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Non-destructive quantification of pharmaceutical tablet coatings using terahertz pulsed imaging and optical coherence tomography

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ABSTRACT

Optical coherence tomography (OCT) and terahertz pulsed imaging (TPI) are two powerful techniques allowing high quality cross-sectional images from within scattering media to be obtained non-destructively. In this paper, we report experimental results of using OCT and TPI for quantitatively characterizing pharmaceutical tablet coatings in the thickness range of 10–140 μm. We found that the spectral OCT system developed in-house has an axial resolution of 0.9 μm, and is capable of quantifying very thin coatings in the range of 10–60 μm. The upper limit of 60 μm within the tablet coating and core is owed to the strong scattering of OCT light, which has relatively short wavelengths in the range of 0.5–1.0 μm. On the other hand, TPI utilizes terahertz radiation that has substantially long wavelengths in the range of hundreds of microns, and thus is less prone to the scattering problem. Consequently TPI has been demonstrated to be able to quantify thicker coatings in the range of 40–140 μm and beyond. We concluded that OCT and TPI are two complementary analytical techniques for non-destructive and quantitative characterization of pharmaceutical tablet coatings.

1. Introduction

Pharmaceutical tablet coating is one of the preferred means to control the release of active pharmaceutical ingredients (API) molecules in the human body [1]. For example, enteric coating is used to protect the API against degradation in the stomach and sustained-release coating is used to obtain an optimum release profile, and hence a desirable API absorption rate [1]. Sustained-release coatings act as a diffusion barrier during drug release. Typically insoluble polymers are used for this purpose and depending on the polymer film thickness and porosity the drug release kinetics is controlled in such a dosage form. The quality of tablet coating will thus have direct implications on product performance. Lack of quality resulting in dose failures such as dose dumping may precipitate legal and commercial consequences for the manufacturer. It is hence of great interest to characterize coating properties such as coating thickness and coating uniformity for the purpose of quality control and quality assurance. A number of methods have been evaluated as a means of coating quality assessment and monitoring. These methods range from coating weight gain to various destructive and non-destructive techniques [2,3]. Routinely in the pharmaceutical industry, tablet coating is controlled by employing calculations on tablet weight gain during the coating processes with respect to the amount of coating solution applied. However, weight gain determination only provides the averaged value for a batch of tablets, and it does not give information on coating thickness and its uniformity on each individual tablet [4]. Terahertz pulsed imaging (TPI) has recently been demonstrated as a powerful technique for quantitatively characterizing coatings of individual pharmaceutical tablets [5–7]. In particular, terahertz radiation can penetrate most pharmaceutical excipients, and this makes TPI an increasingly popular tool for assessing information from various pharmaceutical solid dosage forms. These include coating thickness mapping, coating interface evaluation and tablet dissolution prediction [8]. However, the thinnest coating that could be precisely quantified is about

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40 μm for most common pharmaceutical coatings, using a state-of-the-art TPI system [7,8]. Whilst this is sufficient for characterizing many finished tablet coatings, a better detection limit is highly desirable for the quality assessment of very thin tablet coatings, and for online monitoring of the coating process where such thin coatings (corresponding to the early stage of the coating process) are of particular interest.

Optical coherence tomography (OCT) is also a non-invasive and cross-sectional imaging technique that permits, for example, three-dimensional images with micrometer resolution to be obtained from within the retina [9,10]. However, most commercially available OCT systems are developed and optimized for medical applications. To date, applications of OCT beyond biomedicine have been scarce. Nevertheless, there have been some reports on using OCT for the non-destructive evaluation of thickness of papers [11], and surface roughness, gloss and bulk properties of flat-faced tablets [12]. Very recently, OCT has also been evaluated for characterizing the coating thickness of pharmaceutical tablets [13] and for imaging pharmaceutical tablets [14].

In this paper, we report an experimental investigation of using OCT and TPI for the quantitative characterization of pharmaceutical tablet coatings in the thickness range 10–140 μm. The same set of pharmaceutical tablets was measured using both an in-house OCT system and a commercial TPI system. We found that OCT is better suited for analysis of thinner coatings owing to its high axial resolution whilst TPI is less prone to scattering problems, and thus is well positioned for characterizing pharmaceutical tablets with thicker coatings.

2. Methods and materials

For all TPI measurements reported here a TPI imaga 2000 system (TeraView Ltd., Cambridge, UK) was used and operated at a rapid scan mode, i.e. at an acquisition rate of 30 complete waveforms per second. At each measurement point, the terahertz radiation reflected from a tablet sample was recorded as a function of time over a scan range of a 2 mm optical delay. The TPI imaga 2000 system is specifically developed for the fully automated scan of typical pharmaceutical solid dosage forms that usually have curved surfaces. A six-axes robot system was employed to handle the tablets. This ensures that the tablet is always at the terahertz focus position with its surface perpendicular to the terahertz probe during a TPI measurement [7]. Note that the terahertz radiation used here is broadband, covering a spectral range of 5–100 cm^{-1} (0.15–3 THz). The spot size of the focused terahertz beam at the tablet surface is estimated to be about 200 μm in diameter at its centre frequency of 1.5 THz (50 cm^{-1}).

All OCT measurements were carried out using an in-house OCT system. As shown in Fig. 1, the light from a 50 W halogen lamp was delivered onto the entrance pupil of an interferometer using a multimode fiber. The fiber end was then imaged at a ratio of 1:1 onto the surface of the sample and the reference, using a biconvex lens through a beam-splitter (50:50). The light that was reflected/scattered back from both the reference and sample was collected using another biconvex lens and then imaged back into the entrance slit of a spectrometer. Interference will occur when both the "sample image" and "reference image" are spatially matched in size and orientation within the corresponding transverse coherence distance, and their path lengths are matched within the coherence length of the light source. A PZT actuator was introduced to shift the phase of the reference beam, which allows the phase-shifting method [15] to be used to increase the measurement sensitivity. One distinct feature of our OCT system is the combination of a broadband CCD-based spectrometer with a white light source of an extremely short coherence length. This configuration provides good signal-to-noise ratio and at the same time excellent axial resolution. The multimode fiber used was chosen to have a diameter of 200 μm, to make sure that the OCT light beam and the TPI probe beam have a comparable spot size at the sample surface.

The sample used in the present work was a batch of pharmaceutical tablets with a single coating layer. Tablet cores were biconvex (3 mm in height, 8 mm in diameter and average weight of 252 mg), and contained 10% w/w diprophyllin (API), 84.5% w/w lactose monohydrate (Flowlac® 100), 5% w/w vinylpyrrolidone–vinyl acetate copolymer (Kollidon®V64) and 0.5% w/w magnesium stearate. The coating formulation used is as follows: 50% w/w polyvinyl acetate (Kollicoat® SR 30D), 6% w/w polyvinyl alcohol–polyethyleneglycol graft copolymer (Kolicoat® IR), 0.075% w/w polyoxyethylene(20) sorbitan monooleate (Polysorbate 80), 0.3% w/w glycerolmonostearate, 0.75% w/w triethylcitrate and 42.87% w/w deionised water. The tablets were randomly selected after the following amounts of the sustained-release polymer were applied: 1.8, 3.6, 5.5, 7.3, 9.1, 10.9, 12.7, 14.5 and 18.2 mg/cm^2 [16].

3. Results and discussion

In order to characterize the performance of the in-house OCT system, we firstly measured a layered sample of the polymer film with a known thickness. Fig. 2(a) shows the broadband OCT spectral *interferogram* obtained for the layered sample (curve A), whilst curves B and C are the corresponding spectra of the sample and reference arm, respectively. The measured spectrum of the reference arm (curve C of Fig. 2(a)), which represents the overall spectral range of the instrument including the light source, has a centre wavelength of 700 nm and a full-width-at-half-maximum (FWHM) of 236 nm. The OCT axial resolution Δz is given by $\Delta z = 2\ln 2\lambda_0^2/\pi\Delta\lambda$, where λ_0 is the centre wavelength and $\Delta\lambda$ is the FWHM of the light source. The achieved axial resolution

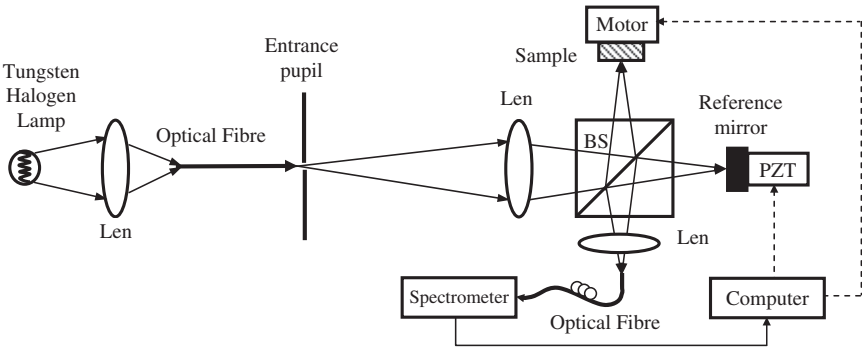

Fig. 1. Schematic diagram of spectral-domain OCT experimental setup. BS—50:50 beam-splitter; PZT—piezoelectric transducer.

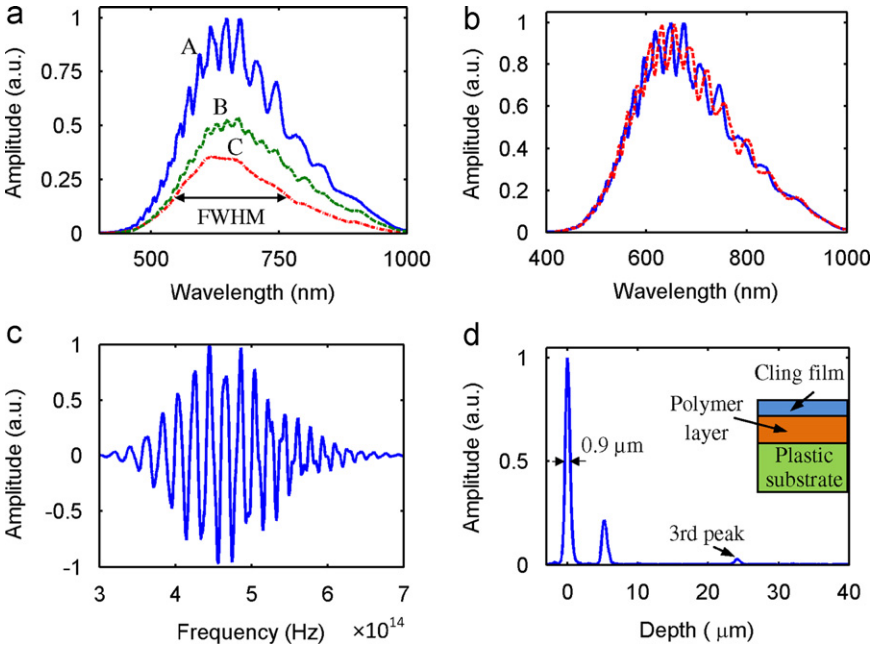

Fig. 2. (a) Extremely broadband OCT spectral interferogram (curve A) obtained by CCD-based interferometer. Curves B and C are the corresponding spectra measured for sample and reference arms, respectively; (b) two OCT spectral interferograms obtained with phase difference of π, using phase-shifting method; (c) differential OCT spectral interferogram obtained after applying phase-shift method and its corresponding OCT-FFT waveform. The axial resolution, defined as FWHM of the main peak of FFT-OCT waveform, was determined to be 0.9 μm. Inset of (d) shows schematic diagram of a layered sample, which is a plastic plate with 6-μm-thick cling film layer and 18-μm-thick polymer layer.

obtained from FWHM is about 0.9 μm in air (Fig. 2(d)), which is amongst the best ever reported [13]. Fig. 2(b) shows two spectral interferograms obtained with a phase difference of π, using the phase-shifting method [12]. The corresponding differential OCT interferogram (the difference of these two interferograms) is shown in Fig. 2(c). This greatly improved the signal-to-noise ratio and the measurement sensitivity. Consequently both coating layers of the sample can be resolved from its corresponding OCT-FFT waveform shown in Fig. 2(d). The thickness of the first and second layer were determined to be 6 and 18 μm, respectively. Note that the third peak (at $z=24$ μm, as indicated in Fig. 2(d)) has an amplitude of 0.027 dB. This feature is very small but is still well above the background noise level (0.0005 dB) confirming that our OCT system has extremely good signal-to-noise ratio and thus good measurement sensitivity.

The axial resolution of the OCT setup was determined to be 0.9 μm with a signal-to-noise ratio of 2000. A set of tablets with a film coating weight gain ranging from 1.8 to 7.2 mg/cm^2 was measured using an OCT spectrometer. Fig. 3(a) shows a typical OCT-FFT waveform recorded for a tablet with a weight gain of 5.4 mg/cm^2. From the OCT-FFT waveform, the tablet core roughness, coating roughness and thickness can be obtained. Unlike the OCT-FFT waveform in Fig. 2(d), where a sharp reflection peak (FWHM of 0.9 μm) from the sample surface is observed, the OCT-FFT waveforms in Fig. 3(a) show a broad surface reflection feature comprising many sharp sparks. This can be explained as follows. (1) As discussed in the previous section the diameter of the OCT light spot size at the sample surface was chosen to be similar to that of the terahertz probe beam (about 200 μm) in order to make a reasonable comparison of the OCT and TPI results. (2) For a sample with a smooth surface, the surface reflection feature across the entire sampling area of 200 μm diameter will appear at the same position ($z=0$ μm). This leads to the sharp peak in the OCT-FFT waveform as shown in Fig. 2(c); in Fig. 3 for a rough surface, the surface height varies over the sampling spot surface. Therefore the feature reflected/scattered from different parts of the surface will appear at a slightly different position ($-\Delta z < z < \Delta z$, where Δz is the surface roughness). This results in a broad envelope comprising many sharp sparks with each spark corresponding to light reflected/scattered from the portion of the surface of the same height.

By fitting the measured OCT-FFT waveforms with a Gaussian function, we are able to quantify the coating thickness as the peak position difference between the two fitted curves (shown as the solid curve in Fig. 3(a)). Fig. 3(b) shows the OCT b-scan maps of the same tablet with a coating polymer weight gain of 9 mg/cm^2, from which the mean thickness of this specific tablet was determined to be 52 μm. Note that the OCT system was also used to measure tablets with a weight gain above 9 mg/cm^2. However, for these samples the OCT signal from the coating/core interface was too weak to be used for reliable coating thickness analysis. This weak OCT signal obtained from the thicker coatings was most likely caused by the strong scattering of the OCT signal within the tablet coating for this specific set of coating/core materials.

After OCT analysis, the same set of tablets was analyzed using the TPI system. Fig. 3(c) shows a typical terahertz waveform recorded for a coated tablet, with Fig. 3(d) showing the corresponding TPI b-scan map. Note here that the results shown in Fig. 3(a)–(d) were obtained using the same tablet with a weight gain of 5.4 mg/cm^2. Again, the coating thickness was calculated as the peak position difference between the surface reflection feature and the coating/core interface reflection feature. The wavelength of the terahertz radiation used for the TPI experiments is about three orders of magnitude larger than that of the OCT light. Therefore, scattering within the tablet coating, the major limiting factor in the OCT measurement, is no longer an issue in the TPI measurement. Consequently, terahertz radiation can penetrate deeper into the tablet sample and TPI is able to quantify thicker coating layers as compared to OCT. As shown in Fig. 4, TPI was successfully used for the quantitative characterization of tablet coatings of a weight gain of 7.3–18.2 mg/cm^2 (thickness range of 40–140 μm). On the other hand, we also found that the thinnest coating layer

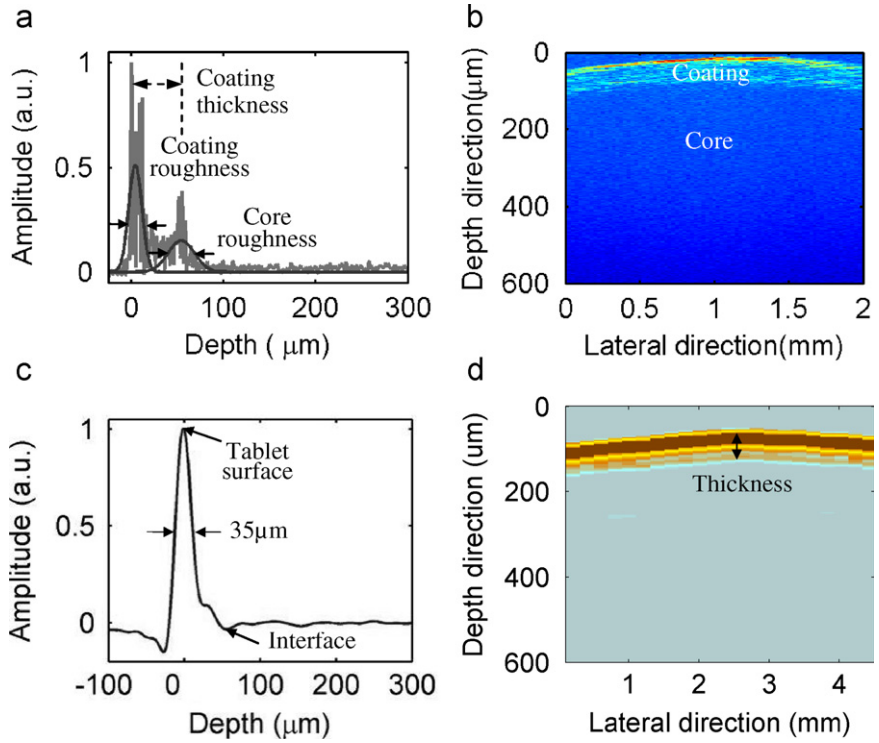

Fig. 3. OCT-FFT waveform (a) and OCT cross-section map (b) recorded for tablet with weight gain of 5.4 mg/cm^2. The solid lines in (a) are the best fitting curves using Gaussian function, and coating thickness was determined to be 52 μm. TPI terahertz waveform (c) and TPI b-scan map (d) were recorded for the same tablet. Note that TPI measures the electric field of reflected terahertz radiation and negative minimum peak at about 52 μm indicates that refractive index of tablet core is larger than that of tablet coating. Note here that results shown in (a)–(d) were obtained using same tablet with weight gain of 5.4 mg/cm^2.

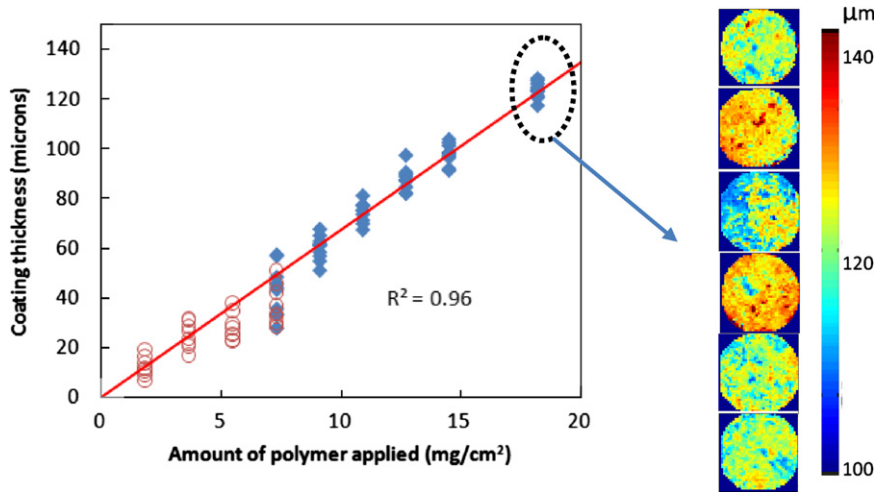

Fig. 4. Correlations between tablet coating thickness and amount of polymer applied. The solid diamonds represent TPI results whilst the open circles represent OCT results; inset on the right-hand side shows TPI coating thickness maps obtained for tablets with same weight gain of 18.2 mg/cm^2. There is large tablet-to-tablet variation in coating thickness for tablets with same weight gain.

that could be precisely quantified using TPI is about 40 μm for this specific set of tablets, which is in good agreement with previous reports [7,16]. TPI technology could not provide precise coating thickness information for tablets with weight gains of 1.8, 3.6 and 5.5 mg/cm^2. In contrast, OCT technology is capable of measuring such thin tablet coatings. As summarised in Fig. 4, a linear relationship (R^2=0.96) between the coating thickness and the amount of polymer applied was observed in the full weight range of 1.8–18.2 mg/cm^2 (thickness range of 10–120 μm) investigated using both techniques. Note that neither TPI nor OCT alone can provide coating thickness information across such a broad range of coating thickness.

4. Concluding remarks

In conclusion, operating at shorter wavelength than TPI, OCT provides high axial resolution, which makes it a better choice to analyze thin coatings. Terahertz radiation has a much longer wavelength, thus being less prone to scattering problems and

hence TPI can be used to analyze thicker coatings as well as for imaging the internal structures deeper inside a tablet. The combination of OCT and TPI would provide the pharmaceutical industry with a complementary and powerful analytical technique for the quantitative characterization of pharmaceutical tablet coatings in a thickness range from a few microns to a few hundreds of microns.

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