



## Research paper

## Terahertz pulsed imaging as an analytical tool for sustained-release tablet film coating

Louise Ho<sup>a,b,c,\*</sup>, Ronny Müller<sup>d</sup>, Keith C. Gordon<sup>e</sup>, Peter Kleinebudde<sup>d</sup>, Michael Pepper<sup>b,c</sup>, Thomas Rades<sup>a</sup>, Yaochun Shen<sup>f</sup>, Philip F. Taday<sup>c</sup>, J. Axel Zeitler<sup>g</sup>

<sup>a</sup> School of Pharmacy, University of Otago, Dunedin, New Zealand

<sup>b</sup> Cavendish Laboratory, University of Cambridge, Cambridge, UK

<sup>c</sup> TeraView Ltd., St. John's Innovation Park, Cambridge, UK

<sup>d</sup> Institute of Pharmaceutics and Biopharmaceutics, Heinrich-Heine-University, Düsseldorf, Germany

<sup>e</sup> Department of Chemistry, University of Otago, Dunedin, New Zealand

<sup>f</sup> Department of Electrical Engineering and Electronics, University of Liverpool, Liverpool, UK

<sup>g</sup> Department of Chemical Engineering, University of Cambridge, Cambridge, UK

## ARTICLE INFO

## Article history:

Received 7 April 2008

Accepted in revised form 19 June 2008

Available online 4 July 2008

## Keywords:

Terahertz pulsed imaging (TPI)

Sustained-release

Film coating

Scale-up

Dissolution

## ABSTRACT

The ability of terahertz pulsed imaging (TPI) to be employed as an analytical tool for monitoring a film coating unit operation and to assess the success of a subsequent process scale-up was explored in this study. As part of a process scale-up development, a total of 190 sustained-release tablets were sampled at 10% increments of the amount of polymer applied, from a lab-scale and a pilot-scale coating run. These tablets were subjected to TPI analysis, followed by dissolution testing. Information on tablet film coating layer thickness and variations in coating density were extracted using TPI. It was found that both terahertz parameters were more sensitive and informative to product quality when compared with measuring the amount of polymer applied. For monitoring the film coating unit operation, coating layer thickness showed a strong influence on the dissolution behaviour for both the lab-scale and the pilot-scale batches. An  $R^2$  of 0.89, root mean square error (RMSE) = 0.22 h (MDT range = 3.21–5.48 h) and an  $R^2$  of 0.92, RMSE = 0.23 h (MDT range = 5.43–8.12 h) were derived from the lab-scale and pilot-scale, respectively. The scale-up process led to significant changes in MDT between the lab-scale and pilot-scale. These changes in MDT could be explained by the differences observed in the film coating density on samples with similar amount of polymer applied between the lab and the pilot-scale. Overall, TPI demonstrated potential to be employed as an analytical tool to help refine the coating unit operation and the scale-up procedure.

© 2008 Elsevier B.V. All rights reserved.

## 1. Introduction

Tablet film coating is a pharmaceutical unit operation modifying simple compressed tablets. Tablets are coated to improve their aesthetic appeal, to mask an odour, to disguise the taste, to improve drug stability, or most importantly to achieve a modified drug release profile [1]. Slight changes in the coating equipment and coating parameters may cause variations in the physicochemical properties of the film and may consequently compromise the coating quality [2]. Coating defects like twinning, cratering and blistering are visible to the naked eye and generally can be picked up by the operator [3]. On the other hand, variations in the film coating thickness and density cannot easily be detected without

the help of a process analytical tool (PAT). Monitoring and controlling coating quality is thus important to prevent output risks including batch reprocessing, batch reject and product recall [2]. Being able to accurately determine coating quality is of paramount significance for a better understanding and appropriate control of the coating process in order to improve manufacturing efficiency and to avoid scale-up delays [4].

Traditionally, weight gain and the amount of coating polymer applied are monitored to determine tablet film coating quality. These parameters are inherently non-specific and often fail to predict the performance of the dosage form in subsequent dissolution testing [5]. Dissolution and bioavailability testing are currently the bench-mark for assessing the success of a scale-up operation in the film coating process [2]. Numerous techniques have been used to study the different aspects of film coating quality, including light and electron-microscopy, magnetic resonance imaging (MRI), near infrared (NIR) spectroscopy, Raman spectroscopy, and laser

\* Corresponding author. School of Pharmacy, University of Otago, P.O. Box 56, Dunedin, New Zealand.

E-mail address: [louise.ho@teraview.com](mailto:louise.ho@teraview.com) (L. Ho).

induced break-down spectroscopy [6–15]. Unfortunately, to determine the coating layer thickness these techniques are often destructive, have no capability to resolve multiple coating layers with a single-point measurement or may require the set-up and maintenance of robust multivariate analysis models for data interpretation.

Terahertz radiation resides in the far-infrared region of the electromagnetic spectrum ( $2\text{--}120\text{ cm}^{-1}$ ). With longer wavelength than NIR, terahertz radiation can penetrate most pharmaceutical excipients with a penetration depth of around 3 mm (depending on the refractive index of the material), thus allowing the non-destructive analysis of most solid dosage forms [16,17]. For coating quality analysis, coating layer thickness and film coating density can be directly determined without recourse to sophisticated multivariate analytical models. These two coating quality parameters are important for the subsequent dissolution performance of a particular film coated dosage form [18,19].

The terahertz pulsed imaging (TPI) has been used to discriminate between an innovator and a generic product by clearly mapping out the coating features of the sugar coat of the two products. Using a single-point measurement the authors concluded that the sugar coating on the innovator product is far more complex than that of the generic product [20]. The detailed set-up for the TPI instrument and the analysis of various solid dosage forms using TPI had been previously described [21], and its capabilities to construct 2D maps and 3D models of film coating defects and to determine coating uniformity has been demonstrated [22]. TPI has also been validated by microscopic imaging with respect to the accuracy of measuring coating layer thickness [22]. A new terahertz parameter (terahertz electric field peak strength/TEFPS) was introduced, and has demonstrated potential alongside coating layer thickness determination to extract information on the density of the tablet film coating [18].

In this study, we investigate how both terahertz parameters (coating layer thickness and TEFPS) can be applied to monitor coating quality. Moreover we assess the success of a film coating scale-up procedure using these terahertz parameters.

## 2. Materials and methods

### 2.1. Sustained-release tablets

Both lab and pilot-scale batches of tablet cores were coated with the same film coating formulation. Tablet cores were biconvex (3 mm in height, 8 mm in diameter and an average weight of 252 mg), and contained 10% w/w diprophyllin (API), 84.5% w/w lactose monohydrate (Flowlac<sup>®</sup>), 5% w/w vinylpyrrolidone–vinyl acetate copolymer (Kollidon<sup>®</sup> VA 64) and 0.5% w/w magnesium stearate. The coating formulation used was as follows: 50% w/w polyvinyl acetate (Kollicoat<sup>®</sup> SR 30 D), 6% w/w polyvinyl alcohol–polyethyleneglycol graft copolymer (Kollicoat<sup>®</sup> IR), 0.075% w/w polyoxyethylene (20) sorbitan monooleate (Polysorbat 80), 0.3% w/w glycerolmonostearate, 0.75% w/w triethylcitrate and 42.87% w/w deionised water.

### 2.2. Coating process (lab-scale)

The lab-scale batch was coated using a BFC5, Bohle Film Coater (L.B. Bohle, Ennigerloh, Germany). The dimensions for the BFC5 coating pan are 316 mm in diameter and 356 mm in pan length, accommodating a 4 kg batch size. A single two-way spray nozzle (type 970/7-1 S75, Düsen-Schlick GmbH, Untersiemau, Germany) was used to apply the coating solution for the lab-scale batch. Ten samples were randomly selected during the coating process, at 10% increments of the amount of sustained-release polymer applied (1.7, 3.7, 5.2, 7.0, 8.7, 10.5, 12.2, 14.0, 15.7 and 17.5 mg/cm<sup>2</sup>).

### 2.3. Process scale-up, coating process (pilot-scale)

A BFC25, Bohle Film Coater (L.B. Bohle, Ennigerloh, Germany) was used to coat the pilot batch (batch size 20 kg). The coating pan dimensions are 546 mm in diameter and 630 mm in length. The coating process was carried out in the same manner as for the lab batch with similar coating parameters (slight changes were necessary to accommodate the increased batch size). Five of the two-way spray nozzles (type 970/7-1 S75) were used (Düsen-Schlick GmbH, Untersiemau, Germany) to spray coat the tablets. Random selection of ten tablets was carried out after the following amounts of sustained-release polymer were applied: 1.8, 3.6, 5.5, 7.3, 9.1, 10.9, 12.7, 14.5 and 18.2 mg/cm<sup>2</sup>. All sampled tablets were stored and measured under the same ambient conditions.

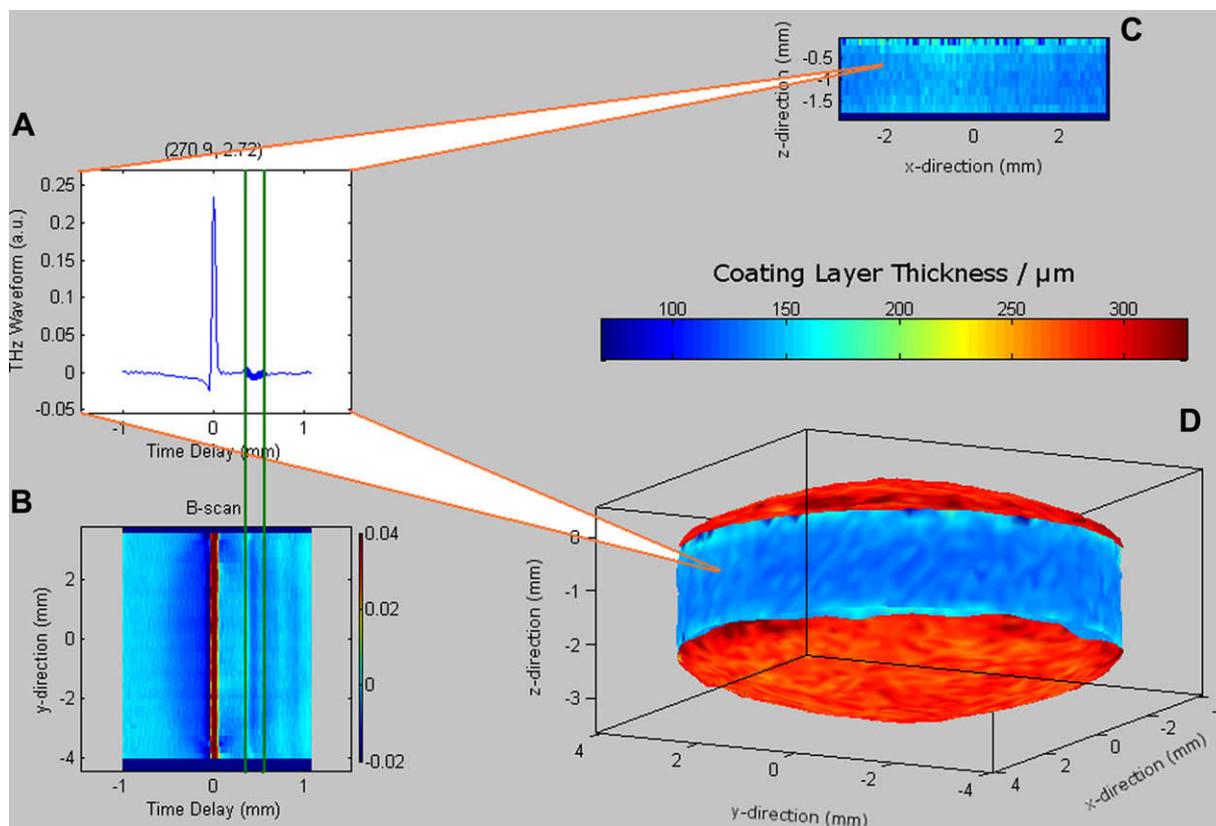
### 2.4. TPI analysis

The imaging process was performed with a TPI Imaga2000 (TeraView, Cambridge, UK), using the same data acquisition process previously detailed [22]. Briefly, ultra-short bursts of coherent broadband terahertz radiation were generated and detected with photoconductive semiconductor devices. Using time-of-flight measurements, the imaging process can either be single-point (measurement time approximately 50 ms) or a whole surface scan (a series of single-point measurements) over the entire solid dosage form. For the tablets examined in this study, the current image acquisition time for a whole surface scan (top and bottom surfaces and the central band of the coated tablet) was around 45 min. The instrument was used in an off-line mode in this study. Due to the transparent or semi-transparent nature of most pharmaceutical excipients in the terahertz region of the electromagnetic spectrum, the incident terahertz radiation is able to travel through the entire film coating. A portion of the radiation is reflected back at each tablet interface due to changes in the refractive indices, resulting in a time-domain terahertz electric field signal. This time-domain signal is the basis for the construction of 2D terahertz surface maps and 3D tablet models, and can be visualised as a cross-sectional image that looks similar to an ultrasound B-scan (Fig. 1).

Both terahertz parameters (coating thickness and TEFPS) were generated from an average of 1200 pixels around the central band of the tablet. The central band was chosen as it is the weakest area of a sustained-release tablet and is rate governing during dissolution [23]. The exact calculations of these parameters were explained in Ho et al. [18,22]. The TEFPS is expressed as a percentage value (%), and was derived from the surface reflection of the sample over the peak intensity of the incident pulse, measured from the reflection off a reference mirror. From the temporal terahertz waveform, using the peak-to-peak or peak-to-trough distance (the direction of the peak is dependent on the change of the refractive index at the tablet coating/core interface) the coating layer thickness ( $d_{coat}$ ) at each pixel can be determined, using the relationship:  $2d_{coat} = \Delta t \ c/n$ , where  $\Delta t$  is the time delay between the terahertz reflections,  $c$  is the speed of light and  $n$  is the refractive index of the coating matrix. Terahertz refractive indices of 1.68 and 1.79 were measured using the spectroscopy set-up in transmission mode and subsequently employed for calculating the film coating layer thickness of the lab and pilot-scale tablets, respectively.

### 2.5. Dissolution testing

Dissolution testing was carried out on the same tablets that were used for TPI analysis and was performed in accordance with the USP guidelines for sustained-release dosage forms. A USP 2 – paddle dissolution apparatus was used. About 900 ml of water



**Fig. 1.** The terahertz time domain waveform depicted in (A) can also be presented as a cross-section B-scan (B), thus the units on the colour bar for the B-scan are also in a.u. The cross-section image is useful for locating various interfaces embedded within the film coating or tablet core. The minimum in the time domain waveform (A) corresponds to the interface between the film coating and the core in (B), highlighted with green lines. The red line in the B-scan is the air/coating surface interface (B), which is the positive peak in the time domain waveform (A). The time domain waveform contains all information required to build a single pixel in the 2D terahertz map (C) and 3D terahertz tablet model (D). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this paper.)

was used as the dissolution medium in each of the beakers with the temperature kept constant at 37 °C and a paddle rotational speed of 100 rpm. The dissolution set-up was in-line, and the drug concentration was determined by UV spectroscopy (Lambda 2 UV/vis, Perkin-Elmer GmbH, Düsseldorf, Germany). The spectrometer detection wavelength was set at 254 nm, corresponding to the maximum absorption of diprophyllin in aqueous solution. Samples were measured automatically at one-minute intervals. The model-independent dissolution parameter, mean dissolution time (MDT), was deduced from the dissolution profiles. For dissolution analysis, a minimum of five tablets from each sampling interval was used. In general, the final product coated under the pilot-scale conditions took 50 h to complete the dissolution process, and 25 h for the lab-scale.

### 3. Results and discussion

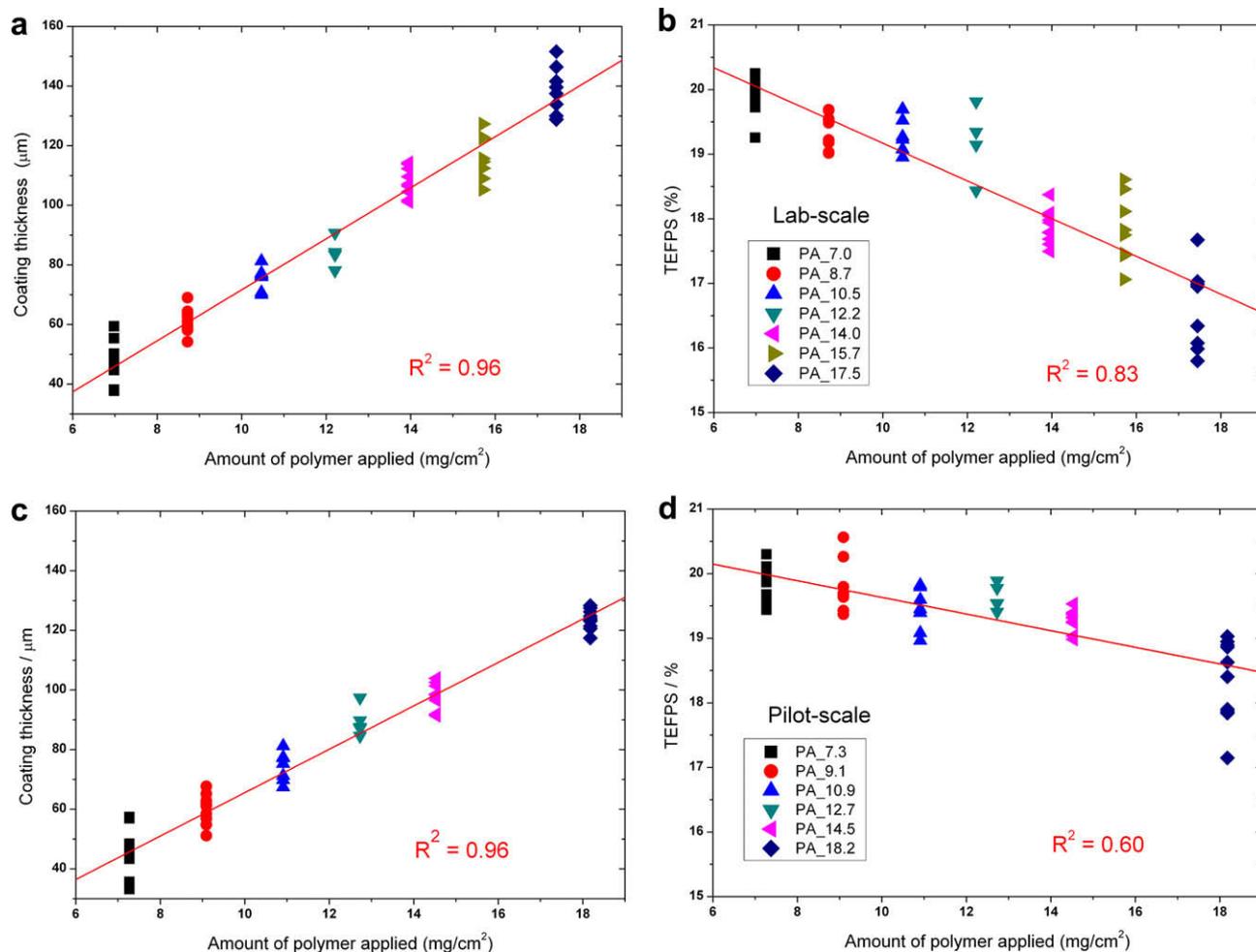
#### 3.1. Terahertz parameters and the amount of sustained-release polymer applied

##### 3.1.1. Coating process in the lab-scale

In a previous study we found that determination of the total coating weight gain alone was insufficient to characterise the quality of the coating process with respect to subsequent dissolution behaviour of the dosage forms [18]. However, the detailed relationship between the terahertz parameters and the amount of polymer applied remained unexplored. In this study, both terahertz parameters (coating layer thickness and TEFPS) were successfully determined for amounts of polymer applied  $\geq 7.0$  mg/cm<sup>2</sup>. For polymer levels of 1.7, 3.7 and 5.2 mg/cm<sup>2</sup> groups, the coating layer

thickness around the tablet central band was below the axial resolution limit of the TPI set-up (minimum depth resolution in the set-up used in this study is around 38  $\mu$ m depending on the refractive index of the coating material concerned) [21].

The relationship between measured coating thickness and the amount of polymer applied is shown in Fig. 2a. The linear correlation ( $R^2 = 0.96$ , RMSE = 7  $\mu$ m, coating layer thickness range = 38–152  $\mu$ m) indicates that the amount of polymer applied should be able to afford an accurate prediction of coating thickness growth throughout the coating process. However, we observed some variability in the growth of the coating layer during the coating process (determined by TPI) that was not reflected in the amount of polymer applied at regular 10% increments of the total amount at each sampling points (Table 1). During the coating run of the lab-scale batch, the coating layer thickness growth varied from 7% to 15%, with only two sampling intervals showing a growth of 10%. Furthermore, the linear correlation between the terahertz parameter TEFPS (indicates coating density) and the amount of polymer applied (Fig. 2b) depicted a  $R^2$  of 0.83 and RMSE of 0.50% (TEFPS range = 15.8–20.3%). Whilst these values showed satisfactory correlations between the two parameters, the amount of polymer applied failed to reflect the subtle changes in coating density as a function of polymer added when measured at different sampling intervals (Table 1). We had previously shown that TPI affords a very high measurement repeatability as well as good long-term measurement precision [22]. The range of coating thickness and TEFPS data depicted with terahertz parameters at each set interval of polymer applied thus revealed non-uniformity or inhomogeneity in the coating process with individual tablet cores gaining a polymer coat at different rates.



**Fig. 2.** Correlations between terahertz parameters (coating layer thickness and TEFPs) and the amount of polymer applied, monitored using samples from the lab-scale (a and b) and pilot-scale (c and d) coating process. PA is the amount of polymer applied in mg/cm<sup>2</sup>.

**Table 1**

Monitoring the film coating unit operation using the three coating quality parameters: amount of polymer applied, coating layer thickness and TEFPs for the lab-scale coating process

Amount of polymer applied (mg/cm <sup>2</sup> )	Increment (%)	Average film coating thickness (µm)	Increment (%)	Average TEFPs (%)	Reduction (%)
7.0		46		19.9	
8.7	10	62	12	19.4	3.0
10.5	10	76	10	19.3	0.6
12.2	10	90	10	18.9	2.4
14.0	10	108	13	17.9	6.0
15.7	10	117	7	17.9	0
17.5	10	138	15	16.6	7.8

### 3.1.2. Process scale-up, coating process in the pilot-scale

Film coating is a complex process and the success of process scale-up depends on a range of process parameters as well as physicochemical properties of the tablet cores [2,24]. These parameters and properties are generally better controlled during a particular coating run (i.e. for a particular film coating unit operation) than

during process scale-up, and often include air temperature, air flow rate, pan speed, spray pattern, tablet rheology, and coating surface attrition. Many of these parameters are likely to contribute to changes in the molecular arrangement of coating polymers on the tablet cores and may influence the TEFPs and thus contribute to coating density and thickness variations [2,18]. We therefore also determined coating thickness and density as a function of polymer applied in a scaled-up batch. The results are shown in Fig. 2c and d.

Samples from the 1.8, 3.6 and 5.5 mg/cm<sup>2</sup> groups were discarded from the coating analysis as the coating layer thickness around the central bands was below the detection limit of the TPI configuration. The coating layer thickness of the lab-scale tablets ranged from 38 to 151 µm whereas it ranged from 28 to 128 µm for the pilot-scale, indicating that the overall coating layer thickness for the pilot-scale tablets was lower than that of the lab-scale tablets (Fig. 2a and c). For the pilot-scale batch, a linear relationship between coating thickness and amount of polymer applied ( $R^2 = 0.96$  and RMSE = 6 µm, coating layer thickness range = 28–128 µm) was observed (Fig. 2c). An  $R^2$  of 0.60 and RMSE of 0.41% (TEFPs range = 17.1–20.3%) were determined for the correlation between TEFPs values and the amount of polymer applied, indicating only a modest correlation between this terahertz parameter and the amount of polymer applied (Fig. 2d). Importantly however, when compared to the lab-scale batch the overall range of TEFPs (film coating density) was higher after the coating process was scaled up (Fig. 2b and d).

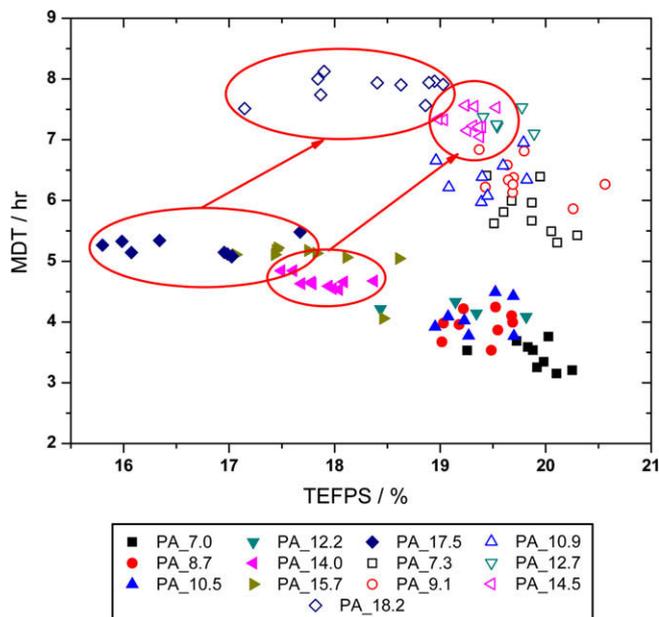
### 3.2. Terahertz parameters and dissolution

#### 3.2.1. Lab-scale batch

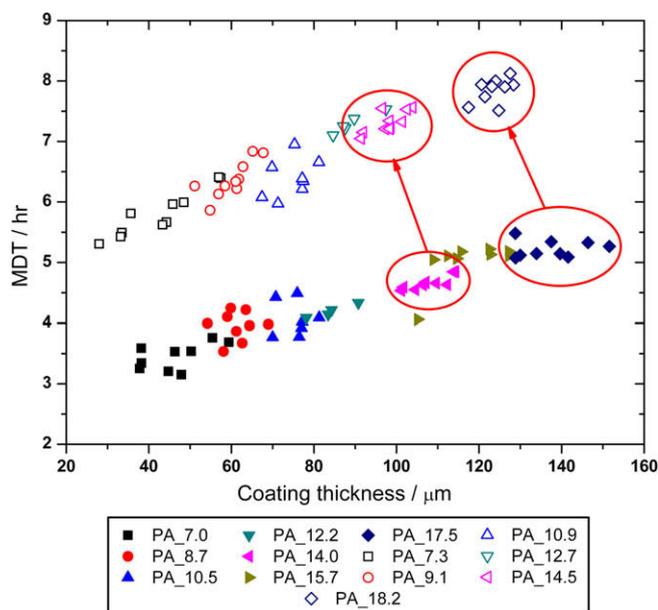
Both coating layer thickness and variations in coating density measured from the lab-scale coating process were correlated to the dissolution profile of the same tablets. A linear regression  $R^2$  of 0.79 and a RMSE of 0.31 h for TEFPs and MDT was yielded (MDT range = 3.21–5.48 h) (Fig. 3), whereas the  $R^2$  was 0.89 (RMSE = 0.22 h) between coating layer thickness and MDT (Fig. 4). The analysis of the correlations between terahertz parameters and MDT revealed that the thicker the film coating, the longer the dissolution process, and the slower the dissolution rate. The relationship between the coating layer thickness and TEFPs observed in a previous study [18] was confirmed here (Fig. 5), where a thinner coating layer corresponded to a higher film coating density (higher TEFPs). In contrast, variations in coating density played a less prominent role in the dissolution behaviour for this particular coating unit operation and correlation was stronger with coating thickness (Figs. 3 and 4). However, for monitoring a film coating run of sustained-release tablets (the film coating consisted mainly of a sustained-release polymer with a pore former), a general pattern of decreasing TEFPs as the process advanced is useful as a process signature (Table 1).

#### 3.2.2. Pilot-scale batch, film coating process scale-up

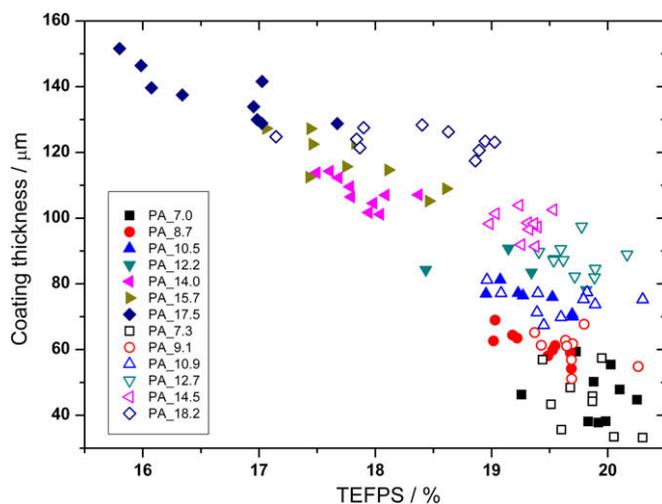
The scale-up operation led to changes in the dissolution profile of the tablets between the lab-scale and the pilot-scale (Fig. 6). When subjected to dissolution testing, samples from the pilot-scale showed a much longer MDT than those of the lab-scale, ranging from 3.21 to 5.48 h for the lab-scale and 5.43 and 8.12 h for the pilot-scale (Figs. 3 and 4). However, in general, similar trends as for the lab-scale batch between terahertz parameters and MDT were also observed for the pilot-scale, exhibiting a strong effect of coating layer thickness on the dissolution behaviour, with a linear regression  $R^2$  of 0.92 (RMSE = 0.23 h) between coating layer thickness and MDT (MDT range = 5.43–8.12 h), and only a modest correlation ( $R^2$  of 0.47 and RMSE of 0.57 h) for TEFPs and MDT (Figs. 3 and 4).



**Fig. 3.** The quality of the film coating, determined as MDT, can be monitored for a scale-up procedure using TEFPs. The lab-scale is presented with solid symbols whilst the pilot-scale is presented with open symbols. PA is the amount of polymer applied in mg/cm<sup>2</sup>. The pilot-scale showed higher film coating density which resulted in the longer MDT.



**Fig. 4.** Relationship between coating thickness and MDT for the pilot and lab-scale samples. The lab-scale is presented with solid symbols whilst the pilot-scale is presented with open symbols. PA is the amount of polymer applied in mg/cm<sup>2</sup>. The coating layer was thinner after the film coating process was scaled up (due to higher film coating density), resulting in a longer dissolution time for the pilot-scale.



**Fig. 5.** Relationship between the two terahertz parameters, coating thickness and TEFPs using samples from both the lab-scale and the pilot-scale. The thicker the coating layer, the lower the TEFPs, which means lower density in the film coating. PA is the amount of polymer applied in mg/cm<sup>2</sup>. The lab-scale is presented with solid symbols whilst the pilot-scale is presented with open symbols.

When comparing TEFPs values from samples with similar amount of polymer applied between the pilot- and lab-scale, pilot-scale samples from the last two polymer weights (14.5 mg/cm<sup>2</sup> and 18.2 mg/cm<sup>2</sup>) showed significantly higher TEFPs values than lab-scale samples taken from similar polymer weights (14.0 mg/cm<sup>2</sup> and 17.5 mg/cm<sup>2</sup>;  $p < 0.001$ ,  $\alpha = 0.05$ ). Higher TEFPs values indicated that the coating density for the pilot-scale was higher than for the lab-scale, resulting in lower water permeability into the film coating. This was evident in the dissolution test, where a longer MDT for the pilot-scale samples was found compared to the lab-scale samples (Fig. 3).

Numerous process and material alterations during process scale-up rendered coating density more dominant in governing the subsequent dissolution behaviour than coating layer thickness

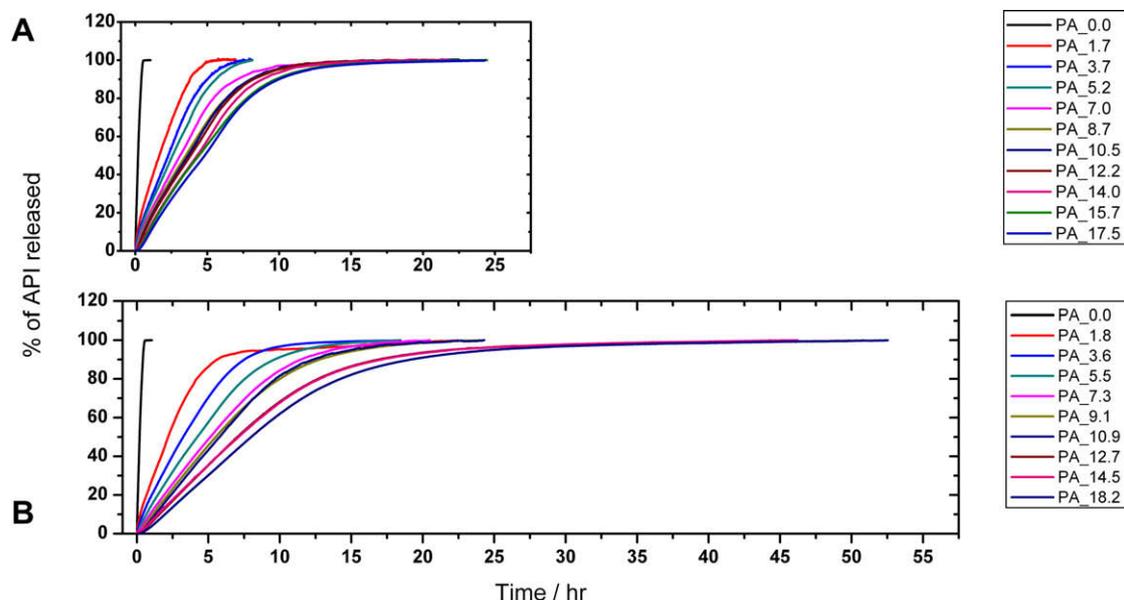


Fig. 6. Drug release versus time profiles for lab-scale (A) and pilot-scale (B) samples. PA is the amount of polymer applied in  $\text{mg}/\text{cm}^2$ .

[18]. The coating layer was noticeably thinner for the pilot-scale, and the difference between the two scales was statistically significant for the last two polymer levels sampled. The average coating layer thickness at  $14.5 \text{ mg}/\text{cm}^2$  for the pilot-scale was  $98 \mu\text{m}$ , when at  $14.0 \text{ mg}/\text{cm}^2$  the lab-scale coating layer thickness was  $108 \mu\text{m}$ . At  $18.2 \text{ mg}/\text{cm}^2$  for the pilot-scale, the average coating thickness was  $124 \mu\text{m}$  as opposed to the  $137 \mu\text{m}$  observed at  $17.45 \text{ mg}/\text{cm}^2$  for the lab-scale. Unpaired two-tailed *t*-tests showed statistically significant differences in coating thickness ( $p < 0.001$ ,  $\alpha = 0.05$ ). The coating thickness variations demonstrated here confirmed the observations made with coating density earlier (Figs. 3 and 4). The tablets from the pilot-scale had thinner films but higher coating densities, and hence lower water permeability into the film coating and slower dissolution rate (longer MDT). Both terahertz parameters deemed the studied scale-up process unsuccessful, however we have further illustrated the importance of a better determination of the features that are specific to the coating processes.

#### 4. Conclusion

In this study we demonstrated how two sustained-release film coating process signatures, coating layer thickness and coating density, can be successfully measured using TPI. These parameters were applied to monitor the coating quality for the film coating unit operation and to assess the success of a scale-up procedure. It was shown that both process signatures were more informative on the product quality when compared with the amount of polymer applied. Whilst the coating layer thickness was the governing factor of the subsequent dissolution behaviour for monitoring a specific film coating unit operation, differences in the film coating density showed a more prominent effect on dissolution during process scale-up. With these measurements it was possible to detect the in-vitro performance differences between the pilot- and lab-scale. TPI demonstrated potential to be employed as an analytical tool to help refine the coating unit operation and the scale-up procedure. The technique affords non-destructive extraction of process signatures on tablet film coatings, which allows for better process understanding and hence optimisation of the product design space for sustained-release tablets.

#### Acknowledgements

We thank Ms. Yvonne Vrede for support in carrying out dissolution measurements. J.A.Z. would like to gratefully acknowledge the financial support from the Research Councils UK Basic Technology Programme (GR/87086/02).

#### References

- [1] G.C. Cole, in: G. Cole, J. Hogan, A. Michael (Eds.), *Pharmaceutical coating technology*, Taylor & Francis Ltd., Philadelphia, 1995, pp. 1–5.
- [2] S.C. Porter, *Scale-Up of film Coating*, Taylor & Francis, New York, 2000.
- [3] M.R. Harris, I. Ghebre-Sellassie, *Aqueous polymeric coating for modified release oral dosage forms*, Marcel Dekker, Inc., New York, 1997.
- [4] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Veterinary Medicine (CVM), O.o.R.A. (ORA), *Guidance for Industry PAT - A Framework for Innovative Pharmaceutical Development, manufacturing, and Quality Assurance*. 2004, pp. 1–16.
- [5] J.D. Perez-Ramos, W.P. Findlay, G. Peck, K.R. Morris, Quantitative analysis of film coating in a pan coater based on in-line sensor measurements, *AAPS PharmSciTech* 6 (1) (2005).
- [6] C.A. Fyfe, A.I. Blazek-Welsh, Quantitative NMR imaging study of the mechanism of drug release from swelling hydroxypropylmethylcellulose tablets, *J. Control. Release* 68 (3) (2000) 313–333.
- [7] J.C. Richardson, R.W. Bowtell, K. Mader, C.D. Melia, Pharmaceutical applications of magnetic resonance imaging (MRI), *Adv. Drug Deliver. Rev.* 57 (8) (2005) 1191–1209.
- [8] M.D. Mowery, R. Sing, J. Kirsch, A. Razaghi, S. Bechard, R.A. Reed, Rapid at-line analysis of coating thickness and uniformity on tablets using laser induced breakdown spectroscopy, *J. Pharmaceut. Biomed.* 28 (5) (2002) 935–943.
- [9] J.D. Kirsch, J.K. Drennen, Determination of film-coated tablet parameters by near-infrared spectroscopy, *J. Pharmaceut. Biomed.* 13 (10) (1995) 1273–1281.
- [10] J.D. Kirsch, J.K. Drennen, Nondestructive tablet hardness testing by near-infrared spectroscopy: a new and robust spectral best-fit algorithm, *J. Pharmaceut. Biomed.* 19 (3–4) (1999) 351–362.
- [11] S. Romero-Torres, J.D. Perez-Ramos, K.R. Morris, E.R. Grant, Raman spectroscopic measurement of tablet-to-tablet coating variability, *J. Pharmaceut. Biomed.* 38 (2) (2005) 270–274.
- [12] S. Romero-Torres, J.D. Perez-Ramos, K.R. Morris, E.R. Grant, Raman spectroscopy for tablet coating thickness quantification and coating characterization in the presence of strong fluorescent interference, *J. Pharmaceut. Biomed.* 41 (3) (2006) 811–819.
- [13] Y. Roggo, N. Jent, A. Edmond, P. Chalus, M. Ulmschneider, Characterizing process effects on pharmaceutical solid forms using near-infrared spectroscopy and infrared imaging, *Eur. J. Pharm. Biopharm.* 61 (1–2) (2005) 100–110.
- [14] M. Donoso, E.S. Ghaly, Prediction of drug dissolution from tablets using near-infrared diffuse reflectance spectroscopy as a nondestructive method, *Pharm. Dev. Technol.* 9 (3) (2004) 247–263.
- [15] M.P. Freitas, A. Sabin, L.M. Silva, F.M. Giannotti, D.A. do Couto, E. Tonhi, R.S. Medeiros, G.L. Coco, V.F.T. Russo, J.A. Martins, Prediction of drug dissolution

- profiles from tablets using NIR diffuse reflectance spectroscopy: a rapid and nondestructive method, *J. Pharmaceut. Biomed.* 39 (1–2) (2005) 17–21.
- [16] J.A. Zeitler, P.F. Taday, D.A. Newnham, M. Pepper, K.C. Gordon, T. Rades, Terahertz pulsed spectroscopy and imaging in the pharmaceutical setting – a review, *J. Pharm. Pharmacol.* 59 (2) (2007) 209–223.
- [17] Y.C. Shen, P.F. Taday, Development and application of terahertz pulsed imaging for nondestructive inspection of pharmaceutical tablet, *IEEE J. Quantum Elect.* 14 (2) (2008), doi:[10.1109/2007.JSTQE.911309](https://doi.org/10.1109/2007.JSTQE.911309).
- [18] L. Ho, R. Müller, K.C. Gordon, P. Kleinebudde, M. Pepper, T. Rades, Y.-C. Shen, P.F. Taday, J.A. Zeitler, Applications of terahertz pulsed imaging to sustained-release tablet film coating quality assessment and dissolution performance, *J. Control. Release* 127 (1) (2008) 79–87.
- [19] J.A. Spencer, Z. Gao, T. Morre, L.F. Buhse, P.F. Taday, D.A. Newnham, Y. Shen, A. Portieri, A. Husain, Delayed release tablet dissolution related to coating thickness by terahertz pulsed image mapping, *J. Pharm. Sci.* 97 (4) (2008) 1543–1550.
- [20] A.J. Fitzgerald, B.E. Cole, P.F. Taday, Nondestructive analysis of tablet coating thicknesses using terahertz pulsed imaging, *J. Pharm. Sci.* 94 (1) (2005) 177–183.
- [21] J.A. Zeitler, Y. Shen, C. Baker, P.F. Taday, M. Pepper, T. Rades, Analysis of coating structures and interfaces in solid oral dosage forms by three dimensional terahertz pulsed imaging, *J. Pharm. Sci.* 96 (2) (2007) 330–340.
- [22] 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, J.A. Zeitler, Analysis of sustained-release tablet film coats using terahertz pulsed imaging, *J. Control. Release* 119 (3) (2007) 253–261.
- [23] L. Ho, R. Müller, K.C. Gordon, P. Kleinebudde, M. Pepper, T. Rades, Y.-C. Shen, P.F. Taday, J.A. Zeitler, Central band – the weakest area on sustained-release coated tablets during dissolution in preparation.
- [24] P. Pandey, R. Turton, N. Joshi, E. Hammerman, J. Ergun, Scale-up of a pan-coating process, *AAPS Pharmscitech* 7 (4) (2006).