Application Note

Pharma and Biopharma

Opaque Container Analysis Capabilities of the Agilent Vaya Handheld Raman Spectrometer

Authors

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Abstract

This study demonstrates the through-opaque-container analysis capability of the Agilent Vaya handheld Raman spectrometer by performing measurements on a range of common excipients and active ingredients within blue barrels. Spatially offset Raman spectroscopy (SORS) is the unique Agilent technology that is the basis of the unique Vaya container subtraction algorithm. This technology can optimize the spectra to provide the clearest signature of contents with the minimum amount of container interference. Verification of raw materials directly through plastic barrels provides efficient raw material identification (RMID) workflows in the warehouse without the need for specialized personnel or controlled sampling environments.

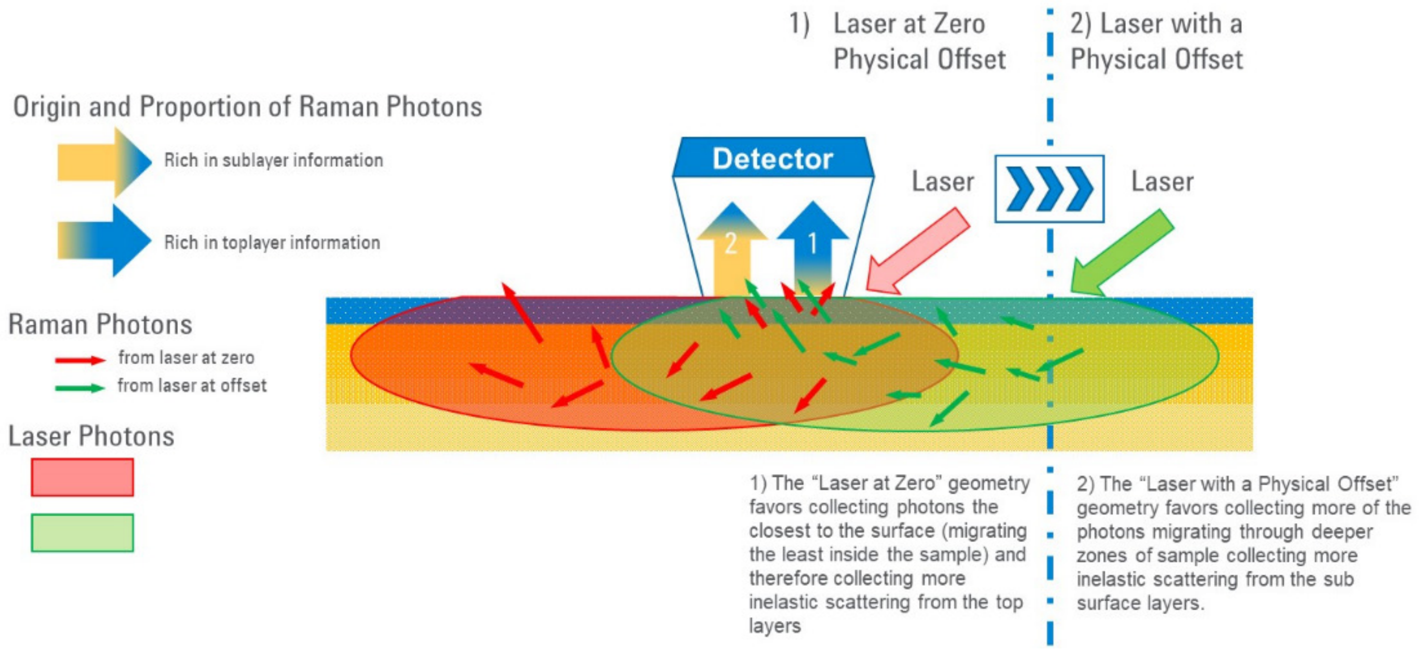
Introduction

Pharmaceutical excipients and active pharmaceutical ingredients (API) are shipped in a variety of containers, including plastic bottles, barrels, and bags, glass bottles, and paper sacks. The choice of container or packaging materials depends on the physical and chemical properties of the stored material, sustainability of the container (reuse and recycling), convenience, and material volume. Plastic barrels are typically made with high density polyethylene plastic, with added pigments for coloration. They typically protect materials from UV degradation and high ambient light, and limit material spills. In conjunction with a low-density polyethylene (LDPE) liner, they can be used for shipping and storing materials. The most common barrel colors are white and blue, with dark blue being commonly selected to inhibit light transfer. The light-blocking properties of dark blue barrels offer challenging conditions for the conducting of identification testing by Raman spectroscopy at receipt. This application note introduces a novel subset of Raman spectroscopy, SORS, capable of optically probing the chemical makeup of subsurface layers of a given analyte. It shows how SORS can be applied to identify a wide variety of materials directly through blue plastic drums to optimize the receipt of raw materials in the pharmaceutical industry.

What is spatially offset Raman spectroscopy?

SORS enables the acquisition of Raman spectra of content material directly through an opaque container wall – the container does not need to be opened. SORS is based on the combination of Raman spectroscopy and light travel properties through diffusively scattering media. The basic principle of SORS is to separate the laser light source and the detector in a Raman spectrometer by a small offset. In this geometry, the light collected by the spectrometer is mostly composed of Rayleigh scattering and Raman photons generated by the laser scattering onto the material inside the container.

Figure 1 shows the basics of light scattering and sorting through the introduction of an offset between the laser and detector. In configuration 1, the laser excitation area is superposed with the signal collection area. This geometry provides surface-related information, as the detected Raman photons mostly originate from the surface (container) of the combination raw material and container. This position is known as Zero. The resulting Raman spectrum is dominated by the container signal, with a low level of contents evident.



1) The "Laser at Zero" geometry favors collecting photons the closest to the surface (migrating the least inside the sample) and therefore collecting more inelastic scattering from the top layers

2) The "Laser with a Physical Offset" geometry favors collecting more of the photons migrating through deeper zones of sample collecting more inelastic scattering from the sub surface layers.

Figure 1. Principles of spatially offset Raman spectroscopy.

Configuration 2 shows the spatial offset or offset laser position, where the laser/excitation area is shifted by several millimeters. This geometry provides subsurface chemistry-rich information, as the collected Raman photons originate mostly from inside the container. The resulting Raman spectrum can be optimized by scaled subtraction of the zero-position spectrum to remove the residual contribution of the surface (container). SORS does not require prior knowledge of the chemical makeup and thickness of the container it will go through.

The Agilent Vaya handheld Raman spectrometer

The Vaya handheld Raman spectrometer uses SORS to enable fast identification testing of incoming raw materials through both transparent and opaque containers. With Vaya, the identification testing process saves time, resources, and money – no sampling/sampling booth or container opening are required. There is no exposure to hazardous materials, no need for consumables (vials, sampling room PPE and consumables), no cross contamination, no waiting for the QC lab, and logistical movements around the warehouse are limited. Vaya is designed for the pharmaceutical and biopharmaceutical industries, and supports compliance with 21 CFR Part 11, USP <858>, USP <1858>, EP 2.248, Chinese Pharmacopeia Raman Spectroscopy (2020 version) chapter 0421, and Japanese Pharmacopeia (Supplement II, 17th Edition) Raman Spectroscopy chapter.

Experimental

Samples

Technical grade acetaminophen, citric acid, ibuprofen salt, lactose monohydrate, polyethylene glycol 8000, povidone, and sorbitol were supplied from Sigma-Aldrich. These materials were chosen as they are frequently used as excipients and APIs in the manufacturing of drug products and exhibit varying Raman cross sections (Raman signal intensity). For example, lactose monohydrate has a small Raman cross section, whereas acetaminophen exhibits a comparatively larger Raman cross section. Upon receipt, all powders (200 grams each) were placed in separate small, clear LDPE bags as primary containers/liners. For demonstration of the Vaya through-barrier capability, an LDPE blue barrel was used (see Figure 2B). A UV-Vis experiment performed with an Agilent Cary 5000 UV-Vis-NIR spectrometer (in transmission mode) revealed that the blue drum exhibits light-blocking properties in the NIR region (854 to 995 nm), where the laser of the Vaya (830 nm) and subsequent Raman photons will interact with the blue drums.

Figure 2. (A) Agilent Vaya handheld Raman spectrometer in operation in a quarantine area. (B) A typical drum used as a secondary container to house excipients.

Instrumentation and data acquisition

The Vaya was used to perform the SORS measurements through the blue drum to isolate the spectrum of the pharmaceutical raw material inside. The Vaya onboard container subtraction algorithm was used to remove any Raman interference of the container.

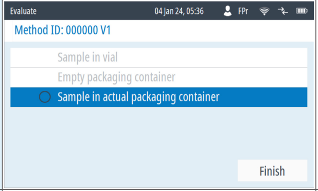
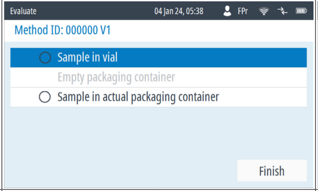
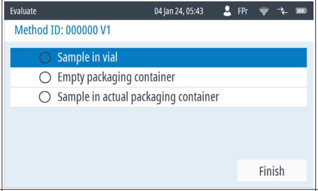
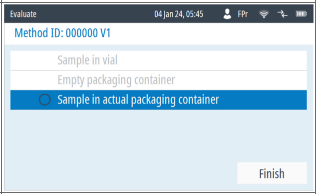
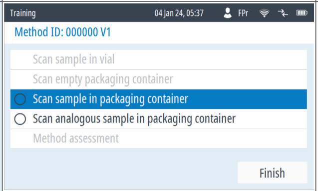
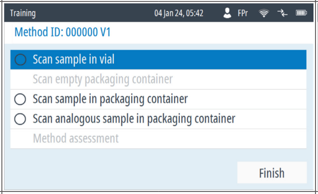
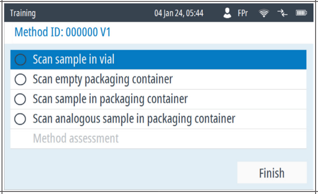
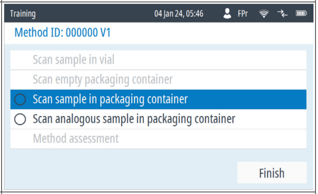
To demonstrate SORS ability to identify materials through an opaque container, an identification method was created for each of the seven raw materials. Each raw material method uses a spectrum model based on a minimum of 10 repeat scans of the corresponding raw material samples. The seven methods were built following the workflow recommended by the onboard wizard system.

How does Vaya address container subtraction?

Vaya is meant to be used by non-spectroscopists, and therefore guides users through method development using a wizard-based workflow, optimized for most combinations of raw materials and containers.

In the method development workflow, the user is asked to select the type of container the measurements will be performed through. Six containers can be selected: glass vial, neat (no primary or secondary container), paper sack, glass, and thin or thick plastic. Vaya then automatically develops a default spectrum acquisition plan with the appropriate laser positions (zero and offset) and a container subtraction methodology based on container type. The first row of Table 1 shows the default position of the laser and the associated default container subtraction algorithm.

Table 1. Method development, container characteristics, and the container subtraction algorithm.

<table>
<tr><th></th><th>Glass Vial</th><th>Neat</th><th>Paper</th><th>Glass</th><th>Thin Plastic</th><th>Thick Plastic</th><th>Custom
(On v1.2 and Up)</th></tr>
<tr><td>Default Laser Positions and Container Subtraction</td><td>Zero
0.6 mm</td><td>Zero
0.0 mm</td><td>Offset
6 mm</td><td>SORS
6 to 0 mm</td><td>Zero
0.0 mm</td><td>SORS
6 to 0 mm</td><td>User choice:
SORS (custom Offset minus custom Zero)
Zero (0 to 1.5 mm)
Offset (4 to 6 mm)</td></tr>
<tr><td>Evaluations Steps</td><td colspan="2"> Method ID: 000000 V1
Sample in vial
Empty packaging container
○ Sample in actual packaging container
 </td><td colspan="2"> Method ID: 000000 V1
○ Sample in vial
Empty packaging container
○ Sample in actual packaging container
 </td><td colspan="2"> Method ID: 000000 V1
○ Sample in vial
○ Empty packaging container
○ Sample in actual packaging container
 </td><td> Method ID: 000000 V1
Sample in vial
Empty packaging container
○ Sample in actual packaging container
 </td></tr>
<tr><td>Method Steps</td><td colspan="2"> Method ID: 000000 V1
Scan sample in vial
Scan empty packaging container
○ Scan sample in packaging container
○ Scan analogous sample in packaging container
Method assessment
 </td><td colspan="2"> Method ID: 000000 V1
○ Scan sample in vial
Scan empty packaging container
○ Scan sample in packaging container
○ Scan analogous sample in packaging container
Method assessment
 </td><td colspan="2"> Method ID: 000000 V1
○ Scan sample in vial
○ Scan empty packaging container
○ Scan sample in packaging container
○ Scan analogous sample in packaging container
Method assessment
 </td><td> Method ID: 000000 V1
Scan sample in vial
Scan empty packaging container
○ Scan sample in packaging container
○ Scan analogous sample in packaging container
Method assessment
 </td></tr>
<tr><td>Possible Automatic Container Subtraction Optimization</td><td>NA</td><td>NA</td><td colspan="2">SORS, Zero, or Offset
(with or without baseline connection)</td><td colspan="2">SORS, Zero minus empty container, or Offset minus empty container
(with or without baseline connection)</td><td>NA</td></tr>
</table>

For example, the default thick plastic container subtraction algorithm is SORS (offset spectrum minus scaled subtraction of the zero spectrum). The surface-rich zero measurement is subtracted from the content (material) rich offset measurement, yielding a typically pure spectrum of the content material that can be used as a reliable and robust identification fingerprint for the material within the container.

In addition to the default options, the Vaya can automatically select from other laser positions and associated container subtraction algorithm types to optimize the spectral quality of the content material. Table 1 shows the different options for optimization. The optimization is based on the comparison of the resulting spectra derived from the different possible subtraction algorithms to the reference spectrum of the content material in a glass vial. This functionality is particularly useful for containers exhibiting variable levels of light absorption across the NIR spectral range. With this strategy, the Vaya also yields the fastest time to response, as it prevents the acquisition of unnecessary data.

To ensure Vaya can achieve the optimal level of container subtraction and the strongest model signature of the content material, it is recommended that an optimized method is built.

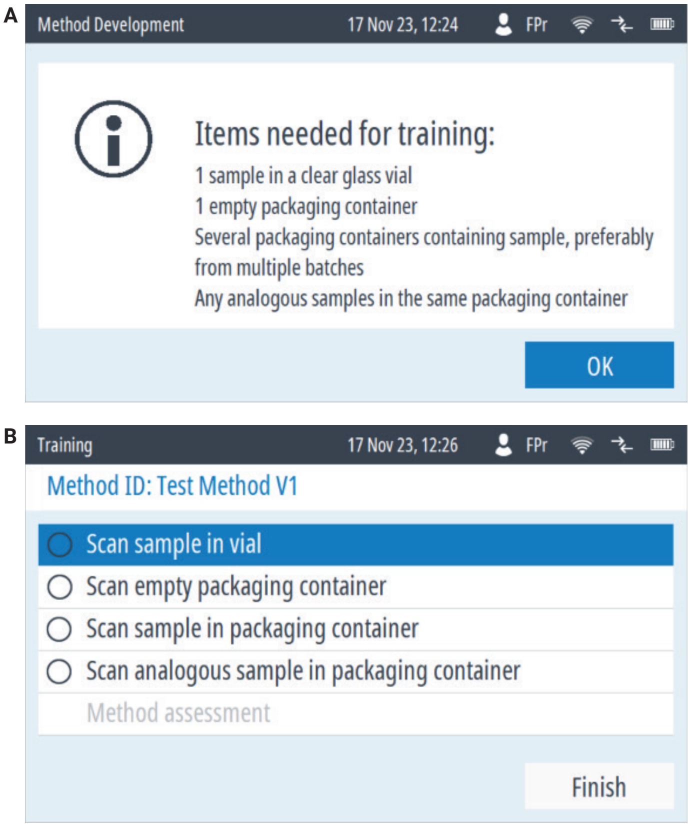
In this process, the following spectral information is necessary for the method:

1. A Raman spectrum of the material in a glass vial (also known as *sample in vial* – a gold standard for comparison for method model building and selection of the container subtraction algorithm).
2. Spectra of the empty container (also known as *empty packaging container scans* – Raman spectra to develop the container model reference needed when the container subtraction algorithm calls for a subtraction of the reference container).
3. Spectra of the raw material in the packaging container or sample in the packaging container – scans of the raw material through container used to make the method model median (typically 10 scans).
4. Spectra of analogous samples in the packaging container (scans of similar content materials added to improve the selectivity of the model). This information is optional, and depends on the existence of materials with similar structure that are at risk of being confused with the method in development.

Once the method contains the aforementioned information (items 1 to 3), the container subtraction algorithm selects from the following options to optimize the analysis:

1. SORS (Offset – Zero)
2. Offset – container reference
3. Zero – container reference
4. Offset
5. Zero

If the minimum information is added to the method (scans of the sample in the packaging container only), then the only available option is the default SORS.



Items needed for training:

1 sample in a clear glass vial
1 empty packaging container
Several packaging containers containing sample, preferably from multiple batches
Any analogous samples in the same packaging container

Method ID: Test Method V1

○ Scan sample in vial
○ Scan empty packaging container
○ Scan sample in packaging container
○ Scan analogous sample in packaging container
Method assessment

Figure 3. (A) Method Development Wizard recommendation on samples needed for method building and (B) Method Development Wizard recommendations on scans needed for method training.

Results and discussion

Figure 4 shows spectra obtained through the blue barrel from the seven content materials using fully optimized methods. The Vaya was able to isolate a unique Raman spectrum for each of the materials in this study, enabling their verification directly in quarantine. In these instances, the Vaya uses the SORS principle, as well as the sensitivity of its charge coupling device detector, to address the intertwined Raman signal challenges inherent to the identification of raw materials through thick opaque colored containers. These include the laser photons blocked by the container, the Raman photons that are absorbed by the container, and the Raman cross section ratio of container-to-content.

The identification verification on the Vaya does not require sample or container preparation before scanning the contents of a container. The user is invited to position the Vaya flush with the container and start the run. During the acquisition of the spectrum, the instrument does not have to be repositioned. The scan time through the blue drums averaged 50 seconds.

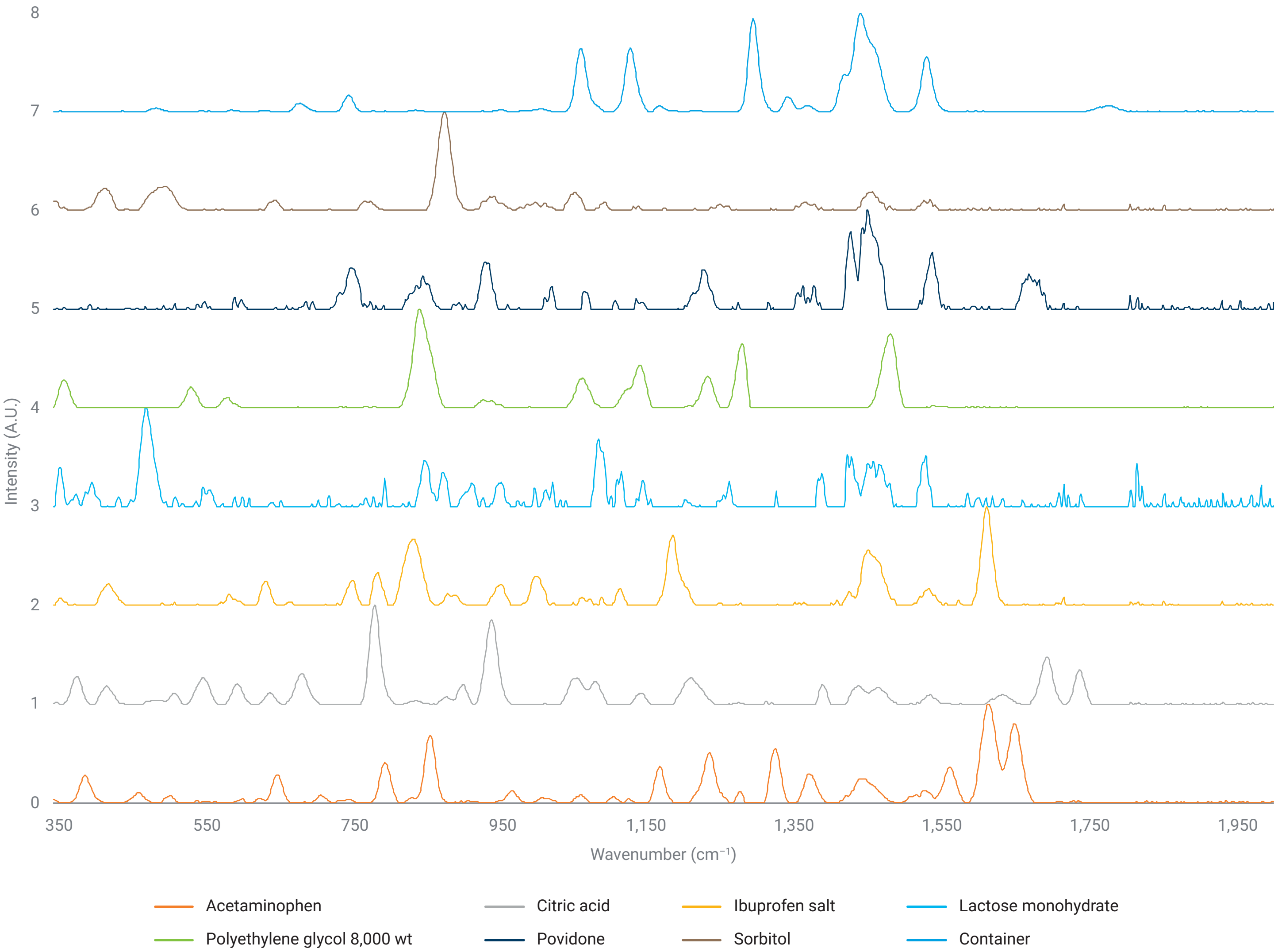


Figure 4. Spectra obtained through blue barrel.

Conclusion

The Agilent Vaya handheld Raman spectrophotometer can scan and verify many materials in blue barrel containers, delivering a clear pass/fail result despite the significant light-inhibiting properties of this type of enclosure. The Vaya is a disruptive solution for raw material identification verification at receipt. It drastically simplifies the receipt process by offering a point-of-need solution in quarantine areas. With the Vaya, one can identify raw material receipts, and address increased production volumes or new sampling requirements like 100% identification with minimal investment.

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