Investigating Dissolution Performance Critical Areas on Coated Tablets: A Case Study Using Terahertz Pulsed Imaging

LOUISE HO,[1,2,3] RONNY MÜLLER,[4] CORNELIA KRÜGER,[4] KEITH C. GORDON,[5] PETER KLEINEBUDDE,[4] MICHAEL PEPPER,[2,3] THOMAS RADES,[1] YAOCHUN SHEN,[6] PHILIP F. TADAY,[3] J. AXEL ZEITLER[7]

[1]School of Pharmacy, University of Otago, P.O. Box 56, Dunedin, New Zealand

[2]Cavendish Laboratory, University of Cambridge, Cambridge CB3 0HE, UK

[3]TeraView Ltd, St. John's Innovation Park, Cambridge CB4 0WS, UK

[4]Institute of Pharmaceutics and Biopharmaceutics, Heinrich-Heine-University, Universitätsstr. 1, Düsseldorf D-40225, Germany

[5]Department of Chemistry, MacDiarmid Institute for Advanced Materials and Nanotechnology, University of Otago, P.O. Box 56, Dunedin, New Zealand

[6]Department of Electrical Engineering and Electronics, University of Liverpool, Brownlow Hill, Liverpool L69 3GJ, UK

[7]Department of Chemical Engineering and Biotechnology, University of Cambridge, New Museums Site, Pembroke Street, Cambridge CB2 3RA, UK

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ABSTRACT: During the process development of coated tablets, knowledge on the formation and the location of film coating 'weak spots' is a key factor to the success of the process and the resulting product batch. It is understood that the performance of the product batch may be greatly limited, and often compromised, by weak spots on the tablet film coat. This study uses circular, biconvex tablets to investigate the ability of terahertz pulsed imaging (TPI) to identify the affected areas on the tablet film coat that are critical for dissolution performance. From the TPI analysis we determined that the tablet central band exhibited the thinnest film coating, lowest coating density and highest surface roughness and thus was the performance limiting area of the film coating. Dissolution tests confirmed that the film coating on the tablet central band was indeed dissolution rate determining, with a faster mean dissolution time (MDT) of 7.4 h in comparison to 10.4 h for the convex top/bottom surface. TPI, as a nondestructive analytical technique, showed potential to be employed as a process analytical tool to probe film coating weak spots during film coating development and to assess the effect on the subsequent dissolution performance. © 2009 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 99:392–402, 2010

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INTRODUCTION

Tablet coating is one of many unit operations involved in the manufacturing of pharmaceutical

Correspondence to: Louise Ho (Telephone: +64-3-479-7275; Fax: +64-3-479-7034; E-mail: lchh2@cam.ac.uk)

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solid dosage forms. This process is usually carried out by applying a polymer coat (either an aqueous polymer dispersion or organic polymer solution) on tablet surfaces to improve the physicochemical properties for aesthetic or therapeutic purposes.[1] In the context of this study, weak spots are defined as affected surface areas on the film coating that subsequently lead to a faster drug release kinetics compared to the release profile from other areas of the tablet. When the coating process is running at optimal conditions, the transit time for each tablet and the exposure of all tablet surfaces through the spray zone should be the same. However in practice, these optimal conditions may be difficult to achieve. Consequently instead of a uniform film coating, defects and weak spots may appear in the finished product. If tablets were coated for therapeutic purposes, deviations in the drug bioavailability from the therapeutic range and batch rejection may be some of the consequences of such weak spots.[2]

The accurate detection and monitoring of weak spots in the film coating unit operation is a pressing issue, vital to the success of the product and process development. Terahertz pulsed imaging (TPI), a mapping technique that operates in the far-infrared region of the electromagnetic spectrum (2–120 cm^{-1}), uses short pulses of coherent broadband radiation to probe information relating to the coating quality of a pharmaceutical dosage form. Subpicosecond pulses of terahertz radiation are directed onto the surface of a tablet and reflections of the pulse are recorded as a function of time as the pulse propagates through the film coating structure. The technique was found to be universal, as most pharmaceutical excipients are either transparent or semi-transparent at terahertz frequencies, thus allowing the nondestructive analysis of the film coating. The axial penetration depth can be as long as 5 mm on the current generation of TPI instruments. In the context of pharmaceutics, the technique has been applied to investigate sugar, enteric and sustained-release coatings.[3–5] A number of parameters can be extracted from the reflected terahertz pulse. One of the parameters that can be measured by TPI directly—coating thickness (CT), was used to investigate the thickness uniformity of the film coat over the entire surface of a tablet and the intra- and inter-batch coating variability.[5,6] The TPI CT measurements were validated by optical microscopy measurements.[6] The terahertz electric field peak strength (TEFPS), which is defined as the magnitude of the reflected terahertz pulse from the tablet surface relative to its initial magnitude, provided information on the relative coating density over the surface of a single tablet. This parameter was subsequently utilised to compare the differences in film coating density of samples from different batches and scales.[7,8] Terahertz interface index (TII) is the magnitude of the reflected terahertz pulse from the interface normalised to that of the reflection from the film coating surface.[9] This parameter denotes the changes in the physicochemical properties at the interface thus is ideal for probing for information at the interface between the film coating and the tablet core. Both CT and TEFPS measurements showed good correlation to the corresponding dissolution performances.[8] In addition, TPI was found to have promising potential as a process analytical tool to study film coating processes in the laboratory scale and for process scale-up.[7] Terahertz parameters (CT and TEFPS) were shown to be more product specific and more informative on the product quality than nonspatially resolved, traditional coating quality parameters (e.g. total tablet weight gain and the amount of polymer applied). Building on our previous work, this study explores the capability of TPI to detect the weakest area of the film coat and assessing its effect on dissolution.

MATERIALS AND METHODS

Sustained-Release Coated Tablets

Tablet cores were round and biconvex (3 mm in height and 8 mm in diameter). The average weight for the tablet core was 252 mg. Tablets contained 10% w/w diprophyllin (API), 84.5% w/w lactose monohydrate (Flowlac®), 5% w/w vinylpyrrolidone–vinyl acetate copolymer (Kollidon® VA 64) and 0.5% w/w magnesium stearate. Two lab-scale (4 kg) batches were coated in the same fashion, with the same coating formulation. The composition of the coating formulation was: 50% w/w polyvinyl acetate dispersion (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. Tablets were coated using a BFC5, Bohle Film Coater (L.B Bohle, Ennigerloh, Germany). The coating pan dimensions were

316 by 356 mm (diameter by length), equipped with a single two-way spray nozzle (type 970/7-1 S75, Düsen-Schlick GmbH, Untersiemau, Germany). Ten samples were randomly selected from the finished product of each lab-scale batch. These were tablets coated at 17.5 mg/cm^2 and cured for 48 h at 60°C. To investigate if the target weight gains for the two batches were comparable, 100 tracer tablet cores were weighed, numbered (with a permanent marker) and incorporated into each batch before the application of a transparent film coating.[8] The target weight gains for the two batches were similar, with a polymer weight gain of around 42 mg obtained for each tablet selected. An additional 60 tablets were also sampled during the coating process of batch I to investigate the formation of the film coating weak spots. These samples were randomly selected at 10% increments of the amount of sustained-release polymer applied from 7.0 mg/cm^2 to the penultimate coating level (7.0, 8.7, 10.5, 12.2, 14.0 and 15.7 mg/cm^2). Tablets below the 7.0 mg/cm^2 were not included in this study as the CT around the central band was below the axial resolution limit of the current TPI set-up, which has a minimum CT requirement of around 38 μm.[7]

Terahertz Parameters

A TPI imaga2000 (TeraView, Cambridge, UK) was used for the terahertz image acquisition. Details concerning the core technology, the data acquisition process and the image analysis procedure have been reported previously.[5,6,10] In this study, all tablets were examined in the point-to-point mapping mode, with a 200 μm step size. A full scan was carried out over all surfaces of every biconvex sample tablet. This took about 45 min to complete for the tablets investigated in this study (around 15 min on each of the three surfaces). The scan involved sequential imaging of the convex top and bottom surfaces (collectively called the top and bottom domain hereafter) and the cylindrical central band.

The terahertz parameters extracted for this study were CT, TEFPS and TII. All terahertz parameters were derived from the terahertz time domain waveform which contained the information for constructing the 2D tablet surface image and the 3D tablet model.[7] For comparison of the terahertz parameters between the top and bottom domain and the central band, the average over the 2600 pixels acquired from the top and bottom domain was determined (1300 pixels on each convex surface) and compared to the average value over 1300 pixels around the central band (Fig. 1). Using terahertz pulsed spectroscopy in transmission mode an average refractive index of 1.68 was determined for the film coating layer in the current study. The determination of CT, TEFPS and TII were described previously.[6,8,9] Briefly, the terahertz parameters were derived as follows:

$$\mathrm{TEFPS} = \frac{S}{R} \times 100, \quad \mathrm{TII} = \frac{I}{S} \times 100$$

$$2\mathrm{CT} = \frac{\Delta tc}{n}$$

where S is the amplitude of the surface reflection off the film coating, R stands for the amplitude of the reference incident terahertz pulse (derived from a mirror) and I is the amplitude of the interface reflection (notwithstanding the direction

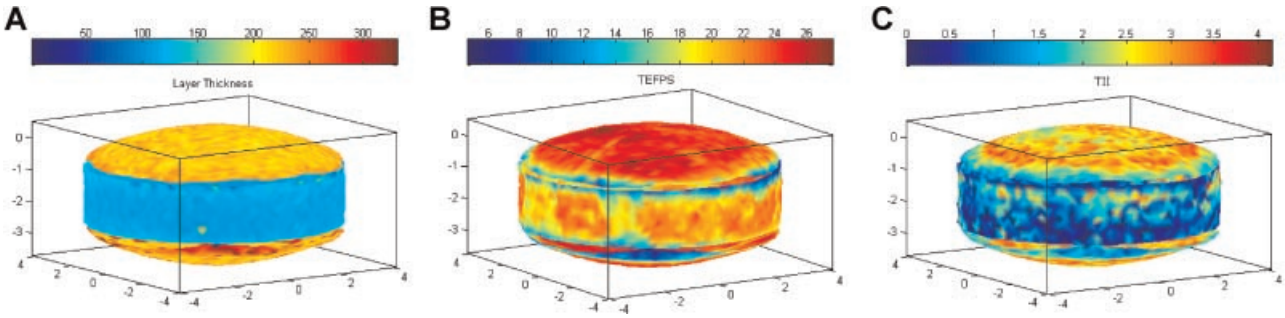

Figure 1. 3D, biconvex tablet models were constructed using the terahertz parameters: CT (A), TEFPS (B) and TII (C). The thickness of the film coating is lower on the central band with a lower TEFPS and TII than the film coat on the top and bottom domain. The units for the colour scales are in μm for CT (A) and % for both TEFPS (B) and TII (C).

of the peaks). Both TEFPS and TII are presented as a percentage value (%). Δt is the time delay between the terahertz reflections, c is the speed of light and n is the refractive index of the coating matrix. CT is expressed in μm.

SEM Imaging

Three film coated tablets from batch I were imaged by scanning electron microscopy (SEM, FEI Philips XL30 sFEG, Philips Electron Optics, Eindhoven, The Netherlands) and micrographs were taken from the top and bottom domain and the central band. The samples were imaged by SEM without the application of a metal coating, as low voltage (1–2 kV) was employed to avoid the build up of the electrostatic charge on the surface of the film coating polymer. The surface images were taken at varying magnification (at 40×, 150×, 300× and 1000×) for visual comparison of surface roughness between the tablets. The images taken at a magnification of 150× were used to measure the droplet deposition size. Cross-sectional images were also obtained from a tablet at a magnification of 270 for the comparison of surface roughness on both domains (top and bottom vs. central band). These cross-sectional images were used for the calculation of the surface roughness factor (R_a). In this study, R_a is defined as follows:

$$R_a = \frac{D}{L}$$

where D is the surface distance of the profile curve and L stands for the sampling length (Fig. 2).

Dissolution Testing

To compare the release behaviour from the top and bottom domain versus the tablet central band, dissolution testing was carried out on tablets from batch I, post terahertz imaging. A further 36 tablets (finished product) were randomly selected from batch I and covered with a waterproof coating (Plasti Dip®, Performix, Petersfield, United Kingdom) on the following surfaces: (a) all surfaces as control (12 tablets), (b) top and bottom domain to observe the release from the central band (12 tablets) and (c) central band and one convex surface to observe the release from the other convex surface (12 tablets) (Fig. 3). The total surface area for each convex surface and the central band is similar at around 0.5 cm^2. Dissolution testing was carried out in accordance with the USP guidelines for sustained-release dosage forms. The in-line dissolution set-up for this study was a USP 2 paddle apparatus (AT 7smart On-line, Sotax, Allschwil, Switzerland) coupled to a UV/VIS spectrometer (Lambda 2 UV/Vis, Perkin-Elmer GmbH, Düsseldorf, Germany). Samples were taken at 1-min intervals and the drug concentration in the dissolution medium was detected by UV spectroscopy at 272 nm, which is the wavelength of maximum absorption of diprophyllin in an aqueous medium. The rotational speed for the paddles was 100 rpm in 900 mL of water, kept at a constant temperature of 37°C. To study the drug release characteristics, the mean dissolution time (MDT) and the zero order release rate (the gradient of the dissolution curve, from the onset of drug release for 3 h) were derived as the model-independent dissolution parameters.

Investigation of Surface Roughness Post Dissolution

Eight tablets were further randomly sampled from batch I to investigate the effect of polymer plasticity on film coating surface roughness, post dissolution.

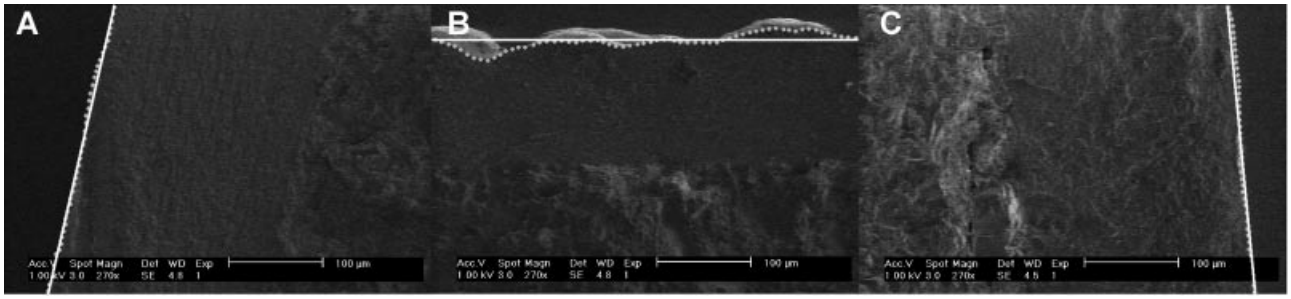

Figure 2. Cross-section images taken by SEM of the top and bottom domain of a coated tablet (A and C) and the central band of a coated tablet (B). R_a was calculated as the ratio of the average surface distance of the profile curve (dotted line) over the sampling length (straight line). All three images were taken at a magnification of 270×. The scale bar is for 100 μm.

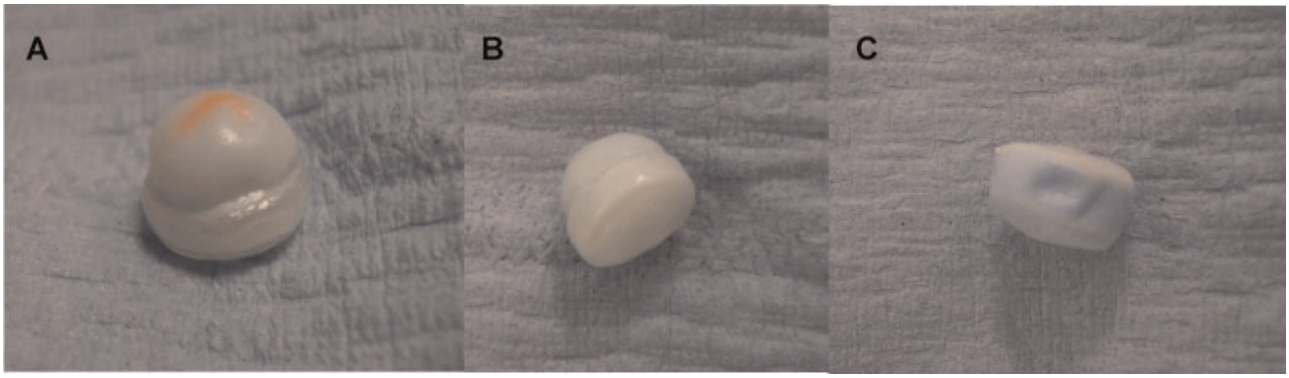

Figure 3. Tablets covered with waterproof coating on the central band and one convex surface to observe the drug release from the other convex surface (A and B). Waterproof coating covered on the top and bottom domain to determine the release from the tablet central band (C).

These tablets were analysed with TPI to investigate the starting physical properties around the central band, and then immersed in the dissolution medium (water) at 37°C. One tablet was taken out of the water after the following time intervals: 5 and 30 s, 2 and 30 min and 2, 8, 16 and 25 h. Each tablet was dried over silica gel for 24 h. Once dried, the central band of these tablets was again examined by TPI and SEM to determine the effect of polymer plasticity on film coating surface roughness during dissolution.

RESULTS AND DISCUSSION

TPI/SEM Analysis of Dry Tablets

The terahertz waveform and the terahertz parameters CT and TEFPS were successfully determined from both lab-scale batches. Distinctive differences were observed in the terahertz waveform derived from the film coating on the top and bottom domain compared with the film coating on the central band. The interface reflection (between the film coating and the tablet core) in the terahertz waveform was a minimum (negative peak) for the film coating on the top and bottom domain. In contrast, the interface reflection was a maximum (positive peak) in the terahertz waveform for the film coating around the central band (Fig. 4). The coating/core interface minimum indicates that the refractive index of the film coating is higher than that of the tablet core for the top and bottom domain. Conversely, the interface reflection maximum observed from the film coating around the central band means the refractive index of the film coating is lower

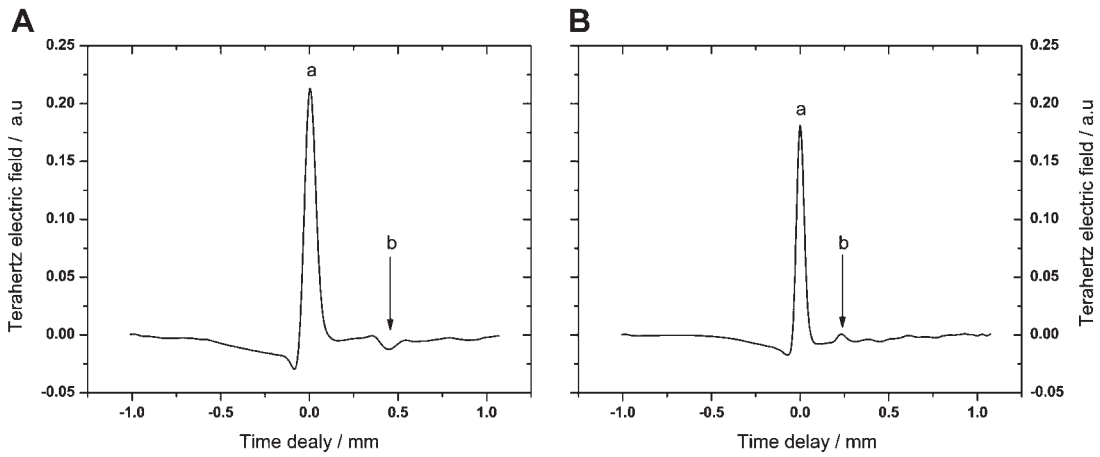

Figure 4. Terahertz waveforms derived from the film coating on the top and bottom domain (A) and the central band domain (B) of a round, biconvex tablet. The interface reflection (b) is a minimum in the terahertz waveform in (A) and a maximum in (B).

than that of the tablet core. Since the refractive index of the tablet core is constant when comparing the two film coating domains (top and bottom vs. central band) on the same tablet, the discrepancy in the direction of the interface reflection indicates the refractive index of the film coating on the top and bottom domain is higher than the film coating on the central band.

An average value was calculated for TEFPS from the 10 sampled tablets and the results for the two lab-scale batches are summarised in Table 1. The average TEFPS derived from the film coating on the top and bottom domain for batch I was 20.6% (±0.5%) and 20.9% (±0.8%) for batch II. The mean TEFPS value for the top and bottom domain was higher than that derived from the central band for both batches; where an average TEFPS of 16.9% (±0.5%) was determined from the central band domain for batch I and 16.8% (±0.3%) for batch II. Two-tailed, paired *t*-tests were carried out on the TEFPS values to compare the film coating characteristics from the top and bottom domain to the central band. A *p*-value of 2.7×10^{-9} and 2.8×10^{-8} were yielded for batches I and II respectively (Tab. 1). As the *t*-test *p*-values for both batches were below the null hypothesis ($\alpha = 0.05$), it denoted the difference in TEFPS between the film coating characteristics on the top and bottom domain compared with the central band was statistically significant. We also observed a statistically significant difference in TII between the two film coating domains (Tab. 1). Like TEFPS, the mean TII value for the top and bottom domain was much higher than that form the central band for both batches. An average TII value of 3.2% (±0.1%) for batch I and 3.1% for batch II were determined from the film coating on the top and bottom domain, whereas 0.9% (±0.1%) for batch I and 0.7% (±0.1%) for batch II were derived from the central band domain.

Table 1. Results on All Terahertz Parameters: TEFPS, TII and CT for Both Lab-Scale Batches

	TEFPS (%)		TII (%)		CT (μm)	
	CB	TB	CB	TB	CB	TB
Batch I						
S1	17.3	21.2	1.0	3.1	130	247
S2	16.0	20.3	0.9	3.2	142	266
S3	17.2	20.5	0.8	3.3	131	250
S4	16.6	21.2	0.9	3.3	120	235
S5	17.5	20.3	1.1	3.1	128	247
S6	16.7	19.9	0.7	3.2	134	255
S7	17.1	20.7	0.9	3.2	121	238
S8	17.7	20.5	0.9	3.2	118	236
S9	17.1	21.5	1.0	3.2	128	246
S10	16.2	20.5	0.9	3.0	142	274
Mean	16.9	20.6	0.9	3.2	129	249
STD	0.5	0.5	0.1	0.1	8	13
t-test	2.7E−09		3.9E−13		1.5E−15	
Batch II						
S1	17.3	21.0	0.7	3.2	163	277
S2	17.1	21.5	0.7	3.3	145	255
S3	16.7	19.7	0.8	3.0	154	270
S4	16.6	21.4	0.6	3.3	153	262
S5	16.5	21.0	0.8	3.0	161	268
S6	16.6	20.9	0.8	3.0	148	261
S7	16.7	21.4	1.0	3.0	148	258
S8	17.1	19.3	0.7	2.9	148	252
S9	16.7	22.1	0.7	3.0	146	255
S10	17.0	20.9	0.7	3.2	149	259
Mean	16.8	20.9	0.7	3.1	152	262
STD	0.3	0.8	0.1	0.1	6	8
t-test	2.8E−08		1.9E−12		7.9E−17	

CB stands for central band and TB stands for the top and bottom domain.

The relationship between TEFPS, the refractive index and the absorption coefficient was previously described in Ho et al.[8] The chemical composition in the film coating across the two domains on the tablet is the same, thus the differences must be physical in nature. As most pharmaceutical coatings are transparent/semi-transparent in the terahertz frequency range, the TEFPS is related to the refractive index of the film coating surface (n_s) via the following equation:

$$R = \frac{n_s - n_{air}}{n_s + n_{air}}$$

where R is the reflection coefficient of the terahertz pulse and n_{air} stands for the refractive index of air.[9] It is clear from the equation that the TEFPS increases with increasing n_s. In this study, the TII results were employed to confirm the observations made with TEFPS. Taken the direction of the interface reflection into account, the TII results indicated that the magnitude of the terahertz reflection from the film coating and tablet core interface was higher from the top and bottom domain and that the refractive index of the film coating on the top and bottom domain was indeed higher than that of the film coating around the central band.

Physical changes in the film coating are the main causes of terahertz signal scattering and refractive index differences between the two tablet domains. TEFPS is sensitive to both signal

scattering (mainly attributed to coating surface roughness) and refractive index changes (an indication of variations in film coating density); the effect of these is not easily deconvolved.[6,8] If the relative difference in surface roughness was marginal, the observed higher refractive index in the film coating on the top and bottom domain for all biconvex tablets measured would indicate solely that the film coating density was higher on these surfaces compared with the film coating around the central band. In this study, we observed patterns of TEFPS and TII non-uniformity as a result of surface roughness around the central band (Fig. 1B and C).

To investigate the surface roughness in the film coating on the central band domain, a further investigation was carried out using SEM. Clear evidence of coating droplet deposition on the surface around the tablet central band was found, whilst the film coating surface on the top and bottom domain was comparatively smooth (Figs. 2 and 5). The size of these coating droplet deposits around the central band was estimated. Ten droplet deposits were randomly selected from the surface of each tablet central band for analysis, thus a total of 30 droplet deposits were investigated. As the droplet deposits were of irregular shapes and sizes, the Feret's Diameter of each droplet deposition was measured in both the x direction and y direction; with an average diameter of 154 μm (range from 63 to 265 μm) in the x direction and 135 μm (range from 61 to 226 μm) in the y direction. Droplet deposition at this size range can cause signal scattering in the terahertz frequency range.[11] Therefore, in addition to the film density differences between the two tablet surface domains (top and bottom vs. central band), signal scattering as a result of surface roughness also attributed to the observed TEFPS variations between the two domains. Attempts were made to quantify the degree of surface roughness on the two tablet domains; a R_a of 1.09 was measured on the tablet central band. This was 6% rougher than the top and bottom domain ($R_a = 1.02$). A similar behaviour in surface roughness was observed in a study by Rowe,[12] who found the surface roughness of the film coating to be higher within the tablet intagliation than on the rest of the tablet surface. The authors attributed this finding to the higher mechanical shear stress on the 'exposed' tablet surface due to inter-tablet 'rubbing' and subsequent smoothing of the film coating surface during the coating process. This inter-tablet contact or mutual rubbing was also documented on round, biconvex tablets that were of the same shape and size as the tablets in our study.[13] As the round, biconvex tablets are not geometrically spherical, preferred orientation is likely to occur as they pass through the spray zone during coating, resulting in variations in the coating uniformity.[14] Moreover, the surface area on the top and bottom domain was 1.07 cm^2; roughly double that of the surface area around the tablet central band (0.50 cm^2). Thus statistically, the central band domain has a smaller chance of coming into mechanical contact with another tablet surface in the tablet bed during the spray coating process than the top and bottom domain. This results in the development of a higher surface roughness in the film coating on the central band domain. To further investigate the coating surface roughness and density difference between the two tablet surface domains (top and bottom vs. the central band) during the film coating process, an average TEFPS value was also derived from 10 samples taken during the

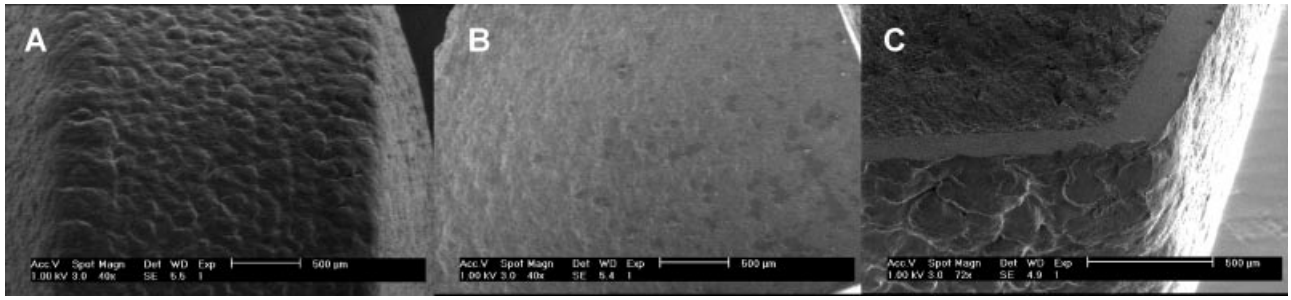

Figure 5. SEM images of the film coating on the tablet central band (A) and the top and bottom domain (B). Polymer droplet deposition on the surface of the central band (A) is visible, whilst the film coating surface on the top and bottom domain (B) is comparatively smooth. The tablet is slightly tilted in (C) to demonstrate the film coating surface roughness on the central band. The scale bar in the micrographs is 500 μm.

film coating process (for batch I) at each of the 10% increments of the amount of sustained-release polymer applied levels. Tablets were randomly selected at polymer levels of 7.0, 8.7, 10.5, 12.2, 14.0 and 15.7 mg/cm^2, and the results are summarised in Table 2. These measurements showed similar trends to the aforementioned results from the final product of batches I and II (Tab. 1), where both TEFPS and TII were higher on the top and bottom domain in comparison to the values derived from the film coating on the tablet central band. This difference was statistically significant and consistent for all polymer levels investigated in this study ($\alpha = 0.05$) (Tab. 2).

Not only the coating density and surface roughness were different for the film coating on the two domains (top and bottom vs. central band), but the thickness of the film coating also differed. This difference was evident for both lab-scale batches, where the CT on the top and bottom domain was higher than that on the tablet central band (Tab. 1). The average CT on the top and bottom domain was 249 μm (±13 μm) for batch I and 262 μm (±8 μm) for batch II. Whereas an average CT of 129 μm (±8 μm) was determined for batch I and 152 μm (±6 μm) for batch II on the central band domain. This thickness difference in the film coating between the two tablet surface domains was statistically significant. Where a *t*-test *p*-value of 1.5×10^{-15} and 7.9×10^{-17} were calculated for batches I and II respectively ($\alpha = 0.05$). As aforementioned, variations in the coating uniformity between the two tablet surface domains is largely attributed to the tablet geometry, subsequently affecting the exposure of each surface to another tablet surface (for mutual rubbing) and the exposure to the coating formulation through the spray zone (for building of CT). A lower CT on the tablet central band than the top and bottom domain as a result of tablet geometry was also reported in Wilson et al. and Pérez-Ramos et al.[6,14,15] This CT difference was also observed in tablets sampled during film coating process. At 10% increments of the amount of polymer applied (from 7 mg/cm^2 upwards), all tablets displayed a higher film CT on the top and bottom domain when compared to the CT around the central band. The average values from 10 tablets sampled at each of the polymer levels are presented in Table 2. The difference in CT between the two tablet domains was statistically significant (*p*-value $= 3.6 \times 10^{-5}$; $\alpha = 0.05$).

Dissolution Testing

The film coating on the central band domain was lower in thickness, lower in density and exhibited a higher surface roughness (thus higher resultant surface area exposed to the dissolution medium) than the film coating on the top and bottom domain. These film coating characteristics suggested faster drug release kinetics on the central band compared to the top and bottom domain, thus the film coating on the central band was subsequently identified as a potential coating weak spot. To assess the effect of the observed differences in the film coating properties on the functional performance, dissolution testing was carried out on tablets covered with waterproof coating on select areas. Dissolution was also carried out on the 10 tablets from batch I (not covered with waterproof coating) that were already analysed with TPI.

The results from dissolution testing showed that drug release from the central band was faster than release from the top/bottom surface (Fig. 6). Only one convex (top or bottom) surface was

Table 2. Average Values for All Terahertz Parameters (TEFPS, TII and CT), Measured from 10 Samples Randomly Selected at 10% Increments of the Amount of Sustained-Release Polymer Applied for Batch I

Amount of Polymer Applied (mg/cm^2)	TEFPS (%)		TII (%)		CT (μm)	
	CB	TB	CB	TB	CB	TB
7.0	19.9 ± 0.3	23.8 ± 0.5	1.7 ± 0.3	3.7 ± 0.3	46 ± 7	110 ± 9
8.7	19.4 ± 0.3	23.4 ± 0.7	1.6 ± 0.2	3.4 ± 0.3	62 ± 4	132 ± 10
10.5	19.3 ± 0.5	22.9 ± 0.7	1.3 ± 0.2	3.1 ± 0.2	76 ± 4	154 ± 8
12.2	18.9 ± 0.6	22.4 ± 0.8	1.3 ± 0.3	2.8 ± 0.2	90 ± 7	183 ± 15
14.0	17.9 ± 0.3	21.5 ± 0.6	0.9 ± 0.2	3.0 ± 0.1	107 ± 4	214 ± 12
15.7	17.9 ± 0.6	21.5 ± 1.0	1.1 ± 0.2	2.9 ± 0.2	117 ± 8	229 ± 12
t-test	9.9E−08		3.8E−06		3.6E−05	

CB stands for central band and TB stands for the top and bottom domain.

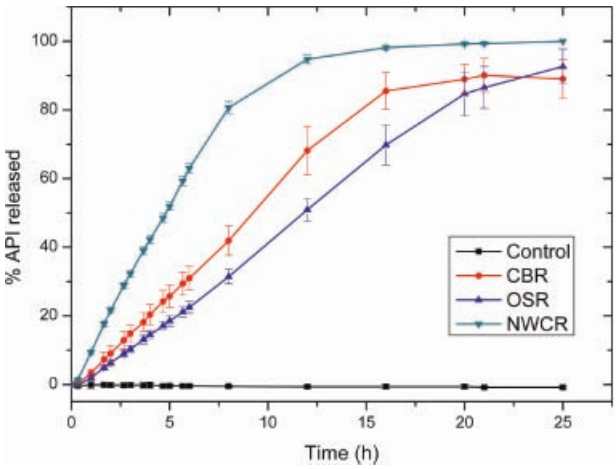

Figure 6. Dissolution profiles for drug release from the tablet central band (CBR), one convex surface (OSR) and tablets with no waterproof coating (NWCR). Each dissolution profile was obtained from an average of at least three tablets.

studied at a time as the surface area for the top and bottom domain is approximately twice that of the central band. All 12 tablets coated on both tablet surface domains as control, showed no signs of drug release throughout the duration of the dissolution testing (25 h). Three out of the 12 tablets that were covered on the top and bottom domain had the waterproof coating still intact at the end of the 25 h dissolution run; an average dissolution profile from these three tablets was obtained to depict the drug release from tablet central band (Figs. 3 and 6). The waterproof coating on all 12 tablets covered on the central band and 1 convex surface remained intact at the end of the dissolution run; an average dissolution profile of all 12 tablets was attained to illustrate the drug release behaviour from the top/bottom convex surface (Fig. 3). The average dissolution profile for both the drug release from the central band and top/bottom surface showed a slower drug release than the expected, normal average dissolution profile from tablets with no waterproof coating due to smaller surface area exposed to the dissolution medium. In addition, neither the drug release from the central band nor from the top/bottom surface reached 100% release at 25 h (Fig. 6). The MDT for the average drug release from the tablet central band was 7.40 h, whilst the MDT for the average drug release from the top/bottom surface was 10.42 h. The zero order release rate for the drug release from the tablet central band (1.1 mg/h) was 38% faster than the drug release from the top/bottom surface (0.8 mg/h). Both MDT and the zero order release rate denoted

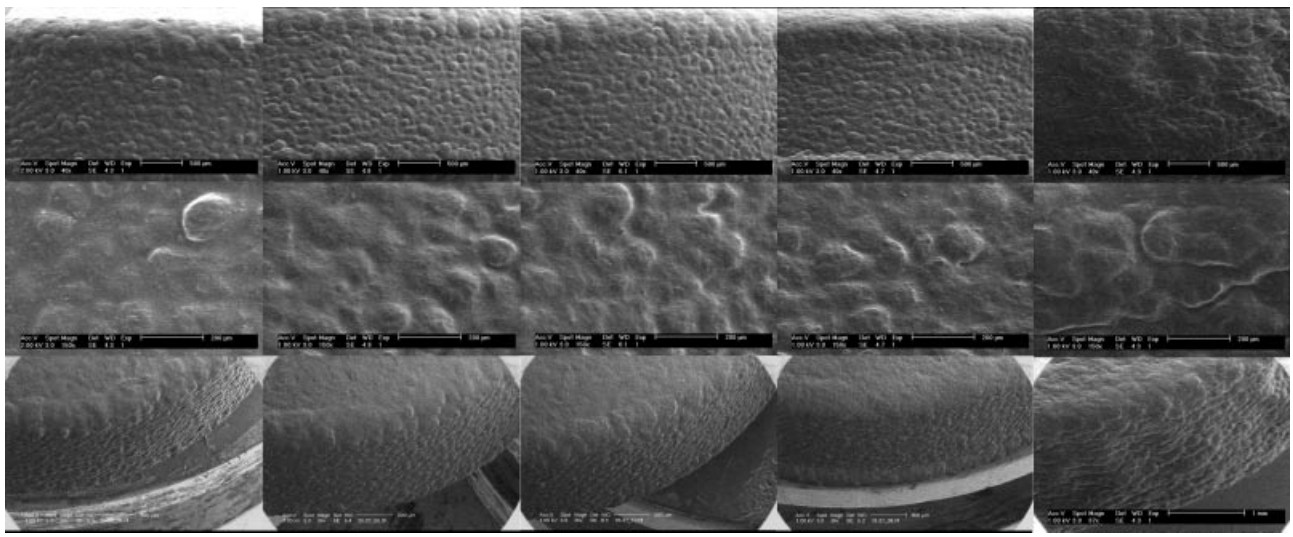

Figure 7. SEM micrographs of the central band of coated tablet retrieved at 5 and 30 s, 2 and 30 min and 2 h into the dissolution process. The top row images are taken at 40× and the second row images at 150×. The third row of micrographs are tilted top view at around 35× for a better appreciation of the extend of the surface roughness of the film coating on the central band. Film coating surface roughness on the central band sustained throughout the dissolution process up to 2 h, irrespective of the high plasticity of the sustained-release formulation.

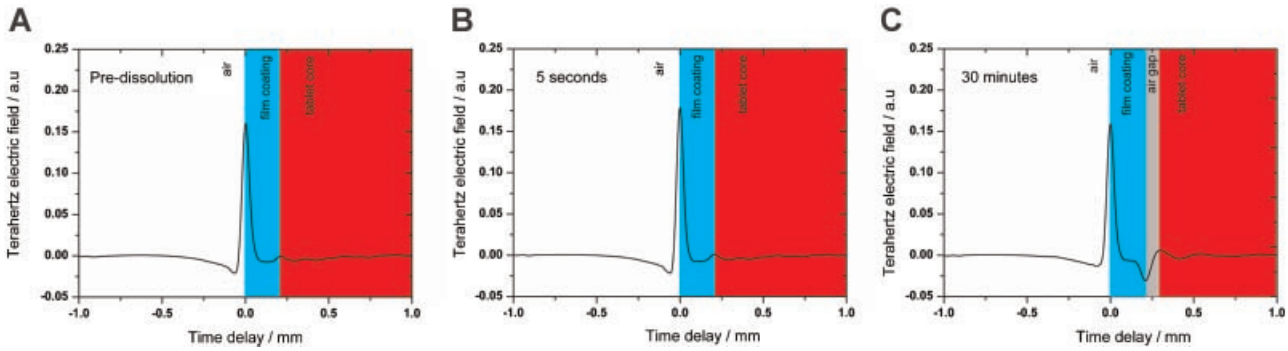

Figure 8. Terahertz waveform of the film coated tablets determined pre dissolution (A) and post dissolution (B and C). Tablets were retrieved from the dissolution medium after 5 s (B) and 30 min (C). No change was observed in the terahertz waveform before (A) and after the dissolution process at the 5-s time point (B), whereas an additional air interface was detected on the tablet that had been exposed to the dissolution medium for 30 min (C).

that the higher surface roughness, lower density and thinner film coating around the tablet central band were dissolution rate determining.

Investigation of Surface Roughness Post Dissolution

The high plasticity of the sustained-release polymer coating employed in this study has been reported to have a self-repairing effect[16] and hence raises the question whether the observed surface roughness (larger surface area exposed to the dissolution medium) around the central band was sustained in the dissolution environment. Tablets that were immersed in the dissolution medium and retrieved beyond the 2 h point could not be analysed as the film coat collapsed after drying over silica gel. TPI analysis was thus only carried out on tablets that had been immersed in the dissolution medium for 3 and 5 s, 2 and 30 min and 2 h. TEFPS indicated no distinctive changes pre- and postdissolution. This inferred that major changes in the surface roughness did not occur on tablets in the dissolution environment for up to 2 h. This was consistent with the surface morphological examination carried out with SEM (once the post dissolution tablets were dried); as no 'smoothing' effect was noticeable (Fig. 7). The terahertz waveform derived from the film coating on the central band, however, showed an additional interface on tablets that had been exposed to the dissolution medium for $\geq$30 min (Fig. 8). This additional interface reflection, depicted as a minimum in the terahertz waveform (between the surface reflection and the coating/core interface reflection), indicated an air gap between the film coating and the tablet core. The width of the air gap increased as the dissolution progressed. This was also monitored with TPI and a 98 μm air gap was recorded after 30 min, which increased to a gap of 114 μm after 2 h of dissolution.

CONCLUSION

In this case study, TPI was successfully applied to probe for coating weak spots and assess the effect on the subsequent dissolution performance. Different physical properties between the polymer coat on the top and bottom domain and the central band of the tablet, such as variations in the film coating density, surface roughness and film CT, were detected using TPI. The tablet central band was identified as the film coating weak spot on round, biconvex tablets and was shown to be dissolution rate determining. TPI showed promise as a process analytical tool for better detection and understanding of film coating weak spots in the development of a film coating unit operation. The technique can be utilised during tablet film coating process development to improve and identify the optimal process conditions, hence achieving a better quality control and helping to minimise product output risks.

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