Quantitative Analysis of Film Coating in a Pan Coater Based on In-Line Sensor Measurements

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ABSTRACT

A method was developed that enables in-line analysis of film coating thickness on tablets during a pan coating operation. Real-time measurements were made using a diffuse-reflectance near-infrared (NIR) probe positioned inside the pan during the coating operation. Real-time spectra of replicate batches were used for modeling film growth. Univariate analysis provided a simple method for in-line monitoring of the coating process using NIR data. An empirical geometric 2-vector volumetric growth model was developed, which accounts for differential growth on the face and band regions of biconvex tablets. The thickness of the film coat was determined by monitoring the decrease of absorption bands characteristic of a component of the tablet core and monitoring the increase of bands characteristic of a component in the coating material. There was good correlation between values estimated from the NIR data and the measured tablet volumetric growth. In-line measurements allow the coating process to be stopped when a predetermined tablet coating thickness is achieved.

KEYWORDS: monitoring, modeling, prediction, film-coating, NIR, diffuse reflectance

INTRODUCTION

Traditionally, the extent of film coating of tablets has been determined by either applying a specified amount of coating material or by measuring the weight gain of tablets until the desired end point is achieved. These methods allow for the evaluation of only the extent of coating at the end of a process.

The use of process analytical technology (PAT) to elucidate and monitor/control pharmaceutical unit operations has recently received increased attention. The Food and Drug Administration PAT initiative combines process understanding with the ability to monitor critical control points to aid in development and manufacturing. The goals include real-time monitoring and control manufacturing processes based on the knowledge generated in development/implementation.[1]

Although film coating is treated as a straightforward operation, little has been done in the pharmaceutical literature to model or monitor the operation beyond those described above. The complexity of this unit operation arises from the fact that multiple variables may influence the quality and degree of coating. These variables are associated with the heat and mass transfer characteristics, the coating curing,[2] the spray configuration, the nature of the coating material, the geometry of the system, the nature of the core, and the rate and extent of coating accumulation. All of this has to be balanced to produce an acceptable coating, and, historically, it is under almost totally empirical control. Monitoring film coating facilitates both process understanding and control.

In real-time monitoring, a sensor is used to monitor the increase or decrease in a signal that is characteristic of the property being monitored until the predetermined end point is achieved. Real-time monitoring has been used in pharmaceutical unit operations such as drying,[3,4] blending,[5-9] and fluid bed coating, but no studies of in-line sensor measurements of film coating in a pan coater have been reported. (Recent studies from Sweden[10,11] monitored the coating of beads in a fluid bed coater.) The model used for this work allows the end point of tablet film coating to be predicted and controlled in real-time without the use of off-line testing.

Spectroscopic sensors offer attractive possibilities for novel process control in the pharmaceutical industry. The use of vibrational spectroscopy, such as near-infrared (NIR) and Raman spectroscopy for monitoring chemical reactions or other unit operations, are the most mature of these.[12-14] Noninvasive measurements for these processes can now be performed through the use of fiber optics. Several literature examples of process analytical chemistry and process monitoring using NIR spectroscopy to obtain both qualitative[15-17] and quantitative[8,18-20] analytical information have been reported. Process applications are well known in the areas of both solids[8,15-17,19,20] and liquids.[18]

Kirsch and Drennen[19] conducted quantitative an NIR analysis of tablet film coating by measuring tablets removed from the process (at-line). Andersson et al[10,11] developed an in-line method for the determination of the extent of coating on tablets in a fluidized bed in which diffuse reflectance NIR spectra were used in a multivariate calibration.

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The objective of this study was to monitor in real-time a pan coating process and to develop a method for quantitative calibration of NIR spectra for the tracking of coating thickness on pharmaceutical tablets and to enable the end point of the process to be determined.

MATERIALS AND METHODS

Materials

Tablets

Sulfanilamide (purum, 98.0%; FLUKA, Buchs SG, Switzerland and Riedel-de Haën, Seelze, Germany), microcrystalline cellulose (Avicel PH-200 NF, FMC, Newark, DE), lactose anhydrous for direct compression (Sheffield Brand Lactose NF, Quest International, Chicago, IL), and magnesium stearate (Witco Corp, Houston, TX) were sieved through a #30 US standard sieve to make the directly compressible formulation for the tablets.

Coating

Hydroxypropyl methylcellulose ([HPMC] Methocel E3 grade, Dow Chemical Co, Midland, MI) and polyethylene glycol 6000 (USP/EP, Dow Chemical Co) were used as received.

Tablet Compression

All of the tablet ingredients were blended in a Tote bin blender. Tablets containing 30% w/w microcrystalline cellulose, 50% w/w lactose anhydrous, 20% w/w sulfanilamide, and 0.2% w/w of total weight for magnesium stearate were compressed with a 7/16-in standard round concave punches to a target weight of 480 mg on a Stokes 16-station B2 tablet press (FJ Stokes Machine Co, Philadelphia, PA).

Coating Solution

An aqueous-based coating solution was prepared, consisting of 10% w/w hydroxypropyl methylcellulose and 1% w/w polyethylene glycol. The polyethylene glycol was added to 7 L of 60°C distilled water. After the polyethylene glycol was dissolved, the hydroxypropyl methylcellulose was slowly added, and the solution was mixed for 20 minutes to fully disperse the polymer. The solution was removed from the heat and allowed to sit for at least 12 hours before use to hydrate the polymer.

Equipment

Film coating experiments were performed in a 24-in diameter Accela-Cota pan coater using a single 2-phase coating spray nozzle. The inlet temperature was controlled with a heat exchanger at 60°C during the coating operation. The pan speed was maintained at 12 rpm during the coating stage of each experiment.

The NIR diffuse reflectance spectra were collected from inside the pan coater using a dispersive single beam instrument (NIR-250L-1.7T2, Control Development Inc, South Bend, IN) equipped with a 35-W tungsten halogen light source. A gold reflector was mounted on the lamp fixture with a focusing lens mounted in front of an optical fiber used for collection. To avoid coating droplets from damaging the sensor, the top and sides of the sensor were protected with a Plexiglass box with a nitrogen purge. The setup and placement of the NIR diffuse reflectance probe inside the pan coater are shown in Figure 1.

The wavelength range scanned by the spectrometer was 1100 to 2200 nm. NIR spectra were collected at 125-ms intervals, and 8 spectra were averaged and saved over an interval of approximately 1 second. During off-line analysis of the NIR data, the spectra were averaged again to obtain 1 spectrum for 20 seconds of data collection.

Software

Spec32 software (version 4.0, Control Development Inc) was used to control the NIR spectrometer and collect the spectra.

METHODS

Four replicate coating experiments were performed as the training set. Each coating experiment consisted of 7 kg of tablets in the pan coater. The tablet bed was allowed to warm up for 15 minutes before the coating operation. The coating solution was applied at a rate of 50 g/min using a

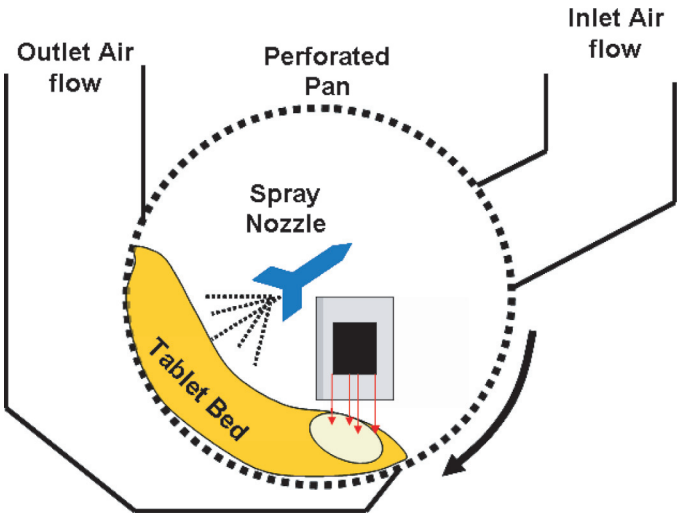

Figure 1. Side-vented pan coater and diffuse reflectance NIR probe equipment setup.

single 2-phase nozzle placed 6 in from the cascading bed of tablets. The inlet air temperature was controlled at 60°C, and the outlet air temperature stabilized at approximately 42°C throughout each coating experiment because of evaporative cooling. The pan speed was maintained at 12 rpm during the coating operation. At the end of the coating step, the pan speed was reduced to 8 rpm, and the heat exchanger was turned off. The coated tablets were allowed to cool down for 20 minutes. Tablet samples of approximately 100 g were collected at 20-minute intervals during the coating experiments. Room temperature was maintained between 21 and 23°C, and the relative humidity was maintained between 19% and 24%, respectively.

Tablet Weight

Following each coating experiment, the individual weights of 100 tablets for each sample time (20-minute intervals) were measured on a Mettler-Toledo AG104 analytical balance (Mettler-Toledo, Columbus, OH). The average weight and SD were calculated from the individual weights.

Tablet Dimensions

After each coating experiment, face thickness measurements were obtained for 100 tablets. Three band diameter measurements per tablet were also obtained for 100 tablets from each sample time using a digital micrometer (Mitutoyo Digimatic Outside Micrometer, Mitutoyo America Corp, Aurora, IL).

Tablet Film Thickness

The thickness of the film coat on individual tablets was estimated based on the tablet dimension measurements using a digital micrometer. Film thickness for uncoated tablets was assumed to be zero (μm), and the tablet dimensional change was assumed to correspond only with the film solids depositing on the surface.

RESULTS AND DISCUSSION

The use of in-line monitoring of coating using NIR spectroscopy in combination with univariate data analysis was investigated. For the system studied, the mass fraction of coating solids on the tablets increased from 0% to 11%, calculated from weight gain, during the pan coating operation. This corresponded to a mean coating thickness of up to 180 μm in the tablet face and 135 μm in the tablet band.

In-line NIR Monitoring

A challenge in using NIR spectroscopy is that NIR spectra are weak overtones and combination bands of fundamental molecular vibrational frequencies. These overtones and combination bands are often overlapping; for example, the 1930-nm overtone for *O*-H stretch is often overlapped by the 1940-nm combination band for water. This problem can often be overcome by the use of multivariate data analysis and chemometrics.

Monitoring the extent of film coating can be accomplished by different methods using NIR. The absorbance bands characteristic of the coating polymer will increase as the thickness of the film coat increases. The increase in concentration can then be correlated to the thickness measured off-line. The reduction in intensity of absorbance bands characteristic of a component of the tablet core can also be correlated to the increase in film coat thickness. As the thickness of the film coat grows, the depth of penetration of the NIR radiation into the tablet core diminishes, effectively decreasing the amount of the core material being analyzed. These are the methods described in this article.

Figure 2 shows the NIR spectra for a cast film of coating solution (top), placebo tablets (middle-top), HPMC polymer powder (middle-bottom), and sulfanilamide crystals (bottom). The tablet core component being tracked, sulfanilamide, has a distinguishing spectral absorbance band at approximately 1965 nm, corresponding mainly to the primary aromatic amine band resulting from the combination of the *N*-H bending and stretching modes. The film coating component being traced, HPMC, has a characteristic intense NIR region around 1735 nm, which corresponds mainly to the first overtone of the C-H stretching vibration from the polymer backbone.

As coating progresses, there are several regions of the spectrum that could be used for univariate analysis (because of intensive changes in peak area and peak height) Some characteristic regions for this system and changes observed

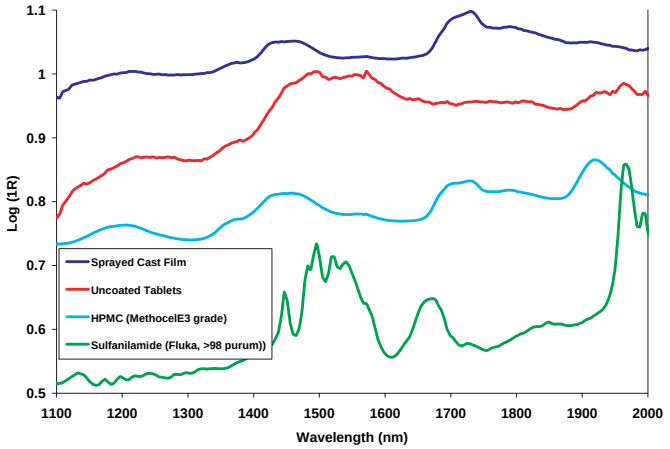

Figure 2. NIR spectra for a sprayed film of coating solution cast in a substrate surface (top), uncoated tablets (top-middle), HPMC powder polymer (bottom-middle), and sulfanilamide crystals (bottom).

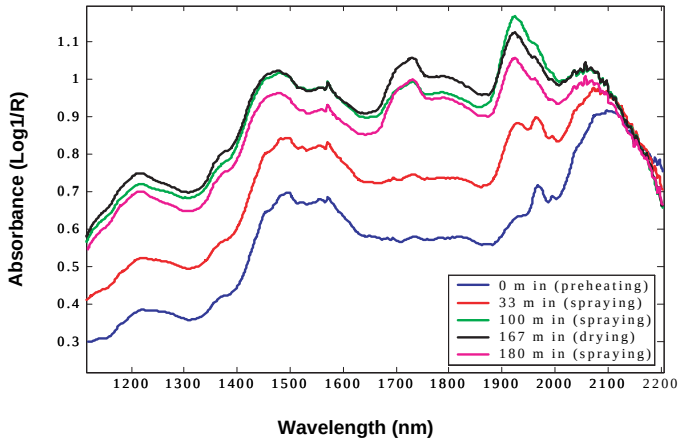

Figure 3. NIR spectra collected at different time points in a single replicate coating experiment for batch 1.

during a coating experiment can be seen in Figure 3. Two main regions were tracked as the coating operation progressed: the region around 1,965 nm, characteristic of the sulfanilamide core active component, and the region around 1,735 nm, characteristic of the HPMC coating polymer. These regions provided information on the process and, thus, could be used to monitor the progress of the coating experiment.

Figure 4 shows peak intensity values for a typical NIR output of the HPMC coating signal at 1,735 nm (top) and the sulfanilamide signal at 1,965 nm (bottom). The peak intensity was calculated by measuring the difference between the absorbance (log [1/R]) of the peak maximum and a baseline point at 1315 nm. Changes occurring during the coating operation are directly observable in the resulting NIR spectra. The tablets are preheated for the first 15 minutes of the experiment. As the coating solution is applied (starting at 15 minutes of elapsed time), the signal corresponding with the core begins to decline, whereas the signal corresponding to the HPMC in the coating grows. Note that the maxima of the HPMC at approximately 1,735 nm shifted slightly as the coating progressed. This was better observed in the second derivative spectra. During the drying stage of the coating experiments, at the end of the addition of the coating solution, the core signal began to increase moderately. This is attributable to the drying and possible curing of the film coat. Film formation occurs when polymeric molecules entangle to form a continuous film.[21,22] As the film coat dries, the film contracts, and the overall thickness of the film may decrease slightly.

The dynamic motion and the behavior of the tablets in a tumbling pan must be taken into account when acquiring diffuse-reflectance NIR measurements. The data collected on the moving bed are affected by changes in the density of material (number of tablets) passing underneath the beam and the distance between the detector and the bed. As the tumbling of the tablet bed proceeds, the cascading motion is additionally agitated by the passing of the baffles in the pan. The dynamic environment of the tablet cascade in the pan means that the number of tablets traveling under the beam is not constant (the baffle signals are periodic) with time. To lessen this problem, the spectral data may be filtered or averaged over a period of time. In the case of the data presented in Figure 4, spectra are collected at approximately 1 second intervals, and 20 spectra are averaged to smooth the fluctuations associated with monitoring a dynamic sample. The quantitative measurements are based on 20-point averages of the spectral data. Spectral averaging diminishes the baseline shifts observed in the signal caused by the dynamic motion of the moving bed and reduces the influence of the baffles on the signal.

Tablet weight and film thickness measurements were collected on samples that were withdrawn during the coating. These data display an increasing trend similar to the NIR signal corresponding with the coating and an inverse of the trend for the signal corresponding to the core. This linear growth rate can be seen in Figure 5 for face film thickness measurements from all of the batches and for band film thickness measurements. However, as seen in Figure 4, a small curvature was observed in the NIR signal with coating time, which could be attributable to a peak shift or saturation of the signal in that region. Hence, there was difficulty in directly relating the nonlinear curvature of the spectral change to a seemingly linearly changing property of film growth. The use of second-derivative spectral processing resulted in a more accurate linear fitting relationship, which allowed ease of use and simplification of statistics.

Calibration of the NIR signal and film thickness can be accomplished by correlating the NIR signal immediately before the collection of coated tablet samples with the film

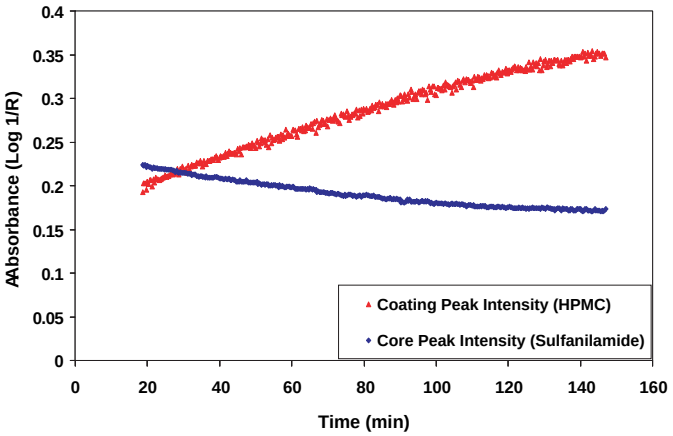

Figure 4. NIR absorbance signal for the 1,735-nm peak (coating solids) and the 1,965-nm peak (sulfanilamide in the tablet core) during the spraying stage of a coating experiment for batch 1. Each data point corresponds with 20 seconds of spectral averaging.

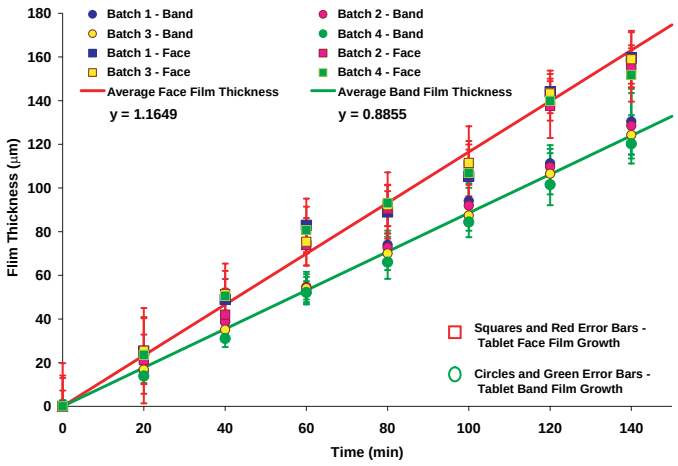

Figure 5. Film growth rate on the face and band of biconvex tablets (SRC-7/16-in tooling) from 4 replicate coating batches. The average growth rates of 3 batches were used to calculate the regression constants for tablet face and band film growth, which were later used to predict the last batch. Bars, film thickness variability for 100 tablets collected at each time point.

coat thickness values estimated from off-line thickness and diameter measurements made with a digital micrometer and optical microscopic measurements. However, as mentioned, the changes of the peak intensities used in the NIR region demonstrate an apparent nonlinear trend, whereas the film coat thickness seems to grow in a linear fashion, although at different rates in the face band directions (Figure 5).

Because NIR does not give an absolute value of the characteristic being measured, all of the NIR data require calibration based on a primary measurement of the characteristic. As such, NIR prediction is only as good as the primary measurement. Film-coated tablet dimensions are commonly used as a measure of film coat thickness.[10,19] Whereas this is an easily implemented method, and statistical robustness can be readily achieved with the simple dimensional analysis of many tablets, care must be taken to account for variability in the dimensions of the tablet cores. If only 1 dimension (face thickness or band diameter) is measured, then the variability in film coat thickness within a single tablet will not be taken into account, because the measurement only records 1 "film thickness" per tablet, and then would assume a uniform coating thickness across the entire tablet. To reduce the amount of variability in the measurement of the tablet core thickness, measurements were made for face thickness, as well as band diameters for each sample time. Compared with face thickness, tablet band diameter measurements are much less variable, because the initial variability of the cores depends on the diameter of the tablet press die orifices and the relaxation behavior of the compact after compression. Therefore, variability in the tablet band diameters corresponds more accurately with real variability in film thickness for tablets within the bed.

The calibration of NIR data to a primary measurement of the characteristic being observed (film thickness) was conducted to account for growth in the band, as well as the face regions of a biconvex tablet. It was determined that a more thorough analysis of the NIR data could be accomplished by observing the changes in the second derivative spectra. The second derivative of a spectrum has its maximum values at the same wavelengths as the peaks in the original diffuse reflectance spectrum, although in the negative direction. There are substantial differences observed when using different numbers of data points in calculating the second derivative spectrum. An example of second-derivative analysis on 1 coating experiment is shown in Figure 6. The second-derivative spectra were obtained for different coating times, and a moving average of 25 nm was used.

The second derivative exhibits some of the same effects as the first derivative: linear (proportional) change in amplitude at small spacings and nonlinear change in amplitude at large spacings There is no shift in the wavelength of the central maxima, although it does broaden relative to the untransformed spectrum. These factors were taken into account during data analysis and soothe the use of calibration or modeling curves based on the second derivative.

In these complex spectra, it can sometimes be difficult to distinguish true spectral features from the artifact peak created by the second-derivative calculation. One characteristic of the second derivative is the narrowing of this peak compared with the original absorbance band. This sharpening effect is accompanied by the creation of 2 artifact peaks, the 2 positive peaks that flank the negative portion of the second derivative. As the wavelengths over which the computed derivative increases, however, this resolution enhancement effect decreases and eventually disappears.[23]

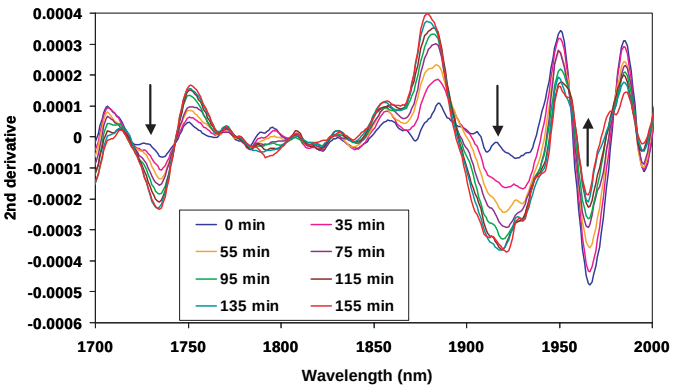

Figure 6. Second derivative spectra (using a moving average with 25 nm spacing) obtained at different time points during the coating experiment for batch 1. Arrows represent regions where significant change in peak area and height allowed univariate analysis to be employed.

Once the second-derivative spectra were calculated, different ratios of the peak heights could be determined and compared. The second-derivative values at a given wavelength were used as a guide for monitoring the extent of film coating and process performance in the same manner as shown previously for single-wavelength monitoring (ie, the HPMC second derivative of absorbance value at 1,735 nm). A moving average of 25 nm resulted in significant noise reduction allowing accurate identification of characteristic regions.

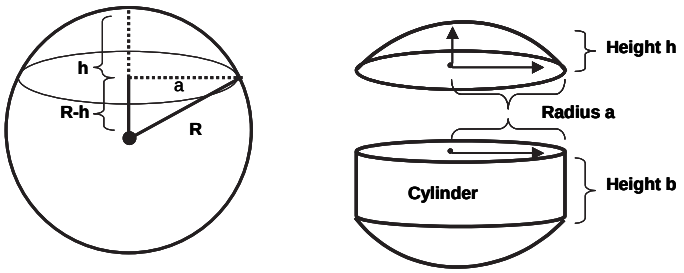

Figure 7. Geometric approach to derive the volume of a biconvex tablet.

Geometric Growth Model

The data analysis correlating the core and coating peak intensities with time yielded a linear fit with R^2 values of 0.96 to 0.97. However, the behavior of the data throughout the plot did not seem linear. To resolve this, a theoretical geometric growth model that has relevance to the dynamic changes in film growth from tablets was developed.

The approach that was chosen is based on the assumption that film growth rate on a biconvex tablet surface is different from that of the band. This is because of the motion of the tablets in the coating pan and preferred orientation of the tablets as they cascade. That is, the larger face spends more time on average oriented toward the spray gun relative to the band or edge. An important assumption is that film thickness is defined by the volume occupied by the coating solids at the surface of the tablet core after coating solids have been applied and water evaporated. Therefore, by quantifying a dry film volumetric growth and using weight gain data of the film coating, a more accurate film density may be estimated than that based on just the literature densities and the amounts of the coating materials present. This approach is more useful than using surface area for estimating film thickness, because it accounts for the mass balance from experimental weight gain measurements. Surface area measurements alone cannot be used to estimate film density from weight gain data. Also, having knowledge of the tablet and film volumes implies that the band face film thicknesses are known. Hence, the NIR signal can be easily correlated to volumetric values, which, in turn, provide tablet face and band film thickness information without having to calibrate for each of these separately. A final inherent assumption here is that the tablets are not changing volumes by any means other than the coating itself. This might be ensured in future studies by measuring the tablet dimensions of tablet core control samples before and after they are subjected to film coating.

For these experiments, tablets were made using 7/16-in Standard Round Concave (SRC) tooling. For a round biconvex tablet, the calculation of the overall surface area for the tablet core was given by Munzel[24] using the surface area of 2 spherical caps from a circle with radius R and a cylinder without top or bottom (Figure 7).

$$SA = 4\pi Rh + 2\pi a \cdot b \tag{1}$$

where a is the radius of the tablet, h is height of the spherical cap, R is the radius of the circle from which the spherical cap was obtained, and b is the height of the tablet edge.

To reconcile weight gain measurements with film growth measurements it was decided that a volumetric approach would be employed. The volume of a biconvex tablet can also be derived in a similar manner.

Because the volume of the spherical cap[25,26] is:

$$V_{spherical\ -cap} = \frac{1}{6}\pi h(3a^2 + h^2) \tag{2}$$

and the volume of the cylinder is:

$$V_{cylinder} = \pi a^2 \cdot b \tag{3}$$

then, the overall volume occupied by the tablet is:

$$V_{Tablet} = \frac{2}{6}\pi h(3a^2 + h^2) + \pi a^2 \cdot b \tag{4}$$

The dimensions of a tablet depend on the type of tooling used, (normal/standard or deep biconcave punches) and can be obtained from punch tip curvature tables produced by the manufacturers. It is also important to assure that the tablet radius a is related to R such that the dimensions of the cap and tablet band coincide precisely. For measurements of volume, the relationship between R and a is given below. Using the Pythagorean Theorem:

$$R^2 = (R - h)^2 + a^2 \tag{5}$$

solve for a^2

$$a^2 = 2Rh - h^2 \tag{6}$$

so the radius of the cap base circle is:

$$a = \sqrt{h(2R - h)} \quad (7)$$

and the volume of the spherical cap becomes:

$$V_{spherical\ -cap} = \frac{1}{3}\pi h^2 (3R - h) \quad (8)$$

However, the height of the tablet edge b does not depend solely on the geometry of the punch but also on the distance traveled by the punches inside the die during compaction. This dimension may not be generally measured by formulators who prefer to measure the total thickness (T_{face}) of the tablet. In this case, the height of the band is calculated from the total face thickness (T_{face}) measured:

$$b = T_{face} - 2h \quad (9)$$

Rearranging equations 4 and 9 gives:

$$V_{Tablet} = \frac{2}{6}\pi h (3a^2 + h^2) + \pi a^2 \cdot (T_{face} - 2h) \quad (10)$$

This equation allows the volume of a tablet to be computed directly from tablet measurements.

In this model, it is assumed that film growth in a biconvex tablet occurs mainly in 2 directions that are normal to the face and the band, respectively. It is also assumed that growth is different in the face direction than in the band direction because of the preferred orientation of the tablets during coating. Another assumption is that growth on either surface is linear with time. Using data from face and band thickness measurements collected from replicate batches, the behavior of film growth for the face and band can be derived from the regression constants for each growth vector. In this case, the coating time is t and the face vector magnitude is defined by:

$$h = Mt + B \quad (11)$$

the band vector magnitude is defined by:

$$a = Kt + C \quad (12)$$

Therefore, for a given time x, the volume of a tablet can be predicted by substituting equations 11 and 12 into equation 4:

$$V_{Tablet} = \frac{2}{6}\pi (Mt + B)\left(\left(3(Kt + C)^2\right)(Mt + B)^2\right) + \pi (Kt + C)^2 \cdot b \quad (13)$$

From equation 10 we obtain:

$$V_{Tablet} = \frac{2}{6}\pi (Mt + B)\left(\left(3(Kt + C)^2\right) + (Mt + B)^2\right) + \pi (Kt + C)^2 \cdot (T_{face} - 2h) \quad (14)$$

Equation 14 allows the volumetric growth of a tablet to be estimated from the regression constants in the two normal directions to the face and band derived from replicate tablet growth measurements. Therefore, this equation can be used to predict and optimize film coating growth on biconvex tablets for a given system and formulation from a limited number of replicate experiments.

This model can also be adapted to a system that exhibits nonlinear film growth by using other types of fitting relationships (polynomial, square root, or cube root) and substituting these, instead of equations 11 and 12, into equation 4 or 10.

Testing the Model

Three initial replicate experiment batches from the training set were used to calibrate for the model, which was later used to predict a fourth replicate batch. For the experiments in this article, face thickness measurements were obtained for 100 tablet samples at 20-minute intervals during the coating operation. With these data, the h values were calculated and plotted for the 3 batches. The slopes and intercepts were averaged, and regression constants for equation 11 were obtained. For the same batch experiments, 300 band diameter measurements were obtained from 100 tablets at each 20-minute interval sample (3 band diameter measurements per tablet; see Figure 5). With these data, the a values were calculated and plotted for the same 3 batches. The slopes and intercepts were averaged, and regression constants for equation 12 were obtained.

Figure 5 shows the difference in the average rate of growth in the face and band directions. The film growth rate in the face direction is higher than in the band direction. This may be because of the difference in exposed surface area during the coating operation, as well as the way that the tablets align themselves as they tumble and cascade in the pan. Preferred orientation of biconvex tablets during the coating process may play a very important role in film thickness variability within tablets.

It has been reported in the pharmaceutical literature that the estimation of the volume of dry film applied to the surface of tablets can be calculated from the proportions of the various components in the formulation (eg, polymers, plasticizers, pigments, etc.) and their respective densities.[27] An overestimation in film thickness can result from ignoring the density of the coating components. The densities of

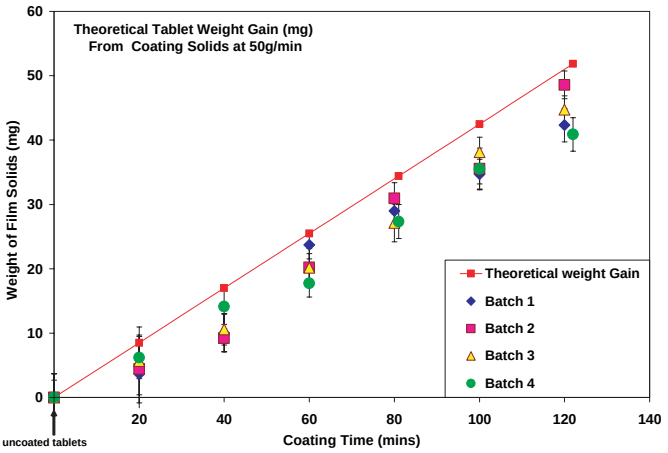

Figure 8. Theoretical tablet weight gain (from coating solids at 50 g/min and load size of 7 kg) and experimental tablet weight gain for 4 replicate batches. Error bars indicate weight variability for 100 tablets collected at each time point.

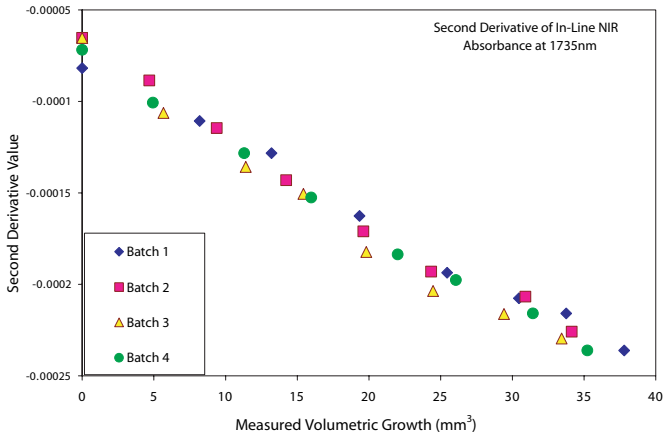

Figure 10. Calculated second-derivative values (using a moving average with 25-nm spacing) of in-line NIR absorbances at 1,735 nm. The R^2 values were ~0.99 for the 4 replicate batches.

the two primary coating excipients used were obtained from Rowe.[28] The theoretical density of the film was estimated to be 1.25 g/mL from the proportions of the two excipients and their respective densities. A comparison of the estimated theoretical weight gain (based on load size and the coating solids pump rate) and the experimental weight gain for the 3 replicate batches can be seen in Figure 8.

Total volumetric growth was calculated for 3 batches of experimental tablet, measurements and total volumetric growth was then predicted for a fourth replicate batch using equation 14. The growth model was developed using constants derived from the first 3 batches, and its ability to predict a fourth replicate batch is demonstrated in Figure 9.

The model and the methods proposed in this article can be of use in estimating the film coating density from tablet weight gain data and tablet volumetric growth. Based on the true densities and the proportions of the film components, the theoretical density was calculated to be ≈ 1.25 g/cm. Figure 9 shows how the estimated volume data obtained from weight gain measurements and the theoretical density of the coating solids correlates with measured volumetric growth for the fourth batch using equation 10. Also shown is the predicted volumetric growth based on the constants derived from the first 3 batches and using equation 14. Any deviation between the estimated volumetric growth from weight gain and the measured volumetric growth is because of an overestimation or underestimation of the actual film density. These data demonstrates that if the volumetric growth rate and the experimental weight gain data are known, then the film density may be closely estimated.

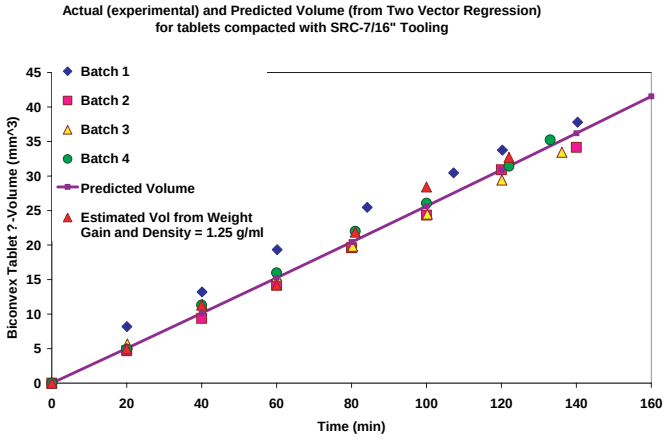

Figure 9. Measured (from off-line dimensional measurements), estimated (from weight gain and theoretical density = 1.25 g/mL), and predicted (from 2-vector model, equation 14) changes in volume during film coating of biconvex tablets compacted with SRC-7/16-in tooling.

Tablet face and band film thickness can be deduced from volumetric growth data by solving for the tablet band and face terms in equation 14 at any given time interval. The correlation between volumetric growth measured from off-line measurements of 3 replicate batches and the second derivative value of the NIR absorbance signal at 1,735 nm is shown in Figure 10. This shows that film thickness can be accurately determined from univariate changes observed in the NIR spectral data. It also shows that the NIR signal obtained can be calibrated to 2 different tablet film thicknesses (face and band) for each coating time interval. In particular, this enables the end point to be determined with high precision.

Because the correlation is based on the NIR signal for tablets to which coating has been applied, the calibration is not very accurate for the NIR signal collected before the start of coating. This was evident during the first 15 minutes of the experiment where the predicted coating thickness was negative. The predicted film coating thickness also

becomes less accurate (but still acceptable) during the drying stage of the coating process (final 30 minutes). This is probably complicated by the loss of moisture from the tablet bed, whereas the change in coating thickness is not very large. The NIR signal overestimates the change in film coat thickness, whereas the moisture content changes significantly. This problem could be addressed by obtaining a separate calibration for the drying stage or by performing a different type of analysis at this stage of the process, such as multivariate.

In summary, the steps involved in implementing a 2-vector film growth model for in-line monitoring of coating of biconvex tablets are: (1) performing 2 or 3 replicate film coating experiments, depending on the formulation used, while monitoring with in-line NIR sensor measurements; (2) obtaining tablet face thickness measurements from representative samples at different time intervals; (3) obtaining tablet side diameter measurements from representative samples at different time intervals; (4) estimating film growth rate in the face and band directions from these measurements to obtain equations 11 and 12, respectively; (5) estimating the tablet volume at any given time interval by substituting equations 11 and 12 into equation 4 to obtain equations 13, or using equation 10 to get equation 14; (6) acquiring tablet weight gain measurements for all of the measured samples; (7) correlating volumetric growth to weight gain and estimating a more accurate film density; (8) obtaining NIR spectral data for all of the components in the tablet cores and all of the components of the film formulation; (9) determining NIR band assignments and defining the appropriate regions to be used for univariate analysis; (10) using in-line NIR spectral data from each coating experiment and corresponding to each sample time interval (univariate analysis may be performed to trace the increasing or diminishing peaks); if necessary, averages of spectra or preprocessing the data, such as a second derivative of spectra, may be used to aid in performing a more accurate univariate analysis fit; (11) correlating the change in the NIR signal with the volumetric growth rate from step 5 to obtain a new film growth calibration curve; and (12) using the calibration curve to predict film growth in the tablet face and band regions at any given time interval and to estimate an accurate film density from a new batch based solely on in-line sensor measurements.

CONCLUSION

A method has been described that enables real-time monitoring and end point determination of tablet film coating during a pan coating operation. NIR spectral data are collected using a NIR diffuse reflectance instrument, which is calibrated against film coat thickness measurements made by direct off-line methods. Univariate analysis of in-line NIR absorbance measurements follows the same trends as observed using traditional tracking techniques, such as tablet weight gain and tablet dimension changes.

An empirical volumetric growth model has been developed for biconvex tablets to account for tablet film growth in 2 orthonormal directions (face and band). The use of tablet volume change during film coating accounts for the mass balance obtained from weight gain measurement data. The density of the film coat itself may be more accurately determined by comparing weight gain data with volumetric growth data.

The changes observed in volumetric growth from off-line measurements throughout a coating experiment correlate well with the change in the second derivative of the NIR absorbance signal at 1,735 nm. Having knowledge of the 2 vector regression constants for a specific coating system allows the film thickness to be estimated in both the face and band of a biconvex tablet. The end point of a coating operation can be accurately determined from in-line NIR measurements.

A prerequisite for this method of in-line monitoring is that a sufficiently fast sampling rate is needed for the NIR measurements and that the fiber optic probe or sensor has been optimized for this purpose. In-line analysis may be additionally developed to provide information on the extent of coating variability within individual film-coated tablets in a pan coating operation. It can also provide information necessary to measure the mechanisms of the coating process and also to measure process performance.

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