

USING HANDHELD RAMAN SPECTROSCOPY TO REDUCE RISKS IN MATERIALS USED FOR MANUFACTURING

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Due to increasing competition, pharmaceutical companies are relocating their manufacturing operations overseas and sourcing raw materials from around the globe in order to help improve efficiencies and cut their production costs.

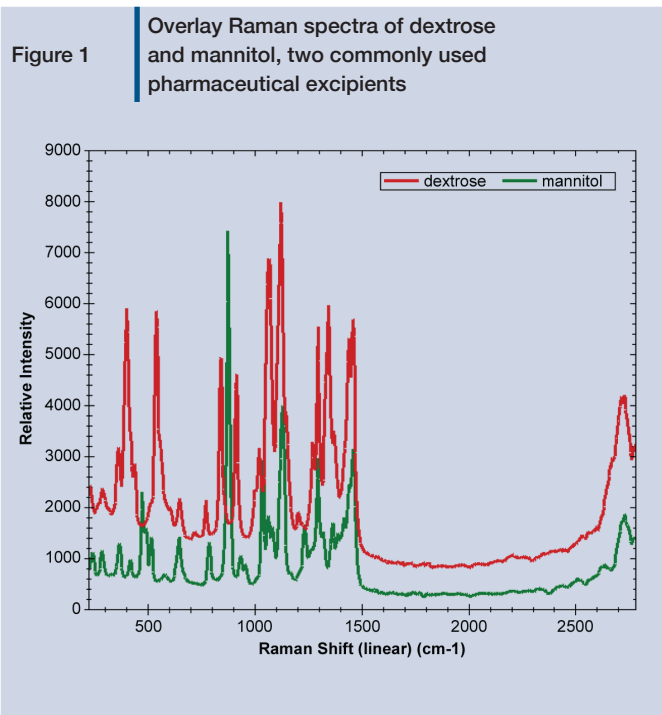
With these changes and the consolidation of the pharmaceutical industry through mergers or consolidation of resources, product quality may be negatively affected. With the risk of impacting quality, there is an increased need for tighter regulatory control to ensure safety and quality of all materials in a pharmaceutical company's production chain in order to mitigate risks; from incoming raw material to real-time monitoring during critical stages of production, and then final product inspection.

According to the ICH Q7, Good Manufacturing Practices for Active Pharmaceutical Ingredients,¹ procedures must be in place for the verification of all incoming raw materials used in production. These guidelines are now more widely adopted and have been published by PIC/S as a more globally-acknowledged GMP guide for pharmaceutical products.² The industry has done an excellent job of creating a strong demand for its products while striving to maintain and even improve the quality and safety to consumers. Regulatory guidance is moving towards required analysis of every container of incoming materials, which is straining the analytical capabilities of many companies and introducing unacceptable production bottlenecks and cost overruns at the manufacturing facilities. This "100% testing" is not sustainable in the long term when done using traditional laboratory testing techniques as prescribed by the monographs in the United States, European and Japanese Pharmacopoeias due to higher costs, increased manpower and additional resources required to perform more testing.³

In order to minimize risks in the quality and identity of raw materials, fuller testing and testing at the point of material receipt is desirable. Full testing of each received container of material can be done most cost effectively by testing methods that do not require sample preparation, and can preferably be done at the point of material receipt using portable technology. Raman spectroscopy, which can be performed with handheld instrumentation, provides a rapid, reliable means of testing in many different environments in manufacturing, including the loading dock. Raman spectroscopy is a form of molecular spectroscopy that like IR spectroscopy provides information about the structure and properties of molecules based on the vibrational transitions that occur. A Raman spectrum provides a fingerprint of a substance, as it contains information about the chemical structure and information related to the morphology (i.e. polymorphic state, crystallinity). It serves as

an important tool in reducing risks in manufacturing without creating bottlenecks due to large movement of materials and many laboratory tests requiring sample preparation, as well as analysis, and reporting of results. The capability of Raman technology for rapid, nondestructive testing and identification of materials in their containers was demonstrated as early as 1998.⁴ The availability of handheld Raman instruments supplied with spectral libraries has increased the adoption of Raman for such testing since they were first available in 2006. The fact that Raman technology is a nondestructive technique that requires no sample preparation, no direct contact with the sample, and has the capability to test a sample through transparent packing material such as glass or plastic has made it an ideal tool for rapid raw material identification. The adoption of this technology can also provide substantial cost savings in terms of quarantine and storage costs for materials that await testing and approval for customer use. In recent years, handheld Raman technology has gained a noticeable market in raw material identification in various industries where traditional analytical techniques like HPLC and FTIR spectroscopy have been the primary technologies. Due to the nondestructive nature of analysis which can be done through transparent packaging, operator exposure to potentially hazardous materials is minimized, as is the need to transport and re-label samples that would need to be submitted to a central laboratory for testing.⁵⁻⁷

Raman technology is accepted as a means of material identification. There are chapters for Raman spectroscopy in the US Pharmacopeia, the European Pharmacopoeia and the Pharmacopoeia of the People's Republic of China, with a new USP general chapter for Raman spectroscopy (858), currently open for

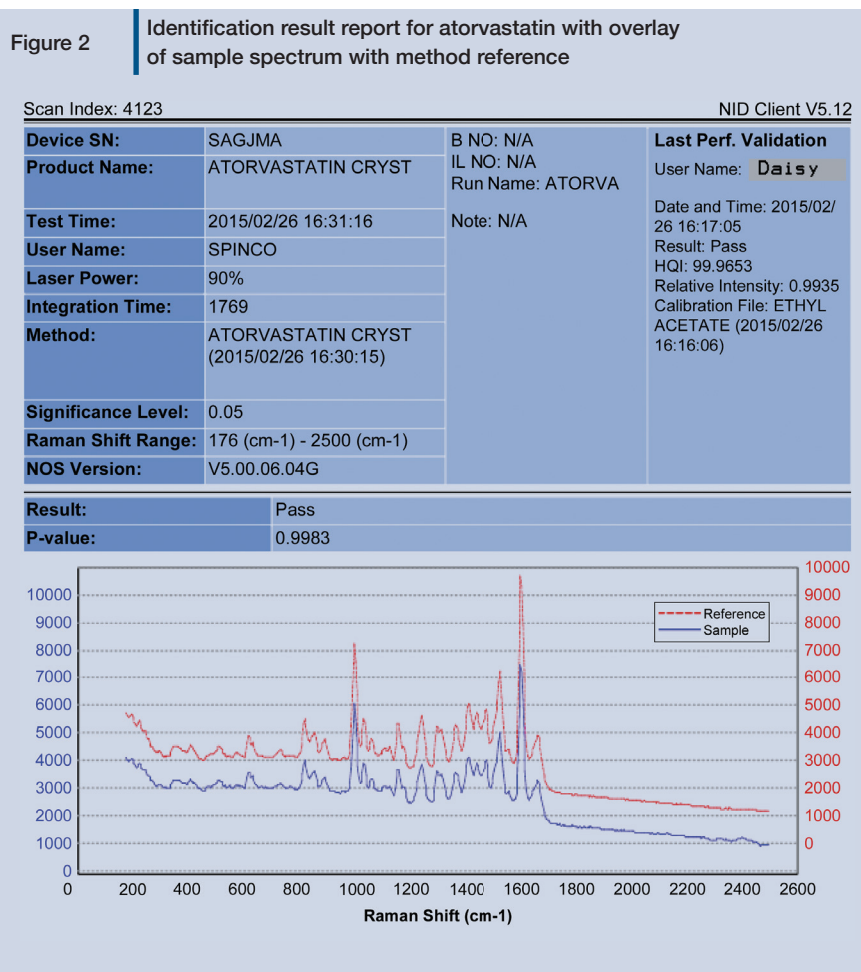


comment.⁸ Because handheld Raman spectrometers are available as reliable, robust instruments providing specificity in identification, their use at the point of material receipt can provide a cost-effective means of full material inspection. Handheld Raman spectrometers offer portability with an instrument providing high quality data for reliable material identification. An intuitive user interface backed by a high quality instrument with robust libraries and identification algorithms make Raman a versatile technology for use by operators and technicians. The Raman spectra of two commonly used excipients, dextrose and mannitol are given in Figure 1, illustrating the differences in a Raman spectrum for chemically similar materials such as these.

Raman spectrometers using on-board spectral libraries as well as intelligent principal component analysis (PCA) model-building software, allow for the rapid development of reliable methods for identification and verification of raw materials. Identification of an unknown compound is achieved in a very short time span (less than 30 seconds for most materials), making it a practical choice for rapid identification and verification purposes. The methodology used makes it easy to develop and validate methods since the methods can be transferred from one instrument to another. This way, the development work does not need to be repeated as more Raman instruments are deployed within a company.^{5,9}

The design of handheld Raman with spectral libraries is intended to make it a tool for use where ever the analysis is needed. The systems provide rapid pass/fail results without the necessity for in-depth data analysis in a laboratory environment. The intent is to increase the testing capabilities without needing to increase the laboratory staff. A typical results report from the measurement and passing identification result for the active pharmaceutical ingredient atorvastatin is shown in Figure 2. Spectral libraries are often provided as part of commercial Raman spectrometers. Many instruments also have the capability of user-created spectral libraries, providing users flexibility in developing methods specific to their analysis needs.

The figures of merit for Raman spectrometers, says John Kauffman, Deputy Director of the FDA, Division of Pharmaceutical Analysis [E-book: Portable Raman Enters a New Era], are spectral range, resolution, signal collection times and signal-to-noise ratio. Additionally, Raman spectroscopy provides high selectivity, making it more powerful for identification than near-infrared spectroscopy. Versatility in availability of sampling accessories optimized for different sample forms makes it easy to apply Raman spectroscopy for rapid identification of samples in different packages, and in the most reproducible means.¹⁰



Raman spectroscopy does have limitations and cannot be used for all types of samples. Though it provides valuable information for organic as well as inorganic materials, it is not capable of analysis of metals. It is also limited in its ability to measure dark and highly colored materials which may heat up and decompose when the laser used for sample excitation interacts with them. Such samples may also have strong fluorescence, which overwhelms the Raman scattering.

User-friendliness is also an issue for handheld instruments, as the methods are most often implemented in the field by non-experts. Some instruments are designed for ruggedness, others for smallness and portability. "One encouraging development," Kauffman says, "is that vendors are improving the user interface to simplify the use of these instruments by non-experts, and some vendors are also developing chemometric tools that offer flexibility for method development scientists." [E-book: Portable Raman Enters a New Era]. The use of a touch screen with intuitive workflow provides an inviting interface for users at all levels.

In addition to identification of raw material (the first step in the manufacturing process to control) Raman spectroscopy also can reduce risk further downstream in manufacturing. Handheld

Raman can be used for the test of finished dosage forms and in the identification of counterfeits. Sometimes even the identification of products manufactured at different facilities can be identified due to the variability within the samples reflected in the Raman spectrum, and the use of PCA-based methods that provide the sensitivity to discriminate between such samples.

Considering Raman spectroscopy more broadly, it can be applied in manufacturing as a powerful tool for process analysis and control, thus contributing to the success of manufacturing quality product with an eye on the process.^{11,12} Raman spectroscopy can be used for quantitative analysis as well as identification purposes. As with identification, the benefits of nondestructive, noncontact sampling with high specificity make it an excellent tool for process monitoring.

Instrumentation is part of the analytical infrastructure of companies, and having the ability to access data and results from numerous locations is important in creating uniform ways of analyzing data, and uniform means of reporting, while also being able to use information and libraries created in one site in other sites, without the need to duplicate work. The use of databases that can be stored on a server or with cloud computing, and access to those databases expand the reach of handheld Raman spectroscopy.

The IT infrastructure and data integrity and security are also important aspects of reducing risks in terms of data loss or infiltration in manufacturing. With the ability to scan barcodes and use the same sample name tracking, the risk of transcription errors is reduced. Wireless communication of handheld Raman allows field users, typically non-experts, to transmit data to a central laboratory where more in-depth analysis can be done. Likewise, wireless communication allows for easy transfer of centrally created libraries to remote users. The ability to integrate Raman data with a LIMS (laboratory information management system) system provides an additional advantage when using handheld Raman in QA applications, as it facilitates the integration of data to the full analysis of materials related to the manufacturing process. LIMS integration of Raman data and results provides a reliable means of data backup and storage within a company's framework for data management. Some handheld Raman spectrometers have the capability for LIMS integration with seamless integration with ready scripts for use with commercial LIMS systems, with defined csv file format of data and results.

Raman spectroscopy is a valuable tool to provide rapid, specific analysis for identification of raw materials, thus reducing the risk

of using substandard or incorrect materials in manufacturing. The utility of handheld Raman increases productivity, and the ability to do full testing without creating bottlenecks in the production process. The integration of the Raman data into a company's data management system provides a secure means of handling data and results, with reduced risk of transcription errors, and data loss.

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