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Research Article

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Prediction of Tablet Film-coating Thickness Using a Rotating Plate Coating System and NIR Spectroscopy

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Abstract. The purpose of this research was to create a calibration model based on near-infrared (NIR) spectroscopy data obtained during a small-scale coating process to predict in-line the coating layer thickness of tablets coated in a side-vented drum coater. The developed setup for the small-scale coating process consisted of a rotating plate with 20 tablets molds that pass a spraying unit, a heating unit, and an in-line NIR spectroscopy probe during one rotation. High-density polyethylene (HDPE) was compressed to flat-faced tablets, and these were coated with a sustained release coating suspension containing Kollicoat IR and Kollicoat SR 30D. The film thickness of these tablets was determined for each tablet individually with a digital micrometer. A calibration model of predicted film thickness *versus* real-film thickness using PLS regression was developed. This model was tested against in-line NIR data obtained from a coating drum process, in which biconvex HDPE tablets were film-coated with the same film-coating suspension. The model predicted a final coating thickness of 240 μm, while the measured average thickness (n = 100 tablets) was 210 μm. Taking into account the use of a different setup and differently shaped tablets, it was possible to predict the coating thickness with accuracy comparable to the one of the digital micrometer. Thus, the small-scale rotating plate system was found to be an efficient means of preparing calibration model for a tablet-coating drum process.

KEY WORDS: drum coater; film-coating thickness; NIR; PLS regression; rotating plate.

INTRODUCTION

Pharmaceutical solid dosage forms are coated to control drug release, protect active pharmaceutical ingredients (APIs) from degradation in the stomach and extend the shelf for moisture and oxygen sensitive APIs. Tablets may also be coated simply for aesthetic reasons and to mask unpleasant taste or smell.

Quality parameters of film coatings, such as coating layer thickness, uniformity, and reproducibility, are often determined via indirect measurements. For example, weight-gain calculations are used to determine the end point of coating processes and can also be used to predict coating mass variability during scale up (1). Such calculations, however, do not offer sufficient information about the coating integrity, which is a major concern in pharmaceutical production. Coating non-uniformity and defects may lead to coating failure with possible consequences including dose dumping. Therefore, in line with the process analytical technology initiative of the Food and Drug Administration (2), there is an interest in analyzing coatings by multi-technique approaches. Laser-induced breakdown spectroscopy (3) and optical microscopy (4) can be used to investigate coating layer thickness and uniformity. But these methods are destructive in this context, as they require the sample to be sliced or cut to determine the coating thickness. Scanning electron microscopy has been used at-line to assess surface roughness of intact tablets (5) and changes in surface morphology during dissolution (6). Atomic force microscopy may also be used offline to investigate coating surface morphology (5), but the sample may be damaged during measurement. Confocal laser scanning microscopy (7,8) is a non-invasive technique and can detect surface defects and defects at the film-core interface. Cross-linking and relaxation behavior of organic coatings during drying has been monitored using confocal Raman microscopy and micro-imaging nuclear magnetic resonance (NMR) (9). It has been shown in the aircraft industry (10) that ultrasound analysis can be used to determine the thickness of thin coatings (<50μm) and, therefore, has a potential for pharmaceutical-coating analysis.

Both near-infrared (NIR) spectroscopy (11) and Raman spectroscopy have been applied in-line to investigate the

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coating process of tablets in a coating pan. Information about coating variability (12,13) and coating thickness (13,14) was obtained using Raman spectroscopy.

Another novel technique to investigate coating quality parameter is terahertz-pulsed imaging (TPI). It has been used to create 3-D images of whole-tablet coatings (4) and has even been able to differentiate between different coating layers (15). The method is based on coherent time domain technology, and therefore, if the refractive index of the coating is known, a calibration model is not required to determine the coating thickness, as is needed when using NIR spectroscopy. TPI can be used to perform whole-surface scans and single point measurements, thus providing the potential for in-line coating thickness measurements.

The European Agency for Evaluation of Medicinal Products (16) has published a detailed guidance for the application of NIR spectroscopy, including principles of method development and validation for qualitative and quantitative analysis. One major restriction of NIR spectroscopy is the time intensive development of a process-specific calibration model if the same batch size and process is used for obtaining the model as for the real production. Therefore, innovative approaches are required to minimize the cost and time for developing robust calibration models, which are capable of appropriate quality control and reliable end-point determination.

Kirsch *et al.* (17–18) have monitored a film-coating process by at-line NIR with the aim of determining layer thickness, tablet hardness, and dissolution rate. For quantitative-coating analysis using in-line NIR spectroscopy, Andersson *et al.* (19) developed a robust and long-lasting calibration model by varying all process conditions after another within one calibration batch. Blanco *et al.* (20,21) have proposed a method to predict the quantity of an API and its polymorphic forms (22) within different production steps (blending, tablet compression, and coating) with a single partial least squares (PLS) or multivariate curve resolution–alternating least squares (23) calibration model. The authors constructed these models using a suitable set of laboratory-scale samples, which included every possible source of physical and chemical variation.

The aim of this study is to introduce a novel small-scale coating system as a time-saving method to prepare a robust and precise calibration model that can be used to predict the coating layer thickness of coatings prepared by a coating drum process.

MATERIALS AND METHODS

Tablet Composition and Compression

The tablets contained 99.9% high-density polyethylene (PE, Inducted, Volketwil, Switzerland; particle size, <10 μm) and 0.1% Aerosil® 200 (amorphous fumed silica; Degussa, Essen, Germany). High-density polyethylene (HDPE) was used in this project to deliberately minimize the chance of migration and interactions between core and coating. Another advantage of HDPE is that it is a strong absorber in the NIR region. This may enable the detection of a core signal even when a thicker coating layer is applied.

The composition was mixed with a Turbula® mixer (Bachofen AG Maschinenfabrik, Basel, Switzerland) for 15min and, afterwards, used to compress two kinds of tablets: flat-faced tablets for the small-scale rotating plate system and biconvex tablets for the coating drum process. Coating with the small-scale rotating plate system requires flat-faced tablets for an equal coating distribution due to the slow drying process, whereas the coating drum process requires biconvex tablets to prevent the tablets sticking together. In addition, flat-faced tablets have a larger sample area, which enables measurement of a single tablet with three scans, thus providing more reliable data for the calibration model. An instrumented single punch tablet machine (Korsch EK0, Erweka Apparatebau, Berlin, Germany) was used for powder compactions. A total of 130 flat-faced tablets and 1 kg (~5,800 tablets) of biconvex tablets with a punch diameter of 9mm were compressed. The tablets (m = 170 mg) were compressed to result in a crushing strength of 50 N.

In preliminary tests, the small-scale rotating plate system was able to monitor migration of water-soluble core material into the coating. For the tablet cores used in this project, migration should not occur, and interactions between core and coating should be limited, in order not to complicate the measurements further. Therefore, HDPE was used as the core material to reduce the risk of migration of core components into the film.

Preparation of Coating Suspension

The composition of the aqueous-based coating suspension was as follows: 50% Kollicoat SR30D® (BASF, Ludwigshafen, Germany) containing 30% polyvinyl acetate and 6% Kollicoat IR®, a polyvinyl alcohol–polyethylene glycol graft copolymer (BASF, Ludwigshafen, Germany), 0.3% glycerol monostearate (BDH Chemicals Ltd., VWR International, Poole, England), 0.075% Tween® 80 V Pharma (Uniqema, Everberg, Belgium), and 0.75% triethylcitrate (Fluka, Buchs, Switzerland). Demineralized water containing Tween® 80 V Pharma (polysorbate 80) was heated to 70°C, glycerol monostearate was added and mixed with a high shear mixer for 20 min. The Kollicoat IR® polymer was dissolved in demineralized water and stirred until it had formed a homogenous solution. This resulting polymer solution was combined with Kollicoat SR30D and the suspension containing polysorbate 80 and glycerol monostearate. Finally, triethylcitrate was added as a plasticizer. The suspension was stirred for 24h prior use.

Film Coating

Rotating plate

A schematic diagram of the novel small-scale rotating plate system is presented in Fig. 1. The small-scale rotating plate system was made of Teflon, containing molds that can accommodate tablets with a diameter of between 7 and 11mm. The rotation speed was constant and set to 1rpm. A spray unit with a pneumatic spraying nozzle was used to mimic the industrial coating process. A peristaltic pump (Watson, Marlow 505S, Watson-Marlow Bredel, Wilmington,

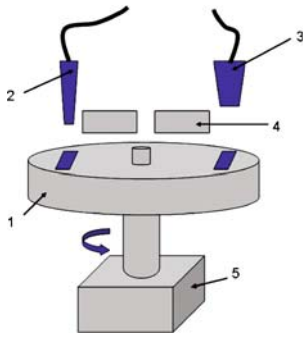

Fig. 1. Schematic setup of the rotating plate coating device: *1* rotating plate, *2* spraying nozzle, *3* near-infrared probe, *4* infrared dryer, *5* motor

MA, USA) was used to pump the coating suspension into the nozzle.

After spraying, the tablets passed under an infrared light heating unit (Sartorius thermo control, Sartorius AG, Göttingen, Germany) and then an in-line NIR spectrometer. Six experiments were performed with 5, 10, 12, 15, 20, and 25 rotations resulting in a coating thickness ranging from 25 to 400 μm. The individual coating processes took between 10 and 50 min. A total of 20 flat-faced tablets for each process were individually labeled, weighed, and their thickness measured at five locations (in the middle of the face and at four points close to the edge of the face) before and after the coating process by a digital micrometer with an error of approximately 10% (Sony digital micrometer U30-F, Sony Magnescale, Tokyo, Japan). Therefore, each NIR spectrum could be assigned to a tablet with a defined coating thickness.

Coating drum

The tablets were film coated using an instrumented laboratory-scale side-vented drum coater (Thai coater, model 15, Pharmaceuticals and Medical Supply Ltd Partnership, Bangkok, Thailand) connected to a digital peristaltic pump (Watson, Marlow 504Du, Watson-Marlow Bredel). Ruotsalainen *et al.* (24) have described the instrumentation and the setup used for the present coater in detail. Process parameters are presented in Table I. The negative air pressure was about 1–2 Pa due to a small open window for the NIR probe fibers.

Table I. Process Parameters Used During the Coating Drum Process

Process parameters	Values
Outlet air flow rate	20 l/s
Pan air temperature	40°C
Negative air pressure (pan)	5.0 Pa
Rotating speed of the pan	7.0 rpm
Temperature (coating liquid)	20°C
Pump speed (flow rate)	3 rpm
Spraying air pressure	300 kPa

Important parameters of the coating process were monitored and are presented in Fig. 2. The inlet air temperature was relatively high (80 ± 5°C) because of the temperature loss resulting from the opening for the NIR probe in the pan. The inlet air temperature is usually about 10°C higher than the temperature of the coating pan. Still, this should have little effect on the coating performance itself as long as the temperature in the coating pan is constant.

The coating batch comprised 1.0 kg tablet cores. Before and after coating, 100 tablets were weighed and their heights were measured in the center of the tablet and at two points close to the edges of the tablet. The biconvex shape resulted in less precise measurements of the edges than of the center of the tablet (error of approximately 10%). The heights were then averaged for each tablet. The final coating thickness was determined by averaging 100 coated tablets.

NIR spectroscopy

In-line measurements were performed with an NIR spectrometer (NIR-256L-2.2T2, Control Development Inc., South Bend, IN, USA) using a thermoelectrically cooled 256-array detector, a tungsten light source, and a fiber-optic reflectance probe, with Teflon serving as a reference (99% reflective Spectralon, Labsphere Inc., North Sutton, New Hampshire, USA). The spectra were recorded in-line within the range of 1,100–2,200 nm with a resolution of 8 nm. The integration time was set to 6 ms resulting in three scans of each tablet during one rotation for the flat-faced tablets. NIR spectra were recorded during the first three rotations, after the spraying was finished. Three of the NIR spectra of each tablet, obtained during drying, were used for the calibration model. NIR spectra were recorded in-line during the entire coating drum process.

Data Analysis

The spectral data obtained from the in-line NIR measurement was analyzed using PLS regression (PLS Toolbox

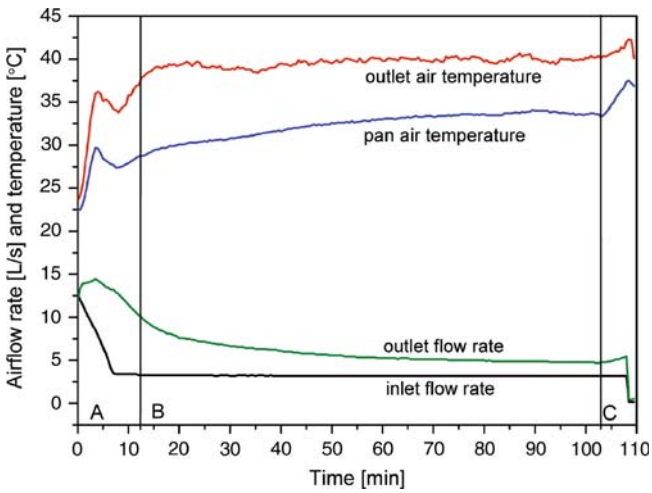

Fig. 2. Changes in temperature and flow rate during the film coating process, with **a** preheating, **b** coating, and **c** drying

4.1.1. Eigenvector Research, Wenatchee, WA, USA) in Matlab 7 (Mathworks, Natick, MA, USA). Two of the three NIR spectra taken of each tablet were selected randomly and used for the calibration set. The remaining third of the NIR spectra was used as a test set. The wavelength range of 1,160 to 1,780 nm was selected. Considering that a PLS model would be needed for processing data obtained by a different experimental setup, the following preprocessing was chosen: the X-block was smoothed, then normalized using standard normal variate (SNV) (25) correction and finally mean-centered (MC). Savitzky–Golay smoothing (26) was performed to remove the baseline offset. For the smoothing process, a filter width of 21 pixels and a second-order polynomial fitting was applied. SNV correction (Eq. 1) removes multiplicative effects, such as scaling and offset effects. Firstly, the average of all the spectral responses in the vector $(\overline{X}_i)$ from each spectrum of original values (X_{ij}) is subtracted, thus centering the spectra about zero. Secondly, each spectrum is divided by its standard deviation, where p is the number of variables (wavelengths) in the spectrum.

$$X_{ij,SNV} = (X_{ij} - \overline{X}_i) \Bigg/ \sqrt{\frac{\sum_{j=1}^{p} (X_{ij} - \overline{X}_i)^2}{p-1}} \quad (1)$$

The Y-block was autoscaled (first mean-centered, then scaled), resulting in variables that have the same mean and standard deviation. Venetian blinds cross-validation (14-way split) was applied to the calibration set. Finally, the PLS model was calculated using the simultaneous partial least squares algorithm (27). The final window width of 21 pixels for the smoothing process was chosen based on the root mean square error of cross-validation (RMSECV). The RMSECV is calculated using Eq. 2, where y_i is the reference value for each run, and $\overline{y_i}$ is the predicted value for each run using cross-validation. I is the number of samples in the calibration set.

$$RMSECV = \sqrt{\frac{\sum_{i-1}^{I} (y_i - \overline{y_i})}{I}} \quad (2)$$

RESULTS AND DISCUSSION

Coating Process

The tablets coated with the small-scale rotating plate system varied in coating thickness within each of the six experiments. The greatest relative variation occurred within the thinner coatings. In the batch with the thinnest coating, the thickness varied between 21.8 and 57.0 μm (62% variation), while for the batch with thickest coating, it varied between 352.6 and 404.2 μm (13% variation). Due to the ineffective nature of the drying process, the tablets dried slowly, resulting in the decomposition of a smooth coating. The tablets coated in the coating drum resulted in a rougher coating as seen in Fig. 3.

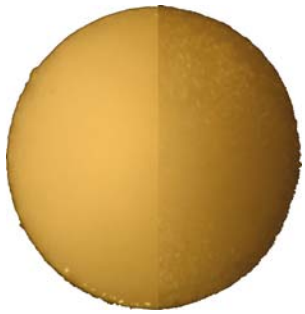

Fig. 3. Tablet coating: the *left side* shows half a tablet coated using the rotating plate (200 μm), and the *right side* shows half of a tablet coated with the coating drum (210 μm)

Multivariate Analysis

PLS regression model of the tablets coated using the rotating plate

Three latent variables (LVs) were chosen for the PLS regression model, as the RMSECVs of the third LV (29.0 μm) and the fourth LV (29.0 μm) were equal. The clustering tendency between several groups of different coating thickness can be seen in the plot of the first two LVs (Fig. 4).

The first LV (y-block variance, 82.13%) shows the greatest potential to separate the data points according to their actual coating thickness. Inspection of the reference spectra of the coated and uncoated tablet cores (Fig. 5a) together with the weights plot (Fig. 5b) reveals that the first LV merely describes general baseline changes.

This may be due to increased scattering during coating. The increasing tablet size and changing surface texture during coating increases absorbance between 1,450 and 1,700 nm (Fig. 5c). Simultaneously, the absorbance of ethylene (core component) between 1,100 and 1,240 nm and 1,700 to 1,750 nm (Table II; Fig. 5c) decreases due to the increasing layer thickness.

The Beer–Lambert law (Eq. 3) forms the basic principle of determining the coating layer thickness. As the coating layer thickens, the ratio of the transmitted light intensity (I_1) to the incident light intensity (I_0) decreases. Thus, the intensity changes in the baseline signal are important for determining the coating thickness. The Beer–Lambert law describes the absorbance (A) in relation to the absorption coefficient (c), the distance that the light travels through the material (d), and the concentration of the absorber (α).

$$A = \alpha dc = \log\left(\frac{I_0}{I}\right) \quad (3)$$

Although the second LV (y-block variance, 11.66%) represents the coating suspension best (Fig. 5a), it does not sort the samples according to their thickness. Nevertheless, it improves the model prediction. The chemical information and thus the signal do not change significantly once the coating suspension is applied. Obviously, the coating thickness determination is less dependent on this signal than the baseline change. The third LV (y-block variance, 0.59%)

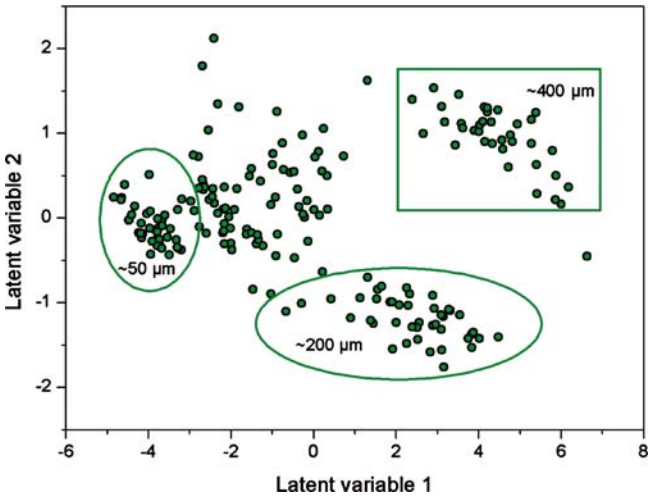

Fig. 4. Latent variable one plotted against latent variable two

mainly represents the tablet core signal (Table II) and, in a similar fashion to the second LV, has no power to predict the coating thickness on its own. Since the core signal decreases as the coating thickens, the third LV still improves the prediction of the model. The complexity of the model shows that a successful coating thickness determination of this system depends on many factors, such as scattering and chemical signals from both the coating and core. Outliers were identified by plotting the Q residuals against the Hotelling T^2 (Fig. 6a). The more thickly the tablets were coated, the higher the Hotelling T^2 values and the Q residuals tended to get. The influence plot revealed that the coating thickness was underpredicted when the thickness exceeded 300 µm (Fig. 6b).

The coating thickness was well predicted in samples with a Y-studentized residual close to zero, while the coating thickness was over- or underpredicted in samples with a strongly positive or negative Y-studentized residual, respectively. For example, the measured coating thickness of one tablet (marked in Fig. 6b with 330 µm) was 330 µm, but the model predicted 230 µm. For this coating suspension, the Beer–Lambert law started to fail at a coating thickness of more than 300 µm, as the coating became too thick to allow a sufficient signal from the tablet core.

In Fig. 7, the predicted coating thickness is plotted against the measured coating thickness for both the calibration and test sets. The root mean square error of prediction was 28.5 µm for the test set and almost identical to the RMSECV of 29.0 µm for the calibration set. The root mean square error of calibration was 28.2 µm.

Application of the PLS model to the drum coating process

When the in-line NIR spectra of the coating drum process were obtained, a problem occurred: some of the spectra contained information about the coating drum every time the mixing baffles passed the probe. Therefore, the model was only fitted to spectra without the coating drum signal. The predicted final coating thickness was 240 µm, while the Sony digital micrometer measured an average thickness of 210µm (Fig. 8). Considering the error of the digital micrometer of about 10%, both measurements (before and after coating) resulted in an error about 30 µm. Thus, the difference of 30 µm between the model prediction and the measured value was still within the error limits.

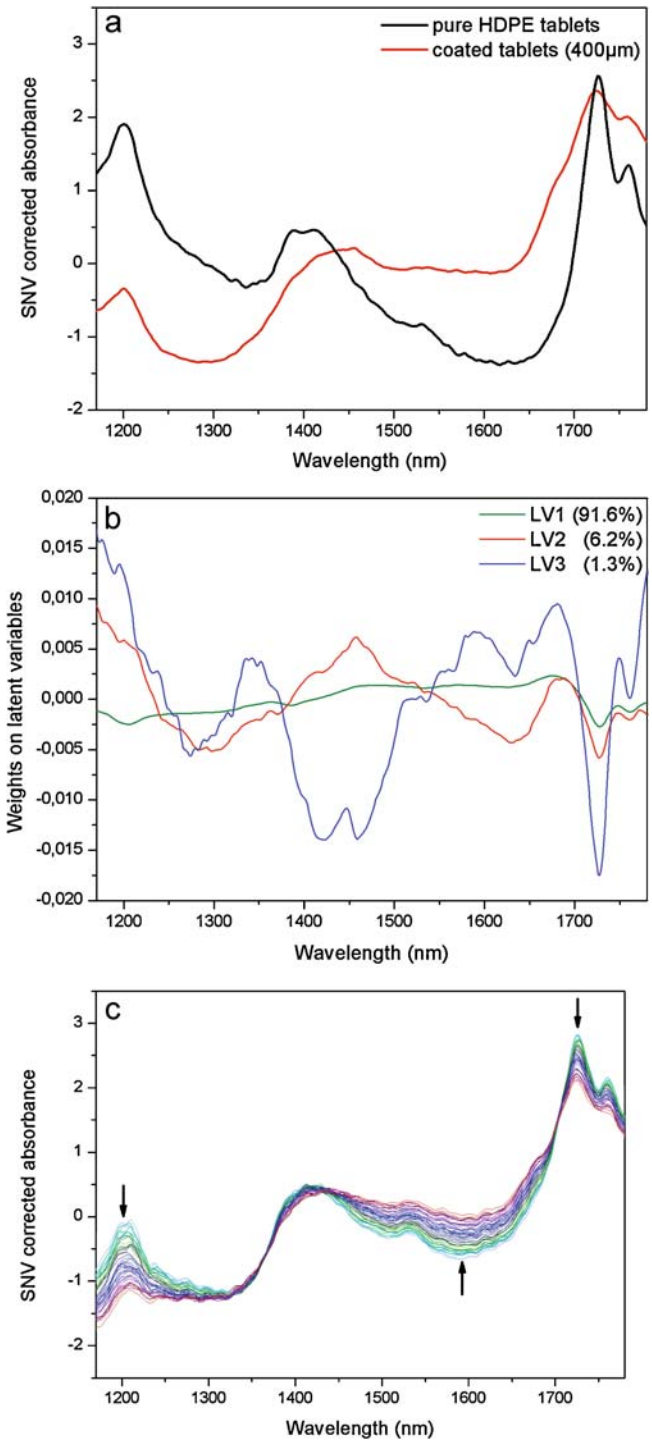

Fig. 5. Reference near-infrared spectra of the pure and coated tablet cores (**a**), weights plot for the first three latent variables (**b**), and data obtained during the entire coating drum process (*green* start; *red* end) (**c**)

Table II. Band Assignment of Polyethylene

	Wavelength (nm)	signal
Ethylene	1,100–1,240	C–H stretch second overtone
	1,400–1,500	C–H stretch first overtone of combination
	1,700–1,750	Aliphatic C–H stretch, first overtone

This higher value determined by the model over prediction may be a result of scattering differences due to differences in shape (flat-faced and biconvex) and movement of the tablets used for calibration and processing. While the tablets on the rotating plate only moved in the horizontal plane, those in the coating drum moved in all three dimensions. In addition, the tablets coated in the drum had a coarser surface due to a more efficient drying process (Fig. 3). Both led to more diffuse scattering of the NIR beam and a decrease in the detected signal intensity. A slightly higher coating thickness prediction was consequently expected. The lower drying efficiency and unequal application of the coating solution in the small-scale setup resulted in a slight overwetting of the tablets and thus in a smoother film. If this issue can be sufficiently addressed, the surface of the coating will be rougher, and this may result in a better prediction.

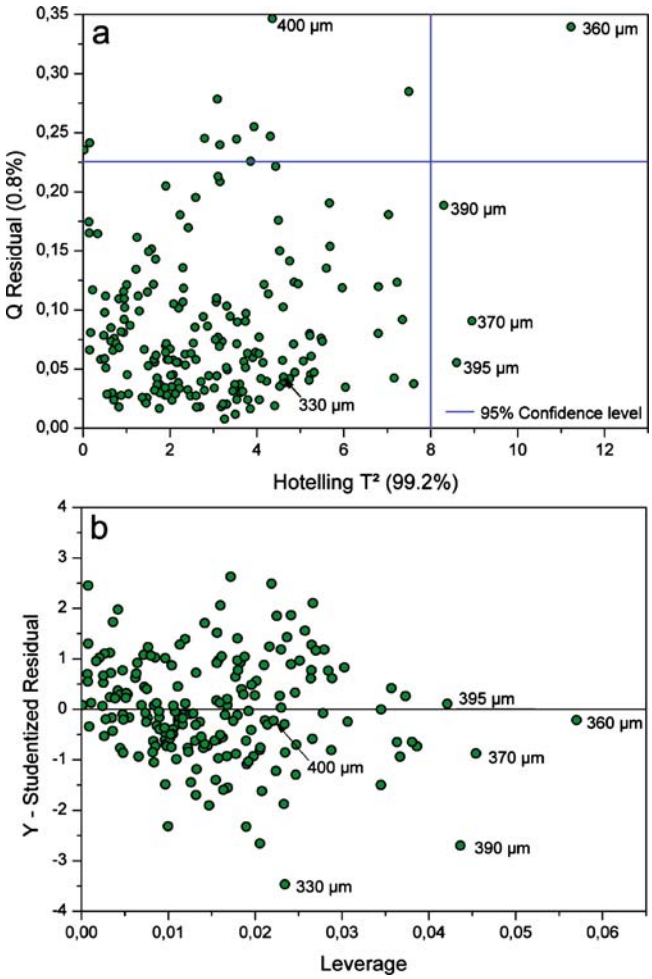

Fig. 6. Q residuals against Hotelling T^2 (**a**) with the outliers and influence plot (**b**) showing the correlation between the measured and predicted values

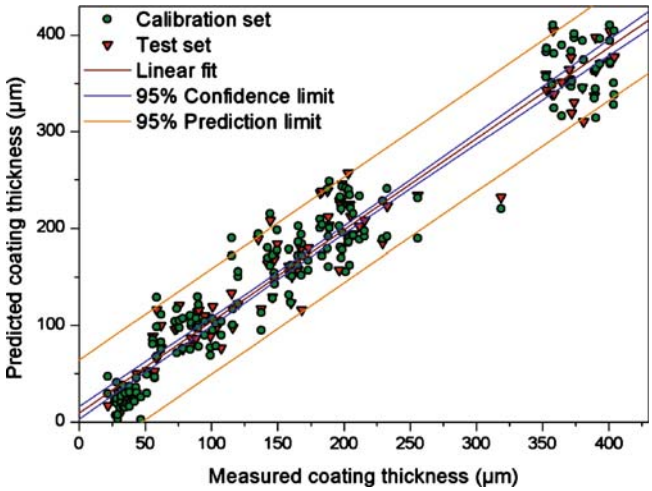

Fig. 7. Coating thickness prediction of the calibration and test sets (near-infrared data obtained during the rotating plate system)

To improve the coating thickness prediction using the small-scale rotating plate system, a better peristaltic pump is needed. The wave-like pumping of the coating liquid caused great variation in relative coating thickness, especially for the thin coatings. The drying efficiency of the setup could also be improved by increasing the temperature and applying a second drying unit in this setup. This may also allow biconvex tablets to be coated and improve the prediction capability and accuracy. In this case, optical microscopy should be used as a reference method, being more accurate than the digital micrometer, used in this study.

One major difference, which cannot be easily changed, is the lack of the pressure difference over the bed, which also influences the film formation process. The negative pressure in the coating drum is used to focus the sprayed coating solution onto the tablets and improves the drying efficiency. If a negative pressure were to be applied to the setup, a closed

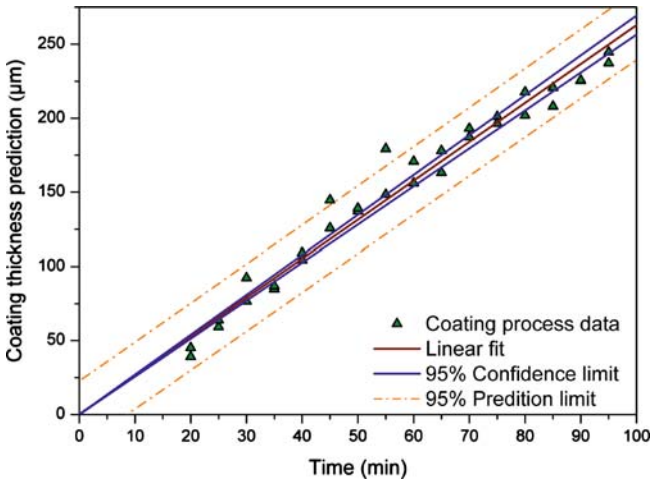

Fig. 8. Coating thickness predicted using in-line near infrared spectroscopy during coating in the coating drum

system would be required, which, in turn, would complicate the placement of probes used to monitor the process.

CONCLUSIONS

In this study, it was shown that a small-scale rotating plate system combined with NIR spectroscopic measurements is a fast and efficient approach to prepare a calibration model for in-line coating analysis. This model was successfully used to determine the coating thickness of tablets in a drum coating process. After the small-scale rotating plate system is further optimized, especially with regards to its drying efficiency, this setup may be useful during the early stage of formulation studies when the amount of drug is limited and formulations are being tested on a small scale.

REFERENCES

1. P. Pandey, M. Katakdaunde, and R. Turton. Modeling weight variability in a pan coating process using Monte Carlo simulations. *AAPS PharmSciTech.* **7**(4): article 83 (2006).
2. FDA, Food and Drug Administration—Guidance for Industry PAT—a framework for innovative pharmaceutical manufacturing and quality assurance. http://www.fda.gov/Cder/guidance/6419fnl.htm (2003).
3. M. D. Mowery, R. Sing, J. Kirsch, A. Razaghi, S. Bechard, and R. A. Reed. Rapid at-line analysis of coating thickness and uniformity on tablets using laser induced breakdown spectroscopy. *J. Pharm. Biomed. Anal.* **28**(5):935–943 (2002).
4. L. Ho, R. Müller, M. Römer, K. C. Gordon, J. Heinämäki, P. Kleinebudde, M. Pepper, T. Rades, Y. C. Shen, C. J. Strachan, P. F. Taday, and J. A. Zeitler. Analysis of sustained-release tablet film coats using terahertz pulsed imaging. *J. Control. Release.* **119**(3):253–261 (2007).
5. P. Seitavuopio, J. Rantanen, and J. Yliruusi. Tablet surface characterisation by various imaging techniques. *Int. J. Pharm.* **254**(2):281–286 (2003).
6. S. Strübing, H. Metz, F. Syrowatka, and K. Mader. Monitoring of dissolution induced changes in film coat composition by H-1 NMR spectroscopy and SEM. *J. Control. Release.* **119**(2):190–196 (2007).
7. M. Ruotsalainen, J. Heinamaki, H. X. Guo, N. Laitinen, and J. Yliruusi. A novel technique for imaging film coating defects in the film-core interface and surface of coated tablets. *Eur. J. Pharm. Biopharm.* **56**(3):381–388 (2003).
8. S. Missaghi, and R. Fassihi. A novel approach in the assessment of polymeric film formation and film adhesion on different pharmaceutical solid substrates. *AAPS Pharmscitech.* **5**(2): article 29 (2004).
9. S. J. F. Erich, J. Laven, L. Pel, H. P. Huinink, and K. Kopinga. Comparison of NMR and confocal Raman microscopy as coatings research tools. *Prog. Org. Coat.* **52**(3):210–216 (2005).
10. V. K. Kinra, and C. Y. Zhu. Ultrasonic nondestructive evaluation of thin (Subwavelength) coatings. *J. Acoust. Soc. Am.* **93**(5):2454–2567 (1993).
11. J. D. Perez-Ramos, W. P. Findlay, G. Peck, and K. R. Morris. Quantitative analysis of film coating in a pan coater based on in-line sensor measurements. *AAPS Pharmscitech.* **6**(1):E127–E136 (2005).
12. S. Romero-Torres, J. D. Perez-Ramos, K. R. Morris, and E. R. Grant. Raman spectroscopic measurement of tablet-to-tablet coating variability. *J. Pharm. Biomed. Anal.* **38**(2):270–274 (2005).
13. J. F. Kauffman, M. Dellibovi, and C. R. Cunningham. Raman spectroscopy of coated pharmaceutical tablets and physical models for multivariate calibration to tablet coating thickness. *J. Pharm. Biomed. Anal.* **43**(1):39–48 (2007).
14. S. Romero-Torres, J. D. Perez-Ramos, K. R. Morris, and E. R. Grant. Raman spectroscopy for tablet coating thickness quantification and coating characterization in the presence of strong fluorescent interference. *J. Pharm. Biomed. Anal.* **41**(3):811–819 (2006).
15. A. J. Fitzgerald, B. E. Cole, and P. F. Taday. Nondestructive analysis of tablet coating thicknesses usign terahertz pulsed imaging. *J. Pharm. Sci.* **94**(1):177–183 (2005).
16. EMEA, European Medicines Agency—Note for Guidance on the Use of Near Infrared Spectroscopy. www.emea.europa.eu/pdfs/human/qwp/330901en.pdf (2003).
17. J. D. Kirsch, and J. K. Drennen. Determination of film-coated tablet parameters by near-infrared spectroscopy. *J. Pharm. Biomed. Anal.* **13**(10):1273–1281 (1995).
18. J. D. Kirsch, and J. K. Drennen. Near-infrared spectroscopic monitoring of the film coating process. *Pharm. Res.* **13**(2):234–237 (1996).
19. M. Andersson, S. Folestad, J. Gottfries, M. O. Johansson, M. Josefson, and K. G. Wahlund. Quantitative analysis of film coating in a fluidized bed process by in line NIR spectrometry and multivariate batch calibration. *Anal. Chem.* **72**(9):2099–2108 (2000).
20. M. Blanco, J. Coello, A. Eustaquio, H. Iturriaga, and S. Maspoch. Analytical control of pharmaceutical production steps by near infrared reflectance spectroscopy. *Anal. Chim. Acta.* **392**(2–3):237–246 (1999).
21. M. Blanco, J. Coello, H. Iturriaga, S. Maspoch, and N. Pou. Development and validation of a near infrared method for the analytical control of a pharmaceutical preparation in three steps of the manufacturing process. *Fresenius J. Anal. Chem.* **368**(5):534–539 (2000).
22. A. de Juan, and R. Tauler. Multivariate curve resolution (MCR) from 2000: Progress in concepts and applications. *Crit. Rev. Anal. Chem.* **36**(3–4):163–176 (2006).
23. M. Blanco, M. Bautista, and M. Alcalá. Preparing calibration sets for use in pharmaceutical analysis by NIR-spectroscopy. *J. Pharm. Sci.* **97**:1236–1245 (2008).
24. M. Ruotsalainen, J. Heinämäki, J. Rantanen, and J. Yliruusi. Development of an Automation System for a Tablet Coater. *AAPS PharmSciTech.* **2**: article 14 (2002).
25. R. J. Barnes, M. S. Dhanoa, and S. J. Lister. Standard normal variate transformation and de-trending of near-infrared diffuse reflectance spectra. *Appl. Spectrosc.* **43**(5):772–777 (1989).
26. A. Savitzky, and M. J. E. Golay. Smoothing and differentiation of data by simplified least squares procedures. *Anal. Chem.* **36**(8):1627–1639 (1964).
27. S. Dejong. SIMPLS - an alternative approach to partial least-squares regression. *Chemometr. Intell. Lab. Syst.* **18**(3):251–263 (1993).