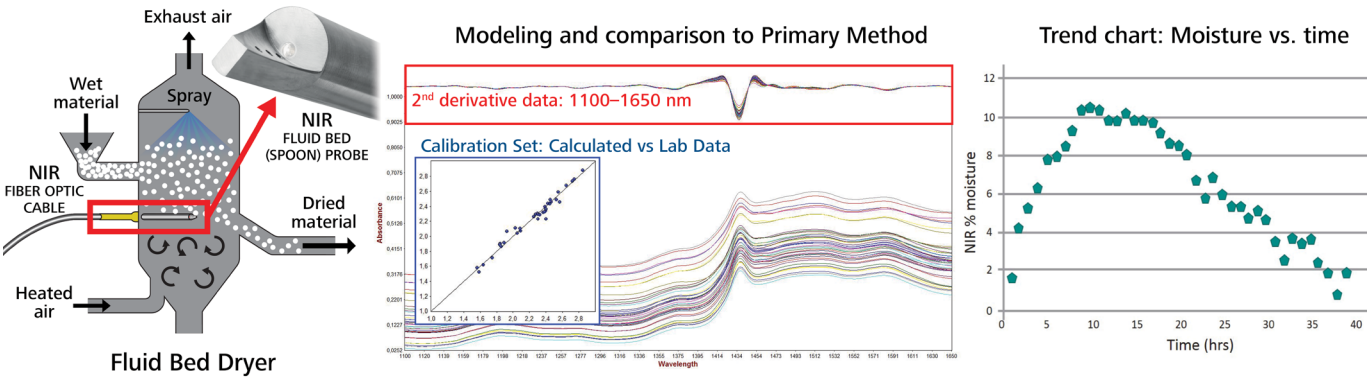
Process Application Note AN-PAN-1048

Inline moisture analysis in a pilot scale granulation process by NIRS

Top spray granulation is a common method of granulation in the pharmaceutical industry. Powder is fluidized in a fluid bed dryer and a liquid binder solution is sprayed on to the product. After spraying the liquid into the 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 the fracture of granules (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 cake. 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Samples are typically withdrawn from the fluid bed with a thief during processing and analyzed offline for moisture content in a laboratory. This delay before analysis results are available to the operator can cause critical processing decisions, like endpoint determination, to be made without optimal product moisture information. Top spray granulation endpoint is often based on time or product temperature—not moisture content.

Using near-infrared spectroscopy (NIRS) technology, the drying process in a fluid bed dryer can be monitored inline for residual moisture level for better process understanding, control and endpoint determination. The figure below shows a calibration model for water determination that correlates NIRS to a reference method performed in the laboratory. A fluid bed probe specifically designed for these applications is used, seen in the diagram inset, with "spoon" and purge vents located on the probe tip. After each NIR spectrum is collected, an air purge exiting through the ports in the probe clears the "spoon" for a new sample.



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

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. 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 process analyzer could be used by the fluid bed dryer's programmable logic controller (PLC) or integrated into SIPAT for closed loop process control decisions. The reduction in reprocessing steps saves both time and money. 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: pharma, granulator, water content, PAT, NIR, spectroscopy, continuous processing, 21 CFR, NIRS PRO

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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 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. 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.

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
- Solvent purity

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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