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On-Line Moisture Detection for a Microwave Vacuum Dryer

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A method has been developed to determine the moisture end point in a microwave vacuum dryer using near-infrared spectroscopy (NIR). Dryer studies were conducted in two T. K. Fielder microwave dryers, a Spectrum 65 and a Spectrum 1200. On-line spectra were collected using a NIRSystems Model 5000 Analyzer with a fiber-optic probe. The calibration equation uses absorbances measured at 1410, 1930, and 1630 nm. Moisture values determined on-line with this equation correlate to within 1% of the Karl Fischer results for samples below 6% moisture. The absolute SEP is 0.6% and the average residual is −0.2%. At levels above 6% moisture, the NIR results do not correlate well with Karl Fischer but the moisture curve can be used to assess the homogeneity of the water in the granulation. The combination of qualitative and quantitative information makes it possible to monitor the drying process and to predict consistently the moisture end point in the microwave dryer.

KEY WORDS: microwave vacuum drying; near-infrared spectroscopy (NIR); moisture analysis; in-process testing.

INTRODUCTION

The manufacture of solid oral dosage forms involves many steps, often including an extended drying period. Products manufactured using a wet granulation are traditionally dried on trays in large ovens. Tray drying is time-consuming and labor intensive, so alternate drying methods have been developed. Fluidized bed dryers have been used extensively throughout the pharmaceutical industry. Microwave vacuum drying is not as common as either fluidized bed dryers or tray dryers, but it has generated considerable interest over the past few years. Microwave drying allows products to be dried quickly without significantly raising the product temperature. A microwave dryer is capable of reducing a multiple-step process (dry mixing, granulation, drying, milling, and lubrication) to a single step using only one piece of equipment (1).

One of the most critical parameters in the drying process is the determination of the end point, usually at a specified moisture content. However, there is currently no direct method for monitoring the moisture level inside the dryer. Indirect methods such as temperature and electric field strength (E-field) have been used (2). The objective of this work was to develop a method for monitoring the moisture content of the granulation inside the microwave dryer. After considering several options, near-infrared spectroscopy (NIR) with a fiber-optic probe was selected. NIR has been used in many pharmaceutical applications, including material identification, moisture analysis, detection of impurities, and potency determinations (3–7). The minimal amount of sample preparation has been a key contributor to the increase in popularity of NIR methods, particularly in the analysis of solids. The use of fiber optics increases that advantage by enabling measurements to be made on-line. The combination of NIR with fiber optics is used here to measure the moisture content of the granulation during drying. The measurement technology and the resulting data are discussed in this report.

MATERIALS AND METHODS

Microwave Vacuum Dryer

Experiments were run on two microwave vacuum dryers. Initial studies were conducted on a lab-scale dryer, the Spectrum 65 (T. K. Fielder Limited, Hampshire, England), which has a dry capacity of 15–25 kg. Additional experiments were run on a Spectrum 1200 (T. K. Fielder Limited), a production-scale dryer with a dry capacity of 250–400 kg. The microwave sources in both units are magnetrons which operate at a frequency of 2.45 GHz. The Spectrum 1200 has 18 air-cooled magnetrons, each with a power rating of 1.5 kW. The magnetrons are located around the upper edge of the dryer. The microwave dryer is held under vacuum at an approximate process pressure of 45 mbar (33.8 Torr).

The bowl of the microwave dryer is made of polished stainless steel. An impeller is located in the bottom of the bowl to stir the material during the drying process. The impeller is not run continuously but rather is pulsed on and off at fixed intervals.

Near-Infrared Instrument and Port

Two instruments were used to collect data during these studies. Calibration studies were conducted using a Model 6500 Near-Infrared Spectrophotometer (NIRSystems, Inc., Silver Spring, MD) equipped with a grating monochromator and an Anhydroguide fiber-optic probe. The ends of the fibers are covered with a slanted sapphire window. A second flat window made of quartz fits over the end of the probe. Data were collected using an IBM PS-2 Model 50Z computer (IBM Inc., Boca Raton, FL) and Near-Infrared Spectral Analysis (NSAS) software (NIRSystems, Inc.). The fiber-optic probe was inserted directly into the product bottle and allowed to rest in the powder. The NIR instrument was set to average 32 scans per sample. The detector was run in the Trans × 1 mode and the wavelength range measured was 1100–2500 nm. Spectra were obtained by inserting the near-infrared probe into the sample jar such that the window was completely covered with sample.

The on-line system is a Model 5000 On-Line NIR Analyzer (NIRSystems, Inc.) equipped with a 4-m-long Anhydroguide fiber-optic probe. The instrument is controlled using a System/2 Model 50Z computer (IBM, Inc.) with NSAS, Near-Infrared Spectral Analysis Software (NIRSystems, Inc.). The spectrophotometer, which is encased in a NEMA 4 enclosure, employs the same grating monochromator as the Model 6500. The instrument was set to collect data automatically, averaging 32 scans per sample, with a 30-sec

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delay. This corresponds to an effective scan rate of 0.73 scans/min. The detector was run in the Trans × 1 mode and the wavelength range measured was 1100–2500 nm. The instrument is run in the reflectance mode using fiber optics arranged in a concentric pattern. The outer ring of fibers carry the light from the white light source to the sample. The inner core of fibers collects the reflected light and transmits it to the monochromator and the PbS detector. The throughput of the fibers varies with wavelength. Transmission above 2200 nm is very low and thus the actual working wavelength region of the system is 1100–2200 nm.

The end of the fiber-optic bundle is protected by a sapphire window. The window is mounted in a stainless-steel casing which fits snugly over the end of the fiber-optic bundle. The ends of the fibers contact the sapphire window and the assembly is held in place using set screws. An index matching fluid (RESOLVE Immersion Oil, Stephens Scientific, Denville, NJ) is used to minimize reflections at the interface.

The window casing is sealed in a port which is located on the side of the dryer just above the level of the impeller. The dryer has a 3-in.-diameter hole in which the port is press-mounted (Fig. 1). The sapphire window extends into the dryer bowl with the slanted edge facing left. The impeller rotates in a counterclockwise motion so the product is moving toward the face of the window. This helps keep the material moving past the window and minimizes caking. The fiber-optic probe is inserted into the window assembly on the outside of the dryer and held in place with set screws.

Reference Method—Karl Fischer Analysis

Laboratory samples were analyzed using Karl Fischer (KF) and NIR on the same day. The Karl Fischer analysis was done using a Mettler DL-18 and each sample was run at least twice. Samples were run more than twice if the first two values differed by more than 0.5% (dried and lubricated) or 1% (wet). A 100-mg sample size was used for the wet samples and a 200-mg sample was used for the dried and lubricated samples. The samples collected from the microwave dryer were stored in watertight containers and analyzed as soon as possible using the same procedure as the laboratory samples.

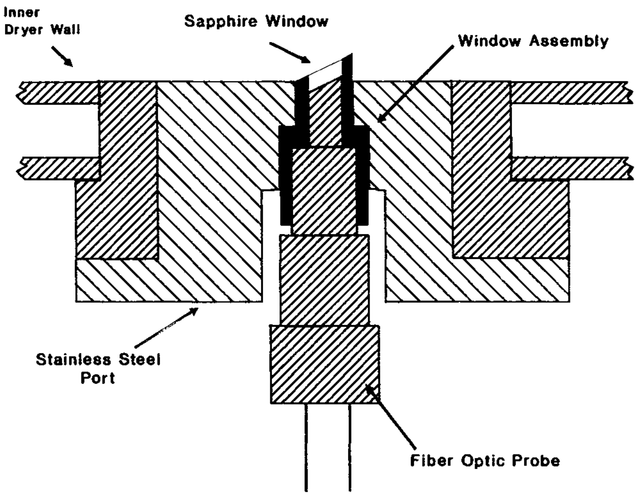

Fig. 1. Cross-sectional diagram of the moisture port.

Calculations

Several statistics are used in this paper to evaluate the accuracy of the NIR method. The residual is calculated by subtracting the Karl Fischer result from the NIR result. The average residual gives an indication of bias in the method. The standard error of calibration (SEC) is a calculation of the standard deviation of the residuals obtained from the calibration set. The SEC is an estimation of the accuracy of the NIR method, and the smaller the value, the better. The standard error of performance (SEP) is the same calculation as the SEC except the residuals are obtained using unknown samples. It is a better indication of the accuracy of the method under conditions of normal use. Ideally, the SEC and the SEP should be equal. Since the moisture content is expressed in terms of percentage, all of these parameters will have units of absolute percentage.

Calculation of Moisture Values

The collection of data is done automatically and is not coordinated with the timing of the impeller. When the process is stopped to obtain samples for evaluation by Karl Fischer, the question arises about which NIR result should be used for comparison. One approach is to use the scan designated by the operator as when the dryer was stopped. A second approach is to use the nearest "peak" moisture reading since that represents the sample collected immediately following the stirring of the granulation. A third option is to take an average of several scans. For these studies, we opted to use the peak values since it would seem to be more representative of the bulk granulation. The question becomes immaterial at the end of the drying cycle where the moisture curve stabilizes. For routine use where the only region of interest is the end of the drying cycle, an average may be a better indicator.

RESULTS AND DISCUSSION

Creation of the Calibration Equation

Calibration studies were performed using material from 20 lots of pharmaceutical granulations. The 63-sample calibration set was collected from three stages of manufacture: 22 wet, 25 tray-dried, and 16 lubricated granulation samples. The wet granulations ranged in moisture content from 22.4 to 25.9%. The dried samples fell in the range of 0.7 to 3.2% water and the lubricated samples had moisture contents between 1.4 and 2.6%. Spectra of the product at different moisture levels are shown in Fig. 2. The water bands are found at 1450 and 1940 nm. The main contributions from the drug are seen around 1700 and 2150 nm.

The NSAS software provides several options for creating calibration equations. The spectra can be smoothed or the data can be transformed using first or second derivatives. The calibration options include a manual stepwise linear regression, an automatic linear regression routine (Autocal), and a partial least-squares (PLS) algorithm. The linear regression options use the entire spectrum to select the opti-

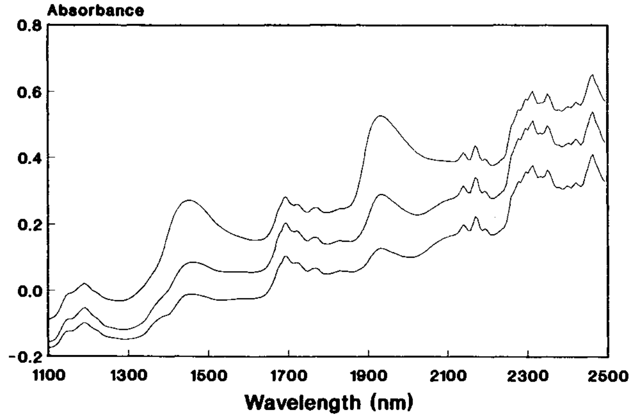

Fig. 2. Near-infrared spectra of the product at three different moisture levels. Moisture contents are 23% (top), 5.6% (middle), and 2.4% (bottom).

mum wavelengths for the correlation but the final equation contains only those selected wavelengths. The PLS routine makes use of the entire spectrum in the calibration method. In developing this application, all of these options were investigated. Because of the large number of options available, the number of equations generated can be unmanageable. The SEC is used to filter out those equations which do not represent an acceptable correlation.

The calibration equations generated using the calibration set are evaluated using a test data set. For this application, a test set was constructed using samples and spectra collected from the microwave dryer. The equation which yielded the lowest SEP and smallest average residual was selected. The optimum equation for the prediction of the moisture end point in the dryer is a three-wavelength equation generated using the Autocal option and the smoothed spectrum (smooth segment = 10):

$$\% \text{ Water} = 171.906 * A_{\lambda=1630} + 24.534 * A_{\lambda=1930} + 150.912 * A_{\lambda=1410} + 4.641$$

where A is the absorbance at the designated wavelength.

Both water bands are contributing to the equation (1930 and 1410 nm) and the measurement at 1630 nm will correct for variability in the background. The standard error of calibration for this equation was 0.6% and the correlation coefficient was 0.997.

Performance of the Method

All of the on-line data used for testing the equation were collected using the Model 5000 Spectrophotometer. Two batches (A1, A2) were run on the Spectrum 65. The potency of one lot (A1) was high by 15%; the potency of another lot (A2) was low by 15%. In the lab-scale studies, all steps of granulation (dry mix, water addition, granulation) and drying were performed in the dryer. NIR spectra were collected continuously throughout the entire process. During the drying cycle, samples for KF analysis were taken from the area in front of the window.

Twenty-one batches (B1–B21) were run on the Spectrum 1200. In the production-scale studies, the wet material was transferred to the dryer after the granulation step and NIR data were collected only during the drying stage. During batch B4, the dryer was stopped three times so samples could be taken for analysis; in all other batches samples were collected only at the end of the drying cycle.

The NIR and KF results for all samples taken from the microwave dryers are shown in Tables I and II. For moisture levels above 6% (Table I), there is an obvious bias in the NIR results. The bias may be a result of sampling limitations. Since the measurement is made only at the edge of the dryer, it probably does not reflect the moisture content of the bulk of the material during the early stages of drying. A second possible cause of the bias is the moisture equation itself. Because of the broad moisture range being examined, a second equation may be necessary to evaluate the high-moisture samples accurately. No attempt was made to optimize the measurement in this region since the end point was the primary concern.

For those samples with a moisture content of less than 6% (Table II), NIR correlates much better with the KF results. The standard error of performance is 0.6% and the average residual is −0.2%. The standard error of performance is the same as the standard error of calibration, indicating that the amount of variability observed in the test samples was not significantly different from that of the calibration samples. The average residual is not significantly different from zero, indicating that there is no bias in the method. The maximum absolute deviation between the NIR and the KF results is 1.1%, well within the accuracy one could reasonably expect for an on-line application.

The predictive power of the equation does not appear to be affected by variations in the sample which are not correlated with water content. Lots A1 and A2 had drug concentrations of +15 and −15% of label, respectively. The residuals for the NIR and KF results are within the range observed for the other microwave lots (Table II). This indicates that the water equation is not sensitive to changes in the drug content of the granulation.

Factors Affecting the Assessment of the Method

Since NIR is a correlation method, it cannot be more accurate than the reference method. In this case the Karl Fischer assay has an average variability of 0.1% water but

Table I. Comparison of NIR and KR Results (% Water >6%)

Run ID	Dryer Model	NIR result (%)	Avg. KF result (%)	Residual (%)
A2	65	5.3	6.8	−1.5
B15	1200	4.5	7.8	−3.3
A2	65	5.8	8.1	−2.3
A1	65	6.0	9.8	−3.8
A1	65	7.2	11.6	−4.4
A1	65	8.1	13.5	−5.4
A2	65	5.4	13.8	−8.4
A1	65	9.7	16.6	−6.9
A2	65	5.2	16.8	−11.6
A1	65	9.6	18.8	−9.2
A1	65	7.1	19.8	−12.7
A2	65	41.7	24.2	17.5
A1	65	39.4	24.4	15.0

Table II. Comparison of NIR and KF Results (% Water <6%)

Run ID	Dryer Model	NIR result (%)	Avg. KF result (%)	Residual (%)
B2	1200	2.7	2.1	0.6
B6	1200	2.6	2.2	0.4
B1	1200	2.9	2.7	0.2
B21	1200	2.2	2.7	−0.5
B19	1200	3.0	2.7	0.3
B5	1200	2.9	2.7	0.2
B17	1200	2.0	2.8	−0.8
B20	1200	2.5	2.8	−0.3
B4	1200	2.9	2.9	0.0
B18	1200	2.2	3.2	−1.0
B7	1200	3.2	3.2	0.0
B16	1200	2.2	3.3	−1.1
A1	65	3.6	3.5	0.1
B4	1200	3.7	3.7	0.0
B3	1200	4.1	3.8	0.3
A1	65	3.8	3.9	−0.1
B9	1200	4.3	4.0	0.3
B13	1200	5.0	4.0	1.0
A1	65	3.9	4.0	−0.1
A2	65	4.6	4.1	0.5
B8	1200	3.8	4.3	−0.5
B12	1200	4.9	4.6	0.3
B10	1200	3.5	4.6	−1.1
B11	1200	3.7	4.6	−0.9
A1	65	4.2	4.7	−0.5
B14	1200	4.5	4.8	−0.3
A2	65	5.2	4.9	0.3
A2	65	5.0	5.6	−0.6
B4	1200	4.8	5.8	−1.0
A1	65	5.1	5.9	−0.8
Avg. residual				−0.2
SEP				0.6

individual samples can yield results which vary by much as 0.6% water. The variability in these measurements affects the ability of the NIR method to correlate well with the KF results and also the ability to predict the "true" moisture value. Compounding the effect are the circumstances in which the NIR samples are obtained. The NIR measurement is made on-line, which introduces some inherent variability (i.e., the sample condition cannot be controlled as easily as an off-line method). Furthermore, the size of the dryer makes it impossible to obtain the exact same sample as being viewed by the NIR probe. Whenever possible, a sample is taken from a location which is close to the sampling window, but that sample may not be representative of the material being analyzed by the NIR probe. The amount of variability in the moisture content due to location is expected to depend upon the uniformity of the drying process. Microwave drying is a favorable technique in this regard, particularly when the moisture content is approaching the end point. However, some variability is expected. This is especially true when the only sample available was taken after the material was removed from the dryer.

The discussion above indicates some of the factors which affect our ability to assess the accuracy of the on-line method. We would expect the NIR method to have a higher variability than the KF method. For this application, increased variability is an acceptable compromise considering that there is currently no way to measure moisture and that the objective is to stop within a certain moisture range rather than at a specific target.

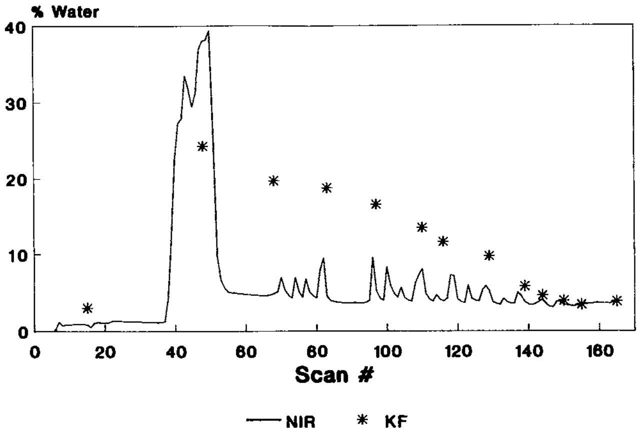

Fig. 3. The moisture curve for a lab-scale lot (A1). The KF values represent samples taken from the dryer during the run.

Assessment of the Moisture Curve

Although the method was developed for end-point detection, data are collected throughout the drying stage. The resulting moisture curves form a distinctive pattern, particularly for studies done using the lab-scale dryer (Fig. 3). At the onset of the drying stage the moisture level drops quickly since the material at the edge dries more quickly than the bulk. When the impeller stirs the material in the bowl, fresh granulation is brought to the window surface. This causes a jump in the apparent moisture content. As the bulk granulation continues to dry, the variation due to stirring decreases, until at the end of the drying period the moisture curve is stable. This indicates that the material in the bowl is homogeneous in terms of moisture content. It is in this region also that the NIR most accurately predicts the moisture content.

The data collected in the production dryer also show fluctuations in the apparent moisture level due to stirring of the granulation (Fig. 4). The curve is not as well defined as

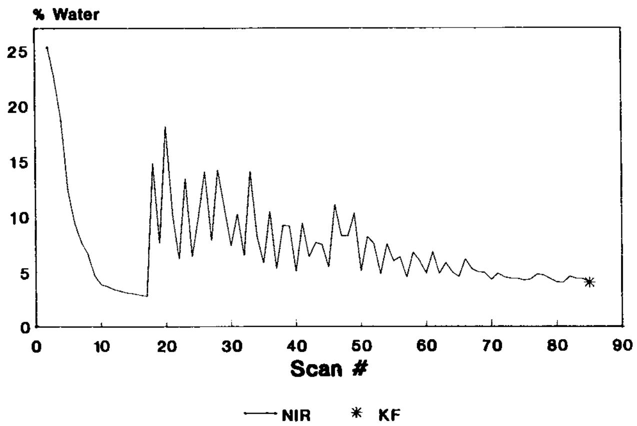

Fig. 4. The moisture curve for a production scale lot (B9). The KF value represents a sample collected at the end of drying.

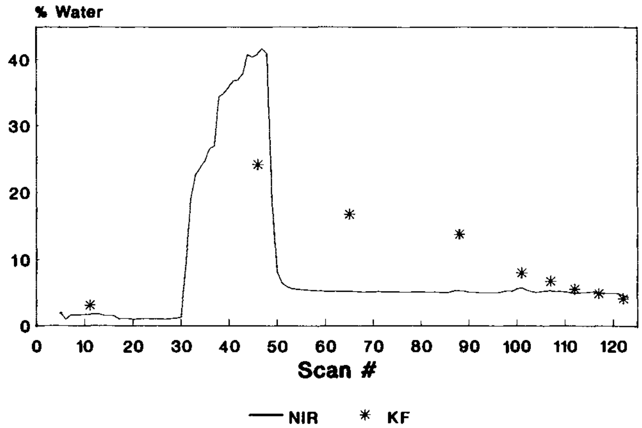

Fig. 5. The moisture curve for a lab-scale lot with the window caked with material (A2). The KF values were obtained from samples taken from the dryer during the run.

in the lab-scale dryer; rather it shows a gradual decline in moisture with small variations superimposed. The pattern remains the same, however, with the highest variability observed at the beginning of the run and the variations gradually decreasing until they disappear at the end of the run. This qualitative information is useful to the operator as an indication that the drying process is nearing the end and that the calculated moisture value is indicative of the moisture level throughout the bowl.

The variation in the moisture curve is also a useful monitor of the measurement process. If the window gets caked over with material which does not get removed during stirring, then the moisture reading will be inaccurate. Figure 5 shows an example of this collected in the lab-scale dryer. When the dryer was emptied, the window was found to be caked over. If during the course of a drying run the operator observes that the moisture level is not fluctuating as the material is stirred, the dryer can be stopped and the window cleared of caked material.

In conclusion, NIR is a useful method for the analysis of moisture in a microwave vacuum dryer. A method has been developed to predict the moisture content of our product granulation at the end of the drying cycle. Additional qualitative information about the drying process and the measurement is obtained by monitoring the moisture curve during the drying run. NIR provides a reliable method for the online determination of the end point of the granulation in a microwave vacuum dryer.

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