



Application Note AN-PAN-1048

Inline moisture analysis in a pilot scale granulation process by NIRS

Top spray granulation is a widely used technique in the pharmaceutical industry for creating granules from damp, powdered substances in fluid bed dryers. It is crucial to maintain residual moisture within defined parameters to prevent particle breakage or clumping (stickiness) of the bulk material. Near-infrared spectroscopy (NIRS) enables real-time monitoring of residual moisture levels in powders post-drying.

During top spray granulation, powder is fluidized in a fluid bed dryer and a liquid binder solution is sprayed onto the product. After spraying the liquid into the

This Process Application Note provides a detailed account of the inline assessment of moisture during a pilot scale granulation process using a 2060 *The NIR Analyzer* from Metrohm Process Analytics. *The 2060 The NIR Analyzer* delivers rapid, reagent-free, and nondestructive analysis of residual moisture in powders, facilitated by a fluid bed probe specially tailored for such applications.

formulation and forming the granule, the product must be dried to the proper moisture level. If the granules are over-dried, movement in the fluid

bed can cause their fracture (creating undesirable fine particles) and can damage the formulation due to hydration changes in some active ingredients and excipients. If the granules contain too much residual moisture, the product will not flow properly and may clump together. This can cause problems with subsequent processing, including a sticky product and product instability during storage.

Samples are typically withdrawn from the fluid bed with a sample thief during processing and then analyzed offline for moisture content in a laboratory. This delay before the analysis results are available to the operator can cause critical processing decisions (e.g., determining when the drying process should end) to be made without optimal product moisture information. Top spray granulation completion is often based on time or product temperature—not

moisture content.

The drying process in a fluid bed dryer can be quickly monitored inline using near-infrared spectroscopy (NIRS) technology. NIRS can help operators to determine the residual moisture level for better process understanding, control, and end of drying process determination. **Figure 1b** shows a trend chart of the moisture content determined by NIRS versus time.

A fluid bed probe specifically designed for these applications is used with a «spoon» and purge vents located on the probe tip (**Figure 1a**). After each NIR spectrum is collected, an air purge exiting through the ports in the probe clears the «spoon» for a new sample.

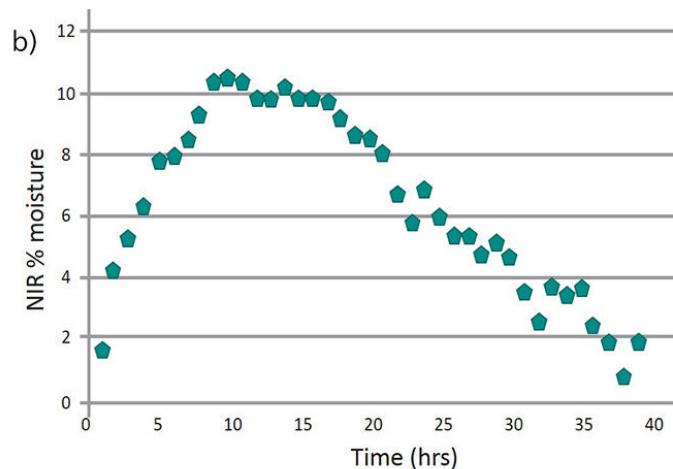
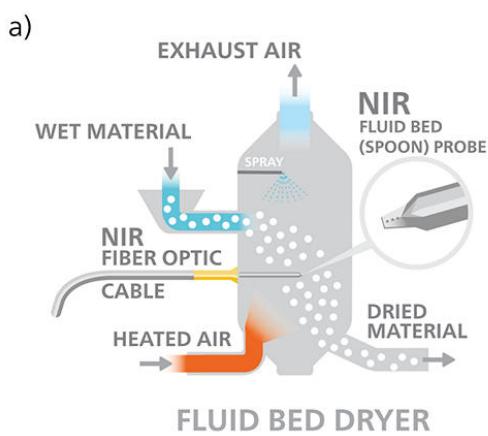


Figure 1. (a) Suggested placement for NIR «spoon» probe in a fluid bed dryer. (b) Trend chart of moisture content as determined by NIRS versus time.

The determination of the end of the drying process can be made when the moisture level asymptotically approaches a lower limit during the drying cycle. The operator is aided in making the decision to end the drying operation before the product is damaged or degraded. The delay caused by waiting for laboratory results before the product can be released for subsequent processing can be minimized or eliminated.

Output from the 2060 *The NIR Analyzer* (Figure 2) can be used by the fluid bed dryer's programmable logic controller (PLC) or integrated into SIPAT (Siemens Industrial Process Analytical Technology) for closed loop process control decisions. The reduction in reprocessing steps saves both time and money, and improvement in the product quality can lead to even higher profits.

Spectroscopy offers numerous advantages over many wet-chemical analytical methods. NIRS is economical and fast, enabling in-situ qualitative and quantitative analyses that are noninvasive and nondestructive. As an indirect test method, NIRS is recommended in **all of the key pharmacopeias** (e.g., Ph. Eur. 2.2.40, USP <1119>) and fits perfectly in the context of continuous processing and the Process Analytical Technology (PAT) initiative of the FDA.

Metrohm Process Analytics offers different versions of the 2060 *The NIR Analyzers* that meet high standards for wavelength precision, reproducibility, and photometric noise. Numerous reference standards and user-friendly software make it easy to check the instrument requirements specified in the pharmacopeias.

The pharmaceutical version of the Vision software is fully validated and compliant with **21 CFR Part 11**.

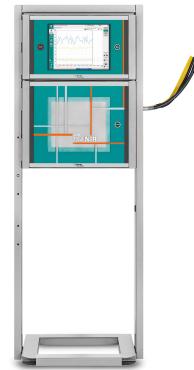


Figure 2. 2060 The NIR Analyzer with fiber optic cable.

Metrohm Process Analytics also offers complete IQ/OQ documentation and instrument performance certification. Documented parameters guarantee that the instrument performs properly.

Routine analysis methods can be developed in the software to include qualitative and quantitative analysis methods. Custom trend charts for real-time visual monitoring as well as electronic process control are also implemented.

APPLICATION

Wavelength range used: 1100–1650 nm. Inline analysis is possible using a micro interactance

reflectance probe with purge on collection tip directly in the fluid bed dryer.

Table 1. Parameters to monitor in a fluid bed dryer.

Analyte	Concentration (%)
Moisture (H ₂ O)	0–60%

REMARKS

A reference method must still be in use. An appropriate range of samples covering the process variability should be analyzed by both methods to build an accurate NIRS model. Correlations are made to process specifications. The correct NIRS probe must

be placed in-situ in a manner that provides sufficient sample contact with the probe tip window. Correct probe design and proper placement in process equipment is of high importance.

Table 2. Dedicated solutions for your NIRS sampling needs.

Probe Type	Applications	Processes	Installation
Micro interactance reflectance probe	Solids (e.g., powders, granules)	Bulk polymerization	Direct into process line
	Slurries with >15 % solids	Hot melt extrusion	Compression fitting or welded flange
Micro interactance immersion probe	Clear to scattering liquids	Solution phase	Direct into process line
	Slurries with <15% solids	Temperature- and pressure-controlled extrusion	Compression fitting or welded flange
Micro transmission probe pair	Clear to scattering liquids	Solution phase	Direct into process line or reactor
	Slurries with <15% solids	Temperature- and pressure-controlled extrusion	Into a side-stream loop
Micro interactance reflectance probe with purge on collection tip			
	Solids (e.g., powders, granules)	Drying of granules and powders	Direct into the fluid bed dryer, reactor, or process line
	Environments where sample amount varies		

CONCLUSION

In conclusion, the implementation of inline analysis with a 2060 *The NIR Analyzer* from Metrohm Process Analytics revolutionizes moisture analysis in pharmaceutical granulation. This inline spectroscopic

analysis approach ensures optimal moisture levels are kept during drying, preventing issues like particle breakage or clumping.

OTHER PROCESS NIRS APPLICATIONS RELATED TO THE PHARMACEUTICAL SECTOR

- Active Pharmaceutical Ingredient (API) content
- Blend homogeneity / Content uniformity
- Solvent purity
- Moisture in Lyophilized Products

AN-NIR-016 Near-infrared spectroscopy for monitoring a single-pot granulator
AB-358 Analysis of residual moisture in a lyophilized

pharmaceutical product by NIRS
AN-PAN-1050 Inline moisture analysis in fluid bed dryers by near-infrared spectroscopy

BENEFITS FOR NIR IN PROCESS

- Optimize product quality and increase profit by fast response time to process variations.
- Greater and faster return on investment.

- No manual sampling needed, thus less exposure of personnel to dangerous chemicals.

BENEFITS FOR NIR IN PROCESS



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CONFIGURATION



2060 The NIR Analyzer

The **2060 The NIR Analyzer** is the next generation of process spectroscopy instruments from Metrohm Process Analytics. With its unique and proven design from the inside out, it delivers accurate results every *10 seconds*. It can provide non-destructive analysis of liquids and solids directly in the process line or in a reaction vessel by using fiber optics and contact probes. It has been designed to connect up to five (5) probes and/or flow-cells. All five channels can be configured independently from each other using our versatile embedded proprietary software.

As part of the **2060 Platform**, the **2060 The NIR Analyzer** has a modular concept and it is available in three other versions: the **2060 The NIR-R Analyzer**, **2060 The NIR-Ex Analyzer**, and **2060 The NIR-REx Analyzer**.