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

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## 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  $\mu\text{m}$  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  $\mu\text{m}$ . 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 **1 INTRODUCTION**

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

19 Several spectroscopic imaging techniques allow such non-destructive analysis for  
20 quality control of tablets including near-infrared (NIR) spectroscopy, Raman  
21 spectroscopy, ultraviolet (UV) imaging and terahertz pulsed imaging (TPI). The NIR  
22 region is defined as the range of the electromagnetic spectrum between 700 and  
23 2500 nm ( $12820 - 3959 \text{ cm}^{-1}$ ) and NIR spectroscopy is a well investigated method for  
24 various pharmaceutical applications (Reich, 2005). Moreover, NIR spectroscopy has  
25 been demonstrated to be a powerful imaging tool for monitoring the API content

26 uniformity and API distribution in single unit tablets (Amigo and Ravn, 2009; Cruz and  
27 Blanco, 2011; Franch-Lage et al., 2011; Lee et al., 2006; Palou et al., 2012). Zhao et  
28 al. applied NIR mapping to visualize the distribution of metoprolol succinate pellets  
29 on the surface of commercially available MUPS tablets (Zhao et al., 2010). Raman  
30 spectroscopy is another frequently applied analytical method for the characterisation  
31 of pharmaceutical formulations. It is based on the inelastic scattering of light, often in  
32 the same range of energy as infrared spectroscopy (Gordon and McGoverin, 2011).  
33 The application of Raman imaging to analyse the tablet ingredient distribution within  
34 single unit tablets is extensively described in the literature (Boiret et al., 2014; Firkala  
35 et al., 2013, Sasić, 2007a, 2007b, Slipchenko et al., 2010; Vajna et al., 2011). The  
36 application of Raman imaging to analyse the structure of MUPS tablets has not yet  
37 been described in the literature, but is also theoretically possible. UV imaging has  
38 also been shown to be applicable for the visualisation of the distribution of  
39 theophylline pellets on the tablet surface (Novikova et al., 2016a). However, UV  
40 radiation does not provide a high penetration depth into a tablet. Therefore, only  
41 pellets directly at the tablet surface are considered in the analysis. With the described  
42 imaging techniques, information on structures below the tablet surface can only be  
43 obtained by destructive and time consuming handling of the tablet (Shen and Taday,  
44 2008).

45 In the present study, terahertz pulsed imaging (TPI) is evaluated as a quality control  
46 tool for MUPS tablets. Terahertz radiation is defined as the range of the  
47 electromagnetic spectrum between microwaves and infrared radiation ( $2\text{-}133\text{ cm}^{-1}$ ,  
48  $0.1\text{-}4\text{ THz}$ ) (Zeitler et al., 2007a). Terahertz radiation propagates through most  
49 pharmaceutical materials, allowing a high penetration depth and thus analysis of the  
50 3D structure of pharmaceutical samples (Fitzgerald et al., 2005; Shen, 2011; Zeitler

51 et al., 2007a). Therefore, terahertz radiation has gained interest in pharmaceutical  
52 research for analysis of solid dosage forms with complex inner structures (Shen and  
53 Taday, 2008). The interfaces separating physical structures with different refractive  
54 indices, such as interfaces between pellets and the matrix in a MUPS tablet, are  
55 visible as peaks in the measured terahertz waveform. Therefore, these features in  
56 the terahertz waveform allow the detection of interfaces below the sample surface.  
57 The main applications of TPI in the pharmaceutical field are the analysis of the  
58 coating thickness (Haaser et al., 2013) and its uniformity (Zeitler and Shen, 2013) as  
59 well as in-line monitoring of coating processes (May et al., 2011). The application of  
60 TPI for chemical imaging as well as for API quantification has also been discussed in  
61 the literature (Cogdill et al., 2006; Shen et al., 2005a). Compared to NIR and Raman  
62 imaging, TPI allows the extraction of chemical and physical information on the  
63 different depths within a sample simultaneously (3D imaging) (Zeitler and Shen,  
64 2013). Therefore, it was possible to perform chemical imaging of lactose and tartaric  
65 acid with TPI in depth within a model tablet (Shen et al., 2005b). However, this model  
66 tablet consisted of polyethylene, which is completely transparent to terahertz  
67 radiation and therefore scattering of the terahertz radiation within the tablet was  
68 minimised (Shen et al., 2005b; Zeitler and Shen, 2013). Nevertheless, this method  
69 holds great potential for chemical imaging within a tablet.

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

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

## 78 **2 MATERIALS AND METHODS**

### 79 **2.1 Materials**

80 Theophylline matrix core pellets obtained by extrusion and spheronisation containing  
81 96.5% theophylline, were supplied by Temmler (Killorglin, Ireland).  
82 Eudragit® NE 30 D was donated by Evonik (Darmstadt, Germany). MCC (Ceolus®  
83 KG-802) was a gift by Asahi Kasei Chemicals (Tokyo, Japan). Hydroxypropyl  
84 methylcellulose (HPMC; Pharmacoat® 603) was purchased from Harke Pharma  
85 (Mülheim an der Ruhr, Germany), polysorbate 80 was obtained from Caelo (Hilden,  
86 Germany), and talc from Fagron (Barsbüttel, Germany).

87

### 88 **2.2 Methods**

#### 89 *2.2.1 Sample preparation*

90 To obtain coated theophylline pellets for manufacturing of MUPS tablets, a  
91 Eudragit® NE coating dispersion was prepared by homogenising HPMC as a gelling  
92 agent in purified water at 40 °C using an Ultra Turrax® (IKA, Staufen, Germany). After  
93 a solution was formed, polysorbate 80 as a plasticiser and talc as anti-tacking agent  
94 were added and dispersed for at least 10 min and subsequently slowly poured into  
95 the Eudragit® NE 30 D dispersion under continuous stirring with a propeller stirrer  
96 (Eurostar 100 digital, IKA, Staufen, Germany) for at least 5 min. The resulting coating  
97 dispersion contained 22.7% Eudragit® NE 30 D, 6.8% talc, 0.7% polysorbate 80, and  
98 0.7% HPMC (w/w). After preparation of the coating dispersion, 400 g of theophylline  
99 pellets (mesh 900 - 1000 µm) were coated in a bottom spray fluidised bed apparatus  
100 (Solidlab 1, Bosch Packaging Technology, Schopfheim, Germany). The coating  
101 parameters were adjusted as follows: inlet air temperature 16 °C; inlet air flow rate  
102 35 m<sup>3</sup> h<sup>-1</sup>; atomising air pressure 1.5 bar; microclimate 0.4 bar; spraying rate



103 1.5 - 3.0 g min<sup>-1</sup>. 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

128 of the terahertz pulse by the matrix. Each 3D measurement thus covered a volume of  
129  $9.7 \times 9.7 \times 3.5 \text{ mm}^3$  ( $49 \times 49 \times 512$  pixels). The scheme of the resulting terahertz  
130 waveform in Fig. 1 shows the peaks originating from the reflection at the front face of  
131 the tablet as well as at the interfaces of the surface-near pellets. As the average  
132 thickness of the pellets' coating layers is below the depth resolution of the used TPI  
133 ( $\approx 35 \mu\text{m}$ ), only two peaks per pellet are observed (e.g. labelled with 2, 3 or 4, 5 in  
134 Fig. 1) even though the coating and the pellet core have different refractive indices.

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

### 140 *2.2.3 X-ray microtomography*

141 The same MUPS tablets that were analysed by TPI were scanned with X-ray  
142 microtomography (Skyscan 1172, Bruker microCT, Kontich, Belgium) applying a  
143 source voltage of 59 kV. The tablets were rotated during the measurement, and 803  
144 transmission images were recorded in steps of  $0.25^\circ$ . The exposure time for each  
145 transmission image was 780 ms. The scan duration for one tablet varied between 43  
146 and 53 min. Reconstruction of the microCT images was performed with NRecon  
147 software (ver. 1.6.8, Bruker microCT, Kontich, Belgium) and further analysis of the  
148 images was conducted with the Dataviewer software (ver. 1.5.2, Bruker microCT,  
149 Kontich, Belgium). The isotropic voxel size of the reconstructed images varied  
150 between  $3.04 \mu\text{m}$  and  $3.98 \mu\text{m}$ .

### 151 3 RESULTS AND DISCUSSION

152 In the present study, the suitability of TPI to analyse the inner structure of MUPS  
153 tablets was investigated. The signals caused by propagation of the terahertz  
154 radiation through the MUPS tablets were correlated with the physical structure of the  
155 tablets. The pulse of terahertz radiation propagates through the tablet and is partly  
156 reflected by interfaces of structures with different refractive indices (Zeitler and Shen,  
157 2013). The time delay  $\Delta t$  between the reflections of two different interfaces can be  
158 measured and used to calculate the actual depth  $d = \Delta tc/2n$ , where  $n$  is the  
159 refractive index of the medium and  $c$  is the speed of light (Shibuya and Kawase,  
160 2013). A sample terahertz waveform resulting from the reflection of the terahertz  
161 pulse at the interface of the structures in a MUPS tablet containing 30% (w/w) of  
162 coated theophylline pellets is presented in Fig. 2a. The terahertz electric field is  
163 plotted versus the time delay relative to the reflection from the surface of the MUPS  
164 tablet (corresponds to 0  $\mu\text{m}$  time delay). The units are propagation distance of the  
165 equivalent length of travel in air ( $n=1$ ). The first reflection peak (1) is caused by the  
166 terahertz pulse being reflected at the tablet surface in the matrix area. Thereafter, the  
167 terahertz pulse propagates into the tablet matrix and is reflected at the interface  
168 between the tablet matrix (MCC) and a coated pellet resulting in a second peak (2).  
169 The contact region between the tablet matrix and the pellet includes both an interface  
170 between the tablet matrix and the coating and an interface between the coating and  
171 the pellet core. However, the coating (coating level 5%) is thinner than the TPI depth  
172 resolution limit of about 35  $\mu\text{m}$  (Haaser et al., 2013). Thus, the reflections at these  
173 interfaces result only in a single peak representing a “combined” interface caused by  
174 the short time delay between these signals. After the reflection at this “combined”  
175 interface, the terahertz pulse further propagates into the theophylline pellet until it

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

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

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

200 For better visualisation of the 3D structure of the MUPS tablet with a theophylline  
201 pellet amount of 30% (w/w), microCT and TPI images at six different depths (24  $\mu\text{m}$ ,  
202 49  $\mu\text{m}$ , 73  $\mu\text{m}$ , 97  $\mu\text{m}$ , 128  $\mu\text{m}$  and 152  $\mu\text{m}$ ) below the tablet surface are presented in  
203 Fig. 3. In the microCT greyscales images, the pellets are visualised by darker grey  
204 colour, as a result of lower density, compared to the MCC matrix. The colours in the  
205 TPI images represent the strength of the terahertz electric field. In this context, the  
206 yellow colour indicates a high electric field and blue colour - a low one. In this proof of  
207 concept study, the coated theophylline pellets embedded in the MCC matrix can be  
208 identified in the TPI images up to a depth of 152  $\mu\text{m}$ . Although the terahertz radiation  
209 penetrates through the entire tablet, the contrast of the pellets' interfaces is very low  
210 at depths  $>152$   $\mu\text{m}$  because of the used optics (i.e. the focal point is at the surface of  
211 the tablet) and scattering losses. A yellow colour of the pixels corresponds to a high  
212 terahertz electric field indicating that the terahertz pulse reaches the surface of the  
213 pellet within the tablet and is reflected at this interface as described above. The first  
214 cross-section image was analysed at the depth of 24  $\mu\text{m}$ . This depth resolution limit  
215 was determined by comparison of the first TPI cross-section image with the microCT  
216 data. As expected, the results show that the signals caused by the back-reflection of  
217 the terahertz pulse from the internal interface still overlap with the signal of the back-  
218 reflected terahertz pulse from the surface of the tablet.

219 The pellets that can be detected based on the TPI data in the first image of Fig. 3 are  
220 marked with a red "1". The TPI results for the pellet distribution at the depth of 24  $\mu\text{m}$   
221 in the tablet were confirmed by the microCT investigation. The depth position of the  
222 pellets below the surface determined by TPI may slightly differ (several  $\mu\text{m}$ ) from that  
223 determined by microCT. This deviation is primarily attributed to the different refractive  
224 indices of MCC, the Eudragit<sup>®</sup> coating of the pellets and the theophylline pellets

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

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

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

250 In a previously performed study on the determination of the coating thickness of  
251 coated tablets with TPI, it was possible to analyse the inner tablet structure up to a  
252 depth of 300  $\mu\text{m}$  (Novikova et al., 2016b). In contrast, in the present study  
253 investigating MUPS tablets it was only possible to detect pellet structures up to  
254 152  $\mu\text{m}$  below the tablet surface (Fig. 3), because of high scattering losses and the  
255 high density of the MUPS tablet components compared to the coating of coated  
256 tablets. Therefore, the location of small objects such as pellets at greater depth is  
257 difficult, as the divergence of the terahertz beam as well as scattering and absorption  
258 losses will further decrease the signal contrast. Nevertheless, the analysis of depths  
259  $>152 \mu\text{m}$  below the tablet surface appears still feasible, because Zeitler et al.  
260 demonstrated that internal interfaces up to 2 mm below the tablet surface of coated  
261 tablets can be detected (Zeitler et al., 2007b).

262 To determine the influence of the pellet amount in the MUPS tablets on the  
263 detectability of the pellets embedded in the MCC matrix, tablets with different  
264 amounts of pellets (expressed as the weight percentage of pellets in the MUPS  
265 tablet) were investigated. As shown in Fig. 3 for a MUPS tablet with a pellet amount  
266 of 30% (w/w), all pellets which were detectable in the microCT images were also  
267 detected in the TPI images. In Fig. 4 [microCT and TPI](#) images of four MUPS tablets  
268 with a pellet amount between 40 and 70% (w/w) are displayed. The images are  
269 presented only at one selected depth per tablet. However, to detect as many pellets  
270 as possible, images at depths below the selected depths were also analysed (data  
271 not shown). Pellets detected in the TPI images at depths below the selected depths  
272 are marked with "1". Furthermore, pellets detected in the TPI images of the selected  
273 depths are marked with "2". In the image of the MUPS tablet with a pellet amount of  
274 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  $\mu\text{m}$ .  
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.



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

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

Pellet amount in MUPS tablet:	30% (w/w) <sup>1</sup>	40% (w/w) <sup>2</sup>	50% (w/w) <sup>2</sup>	60% (w/w) <sup>2</sup>	70% (w/w) <sup>2</sup>
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%

311 <sup>1</sup> Number of pellets detected up to the depth of 49 µm below the tablet surface.

312 <sup>2</sup> Number of pellets detected up to the selected depth below the tablet surface.

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

319 The dividability is an advantage of MUPS tablets. Therefore, rapid and non-  
320 destructive methods for the evaluation of the pellet distribution within the MUPS  
321 tablet are needed. The advantage of TPI compared to surface imaging methods is  
322 the possibility to obtain additional information on the pellet distribution below the  
323 tablet surface. As already mentioned, with the optics of the TPI device it was possible  
324 to analyse the pellet distribution up to 152  $\mu\text{m}$  below the tablet surface. Novikova et  
325 al. investigated the suitability of UV imaging for analysis of the pellet distribution on  
326 the MUPS tablet surface (Novikova et al., 2016a). In this study it could be shown that  
327 the pellet amount in a MUPS tablet can be estimated based on the amount of pellets  
328 determined on the tablet surface. In addition, the pellet amount in a tablet half after  
329 tablet division could be estimated based on the pellet amount determined on the  
330 surface of this tablet half. Based on the data of the present study, the determination  
331 of the pellet amount within a MUPS tablet by TPI analysis of the tablet appears to be  
332 more suitable than a surface method (e.g. UV imaging). Especially for tablets with a  
333 low pellet amount and, thus also a low number of detectable pellets at the tablet  
334 surface, estimation of the pellet amount in the tablets based on TPI images may  
335 improve the quality of the determination. Additionally, Novikova et al. showed that for  
336 thicker tablets the estimation of the pellet amount within a tablet based on the tablet  
337 surface analysis by a UV imager was less precise than for the thinner tablets  
338 (Novikova et al., 2016a).

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

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

#### 347 **4 CONCLUSION**

348 In this study, the suitability of TPI for the detection of coated theophylline pellets  
349 within a MUPS tablet was investigated. It was found, that a pellet in a tablet causes  
350 two peaks: one as soon as the terahertz pulse is back-reflected at the interface  
351 between the tablet matrix and the pellet surface and a second when the terahertz  
352 pulse leaves the pellet and is reflected at the interface between the pellet and the  
353 matrix. Thus, TPI allows the visualisation of the interfaces between the pellets and  
354 the tablet matrix. The first evaluable cross-section TPI images were achieved at  
355 24  $\mu\text{m}$  below the tablet surface. With the applied optics it was possible to detect the  
356 pellets in the TPI images up to at least 152  $\mu\text{m}$  below the tablet surface. Increasing  
357 the amount of pellets within the MUPS tablets appeared to slightly decrease the  
358 pellet detectability. The undetected pellets were located close to the tablet edge or at  
359 the tablet surface. In conclusion, TPI was shown to be a promising technique for ~~fast~~  
360 ~~and~~ non-destructive analysis with a high depth resolution within the MUPS tablets.  
361 Therefore, the present study serves as a proof-of-concept for quality control of MUPS  
362 tablets by means of TPI.

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