Near-Infrared Spectroscopic Monitoring of the Film Coating Process

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Purpose. The purpose of this study was to investigate the potential of near-infrared (near-IR) spectroscopy for non-destructive at-line determination of the amount of polymer coat applied to tablet cores in a Wurster column.

Methods. The effects of coating composition on the near-IR spectroscopic determination of ethylcellulose (Aquacoat ECD-30) or hydroxypropylmethylcellulose (HPMC)-based (Spectrablend) coating were evaluated, as were the performance of several chemometric techniques.

Results. Tablets were coated with up to 30% ethylcellulose or 22% HPMC, and samples were pulled at regular intervals during each coating run. Near-IR reflectance spectra of the intact tablets were then collected. The spectra were preprocessed by multiplicative scatter correction (MSC) or second derivative (D2) calculations, and calibrations developed using either principal components (PCs) or multiple spectral wavelengths. The near-IR method provided predictions of film applied with standard errors of 1.07% w/w or less.

Conclusions. Near-IR spectroscopy can be profitably employed in a rapid and non-destructive determination of the amount of polymer film applied to tablets, and offers a simple means to monitor the film coating process.

KEY WORDS: near-IR spectroscopy; film coating; chemometrics; pharmaceutical analysis; process monitoring.

INTRODUCTION

Modified cellulose polymers are commonly used to film coat tabletted and encapsulated dosage forms to control rates of drug release or to improve their appearance or palatability. Film coating has also been investigated as a means of improving the stability of photosensitive drugs. Several analytical methods have been developed to measure coating levels accurately, including a liquid chromatographic method for determining the amount of hydroxypropylmethylcellulose (HPMC) applied (1) and a method for measuring the amount of titanium dioxide present in coated dosage forms (2). Other studies have been reported which measure the opacity of a coat based upon specular reflectance measurements (3,4). In most production settings, the amount of polymer applied is determined by the percentage increase between the mass of a sample of the uncoated product and the mass of a similar sample after coating. This provides a measure of the theoretical amount applied, but does not account for the loss of mass from the uncoated core prior to coating, reducing the accuracy of this method.

Near-infrared (near-IR) spectroscopy is a rapid and nondestructive analytical method being investigated for a variety of pharmaceutical process monitoring applications, including blending (5,6), microwave vacuum drying (7), and determination of parenteral product sterility (8). Research conducted previously in this laboratory showed the utility of near-IR spectroscopy in the analysis of film coated tablets and indicated the potential of the method for measuring film coat thickness (9). The goal of this research was to evaluate the use of near-IR spectroscopy at-line as a nondestructive means of monitoring film coating in a Wurster column.

EXPERIMENTAL

Materials

Microcrystalline cellulose (Avicel PH101, FMC, Philadelphia, PA), magnesium stearate (Whittaker, Clark, and Daniels, South Plainfield, NJ), ethylcellulose (EC) (Aquacoat ECD-30, FMC, Philadelphia, PA), and a blend of hydroxypropylmethylcellulose (HPMC) and opacifiers (Spectrablend, Warner-Jenkinson, St Louis, MO) were generously donated. Dibutyl sebacate (Sigma, St. Louis, MO), used as a plasticizer in the EC coating, and fast-flo lactose (Foremost, Baraboo, WI), were purchased. All powders were passed through a #20 mesh screen prior to use.

Tablet Compression

All ingredients were blended in an eight quart V-blender (Patterson-Kelley Co., East Stroudsburg, PA). Placebos containing 79% w/w lactose, 20% w/w microcrystalline cellulose, and 1% w/w magnesium stearate weighing 125 mg were compressed with 1/4 inch standard concave punches to a target hardness of 7 kiloponds (kp) on an instrumented 38-station Hata press (Elizabeth-Hata International, North Huntingdon, PA).

Coating

Coating was carried out at 56°C in a Glatt WSG-5 fluid bed apparatus equipped with a 6 inch Wurster column (Glatt Air Techniques, Ramsey, NJ), using 600 g batches of tablets. The inlet air flap was set at 3, and the partition height was 2.2 cm. Each batch was fluidized for 3 minutes prior to initiation of coating in order to equilibrate the tablet bed and column temperatures.

Two coating formulations were investigated. The first consisted of the EC diluted to 20% solids and plasticized with dibutyl sebacate (24% w/w solids). The second was an aqueous HPMC-based formulation, which was prepared at 15% solids w/w. Both formulations were mixed for 0.5 hours prior to coating using a Dyna-Mix mixer (Fisher Scientific, Pittsburgh, PA), with mixing continued during the coating run to maintain homogeneity. Both formulations were applied to the tablets with a Masterflex peristaltic pump (Cole-Parmer Instrument Co., Chicago, IL) at a spray rate of 11 ml/min and an atomizing air pressure of 15 psig. The tablets were coated with 12 or 30% theoretical EC added, or 22% solids added for the HPMC-based formulation.

The Wurster column was retrofitted with a sample thief, allowing withdrawal of 10-tablet samples during coating. For each coating run, samples were collected at 2 minute intervals up to 40 minutes, and at five minute intervals thereafter. Each

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minute of coating corresponded to approximately 0.3% solids added.

The theoretical percent coating added at each time point was calculated by weighing a particular 10-tablet sample, subtracting the mass of a sample fluidized for 3 minutes to account for core attrition prior to coating, then dividing by the mass of the 3-minute fluidized sample.

Near-IR Methodology

Near-IR instrumentation is typically robust, with applications in the agricultural and chemical industries indicating that implementation of such methods on the pharmaceutical process floor is possible. Although development of near-IR calibrations can be a significant undertaking, the actual analysis and prediction of unknown samples is a simple task that will allow plant personnel to use the technique for process control.

For calibration development, performed in the laboratory, the near-IR spectrum for each tablet was collected in triplicate on a Quantum 1200 Plus grating-based spectrometer (LT Industries, Rockville, MD). Spectra were collected in reflectance mode in the 1200 to 2400 nm region. For the at-line study, spectra were collected in duplicate due to time constraints between samples. The CAPCELL™ (Optical Prototypes, Inc., Mars, PA), a parabolic reflector, was used to illuminate all tablet surfaces in a sampling configuration described previously (10). Proprietary programs written in SPEAKEASY® (Speakeasy Computing Corp., Chicago, IL) were used for spectral preprocessing and analysis.

Prior to analysis, the log(1/R) transformation of the spectra was taken. The duplicate or triplicate spectra from each tablet were then averaged to yield one spectrum per tablet.

Sample positioning is a critical concern in the near-IR analysis of tablets. Instrumental error (typically in the 10 μA range for popular commercially available instruments) is overshadowed by such positioning error. The error associated with variable tablet positioning can, however, be significantly reduced through the use of appropriate hardware, software and analytical protocol.

In near-IR analysis of intact dosage forms, differences in sample positioning cause shifting of spectral baselines, which can interfere with calibration development. In order to remove the shifts in spectral baselines due primarily to tablet positioning effects, two preprocessing techniques were examined: second derivative (D2) transformation and the multiplicative scatter correction (MSC) algorithm proposed by Martens *et al.* and summarized by Isaksson and Naes (11).

Most scanning spectrometers are capable of collecting spectra at a large number of wavelengths, and a data reduction step prior to analysis can increase the speed and ease of calculations. Principal component analysis (PCA) is a multivariate statistical technique commonly used to reduce the dimensionality of near-IR spectral data. PCA describes the major sources of variability in the spectra in a small number of orthogonal (uncorrelated) axes, or principal components (PCs).

A brief description of the technique follows. Each wavelength (n) in a near-IR spectrum is an independent variable, which can be plotted in multidimensional space. The number of dimensions in this space corresponds to the number of wavelengths of observation. Each near-IR spectrum is plotted as a single point in this multidimensional space, resulting in a cluster of single-point spectra in n-dimensional space. A set of orthogonal axes is calculated which describes the sources of variability in the cluster. The first PC describes the greatest source of variability, the second axis the second greatest source, and so on, until all sources of variability have been explained. In many cases, the first five or six PCs adequately describe the major sources of variability in the near-IR spectra. In this study, the major source of spectral variability is expected to be due to variations in film thickness.

Three chemometric techniques for calibration and prediction were investigated. In one case, multiple wavelength calibration following MSC was examined. The other methods involved multiple linear regression using PC spectra after preprocessing by either MSC or D2.

RESULTS AND DISCUSSION

Ethylcellulose Coating

Near-IR absorbances are overtone and combination bands arising from the fundamental mid-IR absorbances. The bottom half of Figure 1 shows the near-IR spectra of a tablet core and a cast EC film. Due to the presence of 20% microcrystalline cellulose in the tablet core, the spectra of the film and core show some similarities. Note, however, the increased absorbance of the EC film in the 1650 to 1800 nm region, which lies in the first overtone region and is attributed to C-H stretching. The EC film also shows increased absorbance in the 2250 to 2400 nm region, which is a combination band arising from C-H stretching. The top half of Figure 1 displays spectra of tablet cores coated with up to 30% EC after MSC. Each spectrum corresponds to approximately 3% EC solids added. Again, the increasing absorbances in the 1650 to 1800 nm and 2250 to 2400 nm regions are due to the increased influence of the EC coat on the near-IR spectra. In other spectral regions, however, the absorbance of the tablet decreases as more film is applied (e.g. 1250 to 1300 nm and 1350 to 1600 nm).

Calibrations were developed using samples obtained from the 30% EC coating run. Sixty tablets (two tablets from each sample) were used for the calibration development. For MSC/

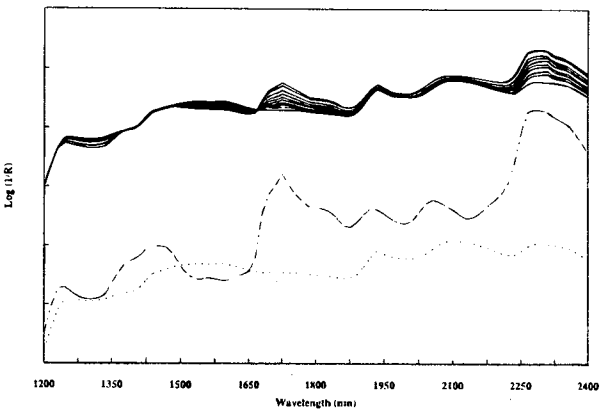

Fig. 1. Near-IR spectra of an uncoated tablet core (dotted line), an EC cast film (dot-dashed line), and a series of near-IR spectra collected during a 30% EC coating run (solid lines). Note EC absorbance peaks in 1650 to 1800 nm and 2250 to 2400 nm regions, and increasing absorbances in these regions as EC coat level increases. Note: spectral baselines offset for clarity.

PCA and D2/PCA calibrations, PCs which contributed significantly to the regression model (i.e. t-values ≥ 3) were used, while for multiple wavelength calibration, the wavelengths most highly correlated with changes in coat applied were employed. Four PCs were significant for the MSC/PCA data treatment, whereas for D2/PCA only two PCs were significant. For multiple wavelength calibration three wavelengths were chosen (1301, 1731 and 2291 nm), one from each of the three wavelength regions with the highest correlation. The standard errors of estimate (SEE) for each calibration method were comparable (MSC/PCA = 0.66, D2/PCA = 0.79, and multiple wavelengths = 0.62% w/w), and all calibrations had R^2 values of 0.993 or better. Thirty tablets (one tablet from each sample and not part of the calibration set) were used to test the models. The standard error of prediction (SEP) for each model, using samples from the same coating run as the calibration set were 1.03% w/w or less. Figure 2 shows the calibration obtained by regressing 4 PCs after MSC.

In order to further test the calibration, two batches of tablets were coated up to 12% w/w theoretical weight gain with EC. In the first batch, samples were collected at two-minute intervals, then analyzed after completion of the coating run. In the second test batch, the near-IR spectrometer was moved to the production site, where samples were pulled and analyzed at-line as the coating run progressed. In both cases, the calibration technique of MSC/PCA, followed by regression with four PCs, provided the lowest SEP. The overall SEP, using the test samples from the calibration test set and the two test batches, was 1.07% w/w. A scatterplot displaying predicted versus actual values for all test samples can be seen in Figure 3.

Although multiple wavelength calibration showed the lowest SEE and SEP for the initial calibration development, calibrations based upon multivariate techniques such as PCA are often more robust, as was evident in this study. However, the performance of the model employing just three wavelengths of observation reveals the potential for the use of simple and inexpensive fixed-filter near-IR instruments in such applications.

HPMC Coating

The second part of this study involved the analysis of tablets coated with 22% w/w theoretical weight gain of the HPMC-based formulation. The lower half of Figure 4 shows

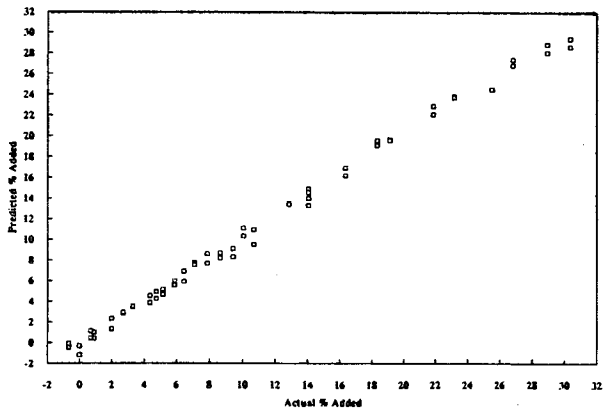

Fig. 2. MSC/PCA calibration obtained for EC coating (n = 60, SEE = 0.66%, R^2 = 0.995).

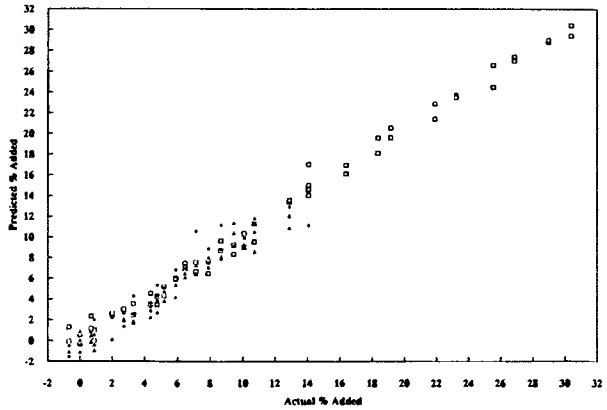

Fig. 3. MSC/PCA-based prediction of 106 samples from three EC coating runs (SEP = 1.07%). Square = prediction set from calibration run, diamond = 12% laboratory run, triangle = 12% at-line run.

the spectra of an uncoated tablet core and a cast film of the blend. This HPMC film has a much lower absorbance across the spectrum than the EC film due to the high concentrations of aluminum lakes (12% w/w) and titanium dioxide (12% w/w), excellent light scatterers, in the HPMC-based formulation. In the upper half of Figure 4, the scatter-corrected near-IR spectra of tablets collected during the coating run are shown. The primary spectral change occurring is a decreasing baseline caused by increasing reflectance as the film thickness increases.

The same calibration development approaches were used for this process. Thirty-two tablets were used for calibration development, and an equal number from the same batch used for validation. For MSC/PCA calibration five PCs contributed significantly to the model, and SEE and SEP values were 0.76 and 0.69% w/w, respectively. Two PCs were significant for the D2/PCA calibration, and an SEE of 1.22% w/w and SEP of 0.85% w/w obtained. Two wavelengths (1600 and 2279 nm) were used for the third calibration, and SEE and SEP values nearly identical to the MSC/PCA calibration obtained: 0.82%

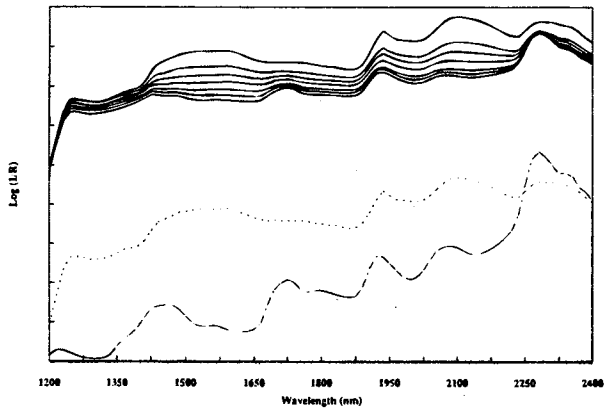

Fig. 4. Near-IR spectra of an uncoated tablet core (dotted line), an HPMC cast film (dot-dashed line), and a series of near-IR spectra collected during a 22% HPMC coating run (solid lines). Note decreasing absorbances across spectrum as coating level increases, due to the presence of titanium dioxide and aluminum lakes. Note: spectral baselines offset for clarity.

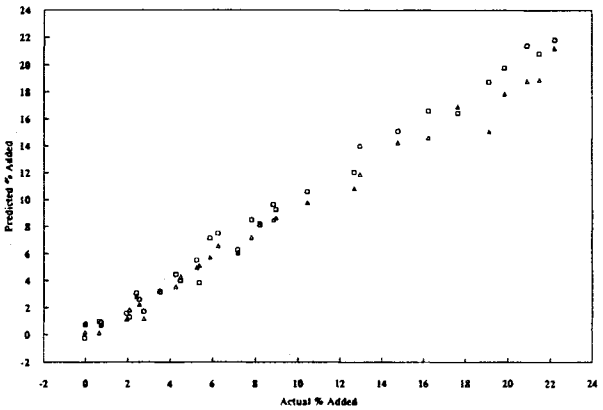

Fig. 5. MSC/PCA-based calibration and prediction plot for HPMC coating run, with 32 samples for each (SEE = 0.76%, R^2 = 0.990, SEP = 0.69%). Squares = calibration samples, triangles = prediction samples.

w/w and 0.70% w/w. Figure 5 shows the plot of both the calibration and validation data sets.

The amount of film added for the calibration batches is higher than would be expected for most coating applications. Two reasons exist for this approach. First, for optimal calibration development, samples whose film concentration varies over a range greater than that expected in production is desired. Also, the authors wanted to determine the linear dynamic range for prediction of coat thickness. Nonlinearity was not observed in the calibrations, indicating that thicker coatings could be monitored by near-IR spectroscopy.

CONCLUSIONS

Near-IR spectroscopy, used at-line, is useful for determining the amount of coating applied to dosage forms. This method provides a means to bypass time-consuming and expensive wet chemical methods for the determination of film added. For example, if a certain dissolution rate is desired and is dependent upon the film applied, near-IR spectra can be collected from the dosage forms prior to dissolution testing, and those spectra corresponding to tablets with desired dissolution rates used to develop a spectral library. The near-IR spectra from subsequent batches can be compared with those from the library using qualitative statistical tests, and coating endpoints determined.

Several near-IR methods have now been accepted by the U.S. Food and Drug Administration. A select group of near-IR instrument manufacturers and chemometric software vendors, recognizing the considerable market potential of the pharmaceutical industry and realizing the importance of validation in this industry, have developed their products to be "validatable" according to current Good Manufacturing Practices.

Work is currently underway to install a fiber-optic probe in a Wurster column to conduct on-line monitoring, providing increased control of this important pharmaceutical process.

ACKNOWLEDGMENT

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REFERENCES

1. D. D. MacLaren and R. G. Hollenbeck, "A High Performance Liquid Chromatographic Method for the Determination of the Amount of Hydroxypropyl Methylcellulose Applied to Tablets During an Aqueous Film Coating Operation," *Drug Dev. Ind. Pharm.*, **13**(12):2179–2197 (1987).
2. J. J. Harrison, I. Lafferty, W. D. Moore, D. A. Rawlins, and P. M. Thwaites, "Titanium Determination as a Method of Quantifying Film-Coat Application on to Tablets," *Drug Dev. Ind. Pharm.*, **17**:149–155 (1991).
3. R. C. Rowe, "The Opacity of Tablet Film Coatings," *J. Pharm. Pharmacol.*, **36**:569–572 (1984).
4. R. C. Rowe, "Quantitative Opacity Measurements on Tablet Film Coatings Containing Titanium Dioxide," *Int. J. Pharm.*, **22**:17–23 (1984).
5. D. J. Wargo and J. K. Drennen, "A Near-IR Method for Assessing Homogeneity of Powder Blends," paper presented at Pittcon '95, New Orleans, Louisiana, 5–10 March 1995.
6. E. W. Ciurczak, "Pharmaceutical Mixing Studies Using Near-Infrared Spectroscopy," *Pharm. Technol.*, **14**(10): 140–144 (1991).
7. J. G. White, "On-Line Moisture Detection for a Microwave Vacuum Dryer," *Pharm. Res.*, **11**:728–732 (1994).
8. L. J. Galante, M. A. Brinkley, J. K. Drennen, and R. A. Lodder, "Near-Infrared Spectrometry of Microorganisms in Liquid Pharmaceuticals," *Anal. Chem.* **62**:2514–2521 (1990).
9. J. D. Kirsch and J. K. Drennen, "Determination of Film-Coated Tablet Parameters by Near-Infrared Spectroscopy," *J. Pharm. Biomed. Anal.*, in press.
10. R. A. Lodder and G. M. Hieftje, "Analysis of Intact Tablets by Near Infrared Reflectance Spectrometry," *Appl. Spectrosc.*, **42**:556–558 (1988).
11. T. Isaksson and T. Naes, "The Effect of Multiplicative Scatter Correction (MSC) and Linearity Improvement in NIR Spectroscopy," *Appl. Spectrosc.*, **42**:1273–1284 (1988).