Investigation of Pharmaceutical Film Coating Process with Terahertz Sensing, Optical Coherence Tomography and Numerical Modelling

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***Abstract*—Terahertz in-line sensing was successfully demonstrated on a production scale setting for measuring the coating thickness of individual pharmaceutical tablets during the film coating process. This paper reports on recent research progress to exploit terahertz in-line sensing, optical coherence tomography and numerical modelling to better understand the pharmaceutical film coating process.**

I. INTRODUCTION

PHARMACEUTICAL film coatings are typically polymeric films formed from an aqueous latex dispersion that are used primarily for prolonging shelf life of the active ingredient and improving the aesthetics of the dosage forms and in advanced dosage forms. The coatings can also serve a functional purpose such as in active coating and controlled release.

Even though pharmaceutical film coating has been performed for more than 100 years, the coating process is still poorly understood. This is in part due to the inherently complex nature of the process stemming from the involvement of many parameters that may be broadly classified as: dosage form properties (shape, size), process conditions (rotation speed, temperature, humidity, airflow) and device parameters (baffle design, nozzle location). To facilitate better process understanding, various non-destructive in-line 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 nevertheless measure coating thickness indirectly and thus require time-consuming calibrations models to be constructed. Furthermore, owing to the inherent high sensitivity, 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] and optical coherence tomography (OCT) [4] are relatively new sensing modalities that show tremendous potential for pharmaceutical coating investigations. In particular, terahertz sensing is well suited for tablet dosage forms with coating thickness in the range of 40 µm to 1 mm, whereas OCT is applicable to tablets and pellets for coating thicknesses of 10 to 80 µm. By combining these two promising techniques together in an in-line setting, *in-situ* and real-time film coating thickness information can be obtained that can subsequently be consolidated with numerical models in order to develop a mechanistic understanding of the film coating process. The aim of this paper is to report on the recent research progress in this area.

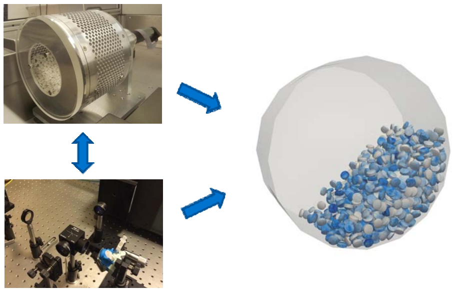

Fig. 1. A numerical model for the pharmaceutical coating process consolidated with process feedback information in the form of film coating thickness measured *in-situ* by in-line SD-OCT and terahertz sensing.

II. METHODS

A two liters laboratory-sized perforated coating pan has been designed and manufactured as shown in Figure 1. We are currently in the process of modifying the coating pan to a fully contained lab scale coating unit in which the batch spray coating of tablets can be performed. The coating unit includes relevant sensors to monitor and record process parameters such as airflow, temperature, humidity and pressure.

In a manner similar that described in [3], the coating unit has been coupled to the TPI Imaga 2000 (TeraView Ltd., Cambridge, UK), where TPI operates at an acquisition rate of 30 Hz to measure the coating thicknesses of tablets. In parallel, a fibre based spectral domain (SD) OCT system operating at 850 nm has been developed with a 300 Hz acquisition rate to generate tablet depth profiles at an offline setting, also shown in Figure 1. In order to assess in-line sensing with both of the modalities, pigment-free film coated bi-convex tablets were measured directly inside the coating unit rotating at 6 rpm. The measurement was limited to 10 minutes duration so as to reduce the amount of attrition to the dosage forms. The film coated tablets were previously coated by a side-vented pan coater (BFC5, L.B. Bohle, Germany) on biconvex 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). Film coating thickness for the tablets was measured by TPI Imaga 2000 and SD-OCT system in an offline setting. Even though it is possible to determine the refractive index of the film coating material at terahertz frequencies for absolute coating thickness computation, the refractive index at optical frequencies remains unknown in this investigation. Such information may, however, be obtained via suitable spectroscopic methods such as spectroscopic ellipsometry.

III. RESULTS

The absolute film coating thicknesses for three randomly selected tablets were measured by TPI to be in the range of 60 to 70 µm with a refractive index of 1.5 [5]. Without accurate knowledge of the refractive of the coating material at the optical frequencies, the film coating thicknesses of the same tablets were measured to be around 80 µm with SD-OCT when a refractive index value of 1.5 was also used for calculation. Figure 2 shows the coating thickness measurement for one side of one of the three tablets measured using TPI and SD-OCT system. The coating thickness distribution across the tablet surface can be mapped out using TPI at a spatial resolution of 200 µm at 1 THz where information on the intra-tablet coating variation can be obtained. Whilst similar information can also be obtained from a SD-OCT B-scan at a higher spatial resolution than terahertz owing to a comparatively shorter wavelength, this information is not obtained in this investigation. Coating thickness from the SD-OCT measurements can be manually determined from inspecting the distance between successive peaks in the A-scans that correspond with the interfaces on the B-scan.

The film coating thickness of the individual tablets measured *in-situ* using terahertz in-line sensing and the integrated SD-OCT sensor Figure 3. Evidently, the coating thickness distribution that is representative of the inter-tablet coating variation as measured with terahertz in-line sensing is centered at 65 µm (Figure 3 top row), which is in close agreement with the offline measured coating thickness. Similarly, the coating thickness distribution measured with SD-OCT is centered about 75 µm (Figure 3 bottom row), which also coincides with the offline SD-OCT measured thickness. Even though the number of tablets reported in the coating thickness distribution with terahertz sensing is greater than with SD-OCT, this value is likely to be lower due to uncertainties in defining thresholds for the various selection criteria [6]. In contrast, the number of tablets detected with SD-OCT is more accurate because the detections can be observed visually as portions of the bi-convex tablet on the measured B-scans. Furthermore, as the acquisition rate for SD-OCT is an order of magnitude greater than that for terahertz, information on intra-tablet coating variation can also be obtained.

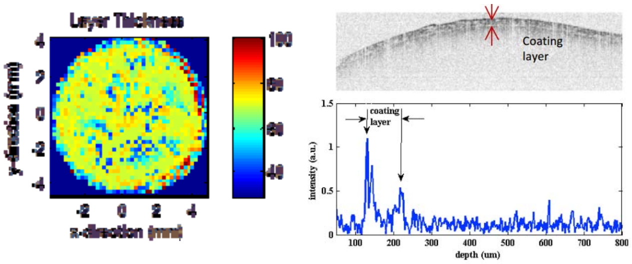

Fig. 2. Coating thickness map of an example tablet as measured using TPI (left) and offline OCT system (right).

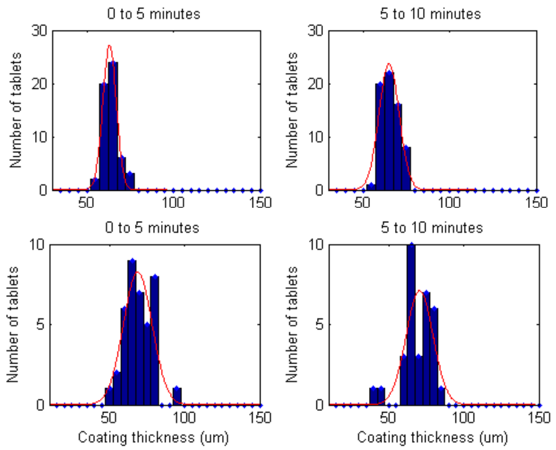

Fig. 3. Coating thickness distribution of the same batch of tablet at 5 minutes time window as measured *in-situ* using terahertz in-line sensing (top row) and SD-OCT system (bottom row).

IV. SUMMARY

We have successfully coupled a lab-scale coating unit to the terahertz system for terahertz in-line sensing and successfully integrated the OCT sensor into the coating unit. In particular, we have validated the inline measured coating thickness against the coating thickness measured offline. Future work aims perform pharmaceutical film coating trials and to utilise both sensing modalities to monitor coating thickness growth for consolidation with numerical modelling.

ACKNOWLEDGEMENT

The authors would like to acknowledge the financial support from UK EPSRC Research Grant EP/L019787/1 and EP/L019922/1.

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