Neural Network-based Non-destructive Quantification of Thin Coating by Terahertz Pulsed Imaging in the Frequency Domain

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Abstract— **Terahertz pulsed imaging (TPI) is a powerful tool for non-destructive quantification of pharmaceutical tablet coatings. In this paper, we present a Neural Network (NN) based method for extracting the coating thickness from the FFT-amplitude of the measured terahertz waveform. We demonstrate that the NN-based frequency domain method outperforms the standard "peak-finding" time-domain method, in terms of quantifying thinner coating thickness, although a learning set of data is necessary.**

I. Introduction

IN the pharmaceutical sector, tablet coating is one of the preferred routes to control the drug release to the human body [1]. Therefore non-destructive techniques for characterizing pharmaceutical tablet coatings become increasingly important. A number of methods, including near-infrared (NIR) spectroscopy [2], optical coherence tomography [3, 4], X-ray computed tomography [5], and terahertz technology [6-8], have been investigated for non-destructive and quantitative characterization of pharmaceutical tablet coatings. Terahertz pulsed imaging (TPI) was recently adopted by the pharmaceutical industry for quantifying tablet coating thickness [2, 6-8]. Usually a "peak-finding" method is used to analyze the time-domain terahertz waveforms: the coating thickness is determined from the time-of-flight between the reflection of the tablet surface and the subsequent reflection from the coating interface. Using this approach a detection limit of about 40 microns is achieved [6, 8], 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 studied the feasibility of using a neural network (NN) based method to enhance the TPI's capability of resolving thinner coating layers.

II. EXPERIMENTS AND METHODOLOGY

In this study, seven batches of pharmaceutical tablets with a coating time of 40, 60, 90, 120, 150, 180, and 210 minutes, were studied. At each process time, 15 tablets were randomly sampled from the coating pan (Oyster Manesty, Knowsley, UK), 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 analyze the tablets. For each tablet a TPI data set comprising approximately 2000 point measurements was recorded. For each point/pixel measurement the terahertz radiation reflected from a sample was recorded as a function of time over a scan range of 2 mm. This provides a terahertz waveform of 512 data points at each pixel. Fourier transforming the recorded terahertz waveform gives a FFT-amplitude spectrum.

A feed-forward back-propagation neural network [9] was used to train the FFT-amplitude of Terahertz waveforms measured for tablets with a coating thickness above 40 microns. The trained network was subsequently used to predict the thickness of tablets with thinner coatings. Fig.1 shows the schematic diagram of a typical three-layered network used in the present work. Each layer consists of several neurons and the layers are interconnected by sets of correlation weights. In the training processing of neural network, FFT-amplitudes of the averaged THz waveform of tablets were used as the input vectors, whist the corresponding coating thickness (that were pre-determined by using the peak-finding method) of the tablets were used as the target vectors. The gradient descent method is employed to calculate the weight of the network and adjusts the weight of interconnections to minimize the output error.

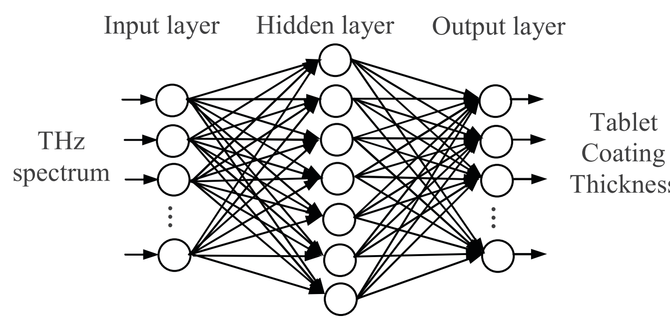

Fig.1 Schematic diagram of a three-layered neural network (an input layer, a hidden layer, and an output layer)

III. RESULTS AND DISCUSSIONS

As example, Fig.2 (a) shows the typical raw time-domain terahertz waveforms measured for the tablets with a coating time of 180 minute, with Fig. 2(b) showing their corresponding FFT-amplitude spectrum. Usually a simple "peak-finding" method was used to analyze the measured time-domain terahertz waveforms, and the coating thickness is calculated directly as the time delay difference between the peak positions corresponding to the terahertz reflections at the tablet surface and at the coating/core interface, divided by the refractive index of the coating material [6, 8]. This peak-finding method is robust and intuitive. However, for thinner coatings, the surface reflection peak and the interface reflection peak may be too close to be resolved precisely. Consequently the achieved limit of detection (the thinnest coating structure that can be precisely quantified) is about 40 microns, even with the state-of-the-art instrument.

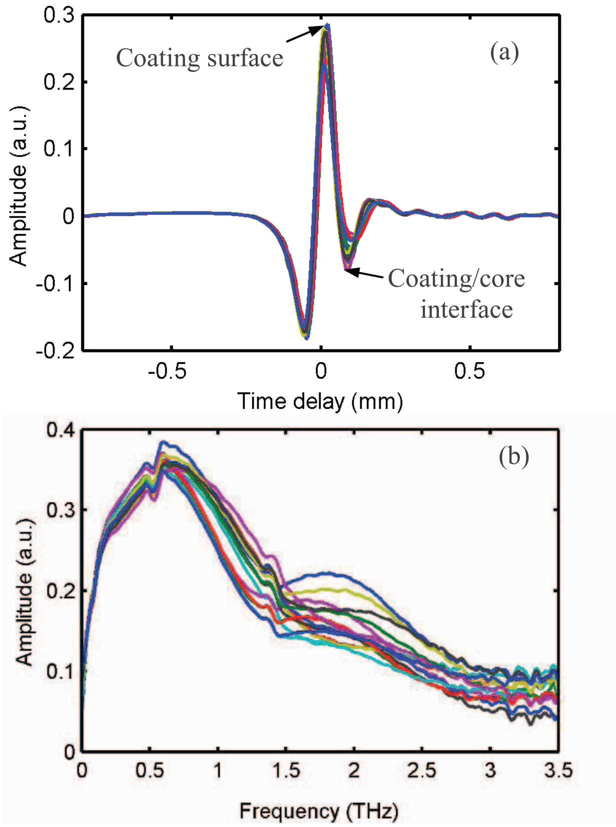

Fig.2 TPI waveforms (a), and their corresponding FFT-amplitude spectra (b), of the tablets with a coating time of 180 minutes.

In order to improve TPI's capability of resolving thinner coating layers, the above-mentioned neural network method was applied to analyze the FFT-amplitude spectra of all the tablets studied. Fig. 3 shows the plot of the predicted tablet coating thickness against the coating time. A linear dependence is evident across the whole coating time range investigated, even for tablets with a coating time below 90 minutes. Thus the NN-based frequency-domain TPI method has demonstrated its potential for analyzing very thin coatings whose thickness is beyond the current detection limit of the peak-finding method. Note that there is large tablet-to-tablet variation in the coating thickness even for the tablet with the same coating time, as shown in the insert of Fig.3. This tablet-to-tablet variation is a true representation of the coating thickness, rather than the measurement error as the application of polymer in the coating process is not uniformly distributed over all tablet cores in the coating pan [2].

In conclusion, we demonstrate that the newly-developed NN-based frequency domain method outperforms the standard "peak-finding" time-domain method, in terms of resolving thinner coatings. However, the NN-based method requires a learning/training data, and further work is needed to study the universality of the developed NN-model.

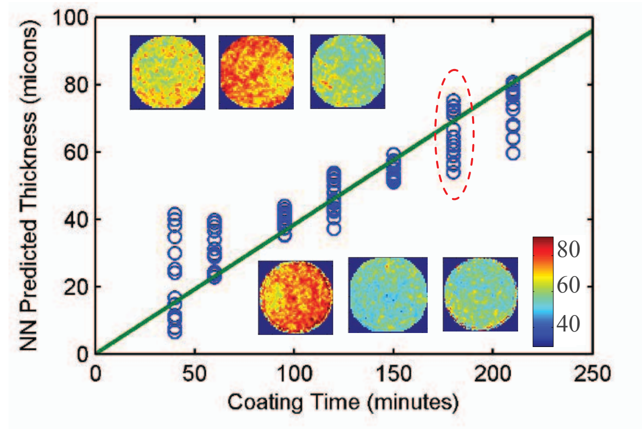

Fig.3 Coating thickness predicted using the NN-based method. The insert shows the 2D coating thickness map of the tablets with 180-minute coating time. The size of the maps is 10 x 10 mm, and the color scale bar is in micrometers.

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