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Manufacturing Benefits of Hyperspectral and Raman Imaging Techniques

By David Bannon at Headwall Photonics

Applications of hyperspectral and Raman imaging techniques have now been extended to pharmaceutical production where they can be used to increase production yields and provide companies with a competitive manufacturing advantage.

Since their development over 25 years ago, spectral imaging techniques have gradually expanded into more commercial application areas such as pharmaceuticals. Recent breakthroughs in the design and performance of optical components have solved many of the limitations associated with older hyperspectral and Raman imaging systems. As a result, there is now significant potential for in-line or at-line applications where imaging performance, reliability and high-speed data transfer are the defining system parameters (1). The US FDA's Process Analytical Technology (PAT) initiative readily lends itself to the benefits of spectral imaging techniques, as does the need to implement a 'quality by design' infrastructure.

By developing spectral imaging equipment that covers the entire wavelength range – from ultra violet (UV), through near infrared (NIR), up to the long wave infrared (LWIR) – sensor manufacturers can address commercial demand for imaging in harsh, critical application areas. The commercial growth of these imaging techniques has exploded in the last five years, mainly in their ability to solve real-world problems associated with, for example, pharmaceutical quality, forensic science, human tissue analysis, non-invasive cancer detection, biomedical microscopy, nanoparticle research, hazardous materials detection, and high-speed waste sorting and recycling (2).

Keywords

Hyperspectral imaging
Raman imaging
Spectroscopy
On-line quality control
Polymorph identification

Principles of Hyperspectral Imaging

All objects reflect, absorb or emit electromagnetic radiation based on their composition. The source of this electromagnetic radiation can either be natural, like sunlight, or man-made – for example, a monochromatic beam of light from a UV/IR lamp or a high-energy laser. The source of radiation is directed onto the surface of a sample and – by utilising a series of collecting, dispersing focusing and detecting optical components – the unique spectral information from the sample can be captured and then used to identify the individual components of a material. This technique is called multi- or hyper-spectral imaging (HSI), because it typically involves collecting multiple spectral channels and spatial bands in the electromagnetic spectrum, anywhere from 200nm to 12µm.

When used to scan, for example, a wide conveyor of moving tablets or pills, multiple two-dimensional (spectral and spatial) image frames are captured as tablets pass by the hyperspectral imager; these individual frames are taken at very high speed and are stacked like a deck of cards to produce a data file commonly called a hyperspectral data cube. The value of each pixel within this hyperspectral data cube represents the spectral intensity of that pixel's small field of view on the scene.

Spectral and spatial resolution is a key consideration for any spectral imaging application. Hyperspectral instruments that are deployed for high-speed, in-line analysis require aberration-corrected sensors that can maintain imaging performance across a wide field of view. These aberration-corrected optics are often peaked for optical efficiency at a specific wavelength within the spectral region of interest in order to maximise signal-to-noise characteristics of the system. Given the demands of pharmaceutical applications, hyperspectral sensors cannot utilise transmissive optics

or prisms that contribute to high levels of stray light and thermal instability.

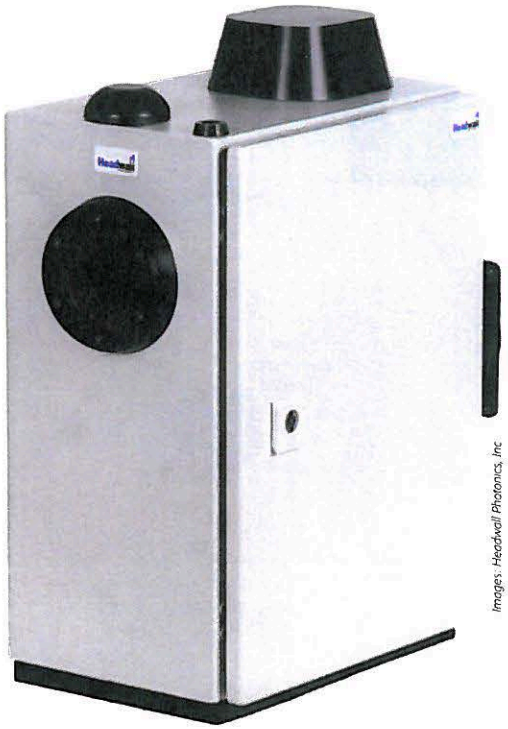
When deployed in-line for process manufacturing environments, system reliability is a key parameter. Hyperspectral instruments (such as Headwall Photonics' Hyperspec® In-Line Inspector system, see Figure 1) have evolved to include not only a hyperspectral sensor core, but also diagnostic routines and calibration modules to ensure accurate, repeatable measurement and thermal management modules that are essential for harsh imaging environments.

Applications in Pharma Production

One of the major areas of growth in spectral imaging has been industrial process monitoring and, in particular, on-line quality control applications found in pharmaceutical production. Applications relating to utilising high-efficiency diffractive optics, hyperspectral and Raman sensors can be configured to offer peak optical efficiency in key wavelengths of interest across broad spectral regions, specific to pharmaceutical compounds; the major advantage here is utilisation for wide area spectral analysis over a conveyor processing line versus an off-line, tablet-by-tablet approach. These sensors thus present a new set of application capabilities, as pharma companies are able to ramp up production with precise control over key steps in the manufacturing process.

Other production areas where spectral imaging holds considerable potential include the monitoring of active pharmaceutical ingredients (APIs), high-volume sampling of raw materials, troubleshooting blending inhomogeniety problems, carrying out polymorphism studies, quality control of spray dry dispersion techniques and post packaging analysis for anti-counterfeit verification and authentication.

Traditionally, capturing precise spectral information from pharmaceutical manufacturing control points has involved machine vision or single point, near infrared (NIR, 900 to 1700nm) spectral instruments deployed in an off-line manner. The main limitation of these systems is that they are only capable of sampling a very small area of the overall product flow and do not lend themselves to high speed production processes. One benefit of using hyperspectral imaging techniques for this type of NIR application is that it enables high sampling rates in a short period of time, resulting in very rapid sample throughput. These hyperspectral imaging instruments can be deployed either as a multi-point solution or a lens-based analyser to scan large volumes of product across the production line.



Images: Headwall Photonics, Inc

Figure 1: Example of an In-Line Hyperspectral NIR Imager manufactured by Headwall Photonics; such instruments are available with optical elements peaked for the specific pharmaceutical application wavelengths

Additionally, when deployed in-line, hyperspectral imaging instruments provide two significant manufacturing benefits. The first is an ability to rapidly and cost-effectively eject poor quality product or foreign material from the process manufacturing line based on spectral discriminators. The second is creation of a wealth of process flow analytics that allow a better understanding of the spectral quality and chemical composition of product flow at various points throughout the development and manufacturing process. This spectral information can be used to track product quality and safety over time from production run to production run, or from one material supply to another – thereby helping increase production yield and process control as manufacturing is scaled to higher volumes.

Hyperspectral imaging instruments greatly enhance knowledge and understanding of pharmaceutical processes by capturing all of the spectral and spatial attributes of material samples within the sensor field of view. When combined with spectral libraries established during the drug discovery phase and the use of multivariate analytical models, hyperspectral sensors can make 'accept or reject' decisions when deployed for 'in-line' or 'at-line' applications. As a result, hyperspectral imaging allows pharmaceutical manufacturers to establish critical control points (CCPs) from the post-discovery phase through pre-production to high-volume manufacturing.

Raman Spectroscopy

Raman spectroscopy measures the vibrational frequencies of various components of a molecule; these

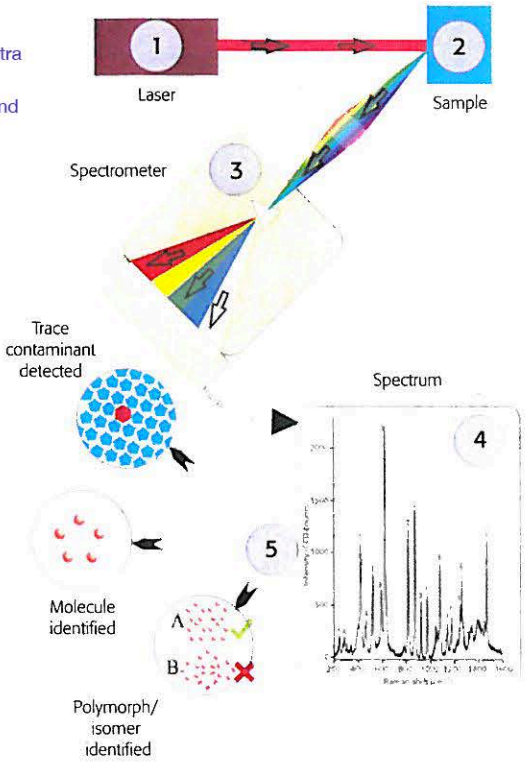


Fig 2: Principles of Raman spectroscopy, showing spectra of a crystaline contaminant in a pharmaceutical compound

frequencies depend on both the bond strength and mass of the bound atoms, as well as other factors such as intermolecular interactions. The pattern of vibrational and rotational frequencies from a molecule is highly characteristic of a given molecular species or the crystalline arrangement of those molecules.

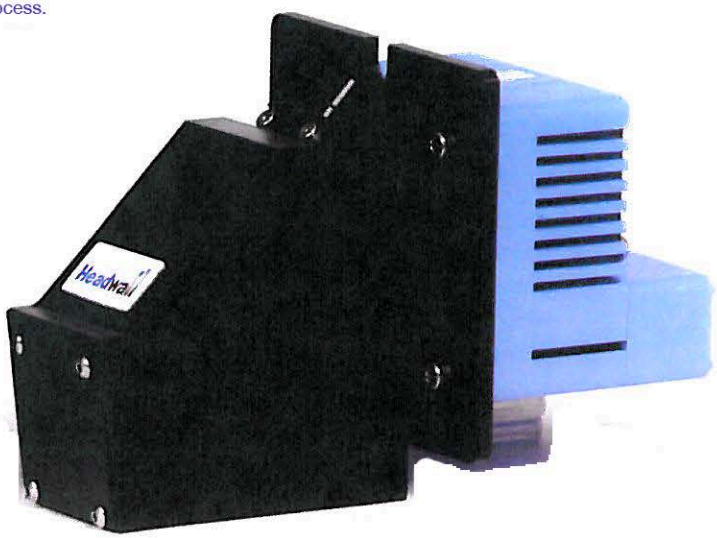
While infrared (IR) spectroscopy is essentially based on illuminating the sample with a broad range of wavelengths of IR light and measuring which are absorbed, a Raman spectrum is obtained by illuminating the sample with a single wavelength of light from a laser, and collecting and analysing the resulting 'scattered' light in the following way:

- Molecules in the sample 'scatter' the incident laser light, providing detailed information about the molecular properties of the sample
- The scattered light is collected and analysed using a Raman spectrometer to produce a Raman spectrum
- Raman spectra are generally well resolved and rich in features enabling unambiguous identification of molecular compounds
- Like traditional chemical imaging techniques that use IR wavelengths, Raman spectra can also be used to rapidly identify unknown compounds
- When coupled with high-powered microscopy, Raman imaging can be a cost-effective drug development tool for evaluating the properties of drug compounds when carrying out *in vitro* cell-based assays (3)

The principles of Raman spectroscopy are shown in Figure 2. A novel Raman approach – known as spatially resolved Raman imaging – provides pharmaceutical manufacturers with numerous advantages over traditional approaches. Specifically, applications such as high throughput screening of polymorphs can take advantage of benefits such as higher resolution across broader sample areas, greater chemical specificity, reduced time and improved sampling statistics.

Whether utilised as a handheld instrument or an in-line process module (see Figure 3), spatially resolved Raman imaging has proven advantages over traditional techniques, providing a greater understanding of tablet composition and chemical structure. Whether used for raw material screening or tablet verification, Raman imaging serves as an essential tool to improve product performance, safety and quality.

Fig 3: Handheld and portable Raman imagers, as well as in-line Raman instruments, serve critical analytical functions throughout the manufacturing process.



Polymorph Identification Using Raman Imaging

A pharmaceutical compound can often have different polymorphic or crystalline forms, which can affect the ease of manufacture and stability of the final formulation. Therefore, detection and identification of the different polymorphs is important throughout the drug development and manufacturing process, so that the optimum form for eventual manufacture can be selected. Additionally, during scale up and manufacture it is important to monitor the material being produced to ensure the drug is of the correct polymorphic form for inclusion in the final product.

Raman spectroscopy coupled with microscopy is an ideal tool for characterising different polymorphic forms

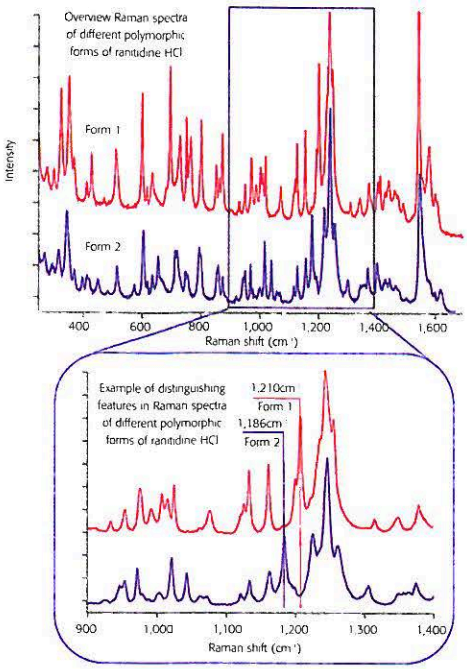


Figure 4: Raman spectra from two different polymorphs of ranitidine obtained from different manufacturers

because the molecules experience different intermolecular forces, resulting in differences in both the frequency and intensity of the vibrational forces observed in the Raman spectrum (4). The sharp, well-resolved features typical of pharmaceutical spectra also facilitate the identification of more subtle spectral differences, which may, for example, indicate low levels of one polymorph in the presence of a larger one. This is exemplified in the spectra of two polymorphs of ranitidine shown in Figure 4; this shows that there are a large number of clearly resolved peaks in the spectral range of 200-1600 cm^{-1}, while a zoomed-in view of the 900-1400 cm^{-1} region shows the characteristic features for each of the polymorphs.

Given the lack of need for sample preparation and the short spectral acquisition times, Raman spectroscopy is also particularly suitable for high throughput identity verification of raw materials. The ability to record spectra through optically transparent containers/windows means that materials can be tested without opening their containers, or in-line as they are fed into the production line.

Conclusion

While hyperspectral imaging has long been established as a proven technology for the harsh environments of military and remote sensing applications, its use in pharmaceutical manufacturing operations has expanded considerably in the past few years. Understandably, a key driver has been the FDA's PAT initiative to gain increased control and process understanding at various points in the production process. Commercially available hyperspectral imaging systems can now be deployed to increase production yields – providing a very attractive return on investment and short payback period, and offering the advantage of much greater, in-depth knowledge of the product during the manufacturing process.

At the same time, spatially resolved Raman spectroscopy has evolved to withstand the rigours of manufacturing applications and has shown itself to be highly sensitive to the different crystalline forms of pharmaceutical compounds. Little sample preparation is required, making it particularly suitable for polymorph identification or high-throughput raw material testing. Raman spectra may be recorded from very small sample volumes, enabling micron-sized particles to be identified or micron spatial resolution, chemically-specific maps to be generated. Additionally Raman spectroscopy coupled with high-powered microscopy has unique capabilities that make it ideal for carrying out in vitro studies to assess the properties of drug compounds in the presence of biological samples during the clinical trials stage of development.

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