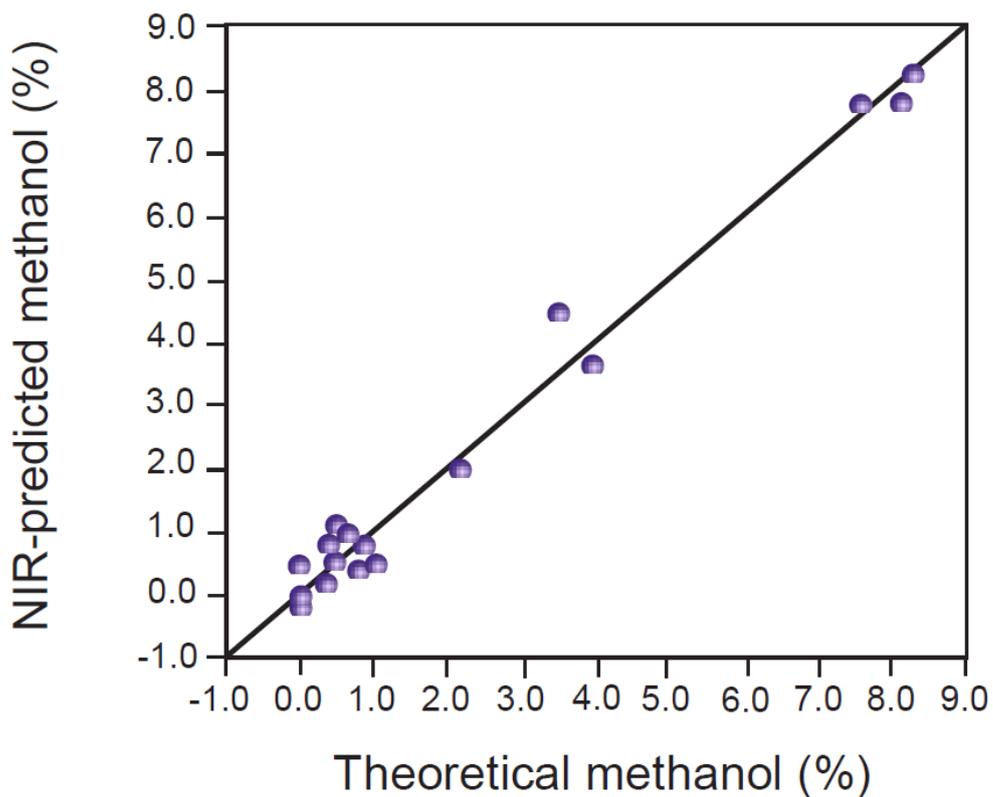# Monitoring a single-pot granulator using near-infrared spectroscopy

This Application Note shows the capability of a novel probe design equipped with a NIRS XDS Process Analyzer for predicting the residual amounts of solvent during the drying phase in a high-shear granulator. This system configuration can reduce the powder sample density variance such that moisture and solvent levels can be accurately modeled and predicted in process.

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Method description

Introduction

Near-infrared spectroscopy (NIRS) is an analytical technique based on absorption measured in the near-infrared region of the electromagnetic spectrum that is between the visible and the mid-infrared. The fundamental absorption bands of functional groups occur in the mid-infrared and are very strong. The overtone absorptions of these fundamental bands occur in the near infrared (NIR) spectral region and allow direct measurement without sample preparation due to the relative weakness of absorption. The OH, CH, NH and SH bonds have the strongest overtone absorbance in the NIR region.

For years many processes have been monitored real-time using NIR spectroscopy and fiber-optic probes. The challenge in high-shear granulator monitoring is the turbulent flow of the powder granules. If a probe is inserted normal to the nominally circular flow direction of the powder, the effect of the turbulence caused by the high-shear chopper and the purge gases constantly and randomly changes the apparent sample density in front of the NIR probe window. This makes analysis impossible due to constant wide range random change in spectral absorbance. When the sample density change is brought within an acceptable, narrow range, NIR analysis can be performed using multivariate methods that account for density variance as well as residual granulating liquid variance. This Application Note discusses the use of a novel probe design that reduces the powder sample density variance to a level at which the granulating solvent level can be accurately modeled and predicted

One of the elements of the PAT initiative is to use in-line analysis to increase process understanding and control and to verify product quality and release it for subsequent processing without delay. Using NIRS, the process can be monitored for low levels of residual alcohol for better process control and end-point determination. NIR spectroscopy is a rapid, nondestructive technique often used for in-process analysis of moisture and alcohols in the manufacturing environment. Measurements can be made and analyzed real-time with no sample preparation and the data can be analyzed and stored automatically. NIRS fits in well with Process Analytical Technology (PAT) initiatives as proposed by the FDA. The process can be monitored for low levels of residual alcohols and other process constituents to yield better process control and quality management.

Methods

The NIR instrument used to collect spectra was the NIRs XDS Process Analyzer. See Figure 1. Spectra were collected in the reflectance mode from 800 to 2100 nm with 0.5 nm data intervals and 32 scans were co-added to produce a single spectrum. Monitoring the removal of granulation liquids such as methanol is important for product purity. Methanol level is typically measured by taking a sample with the sample thief and sending it to the laboratory for GC analysis. GC requires lengthy analysis times and calibration samples must be run often.

Fig. 1. Metrohm NIRS XDS Process Analyzer

Fig. 2. Bohle single-pot high shear granulator used in study

Method description

Fig. 3. The standard Bohle temperature probe was replaced with the angled NIR probe for this study

Experimental

A Metrohm XDS Process Analyzer was set up and connected to a fiber optic probe with a specially designed tip installed into a Bohle VMA 70 single-pot high-shear granulator. See Figure 2 and 3 for photos of the Bohle granulator. The probe in Figure 4 has an angled face that forces the powder sample to divert in a quasi-laminar flow over the measurement window. This maintains a more constant sample density at the window interface.

A 24.0 Kg charge of 91% lactose anhydrous and 9% starch 1500 was prepared and loaded into the granulator. The granulator was run to blend the dry mixture to homogeneity for 10.0 minutes. Moisture, methanol and yellow dye FD&C #6 were sprayed into the mix and blended. The yellow dye FD&C #6 was in the parts per billion range and was not a source of interference with NIR measurements. NIR spectra were collected continuously during the blending and granulation operations and samples for LOD analysis were withdrawn at intervals.

Fig. 4. A novel probe employing an angled sample interface

After all moisture and methanol had been added and blended an agglomeration cycle was run for a period of 6.0 minutes. The heated jacket was energized and a vacuum was pulled to around 200 mBars to start the drying operation. The drying operation was uniform and gradual over a period of about 43 minutes with an agitator speed of 200 RPM and a nitrogen purge at a rate of 1.0 NM3/hr. NIR spectra were collected continuously; approximately two complete scans of 32 co-added scans per minute, during the whole blending, granulating and drying operation resulting in about 150 spectra for a batch. Three test batches and three calibration batches were run. The three calibration batches will be discussed in this Application Note. All spectral data collection and analysis were performed using the Vision® software.
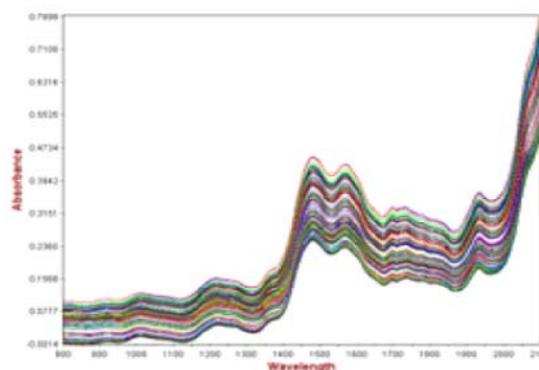
Results and discussion
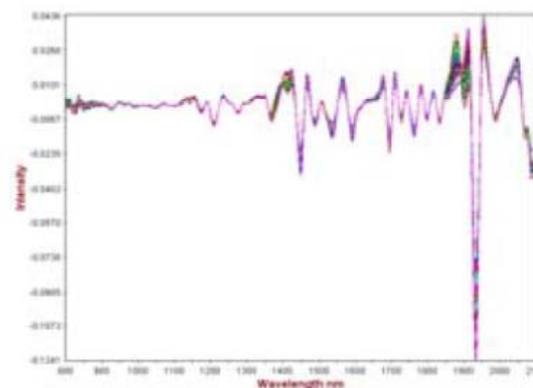

Fig. 5. Raw spectra of drying samples

Fig. 6. 2nd derivative of dryer spectra scanned in-process

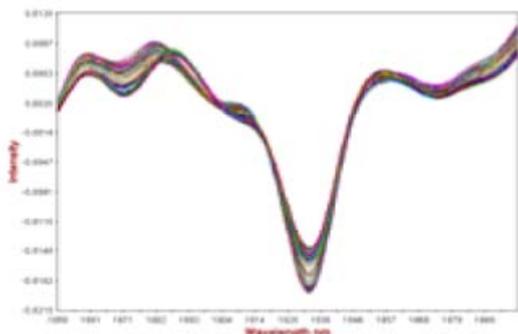**Ω Metrohm**
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Method description

Fig. 7. 2nd derivative spectra in the analytical region

Figure 5 shows the raw spectra from the granulation drying run. Figure 6 shows the second derivative spectra of the analytical region of blend # 5 as an example of the spectra used for prediction of methanol in the lactose anhydrous and starch 1500 blend. Figure 7 shows the enlarged analytical region. The moisture values were subtracted from the LOD values and a model was made from the resulting 17 adjusted values. One spectrum was an outlier according to the qualification library and was not used in the model. As seen in Figure 8, a partial least squares (PLS) regression model was developed using the second derivative intensity over the range 1800 to 2100 nm that resulted in an R^2= 0.9823, SEC = 0.4427. The standard error of cross validation was 0.6224. These samples are not well spaced due to the faster removal of methanol initially. The water was removed in a quasi-linear function of time but the methanol was nonlinear leaving less data in the mid-level. To develop a robust model more data would have to be taken initially. Using GC as reference method would assure more accurate results.
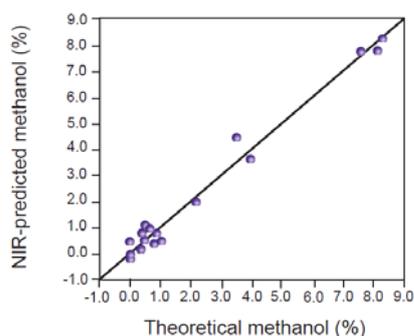

Fig. 8. Calibration set for the PLS model, R^2 value of 0.9823 and SEC of 0.4427% MeOH
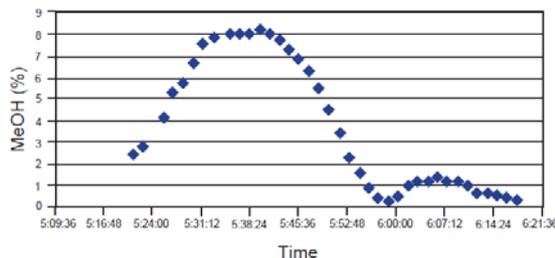

Fig. 9. A process trend chart showing the process from blending to spraying the binder/moisture solution and drying. This is a Vision$^®$ routine analysis output trend chart

Figure 9 is the process trend chart from routine analysis for the granulation and drying operation. These spectra were analyzed in routine analysis, averaging five spectra for each prediction and tested against a qualification library. Some initial samples were not predicted when the average spectrum did not meet library qualification due to high RPM of the granulator and turbulence during the blending cycle. The methanol level appears to reach a minimum and then increase slightly before reaching the final minimum. This is most likely due to "case hardening" of the granules when the "free" methanol is removed and then the granules fracture and release additional interstitial methanol. This phenomenon is due to over aggressive drying. Although the true values are theoretical, the predictions are smooth and reasonable even through the part of the granulation cycle that was not modeled.

Conclusions

The in situ NIR spectroscopic method demonstrated the ability to predict samples of lactose anhydrous and starch 1500 with residual amounts of methanol during the blending, granulation and drying operations. Although accuracy is not known, the trended predictions appear smooth and reasonable from known initial and end point data. The single-pot granulator trial indicates the ability of the NIR process instrument with the novel angled probe to measure a moving sample, in turbulent flow, when it is placed in the sample medium in a manner that provides sufficiently constant sample density. Proper probe placement and design in process equipment is essential for success of the implementation of in situ measurements.

References

R. A. Mattes, Rudolf Schroeder, Vinny Dhopeshwarkar, Robert Kowal, William Randolph, Monitoring a Granulation Drying Process Using Near-Infrared Spectroscopy for *In Situ* Analysis Of Residual Moisture and Methanol, Pharm. Tech. Sept. 2004.

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