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Applications of terahertz pulsed imaging to sustained-release tablet film coating quality assessment and dissolution performance

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Abstract

The potential of terahertz pulsed imaging (TPI) to predict the dissolution performance in sustained-release tablets was investigated in this study. Batches of coated tablets with similar weight gain during the coating process at the lab and pilot scales were subjected to non-destructive imaging by TPI and subsequently analysed by dissolution testing. The results from the dissolution tests revealed significant differences in the product performance between the lab and pilot scales (Student *t*-test, $P<0.05$). The model-independent dissolution parameters in the pilot scale showed a prolonged mean dissolution time. This indicated that the pharmaceutical active ingredient was released at a slower rate in the pilot compared to the lab scale. While weight gain measurements (the traditional coating quality parameter), failed to provide an early indication of the product functional performance; terahertz parameters (terahertz electric field peak strength and coating layer thickness) provided insight into the subsequent dissolution behaviour. Correlations between terahertz parameters and dissolution were much stronger than correlations between weight gain and dissolution; with the R^2 value for terahertz correlations typically around 0.84 as opposed to 0.07 for weight gain correlations. This study presents the initial finding of correlations between terahertz parameters for assessing the coating quality to the dissolution performance of the coated tablet. The contributing factors for these particular correlations are also discussed.

Keywords: Terahertz pulsed imaging; Sustained-release; Tablet coating; Scale up; Dissolution

1. Introduction

Tablets are often coated with polymers in an effort to modify the drug release profile and thus meet certain in-vivo release specifications. Tablets can be coated to alter the initial drug release kinetics to be pH dependent (controlled-release formulations); or to prolong the optimum drug plasma concentration (sustained-release formulations); or to retard the onset of the drug release time (delayed-release formulations) [1]. Most commonly, indirect parameters derived from the final product are employed to indicate the quality of the film coating process. These include the weight gain of the coated tablets and the amount of coating formulation applied during the process.

Numerous coating quality analytical techniques have been investigated and have shown potential in providing information on various physicochemical, coating properties. These include microscopy techniques (scanning electron microscopy, conventional optical microscopy and environmental scanning electron microscopy), spectroscopic techniques (near infrared and Raman) and magnetic resonance imaging [2–8]. Often these techniques are destructive, not fully-automated, are not able to resolve multiple coating layers or provide only limited

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information about the quality of the coating layers below the immediate surface of the tablet.

The ability to characterise pharmaceutical solid-dosage forms and analyse tablet coating quality by terahertz pulsed imaging (TPI) was recently demonstrated [9–11]. Terahertz radiation is able to penetrate through most typical pharmaceutical excipients as it operates in the far-infrared region of the electromagnetic spectrum (2–120 cm^{-1}). In this range, polymers used in film coating are either transparent or semi-transparent. Using pulsed and coherent terahertz radiation, tablet coatings can be analysed non-destructively. TPI provides information on coating layer thickness, coating uniformity, and reproducibility among other coating quality assessments. In the study by Ho et al. coating layer thickness measurements by TPI were validated with microscopy imaging and good measurement precision and repeatability were found [11]. A TPI instrument was constructed that allows the fully-automated analysis of arbitrarily shaped dosage forms using a six-axis robotic arm for the terahertz mapping process [9].

In pharmaceutical research and development, scale-up operations of a processing step such as film coating form a very critical part during the development of a new product. The scale-up is only deemed successful when products from the pilot scale exhibit identical dissolution characteristics to those of the lab scale. However, one of the most persistent problems in the development of coated tablets is the difficulty to achieve such identical dissolution characteristics. Even though well established quality control parameters such as weight gain indicate "identical" coating properties for batches of product manufactured on different scales, the results of subsequent dissolution studies may show vast differences between those batches. The inability of the traditional indicators to reliably predict differences in the performance of the dosage forms emphasises the need to develop novel techniques to accurately characterise coating quality which will thus provide the basis for future rational process engineering during scale-up.

In this study, TPI coating analysis is carried out on two batches of lab scale and two batches of pilot scale sustained-release tablets, to identify whether terahertz parameters for assessing coating quality in the dry-state are able to differentiate between the two scales. Furthermore, we investigated whether the information from the terahertz images can be correlated to the results from dissolution testing and thus hold potential to predict the functional performances of the tablets examined.

2. Materials and methods

2.1. Production of lab and pilot scale tablets

The biconvex tablet cores consisted of 10% w/w of diprophyllin (API), 5% w/w of vinylpyrrolidone–vinyl acetate copolymer (Kollidon® VA 64), 0.5% w/w of magnesium stearate and 84.5% w/w of lactose monohydrate (Flowlac® 100). The tablet cores were coated using Bohle Film Coaters, BFC5 or BFC 25 (L.B Bohle, Ennigerloh, Germany). Two batches of the tablets were coated on the lab scale coater BFC5 (pan diameter = 316 mm, length = 356 mm) and two batches of pilot scale tablets were coated on the pilot scale coater BFC25 (pan diameter = 546 mm and length = 630 mm). The batch size for the pilot scale was 20 kg and 4 kg for the lab scale. All four batches were coated with the same coating formulation onto tablet cores produced in the same fashion. For all batches, two-way spray nozzles (type 970/7-1 S75) were used (Düesen-Schlick GmbH, Untersiemau, Germany). One spray nozzle was used for the lab scale while five nozzles were used for the pilot scale. All tablets were coated with the sustained-release coating formulation at 18 mg/cm^2. The coating composition was as follows: 50% w/w polyvinyl acetate (Kollicoat® SR 30 D), 6% w/w polyvinyl alcohol–polyethyleneglycol graft copolymer (Kollicoat® 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. The coating was transparent. The geometry of a coated tablet was approximately 8 mm in diameter and 3 mm height. The coating process parameters are listed in Table 1.

2.2. Weight gain measurements

For each pilot and lab scale batch, 100 tracer-tablets cores were randomly mixed into the 20 kg pilot scale and 4 kg lab scale tablets before coating. These tracer-tablets were weighed individually and marked using a permanent-marker with a cross on one side of the tablet surface and a number on the other side for identification. Once the tablets were coated with the transparent coating, all tracer-tablets were separated from the other tablets of the batch and subjected to a further drying step in a 60 °C chamber for 48 h prior to weighing. Tablet coating weight gain for all tracer-tablets was derived by subtracting the weight of the tablet core from the total weight of the respective tablets.

Table 1
Coating process parameters for the pilot and lab scales

Process parameters	Lab scale					Pilot scale				
	Dedusting	Preheating	Spraying	Drying	Cooling	Dedusting	Preheating	Spraying	Drying	Cooling
Pan speed (rpm) [on/off (s)]	5	5	20	12	10	3	3	11.6	7	5.8
Air volume (N m^3/h)	–	100	120	120	100	–	545	720	545	545
Negative pressure pan (Pa)	200	30	30	30	30	200	30	30	30	30
Outlet air temperature (°C)	–	45	40	60	30	–	45	40	60	30
Atomization air (mbar)	1500	–	1500	–	–	1500	–	1500	–	–
Pattern air (mbar)	1800	–	1800	–	–	1800	–	1800	–	–
Distance gun to tablet bed (cm)	10	–	10	–	–	10	–	10	–	–
Spray rate per gun (g/min)	–	–	9	–	–	–	–	10.8	–	–
No. of spray guns	–	–	1	–	–	–	–	5	–	–

2.3. Terahertz pulsed imaging analysis

Ten tracer-tablets with similar weight gain were selected from each batch and imaged with pulsed terahertz radiation using an TPI Imaga2000 (TeraView, Cambridge, UK). The technical configuration, including details of the data acquisition process and the image analysis procedure, has been previously described [9,11]. Once a tablet was picked up by the robotic arm of the instrument, the tablet topology was scanned using a 670 nm laser gauge. A model of the tablet topology was then constructed and used for the subsequent scan at the terahertz emitter to construct terahertz 3D tablet models. All terahertz scans were carried out in the point-to-point scan mode with a 200 μm step size and a depth resolution of about 38 μm.

2.4. Terahertz parameters for the analysis of coating quality

The terahertz parameters employed to assess the coating quality were tablet coating layer thickness and terahertz electric field peak strength (TEFPS). These parameters were determined separately for each of the three tablet surfaces (top, bottom and central band). For the purpose of correlating these terahertz parameters to the dissolution data, an average value across the three tablet surfaces was used. This was done to try and achieve a true representation of the coating characteristics, as all three surfaces were completely immersed in the medium during the dissolution study.

The coating layer thickness per pixel was derived from the terahertz temporal waveform in the time domain. The time delay between the initial reflection off the tablet surface and the subsequent reflected signal from the interface between the coating matrix and the core constituted twice the coating layer thickness. Taken the refractive index of the coating structure into account, the coating layer thickness was calculated by converting the time-of-flight terahertz signal into depth (in μm) by multiplying by the speed of light. For an accurate determination of the coating layer thickness, the refractive index of the coating matrix is required. The refractive index of the coating from the lab and pilot scale was measured by terahertz pulsed spectroscopy using an uncoated tablet core as the reference. Refractive indices of 1.68 and 1.79 were derived for the lab and pilot scale respectively. The measurement uncertainty for terahertz refractive indices was previously investigated. Where triplicate samples of some 30 most common pharmaceutical excipients were measured, and standard deviations (between triplicate measurements for all 30 excipients) ranged from 0.005 to 0.03 were observed, indicating good measurement precision [12]. All coating layer thickness (dcoat) calculations were based on the equation $2\text{dcoat} = \Delta t c / n$. The time delay between the reflections was presented by Δt, c is the speed of light and n is the refractive index of the coating matrix [11].

The TEFPS was determined from the signal reflected off the coating surface normalised to the magnitude of the incident pulse. This parameter is thus presented as a percentage. Moreover, multi-dimensional TEFPS maps could be generated in the same fashion as the coating layer thickness maps. An example of the terahertz coating layer thickness and TEFPS 2D maps are given in Fig. 1 along with their respective 3D terahertz models of the tablet imaged.

2.5. Dissolution studies

Dissolution testing has long been employed by the pharmaceutical industry as the bench mark in evaluating the product quality and predicting in-vivo drug release behaviour. When executed accurately, this in-vitro product performance test exhibits good reproducibility and is inexpensive [13]. The in-line dissolution set-up for this study was in accordance with the paddle dissolution apparatus in the European Pharmacopoeia (volume 5.7) section 2.9.3. The rotational speed for the paddles was set at 100 rpm, 900 ml of deionised water for dissolution was utilised as the dissolution medium in each of the beakers and the temperature was kept constant at 37 °C. A UV/VIS spectrometer (Model: Lambada 2 UV/Vis, manufactured by Bodenseewerk Perkin-Elmer GmbH Düsseldorf, Germany) was employed in-line at a wavelength of 254 nm, corresponding to the absorption maximum of the API, to determine the API dissolution at one-minute intervals. Dissolution testing was performed on the same tracer-tablets (10 tablets per batch) that were used for the terahertz imaging analysis.

2.6. Dissolution parameters

Modelling of the dissolution rate for the modified-release dosage forms has proven to be relatively complicated when compared to the immediate release forms. In the current study, the mechanism of drug release was based on the leaching of the API through pores and capillary channels created by the dissolution medium within the coating structure. Factors, such as the extent of the wetting and the inherent physical–chemical properties of the coating structure, would have to be taken into account when developing a dissolution rate model for the drug release. Nevertheless, model-independent dissolution parameters could be described and the following were used for the investigation of their correlation with the terahertz parameters for coating quality assessments: mean dissolution time (MDT) and dissolution rate constant [14–16].

The Mean dissolution time was derived using Eq. (1) [17]. Where, $W_d(t)$ is the cumulative amount of drug dissolved at any time interval, t:

$$\text{MDT} = \frac{\int_0^\infty t W_d(t) dt}{\int_0^\infty W_d(t) dt} \quad (1)$$

The zero order release rate constant is the gradient of the dissolution curve, taken from the onset of drug release for 3 h.

2.7. Discrimination between lab and pilot scales

In order to compare the lab and pilot scales (on all four batches), unpaired two-tailed t-tests were carried out on all coating quality parameters (dissolution parameters, weight gain and terahertz parameters). Prior to the t-test the normal distribution of the dissolution data was confirmed using the Anderson–Darling normality test at significance level $\alpha = 0.05$.

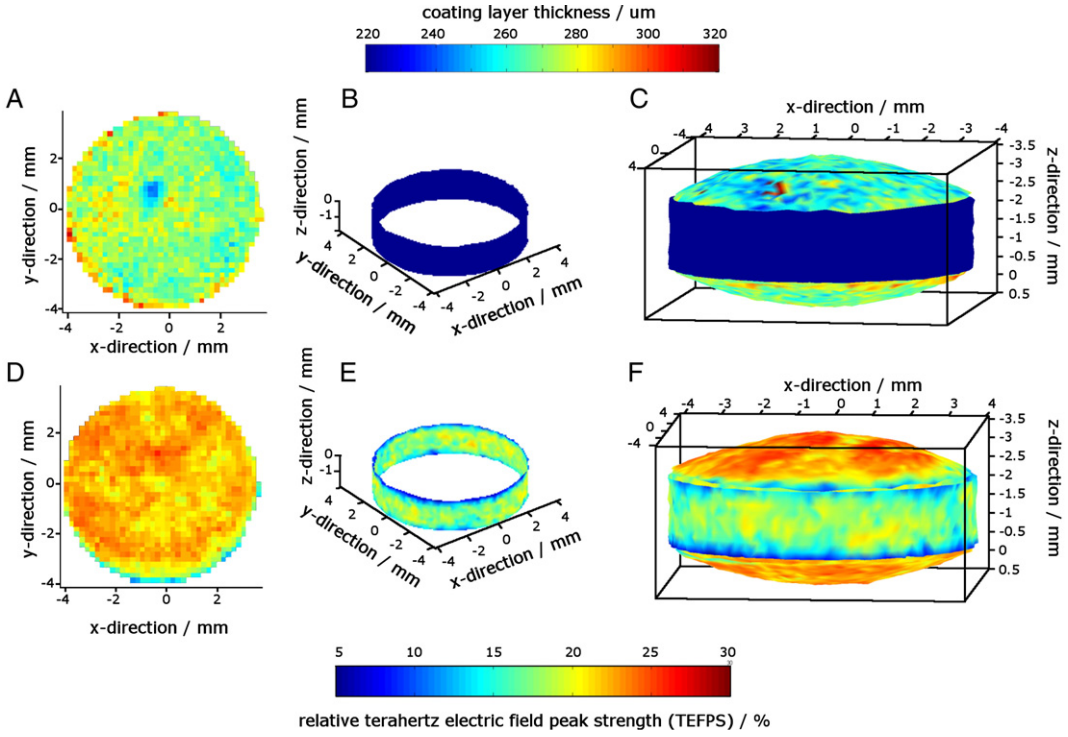

Fig. 1. Tablet 26 of lab scale batch II used as an example used here, where the terahertz 2D maps of surface a is presented in (A) and (D). Where the distribution of the coating layer thickness (colour bar in micron) and TEFPS (colour bar in %) over surface a are shown respectively. (B) and (E) are 3D maps of the tablet central band, with the coating layer thickness distribution displayed in (B) and TEFPS in (E). A 3D tablet model is depicted here in (C) using coating layer thickness information to build the model for all three surfaces (a, b and central band). It is clear that the coating layer thickness around the central band is much thinner than that of surfaces a and b; the colour bar is in the range from 50 to 300 micron. A 3D tablet model is also displayed using TEFPS information derived from all three surfaces, and the model is presented in (F). The colour bar is in the range from 6 to 26%.

All P values generated were above the significance level. Instead of taking an average across two batches of the lab and two batches of the pilot scales, the following batch combinations were employed: pilot scale batch I and lab scale batch I, pilot scale batch I and lab scale batch II, pilot scale batch II and lab scale batch I as well as pilot scale batch II and lab scale batch II. This was done to ensure that the variations investigated were solely attributed to inter-scale differences, circumventing any noise that arose from inter-batch variations.

2.8. SEM measurements

SEM (FEI Philips XL30 sFEG, Philips Electron Optics) images were taken on six tablets of similar film coating weight gain. There were 3 tablets from lab scale I and 3 tablets from pilot scale II. Images were taken at the following magnifications: 40×, 150×, 300×, 1000× and 2500× ; on all three surfaces (top, bottom and the central band) and on a cross-section slice of the tablet. All images derived from the lab scale tablets were compared to their pilot scale counterparts to assess the porosity in the film coating.

3. Results and discussion

3.1. Discrimination between lab and pilot scales

3.1.1. Dissolution

The dissolution analysis employed in this study is regarded as the gold standard post-production test as it is assumed to reveal information on the in-vivo functional performance of the samples involved. This is acknowledged by the pharmaceutical industry and the medicinal regulatory bodies, where dissolution analysis is rigorously implemented as the end-stage quality control technique. The results showed that all four batch combinations demonstrated significant product performance differences between the pilot and the lab scales, when model-independent dissolution parameters were employed to assess the coating quality (Table 2).

In pilot scale batch I and lab scale batch II as an example, the average MDT for pilot scale batch I ($n=10$) was 9.7 h whereas the MDT for lab scale batch II ($n=9$) was 5.4 h. This difference between the two scales was statistically significant at $\alpha=0.05$ ($P=1.01\times10–20$) and indicates that the dissolution of diprophyllin from the lab scale is 80% faster than the pilot scale (Fig. 2). The one missing data point in lab scale batch II was due to mechanical failure of the dissolution set-up for that particular beaker. Tablet number 58 was sucked up by the sampling tube which resulted in the termination of the sampling procedure on the 14th hour out of the 20-hour cycle.

Whilst there was a distinctive difference between the two scales when the dissolution rate constant was employed as a quality parameter, the direction of the relationship was in reverse to that displayed by the MDT. For instance, using lab scale batch II and pilot scale batch II, the average dissolution rate constant for the lab scale was 2.26 mg/h; this was 1.03 mg/h higher than the average rate constant for the pilot scale. This 46% variation was found significant at the 0.05 level, with a P

Table 2
Systematic *t*-test (unpaired, two-tailed) on the comparison of the pilot and lab scale batches using various coating quality parameters

	MDT (h)	Zero order release rate constant (mg/h)	Weight gain (mg)	TEFPS (%)	Coating layer thickness (um)
PBI Mean	9.7	1.29	42.5	20.9	190
PBII Mean	9.8	1.23	42.6	20.7	188
LBI Mean	5.4	2.30	42.8	19.4	200
LBII Mean	5.4	2.26	42.5	19.5	202
PBI and LBI					
SD *	2.2	0.52	0.490	0.815	6.02
RSD ** %	29	29	1.15	4.05	3.09
t-test	2.0E−20	1.0E−17	0.185	9.0E−08	4.1E−08
PBI and LBII					
SD	2.2	0.50	0.738	0.769	7.10
RSD %	29	28	1.74	3.81	3.63
t-test	1.01E−20	3.09E−20	0.930	3.21E−07	5.08E−07
PBII and LBI					
SD	2.3	0.55	0.387	0.744	6.72
RSD	30	31	0.906	3.70	3.47
t-test	3.36E−16	5.89E−18	0.247	5.37E−08	1.02E−10
PBII and LBII					
SD	2.2	0.53	0.686	0.698	7.80
RSD	29	30	1.61	3.46	4.00
t-test	1.36E−15	2.87E−20	0.707	2.24E−07	1.28E−08

PBI and PBII correspond to pilot scale batch I and II respectively, while LBI and LBII are lab scale batch I and II respectively.
* Standard deviation.
** Relative standard deviation.

value of 2.87×10–20 yield. All other batches were also evaluated and results are presented Table 2. These findings clearly indicate that drug release from the lab scale tablets was faster than that of the pilot scale.

3.1.2. Weight gain

The weight gain for all tracer-tablets was recorded prior to the TPI analysis and the subsequent dissolution studies. A comparison of the weight gain between the pilot and the lab scales was carried out. Moreover due to the non-destructive nature of the TPI, the relationships between weight gain, terahertz parameters (for coating quality analysis) to the dissolution performance could be investigated using the same tracer-tablets. All four batch combinations between the lab and the pilot scales were investigated (Table 2). Here pilot scale batch I and lab scale batch II are used as an example. The average weight gain for the lab scale batch II was 42.51 mg ($n=10$) compared to 42.54 mg in the pilot scale batch I ($n=10$). The relative standard deviation of 1.74% indicated low variation in weight gain between the two scales. With the null hypothesis at $\alpha=0.05$, all *P* values generated from the systematic inter-scale *t*-tests on the four batches were above the significance level for weight gain, indicating no significant difference in tablet weight gain between the lab and pilot scales (Table 2). A *P* value as high as 0.93 was obtained between the two scales when the lab batch (batch II) was compared to the pilot batch (batch I). These results show that the tablet weight gain as a sole coating quality parameter is insufficient for the prediction of the dissolution/functional performance of the sustained-release product.

3.1.3. Terahertz parameters

In contrast to the results obtained from the weight gain measurement, both terahertz parameters, TEFPS and coating layer thickness are able to discriminate between the lab and the pilot scale batches. Using the example of the batches pilot scale batch II and lab scale batch I the relationships between the pilot and the lab scales can be illustrated. The derived average TEFPS for the lab scale was 19.4% of the reference reflection from a mirror whilst on average 20.7% of the terahertz pulse was reflected off the surface of a tablet from the pilot scale batch, with a relative standard deviation around 3.7%. This is in contrast to the 0.9% relative standard deviation calculated for the weight gain of the same batch combination. This 3.7% was significant in differentiating the two batches, with a *t*-test *P* value well below 0.05 (Table 2). The average coating layer thickness was around 200 μm. On average, the lab batch exhibited a 12 μm thicker than that of the pilot scale. Between the pilot scale batch II and lab scale batch I a significant variation of around 6% and a relative standard deviation of 3.5% were observed. In general we have found that the terahertz parameters for the analysis of coating quality (derived from the dry tablet) gave a better correlation with the true functional performance than the weight gain.

3.2. Early indications of correlations between terahertz parameters to dissolution

In order to investigate the relationship between the model-independent dissolution parameters and terahertz parameters as well as the tablet weight gain, the correlation coefficient was

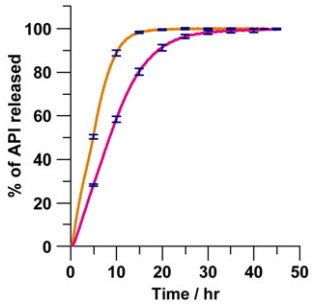

Fig. 2. Dissolution profiles of lab scale batch II (lab scale) and pilot scale batch I. Error bars indicated the intra-batch variation ($n=9$ for lab scale batch II and $n=10$ for pilot scale batch I). Lab scale batch II reached 100% release at 20 h, whereas pilot scale batch I reached 100% release at 40 h. Dissolution data points were collected at 1-min intervals.

calculated. To avoid inter-batch coating variations interfering with the data analysis, coating parameter correlations were carried out systematically on the following batch combinations: pilot scale batch I and lab scale batch I, pilot scale batch I and lab scale batch II, pilot scale batch II and lab scale batch I, pilot scale batch II and lab scale batch II. One way of visualising the correlation behaviour of a terahertz parameter with dissolution is to use a linear regression. The interpretation of the information derived was carried out in a cautionary manner as we acknowledge the regression line effectively runs through two averaged data points (one being the lab and the other being the pilot scale). However, the deviation of each end of the average measurement value was reflected in the correlation coefficient (R) and the coefficient of determination (R^2). For all these batch combinations the R and the R^2 between the MDT and average coating thickness, average TEFPS and weight gain were calculated.

For the batch combination pilot scale batch II and lab scale batch I for example the correlation coefficient between MDT and average TEFPS was 0.89 and with the average coating layer thickness, it was −0.95. These results demonstrate a strong positive correlation for the TEFPS with the MDT and a strong negative correlation with the coating layer thickness. In addition, a R^2 of 0.79 and 0.90 was calculated for the correlation between MDT and TEFPS and coating layer thickness respectively. These results indicate that the 79% and 90% of the MDT dissolution behaviour can be explained by terahertz parameters. All correlations with terahertz parameters were much stronger than the correlation between MDT and weight gain, with the weight gain correlation showing a R^2 of 0.09 (Fig. 3). All other three batch combinations (pilot scale batch I and lab scale batch I, pilot scale batch I and lab scale batch II, pilot scale batch II and lab scale batch II) showed similar trends.

As anticipated, the TEFPS correlates negatively with the zero order release rate constant. The coating layer thickness showed a positive correlation coefficient (0.93), indicating that the thicker the coating layer the faster the dissolution rate. All terahertz parameters yield an R^2 value much higher than that of the weight gain when correlated to the release rate constant. Both terahertz coating quality parameters show strong correlation with the model-independent dissolution parameters while the weight gain alone exhibits a very poor correlation with any of the parameters tested.

3.3. Contributing factor of terahertz correlation to dissolution

The analysis of the correlations between terahertz parameters and the dissolution parameters revealed that the thicker the coating layer, the faster the dissolution rate and the shorter the dissolution process. These findings are counterintuitive and in contrast to the results from the terahertz study by Spencer et al., where the dissolution rate was higher for thinner coating thickness for their enteric coated tablets examined [18]. The coating layer thickness is the major rate determining factor during dissolution for sustained-release tablets, if the quality and the physical structure of the film were consistent for all tablets examined. In the case of the tablets investigated in this study

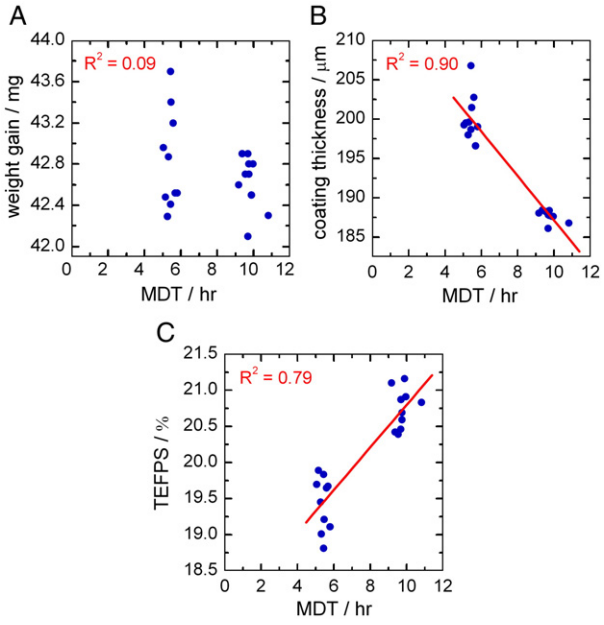

Fig. 3. Using pilot scale batch II and lab scale batch I as an example, correlations of MDT with dry-state coating quality parameters: weight gain, TEFPS and coating layer thickness are shown. Both TEFPS and coating layer thickness generated with TPI showed better correlation than the weight gain. Moreover, when TEFPS and coating layer thickness were employed as coating quality parameters, the pilot and the lab scales were depicted as two distinctive clusters with no overlap. Whereas when the weight gain was employed, overlapping of the data ranges from the two scales were visible. The red trend-line is added to aid visualisation on the direction of the correlation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

with similar weight gain, coating layer thickness is no longer the only dominant parameter that governs the dissolution rate. In addition to the layer thickness, other physical parameters such as the density of the coating have to be taken into account. In general, a change in the film density can be due to properties at the macroscopic level (such as the film porosity) and/or caused by different molecular arrangements of the polymer as a result of variations in the processing conditions (such as a change in drying temperature or drying rate). The variations in the coating process parameters are summarised in Table 1. In the context of a change in coating density, the most significant parameters are pan speed, spray rate and drying air volume. The pan speed was decreased from 25 rpm to 11.6 rpm while the spray rate was increased from 9 to 10.8 g/min during scale-up. Slowing down the pan speed lengthens the tablet transient time through the spray zone. This along with an increased spray rate results in wetter tablets. In order to run the coating process under these conditions it is necessary, among other parameters, to increase the drying air volume. The combination of more suspension being applied per unit time and correspondingly higher drying rate is most likely to lead to a change in density without changes in porosity. Further research is in progress to investigate this further.

In our formulations, the SEM images showed that there was no indication of a significant change in porosity between the different processing scales (Fig. 4). During dissolution, the

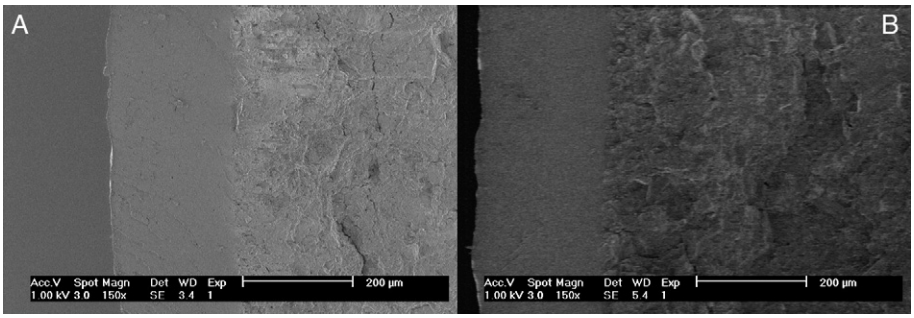

Fig. 4. Cross-section SEM images of a sustained-release tablet from the lab scale (A) and a sustained-release tablet from the pilot scale (B). Some pores are visible in the film coating, with no apparent porosity differences between the pilot and the lab scale.

sustained-release coating used in this study does not erode but is an insoluble porous matrix. The lag time of the dissolution process corresponds to the medium penetrating into the polymer coat, dissolves and leaches the hydrophilic pore former (polyvinyl alcohol–polyethyleneglycol graft copolymer) out of the hydrophobic (polyvinyl acetate) coating matrix [19]. Following this pore formation process in the coating matrix, is the linear part of the dissolution curve, where a zero order kinetic is observed. This provides slow and steady release of the drug over time within the therapeutic range.

Both TEFPS and coating layer thickness determination are strongly influenced by the complex refractive index $\tilde{n}=n+i\kappa$ of the polymer coating, where n is the real refractive index and κ is the extinction coefficient. The reflection of the terahertz pulse is dependent on the real refractive index of the surface (n_s) by $R=(n_s-n_{air})/(n_s+n_{air})$, where n_{air} stands for the real refractive index of air, and its absorption α of the coating material by $\kappa=(\alpha c)/(4\pi\nu)$, where c is the speed of light and ν is the frequency. In addition, the TEFPS is somewhat sensitive to signal scattering losses due to surface coating roughness. As reported earlier, this property makes TPI a valuable tool to detect subtle orange peel defects on the coating structure [11]. When correlating the TEFPS to the dissolution parameters, it was observed that subtle changes in the visible surface roughness on some tablets (visible in TEFPS 2D terahertz maps) did not constitute significant variations in the signal strength reflected back from the surface of the tablet coat. The TEFPS used in this study is an average of about 4000 pixels over the whole tablet surface; hence subtle changes in some of these pixels do not affect the average TEFPS.

In this study the chemical properties of the coating material were identical during the scale-up process: raw materials, relative quantity, volume and composition for the coating formulation were exactly the same for both scales. The only differences between the process scales were of physical nature and the density of the coating matrix was likely to be the physical property primarily responsible for the observed changes in the terahertz parameters. It has been shown in earlier studies that density is a major contributor to changes in the terahertz refractive index [9,20]. The average TEFPS of the pilot scale was higher than that of the lab scale (Table 2) and we therefore conclude that the polymer film prepared under these conditions has a higher density compared to the film obtained in the lab scale process [20]. A higher density film leads to a relatively longer dissolution time and a slower dissolution rate for the pilot scale as the permeability of the dissolution medium into the coating matrix is lower.

The assumption that density variations lead to the changes in TEFPS was further confirmed by the change in coating layer thickness between the two scales. Since the same weight gain resulted in different coating layer thickness for lab scale and pilot scale, the physical structure of the film must be different. At identical weight gain the coating layer was thicker in the lab scale. It can be concluded that the density of the film must be lower in the lab scale. A lower density that results in a higher permeability of the film neatly explains the faster dissolution of the drug from tablets with a thicker film of the same material. In order to estimate the respective film density, the film volume was approximated by multiplying the film thickness with the surface area of the tablet. The ratio of weight gain and film volume gives the estimated density of the film coating. The plot of MDT vs. film density shows that the dissolution is faster in case of a lower density film (Fig. 5).

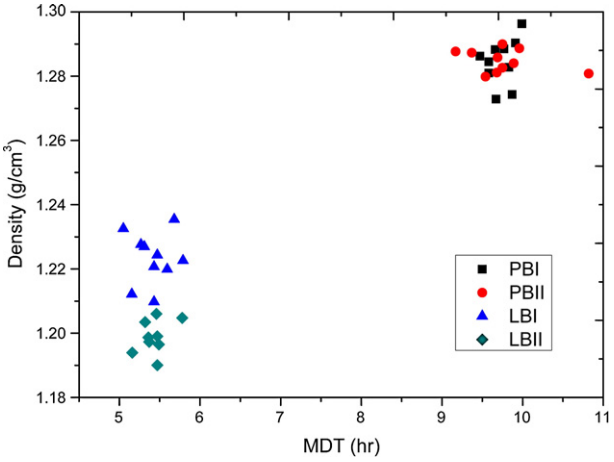

Fig. 5. The relationship between MDT and density is demonstrated here. Both pilot scale batches (PBI and PBII) clustered together, while the same applied for the lab scale batches (LBI and LBII). It is clear that both pilot scale batches exhibit longer MDT (or slower dissolution rate) due to higher coating film density; while both lab scale batches show shorter MDT (or faster dissolution rate) due to lower coating film density.

As illustrated, we have found that the coating matrix for the pilot scale was thinner and denser than that of the lab scale. This change in density corresponds with the dissolution behaviour (longer MDT and slower zero order release rate constant) observed in the pilot scale and is directly reflected in the terahertz signal. Our initial findings reveal the potential of TPI for pharmaceutical coating analysis: not only is it possible to accurately and non-destructively determine the film thickness distribution over the whole surface of the tablet but with TEFPS an additional quality parameter is introduced that correlates directly to the coating performance and can be used to predict the dissolution behaviour in sustained-release coated tablets.

3.4. Inter-batch variations

Whilst the ability to detect intra-batch variations was demonstrated by Ho et al., inter-batch variations remain to be investigated [11]. In this study, inter-batch variations were apparent within each of the scales, thus all coating quality comparisons between the two scales were done with batch combinations as outlined previously. All inter-batch variations in each of the dry-state coating quality parameters were examined. While most of the coating parameters showed statistically in-significant inter-batch differences within each of the scales, the zero order release rate constant measured for the pilot scale batches showed a significant difference. The average drug release rate constant for pilot scale batch I was 1.29 mg/h and 1.23 mg/h for pilot scale batch II. The relative standard deviation between the two batches was 3.49%, and this was a significant inter-batch variation for the pilot scale at $P=0.003$. In contrast to the pilot scale, both batches of the lab scale tablets investigated indicated no major inter-batch variations on all coating parameters examined.

4. Conclusion

This was the first study to directly examine the relationship between terahertz parameters and product performance using sustained-release tablets produced during a scale-up process. Model independent dissolution parameters were used to characterise the differences in product performance between the pilot and the lab scales. Weight gain, the traditional non-destructive indicator for coating quality in the dry-state, failed to reflect the functional performance of the product. Conversely terahertz parameters could be correlated with the actual product performance and showed potential to predict the dissolution behaviour of sustained-release tablets. It was found that in the sustained-release system investigated, the thicker the average coating layer thickness, the shorter the dissolution time; while the stronger the TEFPS, the longer the dissolution time. Terahertz results suggested that this may be a function of the film coating density, and their role was clearly reflected in the dissolution performance. The impact of these dry-state terahertz parameters on dissolution performance was also investigated in this study. These initial findings warrant a more extensive systematic study to provide sufficient statistical power to further understand the extent of the relationship between the dry-state terahertz parameters and product performance.

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