The Electronic Conference on Pharmaceutical Sciences
ECPS2011

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Communication

Terahertz Pulsed Imaging as a PAT Tool for Evaluating the Effect of Coating Methods and Application of Stress Conditions on Applied Film Quality

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Received: / Accepted: / Published:

Abstract: In this study, the effect of two different film-coaters, a fluid bed and a drum coater on the applied film quality was determined by terahertz pulsed imaging (TPI). In addition to the coating application under recommended conditions, stress conditions were applied and investigated. From the terahertz time-domain waveforms, maps of the terahertz electric field peak strength (TEFPS), interface index (TII) and coating thickness (CT) were successfully derived. The results indicated a rougher coating surface for samples coated in the fluid bed coater. Although the amount of coating deposited was found to be the same,

the mean CT for the fluid bed coated samples was higher. Furthermore, it was possible to distinguish an interface between the subsequent coating layers in the CT maps (generated by a coating liquid application stop), which could not be resolved by SEM for all samples. In good agreement with previous studies, the overall thickness of the coating layer was systematically thinner around the centre band compared to the top and bottom surfaces. TPI can be considered applicable for increasing the understanding of complex film coating structures.

Keywords: Terahertz pulsed imaging (TPI); film quality, coating; image analysis; unit operations; process analytical technologies.

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1. Introduction

The application of film coating on solid dosage forms is a pharmaceutical unit operation commonly performed in pharmaceutical manufacturing. The properties of the applied film coatings vary mainly depending on their purpose. Besides taste masking and aesthetic reasons, coatings are applied to modify the active pharmaceutical ingredient (API) dissolution behavior, resulting in sustained, controlled, or delayed drug release profiles. To meet the desired drug release profile not only is it important to choose an eligible coating polymer formulation[1] but also the final film coating uniformity and quality are crucial[2]. Additionally, it is essential to understand and optimize the highly complex coating process with all its variables[3,4].

At present, a wide range of tablet coating systems are used in pharmaceutical industry, e.g. drum, fluid bed, rotary etc. Therefore it is important to identify the possible impacts of the coating device on the final film coating quality. The indirect monitoring methods for controlling the highly complex coating process are in general, the amount of formulation applied and the weight gain of dosage forms. However, their inability to provide specific information on the coating quality makes them inadequate to predict dissolution characteristics. Other monitoring and controlling procedures, on the other hand, have been shown to access certain aspects of the applied film coating quality[5-8]. Nevertheless, most of those techniques are limited in the ability to determine complex coating structures (e.g. distinction between coating layers) and/or the techniques are destructive.

A more recently established non-destructive technique to gain deeper understanding on film-coating properties such as coating thickness, uniformity and quality is Terahertz-Pulsed-Imaging (TPI). Terahertz radiation is part of the far infrared region of the electromagnetic spectrum (2 cm^{-1} and 120 cm^{-1}) hence, most of the well-established polymer formulations used in tablet coatings are transparent or semitransparent to the pulsed coherent light used in TPI[9]. The generated terahertz pulse can penetrate through the sample and the partial reflection caused by interfaces within the

sample structure, such as refractive interface and/or absorption coefficient changes, are measured against time. Thus, single or multiple coating layer thicknesses can be derived from the peak-to-peak distance in the time-domain signal (time delay of the terahertz pulse). Yet, not only parameters like coating thickness but also chemical and physical properties can be investigated by TPI which has been basis for many studies on applied film coatings in the past[10-16].

In this study, TPI was used for coating analysis in order to discriminate between the product performance of the two most common tablet coating devices: fluid-bed and drum coaters. Tablets coated with an enteric coating were imaged and the results verified by scanning electron microscopy (SEM). Furthermore, different stress conditions were applied during the coating process in order to investigate impacts on the applied film coating quality and possible differences between coating performance of both pieces of equipment.

2. Experimental Section

2.1 Materials

Acetylsalicylic acid (ASA) (Rhodia Organique, France), microcrystalline cellulose (MCC) (Avicel PH102, FMC BioPolymer, United Kingdon), magnesium stearate (Fagron, The Netherlands) and talcum (Fagron, The Netherlands) were used as received. Eudragit L30-55 (Evonik Röhm GmbH, Essen, Germany) was redispersed in sodium hydroxide and distilled water as indicated by the manufacturer[17]. The final coating dispersion was prepared according to the recommendations of Evonik for all coating experiments.

2.2 Compression at a Single Punch Tablet Press

The sieved ASA crystals (86% w/w) were mixed with MCC and a 9:1 mixture of magnesium stearate and talcum (5% w/w) in a Turbula mixer for 3 min at 32 rpm (WAB AG, Germany). Ready blends were compacted on an instrumented one punch tablet press (Diaf II, Denmark) by using a biconvex 9.5 mm tooling.

2.3 Coating Experiments

A lab scale fluid bed (Combi Coata, Model CC1/LAB, Niro Atomizer, Denmark) and drum (Hi-Coater, HCT 20, Lödige Maschinenbau GmbH, Germany) coater were used to coat the tablets. A batch size of 250 tablets and 61 grams of coating liquid were used per coating experiment. Coating experiments were carried out under different process conditions: recommended *vs*. stress conditions. Stress conditions included high spray rate (‘wet’ conditions); different curing approaches and a process stop with the aim to incur lamination in the applied coating (‘lamination’). In order to obtain ‘wet’ conditions the inlet air temperature was decreased by 10°C and the spray rate was increased by 3.6 times. As a consequence the airflow rate had to be increased and the total amount of coating liquid applied had to be decreased to 42 g in the drum

coater. The effect of curing was investigated by applying different curing times varying from 0 hours to 120 hours at 40°C. For the 'lamination' experiments the spraying of the coating dispersion was stopped for 30 min when half of the amount of coating dispersion was applied. In case of the fluid bed coater the airflow was cut off, whereas in the drum coater the batch was kept in the slow movement for 30 min.

2.4 Terahertz-Pulsed-Imaging Measurements

Six randomly chosen samples from each batch were imaged individually using a TeraView Ltd. TPI Imaga2000 (TeraView Ltd, Cambridge, UK). The detailed imaging setup employed in this system has been previously described[15]. The fully automated imaging process enables the scanning of the surface area of the whole tablet divided into three stages; top (a) and the bottom (b) side of the tablet, and the central band (c). Terahertz maps were acquired in a point-to-point scan mode with a 150 µm step size in both the *x*- and *y* directions and a 1 mm axial penetration depth in air (*z* direction). The resulting depth resolution limit with this analysis technique lies between 30-40 µm and the spatial resolution is 200 µm. Data analysis was carried out using TPIView TVL imaging software version 3.0.3. To obtain the refractive index (RI) of the coating material in order to determine the accurate CT, terahertz pulsed spectroscopy (TPS) using a TPS Spectra3000 (TeraView Ltd., Cambridge, UK) in a transmission mode was applied according to a previous setup used by Ho et al.[11]. For the used enteric coating the RI was found to be 1.50. In addition to the CT, the terahertz electric field peak strength (TEFPS) and the terahertz interface index (TII) per pixel were determined. TEFPS was used as an indication of surface roughness and relative film coating density, whereas TII was used to gain information on differences in the coating/core interface.

2.5 Scanning Electron Microscopy

One of the 6 samples of each batch analysed by TPI was imaged using a Hitachi S-3400 (Hitachi High Technologies America, Inc., USA) scanning electron microscope (SEM). Images were taken on a cross-sectional area (a side, the central band and an overview image) and from the coating on the surface of the tablets; magnifications of 50×, 470× and 500× were used. The images were then compared with each other and the corresponding TPI results.

3. Results and Discussion

3.1 Comparison of the Coating Equipment Performance

Two standard coating devices, a fluid-bed and a drum coater, have been used to apply the same amount of an enteric coating to biconvex ASA loaded tablet cores under the most similar conditions possible. The coating processes were carried out according to recommended coating conditions for the specific polymer followed by a 2h curing period at 40°C. From the first visual inspection, the tablet surface of samples coated in the fluid-bed device (ASA I) appeared less

glossy than that of tablets coated in the drum coater (ASA II). A glossy coat often refers to a smoother surface whereas a matt coat is supposed to be a result of a rough coating surface[18]. In previous studies, the TPI parameter TEFPS has been successfully correlated to the surface morphology[10,11], as well as to density changes[12]. TEFPS is associated with the RI (density) of the coating material, the values increase/decrease with a increase/decrease of the final film coating RI, respectively[10,12]. In this study, no significant RI differences between ASA I and ASAII could be derived from the TPI maps. Nevertheless, TEFPS values obtained showed a statistically significant lower signal reflection strength from the tablet sides in samples from batch ASA I (*t*-test *P*-value 0.038; null hypothesis, $\alpha = 0.05$), which indicated a rougher surface morphology in the presumption of similar coating RI for both batches.

To further investigate the surface roughness, SEM images of the tablet surfaces were taken to compare both batches (Figure 1). From the images it becomes clear that the sample from batch ASA I (Figure 1A) has a higher number of visible droplets on the surface compared to the sample from batch ASA II (Figure 1B). The partly coalesced polymer droplets at the surface of the ASA I samples indicate that the film formation conditions were not optimal in the fluid bed coater, drying of the droplets was too fast. The size of the droplets at the surface of the sample from the fluid-bed is in the range of 30-50 µm in diameter. Scattering effects due to sample size has been shown to occur if the sample size is in the size range of the terahertz wavelength[19]. Smaller sample sizes which have not been part of the previous investigation however, could still cause scattering[20] but this is not easy to ascertain; more studies need to be done to resolve the impact of scattering effects in the samples presented.

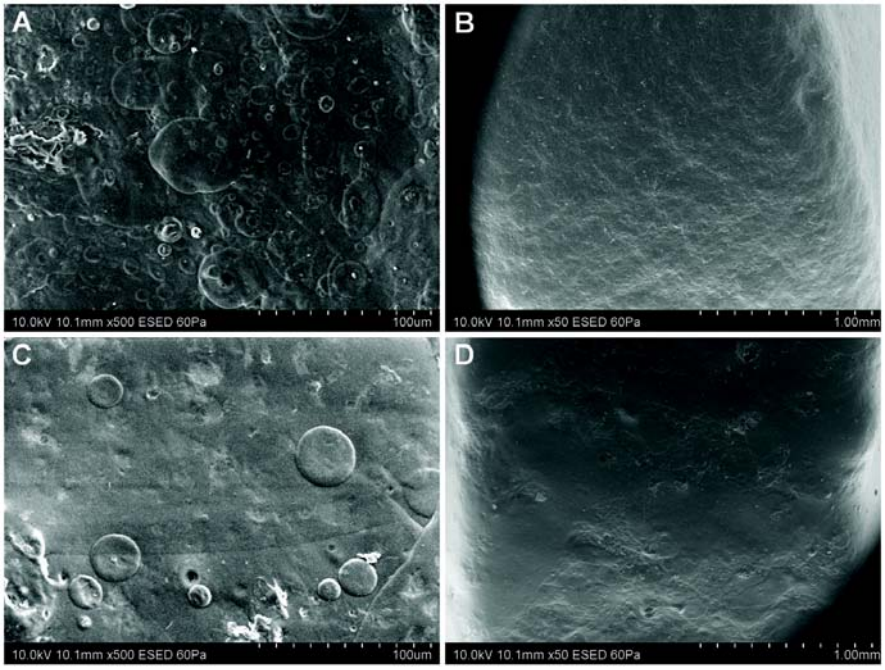

Figure 1. SEM micrographs of the surface of tablets from batch ASA I **(A)** and ASA II **(C)**, with their central band surface images presented in **(B)** and **(D)**, respectively. Coating

droplets are visible on both surfaces but appear more on the tablet in **(A)** than on the tablet in **(B)**. This suggests a rougher surface of the sample from batch ASA I than ASA II. The central band surface morphology also seems rougher in batch ASA I **(B)** than ASA II **(D)**. The scale bar is 100 µm and 1 mm.

Core surface roughness has been suggested to be one reason for a rough coating surface. Further investigations where the TPI parameter TII was used to analyse the coating/core interface were carried out. The mean TII value for samples from the ASA II batch was found to be 5.8%, being less than the value for ASA I batch (7.5%) revealed that the surface roughness in ASA I is not caused by the core surface roughness. Furthermore, the cores used in both runs are from the same batch; as well as the polymer and the amount applied was the same; differences here must be due to the variables like different mechanical shear stress in different equipments, and/or different product bed temperature present during coating. It is well established that the collision forces, tablet-tablet/ tablet-coater, are much higher in a fluid bed coater compared to the ones in a drum coater. This assumption was validated by SEM images showing a more spherical-shaped edge for samples from batch ASA I compared to samples from batch ASA II.

Therefore, the temperature difference effecting the coating polymer behaviour must be a reason for the variation at the coating/core interface. In a drum coater the product bed temperature is usually lower and the amount of air passing through is less, allowing the sprayed polymer particles to coalescence and/or dry slower resulting in a more complete film formation and these conditions make it more likely that the polymer particles have the possibility to adjust to the tablet core surface morphology resulting in a seemingly rougher coating/core interface. Whereas the higher temperature and higher volume of air in the fluid-bed device accelerates drying of the coating liquid resulting in a smoother coating/core interface, and a rougher coating surface as the polymer particle do not get the chance to spread and merge completely before drying.

In addition to the investigation of surface morphology, weight gain measurements were carried out. The average weight gain of tablets was 22.7 mg and 21.6 mg for tablets from ASA I and ASA II batches, respectively. A two tailed, unpaired *t*-test was carried out to compare the efficiency of the two techniques, resulting in a *P*-value of 0.839 (α = 0.05). Despite a similar weight gain in both batches, the average CT obtained from the TPI maps discriminates between the fluid-bed and drum coated samples. The mean CT over the entire tablet from batch ASA I (99 µm) was found statistically significantly higher than the mean CT of batch ASA II (90 µm). SEM micrographs taken, validated the TPI CT measurements. Furthermore, and in good agreement with a previous study[11], thicker coat on average for the sides compared to the mean CT of the central band could be revealed. Different physical conditions present at the central band during the coating process compared to the sides, as well as to the tablet shape, or preferred orientation while passing through the spry zone in both coating devices can be reasons for the thinner CT at the central band[24]. The intra-tablet CT variation found for both batches was minor.

3.2. Impacts of Various Stress Conditions on the Final Film Coating Quality

3.2.1. Coating Formulation Application Stop

Previously, TPI has been shown to be able to detect coating layers of different polymers within the same sample[15,21]. With the purpose of investigating the possibility to detect the interface within the same polymer a spray application stop was applied. So called 'lamination' experiments were performed by stopping the coating application after 50% of the coating liquid was applied; 30 min later the application was continued. Just recently, intra-coating layering due to a process stop has been shown for push-pull osmotic systems (PPOS)[16]. In this study, unlike to the PPOS study, the process stop was intended and it was possible to show the coating/coating interface in the TPI maps for all samples under investigation. According to the terahertz signal, the CT for the first layer was found to be roughly half of the entire CT which is in agreement to the point in the coating process where the spray application was stopped. Figure 2A and B show the terahertz waveform and the corresponding cross-sectional B-scan. A weak peak can be observed between the air/coating interface and the coating/core interface signal in the time domain terahertz waveform, indicating the coating/coating interface. The associated SEM images taken from the same sample verify the obtained TPI results (Figure 2C).

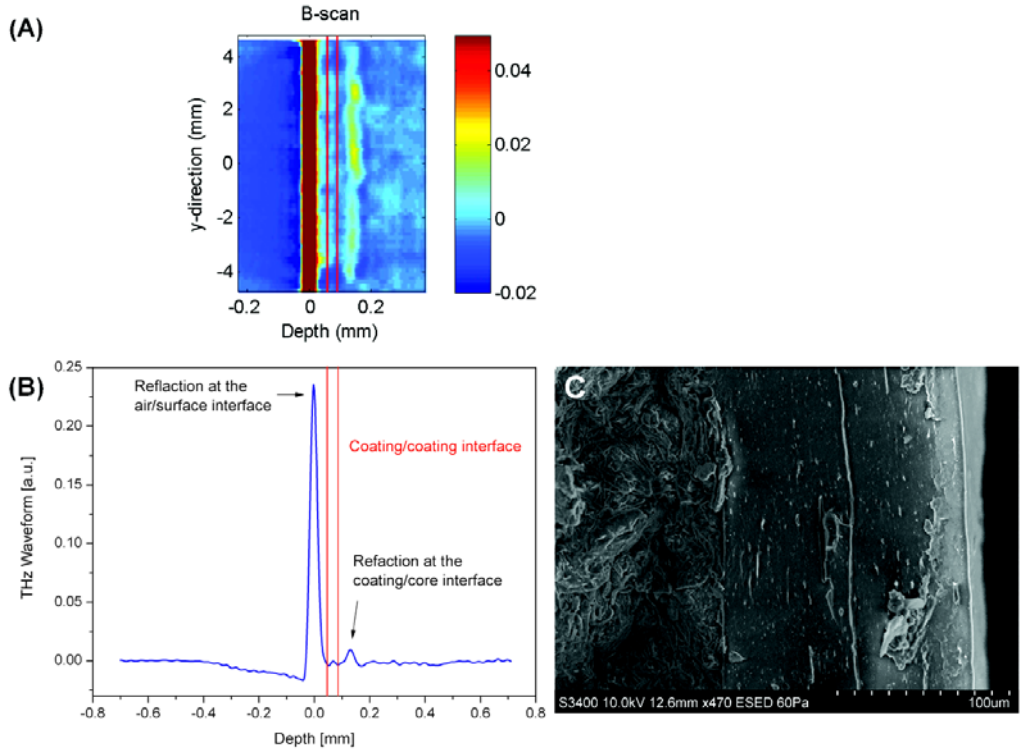

Figure 2. Time domain terahertz waveform **(B)** and corresponding B-scan **(A)** from a single pixel for a sample from batch ASA III. The weak peak between the air/coating and coating/core signal in the waveform represents the coating/coating interface signal shown as a light blue line in the associated B-scan **(A)**. The corresponding SEM image is

presented **(C)**; a fine line indicating the process stop is clearly visible in the coating structure.

The layering effect was found for the both sides of the tablets and the central band in both batches (Figure 3). Interestingly, the average amount of signal containing pixels in all 3D-TPI maps of the tablets coated in the drum coater were less than the amount of pixels of the fluid-bed coated tablets, 57.0 % and 69.0 %, respectively. An explanation for this could be that the tablets were kept in movement during the coating formulation application stop in the drum coater allowing the later applied coating liquid, i.e. polymer particles, to merge with previously applied film. Additionally, tablet cores in the drum coater were warm which could encourage a complete coalescence between the two coating layers. Furthermore, SEM images taken from a sample of batch ASA IV did not reveal a coating/coating interface within the coating structure as anticipated. Nevertheless, even though not visible under the SEM a change in the density and therefore in the RI within the first coating layer may has occurred as the tablets were cured to a certain extent during the 30 min spray stop before a new layer of coating was applied.

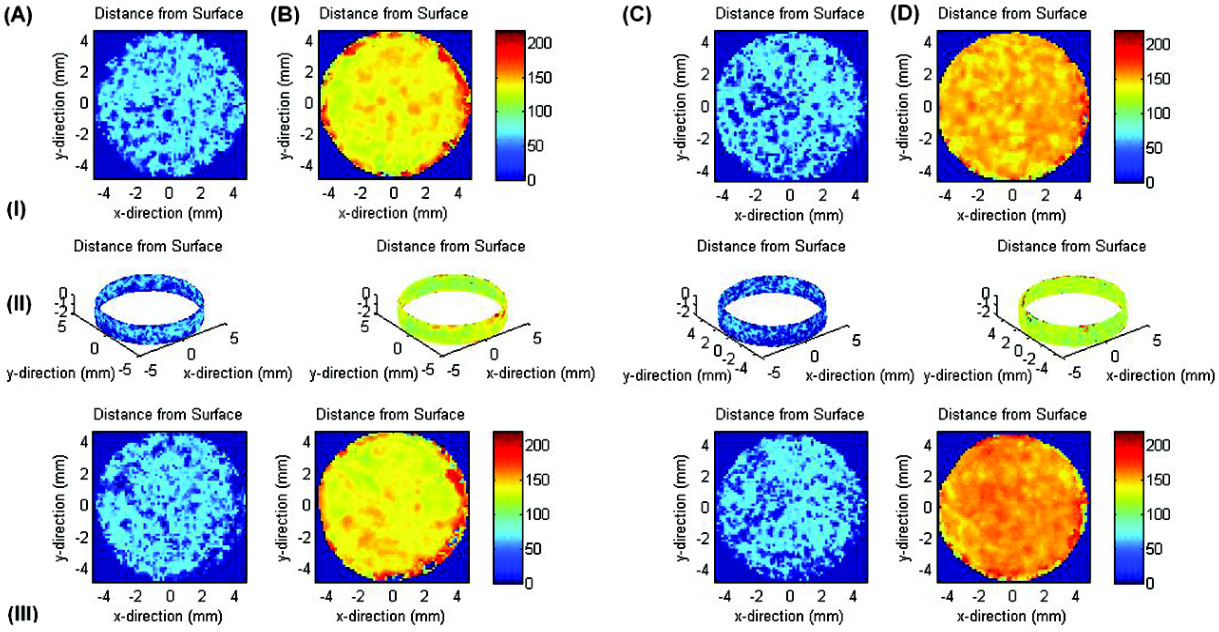

Figure 3. The false-color image of the terahertz parameter coating thickness (CT). The CTs of a sample from batch ASA III **(A** and **B)** and of a sample from batch ASA IV **(C** and **D)** are shown. The light blue images represent the first layer for both sides **(A I**, **III**; and **C I**, **III**, respectively) and the central band (A II and C II) of each sample, whereas the orange/ light green images show the total CT of all sides (**B I-III** and **D I-III**).

3.2.2 Impact of Different Curing Times on the Final Film Coat Quality

With the aim to investigate the effect of various curing times on the final film coating characteristics, all batches were divided into three and cured at 40°C either for 2 h (recommended), 120 h (overcured), or were left uncured (uncured). Typically, curing is carried out to prevent any

further coalescence of polymer particles and consequently avoiding changes in the coating characteristics during the storage. The terahertz parameters for all batches and conditions under investigation were obtained and compared. Student's *t*-tests carried out on the CT and TEFPS indicated no statistically significant differences due to the various curing times Only the batches coated under 'wet' conditions (fluid-bed and drum coater) showed statistically relevant changes in the TEFPS values between the uncured and 120 h cured samples. Here, the TEFPS values increased with increasing curing time suggesting an increase in the surface RI and therefore in the density of the applied film coating.

4. Conclusions

For the first time the performance of two pieces of coating equipment, a fluid-bed and a drum coater, have been investigated using TPI and their results compared. The non-destructive character of TPI enabled a deeper insight to be gained into the performance of the different devices and their impact on CT, uniformity, and quality. The results revealed significant differences in coating surface morphology, coating uniformity across a single tablet, coating/core interface and CT between the two coating devices. SEM was used to confirm the results obtained by TPI. In addition to the comparison of both techniques, different stress conditions were successfully evaluated. Intra-coating layering due to a coating liquid application stop could easily be detected by TPI even if the layering effect was not visible in SEM images. Furthermore, other impacts on the final film coating quality such as density changes due to 'wet' coating conditions and/or various curing times after coating were accessed. TPI can be considered as a potential PAT tool, providing valuable information on the performance of the equipment used to apply film coatings and impacts of various stress conditions on the final film quality.

Acknowledgements

This work was financially supported by University of Otago PhD Scholarship (MH). Drug Research Academy and Lundbeckfonden (grant decision R50-A3631) are acknowledged for their financial support.

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