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Research paper

Evaluation of critical process parameters for inter-tablet coating uniformity of active-coated GITS using Terahertz Pulsed Imaging

Daniela Brock [a], J. Axel Zeitler [b], Adrian Funke [c], Klaus Knop [a], Peter Kleinebudde [a,*]

[a] Institute of Pharmaceutics and Biopharmaceutics, University of Düsseldorf, Düsseldorf, Germany
[b] Department of Chemical Engineering and Biotechnology, University of Cambridge, Cambridge, United Kingdom
[c] Global Chemical & Pharmaceutical Development, Bayer Pharma AG, Berlin, Germany

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ABSTRACT

The aim of this study was the evaluation of critical process parameters (CPP) for inter-tablet coating uniformity in an active pan coating process using nondestructive Terahertz Pulsed Imaging (TPI). Coating uniformity was assessed by calculating the coefficient of variation (CV) of coating thickness measured by TPI, and the CV of API content measured by high performance liquid chromatography (HPLC). A design of experiments (DoE) was performed at pilot scale with drum load, drum speed, spray rate, run duration and spray pressure as factors. Good agreement in the CV of both analytical techniques was shown. The DoE models both revealed the same CPP: a low drum load, high drum speed, low spray rate and high run duration were beneficial for coating uniformity. The spray pressure was only significant in one of the DoE models. It was further shown that the negative impact of a high drum load on the CV cannot only be compensated by high drum speed, but also be compensated by a low spray rate and long run duration. It was demonstrated that TPI is a feasible tool for the measurement of inter-tablet coating uniformity and for the evaluation of CPP in an active pan coating process.

1. Introduction

In recent years, Terahertz Pulsed Imaging (TPI) has aroused interest in the pharmaceutical sciences as a technique to nondestructively measure coating thickness distributions of both, external and buried layers, over the entire tablet surface. Detailed information on the measurement technique is given in [1,2].

Various applications of TPI have since been reported in the literature. For example, TPI was used as a tool to monitor the increase in film thickness throughout a coating process [3–5] or to evaluate the three-dimensional structure of solid drug dosage forms [6,1] and to identify defects in coating layers [7].

Several studies also deal with the use of TPI to evaluate coating uniformity, utilising the high spatial and axial resolution of the technique. Coating uniformity can be subdivided into intra-tablet uniformity, describing the uniformity of the film coating within a single tablet, and inter-tablet uniformity, which corresponds to the uniformity of the film coating between multiple tablets of a batch. While several studies deal with the investigation of intra-tablet uniformity using TPI [7–10], only [4] made a first approach to use in-line terahertz measurements to evaluate inter-tablet coating uniformity. Up to now, no literature is available that has systematically evaluated the use of TPI in the analysis of inter-tablet coating uniformity.

In the film coating unit operation, a high inter-tablet coating uniformity is desired to maintain a constant product quality of each individual dosage unit in the batch. Inter-tablet coating uniformity is of particular importance in functional film coatings, such as sustained-release coatings or active coatings, where the drug release and API content, respectively, determine the effectivity of the drug product.

Drug dosage forms comprising an active coating need to meet the requirements on uniformity of dosage units described in major pharmacopoeias [11–13]. Herein, the API content of the final product as well as the content uniformity within the batch is assessed. An acceptance value (AV) is calculated to determine whether both API content and content uniformity are within a specified range:

$$AV = |M - \overline{X}| + ks \quad (1)$$

* Corresponding author. Institute of Pharmaceutics and Biopharmaceutics, University of Düsseldorf, Universitätsstrasse 1, 40225 Düsseldorf, Germany. Tel.: +49 211 8114220; fax: +49 211 8114251.
E-mail addresses: daniela.brock@uni-duesseldorf.de (D. Brock), jaz22@cam.ac.uk (J. Axel Zeitler), adrian.funke@bayer.com (A. Funke), klaus.knop@uni-duesseldorf.de (K. Knop), kleinebudde@uni-duesseldorf.de (P. Kleinebudde).

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Here, $\overline{X}$ is the arithmetic mean of the individual contents of the dosage units expressed as a percentage of label claim. M is a reference value that varies depending on the actual $\overline{X}$ of the batch, k is the acceptability constant and s is the sample standard deviation. The acceptability constant k is defined by the number of investigated dosage units (k = 2.4 for 10 dosage units, k = 2.0 for 30 dosage units).

The term $|M - \overline{X}|$ accounts for the average amount of API that is incorporated in the dosage form. If the API content is between 98.5 and 101.5 % of label claim, the term can be neglected and does not contribute to the AV. In that case, only the second term, ks, affects the AV. It accounts for the variability of API content among the dosage units in the batch – the inter-tablet uniformity.

In compliance with the pharmacopoeial regulation, an AV $\leqslant$15 has to be met. In the case that a mean content of 98.5% $\leqslant \overline{X} \leqslant$ 101.5% is achieved, a relative standard deviation of $\leqslant$6.25% is sufficient to meet the pharmacopoeial requirements on uniformity of dosage units (for n = 10 dosage units, k = 2.4). If $\overline{X}$ exceeds these limits, s needs to be lower to attain an AV $\leqslant$ 15.

It is evident that both, the accurate determination of the coating endpoint and the achievement of a low standard deviation, are of key importance to meet the required AV.

In the present study, the active coating process of a recently developed dosage form – an active-coated push–pull osmotic system – is investigated. Ref. [14] showed that the accurate API content at coating endpoint can be precisely determined and controlled via in-line Raman measurements. To achieve a high inter-tablet coating uniformity as the second premise for an acceptable AV, the critical process parameters (CPP) in the active coating process need to be identified and a parameter space needs to be defined within which the requirements on coating uniformity are met.

In the literature, several articles address the influence of process parameters on inter-tablet coating uniformity and the mixing behaviour of tablets in the coating drum. They determine inter-tablet coating uniformity by (i) the weight variability of the coated and uncoated tablets [15,16] or the individual coating weights [17], (ii) the variability in tablet diameter or in layer thickness determined by NIR [18], and (iii) dyes or marker substances in the coating to quantify the amount of coating that is applied to the individual tablets [19,20]. Other approaches to investigate inter-tablet coating uniformity are based on computer simulations [21–24]. Up to now, no literature is available that has evaluated the use of TPI in the assessment of inter-tablet coating uniformity and the related CPP in pan coating processes.

The aim of this work was the evaluation of critical process parameters for inter-tablet uniformity in an active pan coating process using Terahertz Pulsed Imaging. As a first step, the linear correlation of layer thickness and CAN content at coating endpoint is evaluated. A high correlation over a broad range of layer thickness and API content was already reported by [5]. The coefficient of variation (CV) of content and layer thickness obtained by HPLC – as a well-established analytical tool – and TPI are then compared for a number of batches. Subsequently, a design of experiments is investigated by both, HPLC and TPI to evaluate whether TPI can resolve the same CPP as HPLC does and to identify a parameter range within which acceptably low CV can be achieved.

2. Materials and methods

2.1. Materials

Gastro-intestinal therapeutic systems (GITS, Bayer Pharma AG, Berlin, Germany) were used as starting material in the active coating process. The tablets were made from a two-layer tablet core surrounded by a semipermeable membrane consisting of cellulose acetate and polyethylene glycol 3350. One half of the tablet core contained the active pharmaceutical ingredient nifedipine (NIF). Given its colour, this face of the tablet is referred to as the yellow tablet face in the remainder of this work. An osmotic blend was incorporated in the other half of the tablet core. Owing to its high content in iron oxide, this face is referred to as the red tablet face. A laser-drilled hole was positioned in the semipermeable membrane on the centre of the yellow tablet face, to enable the release of NIF from the dosage form by contact with water. Three different dose strengths of the GITS were used in this study. The GITS with a drug load of 20 mg NIF were 8.4 mm in diameter and 4.3 mm in height with a mass of 217 mg per tablet. GITS with a drug load of 30 mg NIF were 9.1 mm in diameter and 4.8 mm in height with a mass of 280–283 mg per tablet and GITS with a drug load of 60 mg NIF were 10.6 mm in diameter and 6.6 mm in height with a mass of 531 mg per tablet.

2.2. Pan coating

2.2.1. Preparation of the coating suspension

The aqueous coating suspension consisted of 40% (wt/wt) candesartan cilexetil (CAN) as API and 60 % (wt/wt) polyvinyl alcohol based polymer mixture (Opadry®, Colorcon, Dartford, UK) at a total solid content of 29% (wt/wt). The API was dispersed in water using either an Ultra-Turrax homogeniser (batches A and B, TP18/10, Janke und Kunkel, Staufen, Germany) or a dissolver stirrer (other batches). Subsequenty, Opadry® was added and the suspension was stirred for at least 45 min until all polymer particles had dissolved.

2.2.2. Coating trials in lab scale

Pan coating in lab scale (3 and 8 kg) was performed using side-vented pan coaters (BFC5 and BFC5/10, L.B. Bohle, Ennigerloh, Germany). The process conditions and theoretical API content at process endpoint are listed in Table 1. In batches A and B the spray rate was increased from 8 g/min to 12 g/min after 60 min process time.

2.2.3. Design of experiments in pilot scale

Pan coating in pilot scale (38–43 kg) was performed using a side-vented pan coater (BFC50, L.B. Bohle, Ennigerloh, Germany). A 2^{5-1} fractional factorial design of experiments (DoE) was performed using GITS with a drug load of 30 mg NIF. Drum load

Table 1
Process parameters and API contents in the fixed-dose combination for the investigated lab scale batches of active-coated GITS at different scales.

Batch no.	loa (kg)	rpm (rpm)	spr (g/min)	dur (min)	pres (bar)	NIF load (mg/tablet)	CAN load (mg/tablet)
A	3	18	8/12	340	0.8	20	32
B	3	18	8/12	348	0.8	20	32
C	8	15	25	396	1.1	20	32
D	8	15	21	180	1.0	60	32
E	40.1	11	123	80	1.5	30	8
F	40.1	11	126	150	1.5	30	16
G	44	11	78	140	1.5	60	16

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Table 2
Overview of the factors and factor levels in the design of experiments at pilot scale [25].

Factor	Unit	Abbr.	Factor level		
			−1	0	1
Drum load	tablets × 1000	loa	133	143	153
Drum rotation speed	rpm	rpm	12	13	14
Spray rate	g/min	spr	60	90	120
Run duration	min	dur	150	225	300
Spray pressure	bar	pres	1.7	1.8	1.9

(*loa*), drum rotation speed (*rpm*), spray rate (*spr*), run duration (*dur*) and spray pressure (*pres*) were used as factors [25]. The factors and factor levels in the DoE are given in Table 2. Three replicates were performed at the model's centre point.

The target API content at process endpoint varied from batch to batch and is a result of the factor combination of *loa*, *spr*, and *dur*. The drum load determines the number of tablet cores in the batch. At higher drum loads the coating suspension is distributed over a higher number of tablets and hence less coating suspension is applied to each individual tablet. The combination of spray rate and run duration yields the total amount of coating suspension applied to the batch and the drum load then determines the amount of coating suspension per tablet. As a result of the factor combinations, drug loads between 6.6 and 32.0 mg CAN were applied in the individual batches, covering a therapeutically meaningful CAN dose strength range.

Analytical samples for HPLC and TPI analysis were withdrawn from the final product.

2.3. Terahertz Pulsed Imaging

Terahertz Pulsed Imaging was performed using a TPI imaga 2000 (TeraView Ltd., Cambridge, UK). The tablet surface was mapped in point-to-point mode at a lateral resolution of 200 μm × 200 μm and a penetration depth of 2 mm in air. Either 10 tablets (batches 1–5, 7–19), 11 tablets (batch 6) or 36 tablets (A–G) were measured. Coating thickness analysis was performed using TPIView software version 3.0.3 (TeraView Ltd., Cambridge, UK). As the real refractive index, n_{real}, of the film coating was unknown, it was set to $n_{estimated} = 1.53$, which is an average value for commonly used polymer formulations and the default value in the software [1].

All subsequent numerical analysis was performed using Matlab (Mathworks, Natick (MA), USA). For each tablet the average film thickness was determined on the top and bottom tablet face individually. To avoid artefacts from scattering of the THz pulse at the tablet edges and in the region of the laser drilled hole, a region of interest (ROI) was applied within which the TPI data were used for numerical analysis. For further details on measurement artefacts in TPI the reader is referred to [25].

The applied ROI had a torus shape with an inner radius of r_i=1.5 mm and an outer radius of $r_o = 3.5$, 4, and 4.5 mm for the 20, 30, and 60 mg GITS, respectively. The dimensions of r_o were adjusted to the tablet size in a way that error-prone measurement points were excluded from coating analysis in all investigated batches, while r_i was defined by the area within which the laser drilled hole could potentially be located. For consistency, the same ROI was applied to both, the tablet face with and without the laser drilled hole.

2.4. HPLC analysis

2.4.1. Sample preparation

The active coating layer of an individual tablet was dissolved by adding 10 mL deionised water to the active-coated GITS. After 10 min the mixture was subdued to ultrasonication for 20 min (Sonorex Super 10P, Bandelin, Berlin, Germany). Subsequently, 80 mL methanol was added to the mixture followed by a 20 min ultrasonic treatment. The mixture was then filled with methanol to 100.0 mL and was centrifuged for 5 min at 300 rpm (Heraeus Multifuge 1L, Thermo Scientific, Waltham (MA), USA). Finally, a 10% (v/v) dilution was prepared and was filtered using disposable filters of 0.45 μm pore size.

2.4.2. Method 1

Ten tablets from batches A–C were subdued to HPLC analysis subsequent to the TPI measurements. HPLC analysis was performed using an Elite LaChrom HPLC system (VWR Hitachi, Darmstadt, Germany). A C18-column (X-Bridge, Waters, Eschborn, Germany) with 3.5 μm particle size, 3 mm diameter and 150 mm length with precolumn (3.5 μm particle size, 3 mm diameter, 20 mm length) was used. The eluent consisted of 80% (v/v) methanol and 20% (v/v) phosphate buffer (5 mmol, pH 3). The flow rate was set to 0.6 mL/min. The oven temperature of the column was set to 40 °C. Detection was achieved by measuring the UV absorption at 260 nm. Each sample was measured in triplicate (injection volume: 5 μL) and the mean content as well as standard deviation was calculated using external standard calibration. Data analysis was performed using EZChrom Elite software (VWR Hitachi, Darmstadt, Germany).

2.4.3. Method 2

HPLC data of the remaining batches were provided by Bayer Pharma AG (Berlin, Germany). 30 Tablets per batch (10 tablets for batch D) were investigated using an Agilent 1100 HPLC (Agilent Technologies, Germany) with a Zorbax Eclipse XDB C-18 column (75 × 4.6 mm, 3.5 μm particle size). A gradient programme was performed using water +0.05% trifluoroacetic acid and methanol as eluents. The oven temperature was set to 40 °C and UV detection was performed at 225 nm. The API content was calculated using external standard calibration [25].

3. Results and discussion

3.1. Correlation between HPLC and TPI data at coating endpoint

A high correlation between API content and layer thickness measured by TPI over a broad range of API content and layer thickness was already shown by [5] for the present dosage form. To evaluate the linearity in a narrower range, the layer thickness and CAN content in three batches of tablets (A–C) were investigated at coating endpoint. Ten tablets of each coating run were subdued to TPI and subsequent HPLC analysis to obtain the layer thickness and CAN content from the same tablets.

Fig. 1 and Table 3 describe the correlation of CAN content and layer thickness. All three batches show a high correlation with an $R \geqslant 0.999$. While batches A and C reveal a low RMSE (RMSE = 1.25 and 1.24), the RMSE in batch B is much higher (RMSE = 2.19). The narrow data range as well as an outlier at 37.2 mg CAN content led to a broad point cloud and hence a higher RMSE.

It is immediately obvious that the CAN content is a function of the layer thickness over the entire tablet surface rather than of the layer thickness of only an individual tablet face. Still, measurement artefacts can occur in TPI due to scattering losses of the THz pulse close to the tablet edges and in the region of the laser drilled hole. Ref. [25] showed that scattering losses may lead to weak TPI signals without sharp interface reflections. These signals do not allow an accurate coating thickness measurement and may bias the subsequent numerical analysis of layer thickness. Hence, an exclusion of these areas from numerical analysis of the coating

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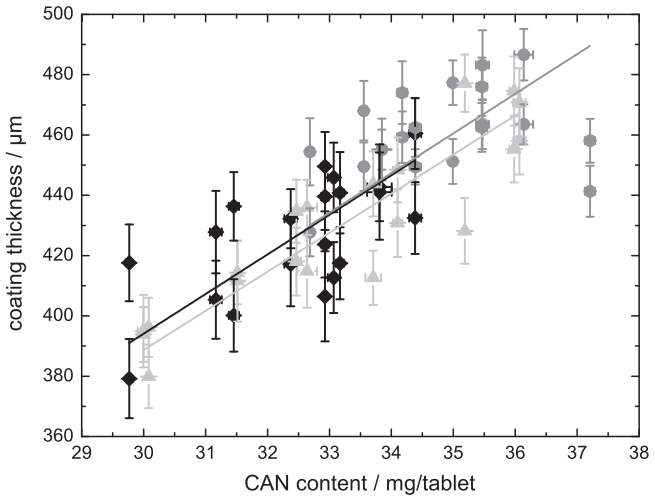

Fig. 1. Correlation of CAN content (measured by HPLC) and layer thickness on the two tablet faces (measured by TPI). The data points represent the average layer thickness on each tablet face (ROI: $1.5 \leqslant r_t \leqslant 3.5$ mm) and the corresponding CAN content of the same tablet ($n = 20$ data points per batch, *i.e.* 2×10 tablet faces). Black = batch A, dark grey = batch B, light grey = batch C. Linear equations are given in Table 3.

Table 3
Linear regression analysis of layer thickness as a function of CAN content using a fit to the equation $y = ax$. For the fit the squares of the distance were weighted using the reciprocal variance of the y-values of the respective data points.

Batch no.	a (µm/mg/tablet)	R	RMSE (µm)
A	13.14	0.999	1.25
B	13.16	0.999	2.19
C	12.96	>0.999	1.24

thickness data makes sense to avoid biasing coating thickness data. The investigation of only the tablet faces – especially with the limitation to a region of interest that excludes error-prone TPI signals – does not comprise all areas that contribute to the total CAN content. Still, with the prospect of in-line coating thickness measurements [4], it is interesting to see to which extent layer thickness measurements solely on the tablet faces can give information on the CAN content of the individual tablets. Furthermore, a restriction of the sampling area in the TPI measurement can significantly reduce the measurement time and hence speed up the coating thickness determination.

As a measure of inter-tablet coating uniformity the coefficient of variation of layer thickness, CV_{TPI}, and CAN content, CV_{HPLC}, was calculated from the average layer thicknesses of the individual tablet faces and the CAN content of the individual tablets, respectively:

$$CV_{HPLC,TPI} = \frac{\sqrt{\frac{1}{n-1}\sum (X_i - \overline{X})^2}}{\overline{X}} \quad (2)$$

As the coating density and refractive index are unknown for the present dataset and coating thickness values cannot be calculated accurately in µm, the coating uniformity was analysed using the relative standard deviation (in %) instead of the absolute standard deviation in μm (Eq. (2)). Using this approach, a comparison of %RSD from batch to batch is possible and a statistical analysis of the DoE can be performed.

It is not feasible to determine density, or n, of the coating layer directly with sufficient accuracy. There is currently no feasible method available that allows the evaluation of the coating density or n on this type of tablet with any technique other than TPI itself. A recently published method by Russe et al. [26] utilises X-ray micro computed tomography to calibrate n for terahertz coating thickness measurements. This technique is feasible for tablets that exhibit high X-ray contrast between the tablet core and coating layer, e.g. due to a high amount of transition metal elements in the coating formulation. However, the present active-coated GITS do not provide sufficient contrast to use this technique (data not shown). Other techniques such as transmission measurements of coated and uncoated cores are not an option due to strong absorption of the THz radiation from the tablet core and the generally poor reliability of this method [26]. Other techniques use model systems such as sprayed or cast films, which is not feasible either as the impact of different process conditions on n cannot be assessed using the model systems.

The assumption we make is that the refractive index (and in turn the coating density) is constant within a single batch of tablets, which we believe to be a fair assumption to make based on the results presented in the paper by Russe et al. and May et al. [26,27] as well as the study of Niwa et al. which shows that subtle changes in moisture levels within a coating layer have no significant effect on the TPI results [28].

Similar to the high linear correlation that was found between API content and coating thickness data, the CV_{HPLC} and CV_{TPI} in batches A–C are on the same order of magnitude (Table 4). Batches D–G were also investigated with respect to the CV of CAN content and layer thickness and good agreement was found in most batches. Other than in batches A–C, HPLC and TPI analysis were assayed on different tablets. This could be one reason for the high discrepancy of CV in batch D. Additionally, only ten tablets were subdued to HPLC analysis in batch D, while a total of 36 tablets was investigated via TPI.

Despite the irregular CV in batch D, the investigation immediately suggests that the prediction of content uniformity via TPI measurements of the inter-tablet coating uniformity is possible. Consequently, in the next step a design of experiments was conducted to evaluate whether TPI is a suitable technique to identify the CPP in the active coating process.

3.2. Experimental design to identify critical process parameters

3.2.1. Current state of knowledge

In the literature on inter-tablet coating uniformity, several authors describe that an increase in drum rotation speed improves coating uniformity [20,19,15]. These findings can be explained by a better mixing behaviour of the tablets in the coating drum [22,23] and more frequent but shorter visits to the spray zone [29]. Only [17] did not find a significant effect of the drum rotation speed on coating uniformity in their investigated parameter space.

A reduction in the drum load was also beneficial for coating uniformity and could again be related to a better mixing behaviour

Table 4
Coefficient of variation (CV) measured by HPLC and TPI and the appropriate sample amount.

Batch no.	CV_{HPLC} (%)	CV_{TPI} (%)	Sample amount (tablets)	
			HPLC	TPI
A*	4.20	3.86	10	36
B*	3.83	4.05	10	36
C*	6.71	6.23	10	36
D	4.36	6.96	10	36
E	11.13	11.00	30	36
F	8.53	9.65	30	36
G	9.79	9.82	30	36

* HPLC data were collected from a subset of the TPI samples.

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Table 5
Factor levels, average API content, model responses CV_{HPLC} (n = 30 tablets) and CV_{TPI} (n = 10 tablets, n = 11 tablets in batch 6) and the absolute difference between CV_{HPLC} and CV_{TPI}, anf yield. [25,10].

Batch no.	loa (tablets x1000)	rpm (rpm)	spr (g/min)	dur (min)	pres (bar)	CAN content (mg/tablet)	CV_{HPLC} (%)	CV_{TPI} (%)	|ΔCV| (%-points)	Yield (%)
1	133	12	60	150	1.9	6.8	5.30	4.23	1.07	85.6
2	153	12	60	150	1.7	6.6	5.82	6.99	1.17	95.1
3	133	14	60	150	1.7	6.7	3.97	5.7	1.73	83.9
4	153	14	60	150	1.9	6.7	4.66	4.48	0.18	97.0
5	133	12	120	150	1.7	16.1	6.45	7.4	0.95	101.3
6	153	12	120	150	1.9	13.6	11.12	9.35	1.77	98.6
7	133	14	120	150	1.9	16.2	6.09	4.60	1.49	101.6
8	153	14	120	150	1.7	14.3	6.89	6.04	0.85	103.3
9	133	12	60	300	1.7	14.8	4.27	5.96	1.69	92.7
10	153	12	60	300	1.9	13.4	4.11	5.75	1.64	96.5
11	133	14	60	300	1.9	15.0	3.18	3.35	0.18	94.0
12	153	14	60	300	1.7	13.2	2.72	3.38	0.66	95.6
13	133	12	120	300	1.9	32.0	5.48	3.85	1.63	100.6
14	153	12	120	300	1.7	27.8	8.17	8.95	0.78	100.5
15	133	14	120	300	1.7	31.4	5.43	4.21	1.23	98.5
16	153	14	120	300	1.9	27.3	4.26	5.91	1.65	98.5
17	145	13	90	225	1.8	16.4	5.62	6.11	0.49	98.4
18	143	13	90	225	1.8	16.1	5.33	5.62	0.29	96.8
19	143	13	90	225	1.8	15.8	4.67	4.75	0.08	94.9

Table 6
Excluded interactions after backward regression in the HPLC and TPI model.

HPLC model	TPI model
loa × pres	rpm × dur
rpm × dur	dur × pres
spr × pres	

Table 7
Model quality of HPLC and TPI model and the appropriate requirements according to [30].

	Requirement	HPLC model	TPI model
$R^2_{adj.}$		0.966	0.935
Q^2	>0.5	0.947	0.947
$\lvert R^2 - Q^2 \rvert$	<0.2–0.3	0.019	0.012
Model validity	>0.25	0.943	0.954
Reproducibility	>0.5	0.938	0.865

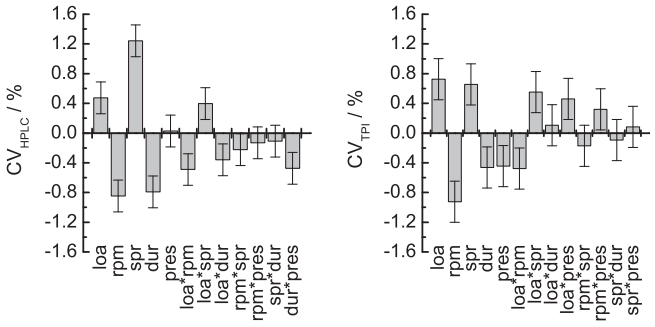

Fig. 2. Coefficient plots for the HPLC and TPI model. All included factors and interactions are displayed. The errorbars depict the confidence intervals at α = 0.05.

in the coating drum [22], a more uniform circulation time distribution [24] or a wider spray zone [21]. A contrasting effect was described by [23], who found that an underloading of the coating drum to only 67% capacity deteriorated coating uniformity. They also related this to a poor mixing behaviour. Still, they showed that an increase in drum rotation speed diminished the effect of a too low fill level.

The impact of process time on coating uniformity was further evaluated. An increase in coating time [20] and a higher amount of coating applied [17] or the dilution of the coating solution [17], which also lead to longer process times, improved coating uniformity. In contrast, [19] found an increase in CV at higher amounts of coating applied.

[22] described that the CV was reduced with the square root of the number of pan revolutions, which is the product of high drum rotation speeds and extended process times.

[21] found that smaller tablet sizes are beneficial for coating uniformity. They confirm the results by [29] who found that the time that tablets spend in the spray zone throughout a single visit is shorter with smaller tablet size.

Simulations investigating the influence of the spray pattern on the inter-tablet coating uniformity revealed that a wide spray zone is advantageous [21,22] as more tablets can receive coating at the same time. [16] showed that a low atomizing air pressure enlarges the mass variance of tablets and related this to an increase in droplet size and droplet size distribution. At higher atomizing air pressures the authors found no significant differences in the mass variance. Both, [19,20] described that a uniform spray pattern improves the inter-tablet coating uniformity.

[20] also studied the effect of inlet air flow and temperature on inter-tablet coating uniformity, but did not find any significant effects.

3.2.2. Experimental setup

A 2^{5-1} design of experiments (DoE) was performed for the active coating process at pilot scale. The centre point was conducted in triplicate. The investigated factors and factor levels are displayed in Table 2. They comprise those factors that were described as most critical in terms of coating uniformity in the aforementioned literature.

The drum rotation speed only covers a narrow range of values. The high factor level was defined as the highest technically operable level, where the tablets did not yet bounce in the coating drum. As according to literature a high drum rotation speed is advantageous for the inter-tablet uniformity, the centre point and the low level were only chosen little below the high level.

Both, spray rate and run duration were included although they are closely related to each other. This way, the impact of both factors on the inter-tablet uniformity can be investigated independently.

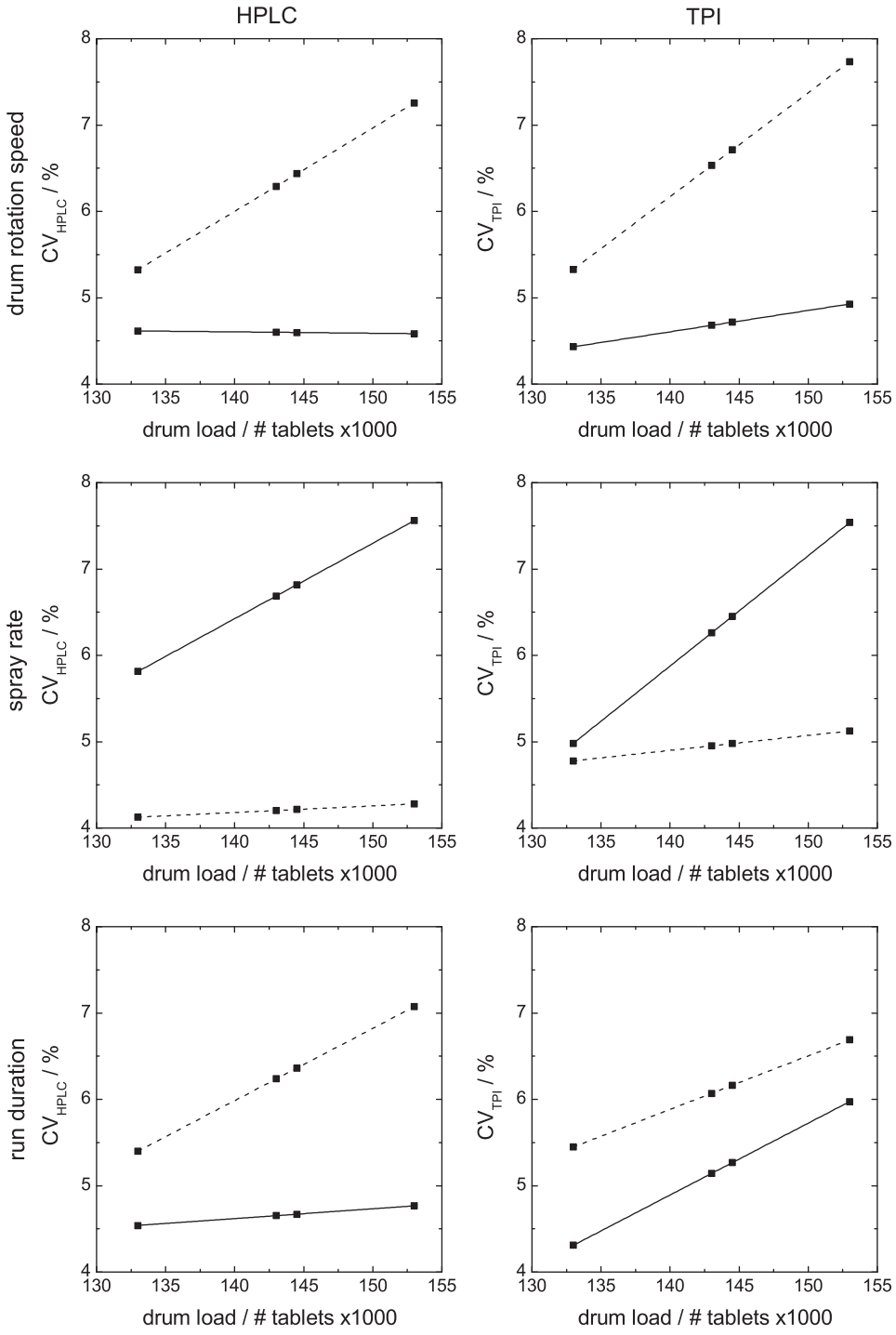

Fig. 3. Interactions of drum load with drum rotation speed, spray rate, and run duration in the HPLC (left) and TPI model (right). Dashed line: low factor level, solid line: high factor level.

Table 8
Drug dissolution of CAN after 15, 30, 45, and 60 min in 4 different DoE batches expressed as % of theoretical API content.

Batch	CAN (mg/tablet)	15 min	30 min	45 min	60 min	Conditions
16	27.7	51	78	86	89	dry
10	13.8	76	87	89	91	dry
14	27.7	58	88	96	98	wet
6	13.8	76	90	94	95	wet

With the selected factor levels the coating endpoint comprises the therapeutically meaningful CAN dose strength range of 8–32 mg/tablet.

The drum load at the low level just covered the baffles in the pan coater, such that excessive spraying onto the baffles and with this a loss of coating suspension can be avoided. For the definition of the high level, the increase in bed height due to the mass application in the coating process was considered. It was defined, such that no overloading of the drum took place at coating endpoint

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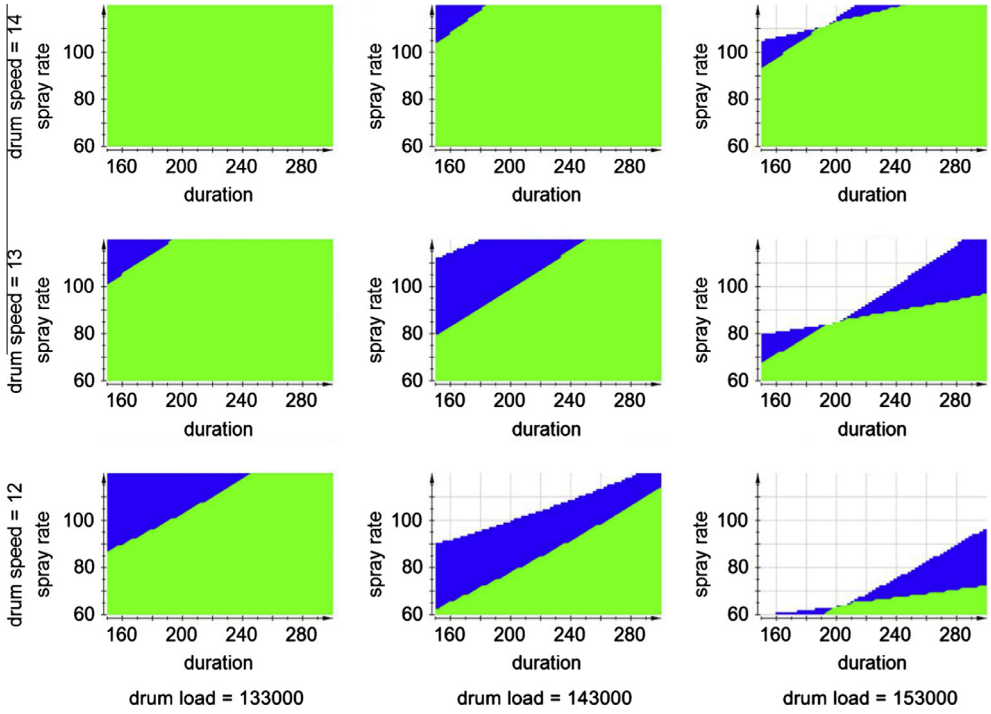

Fig. 4. Sweet spot plot of CV_{HPLC} and CV_{TPI} for a target CV ⩽ 6.25%. Green = both models meet the target CV, blue = only one model meets the target CV. Data displayed for *pres* = 1.9. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

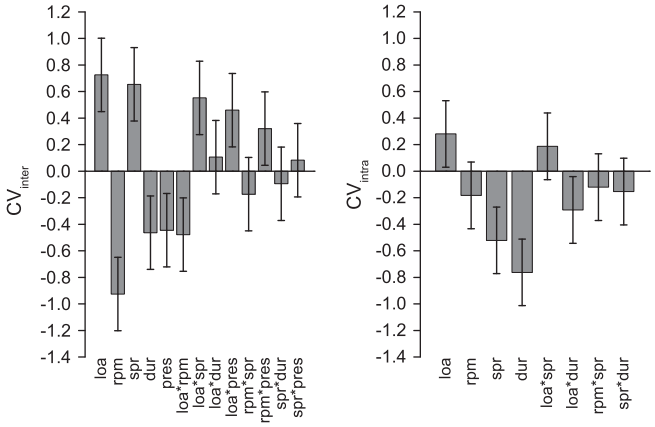

Fig. 5. Coefficient plots for the TPI model on inter-tablet coating uniformity (left) and intra-tablet coating uniformity (right), adapted from [10].

when the maximum amount of coating suspension was applied (36 kg suspension at high spray rate and run duration).

Details on the process conditions and final API content in the individual batches of the DoE are given in Table 5.

Tablet samples from the coating endpoint were subdued to TPI (10 tablets) and HPLC (30 tablets) analysis. The analyses were performed on different subsets of samples.

3.2.3. Quality of the obtained models

Table 5 gives an overview of the obtained responses (CV_{HPLC} and CV_{TPI}) in the DoE. Models were fitted to the datasets using multiple linear regression. The models were optimised by backward regression, where the insignificant interactions were excluded until no further improvement of the model was achieved (see Table 6).

Table 7 gives an overview of the model quality. Both, HPLC and TPI model show a high adjusted goodness of fit ($R^2_{adj.}$) and goodness of prediction (Q^2) as well as a high model validity and reproducibility according to the criteria specified by [30]. In both models, different interactions (except *rpm* × *dur*) had to be excluded in the backward regression step to guarantee the best model for each analytical method.

3.2.4. Critical process parameters

The range of CV measured by HPLC and TPI was 2.72–11.12% and 3.35–9.35%, respectively. CV_{HPLC} and CV_{TPI} show a discrepancy of up to 1.77%-points in some batches. This can be explained by the fact that both analytical methods were not performed on the same subset of tablets. Furthermore, only 10 tablets were subdued to TPI analysis on the basis of limited measurement times while 30 tablets were used for HPLC analysis.

Both models reveal that a high drum load (*loa*), a low drum rotation speed (*rpm*), a high spray rate (*spr*) and a short run duration (*dur*) deteriorate the inter-tablet uniformity in the investigated parameter space and were thus identified as CPP (Fig. 2). The extent to which the parameters impact on the CV is different in the two models. While *spr* and *rpm* have the highest effect on CV_{HPLC}, *loa* and *rpm* have the highest effect on CV_{TPI}. A high spray pressure was beneficial for the CV according to the TPI model whereas in the HPLC model no significant effect was observed.

The impact of *loa*, *rpm*, *spr* and *dur* on the inter-tablet uniformity is consistent with the previously described literature. Differences in the extent of the effect in the two models on the CV might be due to the differences in the CV measured by the two techniques. Possibly, a higher amount of samples in TPI (only 10 tablets per batch were measured) could harmonise the CVs and with this the DoE models.

Both, HPLC and TPI model revealed that the drum load was subject to interactions (Fig. 3). High drum rotation speeds compensated the negative effect of the drum load on the CV. This result confirms the work of [23] who found that an increase in drum rotation speed diminished the effect of the fill level due to the improved axial mixing in the coating drum in their DEM simulations.

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Additionally, the HPLC and TPI model showed that a low spray rate can reduce the negative effect of a high drum load, as well. The HPLC model also revealed that longer run durations can compensate high drum loads while TPI could not confirm this result. The interaction of drum load and spray pressure (*pres*) that was investigated in the TPI model was excluded from the HPLC model and could therefore not be detected.

Only in the TPI model, a significant influence of *pres* on the CV was observed. The HPLC model showed no effect of *pres* on the inter-tablet coating uniformity. This is consistent with [16]. In their study, *pres* had no effect on the inter-tablet coating uniformity with the exception of a very low spray pressure of 0.5 bar. The discrepancies between CV_{HPLC} and CV_{TPI} in some batches could again be the reason for the different effects of *pres* in the two models.

The drug dissolution of CAN from the active coating layer was not influenced by the applied coating parameters. Dissolution data were compared for two different dose strengths of CAN: 27.7 mg/tablet (batches 16 and 14) and 13.8 mg/tablet (batches 10 and 6). The batches differed in the applied coating parameters in that batches 14 and 6 were processed at very humid conditions in the pan coater. A high drug load, low drum rotation speed and high spray rate were applied, leading to poor mixing and local overwetting of the tablet cores (tablets sticking to the coater walls). In contrast, batches 16 and 10 were processed at relatively dry process conditions and no signs of overwetting were found during the process. No difference in dissolution of CAN was observed between tablets that were produced at dry or wet process conditions (cf. Table 8). The tablets with 27.7 mg/tablet CAN load in the active coating show a slower increase in drug dissolution, which can be explained by the thicker active coating layer, which needs more time to dissolve compared to the thin layer at 13.8 mg/tablet CAN load.

Furthermore no significant impact of the active coating layer on the drug dissolution of NIF from the tablet core was observed. The uncoated and active coated GITS showed a drug release of 63% and 60% NIF after 12 h, respectively.

According to the test on uniformity of dosage units, a $CV \leqslant 6.25\%$ is sufficient to meet an $AV \leqslant 15$ ($n = 10$ dosage units, $98.5\% \leqslant \overline{X} \leqslant 101.5\%$). An acceptable parameter range to meet the $CV \leqslant 6.25\%$ in the investigated coating process at pilot scale can be derived from the design of experiments. This range is illustrated in Fig. 4 in the form of a sweet spot plot. Herein, the green areas indicate the parameter region within which both, HPLC and TPI model predict a $CV \leqslant 6.25\%$, while in blue areas, only one of the two models predicts a $CV \leqslant 6.25\%$. Depending on the target CAN content of the batch, which is the result of the factor combination of *spr*, *dur* and *loa*, feasible factor combinations for a target of $CV \leqslant 6.25\%$ can be deviated from the sweet spot plot. It is obvious that, in the case of a low drum load and high drum speed a $CV \leqslant 6.25\%$ is yielded for all combinations of spray rate and run duration within the investigated parameter space (upper left plot in Fig. 4). A range of target CAN content between 8–32 mg/tablet can be covered within that range.

The same dataset was analysed regarding the intra-tablet coating uniformity by [10]. Similar to the critical process parameters for inter-tablet uniformity, the authors described that a low drum load, high drum rotation speed and long run duration are beneficial for intra-tablet uniformity, reducing the variability in film thickness on the individual tablet faces (cf. Fig. 5). But while a low spray rate was beneficial for inter-tablet uniformity, the low spray rate led to a higher intra-tablet coating variability. The authors assumed that the negative effect on intra-tablet uniformity was due to the lower humidity of the coating that could not spread well over the tablet surface during the coating process, leading to a less uniform coating layer. For further details on critical process parameters for intra-tablet uniformity the reader is referred to [10].

4. Conclusion

This study described the use of TPI as a tool to evaluate critical process parameters for inter-tablet coating uniformity in an active coating process.

A high correlation of API content and layer thickness was found not only over a broad range of values (as shown previously [5]) but also within a narrow range of values. Accordingly, the CV_{HPLC} and CV_{TPI} corresponded in most batches.

In the DoE, the TPI model identified the same CPP as the HPLC model, only the magnitude of the effects was different.

A low drum load, a high drum rotation speed, a low spray rate, and a high run duration was beneficial for the inter-tablet coating uniformity. These findings are in agreement with the results in previously published literature. An interaction of drum load and drum rotation speed as described by Dubey et al. [23] could be confirmed, as well. Additionally, the models showed that the negative impact of high drum loads on the inter-tablet uniformity cannot only be compensated by high drum rotation speeds, but also by reduced spray rates and prolonged run durations. On the basis of the two DoE models, a parameter range within which a $CV \leqslant 6.25\%$ is reached could be described. In the case of a high drum speed and a low drum load, all factor combinations of spray rate and run duration within the investigated parameter range yielded a $CV \leqslant 6.25\%$, which is a satisfactory high coating uniformity with respect to the test on uniformity of dosage units (given that the average API content is within 98.5% and 101.5% of label claim).

Overall, TPI is a useful and nondestructive alternative in the evaluation of inter-tablet coating uniformity. The developed models are solely based on layer thickness data of the tablet faces. This is advantageous in terms of the measurement procedure. The measured area on the tablet surface can be restricted to only a limited radius on the tablet faces, which speeds up the measurements significantly and makes TPI a quick analysis tool. Due to its nondestructive nature, further quality control tests can be performed on the same tablets after the TPI measurements, *e.g.* dissolution tests. In comparison to NIR methods TPI has the advantage of higher measurement speed and not requiring any chemometric models to correlate between a spectral response and the coating thickness given that it directly measures the layer thickness while in comparison to weight gain measurements it has the clear advantage of its results being independent of any variation in the tablet core matrix. The current limitations of the TPI method have been discussed previously in [25]. In addition to the factors discussed in this paper the relative immaturity of the technology with the associated costs and stability limitations need to be taken into consideration.

With regards to a potential future implementation of the TPI technology as in-line tool, our results clearly support the idea of using TPI beyond a use of simple endpoint determination of the coating process, but also for a nondestructive in-line evaluation of inter-tablet coating uniformity as previously demonstrated [4]. The fact that the tablet faces of most typical geometries align with the coating pan mesh will lead to similar data during the coating process as discussed in this study. This will make it possible to resolve inter-tablet inhomogeneities during the coating operation and use this real-time information to better control the process in oder to minimise such undesired variation.

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Appendix A. Abbreviations

API = active pharmaceutical ingredient
AV = acceptance value
CAN = candesartan cilexetil
CPP = critical process parameters
CV = coefficient of variation
DEM = discrete element method
DoE = design of experiments
dur = run duration
GITS = gastro intestinal therapeutic system
HPLC = high performance liquid chromatography
loa = drum load
NIF = nifedipine
NIR = near infrared
OROS = osmotic release oral system
pres = spray pressure
RMSE = root mean square error
ROI = region of interest
rpm = rounds per minute/drum rotation speed
RSD = relative standard deviation
spr = spray rate
TPI = Terahertz Pulsed Imaging

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