

Rapid in-process moisture determination on a fluid bed dryer

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Figure 1. Antaris MX FT-NIR analyzer.

Abstract

The ability to quantify moisture in real-time is critical for optimizing the operation of production dryers. This is especially true for fluid bed dryers in the pharmaceutical industry since ruining one batch of product can be very costly. The goal in any drying process is to reach optimum product moisture using the least amount of energy in the quickest amount of time without sacrificing product quality. If product is over-dried it might not be suitable for sale, energy would have been wasted in the drying process, and the throughput of the dryer would not have been optimized. If product is under-dried it creates operational inefficiency since the dryer will need to be stopped and restarted several times in order to sample for moisture verification. Also, high-moisture product could cause product stability issues during storage and could stick to the faces of tablet presses. This study demonstrates that moisture can be accurately measured in-line using the Thermo Scientific™ Antaris™ MX FT-NIR process analyzer (Figure 1) equipped with a fiber optic purge probe inserted into a fluid bed dryer.

Introduction

Drying in the solid oral drug industry is a central step in the manufacturing of tablets and granulates which make up 80% of the drugs in the marketplace. Drying is the science of evaporating water or an organic solvent using heat. Different temperatures and times are required depending upon the product's quality and the desired residual moisture. As the evaporation of the solvent cools the product, relatively high temperatures can be used for drying without overheating the product. At the same time, it is important to mix the product well during drying.

Fluid bed dryers are effective for solid drying in the pharmaceutical industry. The heat transfer is excellent and the drying time is ideal for gentle drying of the product. The whole surface of each individual particle is available for drying due to the fluidization of product in the dryer. A homogeneous product temperature and a uniform drying of the starting product are achieved as a result of the continuous and thorough mixing in the dryer. This cannot always be guaranteed in the case of contact and radiation dryers.

Types of fluid bed dryers

Batch fluid bed dryers are used whenever reproducible product quality and comprehensive process documentation are required. They provide a high level of economy with gentle product handling. The drying process starts with moist product being fed into the dryer. The product is mixed vigorously by the heated-air stream coming from the bottom of the dryer. The product is suspended as it is mixed and dried by the heated air stream. The optimum amount of heated air blown into the dryer depends on the particle size and density of the product.

The temperature of the air can be adjusted during the drying process. Once the product is dry, it can be cooled before the dryer is emptied. This process dries the product to the desired moisture content efficiently.

Continuous fluid bed dryers are used whenever high throughput is required. They offer unrivaled economy for reproducible product quality with gentle product handling. The steps that are carried out for each batch in the above process are carried out in different places in the continuous process. Moist starting product is fed in continuously and moves through the drying system. Effective drying is accomplished using different temperatures of the incoming air for the different chambers. If the last chamber is operated with cold air, the dry product can be cooled before leaving the drying system.

The batch fluid bed drying systems are the most popular in pharmaceutical manufacturing. There are basically three different types of dryers based on what direction the heated air is blown into the dryer: top spray, bottom spray, and tangential spray. NIR is an accepted analysis technique in the pharmaceutical industry (European Pharmacopeia (Ph.Eur.) 2.2.40 1997, ASTM NIR Method E 1944, USP Chapter <1119> and the Japanese Pharmacopeia). NIR is non-destructive and provides real-time data; it is finding widespread use for in-process analysis of moisture in multiple industries.

FT-NIR is an excellent tool for implementing Process Analytical Technology (PAT) in the pharmaceutical drying process. PAT means incorporating science into manufacturing by conducting analysis in real-time to control the process. Currently, pharmaceutical companies rely on recipe-based manufacturing (heat for 2 hours, mix for 25 minutes, etc.). This does not lead to any kind of process understanding so entire batches can simply be thrown out without understanding the root cause of failure. Processes are still tethered to one-off QC lab testing that determines the fate of an entire batch. PAT aims to work process understanding into the pharmaceutical manufacturing process which mitigates risk and improves the bottom line.

FT-NIR spectroscopy can play a large role in PAT since it can meet the requirements across the product development lifecycle from R&D to manufacturing. Antaris FT-NIR analyzers use a common platform so that transfer of methods between instruments from lab to process can be done without a decrease in method performance. In addition to in-line dryer analysis, FT-NIR has been used for other process analyses including raw material ID, blend uniformity, tablet content uniformity, and API quantification.

FT-NIR has many advantages over traditional Karl Fischer and Loss on Drying methods for moisture analysis (Table 1) including increasing dryer operational efficiency and lowering operating cost without sacrificing accuracy or precision.

FT-NIR	Karl Fischer/Loss on drying
Non-destructive	Destructive
Uninterrupted sampling	Interrupted sampling
No operator training needed for analysis	Chemistry and method training for operator
No sample preparation or solvents	Sample preparation and solvents
Results in seconds	Results in 15 minutes or more
Allows for closed loop control	No ability for closed loop control
Multi-component analysis on dryer samples	Additional tests on samples would take a long time
NIR can be used online, inline or at line	Can only be run in the laboratory – can't go online

Table 1. Advantages of FT-NIR over laboratory moisture analysis.

Experiment

The challenge in any moisture determination whether in-line or in the lab is getting a representative sample to the instrument. Fluid bed dryers use the action of hot gas and fluidization to dry product as it swirls around inside the dryer. This swirling action results in a variable distance and density of the product in front of a measurement probe. This negative can be overcome by chemometric processing and the averaging of large amounts of spectral data.

Another issue is whether the product will form a crust or leave a residue at the probe-sampling interface. Instruments that analyze using sight glasses on the side of a dryer cannot overcome this obstacle since there is no way to clean the glass while the dryer is running. Also, the material that is adhered to the sight glass is not representative of the product that is in the dryer. This issue can be overcome with a purgeable tip or retractable probe with a self contained cleaning system. The purgeable tip probe (Figure 2) removes powder or sample crust using pressurized N₂ blown through the holes on the end of the probe. The retractable probe (Figure 3) can be cleaned automatically by solvents in a separate self-contained chamber. The purgeable tip probe works best for product under 15% moisture since it can be easily blown off the end of the tip. For product that cannot be removed from the purgeable tip probe (higher moisture product), the

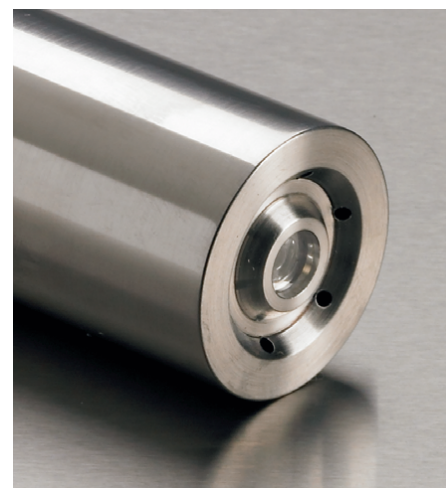


Figure 2. Purgeable-tip probe.

retractable probe is the best choice. The retractable probe can be mechanically cleaned in between each measurement and then solvent cleaned and dried in between each dryer run. The movement, purging and data collection of these two probes can be controlled automatically using Thermo Scientific RESULT™ software with the process controller.

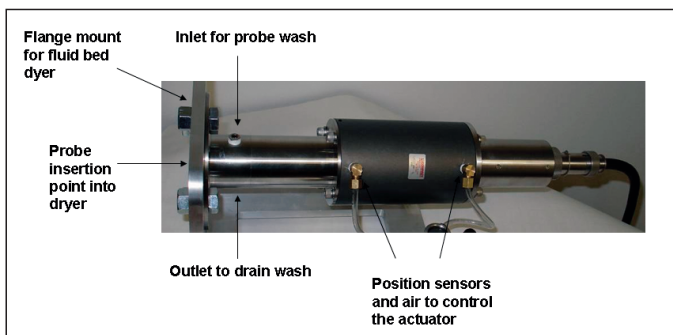


Figure 3. Retractable probe with internal cleaning chamber.

For this study, a diffuse reflectance fiber optic probe with purgeable tip was installed into a fluid bed dryer (Figure 4). The dryer ran in a cycle of 120 seconds of purge drying followed by 10 seconds of filter shaking. Spectra were collected during the 10 seconds of filter shaking because of



Figure 4. Fluid bed dryer.

better reproducibility of results than collecting spectra during the purge step. This allowed a new data point to be produced every 2 minutes. An Antaris MX FT-NIR analyzer was used for the spectral collection. The instrument acquired 12 scans per sample at 8 cm⁻¹ resolution from 4800-10000 cm⁻¹. The primary method analysis was done by Karl Fischer with each sample being run in duplicate which took about 10 minutes. A large set of dryer batches were sampled with the samples ranging from 1-23% moisture.

The method developed for moisture determination used the Partial Least Squares (PLS) algorithm with 5 factors. The spectra were pre-processed before method development using 1st derivative, Multiplicative Scatter Correction (MSC) and a Savitzky-Golay filter with a data point of 7 and polynomial order of 3 for smoothing. The MSC processing helped to account for differences in effective pathlength caused by the varying distance of the sample from the

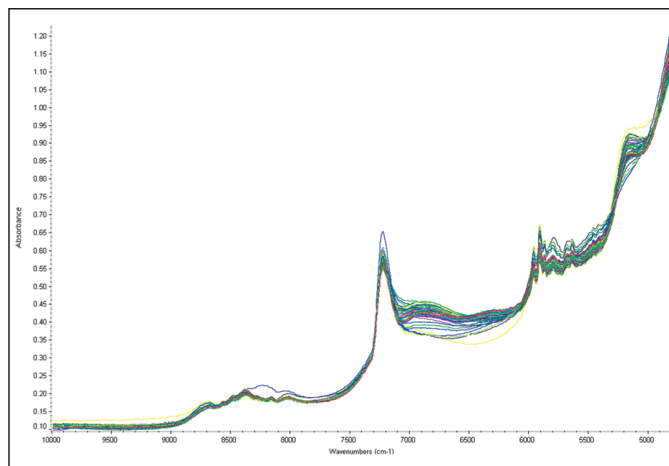


Figure 5. Unprocessed spectra of calibration standards.

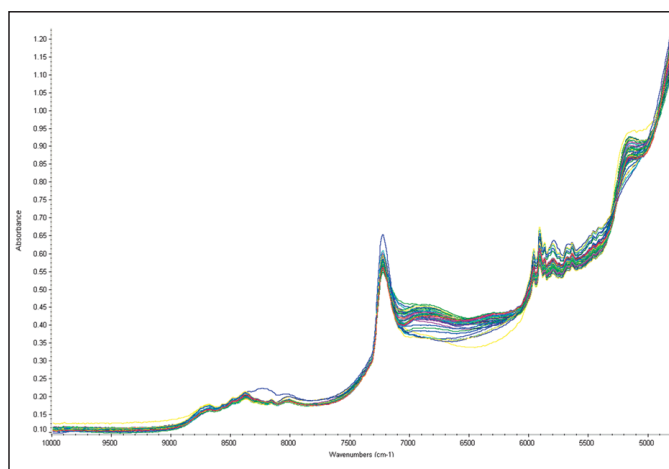


Figure 6. 1st overtone for water.

probe and also the effects of light scattering due to the different particle size of the samples. The 1st derivative helped peak resolution and also removed unwanted baseline features. The spectral region used in the method was 4850-9980 cm⁻¹. This region incorporates the combination band for water at 5150 cm⁻¹ and the 1st overtone for water at 7000 cm⁻¹. As seen in Figures 5 and 6 the region around 7000 cm⁻¹ shows significant variation in absorbance due to the large range in moisture (1-23%).

Results

Quantifying water in most compounds is very easy and straightforward by NIR. This is due to the fact that water is the most sensitive compound that can be measured by NIR. Most compounds can be detected reliably down to 0.05-0.1% while water sensitivity is roughly an order of magnitude better.

The method for moisture determination produced a RMSEC (root mean square error of calibration) of 0.56 with a correlation coefficient of 0.995 as shown in Figure 7. The RMSECV (root mean square error of cross validation) for the method was 1.05 with a correlation coefficient of 0.981.

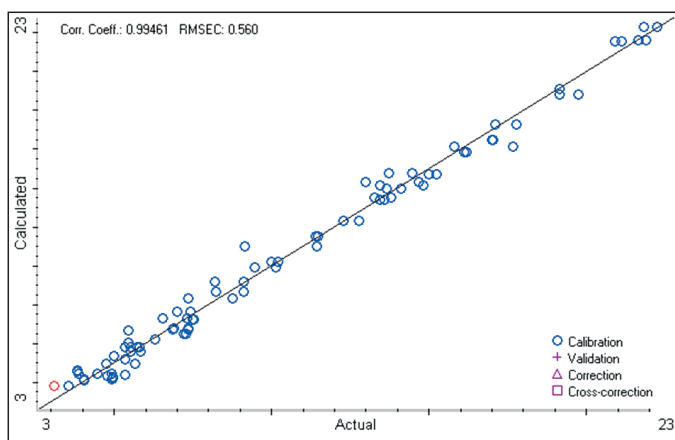


Figure 7. Calibration plot for moisture.

Conclusions

The Antaris MX FT-NIR analyzer equipped with a purgeable tip fiber optic reflection probe can accurately measure moisture in a fluid bed dryer. The fit of the calibration method ($R=0.995$) has proven to be excellent across a wide range in moisture (1-23%). The speed at which real time moisture analysis data is available using the Antaris MX makes determining the dryer endpoint much easier than thief sampling for primary wet chemistry analysis. The dryer endpoint can be determined based on when the moisture concentration hits a control value. The need for lab equipment, solvents, and personnel to constantly analyze dryer samples is eliminated. The accuracy, precision, linearity, and speed of analysis by FT-NIR allows for a definitive determination of dryer endpoint. Knowing exactly when a dryer has reached its endpoint will save companies energy, eliminate the destruction of product due to over-drying, and increase the overall efficiency of the drying process.

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