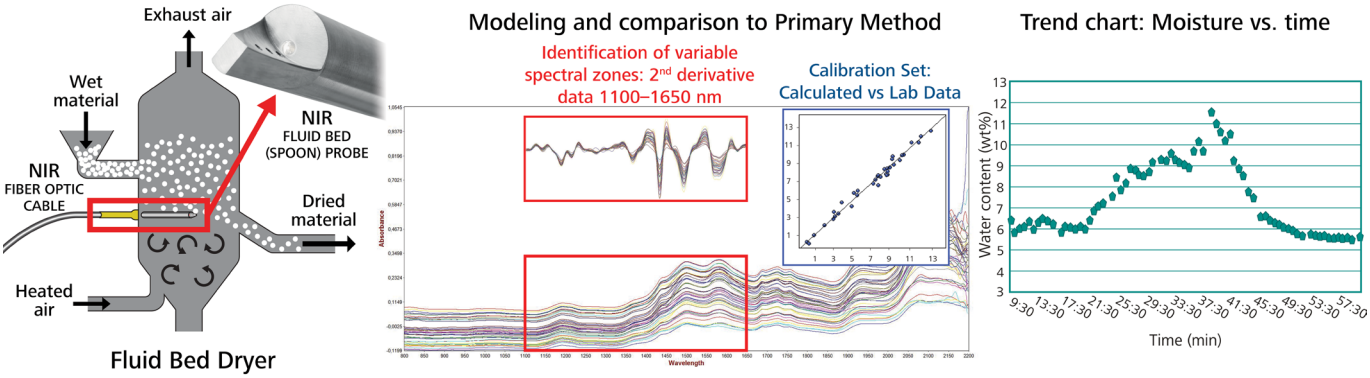
Process Application Note AN-PAN-1050

Inline process monitoring of moisture levels in a fluid bed dryer

In the pharmaceutical sector, the fluid bed granulator/dryer is an integral point in the manufacture of powdered materials (active ingredients or excipients). Particle size can be affected by several factors, among them the moisture content of the product in the fluid bed dryer. If over-drying occurs, the granules can fracture, resulting in fine particles which can adversely affect the final formulation. Product that is left too moist at the end of the process can clump together and cause blockages in the flow, as well as causing other manufacturing problems.

Moisture content of the powder is determined via slow offline laboratory techniques such as loss of weight (10–30 minutes), after physical removal from the process with a sample thief. This manual sampling results in a delay, which can cause problems whenever critical processing decisions must be made, such as endpoint determination. Monitoring the moisture content directly leads to a more informed operator.

Real-time analysis of the moisture content in powders can be performed inline via near-infrared spectroscopy (NIRS) technology, which fits well within the Process Analytical Technology (PAT) initiative as recommended by the FDA. The drying process can be monitored constantly without manual intervention, allowing for better process understanding, control and endpoint determination. Development of a calibration model which properly correlates NIRS results to a laboratory reference method is necessary first. A fluid bed "spoon" probe designed specifically for this purpose is inserted directly into the dryer, as seen in the diagram below. After each NIR spectrum is collected, an air purge exiting through the ports located in the probe tip clears 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.



Suggested placement for NIR "spoon" probe in a fluid bed dryer. Raw and 2nd derivative spectra of the dryer samples shows strong water absorption around 1400 nm. The 2nd derivative intensity (1100–1650 nm) was used to create a prediction model.

Product release delays caused by waiting for laboratory results can be minimized or eliminated as endpoint determination 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. Output from the process analyzer could 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 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

Keywords: powder, water content, pharma, PAT, NIR, spectroscopy, continuous processing, 21 CFR, NIRS XDS

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recommended in **all of the key pharmacopoeias**, from the European (2.2.40) to the American (USP 1119) and fits perfectly in the context of continuous processing and the PAT initiative of the FDA. Metrohm Process Analytics offers instruments that meet the standards for wavelength precision, reproducibility, traceability, and photometric noise. Numerous reference standards and user-friendly software make it easy to check the instrument requirements specified in the pharmacopoeias. The pharmaceutical version of the Vision software is fully validated and compliant with 21 CFR Part 11. 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 and custom output graphics for real-time visual monitoring as well as electronic process control.

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. Related application: **AN-PAN-1048**

Typical Range: 0–60% H_2O

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

Other Process NIRS applications related to the Pharmaceutical sector:

- Active Pharmaceutical Ingredient (API) content
- Blend homogeneity / Content uniformity
- Solvent purity

NIRS XDS Process Analyzer

Related Application Notes and Bulletins:

- **Pharmaceutical manufacturing process**
- **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
- **TA-048** Near-infrared spectroscopy for pharmaceutical analysis

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

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