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Investigating Intra-Tablet Coating Uniformity With Spectral-Domain Optical Coherence Tomography

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ABSTRACT

Spectral domain optical coherence tomography (SD-OCT) has recently attracted a lot of interest in the pharmaceutical industry as a fast and non-destructive modality for direct quantification of thin film coatings that cannot easily be resolved with other techniques. While previous studies with SD-OCT have estimated the intra-tablet coating uniformity, the estimates were based on limited number of B-scans. In order to obtain a more accurate estimate, a greater number of B-scans are required that can quickly lead to an overwhelming amount of data. To better manage the data so as to generate a more accurate representation of the intra-tablet coating uniformity without compromising on the achievable axial resolution and imaging depth, we comprehensively examine an algebraic reconstruction technique with OCT to significantly reduce the data required. Specifically, a set of coated pharmaceutical tablets with film coating thickness in the range of 60-100 μm is investigated. Results obtained from performing the reconstruction reveal that only 30% of the acquired data are actually required leading to a faster convergence time and a generally good agreement with benchmark data against the intra-tablet coating uniformity measured with terahertz pulsed imaging technology.

Introduction

The process of coating one or more layers of polymer onto tablets is almost ubiquitous in pharmaceutical manufacturing in order to achieve uniformity of color, light protection, taste masking, and, more recently, advanced coatings such as active coatings and sustained release, where the drug release kinetics can be controlled thereby increasing the therapeutic efficacy of tablets.[1] In addition to average coating thickness, other benchmarks that govern the quality of the finished product include intra- and inter-tablet coating uniformity. Inter-tablet coating uniformity refers to the variations in coating thickness between different tablets within a batch, and a low level of variation is desired to ensure consistent quality across the batch. In contrast, intra-tablet uniformity describes the variation in coating thickness on an individual tablet, and achieving a high level of intra-tablet uniformity is especially important in functional film coating, for instance, in sustained release formulations, where the drug release rate depends on the layer thickness of the film coating. To date, various measurement techniques have been employed for assessing the intra-tablet coating uniformity. These include laser-induced breakdown spectroscopy,[2] which is destructive in nature, and other non-destructive techniques such as hyperspectral near-infrared imaging,[3,4] ultraviolet (UV) chemical imaging,[5] X-ray micro-computed tomography,[6] terahertz pulsed imaging (TPI),[7,8] and, more recently, spectral-domain optical coherence tomography (SD-OCT).[9-11] However, near-infrared spectroscopy is inherently an indirect method as it needs additional reference techniques to build a calibration model. UV chemical imaging is able to map and differentiate the different types of coating defects[5] but it does not provide quantitative coating thickness information because of limited penetration depth of UV light into thick coatings. TPI and laser-induced breakdown spectroscopy can be used for quantifying

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thick coatings. Laser-induced breakdown spectroscopy requires high-energy laser pulses (100 mJ) which have relatively large spot size of 150 μm diameter and low repetition rate of 10 Hz.[2] TPI can achieve higher data acquisition rate of hundreds of waveforms per second and high axial resolution of better than 40 μm, but its lateral resolution is fundamentally limited by the relatively longer wavelength of THz radiation (300 μm at 1 THz). On the other hand, X-ray micro-computed tomography provides micrometer resolution image of a tablet in all 3 dimensions but the data acquisition time is slow (1.8-3.5 h for each tablet[6]).

SD-OCT is thus fast gaining popularity as a non-destructive method for quantitative evaluation of pharmaceutical coatings because it offers both high data acquisition rate (27,800 waveforms per second[12]) and high spatial resolution (the lateral and axial resolutions are better than 10 and 5 μm,[12] respectively). While the previous studies with SD-OCT have been demonstrated to be able to estimate the intra-tablet coating uniformity, the estimates were based on limited number of B-scans such as 192 B-scans[10] and 100 B-scans[13] resulting in a limited area for the tablet's three-dimensional (3D) reconstruction. Understandably, the reason for this is because of the overwhelming size of the acquired dataset that can quickly become unmanageable. For example, for a tablet of diameter 8 mm, scanning it with an optical spot size of 10 μm would generate a dataset greater than 1 GB. Algebraic reconstruction technique (ART)[14,15] with OCT, which is based on a similar concept to the recently developed compressive sensing technology,[16,17] was proposed very recently to significantly reduce data acquisition without compromising on axial resolution and imaging depth. In order to establish SD-OCT as a useful and practical modality for assessing the entire tablet surface, the number of measurement points should be kept down but still sufficient to provide an accurate representation of the intra-tablet coating uniformity. This article comprehensively examines the use of an ART-OCT to determine the optimal number of measurements required without loss of information.

Materials and Methods

Tablet Production

The samples used in this study comprise a batch of pharmaceutical tablets with a single sustained-release polymer coating layer. The tablet cores were biconvex shaped and contained 10% wt/wt diprophyllin (API), 84.5% wt/wt lactose monohydrate (FlowLac® 100), 5% wt/wt vinylpyrrolidone-vinyl acetate copolymer (Kollidon® V64), and 0.5% wt/wt magnesium stearate. The transparent coating suspension has the following formulation: 50% wt/wt polyvinyl acetate (Kollicoat® SR 30D), 6% wt/wt polyvinyl alcohol-polyethyleneglycol graft copolymer (Kollicoat® IR), 0.075% wt/wt polyoxyethylene (20) sorbitan monooleate (Polysorbate 80), 0.3% wt/wt glycerolmonostearate, 0.75% wt/wt triethylcitrate, and 42.87% wt/wt deionized water. The tablet cores were coated in a pilot scale coater BFC25, Bohle Film Coater (L.B. Bohle, Ennigerloh, Germany). The coating pan dimensions were 546 mm in diameter and 630 mm in length and the batch size was 20 kg. The coater used 5 two-way spray nozzles (970/7-1 S75; Düsen-Schlick GmbH, Untersiemau, Germany) to spray coat the tablets. The geometry of a coated tablet is approximately 4 mm in height and 8 mm in diameter. A tablet was randomly selected after the following amounts of the sustained-release polymer were applied: 3.6, 5.5, 7.3, 9.1 mg/cm^2 on a pilot scale study.[18]

Terahertz Pulsed Imaging Measurements

TPI measurements on the top and bottom surfaces of the tablets were performed using a TPI Imaga 2000 system (TeraView Ltd., Cambridge, UK). At each measurement point, the terahertz radiation reflected from a tablet sample was recorded as a function of time over a scan range of 2 mm. 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 6-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.[8] 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 center frequency of 1.5 THz (50 cm^{-1}). For the accurate determination of the coating layer thickness, the refractive index of the coating matrix is required. The refractive index of the coating was measured by terahertz time-domain spectroscopy using an uncoated tablet core as the reference. Using this method, a refractive index of 1.68-1.79 was determined[18] and a value of 1.74 was used for thickness quantification.

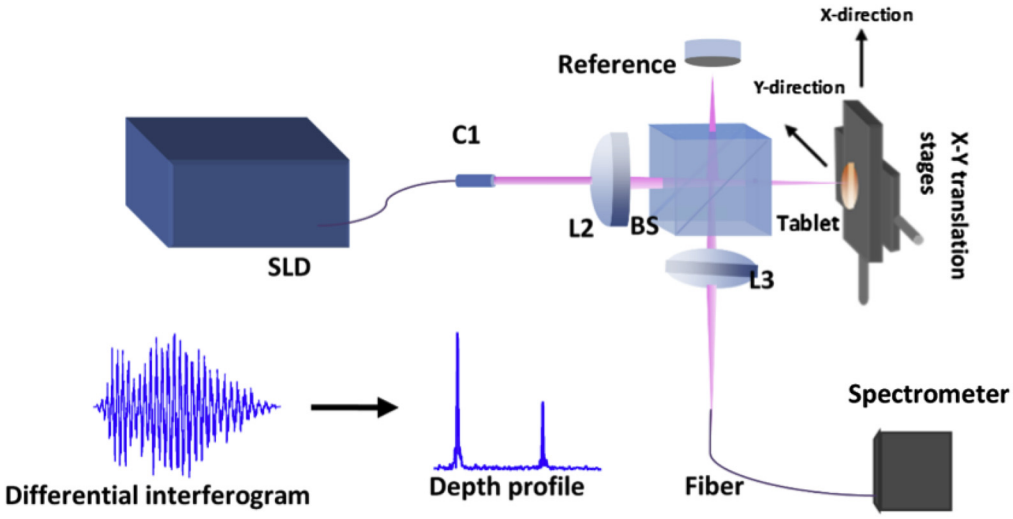

Figure 1. Schematic diagram of experimental setup. C1, collimator; L2 and L3, lenses; BS, 50:50 beam splitter; SLD, superluminescent diode. The insets are a typical differential interferogram and depth profile.