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Research Paper

Evaluation of critical process parameters for intra-tablet coating uniformity using terahertz pulsed imaging

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ABSTRACT

The purpose of this study was to evaluate the intra-tablet coating uniformity and the identification of critical process parameters in an active pan coating process using terahertz pulsed imaging (TPI). A design of experiments (DoE) was performed with drum load, drum speed, spray rate, run duration and spray pressure as factors. Different measures of intra-tablet uniformity were investigated: the average thickness on the individual tablet faces, spatial variation in layer thickness over the tablet surface, and the coefficient of variation (CV_{intra}). Data analysis revealed that the process parameters in the investigated parameter space had hardly any influence on the difference in layer thickness of the tablet faces and centre band. No increase or decrease in layer thickness – as described in the literature – was found towards the edges of the tablet face. In overwetted process conditions a higher layer thickness at the centre band edges could be observed. Still, the highest variability in coating thickness was found along the circumference of the centre band rather than the height. In general, higher CV_{intra} of layer thickness were found on the centre bands in comparison with the tablet faces. The analysis of the DoE model revealed that the run duration had the highest influence on the CV_{intra} on the tablet faces. TPI showed high potential in the assessment of intra-tablet uniformity and layer thickness distributions over the whole tablet surface. It was successfully used to identify critical process parameters regarding intra-tablet coating uniformity.

1. Introduction

In the assessment of film coating quality, the uniformity of the film coating plays an important role. Inter-tablet coating uniformity describes how strongly the layer thickness varies between different tablets in a batch, and a high uniformity is necessary to guarantee consistent functionality in each individual dosage form of the batch. Intra-tablet uniformity describes the variation in layer thickness within an individual tablet, *e.g.*, the differences in layer thickness between the tablet surfaces (faces and centre band) or on a single surface.

High intra-tablet uniformity is especially important in functional film coating, for instance, in prolonged release formulations, where the drug release rate depends on the layer thickness of the film coating. In addition, a poor optical appearance may impact on the patient's adherence to therapy.

To date, only few studies have investigated the influence of process parameters on intra-tablet coating uniformity. These previous studies employed various techniques including terahertz pulsed imaging (TPI), near-infrared chemical imaging (NIR-CI), laser-induced breakdown spectroscopy (LIBS), X-ray micro computed tomography (XμCT) and computer simulations. In several of these studies, it was found that layer thickness on the tablet centre bands is lower than on the tablet faces [5,8,15,13,9,3]. One study investigated the influence of the drum rotation speed on the centre band thickness [15], while differences in layer thickness on the two tablet faces were reported in two other studies [5,4].

The distribution of layer thickness on individual tablet faces was the subject of a number of studies [7,10,3,11,9,16]. Contradictory results were reported, either showing an increase [7,10,11] or decrease [3] in layer thickness towards the tablet face edges compared to the centre of the tablet surface. Thus far, the influence of process parameters on the coefficient of variation in layer thickness, as a measure of intra-tablet uniformity, was only investigated by means of computer simulations [3], and systematic experimental data are missing in this context.

TPI is a nondestructive imaging technique that can be used to measure the spatial distribution of layer thickness on pharmaceutical tablets. Due to its relatively high spatial resolution, it shows

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potential as a tool to evaluate intra-tablet coating uniformity. Details on the technique were reported by Zeitler et al. [16] and Shen and Taday [12].

The aim of this study was to use TPI for the quantification of layer thickness uniformity in multiple batches of active-coated tablets. Using a design of experiments (DoE), process parameters were systematically modified, and their influence on intra-tablet coating uniformity was assessed by measuring the differences in layer thickness on the three tablet surfaces (both tablet faces and centre band). Together with the spatial distribution of layer thickness, the coefficient of variation on the tablet surfaces was quantified.

2. Materials and methods

2.1. Materials

Gastrointestinal therapeutic systems (GITS, Bayer Pharma AG, Berlin, Germany) were used as starting material for the subsequent coating process. The GITS consist of a two-layer tablet core with the active pharmaceutical ingredient (API) nifedipine in one part (yellow coloured part of the tablet core) and an osmotic blend in the other part (red coloured). A diffusion membrane is coated on top of the two-layer tablet core, consisting of cellulose acetate and polyethylene glycol. The GITS dimensions were 9.1 mm in diameter and 4.8 mm in height with a mass of 280–283 mg per tablet.

2.2. Pan coating

The aqueous coating suspension consisted of 40% (wt/wt) candesartan cilexetil as API and 60% (wt/wt) polyvinyl alcohol based polymer mixture (Opadry®, Colorcon, Dartford, UK) at a total solids content of 29% (wt/wt). Candesartan cilexetil was dispersed in water using a dissolver stirrer (IKA-Werke GmbH & Co. KG, Staufen, Germany); then, the polymer mixture was added, and the suspension was stirred for 45 min.

Pan coating was performed using a side-vented pan coater (BFC50, L.B. Bohle, Ennigerloh, Germany) with a pan diameter of 700 mm and a pan length of 630 mm (cylindrical part of the coating drum). A 2^{5-1} fractional factorial design of experiments was executed with drum load (loa), drum rotation speed (rpm), spray rate (spr), run duration (dur) and spray pressure (pres) as factors. Three replicate runs were prepared at the centre point of the design space. The range of process parameters is detailed in Table 1, and the process parameters for the individual batches are listed in Table 2.

Three of the investigated factors impact on the amount of coating material applied per tablet. The drum load determines the number of tablets in the batch. With a higher drum load, the coating suspension is distributed on more tablets, and the amount of suspension per tablet is reduced when compared to a lower drum load. Both spray rate and run duration were included in the experimental design separately to investigate their effect on coating uniformity. The factor combination of spray rate and run duration determines the total amount of coating suspension applied to the batch. The drum load then determines the amount of coating suspension per tablet. Hence, the amount of coating suspension per tablet varies from batch to batch and is the result of the factor combination of drum load, spray rate and run duration. Depending on the factor combinations in the individual batches, drug loads between 6.6 and 32.0 mg/tablet CAN (covering a therapeutically meaningful CAN dose strength range) were applied (see Table 2). This resulted in an amount of coating mass (*i.e.* mass increase of the tablets) between 16.5 and 80 mg/tablet.

Table 1
Range of process parameters in the design of experiments.

Parameter		Abbr.	Range
drum load	[tablets × 1000]	loa	133–153
drum speed	[rpm]	rpm	12–14
spray rate	[g/min]	spr	60–120
run duration	[min]	dur	150–300
spray pressure	[bar]	pres	1.7–1.9

Samples were withdrawn from the final product.

2.3. Terahertz pulsed imaging

Terahertz pulsed imaging was performed using a TPI imaga 2000 system (TeraView Ltd., Cambridge, UK). The tablets were scanned in full scan mode (both tablet faces and centre band) at a point spacing grid of 200 μm × 200 μm. In total, approximately 1900 and 1700 data points were collected for each tablet face and centre band, respectively. The penetration depth was set to 2 mm in air. Ten tablets per batch were measured, except for batch No. 6, where 11 tablets were measured. A total number of 191 tablets were included in this study.

TPIView software version 3.0.3 (TeraView Ltd., Cambridge, UK) was used for layer thickness analysis. The layer thickness was calculated as $2d_{TPI} = \Delta t\ c/n$, where Δt is the time delay between two subsequent reflection pulses of the incident terahertz pulse, c is the speed of light and n is the refractive index of the coating layer. The refractive index was set to $n = 1.53$, which is the default value and represents the refractive index of a typical pharmaceutical coating polymer [16]. Experimental values of n were not determined for the individual batches, and hence, the layer thickness values in this study are not absolute. In Brock et al. [1], it was shown that n is likely to change between batches with different process conditions. As a consequence of the unknown absolute value of n and the different amounts of coating suspension applied in each batch, the comparison of batches to each other will only be performed using relative numbers. Using X-ray microcomputed tomography as a reference technique to measure the absolute coating thickness, Russe et al. [11] showed excellent agreement of the spatial variation in layer thickness determined by TPI. Hence, it is assumed that the spatial variation in layer thickness over the tablet surface can be accurately described using TPI. As demonstrated previously, optical microscopy is an inadequate reference technique due to the deformation of the film coating during the sample preparation [2] and the fact that only a cross-section with a limited number of measurement points can be used to investigate coating uniformity.

Numerical data analysis was performed using Matlab R2011b (The Mathworks, Natick, USA). Differences in the time-domain signals on the two tablet faces due to the inhomogeneous composition of the bilayered tablet core were reported in Brock et al. [1]. The location of the laser drilled hole, and the fact that the red and yellow part of the tablet core exhibit different time-domain signals, made it possible to assign the coating thickness data to the specific face of the tablet core. According to the colour of the tablet core parts, the yellow part of the GITS is referred to as the 'yellow tablet face', while the red part of the GITS is called 'red tablet face' in this article. In order to remove artefacts in the TPI measurements close to the tablet edges, a region of interest of 1.5–4 mm radius from tablet face centre was chosen for numerical analysis. For the centre bands, only data points >0.15 mm edge distance were included in the analysis. Further details on measurement artefacts in this specific sample system can be found in Brock et al. [1].