VIAVI Solutions

eBook

NIR Spectroscopy

A Powerful Tool for Quality and Productivity

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MicroNIR™ Handheld and Process Spectrometers

One product line, one solution for all your process control requirements

VIAVI MicroNIR™ spectrometers are designed for one purpose: to help you improve the quality and reduce the cost of your products. With models and accessories to suit every stage of pharmaceutical manufacturing, full GMP compliance, and low total cost of ownership, MicroNIR instruments are ready and able to take you where you want to go.

- Use the handheld, wireless OnSite-W at the loading dock for raw material identification and qualification (RMID)
- Use the USB-powered PAT-U for real-time monitoring of drying, granulation, tableting, and coating
- Use the compact, wireless PAT-W on a tumble blender for a rotation-by-rotation read out of blend uniformity

MicroNIR Pro software, a complete, easy-to-use chemometric modeling suite, is included with every instrument and supports compliance with USP 1856 and EP 2.2.40 standards.

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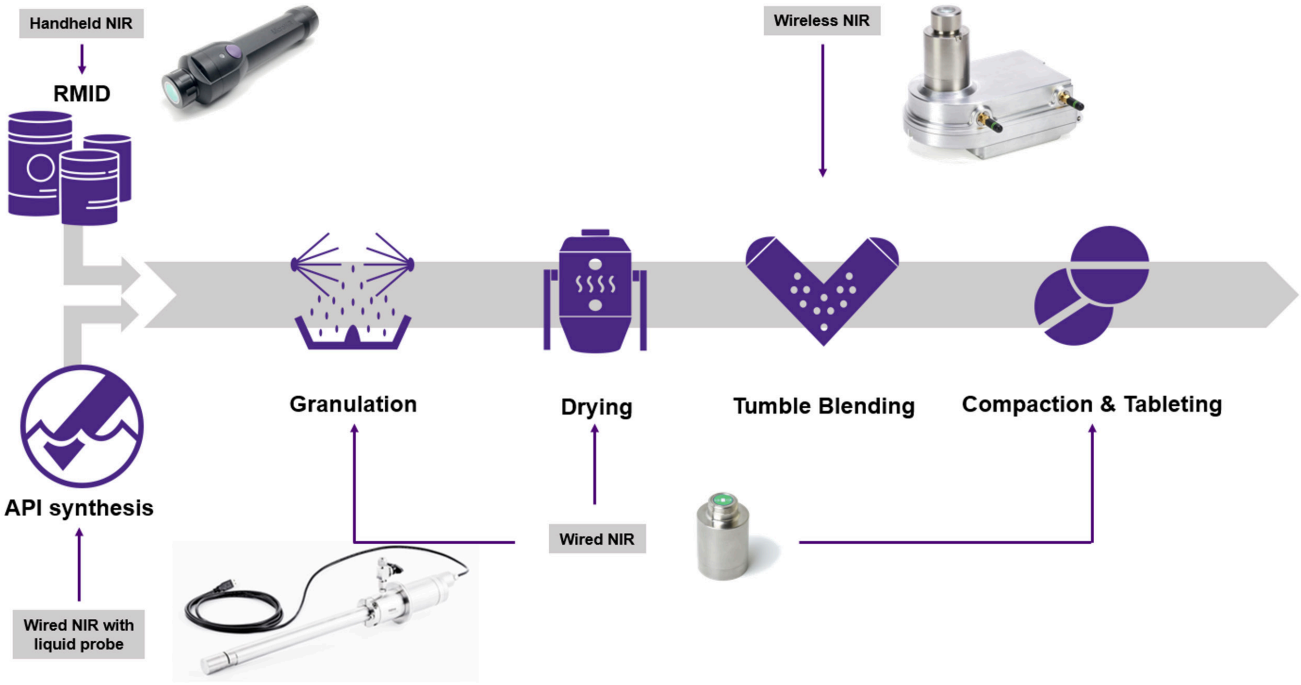
VIAVI Solutions

Near Infrared Spectroscopy Enables Quality by Design and Lean Pharmaceutical Manufacturing

Manufacturers of pharmaceuticals face a host of demanding and evolving challenges. The need to diligently protect patient health and well-being is always primary, and the need to minimize risk oftentimes conflicts with manufacturers' desire to make advantageous process improvements. At the same time, the obligations of USP and EP compliance can push manufacturers into costly and time-consuming processes that challenge their organization's obligation to deliver profit to shareholders. In response to those challenges, scientists and process engineers have been migrating traditional batch-processing of drugs to leaner methods and, increasingly, to continuous or semi-continuous processes. Key to all these trends is PAT – Process Analytical Technology – as a means to increase quality and productivity and gain critical process insights that drive additional innovation.

Batch processing typically depends on frequent laboratory analysis to assure quality at each stage of the manufacturing process. The laboratory analysis of raw materials, intermediates, and finished products, commonly defined as Quality by Testing or QbT, is time-consuming, carries many low value-added steps, and does not always prevent material waste. By contrast, in a Quality by Design (QbD) environment, raw materials are qualified directly in the receiving area; dryers, granulators, and mixers are equipped to continuously monitor moisture content and particle size of intermediates; blend uniformity is verified in real time with no need for systematic thief sampling; and tablet presses monitor the consistency of the powder flow before compression. PAT assures that the final product is as intended, requiring periodic lab analysis only for confirmation and fine-tuning the PAT calibration. As any Lean initiative, QbD upfront costs are readily recovered through significant increase in productivity and reduced waste.

Near infrared spectroscopy (NIRS) has proven to be a powerful tool in the PAT ecosystem because it can provide critical analytical information while being minimally invasive, non-destructive, and fast. The newest generation of PAT NIR spectrometers embodies fit-for-purpose performance, speed of analysis, ease of integration with PAT/HMI software platforms, low cost of ownership, and optional hazardous location safety compliance. In the following chapters, we review how NIRS can be applied to each major stage of pharmaceutical manufacturing (see Figure 1) to increase quality, decrease cycle time, reduce waste, and ultimately improve your organization's productivity and profitability.



Example of typical pharmaceutical manufacturing process steps and the place of NIR spectroscopy in a Quality by Design environment.

Chapter 1

Raw Material Identification

Introduction

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

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% material testing, and the volume of analysis performed in quality control laboratories became burdensome. This regulatory change, now global, pushed instrument manufacturers to design "fit for purpose" solutions. In the early phase of the implementation of "fit for purpose solutions," many industries adopted NIR laboratory systems, redesigned for warehouse operation and equipped with fiber optic probes. Those systems often lacked the cost, ease of use, and ergonomic attributes appropriate for broad deployments in factory and warehouse environments. Recently, the miniaturization of spectroscopy techniques such as NIR and Raman have enabled portable, fit-for-purpose instruments that deliver a satisfying user experience, low 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 routine laboratory characterization and avoid material movement
- Dramatically reduce cycle time
- Increase quality

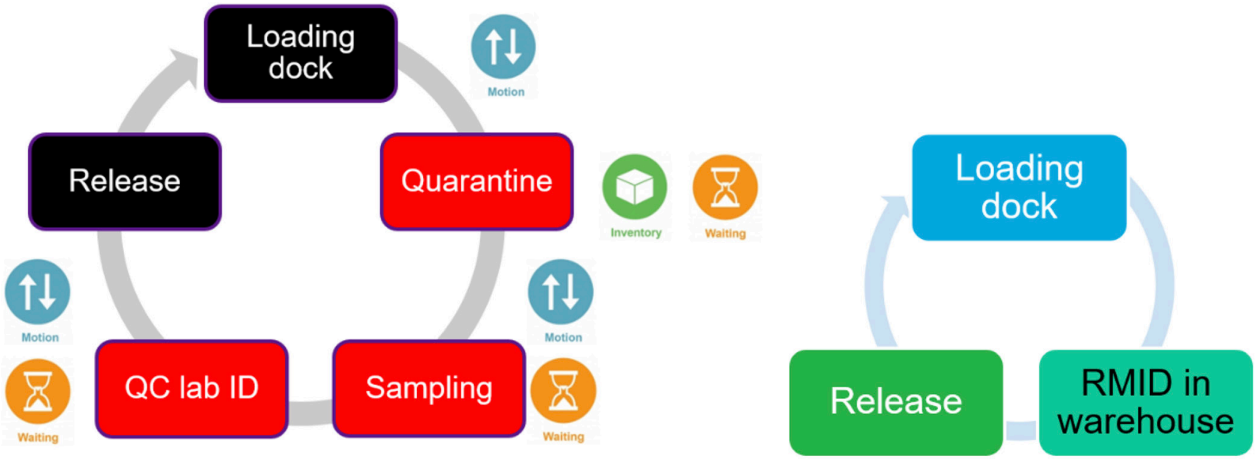


Figure 1. Traditional RMID process cycle (left) compared to RMID performed in the manufacturing area (right).

Several instruments are now available on the market for RMID purposes, primarily Raman and NIR handheld spectrometers. 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 significantly 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 is 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

Figure 2. In this RMID example, Raman is able 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.

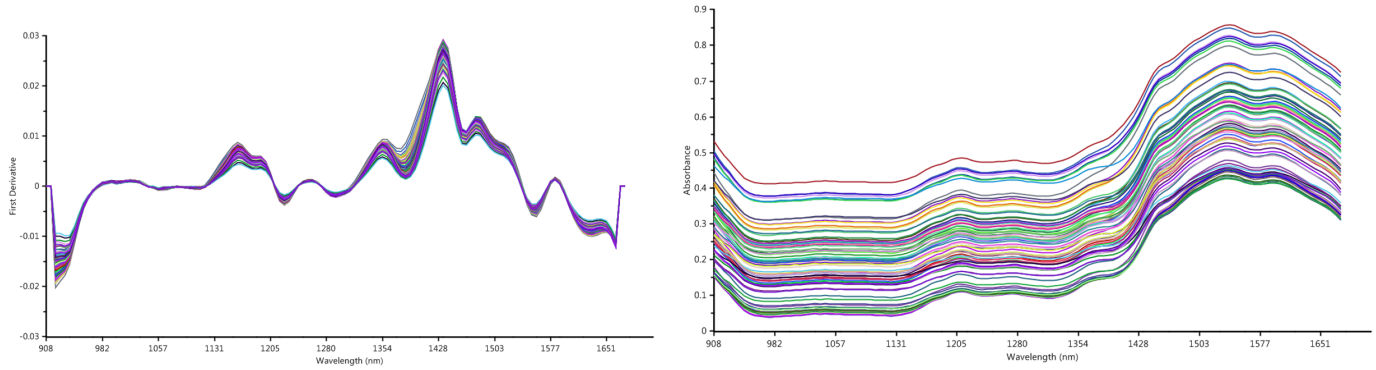


Figure 3. Material composition, moisture, and particle size affect NIR spectra enabling material ID and qualification. Left: SNV-corrected NIR spectra of moisture change in a drying process. Right: raw data NIR spectra of particle size change in a high shear mixing process.

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.

How to configure the MicroNIR OnSite-W NIR handheld for RMID

MicroNIR Pro software is a complete data acquisition, chemometric model development, and prediction package, and is included with every MicroNIR instrument kit. The MicroNIR Pro workflow accommodates multiple criteria of qualification, including spectral match (SMV) for identification and partial least squares (PLS) to quantify concentrations of species or measure continuously 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 or calibration. Preliminary work consists of developing the materials library and, if necessary, the calibration models for other properties:

- Connect the instrument to the tablet PC or laptop via 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 loading dock 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 presentation of powder samples. A long-lasting battery (one that can operate for several days after a single charge 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.

Figure 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 case-study

Several common pharmaceutical 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 (Spectral Match Value, or 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 (particle size) 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.

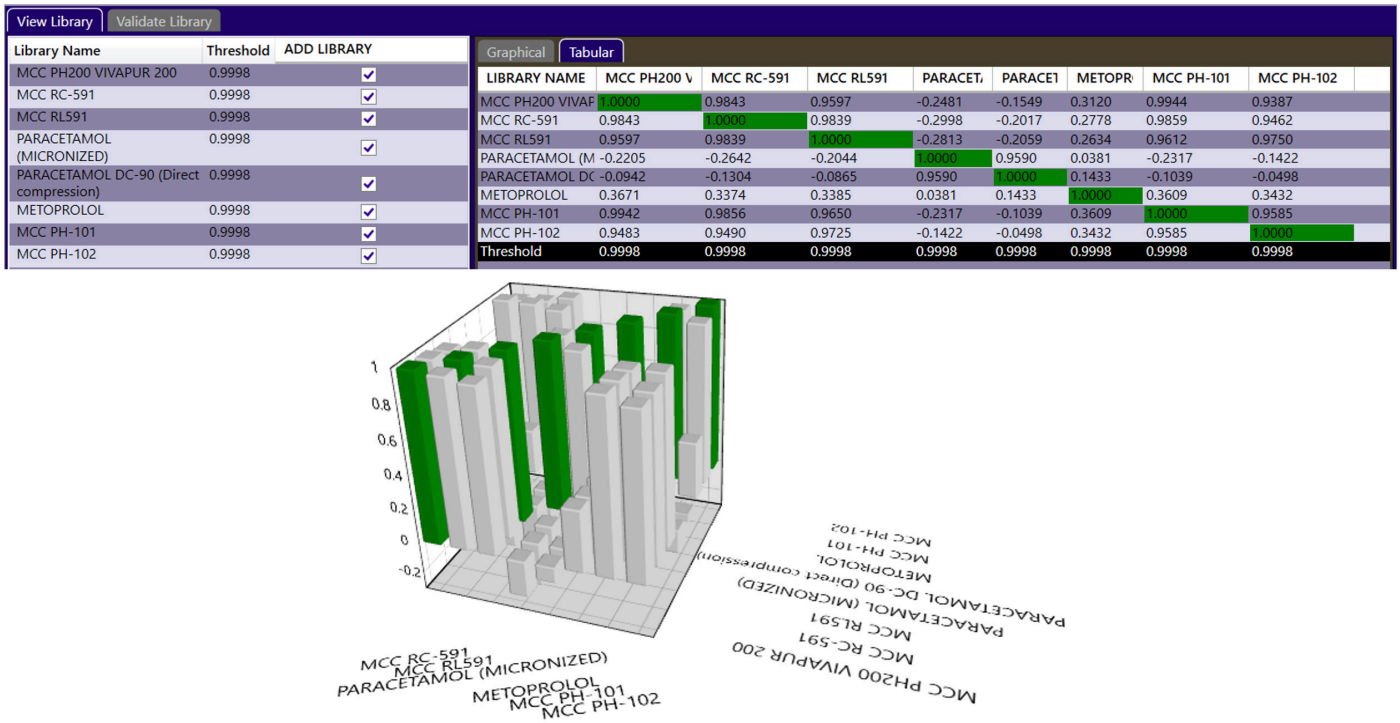


Figure 5. RMID library validation. By performing cross-SMV between library materials and validation batch, the developer can instantly verify the robustness (uniqueness) of the library, where green scores indicate certainty, yellow uncertainty between two very similar materials and red, an insufficient 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 included SMV algorithm or can also be imported from third party tools. Quantitative criteria – moisture and particle size – are developed from a PLS (Partial Least Squares) 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.

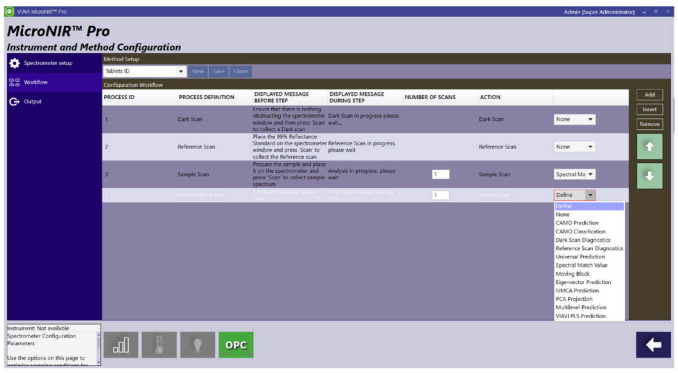


Figure 6. The workflow development of MicroNIR Pro software allows multiple data analysis steps. SMV can be used to identify the spectrum, while chemometric models can be added to quantify a specific material property.

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.

Chapter 2

Immersion Monitoring of API Crystallization

Monitoring the dynamics of the API synthesis in production vessels by means of NIR spectroscopy allows for cost optimization and the potential to improve yield. The primary advantage is the reduced need for laboratory analysis to assess the batch specifications and the consequential savings in cycle time. The secondary advantage is the capability to detect process anomalies, take corrective actions (CAPA) and possibly reduce waste of material and time. Unlike traditional benchtop instruments, new generation NIR spectrometers optimized for PAT deploy the speed of analysis and signal to noise (typically, 100 averaged scans per second) adequate for most chemometric model development purposes. The absence of moving parts, fiber optics and misalignment minimize the cost of ownership, while compliance with ATEX, NEC and IECEx hazardous locations requirements make real-time API crystallization monitoring cost effective and safe. The MicroNIR PAT-L and -Lx are designed

Figure 1. MicroNIR PAT-L Immersion Spectrometer

for installation on vessels in standard and hazardous locations, respectively. They are configurable at order in a variety of pathlengths, immersion depths, probe materials, temperature and pressure resistance, and other properties to fit most applications. The all-in-one design allows ease of implementation, low cost of ownership and it is based on industry-standard process probe technology. The MicroNIR PAT-L and PAT-Lx will be available in the first half of calendar 2021, along with supporting Application Notes and Case Studies.

Chapter 3

Granulation and Drying

Once incoming raw materials are identified and qualified, they are ready to proceed to the next stage of production. Subsequent processes can also be equipped with NIR spectrometers to monitor the evolution of a process and control its end point. In this chapter we look at granulation and drying, intermediate steps no less critical to quality than any other.

Fluid bed dryers, granulators and high-shear mixers provide readouts of air and product temperature, air humidity, and torque. These indicators can indirectly reflect the progress of an ongoing process, but do not directly measure moisture content and particle size, which are typically critical-to-quality (CtQ) parameters. NIR spectroscopy is very sensitive to both moisture and particle size and can provide direct measures, so integrating NIR spectrometers in FBGDs and HSMs opens a clear window on the dynamics of dry mixing and primary and massing granulation. The insight gained allows the process engineer to understand process variables and variability, identify and define end points, increase process consistency, and minimizing process time.

Supervised chemometric modeling (e.g., PLS) provides moisture and particle size values with prediction error often comparable to LOD and particle size analysis. Supervised methods, however, require prior development of calibration models specific to each intermediate. The alternative approach is to use unsupervised methods (requiring no prior calibration) such as moving block standard deviation (MBSD) and principal component analysis (PCA). These approaches do not provide concentration or median diameter values but analyze spectral variation over time that can be correlated to reference values. Once the dynamics of the process are well understood and repeatable, the desired end point and acceptable limits can be set. The result of real-time monitoring is batch to batch consistency, faster cycle time, and lower laboratory analysis cost.

The following paper, co-authored with researchers at the prominent pharmaceutical-equipment maker Freund-Vector, details a study comparing unsupervised and supervised methods of monitoring granulation and drying. It has been lightly edited for clarity and condensed.

Drying monitoring by MicroNIR PAT-U: PCA vs. supervised approach (PLS)

Andrea Gelain[1], Giuseppe Buratti[1], Emiliano Genorini[2], Gabriele Inverni[1]

Freund-Vector European Lab[1], Villasanta (MB); Viavi Solutions Italia[2], Vimercate (MB)

Introduction

The following experiment was performed to assess the capability of NIR technology to provide real time granulation and drying information traceable to laboratory analysis. A couple of batches were used to perform a preliminary study and acquire data for the development of two post processing methods: (1) Principal component analysis (PCA, a calibration-free approach), aimed to verify whether, under the same process conditions NIR can provide comparable

trend profiles, and (2) partial least squares (PLS), a quantitative calibration model, to assess the error of prediction of moisture content (MC) and d50 particle size distribution (PSD) against the primary techniques reference values. Multiple batches of similar composition were then analyzed in real-time throughout the granulation and drying process.

Preliminary study

The first experiment consisted of preparing the placebo formulation shown in the following table and applying a top spray granulation in the fluid bed under the process parameters as shown in Table 1.

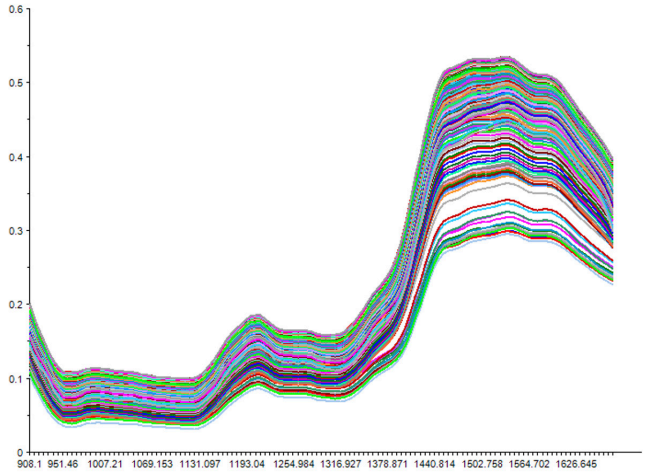
Formulation - Blend		
Component	*Quantity (g)*	*%*
Lactose 200 mesh	1000	50
Pregel. Starch	700	35
MCC	300	15
Total	*2000*	*100*
Formulation - Binding solution		
PVP K30	100	10
DI Water	900	90
Total	*1000*	*100*

Process Parameters			
Inlet air Temp. (°C)	50 - 60	Process time (min)	90
Product Temp. (°C)	27 - 28	Spray Rate (g/min)	25 - 30
Airflow (m^3)	80 - 110	LOD (%)	3 - 10

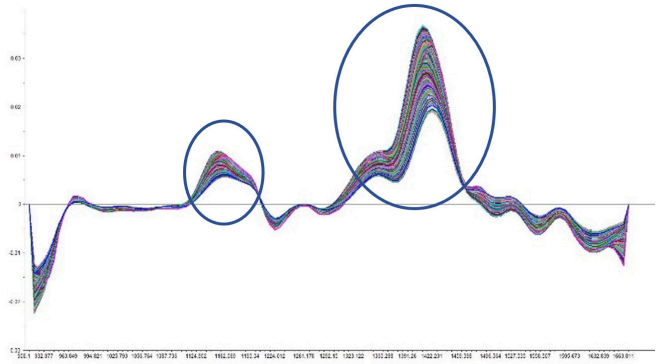
Table 1.

The NIR spectrometer, a MicroNIR PAT-U, was fitted inside the process chamber and set to acquire a spectrum every 20 seconds. Moisture content and LOD parameters were manually analyzed every 5 minutes by means of a Mettler Toledo MJ33 moisture analyzer and a QICPIC with RODOS/L and VIBRI/L which provides high speed image analysis by using a pulsed light source. The less than 1 nanosecond exposure time creates a steady image of the particles while a high-resolution, high-speed camera captures the particle projections with a frequency of up to 500 frames per second. The raw spectra in the following figure (top) show a baseline shift, typical of particles size changes (the finer the powder, the lower the absorbance) while the 1st derivative computed spectra (bottom) highlight the typical absorption regions of water.

2a.



2b.



PCA, unsupervised analysis

The PCA trend analysis showed very similar profiles from one batch to another, as well as distinct patterns indicating the mixing, granulation, granulation endpoint, drying and the endpoint of the drying process phases (Fig. 3).

PLS, supervised analysis

The same data set was used to build a calibration model based on the actual values obtained by MC and

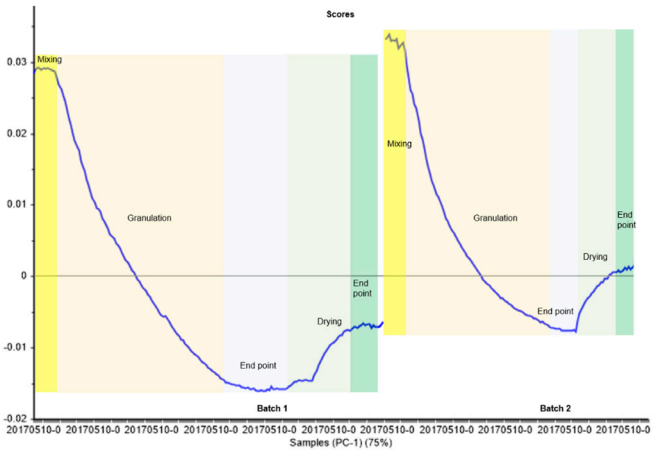
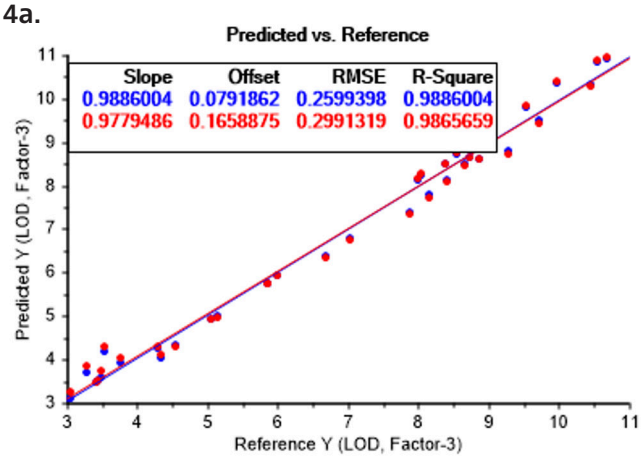


Figure 3.

4a.



4b.

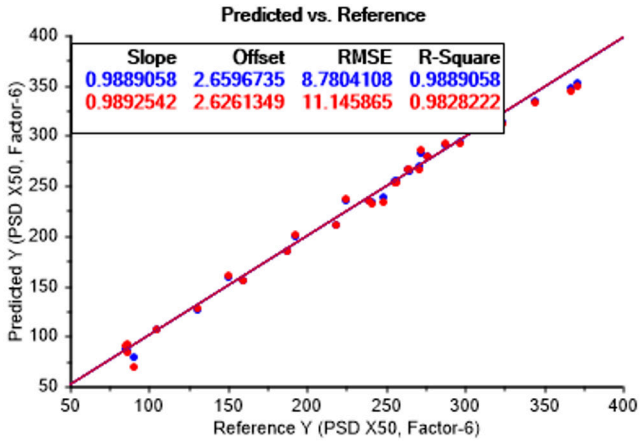


Figure 4a and 4b. Correlation between primary technique Reference and secondary technique (NIR) Predicted values respectively of loss on drying (LOD, Figure 4a) and d50 particle size distribution (PSD, Figure 4b)"

PSD techniques. The obtained correlations of both MC and PSD show good alignment between primary and secondary (NIR) techniques, with R2 very close to 1.0 (perfect correlation).

Process monitoring

Based on the successful preliminary study outcomes, four placebo batches were granulated with top spray technology under identical process parameters, as per tables 5a and 5b below. Process parameters like solution flow rate and inlet air temperature have been automatically regulated by the fluid bed dryer software to ensure reproducibility. The data acquired from three batches were combined to build a calibration for both MC and PSD, while the fourth batch was measured in real time.

Formulation - Blend		
Component	*Quantity (g)*	*%*
Lactose 200 mesh	2000	50
Pregel. Starch	2000	50
Total	*4000*	*100*
Formulation - Binding solution		
PVP K30	200	10
DI Water	1800	90
Total	*2000*	*100*

Table 5a.

Process Parameters			
Inlet air Temp. (°C)	50 - 60	Process time (min)	90-120
Product Temp. (°C)	27 - 28	Spray Rate (g/min)	25
Airflow (m^3)	90 - 120	LOD (%)	3 - 10

Table 5b.

The Predicted vs. Reference real time measurements (figure 6a and 6b) confirmed good correlation and shown a prediction error (tables 7a and 7b) within an acceptable range.

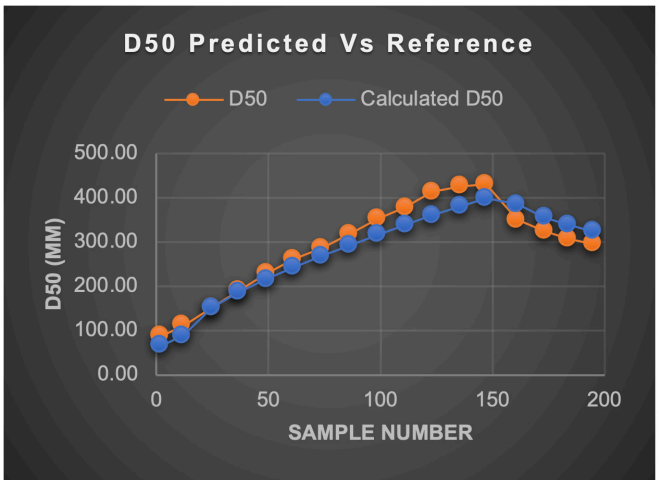


Table 6a.

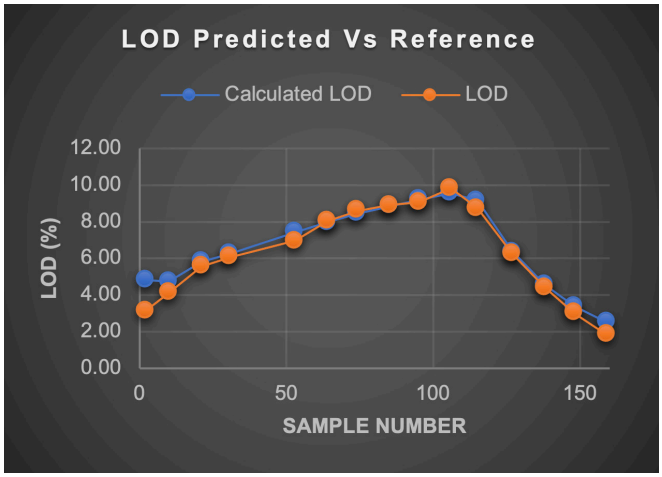


Table 6b.

Conclusions

The PCA profile endpoint is typically obtained by repeated tests, where no further significant changes can be observed within a certain period of time. By specifying the number of repeated values, the range of PCA score variation and implementing event triggers, the equipment can be instructed to automatically stop at the end point. This approach does not require prior calibration data acquisition and modeling, but repeatability studies for each blend and process conditions. The PLS calibration alignment with primary techniques and acceptable error of prediction showed the potential of the MicroNIR PAT-U to significantly reduce laboratory analysis and implement batch-to-batch continuous monitoring for increased quality assurance, at lower cost.

Batch 20170727_02		
Sample	***LOD***	***Calculated LOD***
2	3.13	4.83
10	4.11	4.75
21	5.56	5.82
31	6.08	6.25
53	6.97	7.42
64	8.04	7.98
74	8.59	8.45
85	8.92	8.84
95	9.07	9.19
106	9.84	9.55
115	8.74	9.16
127	6.25	6.37
138	4.39	4.55
148	3.00	3.39
159	1.84	2.53

Table 7a.

Batch 20170804_01		
Sample	***D50***	***Calculated D50***
2	87.58	65.47
12	111.16	89.49
25	153.36	153.12
37	190.63	187.72
49	228.66	216.38
61	261.74	242.55
74	287.20	269.39
86	318.07	291.23
99	352.98	316.52
111	378.39	338.70
123	414.01	360.93
136	426.08	381.09
147	431.06	399.44
161	350.76	385.97
173	324.35	355.80
184	307.05	338.53
195	295.06	323.64

Table 7b.

Chapter 4

Blending Optimization

Introduction

Once raw materials and intermediates are prepared and qualified, they must be blended uniformly to ensure that every unit dose contains an identical ratio of constituents. Blenders take various forms, but one of the primary methods is tumble blending. Tumble blenders present a unique challenge for real-time monitoring since it is not possible to connect a cabled instrument to a piece of rotating machinery. The MicroNIR PAT-W is a unique, lightweight, wireless instrument that can be readily attached to almost any size tumble blender to bring the power of NIR spectroscopy to real-time blend monitoring.

Traditional Methods

Blend uniformity testing in the pharmaceutical industry is traditionally carried out by stopping the blender after a given time, typically defined by existing procedures. The operator then withdraws 10 samples at predefined locations specified by the current International Conference on Harmonization (ICH) guidelines. The samples are then analyzed offline in the QC/QA laboratory by means of HPLC, UV-Vis and/or other laboratory techniques. The approach has several disadvantages:

- The blender must be stopped to withdraw samples, costing time and money
- Thief sampling causes perturbation of the finished blend
- Laboratory characterization is labor intensive and time-consuming
- Operator exposure to API and solvents may require extra safety measures
- The blend is exposed to the environment

Thief sampling is the most underestimated aspect of this list. In fact, introducing a thief and withdrawing samples causes perturbations in the blend, creating segregation in the powder beds. This is well explained in a recent article by Kim Esbensen, Rodolfo Romañach and coworkers.

Real-time Monitoring

Installing a near infrared (NIR) spectrometer online can be an effective solution to overcome the drawbacks listed above. The MicroNIR PAT-W from Viavi Solutions monitors tumble blending continuously in real time, with no need to stop the blender for sample withdrawal and further laboratory analysis. In the pharmaceutical industry, the direct monitoring approach enables the implementation of QbD (Quality by Design), encouraged by the FDA . In other industries, the direct monitoring of the blending process represents a significant advance toward LEAN manufacturing.

Real-time blend monitoring is a fundamental step of the transition from process validation to continuous process verification, in which every step of every batch is controlled during the production phase.

This note describes how the MicroNIR PAT-W can be integrated into a commercial manufacturing environment for the purpose of optimizing the endpoint of a blend.

System Configuration

Setting up the MicroNIR PAT-W to monitor powder blending is fast and easy. The steps include:

- Mounting the NIR sensor on the blender lid equipped a standard triclover clamp
- Connecting the instrument via Wi-Fi to the computer
- Adjusting the acquisition parameters so that data are collected exclusively when the blend covers the instrument's sapphire process window. (The PAT-W includes an onboard accelerometer used to trigger data acquisition.)

With some minor additional software settings, the system is ready to display the progress of blend uniformity, allowing a direct and non-invasive readout of blend dynamics inside the blender. Typically, 50-100 rapid acquisitions are averaged into a single spectrum, representing a single blender rotation. Total time to acquire a single spectrum is in the range of 450-900 ms.

The MicroNIR PAT-W is IP 65/67 rated and is completely isolated from the blend by a sapphire window, allowing non-contact operation. When the blending process is complete, CIP (Cleaning in Place) and SIP (Sterilization in Place, if required) can be accomplished without disassembly. Materials used in the PAT-W are FDA approved. In the following section, we describe methods of monitoring blend process in real-time.

From real-time data to executable information

Unlike many NIR applications, blend uniformity can be monitored with no need for chemometric data modeling. Starting from the initial loading of pure ingredients, blend uniformity is monitored throughout the blending cycle by plotting the standard deviation of the acquired spectra over time. This provides an easily interpreted numerical value that reflects the degree of uniformity of the mixture: as the blend becomes increasingly uniform, successive spectra become increasingly similar and the corresponding standard deviation decreases asymptotically.

The data processing, based on the calculation of standard deviation as an index of similarity, is called Moving Block Standard Deviation (MBSD) (Figure 1). At the beginning of the blending cycle the materials are well separated. Spectral variability from one rotation to the next and the resulting block standard deviation are high. As the material becomes well blended the MBSD decreases to a low, nearly constant level. Blending is complete when the calculated value falls below a user-defined threshold and remains consistent over a meaningful number of blender revolutions. The threshold may be manually set or mathematically defined by Fisher statistics at a 95% confidence interval. Up to four separate spectral regions can be monitored simultaneously. Data acquisition and analysis are accomplished by the VIAVI MicroNIR Pro software, which is compliant with Title 21 CFR Part 11, USP chapter 1119 and E.P. chapter 2.2.40.

Case study

The product in this case study consisted of one active ingredient and four excipients. The standard blending time for the chosen process was 20 minutes, or approximately 450 rotations. After the endpoint was reached, the last steps of the process included the

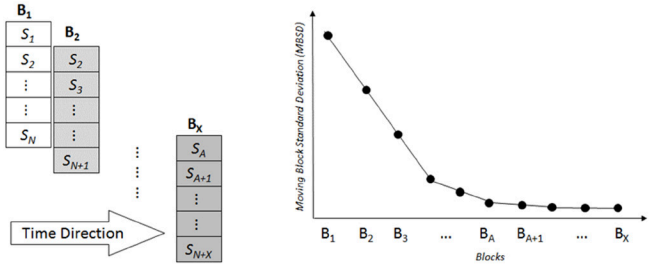


Figure 1. How the MBSD algorithm works

addition of a lubricant, followed by a final blending time of 1 minute. A MicroNIR PAT-W was installed on the blender lid (Figure 2) equipped with a welded sanitary flange and sapphire process window.

The built-in rechargeable Li ion battery of the MicroNIR PAT-W allows >8 hours of continuous operation and the dedicated wireless channel addresses network security concerns.

Figure 2. Interface of the MicroNIR PAT-W into the lid of a bin blender

The MicroNIR PAT-W uses VIAVI Linear Variable Filter (LVF) technology and has no moving parts or optical fiber couplings, permitting the instrument to deliver highly reproducible spectral data at a rapid rate. Dual onboard tungsten lamps provide stable operation with an extremely long lamp life.

Acquisition parameters used to collect data are reported in Table 1.

Delay time refers to the time difference between the gravity-activated trigger and the measurement cycle,

Acquisition Mode	Diffuse Reflectance
Integration Time (ms)	8.9
Scan Count	100
Scan Mode	Autonomous (Gravity)
Delay Time (ms)	600

Table 1. Acquisition parameters

and is set during configuration to ensure the blend covers the process window during measurement. The NIR spectral profiles of the entire process are shown in Figure 3a. Visibly different spectra reflect the inhomogeneity of the powder mix at the beginning of the cycle, clearly showing that blend uniformity is embodied within the collected data.

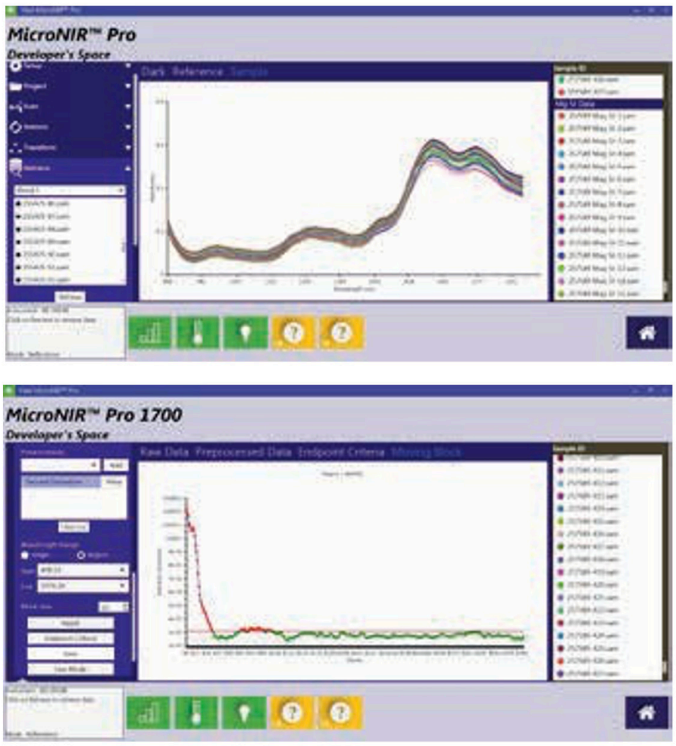


Figure 3. a) Spectra acquired during blending. b) Moving Block Standard Deviation of spectra plotted over time.

In the present case study, the MBSD profile of Figure 3b indicated that the process endpoint occurred after 150 rotations, while the traditional approach standard procedure was set to 450 rotations with subsequent laboratory analysis. Once validated, the PAT approach greatly reduces the need for lab analysis and increases uptime and product throughput. In many cases, NIR monitoring can also reveal over-blending, resegregation, and the production of fines.

Advanced approach

The ability to monitor the homogeneity of a blend with no need for data modeling and prior analytical method development applies to a wide range of formulations, regardless of the chemical composition, number, or nature of the ingredients. When complex blending dynamics need to be understood, more advanced data analysis tools can be applied. Mixtures can be monitored by narrowing the spectral region to the unique signatures of specific ingredients while simultaneously displaying the profile of multiple constituents. Alternatively, data reduction with PCA (Principal Component Analysis) prior to performing the MBSD computation allows the monitoring of ingredients characterized by chemical similarities or by particle size inhomogeneity among the mixture constituents, again with no need for chemometric modeling.

Conclusions

In summary, blend uniformity continuous monitoring by means of the MicroNIR PAT-W is a critical step toward the implementation of QbD in pharmaceutical manufacturing and/or LEAN manufacturing in any industry and can be successfully used to:

- Enable process monitoring from laboratory to production through a scalable path
- Acquire actionable information within process development and deployment
- Avoid overprocessing, such as production of fines and material segregation
- Reduce blending time and increase manufacturing productivity

The MicroNIR PAT-W is suited to many applications, from small-batch pilot laboratories to identify the optimal blending time of new formulations, up to the production floor, through OPC integration, IP 65/67 compliance and fit-for-purpose industrial design.

References

1. Esbensen et al., International Journal of Pharmaceutics (2016) 499, 156 DOI: 10.1016/j.ijpharm.2015.12.038
2. PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pat-framework-innovative-pharmaceutical-development-manufacturing-and-quality-assurance

Chapter 5

Real-time monitoring of tablet presses

Introduction

Tableting is one of the final steps in pharmaceutical, nutraceutical and other solid-forms manufacturing. NIR monitoring of moisture, particle size and blend uniformity throughout the process is essential to avoid out-of-specification intermediate mixtures, but problems may still arise at the very last – tableting – step. Sticking, one of the major defects associated with tablet manufacturing, can be due to the inaccurate addition of excipients or errors in the granulation process. Lamination, another typical tableting issue, can be created by fines, excess trapped air between particles, or inadequate moisture in the powder blend. Physical defects are generally easy to detect, often by visual inspection of the finished tablets. However, identifying the source of the physical defect requires laboratory analyses, after which corrective action can only be taken on future production. The defective batch must be scrapped, which results in material waste and lost time. In absence of tablet physical defects, out-of-specification tablets would be detected only after laboratory analysis and may lead to risk management corrective actions, including product recalls. The implementation of NIR sensing in a tablet press enables the detection of anomalies in the formulation before the compression stage and allows real-time root cause analysis of the problem and immediate corrective action.

In summary, the disadvantages of post-tableting quality control are:

- Time consuming and expensive root-cause analysis of physical defects
- Possible waste of material, lost time, and inconsistent production yield
- Late detection of out-of-specification tablets with potential risk of product recall

Installing an NIR sensor directly on-line can be an effective solution to avoid all these drawbacks. Specifically, the MicroNIR™ PAT-U miniature process spectrometer allows continuous monitoring of powder mixtures before the compression stage, in real-time. In the pharmaceutical industry, the direct monitoring approach based on PAT (Process Analytical Technology) enables the implementation of QbD (Quality by Design), which is now advocated by the FDA (see, e.g., the Guidance for Industry PAT - A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance). In other industries, the direct monitoring of the process represents a valuable advancement toward LEAN manufacturing.

Real time powder flow monitoring before tablet compression is a fundamental step in the transition from process validation to continuous process verification, in which every step of every batch is controlled during the production phase.

This document describes how the MicroNIR PAT-U can be integrated into commercial manufacturing equipment for the purpose of identifying sources of tableting defects and out-of-specification formulations, directly on-line in real time.

System Configuration

Setting up the MicroNIR PAT-U to monitor powder mixtures in a tablet press is a quick and easy procedure. The system setup steps are:

- Mounting the NIR sensor on the press equipped with a standard quick release clamp
- Connecting the instrument to the computer via a USB cable
- Adjusting the acquisition time interval to fit the dynamics of the powder flow

With some minor additional software settings, the system is ready to display the consistency of the powder blend feeding the press, allowing a direct and non-invasive monitoring of the dynamics occurring in the feed frame, or chute.

The MicroNIR PAT-U is completely isolated from the blend by a sapphire window, which allows non-contact operation. When the tableting process is complete, CIP (Cleaning in Place) and SIP (Sterilization in Place, if needed) can be accomplished without disassembling the system. In case of mechanical / space constraints due to the press equipment design, an optional extended probe allows the installation of the instrument on the feed frame with additional flexibility, with no impact on the instrument performance. The HazLoc version of the instrument – the MicroNIR PAT-Ux – is safe in the presence of flammable gases, vapors, and dust, and enables the above capabilities in hazardous locations.

From real-time data to executable information

Powder blend uniformity can be monitored in real-time with no need for a priori data modeling. Principal Component Analysis (PCA) is a powerful mathematical tool for tracking changes in the spectral "fingerprint" of the blend over time. PCA is an "unsupervised" data processing algorithm that does not require pre-calibration and explains the variance of a data set with no need for additional information. The PCA algorithm transforms information embodied in the spectra into new variables, called Principal Components (PCs), that correspond to specific spectral absorptions. The uniformity of the pre-blended material is monitored throughout the feeding cycle by plotting the trajectories of PCs over time. In the ideal case where the composition, moisture, particle size, and other critical parameters remain constant, the trajectory of the principal component(s) over time remains flat or stationary within set limits of variation. Any anomaly in the PCA plot pattern, including slopes or steps, indicates either a continuous variation in the blend, or one or multiple undesirable variations over time.

Moving Block Standard Deviation (MBSD) is another unsupervised method to monitor product uniformity in real time. While MBSD can be used for the same purpose, PCA has the advantage of providing potentially useful information to explain the nature of an anomaly. The interpretation of an anomaly is possible by jointly interpreting the PCs trajectory and the loadings profile, which is a dedicated graph that represent the contribution of each absorption band to the new variables (PCs).

Let us call the first principal component PC-1 and the second principal component PC-2. Each of these PCs explains some fraction of the observed variance in the product, with PC-1 explaining the largest part, PC-2 the next largest, etc. By examining the loadings, if the PC-1 loadings profile has a high contribution (absolute value) in the typical region of water absorptions, for example, it is possible that the process variation is

Figure 1. MicroNIR PAT-U and optional extended probe

due to an increase or decrease in the concentration of moisture. Once the PCA trajectory of a specific process is confirmed by multiple repetitions, the user can define thresholds, enable triggers to stop the equipment and avoid the production of out-of-specification tablets.

Tablet Press – A case-study

To demonstrate the capability of the MicroNIR PAT-U to detect changes in the powder mix flow, a tablet press was fitted with an instrument and sequentially loaded with blends of the same ingredients (lactose, talc, and magnesium stearate) in different ratios as reported in Table 1. Data processing procedure included both PCA and MBSD methods.

The absence of moving parts in the MicroNIR line of spectrometers allows rapid data acquisition and averaging of 100 spectra in one second, delivering excellent signal to noise data and the collection speed required for continuous monitoring. The MicroNIR PAT-U acquisition parameters used to collect data are reported in Table 1.

Ingredients	Blend 1	Blend 2	Blend 3
Lactose	98%	93%	94%
Talc	1%	3%	5%
Mg stearate	1%	1%	1%

Table 1. Powder blends composition.

Results and discussion

The acquired spectra were preprocessed using Standard Normal Variate (SNV) and first derivative (1der) transforms. The preprocessed NIR absorbance spectra for the duration of the entire experiment are shown in Figure 2. At a first glance, the spectra appear very similar, except mainly in the 1354-1550 nm region where slight variations are observed. Those slight variations represent significance in the data.

Acquisition Mode	Diffuse Reflectance
Integration Time (ms)	8.9
Scan Count per Spectrum	100

Table 2. Acquisition parameters.

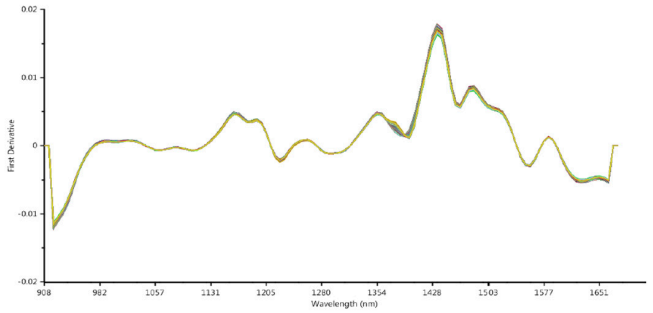


Figure 2. SNV and first derivative processed spectra of the entire experiment.

Variations in the process are reflected by structured variations in the PCA and MBSD analyses of the time-series data. With reference to Figure 3, both the MBSD profile (3a) and the trajectory of the first PC (PC-1) (3b) indicate three distinct steps or stages of the process.

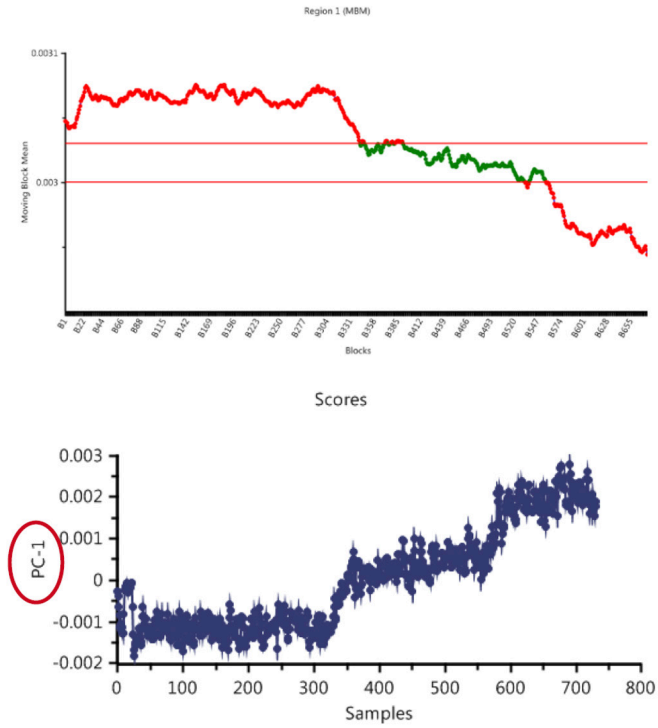


Figure 3. a) Moving block standard deviation (mean); b) PCA PC-1 trajectory

A closer examination of the PCA results shows that PC-1 is accounting for almost the entire variability of the system (Figure 4a) and it is mainly ascribable to variations in the talc absorption band, highlighted in Figure 4b. Thanks to PCA it was possible to demonstrate that, despite its low value (that varies by a factor of 5), the variations in talc concentration are detectable in real time by means of NIR spectroscopy.

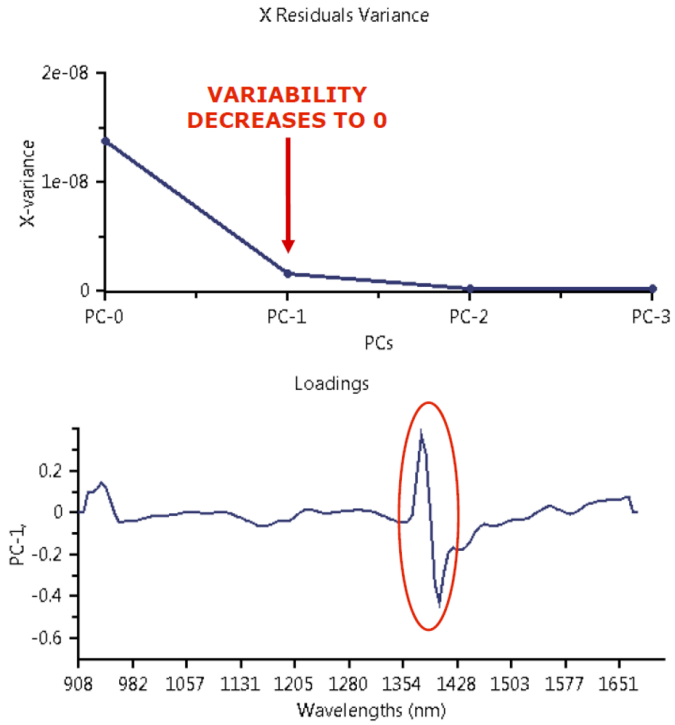


Figure 4. a) PCA explained variance; b) PC-1 loading plot

Further insight can be gained by examining the score plot in which PC-1 and PC-2 define a new orthogonal space. On this plot, the spectra are represented as points in a scatter chart. The score plot in Figure 5 shows three distinct trajectories and two intermediate trajectories. This graph represents the powder flow dynamics, from blend 1 with 1% talc concentration to blend 3 with 5%, and the two transitions between as the process changes from one blend to the next. The goal of process development should be a uniform and consistent flow, which would be represented in a PC-2 vs. PC-1 plot as a single cluster of scores, without separations or outliers.

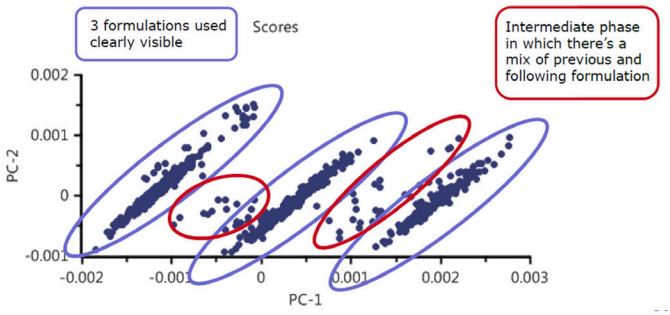


Figure 5: PC-1 and PC-2 score plot.

Figure 5. PC-1 and PC-2 score plot.

Conclusions

Powder flow continuous monitoring in a tablet press by means of the MicroNIR PAT-U and PCA analysis can yield a deeper understanding of your process, a critical step toward the realization of QbD in pharmaceutical manufacturing. This statement applies equally to LEAN manufacturing in any industry compressing tablets or employing analogous manufacturing processes. The PAT-U and can be successfully used to:

- Enable process monitoring, from laboratory to production, through a scalable path
- Acquire actionable insight on variations in the process
- Minimize time and material waste by improving yield
- Minimize out-of-specification and potential product recall risks

The MicroNIR PAT-U can also be used to enhance process understanding on other manufacturing equipment including High Shear Mixers (HSMs) and Fluid Bed Dryer (FBDs), and ribbon blenders. The MicroNIR line of compact process and handheld instruments is IP65/67 rated and supported by a GMP-compliant software suite and optional OPC process control interfaces. MicroNIR instruments can help simplify and accelerate the entire journey from pilot laboratory experiments through manufacturing process development, process optimization, and all the way up to full-scale mass production.

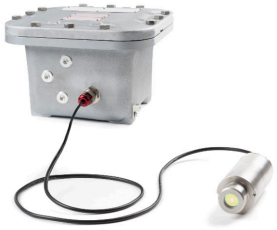
Conclusions

Quality by Testing forms a bottleneck in development, when trying to reduce time to market, and in production, when trying to reduce in-process cycle time and optimize processes in pharmaceutical, nutraceutical, and CDMO manufacturing. By contrast, Quality by Design represents a significant opportunity for improvement toward LEAN in traditional processes and is a mandatory component of Continuous Manufacturing (CM) implementations. Modern PAT instruments like the MicroNIR product line are engineered to be fit-for-purpose: rugged and stable with process-matching speed and low total cost of ownership. Using NIR instruments in a PAT/QbD environment allows the process engineer to accelerate the development of new formulations, reduce in-production cycle time, enhance product consistency, and reduce costs.

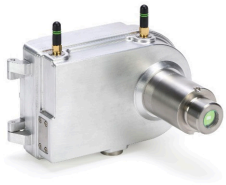
Appendix A

Hazardous Locations and Liquid Streams

Each MicroNIR PAT system is also available as an ATEX/NEC/IECEx certified version that allows the continuous monitoring of various process steps in potentially hazardous environments (solvents, fine powders etc.). A high flow rate liquid cell is also available for on-line monitoring of liquids, including moisture content in organic solvents.



MicroNIR PAT-Ux



MicroNIR PAT-Wx

MicroNIR PAT-L(x)

Appendix B

Integration with Process Controllers and PAT Software

The ultimate purpose of MicroNIR systems is to make production equipment "smarter" through the deployment of real time quality assessment of intermediates, but also by working in synergy with process control software. The optional MicroNIR OPC DA and UA software add-in allows full integration (e.g., event triggering) while the lightweight VIAVI Spectral Server integrates directly with PAT platforms such as Siemens SiPAT. MicroNIR drivers are also included in SynTQ by Optimal and Pulse by Camo Analytics, so MicroNIR solutions can be deployed across a wide range of process control environments.

VIAVI Solutions

MicroNIR™

Rugged NIR Spectrometers for Field and Process Applications

Reliable, repeatable, and maintenance-free, MicroNIR spectrometers are designed to solve your material analysis problems no matter where you are - factory, loading dock, lab, or field. Based on VIAVI linear variable filter (LVF) technology developed for NASA interplanetary spacecraft, MicroNIR instruments have no moving parts, no fiber optics, and no free-space optics for thousands of hours of stable and repeatable operation. MicroNIR spectrometers are ideal for chemical, pharmaceutical and agricultural applications, as well as feed analysis and food diagnostics.

The MicroNIR product line has recently grown to include instruments certified for use in hazardous locations and instruments for liquid vessels. To learn more about these exciting new and offerings, visit www.micronir.com.

For more information on the MicroNIR family of products, please contact your local VIAVI account manager or VIAVI Customer Service at 1-800-254-3684.

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