



Application Note AN-PAN-1050

Inline moisture analysis in fluid bed dryers by near-infrared spectroscopy

In the pharmaceutical industry, the fluid bed granulator/dryer is an integral point in the manufacture of powdered materials. Residual moisture must be kept within certain specifications to avoid fracturing of particles or caking (stickiness) of the bulk material.

Current methods for moisture measurement in pharmaceuticals are slow and cumbersome, which can lead to damaged or degraded product. The ability to monitor the residual moisture content of powders

inline after drying is possible with near-infrared spectroscopy (NIRS).

This Process Application Note details the inline analysis of moisture during the drying process with NIRS. The 2060 *The NIR Analyzer* from Metrohm Process Analytics offers fast, reagent-free, nondestructive moisture analysis in powders. The analyzer can be used with a fluid bed probe specifically designed for these applications.

Powdered APIs (Active Pharmaceutical Ingredients) and excipients are important in pharmaceutical formulation. They are easy to use and allow for accurate dosing. Additionally, they help ensure consistent formulation. They are fundamental in achieving precise drug delivery and efficacy.

The fluid bed dryer is essential in the manufacturing process for removing moisture from wet granules or particles. This step is of paramount importance as it enhances the stability and shelf-life of the final pharmaceutical product.

Additionally, the moisture content during the fluid

bed drying stage significantly impacts particle size [1]. Therefore, meticulous control over moisture levels in the fluid bed dryer is imperative in pharmaceutical manufacturing.

If over-drying occurs, the granules can fracture [2], resulting in fine particles which can adversely affect the final formulation. If the product is too moist it can clump together. This causes flow blockages as well as other manufacturing problems.

The moisture content of the powder is generally determined via slow offline laboratory techniques. Often, this is done with loss on drying (10–30 minutes) after physical removal from the process with a sample thief.

Manual sampling results in delays which can cause problems whenever critical processing decisions must be made. Here, stopping the drying process at the optimal point is key.

Real-time moisture analysis in powders can be performed inline via near-infrared spectroscopy

(NIRS). NIR spectroscopy fits well within the Process Analytical Technology (PAT) initiative as recommended by the FDA [3].

NIRS can determine the residual moisture inline without manual intervention. This leads to better process understanding, optimization, and more precise determination of the end of drying. NIRS technology for moisture control is an excellent fit due to its sensitivity to the -OH functional group.

The development of a calibration model which properly correlates NIRS results to a laboratory reference method is necessary. A fluid bed «spoon» probe designed specifically for this purpose is inserted directly into the dryer (Figure 1a). After data is collected, air purges the probe tip through integrated ports to clear the «spoon» for a new sample. Each scan takes 30 seconds, ensuring there is always an accurate snapshot of the drying process at any time (Figure 1b).

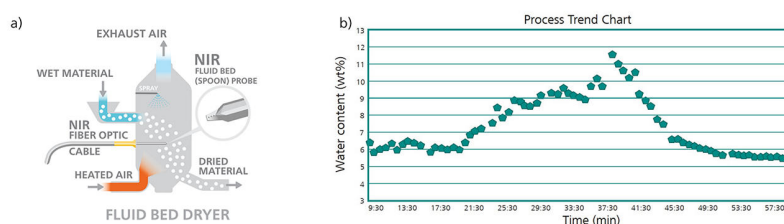


Figure 1. (a) Suggested placement for NIRS «spoon» probe in a fluid bed dryer. (b) Trend chart of water content determined via NIRS versus time.

Product release delays caused by waiting for laboratory results can be minimized or eliminated with inline NIRS analysis. Determination of the end of the drying process is made when the moisture level asymptotically approaches a lower limit. The operator is aided in making the decision to end the drying operation before the product is damaged or degraded.

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 Industry Process Analytical Technology) for closed-loop process control decisions. The reduction in reprocessing steps saves manufacturers time and money. Improvement in the product quality can lead to even higher profits.

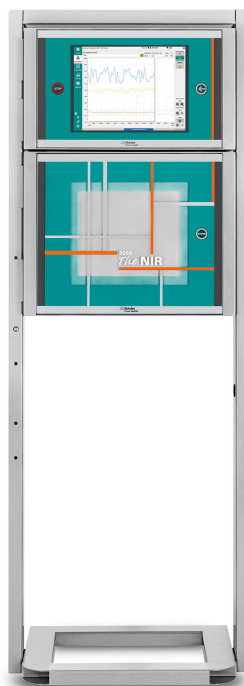


Figure 2. 2060 The NIR Analyzer from Metrohm Process Analytics.

APPLICATION

Wavelength range used: 1100–1650 nm. Inline NIRS analysis is possible directly in the fluid bed dryer using

a micro interactance reflectance probe with purge on collection tip.

Table 1. Quality control parameters to monitor in a fluid bed dryer with NIRS.

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

REMARKS

A primary 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. More NIRS probe types can be found in Table 2.

Table 2. Dedicated solutions for your 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
			Compression fitting or welded flange
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		Compression fitting or welded flange

CONCLUSION

Moisture monitoring in pharmaceuticals with nearinfrared spectroscopy (NIRS) is fast and nondestructive. This method ensures inline moisture control in fluid bed dryers, preventing particle damage or clumping.

The 2060 *The* NIR Analyzer from Metrohm Process Analytics enables real-time analysis. This gives process operators more control and reduces product release delays. Integrating NIRS data into the process control

system enhances process understanding and improves product quality, leading to increased profits. However, proper calibration and probe placement are essential for accurate results.

Embracing this technology aligns with the PAT initiative and enhances pharmaceutical manufacturing efficiency. Overall, NIRS optimizes drying processes in the pharmaceutical industry.

REFERENCES

1. Fu, H.; Teng, K.; Shen, Y.; et al. Quantitative Analysis of Moisture Content and Particle Size in a Fluidized Bed Granulation Process Using Near Infrared Spectroscopy and Acoustic Emission Combined with Data Fusion Strategies. Rochester, NY June 8, 2023. <https://doi.org/10.2139/ssrn.4473523>.
2. De Leersnyder, F.; Vanhoorne, V.; Bekaert, H.; et al. Breakage and Drying Behaviour of Granules in a Continuous Fluid Bed Dryer: Influence of Process Parameters and Wet Granule Transfer. *Eur. J. Pharm. Sci.* **2018**, *115*, 223–232. <https://doi.org/10.1016/j.ejps.2018.01.037>.
3. Aoki, H.; Hattori, Y.; Sasaki, T.; et al. Comparative Study on the Real-Time Monitoring of a Fluid Bed Drying Process of Extruded Granules Using near-Infrared Spectroscopy and Audible Acoustic Emission. *Int. J. Pharm.* **2022**, *619*, 121689. <https://doi.org/10.1016/j.ijpharm.2022.121689>.

OTHER PROCESS NIRS APPLICATIONS RELATED TO THE PHARMACEUTICAL SECTOR

- Active Pharmaceutical Ingredient (API) content

AN-NIR-016 Near-infrared spectroscopy for monitoring a single-pot granulator

AN-PAN-1048 Inline moisture analysis in a pilot scale granulation process by NIRS

- Blend homogeneity / Content uniformity
- Solvent purity

AN-PAN-1060 Inline process monitoring of moisture content in tetrahydrofuran

AB-358 Analysis of residual moisture in a lyophilized pharmaceutical product by NIRS

BENEFITS FOR NIRS 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



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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**.