In-Line Monitoring of Coating Thickness of Pharmaceutical Tablets during Production Scale Film Coating by Terahertz Imaging

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***Abstract*— We present preliminary results from in-line Terahertz pulsed imaging (TPI) measurements of coating thickness on pharmaceutical tablets made during production-scale film coating. Results of these real-time TPI measurements are compared to those from off-line TPI measurements, as well as weight-gain measurements made on sample tablets removed at discrete time-intervals during production. The results, and their repeatability, demonstrate that real-time monitoring of pharmaceutical tablet coating is not only possible but provides substantially more information than the standard quality control method.**

I. Introduction

The process of film coating in pharmaceutical tablet production has a variety of purposes. For cosmetic coatings and those used to disguise tablet taste, tablet coating quality is not so important. However, for those used in controlled release of active pharmaceutical ingredients (API), coating quality is critical. An enteric coat must be suitably uniform to ensure the tablet core containing API is not exposed. Film coating is applied repeatedly as an atomized spray that dries on the tablet surface until a suitably thick coating layer is achieved. During production, the coating process is monitored by estimating the average weight gain per tablet. When the target weight gain, as a percentage of core weight, has been achieved the coating process is stopped. Typically, a small number of tablets are removed and tested in bulk at regular intervals.

Terahertz pulsed imaging (TPI) provides a mean of non-destructively measuring the thickness of tablet coating layers directly[1,2]. Furthermore, in-line TPI offers the possibility of continuously sampling many more sample tablets during coating without the need to remove tablets – an important consideration when toxic materials are involved. In addition to measuring coating thickness, TPI can also yield further information such as refractive index of the tablet surface.

II. Results

An in-line TPI sensor system (TeraView Ltd.) was developed and installed on a production-scale side-vented tablet coater (Premier 200, OYSTAR Manesty). 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 (Figs. 1,2). The system was tested during a five hour coating trial in which film coating was applied to 10 mm diameter, bi-convex tablets to achieve a target weight gain of 12%. The coating process was performed under full industrial production scale conditions (175 kg batch size). Reflected time-domain waveforms were recorded at a rate of 120 Hz. 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 tablets surface and any subsequent interfaces between coating(s) and the tablet core. The thickness of coatings at a given point on a tablet surface is directly proportional to the separation between adjacent reflection peaks in the time-domain. For thin coatings, more sophisticated processing techniques[3] were used to distinguish reflections peaks. Not all recorded waveforms contain suitable tablet reflections and signal processing was used to identify those that do. It is estimated that between 0.5% and 5% of the collected waveforms contained useful reflections from moving tablets.

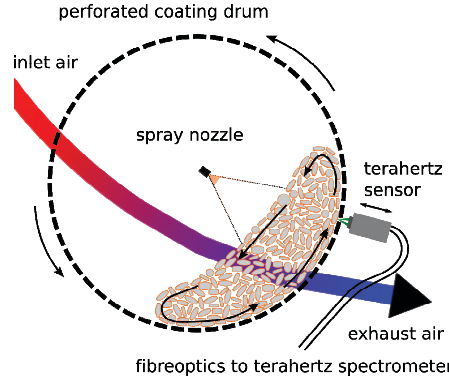

Fig. 1: Schematic detailing the position of the in-line terahertz sensor in the coating unit. The sensor is placed such that the terahertz pulse train is focused just behind the mesh of the perforated coating drum.

Fig. 2: Photograph of the terahertz sensor unit attached to the production scale film coater.

For reference purposes TPI measurements of sample tablets removed during the coating trial at intervals of between 30 and 60 minutes were made using a TPI Imaga 2000 (from TeraView Ltd.). The TPI maps of the tablets were used to check the coating uniformity over the entire surface of the tablets in the coating drum. The off-line measurements also provided estimates of the average coating thickness at 10 sample points in the coating trial. In addition, weight gain measurements were made on 20 tablets removed from the coater every hour. The results of the coating trial are shown in Fig. 3.

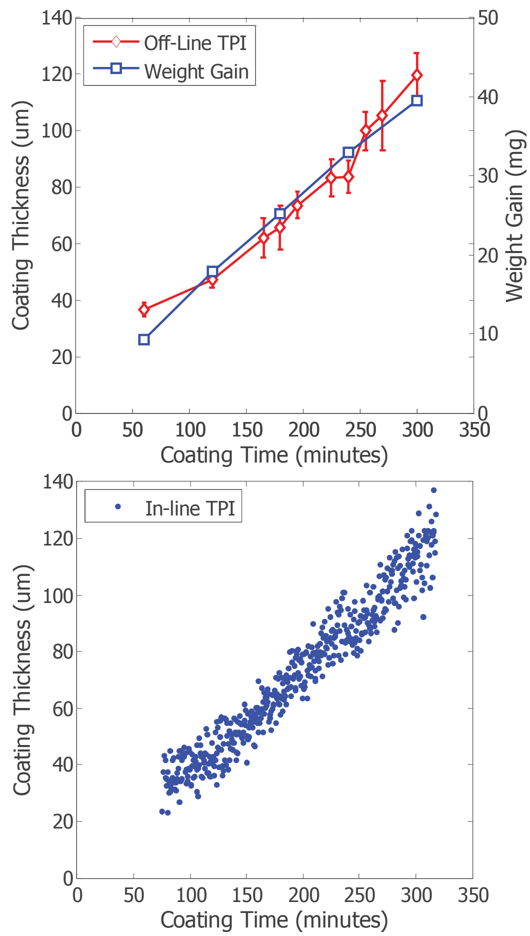

Fig. 3. Off-line TPI and weight gain measurements (top). In-line TPI measurements (bottom).

Excellent agreement was found between the measurements acquired using the terahertz in-line sensor and both the TPI off-line images and the weight gain measurements.

Compared to near-infrared or Raman process sensors the terahertz measurements provide a direct method of determining the coating thickness as no chemometric calibration models are required for the quantification. The calibration free measurement method makes the terahertz sensor very powerful from the early product development phase onwards as small changes in the coating formulation have no impact on the coating thickness measurement, which is ideal at a stage where changes in formulation occur quite frequently. The results from the in-line sensor were reproduced in eight coating runs. Our experiments show that real-time monitoring of pharmaceutical tablet coating is not only possible but provides substantially more information of the coating quality than the standard quality control method.

Rather than providing an average coating thickness the terahertz sensor provides the coating thickness of up to 100 individual tablets per minute (data not shown)[4]. Again, such a measurement cannot be achieved with the currently available optical techniques where each measurement point represents the time and spatial average over up to hundreds of tablets. Using the information of the single tablets acquired with the terahertz in-line sensor the operator can get additional information about the thickness distribution in the coating pan and adjust the process accordingly.

We have demonstrated how terahertz technology can be used to quantitatively measure the coating thickness of randomly moving tablets during film coating *in situ* using an in-line sensor under industrial production conditions. In the development laboratory the time to acquire a coating thickness map over the surface of an entire tablet can be as much as 60 minutes using a TPI instrument. In contrast, the in-line sensor is able to non-invasively assess the average thickness of a single tablet in less than 9 ms without interfering with the coating process. In principle this development allows terahertz sensors to make their way from the development laboratory to the manufacturing floor. We envisage that this sensor could have considerable impact in process analytical technology (PAT) and quality-by-design (QbD), two recent initiatives to improve the manufacturing quality and efficiency in the pharmaceutical industry, of film coating processes.

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