIR has also been used to monitor the moisture uptake of intact hard gelatin capsules [1]. These tests employed a specially designed conical reflector [1, 4] that positions the capsule along the axis of rotation of the conical reflector, thereby maximizing diffuse reflectance (signal) while minimizing specular reflectance (Figure 1). The study exposed capsules to water inside a desiccator for as long as 120 hours, and their weight gain was monitored to determine water uptake. The NIR spectra of the capsules showed a strong correlation to increases in capsule mass due to their exposure to moisture (Figure 2). Predicted weight gain was calculated using the PCR values from the NIR spectra against the gravimetric values. Determining the water content of intact gelatin capsules using NIR saves time, effort, and expense over traditional methods of moisture analysis, such as Karl Fischer titration.

FIGURE 2

NIR spectra of capsules show a strong correlation to increase in capsule mass after exposure to moisture (22°C at 100% RH). Adapted from Cogdill et al. [3].



Excipient contaminants. Trace amounts of contaminants in excipients have been shown to interact with gelatin capsules. Formaldehyde, just one of a variety of reagents and contaminants capable of interacting covalently with gelatin, has been studied most extensively [5]. In one study, hard gelatin capsules exposed for as long as 24 hours to a simulated atmosphere containing a small amount (parts per billion) of formaldehyde were filled with a commercially sourced amoxicillin formulation. The capsules were scanned using NIR, after which each exposure group was subjected to dissolution testing (figures 3 and 4). A strong correlation was established between the first six principal components and the percentage of amoxicillin dissolved in pH 1.2 media for 45 minutes [6].

Polyethylene glycol (PEG)—a common component of softgel fill materials—is known to contain trace amounts of formaldehyde, which can migrate into the gelatin shell. In a study of how NIR can monitor that migration [7], five treatment groups of softgels were filled with PEG 400 that contained 0, 0.05, 0.10, 0.20, and 0.40 percent (v/v) of aqueous formaldehyde. These were stored for 48 hours, after which the PEG 400 was emptied from the capsules, and NIR scans were obtained from each treatment group (Figure 5). The results showed excellent correlation between the actual concentration of formaldehyde in the PEG-filled capsules and the principal-component values obtained from the NIR spectra (Figure 6). The crosslinking reaction—which the study's authors had hypothesized would occur—was confirmed by spectral changes that occurred in the NIR.

Figure 3

NIR spectra of hard gelatin capsules exposed to formaldehyde for different periods. Adapted from Gold et al. [6].

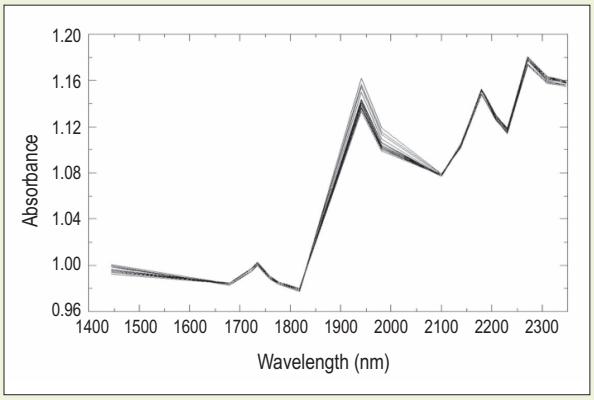


Figure 4

Correlation of the actual dissolution of drug from hard gelatin capsules that were exposed to formaldehyde to the dissolution predicted from NIR spectral data. Cross-validation samples are superimposed on the calibration line; error bars represent the range (extreme values). Adapted from Gold et al. [6].

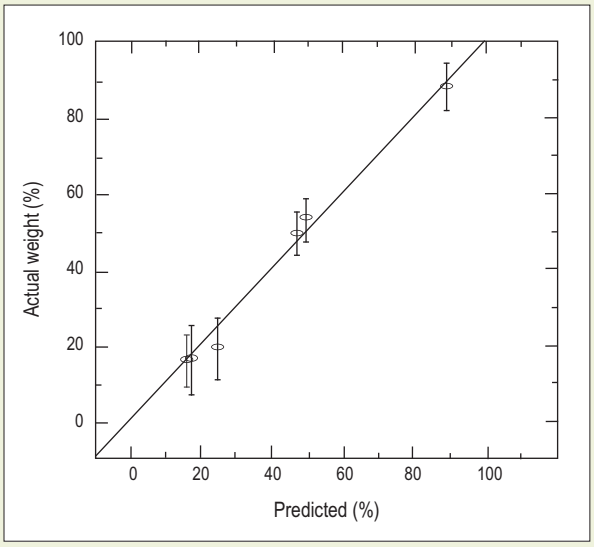


Figure 5

NIR spectra of empty soft gelatin capsules that had been filled with a PEG solution containing different amounts of formaldehyde. Adapted from Gold et al. [7].

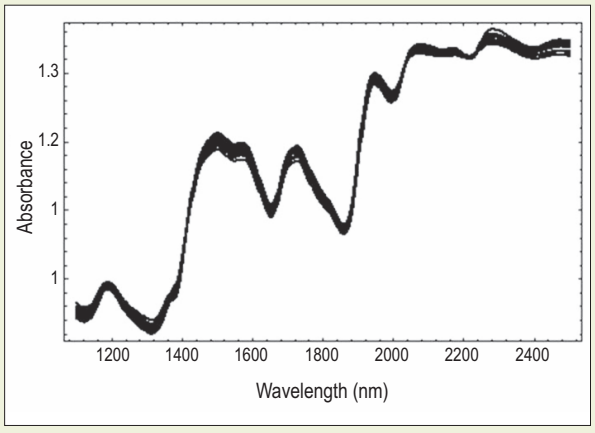
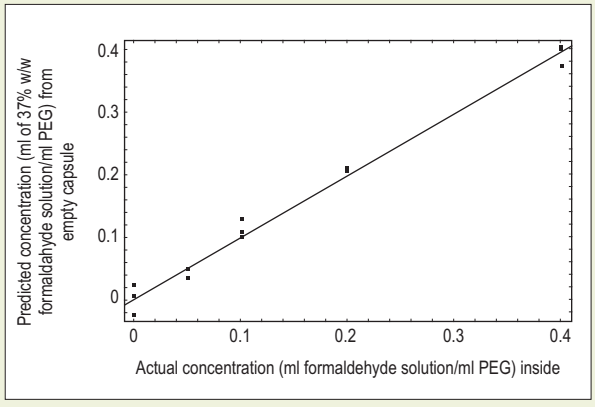


Figure 6

Correlation between the actual concentration of formaldehyde in PEG-filled capsules and the principal-component values obtained from the NIR spectra. The calibration line (r2=1) is shown superimposed on the data points. Adapted from Gold et al. [7].



Tablet dissolution. NIR spectroscopy can also predict the dissolution rates of tablets, as demonstrated in a study of intact carbamazepine tablets [8]. Moreover, the authors showed that branded and generic carbamazepine tablets reacted differently when exposed to high humidity.

In an earlier study, Lodder et al. showed how forensic chemistry might benefit from non-invasive NIR spectroscopy to detect adulteration in both prescription and over-the-counter drug products [4]. Although it is impossible to predict what contaminant might be placed in a particular product, the authors argued that with a well constructed training/calibration set for each brand and SKU of product, a multivariate analysis technique could mathematically distinguish an outlier dosage form from a good one. In other words, the study's NIR method could be used to qualitatively determine whether a finished product was genuine or adulterated.

Future uses

NIR spectroscopy is a powerful tool that has just begun to be used in pharmaceutical development and manufacturing settings. Several manufacturers of NIR instruments have made implementation of raw-material identity testing very accessible. Yet the quantitative aspects of NIR spectroscopy have not been fully realized. For example, less conventional dosage forms, as well as single-unit operations, should benefit from in-process testing that can determine the amount of drug or other analyte present. Roller compaction is a good example. It would benefit from NIR's ability to rapidly and non-invasively determine drug content and ribbon density. NIR could also supplement diffusion/erosion modeling of drug release from matrix tablets. It may also emerge as a means of determining the effectiveness of drug layering on pellets, sugar spheres, and tablets. Finally, NIR's contribution to identifying counterfeit and adulterated drug products should not be underestimated. *T&C*

References

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