Technical Overview

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Benefits of Using the Agilent Vaya Handheld Raman for Hazardous Materials ID Testing

Avoid handling and exposure to hazardous raw materials or highly potent active pharmaceutical ingredients during ID testing

Introduction

The handling of hazardous materials is a long-standing issue in the pharmaceutical industry. However, the risks associated with product handling have increased in recent years due to the growing number of drug development pipelines that use High Potency Active Pharmaceutical Ingredients (HPAPIs).

To mitigate, reduce, or eliminate these risks, pharmaceutical companies have adopted various strategies. Some organizations use contract manufacturing organizations (CMOs) or contract development and manufacturing organizations (CDMOs) that specialize in handling toxic substances during manufacturing. Other companies have updated their processes to adopt safer procedures, such as better containment during the handling of powders and liquids.

Figure 1. Typical raw material packaging.

Exposure to hazardous raw materials may occur during the quality control (QC) processing of raw materials and APIs upon receipt. This risk is higher in low-containment manufacturing facilities where hazardous materials are not strictly isolated. As a minimum, QC at receipt requires identification (ID) testing or ID verification of raw materials.

Typically, pharmaceutical raw materials are packaged in primary containers such as drums, bags, or containers made of materials such as plastic or glass. These primary containers are often placed into secondary containers or packaging for extra protection during storage and transportation. The secondary packaging can include paper sacks, cardboard boxes or cartons, or plastic drums.

If a molecular spectroscopy technique such as infrared (IR), near infrared (NIR), or conventional Raman spectroscopy (CRS) is used to ID the material, the secondary (outer) packaging must be opened. The primary container will also be opened if sampling of the material is necessary.

Before opening secondary and primary packaging of pharmaceutical raw materials, several safety measures are typically taken to ensure the protection of personnel and the integrity of the chemicals. The raw materials are typically handled by operators wearing full personal protection equipment (PPE) such as a full gown, gloves, and a mask, often under a controlled airflow in a specially designed sampling booth. Despite all the safety precautions, opening and handling the contents of the secondary container—and especially the primary container—increases the potential for worker-exposure to hazardous materials.

However, spatially offset Raman spectroscopy (SORS), a form of Raman spectroscopy, can be applied to the QC of raw materials, ensuring a faster and safer ID test process. SORS, an Agilent proprietary technique, was developed in 2005 for the deep probing of turbid material.[1] When applied to ID testing of raw materials, SORS can identify the contents of a packaged material through non-transparent and transparent containers. When used for ID testing, the SORS technique simplifies the procedure with the following benefits:

- No need to open the container to sample the material, speeding up the analysis
- No exposure to hazardous materials, ensuring worker safety
- No cleanup after the analysis, minimizing waste and improving productivity

How does SORS work?

Raman spectrometers probe materials using monochromatic laser light, usually at visible or near-infrared (NIR) wavelengths. Conventional Raman spectroscopy involves illuminating a sample with a laser followed by the detection of scattered light, whereas SORS through-barrier mode uses multiple measurements to probe the subsurface of a sample. For the analysis of a pharmaceutical raw material (analyte) through a container using SORS, the laser automatically fires at different positions on the container and two Raman spectra are measured. The first spectrum is collected when the area of excitation coincides with the light collection area. The second spectrum is then collected when these two areas no longer fully overlap. Typically, the first "zero" spectrum will be rich in surface information (i.e., container) while the second "offset" spectrum will be richer in subsurface information (i.e., raw material). The software then performs a scaled subtraction of the two spectra that results in a spectrum that represents the raw material alone, without interference from the container. This container-free raw material spectrum is then matched against a reference library containing SORS spectra for ID verification.

Figure 2 shows the measurement of sucrose through a 1.5 mm thick polypropylene (PP) container using conventional Raman and SORS. The two spectra obtained using conventional Raman (A and B) show that the technique was unable to measure the sucrose due to the non-transparency and fluorescence from the PP packaging. In contrast, SORS produces a high-quality spectrum of sucrose through several millimeters of opaque plastic, as shown by the clear match of the sample spectrum (C) with the library reference spectrum (D).

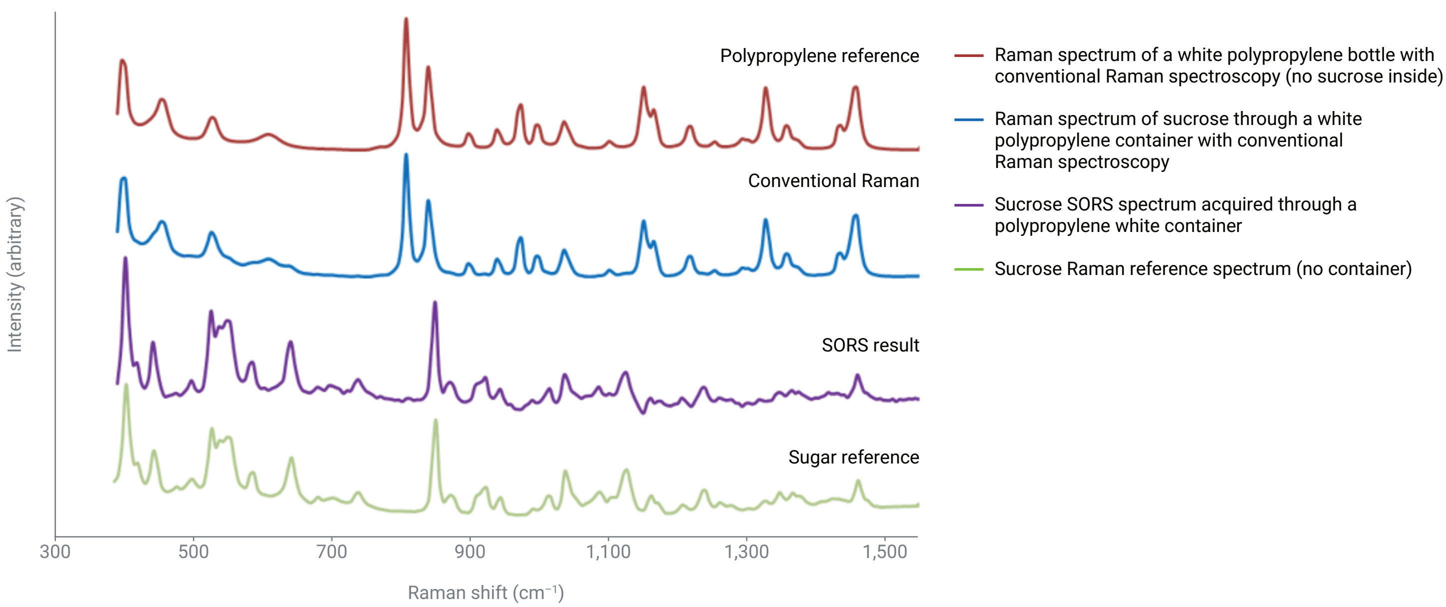

Figure 2. Overlay of SORS and conventional Raman spectra for the analysis of sucrose through a white polypropylene container.

What is the Vaya Handheld Raman Spectrometer?

The Agilent Vaya can be used as part of any hazardous materials handling program. It is a handheld SORS spectrometer capable of ID testing through transparent and opaque containers. It dramatically reduces exposure to hazardous raw materials and highly potent APIs as it minimizes the opening of the secondary and/or primary container during QC testing. Vaya is easy to use and can be used by any operator. When a measurement is taken, a simple a pass/fail ID result is displayed on the screen following the testing of materials through containers such as blue drums, paper sacks, amber bottles, and white totes. Vaya provides a superior and future-proof workflow; it is fast, fully compliant, easy to deploy, and simple to use, requiring minimal training or operator skills. It also helps achieve sustainability goals by minimizing resource usage and avoiding waste-intensive raw material sampling processes.

Vaya is less likely to degrade or burn analytes under investigation, as it uses a divergent laser that lowers the power density of the laser spot on the analyte.[2] Heat-sensitive materials such as nitrocellulose and picramic acid used in the pharmaceutical and cosmetics industries can therefore be probed by Vaya for ID purposes, as shown in Figure 3.

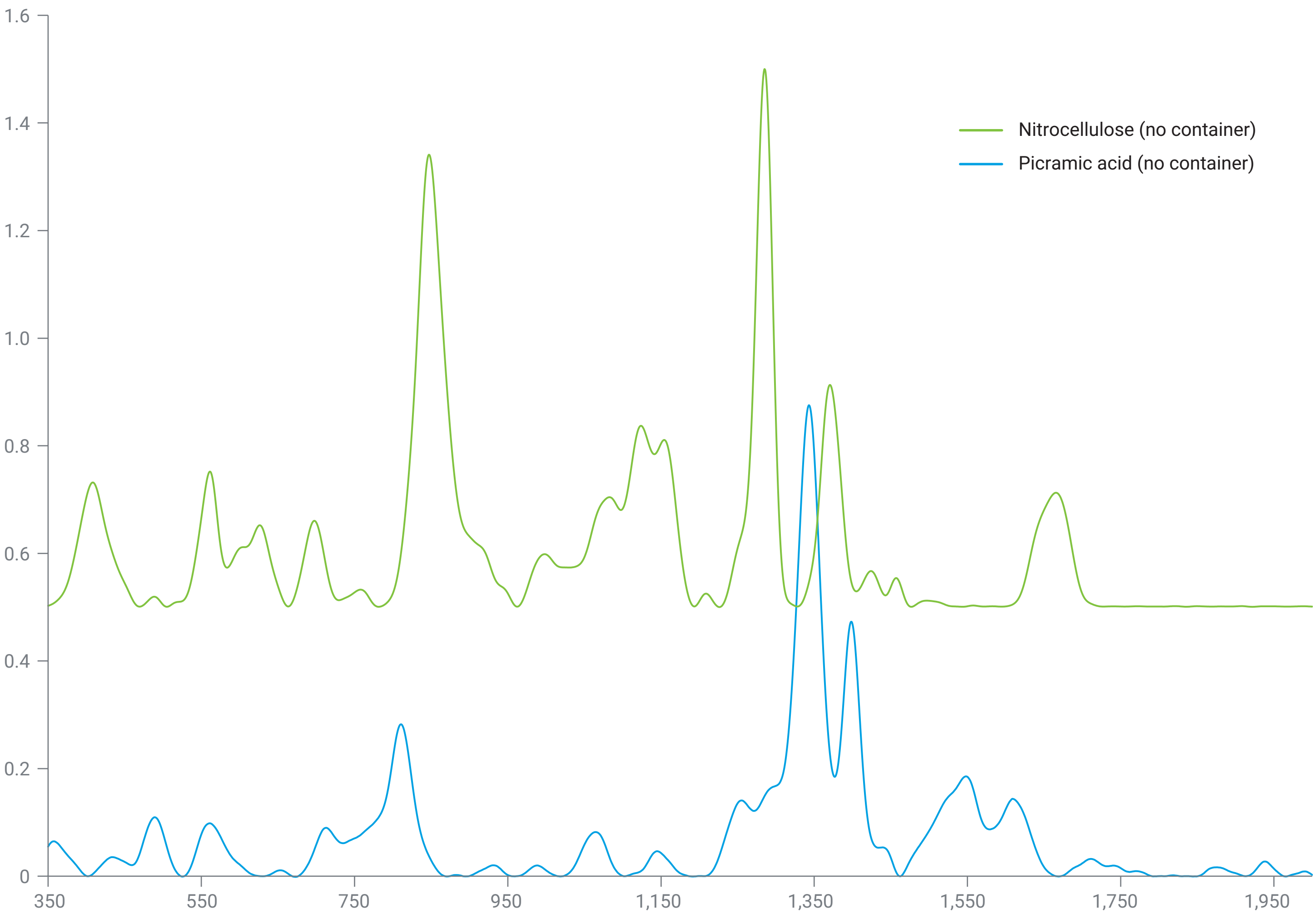

Figure 3. Example of neat Raman spectra of two sensitive explosive materials, obtained by SORS with a laser power set to 450 mW. **Note**: Use care and caution when scanning heat-sensitive materials such as explosives. Conduct a thorough risk assessment and follow normal safe operating procedures.

What hazardous excipients or potent APIs can Vaya ID?

The SORS technique is based on the core principle of Raman spectroscopy, where a monochromatic light source illuminates an analyte, and the resulting scattered light, which may be shifted to the blue or red end of the spectrum, is collected. The sample-specific spectrum probes for the presence of molecular vibrations and phonons in the analyte, which are typically associated with covalent bonds. The Raman effect is therefore observed in organic and inorganic molecules that contain covalent bonds, where changes in polarization provide valuable information about the molecular structure and composition of a sample.

Most excipients and APIs used in the pharmaceutical industry exhibit a Raman fingerprint that can be used for ID purposes. The sample-types include hazardous materials necessary to the drug manufacturing processes such as cytotoxics, flammable solvents, hormones, formaldehyde, and radioactive materials. Although these materials are typically shipped in containers, such as glass bottles and blue high-density polyethylene (HDPE) drums with liners, Vaya can identify them in a matter of seconds.

Figure 4 shows examples of Raman "fingerprint" spectra for methanol obtained through an amber bottle, formaldehyde solution through a clear vial, fluorouracil through a transparent low density PE (LDPE) bag, and benzoyl peroxide through an amber bottle measured using Vaya.

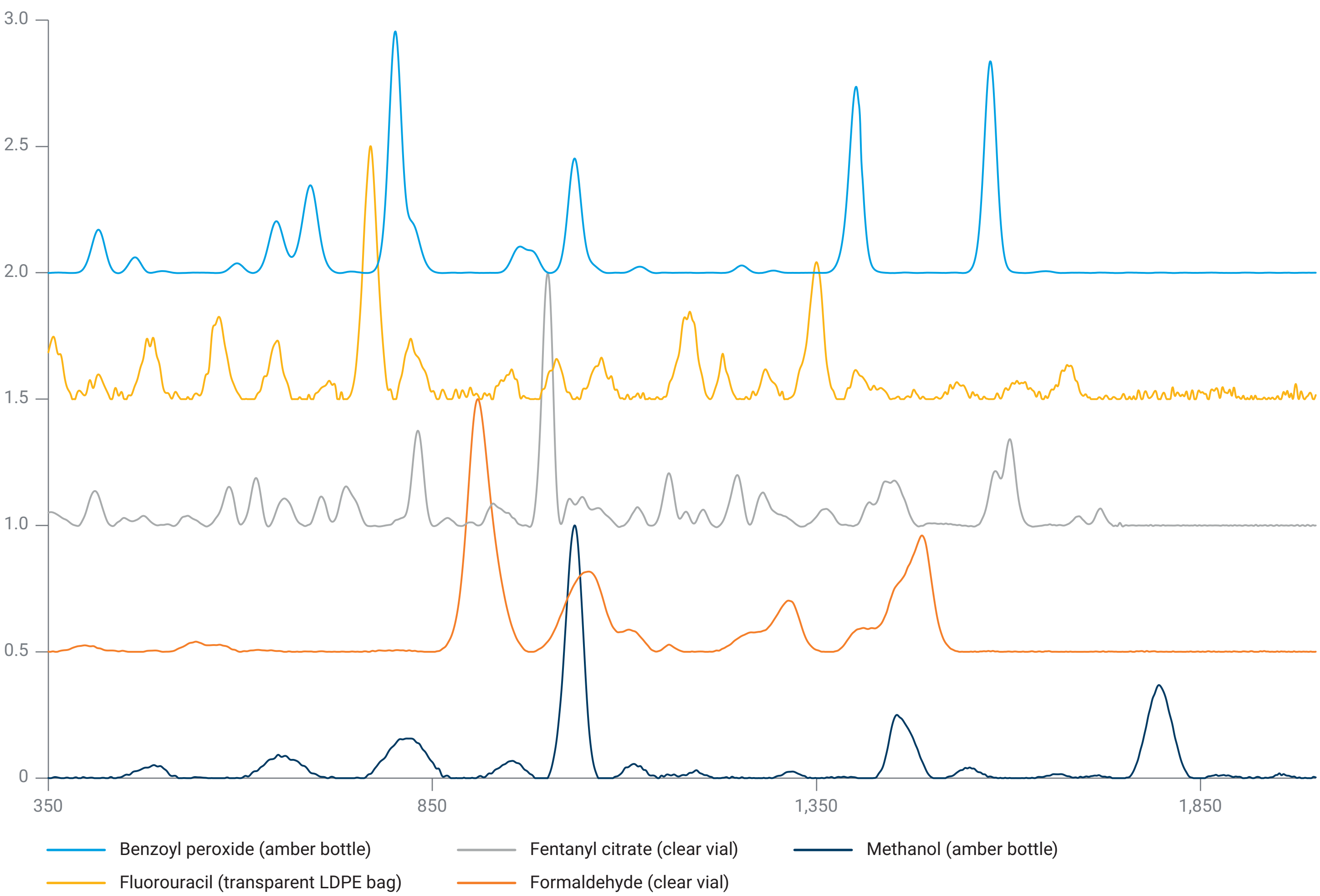

Figure 4. Example of Raman spectra of hazardous materials in a variety of packaging containers obtained by SORS.

Conclusion

The Agilent Vaya handheld Raman spectrometer brings unique SORS capability to the rapid ID testing of pharmaceutical raw materials on delivery, in a sampling booth, or in the warehouse.

The SORS technique enables the effective probing of all types of materials—including hazardous materials and high potency APIs—directly through the container, protecting staff from exposure to the raw materials and avoiding cumbersome and potentially risky safety measures.

As shown in the paper, the Vaya successfully identified sucrose through multiple layers of paper or many millimeters of colored glass, an impossible application for non-SORS-based techniques. Due to the relatively low power-density of the SORS laser, the mobile spectrometer also produced clear spectra for the ID of heat-sensitive materials, such as nitrocellulose and picramic acid. Clear spectra were also obtained for a series of hazardous materials including formaldehyde, fluorouracil, and benzoyl peroxide, directly inside different types of containers.

Compared to using FTIR or traditional Raman spectroscopy for ID testing, the Vaya handheld Raman spectrometer simplifies and streamlines the procedure. With Vaya, there is no need to sample materials or transfer containers to and from quarantine areas for analysis, and therefore no cleaning tasks post-analysis. Vaya also maintains the sterility of raw materials and minimizes any associated spoilage expenses, which may be significant for hazardous materials.

References

1. Matousek, P.; Clark, I. P.; Draper, E. R. C. *et al.* Subsurface Probing in Diffusely Scattering Media Using Spatially Offset Raman Spectroscopy. *Applied Spectroscopy*. **2005**, *59(4)*, 393–400.
2. Stokes, R.; Presly, O.; Screening for Sensitive Explosives with Agilent Resolve—a Handheld SORS System, *Agilent Technologies application note*, publication number 5991-8871EN, **2018**.

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