

## In-line Process Analysis of Residual Moisture in a Fluid Bed Granulator–Dryer Using NIR Spectroscopy

The authors describe the in-line moisture measurement of a pharmaceutical granulation of lactose, microcrystalline cellulose and crospovidone in a fluid bed granulator–dryer using top sprayed granulating liquid. A near-infrared (NIR) prediction model was developed for moisture on spectra collected during a calibration run. Subsequent granulations were analyzed for moisture content real-time throughout the granulation and drying process using the NIR process instrument.

Robert A. Mattes, Denise E. Root, and Andrew P. Birkmire

**G**ranulation is an important step in pharmaceutical solid dosage form processing. The flow and compression characteristics of a formulation are improved through granulation. Also, the content uniformity of the formulation is maintained after blending by the agglomeration of smaller particles to form larger particles through granulation (1).

A common method of pharmaceutical granulation is top spray granulation, where the powder is fluidized in a fluid bed dryer and liquid binder solution is sprayed onto the product layer from the top counter-currently to the fluidizing gas. 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 the action of the fluid bed can cause the fracture of granules creating undesirable fines and can damage the formulation due to hydration changes in some actives and excipients (2). If the granules are not dry enough the product will not flow properly and can cake and cause problems with subsequent processing, including product sticking to the faces of the tablet press punches and problems with product stability during storage. Samples typically are withdrawn from the fluid bed with a thief during processing and analyzed off-line in a laboratory for moisture content. Commonly there is a delay before analysis results are available to the operator that causes processing decisions, like end-point determination, to be made without optimal product moisture information. Top spray granulation end point is often based on time or product temperature and not moisture content.

Near-infrared (NIR) spectroscopy is a rapid non-destructive technique often used for in-process analysis of moisture in the manufacturing environment (3). Real-time measurements can be

made with no sample prep and the data can be analyzed and stored automatically. NIR fits in well with the Process Analytical Technology (PAT) initiative as developed by FDA (4–7). One of the elements of the PAT initiative is to use in-line analysis to increase process understanding and control to verify product quality and release it for subsequent processing without delay (8). Using NIR the process can be monitored for low levels of residual moisture and alcohols and other process constituents to yield better process control and end-point determination (9).

### Experimental

All NIR spectra contained in this study were collected using a FOSS NIRSystems XDS Process Analyzer and Vision software. Each spectrum consists of 16 co-added scans of sample and reference in the NIR range of 800–2100 nm. The process instrument is a rugged design that can be equipped for explosion-proof environments. It has a fiber optic probe that can be inserted into a process vessel at a location remote from the instrument.

The process instrument was set up and allowed to equilibrate to temperature. A probe of novel design, specifically for the fluid bed application, was inserted into a Niro MP 2/3 Precision Granulator at a 45° angle to the central axis of the product container as seen in Figures 1 and 2. Note the collection “spoon” and purge vents located on the probe tip. After each NIR spectrum was collected, the software sent a “data complete” signal that energized an air purge exiting through the ports in the probe and cleared the “spoon” for a new sample.

A charge of lactose (Pharmatose 200M, DMV), microcrystalline cellulose and (Avicel PH 101, FMC), and crospovidone



Figure 1. The 1-in. NIR probe is inserted in the port at a 45° angle in the product container of the fluid bed dryer.

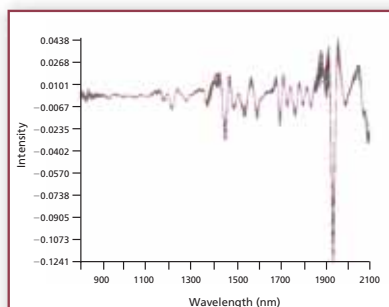


Figure 4. Second derivative of spectra taken in-process in the fluid bed dryer.

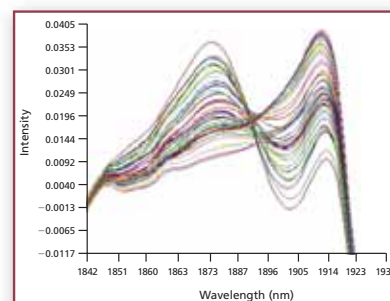


Figure 5. An analytical wavelength region used for moisture analysis.



Figure 2. The novel design fluid bed NIR probe inserted into the product container of the fluid bed dryer. Note the collection "spoon" and purge vents.

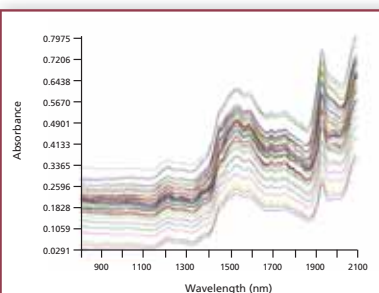


Figure 3. Raw spectra taken in-process in the fluid bed dryer.

(Polypladone XL 10, ISP) was prepared by Niro and loaded into the product container. The product was fluidized for 5 min to blend and dry the mixture to homogeneity. An aqueous solution of 15% polyvinyl pyrrolidone (Plasdone K29/32) was added by top spray at 1.5-bar atomization pressure. The fluidizing airflow and liquid spray rate were increased twice during the batch as the granules formed. NIR spectra were collected every 40 s during the blending operation and samples for loss on drying (LOD) analysis were withdrawn at approximately 5-min intervals. A 2.0-g sample was analyzed for LOD at 160 °C for 15 min using the Mettler Toledo (Columbus, OH) HR73 halogen moisture

analyzer. When the water–binder solution pump was stopped the drying process began. The drying operation was uniform and gradual over a period of 15 min.

### Results and Discussion

Figure 3 shows the raw spectra of the dryer samples. Water absorbs strongly in the NIR around 1400 nm and 1900 nm as evidenced by the peaks in those regions. Figure 4 shows the second derivative of the same spectra. The second derivative math treatment is used commonly in NIR spectroscopy to minimize baseline offset caused by scattering and enhance absorbance peaks (10). The second derivative spectral peaks appear inverted with

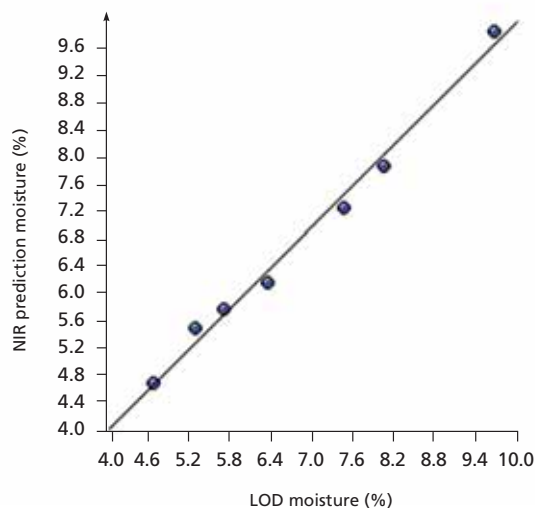


Figure 6. A PLS model was developed with an  $R^2$  value of 0.9896 and a SEC of 0.2171.

## In-Line Moisture Analysis

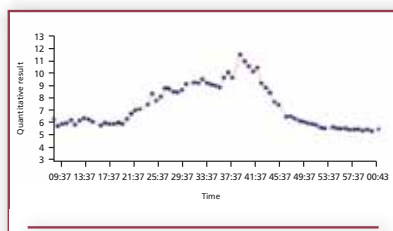


Figure 7. Process trend chart from routine analysis for granulation/drying operation. This typical software routine analysis output shows the predicted moisture trend during granulation and drying.

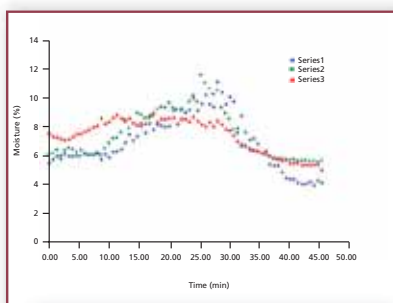


Figure 8. Three NIR moisture prediction runs monitoring the fluid bed granulator/dryer.

respect to the raw spectra (11). Figure 5 shows an enlargement of a spectral region that was used to model the moisture in the samples. A two-factor partial least squares (PLS) regression model was developed with spectra from a calibration run and loss-on-drying (LOD) reference values (see Table I). The second derivative intensity over the range 900–2100 nm was used to develop a prediction model with an  $R^2$  value of 0.9896 and a standard error of calibration (SEC)

of 0.2171. See Figure 6 for a plot of NIR predicted versus LOD % moisture. Although the prediction model performed well, it would be more robust with more calibration samples included.

Figure 7 shows a typical routine analysis output trend chart. 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.

Figure 8 shows moisture predictions for three top spray granulations using 1.5-bar atomization pressure plotted on the same graph. Table II shows compar-

ative data of NIR versus LOD for the same three granulations. The LOD values demonstrated from 0.03 % to 0.58 % moisture repeatability error with higher error at the higher moisture levels. There also are errors due to LOD sampling and the representative capability of the thief system.

Figure 9 shows the NIR predicted moisture versus LOD value. The standard error of prediction is 0.4232%. The LOD standard error was estimated to be 0.33% moisture and there was a delay of more than a week between sample collection and analysis that accounts for deviations. The model accuracy would be improved with Karl Fischer reference data analyzed in a more timely manner.

The endpoint determination can be made when the moisture level asymptotically approaches a lower limit during the drying cycle. As seen in Figure 8, the change in moisture reaches a minimum when the product is dry. The operator is aided in making the decision to end the drying operation before the product is damaged or degraded. The delay caused by

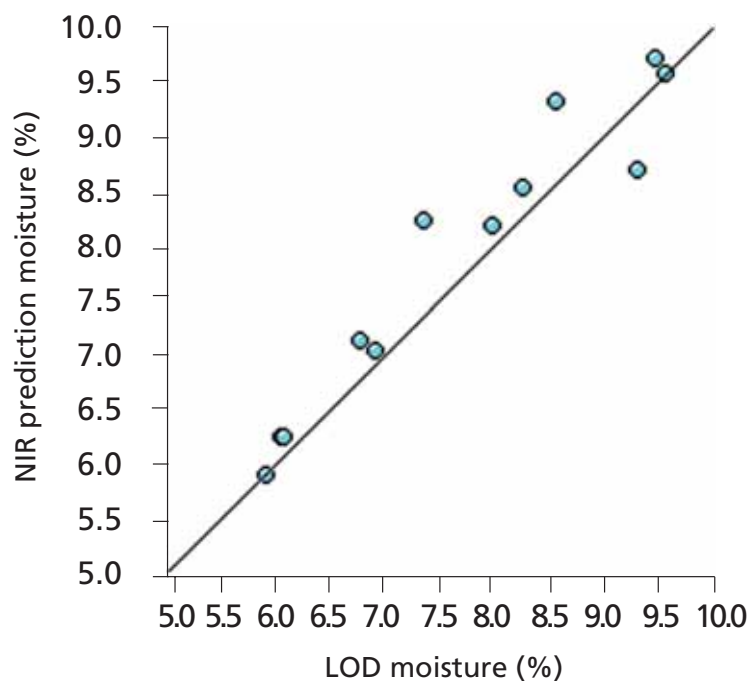


Figure 9. NIR predicted versus LOD values of validation set. The standard error of prediction is 0.4232.

Table I. Calibration sample set data.

Sample #	NIR Prediction %	LOD %	Residual %
0019	5.80	5.7	0.10
0039	7.26	7.46	-0.20
0059	9.83	9.64	0.19
0081	7.88	8.04	-0.16
0089	6.19	6.36	-0.17
0095	5.51	5.3	0.21
0103	4.72	4.69	0.03

Table II. NIR versus LOD values for three top spray granulations.

Batch	Elapsed Time (min.)	NIR	LOD	Residual
9/14#3	12.00	7.04	6.92	0.12
9/14#3	18.66	8.18	7.98	0.20
9/14#3	27.33	9.56	9.55	0.01
9/14#3	34.66	6.27	6.06	0.21
9/14#4	14.66	7.13	6.77	0.36
9/14#4	22.66	9.33	8.56	0.77
9/14#4	28.66	9.71	9.46	0.25
9/14#4	37.99	6.27	6.07	0.20
9/16#2	9.33	8.22	7.34	0.88
9/16#2	18.66	8.53	8.25	0.28
9/16#2	22.66	8.69	9.3	-0.61
9/16#2	36.66	5.92	5.92	0.00

waiting for lab results before the product can be released for subsequent processing can be minimized or eliminated. Output from the NIR computer could be used by the fluid bed dryer's programmable logic controller (PLC) for closed loop process control decisions.

the ability of the novel fluid bed probe to measure a fluidized sample for residual moisture. Although the prediction model performed well, it would be more robust with more calibration samples included. The model accuracy would be improved with Karl Fischer reference data analyzed in

## References

1. A.G. Rogers, "Granulation and Drying Principles", "Hands-on" Postgraduate Course in Tablet Technology, Univ. Tenn., Memphis (2003).
2. S.M. Maggard, D. E. Root, and M. Duell, *J. Process Analytical Chemistry* 7(1) (2002).
3. K.A. Bakeev, *Spectroscopy* 19(1) (2004).
4. M.L. Balboni, *Pharm. Tech.* 27(10) (2003).
5. US FDA Draft Guidance "PAT – A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance," August 2003, <http://www.fda.gov/cder/OPS/PAT.htm>.
6. H. Forcinio, *Spectroscopy* 18(9) 16–24 (2003).
7. R.C. Lyon, E.H. Jefferson, C.D. Ellison, L.F. Buhse, J.A. Spencer, M.M. Nasr, and A.S. Hussain, *Am. Pharm. Rev.* 6(3) (2003).
8. A.M. Afnan, *J. Process Analytical Technology* 1(1) (2004).
9. R.A. Mattes, R. Schroeder, V. Dhopeswarkar, R. Kowal, and W. Randolph, "Monitoring Granulation Drying Using Near-Infrared Spectroscopy for In Situ Analysis of Residual Moisture and Methanol", *Pharmaceutical Technology, Process Analytical Technology Supplement*, September 2004.
10. T.C. O'Haver and T. Begley, *Anal. Chem.* 53, 1876–1878 (1981).
11. H. Mark and J. Workman Jr., *Spectroscopy* 18(4) (2003). ■

**Robert A. Mattes** is an instrumentation scientist and **Denise E. Root** is marketing and process instrument manager at FOSS NIRSystems, Inc. (Laurel, MD).

**Andrew P. Birkmire** is a process engineer at Niro Pharma Systems, Inc. (Columbia, MD). Address correspondence to: [rmattes@foss-nirsystems.com](mailto:rmattes@foss-nirsystems.com).

## ONE OF THE ELEMENTS OF THE PAT INITIATIVE IS TO USE IN-LINE ANALYSIS TO INCREASE PROCESS UNDERSTANDING AND CONTROL TO VERIFY PRODUCT QUALITY AND RELEASE IT FOR SUBSEQUENT PROCESSING WITHOUT DELAY.

### Conclusion

The NIR process instrument demonstrated the ability to predict the moisture content of a pharmaceutical granulation of lactose, microcrystalline cellulose and crospovidone being dried after wet granulation in a fluid bed dryer. Endpoint determination can be made when the moisture level asymptotically approaches a lower limit during the drying cycle. This trial also demonstrated

a timely manner. The correct NIR probe must be placed in the product container 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 for success of NIR implementations. Future work will evaluate the ability to monitor other residual granulating liquids and constituent levels using the same instrument/probe configuration.

© Reprinted from SPECTROSCOPY, January 2005 AN ADVANSTAR PUBLICATION Printed in U.S.A.

Copyright Notice Copyright by Advanstar Communications Inc. Advanstar Communications Inc. retains all rights to this article. This article may only be viewed or printed (1) for personal use. User may not actively save any text or graphics/photos to local hard drives or duplicate this article in whole or in part, in any medium. Advanstar Communications Inc. home page is located at <http://www.advanstar.com>.



Niro Pharma Systems

AEROMATIC  
BUCK  
COLLETTE  
COURTOY  
FIELDER  
NICA  
NIRO

Niro Inc. • 9165 Rumsey Road • Columbia, MD 21045 • USA  
Tel: +1-410-997-8700 • Fax: +1-410-997-5021  
E-mail: [info@niroinc.com](mailto:info@niroinc.com) • Web: [www.niroinc.com](http://www.niroinc.com)