VIAVI Solutions

White Paper

Raw Material Identification by NIR Spectroscopy

Raw Material Identification (RMID) is the first and a fundamental step in a Quality by Design (QbD) process implementation. Ensuring that the material used in the manufacturing process conforms to the desired quality standard is essential to prevent potential failures in the finished product.

Introduction

Historically, RMID sampling criteria specified square root of N+1, where "N" represented the number of containers of both, excipients, and API. More recently, the European Pharmacopoeia raised the RMID requirements to 100% of material testing, and the volume of analysis performed in quality control laboratories became unsustainable. This regulatory change, now global, pushed instrument manufacturers to design "fit for purpose" solutions. In the early phase, many industries adopted NIR laboratory systems, redesigned for warehouse operation and equipped with fiber optic probes. Recently, the miniaturization of spectroscopy techniques such as NIR and Raman have enabled portable, fit-for-purpose instruments that deliver an enhanced user experience, lower cost of ownership, and results as reliable as laboratory instruments.

Why RMID performed at the receiving point?

Receiving-point RMID is a critical step in QbD and LEAN implementations and allows manufacturers to:

- Significantly reduce the need for material quarantine, floor space, and sampling area
- Eliminate laboratory characterization and avoid material movement
- Dramatically reduce cycle time while increasing quality

Fig. 1: Traditional RMID process cycle (left) compared to RMID performed in the manufacturing area (right).kept to a minimum.

Several instruments are now available on the market for RMID purposes, primarily Raman and NIR handhelds. None by itself represents a total solution for the variety of materials and containers typically used in pharmaceutical, chemical, or food ingredients manufacturing sites. Most Raman systems are generally affected by fluorescence, a severe limitation that drastically reduces the number of measurable materials. Some Raman instruments reduce the limitation by using different wavelength excitation lasers, while others allow sampling through thick plastic containers. No matter which Raman instrument is used, due to other material properties including moisture content and particle size, the "identification" is often insufficient to qualify the material and laboratory analysis (LOD and particle size) is still required. This why NIR and Raman are complementary in the RMID process. This complement is shown in Figure 2.

		Raman only		**Raman and NIR combined**	
Material	Container	Raman ID	QC Lab	Raman and NIR ID	QC Lab
API 1	Poly bag (LDPE 8 MIL)	Validated	n.a.	Validated	n.a.
API 2	Poly bag (LDPE 8 MIL)	Validated	n.a.	Validated	n.a.
API 3	Poly bag (LDPE 8 MIL)	Validated	n.a.	Validated	n.a.
API 4	Poly bag (LDPE 8 MIL)	Validated	n.a.	Validated	n.a.
API 5	Poly bag (LDPE 8 MIL)	Validated	n.a.	Validated	n.a.
API 6	Poly bag (LDPE 8 MIL)	Validated	n.a.	Validated	n.a.
API 7	Poly bag (LDPE 8 MIL)	Uncertain	Yes	Validated	n.a.
API 8	Poly bag (LDPE 8 MIL)	Uncertain	Yes	Validated	n.a.
Excipient 1	Poly bag (LDPE 8 MIL)	Validated	n.a.	Validated	n.a.
Excipient 2	Poly bag (LDPE 8 MIL)	Validated	n.a.	Validated	n.a.
Excipient 3	Poly bag (LDPE 8 MIL)	Validated	n.a.	Validated	n.a.
Excipient 4	Poly bag (LDPE 8 MIL)	Validated	n.a.	Validated	n.a.
Excipient 5	Poly bag (LDPE 8 MIL)	Uncertain	Yes	Validated	n.a.
Excipient 6	Poly bag (LDPE 8 MIL)	Fluorescence	Yes	Validated	n.a.
Excipient 7	Poly bag (LDPE 8 MIL)	Fluorescence	Yes	Validated	n.a.
Excipient 8	Poly bag (LDPE 8 MIL)	Fluorescence	Yes	Validated	n.a.
Excipient 9	Bottle light brown	Validated	n.a.	Validated	n.a.
Solvent 1	Bottle light brown	Validated	n.a.	Validated	n.a.
Solvent 2	Bottle light brown	Validated	n.a.	Validated	n.a.
Solvent 3	Bottle dark brown	Validated	n.a.	Validated	n.a.
Solvent 4	Bottle dark brown	Validated	n.a.	Validated	n.a.
Solvent 6	Bottle dark brown	Not measurable	Yes	Not measurable	Yes
Solvent 7	Bottle dark brown	Not measurable	Yes	Not measurable	Yes
Excipient 10	Bottle LDPE white	Not measurable	Yes	Not measurable	Yes

Fig. 2: In this RMID example, Raman is adequate to identify 15 of 24 samples, requiring 9 to go to the lab. Combining Raman and NIR expands the capability to 21 of 24, reducing the lab load to 3 samples. NIR also adds the ability to qualify materials for moisture and particle size, which Raman is unable to do.

When moisture content and particle size matter, identification by itself is insufficient to qualify the material for production.

Unlike Raman, NIR spectroscopy is very sensitive to moisture content and particle size, is not affected by fluorescence, and can qualify materials by characterizing multiple properties, as illustrated in Figure 3.

The VIAVI MicroNIR™ OnSite-W wireless NIR spectrometer embodies these advantages in a robust, compact, and repeatable handheld form factor ideally suited to the rigors of warehouse deployment.

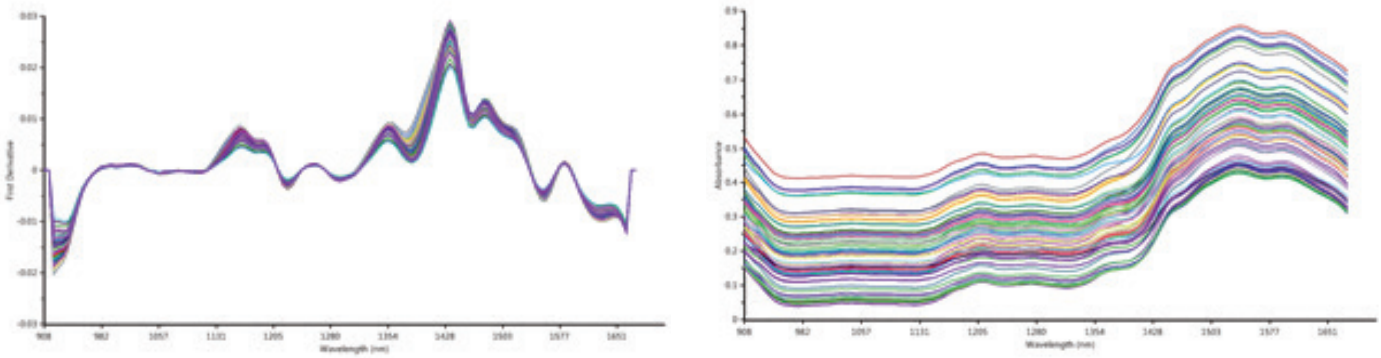

Fig. 3: Material composition, moisture, and particle size affect NIR spectra enabling material ID and qualification. Left: SNV-corrected NIR spectra of moisture change in a drying process. Right: raw data NIR spectra of particle size change in a high shear mixing process.

This document describes how to configure the MicroNIR OnSite-W NIR handheld for RMID.

The MicroNIR Pro software workflow allows multiple criteria of qualification, including spectral match (SMV) to identify and partial least square (PLS) to quantify species, or variable characteristics like moisture and particle size.

System Configuration and Results

Setting up the MicroNIR OnSite-W to perform material identification and qualification is fast and easy. The instrument does not require any setup; the essential preliminary work consists in the development of the materials library and, if necessary, the calibration models for other properties:

- Connect the instrument to the tablet PC / laptop Bluetooth
- Acquire spectra of reference materials
- Create the materials identification library and quantitative models for qualification
- Design the workflow and assign access to user
- Perform RMID on the floor

NIR measurements can be performed through plastic sacks to avoid possible contamination, exposure to atmosphere, and exposure of the operator to hazardous materials. The OnSite-W standard features and functions optimize accuracy, productivity, and ease of use. The included flat plate measurement collar ensures consistent sample presentation. A long-lasting battery (several days in typical use) yields high productivity. The instrument's light weight (8 oz./250 gr), ergonomic handle, single pushbutton operation, and rapid measurement cycle minimize operator fatigue (even with three repetitions, an operator can qualify a material in only a few seconds). Finally, when paired to a BCR equipped tablet PC, the operator can enter material details directly from its bar code, eliminating potential typing errors.

Fig. 4: The sampling collar, single push-button operation, rapid measurement cycle, and lightweight of the MicroNIR OnSite-W minimize sampling errors and fatigue. Results are displayed rapidly on the Bluetooth-connected tablet PC.

How to achieve highest confidence in the result? A real case-study.

Several materials were analyzed with the MicroNIR OnSite-W, using qualitative and quantitative chemometric models built in MicroNIR Pro software. The model library was developed by sampling six batches of each material. The collection time per batch was under 30 seconds in total, at default instrument data collection parameters. An additional set of data (1 batch of each material) was created to perform the library validation. The library included both excipients and APIs.

The MicroNIR Pro software includes a powerful algorithm (SMV) and library development kit designed to provide the highest degree of confidence in the results, including: material independent spectral pre-treatment and threshold, as well as numerical and visual library validation and nearest neighbor ID option.

- Some materials have minor structural and morphological differences and therefore may or may not require data pre-treatment. Materials of identical composition and different mesh would require raw data (see Fig. 3) to preserve the information relative to particle size, such as the baseline shift. Other materials very similar in all aspects may require SNV and 1st or 2nd derivative preprocessing to enhance the algorithm identification performance.
- The built-in diagnostic of MicroNIR Pro generates the SMV value of each material when compared to all others helping to verify uniqueness of the material ID (green) possible uncertainty between two materials of very similar composition and spectra (yellow) and insufficient threshold to uniquely identify materials with a higher degree of spectral difference (red). This diagnostic tool is fully automated and presented in tabular and graphical way to the library developer.
- The nearest neighbor function allows to identify the closest material to the new sample, as well as other materials, for enhanced confidence in the uniqueness of the ID result.

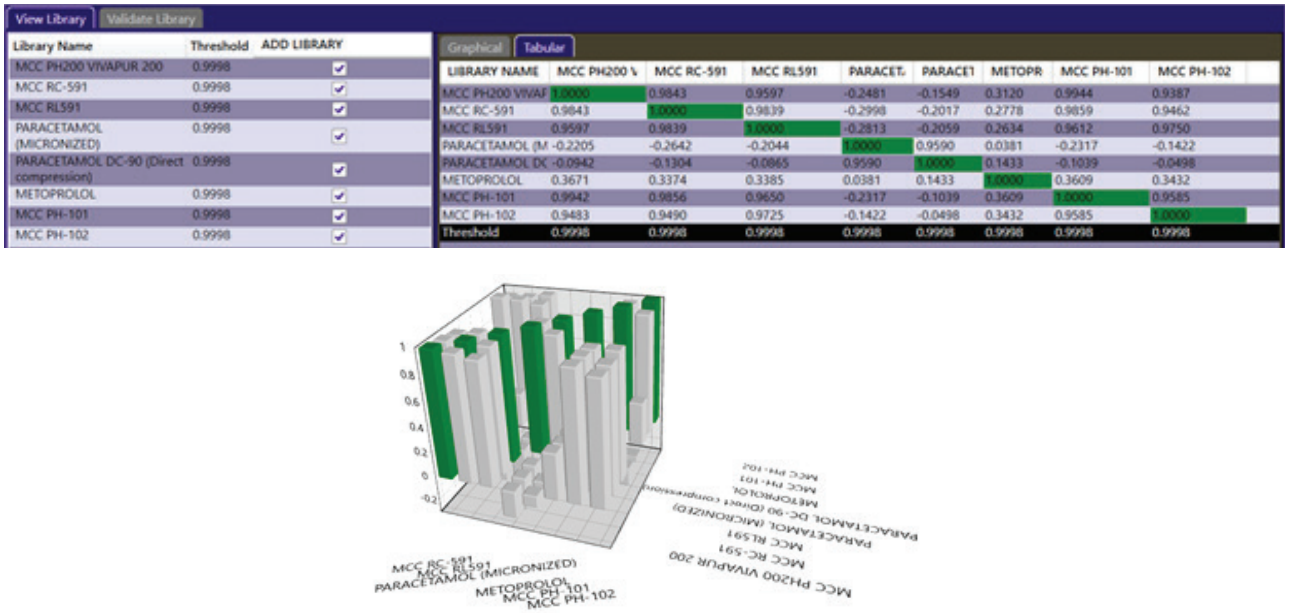

Fig. 4: RMID library validation. By performing cross-SMV between library materials and validation batch, the developer can instantly verify the robustness (uniqueness) of the library, where green scores indicate certainty, yellow uncertainty between two very similar materials and red, an insufficient threshold. The score of the materials is also presented in a histogram, where each material column must be sufficiently lower than the green ones (higher SMV distance).

Advanced approach – combined qualitative and quantitative modeling

The ability of MicroNIR Pro software to apply multiple analytical criteria to the workflow allows the developer to combine qualitative and quantitative results. Qualitative (identification) criteria are developed using the SMV algorithm, or can also be imported from third party tools. Quantitative criteria – moisture and particle size – are developed from a PLS model built on samples characterized in a laboratory (loss on drying for moisture, for example, and particle size analysis). Each of these samples can be named to include the relevant properties, for example "Avicel MCC PH200 PS 180 Moisture 2%" for the material with 180 micron particle size and 2% moisture. A model built this way will immediately tell the operator whether the incoming material passes or fails and what parameters are in or out of bounds. Clearly, once these methods are deployed on the loading dock, laboratory effort, reagent use, and cycle time can be dramatically reduced.

Fig. 4: The workflow development of MicroNIR Pro software allows multiple data analysis steps. SMV can be used to identify the spectrum, while chemometric models can be added to quantify a specific material property.

Conclusions

Material identification and qualification is an essential step of QbD and LEAN. 100% RMID is an established common practice in the pharmaceutical industry and NIR is one of the best fit-for-purpose analytical techniques to perform such tasks. Unlike other technologies, NIR can identify materials and qualify them by multiple properties including moisture content and particle size, all while reducing workload on the quality control laboratory. The MicroNIR OnSite-W offers unique value to perform warehouse characterization of incoming materials, including:

- Identification and qualification of materials, including Raman fluorescing ones
- Confidence in the results by diagnostic tools and nearest neighbors' ID scores
- Ease of use achieved by lightweight, single push-button operation and streamlined user interface
- Long lasting battery operation for uninterrupted work on the production floor

The MicroNIR OnSite-W can be used in place of LOD/titration for moisture content speciation, or to minimize the need for lab-based particle analysis. The industrial design is water and dust proof (IP65/67) and its Bluetooth connectivity allows the use of tablet PCs which, if equipped with bar code reader, can also eliminate sample information typing errors. The MicroNIR OnSite-W can uniquely identify and qualify a wide variety of materials and represents an excellent solution for RMID, or a perfect complement to existing Raman-based processes.

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