Quantification of Thin-film Coating Thickness of Pharmaceutical Tablets using Wavelet Analysis of Terahertz Pulsed Imaging Data

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***Abstract*— Terahertz pulsed imaging (TPI) is a powerful tool for nondestructive and quantitative characterization of pharmaceutical tablet coatings. In this paper, we present various processing methods for determining coating thickness from the measured terahertz waveform. We demonstrate that a wavelet-based method can be used to characterize the tablet coating with a thickness down to 25 microns, which is better than a conventional "peak-finding" method. Experimental results demonstrated that this new method is also applicable to real-time in-situ monitoring and control of pharmaceutical manufacture processes.**

I. Introduction

PHARMACEUTICAL tablet coating is one of the preferred routes to control the release of drug molecules in the body[1]. As summarized in a recent review article[2], four main methods have been proposed to assay the tablet product performance through evaluating the physical and chemical uniformity inside a tablet. These are X-ray computed tomography (CT), magnetic resonance imaging (MRI), infrared (IR) spectroscopy and Terahertz pulsed imaging (TPI)[2-7]. X-ray CT is a high-resolution and high-penetration method. However, there are safety concerns about using ionizing X-ray radiations and the contrast is often quite poor. MRI is generally regarded as destructive because it requires the interaction of a liquid phase with the sample and hence better suited to study dissolution processes. In addition, X-ray CT requires either the sample or the instrument to be rotated, which is not ideal for on-line monitoring applications. NIR techniques have been used for on-line applications but require a learning set of tablets to build a calibration model and thus is not a direct method[4]. TPI, on the other hand, is a direct and non-ionizing method. Recently it has been demonstrated that TPI is a powerful tool for nondestructive and quantitative characterization of pharmaceutical tablet coatings[4-7]. The state-of-the-art TPI instrument has a detection limit of 40 m which is sufficient to characterize most finished solid dosage form products. However, for on-line applications, a better detection limit is needed in order to identify any issues at an early stage of the coating process. In this paper we demonstrate that a wavelet analysis method can be used to enhance the capability of TPI for characterizing thinner pharmaceutical coatings.

II. Experiments and Methodology

In this study, eight batches of pharmaceutical tablets with various coating thickness were measured. The tablet core is a mixture of lactose, microcrystalline cellulose, aluminum oxide and magnesium stearate. The tablets were taken at various intervals (10 to 80 minutes) during a continuous coating run on the Manesty Lab01 coater whilst being sprayed with 20%w/w Opadry II solution (Colorcon Ltd, Dartford, UK).

A TPI imaga 2000 (TeraView Ltd, Cambridge, UK) was used to analyse the tablets. Fig.1 shows the schematic diagram of the instrument. Terahertz radiation is generated by pumping a biased photoconductive antenna with a laser pulse from a Ti:Sapphire femtosecond laser at 800 nm. The emitted terahertz pulse is collected, collimated, and then focused onto a coated tablet. The reflected and backscattered terahertz pulse is then collected and focused onto an unbiased photoconductive antenna for the laser-gated terahertz detection. A six-axis robot system was employed to handle the tablet. This ensures that the tablet is always at the terahertz focus position with its surface always perpendicular to the terahertz probe during TPI measurement. For each tablet a TPI data set comprising approximately 2600 point measurements was recorded. Each point measurement on the surface of the tablet gives a terahertz waveform of 512 data points.

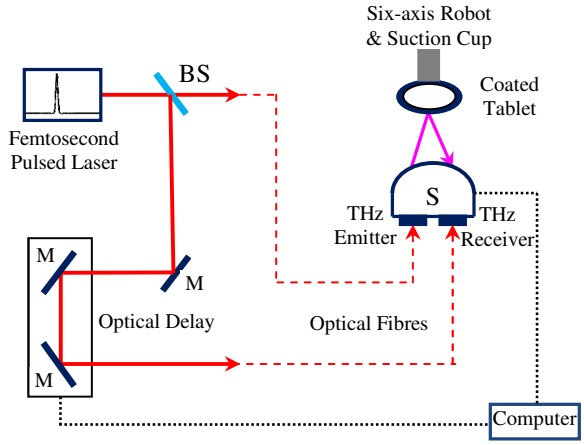

Fig.1 Schematic setup of the TPI imaga 2000 system. A six-axis robot system was used to handle the coated tablet. SL: silicon lens system; BS: Beam Splitter; M1, M2 and M3: Metallic mirrors.

For the coating thickness analysis of tablets, the prediction method used in the present work is based on the stationary waveform transform (SWT)[8-9]. The methodology of the proposed method is based on SWT decomposition of TPI data

into approximate coefficients ($\tilde{c}_{j+1,k}$) and detail coefficients ($\tilde{d}_{j+1,k}$) which are represented as follows:

$$\tilde{c}_{j+1,k} = \left\langle f(x), \frac{1}{2^{(j+1)/2}}\phi\left(\frac{x-k}{2^{(j+1)}}\right)\right\rangle = \sum_{l=-\infty}^{+\infty} h(l)\,\tilde{c}_{j,k+2^j l}$$

$$\tilde{d}_{j+1,k} = \sum_{l=-\infty}^{+\infty} h(l)\,\tilde{d}_{j,k+2^j l}$$

where $\tilde{c}_{j,k} = \left\langle f(x), \frac{1}{2^{j/2}}\phi\left(\frac{x-k}{2^j}\right)\right\rangle$, $\tilde{d}_{j,k} = \left\langle f(x), \frac{1}{2^{j/2}}\psi\left(\frac{x-k}{2^j}\right)\right\rangle$, and ϕ is the scaling function, $\psi(x)$ is the mother wavelet and h is the impulse response of low-pass paraunitary quadrature mirror filters.

III. Results and Discussions

Fig.2 shows a typical waveform and its SWT detail coefficient. In the figure, the two dots in SWT detail coefficient indicate the surface and coating/core interface of a tablet, respectively. Fig.3 (a) plots the averaged thickness of each tablet, obtained using the standard peak-finding method[5], against the coating time. In general, the coating thickness increases with coating time, except for the coating thickness obtained for 10 and 20 minutes where the coating thickness is below the detection limit. Note that the coating thickness varies from tablet to tablet, even for the tablets with the same coating time. As shown in Fig.3 (c), the coating thicknesses of three tablets are different although they have the same coating time of 50 minutes.

Fig.3 (b) shows the thickness predicted by the newly developed SWT method. Using this approach the limit of the thinnest coating thickness that can be measured reliably can be improved to about 25 microns, which is better than the 40 m obtained using a conventional "peak-finding" method. We believe that this improved detection limit is of significant importance. In the coating process there are many variables such as temperature, moisture, the speed of coating drum and air flow that may affect the final quality of the product. This result is important in the context of on-line monitoring of the coating thickness, especially in the early stage of the coating process when the coating is relatively thin. TPI techniques, together with this newly developed SWT analysis reported here, may provide a powerful technique for real-time in-situ monitoring and control of pharmaceutical manufacture processes.

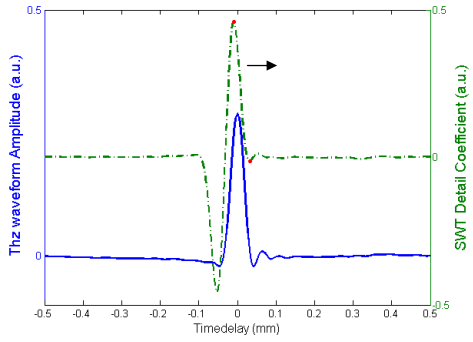

Fig.2 A typical THz waveform and its SWT detail coefficient

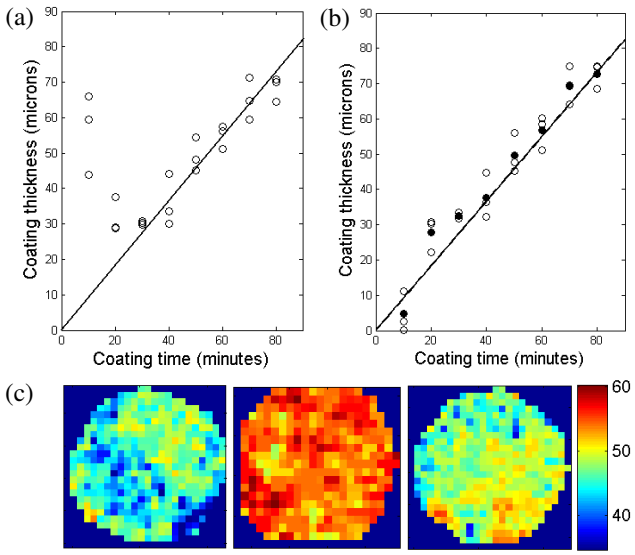

Fig.3 The averaged coating thickness of each tablet predicted using the peak-finding method (a), and the wavelet-based method (b). The solid dots are the coating thickness averaged over 3 tablets of the same coating time. (c) Coating thickness map (in microns) of 3 tablets with a coating time of 50 minutes, showing tablet-to-tablet variations.

Acknowledgement

The authors would like to acknowledge financial support from UK Technology Strategy Board (AB293H). JAZ would like to thank Gonville & Caius College for funding through a research fellowship.

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