Monitoring the Film Coating Unit Operation and Predicting Drug Dissolution Using Terahertz Pulsed Imaging

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ABSTRACT: Understanding the coating unit operation is imperative to improve product quality and reduce output risks for coated solid dosage forms. Three batches of sustained-release tablets coated with the same process parameters (pan speed, spray rate, etc.) were subjected to terahertz pulsed imaging (TPI) analysis followed by dissolution testing. Mean dissolution times (MDT) from conventional dissolution testing were correlated with terahertz waveforms, which yielded a multivariate, partial least squares (PLS) model with an $R^2$ of 0.92 for the calibration set and 0.91 for the validation set. This two-component, PLS model was built from batch I that was coated in the same environmental conditions (air temperature, humidity, etc.) to that of batch II but at different environmental conditions from batch III. The MDTs of batch II was predicted in a nondestructive manner with the developed PLS model and the accuracy of the predicted values were subsequently validated with conventional dissolution testing and found to be in good agreement. The terahertz PLS model was also shown to be sensitive to changes in the coating conditions, successfully identifying the larger coating variability in batch III. In this study, we demonstrated that TPI in conjunction with PLS analysis could be employed to assist with film coating process understanding and provide predictions on drug dissolution.

INTRODUCTION

Film coating is generally carried out as the penultimate step to packaging, in the manufacturing processes for tablets. Therefore, it is axiomatic that the quality of the film coating is...
pertinent to the aesthetic and performance properties of the final product.\(^1,2\) Fast and easy measurements like tablet film coating weight-gain and determination of the amount of coating polymer applied are process signatures most commonly monitored to control the progress of the film coating unit operation and the film coating quality of the batch. However, neither tablet film coating weight-gain, nor the amount of coating polymer applied could afford information on the film coating uniformity, thickness and density; thus they are often inadequate to accurately reflect the progress of the film coating process and predict the in vitro dissolution performance of the final product.\(^3-6\)

The film coating unit operation has been closely examined using spectroscopic techniques like near-infrared (NIR), X-ray photoelectron (XPS) and Raman spectroscopy to gain a better understanding of the processes in order to achieve a built-in product quality or to improve the product design space.\(^7,8\) Coupled with multivariate analyses, both Raman and NIR spectroscopy demonstrated their capabilities in investigating the film coating unit operation in a qualitative and quantitative manner.\(^3,8-13\) Moreover, NIR in particular has been applied to predict drug dissolution. NIR spectra of uncoated carbamazepine tablets were used to predict the dissolution rate using principle component regression (PCR).\(^14\) Similarly a series of statistical models were built, including using partial least squares (PLS) analysis to investigate correlation of the dissolution profiles at five time points (15, 30, 60, 90 and 120 min) with the NIR spectra of uncoated theophylline tablets compressed at different forces.\(^15\) PLS models were also developed from NIR spectra to predict dissolution of uncoated clonazepam tablets at seven time points in three different media.\(^16\) Furthermore, both transmittance and diffused reflectance NIR spectra of uncoated indomethacin tablets were used to construct PCR models to study the effect of varying compression forces on dissolution, in particular correlations to the time required at 75% dissolution and mean dissolution time (MDT).\(^17\) A PCR model was also built using NIR spectra of uncoated theophylline tablets and tablets coated with 2% and 3% ethyelcellulose to predict the dissolution time at 50% drug release.\(^16\) Recently, Felton and coworkers\(^19\) in a study using XPS in concert with PCA have demonstrated that images of the film–tablet interface may be obtained to study the relationship between atomisation air pressure and the thickness of the film–tablet interface. By changing the atomisation air pressure during the coating process, Felton and coworkers\(^19\) were able to establish that higher atomisation air pressure resulted in thinner film–tablet interface, thus highlighting the role of coating process parameters in the physical changes in the tablet–film interface.

Imaging of pharmaceutical solid dosage forms with terahertz radiation (2–120 cm\(^{-1}\)) has evolved from a single point (single pixel) measurement capability to fully automated imaging, covering the entire area or selected regions of the sample surface (thousands of pixels depending on the size of the sample).\(^20,21\) Whilst the fast single point measurement (50 ms) is geared towards on-line applications, the off-line whole surface scan (45 min on a biconvex tablet with an 8 mm diameter and 3 mm height, at a step-size of 200 μm) has played an important role in gaining an insight into the coating processes. This can be attributed to the penetration depth of terahertz radiation of up to 5 mm into the sample, which renders non-destructive construction of virtual cross-sections and three-dimensional modelling of the sample structure possible. These are important tools in defect diagnostics (even when the defects are buried below the surface of the coating) and resolving multiple layers of a complex film coating.\(^22,23\)

Details of the technical set-up and the imaging process have been reported previously.\(^24,25\) In short, photoconductive semiconductor antennas are used to generate and receive terahertz radiation (which resides in the far-infrared region of the electromagnetic spectrum). The current set-up is time-gated by the arrival of the femtosecond laser beams, where the pump beam excites the emitter to generate pulses of terahertz radiation and the probe beam illuminates the receiver. Most pharmaceutical excipients are either transparent or semitransparent in the far-infrared region. Thus pulses of terahertz radiation can penetrate most coating structures and internal physico-chemical changes are generally visible as echoes in the time domain waveform. This time domain waveform can then be exploited to generate information on film coating thickness, surface roughness and variations in film coating density.\(^5\) Terahertz pulsed imaging (TPI) has been employed to investigate the film coating quality of commercial products\(^21\) analysing batch variability in film coating thickness and detecting coating defects,\(^22\) exploring the reason behind a film coating scale-up failure\(^4\) and assessing the
testing. The tablet imaging process has been previously described in detail.\textsuperscript{22} Briefly, a 670 nm laser was used to build the topological model of the tablet. Once the sample had been scanned in front of the 670 nm laser gauge, the robotic arm presented the sample to the terahertz gauge for terahertz mapping. The tablet central band was mapped out in point-to-point mode with 200 μm steps. The tablet central band was chosen as it has previously been shown to be the weakest area of the film coat and is dissolution rate determining.\textsuperscript{2,26}

For this study, an average terahertz time domain waveform (corresponding to an optical delay length of −1 to 1 mm) over 1,200 pixels around the central band was extracted from each tablet for PLS analysis. The entire terahertz waveform (from −1 to 1 mm) was employed in the analysis. The optical delay in the time-domain was converted from seconds into millimetres to allow for quick coating thickness interpretations.

**Dissolution Studies**

Dissolution analysis was performed conforming to the USP guidelines for sustained-release dosage forms. A paddle dissolution apparatus (AT 7smart On-line, Sotax, Allschwil, Switzerland) was used with a paddle rotational speed of 100 rpm. The dissolution medium was 900 mL of water in each beaker and the temperature was kept constant at 37°C. A UV spectrometer (Lambda 2 UV/Vis, Perkin-Elmer GmbH, Düsseldorf, Germany) was employed to determine the drug concentration inline. Automatic sampling at 1 min intervals was carried out through the entire dissolution process (25 h). The UV detection wavelength was set at 272 nm—the maximum absorption of diprophyllin in an aqueous solution. The MDT was derived from the dissolution profiles as the model independent dissolution parameter and included in the PLS analysis. Differing from other model independent dissolution parameters like \( t_{20\%}, t_{50\%} \) and \( t_{90\%} \), MDT takes the shape of the dissolution curve into account and therefore is more robust in reflecting the true dissolution performance of sustained-release tablets.\textsuperscript{27} The MDT was calculated from the following equation:\textsuperscript{28}

\[
\text{MDT} = \frac{\int_{0}^{\infty} t W_d(t) dt}{\int_{0}^{\infty} W_d(t) dt}
\]
where, $W_d(t)$ is the cumulative amount of drug dissolved and $t$ the time interval.

**PLS Analysis of Terahertz Waveforms**

Terahertz waveforms contain film coating quality information including film coating thickness, variations in film coating density, surface roughness and film coating uniformity at the film/core interface. Traditionally (Fig. 1) this information is extracted from parts of the terahertz waveform; by determining the distance between the surface reflection and interface reflection for coating thickness and other terahertz parameters like terahertz electric field peak strength (TEFPS) and terahertz interface index (TII) to investigate surface roughness and variations in coating density.

We have demonstrated the importance of these terahertz parameters to MDT through univariate analysis. Here, for the first time, we explore multivariate analysis by employing PLS regression, where the entire waveform was taken into account and the regression algorithm cross-correlates the $X$ matrix (terahertz waveforms) and the $y$-variable (MDT). This cross-correlation between the $X$ matrix and the $y$-variable ensures any variances from the terahertz waveforms ($X$ matrix) described in the PLS model are related to the changes in the MDT. Further details of the mathematical algorithms are available in the literature.

**Model Development**

From batch I, a minimum of five tablets from each sampling interval (at 1.7, 3.7, 5.2, 7.0, 8.7, 10.5, 12.2, 14.0, 15.7, 17.5 mg/cm$^2$ amounts of polymer applied) and from the final cured tablets (finished product) were included in the $X$ matrix. This PLS model was then implemented to predict the MDTs of the finished product from other lab-scale coated batches.

In this study, the terahertz waveform from the sample depicts meaningful information on film coating surface roughness and variations in coating density. All terahertz waveforms were preprocessing with signal deconvolution. This signal deconvolution deals with the baseline shifts and any instrumental dependency so that any nonspecific noise is removed. A flow diagram of the deconvolution process is presented in Figure 2.

Full cross-validation was carried out on the calibration set. The quality of the model was assessed with the following parameters: $R^2_{cal}$ (correlation of determination on the calibration set), $R^2_{val}$ (correlation of determination on the validation set), root mean square error of calibration (RMSEC) and root mean square error of cross validation (RMSECV). $R^2_{cal}$ shows how well the terahertz waveforms and MDT are correlated in subsequent dissolution testing on the same tablets (this was possible as TPI is a nondestructive technique). PLS algorithm directly uses the $y$-variable to decompose the $X$ matrix, deducing the loading-weights matrix $W$. This $W$ matrix is then used as inputs for calculating the $X$ space, $T$ scores matrix. Thus the PLS regression model achieves $X$ matrix and $y$-variable interdependently by maximising the $(t,y)$ covariance to reach the optimum number of PLS components (PCs) that describe terahertz waveforms in relation to the respective MDT (and vice versa) adequately.

Further details of the mathematical algorithms are available in the literature.

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**Figure 1.** A 3D terahertz tablet scan of a round, biconvex tablet. The scales in the $x$, $y$ and $z$ directions are in mm. The colour scale bar depicts layer thickness and the unit is in $\mu$m.
the calibration model, while $R^2_{\text{val}}$ indicates the predictive ability of the PLS model. Generally, a model is of a high quality and has robust predictive ability when; $R^2_{\text{cal}}$ and $R^2_{\text{val}}$ are high (close to 1), RMSEC and RMSECV are low, the correlation coefficients ($R^2_{\text{cal}}$ and $R^2_{\text{val}}$) are similar to each other and RMSEC is of similar magnitude as that of RMSECV.

RESULTS AND DISCUSSION

PLS Model—Evaluation of the Scaling

The data for the PLS analyses are presented in Table 1. These data show that scaling the waveform with either UV or MC methods has little effect on the model. UV scaling is generally recognised as the most objective scaling approach to give all variables relatively similar footing in the subsequent multivariate analysis, especially when variables are expressed in different units. UV scaling ensures that each variable in the X matrix has equal variance by attaining the standard deviation ($S_k$) for each column (variable) for the calculation of the scaling weight ($1/S_k$), which is then multiplied with each column of the X matrix. However this scaling step was not advantageous in this study. All the variables in the terahertz waveforms were of the same unit (in terahertz signal/a.u.) and the column ‘spread’ in each variable of the terahertz waveforms in fact represented the ‘real spread’ of the coating quality within the batch. The deconvoluted terahertz waveforms are extremely sensitive to any physicochemical changes in the film coating. Consequently, slight changes encoded in the terahertz waveform usually express coating quality related information.

Additionally, all samples were randomly selected at each sampling interval during the coating process and from the finished cured product. This assured the sample set included tablet coatings with defects that may subsequently result in abnormal dissolution profiles for a fair representation of the quality of the batch. It was thus important to keep the X-column (variable) ‘spread’ in order to build not only a good quality model but also a working model that was robust enough to predict the subsequent dissolution from products of the same batch and reflect the dissolution behaviour of products from other batches accurately.

Both the unscaled and the MC scaled models expressed a $R^2_{\text{cal}}$ of 0.92 and 0.91 for $R^2_{\text{val}}$. The calibration error/RMSEC was 0.31 h (MDT range = 3.21–5.61 h) and the prediction error/RMSECV was 0.34 h (Fig. 3). The calibration and validation correlation of determination values were similar, with RMSEC and RMSECV both lying within 10% of each other, indicating the model generated is of good quality. In comparison with a previous NIR dissolution prediction study using PLS models, our PLS models showed much higher similarity between the calibration and validation correlation coefficients. Our best fit values agreed with the optimal values in Freitas et al., with a much more extensive coverage of

Table 1. Effect of Different Scaling Methods for Terahertz Waveforms on the Quality of the Subsequent PLS Models

<table>
<thead>
<tr>
<th>Pre-Processing Method</th>
<th>Scaling</th>
<th>PLS Factors</th>
<th>$R^2_{\text{cal}}$</th>
<th>$R^2_{\text{val}}$</th>
<th>RMSEC (h)</th>
<th>RMSEP (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deconvolution</td>
<td>None</td>
<td>2</td>
<td>0.92</td>
<td>0.91</td>
<td>0.31</td>
<td>0.34</td>
</tr>
<tr>
<td></td>
<td>UV</td>
<td>2</td>
<td>0.94</td>
<td>0.92</td>
<td>0.27</td>
<td>0.30</td>
</tr>
<tr>
<td></td>
<td>MC</td>
<td>2</td>
<td>0.92</td>
<td>0.91</td>
<td>0.31</td>
<td>0.34</td>
</tr>
</tbody>
</table>
the dissolution profile (using MDT as the y-variable instead of a single time point in the dissolution profile). Since MC scaling added no additional benefit in improving the model quality, the unscaled model was used to further understand the coating process and prediction of the MDT data of two other lab-scale batches.

**PLS Assisted Coating Process Understanding**

The PLS dissolution prediction model was built with two PCs. Two PCs were chosen so that the model maximised the relationship between terahertz waveforms and MDT values without over fitting. The first component (PC1) explained 69% of the information in the terahertz waveforms and 88% of the MDT data. In addition, the second component (PC2) depicted 8% of the terahertz information and 4% the dissolution information. The X loading weights indicate the regions of the terahertz waveform that have contributed towards each PC.

PC1 mainly illustrated the changes in the TEFPS as the coating process progressed (Fig. 4). TEFPS is the ratio of the amplitude of the sample surface reflection over the amplitude of the surface reflection from a reference mirror. This was well described by the two positive and one negative peaks in the PC1 loadings, characterising the main changes in the surface reflection of the terahertz waveforms as the coating process progressed. TEFPS describes variations in film coating density and the degree of surface roughness which are both important factors governing the dissolution behaviour. The scores plot showed that PC1 (TEFPS) alone can trace the coating progress reasonably well—spreading from tablets coated at the lowest polymer level (1.7 mg/cm$^2$) from the left moving towards tablets coated with the highest polymer level (17.5 mg/cm$^2$) on the right (Fig. 5). This distribution in general, followed the changes in film coating refractive index as a result of the film formation and effectively trailed the changes in the film coating density during the coating process. Moreover, the distribution characterised by PC1...
in the scores plot did not show a consistent growth pattern, indicating the extensive film coating variability within the batch and the presence of film coating surface roughness.

PC2 primarily differentiated the 3.7 and 5.2 mg/cm² cluster from the rest of the tablets coated at other polymer levels (Fig. 5). As previously illustrated, the time delay position of the interface reflection is important for the calculation of coating thickness. However, for tablets coated at 1.7, 3.7 and 5.2 mg/cm², the coating/core interface reflection was not clearly resolved as the coating thickness was under 38 μm (the current TPI axial resolution). Instead, exhibiting ‘flattening’ of the postsurface reflection dip (at 0.04 mm time delay) for tablets coated at 1.7 mg/cm² and the ‘emergence’ of partially formed interface peaks for tablets coated at 3.7 and 5.2 mg/cm² (Fig. 6a). For clarity, this ‘emergence’ of the interface reflection peak is also depicted in the schematic diagram in Figure 7. This schematic diagram illustrates the convolution of the surface reflection and the interface reflection at very thin coating thicknesses below the resolution limit of the TPI system. Waveforms for tablets coated at 1.7 and 3.7 mg/cm² correspond to waveforms in Figure 7a and b respectively. Moreover, waveforms for tablets coated at 5.2 mg/cm² share resemblance to waveforms in Figure 7c.

The negative peak at 0.04 mm and the positive peak at 0.11 mm time delay in the PC2 loading-weights plot detected the difference between the partially formed and the complete interface reflection in the waveforms (Fig. 4). Hence PC2 was able to harvest information on the formation of the film coating both below and above the TPI axial resolution and separated out the 3.7 and 5.2 mg/cm² cluster from tablets coated at 7.0 mg/cm² and upwards (the coating thickness was above 38 μm for tablets coated at 7.0 mg/cm²). The fact that PC2 could characterise the formation of film coating below the current axial resolution, extended the breadth of the design space for monitoring the film coating unit operation.

It is important to note nevertheless, that the film coating formation on tablets coated at 1.7 mg/cm² was not characterised by PC2, but PC1 alone. Although PC1 mainly illustrated the changes in the TEFPS, it also partly described the shifts in the time delay position of the interface reflections as the coating process progressed (Fig. 4). Hence PC1 also depicted some information on the growth of coating thickness. Similarly, in addition to representing the coating thickness information on
the lower polymer levels, PC2 also represented some information on TEFPS. As aforementioned, TEFPS is characterised by the surface reflection at 0 mm time delay. At this position, PC2 was above 0 loading weights as shown in Figure 4. Therefore the effect of TEFPS (describes variations in film coating density and surface roughness) and coating thickness in the two PCs are not mutually exclusive and both are related to the changes observed in MDT. This finding with the PLS analysis is consistent with our previous univariate analysis study, where it was indicated that coating thickness may not have been the sole factor that attributed to the changes in the MDT; thus both terahertz parameters (TEFPS and coating thickness) should be taken into account as important process signatures when considering the design space for analysing sustained-release tablets.

Prediction of MDT

Ten additional samples from the finished product (cured tablets coated at the final polymer level of 17.5 mg/cm²) were selected from batch I to further validate the PLS model. These tablets were subjected to terahertz imaging to obtain the necessary average waveforms from the tablet central bands to implement into the PLS model for the prediction of the subsequent MDT values. To validate the predicted MDT values, conventional dissolution tests were carried out on the same 10 tablets post terahertz imaging. The average dissolution profiles from conventional dissolution testing for batches I, II and III are depicted in Figure 8. The average MDT predicted and the reference results (obtained from dissolution testing) are shown in Table 2, excluding data from one tablet that was lost to a mechanical problem during dissolution testing. A two-tailed, paired t-test was performed and a p-value of 0.07 was calculated. The p-value was above the null hypothesis α = 0.05, indicating no statistically significant difference between the predicted and reference means in MDT. Although this demonstrated the desirable capability of predicting the drug dissolution with the terahertz PLS model, it is interesting to note that the average predicted values were, on the whole, lower than that of the reference average MDT values generated from dissolution testing (Tab. 2). This may be due to sample selection and preparation for the PLS model. The PLS model was built largely on uncured tablets from batch I whilst the additional 10 samples selected for validation were cured tablets from the finished product. Furthermore, tablets from batches II and III for dissolution prediction were also cured.
Using samples from batch I as an example, the coating thickness was lower and the coating density was higher for the cured tablets when compared to the uncured tablets coated at the same polymer level (17.5 mg/cm²). The coating thickness was derived from the distance between the surface reflection and the interface reflection between the film coating and the core. It was visible that the interface reflection of the cured tablets shifted to the left of that of the uncured tablets with the same amount of polymer applied (Fig. 6b). Using the following equation $2d_{coat} = \Delta t c/\Delta n$ ($\Delta t$ is the time delay between the terahertz reflections, $c$ is the speed of light and $n$ is the refractive index of the coating matrix), the coating thickness ($d_{coat}$) of each waveform was determined for both cured and uncured groups. Cured tablets on average were around 7 μm thinner than that of the uncured tablets. With a similar surface roughness observed around the central band of all tablet examined, a difference of 0.3% in TEFPS (expressed in %) on the cured (16.9%) and uncured (16.6%) tablets was observed. This inferred the film coating density for the cured tablets was higher, which concurred with the lower film coating thickness observed. Higher film coating density after curing would theoretically lead to slower water permeability into the film and a longer MDT should be expected. The average MDT for the cured tablets (5.33 h) was slightly longer (0.11 h) than the uncured tablets (5.22 h) coated at 17.5 mg/cm². If the PLS model was built solely from cured tablets at each 10% increments of polymer interval, one would expect the predicted MDT to be longer and thus closer to the reference values derived from the finished product (cured tablets). Further research is currently in progress to investigate the effect of curing on the subsequent dissolution more in-depth.

The same relationship between predicted and reference MDT values was also observed with batches II and III, where the majority of the PLS predicted MDT values were slightly lower than those of the reference values. A two-tailed, paired t-test was also carried out, which yielded a p-value of 0.07 (null hypothesis $\alpha = 0.05$) for batch II. This showed good agreement between the terahertz predicted and reference MDT values, confirming that not only the terahertz PLS model was capable of predicting the MDT values of tablets from the same batch, but also robust enough to predict the MDT values of tablets of other batches coated with the same process parameters and under similar environmental conditions. Batch III was coated with the same process parameters as the other two batches, but at a lower relative humidity (RH). During the film coating process, the RH in the coating drum for batch III was much lower in comparison to the other two batches and it eventually dropped below 20% RH at the end of the coating process. The RH for batches I and II was kept above 25% RH throughout the coating process. The inlet and outlet air temperatures were also monitored during the coating process. Whilst both of these parameters were similar between the three batches, batch III was coated on a hot summer day where the RH in the ambient air was already lower than the other 2 days when batches I and II were coated. The PLS model successfully detected this larger coating variability in batch III, where the t-test p-value was 0.01 (null hypothesis $\alpha = 0.05$). This result demonstrates the sensitivity of the terahertz PLS model to subtle physicochemical changes in the film coating as the consequence not only of changes in the coating process parameters but also the environmental conditions under which the batch was coated.

Table 2. Average Predicted and Reference MDT Values. Predicted MDT Values Were Those Derived Using the PLS Model for All Three Batches and Reference Values Were Those Obtained from Conventional Dissolution Testing Subsequent to Terahertz Imaging

<table>
<thead>
<tr>
<th>Batch</th>
<th>Predicted MDT (h)</th>
<th>Reference MDT (h)</th>
</tr>
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<tbody>
<tr>
<td>I (n = 9)</td>
<td>5.25 ± 0.24</td>
<td>5.43 ± 0.17</td>
</tr>
<tr>
<td></td>
<td>t-test p-value = 0.07 ($\alpha = 0.05$)</td>
<td></td>
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<tr>
<td>II (n = 10)</td>
<td>5.35 ± 0.13</td>
<td>5.56 ± 0.19</td>
</tr>
<tr>
<td></td>
<td>t-test p-value = 0.07 ($\alpha = 0.05$)</td>
<td></td>
</tr>
<tr>
<td>III (n = 10)</td>
<td>5.14 ± 0.22</td>
<td>5.42 ± 0.23</td>
</tr>
<tr>
<td></td>
<td>t-test p-value = 0.01 ($\alpha = 0.05$)</td>
<td></td>
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</table>

CONCLUSIONS

Multivariate analysis was employed in this study. By coupling the conventional dissolution parameter (MDT) to terahertz waveforms, the resultant terahertz PLS model provided insight into not only physicochemical changes in the film coating (as a consequence of changes in the
environmental conditions), but also predictions on the corresponding in vitro dissolution whilst the tablets were still intact. MDTs obtained from conventional dissolution testing were correlated to terahertz waveforms on tablets sampled from batch I. Using the terahertz PLS model, the MDT values for tablets from batch II was successfully predicted in a nondestructive manner. The PLS model was also sensitive to the increased coating variability in batch III, possibly as a result of environmental changes during the film coating process. The concept presented in this study potentially opens new avenues to achieving a greater understanding and better control of the coating unit operation.

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