Non-Destructive Evaluation of Polymer Coating Structures on Pharmaceutical Pellets Using Full-Field Optical Coherence Tomography

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ABSTRACT: Full-field optical coherence tomography (FF-OCT) using a conventional light-emitting diode and a complementary metal-oxide semiconductor camera has been developed for characterising coatings on small pellet samples. A set of *en-face* images covering an area of 700 × 700 μm^2 was taken over a depth range of 166 μm. The three-dimensional structural information, such as the coating thickness and uniformity, was subsequently obtained by analysis of the recorded *en-face* images. Drug-loaded pharmaceutical sustained-release pellets with two coating layers and of a sub-millimetre diameter were studied to demonstrate the usefulness of the developed system. We have shown that both coatings can be clearly resolved and the thickness was determined to be 40 and 50 μm for the outer and inner coating layers, respectively. It was also found that the outer coating layer is relatively uniform, whereas the inner coating layer has many particle-like features. X-ray computed microtomography measurements carried out on the same pellet sample confirmed all these findings. The presented FF-OCT approach is inexpensive and has better spatial resolution compared with other non-destructive analysis techniques such as terahertz pulsed imaging, and is thus considered advantageous for the quantitative analysis of thin coatings on small pellet samples.
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INTRODUCTION

An ever increasing number of modified release technologies are available to the pharmaceutical industry for the purpose of improving drug therapy via oral administration.[1] Small-sized pellets of sub-millimetre diameter have been used to control the release rate of active pharmaceutical ingredients (APIs) in the human body. They are designed to be coated and filled into capsules or compressed into other solid dosage form. The use of pellets allows a more even spread of drug after the dissolution of capsule shell and thus ensures the drug absorption within gastrointestinal tract[2] as well as avoiding dose-dumping problems because of local defects in the coating structure which are much more severe in a monolith as opposed to a multi-particulate release system. Depending on the required dissolution profile, the API can be contained in the pellet core, or directly coated onto a core bead typically made of sugar or polymer excipients. By using sophisticated coatings such as enteric coatings and complex layer structures applied on pellets, it is possible to direct and extend the release time to attain full therapeutic efficiency. As the coating quality has a direct impact on the therapeutic efficiency, there is a critical need for analytical techniques to non-destructively assess the coating structures on pharmaceutical pellets.

The current quality control procedures during film coating processing generally evaluate the coating quality of pellets in terms of the average weight gain.[3] The measurement is non-specific and the weight gain may fail to reflect the coating structure of the sample.[4] Investigation into the physical characteristics of pellets is commonly undertaken with microscopy techniques. Images are generally recorded from cross-section cuts of pellets, and coating thicknesses are evaluated by measuring the distance between manually marked points on the coating borders.[5] However, this method is very time consuming, it is destructive and can induce artefacts because of plastic deformation during the preparation of cross-sections.[6]

Near infrared (NIR) spectroscopy, which is a non-destructive method, has long been used to evaluate pellet coatings in the pharmaceutical industry. However, NIR spectroscopy is inherently an indirect method as it needs additional reference techniques to build a calibration model.[7] Terahertz pulsed imaging (TPI) has also been demonstrated as a powerful method for the non-destructive evaluation of coatings on large pharmaceutical tablet.[8–10] It is an excellent technique to study the coating structure of relatively large pharmaceutical tablets because of its high penetration depth. For small pellets such as the ones studied here which make up the bulk of pharmaceutically used pellets, however, TPI cannot comprehensively resolve the layer structures because of its inherently low lateral resolution, which is fundamentally limited by the relatively large wavelength of terahertz radiation (e.g., 300 μm at 1 THz), thus leading to strong scattering from sub-millimetre size pellets.

Recently, we and other groups have demonstrated that optical coherence tomography (OCT) can be used for characterising the coating thickness of pharmaceutical tablets[11,12] and for imaging pharmaceutical tablets.[13] Tablet coatings with a layer thickness range of 10–60 μm were measured quantitatively.[11] In all these studies, single-point frequency domain OCT systems were used where the depth profile (A-scan) at a given

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transverse location was obtained using a focused probe beam from a broadband light source. A succession of these A-scans along one dimension of the transverse plane provides a two-dimensional cross-section map (B-scan). A full three-dimensional volume is obtained by collecting successive B-scans. Therefore, a full OCT measurement requires electromechanically scanning either the sample or the OCT optics in two lateral dimensions. For small pellet samples, however, this approach proves to be difficult and inefficient to perform OCT measurements because of the small size (pellet diameter is less than 1 mm).

In this work, we report the development of a full-field OCT (FF-OCT) system for characterising small size pellets. Our FF-OCT system uses an inexpensive conventional infrared light-emitting diode (LED) as the broadband light source and a complementary metal-oxide semiconductor (CMOS) camera as the detector. The measurement is done in parallel. The sample is full-field illuminated and *en-face* imaged with the CMOS camera, hence eliminating the need for an electromechanical lateral scan. We demonstrate that small-sized pharmaceutical pellets can be imaged easily using the presented FF-OCT system, with a high-spatial resolution of 3.6 and 11 μm in axial and lateral directions, respectively.

EXPERIMENTAL

FF-OCT Imaging Setup

Figure 1 shows the schematic diagram of a table-top FF-OCT system which was based on a Michelson interferometer. Broadband light from a conventional infrared LED source ($\lambda_0 = 850$ nm, $\Delta\lambda = 90$ nm) was first split into reference and sample arms by a non-polarising 50/50 beam-splitter. Light back scattered by the sample was recombined with the light reflected off the reference mirror at the beam splitter and finally captured with a Firefly MV CMOS camera (Point Grey Research Inc, Richmond, British Columbia, Canada). Interference would occur when the optical path length difference between the reference and sample arms is within the coherence length of the light source.

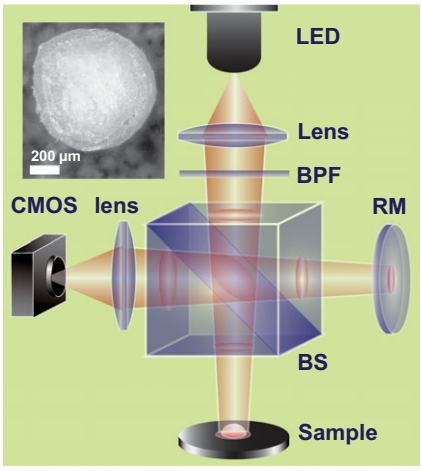

Figure 1. A schematic diagram of the FF-OCT system. The inset shows the microscope image of the cross-section through a pellet sample which is spherical with a diameter of about 850 μm. LED, infrared LED light source; BPF, band-pass filter; BS, beam splitter; RM, reference mirror.

For a full OCT measurement, a series of *en-face* images was acquired at a rate of 120 frames per second while the reference mirror on a motorised stage was moving at a constant speed of 3 μm/s. This resulted in a fixed 25 nm depth interval between successive *en-face* images. Each *en-face* image is composed of 180 × 180 pixels (about 4 × 4 μm^2 per pixel) covering a sample area of 700 × 700 μm^2. The stage was scanned over a depth of 166 μm, thus the system eventually acquired a full OCT data cube covering a volume of 700 × 700 × 166 μm^3.

X-Ray Computed Microtomography

The same pellet sample was analysed using a SkyScan1172 high-resolution X-ray computed microtomography (XμCT) scanner (Bruker-microCT, Kontich, Antwerp, Belgium). The sample was imaged at an isotropic voxel resolution of 1.2 μm over a total of 5 h acquisition time and a subsequent image reconstruction time of about 4 h, using the NRecon program (version 1.6.8.0, Bruker-microCT).

The sample used in the presented work was a pellet with two coating layers. The core is a microcrystalline cellulose (MCC) sphere (Celphere MCC seed core CP-507, Asahi Kasei Corp., Tokyo, Japan). The inner coating layer is a drug-loaded layer containing 10% API and 90% hydroxypropyl methylcellulose (HPMC). The outer coating formulation contains a combination of ethyl cellulose and hydroxypropyl cellulose. As shown in the inset of the Figure 1, the coated pellet is approximately spherical with an outer diameter of about 850 μm.

RESULTS

Figure 2a shows a typical raw interferogram signal which is extracted from the volumetric OCT data cube recorded for a coated pellet sample. The tomography signal (Fig. 2b), which is a more intuitive and better representation of the sample depth profile, is calculated by demodulating the raw interferogram signal using a Hilbert Transform.[14] A mean refractive index of 1.5 was used in all calculations. Several interference patterns are clearly visible. The first major interference feature at $z = 0$ corresponds to the reflection/scattering from the pellet surface. The full width at half maximum (FWHM) of the envelope of this main interferogram feature, which corresponds to the axial resolution achieved here, is determined to be 3.6 μm, as shown in the inset of Figure 3a. Note that the axial resolution of an OCT system is ultimately determined by the coherence length of the light source and can be calculated using the following equation[15]:

$$l_c = 0.44\frac{\lambda_0^2}{\Delta\lambda}$$

where $\lambda_0 = 850$ nm is the centre wavelength and $\Delta\lambda = 90$ nm is the spectral bandwidth of the LED light source used in our experiment. The axial resolution is thus theoretically calculated to be 3.5 μm which agrees very well with the measured resolution of 3.6 μm.

A set of cross-sectional images (B-scan images) was reconstructed from the recorded volumetric OCT data cube. Figure 3a shows one such B-scan image of the pellet sample, revealing its internal structures. A scale bar calibrated in decibel units is included. Black corresponds to the highest signal and white corresponds to the lowest. As shown in Figure 3a, two

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