In-Line Monitoring of a Pharmaceutical Pan Coating Process by Optical Coherence Tomography

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ABSTRACT: This work demonstrates a new in-line measurement technique for monitoring the coating growth of randomly moving tablets in a pan coating process. In-line quality control is performed by an optical coherence tomography (OCT) sensor allowing nondestructive and contact-free acquisition of cross-section images of film coatings in real time. The coating thickness can be determined directly from these OCT images and no chemometric calibration models are required for quantification. Coating thickness measurements are extracted from the images by a fully automated algorithm. Results of the in-line measurements are validated using off-line OCT images, thickness calculations from tablet dimension measurements, and weight gain measurements. Validation measurements are performed on sample tablets periodically removed from the process during production. Reproducibility of the results is demonstrated by three batches produced under the same process conditions. OCT enables a multiple direct measurement of the coating thickness on individual tablets rather than providing the average coating thickness of a large number of tablets. This gives substantially more information about the coating quality, that is, intra- and intertablet coating variability, than standard quality control methods. © 2015 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 104:2531–2540, 2015

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INTRODUCTION

Although tablet coating is a well-established unit operation in pharmaceutical industry, the achievable quality of coating is still limited by the fact that it is a highly complex process depending on many parameters, such as coater geometry, air pattern, degree of filling, rotation rate, spray suspension properties, spray gun numbers, spray patterns, thermal management, and tablet shape.[1–3] This is specifically critical for a functional tablet coating, which requires a uniform layer with a specified thickness and density to fulfill its purpose. The aim of such coatings is to control the rate of drug release as a function of the environment, that is, the initial drug release kinetics should be aligned with the pH of the environment. There are significant gaps remaining in the full scientific understanding of the process, which makes it a difficult task to produce tablets with an exact thickness and density and with only small tablet-to-tablet variations between batches or even within one single batch. As mixing of the tablets in the coater, and their appearance in the spray zone, are stochastic processes, the coating thickness of the final product will always follow a distribution. The goal is to make this distribution as narrow as possible. On the one hand, the understanding of the process can be improved through advances in the field of modeling film coating processes.[2–4] On the other hand, the use of process analytical technology (PAT) facilitates the understanding of physicochemical changes of the film during manufacturing. This is also relevant in view of real-time release, which is the ultimate goal of pharmaceutical manufacturing.

In-line monitoring of film coating has been reported previously. Several studies highlighted the application of spectroscopic sensors, such as near-infrared and Raman spectroscopy to monitor the coating thickness,[5,6] dissolution time,[7,8] or coating deposit mass.[9] Nevertheless, spectroscopic methods typically measure the characteristic coating property indirectly, by correlating reference measurements from samples with the attenuation of spectral features of one of the mutually exclusive constituents in the product substrate or in the coating formulation. This approach therefore requires reference measurements of samples, which are combined with the spectral information in a multivariate calibration model. Such a model then allows the prediction of the characteristic coating property, that is, the actual coating thickness. The development and validation of such chemometric models is tedious and even slight variations in the process conditions or raw material properties may render the model invalid.

Consequently, a calibration-free direct measurement of coating properties is highly desirable. The most promising methods allowing a direct in-line measurement of the coating thickness are terahertz pulse imaging (TPI) and optical coherence tomography (OCT). TPI was successfully applied to quantitatively measure the coating thickness of tablets in a pan coater.[10] However, TPI has limited resolutions [i.e., a transversal of 200 μm and axial (depth) resolution of 2 μm for layers greater than

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40 μm] and requires relatively long measurement times (in the range of 5 ms for one single depth measurement). Both drawbacks of TPI can be overcome by OCT, which can achieve resolutions below 10 μm and allows the acquisition of hundreds of frames per second. One has to mention, however, that OCT has limited capabilities in terms of penetration depth compared with TPI, and in some cases OCT fails to image through the coating or does not show a clear tablet/coating interface (e.g., when the refractive index of tablet and coating materials are too similar).

This study reports that OCT is used to nondestructively measure the thickness (and variability) of tablet coating layers directly inside the coating pan. OCT is a high-resolution imaging technique providing depth profiles of semitransparent and turbid materials in a contactless and nondestructive manner. In OCT, an optical beam generated by a broadband light source is focused onto the surface of the tablet. The main part of the light is directly reflected by the surface of the tablet. A substantial fraction of the light penetrates into the coating structure and is then back-reflected by subsequent interfaces separating two media with different index of refraction, for example, coating and tablet core. The OCT image contrast thus results from a combination of absorption and scattering. The principal disadvantage of OCT is that light is highly scattered by some coatings, and attenuation from scattering limits the image penetration depths, reducing the imaging contrast and resolution of the OCT system. Consequently, these scattering effects limit the maximum coating thickness that can be resolved accurately. However, the coating thickness at a given point on a tablet surface (oriented perpendicular to the incident beam) is in general directly proportional to the separation between adjacent reflection peaks in the time-domain OCT signal and is determined as $d = \Delta t/(2n)$, where d is the coating thickness, Δt is the peak separation, and n is the refractive index of the coating. A number of studies have already demonstrated the applicability of OCT for measuring the coating thickness of film-coated tablets off-line,[11,12] as well as for in-line monitoring of the film formation during fluid-bed coating.[13] In addition, it was shown that OCT allows the in-line analysis of both tablet-to-tablet (intertablet) coating variations and the coating homogeneity of each measured tablet (intratablet).[14]

MATERIALS AND METHODS

Tablet Core and Coating Material

Round bi-convex tablets without break lines were used in the experiments. The tablet cores contained 50 mg acetylsalicylic acid as an API, lactose monohydrate, microcrystalline cellulose, highly dispersed silicone dioxide (SiO_2), starch, talc, and triacetin. Tablet diameter (7.14 mm), thickness (3.75 mm), curvature radius (7.56 mm), and weight (149.7 mg) were measured and averaged over 20 tablet cores. The composition of the applied enteric coating is listed in Table 1.

Tablet Coating

The coating process was carried out with a laboratory-scale pan coater (ProCepT, Zelzate, Belgium) equipped with a 1-L drum with an inner diameter $D_{drum} = 200$ mm and a Schlick spray nozzle with a 0.8-mm tip. This nozzle generates an elliptical spray pattern. Wing-like baffles were mounted on the perforated pan to achieve good mixture of the tablets and a uniform coating distribution. Each coating experiment started with 350 g of tablets in the pan. The process conditions for coating, that is, pan speed, spray rate, inlet air flow rate, inlet air temperature, were kept constant at 40 min^{-1}, 1.40 g/min, 0.4 m^3/h, and 42°C, respectively. Exhaust air temperature and tablet temperature were monitored during the coating runs at temperatures of 34.1 ± 0.3° and 34.8 ± 0.8°, respectively. The process was stopped at a total mass of 120 g coating material sprayed onto the tablets. This was determined by measuring the weight loss of the coating material in the storage vessel using a weighing scale.

Tablet samples of approximately 1.50–2.25 g (10–15 tablets) were drawn every 8 min. To assess reproducibility, every coating experiment was repeated three times (referred to as B01, B02, and B03) under exactly the same process conditions.

Table 1. Composition of the Enteric Coating Suspension

Function	Ingredient	Quantity (g)	Quantity (%)
Polymer	Eudragit® L30 D-55	213.4	42.3
Plasticizer	Triethyl citrate	6.2	1.2
Antitacking	Talc	31.2	6.2
Diluent	Water	254.1	50.3
Total		504.9	

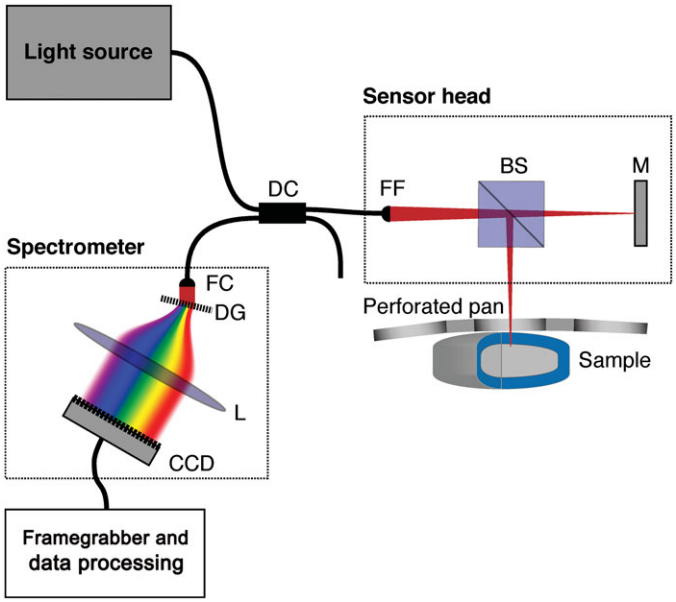

Figure 1. Schematic of OCT system. DC, directional coupler; FF, fiber focuser; BS, beamsplitter; M, mirror; FC, fiber coupler; DG, diffraction grating; L, lens; CCD, charged coupled device.

Optical Coherence Tomography

A spectral-domain (SD) OCT system was developed for the in-line application. This system is modularly designed allowing separation of the sensor head from light source, spectrometer, and processing unit, as schematically illustrated in Figure 1. A superluminescent diode Broadlighter (Superlum Diodes Ltd.,

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