# Optimization of the inter-tablet coating uniformity for an active coating process at lab and pilot scale

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## ARTICLE INFO

## ABSTRACT

The objective of this study was to enhance the inter-tablet coating uniformity in an active coating process at lab and pilot scale by statistical design of experiments. The API candesartan cilexetil was applied onto gastrointestinal therapeutic systems containing the API nifedipine to obtain fixed dose combinations of these two drugs with different release profiles. At lab scale, the parameters pan load, pan speed, spray rate and number of spray nozzles were examined. At pilot scale, the parameters pan load, pan speed, spray rate, spray time, and spray pressure were investigated. A low spray rate and a high pan speed improved the coating uniformity at both scales. The number of spray nozzles was identified as the most influential variable at lab scale. With four spray nozzles, the highest CV value was equal to 6.4%, compared to 13.4% obtained with two spray nozzles. The lowest CV of 4.5% obtained with two spray nozzles was further reduced to 2.3% when using four spray nozzles. At pilot scale, CV values between 2.7% and 11.1% were achieved. Since the test of uniformity of dosage units accepts CV values of up to 6.25%, this active coating process is well suited to comply with the pharmacopoeial requirements.

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## 1. Introduction

Tablet coating is a common process for drug manufacturing. The majority of coating processes are performed to provide protection for the tablet core or to modify the drug release of tablets. Incorporating active pharmaceutical ingredients (APIs) into the coating layer enables the development of fixed dose combinations of a sustained release dose in the tablet core and an immediate release dose in the coating layer (Rege et al., 2002).

In an active coating process in particular, the coating uniformity is a critical quality attribute as coated tablets have to pass the test on uniformity of dosage units according to the pharmacopoeias (European Pharmacopoeia, 2011; Japanese Pharmacopoeia, 2011; United States Pharmacopoeia, 2011). The regulatory requirements are met if the acceptance value is less or equal to 15. The CV of the API content in the tablet coat must not exceed 6.25% provided that the correct coating endpoint is met. To comply with the pharmacopoeias' acceptance value for content uniformity of the coating layer, process understanding is essential. Experimental

investigations are crucial to gain this process understanding. Rege et al. (2002) achieved less than 6% relative standard deviation of drug content whereas Chang and Leonzio (1995) obtained a CV of 10.75%.

The coating uniformity can be differentiated between the intra-tablet coating uniformity and the inter-tablet coating uniformity (Tobiska and Kleinebudde, 2003). The intra-tablet coating uniformity relates to the homogeneity of the film on a single tablet and can be characterized for instance by terahertz pulsed imaging (TPI), which enables the measurement of coating thickness distributions (Ho et al., 2007) or by optical coherence tomography (OCT) (Koller et al., 2011). The inter-tablet coating uniformity on the other hand refers to the homogeneity between different tablets within one batch. It can be determined by TPI, mass uniformity or content uniformity, for instance. Computational simulation tools like the discrete element method (DEM) also allow for the investigation of the inter-tablet coating uniformity (Kalbag et al., 2008; Suzzi et al., 2012). In the context of quality by design (QbD), coating process simulations can be used as a tool to enhance process understanding. In order to conduct these simulations, the impact of formulation parameters and process variables on the process and product quality has to be assessed. However, the evaluation of critical process variables which impact the coating uniformity and the validation of DEM model predictions require experimental studies.

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Thus, combined experimental and computational simulation approaches can contribute towards an overall mechanistic pharmaceutical process understanding. On the basis of this knowledge and in combination with experimental validation, process optimization can be performed to build quality into the product.

A coating process consists of simultaneous spraying, mixing, and drying processes. These components and their respective parameters have to be considered with regard to the coating uniformity. In general, the coating variability can be influenced by the tablet movement in the coater and by the spray properties (Pandey et al., 2006b). Several authors evaluated critical process parameters on the inter-tablet coating uniformity by statistical design of experiments (DOE). This tool enables the simultaneous variation of the parameters potentially affecting the coating uniformity. Porter et al. (1997) found the pan speed to have the largest influence on the coating uniformity, followed by the spray rate, the inlet air temperature, and the number of spray nozzles. An increase in the pan speed as well as in the number of spray nozzles reduced the coating variation. According to Rege et al. (2002), the atomization pressure was the most influential variable, followed by the pan speed and the coating time. With a lower atomization pressure, higher pan speed, and longer coating time, a better coating uniformity was achieved. Patel et al. (2009) identified the spray rate, inlet air temperature, and pan speed as most critical process parameters. Mathematical models were also developed to predict the coating uniformity. It was found that the coefficient of variation (CV) was inversely proportional to the square root of the coating time (Chen et al., 2010; Cheng and Turton, 2000; Mann, 1983).

The pattern pressure influences the spray geometry, i.e., spray width and height. Mueller and Kleinebudde (2006) adjusted the corresponding pattern pressure depending on the atomization pressure, to gain an ellipsoid spray cone of maximal spray width without forming a dumbbell pattern. An ellipsoid spray cone resulted in a more uniform film layer than a round spray cone, as more tablets received coating (Pandey et al., 2006a).

The average residence time per pass, i.e., the time a tablet spends in the spray zone per visit, decreases with increasing pan speed and fill level (Leaver et al., 1985; Pandey and Turton, 2005; Yamane et al., 1995). The coefficient of mass variation depends on the average circulation time, the circulation time distribution, the average coated weight per pass, and the coat weight distribution per pass. These parameters correlate with the circulation of the tablets through the spraying zone. Leaver et al. showed that the circulation time was reduced by increasing the pan speed but by the decreasing fill level (Leaver et al., 1985). Increasing pan speed or decreasing spray rate decreased the coefficient of mass variation as the tablets passed the spray zone more frequently and the tablet bed mixing was improved. Applying more film coating or diluting the coating formulation resulted in a reduced coating mass variability due to a prolonged coating time (Chang and Leonzio, 1995). The number of spray nozzles and their distance to the tablet bed also impacts the coating uniformity. Increasing the gun-to-bed-distance resulted in lower droplet velocities (Aulton and Twitchell, 1995).

In this study, an active coating process was performed at the lab and pilot scale to produce fixed dose combinations of two drugs with different release profiles. The API candesartan cilexetil was coated on gastrointestinal therapeutic systems (GITS) containing the API nifedipine. The objective was the improvement of the inter-tablet coating uniformity in this active coating process in order to achieve the requirements of the pharmacopoeias. Statistical design of experiments was used to systematically investigate the influence of coating parameters on the inter-tablet coating uniformity and to identify optimal coating process conditions.
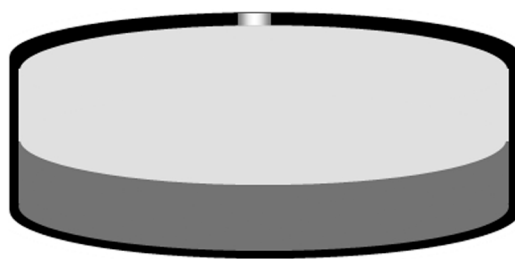


**Fig. 1.** Schematic of GITS: API layer (light grey), osmotic blend layer (dark grey), and diffusion membrane coat (black) with laser drilled hole.

## 2. Materials and methods

### 2.1. Materials

Gastrointestinal therapeutic systems (GITS) were used as starting material in this study (Bayer Pharma AG, Leverkusen, Germany).

These GITS were coated biconvex two-layer tablets (280 mg, 9.1 mm diameter, 4.8 mm height) comprising the API nifedipine, an osmotic blend and a diffusion membrane coating of cellulose acetate and polyethylene glycol (Fig. 1).

The aqueous coating suspension contained the API candesartan cilexetil and a polyvinyl alcohol-based lacquer (Opadry® II 85F clear, Colorcon, Dartford, UK). The solid content of the coating suspension was about 30%. The active-coated GITS were of 9.4 mm diameter and 5.4 mm height and the mass was 320 mg.

### 2.2. Preparation of the coating suspension

#### 2.2.1. Lab scale

The amount of coating suspension was calculated to reach a target dose of 16 mg candesartan cilexetil per tablet (40% API content). A spray loss of 1.5% was taken into account. The coating suspension was prepared by dispersing the blend of API and lacquer in water. The suspension was stirred overnight and during the whole coating trial with a dissolver stirrer (IKA Euro-ST PB, R 1302 dissolver stirrer, IKA-Werke GmbH & Co. KG, Staufen, Germany).

#### 2.2.2. Pilot scale

The amount of the coating suspension was calculated based on the intended spray rate and spray time resulting in different candesartan cilexetil doses. The coating suspension was prepared by dispersing the API and subsequently the lacquer in water by vigorous stirring using a dissolver stirrer (IKA Euro-ST P-DV, IKA-Werke GmbH & Co. KG, Staufen, Germany) for at least one hour. The suspension was then gently stirred overnight and during the whole coating process.

### 2.3. Active coating process

#### 2.3.1. Lab scale

At lab scale, a side-vented pan coater (BFC 5, L.B. Bohle, Ennigerloh, Germany) with two (nozzle diameter 1 mm) and with four (nozzle diameter 0.8 mm) spray nozzles (ABC 970/7-1 S75, 970/7-1 S89, Duesen-Schlick, Untersiemau, Germany) was used. The dimensions of the pan were 360 mm (length of the cylindric part of the pan) and 320 mm (pan diameter). The atomization air pressure was kept constant at 0.8 bar for all coating trials. The pattern pressure was adjusted according to the atomization pressure at 0.7 bar. The distance of the spray nozzles from the tablet bed was 10 cm. The inlet air temperature was adjusted to obtain an exhaust air temperature of 40 °C. The inlet air rate was constant at 160 m³/h. Subsequent to the spraying process, the tablets were dried in the pan at 60 °C inlet air temperature for 10 min.