NIR Chemical Imaging as a Process Analytical Tool

NIR chemical imaging greatly extends the capability of NIR spectroscopy, and is the only PAT-applicable blend monitoring technique that gives both statistical and direct information about individual sample components on the micro scale.

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While it is generally assumed that the manufacturing steps performed to transform a collection of raw materials into a finished pharmaceutical product significantly impact manufacturability and product performance, an understanding of these phenomena seem to be either illusive or – even worse – neglected. In fact, it has led some sources to label the apparently simple process of dry-blending pharmaceutical ingredients as a ‘black art’ or even ‘alchemy’ (1).

A chief reason why this process is not well-characterised is the lack of analytical technology capable of delivering detailed information of the blending process at both the macro- and micro-scale. In addition to providing blending data for all components – active pharmaceutical ingredients (APIs) and excipients alike – an ideal technique would also perform these measurements in real-time and non-invasively – that is, without having to remove sample from a blend vessel. The accepted standard in the industry is currently to perform HPLC on samples that have been removed from the vessel. This approach is time-consuming and not considered to be compatible with US FDA Process Analytical Technology (PAT) regulations (2), as it does not provide an understanding of the blending process – it simply gives an assessment of whether or not an end-point has been reached with respect to the bulk distribution of the active ingredient.

Non-wet chemistry approaches that may be appropriate for PAT are being evaluated by the industry, including near-infrared (NIR) chemical imaging, single point NIR spectroscopy, acoustic spectroscopy and effusivity. Except for NIR chemical imaging, these alternative techniques can only deliver data on macro-scale blending characteristics, as they track only average mixing...
progress, and cannot monitor the micro-mixing characteristics and domain sizes of individual components. NIR chemical imaging, though, can provide quantitative information about both the spatial and chemical characteristics of individual blend components at the micro scale. As such, it can be utilised to elucidate domain sizes and spatial distributions of both the API and excipients simultaneously. It is the only method of those considered to be relevant to PAT that is a primary technique – that is, it does not need to be correlated with other physical properties, or results from other methods.

**NIR CHEMICAL ANALYSIS**

A typical NIR chemical imaging instrument collects many thousands of spatially distinct NIR spectra simultaneously in a single data-set. These spatially resolved data can be acquired over a microscopic or macroscopic portion of a sample, and provide qualitative and quantitative insight into the functionality of heterogeneous samples such as pharmaceutical tablets, polymer laminates, or agricultural and biological materials. First commercialised five years ago, NIR chemical imaging is a relatively new addition to the analytical toolbox; however, its demonstrated utility in solving real-world problems has encouraged its rapid acceptance.

Currently, NIR chemical imaging instrumentation is predominantly deployed in laboratory settings for product development and formulation R&D, and as a trouble-shooting tool for manufacturing. Because it builds on the analytical capabilities of NIR spectroscopy, it is a well-understood and well-characterised tool, and the underlying physical principles of how and why it works are fully established and accepted. It retains many of the attributes of traditional NIR bulk spectroscopy – such as minimal sample preparation, flexible sample presentation, robust and easy-to-use instrumentation, and rapid data acquisition. It can also get around some of the more tricky aspects of NIR spectroscopy – such as the need for calibration sets and transfer of calibration between instruments.

Although novel analytical techniques tend to begin their life cycle viewed as more of an art form than a science, the most useful and robust techniques do move into the mainstream. NIR imaging has made that transition and is deployed in a variety of industrial settings elucidating novel critical product performance attributes. Although novel analytical techniques tend to begin their life cycle viewed as more of an art form than a science, the most useful and robust techniques do move into the mainstream. NIR imaging has made that transition and is deployed in a variety of industrial settings elucidating novel critical product performance attributes. In addition, by providing robust, reliable and automated data collection capabilities, coupled tightly with quantitative, statistical, objective, reproducible and automated data processing tools, NIR chemical imaging has moved rapidly from a specialised technology into a routine and highly desirable quantitative analytical tool. Robust instrumentation, modular software that enables
the development of turnkey solutions and instrument platforms that transition from R&D to process environments are just some of the attributes that contribute to the usefulness of NIR chemical imaging as a routine QA/QC tool. Current developments in chemical imaging have focused on the implementation of numerical strategies, algorithms and routine software tools to automate data-mining and enable turnkey analytical solutions to be developed.

**INSTRUMENTATION AND DATA COLLECTION PROTOCOL**

The basic data construct for global spectroscopic imaging systems is shown in Figure 1a. The data-set, commonly referred to as a hypercube, consists of a sequence of images of a sample recorded over a series of infrared wavelengths or frequencies. The data can be viewed as a collection of frequency-resolved images (see Figure 1b) or – as a spectroscopist would view it – a series of spatially resolved spectra (see Figure 1c). The chemical image in Figure 1b is that of a whole tablet, demonstrating a field of view (FOV) of approximately 13 x 10mm. In this example, because the full data-set contains 81,920 spectra, a single micro-spectrum samples a location on the tablet surface of approximately 40x40 microns. This magnification is configurable, and can be increased or decreased by the simple selection of the appropriate image formation optics.

To create a hypercube, data can be collected one image at a time, one spectrum at a time or one line image at a time. However, not all of these approaches are relevant for process instrumentation. Building up a data-set through point- or line-mapping – which are both mechanically-driven scanning approaches – does not afford the speed necessary for process monitoring applications. In addition, because of the delicate moving parts, they are not as rugged an instrumental approach as global imaging. Furthermore, some of the unique capabilities of global imaging – such as the ability to have standards or pure components in the same field of view as the sample – are negated with the point- and line-mapping approaches. Global imaging using a solid state tunable filter and focal plane array – a common approach to NIR imaging – is currently the only approach relevant to process applications. Below, we describe a specific focal plane/tunable filter approach that provides a no-moving parts, solid state and rugged instrument platform.

**IMAGING OF BLEND PROGRESSION**

As an example of the qualitative and quantitative information that NIR chemical imaging can provide for pharmaceutical blending, we present a simple example – a 50:50 blend of lactose and an active pharmaceutical ingredient (API). NIR spectral information can be used to produce images that visualise the abundance, distribution and domain size of the API within the lactose matrix. The images reveal the extent of the blending at each time interval. Data was processed by taking a second derivative and normalising the results. Figure 2 shows
NIR chemical images of this model pharmaceutical blending process at the three blending-time intervals: 3, 6 and 10 seconds respectively for 2a, 2b and 2c. The contrast in these images is based on the strong API feature (red domains) relative to lactose (blue background) at 1632nm. Looking at these images, an observer could make several subjective observations; the API domain sizes appear to decrease with increased blending time, and also appear to become more homogeneously distributed. However, for a technique to be useful in a process monitoring application – or any analytical application – the results obtained must be objective, reproducible, automated and quantitative. NIR chemical imaging is able to do this.

One approach for deriving numerical information is to represent image data as histograms, enabling statistical and objective analysis of the images. Figures 3a-3c show the histogram representation of the 3, 6 and 10 second blend images, respectively. Table 1 summarises the resulting statistical analysis. Qualitatively, the brighter the pixel, the more similar it is to API, and these pixels appear to the right on the x-axis. The more homogeneously the API is distributed, the narrower the distribution will be. The standard deviation values in Table 1 decrease with increased blending time, verifying that the blend is becoming more homogeneous – that is, the distribution of pixel intensities is becoming narrower, and the bulk of pixels are becoming more similar to each other.

A positive skew indicates that the tail on the right side of the distribution is longer – in this case, representing a population of pixels with high API content. As the skew decreases with blending time, it means that these high API content domains are mixing with lactose and moving toward a mean blending value. The final category in the table, kurtosis, is a measure of the ‘peakedness’ of a distribution, or alternatively the size of the tails. A large positive number indicates that the distribution tails are large, implying that a significant population of pixels does not lie close to the mean. There is no trend relating kurtosis and blending time, although the 6- and 10-second values are lower than the 3-second value. In other words, although we can see progress of mixing in the overall homogeneity based on standard deviation and skew values, there are still noticeable domains of API present in the mixture. This is visualised in the images, where API-rich domains are still readily apparent after 10 seconds of blend time. It is worth noting here that other methods for monitoring pharmaceutical blending produce a single ‘average’ value for the composition at any given time point.

![Figure 3: Histogram representations of the corresponding images in Figure 2](image)

**Table 1: Statistical analysis of the image data shown in Figures 3a to 3c**

<table>
<thead>
<tr>
<th></th>
<th>3 seconds</th>
<th>6 seconds</th>
<th>10 seconds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean value</td>
<td>-0.0332</td>
<td>-0.0357</td>
<td>-0.0301</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>0.048</td>
<td>0.042</td>
<td>0.036</td>
</tr>
<tr>
<td>Skew</td>
<td>1.944</td>
<td>1.648</td>
<td>1.522</td>
</tr>
<tr>
<td>Kurtosis</td>
<td>5.882</td>
<td>5.565</td>
<td>5.698</td>
</tr>
</tbody>
</table>

![Figure 4: A schematic representation of the spatial distribution of two components present in a 50:50 proportion as blending progresses](image)
measurement point. From these data distributions, it is obvious that the average value (centre of the distribution) is only one measure of the state of the blend and the ‘range’ of states – reflected in the distribution width is also critically important.

A schematic representation of six different blends all with 50% API is shown in Figure 4. Red and yellow squares show domains of API and excipient, and orange squares indicate domains of mixed API and excipient. As blending progresses, the mixture evolves from isolated domains of pure API domains, to smaller yet still distinct API domains, and ultimately to a purely homogeneous distribution of API and excipient. The overall ‘brightness’ of these ‘images’ moves towards a mean represented by the orange squares. Obviously, the definition of a homogeneous pixel is also a function of magnification. If the image is broken down into even smaller pixels, orange regions may appear as a collection of solid red and yellow pixels again. Interestingly, a bulk approach such as HPLC would discern no difference between these six blends. And in most circumstances, the extreme variation in homogeneity between these blends would directly influence physical characteristics such as dissolution. The ability to characterise the heterogeneity of a sample is what distinguishes NIR chemical imaging, and makes it such a valuable analytical tool.

**PROCESS INSTRUMENT PROTOTYPE**

A prototype NIR chemical imaging blend monitor mounted to a V-blender is shown in Figure 5. This implementation is an LCTF-based global imaging system, in which an imaging fibre bundle is used to collect and transmit NIR spectral information from the blend to the NIR imaging spectrometer. The same type of data analysis that has been demonstrated in this article can be performed with this system. Its utility for blend monitoring in a process environment is currently being evaluated. Further development to simplify the implementation, streamline data acquisition and turnkey data analysis is underway.

**CONCLUSION**

NIR chemical imaging is the only PAT technique currently being considered for blend monitoring that gives both statistical and direct information about individual sample components on the micro scale. It has evolved from being a specialised laboratory-based analytical technique – providing mostly qualitative assessment of sample heterogeneity – into a robust process-ready technique that provides reliable quantitative data derived directly or indirectly, from single or multiple samples. Today, NIR chemical imaging is being used to measure spatial heterogeneity and component distribution in powder blends, and make direct measurements of coating thickness, particle sizes and associated distribution statistics in complex multi-component samples. In addition, it is being used to locate and identify contaminants in single or multiple samples, and perform conventional NIR spectroscopy in a high-throughput modality. All of this is being accomplished using both microscopic and macroscopic optics on samples that differ in size by several orders of magnitude.

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**References**
