Hyperspectral Monitoring of Continuous Pharmaceutical Manufacturing

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Pharmaceuticals, food, and other materials manufactured on roll-to-roll equipment can possess spatially nonuniform concentrations that manufacturers need to monitor to insure quality and to improve manufacturing processes. Manufacture of transdermal products, such as patches that deliver nicotine, glyceryl nitrate, or estradiol transdermally, typically occurs on such equipment.

As early as 1975, scientists recognized the need to monitor the compositional distribution across a web-type line that manufactures pharmaceuticals [1], but the technology to monitor the entire area for compositional differences was not available. In manufacturing transdermal patches, pull samples are not ideal because the practice creates areas cut out of the web. The manufacturer must handle these areas as exceptions further downstream when the manufacturing process laminates the release liner, adhesive backing, packaging, and other layers onto the substrate and cuts the final product to the unit-dose size.

Near-infrared (NIR) spectroscopy is a widely used tool now for identifying materials and for monitoring composition of products, coating thickness, blend uniformity, and other pharmaceutically relevant parameters [2]. This technology is fast and nondestructive and can provide quantitative analyses of pharmaceuticals, both in development and on the production line [3, 4]. Hardware advances in spectrographs, computing power, and photodetectors now allow companies to combine spectroscopy with imaging technology, creating so-called Hyperspectral Imaging Systems (HSI).

The FDA's initiative for Process Analytical Technology (PAT) is driving the development of manufacturing processes that move pharmaceutical quality to a new level [5]. As its basic premise, the PAT initiative suggests that understanding and monitoring critical steps in the manufacturing process can provide a reduction in costly and disruptive failure rates. The manufacturer must conduct in-process evaluations that allow needed corrections to be made before a manufacturing run is completed. PAT emphasizes designing quality into the product rather than relying on product testing on the back end as a means of identifying off-specification products.

Hyperspectral imaging during manufacture is a new analytical technique for continuously monitoring manufactured products in pharmaceutical and other industries. For measurement of composition, manufacturers most commonly use the near-infrared wavelength range. By combining spectroscopic technology with an imaging camera, manufacturers can monitor the entire surface of pharmaceutical products continuously during roll-to-roll manufacturing. The end result is a full spectrum containing chemical information at each spatial point. From this nondestructive method, the manufacturer can obtain information on several important aspects of the product, including variations in concentration, nonhomogeneous distribution of components, and spatial locations of contaminants.

Manufacturers have used HSI in the pharmaceutical industry:

- To identify counterfeit drugs [6, 7]
- To detect dissolution differences between tablets at the microscopic level [8]
- To monitor process development [9] and stages of pharmaceutical production [10]

Manufacturers cannot define the distribution of the active pharmaceutical ingredients (APIs) and the excipients with a single bulk concentration. They also must verify an additional dimension, the spatial distribution of the API and excipients [11, 12]. Variation may exist in several aspects of the extruded or deposited, medicated layer of a transdermal product.

In the axial-pull direction, the variation can be due:

- To the composition of the layer, which may vary over time due to settling in the applicator module
- To the thickness of the layer, which can be inconsistent due to variations in the temperature or viscosity of the deposited mix of materials

In the cross-web direction, the variation can be due:

- To nonuniformity of the mechanism for layer deposition
- To local temperature variations at the point of the deposition
- To edge effects toward the sides of the web

Methodology that uses NIR spectroscopy is useful for analyzing materials for transdermal [13] and thin-film drug delivery. Fountain et al found NIR to be an effective and nondestructive method of determining the content uniformity of testosterone in thin-film composites [14].

Hyperspectral Imaging

The term hyperspectral imaging or chemical imaging refers to the technique where each point in the surface of a sample has a respective spectrum from which a scientist can calculate the chemical composition. The spectra can be UV, visible, near-infrared, or mid-infrared, depending on which region is most useful for the application. As Figure 1 shows

Figure 1

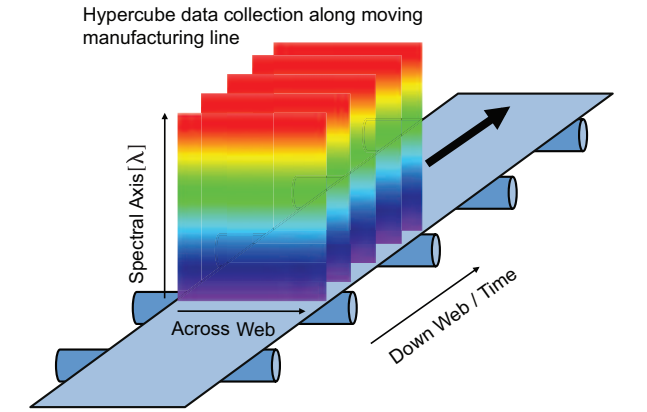

Figure 1. Shows hyperspectral data collection: The system collects a full spectrum for each point on a line across the transdermal web. As the web moves past the camera, the system forms the complete hypercube.

schematically, each point in the down-web and across-web directions has a complete spectrum associated with it.

The compilation of this information, called the hypercube, can be a massive amount of data, depending on the spatial and spectral resolution. In off-line applications for laboratories, the system collects the data for the hypercube all at once and saves it for further processing. In a continuously moving sample, the data processing must keep pace in real time with this high rate of data collection and compress the information for recording. The system also can report data continuously for use in real time by process-control computer systems.

The hyperspectral camera consists of a lens, a spectrograph, and a focal plane array (FPA) sensor. The lens captures the image of a line from the sample to the entrance slit of the spectrograph, which in turn creates images of each point on this line, breaking it

Figure 2

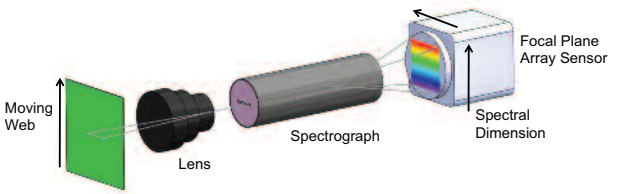

Figure 2. A hyperspectral camera includes a lens, a spectrograph, and a focal plane array sensor.

down into its spectral components and projecting it onto the FPA (Figure 2). Using specialized lenses, the same camera system can perform noncontact monitoring of the features on a 30-inch web, or with a different lens, it can detect particles as small as 30μm.

Issues in Hyperspectral Measurement for Transdermal Applications

A complete measurement system consists of an illumination module, a hyperspectral camera with its controller module, power supplies, and a data collection and processing system. Figures 3 (a) and (b) show the two basic optical arrangements.

Figure 3

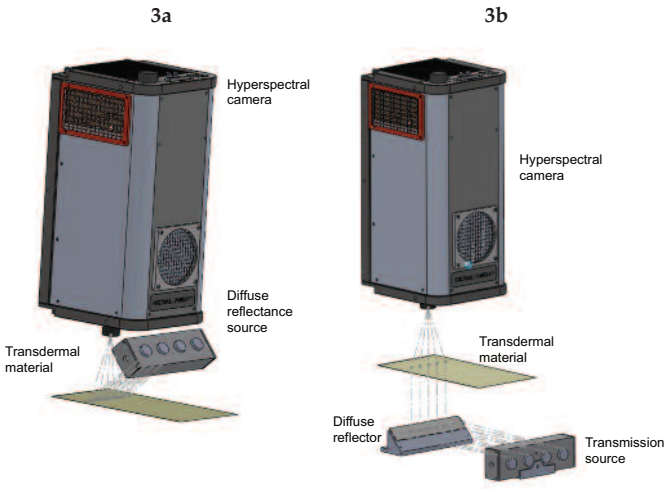

Figure 3: (a) Shows the optical arrangement for reflectance-mode imaging: The system directs light at the surface of the material, and the camera above measures the reflectance. (b) Shows the optical arrangement for transmission-mode imaging: The system directs light at a diffuse reflector, which redirects the light through the material. The material absorbs light at characteristic wavelengths, and the camera measures the remaining light intensity.

When choosing placement and arrangement for measurement, the manufacturer must consider the spectral characteristics of the transdermal product. For example, the spectrum of a 0.075mg-per-day estradiol patch shows approximately 0.4 to 0.5 peak-to-valley absorbance in both transmission and reflectance, which is a reasonable intensity for quantitative work in either mode (Figure 4).

Figure 4

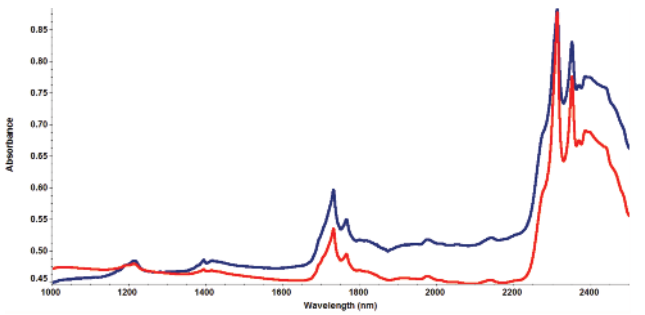

Figure 4. Shows the near-infrared spectra under transmission-measurement (red) and reflectance-measurement (blue) modes of a 0.075mg-per-day estradiol patch.

In contrast, other products may limit measurement to either transmission or reflectance only. For transdermal products in general, the transmission-measurement mode is preferable because the light usually passes through the entire cross-section of the product. It is generally a good practice to choose a measurement point physically closest to the location where the manufacturing process deposits the API-containing-material and where the process has not yet applied the additional layers.

In the example for the estradiol patch, the manufacturer can observe good-quality spectra even with the peel-off layer in place. The peel-off layer, however, is thin with smooth and parallel sides that produce residual fringing when the system transmits light through the whole stack, introducing yet another variable into the measurement (Figure 5).

Figure 5

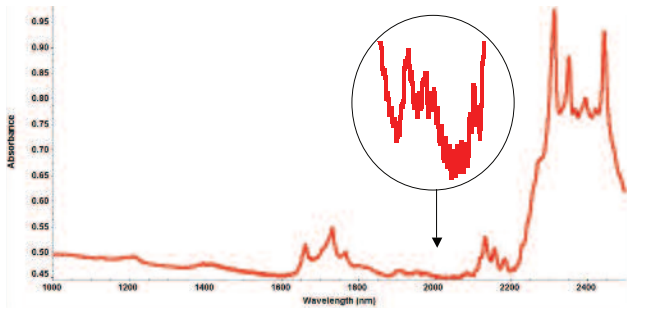

Figure 5. Shows the near-infrared spectrum of a 0.075mg-per-day estradiol patch with the peel-off layer in place. Note the interference fringing around 2000nm magnified above.

Calibration

NIR spectra are relatively featureless and the spectra of the different components in the sample usually overlap. To predict composition, the manufacturer usually must use multivariate calibration rather than univariate calibration at a single wavelength. Also, multivariate measurement maximizes sensitivity, which usually is desired because the time available for one measurement is often limited, especially in on-line situations.

The calibration is a mathematical model that the manufacturer establishes during the preparatory phase of the process installation and that relates the measured spectra to physical characteristics of the sample, such as concentration. Manufacturers create calibrations for a specific set of substrate, API, camera, white reference material, and illumination. See Miller [15] for a more detailed general description of the steps of calibration development.

Scientists base multivariate spectral calibrations on classical least-squares methods or on statistical approaches like partial least squares (PLS) or principal component regression (PCR). They typically use the latter in more challenging applications as are often found in conventional NIR or in imaging [16, 17], which Gendrin reviewed [18].

The statistical approach to calibrating measurement instruments requires calibration standards with known and varying concentrations in the analyte and excipients. In practice, this approach requires production of several different, off-specification products that the scientist uses for the calibration. Creating these standards costs time and money and is often challenging due to practical limitations associated with varying the process. The statistical approach also makes testing and validating a challenge because the inner working of the *black box* calibration algorithms is not transparent to the user or regulator.

The Science Based Method of Calibration (SBC)

For process monitoring of pharmaceuticals where ingredients are well-known, manufacturers usually can use an alternative method, the so-called science-based method of calibration (SBC). This technique [19 to 21] makes use of an understanding that led to the mathematical definition of selectivity in the multivariate case [22]: *All* calibration methods, including not only PLS and PCR but also the traditional *classical* methods, produce a result that can be written in the same mathematical form (Equation 1).

$$b_c = \frac{\Sigma_c^{-} g_c}{g_c^{T} = \Sigma_c^{-} g_c}$$

In this equation:

- The parameter b_c is the regression-vector result.
- The parameter g_c is the estimate of the response spectrum of the analyte.
- The parameter Σ_c is the estimate of the covariance matrix of the spectral noise.

Assume a transdermal application where the analyte of interest is the mass-area density of the API (g/cm^2) and the measured spectra are in absorbance units [AU].

In this example:

- The response spectrum g_c has units of AU/(g/cm^2).
- The inverse covariance matrix Σ_c^{-} has units AU^{-2}).
- The regression vector b_c has units (g/cm^2)/AU.

In the older classical calibration methods, which are based on spectral fitting, the user defines the signal g_c, but the algorithm implicitly defines the noise estimate Σ_c, which therefore is not under the direct control of the user. In statistical calibrations like PLS, the algorithm implicitly defines both the signal and the noise estimates.

SBC is simple to explain because it puts both estimates under the user's control; that is, the user must define both parts explicitly and then put them into Equation 1.

As an example, assume that a scientist is measuring spectra from a running process, and somehow, he or she can fix the concentration of the analyte at some value, say, 0.75 g/cm^2. The variation of the measured

spectra is then the spectral noise; that is, Σ_c is the sum of variances from all spectral effects other than the analyte, including changes in excipient concentrations, sampling noise, and hardware noise. In practice, scientists can determine the covariance matrix Σ_c from a large number of measured spectra regardless of whether the analyte is fixed or not, although some precautions may be necessary in the latter case [22]. Since these spectra do not require lab reference values, determination of Σ_c is relatively easy. The computation itself is analogous to computing a standard deviation in the univariate case.

Next, assume that all spectral-noise effects, even the hardware noise, are somehow frozen in time. The only variation in the measured spectra then comes from changes in the analyte concentration. This condition defines the application-specific, analyte response spectrum g_c, which depends not only on the chemistry but also on the physical characteristics of the sample, such as its optical scattering, and on the chosen geometry of the sampling optics. In practice, a few measurements in the lab can determine the response spectrum, simulating the conditions of the actual on-line application.

When the scientist matches the signal and noise estimates used in the calibration, g_c and Σ_c, to the reality of the measurement situation, $g_c \cong g_{true}$ and $\Sigma_c \cong \Sigma_{true}$, then the result of Equation 1 is the spectrometric version of the well-known matched filter, which has widespread use in time-signal processing equipment such as radar or mobile phones. The matched-filter solution is the globally best solution in the mean-square error sense; that is, it can achieve selectivity at the best possible sensitivity, thus achieving minimum standard error. Typically, a user's spectroscopic expertise and application knowledge can produce estimates that are superior; that is, better matched, than the estimates that algorithms implicitly make. Compared to classical calibrations, matched-filter solutions have in most cases a significant advantage in sensitivity. Compared to PLS and other statistical methods, the matched-filter solution has an advantage in selectivity and often also in sensitivity.

Prediction of the Analyte Concentration

As in other calibration methods, prediction of the analyte concentration in hyperspectral-measured spectrum **x** is by dot-multiplication with the *b*-vector (Equation 2).

$$\hat{y}=(x-x_{OP})^T \bullet b_c + y_{OP}$$

Where y_{OP} and x_{OP} describe the *operating point* of the measurement.

Usually, a scientist chooses these points as the mean values but sometimes also chooses other operating points, such as $y_{OP} = 0$ and $x_{OP} = x_{Clean}$ for an impurity measurement. The *b*-vector is the end-result of the calibration effort, and the high-speed computing equipment uses it to predict the composition. During a manufacturing run, the sensors are not always looking at the type of material for which they were calibrated because:

- The process may not apply some layers at the beginning or end of a run.
- Sample areas could be cut out of the film.
- The camera may be looking at a wider swath than the product web.

Manufacturers must implement outlier-detection methods to ensure that the camera detects spectra that lie outside the valid calibration range and that the control system reacts according to predetermined rules. Simple application-specific algorithms can detect various forms of rough outliers.

The Mahalanobis' distance, which is a sensitive multivariate measure of distance, can detect subtle changes in the spectral features that otherwise would be difficult to detect. The manufacturer computes this distance based on the $\bar{\Sigma}_c$ estimate that the user made in SBC or that the algorithm defined in PLS or PCR. The manufacturer thus can detect sample points outside the expected range and block the prediction for that point. This practice is usually a standard part of the prediction-software routine.

Compared to PLS, matched-filter calibration (SBC) can significantly reduce the cost and the time required for multivariate calibration, often by as much as 80%, and at the same time, improve the selectivity and sensitivity of the multivariate measurement [22]. Thus, it is prudent to try the SBC approach first.

For complex cases where the analyte of interest is not an identifiable and separately measurable chemical entity, such as in the case of chemical interactions or of phase transitions of ingredients, SBC is not the method of choice. In such cases, manufacturers can use statistical correlative methods like PLS, which in challenging cases may require hundreds of calibration samples with known reference values. In all cases, the manufacturer must use independent validation samples to test the performance of the calibration.

Example of Hyperspectral Monitoring in a Patch

Since transdermal products are different proprietary formulations using a variety of opaque or transparent substrates, the manufacturer must analyze each application separately. To illustrate a hyperspectral analysis, Figure 6 shows a scan of an over-the-counter patch. The authors recorded the spectra in reflectance in the 1000 to 2500nm range and processed the data using the above mentioned SBC algorithm [23].

For the prediction, the authors used the spectrum of liquid nicotine as the pure analyte, and applied no additional slope or bias correction. In this example, thickness changes in the layer as well as the concentration distribution of the API in the matrix affected the relative abundance of the API. A hyperspectral imaging system can perform the same or similar measurements and predict the distribution of ingredients on-line at the rate of the process to evaluate uniformity of the product during manufacturing.

Figure 6

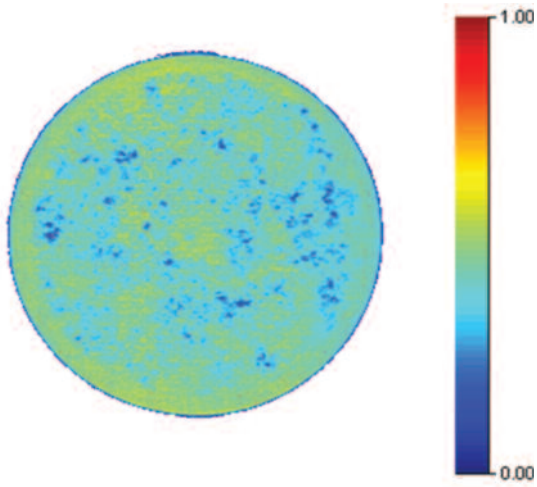

Figure 6. Shows predicted nicotine levels in a 21mg over-the-counter patch. Colors toward the red indicate higher amounts of nicotine; those toward the blue indicate lower relative amounts.

From Laboratory to On-Line Process Monitoring

Hyperspectral push-broom, line-imaging cameras are ideally suited for continuously moving industrial samples, producing high-resolution spectra of every point of a line at very high speed [24]. Fully parallel spectral measurements allow the scanning of moving samples to monitor the entire surface. The manufacturer can arrange the illumination and the sample in diffuse reflectance or diffuse transmittance as described above. An important advantage of hyperspectral imaging is that the manufacturer can test and calibrate the camera in the laboratory and then transfer it to the production line to monitor the manufacturing process.

A typical hyperspectral monitoring system for a transdermal or other roll-to-roll manufacturing process consists of the following equipment (Figure 7):

- **A hyperspectral camera, such as a short wave infrared (SWIR) camera, typically capable of producing 320 spatial points with 256 spectral points each, at a rate of up to 100 frames per second**

  The spectral points span wavelengths from 1000 to 2500nm. For example, the density of measurement points for a 40-centimeters-wide web moving at a rate of 60 centimeters per minute can be 800 points per square centimeter; that is, eight points per centimeter across the web and 100 points per centimeter down the web. Manufacturers typically use averaging of spectral data to increase the signal to noise at the expense of reducing the spatial resolution.

- **A high-speed device to process the spectral data, such as the Hyperspectral Prediction Engine™ (Middleton Research, Middleton, Wisconsin USA)**

  The process requires a very fast, dedicated computing device to process the hyperspec-

tral data according to the predetermined calibration algorithm and to send the results to the monitor computer to be further analyzed and displayed. The manufacturer places this device in the data path between the camera and the monitor computer for the process.

- **A computer that allows the user to view prediction data, set camera parameters, and interact with a central process server**
- **A line-transmission source or reflectance line source, as necessary, to illuminate the sample**
- **White reference material to account for actual levels of illumination across the web**
- **A frame to mount the camera over the manufactured material, the light source under the material, and the optical reference material**
- **A validation system consisting of a protocol and traceable standards to test wavelength accuracy, spectral noise, and linearity**

Figure 7

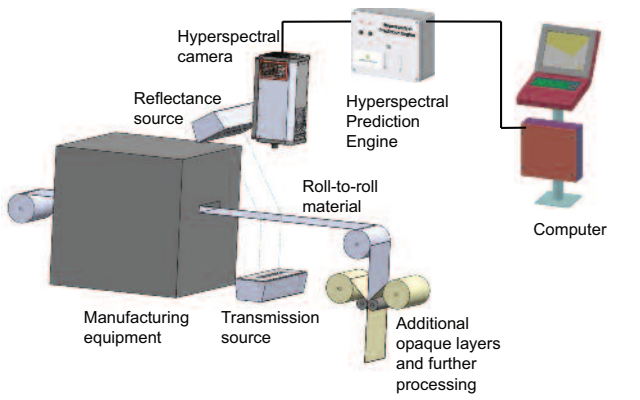

Figure 7. Hyperspectral monitoring system

Challenges

Analyzing the composition of a complex pharmaceutical product during manufacturing is a significant challenge. Some applications are more difficult due to low concentrations of the monitored ingredients. In addition, changes in product characteristics may occur throughout the production process, such as changes in temperature and related consistency, evaporation of solvents, and phase transitions of materials due to melting or crystallization. Consequently, customization of the hyperspectral monitoring system must include measurement-point analysis and understanding of methods necessary to optimize this technique.

Conclusion

Monitoring of continuous pharmaceutical production is a new challenge in the light of the PAT initiative. Manufacturers can monitor transdermal and other roll-to-roll production using high-speed, hyperspectral instrumentation if the analytical task lends itself to spectroscopic monitoring using reflectance or transmission, near-infrared measurements. Pull samples in manufacturing are disruptive and costly, and manufacturers can replace them with process monitoring that constitutes 100% inspection using a hyperspectral camera system. The manufacturer can perform feasibility measurements in the lab and then can move the hyperspectral device to the production floor and integrate it into the process-monitoring and process-control system.

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