PHARMACEUTICAL TECHNOLOGY

Terahertz In-Line Sensor for Direct Coating Thickness Measurement of Individual Tablets During Film Coating in Real-Time

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ABSTRACT: We present a new in-line measurement technique to determine the coating thickness of individual pharmaceutical tablets during film coating in a pan coating unit using pulsed terahertz technology. Results of these real-time terahertz measurements acquired during a production scale coating run are validated using both off-line high-resolution terahertz pulsed imaging of the whole dosage form as well as weight-gain measurements made on sample tablets removed at discrete time intervals during the process run. The terahertz measurements provide a direct method of determining the coating thickness, and no chemometric calibration models are required for the quantification. The results, and their repeatability, demonstrate that real-time monitoring of pharmaceutical tablet coating is not only possible but also provides substantially more information of the coating quality than the standard quality control method. Rather than providing the average coating thickness of a large number of tablets, the terahertz sensor provides the thickness of up to 100 individual tablet coatings per minute. Using this information, the operator can get additional information about the thickness distribution in the coating pan and adjust the process accordingly. At present, a minimum coating thickness of 40 μm is required to determine the coating thickness. The technique is applicable for coatings up to 1 mm in thickness. Within that range, it provides thickness measurements of sub-micron resolution. Terahertz in-line coating process measurements show considerable potential for applications in real-time release, process analytical technology and quality by design. © 2010 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 100:1535–1544, 2011

Keywords: coating; processing; unit operations; formulation; coating thickness; analysis; terahertz pulsed imaging; in-line sensor; quality by design; process analytical technology

INTRODUCTION

Interest in coating tablets with one or multiple polymer film layers is steadily increasing within the pharmaceutical industry. Although initially film coating was predominantly performed for aesthetic or taste masking purposes, recent development efforts are directing coating technology more towards functional coatings for controlled release applications.[1] Coating is a well established unit operation in pharmaceutical manufacture, yet the quality of coating achieved to date is limited by the fact that it is a highly complex process dominated by empirical knowledge with large gaps remaining in the full scientific understanding of the process.[2] Although it is possible to readily achieve a uniform coating on the industrial process scale, it is much more difficult to produce coated tablets to exact thickness and density specifications both in terms of tablet-to-tablet variations within a batch or

between batches and production scales. Nevertheless, process understanding is increasing steadily through advances in the field of modelling film coating on the process scale[3,4] as well as understanding the physico-chemical changes of the film formation itself on the micro scale.[5,6]

In order to reduce process time and improve the quality of the coating process, a number of optical sensors, for example, at near-infrared frequencies[7,8] or using Raman spectroscopy,[9,10] have been developed previously to monitor the coating operation and to determine the process endpoint. Conceptually, both of these techniques measure the coating thickness indirectly in that they either track the attenuation of the spectral features of one of the constituents, which is exclusive to the tablet core matrix, or the buildup in intensity of the spectral features in a component that is only found in the coating formulation but not in the tablet core. This approach relies on reference measurements of samples, with well-defined coating thickness spanning the entire thickness range of the coated product throughout the process, having to be acquired prior to the in-line measurement in the process development phase. Typically, the datasets are combined in a multivariate calibration model which is then used to quantitatively correlate the spectral information to the actual coating thickness. The development and validation of such chemometric models is very labour-intensive and slight variations in process conditions can shift the spectral response such that the model loses its quantitative prediction power. This approach is further complicated by the fact that the optical probes used for the acquisition of the calibration models can be different to the actual process sensor and hence models for the transferability of the measurement from one instrument to another are required.

As a consequence, the availability of a calibration-free direct measurement is highly desirable. Here, we show that terahertz pulsed imaging (TPI) could be a suitable alternative technology to non-destructively measure the thickness of tablet coating layers directly within the coating pan. TPI was recently introduced to characterise pharmaceutical coating structures.[11–13] The measurement principle is fundamentally different to the previously mentioned optical sensor technologies: in TPI a sub-picosecond pulse of terahertz radiation is focused onto the surface of a tablet. The main part of the pulse is reflected directly from the surface of the tablet. However, due to the transparency of most polymer materials at terahertz frequencies, a considerable portion of the pulse penetrates into the coating structure and is then reflected back at any subsequent coating structure interface where a change in refractive index is observed. Using the delay time between the two reflection pulses, the coating thickness can be determined directly. To

date, a number of studies have highlighted how this technology can be used in coating development by imaging the coating thickness distribution over the surface of solid dosage forms and correlating the findings to drug release characteristics in dissolution testing.[14–20] In addition to measuring coating thickness, TPI can also yield further information such as the refractive index of the tablet surface which in turn can be critical to drug release from coated tablets.[15]

MATERIALS AND METHODS

An in-line TPI system (TeraView Ltd., Cambridge, UK) was developed and installed on a production-scale, side-vented tablet coater (Premier 200, Oystar Manesty, Merseyside, UK). The sensor was externally mounted onto the perforated coating pan such that the surfaces of tablets moving inside the rotating coating pan are presented at the focus of a continuous train of terahertz pulses (Fig. 1a). The perforated drum had a diameter of 1.3 m. Each circular perforation of the drum was 3 mm in diameter with 51% of the external surface of the drum being open. The coating pan was fitted with tubular mixing baffles. The terahertz sensor is designed such that it maintains a constant distance between the sensor optics and the mesh of the perforated coating pan throughout the process. The system was tested during a 5 h coating trial in which a polymer film (Acryl-EZE®, Aqueous AcrylicEntericSystem yellow and pink, Colorcon Ltd., Dartford, UK) was applied to a batch of tablets. The batch size of uncoated tablet cores was 175 kg. The tablets were bi-convex (10 mm diameter, 370 mg) and consisted of direct compressed lactose monohydrate (Meggle, Wasserburg, Germany). Coating was performed using three spray guns at a spray rate of 300 mL/min operating at an atomising air pressure of 1.5 bar. The coating drum was rotated at 6 rpm. The inlet air flow was set to 2200 m³/h at a temperature of 52°C and an absolute water content of 7.6 g/kg. The exhaust temperature was maintained at 38°C–40°C. Reflected time-domain waveforms were recorded at a rate of 120 Hz (acquisition time of a single waveform 8.3 ms). No signal averaging was performed. When reflected at a suitable orientation from the surface of a tablet, the reflected waveform contains one or more peaks due to reflections from the external surface of the tablets and any subsequent interfaces between coating(s) and the tablet core (Fig. 1b). The thickness of the coatings at a given point on a tablet surface is directly proportional to the separation between adjacent reflection peaks in the time domain and is determined as $2d = \Delta tc/n$, where d is the coating thickness, Δt is the peak separation, c is the speed of light in vacuum and n is the refractive index of the coating. No further assumptions are required for the thickness measurement. The minimum coating thickness that
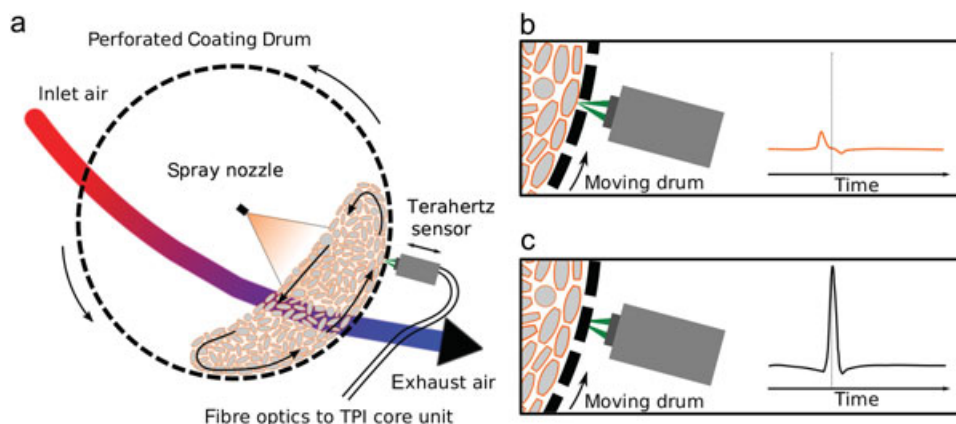
Figure 1. (a) Schematic diagram of the pan coater fitted with the terahertz coating sensor, (b) successful terahertz measurement of the coating thickness of a tablet in the coating pan through a single hole of the drum mesh and (c) measurement of a reference reflection from the mesh. The terahertz pulse is shifted in phase and is much larger in amplitude allowing an easy discrimination between the reference waveforms from the drum mesh and the coating measurements from the tablets in the coater.

can be resolved with this analysis technique is in the range of 30–40 µm.[12,13] For thin coatings, it is possible to use more sophisticated processing techniques to distinguish reflection peaks in the time domain.[21] The identification of the reflection from the tablet surface is facilitated by the fact that reflections from the drum mesh can be easily distinguished from tablet reflections (Fig. 1c).

In order to determine the coating thickness of the tablets in the coating drum in real-time, the data stream from the coating sensor is analysed using a specifically developed waveform processing and analysis algorithm (Matlab R2009b, The MathWorks Inc., Natick, Massachusetts). The algorithm initially performs a signal-processing step which involves signal deconvolution as well as a stationary wavelet transform. In a second step, the algorithm is able to automatically select suitable waveforms from the data stream which represent reflections from the coated tablets that are both in the focus of the terahertz beam and aligned at normal angle to the terahertz optics. This is achieved by specifying selection criteria that describe the amplitude, position, width and separation of the reflection pulses. The third step is the calculation of the coating thickness using the equation specified in the last paragraph. The processing, selection and measurement process is fully automated and runs unattended and in real-time on the raw data stream from the terahertz sensor. According to the type of tablets and coating, it is possible to adjust the waveform selection criteria that determine which waveforms are selected in the second step of the algorithm. In the present study, we saved the entire data stream of raw and processed waveforms in order to allow further off-line analysis and for reference purposes. In a production environment, it is possible

to discard all but the waveforms of the tablet hits in order to reduce the amount of data that need to be stored. In the present configuration, the coating thickness data are directly displayed on the screen of the coater unit in real-time to inform the operator about the progress of the coating process.

For reference purposes, and in order to validate the in-line sensor data, 20 tablets were removed randomly from the coating pan after 60, 120, 165, 180, 195, 225, 240, 255, 270 and 300 min. A minimum of six tablets from each time point were imaged using a TPI imaga 2000 (TeraView Ltd.). For the TPI maps, the top and bottom surface of the tablets were imaged each at 200 µm lateral resolution using the point-to-point spacing mode (>1000 data points per surface). In addition to TPI, the average weight gain was determined on 20 tablets removed from the coater at the same time points.

RESULTS AND DISCUSSION

In order to obtain a quantitative measurement of the coating thickness, the tablets need to be aligned at the focal point and normal angle to the terahertz sensor. Within a pan coater, the tablets have a tendency to align themselves with their faces towards the mesh of the pan. This effect is exploited by focusing the terahertz pulses from outside the drum into the coater where the tablets exhibit a preferred orientation towards the sensor. The terahertz beam is focused just behind the inner surface of the mesh. Tests using different tablet sizes and geometries indicate that this sampling protocol is universally applicable for most commonly used pharmaceutical tablets (Fig. 2). Between 0.5% and 5% of all recorded waveforms contain suitable tablet reflections where the tablet surface is
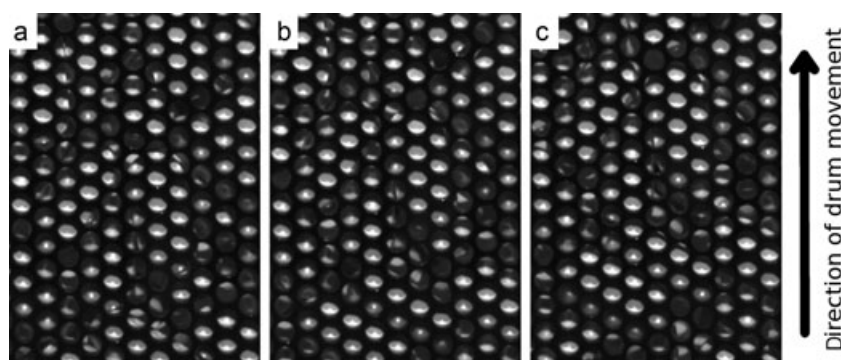
Figure 2. Photographs acquired using a high-speed camera from the exhaust area of the coater looking into the pan at the position of the terahertz sensor. The coating drum is rotating at 6 rpm. The photographs show three frames at 20 min intervals of oblong tablets in the coater unit (a video is available in the supplementary materials). The holes of the perforated coating drum have a diameter of 3 mm.

in focus and the tablet is oriented at normal angle to the sensor optics.

Before attempting to measure the reflections by moving tablets within the pan coater, a proof-of-principle experiment was performed to evaluate whether it is possible to obtain quantitative thickness measurements from terahertz reflections acquired through the steel mesh. For this purpose, a piece of the mesh was screwed flat on top of an aluminium tablet holder. The tablet holder was designed such that it could hold up to six tablets at slightly different angles relative to the mesh (Fig. 3). Five tablets were placed into the holder and a two-dimension terahertz reflection image was acquired by mapping the terahertz reflections in 200 μm step size in x and y direction over the entire test piece (Fig. 4). Three of the five tablets were in a suitable orientation to yield good quality reflections through the mesh. No diffraction artefacts were observed from the pixels at the centre of each aperture. The coating thickness measured from the centre pixels acquired through the aperture agreed very well with the thickness measurements acquired for the same tablets on the TeraView imaga 2000 imaging system.

Even though the terahertz sensor was positioned in the exhaust of the coater, the sensor optics remained clean throughout the coating process and data were acquired throughout the coating operation. The reason for this is most likely the very close proximity of the sensor lens to the mesh (<5 mm). In addition, the velocity of any of the dried polymer droplets that are not deposited on the tablet will rapidly decrease upon reaching the exhaust area due to the sudden increase in volume of the exhaust. Consequently, the far side of the exhaust area exhibits a deposit of fine particular dust which builds up predominantly on the base plate. The contamination of the sensor is further prevented by the fact that the optics are slightly above the level at which the spray guns discharge the coating sus-

pension on the tablet bed. Even though we did not observe any significant deposition of coating material onto the sensor, it is possible that the optics could become coated by a polymer film if the coater is operated under unsuitable temperature conditions (i.e. the temperature of the tablet bed is too low). In this case, the sensor could be easily cleaned or sealed with a user replaceable polymer cover, which is transparent to terahertz radiation. The coating performance of the coater was the same with or without the sensor in place.

The coating thickness measurements obtained using the in-line terahertz sensor agree very well with both the off-line TPI and weight gain measurements (Fig. 5a). As expected, a steady increase in coating thickness build-up is observed over process time with all three techniques. The in-line measurements, though obtained only from a single spot of the moving tablets in the coating pan, show an excellent agreement with the average thickness as determined over the entire surface of the corresponding tablets by TPI. The TPI maps reveal that the polymer layer is evenly distributed over the surface of the individual tablet faces (Figs. 6 and 7).

Even though there is an excellent agreement between the overall trend of the in-line sensor data, the weight gain and the TPI measurements, the slope of the TPI results is slightly lower than that of the weight gain and the in-line results. The reason for this deviation—which becomes more evident at longer coating times and hence thicker coatings—could be due to changes in the coating thickness after the coating operation is finished. Due to the long data acquisition time, the TPI measurements were carried out over a couple of weeks after the coating run. Even though the tablets were stored in a sealed plastic bag under ambient conditions, it is possible that the polymer film has cured during this time and hence increased in density. This would explain the slight
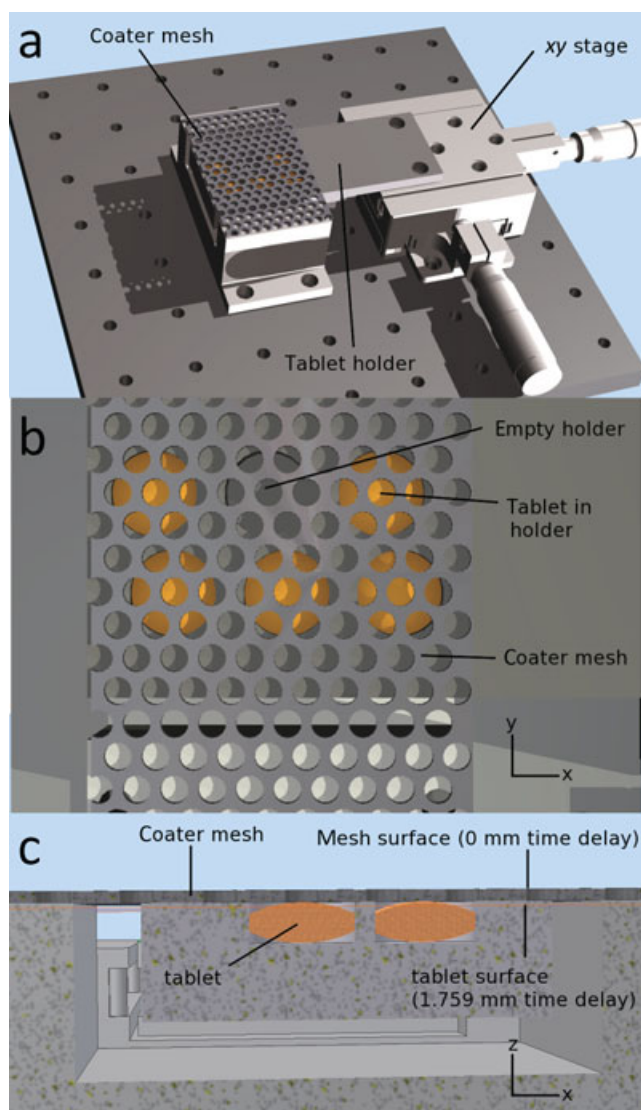
Figure 3. Schematic representation of the sample holder prepared to test whether quantitative terahertz reflection pulses can be acquired through the mesh of a pan coater. (a) The tablets are mounted in a holder which is placed behind a flat piece of mesh from the pan coater. Using a *xy* stage, the position of the tablets can be adjusted relative to the mesh. (b) Five tablets are placed in the holder at slightly different angles. (c) Cross-section through the test piece.

discrepancy in absolute thickness between the TPI reference measurement and the in-line sensor data despite the excellent agreement with the change in tablet mass. The slope of the linear fit of the in-line measured data points is 0.38 µm/min [$R^2 = 0.91$, root mean squared error (RMSE) = 5.8 µm] compared with 0.33 µm/min ($R^2 = 0.99$, RMSE = 3.3 µm) for the TPI off-line measurements (Fig. 5b). These results suggest that the coating shrinks by 13% during storage. However, this hypothesis is subject to further investigation by a detailed time-resolved study into the physico-chemical changes of the coating layer during storage.

Using a terahertz sensor, the coating thickness is measured directly as the time-of-flight between two reflection pulses from the coating surface and the interface with the tablet core.[11–13] This approach is conceptually similar to a radar measurement, and apart from the refractive index of the coating layer, no prior knowledge is required to quantify the coating thickness. Previous work showed that the refractive index of the coating polymer does not change significantly during process time.[16] Together with the above-mentioned study into the physico-chemical changes of the polymer film upon storage after the coating operation, future research will also explore how the refractive index is affected by the process conditions in the coating drum. Until now, it was not possible to investigate such processes in detail as no measurement technique was available to perform studies at the time scales and process conditions required for such experiments. We have performed a preliminary study into whether moisture in the coating layer impacts on the accuracy of the coating measurements. In this experiment, tablets were stored at room temperature, measured by TPI, dried in an oven at 60°C for 1 h, measured immediately by TPI, placed back into the oven at 60°C for 24 h and measured by TPI again. No significant changes were detected between the different measurements. It is also worth noting that though this study focuses on the measurement of the coating thickness in the coating drum, it might be possible to use the sensor to determine additional parameters such as the film density from the same measurement.[15,22]

In order to test the robustness of the terahertz sensor measurements, the colour of the coating was modified during the coating operation by switching from Acryl-EZE® yellow (Aqueous AcrylicEntericSystem, Colorcon Ltd.) to Acryl-EZE® pink, 180 min into the run. The change in colour had no effect on the coating thickness measurement (Fig. 5a). This finding further emphasises the robustness of the terahertz method when compared with other optical sensor techniques which have to be recalibrated for different colours. Even though most polymers used in pharmaceutical coating fall into a relatively narrow band of refractive indices at terahertz frequencies ($n = 1.3$–1.7), the difference in refractive index is typically sufficient to distinguish between different coating layers.[11–14] However, in most cases, the pigments and lakes that are used to alter the visual appearance of the coating have no significant influence on the refractive index at the concentration used in coatings and therefore no influence on the coating thickness measurement is observed.

In the current configuration, the sensor is able to measure the coating thickness of up to an average of 30–40 tablets during 30 s process time (Fig. 8). In addition to its direct measurement capabilities (i.e.
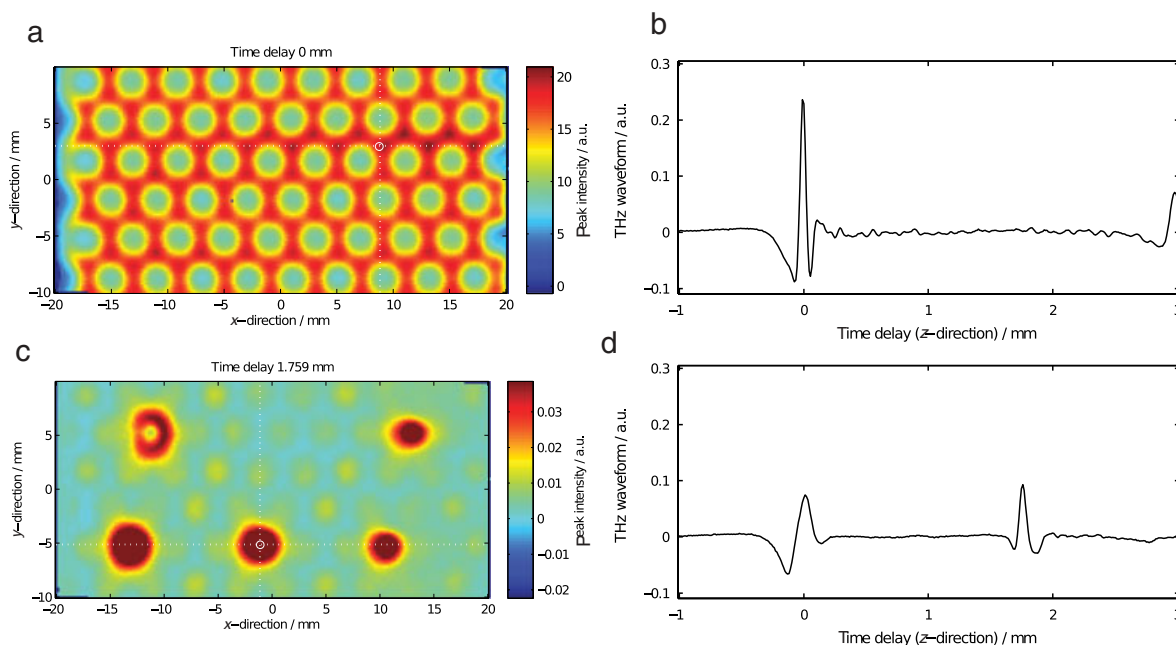
Figure 4. Terahertz maps from the feasibility study using 50 mm focal length terahertz optics. (a) Two-dimensional terahertz reflection map of the surface of the coating mesh (0 mm time delay). (b) Unprocessed terahertz waveform reflected from the metal mesh. The strong reflection at 0 mm time delay is from the metal mesh, whereas the reflection at 3 mm is from the aluminium sample holder below. (c) Map from the plane just below the surface of the mesh (1.759 mm time delay). Three tablets on the left yield strong reflections. The two tablets on the right are slightly tilted and not exactly at normal angle to the terahertz optics hence their reflection is slightly lower than for the other three tablets. (d) Waveform of the reflected terahertz pulse acquired at the centre of the sample in the middle of the bottom row. The first reflection originated from the mesh, whereas the second reflection at 1.759 mm is from the tablet surface.

no calibration models or chemometric data analysis are required) and its robust measurement approach, the terahertz sensor has the additional advantage that it provides the distribution of coating thickness in the coating drum at any given time during the process (Fig. 9). The ability to measure the coating thickness distribution in the coating pan *in situ* cannot be achieved using any of the currently available near-infrared or Raman sensor technology, as each measurement point acquired with these techniques inherently represents the temporal and spatial average over a large number of tablets compared with the single tablet measurements made using the terahertz sensor.

The additional information captured by the terahertz sensor could be a useful critical quality attribute—'a physical, [or] chemical [...] property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality'—for the development of film coating processes within the process analytical technology (PAT)/quality-by-design (QbD) framework.[23] Further work needs to investigate how the *in situ* coating thickness distribution in the coating drum impacts on the quality of the final coated batch.

By measuring the coating thickness over a large number of tablets in the coating drum, the full extent of the coating thickness distribution can be quantified (Fig. 9). The thickness distribution ranges more than $\pm 100\%$ at any given process time. For the present study, it is possible that the distribution in Figure 9 is slightly over-representing thicker coatings due to the very conservative acceptance criteria in our waveform selection algorithm and the current limitation in reliably identifying coatings below 40 µm thickness in this proof-of-principle study. The ability of the in-line technique to sample a far greater number of tablets then is practicable with the off-line analysis means that the full distribution range of coating thickness within the coating pan can be resolved for the first time. In this study, the sample size of the in-line measurements is increased by more than one order of magnitude in comparison with the off-line analysis. The current sensor configuration allows considerable room for improvement in terms of increasing the number of individual tablets that can be measured during the process. By further compensating for subtle irregularities in the geometry of the coating drum in the mount of the sensor and through further improvements of the waveform acceptance criteria,
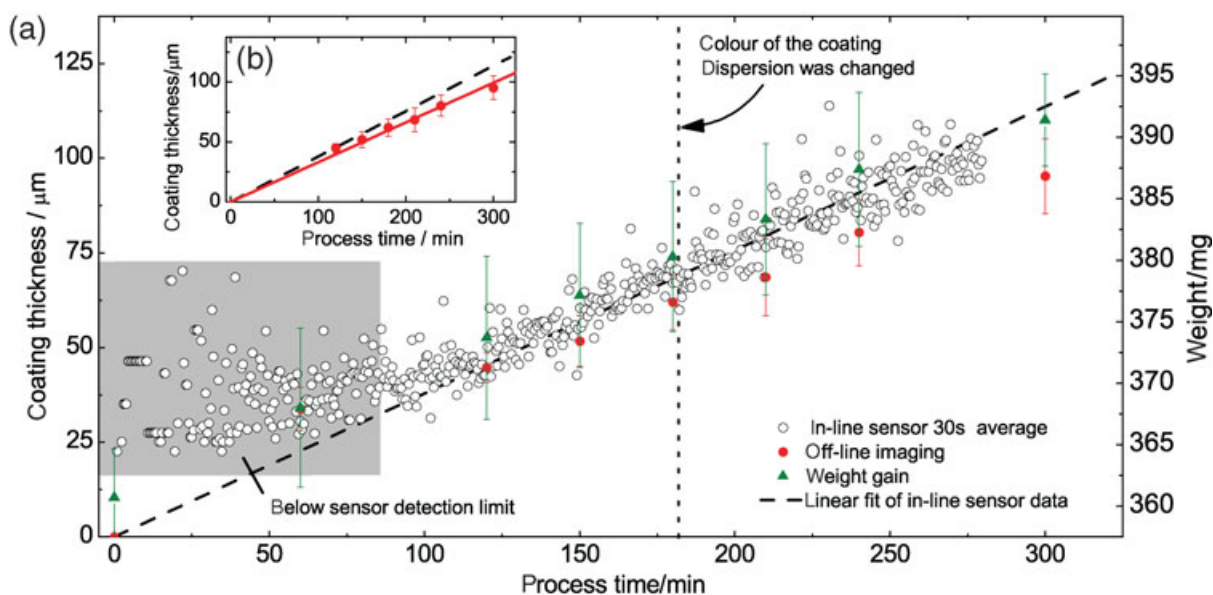
Figure 5. (a) Coating thickness measured by the in-line process sensor as a function of process time (open circles). For clarity, the measurements are subdivided into bins of 30 s duration and the data points correspond to the average thickness during each 30 s bin. The black dashed line indicates the trend line based on the linear fit over all in-line data points above the sensor detection limit indicated in the figure by the shaded region. The closed red circles correspond to the coating thickness as measured by off-line terahertz pulsed imaging (TPI). Each data point represents the average coating thickness over both surfaces of six tablets removed from the coating pan. The closed green triangles indicate the average weight gain of 20 tablets. Before 80 min process time, the coating thickness was below the minimum resolution. After 180 min process time (indicated by the vertical dotted line), the colour of the coating dispersion was changed. (b) Linear fit of the TPI off-line measurements of the tablets after storage compared with the linear fit of the in-line data.

which is used to select suitable reflection signals, the hit rate could be increased to at least 100 tablets per minute.

The instrument in the configuration of this study is already able to measure around 10,000 individual tablets over a 6 h total run duration, which amounts to more than 20% of all tablets in the coating drum. During 30 min process time, an equivalent of up to 3% of all tablets can be sampled. It is possible that some tablets are measured more than once during this process; however, the probability for this is low.

The experimental observation of such a wide thickness distribution during the coating operation further highlights the need for better process understanding in order to achieve uniform coating throughout the batch. Under ideal mixing and spray conditions, a uniform coating thickness distribution over the surface of the tablet would be expected. However, in previous studies, we identified an intra-tablet coating inhomogeneity in standard biconvex tablets where the coating layer on the central band area of the tablet is thinner compared with the two main faces of the
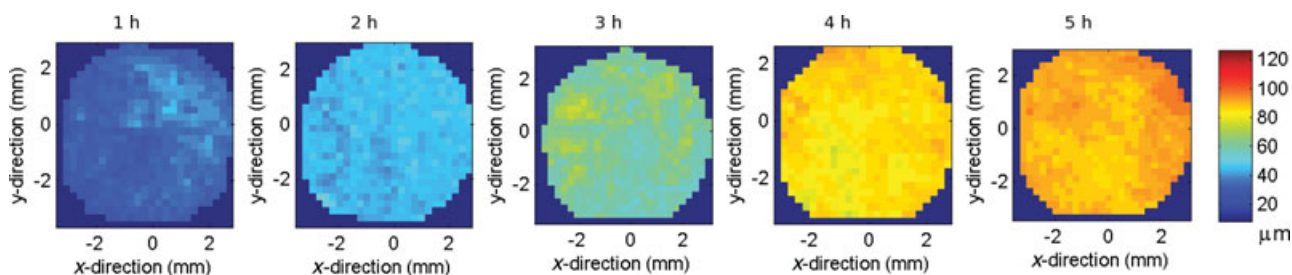
Figure 6. Coating thickness maps from off-line terahertz pulsed imaging measurements at five different time points in the coating trial. Each map represents the surface of one of the tablets removed at hourly intervals during the coating process.
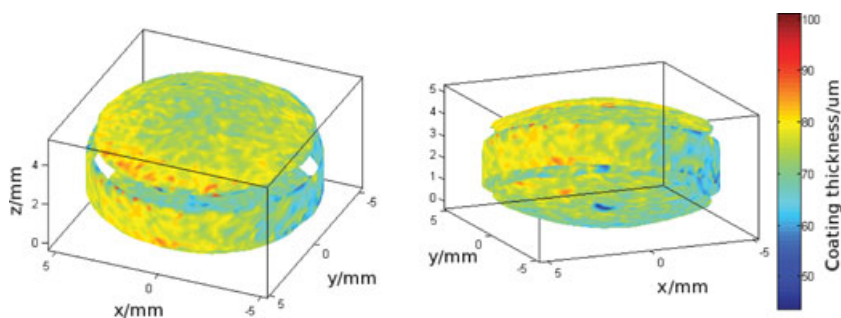
Figure 7. Three-dimensional map of the coating thickness distribution over the entire surface of a tablet after 180 min coating. The thickness of the coating around the centre band of the tablet is identical to that on the top and bottom surface.
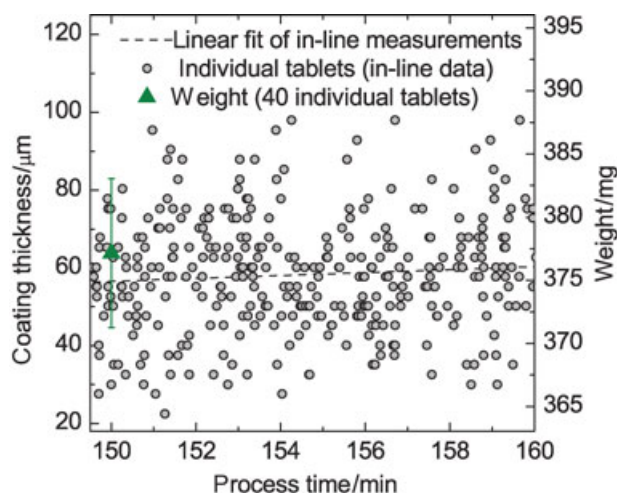
Figure 8. Thickness measurements of 352 individual tablet hits identified during 10 min process time. The black dashed line indicates the trend line based on the linear fit over all data points to guide the eye. The green full triangle indicates the tablet weight of 40 tablets removed at 150 min process time.

tablet.[14] This inhomogeneity appears to be quite common in coated biconvex tablets and it was found to have a significant effect on the drug release kinetics in sustained release coated tablets.[15,18] Even though the coating in this study does not exhibit this defect (Fig. 7), the tablet-to-tablet coating thickness variability itself is expected to have a significant impact on the performance of the product. This effect is expected to be particularly pronounced when the product has an active or a sustained release coating.

The results from this study further question the significance of the quality tests that are implemented across the different pharmacopoeias at present. These end product tests, which form the basis of whether or not a product is deemed safe and is released to the market, assess no more than 30 individual tablets. The histograms presented in Figure 9 clearly demonstrate that sampling such a small fraction of tablets

from an entire batch leads to an almost meaningless result.

Due to the fact that the weight of the uncoated tablet cores varies considerably and because it is not possible to trace individual tablets during the coating run, it is not possible to measure the variation in coating thickness by weight gain measurements: the weight gain of an individual tablet from the coating step is about 31 mg ($\approx$10%) in this study, and the standard deviation in mass of both the uncoated tablets and the coated tablet at the end of the run is $\pm$4 mg each.

Besides the application in the coating drum, the sensor that is introduced in this study could also be used for in-line quality testing of the end product just prior to packaging. It could be used to test the coating thickness of every individual tablet before blistering. The fact that during the packaging process the tablets are individually aligned into the blister packages makes it possible to ensure an ideal reflection from almost every tablet. Using this technology, tablets which deviate from the target thickness could be automatically removed from the product line and film-coated products could be filed for real-time release to the regulatory bodies. Such an application of the sensor technology could be used to improve the quality of the medication that is released to the patient. However, this approach should be regarded as a short-term improvement as this solution would not address the fundamental problem of insufficient process understanding which is causing the sub-standard quality of the film coated product in the first place and this approach would furthermore result in a lot of waste product.

We are currently working on more sophisticated signal processing techniques that will allow us to reduce the minimum film thickness we can resolve. Such development will allow a reliable measurement of the coating thickness earlier in the process. Together with theoretical modelling work of the coating process,[24] this in-line terahertz sensor could be used to study how to achieve and maintain a very narrow
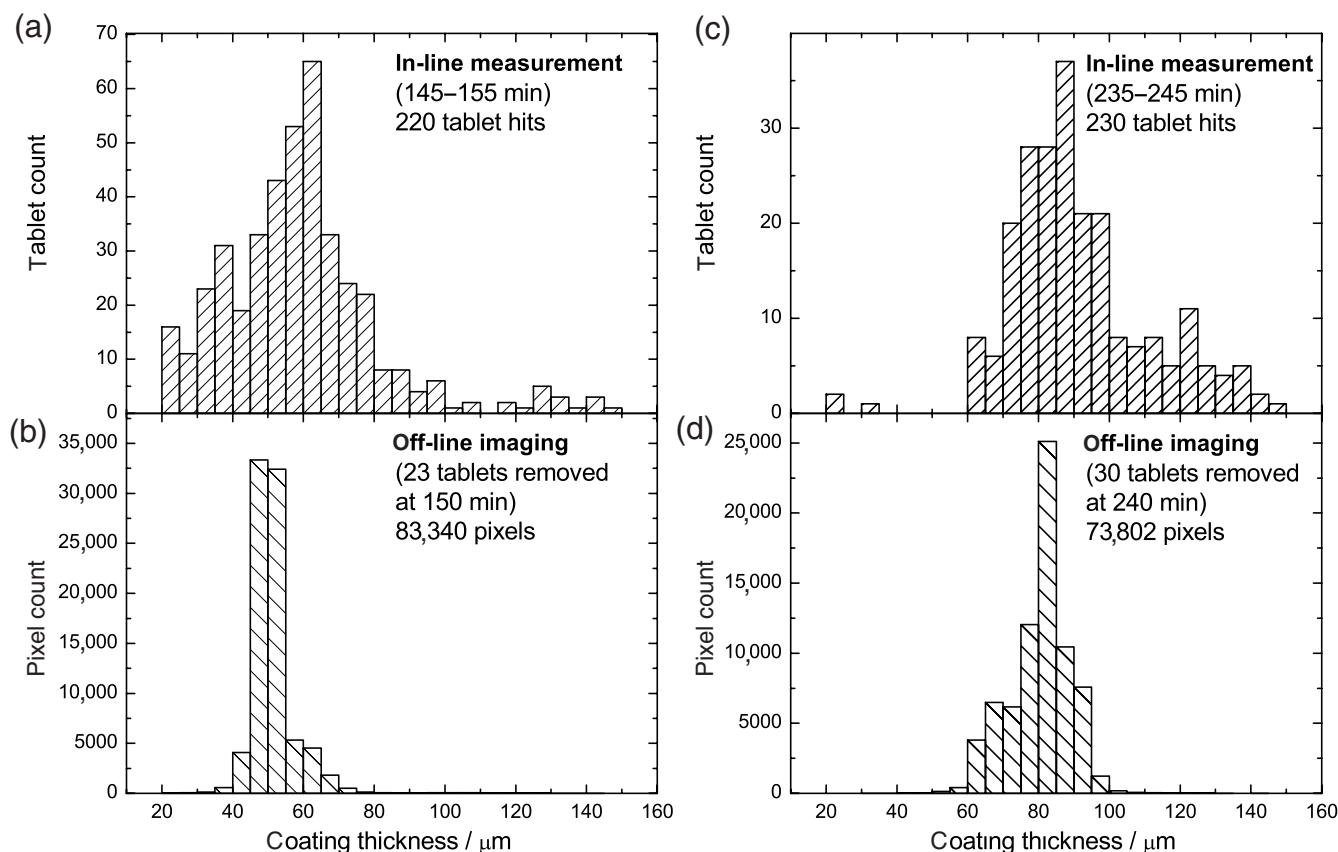
Figure 9. Coating thickness distribution between 145–155 and 235–245 min process time. (a and c) measured using the in-line sensor and (b and d) the corresponding off-line imaging analysis by terahertz pulsed imaging (TPI). The histogram of the off-line measurement represents all pixels of the TPI coating maps generated over the entire surface of 23 or 30 tablets, respectively.

thickness distribution within the coating pan during the entire process. Once the critical process parameters are identified, the sensor could be used to actively control the coating process via feedback loops not only to determine the process endpoint but also to ensure optimum coating conditions throughout the process.

CONCLUSIONS

We have demonstrated for the first time how terahertz pulsed technology can be used to quantitatively measure the coating thickness of randomly moving tablets in a pan coater using an in-line sensor. The acquisition time to produce a coating thickness map of an entire tablet can be as much as 60 min, using the reference high-resolution TPI method. In contrast, the in-line sensor is able to assess the thickness of a single tablet in less than 9 min during process conditions without interfering with the coating process. Direct thickness measurements of film coatings ranging from 40 µm to 1 mm in thickness are achieved with sub-micron resolution and no need for any prior chemometric

calibration models. In principle, this development allows terahertz sensors to make their way from the development laboratory to the manufacturing floor. We envisage that the terahertz coating sensor could have considerable impact in process understanding, PAT and QbD developments of film coating processes. However, future research is required to assess the full potential of this new sensor technology, and development work is ongoing to make the technology more readily available.

ACKNOWLEDGMENTS

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