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Optical coherence tomography as a novel tool for in-line monitoring of a pharmaceutical film-coating process

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ABSTRACT

Optical coherence tomography (OCT) is a contact-free non-destructive high-resolution imaging technique based on low-coherence interferometry. This study investigates the application of spectral-domain OCT as an in-line quality control tool for monitoring pharmaceutical film-coated tablets. OCT images of several commercially-available film-coated tablets of different shapes, formulations and coating thicknesses were captured off-line using two OCT systems with centre wavelengths of 830 nm and 1325 nm. Based on the off-line image evaluation, another OCT system operating at a shorter wavelength was selected to study the feasibility of OCT as an in-line monitoring method. Since in spectral-domain OCT motion artefacts can occur as a result of the tablet or sensor head movement, a basic understanding of the relationship between the tablet speed and the motion effects is essential for correct quantifying and qualifying of the tablet coating. Experimental data was acquired by moving the sensor head of the OCT system across a static tablet bed. Although examining the homogeneity of the coating turned more difficult with increasing transverse speed of the tablets, the determination of the coating thickness was still highly accurate at a speed up to 0.7 m/s. The presented OCT setup enables the investigation of the intra- and inter-tablet coating uniformity in-line during the coating process.

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1. Introduction

In pharmaceutical manufacturing, good manufacturing practices (GMP) and numerous quality tests were introduced to guarantee the quality and safety of pharmaceutical products. More recently, a number of regulatory approaches, including Quality by Design (QbD) and Process Analytical Technology (PAT), have raised the interest in an in-depth understanding of a process, product characteristics and in-line monitoring of product quality (FDA, 2004; ICH, 2009). A detailed understanding of the effect that the key process and material parameters have on the product quality can only be achieved by measuring quality attributes of the intermediate or final product and relating them to the key process parameters (Koller et al., 2011a,b; Scheibelhofer et al., 2013). Implementing an appropriate control strategy, including real-time measurements, is essential for process improvement, optimisation and quality assurance.

Manufacturing of pharmaceutical solid dosage forms often involves film coating as a final process. Typically, a thin continuous solid layer that controls the rate of drug release as a function of the environment is applied. The main functionality of such modified-release coatings (i.e., enteric coatings) is to align the initial drug release kinetics with the pH of the environment. In some cases the coating also contains an active pharmaceutical ingredient (API). However, tablets may also be coated for visual attractiveness, taste masking or brand recognition (Suzzi et al., 2010).

The main challenges of film coating are to apply spray droplets uniformly on the surface of a tablet and among the whole batch, and to dry the (typically aqueous) coating materials at a proper evaporation rate. There is still a lack of understanding of how in detail the material and operating parameters affect the product quality. Thus, defects do occur. The most common tablet coating defects are: (1) overwetting/picking (i.e., a part of the film coating is pulled off one tablet and deposited on another), (2) twinning (i.e., two or more of the tablet cores are stuck together), (3) orange peel (i.e., roughened film due to spray drying), (4) bridging (i.e., the film coating protrudes from the tablet logo), (5) cracking (i.e., internal stress in the film), (6) coating thickness variations (i.e., within a batch due to poor process and equipment design) and coating

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inhomogeneities (i.e., either a visible colour variation from tablet to tablet or an unacceptable release profile of the tablets), (7) tablet attrition/erosion (i.e., some portion of the product substrate has a high level of friability), (8) core erosion (i.e., attrition due to overwetting of the tablet), (9) peeling (i.e., large pieces or flakes of the film coating fall off the tablet core), (10) loss of logo definition (i.e., the tablet logo is no longer clearly legible), (11) core stability issues (i.e., discoloration or degradation of the core) and (12) tablet marking (i.e., black marking on the tablet face) (Koller et al., 2011a; Porter et al., 2009).

An imperfect coating may result in ineffective gastric-juice resistance and render the drug useless. In contrast, too much coating material may interfere with drug absorption in the small intestine (Porter et al., 2009). Thus, traditional biopharmaceutical parameters (i.e., disintegration time, dissolution profile) may be impacted by the coating process and it is important to understand the processing steps and their effect on the final product (Zeitler and Gladden, 2009). Since thickness and homogeneity of the coating are known to be critical for the drug release rate, their direct or indirect monitoring is essential.

Generally, the methods for film analysis can be categorised as destructive and non-destructive. Scanning electron microscopy (SEM) and confocal laser scanning microscopy (CLSM), for example, are destructive since they require a cut through the tablet and cannot be used for in-line monitoring. For a quick feedback, a measurement method should resolve the structure of the dosage form fast and non-destructively. Spectroscopic techniques, such as near-infrared (NIR) and Raman spectroscopy, offer an opportunity of solid dosage form characterisation and coating processes monitoring. The quantitative determination of the coating thickness via NIR and Raman has already been performed for off-line and in-line product characterisation (Cahyadi et al., 2010; Kirsch and Drennen, 1995; Romero-Torres et al., 2006). In combination with multivariate data analysis (MVDA), these methods allow real-time non-invasive and quantitative process monitoring (Müller et al., 2012; Römer et al., 2008). The major drawbacks of spectroscopic techniques are that they do not provide an absolute value of the coating thickness directly and have a limited capability for inter- and intra-tablet coating uniformity analysis. Since a calibration based on primary measurements (e.g., SEM) providing an absolute value is required, the prediction of the coating thickness is only as accurate as the reference measurements.

The above mentioned disadvantages can be overcome by using tomographic methods, which provide spatially (transversally and axially) resolved information regarding the coating. Several tomographic techniques are available, such as X-ray computed microtomography (XμCT), magnetic resonance imaging (MRI), terahertz pulse imaging (TPI) and optical coherence tomography (OCT) (Zeitler and Gladden, 2009). Most of them have already been successfully applied for the tablet coating analysis. However, only TPI and OCT fulfil the requirements for an in-line measurement system, such as high spatial (transverse and axial) resolution, high sensitivity regarding the detection of coating layers and impurities, large penetration depth, and separation of sensor head and processing module.

TPI is highly suitable for pharmaceuticals characterization, since terahertz radiation easily penetrates the excipients used in pharmaceutical tablets and reveals a contrast between them. (Shen and Taday, 2008). TPI's high potential as an in-line coating process measurement was demonstrated by May et al. (May et al., 2010) who successfully applied an in-line sensor for terahertz measurements of the film coating ranging from 40 μm to 1 mm. However, the transversal and axial spatial resolutions in TPI are limited to 50 μm and 40 μm, respectively. Since the coating thickness of most commercially-available pharmaceutical tablets ranges from 5 μm to 200 μm, a better axial resolution would be preferable. Moreover, TPI is expensive and requires relatively long measurement times.

These problems may be overcome using OCT, which is easily deployable and has a high data acquisition rate, a good transversal resolution and an extremely high axial resolution. OCT is a contact-free non-destructive high resolution imaging technique that originates from the field of biomedicine with the main applications in ophthalmology (Sakata et al., 2009), cardiology (Bezerra et al., 2009), dermatology (Welzel, 2001), gastroenterology and endoscopy (Adler et al., 2009). However, over the last years, the number of OCT applications in non-destructive testing and evaluation (NDT, NDE) of non-biological materials has substantially increased (Stifter, 2007).

OCT off-line applications for determining the coating thickness and detecting film defects have been studied in the literature and have been compared to other measurement techniques (Koller et al., 2011a; Mauritz et al., 2010; Zhong et al., 2011). In the current study, the feasibility of OCT as an in-line method for monitoring of pharmaceutical tablet film coating is reported. First, the feasibility of OCT for the analysis of the tablet coatings was examined. Off-line investigations of several different commercially-available tablets with film coating were conducted using two spectral-domain (SD)-OCT systems. Secondly, the influence of a moving tablet bed on OCT images was analysed in a static tablet bed by moving the sensor head along the tablet bed. The effect of the movement on the OCT image was examined and verified via experimental data.

2. Materials and methods

2.1. Optical coherence tomography

OCT is used to generate cross-sectional depth-resolved two- and three-dimensional images of translucent materials. Physically, OCT is based on low-coherence interferometry (LCI) and uses light sources with high spatial and low temporal coherence (i.e., a large bandwidth spectrum corresponding to coherence lengths of several microns). Since OCT is an interferometric approach, such a short coherence length acts as a temporal filter for photons that are back-reflected and back-scattered from different sample structures, such as interfaces, impurities, pores and cells. A depth scan is performed by comparing the arrival times of single scattered photons with a reference light beam. Low-coherence light sources generally have a coherence length in the region of 1–15 μm, and enable therefore an excellent axial-(depth) resolution (Fercher et al., 2003). The axial resolution λ_c is defined as half of the coherence length l_c, which is limited by the centre wavelength λ_c and the full width at half maximum (FWHM) bandwidth $\Delta\lambda$ of the light source:

$$\delta z = \frac{l_c}{2} = K\frac{\lambda_c^2}{\Delta\lambda}. \tag{2.1}$$

K is a constant factor given as 0.44 for a source with Gaussian spectral distribution.

The depth-resolved OCT signal can be acquired either in the time-domain or in the Fourier-domain. In the time-domain, the reference arm in the interferometer is varied and a signal is detected only when the photons reflected from both interferometer arms have travelled the same optical distance to the photodetector. The mechanical movement of a reference mirror can cause mechanical instabilities and noise. Acquiring the signal via OCT in the Fourier-domain has advantages in terms of imaging speed and sensitivity and can be used for in-line process monitoring. In this approach the reference arm is fixed and the interference signal of the light that back-reflects and back-scatters from the reference mirror and the sample is detected in a spectrally resolved way. This

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