Steps towards numerical verification of the terahertz in-line measurement of tablet mixing by means of discrete element modelling

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Abstract: In recent years terahertz in-line sensing has been used to monitor the film coating thickness of individual pharmaceutical tablets during the coating process. In the previous work, the in-line measurements were verified against off-line measurements of samples from the same population. Here we report on our recent progress to further verify the validity of the terahertz in-line measurement modality using discrete element modelling for an artificial lab-scale tablet mixing process inside a tablet pan coater. By coupling discrete modelling with a ray-tracing method it is then possible to estimate the cumulative measurements taken, which in turn can guide towards the fine-tuning of the selection criteria as part of measurement analysis.

1. Introduction

Pharmaceutical film coatings are typically polymeric films formed from an aqueous latex dispersion. The films are used primarily to extend the shelf life of the active ingredient and improve the aesthetics of the dosage forms. In addition, they can also serve a functional purpose as in the case of active coatings and controlled release applications. To facilitate better coating process understanding, various non-destructive in-line sensing techniques have been demonstrated. Whilst near-IR [1] and Raman spectroscopy [2] have proven to be popular techniques, largely because of the wide availability of sources and detectors, these techniques measure coating thickness indirectly and thus require time-consuming calibration models to be constructed. Furthermore, owing to the inherent high sensitivity to variations, temporal and spatial averaging of the measurements are necessary and therefore information specific to each of the dosage form, such as the inter-tablet coating variation, cannot be captured.

Terahertz in-line sensing [3, 4] and optical coherence tomography (OCT) [5] are relatively new sensing modalities that show tremendous potential for pharmaceutical coating investigations. In particular, terahertz sensing is well suited for studying tablets with a coating thickness in the range of 40 µm to 1 mm, whereas OCT is applicable to tablets and pellets of suitable coating materials [6, 7] with thicknesses of 10 to 80 µm. The two modalities have been combined recently [8] and can potentially be used to reveal more process insights than previously possible. Methods of verifying these in-line measurements were performed by either intermittent offline measurements [3, 4] or using another independent sensor such as OCT [8]. To further verify the terahertz in-line measurement modality, here we report on the consolidation of our measurements with prediction from discrete element modelling (DEM).

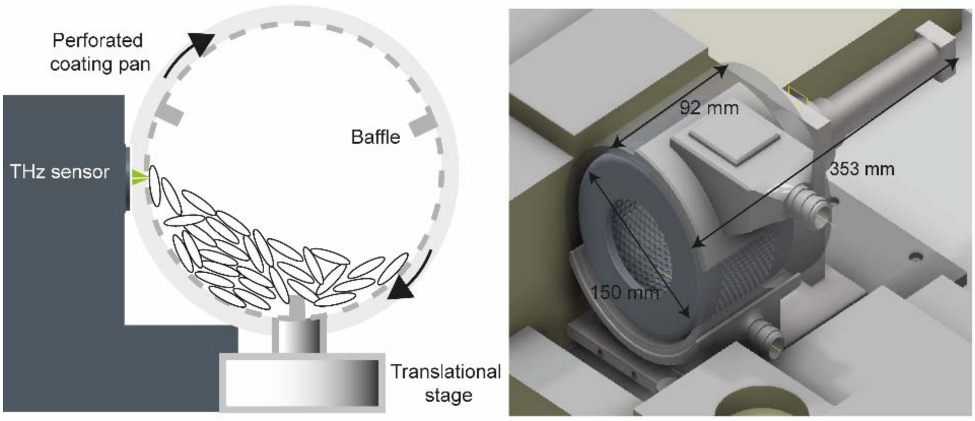

Fig. 1 - Schematic of the pan coater for performing terahertz in-line sensing (left) and a 3D model of the pan coater in perspective view (right).

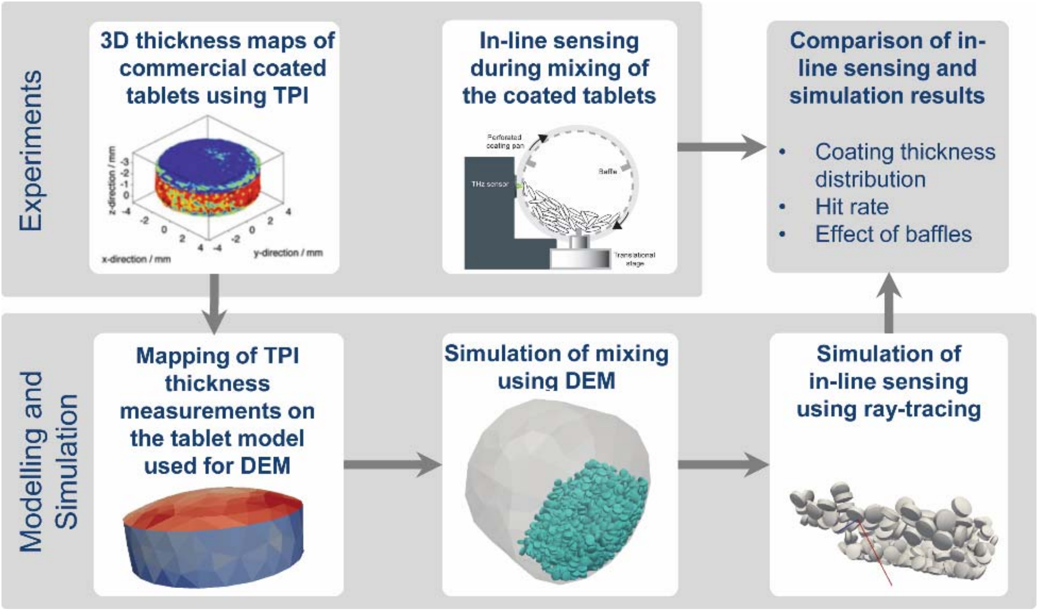

Fig. 2. **– A flowchart describing the steps taken in this study to reconcile the in-line measurements against predictions made with numerical simulations combined with ray-tracing method.**

2. Method

2.1 Tablet mixing

A 1.2 litre laboratory-sized perforated coating pan was custom designed for terahertz in-line measurement using the TPI Imaga 2000 (TeraView Ltd., Cambridge, UK) as shown in Figure 1. The height of the coater was adapted to the height of the terahertz sensor such that surfaces of tablets on the mesh would lie in perpendicular orientation to the propagation direction of the incident terahertz beam to ensure an accurate thickness measurement. To allow for the precise positioning of the perforated coating pan relative to the fixed terahertz sensor, the coating unit was mounted on a manually adjustable linear translational stage. The rotational movement was driven by an A-max 32 permanent magnet DC motor (Maxon Motor AG, Sachseln, Switzerland) supplied with 24 V. A PWM servo controller (ESCON Module 50/5) was used to maintain closed loop speed control by comparing and dynamically adjusting the speed measured by a 3-channel 100 kHz encoder HEDL 5540 (Maxon Motor AG), against the speed set point configured on the ESCON Studio via USB 2.0 interface. The coating unit had a computer numerical control (CNC) machined perforated coating pan of 3-mm wall thickness and an overall outer diameter of 150 mm, whereas each circular perforation had a diameter of 4.2 mm. These perforations are spatially patterned over the surface of the pan as shown in Figure 1. Given the area of each of the perforations and the entire external surface area of the pan, this therefore amounted to an overall 45% of the pan surface being open to airflow. To facilitate the mixing of the tablet bed, the coating pan was additionally fitted with one, three and six drive bars (baffles) where for three and six baffles configurations, the baffles were spaced out at 120° and 60°, respectively. Each baffle has a length of 70 mm corresponding to the longitudinal axis of the coating pan, a thickness of 6.2 mm, and a length of 6 mm toward the centre of the coating pan.

An artificial mixing experiment using a small batch of pigment-free film coated bi-convex tablets were performed directly inside the coating pan rotating at 15 rpm ($0.11\ \mathrm{ms}^{-1}$). The measurement was limited to 10 minutes duration so as to reduce the amount of attrition to the dosage forms. The film coated tablets used for the mixing experiments were coated by a side-vented pan coater (BFC5, L.B. Bohle, Germany) on bi-convex placebo cores (tablet radius = 4 mm, radius of curvature = 9 mm). The coating formulation consisted of 75% Walocel HM5 PA2910 (Hypromellose, Wolff Cellulosics, Germany) and 25% polyethylene glycol 1500 (wt % solids). Prior to tablet mixing, the film coating thickness distribution for 24 tablets was measured off-line by TPI Imaga 2000, where a refractive index of 1.5 was used to determine the absolute film coating thickness [7].

2.2 Terahertz in-line measurement and analysis

To ensure that the generated terahertz pulses were focused onto the surface of tablets inside the coating pan, the sensor was kept at a fixed distance that matched to the 7 mm focal length of the terahertz sensor optics from the inner wall of the coating pan. Taking into account the distance of travel on the mesh and the tablet tangential speed, reflected time-domain waveforms were recorded at a rate of 30 Hz (acquisition time of a single waveform 33.3 ms) with no signal averaging to ensure that the likelihood of multiple measurements on a single tablet is minimised. The measurements were saved and processed off line (Matlab R2015b; The MathWorks Inc., Natick, MA) using a previously developed analysis algorithm [3, 4]. Deconvolution was performed for all of the acquired raw pulse waveforms with a reference waveform, which was acquired from the outer metallic mesh wall of the coating pan [3]. This was necessary in order to obtain time-domain waveforms of a sufficiently high signal-to-noise ratio that

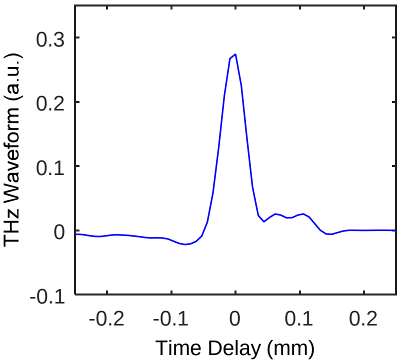

Fig. 3. – An example processed waveform acquired from the tablet surface using TPI in off-line.

clearly reveal individual reflections from interfaces across which changes in refractive index occur. By applying a set of pre-determined selection criteria from theoretical estimations and analysing off-line measurements, only the waveforms that originate from the surface of a coated tablet within a range of normal orientation to the terahertz sensor were selected for the subsequent coating thickness calculation. The selection criteria are composed of position and amplitude limits such that the reflection peaks of interest in a given sample waveform must fall within it. Each processed waveform must contain a primary reflection peak and the position and amplitude of which must lie within the respective limits. As an example, the position and amplitude of the primary peak must lie between -0.2 mm and 0.2 mm and between 0.02 and 0.3 in magnitude, respectively, from the off-line measurement shown in Figure 3. The positioning values are consistent with theory especially considering that a 7 mm focal length lens is used in TPI to achieve a Rayleigh range of approximately 0.5 mm. This therefore implies that for measurements taken outside this distance, the measured signal amplitude would deteriorate that in turn are no longer reliable. The upper limit of the amplitude is set to 0.3 from the off-line measurement in order to record a greater number of hits. This value is also an indicator of the refractive index of the tablet surface and can be estimated from Fresnel's equation at normal incidence. When the primary reflection peak does satisfy both the position and amplitude criteria, analysis is performed using stationary wavelet transform to identify the presence of a secondary reflection peak within a realistic pulse delay range (30–200 µm). In particular, Haar wavelets were used with four levels of decomposition because such settings have shown to be a more robust peak finding method [3, 4, 6]. The amplitude of the secondary peak within the position range must also exceed a certain limit for coating thickness to be reliably calculated. The strength of this value is an indicator of the physical or chemical composition at the interface and is generally estimated from off-line measurement. Finally, as coating thickness is directly proportional to the time lapse between consecutive reflection peaks in the time domain and inversely proportional to the refractive index, the coating thickness d is determined as $2d = \Delta tc/n$, where Δt is the time lapse, n is the coating refractive index taken as 1.5 and c is the speed of light in vacuum. It should be noted here that the recommendations for determining the limits as part of the selection criteria are mere guidelines with realistic uncertainties especially considering differences in core roughness and coating thickness in a population of coated tablets.

2.3 Discrete element modelling and ray-tracing

There is a growing interest towards mechanistic modelling based on solid and gas phase motions such as DEM and computational fluid dynamics in order to comprehensively explain the process in terms of inter- and intra-tablet uniformity of the coating process [10-15]. Inputs to the DEM model typically include material properties, process parameters and coater geometry, with the predicted outputs being inter-tablet and intra-tablet coating uniformity. Quality of the predictions are, however, subjected to the accuracy of the input data that are measured or estimated from realistic conditions. Here, we make our best effort to replicate the experiment numerically. For example, the dimensions of the coating pan and baffles simulated coincided with physical dimensions of the coating pan, the bi-convex shape of the tablet was approximated using the multi-sphere method, and the coating distribution thereof were mapped onto meshed tablet models with values from the off-line thickness distribution as measured by TPI. For each tablet, thickness mapping was performed using a triangulation-based nearest neighbour interpolation method in Matlab whereby each triangle on a tablet equals to the coating thickness of the 'nearest' off-line point measurement as shown in Figure 4.

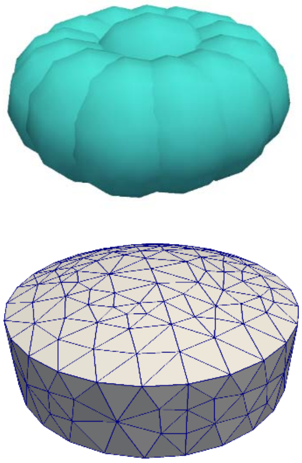

Fig. 4. - The multi-sphere tablet is used in DEM simulations (top) while the meshed tablet is used in the ray-tracing process (bottom).

As it would be prohibitively long to measure the entire batch of tablets off-line, here coating thicknesses of 24 tablets were measured off-line using TPI thus generating 24 coating thickness maps. These maps were sequentially applied onto the entire 230 meshed tablet models.Mixing motions of these coated tablet models inside the coating pan were then simulated mechanistically using DEM. The open source software package LIGGGHTS 3.1.0 [16] was used to compute the dynamics of the multi-sphere tablets in the mixing process. The contacts between constituent spheres from different tablets were calculated based on the Hertz-

Mindlin contact model [17]. The multi-spheres were treated as rigid bodies that follow Newton's second law of motion using a quaternion rigid body algorithm. In order to mimic the sampling mechanism used in terahertz in-line sensing with TPI, here we take into account of the angle of incidence and the sampling frequency using a ray-tracing method. It should be noted that the ray tracing method was used previously as part of DEM simulations for tablet coating as opposed to tablet mixing in order to mimic the trajectories of discrete spray droplets [10, 14]. The ray-tracing method as shown in Figure 5 used in this study represented the trajectories taken by the terahertz beam. In particular, an incoming ray was fired onto the tablet population at an oblique angle of incidence. When the incident ray does intersect with a triangular point on a tablet, a ray is reflected at a direction pending on the tablet orientation. A successful hit of the ray is achieved only when two conditions are fulfilled; 1) when the intersection point on the tablet is approximately 7 mm away from where the incoming ray was fired from; and 2) when the distance between the firing of the incident ray and receiving the reflected ray is approximately 8 mm in order to account the realistic separation distance between the emitter and detector probes of the terahertz sensor. Further, the reflected ray should not be obstructed by either the metallic mesh or other tablets in order for a hit to be registered. The build-up of droplets as the accumulation of successful hits between the ray and the triangle on the table in turn provided information on the coating thickness distribution.

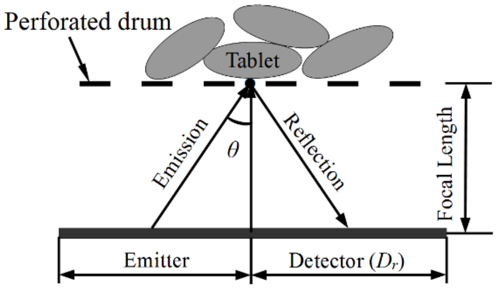

Fig. 5. – The ray-tracing method in reflection mode at incident angle θ. A hit is considered when there is an intersection between the ray and a tablet within focal length and the ray is reflected back to the detector probe of the terahertz sensor.

3. Results and discussions

3.1 Fine-tuning waveform selection

In light of the uncertainties associated with the settings of the selection criteria used as part of waveform analysis, DEM combined with ray-tracing can be used to fine-tune these settings because the simulation results ultimately represent an ideal scenario. As an example, Figure 6 shows the cumulative hits or successful measurements achieved over the 5-minute interval between measurements and simulation for three magnitudes of the secondary peak for varying number of baffles used. The three magnitudes used coincided to settings that are considered to be stringent, relaxed and closer to DEM simulated results, respectively. By applying these settings to the waveforms selection, a significant mismatch in tablet hits between measurement and simulation can be observed especially when stringent and relaxed settings were applied, where the level of mismatch becomes more apparent when the number of baffles used is greater than one. By using the simulation as a guide, magnitude of the secondary peak can be fine-tuned that could result in a closer match. The fine-tuned magnitude here was the same for both 1 and 3 baffles mixing process, while this value was marginally lower for the

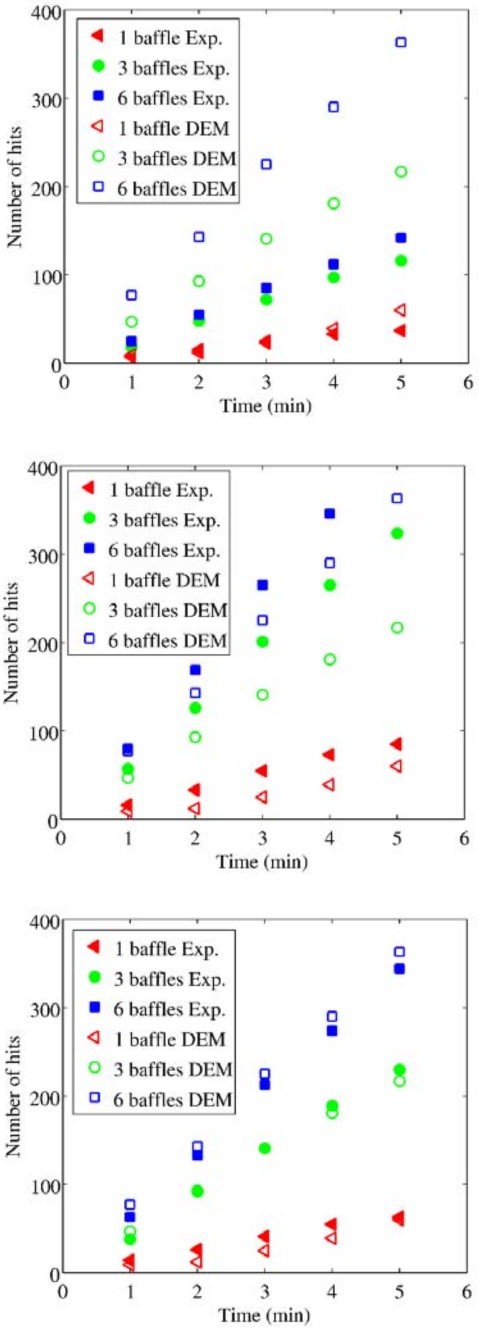

Fig. 6. – Cumulative hits for varying number of baffles over a 5 minutes interval between simulations and measurements processed using stringent (top), relaxed (middle) and normal (bottom) selection criteria.

6 baffles process. It is not understood why this is the case and is the subject of ongoing investigation.

3.2 Hit rate

From the fine-tuned settings, we can then compare the hit rates between the measurement against the simulation, as shown in Figure 7. It can be seen that the hit rates from simulations are generally within two standard deviations (error bars in Figure 7) of the measurements, which present an excellent agreement between measurements and simulations for the different number of baffles used in this study. As expected, hit rate increases with the number of baffles due to the small number of tablets investigated. It additional, it can be seen that the measurement becomes more meaningful when the number of baffles used is equal to or greater than three for the small number of tablets investigated in order to ensure that the tablets can be lifted high enough relative to the location of the terahertz sensor so that there would be an increased probability of interacting with the incoming ray.

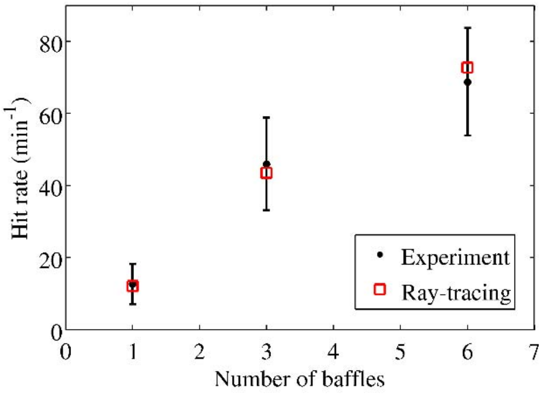

Fig. 7. – Hit rates in measurements and ray-tracing simulations with varying number of baffles.

3.3 Coating thickness distribution

The fine-tuned settings that generated a comparable number of hits between measurement and simulation in turn results in coating thickness distributions shown in Figure 8, which is plotted against the predictions using DEM combined with ray-tracing for various number of mixing baffles, similar to what was recently presented [18]. As can be seen, there is generally a good agreement between measurement and simulation especially between the thickness range of 50 to 90 µm. In particular, for the 24 off-line measurements, the mean coating thickness and relative standard deviation are 59.4 µm and 0.21, respectively, and in the range of 65 to 67 µm and 0.2 – 0.22 for the in-line measurements. The statistics of ray-traced data are closer to the off-line measurements and shows a slight difference from the in-line measurements. The differences between the distributions may be due to under representing the entire tablet population in the simulation where only 10% of randomly selected tablets, as well as the use of interpolation as part of mapping the off-line thickness measurement onto tablet models.

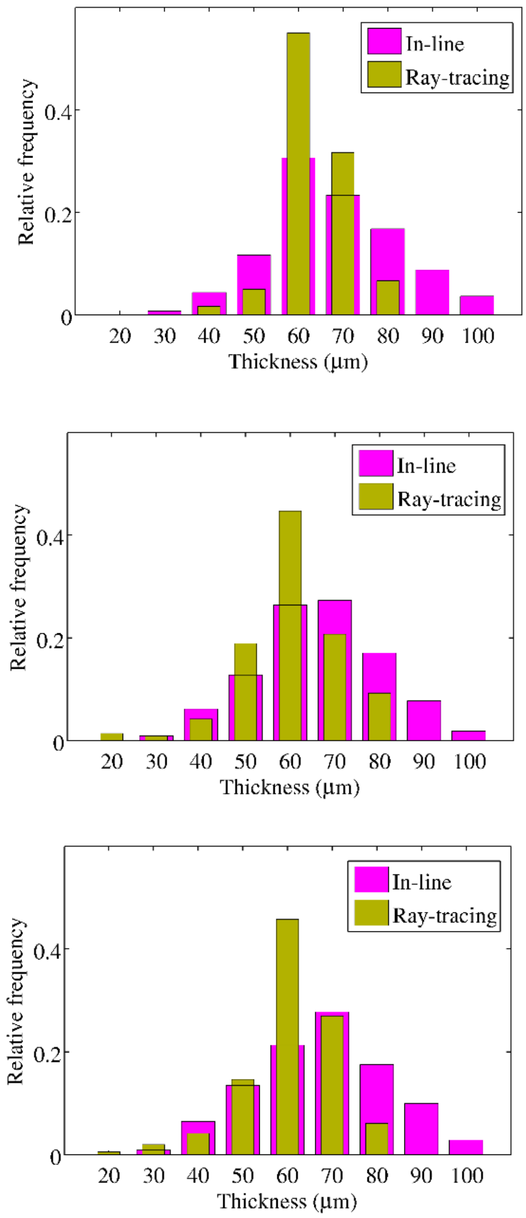

Fig. 8. – A comparison of measured in-line coating thickness distribution against the predictions using DEM combined with ray-tracing for one (top), three (middle) and six (bottom) mixing baffles.

4. Conclusion

Using numerical modelling as a guide to fine-tune the settings of the selection criteria, which presently can only be estimated from the off-line measurements alone, such as the strength of the reflection from the buried surface, we have successfully verified terahertz in-line measurement for an artificial lab-scale tablet mixing process. Benchmarks of comparisons in this study were the hit rates and coating thickness distribution taken when the process included one, three and six mixing baffles. It is also worthwhile to note that from the numerical modelling perspective, this study also presents an interesting method for comparing against time-resolved in-process measurements as opposed to only off-line measurements at process endpoints. Future work aims to extend the model in order to develop a mechanistic understanding of the pharmaceutical film coating process.

5. Acknowledgments

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