A non-destructive method for quality control of the pellet distribution within a MUPS tablet by terahertz pulsed imaging

Anna Novikova[a]
Daniel Markl[b]
J. Axel Zeitler[b]
Thomas Rades[c]
Claudia S. Leopold[a,*]

[a] University of Hamburg, Dept. of Chemistry, Div. of Pharmaceutical Technology, Bundesstraße 45, 20146 Hamburg, Germany, anna.novikova@chemie.uni-hamburg.de, claudia.leopold@uni-hamburg.de

[b] University of Cambridge, Dept. of Chemical Engineering and Biotechnology, Philippa Fawcett Drive Cambridge, CB3 0AS, United Kingdom, dm733@cam.ac.uk, jaz22@cam.ac.uk

[c] University of Copenhagen, Dept. of Pharmacy, Universitetsparken 2, 2100 Copenhagen, Denmark, thomas.rades@sund.ku.dk

*Corresponding author: Prof. Dr. Claudia S. Leopold
University of Hamburg
Dept. of Chemistry
Div. of Pharmaceutical Technology

Bundesstraße 45
20146 Hamburg
Germany
Phone: +49 40 42838-3479
Fax: +49 40 42838-6519
e-mail address: claudia.leopold@uni-hamburg.de

ABSTRACT

Terahertz pulsed imaging (TPI) was applied to analyse the inner structure of multiple unit pellet system (MUPS) tablets. MUPS tablets containing different amounts of theophylline pellets coated with Eudragit® NE 30 D and with microcrystalline cellulose (MCC) as cushioning agent were analysed. The tablets were imaged by TPI and the results were compared to X-ray microtomography. The terahertz pulse beam propagates through the tablets and is back-reflected at the interface between the MCC matrix and the coated pellets within the tablet causing a peak in the terahertz waveform. Cross-section images of the tablets were extracted at different depths and parallel to the tablet faces from 3D terahertz data to visualise the surface-near structure of the MUPS tablets. The images of the surface-near structure of the MUPS tablets were compared to X-ray microtomography images at the same depths. The surface-near structure could be clearly resolved by TPI at depths between 24 and 152 µm below the tablet surface. An increasing amount of pellets within the MUPS tablets appears to slightly decrease the detectability of the pellets within the tablets by TPI. TPI was shown to be a ~~fast and~~ non-destructive method for the detection of pellets within the tablets and could resolve structures thicker than 30 µm. In conclusion, a proof-of-concept was provided for TPI as a method of quality control for MUPS tablets.

Key words: *MUPS tablets, terahertz pulsed imaging, 3D mapping, pellet distribution analysis, spectroscopy, quality control.*

1 INTRODUCTION

Multiple unit pellet system (MUPS) tablets have great potential as solid oral dosage forms, as they combine the advantages of coated single unit tablets with pellet containing capsules (Abdul et al., 2010; Bodmeier, 1997). The active pharmaceutical ingredient (API) in MUPS tablets is present in form of small coated pellets surrounded by a tablet matrix (Collet and Moreton, 2002). MUPS tablets disintegrate fast in the stomach resulting in the coated pellets to be released. These pellets pass the pylorus faster and at a more predictable rate than a coated single unit tablet (Bechgaard and Nielsen, 1978). A further advantage of MUPS tablets compared to coated single unit tablets is their divideability without losing the pellet coating functionality and thus providing high dosage flexibility (Bodmeier, 1997). However, to allow dividability, a homogeneous distribution of the API pellets within the tablet matrix is crucial and should be controlled and monitored during the manufacturing process. As a MUPS tablet formulation often contains pellets together with powder excipients, which strongly differ in terms of particle size, density and shape, segregation at various steps of the manufacturing process may occur (Reich, 2005; Wagner et al., 2000; Wagner et al., 1999). A fast and non-destructive method for quality control of the API pellet distribution within a MUPS tablet is thus needed.

Several spectroscopic imaging techniques allow such non-destructive analysis for quality control of tablets including near-infrared (NIR) spectroscopy, Raman spectroscopy, ultraviolet (UV) imaging and terahertz pulsed imaging (TPI). The NIR region is defined as the range of the electromagnetic spectrum between 700 and 2500 nm (12820 - 3959 cm^{-1}) and NIR spectroscopy is a well investigated method for various pharmaceutical applications (Reich, 2005). Moreover, NIR spectroscopy has been demonstrated to be a powerful imaging tool for monitoring the API content

uniformity and API distribution in single unit tablets (Amigo and Ravn, 2009; Cruz and Blanco, 2011; Franch-Lage et al., 2011; Lee et al., 2006; Palou et al., 2012). Zhao et al. applied NIR mapping to visualize the distribution of metoprolol succinate pellets on the surface of commercially available MUPS tablets (Zhao et al., 2010). Raman spectroscopy is another frequently applied analytical method for the characterisation of pharmaceutical formulations. It is based on the inelastic scattering of light, often in the same range of energy as infrared spectroscopy (Gordon and McGoverin, 2011). The application of Raman imaging to analyse the tablet ingredient distribution within single unit tablets is extensively described in the literature (Boiret et al., 2014; Firkala et al., 2013, Sasić, 2007a, 2007b, Slipchenko et al., 2010; Vajna et al., 2011). The application of Raman imaging to analyse the structure of MUPS tablets has not yet been described in the literature, but is also theoretically possible. UV imaging has also been shown to be applicable for the visualisation of the distribution of theophylline pellets on the tablet surface (Novikova et al., 2016a). However, UV radiation does not provide a high penetration depth into a tablet. Therefore, only pellets directly at the tablet surface are considered in the analysis. With the described imaging techniques, information on structures below the tablet surface can only be obtained by destructive and time consuming handling of the tablet (Shen and Taday, 2008).

In the present study, terahertz pulsed imaging (TPI) is evaluated as a quality control tool for MUPS tablets. Terahertz radiation is defined as the range of the electromagnetic spectrum between microwaves and infrared radiation (2-133 cm^{-1}, 0.1-4 THz) (Zeitler et al., 2007a). Terahertz radiation propagates through most pharmaceutical materials, allowing a high penetration depth and thus analysis of the 3D structure of pharmaceutical samples (Fitzgerald et al., 2005; Shen, 2011; Zeitler

et al., 2007a). Therefore, terahertz radiation has gained interest in pharmaceutical research for analysis of solid dosage forms with complex inner structures (Shen and Taday, 2008). The interfaces separating physical structures with different refractive indices, such as interfaces between pellets and the matrix in a MUPS tablet, are visible as peaks in the measured terahertz waveform. Therefore, these features in the terahertz waveform allow the detection of interfaces below the sample surface. The main applications of TPI in the pharmaceutical field are the analysis of the coating thickness (Haaser et al., 2013) and its uniformity (Zeitler and Shen, 2013) as well as in-line monitoring of coating processes (May et al., 2011). The application of TPI for chemical imaging as well as for API quantification has also been discussed in the literature (Cogdill et al., 2006; Shen et al., 2005a). Compared to NIR and Raman imaging, TPI allows the extraction of chemical and physical information on the different depths within a sample simultaneously (3D imaging) (Zeitler and Shen, 2013). Therefore, it was possible to perform chemical imaging of lactose and tartaric acid with TPI in depth within a model tablet (Shen et al., 2005b). However, this model tablet consisted of polyethylene, which is completely transparent to terahertz radiation and therefore scattering of the terahertz radiation within the tablet was minimised (Shen et al., 2005b; Zeitler and Shen, 2013). Nevertheless, this method holds great potential for chemical imaging within a tablet.

The suitability of TPI for the analysis of the inner structure of MUPS tablets was investigated in this study. For this purpose, MUPS tablets containing varying amounts of theophylline pellets coated with Eudragit® NE 30 D were compressed with microcrystalline cellulose (MCC) as a cushioning agent and thereafter analysed by TPI. The effect of the depth resolution limit and the influence of the coated pellet amount in the MUPS tablets on the detectability of the pellets below the tablet

surface was investigated. The TPI results were compared to X-ray microtomography (microCT) measurements as reference method.

2 MATERIALS AND METHODS

2.1 Materials

Theophylline matrix core pellets obtained by extrusion and spheronisation containing 96.5% theophylline, were supplied by Temmler (Killorglin, Ireland). Eudragit® NE 30 D was donated by Evonik (Darmstadt, Germany). MCC (Ceolus® KG-802) was a gift by Asahi Kasei Chemicals (Tokyo, Japan). Hydroxypropyl methylcellulose (HPMC; Pharmacoat® 603) was purchased from Harke Pharma (Mülheim an der Ruhr, Germany), polysorbate 80 was obtained from Caelo (Hilden, Germany), and talc from Fagron (Barsbüttel, Germany).

2.2 Methods

2.2.1 Sample preparation

To obtain coated theophylline pellets for manufacturing of MUPS tablets, a Eudragit® NE coating dispersion was prepared by homogenising HPMC as a gelling agent in purified water at 40 °C using an Ultra Turrax® (IKA, Staufen, Germany). After a solution was formed, polysorbate 80 as a plasticiser and talc as anti-tacking agent were added and dispersed for at least 10 min and subsequently slowly poured into the Eudragit® NE 30 D dispersion under continuous stirring with a propeller stirrer (Eurostar 100 digital, IKA, Staufen, Germany) for at least 5 min. The resulting coating dispersion contained 22.7% Eudragit® NE 30 D, 6.8% talc, 0.7% polysorbate 80, and 0.7% HPMC (w/w). After preparation of the coating dispersion, 400 g of theophylline pellets (mesh 900 - 1000 µm) were coated in a bottom spray fluidised bed apparatus (Solidlab 1, Bosch Packaging Technology, Schopfheim, Germany). The coating parameters were adjusted as follows: inlet air temperature 16 °C; inlet air flow rate 35 m^3 h^{-1}; atomising air pressure 1.5 bar; microclimate 0.4 bar; spraying rate

103 1.5 - 3.0 g min^{-1}. The nozzle diameter was 0.8 mm. The obtained coated pellets were
104 subsequently dried in an oven at 40 °C for 48 h. The total coating applied to the
105 pellets amounted to a 5% weight gain in polymer mass.

106 The coated theophylline pellets were mixed with MCC powder to obtain five batches
107 of tablets with varying amounts of pellets (30%, 40%, 50%, 60%, and 70% (w/w)).
108 250 mg of each formulation were manually filled into the die and compacted at
109 255 MPa using the single punch mode of an instrumented rotary press (Fette 102i,
110 Fette Compacting, Schwarzenbek, Germany), equipped with 10 mm flat-faced
111 punches, resulting in tablets between 2.2 and 2.4 mm thickness. The tablet thickness
112 and tensile strength were determined with a tablet hardness tester (Erweka TBH425,
113 Heusenstamm, Germany). The tensile strength of the produced tablets was above 3
114 MPa to ensure tablets of significant hardness comparable to industrially produced
115 tablets.

116 *2.2.2 Terahertz pulsed imaging*

117 Five MUPS tablets, one from each batch, were imaged with a commercial TPI system
118 (TPI™ imaga 2000, TeraView, Cambridge, UK) which represents an automated
119 tablet scanner. As shown in Fig. 1 the TPI system scans across the *x*- and *y*-
120 direction of the top and bottom face of the sample tablets and thereby records single
121 depth profiles at 200 µm lateral resolution. The scanning procedure is based on a 3D
122 model of the surface, which is generated prior to the terahertz measurements. This
123 3D model is further required for analysis of the terahertz data to locate each
124 waveform and thus to enable the 3D reconstruction of the sample. Each terahertz
125 waveform within a sample tablet represents a depth profile equivalent to 3.5 mm
126 pulse propagation in air (refractive index, $n=1$). The actual penetration depth is
127 dependent on the actual refractive index of the tablet matrix as well as the absorption

of the terahertz pulse by the matrix. Each 3D measurement thus covered a volume of 9.7 x 9.7 x 3.5 mm^3 (49 x 49 x 512 pixels). The scheme of the resulting terahertz waveform in Fig. 1 shows the peaks originating from the reflection at the front face of the tablet as well as at the interfaces of the surface-near pellets. As the average thickness of the pellets' coating layers is below the depth resolution of the used TPI (≈ 35 µm), only two peaks per pellet are observed (e.g. labelled with 2, 3 or 4, 5 in Fig. 1) even though the coating and the pellet core have different refractive indices.

The data acquisition time for one tablet face was 25 min. Analysis of the images was performed with Matlab (ver. 8.1, Mathworks, Natick, USA). Wavelet denoising was applied on each terahertz waveform using 4-layer Daubechies wavelets and performing the wavelet decomposition at level 8. This procedure helped to highlight inner structures and supressed noise in the terahertz waveforms.

2.2.3 X-ray microtomography

The same MUPS tablets that were analysed by TPI were scanned with X-ray microtomography (Skyscan 1172, Bruker microCT, Kontich, Belgium) applying a source voltage of 59 kV. The tablets were rotated during the measurement, and 803 transmission images were recorded in steps of 0.25°. The exposure time for each transmission image was 780 ms. The scan duration for one tablet varied between 43 and 53 min. Reconstruction of the microCT images was performed with NRecon software (ver. 1.6.8, Bruker microCT, Kontich, Belgium) and further analysis of the images was conducted with the Dataviewer software (ver. 1.5.2, Bruker microCT, Kontich, Belgium). The isotropic voxel size of the reconstructed images varied between 3.04 µm and 3.98 µm.

3 RESULTS AND DISCUSSION

In the present study, the suitability of TPI to analyse the inner structure of MUPS tablets was investigated. The signals caused by propagation of the terahertz radiation through the MUPS tablets were correlated with the physical structure of the tablets. The pulse of terahertz radiation propagates through the tablet and is partly reflected by interfaces of structures with different refractive indices (Zeitler and Shen, 2013). The time delay Δt between the reflections of two different interfaces can be measured and used to calculate the actual depth $d = \Delta tc/2n$, where n is the refractive index of the medium and c is the speed of light (Shibuya and Kawase, 2013). A sample terahertz waveform resulting from the reflection of the terahertz pulse at the interface of the structures in a MUPS tablet containing 30% (w/w) of coated theophylline pellets is presented in Fig. 2a. The terahertz electric field is plotted versus the time delay relative to the reflection from the surface of the MUPS tablet (corresponds to 0 µm time delay). The units are propagation distance of the equivalent length of travel in air ($n=1$). The first reflection peak (1) is caused by the terahertz pulse being reflected at the tablet surface in the matrix area. Thereafter, the terahertz pulse propagates into the tablet matrix and is reflected at the interface between the tablet matrix (MCC) and a coated pellet resulting in a second peak (2). The contact region between the tablet matrix and the pellet includes both an interface between the tablet matrix and the coating and an interface between the coating and the pellet core. However, the coating (coating level 5%) is thinner than the TPI depth resolution limit of about 35 µm (Haaser et al., 2013). Thus, the reflections at these interfaces result only in a single peak representing a “combined” interface caused by the short time delay between these signals. After the reflection at this “combined” interface, the terahertz pulse further propagates into the theophylline pellet until it

once again is reflected at the “combined” interface between the pellet and the tablet matrix resulting in a third peak (3).

Another example of the waveform caused by the terahertz pulse that propagates into the MUPS tablet is outlined in Fig. 2b. The first peak (4) is again caused by terahertz pulse reflection at the surface of the tablet. In this case, however, the signal for the reflection of the terahertz pulse at the interface between the tablet matrix and pellet core is not detectable because this particular pellet is too close to the tablet surface and its signal is overlapped by the first peak. After that reflection, the terahertz pulse further propagates into the theophylline pellet. Subsequently, the second peak (5) is the result of the reflection at the interface between the pellet core and the tablet matrix. This described waveform is presented for a pellet, which is located close to the surface and has lost its spherical shape during compression.

As the measured terahertz waveform is the result of the convolution of the incident terahertz pulse and the impulse response function of the sample, features of the incident terahertz pulse (e.g. negative peaks) are also visible in the measured waveform. In the majority of cases, this is corrected by a deconvolution using a reference waveform (e.g. the reflection measurement of a mirror). Such deconvolution amplifies high-frequency noise, which can be reduced by applying a filter. In the present study a deconvolution was applied and different filters (double Gaussian and Wiener filter) were tested, which improved the overall signal to noise ratio. However, the filters introduced artificial features causing a misdetection of pellets and it suppressed characteristic peaks originating from the pellet interfaces. Therefore, the raw terahertz waveforms were used for comparison with the microCT data.

For better visualisation of the 3D structure of the MUPS tablet with a theophylline pellet amount of 30% (w/w), microCT and TPI images at six different depths (24 µm, 49 µm, 73 µm, 97 µm, 128 µm and 152 µm) below the tablet surface are presented in Fig. 3. In the microCT greyscales images, the pellets are visualised by darker grey colour, as a result of lower density, compared to the MCC matrix. The colours in the TPI images represent the strength of the terahertz electric field. In this context, the yellow colour indicates a high electric field and blue colour - a low one. In this proof of concept study, the coated theophylline pellets embedded in the MCC matrix can be identified in the TPI images up to a depth of 152 µm. Although the terahertz radiation penetrates through the entire tablet, the contrast of the pellets' interfaces is very low at depths >152 µm because of the used optics (i.e. the focal point is at the surface of the tablet) and scattering losses. A yellow colour of the pixels corresponds to a high terahertz electric field indicating that the terahertz pulse reaches the surface of the pellet within the tablet and is reflected at this interface as described above. The first cross-section image was analysed at the depth of 24 µm. This depth resolution limit was determined by comparison of the first TPI cross-section image with the microCT data. As expected, the results show that the signals caused by the back-reflection of the terahertz pulse from the internal interface still overlap with the signal of the back-reflected terahertz pulse from the surface of the tablet.

The pellets that can be detected based on the TPI data in the first image of Fig. 3 are marked with a red "1". The TPI results for the pellet distribution at the depth of 24 µm in the tablet were confirmed by the microCT investigation. The depth position of the pellets below the surface determined by TPI may slightly differ (several µm) from that determined by microCT. This deviation is primarily attributed to the different refractive indices of MCC, the Eudragit® coating of the pellets and the theophylline pellets

causing variations in the propagation velocity of the terahertz pulse while it propagates through the tablet. In addition to that, it was difficult to accurately superimpose both datasets in 3D.

In the second image of Fig. 3 (depth of 49 µm) a change of the yellow colour to green or blue for various pellets that are marked with “1” can be observed. This change results from the decrease of the terahertz electric field after the peak maximum. However, the differentiation between various pellets that are marked with “1” and the tablet matrix is impossible at this depth because there is no interface present. Therefore, to analyse the pellet distribution deep below the tablet surface of a MUPS tablet, the TPI images at several depths should be analysed instead of TPI image at one preselected depth. Pellets which were first detectable at the depth of 49 µm are marked with “2” (Fig. 3, image 2).

The pellets contain 96.5% of theophylline and are coated with a flexible polymer (please refer to section 2.1), resulting in soft pellets, which have lost their spherical structure during compression. Therefore, the shape of the pellets may vary depending on their location below the surface of the MUPS tablet. Thus, several interface spots between the pellet and the matrix exist for one pellet at varying depths. The terahertz pulse is reflected at these interfaces resulting in a high terahertz electric field (yellow colour) for one pellet at varying depths. This can be observed for the pellets marked with “1” in the lower left corner of the TPI images. These pellets are characterised by a high terahertz electric field in the first image and then again especially in the fourth image. As described above, the detectable interface spots of these pellets increase at the depth of 97 µm leading to new interfaces resulting in back-reflection of the terahertz pulses and therefore in high terahertz electric field values (yellow colour).

In a previously performed study on the determination of the coating thickness of coated tablets with TPI, it was possible to analyse the inner tablet structure up to a depth of 300 µm (Novikova et al., 2016b). In contrast, in the present study investigating MUPS tablets it was only possible to detect pellet structures up to 152 µm below the tablet surface (Fig. 3), because of high scattering losses and the high density of the MUPS tablet components compared to the coating of coated tablets. Therefore, the location of small objects such as pellets at greater depth is difficult, as the divergence of the terahertz beam as well as scattering and absorption losses will further decrease the signal contrast. Nevertheless, the analysis of depths >152 µm below the tablet surface appears still feasible, because Zeitler et al. demonstrated that internal interfaces up to 2 mm below the tablet surface of coated tablets can be detected (Zeitler et al., 2007b).

To determine the influence of the pellet amount in the MUPS tablets on the detectability of the pellets embedded in the MCC matrix, tablets with different amounts of pellets (expressed as the weight percentage of pellets in the MUPS tablet) were investigated. As shown in Fig. 3 for a MUPS tablet with a pellet amount of 30% (w/w), all pellets which were detectable in the microCT images were also detected in the TPI images. In Fig. 4 microCT and TPI images of four MUPS tablets with a pellet amount between 40 and 70% (w/w) are displayed. The images are presented only at one selected depth per tablet. However, to detect as many pellets as possible, images at depths below the selected depths were also analysed (data not shown). Pellets detected in the TPI images at depths below the selected depths are marked with “1”. Furthermore, pellets detected in the TPI images of the selected depths are marked with “2”. In the image of the MUPS tablet with a pellet amount of 40% (w/w) all pellets which were present in the microCT image, were also detected

275 in the TPI image. In the microCT image of the MUPS tablet with a pellet amount of
276 50%, two pellets (marked with “0”) were found, which were undetectable in the TPI
277 images (Fig. 4b). Interestingly, these pellets were visible with microCT on the tablet
278 surface. Thus, the peak caused by the back-reflection of the terahertz pulse at the
279 interface between the pellet and the matrix may have overlapped with that at the
280 interface between air and tablet surface (matrix), or this surface peak is already
281 caused by the back-reflection at the interface between air and pellet surface. The two
282 undetected pellets are located close to the edge of the tablet. In the TPI image of the
283 MUPS tablet with a pellet amount of 60% (w/w) again two pellets (marked with “0”),
284 which were also located close to the edge of the tablet, were not found in the TPI
285 images. Apparently, edge effects are occurring in the terahertz waveforms acquired
286 close to the tablet edge because of a diffraction-limited focal spot of about 200 µm.
287 As shown in Fig. 4d, for the MUPS tablet with a pellet amount of 70% (w/w) the
288 number of undetected pellets increases to six (marked with “0”), compared to the
289 MUPS tablets with lower pellet amounts. Three of the undetected pellets were again
290 located close to the tablet edge confirming the assumption that the applied optics
291 decreases the pellet detectability at the edge of the tablet. The other three of the
292 undetected pellets were not located close to the tablet edge, but are already visible
293 on the tablet surface. This confirms the hypothesis that the back-reflection peak of
294 the terahertz pulse beam at the interface between matrix and pellets which are visible
295 on the tablet surface may overlap with the back-reflection peak of the terahertz pulse
296 at the tablet surface. However, in general, the detectability of pellets based on the
297 TPI images appears to decrease slightly with increasing pellet amount in the MUPS
298 tablet. Nevertheless, it should be mentioned that these pellets may still be detected
299 based on terahertz electric field values at other depths below the tablet surface.

In Table 1 the results regarding the number of pellets detected in the TPI and microCT images of MUPS tablets up to the depths presented in Fig. 4 are summarized. For better comparison of the results for the different pellet amounts within the MUPS tablets the percentage of the number of pellets detected in the TPI images with regard to the actual number of visible pellets in the microCT images was calculated. For tablets with a low pellet amount (30 and 40% (w/w)) all pellets that were visible in the microCT images, could also be detected in the TPI images. In the TPI images of tablets with pellet amounts of at least 50% (w/w) more than 87% of pellets that were visible with microCT, could be detected.

Table 1: Comparison of the number of pellets detected in MUPS tablets with varying pellet amounts by microCT and TPI.

Pellet amount in MUPS tablet:	30% (w/w)[1]	40% (w/w)[2]	50% (w/w)[2]	60% (w/w)[2]	70% (w/w)[2]
Number of pellets detected in microCT images	18	16	19	25	45
Number of pellets detected in TPI images	18	16	17	23	39
Percentage of pellets detected by TPI compared to microCT	100%	100%	89%	92%	87%

[1] Number of pellets detected up to the depth of 49 µm below the tablet surface.

[2] Number of pellets detected up to the selected depth below the tablet surface.

In general, it can be stated that it was possible to detect most of the pellets in the TPI images up to the selected depth regardless of the pellet amount in the MUPS tablets and to confirm these results with the microCT images. TPI has been shown to be a faster ~~and safe~~ method than microCT, with a pixel size in depth of 4.9 µm and the possibility to precisely resolve structures thicker than about 30 - 40 µm for the analysis of the surface-near structure of MUPS tablets.

The dividability is an advantage of MUPS tablets. Therefore, rapid and non-destructive methods for the evaluation of the pellet distribution within the MUPS tablet are needed. The advantage of TPI compared to surface imaging methods is the possibility to obtain additional information on the pellet distribution below the tablet surface. As already mentioned, with the optics of the TPI device it was possible to analyse the pellet distribution up to 152 µm below the tablet surface. Novikova et al. investigated the suitability of UV imaging for analysis of the pellet distribution on the MUPS tablet surface (Novikova et al., 2016a). In this study it could be shown that the pellet amount in a MUPS tablet can be estimated based on the amount of pellets determined on the tablet surface. In addition, the pellet amount in a tablet half after tablet division could be estimated based on the pellet amount determined on the surface of this tablet half. Based on the data of the present study, the determination of the pellet amount within a MUPS tablet by TPI analysis of the tablet appears to be more suitable than a surface method (e.g. UV imaging). Especially for tablets with a low pellet amount and, thus also a low number of detectable pellets at the tablet surface, estimation of the pellet amount in the tablets based on TPI images may improve the quality of the determination. Additionally, Novikova et al. showed that for thicker tablets the estimation of the pellet amount within a tablet based on the tablet surface analysis by a UV imager was less precise than for the thinner tablets (Novikova et al., 2016a).

NIR mapping has also been shown to be applicable for visualization of the pellet distribution on the surface of MUPS tablets (Zhao et al., 2010). Nevertheless, NIR, such as NIR mapping in reflection, is a surface-biased method and may not be applicable for tablets with a low amount of pellets on the tablet surface or for thicker MUPS tablets. As described in the introduction, Raman imaging has not yet been

applied for analysis of the pellet distribution within MUPS tablets. Moreover, Raman is also a surface biased technique. Therefore, depth information may only be obtained by microtoming the samples and successively imaging every plane.

4 CONCLUSION

In this study, the suitability of TPI for the detection of coated theophylline pellets within a MUPS tablet was investigated. It was found, that a pellet in a tablet causes two peaks: one as soon as the terahertz pulse is back-reflected at the interface between the tablet matrix and the pellet surface and a second when the terahertz pulse leaves the pellet and is reflected at the interface between the pellet and the matrix. Thus, TPI allows the visualisation of the interfaces between the pellets and the tablet matrix. The first evaluable cross-section TPI images were achieved at 24 µm below the tablet surface. With the applied optics it was possible to detect the pellets in the TPI images up to at least 152 µm below the tablet surface. Increasing the amount of pellets within the MUPS tablets appeared to slightly decrease the pellet detectability. The undetected pellets were located close to the tablet edge or at the tablet surface. In conclusion, TPI was shown to be a promising technique for ~~fast and~~ non-destructive analysis with a high depth resolution within the MUPS tablets. Therefore, the present study serves as a proof-of-concept for quality control of MUPS tablets by means of TPI.

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