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Optimization of an industrial scale low-dose dosator capsule filling process for inhalation products

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"It is a profound and necessary truth that the deep things in science are not found because they are useful; they are found because it was possible to find them."

J. Robert Oppenheimer

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Abstract

Capsule filling is widely applied in the pharmaceutical industry. Precise dose filling in the lower mg-range, which is required for inhalation therapies, is essential for the successful manufacturing of high-quality products. One of the greatest challenges for effectively developing low-dose inhalation products is dose uniformity. Although several studies have reported that many powder and processing parameters affect the quality of filled capsules, little research has been performed with regard to low-dose dosator capsule filling processes. Up to now, the main challenge is the powder layer inhomogeneity of very fine powders with low density particles, i.e., particle sizes smaller than 10 µm, exhibiting poor flowability and high cohesivity. Currently, no systematic understanding exists of how the evolution of the powder layer during the capsule filling process contributes to critical quality attributes such as the fill weight and the weight variability.

The goal of this thesis is to analyze and optimize the dosing process with different experimental approaches to gain an advanced process understanding and enhance the filling performance, thus reduce fill weight variability of low doses (1-50mg). We mainly focused on three grades of lactose excipients, but also studied carrier-based DPI products (formulated as dry powders of API in the presence of excipient particles – the carrier) and various silicified microcrystalline cellulose excipients. The three lactose excipients were extensively characterized and filled into hard gelatin size 3 capsules using two different capsule filling modes, i.e. dynamic and static mode tests. Dynamic tests refer to filling of capsules in a regular lab-scale, low-dose dosator capsule filling machine (Labby, MG2, Bologna) with special low-dose equipment adaptations. Static tests were conducted using a novel filling system developed by us. The influence of the gap at the bottom of the powder container and the effect of mechanical vibrations on the quality of filled capsules were assessed.

In dynamic mode trials, the layer uniformity, the fill weight and the weight variability strongly depend on the powder characteristics and the instrumental settings. When filling powder mixtures (i.e., an adhesive powder blend containing an API) we found two distinct performance indicating properties of carrier and API in terms of capsule filling and in vitro aerosolization performance for the investigated system, i.e. carrier surface properties for capsule filling and API properties for in vitro aerosolization.

The findings of the static mode trials suggest that for low-dose dosator capsule filling it is strongly recommended to continuously control instrumental settings, i.e., gap between the lowest point of the dosator and the bottom of the box, as well as mechanical vibrations that clearly affect the fill weight and weight variability.

Based on the generated data where the powder layer inhomogeneity was found to be one of the main challenges, at a later stage the focus was on the latter to optimize the filling process. The most promising process analytical technology (PAT) analyzer capable to continuously measure the layer uniformity of the powder bed was evaluated for its applicability for a capsule filling process. A novel approach to quantify density variations in a moving powder bed by means of terahertz technology was developed, and the sensitivity of the method was assessed. Relative densities predicted from terahertz reflection measurements were correlated to off-line weight measurements (i.e. collected filled capsules). In all cases predicted relative densities were in good agreement with the respective fill weight of filled capsules. The results demonstrate that it is feasible to analyze powder density variations in a rotating container by means of terahertz reflection measurements and to predict the fill weight of collected capsules, a further step towards capsule filling process optimization.

Kurzfassung

In der pharmazeutischen Industrie ist das Befüllen von Kapseln eine weit verbreitete Methode. Die genaue und zuverlässige Dosierung von Dosen im unteren mg-Bereich (1-50mg) ist eine der größten Herausforderungen für eine erfolgreiche Produktentwicklung. In der Literatur berichten zwar mehrerer Studien vom Einfluss verschiedener Pulver- und Prozessparameter auf die Qualität gefüllter Kapseln, jedoch ist in Bezug auf das genaue und zuverlässige Dosieren von kleinsten Dosen in Kapseln wenig bekannt. Kürzlich durchgeführte Studien zeigen, dass für das Befüllen geringer Dosen die Pulverbettinhomogenität eine große Herausforderung darstellt, vor allem wenn sehr feinkörnigen Materialien mit geringen Dichten einzelner Partikel, das heißt Materialien mit einer Partikelgröße unter 10 µm welche schlechte Fließfähigkeiten und hohe Kohäsionskräfte aufweisen verwendet werden. Gegenwärtig gibt es jedoch kein systematisches Verständnis darüber, wie sich diese Pulverbettinhomogenität und deren Veränderung während des Prozesses auf die kritischen Qualitätsattribute von gefüllten Kapseln auswirken.

Das Ziel dieser Arbeit ist es, den Dosierprozess mit verschiedenen experimentellen Methoden zu analysieren und zu optimieren. Auf diese Weise sollen Füllgewichtsschankungen von Kapseln gefüllt mit sehr niedrigen Dosen (1-50 mg) reduziert werden. Hierzu konzentrierten wir uns auf hauptsächlich auf drei Klassen von Laktose Hilfsstoffen, untersuchten aber auch Pulvermischungen von Wirkstoffpartikeln auf grobkörnigem Trägermaterial welche häufig im Inhalationsbereich verwendet werden, und zusätzlich verkieselte mikrokristalline Cellulose Hilfsstoffe. Die drei Laktose Hilfsstoffe wurden umfangreich charakterisiert und in Hartgelatinekapseln auf zwei unterschiedliche Arten gefüllt, im dynamischen und statischen Modus. Für den dynamischen Modus wurde ein herkömmliches Labormaßstab-Kapselfüllgerät mit speziellen Ausrüstungsanpassungen für das Dosieren kleiner Mengen (Labby, MG2, Bologna) verwendet. Statische Tests wurden mit einem neuartigen Füllsystem durchgeführt, welches von uns selber entwickelt wurde.

In dynamischen Testversuchen hängen die Pulverbetthomogenität, das Füllgewicht und die Füllgewichtsschankung stark von den Pulvereigenschaften und den instrumentellen Einstellungen ab. Weiters stellten wir fest, dass beim Befüllen von Pulvermischungen in Kapseln der Füllprozess hauptsächlich durch die Eigenschaften des Trägermaterials beeinflusst wird, wohingegen die Inhalationsperformance von den Wirkstoffpartikeleigenschaften bestimmt wird.

Die Ergebnisse der statischen Testversuche verdeutlichen, dass für das Befüllen von Kapseln mit sehr niedrigen Dosen eine kontinuierliche Kontrolle der instrumentellen Einstellungen notwendig ist. Hierzu zählen Faktoren wie der Abstand zwischen dem tiefsten Punkt des Dosators und dem Behälterboden, sowie auftretende mechanische Vibrationen, welche sich eindeutig auf das Füllgewicht und Füllgewichtsschankungen auswirken.

Basierend auf den generierten Daten, bei denen die Pulverbettinhomogenität als kritischer Faktor festgestellt wurde, lag der Fokus zu einem späteren Zeitpunkt darauf den Prozess diesbezüglich zu optimieren. Die vielversprechendste prozessanalytische Technology (PAT) Methode welche in der Lage ist die Pulverbettinhomogenität kontinuierlich zu messen wurde auf ihre Anwendbarkeit für den Kapselfüllprozess bewertet. Ein neuartiger Ansatz zur Quantifizierung von Dichtevariationen in einem sich bewegenden Behälter mittels Terahertz Technology wurde entwickelt und die Sensitivität der Methode beurteilt. Relative Dichten, welche von den Terahertz-Reflexionsmessungen vorhergesagt wurden, korrelierten sehr stark mit off-line Gewichtsmessungen (gesammelte gefüllte Kapseln). Mit unserer entwickelten Methode ist es möglich Pulverdichtevariationen in einem rotierenden Behälter mittels Terahertz-Reflexionsmessungen vorherzusagen, ein weiterer Schritt in Richtung Optimierung eines Kapselfüllprozesses.

Contents

Contents

Abbreviations

Abbreviation	Meaning
AE	aerated energy
AIF	angle of internal friction
AOR	angle of repose
API	active pharmaceutical ingredient
AR	aeration ratio
BD	bulk density
BET	Brunauer, Emmett, and Teller
BFE	basic flowability energy
BJH	Barrett, Joyner, and Halenda
BR EMA	Bruggeman effective medium approximation
C	cohesion
CMA	critical material attribute
CI	Carr's index
COPD	chronic obstructive pulmonary disease
CP	compression
CPH	capsules per hour (filling speed)
CPP	critical process parameter
CQA	critical quality attribute (capsule fill weight and weight variability)
QbD	Quality by Design
QTPP	quality target product profile
DCL	dosing chamber length
DIA	dosator diameter
DOE	design of experiments
DPI	dry powder inhalation
DS	design space
DSC	Differential scanning calorimetry
ED	emitted dose
Eq	equation

EQPC	circle of equal projection area
FDA	Food and Drug Administration
FEA	finite element analysis
FFc	flow function coefficient
FPD	fine particle dose
FPF	fine particle fraction
HDPE	high-density polyethylene
HPLC	High Performance Liquid chromatography
HPMC	hydroxypropyl methylcellulose
HR	Hausner ratio
Hz	Hertz
ICH	International Conference on Harmonisation
JMSS	jet-milled salbutamol sulphate
kPa	kilopascal
LAC_E	lactose engineered
LAC_R	lactose raw material
LD	low density
LH	Lactohale
MDIs	non-pressurised metered dose inhalers
MMAD	mass median aerodynamic diameter
NGI	next generation impactor
NIRS	near-infrared spectroscopy
OCT	Optical coherence tomography
PAT	process analytical technology
PBH	powder bed height
PD	air pressure drop
PM	air permeability
pMDIs	pressurized metered dose inhalers
PSD	particle size distribution
RH	relative humidity
RI	refractive index

RSD	relative standard deviation (weight variability)
SDSS	spray dried salbutamol sulphate
SEM	scanning-electron microscopy
SMCC	silicified microcrystalline cellulose
SS	salbutamol sulphate
SSA	specific surface area
SWAXS	small and wide angle X-ray scattering
TD	tapped density
THz	terahertz
THz-TDS	terahertz time-domain spectroscopy
TPI	terahertz pulsed imaging
USP	United States Pharmacopeia
VMD	volumetric mean diameter
XμCT	X-ray computed microtomography

1. Introduction and motivation

For many years there has been growing interest in delivering medicinal products through the lung. This mode of drug delivery ensures rapid onset, allows local and systemic mode of action, circumvents the first-pass effect and enables delivery also of large molecules. In particular, in the past few years, the lung has emerged as an alternative route for the systemic delivery of peptides, proteins, anti-viral vaccines and drugs requiring fast onset of action (Hoppentocht et al., 2014). Different delivery technologies exist. Dry Powder Inhaler (DPI) devices that utilize capsules as a dose-holding system are the most rapidly-expanding field in pulmonary drug delivery (Islam and Gladki, 2008). However, filling inhalation powders into capsules often requires specialized equipment that can handle the very low fill weight (Edwards, 2010) in the range of a few tens of milligrams. For the currently available low-dose capsule filling systems, the dosator method is often used (Faulhammer et al., 2014b).

One of the biggest problems in the manufacturing of high-quality low-dose inhalation products is dose uniformity (Islam and Cleary, 2012). Although there is a considerable body of literature on identifying and assessing critical material and process parameters that affect the product quality for standard doses (Tan and Newton, 1990a; S. B. Tan and Newton, 1990b; Patel and Podczeck, 1996; Podczeck and Newton, 1999; Podczeck and Newton, 2000; Heda et al., 2002; Nalluri et al., 2013; Osorio and Muzzio, 2013; Llusa et al., 2013; Llusa et al., 2014a; Faulhammer et al., 2015; Faulhammer et al., 2015b; Moolchandani et al., 2015; Moolchandani et al., 2016; Loidolt et al., 2017; Wagner et al., 2018;), little attention has been paid to low-dose dosator capsule filling processes. For the latter there are still some obstacles to be overcome, in particular the filling of very fine powders poses a major challenge (Faulhammer et al., 2014b).

In the scope of this thesis, a low-dose dosator nozzle capsule filling process was investigated using three grades of lactose excipients (Lactohale 100, Lactohale 200, Lactohale 220) that are commonly applied as carriers in inhalation therapies (Kou et al., 2012a), carrier-based DPI products (formulated as dry powders of API in the presence of excipient particles – the carrier) and various silicified microcrystalline cellulose excipients (Prosolv® SMCC 50, Prosolv® SMCC 50 LD, Prosolv® SMCC 90). The applied experimental approaches are not only relevant for a low-dose capsule filling process, but also for other pharmaceutical unit operations like e.g. standard capsule filling as well as tableting.

The gained knowledge of the effects of various process parameters on the capsule filling efficiency may improve current filling systems, the product quality of low-dose capsules for inhalation and, ultimately, patients' health.

For improving existing capsule filling solutions, considering in particular a lab-scale capsule filler (Labby, MG2, Italy) and an industrial scale capsule filler (Planeta 100 MG2, Italy), and gain deeper knowledge about the processability of excipient powders and carrier-based DPI formulations, the following scientific approaches were applied:

(1) Characterization of excipient powders using standardized methods (such as particle size, bulk powder density and FT4 powder rheometer measurements) and advanced measurement techniques to assess the powder's flowability in detail. For the latter a dynamic test method (the avalanching test method) was applied, via which the flowabilty of powders can be assessed by measuring their avalanching behavior related to cohesivity and flowability (Kaye, 1997). This knowledge about powder properties and how they can be translated to downstream processing were investigated through accurate filling studies with different combinations of capsule filing settings. In the present study the focus was put on the condition of the powder layer, i.e. powder bulk density as well as visible or hidden channels, holes, compacted, loosened, or segregated areas within the powder mass, which is known as critical factor affecting the quality of filled capsules in terms of fill weight and weight variability.

(2) Decoupling and comparison of the filling process in dynamic and static tests to identify possible emerging critical process parameters. Moreover, the filling performance from the static tests carried out with the in-house developed stand-alone test tool, are used as experimental input data for simulation studies of the dosator dipping step. For details about the respective DEM simulations and developed simulation model we refer to the previously published work (Loidolt et al., 2017a) and book chapter (Loidolt et al., 2018). The in-house developed novel test tool used for static tests is beneficial for executing pre-tests for optimal process settings of new powders (or powder mixtures) with a limited amount of powders. More precisely, it could help formulation and process developers to rapidly screen the required process parameters based on the specific properties of the powders used. From industrial perspective, this tool will support manufacturer's clients in selecting optimal process parameters for their products. Moreover, it can be used to test new dosators or industrial scale dosators to facilitate a rapid scale-up of the process.

(3) Monitoring the state and changes of the powder conditions inside the rotary container in terms of layer uniformity using Process Analytical Technology (PAT) analyzers. The identified technology, i.e. the terahertz technology, is capable of measuring powder density variations in a rotating container from which the dosator collects the powder. In general, the implementation of a process analyzer in capsule filling processes could significantly reduce the fill weight variability of filled capsules. The powder bed density at the position where the dosator collects the powder could be measured by placing the terahertz probe at the respective position. The knowledge about the state of the powder bed throughout the process will help in designing production machines, e.g. introduction of tools to stabilize the powder bed condition, which are capable to maintain a constant powder bed density and thus reduce process induced variability of final products.

(4) Study the interplay between particle engineering, particle properties, their downstream processability and aerodynamic performance of carrier-based DPI products. This specific knowledge base will help in the pre-selecting of suitable API carrier combinations, in terms of their engineering routes and downstream process parameters based on particle characteristics.

Overall, the findings of all these approaches contributed/will contribute in several ways to expanding the understanding of downstream processability of powers and required capsule filler settings along with special adaptations. Moreover, the studies raised the awareness on the urgency of process analyzers capable of continuously monitoring the powder bed conditions. The suggested optimization strategies tested at lab-scale can be translated to industrial scale capsule fillers to improve current filling systems, the product quality of low-dose capsules and, ultimately, patients' health.

1.1 Granular materials

Granular materials, described as discrete solid, macroscopic particles (Holdich, 2002), are ubiquitous in our daily lives and in industrial applications (Lumay et al., 2012). Handling granular materials, including powders, plays a crucial role in many industries (such as pharmaceutics, agriculture, food and cosmetic production, mining, catalysis technology, chemical processing and environment) and modern technologies (such as additive manufacturing). In fact, most of the raw materials used for manufacturing end products are granular materials, whose handling (e.g. transporting, conveying, storing, dosing) is known to be challenging due to their application-dependent performance and their material attributes that hinder an establishment of general constitutive equations relating shear rates and stresses (Schulze, 2007; Stiess, 2008; Duran, 2012).

Granular materials, and in particular powders, are considered to be two-phase systems consisting of a dispersed phase of solids of various sizes and gas as the continuous phase. Consequently, the behavior of powder materials depends on the properties of the particle as an individual entity, the properties of an assembly of particles, and the interactions between those assemblies and the continuous phase (Ortega-Rivas, 2009). Compared to liquids and gasses, the understanding of the granular state properties is poor. In fact, a granular material is a complex system which exhibits non-trivial transitions between the static, the quasi-static and the dynamical states. The motion and jamming of grains inside a pile are mainly influence by steric repulsions (related to the geometry of the particles), friction forces (influences by surface properties and the chemical nature of the grains) and cohesive forces (related to liquid bridges, electric charges, van der Waals interactions and magnetic dipole-dipole interactions). Any progress in the understanding of the granular material behaviors is highly relevant for the industry, in particular during the development or the optimization of an industrial process (Lumay et al., 2012). Regarding powder properties relevant in capsule filling processes, most of the literature is focused on the effect of powder flowability on fill weight variability (S B Tan and Newton, 1990a; S B Tan and Newton, 1990b; Patel and Podczeck, 1996). However, flowability was also suggested to affect fill weight (Patel and Podczeck, 1996). Moreover, Eskandar et al. (2011) reported that successful and accurate dosing of low powder masses <10 mg is considered to be challenging due to the limitations of current powder volumetric dosing technologies that rely on powder's having a "good" flowability (Eskandar et al., 2011).

It is well known that many factors affect the flowabilty of any given powder. This includes surface properties, shape and size distribution on the one hand and the geometry of the physical system on the other. Thus it is obvious that one general theory can hardly be applicable to all powders and all possible conditions that may develop in practice (Peleg, 1977). For example, in a dosator nozzle capsule filling process powders must have good flowabilty and be non-adhesive yet compressible enough to form plugs (Loidolt et al., 2018). However, since during a dosator capsule filling process the powder blend rotates in a powder container, a good flowabilty does not necessarily guarantee a good filling performance. Segregation can occur over longer processing time. This segregation tendency may be a result of differences in powder density, particle mobility induced by the different shapes of particles and, above all, the particle size (Cullen, 2009). In contrast, for highly compressible powders, jamming and blocking of the piston has to be considered critical (Tan and Newton, 1990c).

In fact, it is thus evident to extensively characterize the powder properties, and relate them to the respective filling performance, to use it as a knowledge basis for required instrumental adaptations of current filling solutions. This enhanced understanding of processability of different powder groups, in our case on a dosator nozzle system, will help to optimize current filling systems and ultimately high quality end products. In general terms, powder's characteristics needs to be translated into needed instrumental settings required to successfully produce capsules with a constant fill weight and low weight variability to achieve product-specification compliance.

1.2 Dry powder filling of hard capsules

Capsule filling is widely applied in the pharmaceutical industry. Capsule filling machines can be classified as manually, semi-automatic and fully automated. Furthermore, as shown in Figure 1, the semi- and fully automated systems can be categorized due to their filling principle in direct and indirect machines. In the former principle the machines use the capsule body to directly measure the dose, which is filled as a loose mass. The auger filling mechanism, a direct filling system, uses a hopper with a built in auger which is filled with powder. Capsules are placed on a rotating plate at the outlet of the hopper, which are then filled with powder due to the motion the auger. Another technique in this category is vibration-assisted filling. The powder is filled in a container with an oscillating sieve at the bottom, thus the powder percolates through the sieve

and is filled into the capsule which is placed below the container. Indirect filling can be done with a dosator nozzle system, a tamp filler, a vacuum drum filler or a vacuum dosator. The tamping principle uses tamping pins to sequentially compress little amounts of a powder bed into dosing bores to form a powder plug which is subsequently filled into the capsule. The vacuum drum filling principle, which applies vacuum to take up powder into the cavity of a dosator and subsequently fill it into the capsule, and the dosator system belong also to the indirect filling category, and are preferentially used for low-dose capsule filling (Podczeck and Jones, 2004). The indirect method of capsule filling is used in the vast majority of commercial filling operations, with the two principle methods for making a plug, the dosing disks and the dosator method (Hoag, 2016). The work of Lightfoot (2017) reviews the history of capsule filling which started in the United States around 1900, and provides a detailed discussion of capsule filling machines.
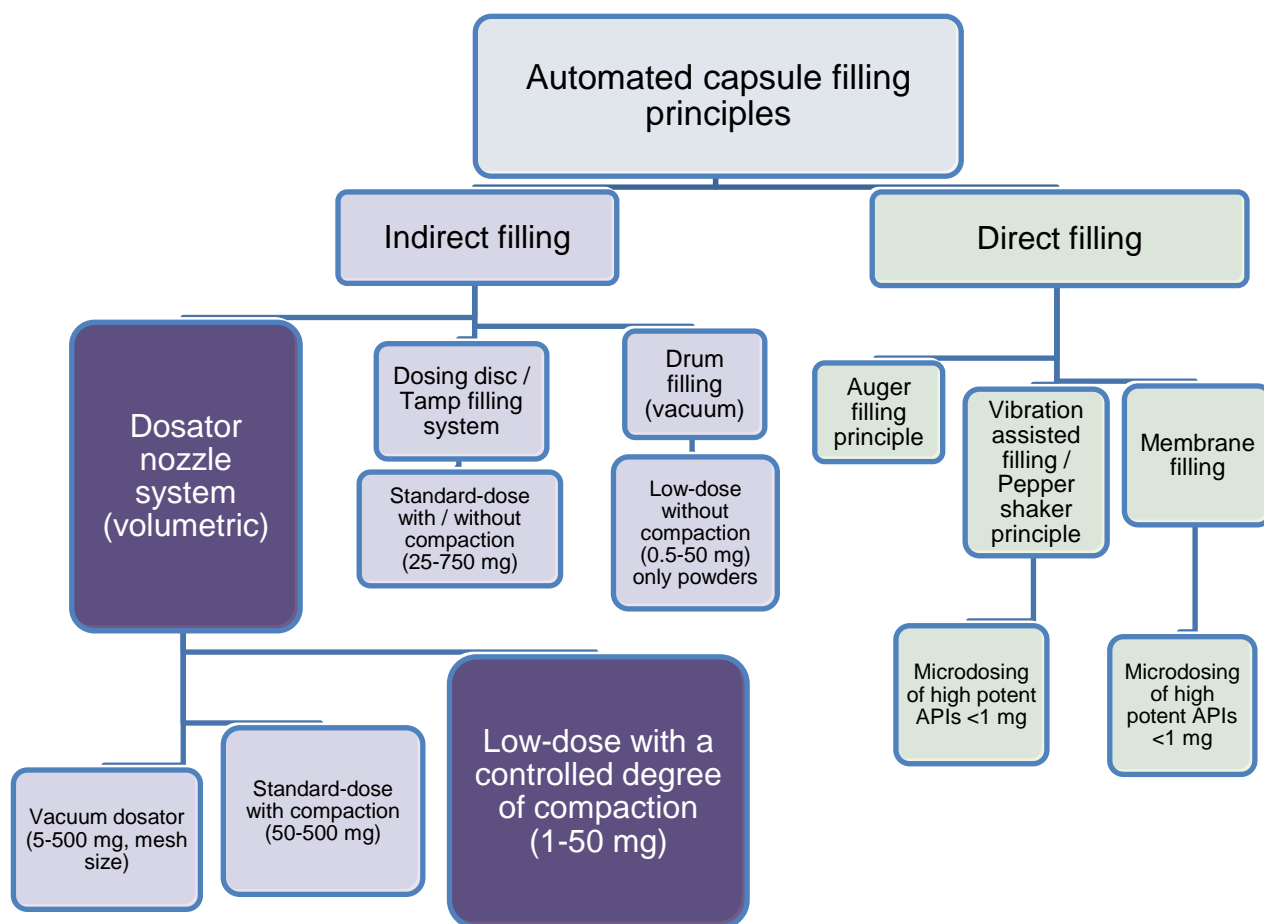

Figure 1: Overview of automated capsule filling principles

Data from several sources have identified and assessed material and process parameters affecting the quality of filled capsules for standard doses (Tan and Newton, 1990a; S. B. Tan and Newton, 1990b; Patel and Podczeck, 1996; Podczeck and Newton, 1999; Podczeck and Newton, 2000; Heda et al., 2002; Nalluri et al., 2013; Osorio and Muzzio, 2013; Llusa et al., 2013; Llusa et al., 2014a; Faulhammer et al., 2015; Faulhammer et al., 2015b; Moolchandani et al., 2015; Moolchandani et al., 2016; Loidolt et al., 2017; Wagner et al., 2018).

For example, a series of studies investigated in detail the material and process parameters of a dosator nozzle machine affecting the critical quality attributes of filled capsules, i.e. fill weight and weight variability. The effects of mechanical vibrations (Llusa et al., 2013), the compressibility of powders (Llusa et al., 2014a), the impact of particle modification (Faulhammer et al., 2015b), to name a few, were evaluated and translated into the capsule filling performance.

More recently, Moolchandani et al. (2016) studied the relationship between the physicochemical and mechanical properties of lactose that could affect product formulation and processing end performance of a dosing disc capsule filling machine. In particular, the effects of drug load and change in machine operating variables on formulations derived from different lactose types were evaluated in terms of resulting plug characteristics and their capsules. It was found that both formulation and machine operating variables had major impacts on the physical, mechanical and drug release rate properties of the capsules prepared.

A recent study by Loidolt et al. (2017) investigated the filling of a dosator nozzle when dipping into a powder bed using the Discrete Element Method (DEM). Basically, this method offers the opportunity to freely modify powder properties and to observe quantities that are not measurable experimentally, making it a great complementary tool to experiments. This study was the first attempt of a mechanistic modeling of the dosator filling process. The main findings relevant for our purpose are summarized and discussed in section 1.3.

Since the pharmaceutical industry is moving from batch towards continuous processing (Davies et al., 2005; Buchholz, 2010; Poechlauer et al., 2012), the recently published work by Wagner et al. (2018) suggests a process model for controlling a continuous capsule filling process, a next step towards predicting the optimal processing conditions for a new capsule filling task.

1.2.1   Low-dose dosator nozzle technique

Capsule filling by nozzle dosators has been broadly investigated (Jones, 2001; Podczeck and Jones, 2004; Llusa et al., 2013; Llusa et al., 2014a; Faulhammer et al., 2014b; Faulhammer et al., 2015; Faulhammer et al., 2015b; Loidolt et al., 2017) and is an important technology applied in the pharmaceutical industry today. Especially in DPI (Dry powder inhaler) filling the dosator principle plays an important role, as the doses need a controlled degree of compaction, to ensure that the DPI can reliably turn the plug back into a powder for efficient dose delivery (Faulhammer et al., 2014b).

Precise dose filling in the lower mg-range, which is required for inhalation therapies (Edwards, 2010), is essential for the successful manufacturing of high-quality products. In addition, the final product, i.e. capsule-based dry powder inhalation therapy (DPI) system, has to provide effective mono-dose packing of the inhalation formulation, secure the release from the capsules through ease of opening in the device (e.g. piercing, shearing) and the complete ejection of the fine particles from the capsules (Stegemann et al., 2018). Several low-dose capsule filling systems are currently available. The work of Edwards (2010) provides an excellent overview of applications of capsule dosing techniques for use in dry powder inhalers. As stated above, the dosator principle with its ability to fill powder with a controlled degree of compaction to ensure that for efficient dose delivery the plug can be turned back into a loose powder plays an important role in DPI product filling. In the following, the dosator nozzle technique is described in more detail, because it is the filling principle, which was used in the experimental part of this thesis.

Figure 2 depicts the multiple steps of a continuous dosator nozzle machine. Here, the powder is fed from a powder hopper into a rotating powder container. The dosator nozzles (1 in lab-scale machines; 2-32 in industrial scale machines) are fixed in a turret which has a smaller diameter than the rotary container and is slightly off-center, whereas both rotate in the same direction. At first, the dosator nozzle moves into the powder bed and collects the desired volume of powder from the powder layer out of a rotating container. This volume is determined by a spring inside the nozzle, which pushes the piston up until the dosing chamber is reached. For inhalation products, the capsules are filled with a controlled degree of compaction or even without compaction (Figure 2, step 4b), to ensure that the plug is turned back into a powder for efficient drug delivery. After collecting the powder, the nozzle and piston are first withdrawn from the powder bed, then move through a cleaning unit (Figure 2, step 8), and finally the plug is placed

into the body of the capsule. Due to the dosing principle, the powder has to be retained in the dosing chamber, while this section is in motion. Thus, for the retention of the powder in the nozzle during transfer, the powder must be able to form an arch. If no compaction is applied and no plug is formed the transfer step is very critical. Moreover the adhesion of the powders plays an important role (Podczeck and Jones, 2004; Faulhammer et al., 2014b; Hoag, 2016; Loidolt et al., 2018).
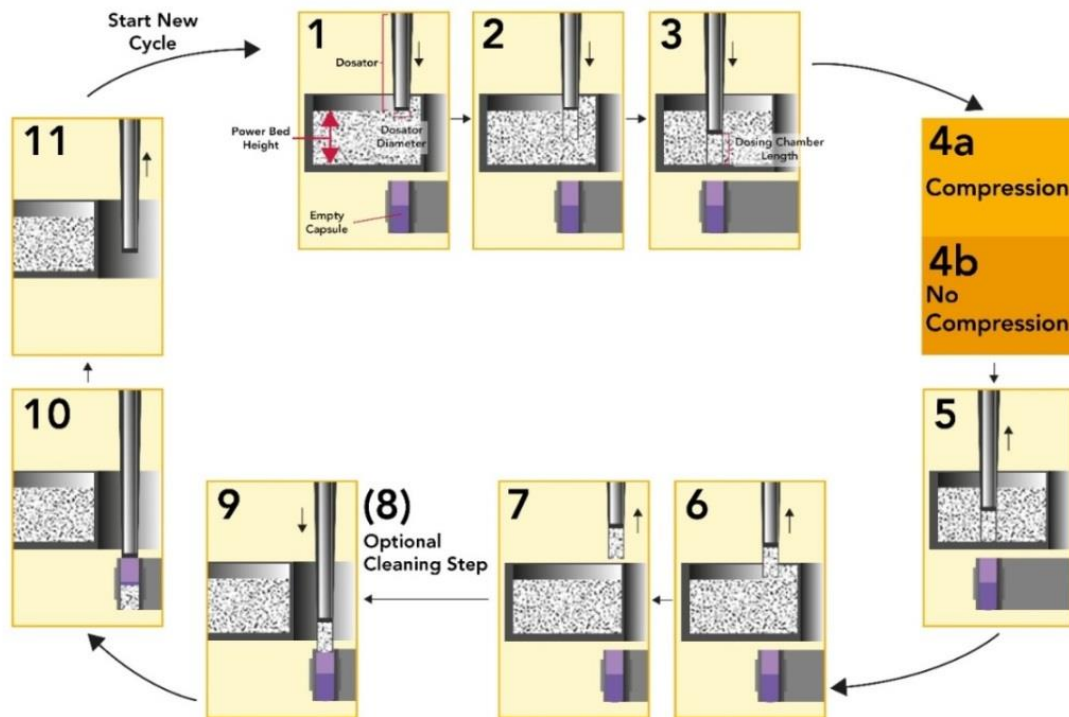

Figure 2: Continuous capsule filling with dosator nozzles (Loidolt et al., 2018).

Although, as stated in the previous section, several studies have reported the impact of material and process parameters on the capsule filling performance for standard doses, little research has been performed with regard to low-dose dosator capsule filling processes. To the best of our knowledge, the studies of Faulhammer et al. (2014a) and Seyfang et al. (2014) were the first attempts to scientifically qualify dosator nozzles for low-fill-weight capsule filling. The main challenge in their experiments was the powder layer inhomogeneity of very fine powders with low density particles, i.e., particle sizes smaller than 10 μm, exhibiting poor flowability and high cohesivity (Faulhammer et al., 2014a; Seyfang et al., 2014). Currently, no systematic

understanding exists of how the evolution of the powder layer during the capsule filling contributes to critical quality attributes such as the fill weight and the weight variability.

1.3 Powder bed

In a dosator nozzle capsule filling process the powder to be filled in a capsule is presented in the form of a powder bed from which the dosator collects the desired volume of powder and transfers it into a capsule (Podczeck and Jones, 2004).

It is well known that powder density variations during manufacturing can detrimentally influence the quality of final products. This is frequently prescribed (amongst others) for two commonly used oral dosage forms, i.e. tablets and capsules. In tablet production powder density variations may impact tablet mass and hardness as well as the dissolution performance and it hence affects the amount of drug delivered to patients (Singh et al., 2015). In filling capsules with powder or with pellets, the content of capsules, i.e. the fill weight, needs to be constant according to regulatory requirements. Fill weight variability and content uniformity are therefore considered as critical quality attributes (CQAs) within the Quality-by-Design (QbD) framework (Faulhammer et al., 2014c). For example, Faulhammer et al. (2014b) reported that for low-fill weight (1–50 mg) capsule filling using the dosator nozzle method, the powder density is one of the most relevant material attributes affecting the weight variability of final products, i.e. filled capsules. Moreover it was found that the influencing process parameters differ for the tested powders, whereas particular process parameters are required to successfully fill different types of powders into capsules. The recently published work by Loidolt et al. (2017a), where the Discrete Element Method (DEM) was used to describe the filling of the dosator nozzle when moving into the powder bed, showed the influence of powder properties on the amount of dosed mass. The powder packing inside the dosator nozzle and in turn the powder mass was affected by (1) the ratio between the particle and dosator diameters, and (2) the flow behavior of the powder which modifies the filling and compression behavior. In particular, cohesive powders pack less densely inside the powder bed, resulting in a lower amount of dosed powder. In contrast, cohesive powders are more compressible and thus the powder density inside the dosator nozzle increases during the dosing process. Evidently, the densification of the powder during the dosing step increases with powder compressibility, poorer flowability and a higher pre-compression ratio (i.e. the ratio between the dosing chamber length and the powder bed height). Moreover, the dosing

speed has an impact on the resulting fill weight, but its impact is rather complex and it is still unclear whether the increase in fill weight over time is due to the increased nozzle dipping speed or the densification of the power bed caused by machine vibrations and other forces. Likely, for different powders different effects are dominating (Loidolt et al., 2017a). In general, the major challenge is that the dose in the capsule is specified by weight, while the filling systems work based on a volumetric principle (Brian E Jones, 2001; Podczeck and Jones, 2004a). This implies, that when dosing the same volume of powder into a capsule, the fill weight may vary due to natural variations in the bulk density of the powder (Loidolt et al., 2018)

1.3.1 Bulk powder density

The relative density of the intermediate and final product is therefore highly critical for the product quality and it needs to be monitored and controlled to assure a consistent product performance. In general, the bulk powder density can be a useful parameter for the design, optimization, and scale-up of manufacturing processes, where density could be used as an equipment-independent scaling parameter (Hancock et al., 2003). Furthermore, as the pharmaceutical industry is moving from batch towards continuous processing (Davies et al., 2005; Buchholz, 2010; Poechlauer et al., 2012), real-time monitoring of the product quality is inevitable and robust quality descriptors are essential to realize process control (Vanarase et al., 2010). In this respect, the process analytical technology (PAT) is frequently prescribed as an essential step forward in the pharmaceutical industry. Real-time analyzers will provide timely data on quality properties, and thus are powerful tools for this industry, for process understanding, process and quality monitoring, detection of abnormal situations and for improving product quality and process reliability (Kourti, 2006). Based on previous studies of our working group where the powder layer inhomogeneity was found to be a critical factor resulting in poor quality of end products, a PAT strategy is highly recommended to improve the capsule filling performance (Faulhammer et al., 2014a; Faulhammer et al., 2014b).

1.4 Process analytical technology (PAT)

Food and Drug Administration's (FDAs) PAT initiative

In general, the complexity of many processes makes it very difficult to determine the product quality during processing. Pharmaceutical developments and manufacturing practices often rely

on a number of off-line tests to test whether a final product meets the quality requirements. To overcome this, the FDA and other regulatory organizations are encouraging the development of process analytical technologies (PATs) with the goal to build quality assurance into the manufacturing process by acquiring process data on-line. A key requirement of the initiative is the ability to measure critical quality attributes on-line for process monitoring and to verify product quality (McKenzie et al., 2006). Since 2004, a series of guidelines regarding Process Analytical Technology (PAT) and Quality by Design (QbD) have been released by the FDA (FDA, 2004) and ICH (Q8–Q11).

Quality by design (QbD)

One of the basic ideas of the PAT Guidance (FDA, 2004) is that quality of the end-product "should be built-in or should be design" and that PAT procedures "would be consistent with the basic tenet of quality by design". The QbD framework has led to an important paradigm change by allowing pharmaceutical companies to develop well-controlled and consistently optimized manufacturing processes. The studies on the QbD procedures are emerging as a specific area with its own vocabulary represented by a set of abbreviations, such as QTPP (quality target product profile), CPP (critical process parameter), DS (design space), and CQA (critical quality attribute) (Pomerantsev and Rodionova, 2012).

Design space (DS)

The development of a PAT method requires an in-depth understanding of the physical and chemical properties affecting the product quality, as well as how changes in process parameters affect these properties (such as, e.g. impeller speed). For this, a design space approach is recommended in order to understand the complex relationship between the input variables and the process parameters and their impact on product quality. The design space is defined as "a multidimensional combination and interaction of input variables (e.g. material attributes) and process parameters that have been demonstrated to provide assurance of quality". The DS is a subset of the knowledge space. The knowledge base represents what is known about the process, including failure regions, and the DS refers to the set of operating situations where the final product quality is acceptable. Another subset is the control space, which is used to further optimize the process to define a target range for normal operation. The DS is useful to understand how a product performs under different operating conditions and to develop robust processes

where variability in materials, process parameters and equipment can be accommodated (FDA, 2004; ICH (Q8–Q11)).

Design of experiments (DoE)

In conjunction with a design space, the statistical approach known as design of experiment (DoE) is often used to understand the complex relationship between variables. Basically, experiments are designed to identify the root cause of variability and how it affects the process as a whole (Box et al., 1978).

Monitoring process variability

Based on the FDA's PAT initiative (FDA, 2004), the following real time measurement modes can be performed in order to monitor variables of a process: (1) At-line, where the sample is removed and analyzed in close proximity to the process stream, (2) On-line, where the sample is diverted from the manufacturing process, and may be returned to the process stream and (3) In-line, where the sample is not removed from the process stream and can be invasive or non-invasive.

Much of the current literature in the manufacturing of solid dosage forms pays particular attention to techniques for in-line monitoring of the blend uniformity, with the most common employed process analyzer being near-infrared spectroscopy (NIRS) (Reich, 2005a; El-Hagrasy and Drennen, 2006; Li et al., 2006; Moes et al., 2008; Lin et al., 2015; Corredor et al., 2014;). Other non-destructive techniques such as Raman spectroscopy (Hausman et al., 2005; Wikström et al., 2006; Arruabarrena et al., 2014), light induced fluorescence (Karumanchi et al., 2011), and chemical imaging (El-Hagrasy et al., 2001; Lyon et al., 2002; Ma and Anderson, 2008; Osorio et al., 2014) are commonly used for on-line or in-line measurement of the blend uniformity (H. Wang et al., 2017). However, even if blend uniformity is adequate, density changes in the product may lead to undesirable variations in the product performance. Density variation can either cause an excess/lack of drug in a single dose or it can impact the microstructure which also influences the dissolution behavior of the final product (Markl et al., 2017a). Thus, it is crucial to not only control the drug concentration but also the relative density during processing. To date, only a few studies have attempted to monitor density variations of a powder bed. For example, the work by Singh et al. (2015) proposes a novel method for real-time monitoring of bulk powder density using a NIR sensor. Sensitivity analysis to quantify the effects of bulk powder density on

critical quality attributes of pharmaceutical tablets has been performed. Recently, NIRS calibration models for real-time prediction of powder density (tap, bulk and consolidated) were developed for a pharmaceutical formulation (Román-Ospino et al., 2016). Moreover, other approaches related to monitoring powder bulk densities are reported in the literature such as an analytical ultrasound method (Leskinen et al., 2010), an air-coupled acoustic technique (Akseli et al., 2010), photo-acoustic testing (Ketolainen et al., 1995), acoustic emission measurements (Hakanen and Laine, 1995), microwave measurements (Trabelsi et al., 1998; Trabelsi and Nelson, 2004), X-ray based methods (Akseli et al., 2011), thermal effusivity monitoring (Ghorab et al., 2007), and electrical tomography (Davies et al., 2005). However, quantitative real-time measurements of bulk powder density variations in a moving powder bed remains a challenge (Singh et al., 2015). Terahertz time-domain spectroscopy (THz-TDS) has recently emerged as a promising analytical tool for characterizing the pore structure of tablets (Markl et al., 2017b). In general, within the last ten years, a rapid development of terahertz systems and their commercialization driven by their inherent potential for quality control have created many exciting opportunities in the pharmaceutical sector (Y. C. Shen, 2011).

1.5 Terahertz technology

Terahertz electromagnetic radiation covers the spectral range from 2 to 130 cm^{-1} (60 GHz–4 THz) (Zeitler et al., 2007), as shown in Figure 3. It spans in the range between mid-infrared (IR) and microwave radiation, thus terahertz can also be named far-infrared radiation. In contrast to the IR region, which is related to intra-molecular vibrations, terahertz region is dominated by inter-molecular vibrations, corresponding to coherent, delocalized movements of large number of atoms and molecules (Korasa and Vrečer, 2018). As the radiation lies between the electronics and optics, terahertz radiation can be obtained with both technologies. Terahertz combines advantageous properties of both regions: It can penetrate through most dielectric materials like microwaves do, and it features spectral absorption of most polar molecules such as in infrared which can be used for chemical identification and sensing applications (Ellrich et al., 2011). Compared with NIR, mid-IR, and Raman spectroscopy, THz-TDS is inherently less vulnerable to scattering effects from powders due to operating at much longer wavelength (Markl et al., 2017b). Excipients most commonly used for the formulation of solid dosage forms are transparent, or semi-transparent, to terahertz radiation. Hence, the pulse of terahertz light can

penetrate into and through a specimen leading to a large representative sample volume. The penetration depth of the terahertz radiation into the sample material is dependent on the material and the power of the terahertz pulse. At present, penetration depths into typical pharmaceutical formulations have been demonstrated up to 5.3 mm (Markl et al., 2017a).
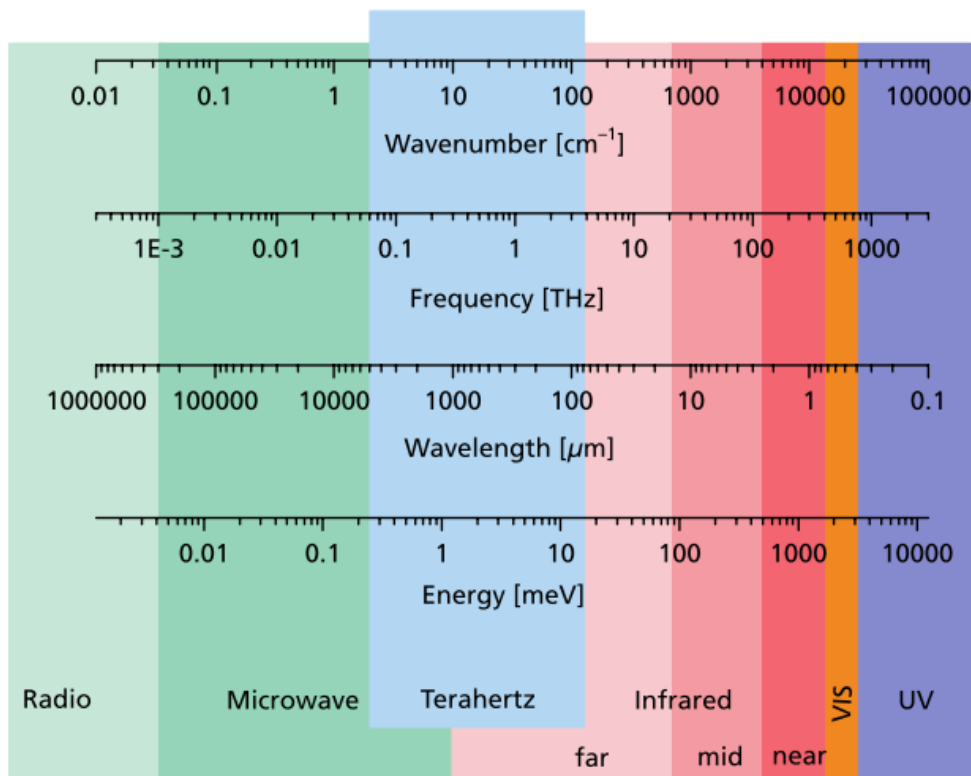

Figure 3: The electromagnetic spectrum showing terahertz radiation in relation to adjacent spectral regimes (Zeitler et al., 2007).

Detectors can be either homodyne or heterodyne. Homodyne detectors measure a physical property (e.g. volume, electric and dielectric properties) and in heterodyne detectors incoming terahertz signals are blend with an additional signal from a local oscillator which results in an intermediate frequency signal. Alternatively optoelectronic detectors can be used such as optically gated terahertz photoconductive antennas or nonlinear electro-optic crystals (Saeedkia and Safavi-Naeini, 2008). Details about detectors (using a solid-state receiver) to detect and measure terahertz pulses can be found elsewhere (Zeitler and Gladden, 2009).

Detailed description of the terahertz theory, device and system has been provided by numerous earlier studies and reviews (Jepsen et al., 1996; Ferguson and Zhang, 2002; Schmuttenmaer,

2004; Chan et al., 2007; Jansen et al., 2010). Excellent and detailed reviews on pharmaceutical applications of terahertz pulsed spectroscopy and imaging were published recently by Zeitler et al. (2007b), Ho et al. (2007), Taday (2004, 2009), Y.-C. Shen (2011) and Dave et al. (2017). In addition many reviews on other applications e.g., the food and agri-food industry (Gowen et al., 2012; Qin et al., 2013; K. Wang et al., 2017), imaging of biologically related applications (Parvathi Devi et al., 2014), fundamental research and industrial applications (El Haddad et al., 2013) to name a few, are reported. Recently, an excellent comprehensive overview and summary of recent advances and applications of terahertz spectroscopy was published by Prabhu (2018).

In terms of terahertz as a potential technology for monitoring the density variations of particulate material (off-line or in real time) valuable approaches in very similar fields are reported. For example, the work by Palermo et al. (2008) demonstrates the ability to quantitatively measure density maps of a tablet using terahertz pulsed imaging (TPI). As shown in Figure 4 it was possible to quantify the effect of the compaction force on the refractive index of the solid oral dosage forms using terahertz spectroscopy. Using a chemometric model, the density distribution over the surface of flat tablets was predicted from the TPI maps.
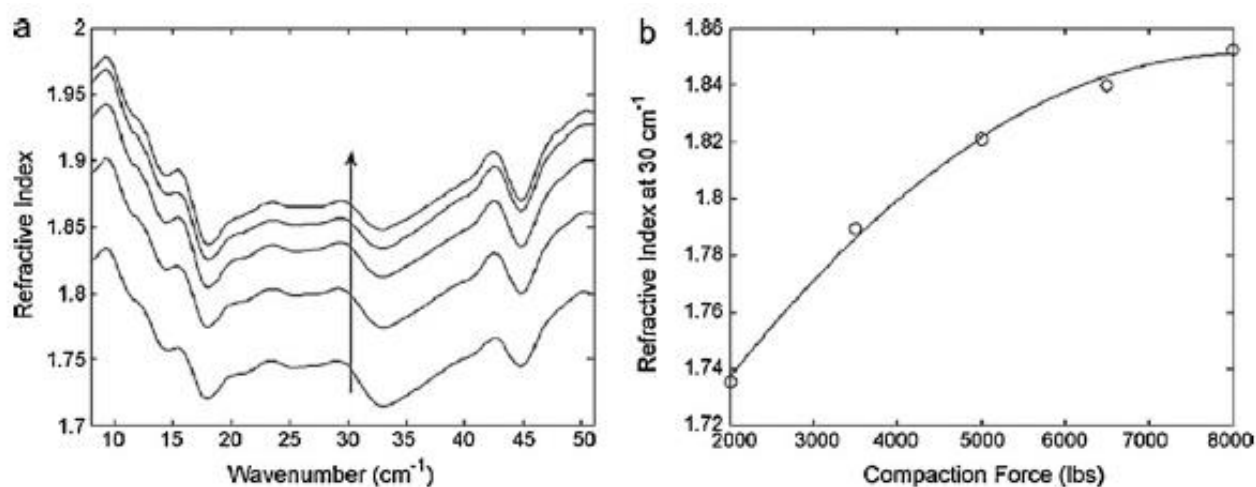

Figure 4: Effect of compaction force (2000, 3500, 5000, 6500 and 8000 lbs) on the mean refractive index spectra of all compacts. The arrow indicates the direction of increasing force.

In a further study, May et al. (2013) applied TPI for the analysis of the "hardness" (crushing strength) of pharmaceutical tablets. Radially symmetric spatial distributions in tablet density due to the shape of the punch used in the tablet manufacture were observed. A strong correlation between TPI results and those from diametric compression tests as well as finite element analysis (FEA) simulations was found. In a related study, Juuti et al. (2008) investigated the surface roughness and bulk properties of starch acetate tablets. The time delay of the terahertz pulses transmitted through a tablet was found to be correlated with the porosity of the tablet across a range of compression pressure. In a different study, the transmission terahertz spectra of porous media were also studied by Juuti et al. (2008).

In a further recent attempt to non-destructively measure the porosity of pharmaceutical tablets, the work by Ervasti et al. (2012) showed that in the absence of terahertz scattering, the effective refractive index (RI) that is obtained by the detection of the terahertz pulse delay correlates with the porosity of the tablet. Additionally, it was proposed that the broadening of the terahertz pulse could be a measure of porosity of tablets that scatter terahertz radiation (Ervasti et al., 2012). Parrott et al. (2009) have investigated the frequency-dependent RI and the absorption coefficient of porous media in the case of media that exhibit low porosity and weak scattering of terahertz radiation (Parrott et al., 2009) using the Maxwell Garnett effective medium model (Garnett, 1905). Furthermore, they have also considered the Bruggeman model (Bruggeman, 1935) for a case when the porosity of a sample can be relatively high. The work by Bawuah et al. (2014) investigated the dependence of porosity on other physical quantities such as gloss and surface roughness and furthermore introduced a method for the non-destructive and the non-invasive estimation of the porosity of sample pellets measured with terahertz pulse delay and using the Bruggeman effective medium approximation (BR EMA) (Bawuah et al., 2014).

More recently, the results from the terahertz measurements are complemented and compared with characteristic pore structure parameters extracted from X-ray computed microtomography (XμCT). It was demonstrated that the long acquisition times (several hours) and safety concerns of X-ray computed microtomography measurements can be overcome by terahertz technology, which is a fast, non-ionizing, contactless, and non-destructive method. The high potential of this technology to analyze the pore structure was emphasized by an $R^2 = 0.99$ from the correlation between the porosity predicted from terahertz measurements and the nominal porosity (Markl et al., 2017b). It should also be noted, that some materials have a characteristic fingerprint in the terahertz region, which makes it an important technique for identification of various compounds

17

(Dave et al., 2017). All these results suggest that the terahertz technology is suitable for non-destructive monitoring and analysis of pharmaceutical manufacturing processes. It is also suggested that TPI could also be useful for characterizing (tablet) bulk properties non-destructively. Terahertz is considered to be an attractive PAT tool for monitoring, quality assessing and investigating the microstructure of solid dosage forms. Some limitations like the relatively high wavelength (i.e. the spatial resolution limits) could be overcome by coupling with other techniques such as NIR imaging (Dave et al., 2017). Furthermore, the low absorption of pharmaceutical excipients at terahertz frequencies would make OCT (optical coherence tomography) a particularly attractive technique to bring together high resolution, high penetration and strong contrast (Shen et al., 2008). However, for a OCT-THz coupling, more powerful detectors are needed (Zeitler and Gladden, 2009). In the near future, more improvements are needed to further allow using the terahertz technology as real-time and on-line PAT tool, and enhance its applications in various aspects of pharmaceutical development (Zeitler and Gladden, 2009).

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2. The effect of material attributes and process parameters on the powder bed uniformity during a low-dose dosator capsule filling process

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Graphical Abstract
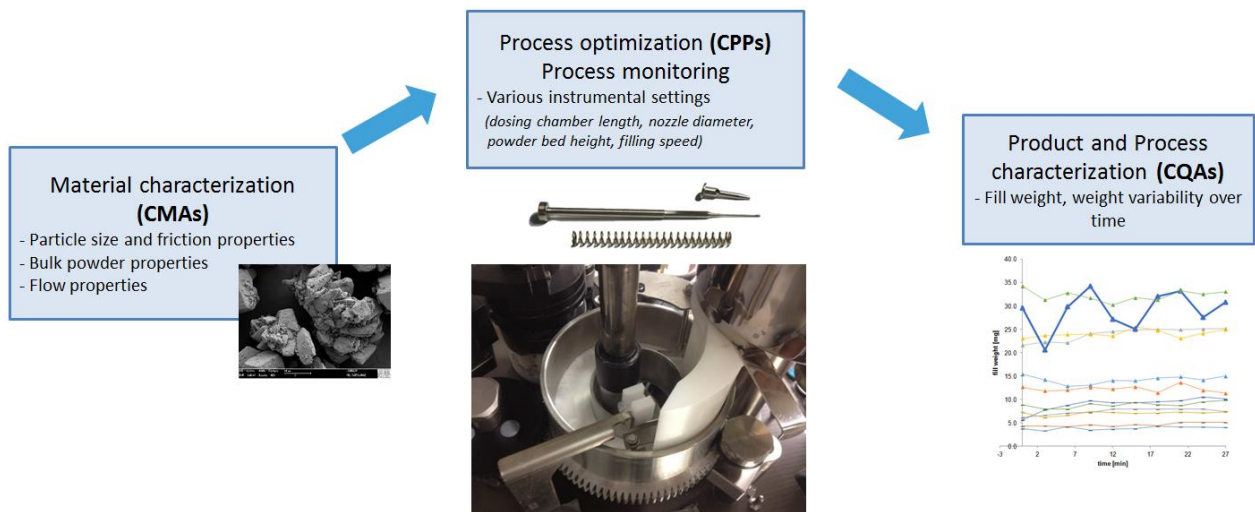
The effect of material attributes and process parameters on the powder bed uniformity during a low-dose dosator capsule filling process

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ABSTRACT

The objective of this work was to assess the effect of process parameters of a dosator nozzle machine on the powder bed uniformity of inhalation powders with various characteristics during a low-dose dosator capsule filling process. Three grades of lactose excipients were extensively characterized and filled into size 3 capsules using different dosing chamber lengths (2.5, 5 mm), nozzle diameters (1.9, 3.4 mm), powder bed heights (5, 10 mm) and filling speeds (500, 3000 capsules/hour).

The fill weight and the weight variability of Lactohale 100 (large particles, good flowability, low cohesion) remained almost the same, regardless of the process parameters throughout the capsule filling run time. Moreover, for this powder an increase in the fill weight at a higher filling speed was observed in all cases. Fill weight variability was significantly higher for lower dosing chamber volumes at a filling speed of 3000 capsules per hour. Lactohale 220 (small particles, poor flowability, high cohesion) delivered entirely different results. After a certain run time, depending on instrumental settings, a 'steady-state' with constant fill weights and low weight variability was achieved. For this highly cohesive powder, a high dosing chamber volume

27

requires a low filling speed in order for the powder to completely fill the dosator nozzle. Moreover, it was established that a dosing chamber length of 2.5 mm and a powder bed height of 10 mm were required due to the powder's high fill weight variability over time, while the dosator size had no effect on it.

In summary, the layer uniformity, the fill weight and the weight variability strongly depend on the powder characteristics and the instrumental settings. The results indicate that Lactohale 220 requires special attention during low-dose capsule filling. The study presents excellent insights into the effect of material attributes and process parameters on the layer uniformity and the quality of end product.

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2.1 Introduction

Capsule filling is widely applied in the pharmaceutical industry. Different methods exist, including tamping systems and the nozzle-dosator technique, which is especially relevant for filling capsules for inhalation application (Faulhammer et al., 2014b). Precise dose filling in the lower *mg*-range, which is required for inhalation therapies (Kou et al., 2012b), is essential for the successful manufacturing of high-quality products. One of the greatest challenges for effectively developing low-dose inhalation products is dose uniformity (Islam and Cleary, 2012). Although several studies have reported that many powder and processing parameters affect the quality of filled capsules (Faulhammer et al., 2014b; Nalluri et al., 2013; Podczeck and Newton, 1999; Podczeck and Newton, 2000; Patel and Podczeck, 1996; Tan and Newton, 1990; S. B. Tan and Newton, 1990) little research has been performed with regard to low-dose dosator capsule filling processes. To the best of our knowledge, the studies of Faulhammer et al. (2014a) and Seyfang et al. (2014) were the first attempts to scientifically qualify dosator nozzles for low-fill-weight capsule filling. In these systems the powder is forming a layer in a rotating bowl from which periodically material is sampled via the dosator nozzle and filled into empty capsule bodies. The main challenge in their experiments was the powder layer inhomogeneity of very fine powders with low density particles, i.e., particle sizes smaller than 10 μm, exhibiting poor flowability and high cohesivity (Faulhammer et al., 2014a; Seyfang et al., 2014). Currently, no systematic understanding exists of how the evolution of the powder layer during the capsule filling contributes to such critical quality attributes as the fill weight and the weight variability.

The objective of this work was to assess the effect of process parameters of a dosator nozzle machine on the powder bed uniformity of powders with various characteristics during a low-dose dosator capsule filling process. A lab-scale, low-dose dosator nozzle capsule filling machine (Labby, MG2, Bologna) with special low-dose equipment adaptations (i.e., smaller nozzles, a cleaning unit for the removal of excess powder from the dosator, special blades to create the powder layer) was used in this study. The evolution of the powder bed for three grades of lactose and the combination of various process parameters was assessed by measuring the weight of filled capsules for a total run time of 30 minutes. The effect of combinations of various material attributes and process parameters was investigated with respect to fill weight and weight variability over time. Compared to previous studies in the field of assessing the capsule filling performance, a key strength of this study was the ability to demonstrate the changes in fill weight

and weight variability not only depending on the instrumental settings, but also their changes over time.

This study provides new insights into the significance of powder layer monitoring during a low-dose dosator capsule filling process in order to achieve product-specification compliance.

2.2 Materials and methods

Three grades of lactose excipients commonly used as carriers in inhalation therapies (Kou et al., 2012b) were used as received from the supplier (DFE pharma). The sieved Lactohale 100 and two milled powders Lactohale 200 and Lactohale 220 were selected since for powders with different characteristics (such as compressibility) a certain combination of instrumental settings is required in order to successfully fill a dosator nozzle machine. A recent study by Faulhammer et al. (2014a) describes the processability of two groups of powders (group 1 – coarse carriers; group 2 – fine carriers and API). In our study the described classification of powders will be extended by introducing another group -'intermediate group' - to enhance the process understanding. Each of the three used lactose excipients will act as a representative for one group. Table 1 shows the parameters which were used for grouping the powders. In order to minimize manufacturer and batch-to-batch variations, experiments were carried out using powders from one batch and one supplier (DFE pharma).

Table 1: Material classification

Group	Representative powder	Particle size [x50]	Bulk density [g/ml]
Small	Lactohale 220	< 10 μm	< 45 g/ml
Intermediate	Lactohale 200	10-150 μm	45-65 g/ml
Large	Lactohale 100	> 150 μm	> 65 g/ml

2.2.1 Powder characterization

All experiments were carried out under controlled environmental conditions (20-24 °C, 40-60 % relative humidity). The following material attributes were established in triplicate: Particle size was measured via QICPIC (OASIS/L wet and dry dispersing system, Sympatec GmbH, Clausthal-Zellerfeld, Germany) and Helos KR (Sympatec GmbH, Clausthal-Zellerfeld, Germany). Dynamic image analysis of millions of particles in each sample was performed to determine the size distribution and the volumetric mean diameter (VMD) and median particle size.

The bulk (BD) and tapped densities (TD) were analyzed using the Pharmatester (PT-TD200) and the standardized method described in the United States Pharmacopeia (USP 2015). To this end, a certain mass of powder was filled into a cylinder and the level was recorded. After mechanically tapping the powder sample, the tapped density was determined. The true density was measured with a helium pycnometer (AccuPac II 1340, Micromeritics, Norcross, USA).

The compressibility, air permeability, flow function coefficient, cohesivity, angle of internal friction, basic flowability energy and wall friction angle were measured with the FT4 powder rheometer (Freeman Technology, Malvern, United Kingdom). Compressibility was determined by assessing the volume change of a conditioned sample when it was compressed under a specific normal force. For this purpose, the conditioned sample was compressed with normal forces starting at 0.5 kPa up to 15 kPa. The ratios between the density and bulk density of each compaction step were recorded. Air permeability was measured by transmitting air though a bulk and detecting the air pressure drop across the powder bed. Pressured dry air (2 mm/s air velocity) was used for the permeability test. In order to determine the flow function coefficient and cohesion, a 1 ml shear-cell module at a maximum pressure of 3 kPa was used. High flow function coefficient values (>4, or more strictly >10) represent powders with good flowability. The cohesivity C provides information about inter-particle interactions due to electrostatic, capillary or van der Waals forces. The angle of internal friction for a given soil is the angle on the graph in Mohr's Circle (shear stress vs. normal stress) at which shear failure occurs. The basic flowability energy indicates the amount of energy that is required for establishing a particular flow pattern in a conditioned, precise volume of sample. The wall friction angle determines the friction force a powder can sustain as a function of normal forces at a surface. We used a stainless steel plate

with a nominal roughness of 0.2 µm (Ra), of which MG2 nozzles are typically made (Freeman, 2007a).

Furthermore, a dynamic test method (the avalanching test method) was applied, via which the flowability of powders can be assessed by measuring their avalanching behavior related to cohesivity and flowability (Kaye, 1997). The avalanching test can be conducted with different types of equipment, including rotating drums and vibratory feeders (Hancock et al., 2004; Hickey and Concessio, 1994). Unlike the shear-cell method mentioned above, the avalanching test method using a rotating drum is dynamic in nature (Kaye, 1997). Therefore, it may be more applicable to low-shear processes, such as low-dose capsule filling without an additional compaction step. In the drum revolving at a fixed speed, the powder is subjected to stress as a result of rotation. The applied stress causes the powder to shear, leading to avalanching events (Boothroyd et al., 2000) which can be monitored via an optical sensor system. In this study, a rotating drum was used for powder characterization. Samples of about 100 ml corresponding to 50 % fill level were introduced into a metallic drum secured with conductive glass covers. The internal diameter of the drum was 100 mm and its depth was 25 mm. The drum was rotated at a speed of 2 rotations per minute for 10 minutes. The movement of the drum and powder was recorded with a digital camera (Casio Exilim EX-F1) using a diffused backlight. Video resolution was 640 x 480 pixels with a frame rate of 30 frames per second. The videos were analyzed via an in-house OpenCV-based Python program. The first step of this analysis was to select a circular region of interest and a binarization threshold value. The main feature of interest was the border between the air and the powder. The border was simplified to three segments using a Ramer-Douglas-Peucker algorithm, which preserves points with the largest distance to the segments. For further analysis, the angle of each segment and the normalized border length were saved for each frame. The distribution of angles of the middle segments was analyzed in detail and it was fitted to a gaussian function in order to eliminate the outliers caused by some avalanches. The border length was normalized by dividing it by the diameter of the region of interest and obtaining values larger or equal to 1. A snapshot of all three powders tested and evaluated using our software can be seen in Figure 1. The structure of border between the powder and air indicates the level of cohesiveness.
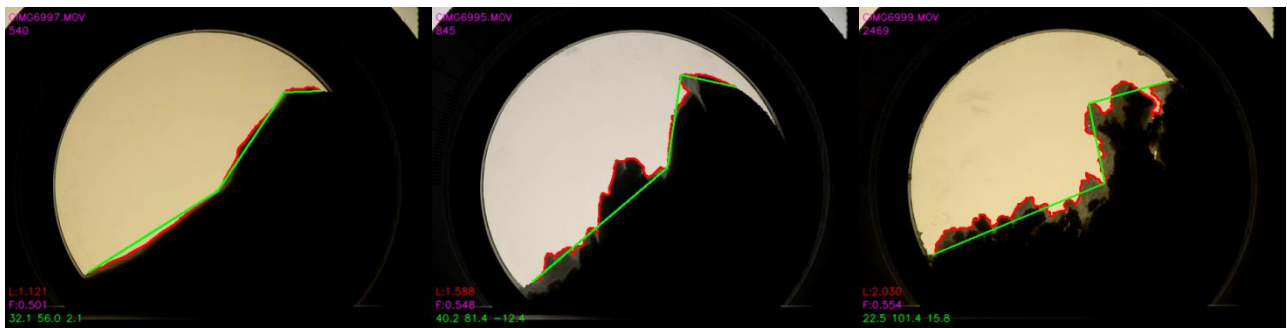
Figure 1: Exemplary powder behavior under dynamic testing for LH100, LH200 and LH220. Red line represents the border length, which was used in normalized border length calculation and the green line represents a three segment simplification of the border line, which was used for angle determination.

2.2.2 Capsule filling

Capsule filling experiments were performed using different combinations of four process parameters: the dosator diameter (dia), the dosing chamber length (dcl), the powder bed height (pbh) and the capsule filling speed in capsules per hour (cph). In order to obtain small fill weights, small dosing chambers were used and filling was performed without compaction (which is an optional step in dosator filling). Two dosing chamber length (2.5, 5 mm), two dosator sizes (1.9, 3.4 mm), two powder bed heights (5, 10 mm) and two filling speeds (500, 3000 cph) were used in the experiments.

Powders were filled into hard gelatin capsules of size 3 (supplied by Capsugel) in a lab scale capsule filling machine (Labby, MG2, Bologna) adopted for special low-dose equipment, as reported in Faulhammer et al. (2014a).

The study was performed under humidity-controlled conditions (45-55 % relative humidity). In order to create an initial powder bed without densification, the layer was adjusted manually and the powder was initially not supplied from the hopper. The capsules were collected as described below. Powder feeding from the hopper to the rotary container was adjusted according to the amount of powder collected during the capsule filling. Figure 2 shows a sketch of the used capsule filling machine. After each run, the powder was removed from the rotary container, all equipment was cleaned and a new powder layer was created. The collected capsules were stored in cups sealed with Parafilm until their fill weight and weight variability were analyzed.

Figure 2: Sketch showing the rotary container with the powder layer, the hopper and the dosator.

2.2.3 Sampling

After setting all machine parameters and creating a smooth powder layer without densification, capsule filling experiments were carried out. The capsule filling process consists of several steps. First, the dosator moves towards the powder layer of the rotary container. Next, the dosator dips into the powder bed and a predefined volume of powder (volume of dosing chamber) is collected. During this step, depending on the material characteristics, a certain stress state in the powder is established, resulting in a more or less stable plug, which can be lifted by the nozzle and filled into a capsule. The speed of the dosator's dipping and ejection steps depends on the production speed of the machine. After each dosator dipping step, the container with the powder rotates in order to enable the voids in the layer to be filled with the powder prior to the next dosing event.

In addition, the mounted dosator rotates but at a different rotational speed. Since the dosator needs 25 rotations of the rotary container to reach exactly the same point in the powder layer as for time point 0, the capsules were collected at time point 0, after 25, 50, 75, 100, etc., rotations of the container for a total run time of 30 minutes. This means a total of 11 collected capsules for the low filling speed (500 cph) and 61 for the high filling speed. For each run three repetition experiments were carried out. This way, the dynamics of the powder layer creation (i.e., removing powder from the layer vs. re-establishing a uniform powder bed) could be studied as well as the impact on capsule fill-weight variability.

2.2.4 Analysis of capsule fill weight and variability

The weight of collected samples was measured with a Denver (SI-234A) analytical scale. Due to a relatively high weight of empty capsules and their variability, the collected filled capsules were first weighted and then emptied and re-weighed. An air pistol was used to make sure that no powder was left in the capsule after it was emptied.

2.3 Results and discussions

2.3.1 Powder characterization

Table 2 presents the particle size, friction angles, bulk and flowability properties of the three lactose excipients studied. It shows that powders with completely different characteristics were used to assess their influence on the processability and, more precisely, on the powder layer uniformity during the capsule filling process. In 2004, Podczeck reported that particles with a median size larger than 150 µm (due to too good flowability) and particles with a median size below 20 µm (due to too poor flowability) were either difficult or impossible to fill with a dosator nozzle machine (Podczeck, 2004). In contrast, Faulhammer et al. (2014) successfully filled powders with small particle sizes by adding special features to the equipment (MG2). However, filling very fine powders proved to be highly challenging, indicating that further investigations were required (Faulhammer et al., 2014b).

The current study aims to determine or, at least, provide an insight into the behavior of these challenging powders during the low-dose capsule filling process.

Table 2: Material attributes for the three grades of lactose excipients used in this study. Each measurement was performed in triplicate. Mean and SD are shown.

	Lactohale 100	Lactohale 200	Lactohale 220
Particle size and friction properties			
Volumetric mean diameter [µm]	160.02 ±0.62	83.63 ±n.a.	16.38 ±n.a.
Particle size x10 [µm]	100.52 ±0.52	10.93 ±0.07	2.41 ±0.01
Particle size x50 [µm]	155.24 ±0.58	78.72 ±0.44	13.40 ±0.01
Particle size x90 [µm]	229.14 ±0.75	162.54 ±0.38	33.76 ±0.10
Angle of internal friction [°]	18.43 ±0.49	21.24 ±0.53	25.73 ±2.66
Wall friction angle (3 kPa 0.2 Ra) [°]	7.70 ±0.02	11.46 ±0.82	19.97 ±3.82
Bulk powder properties			
Bulk density (BD) [g/ml]	0.697 ±0.004	0.622 ±0.003	0.400 ±0.007
Tapped density (TD) [g/ml]	0.828 ±0.013	0.996 ±0.002	0.785 ±0.007
True density [g/ml]	1.539 ±0.003	1.543 ±0.002	1.547 ±0.004
Compressibility at 8 kPa (ρ_{comp}/ρ_{BD}) [%]	1.05 ±0.00	12.66 ±0.29	36.95 ±0.16
Air permeability at 8kPa [mbar]	1.05 ±0.02	7.00 ±0.10	12.04 ±0.55
Flowability			
Basic flowability energy [mJ]	910.67 ±43.00	1722.85 ±27.00	667.32 ±10.80
Flow function coefficient	6.58 ±0.01	4.04 ±0.01	1.65 ±0.01
Cohesion [kPa]	0.24 ±0.02	0.39 ±0.01	1.05 ±0.13

Particle size and friction

In a capsule filling process the particle size, which is known to have an impact on the bulk behavior of powders (Fu et al., 2012a), has to be regarded as a critical factor. It is one of the major factors correlating with the capsule fill weight and the fill weight variability (Faulhammer et al., 2014c). According to the powder classification in the USP 2011, Lactohale 100 is a fine powder and Lactohale 200 and 220 are very fine powders. The particle size affects the flowability and cohesivity of a bulk powder, with smaller particle sizes typically showing higher cohesivity (Jolliffe and Newton, 1982; Fu et al., 2012). By now, powders with a particle size <10 µm are known to be challenging with regard to the dosator nozzle technique (Faulhammer et al., 2014b). However, not only the particle size, but also the particle size distribution has to be regarded as critical in capsule filling mainly because of its impact on powder compressibility as reported by Llusa et al., 2014. The range of the particle size distribution can be assessed using the span parameter (Span = (x90- x10)/x50).

Bulk powder properties

The compressibility of powder describes the extent of volume change in a conditioned sample when it is slowly compressed under a specific normal force. Figure 3 shows the volumetric change under the effect of compaction. Especially in fine powders (Lactohale 220), high volume changes may occur upon compression.
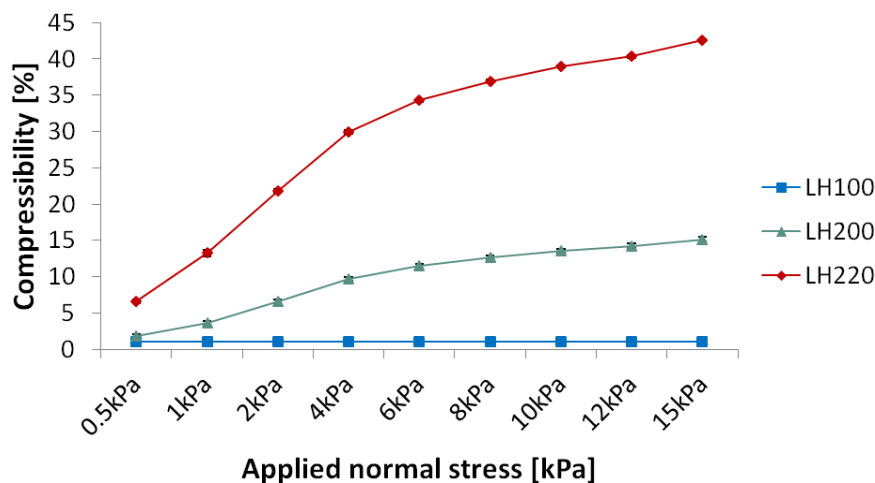

Figure 3: Percentage of compressibility in the range from 1 to 15 kPa.

The compressibility of a material is a crucial factor for dosator filling since it correlates with the fill weight (Faulhammer et al., 2014c). Since the dosator volume is fixed, compressibility determines how much powder enters the nozzle, depending on the stress created. During the dosator dipping step, depending on the mode of filling, the powder is compressed to some degree to improve its retention inside the nozzle. During a standard dose dosator filling process, a piston inside the nozzle is moved downwards (vertical compressive stress) to form a plug. Since the plug has to be ejected later, this force should be low (Jolliffe et al., 1980). In contrast, during low-dose filling, no piston compaction step is performed and the powder is only compacted if the powder bed height is higher than the dosing chamber length since in this case pre-compression occurs when the nozzle dips into the powder bed.

Flowability

It is known that powder flowability affects the filling performance (weight variability) of a dosator with a standard nozzle (Freeman and Fu, 2008; Freeman, 2007; Podczeck and Mia, 1996; Prescott and Barnum, 2000). Faulhammer et al. (2014a) reported that flowability plays a particularly important role in low-dose dosator capsule filling that involves higher weight variability of high cohesive powders (Faulhammer et al., 2014b). According to the flow function coefficient and cohesion values, Lactohale 100 has the best flowability, followed by Lactohale 200 and Lactohale 220 (with a flow function coefficient of 1.65 ± 0.01 and a C of 1.05 ± 0.13 kPa), which exhibits poor flowability.

Avalanching behavior

The average and the standard deviation of the angle of the second segment was increasing for the samples in the following order: Lactohale 100, Lactohale 200 and Lactohale 220 (Table 3). Higher values of average values as well as its spread indicate worse flowability. It can be seen that the average value of Lactohale 220 is nearly 90°, which can be considered as very bad flowability. The values of normalized border length follow the same trend and can therefore be used a simple parameter for evaluation of powder cohesiveness.

Table 3: Dynamic behaviour for the three grades of lactose excipients used in this study. Mean and SD are shown.

	Lactohale 100	Lactohale 200	Lactohale 220
Upper angle [°]	52.69 ± 4.25	72.84 ± 12.99	86.17 ± 21.82
Normalized border length [-]	1.085 ± 0.017	1.459 ± 0.090	1.728 ± 0.206

Additionally, a frequency analysis using Fast Fourier Transform (FFT) was performed on the normalized borderline length time series in order to study the dynamics of the avalanching behaviour. The power spectra show that LH100 had a peak at the lowest amplitude of around 500, and frequencies of up to 2.5 Hz were more pronounced, corresponding to the formation of small and frequent avalanches. The power spectrum of LH220 shows much higher amplitudes (around 150,000) and frequencies up to about 0.3 Hz. These results indicate significant avalanching of larger powder assemblies. This means that avalanches of this powder are rarer and stronger than those for LH100, which can lead to poorer powder filling.
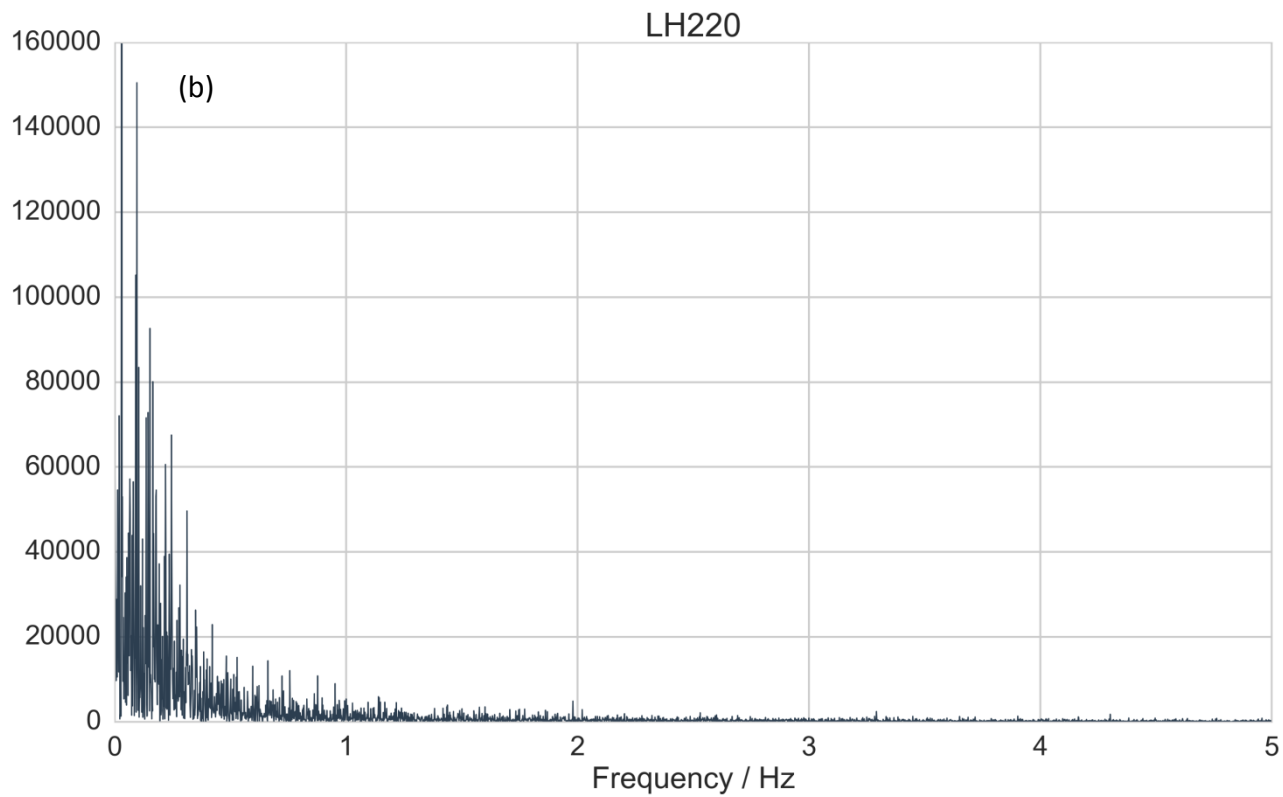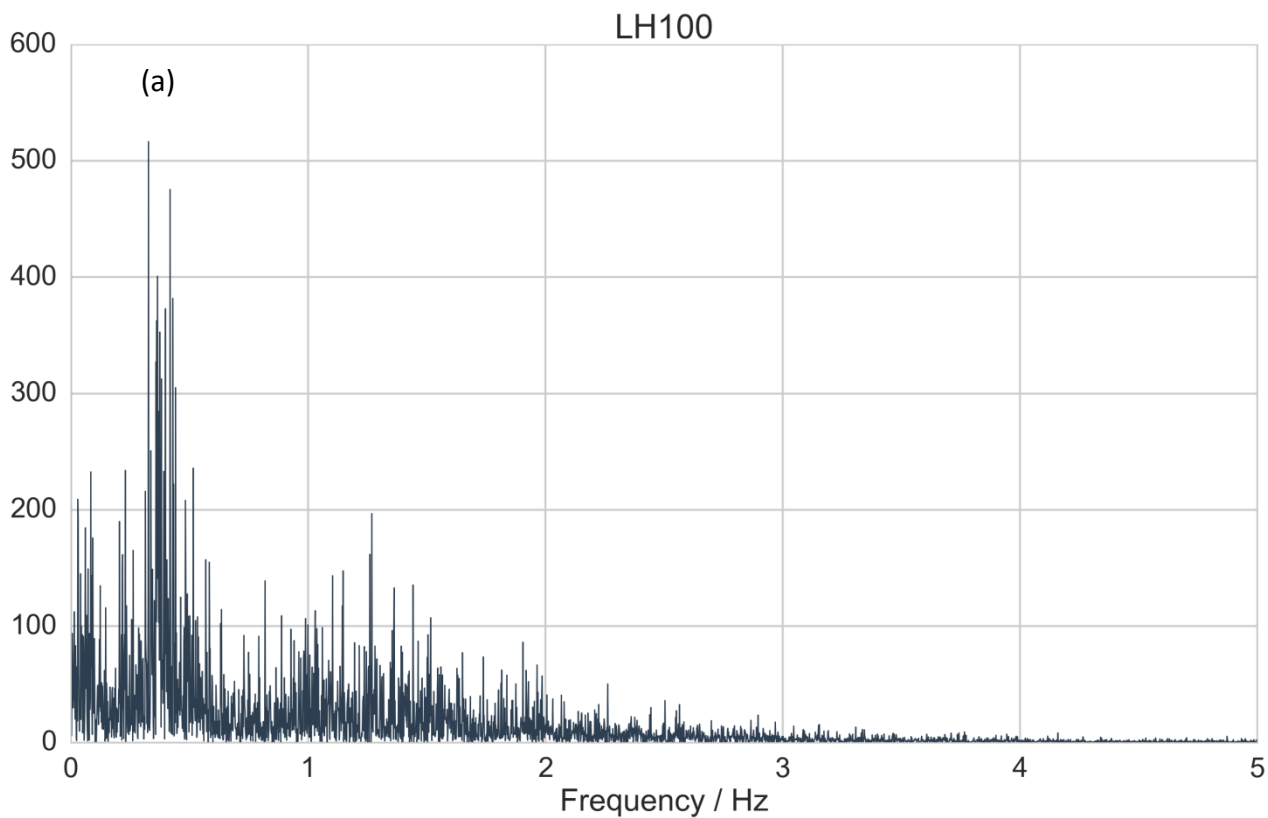
Figure 4: Power spectra of (a) LH100 and (b) LH220.

2.3.2 Capsule filling

Table 4 presents the experimental plan (DOE) for capsule filling with a dosator size of 3.4 mm, i.e., the values of the four process parameters, the fill weight and the weight variability (RSD), as well as the obtained results. In some cases powder could not be filled successfully into capsules (details described below). These runs are marked with f.n.p., which stands for "filling not possible".

Table 4: Low-dose capsule filling study: 8 experimental runs with 3 repetition experiments

					Lactohale 100		Lactohale 200		Lactohale 220	
RUN	Speed [cph]	Diameter [mm]	Dosing chamber length [mm]	Layer [mm]	Weight [mg]	RSD [%]	Weight [mg]	RSD [%]	Weight [mg]	RSD [%]
1	500	3.4	2.5	5	22.6	1.6	25.5	3.6	12.3	10.4
2	3000	3.4	2.5	5	23.6	4.7	27.7	3.1	14.0	13.3
3	500	3.4	5	5	f.n.p.	f.n.p..	f.n.p.	f.n.p.	f.n.p.	f.n.p.
4	3000	3.4	5	5	f.n.p.	f.n.p.	f.n.p.	f.n.p.	f.n.p.	f.n.p.
5	500	3.4	2.5	10	23.1	2.4	29.5	2.0	24.1	5.2
6	3000	3.4	2.5	10	25.0	1.3	29.5	1.1	24.1	8.9
7	500	3.4	5	10	37.7	1.3	46.4	1.0	32.2	7.9
8	3000	3.4	5	10	39.5	3.5	45.0	7.3	30.0	18.9

From Table 4 it can be seen that the fill weight is a function of the chamber length and the depth of the powder bed. For experiments for powders with the same chamber length and layer depth no sufficient compression was obtained such that the plug in the nozzle was not stable. Thus, the layer depth needs to be larger than the chamber length for successful dosing. As can be seen as well, the weight correlated with the chamber volume. For the most compressible powder (LH 220), however, the powder bed layer depth has also a very strong impact on the fill weight.

Capsule filling speed has a moderate impact on the fill weight, with higher speeds mostly (not always) leading to higher fill weights, due to an increased densification of the powder associated with a higher level of vibrations of the machine.

The highest capsule fill weights were obtained for Lactohale 200, followed by Lactohale 100 and Lactohale 220. The fill weight correlates with the measured tapped densities of the powders, indicating that the powder layer densifies during the filling experiments.

In terms of dependence on the fill weight and speed, the more cohesive powders (Lactohale 200 and 220) behaved differently from Lactohale 100. The fill weight of Lactohale 100 increased at a higher filling speed in all combinations of instrumental settings. A possible explanation for these results is that when using a lower filling speed powder is more likely be lost during the transfer step from the powder bed to the capsule body compared to a higher filling speed.

In contrast, for Lactohale 200 and 220, a different dependence on the filling speed and fill weight was observed. As shown in Table 4, the combination of a high dosing chamber volume and a high filling speed (run 8) resulted in a slightly lower fill weight compared to a low filling speed (run 7). When analyzing the weight variability of more cohesive powders, the combination of a high dosing volume and a high filling speed (run 8) significantly increased the fill weight variability. The hypotheses for this observed dependence of fill weight and weight variability of more cohesive powders are that (1) a high dosing chamber volume needs more time to be completely filled with powder and (2) the increase in weight variability is caused by the fact that for a higher powder bed height, inhomogeneities are more likely to be present compared to a smaller powder bed height. Thus, dosing of larger amounts of powders can lead to higher fill weight variability.

With respect to fill weight variability of all three powders, Lactohale 100 shows the most uniform filling performance with RSD's below 5 %, as also described by Faulhammer et al. (2014a). For Lactohale 220, overall relatively high RSDs were obtained. The powder layer was not smooth and had cracks and agglomerate formations. Feeding and filling up the voids in the powder layer after a dosator dipping step was obviously difficult to achieve due to the low flowability and high cohesivity of the powder. Since the dosator filling technique is based on volumetric filling, the powder bed inhomogeneity is a critical factor since possible densifications or entrapped air can introduce fill weight variability as reported by Faulhammer et al. (2014a) and Seyfang et al.

(2014). The filling performance of the 'intermediate' powder LH 200 with RSD's up to about 8 % was, as expected, inferior to that of Lactohale 100 but better than that of Lactohale 220.

Furthermore we found out that at a dosing-chamber-to-powder-bed height compression ratio of 1:1, none of the three powders could successfully be filled due to insufficient compression. Hence, large dosator sizes require a larger compression ratio (>1:1) for a successful transfer of powders into the capsules.

Table 5 shows the experimental plan and the results for the dosator size of 1.9 mm. As described earlier, the abbreviation f.n.p. was used for runs for which filling was not possible. The weights were significantly smaller, i.e., in the range of a few mg. As in the case of the dosator size 3.4 mm, the fill weights of Lactohale 200 were higher than those of Lactohale 220 for all instrumental settings and mostly higher than for Lactohale 100. Using the smaller dosator size (1.9 mm) rather than the larger dosator size (3.4 mm) resulted in a higher weight variability in all cases.

Interestingly, at a dosing-chamber-length-to-powder-bed height compression ratio of 1:1 (i.e., no pre-compression of powder during filling) Lactohale 100 could be filled at a low filling speed and Lactohale 220 both at low and fast speeds. However, during the filling process many capsules were not filled with powder, resulting in very high weight variability. As reported by Faulhammer et al. (2014a) for highly cohesive powders the fill weight is - in contrast to powders with lower cohesivity - additionally affected by frictional characteristics (wall friction angle). This could be a reason why the highly cohesive powder was occasionally transferred into capsules. For the less cohesive powder Lactohale 100, the presence of inter-particle interactions (due to electrostatic, capillary or van der Waals forces) which supports arching may be the reason for the partially successful filling of capsules.

In general filling at a dosing-chamber-length-to-powder-bed height compression ratio of 1:1 proved to be unsuitable, since Lactohale 100 (except for low speed) and 200 could not be filled at all due to the lack of compaction and arching and for Lactohale 220 only some capsules could be filled but with a very high fill weight variability.

With a dosator size of 3.4 mm, Lactohale 100's fill weight increased at a higher filling speed. However, this increase was lower with a dosator size of 1.9 mm. Moreover, filling Lactohale 100 at a higher filling speed resulted in all cases (run 2, 6, 8) in a higher weight variability. This

means that filling inhalation powders that have large particles and good flowability should be performed at a lower filling speed when using a small dosator size.

Interestingly, no significant loss in fill weight was detected using a smaller dosator size when a combination of a large dosing chamber volume and a high filling speed (run 8) was applied to Lactohale 200 and 220. This finding suggests that in contrast to the 3.4 mm dosator for a smaller dosator size a high filling speed can also be used for high dosing chamber volumes.

Table 5: Low-dose capsule filling study – 8 experimental runs with 3 repetitions each.

					Lactohale 100		Lactohale 200		Lactohale 220	
RUN	Speed [cph]	Diameter [mm]	Dosing chamber length [mm]	Layer [mm]	Weight [mg]	RSD [%]	Weight [mg]	RSD [%]	Weight [mg]	RSD [%]
1	500	1.9	2.5	5	7.4	5.1	7.0	4.0	4.6	13.0
2	3000	1.9	2.5	5	7.6	12.5	7.5	4.7	3.9	13.9
3	500	1.9	5	5	4.6	16.8	f.n.p.	f.n.p.	4.8	23.6
4	3000	1.9	5	5	f.n.p.	f.n.p.	f.n.p.	f.n.p.	4.7	47.3
5	500	1.9	2.5	10	7.2	3.6	8.3	6.7	7.1	7.6
6	3000	1.9	2.5	10	7.4	11.5	9.3	4.1	7.5	9.0
7	500	1.9	5	10	9.1	5.2	12.6	4.5	9.0	11.1
8	3000	1.9	5	10	10.3	12.1	12.7	5.4	9.0	15.3

In order to investigate if the three powders exhibit volumetric filling, the mean fill weight as a function of the dosator volume was examined (Figure). Volumetric filling is achieved if the mass correlates with the volume (i.e., doubling the dosing chamber volume leads to double the fill weight). It is apparent from the two plots that the three powders did not show volumetric filling.

In order to analyze the effect of doubling the dosing chamber volume in more detail, Table 6 presents the percentage change in fill weight for the three powders and the two dosator sizes (1.9 mm, 3.4 mm). When analyzing the results obtained with the large dosator size (3.4 mm), it can be

clearly seen that for none of the three powders volumetric filling can be observed. The fill weight of Lactohale 100 and 200 increased to a higher extent compared to the highly cohesive Lactohale 220. Interestingly, for the small dosator size (1.9 mm) the largest changes in fill weight were observed for Lactohale 200 at a low filling speed. Using the high filling speed again, Lactohale 100 and 200 show a higher increase of fill weight compared to Lactohale 220, but with a significant lower extent as for the larger dosator size. Contrary to expectations, this study did not find a volumetric filling for any of the used powders. However, the larger increase in fill weight of Lactohale 100 and 200 supports the idea that the fill weight of powders with properties similar to those materials is mainly affected by the diameter of the dosator and the length of the dosing chamber as reported by Faulhammer et al. (2014a).

The fact that ideal volumetric filling was not observed may be due to sampling at exactly the same point of the powder layer, in contrast to earlier studies. Additionally, sampling of capsules was carried out for a longer run time. Nevertheless, these results highlight once again that is difficult to predict the fill weight for arbitrary powders and that even a systematic interpretation of the capsule weight results is difficult. Thus, unless advanced computational methods are introduced experiments are necessary to establish fill weight as a function of powder and operating variables.
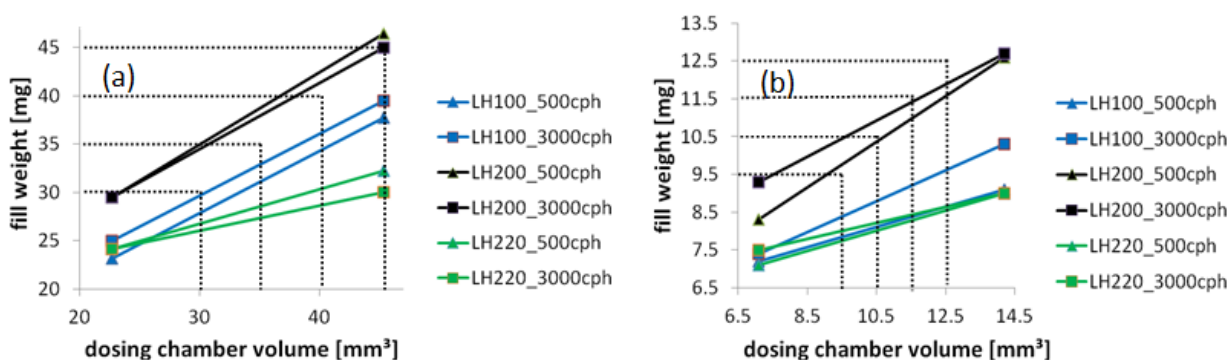

Figure 5: Effect of increasing the dosing chamber volume on the filling behavior (fill weight) of LH 100 (blue) LH 200 (black) and LH 220 (green): (a) dosator diameter of 3.4 mm, (b) dosator diameter of 1.9 mm.

Table 6: Overview of obtained change in fill weight [%] for dosator size 3.4 mm and 1.9 mm.

Powder	LH100		LH200		LH220	
Filling speed	500cph	3000cph	500cph	3000cph	500cph	3000cph
Dosator size 3.4 mm						
Change in fill weight [%]	63 %	58 %	57 %	53 %	34 %	24 %
Dosator size 1.9 mm						
Change in fill weight [%]	26 %	39 %	52 %	37 %	27 %	20

2.3.3   Effect of the compression ratio (chamber length/ powder bed height) on the fill weight

As discussed above, the three Lactose excipients have a significantly different compressibility. In our study, the effect of compressibility was investigated using different powder bed heights and a constant dosing chamber length. Results are shown in Table 7. Here the expected fill weight based on bulk density, the compression ratio and the actual fill weight, and the increase of fill weight with compression ratio in [%] is shown.

Table 7: Change in fill weight using two compression ratios (chamber length/powder bed height)

Powder	Settings							Filled powder [mg]	Change in fill weight [%]
	Dosing chamber length [mm]	Diameter [mm]	Dosing chamber volume [mm^3]	Fill weight based on BD [mg]	Speed [cph]	Layer [mm]	Compression ratio		
LH 100	2.5	1.9	7.1	4.9	500	5	1:2	7.4	-2.7
						10	1:4	7.2	
					3000	5	1:2	7.6	-2.7
						10	1:4	7.4	
		3.4	22.7	13.1	500	5	1:2	22.6	2.2
						10	1:4	23.1	
					3000	5	1:2	23.6	5.9
						10	1:4	25.0	
LH 200	2.5	1.9	7.1	4.4	500	5	1:2	7.0	18.6
						10	1:4	8.3	
					3000	5	1:2	7.5	24.0
						10	1:4	9.3	
		3.4	22.7	15.8	500	5	1:2	25.5	15.7
						10	1:4	29.5	
					3000	5	1:2	27.7	6.5
						10	1:4	29.5	
LH 220	2.5	1.9	7.1	2.8	500	5	1:2	4.6	54.3

				10	1:4	7.1	
			3000	5	1:2	3.9	92.3
				10	1:4	7.5	
3.4	22.7	12.4	500	5	1:2	12.3	95.9
				10	1:4	24.1	
			3000	5	1:2	14.0	72.1
				10	1:4	24.1	

For Lactohale 100, the experimentally obtained fill weight is about 35 % and 45 % higher than the expected fill weight based on BD for the small dosator size (1.9 mm) and the larger dosator size (3.4 mm), respectively. A higher filling speed always resulted in higher fill weights. This supports the finding by Faulhammer et al. (2014a) that in low-dose capsule filling experiments powders with a VMD bigger than 100 µm are affected by the capsule filling speed, most likely by densification of the powder due to higher levels of vibrations at higher speeds. Interestingly, the fill weight decreased slightly when the compression ratio was increased for the smaller dosator. For the larger dosator there was a modest increase of a few percentage, reflecting the poor compressibility of the powder.

For Lactohale 200 (intermediate size), for both dosator sizes (1.9 mm, 3.4 mm) and a powder bed layer of 10 mm, the experimentally obtained fill weight is about 50 % higher than the expected one (based on BD), and for a powder bed layer of 5 mm it is about 40 % higher. Again, higher fill weights (except for the combination of a larger dosator and a larger powder layer height) could be observed using a higher filling speed. Thus, also for powders with a VMD lower than 100 µm the capsule filling speed has an effect on the expected fill weight. Upon increase in compression ratio there was a significant increase in fill weight, dependent on the size and filling speed.

For Lactohale 220, the fill weight experimentally obtained with the small dosator size (1.9 mm) is 30 % and 60 % higher than the expected fill weight (based on BD) with powder layers of 5 mm and 10 mm, respectively. For the large dosator size (3.4 mm), the experimentally obtained fill weight is 10 % and 50 % higher than the expected fill weight with powder bed heights of 5 mm and 10 mm, respectively. As expected, for the highly cohesive Lactohale 220, the change in the

powder bed height from 5 mm to 10 mm at a constant dosing chamber length resulted in a significant increase in the fill weight for both dosator diameters. This can be correlated with the high compressibility of this powder, as shown above. For all three powders, the experimentally obtained fill weights are in all cases higher than the expected fill weights (calculated based on bulk density). A correction factor that takes into account compressibility behavior and bulk density of powders could help to predict the fill weight changes of various powder bed heights.

Since for Lactohale 220 the biggest fill weight changes were obtained, the results for this powder were examined in more detail. The powder bed height (and thus the compression ratio) clearly affects the filling of this highly cohesive powder much more than it does powders with less compressibility. Moreover, for Lactohale 220 a significant effect of filling speed on the fill weight was observed. In the case of the large dosing chamber volume and a low filling speed, the fill weight increased much more than it did in the case of the small dosing chamber volume. At a higher filling speed, a lower increase in the fill weight was observed for the large dosing chamber volume. It can be expected that there is more air entrapped in the large dosing volume than in the small one, resulting in a lower increase in the fill weight. All of the above findings indicate that highly cohesive powders require a lower filling speed when the dosing volume is increased.

2.3.4 Fill weight dynamics

Figure 6 shows the results of the experiments for the three lactose excipients (Lactohale 100, 200, 220) with various combinations of process parameters (dosator size, dosing chamber length, powder bed height, speed) as a function of time. Each data point corresponds to a triplicate determination of the capsule fill weight. The plots indicate that for Lactohale 100 and 200 the fill weight remained almost constant for all instrumental settings and is mainly a function of the chamber volume. There is no significant change of capsule weight over time, which indicates that no powder caking in the rotary container during the capsule filling process occurred. A visual inspection of the reconstitution of the powder layer throughout the entire process indicated that the holes introduced by each dosator dipping step were completely filled with powder and the powder layer could be recreated with a smooth surface. Again, it can be clearly seen that for Lactohale 100 a change of the powder layer height (from 5 mm to 10 mm) at a constant dosing chamber length of 2.5 mm resulted in almost the same fill weights throughout the process.

For Lactohale 200, the fill weight slightly increased after doubling the powder layer height at a constant dosing chamber length due to the higher compressibility (see Fig. 2). These results also

agree with a previous study by Faulhammer et al. (2014a), indicating that the fill weight is dependent on the powder layer height.

In contrast, for Lactohale 220 a different behavior was observed. The powder layer was more uneven and the surface appeared to crack easily. It became clear from a visual examination that the powder bed did not reach a final homogeneity. The poor flowability and high cohesivity of this powder made the filling of holes of the powder layer generated by the nozzle more challenging. Thus, a high weight variability over time could be detected for this powder. The most noticeable variations in the fill weights over time were obtained for the combination of the large dosing chamber volume, a filling speed of 3000 cph and a high powder bed height. This is shown in Figure 6 (turquoise line) and in Figure 7 which presents the RSD over time for LH 220. Obviously, a larger powder bed height leads to less homogenous beds than a shallower one because of a significant amount of air entrapped in the powder layer, resulting in large fill-weight variability.

Furthermore, we detected a significant increase of fill weight with time throughout the total run time of 30 minutes for a combination of a dosing chamber length of 2.5 mm and a powder bed height of 10 mm as shown in Figure 8. These findings suggest that for powders with poor flowability and high cohesion (especially when using a larger powder bed layer height) the monitoring of the evolution of the powder bed density over time would be crucial for detection of variations followed by any corrective actions.
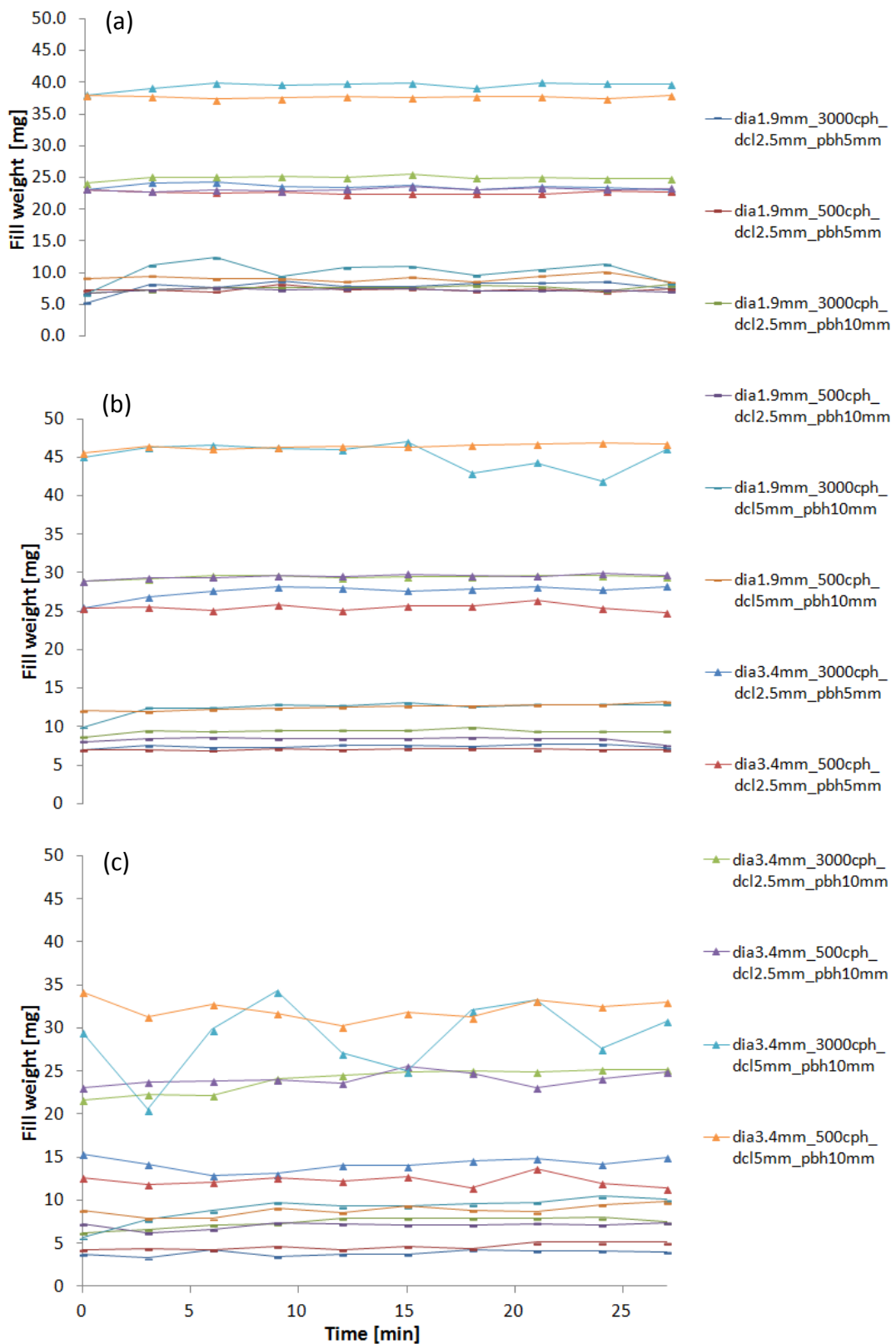
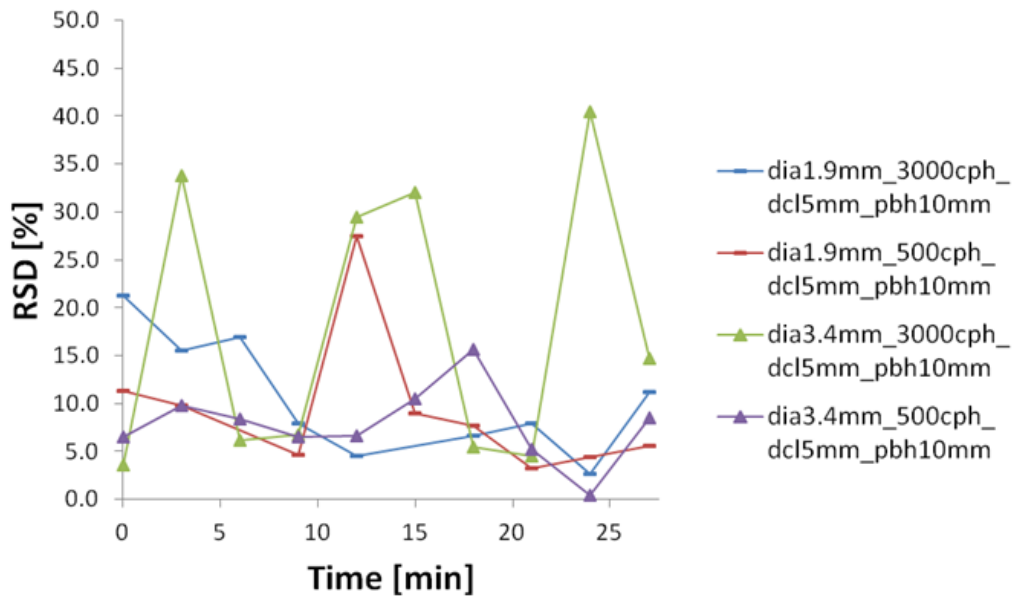**Figure 6:** Fill weight over time: (a) Lactohale 100, (b) Lactohale 200, (c) Lactohale 220.

Figure 7: Weight variability of Lactohale 220 over time.
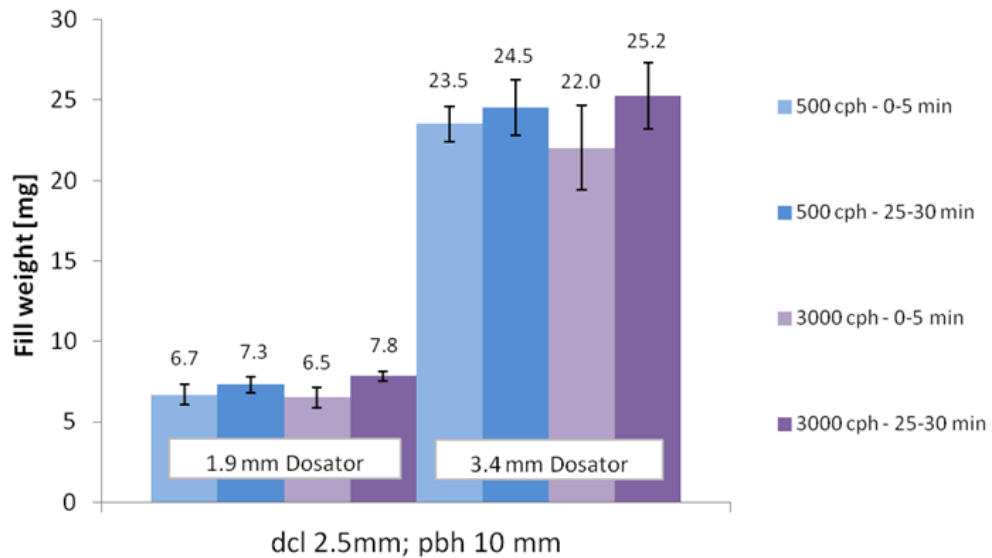

Figure 8: Change of fill weight after a total run time of 30 minutes for a combination of a dosing chamber length of 2.5 mm and a powder bed height of 10 mm for both dosator sizes for LH 220.

Figure 9 shows the weight of the capsules for Lactohale 220 as a function of time in more detail for the high filling speed of 3000 cph. Clearly, as shown above, the height of the powder bed for a constant dosing chamber volume significantly influences the fill weight. For the 10 mm height, the powder bed required a longer time period to reach a 'steady-state of fill weight'. For the 1.9 mm dosator using a combination of a low dosing chamber length (2.5 mm) and a larger powder bed height, after 15 minutes a constant fill weight could be obtained. Using the same settings for experiments with the 3.4 mm dosator the weight variability was much higher which makes it more difficult to reach 'steady-state' after a certain filling time.

Furthermore, filling the highly cohesive Lactohale 220 using a dosing chamber length of 5 mm is challenging, regardless of the dosator size. A high fill weight variability was observed over the entire sampling period. The effect of powder bed height on the fill weight of high cohesive powders can possibly be explained by a densification of the powder layer, which could be caused by inherent machine vibrations, as described by Llusa et al. (2013), or by a continuous powder accumulation in the lower part of the powder bed due to high pressure generated at the lowest point of a dosator dipping step (Pinzon, 2012). For the latter, it may be the case that after the dosator dipping step, a small amount of powder remains at the bottom of the rotary container. Dosing from the same spot in the powder layer may lead to compaction of the remaining powder, resulting in a higher fill weight after a certain run time. Since capsule filling is a dynamic process with multiple steps over a short period of time, the effect of instrumental settings on the fill weight and weight variability has to be monitored over a certain run time to obtain reliable data, as described in this study.
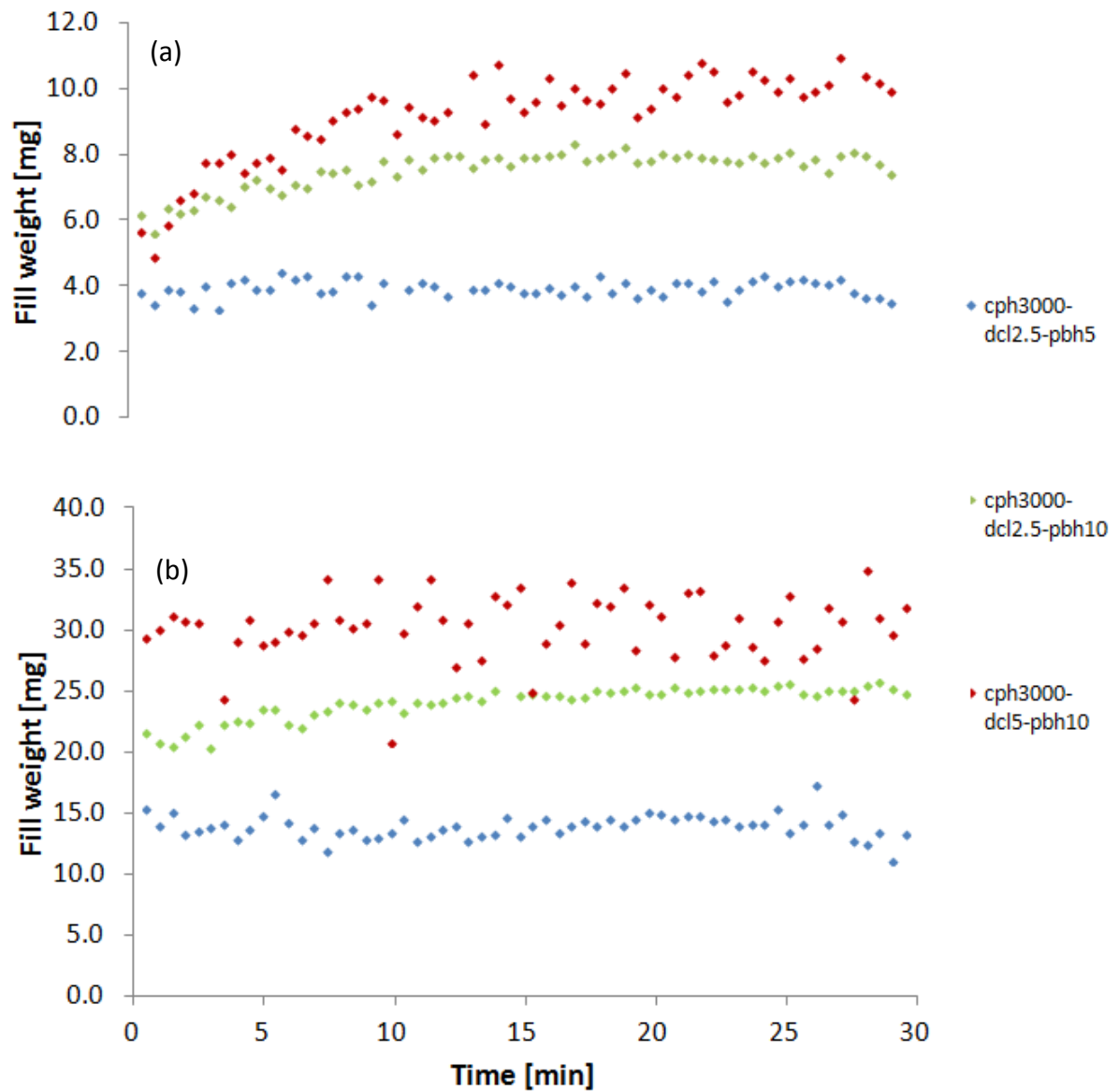
Figure 9: The change of fill weight of Lactohale 220 over time: (a) dosator diameter of 1.9 mm, (b) dosator diameter of 3.4 mm for a filling speed of 3000 cph.

2.4 Conclusion and outlook

The present study focused on the change in the powder layer over time during low-dose capsule filling. Three grades of lactose excipients were thoroughly characterized in order to relate their powder attributes to the filling performance in various instrumental settings. The off-line measured compressibility of the powder, with a high increase in the cohesive Lactohale 220 of up to 37 % for an applied normal stress of 8 kPA, correlates with the densification behavior during the capsule filling process. During the filling process, the compression ratio (dosing chamber length/powder bed height) of Lactohale 220 determined the change in the fill weight over time. With that regard, a high compression ratio (1:4) combined with a large powder bed height (10 mm) results in densification of the powder bed. This densification of powder bed leads to an increase of the fill weight over time with significantly higher fill weights at the end of the total run time of 30 minutes. Interestingly, the biggest change in the fill weight over time was obtained for Lactohale 220 using a high capsule filling speed (3000 cph), a small dosator diameter (1.9 mm), a large powder bed height (10 mm) and a dosing chamber length of 2.5 mm. The reason could be because in the beginning a large quantity of air of entrapped in the powder layer is filled instead of powder, which is more critical for smaller filling amounts than for bigger amounts of powder filled with a higher dosing chamber volume. Taken together, our findings suggest that for low-dose capsule filling with a dosator nozzle system, the desired target fill weight of capsules filled with powder strongly depends on both the material characteristics and the instrumental settings. The implemented classification of powders according to their processability during capsule filling can help to choose appropriate instrumental settings for initial test runs of new formulations.

An issue that was not addressed in this study was the influence of powder mixtures (e.g., powder with API) on the powder bed uniformity. Further investigation of this issue and experiments are strongly recommended, as well as continuous control of the material variations inside the rotary container during the manufacturing process. The implementation of process analytical technology (PAT) tools can significantly reduce the fill weight variability via complete monitoring of all process steps.

2.5 Acknowledgments

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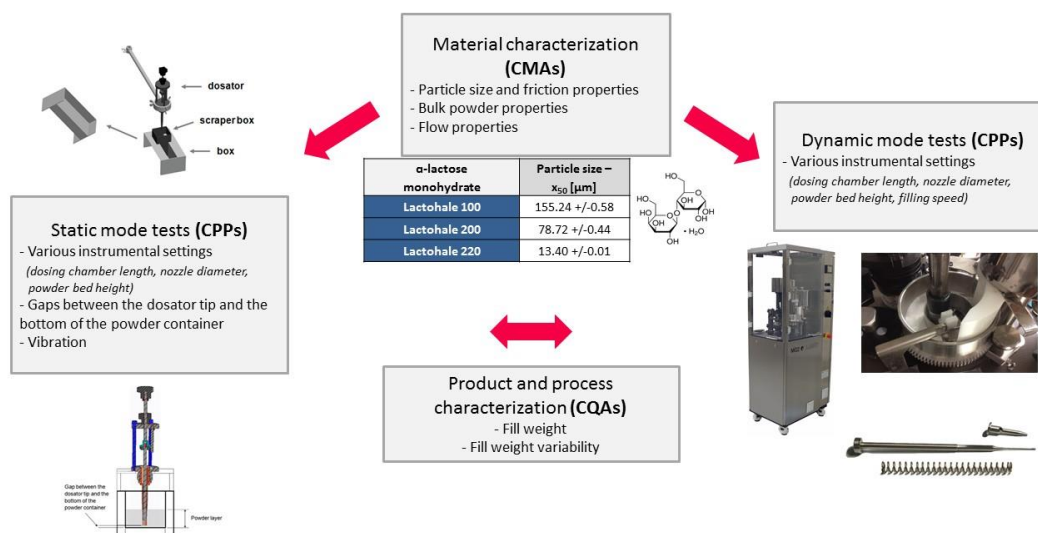
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3. Study of a Low-dose Capsule Filling Process by Dynamic and Static Tests for Advanced Process Understanding

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Graphical Abstract

Study of a low-dose capsule filling process by dynamic and static tests for advanced process understanding

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ABSTRACT

Precise filling of capsules with doses in the mg-range requires a good understanding of the filling process. Therefore, we investigated the various process steps of the filling process by dynamic and static mode tests. Dynamic tests refer to filling of capsules in a regular laboratory dosator filling machine. Static tests were conducted using a novel filling system developed by us. Three grades of lactose excipients were filled into size 3 capsules with different dosing chamber lengths, nozzle diameters and powder bed heights, and, in the dynamic mode, with two filling speeds (500, 3000 caps/h). The influence of the gap at the bottom of the powder container on the fill weight and variability was assessed. Different gaps resulted in a change in fill weight in all materials, although in different ways. In all cases, the fill weight of highly cohesive Lactohale 220 increased when decreasing the gap. Furthermore, experiments with the stand-alone static test tool indicated that this very challenging powder could successfully be filled without any pre-compression in the range of 5 mg to 20 mg with acceptable RSDs. This finding is of great importance since for very fine lactose powders high compression ratios (dosing-chamber-length-to-powder-bed height compression ratios) may result in jamming of the piston. Moreover, it shows that the static mode setup is suitable for studying fill weight and variability.

Since cohesive powders, such as Lactohale 220, are hard to fill, we investigated the impact of vibration on the process. Interestingly, we found no correlation between the reported fill weight changes in dynamic mode at 3000 cph and static mode using similar vibration. However, we

could show that vibrations during sampling in the static mode dramatically reduced fill weight variability.

Overall, our results indicate that by fine-tuning instrumental settings even very challenging powders can be filled with a low-dose dosator capsule filling machine. This study is a further step towards a scientific qualification of dosator nozzles for low-fill weight (1–45 mg) capsule filling.

Keywords: Low-dose capsule filling, critical process parameters, process decoupling, powder bed density, vibration, dosator nozzle machine, Inhalation powders

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3.1 Introduction

For many years there has been significant interest in delivering medicinal products through the lungs. This mode of drug delivery ensures fast onset, allows local and systemic modes of action, circumvents the first-pass effect and enables delivery also of large molecules. Different delivery technologies exist. Dry Powder Inhalers (DPI) devices that utilize capsules as a dose-holding system are the most rapidly-expanding field in pulmonary drug delivery (Islam and Gladki, 2008). However, filling inhalation powders into capsules often requires specialized equipment that can handle the very low fill weight (Edwards, 2010) in the range of a few tens of milligrams. For the currently available low-dose capsule filling systems, the dosator method is often used (Faulhammer et al., 2014b). However, the precise filling of very fine powders remains challenging.

One of the biggest problems in the manufacturing of high-quality low-dose inhalation products is dose uniformity (Islam and Cleary, 2012). Although there is a considerable body of literature on identifying and assessing critical material and process parameters that affect the product quality for standard doses (Faulhammer et al., 2014b; Nalluri et al., 2013; Podczeck and Newton, 1999; Podczeck and Newton, 2000; Patel and Podczeck, 1996; Tan and Newton, 1990; S. B. Tan and Newton, 1990), little attention has been paid to low-dose dosator capsule filling processes. The current study examines this issue and should be regarded as a continuation of the research efforts of Faulhammer et al. (2014), Faulhammer et al. (2015) and Stranzinger et al. (2017), who assessed the effect of critical material attributes and process parameters on a low-dose dosator capsule filling process. These recent studies demonstrated that the low-dose filling of very fine carriers with a dosator system is challenging, and further investigations are required in order to achieve the required product specification compliance. Moreover, different filling behavior of powders with varying material characteristics using different combinations of process parameters has been reported.

The two primary aims of this study are:

1. to investigate the effect of gaps between the dosator tip at the end of the stroke and the bottom of the powder container box with different carrier materials. Although this process parameter is expected to affect the fill weight and variability, it has received minimal attention to date.

2. to take a closer look at the filling behavior of challenging fine carrier materials. It was

assumed that the mechanical vibration of the powder drum induces particle movement/rearrangement in the drum and, possibly, segregation (Metzger et al., 2011; Majid and Walzel, 2009; Ellenberger et al., 2006; Rosato et al., 2002; Elperin and Golshtein, 1997). To that end, the vibration present in the drum was measured to assess its intensity (specifically acceleration and frequency). Subsequently, the vibration was recreated in a laboratory setup to isolate the effect of vibrations, separating it from the dosing process and drum rotation.

For the purpose of this study, a lab-scale, low-dose dosator capsule filling machine (Labby, MG2, Bologna) with special low-dose equipment adaptations (i.e., smaller nozzles, a cleaning unit for the removal of excess powder from the dosator and special blades to create the powder layer) and a stand-alone static test tool were used. In the latter, material is dosed from a stationary container. Thus, the main achievement of this study was separating the different effects occurring in capsule fillers. This was accomplished by using dynamic (rotating bowl) and static (stationary container) tests to establish how specifically the process parameters affect the quality of filled capsules.

The filling behavior of three grades of lactose using a combination of various process parameters was assessed in terms of fill weight and weigh variability. Our study provides insights into exactly what occurs during the capsule-filling process, from the start of capsule opening to the end of filled capsule ejection. A deeper understanding of the effects of various process parameters on the capsule filling efficiency may improve current filling systems, the product quality of low-dose capsules for inhalation and, ultimately, patients' health.

3.2 Materials and methods

3.2.1   Materials

Three grades of lactose excipients that are commonly applied as carriers in inhalation therapies (Kou et al., 2012a) were used as received from the supplier (DFE pharma, Goch, Germany). Sieved Lactohale 100 and two milled powders Lactohale 200 and Lactohale 220 were selected, since, as stated in the introduction, the present work is a continuation of the research efforts of our group, focusing on the powder characteristics that have not been investigated yet.

3.2.2 Powder characterization

Powder characterization was carried out in order to examine the influence of powder attributes (e.g., particle size and distribution, powder flow and surface properties) on the capsule filling performance. All experiments were carried out under controlled environmental conditions (20–24 °C, 40–60% relative humidity) and each measurement was made in triplicate (n = 3).

3.2.3 Particle size and size distribution

Particle size and size distribution of the carrier material was measured via the laser diffraction technique (HELOS/KR, Sympatec GmbH, Clausthal-Zellerfeld, Germany). For powder dispersion, a dry dispersing system (Rodos/L, Sympatec) and a vibrating chute (Vibri, Sympatec) was used. A dispersion pressure of 2.5 bar was applied. The typical sampling time was 30 seconds. Data were evaluated using the software Windox 5.6.0.0 (Sympatec, Clausthal-Zellerfeld, Germany).

The particle size distribution (PSD), the volumetric mean diameter (VMD) and the median particle size (x_{50}) were determined. The latter is defined as the particle diameter corresponding to 50% of the cumulative undersize distribution. Cumulative volume-based (Q_3) particle size distribution plots were analyzed. Evaluation of the data was performed using the software Windox 5 (Sympatec). To describe the width of the PSD, we used the span (see Eq (1)) where the x_{10} and x_{90} are defined analogous to x_{50}.

$$Span = \frac{(x_{90} - x_{10})}{x_{50}}$$
Eq (1)

3.2.4 Powder flowability and density

The angle of repose (AoR) was determined by using a glass funnel and the standardized method described in the United States Pharmacopeia (USP 2017, 1174). The static angle of repose is defined as the angle at which a material will rest on a stationary heap or the angle θ formed by the heap slope and the horizontal when the powder is dropped on a platform (Juliano and Barbosa-Cánovas, 2010). The bulk density (BD) and tapped density (TD) were measured as described in Stranzinger et al. (2017) and the Hausner ratio was computed (as described in USP 2017, 616) as another indicator for flowability and cohesivity.

3.2.5 Specific surface area (SSA)

The specific surface area (SSA) of the three grades of lactose excipients was determined using the Micromeritics Tristar II 3020 (Micromeritics Instrument Corp., Norcross, GA, USA). Samples were initially out-gassed in the Micromeritics VapPrep 061 degas unit (Micromeritics Instrument Corp., Norcross, GA, USA) for at least one day at room temperature. The measurements were performed using nitrogen gas. The Brunauer, Emmett and Teller (BET) absorption method was applied for calculating the specific surface areas, with a pressure range of 0.05–0.20 normalized to the saturation pressure of the adsorbate. The Barrett, Joyner and Halenda (BJH) method was used to calculate the pore size distributions based on experimental isotherms from the Kelvin model of pore filling.

3.2.6 Capsule filling

Capsule filling experiments were performed under humidity-controlled conditions (45–55% relative humidity). Various combinations of four process parameters were considered: the dosator diameter (dia), the dosing chamber length (dcl), the powder bed height (pbh) and the capsule filling speed in capsules per hour (cph). In order to obtain the fill weight of up to 40 mg that is typical for inhalation applications (Edwards, 2010), the capsules were filled using two dosing chamber lengths (2.5, 5 mm), two dosator sizes (1.9, 3.4 mm), two powder bed heights (5, 10 mm) and two filling speeds (500, 3000 cph).

3.2.6.1 Dynamic mode tests

Powders were filled into size 3 transparent hard gelatin capsules supplied by Capsugel using a lab-scale capsule filling machine (Labby, MG2, Bologna) adopted for special low-dose equipment, as reported in Faulhammer et al. (2014). Dynamic mode tests were performed as described in our previous work, e.g., Stranzinger et al. (2017). Note that in this setup, the powder bowl rotates and the dosator samples material from various locations of the bowl. The dosator nozzle matches the speed of the bowl, and thus, during sampling there is no relative horizontal speed of the nozzle with respect to the powder bed. The powder bed is continuously reconstituted by feeding powder from a hopper. A static scarper on top of the bed defines the powder bed height and creates a flat and smooth surface. In front of the scraper typically powder accumulates. A certain level of densification apparently occurs during the scraping.

3.2.6.2 Static mode tests

The static mode tests, using a novel test setup, were carried out in a stand-alone static test tool (Figure 1). Capsule-filling experiments were conducted using the same combination of process settings and environmental conditions as the dynamic mode tests. The difference was that the powder was sampled from a static powder bed rather than from a rotating drum, which allows the study of the effect of the powder layer homogeneity on the capsule quality attributes and to achieve a mechanistic understanding of the powder compaction behavior inside the dosing chamber. Additionally, the static mode setup can help to determine the effect of forces that are always present in a lab-scale capsule filling machine (e.g., the centrifugal force) by simply excluding them using a static powder bed. Furthermore, the stand-alone test tool provides an opportunity to fine-tune certain process parameters, such as the gap between the lowest point of the dosator and the bottom of the powder box. In this way, the parameter limitations and the optimal parameters settings can be identified for various powders before filling up the hopper and the bowl of an industrial scale machine with expensive material available in a limited quantity in early stages of the development process.
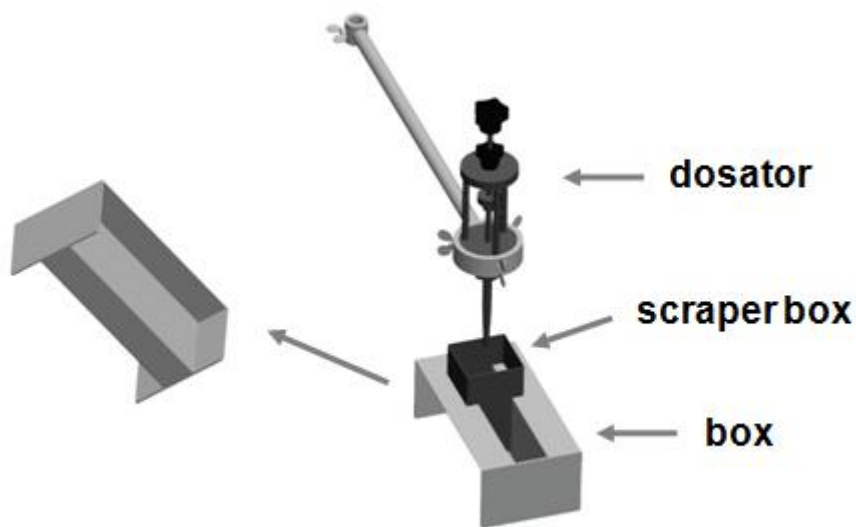

Figure 1: Sketch of the stand-alone static test tool including a bottom view of the box.

The following sets of experiments were carried out using the static device:

- *Experiments without vibration*: In each case, capsule-filling experiments were performed as follows: In order to create an initial powder bed layer without densification, a defined volume of powder was poured into a scraper box, which was moved from the left to the right side of the metal box to create a homogeneous powder layer. Subsequently, at a pre-determined point a dosator dipping step was performed and the collected powder was transferred into a capsule. Once again the layer was adjusted by moving the scraper box from the left to the right side of the metal box. Another dosator dipping step was carried out at the same pre-determined point as before. For each instrumental setting 30 capsules were collected.

- *Experiments with vibrations*: Here the static test tool was placed on top of a Vibration Test System TV 51120 (Tira GmbH, Schalkau, Germany), which can vibrate the powder box under controlled conditions during the capsule-filling experiments. All experiments were initially carried out in the same manner as the experiments without vibration (see above). For each instrumental setting 15 capsules, a sample size which was proved to be sufficient based on preliminary testing, were collected. Next, the powder box was subjected to vibration triggered by a vibration plate (adaption of the vibration settings explained in more detail in the following section). The procedure was repeated after 5 min and 30 min. By detecting the fill weight and weight variability over time, the evolution of the powder bed due to instrumental settings and powder characteristics can be monitored. Note that the overall procedure was performed using the same batch of powder during experiments, which was guaranteed by using an excess of powder in the scraper box at the beginning.

3.2.6.3 Adjusting the vibration parameters

Vibrations in the lab-scale capsule filling machine (Labby, MG2, Bologna) were recorded with a dynamic accelerometer (Seika BDK 100, Seika Mikrosystemtechnik GmbH, Wiggensbach-Ermengerst, Germany) which contains a capacitive spring-mass accelerometer with integrated sensor electronics, resulting in a resolution of $< 0.1g$, and a measurement frequency of 1651.61 Hz. Signal acquisition was performed using a NI-9234 (National Instruments GmbH, Salzburg-Bergheim, Austria) ETC high-accuracy analog input module specifically designed for high-

channel-count vibration applications and LabVIEW (National Instruments GmbH). The data were further analyzed via MatLab (R2014b, The Mathworks Inc, Natick, U.S.A.).

Due to the rotation of powder drum, it was impossible to directly attach the sensor to the bowl. Thus, several positions in proximity to the bowl were tested, and the one that yielded the largest vibration readouts was used further. The machine settings relevant to industrial production, with the minimum and maximum vibrations expected, were measured and analyzed.

The laboratory vibration setup (Vibration Test System TV 51120, Tira GmbH, Schalkau, Germany) consisted of an electrical amplifier, a cooling blower and a vibration exciter. A module NI 9263 (National Instruments GmbH) provides an analogue output for the amplifier. The same sensor as mentioned above was mounted on the vibrated plate to produce consistent results. Control of the acceleration occurred via a PID loop, as described in the work of Reif (2014).

3.2.6.4 Analysis of capsule fill weight and weight variability

The collected samples were weighed on a Denver (SI-234A) analytical scale. Due to a relatively high weight of empty capsules and their variability, the collected filled capsules were weighed, emptied and re-weighed. An air pistol was used to ensure that no powder was left in the capsule after it was emptied.

3.3 Results and discussion

3.3.1 Powder characterization

In the literature, it is well-known that numerous particle and powder attributes (and their combinations) affect the performance of a pharmaceutical unit operation. For example, Jones (2001) reviewed all the powder flow measurements that correlated with capsule-filling performance published in the literature up to 2001. Osorio and Muzzio (2013) updated this information in light of recent progress in the measurement techniques. In our work, we characterized the powders in terms of particle size distribution, flowability and powder porosity to enhance process understanding.

Particle size and size distribution

In capsule filling, the particle size (and size distribution) and shape are considered critical material attributes, since they are known to significantly affect the powder's flow characteristics over a wide range of stress conditions (Fu et al., 2012a). Furthermore, when filling capsules with various powders, the compressibility of powders, which is also affected by the size and shape of the particles (Llusa et al., 2014), requires special attention. The compressibility of powders plays an especially important role in standard dosator filling processes with the piston inside the nozzle moving downwards (vertical compressive stress) to form a plug. Also in low-dose dosator capsule filling processes that do not require a piston compaction step, compressibility is critical: the powder can be compacted if the powder bed height is higher than the applied dosing chamber length since in this case pre-compression occurs when the nozzle dips into the powder bed. For this process the minimum gap between nozzle tip and bottom of the container is a critical parameter as shown by the first computational work analyzing the dosator process (Loidolt et al., 2017b).

Table 1 presents the results for the particle size. Clearly, the width of PSD represented by the span value increases (within an acceptable range) for smaller particles.

Table 1: Particle size and size distribution of the three grades of lactose excipients (n = 3).

	Lactohale 100	Lactohale 200	Lactohale 220
Volumetric mean diameter [µm]	160.0 ± 0.6	$83.6 \pm$ n.a.	$16.4 \pm$ n.a.
x_{10} [µm]	100.52 ± 0.5	10.9 ± 0.1	2.4 ± 0.0
x_{50} [µm]	155.2 ± 0.6	78.7 ± 0.4	13.4 ± 0.0
x_{90} [µm]	229.14 ± 0.75	162.5 ± 0.4	33.8 ± 0.10
Span = $(x_{90} - x_{10}/x_{50})$ [µm]	0.83	1.93	2.34

Powder flowability

Many methods exits to characterize the flowability of powders (Peleg, 1977, Prescott and Barnum, 2000). Note that flowability is not a strictly defined quantity, such as powder density. In the present study we characterized the flowability of powders using the angle of repose (AoR)

method. In general, the AoR can be related to the inter-particulate friction or the resistance to movement between the particles. One of our main reasons for choosing this method was that it is commonly used in the pharmaceutical industry and that the literature contains a number of examples demonstrating its value in terms of predicting the manufacturing problems ("USP-NF Online," 2017). Another important reason was that this relatively simple method allows collecting input data for future *in silico* simulation studies (i.e., for calibrating a model to simulate the powder behavior in the process later on).

Table 2 presents the results of the angle of repose (AoR) flowability measurements of the carriers investigated and the corresponding qualitative description of the powders' flow properties according to the classification proposed by Carr (Carr, 1965). A value of 25–30° indicates an excellent flow and a value of >66° suggests a extremely poor flowability. The intermediate scale includes the ratings good (θ between 31–35°), fair (θ between 36–40°), passable – may hang up (θ between 41–45°), poor – must be agitated or vibrated (θ between 46–55°) and very poor (θ between 56–65°). According to this classification, the flowability of Lactohale 100 can be classified as good, Lactohale 200 as poor and Lactohale 220 as passable.

Table 2: Results of the AoR measurements (left) of the three grades of lactose excipients and qualitative description of the flow properties according to Carr (right).

	Measured Angle of Repose [°]	Flowability	Angle of Repose [°]
Lactohale 100	33.5 ± 0.7	good	31–35
Lactohale 200	51.9 ± 0.9	poor – must agitate, vibrate	46–55
Lactohale 220	43.7 ± 1.1	passable – may hang up	41–45

Table 3: Bulk and tapped densities and Hausner Ratio of the three grades of lactose excipients (n = 3).

	Lactohale 100	Lactohale 200	Lactohale 220
Bulk density (BD) [g/ml]	0.697 ±0.004	0.622 ±0.003	0.400 ±0.007
Tapped density (TD) [g/ml]	0.828 ±0.013	0.996 ±0.002	0.785 ±0.007
Hausner Ratio (HR)	1.187 ±0.024	1.601 ±0.006	1.964 ±0.044

Specific surface area (SSA)

Specific surface area (SSA) is a property of solids defined as the total (inner and outer) surface area of a material per unit of mass (Everett, 1972). The specific surface of the three grades of lactose excipients were investigated using the BET method, which is generally applied to measure the surface of accessible internal pore networks interconnected with the particle surface with spatial dimensions above 2 nm. More precisely, surface asperities, surface pores, as well as open pore networks interconnected with particle surface that is of spatial dimension above 2 nm, are accessible using this method.

Table 4 lists the results of the specific surface measurements, which are between 0.1 and 0.9 m^2/g. Significant differences in the specific surfaces were observed for the three excipients, which can be attributed to the distinct methods of powder manufacturing. Milled grades (i.e., Lactohale 200 and Lactohale 220) have consistently higher BET surface areas than the coarser sieved grades (i.e., Lactohale 100). The low values show that the particles have small internal surface area. (The external surface area of a spherical 10 (100) µm lactose particle should be approximately 0.4 (0.04) m^2/g). This indicates that for our powders have low porosity, and thus, the external surface area which can be an indicator for surface interaction, cohesivity, and thus, flowability.

Therefore, in terms of capsule filling, determining a specific surface area may help to classify powders in terms of the expected flowability behaviour.

Table 4: Specific BET surface area of the three grades of lactose excipients (n = 3).

	Specific BET surface area [m^2/g]
Lactohale 100	0.131 ± 0.005
Lactohale 200	0.256 ± 0.003
Lactohale 220	0.880 ± 0.014

3.3.2 Capsule filling: static and dynamic mode tests

Dynamic and static mode tests were performed in order to achieve a good understanding of the effect of (1) gaps between the dosator tip and the bottom of the box and (2) vibrations, which are known to be an important issue for dosator nozzle machines.

3.3.2.1 Decoupling to detect the effect of gaps on the fill weight and weight variability

In order to evaluate the influence of gaps between the lowest point of the dosator and the bottom of the powder box (Figure 2) on the fill weight and weight variability, three gap widths were examined: the standard gap for a lab-scale filler (Labby, MG2, Bologna) (gap B), a gap for low-dose capsule filling for an industrial scale filler (Planeta, MG2, Bologna) (gap C) and a gap smaller than the standard lab-scale gap (gap A). To be able to draw conclusions about the effect of the gap on the filling behavior, it is important to note the following sequence of distances: gap C > gap B > gap A. Thus, gap A is the smallest gap.

Table 5 presents the experimental plan (DoE) for the static mode tests with two dosator sizes (1.9 mm and 3.4 mm), i.e., the values of the four process parameters and the obtained fill weight and weight variability (RSD) for each setting. All experiments were carried out at a constant dosator dipping speed of 0.253 cm/s. If the powder could not be successfully filled into capsules (details described below), the runs were marked f.n.p., which stands for 'filling not possible'.
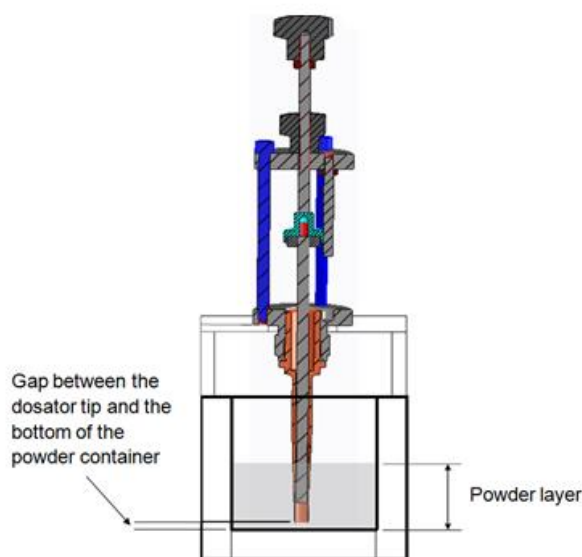

Figure 2: Sketch of the static test tool. The gap between the dosator tip and the bottom of the container are shown.

Table 5: Static mode tests: 24 experimental runs with 3 repetition experiments (gap A = gap smaller than the standard lab-scale gap, gap B = standard gap used for a lab-scale filler and gap C = gap for low doses for industrial scale filling).

				Lactohale 100		Lactohale 200		Lactohale 220	
RUN	Gap [mm]	Diameter [mm]	Powder bed height [mm]	Dosing chamber length [mm]	Weight [mg]	RSD [%]	Weight [mg]	RSD [%]	Weight [mg]	RSD [%]
1	Gap A	1.9	5	2.5	6.5	2.5	7.5	4.4	5.4	6.1
2	Gap A	1.9	5	5	5.8	54.5	3.9	117.2	6.2	9.7
3	Gap A	1.9	10	2.5	6.8	3.2	8.2	2.8	6.5	9.3
4	Gap A	1.9	10	5	11.8	4.1	13.6	3.6	8.2	15.6
5	Gap A	3.4	5	2.5	22.8	0.9	26.4	1.3	18.6	15.4
6	Gap A	3.4	5	5	f.n.p.	f.n.p.	24.2	56.9	20.4	8.2
7	Gap A	3.4	10	2.5	23.7	1.1	26.8	1.4	22.2	7.8
8	Gap A	3.4	10	5	38.4	0.6	45.4	0.7	29.8	11.6
9	Gap B	1.9	5	2.5	6.1	3.9	6.3	11.0	3.1	39.1
10	Gap B	1.9	5	5	f.n.p.	f.n.p.	f.n.p.	f.n.p.	3.6	51.5
11	Gap B	1.9	10	2.5	6.0	2.6	7.5	3.4	6.0	7.1
12	Gap B	1.9	10	5	9.9	5.5	12.6	5.2	7.1	18.3
13	Gap B	3.4	5	2.5	21.4	2.5	25.5	7.8	15.3	11.2
14	Gap B	3.4	5	5	f.n.p.	f.n.p.	f.n.p.	f.n.p.	f.n.p.	f.n.p.
15	Gap B	3.4	10	2.5	22.9	1.4	27.5	2.3	20.1	4.0
16	Gap B	3.4	10	5	38.9	1.7	47.7	0.8	26.7	13.2
17	Gap C	1.9	5	2.5	4.2	51.4	5.9	11.3	3.2	31.1
18	Gap C	1.9	5	5	f.n.p.	f.n.p.	f.n.p.	f.n.p.	3.3	42.6

19	Gap C	1.9	10	2.5	5.5	4.3	6.6	4.9	4.7	10.1
20	Gap C	1.9	10	5	10.2	5.1	11.9	1.6	6.7	12.2
21	Gap C	3.4	5	2.5	19.1	3.2	22.0	3.7	12.8	7.3
22	Gap C	3.4	5	5	f.n.p.	f.n.p.	f.n.p.	f.n.p.	f.n.p.	f.n.p.
23	Gap C	3.4	10	2.5	20.0	1.6	23.3	1.4	19.0	8.9
24	Gap C	3.4	10	5	36.7	1.2	43.1	1.2	25.9	8.7

Table 5 shows that the fill weight of the three powders is affected by varying gaps, but in different ways. For the most compressible powder (Lactohale 220), the fill weight correlated with the gaps (gap C > gap B > gap A), increasing when smaller gaps existed in all combinations of instrumental settings. These findings are discussed in more detail in below. For the 'intermediate' Lactohale 200, the correlation between the fill weight and the gaps was observable only in the case of the smaller dosator (1.9 mm). The fill weight of Lactohale 100 (large particles, good flowability, low cohesion) did not correlate with the varying gaps. Interestingly, for the larger dosator (3.4 mm) the fill weight of Lactohale 100 and 200 powders varied only slightly for the two gaps used on the lab-scale (standard and smaller gap) and significantly dropped in the case of the gap used on the industrial scale for low doses. Thus, it can be hypothesized that for these powders the critical part determining the fill weight is the lowest part of the dosator dipping step, close to or at the end of the stroke. This can be explained by viewing a powder plug mass as a function of the particle size, i.e., as a geometric effect that may be more relevant for larger particles: more compression of big particles occurs near to the bottom due to earlier confinement of particles, resulting in higher fill weight (Loidolt et al., 2017b). Additionally, it can be expected that when a larger gap is used, it is much easier for the powders with good or moderate flowability to escape from underneath the dosator than in the case with a lower gap and for highly cohesive powders (due to the lack of powder mobility caused by large inter-particle interactions triggered by cohesive forces). Similar findings were also reported in a recently published study by Loidolt et al., 2017. These findings demonstrate that special care has to be taken when capsule filling is performed on different machines, as well as for predicting fill weight after scaling up the process from a lab-scale to an industrial scale one.

In terms of the fill weight variability (RSD), the highly cohesive powder Lactohale 220 had the highest one, as expected. For all three powders, no clear trend between the instrumental settings and the weight variability was observed, except for the dosator size (a higher weight variability occurred for a smaller dosator, which was already discussed in our recent work, e.g., Faulhammer et al., 2014a; Faulhammer et al., 2015; Stranzinger et al., 2017).

Valuable insights into avoiding a pre-compaction step during capsule filling were obtained, which is especially relevant for inhalation applications, since the plug has to revert to a loose powder to guarantee an efficient dose delivery (Faulhammer et al., 2014b). The highly cohesive powder could be filled successfully (with the acceptable weight variability below 10 %) using the smallest gap at a dosing-chamber-length-to-powder-bed height compression ratio of 1:1 (i.e., no pre-compression of powder during filling). As reported by Faulhammer et al. (2014a), the fill weight of powders with smaller particles and lower densities is significantly affected by frictional (wall friction angle) and powder flowability characteristics. Therefore, for highly-cohesive powders it can be expected that a combination of the friction effect and greater inter-particle forces in highly cohesive powders are sufficient to keep them inside the nozzle.

Figure 3 depicts the results for the highly cohesive powder Lactohale 220 in more detail. It is clear that the powder was successfully filled in all combinations of process settings (except for the combination of a larger dosator and a dosing-chamber-length-to-powder-bed height compression ratio of 1:1). Based on these results, particular combinations of settings can be suggested for this powder. When a smaller dosator (1.9 mm) is used for capsule filling, the best filling performance in terms of weight variability (low RSD's) can be achieved using a small dosing chamber length (2.5 mm) with a large powder bed height. A short dosing chamber length with a powder bed height of 5 mm is also recommended for accurate capsule filling, but only with the smallest gap. Based on these observations, we hypothesize that at a compression dcl/pbh-ratio of 1:4, the gap size is irrelevant: in all cases the compression due to the dosator moving down through a considerable powder bed height is sufficient to reduce any variations within the dose that is collected during dosing. In the case of a smaller powder bed heights, a very small gap is required to obtain the critical compression of powder required for a low variation inside the dosator, In other words, for filling with low RSDs not only the combination of a certain dosing chamber length and powder bed height is critical, but also the gap has to be taken into account. This is highly relevant for achieving content uniformity of inhalation capsules.
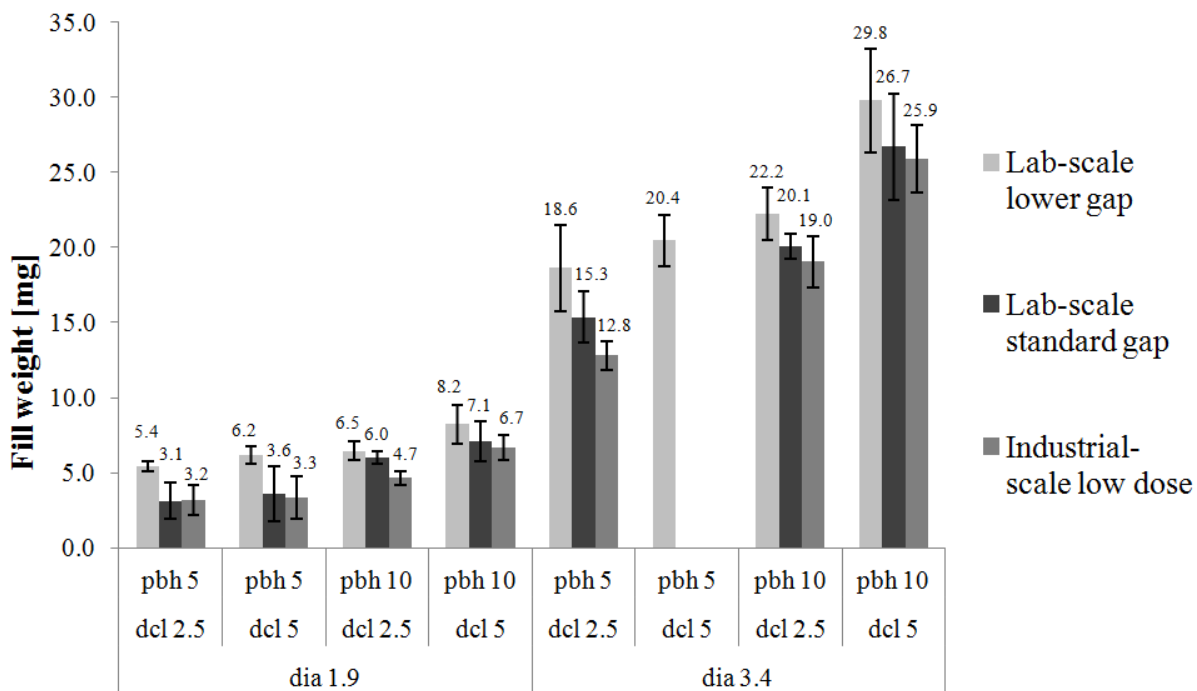
Figure 3: Fill weight and weight variability of Lactohale 220 for different gaps. Pbh = powder bed height, dcl = dosing chamber length, dia = diameter of dosator

Another interesting aspect of the data (see Table 5 and Figure 3) obtained from the static mode tests for the highly cohesive Lactohale 220 is that at the low gap setting the powder could be filled using both dosator sizes (1.9 mm, 3.4 mm) at a dcl/pbh-ratio of 1:1 with an acceptable weight variability (below 10%). This means that lowering the gap makes it possible to fill the very fine Lactohale 220 within a range of 6 mg to 20 mg with RSDs below 10% without any pre-compression. This discovery is highly valuable since (1) filling lactose powders (especially fine lactose powders) at high compression ratios tends to be challenging due to jamming and blocking of the piston (Tan and Newton, 1990b) and (2) filling very fine lactose powders can be beneficial in terms of density similarity with APIs (Stegemann and Bornem, 2002), meaning that pure API can be filled into capsules even on the industrial scale. The latter is particularly important since during a dosator capsule-filling process the powder blend (lactose powder and API) rotates in a powder container, possibly leading to segregation due to differences in powder density, particle mobility induced by the different shapes of particles (a non-spherical shape leads to non-isotropic

particle orientation and a different particle mobility) and, above all, the particle size (Cullen, 2009). Segregation results in poor blend uniformity and high dosage variability. To prevent segregation and to ensure a high product quality, filling excipients with small particle sizes together with APIs with an aerodynamic diameter of 1 µm – 5 µm for the DPI applications (Daniher and Zhu, 2008) could be advantageous

3.3.2.2 Effect of vibration on the fill weight and weight variability of Lactohale 220

Since fine and cohesive powders are notoriously hard to fill, we extend here our previous findings on the fill weight increase over time for highly cohesive Lactohale 220 (Stranzinger et at. 2017). To the best of our knowledge, to date it has not been established which parameters have the greatest influence on the reported increase in the fill weight of this fine powder over time during low-dose dosator filling, as reported before. To examine this effect more closely, we selected a combination of process settings in the Labby that resulted in the most significant changes in the fill weight: a dosator diameter of 1.9 mm, a dosing chamber lengths of 5 mm and a powder bed height of 10 mm at a filling speed of 3000 cph (Stranzinger et at. 2017).

Vibrations are known to be an important issue when filling capsules with a dosator nozzle system. Typically, capsule fillers are equipped with a rotating bowl that contains a powder bed from which a desired volume of powder is collected and loaded into a capsule. The powder bowl is subjected to vibration when it rotates. As a result, the powder in the container is densified to a certain extent. For example, Llusa et al. (2013) confirmed a correlation between the powder densification under more intense vibrations and a higher fill weight.

In our study, we used a stand-alone static test tool to understand the effect of vibration on the critical quality attributes, which in our case were the capsule fill weight and weight variability. To this end, we subjected the powder in the static powder bed to a similar level of vibrations as the ones observed in the Labby operated at a speed of 3000 cph. The experimental setup is described above. Samples were taken over a run time of 30 min.

Recordings of the vibrations on the Labby were done for several minutes and subsequently analyzed. A histogram of the measured acceleration is shown in Figure 6. Note that, due to the off-site placement of the sensor, the accelerations in the acceleration sensor may not be identical to the real accelerations inside the powder bowl. To identify the dominant frequencies, a Fast-Fourier-Transformation was applied to the accelerometer data. The power spectrum is also shown

in Figure 6. As expected, the signal indicates a major background noise due to the effect of stainless steel parts of the machine, which reflected and distorted the vibrations during measurements. Evidently, the amplitudes at low frequencies are very low. This is consistent with our visual observations that did not suggest clearly detectable vibrations. Nonetheless, some dominant frequencies were observed and chosen for the laboratory application.

An acceleration in the sine-wave form was selected to represent the more complex accelerations of the actual machine. The direction was vertical (i.e., parallel to gravitational acceleration), the same way the powder drum is installed in the capsule filling machine, with a spindle preventing the lateral movement of the drum and making only a vertical movement possible.

To represent vibration as a sine wave, the dominant frequencies and the corresponding maximum (i.e., the limits of the 95% area of the histogram) were chosen to be 0.842 g (8.26 m/s²) at 374 Hz at 3000 cph and 0.278 g (2.73 m/s²) at 579 Hz at 500 cph, resulting in very low amplitudes. Since it was not clear if the measurement positions represented the powder drum, additional experiments were performed at the same frequencies, yet with larger amplitudes and accelerations in order to induce clearly-observable reactions in the powder bed.
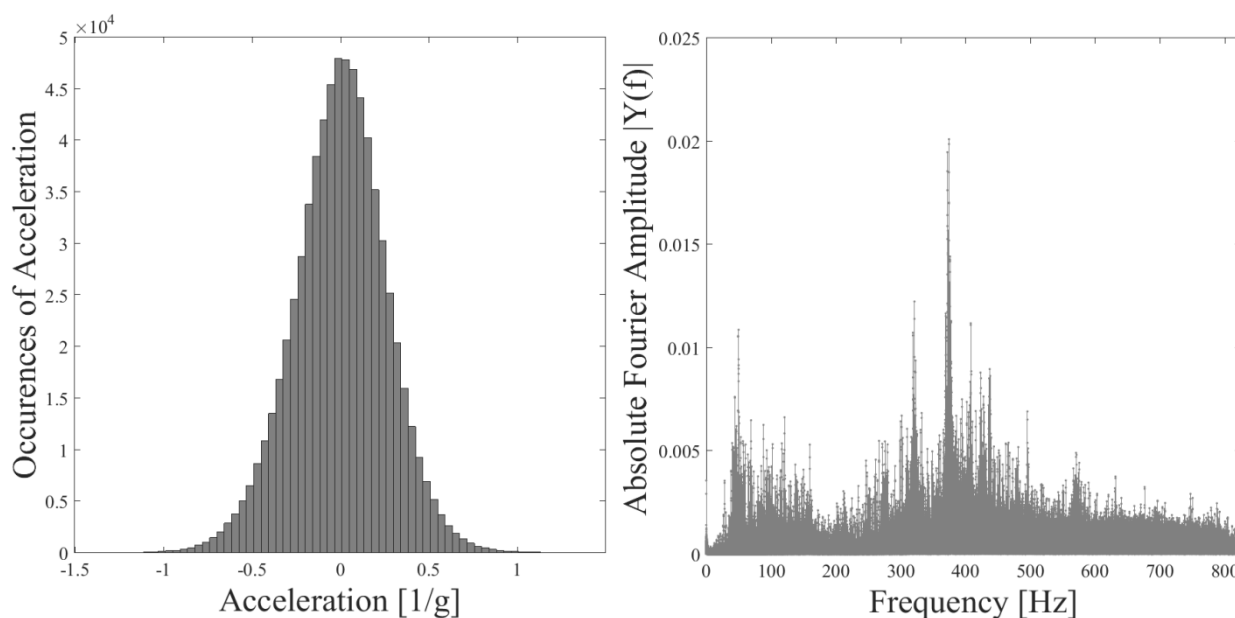
Figure 6: Vibration measurements at an operating speed of 3000 capsules per hour in the Labby. Left: Histogram of accelerations. Right: Fourier Transformation of the acquired signal, showing the dominant frequencies.

Figure 7 presents a comparison of the results of experiments carried out in the dynamic mode at 3000 cph, in the static mode without vibration and in the static mode with vibration adjusted to be similar to the machine running at 3000 cph. The initial fill weight and weight variability are shown, as well as results at 30 min.
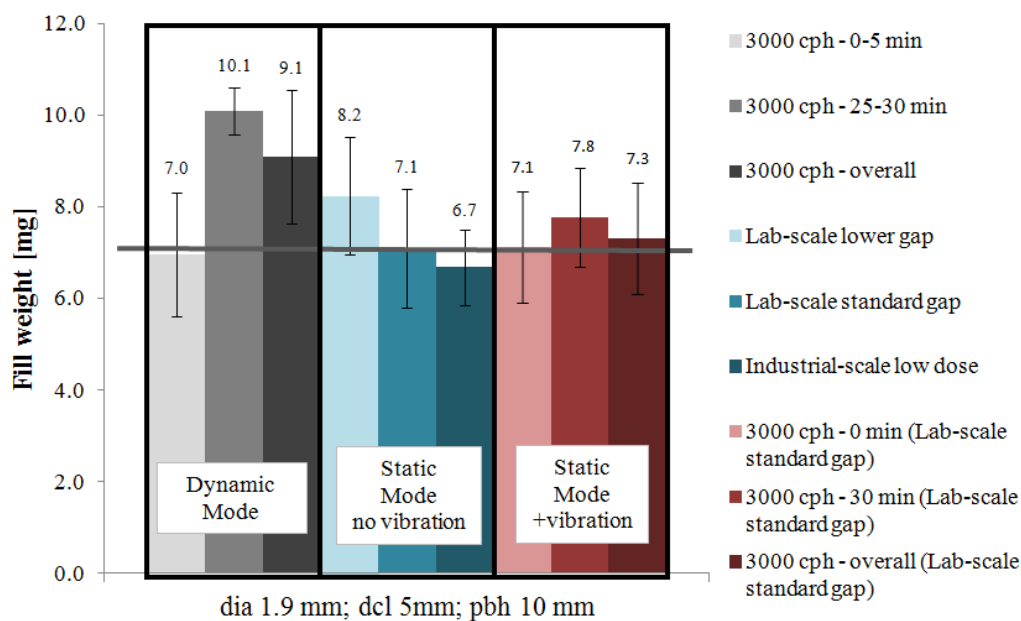

Figure 7: Fill weight and weight variability of Lactohale 220 for experiments in the dynamic mode, static mode without vibration and static mode with vibration. The lab-scale standard gap (gap B) was used in dynamic mode and in static mode with vibration. In static mode without vibration the gaps A-C were tested.

Interestingly, the results of static mode tests with vibrations (0.842g at 374 Hz, comparable to those in dynamic mode at 3000 cph) did not show a major change in the fill weight over a run time of 30 min (7.1mg to 7.8 mg, yet with large RSD). However, there are significant differences in the results obtained with the static and dynamic mode. There are several possible explanations of differences in the results obtained using the two modes of capsule filling:

(1) In the static mode, the powder is collected from a non-rotating rectangular powder box and the powder layer is created by manually moving the scraper box (with powder) from one side to the other. In the dynamic mode the powder layer is formed by scrapers that are

mounted on a fixed position above the powder container to continuously smooth the powder bed surface with each rotation. Consequently, the formation in the powder bed is different, introducing differences in the observed data.

(2) The scraper could be responsible (in addition to the vibrations) for densifying the powder over time, resulting in an increase of the powder density. Typically powder accumulates in front of the scraper, forming a little hill and being compacted. This is quite possible for Lactohale 220 since the powder enters the powder bowl with poured bulk density and the tapped density is much higher, i.e., the HR of this powder is 1.964 ±0.044. In contrast the increase in fill weight for the non-cohesive Lactohale 100 (Stranzinger et at., 2017), was very low, due to the low HR of this powder (1.187 ±0.024).

(3) The effect of the applied mode of vibrations (horizontal versus vertical) may play a role. For example, Deparlment and Road (1984) found that the application of vibration in the vertical mode markedly increased the uniformity of the powder packing, while horizontal vibrations were less effective in this respect. In our experiments, the powder bed in the static mode was subjected to vertical movements only, whereas in the dynamic mode the powder bed was exposed to vertical movements and also to some degree to horizontal vibrations. In principle, a spindle should prevent the lateral (horizontal) movement of the drum, however, it is expected that some minor lateral movement of the drum cannot be avoided. Furthermore, as the powder drum rotates during processing, rotational movement also needs to be taken into account.

(4) Different sampling conditions may have an effect. In the dynamic mode, the dosator dips into the powder bed, which is continuously subjected to vibration, whereas in the static mode sampling is performed after switching the Vibration Test System off. Hence, it can be expected that, in the dynamic mode, during the descent of the dosator into the moving rotary container the powder is likely to move inside the dosator. To understand the effect of sampling with/without continuous vibration, additional static mode tests using a different sampling strategy, as described in the following paragraph, were performed.

In addition to the static mode experiments with adjusted 3000 cph vibrations, we performed experiments with more intense vibration (maxG) and experiments using another sampling strategy "dosing under vibration". For this, the vibration plate remains switched on throughout

the duration of the experiment (incl. during sampling) in contrast to our previous described experiments where the vibration plate was turned off for each sampling step.

Figure 8 presents the fill weight and weight variability after a run time of 30 minutes. No significant increase in the fill weight was observed when subjecting the powder bed to more intense vibration (two bars on the left). However, the most interesting discovery in terms of weight variability was made by changing the sampling strategy. Dosing in the presence of vibration decreased the weight variability much more than dosing when the vibrations were turned off for the sampling procedure: it was reduced from 14.0% RSD to 4.5% RSD for the adjusted 3000 cph vibration and from 18.8% RSD to 6.5% under more intense vibration (maxG). Moreover, the dosed mass increased significantly with the intensity of vibrations, from an average of 8.1mg to 9.8 mg. The effects of vibro-fluidization of powders that achieves fluid-like behavior, as described in the work of Reif (2014), may explain this phenomenon. This in turn may lead to a more uniform dosing mass, as expressed by a low weight variability. Thus, exposing the system to systematic vibrations (in addition to the naturally occurring ones) might improve the capabilities of current dosator systems. In summary, these results show that the most critical process step that determines fill weight and variability is the way and mode at which powder enters the nozzle.
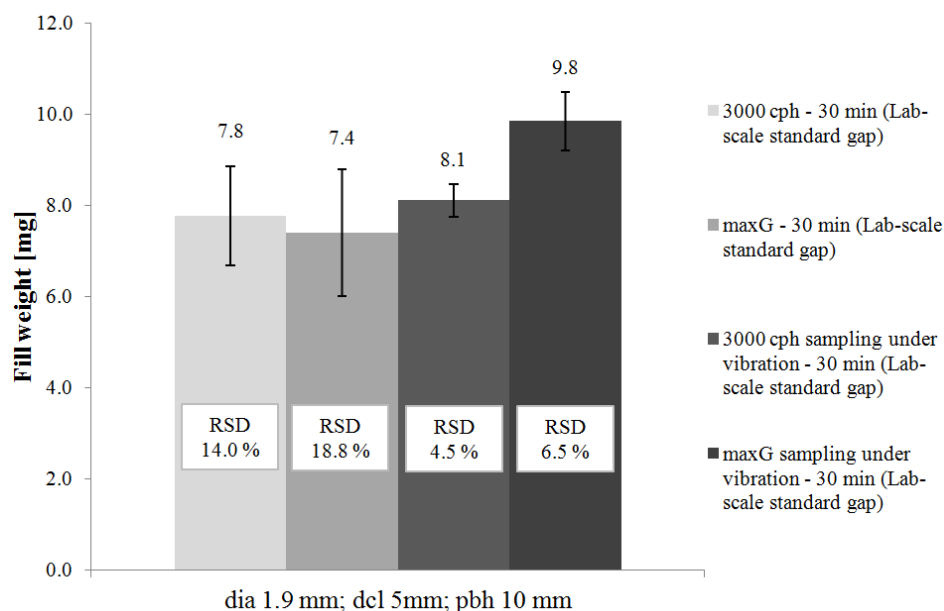

Figure 8: Fill weight and weight variability of Lactohale 220 for experiments in the static mode with different vibrations and using different sampling methods (run time 30 min).

3.4 Conclusions and outlook

The present study was designed to assess factors that influence the quality of capsules filled via a dosator nozzle system by decoupling the process in the dynamic and static mode tests. The effects of (1) gaps between the lowest point of the dosator and the bottom of the box and (2) vibrations, which are known to be an important issue for a dosator nozzle process, were examined.

The investigation of gaps between the lowest point of the dosator and the bottom of the powder box indicated that, generally, the fill weight of all three powders in question was affected by varying the gaps, but in different ways. The most significant changes in the fill weight were observed in the highly cohesive Lactohale 220, with a distinct correlation between the gaps and the fill weight: the smaller the gap, the higher the fill weight. These findings clearly demonstrate that special care has to be taken when capsule filling is performed on different machines and can be used for predicting the fill weight and weight variability after scaling up the process from the lab scale to the industrial one.

Another significant finding of the static mode tests was that with a small gap it was possible to fill the highly cohesive Lactohale 220 within a wide range, from 6 mg to 20 mg, with RSDs below 10% without any pre-compression. This is important with regard to filling capsules with very fine powders since compressing the powder into the dosator may lead to jamming the piston, blocking the dosator and stopping the process.

Interestingly, in terms of vibration no change in the fill weight of highly cohesive Lactohale 220 over time, as previously reported by Stranzinger et al. (2017), was observed in the static mode dosator dipping tests. This may be explained by the different modes of applied vibration (i.e., horizontal and vertical vibration), different sampling conditions and different powder layer re-conditioning strategies. Interestingly, we found that the sampling method, i.e., sampling with or without vibration, plays a key role in terms of weight variability.

Generally, our findings suggest that for low-dose dosator capsule filling it is strongly recommended to continuously control instrumental settings, i.e., gaps between the lowest point of the dosator and the bottom of the box, as well as vibration that clearly affects the fill weight and weight variability. Researching the effect of certain process parameters of various powder materials on the filling performance provides valuable insights into a dosator nozzle filling

process, step by step. Our results could help machine manufacturers to achieve product-specification compliance by fine-tuning the process parameters depending on the powders used.

Since this study was focused on the filling performance of pure carrier material, further research should be conducted to investigate the filling behaviour of powder mixtures (e.g., a powder with an API). In the end, a stepwise mechanistic process understanding could be developed, with the ultimate goal of creating a platform indicating the required instrumental settings for a range of various materials.

3.5 Acknowledgments

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4. Measuring bulk density variations in a moving powder bed via terahertz in-line sensing

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Graphical Abstract
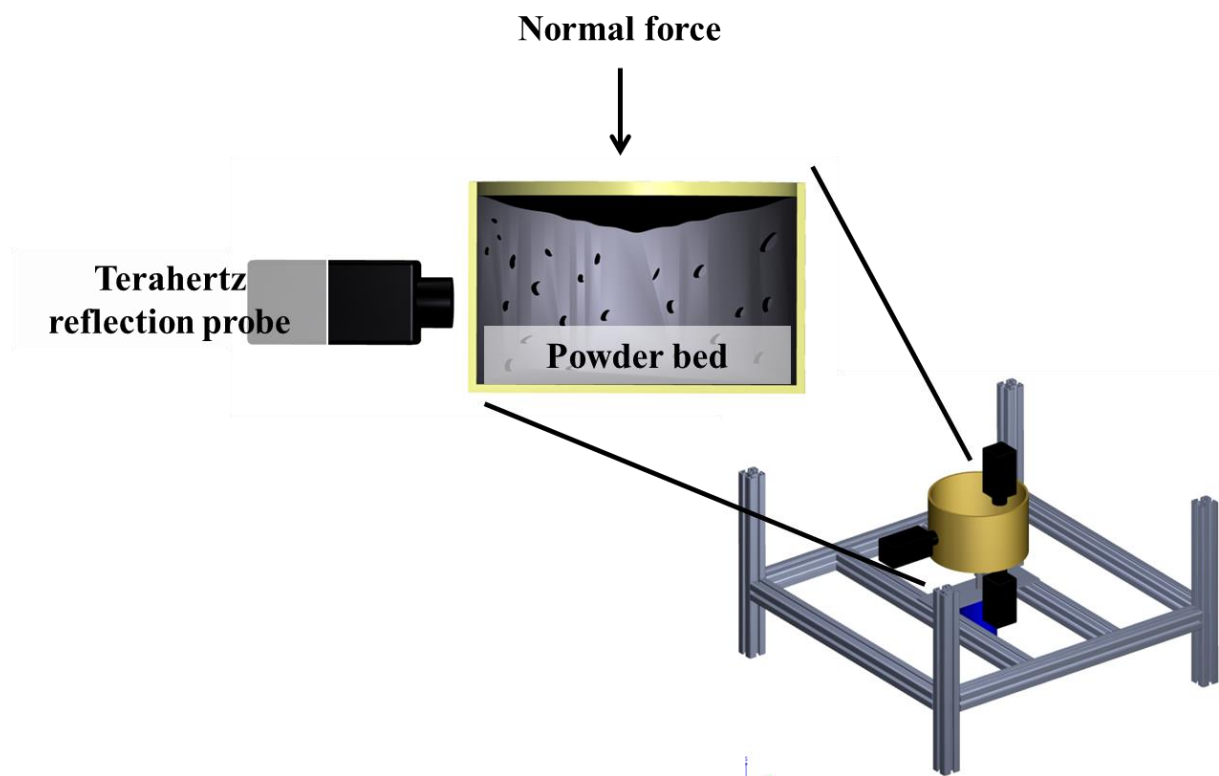
Measuring bulk density variations in a moving powder bed via terahertz in-line sensing

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ABSTRACT

Monitoring the relative density of static or moving powder inside a process line is essential for manufacturing high-quality products. The aim of this study was to quantify density variations in a moving powder bed using terahertz reflection technology. We systematically investigated three grades (varying true density and particle size) of two materials: lactose and silicified microcrystalline cellulose (SMCC). These six powders specifically differ in their compressibility, which can be applied to assess the sensitivity and applicability of our method. The powders were filled into a round container, and terahertz reflection measurements were acquired continuously during the container's rotation. The setup allowed to adjust the relative density by compacting the powders into specific powder bed heights. Each powder was compacted to various relative densities (compression pressures up to 100 kPa). We calculated the surface refractive index based on the in-line terahertz measurements acquired during rotation, which has a linear dependence on the relative density of the powder. This was confirmed by correlating the refractive index values with the theoretical relative densities based on the bulk and true densities of the powder. The coefficient of determination (R^2) was larger than 0.962 (Lactohale 100) for all six powders, with the highest coefficients for Lactohale 220 ($R^2 = 0.996$) and SMCC 50 LD ($R^2 = 0.995$). The results suggest that the proposed method can resolve relative density variations that are as small

as 0.3% (Lactohale 100). The high acquisition rate of the terahertz system (15 Hz) made it possible to determine the powder density in 230 positions uniformly distributed throughout the container, facilitating the investigation of the relative density uniformity in the container as a function of the powder bed height. It was observed that SMCC powders undergo a smaller change in the relative density variations upon compaction than the lactose powders. Moreover, the relative density maps clearly indicate local density differences in the powder bed for all powders. The relative density variations (in the horizontal direction) that were introduced by packing of the container prevailed throughout the compaction process for all samples with the exception of Lactohale 220. The presented approach allows a precise resolution of the spatial distribution of relative density, which facilitates an in-depth analysis of powder behavior upon compaction.

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4.1 Introduction

Handling granular materials, including powders, plays a crucial role in many industries (such as pharmaceutics, agriculture, food and cosmetic production, mining, catalysis technology, chemical processing and environment) and modern technologies (such as additive manufacturing). In fact, most of the raw materials used for manufacturing end products are granular materials, whose handling (e.g. transporting, conveying, storing, dosing) is known to be challenging due to their application-dependent performance and their material attributes that hinder an establishment of general constitutive equations relating shear rates and stresses [1–3]. Granular materials, and in particular powders, are considered to be two-phase systems consisting of a dispersed phase of solids of various sizes and gas as the continuous phase. Consequently, the behavior of powder materials depends on the properties of the particle as an individual entity, the properties of an assembly of particles, and the interactions between those assemblies and the continuous phase [4]. Even though bulk properties are known to have an important effect on many processes and unit operations that involve powders and particulates [4], measuring the process/raw material variability in real-time and initiating corrective actions before it can influence the product quality is still a major challenge [5].

This is particularly important for the manufacturing of pharmaceutical solid dosage forms. The production of pharmaceuticals comprises various processes, and the majority of operations (i.e., roller compactors, twin-screw granulators, tableting machines, additive manufacturing and capsule filling) require a densification of the raw or intermediate material. As such, the relative densities of the intermediate and final product are highly critical for the product quality and need to be monitored and controlled to assure a consistent product performance. In general, the powder density can be a useful parameter in the design, optimization and scale-up of manufacturing processes, where density could be used as an equipment-independent scaling parameter [6]. Furthermore, as the pharmaceutical industry is moving from batch to continuous processing [7–9], real-time monitoring of the product's quality is inevitable, and robust quality descriptors are essential for realizing the process control [10].

Much of the current literature on the manufacturing of solid dosage forms pays particular attention to techniques for in-line monitoring of the blend uniformity, with near-infrared spectroscopy (NIRS) being the most widely-employed process analyzer [11–17]. Other non-destructive techniques, such as Raman spectroscopy [18–20], light induced fluorescence [21],

and chemical imaging [22–25], are used for on- and in-line measuring of the blend uniformity [26]. However, even if the blend uniformity is adequate, density changes in the product may lead to undesirable variations in the product performance. Density variations can either cause an excess/lack of drug in a single dose or affect the microstructure, which may influence the dissolution behavior of the final product [27]. Thus, it is crucial to control not only the drug concentration but also the relative density during processing.

To date, only a few studies have attempted to monitor density variations in a powder bed. For example, Singh et al. [5] proposed a novel method for real-time monitoring of powder bulk density using a NIR sensor and performed a sensitivity analysis to quantify the effects of the powder's bulk density on the critical quality attributes of pharmaceutical tablets. Recently, NIRS calibration models for real-time prediction of powder density (tap, bulk and consolidated) were developed for a pharmaceutical formulation [28]. Moreover, other approaches for monitoring powder bulk densities have been reported in the literature: an analytical ultrasound method [29], an air-coupled acoustic technique [30], photo-acoustic testing [31], acoustic emission measurements [32], microwave measurements [33,34], X-ray based methods [35], thermal effusivity monitoring [36] and electrical tomography [37]. However, quantitative real-time measurement of bulk density variations in a moving powder bed remains a challenge [5].

Terahertz time-domain spectroscopy (THz-TDS) has recently emerged as a promising analytical tool for characterizing the pore structure of tablets [38]. In general, within the last ten years, a rapid development of terahertz systems and their commercialization driven by their inherent potential for quality control have created many exciting opportunities in the pharmaceutical sector [39]. The terahertz spectral region, which can be explored using typical commercial systems, covers the range from 0.1 to 4 THz or 3 mm to 30 μm, respectively [40]. Compared with NIR, mid-IR and Raman spectroscopy, THz-TDS is inherently less vulnerable to the scattering effects in powders since it operates at a much longer wavelength [38]. Excipients that are most commonly used for the formulation of solid dosage forms are transparent or semi-transparent to terahertz radiation, and a pulse of terahertz radiation can easily penetrate a sample matrix [41]. This makes it possible to perform transmission measurements through tablets with a thicknesses of up to 5.3 mm [27]. In order to use THz-TDS to quantify the porosity and relative density of powders and porous media, pulses of terahertz radiation are propagated through the material of interest and the pulse delay is used to calculate the refractive index of the samples. This information can be combined with an effective medium theory to extract a range of the sample's

properties, including pore structure [37,42]. For example, May et al. [43] proposed terahertz pulsed using imaging (TPI) reflection measurements for determining the tablet density, reporting a strong correlation between the TPI results and tablet bulk density and how these relate to the tablet hardness.

This work had two objectives. The first one is the development of a novel approach to quantify density variations in a moving powder bed by means of terahertz technology. In contrast to previous publications, in our case the terahertz probe was applied in the reflection geometry. Powder samples of model excipients, i.e., lactose and silicified microcrystalline cellulose (SMCC) of varying densities and particle sizes, were systematically investigated at various stages of compaction in a moving powder bed. Refractive index values were extracted from the terahertz reflection measurements and the average relative density of the powder in the container was estimated based on the refractive index data. The second part of the paper introduces the method we developed for (1) studying the dependence of relative density on the compression pressure and (2) providing spatially resolved relative density variations in the powder bed for each powder.

4.2 Materials and methods

4.2.1 Materials

Three grades of lactose excipients (Lactohale 100, Lactohale 200, Lactohale 220) supplied by DFE Pharma (Goch, Germany) and three microrystalline cellulose (MCC) excipients (Prosolv® SMCC 50, Prosolv® SMCC 50 LD, Prosolv® SMCC 90) supplied by JRS Pharma (Rosenberg, Germany) were used as received. In order to minimize the manufacturer and batch-to-batch variations, the experiments were carried out using powders from the same batch and one supplier.

4.2.2 Powder characterization

All experiments were carried out under controlled environmental conditions (T = 20–24 °C, 40–60% relative humidity). The following material attributes were determined in triplicate: the true density was measured with a helium pycnometer (AccuPac II 1340, Micromeritics, Norcross, USA); the bulk (BD) and tapped density (TD) values and the median particle size (d50) for the lactose excipients were measured previously for the same batch of material [44–45]. BD, TD

values and the median particle size (d50) for MCC excipients were taken from the technical data sheets (i.e., product sample certificate of analysis) provided by the supplier.

Table 1 presents the bulk powder properties of the excipients and the theoretical amount of powder needed to fill the sample container to an initial target powder layer height of 30 mm.

Table 1: Densities and particle size (d50) of the lactose and MCC excipients used in this study. The mass in this Table refers to the theoretical weight of the powder filled in the container, in order to achieve a fill height of 30 mm.

Material	Bulk density (g cm^{-3})	Tapped density (g cm^{-3})	True density (g cm^{-3})	Particle size x50 (µm)	Mass (g)
Lactohale 100	0.697 ±0.004	0.828 ±0.013	1.5385 ± 0.0028	155.24 ±0.58	212.8
Lactohale 200	0.622 ±0.003	0.996 ±0.002	1.5426 ± 0.0024	78.72 ±0.44	189.9
Lactohale 220	0.400 ±0.007	0.785 ±0.007	1.5466 ± 0.0042	13.40 ±0.01	122.1
SMCC 50	0.31 (0.25 - 0.37)	0.44 (0.37 - 0.50)	1.5910 ± 0.0045	64 (45 - 80)	94.7
SMCC 50 LD	0.24 (0.20 - 0.30)	0.39 (0.34 - 0.47)	1.5866 ± 0.0041	50 (35 - 65)	73.3
SMCC 90	0.31 (0.25 - 0.37)	0.43 (0.37 - 0.50)	1.5852 ± 0.0037	122 (90 - 150)	94.7

All parameters are given as average values ± SD. The values in brackets for MCC are the specified limits, as listed in the technical data sheets.

4.2.3 Experimental setup

4.2.3.1 Rotary container and compression unit

A schematic of the experimental setup is shown in Figure 1. The container was made of high-density polyethylene (HDPE), which is transparent to terahertz radiation. The height of the container's interior was 45 mm. The compression unit consisted of a metal ring with a thickness

of 10 mm combined with a sensor block with a thickness of 63 mm. The pressure in the powder bed was adjusted by tightening a nut on the central screw that was used to assemble the compression unit and the powder container (Figure 1). Three load sensors (see Supporting Information) connected to a computer via an Arduino Uno (Arduino, Somerville, US) were used to measure the applied force, which was measured prior to each compaction stage.

The average relative density, $\bar{\varrho}_r$, of the powder was calculated as

$$\bar{\varrho}_r = \frac{m}{V\varrho_t} = \frac{m}{Ah\varrho_t} \qquad \text{Eq. 1}$$

where A and h are the cross-section area of the container and the fill height, respectively. ϱ_t is the true density (Table 1). $A = 2827$ mm² was kept constant throughout all measurements and was determined as

$$A = \left(\frac{D_o - D_i}{2}\right)^2 \pi \qquad \text{Eq. 2}$$

with $D_o = 138$ mm and $D_i = 78$ mm as the outer and inner diameter of the interior of the container. As mentioned previously, the pressure on the powder bed was adjusted by displacing the compression unit. This displacement was measured in eight positions from the top of the compression unit to the bottom of the container using a digital caliper prior to every measurement. An average value of the displacement was subsequently used to calculate the average fill height, $\bar{h}$, and eventually to determine $\bar{\varrho}_r$ (Eq. 1). A motor speed of 4 rpm was applied in each experiment.
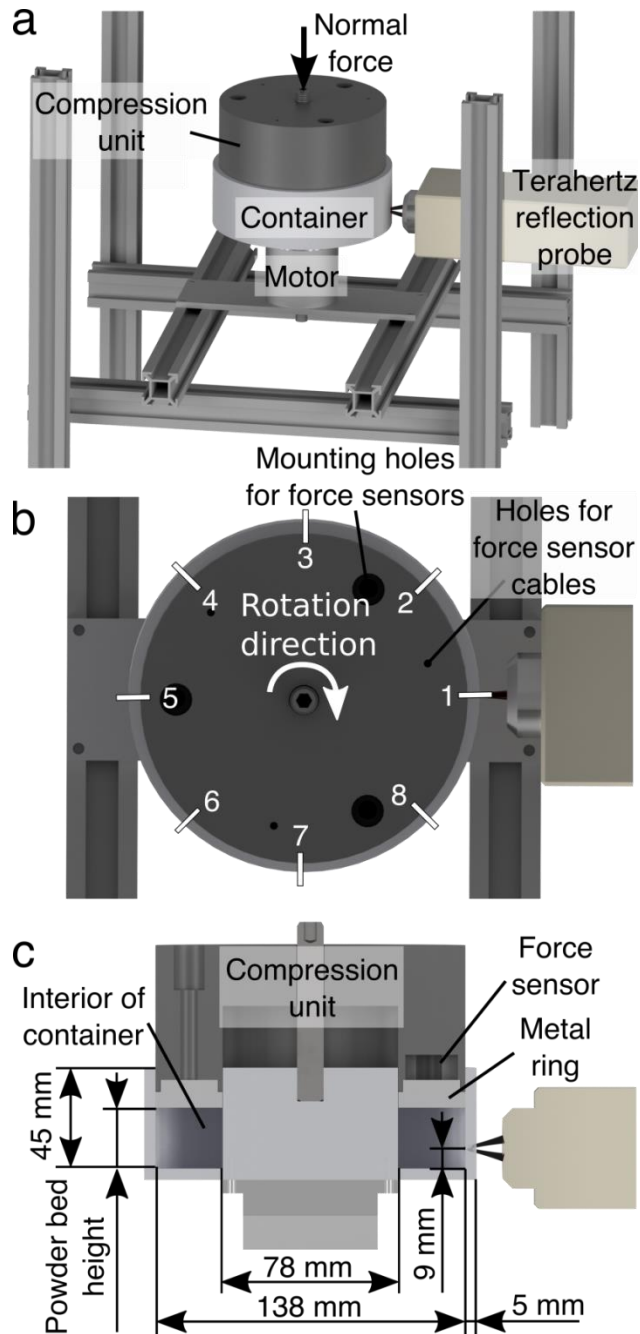
Figure 1: Schematic of the experimental setup for the terahertz reflection measurements. (a) A force is applied to the powder in the container by tightening a nut on the screw. (b) Top view of the setup, indicating the direction of the container's rotation and the displacement measurement positions (labelled as 1 to 8 in red). (c) Cross-section through the center of the container. The interior of container is filled with the powder. The powder bed height is determined in eight different positions, as indicated in (b).

4.2.3.2 Terahertz pulsed imaging

A commercial time-domain terahertz spectrometer (TeraPulse 4000, TeraView Ltd, Cambridge, UK) coupled with a fiber-based flexible reflection probe was used in this study. The system was configured to acquire the reflected terahertz pulse over an optical time delay of 45 ps at an acquisition rate of 15 Hz. The reflection probe had a silicon lens with a focal length of 18 mm. The beam waist at the focus was ≈600 μm. At each compression step, 2000 terahertz waveforms were acquired continuously while the container was rotating, which yielded a total measurement time of 133 s. These 2000 measurements covered about 8.5 rotations of the container. A narrow strip of copper foil was fixed to the outside of the container to reflect the terahertz pulse and serve as a datum to enable an automatic detection of a full rotation based on the terahertz waveforms. Seven full rotation were averaged, yielding $N = 230$ terahertz waveforms uniformly distributed around the container.

The focal point was set on the container/powder interface in order to detect the reflected terahertz pulse originating from it. A reduction in the amplitude of the reflected pulse from the container/powder interface related to an increase in the refractive index of the powder, n_p, which can be calculated using the Fresnel equation for reflection. We would like to emphasize that the calculation of the refractive index based on terahertz reflection measurements differs from determining it via a transmission setup that was employed for studying the porosity of powder compacts [37, 46–49].

In order to simplify the calculation of n_p based on the reflection measurements, we assumed that the terahertz beam is focused on a normal incidence on the HDPE container and that absorption of the HDPE container and the reflection from the air/container interface are negligible. Although these assumptions introduce a minor systematic error to the absolute magnitude of the calculated n_p, they do not affect the prediction of relative density based on the terahertz measurements.

In the case of normal incidence of the terahertz beam on the container, the Fresnel reflection coefficient, r_{cp}, can be expressed as

$$r_{cp} = \frac{n_c - n_p}{n_c + n_p}, \qquad \qquad \text{Eq. 3}$$

where n_c and n_p are the refractive indices of the container and the powder, respectively. The refractive index of the HDPE container is $n_c = 1.54$ [50]. Eq. 3 can then be rearranged as

$$n_p = \frac{n_c(r_{cp}+1)}{n_c - r_{cp}}. \qquad\qquad \text{Eq. 4}$$

r_{cp} was calculated by relating the amplitude of the reflected pulse from the container/powder interface to a reflection from the copper foil on the container. This reference reflection from the copper foil was acquired prior to every experiment. Details of data processing can be found in Supporting Information.

4.3 Results

4.3.1 Method development

4.3.1.1 Terahertz reflection measurements

The terahertz reflection measurements were acquired continuously during the rotation of the container. Since the container does not have a perfectly uniform diameter, the phase of reflection of the container/powder interface varied slightly. Variations due to the container's non-uniformity were corrected by applying the terahertz reflection data for an empty container (see Supporting Information).

In each experimental run, the required amount of powder (as shown in Table 1) was manually filled into the rotary container. A scraper was used to smoothen the powder layer prior to measuring the powder layer height and subsequent mounting the metal ring and the compression unit. As outlined in Section 4.2.3.1, the powder's relative density was adjusted by displacing the compression unit. For each compaction step the applied pressure on the powder bed was measured using the integrated force sensors. Moreover, a change in the powder layer height was measured at each compaction step with a digital caliper.

The terahertz pulse reflected from the container/powder interface appears negative in the terahertz time-domain waveform (Figure 2) as $n_c > n_p$. Decreasing the powder bed height results in an increase in n_p in the relative density. The difference between the container and the powder refractive indices ($|n_c - n_p|$) decreases, which reduces the amplitude of the reflected terahertz pulse. In theory, n_p ranges from 1 (only air) to the intrinsic refractive index of the powder, i.e., the refractive index of the solid skeleton material without any air voids. The refractive indices of pure α-lactose monohydrate and MCC at 1 THz were reported as ≈1.67 [51] and ≈1.85 [48],

respectively. However, the intrinsic refractive indices of the powders used in this study may slightly vary from this value.
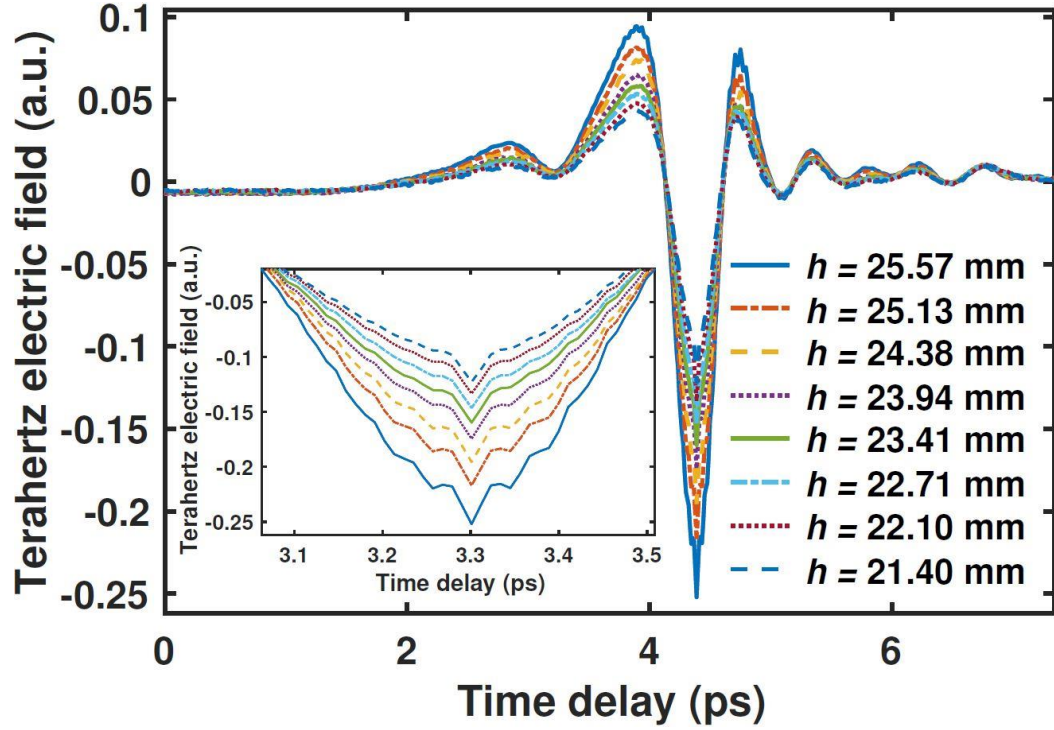

Figure 2: Aligned and averaged terahertz time-domain waveforms for various displacements of the experiment with Lactose 220 at a motor speed of 4 rpm.

4.3.1.2 Relationship between measured n_p and relative density

As shown in Figure 3, there is a linear relationship between the measured refractive indices and the relative densities of the six powders within the range of relative densities studied. In particular, the refractive index measurements of Lactohale 220 ($R^2 = 0.996$) and SMCC 50 LD ($R^2 = 0.995$) correlated strongly with the respective densities (Table 2). These observations are in line with previous studies on the porosity of powder compact, which reported that the refractive index has a linear relationship with the porosity [42]. As such, a linear model was fitted to this calibration data, which is expressed as

$$\bar{\varrho}_r = a_0 + a_1 \bar{n}_p \qquad \text{Eq. 5}$$

where a_0 and a_1 are fitting parameters, $\bar{\varrho}_r$ is the average relative density from Eq. 1 and $\bar{n}_p = \sum_{i=1}^{N} n_{p,i}$ is the average refractive index with $n_{p,i}$ calculated by using Eq. 4 and the terahertz reflection measurement in position i. The dimensions and speed of the container and the acquisition rate of the terahertz system yielded $N = 230$ terahertz measurements per container rotation. Position i corresponds to a certain angle in the container (e.g., $i = 100$ corresponds to an angle of 157°) measured from the copper foil in the counter-clockwise direction. The noise was reduced by applying a moving average filter with a size of 5: the amplitude of reflection peak 0 of 5 waveforms was averaged before calculating $n_{p,i}$. The fitting parameters a_0 and a_1 were determined for every powder separately. These models were subsequently used to predict the relative densities in each position in the container based on the terahertz reflection measurements.
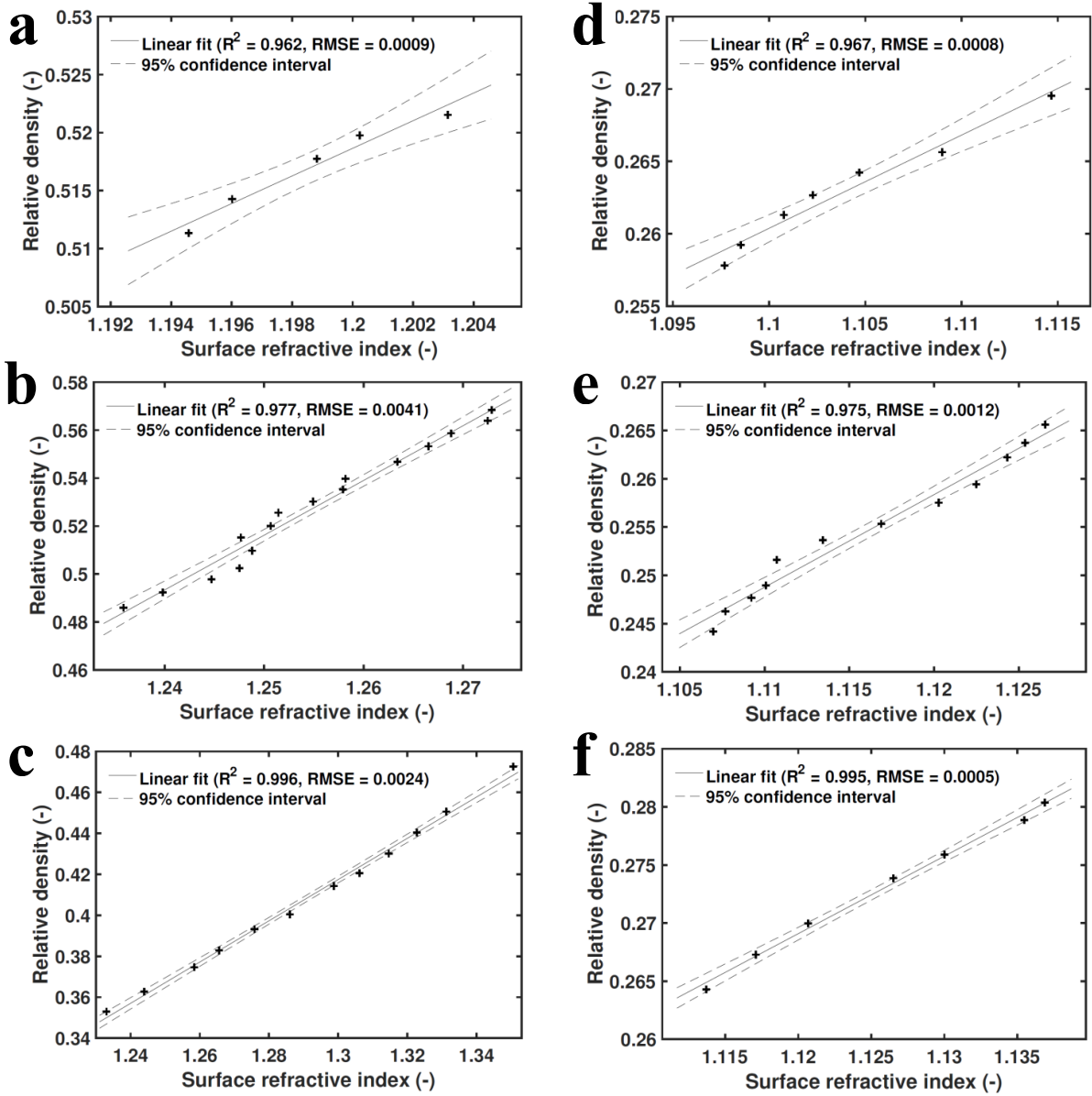
Figure 3: The relative density as a function of surface refractive index calculated based on the terahertz measurements for various powder bed heights. The relative density, $\bar{\varrho}_r$, and the refractive index, $\bar{n}_p$, were calculated using Eq. 1 and Eq. 4, respectively. (a) Lactohale 100, (b) Lactohale 200, (c) Lactohale 220, (d) SMCC 90, (e) SMCC 50 and (f) SMCC 50 LD.

Table 2: Fitting parameters and assessment of goodness of fit for the various powders.

Material	Fitting parameters		Goodness of fit	
	a_0	a_1	RMSE	R^2
Lactohale 100	-0.910 ± 0.163	1.190 ± 0.136	0.0009	0.962
Lactohale 200	-2.336 ± 0.117	2.281 ± 0.093	0.0041	0.977
Lactohale 220	-0.892 ± 0.026	1.007 ± 0.020	0.0024	0.996
SMCC 50	-0.816 ± 0.054	0.959 ± 0.049	0.0012	0.975
SMCC 50 LD	-0.478 ± 0.024	0.667 ± 0.021	0.0005	0.995
SMCC 90	-0.447 ± 0.059	0.643 ± 0.053	0.0008	0.967

RMSE: root mean squared error; the fitting parameters are shown with their standard errors.

The range of relative densities varied depending on the powder. The powders in this study have different compressibility values (volume change when compressed under a specific normal force), as demonstrated in our previous study [44]. We reported a compressibility at 8 kPa of 1.05%, 12.66% and 36.95% for Lactohale 100, Lactohale 200 and Lactohale 220, respectively. This influenced the calibration in that it limited the maximum displacement that could be achieved by the compression unit. In particular, the maximum relative displacement (related to the initial powder bed height) and maximum pressure (in brackets) values were 2% (97.7 kPa), 17% (85.5 kPa) and 51% (72.4 kPa) for Lactohale 100, Lactohale 200 and Lactohale 220, respectively. Therefore, the compressibility and the maximum displacement are in good agreement with our previous work, provided that a smaller displacement corresponds to a lower compressibility. The pressure on the powder was calculated based on the measured force using the integrated force sensors.

Given its limited compressibility, it was impossible to significantly vary the relative density of Lactohale 100 in the current experimental setup (Figure 3a). This means that the predictability of the linear model for Lactohale 100 is only valid within a small range of relative densities. The investigation of such small density changes for Lactohale 100, however, indicates that the

terahertz method resolved density variations that are as small as 0.3% ($\min_{k \in S}(1 - \bar{\varrho}_r(k)/\bar{\varrho}_r(k+1))$), with $S = \{1 \dots K - 1\}$ and K=the number of compression steps). In contrast, given the higher compressibility of Lactohale 200 and Lactohale 220, a much larger range of powder bed heights could be tested, resulting in a broader range of relative densities (Figure 3b-c).

In the preliminary experiments we investigated the effect of various motor speeds on the measurements. The results indicate that the motor speed (in the range of 4 to 16 rpm) has no influence on the average surface refractive index. However, a faster rotation of the container causes a lower spatial resolution of the terahertz measurements in the container since N decreases with an increasing motor speed at a fixed acquisition rate. As such, we applied a motor speed of 4 rpm in all experiments, which resulted in a spatial resolution of 1.57°.

4.3.2   Predicting relative density based on terahertz reflection measurements

The relative density variations of the powder bed were studied via the linear models, as discussed in Section 4.3.1.2. The relative density was subsequently determined based on the linear model (Eq. 5) as a function of the container angle and the powder bed height.

4.3.2.1 Dependence of relative density on the compression pressure

Data acquired by the force sensors (see Section 4.2.3.1) were used to develop an in-depth analysis of the relationship between the pressure applied and the relative densities predicted for the two powder types, i.e., lactose and MCC excipients. Data in Figure 4 suggest that, due to the powders' different compressibility, the range of relative density that can be explored in the rig varies between the two excipients. A broader relative density range for the lactose excipients compared to that of the MCC excipients is attributed to differences in the compaction behavior, which is significantly affected by the physicochemical and mechanical properties of the material [52]. Heckel [52] proposed density-compression force relationship, the Heckel plot analysis, which is often used to describe the plasticity of materials. For example, Teixeira [53] reported that, compared to lactose excipients, MCC excipients have a greater plasticity or plastic deformation at relatively low pressure and a lower brittle fraction. Lactose is commonly regarded as a predominately brittle material that breaks easily at relatively low deformation [54], whereas MCC is considered relatively ductile material that can undergo a significantly higher elastic and plastic deformation [54].
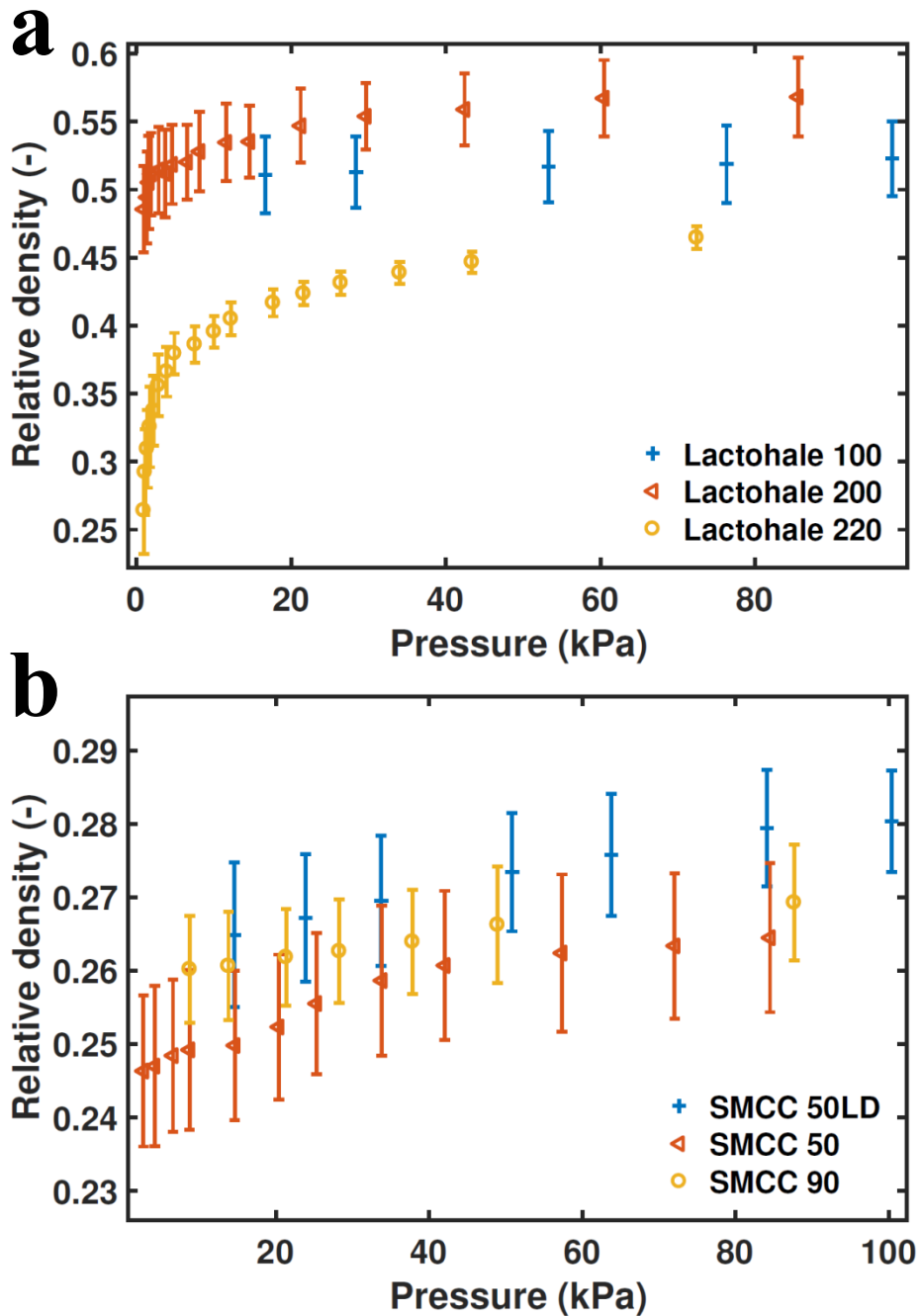
Figure 4: The relative density (calculated from the terahertz measurements) as a function of increasing pressure applied to the powder bed. The relative density, ϱ_r, and the refractive index, n_p, were calculated using Eq. 1 and Eq. 4, respectively. (a) lactose excipients (Lactohale 100, Lactohale 200, Lactohale 220); (b) microrystalline cellulose (MCC) excipients (SMCC 90, SMCC 50, SMCC 50 LD).

4.3.2.2 Spatially-resolved relative density variations

As described in the previous Section, in this setup we were able to spatially resolve relative density variations in the container. Moreover, a precise measurement of the powder bed height in eight positions (see Figure1b) of the container facilitates the investigation of density variations and powder bed height variations at a specific angle of rotation. The resulting maps of relative density and powder bed height variation resolved via the angle of rotation for each powder are shown in Figure 5 and Figure 6 for lactose and MCC, respectively.

Please note that the prediction of relative density values for Lactohale 100 was only calibrated over a small density range (51 – 52%) and the values outside this range were determined via a linear extrapolation. However, despite this limitation, significant density variations were clearly established in the powder bed for Lactohale 100 (Figure 5a). Comparing these local density variations as a function of container angle with the measured powder bed height variations (Figure5d) makes a relationship between those two parameters evident. In theory, a large powder bed height (yellow in Figure 5d-f and in Figure 6d-f) results in a low relative density (blue in Figure 5a-c and Figure 6a-c). This was observed for all powders except for Lactohale 220, which has the largest compressibility factor. Since the terahertz reflection measurement is performed about 9 mm above the bottom surface of the container, the powder bed height variations for Lactohale 220 are compensated for by the powder between the position of the terahertz reflection measurement and the top surface of the powder bed. This also suggests that the powder bed density varies significantly in the vertical direction. This could be investigated in the future by acquiring terahertz reflection measurements in various vertical positions at each compression step.

The data for Lactohale 100 indicate that applying normal stress to the powder bed in order to decrease the powder bed height does not affect the homogeneity of the powder bed, as reflected by the horizontal color distribution along vertical direction. Moreover, we compared local density variations for Lactohale 200 with those for Lactohale 100, which is a more non-uniform density powder bed upon compaction (Figure 5b and e). The results suggest that significant density variations in the container (in the horizontal direction) are introduced when the bed is packed and remain there throughout the compaction process. Based on this observation, we conclude that the filling process for such powders is particularly crucial since an initial variation in the powder bed height will yield a non-uniform relative density distribution even after several compression steps.

In contrast, Lactohale 220 has several stages of powder bed variations during compaction. In the beginning, moderate relative density variations in the horizontal direction were detected, which increased upon compaction and decrease again at the smallest powder bed height (Figure 5c,f). The reason may be that this highly cohesive powder has different stages of particle reorganization upon compaction. Moreover, the findings are possibly linked to a significant amount of air entrapped in the powder layer, which may introduce inhomogeneity and variations in the relative densities throughout compaction.
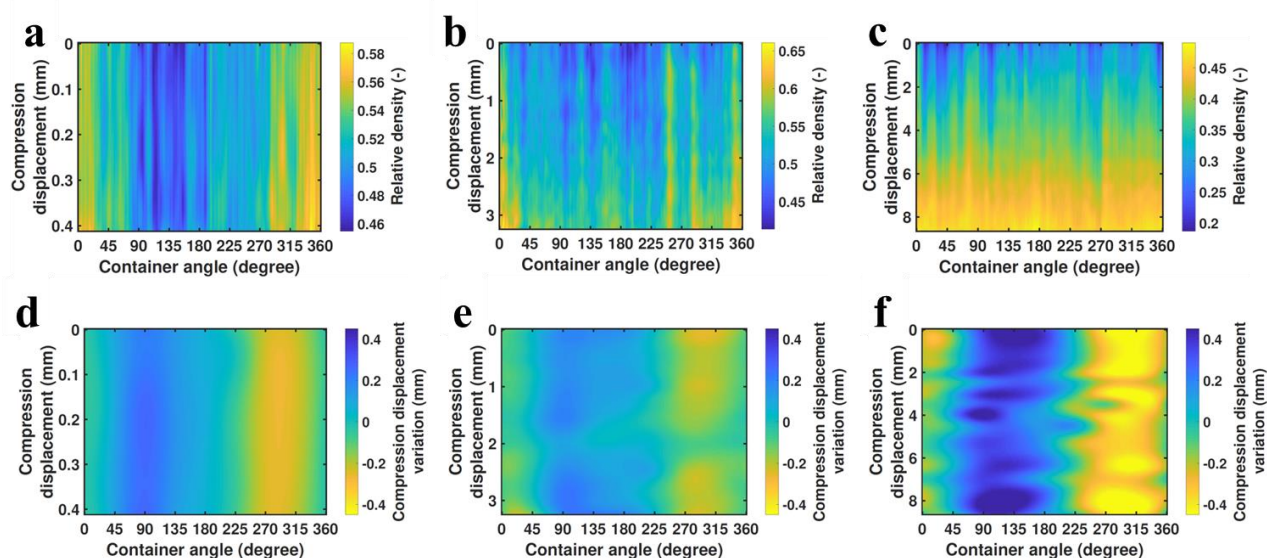
Figure 5: Maps of relative density distributions (a-c) and powder bed height variations (d-e) as a function of average powder bed height, $\bar{h}$, and the angle on the container. (a,d) Lactohale 100, (b,e) Lactohale 200, (c,f) Lactohale 220. The data were interpolated using a cubic interpolation. The compression displacement represents the change of powder bed height from its initial height.

Compared to lactose, MCC excipients undergo a smaller change in the relative density variations, but have a notable local density differences within the powder bed. The predicted relative density variations are reflected by variations in the powder bed height for all MCC materials. The resulting maps of relative density variations (at the top half of Figure 6) clearly show similarities between SMCC 90 (Figure 6c) and SMCC 50 LD (Figure 6b). This result is rather surprising if we consider the different material attributes of those powders, e.g., the particle size. Since the

particle size, along with the particle shape, elasticity, plasticity and brittleness, is known to affect the strength of bonds and arrangements of particles in a tablet [27,55], we would expect similar distribution maps for SMCC 50 (Figure 6a) and SMCC 50 LD (Figure 6b). However, if one considers the bulk densities of the two powders, SMCC 50 and SMCC 50 LD, the latter has a lower bulk density, as also evident from the sample label "LD" (low density). It is well known that a lower density (higher porosity) may facilitate compressibility, i.e., the densification of a powder bed due to the application of a stress [56]. Therefore, a higher relative density (more precisely local areas with higher relative density) observed upon compression of the powder bed for the SMCC 50 LD (see Figure 6b) may be attributed to differences in the bulk densities rather than in the particle sizes. These findings are also reflected in the resulting maps of powder bed height variations (Figure 6d-f), which confirm the presence of local density variations in the powder bed.
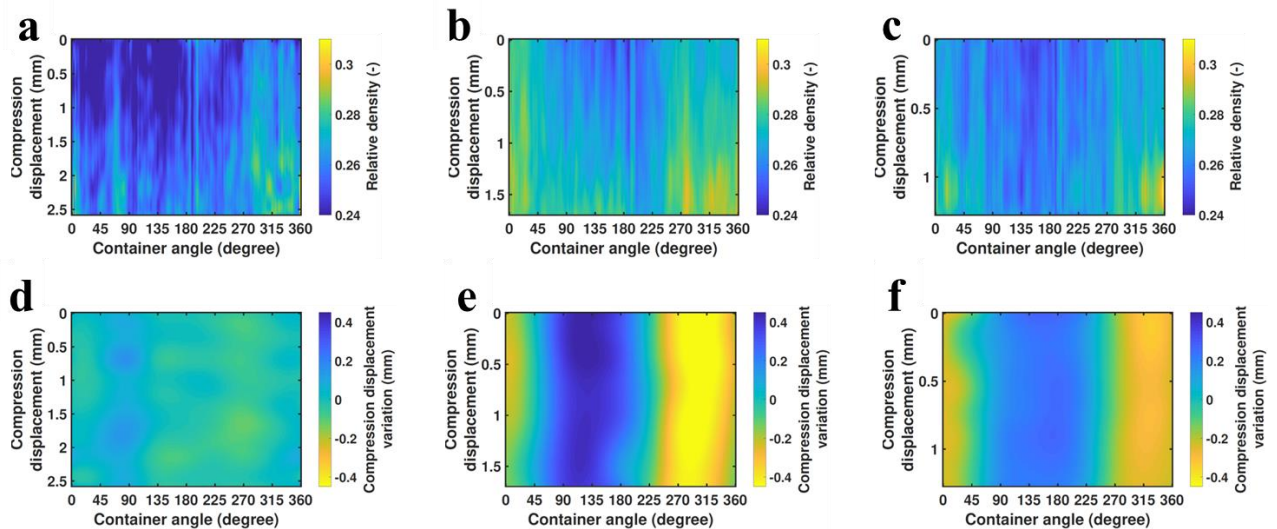

Figure 6: Maps of relative density distributions (a-c) and powder bed height variations (d-e) as a function of average powder bed height, $\bar{h}$, and angle on the container. (a,d) SMCC 50, (b,e) SMCC 50 LD, (c,f) SMCC 90. The compression displacement represents the change of powder bed height from its initial height.

4.4 Conclusions

This study presents an analysis of powder density variations in a rotating container via terahertz reflection measurements. The ability to spatially resolve density variations in a powder bed is relevant for a wide range of industrial applications, processes and unit operations, and especially for processes in which density variations of the bulk powder can result in out-of-spec end products. In the case of tableting process, the proposed method would facilitate the development of an in-depth understanding of the effect of compaction force and compression speed on the density variations and the porosity of a tablet, which is known to be one of the most important contributors to the disintegration of immediate-release tablets [55]. Another application example is a direct measurement of powder density variations during capsule filling. In particular, the method could be adjusted for implementation as an in-line process analyzer to determine the bulk density variations inside a dosator nozzle when the powder is collected from a moving powder bed and transferred into a capsule. Establishing a correlation between the bulk density inside the nozzle and the resulting fill weight and fill weight variation of filled capsules, which are known as critical quality attributes [57], would enhance process understanding and lead to process optimization. Although real-time measurement of density variations remains a challenge, it is highly desired to enhance the product quality [5]. Overall, our method has great potential to quantitatively measure bulk density variations in static or moving powder bulk/powder streams and can be implemented as a process analyzer to continuously control the material variations during a batch or continuous manufacturing process (in such industries as pharma, food, cosmetic, etc.).

4.5 Acknowledgments

4.6 References

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5. Predicting capsule fill weight from in-situ powder density measurements using terahertz reflection technology
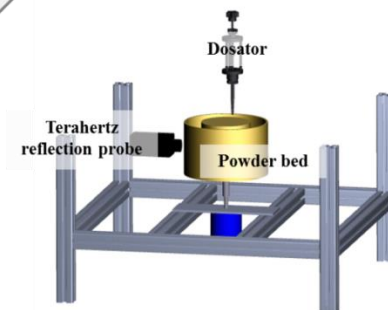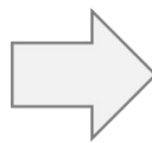
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Graphical Abstract

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Experimental setup that mimics *LABBY*

Predicting capsule fill weight from in-situ powder density measurements using terahertz reflection technology

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ABSTRACT

A good understanding of the powder behavior during the manufacturing of solid oral dosage forms that consist of powder is essential to assure high quality products. This is particularly relevant for a capsule filling process, where the powder bulk density plays an important role in controlling the fill weight and weight variability of the final product. In this study we present a novel approach to quantitatively measure bulk density variations in a rotating container by means of terahertz reflection technology. The terahertz reflection probe was interfaced to an experimental setup that mimics a lab-scale capsule filling machine including a static sampling tool. Three grades of lactose excipients were systematically investigated at five compression stages. Relative densities predicted from terahertz reflection measurements were correlated to off-line weight measurements (i.e. collected filled capsules). The predictions and the measured weights of the powder in the capsules were in excellent agreement, where the relative density measurements of Lactohale 200 ($R^2 = 0.995$) showed the strongest correlation with the respective fill weight. We also studied how the uniformity of the powder bed is impacted by the dosing and the subsequently filling of the holes which were introduced in the powder bed after

the dosing. Even though the holes seemed to be filled with new powder (by visual inspection), the relative density in these specific segments clearly differ from the powder bed state prior to dosing. The results demonstrate that it is feasible to analyze powder density variations in a rotating container by means of terahertz reflection measurements and to predict the fill weight of collected capsules.

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5.1 Introduction

Powder bulk properties are known to be crucial for the operation of many pharmaceutical processes and the quality of final products, such as tablets and capsules. In tablet production powder density variations may impact tablet mass and hardness, as well as the dissolution performance, hence affecting patients (Singh et al., 2015). Capsules are typically filled with powder or pellets. First of all, filling processes are typically volumetric, i.e., a certain volume of powder is filled into capsules. Thus, only if the density remains constant throughout the process the same mass is filled in every capsule. Second, the fill weight is considered to be directly related to the drug content. Since this requires a uniform blend, both the fill weight variability and content uniformity are critical quality attributes (CQAs) as defined within the Quality-by-Design (QbD) framework (Faulhammer et al., 2014c).

The ability to monitor the powder density during processing of pharmaceutical solids thus would be an enormous benefit, guaranteeing high quality end products. Powder density is also used as a key parameter for the design, optimization, and scale-up of many other manufacturing processes by using it as an equipment-independent scaling parameter (Hancock et al., 2003). Furthermore, as the pharmaceutical industry moves from batch towards continuous processing (Plumb, 2005; Buchholz, 2010, Subramanian, 2013), with solid oral dosage forms as one of the primary candidates (Poechlauer et al., 2012), real-time quality monitoring of in-process material is required (Vanarase et al., 2010), possibly leading to real-time release (RTR). Powder density measurements could provide important information in synergy with the process analytical technology (PAT) initiative (Fda, 2004) to enhance end product quality (Singh et al., 2015). However, in-line monitoring of powder density still is an unsolved challenge due to two main reasons:

(1) the powder density is dependent on the type of measurement and the history of processing (Hancock et al., 2003). There are two basic methods of evaluating the density of a powder, the aerated powder (bulk) density and the tapped density (random dense packing). The aerated powder density is determined by allowing the dispersed powder to settle in a container under the influence of gravity. This is often called bulk density. The tapped density is obtained by tapping a container filled with a sample which forces the particles to rearrange leading to a higher density value than the bulk density (Abdullah and Geldart, 1999). This type of analysis provides accurate values for density but can only

be performed off-line.

(2) the handling of particulate materials and segregation that may occur since blends consist of aggregates of different particle size (Hastie, 2015) pose a challenge in the development of an in-line powder density monitoring method. In addition, processing effects such as compressive stresses at different levels of the feeders, shear stresses during blending and particle size distribution affect powder density (Frake et al., 1998; Freeman, 2007; Fu et al., 2012; Jallo et al., 2012).

The most common process analyzer in the manufacturing of solid dosage forms is near-infrared spectroscopy (NIRS), which has been extensively described in the literature for in-line monitoring of blend uniformity (Reich, 2005a; El-Hagrasy and Drennen, 2006; Li et al., 2006; Moes et al., 2008; Corredor et al., 2014; Li and Qu, 2014; Lin et al., 2015). Other non-invasive techniques, such as Raman spectroscopy (Hausman et al., 2005; Wikström et al., 2006; Arruabarrena et al., 2014), light induced fluorescence (Karumanchi et al., 2011), and chemical imaging (El-Hagrasy et al., 2001; Lyon et al., 2002; Ma and Anderson, 2008; Osorio et al., 2014) are also commonly used for determining the uniformity of a blend in an on-line or in-line setting (H. Wang et al., 2017). However, even when blend uniformity is adequate, density changes during the process will cause undesirable variations in capsule weight leading either to an excess or lack of the active pharmaceutical ingredient (API). It is thus crucial to integrate process analyzers that are capable of controlling the drug concentration and powder density. To date, only a few studies have demonstrated the monitoring of density variations of a powder beds. Examples are the work by Singh et al. (2015) who proposed a method for real-time monitoring of powder bulk density based on NIRS. They also conducted a sensitivity analysis to quantify the effects of powder bulk density on critical quality attributes of pharmaceutical tablets. Recently, NIRS calibration models for real-time prediction of powder density (tap, bulk and consolidated) were developed for a pharmaceutical formulation (Román-Ospino et al., 2016). Other examples for measuring powder density are ultrasound technology (Leskinen et al., 2010), air-coupled acoustic technique (Akseli et al., 2010), photo-acoustic testing (Ketolainen et al., 1995), acoustic emission measurements (Hakanen and Laine, 1995), microwave measurements (Trabelsi et al., 1998), X-ray based methods (Akseli et al., 2011), thermal effusivity monitoring (Ghorab et al., 2007), and electrical tomography (Davies et al., 2005).

A very promising method to study the density variations of particulate material is terahertz technology. The terahertz spectral region covers the range from 0.1 to 4 THz or 3 mm to 30 µm,

respectively (Bründermann et al., 2012). Compared with NIR, mid-IR, and Raman spectroscopy, Terahertz time-domain spectroscopy (THz-TDS) is inherently less vulnerable to scattering effects due to its longer wavelength and it is, therefore, a very attractive technique to characterize porous materials. Excipients most commonly used for the formulation of solid dosage forms are transparent, or semi-transparent, to terahertz radiation. Hence, the pulse of terahertz light can penetrate into and through a specimen leading to a large representative sample volume. The penetration depth of the terahertz radiation into the sample material is dependent on the material and the power of the terahertz pulse. At present, penetration depths into typical pharmaceutical formulations have been demonstrated up to 5.3 mm (Markl et al., 2017a).

The terahertz technology can also be employed to measure the effective refractive index of a sample in a non-destructive manner (Bawuah et al., 2016; Markl et al., 2017; Markl et al., 2017a). The effective refractive index is a function of the fill fractions of each constituent and the total porosity. It can therefore be used to determine the porosity of a tablet within seconds by knowing the other fill fractions (e.g., knowing the formulation). Recently, we have demonstrated that powder density variations in a rotating container can be captured and analyzed by means of terahertz pulsed imaging (Stranzinger et al., 2018a). This setup and methodology were capable of spatially resolving density variations as small as 0.3% (Lactohale) in a moving container.

We utilize the method reported by Stranzinger et al. (2018a) in this study to investigate the correlation of the measured powder density with the fill weight in a capsule of three grades of lactose excipients at two different terahertz probe positions, i.e. from the side (terahertz probe position 1) and the bottom (terahertz probe position 2) of the rotary container. Small quantities were drawn from the powder bed using a novel sampling system that mimics the capsule filling process (Stranzinger et al., 2018b). We further analyzed the effect of sampling on the density of the powder bed for the different materials.

5.2 Materials and methods

5.2.1 Materials

Three different grades of lactose excipients (Lactohale 100, Lactohale 200, Lactohale 220) supplied by DFE Pharma (Goch, Germany) were used as received. In order to minimize manufacturer and batch-to-batch variations, experiments were carried out using powders from

one batch and one supplier. Table 1 depicts the bulk, tapped, true densities and median particle size (x50) of the used materials, as well as the required mass which results in a layer of powder in the container with a height of 10 mm.

Table 1: Properties of the various lactose excipients used in this study. The mass in this table refers to the theoretical weight of the powder filled in the container (calculated based on the bulk density of the respective powder).

Material	Bulk density (g cm^{-3})		Tapped density (g cm^{-3})		True density (g cm^{-3})	Particle size x50 (μm)	Mass (g)
Lactohale 100	0.697	±0.004	0.828	±0.013	1.5385 ± 0.0028	155.24 ±0.58	70.9
Lactohale 200	0.622	±0.003	0.996	±0.002	1.5426 ± 0.0024	78.72 ±0.44	63.3
Lactohale 220	0.400	±0.007	0.785	±0.007	1.5466 ± 0.0042	13.40 ±0.01	40.7

5.2.2   Experimental setup

A schematic of the experiments setup, comprising the rotary container, the terahertz fiber-based flexible reflection probe (at position 1 and 2) and the static test tool, is depicted in Figure 1. The rotary container is made of high-density polyethylene (HDPE), which is transparent to terahertz radiation. The height of the interior of the container is 45 mm. A metal ring with a thickness of 10 mm combined with a sensor block with a thickness of 63 mm, both components later referred to as compression unit, were used to apply pressure on the powder bed causing a change of the relative density. The pressure on the powder bed was adjusted by tightening a nut on the screw to increase the compaction pressure on the powder bed. Three load sensors connected to a computer via an Arduino Uno (Arduino, Somerville, US) were used to measure the applied force, which was only measured prior to each compaction stage. For details about the force sensors and installation we refer to our previously published work (Stranzinger et al., 2018a).
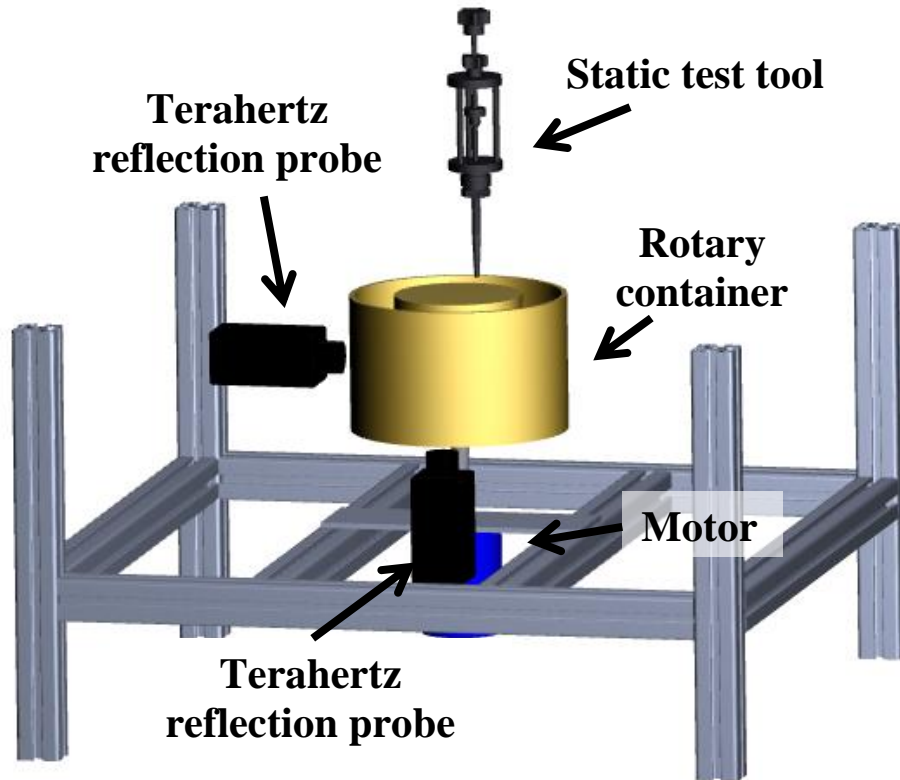
Figure 1: Schematic of the experimental setup for terahertz reflection probe position 1 and terahertz reflection probe position 2, respectively.

The experimental setup was developed to closely mimic a conventional dosator nozzle capsule filling process (Figure 2). Clockwise rotating the container filled with powder enables the holes, which are introduced in the powder bed after a dosing step, to be filled with the excess of powder which is placed behind the scraper. Several rotation cycles are typically needed to completely fill the holes in the powder layer. To date, the filling of the holes has only been detected visually from the top of the powder layer. Terahertz reflection measurements at both positions were performed to gain more insights the powder bed state after dosing.
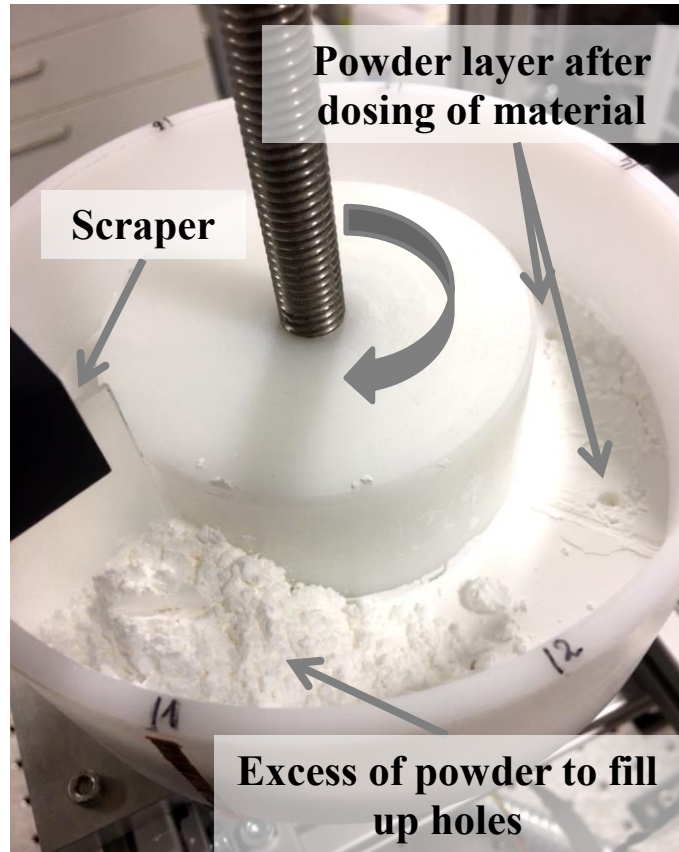
Figure 2: Experimental setup for simulating a conventional dosator nozzle capsule filling process.

5.2.3 Powder bed preparation

For each experimental run, the needed amount of powder (as shown in Table 1) was manually filled into the rotary container. A scraper was used to smoothen the powder layer prior to measuring the powder layer height and subsequently mounting the compression unit. The pressure on the powder bed was changed by displacing the compression unit. This displacement was measured at eight different positions from the top of the container to the entire block by a digital caliper prior to the start of every measurement. An average value of the displacement was then used to calculate the fill height, $\bar{h}$, and eventually to determine $\bar{\varrho}_r$ (Eq. 1). Moreover, for each compaction step the applied pressure on the powder bed was measured using the integrated

force sensors (see section 2.2). The motor speed of 4 rpm was constant throughout all experiments. For each experiment the average relative density, $\bar{\varrho}_r$, was calculated by

$$\bar{\varrho}_r = \frac{m}{V\varrho_t} = \frac{m}{A\bar{h}\varrho_t} \qquad \text{Eq. 1}$$

where A is the cross-section area of the container and ϱ_t is the true density (shown in Table 1). A was constant throughout all measurements and is given as

$$A = \left(\frac{D_o - D_i}{2}\right)^2 \pi \qquad \text{Eq. 2}$$

with $D_o = 138$ mm and $D_i = 78$ mm as the outer and inner diameter of the interior of the container.

5.2.4 Terahertz reflection measurements and prediction of relative density variations

Terahertz reflection measurements were continuously acquired for three independent experimental runs per material, and the average relative densities of the five different compaction steps in each run were predicted. A commercial time-domain terahertz system (TeraPulse 4000, TeraView Ltd, Cambridge, UK) coupled with a fiber-based flexible reflection probe was used in this study. The system was configured to operate at an optical time delay of 45 ps and an acquisition rate of 15 Hz. The reflection probe was equipped with a silicon lens with a focal length of 18 mm. The beam waist at the focus is ≈ 600 µm. 2000 terahertz waveforms were acquired continuously for each compaction step, which yielded a total measurement time of 133 s. These 2000 measurements covered about 8.5 rotations of the container. A thin strip of copper foil was adhered onto the outside of the container, which reflected the terahertz pulse and facilitated the automatic detection of a full rotation from the terahertz waveforms. Seven full rotation were averaged which yielded N = 230 terahertz waveforms uniformly distributed around the container.

The refractive index of the powder, n_p, was calculated by measuring the reflection coefficient, r_{cp}, (from container and powder) and utilizing its relationship which is given as

$$r_{cp} = \frac{n_c - n_p}{n_c + n_p}, \qquad \text{Eq. 3}$$

where $n_c = 1.54$ (refractive index of the HDPE at terahertz frequencies (Wietzke et al., 2011)) is the refractive index of the container. Eq. 3 can then be rearranged to

$$n_p = \frac{n_c(r_{cp}+1)}{n_c - r_{cp}}. \qquad \text{Eq. 4}$$

r_{cp} was calculated by relating the amplitude of the reflected pulse from the container/powder interface to a reflection from the copper foil on the container. This reference reflection from the copper foil was acquired prior to every experiment.

A linear relationship between the measured refractive indices and the relative densities of the powder in the container was observed (for details see (Stranzinger et al., 2018a)), and therefore a linear model was fitted to the calibration data. In particular, the model is expressed as

$$\bar{\varrho}_r = a_0 + a_1 \bar{n}_p \qquad \text{Eq. 5}$$

with a_0 and a_1 as fitting parameters. $\bar{\varrho}_r$ is the average relative density from Eq. 1 and $\bar{n}_p = \sum_{i=1}^{N} n_{p,i}$ is the average refractive index with $n_{p,i}$ calculated by Eq. 4 and the terahertz reflection measurement at position i.

The noise in the terahertz data was reduced by applying a moving average filter with a size of 5 to the data: the reflection coefficient of 5 successive terahertz time-domain waveforms were averaged.

5.2.5 Static mode tests for off-line weight measurements

Off-line weight measurements of powder samples were performed on samples drawn from the rotary container by a novel test setup, i.e., a stand-alone static test tool (Figure 3a), which was previously introduced by us (Stranzinger et al., 2018b). Essentially, the static test tool takes samples via a dosator head from a static powder bed, mimicking the dosing step in a dosator capsule filler. As shown in Figure 3b, the static test tool was placed next to the rotary container. Dosator dipping steps, i.e., downward movement of the dosator, collecting of powder from the rotary container and ejection of powder into a capsule were performed using the following process parameters: a dosing chamber length of 5 mm, a dosator diameter of 3.4 mm and an initial powder layer height of 10 mm. This resulted in a pre-compression ratio (i.e., the ratio between the dosing chamber length and the powder layer height) of 1:2. Dosator dipping steps were performed at the eight different positions shown in Figure 4. The collected capsules were

stored in cups sealed with Parafilm until their fill weight and weight variability were analyzed (as described in Section 2.6).
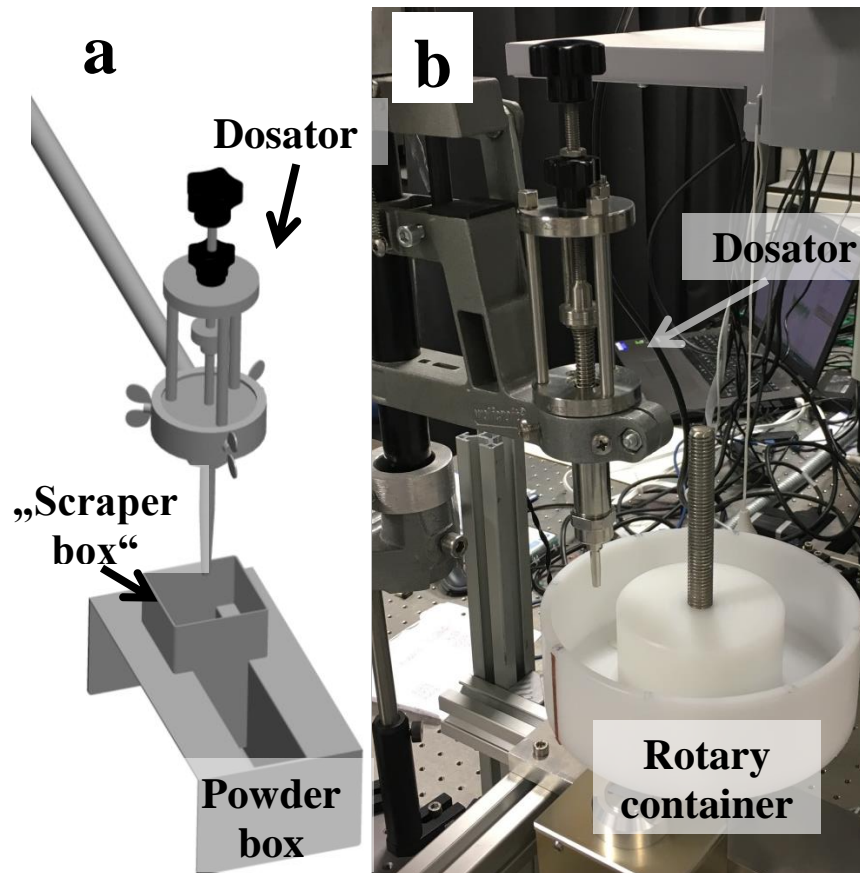

Figure 3: (a) Schematic of the stand-alone static test tool including a rectangle powder box. (b) The static test tool setup used in the present study, i.e. the tool is placed next to the rotary container filled with powder.

Figure 4 depicts the eight different positions around the rotary container (M01–M08) from where powder was sampled for off-line weight measurements. For each material and compression step the fill weight of eight samples was averaged.
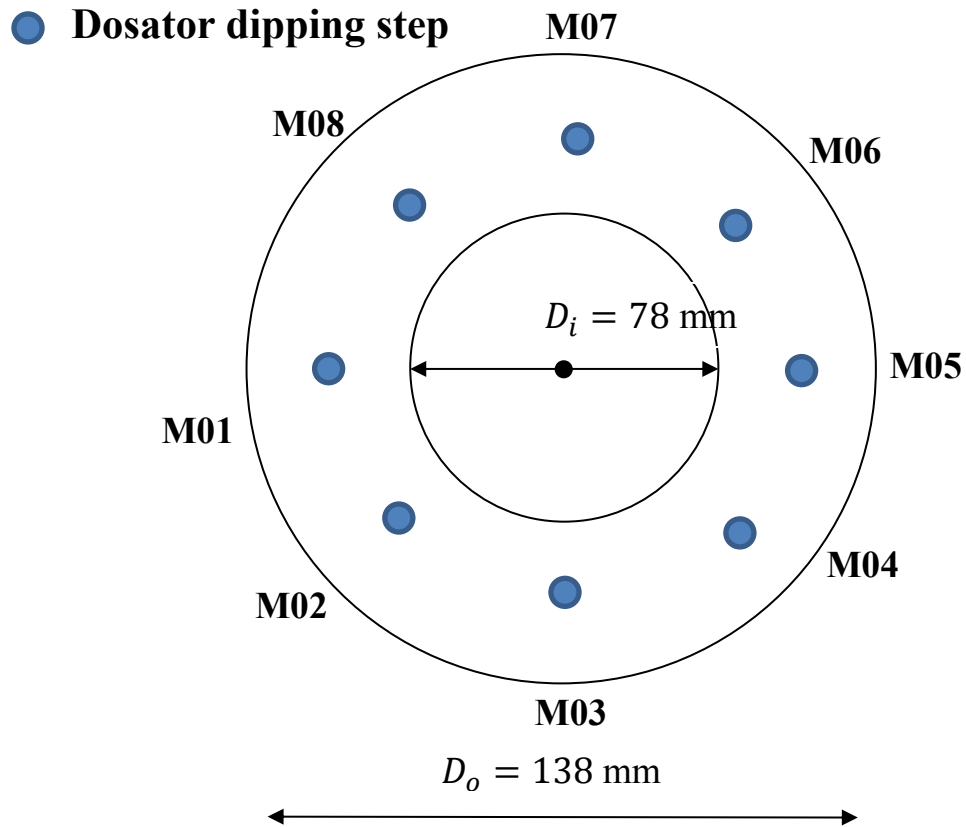
Figure 4: Schematic of the rotary container dimensions and the eight off-line sampling positions (M01–M08).

5.2.6 Analysis of capsule fill weight and weight variability

The collected samples were weighed on a Denver (SI-234A) analytical scale. Due to a relatively high weight of empty capsules and their variability, the collected filled capsules were weighed, emptied and re-weighed. An air pistol was used to ensure that no powder was left in the capsule after it was emptied.

5.3 Results

5.3.1 Correlation between in-line predicted relative densities and off-line weight measurements

Firstly, a linear model between the measured refractive index and the nominal relative density was developed. We observed an excellent linear relationship between the measured refractive index and the relative density for each powder, as reflected by the correlation coefficient (R^2) and root mean square error (RMSE) in Table 2. One linear model was developed per material, which was then used to predict the relative densities for all three experiments per material.

Table 2: Correlation coefficient and root mean square error (RMSE) for the linear model (Eq. 5) relating the measured refractive index to the relative density for the three different powder.

Material	R^2	RMSE
Lactohale 100	0.982	0.002
Lactohale 200	0.996	0.003
Lactohale 220	0.995	0.003

The predicted relative densities of all three experiments were averaged and then correlated with the off-line weight measurements (Figure 5). We observed the highest correlation coefficient ($R^2 = 0.995$) for Lactohale 200, which emphasizes that in-line measured relative bulk densities are highly suitable to predict the change in fill weights of off-line samples. A significant increase in fill weights from 43.1 to 47.1 mg was observed for this powder. This can be correlated with the compressibility of the powder as previously discussed by Stranzinger et al. (2017), where a compressibility at 8 kPa of 12.66% for Lactohale 200 was reported. In terms of fill weight variability, very low relative standard deviations ($< 3\%$) could be achieved for this powder, which is highly relevant to guarantee a high quality product.

A correlation coefficient of $R^2 = 0.870$ was obtained for Lactohale 100. Given the limited compressibility (1.05% at 8 kPa (Stranzinger et al., 2017)) it was not possible to significantly

vary the relative density of Lactohale 100 using the experimental setup. The setup would need a significant modification in order to make it suitable for higher compression forces. However, such high forces are not expected to be relevant for typical capsule filling processes.

A correlation coefficient of $R^2 = 0.864$ was observed for the highly cohesive Lactohale 220 powder. The fill weights significantly increased from 24.4 to 34.1 mg as a function of applied normal forces, owing to the high compressibility (36.95% at 8 kPa (Stranzinger et al., 2017)). As expected, the highly cohesive powder yields the highest fill weight variability among the three powders. These results are in line with the previously reported weight variability of this powder (Stranzinger et al., 2017; Stranzinger et al., 2018b). In the latter study, Stranzinger et al. (2018b) detected a higher weight variability for this highly cohesive powder when sampled without vibration, which was the mode of sampling strategy in the present study. Another interesting discovery in terms of weight variability of this powder was observed by visually examining the powder bed after dosing (Figure 6a and b): It can be clearly seen that in some cases the dosator collected more powder, i.e., the bottom of the container is visible, whereas in other cases some powder remained in the container. This phenomenon in turn is expected to be relevant for fill weight variability of collected capsules. An important fact to be considered for this type of powder is that the fill weight for highly cohesive powders is additionally affected by frictional characteristics (wall friction angle) (Faulhammer et al., 2014c). For highly cohesive powders it can be expected that a combination of the friction effect and greater inter-particle forces in highly cohesive powders are sufficient to keep them inside the nozzle. However, as reported by Stranzinger et al. (2018b), a pre-compression ratio of 1:2 would require a smaller gap (i.e., the difference between the lowest point of the dosator and the bottom of the container) than the gap used in the present study. A smaller gap could provide the critical compression of the powder required for a low variation inside the dosator. In other words, it is highly relevant to also consider the gap as emphasized by the previous work by Stranzinger et al. (2018b) in addition to critical process parameters investigated in earlier studies (Faulhammer et al., 2014a; Faulhammer et al., 2014b; Stranzinger et al., 2017).
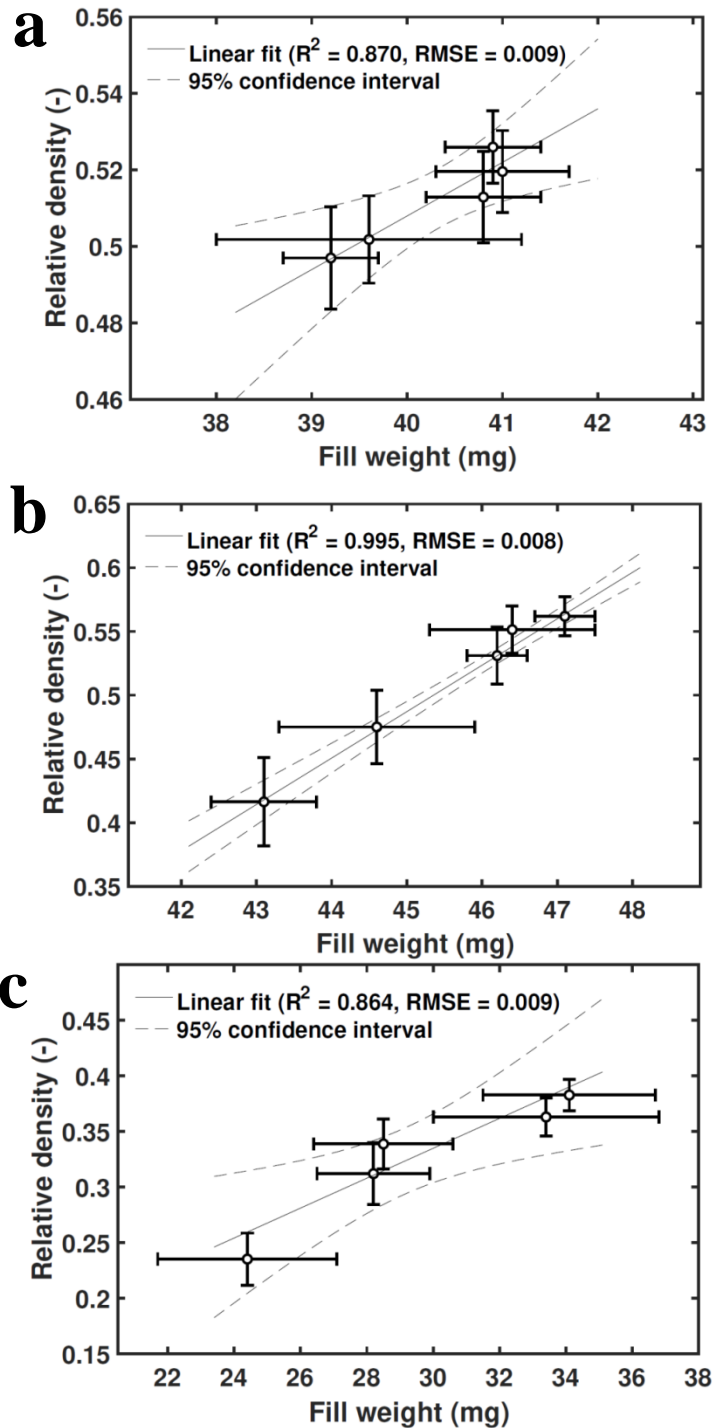
Figure 5: Comparison of the relative density from in-line terahertz reflection measurements and off-line weight measurements. a) Lactohale 100, b) Lactohale 200 and c) Lactohale 220. The relative density predictions were averaged for three experiments per material. The fill weight is the average of eight samples per material and compression step.
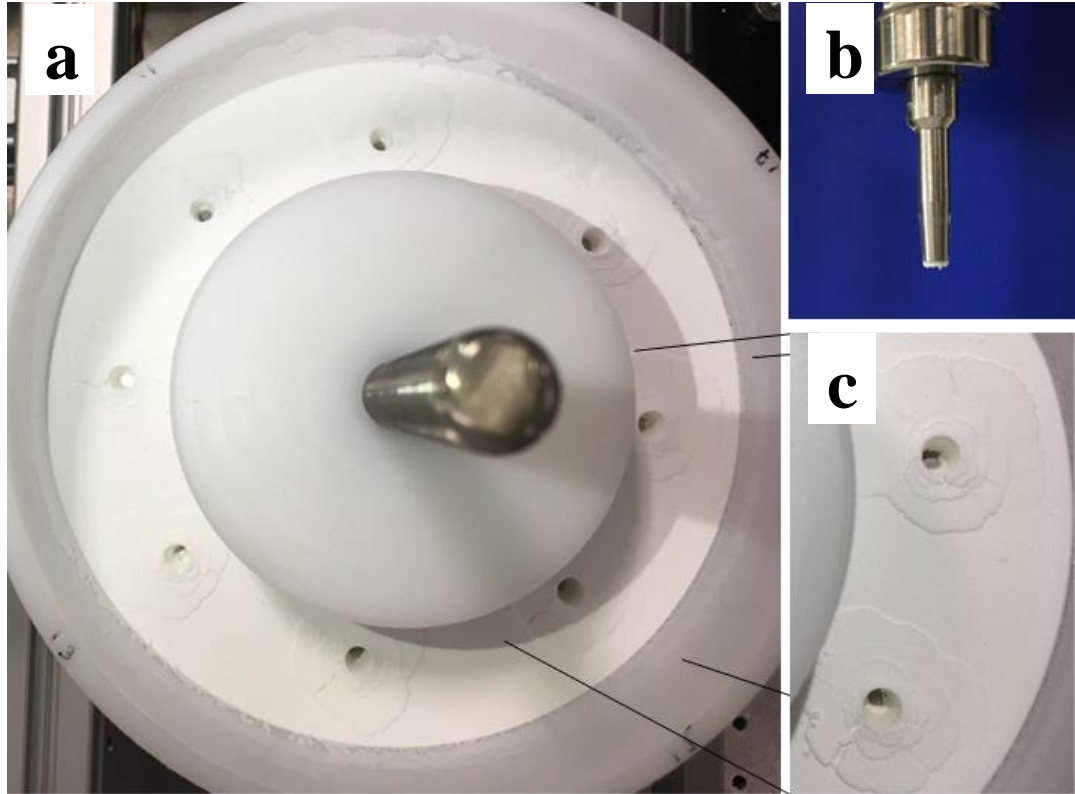
Figure 6: Experiments with Lactohale 220. (a) Powder bed after dosing of material. (b) Dosator with the collected powder after the dosator dipping step. (c) Holes in the powder layer after dosing of material.

5.3.2 Effect of dosing of material on powder bed state

In order to evaluate the impact of dosing of material on the relative density of the powder bed, terahertz reflection measurements (using terahertz probe position 2) were acquired continuously during rotation of the container for three different conditions (1) powder bed with the compression unit for displacement position max (i.e., maximum applied normal force), (2) powder bed after removing the compression unit and before dosing, and (3) powder bed without compression and after dosing of material. As shown in Figure 7, dosing of material considerably affects the state of the powder bed, but to a different extent for the three materials under investigation. Not surprisingly, the largest range of relative densities was observed for Lactohale 220, i.e. the powder that undergoes the largest volume change when it is compressed.

Interestingly, relative densities of Lactohale 100 as a function of the container angle (i.e., local relative densities) varied to a greater extent for the different specific angle positions compared to Lactohale 200 and Lactohale 220, indicating a more non-uniform powder bed upon compaction. This is in line with our previous study Stranzinger et al. (2018a), where maps of relative density distributions around the container (in horizontal direction) showed a similar trend for this powder. Thus, for such powders the filling process seems to be a crucial part during processing, whereas for powders with characteristics similar to Lactohale 200 and Lactohale 220 the dosing step itself has to be regarded critically, since it greatly impacts the powder bed condition and consequently the quality of the end product, i.e., the filled capsules.

As described in section 2.2 (Figure 2), the developed method was tested for its applicability in a conventional dosator nozzle capsule filling process. In those experiments after conditioning the powder layer, i.e., having a smooth powder layer of specific powder layer height, eight dosator dipping steps were carried out, followed by rotating the container to fill the introduced holes in the powder bed. Terahertz reflections measurements (using terahertz position 2) were continuously acquired throughout the entire process, i.e., rotating the container for 2 min to fill the holes. The data in Figure 8 and Figure 9 reveal that at each dosing position the spatially resolved relative densities are notably lower compared to the rest of the powder layer where no samples were taken. Interestingly, these variations of relative densities for segments where powder was collected are visible throughout the filling process (Figure 9). This finding indicates that even though the holes seemed to be filled (by visual inspection), the relative density in these specific segments differ from the initial powder bed state.

By measuring the actual relative density of those spots of interest in the powder bed, the developed method will improve existing solutions in terms of predicting the target fill weight and weight variability. Moreover, these results encourage the applicability of this method for monitoring powder bulk densities throughout the entire capsule filling process. It is of utmost importance to measure the relative density at sampling positions to detect any deviations from the target relative density of the powder bed. Powders with characteristics, such as small particles, poor flowability, high cohesion, are prone to densify under mechanical vibrations of the powder drum during the filling process, resulting in higher fill weights over time (Stranzinger et al., 2017). This was also discussed in the study by Llusa et al. (2013), where they found a clear correlation between more intense mechanical vibrations during capsule filling and fill weight changes. The information of changes of the powder bulk density from in-situ terahertz reflection

measurements could trigger corrective actions, such as adaption of the dosing chamber length, the powder bed height, or even the gap between the lowest point of the dosator at the end of a stroke and the bottom of the powder container. The latter parameter was recently reported by Stranzinger et al. (2018b) to be a critical process parameter for the filling of powder using a dosator nozzle machine for capsule filling.
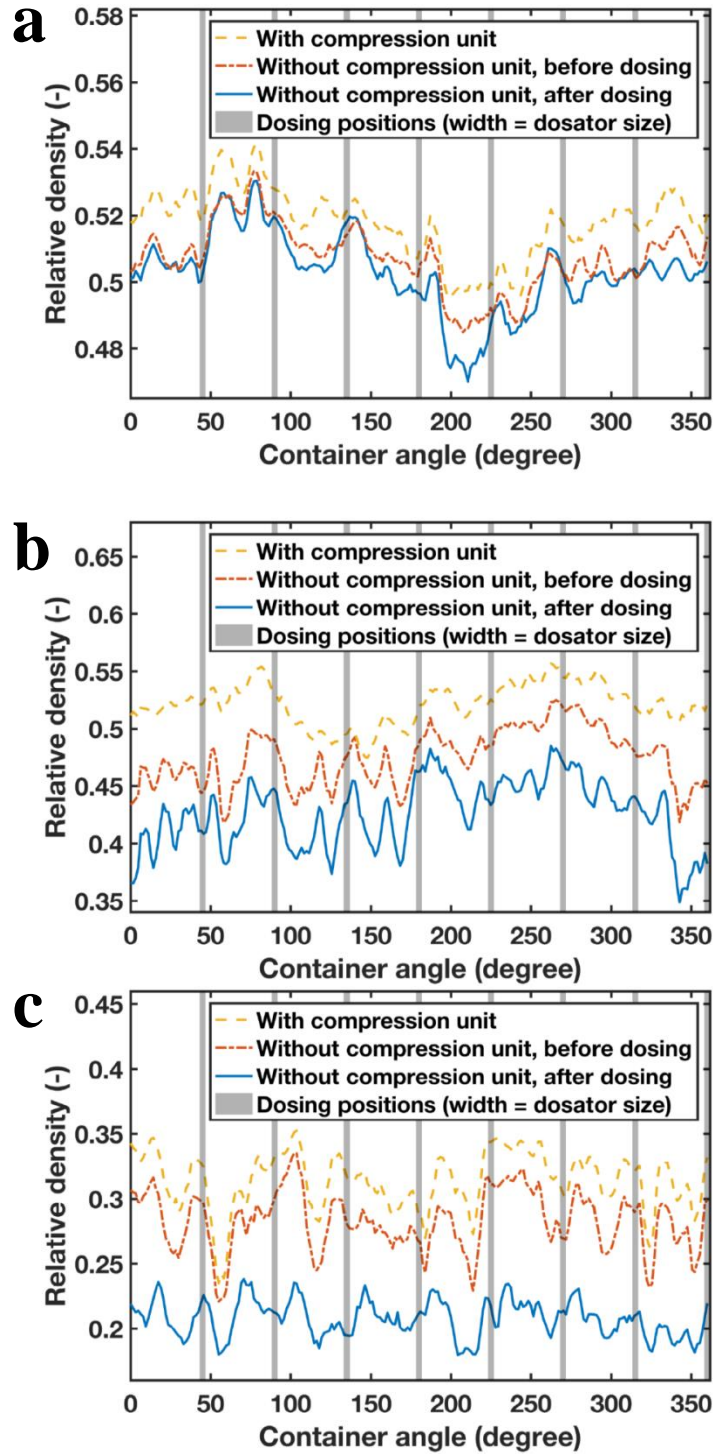
Figure 7: Impact of dosing of material on the powder bed state. The relative densities of the powder bed as a function of the container angle are shown with the sensor block (yellow), without the sensor block (orange) and after dosing (blue). (a) Lactohale 100, (b,) Lactohale 200, (c) Lactohale 220.

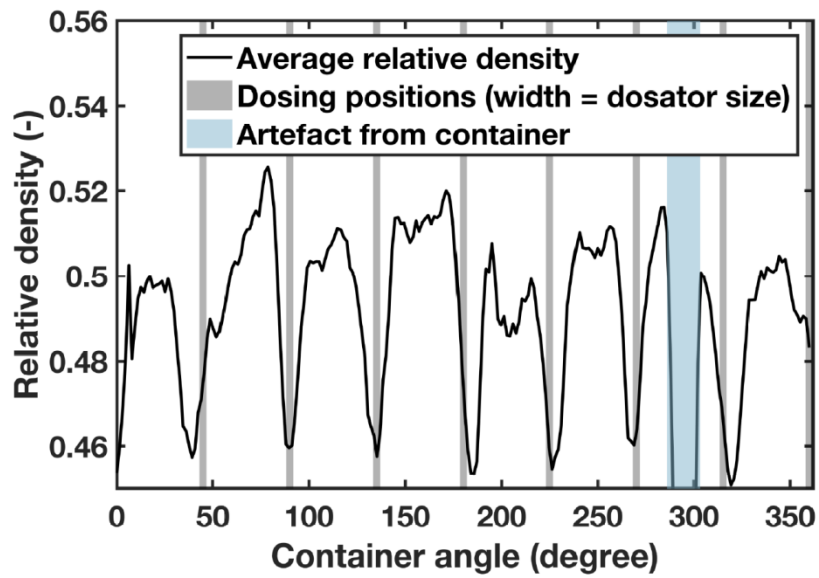**Figure 8:** Average relative density of the powder bed after dosing of material as a function of the container angle for Lactohale 100.
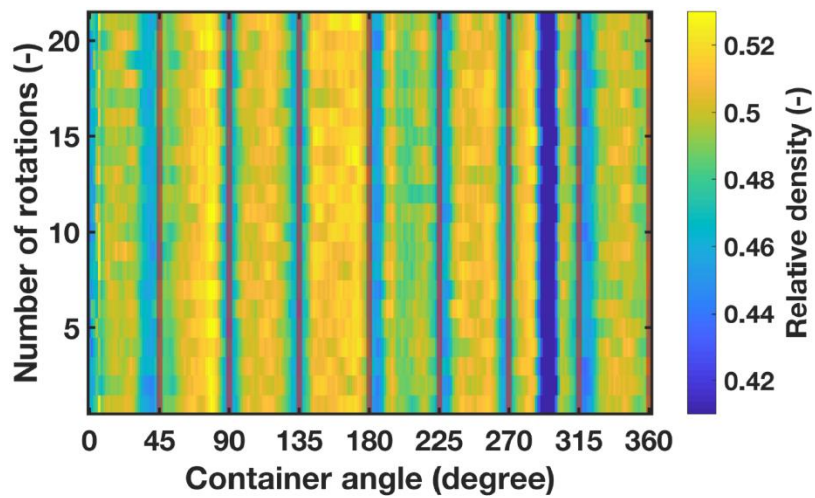

Figure 9: Map of relative density distributions as a function of increasing number of rotation of the container and the angle on the container for Lactohale 100. The dark blue region (very low relative density) is an artefact from the container.

5.4 Conclusion

We demonstrated the applicability of the terahertz technology as a new process analyzer to determine powder bulk density variations in a moving powder bed. Terahertz reflection technology was employed to measure changes in the bulk density non-destructively throughout the process time, which were further correlated to weight measurements of collected off-line samples. The high potential of this technology was emphasized by the determined correlation coefficients of $R^2 = 0.870$, $R^2 = 0.995$ and $R^2 = 0.864$ for Lactohale 100, Lactohale 200 and Lactohale 220, respectively between the predicted relative densities from in-line terahertz measurements and off-line weight measurements. The findings of this study provide a new perspective of the terahertz technology to be used as an in-line monitoring tool for manufacturing processes where powder bed variations are directly linked to the quality of final products, e.g. feeder, rotary container used in a dosator or tamping pin capsule filling process. A critical factor of the presented methodology is the positioning of the terahertz probe relative to the moving container. The powder bed density at the position where the dosator collects the powder could be measured by placing the terahertz probe at the respective position.

The implementation of a process analyzer in capsule filling processes could significantly reduce the fill weight variability in capsules. The knowledge about the state of the powder bed throughout the process will help in designing production machines, e.g., introduction of tools to stabilize the powder bed condition, which are capable to maintain a constant powder bed density and thus reduce process induced variability of final products.

5.5 Acknowledgments

5.6 References

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6. Performance indicators for carrier-based DPIs: Carrier surface properties for capsule filling and API properties for in vitro aerosolisation

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Graphical Abstract
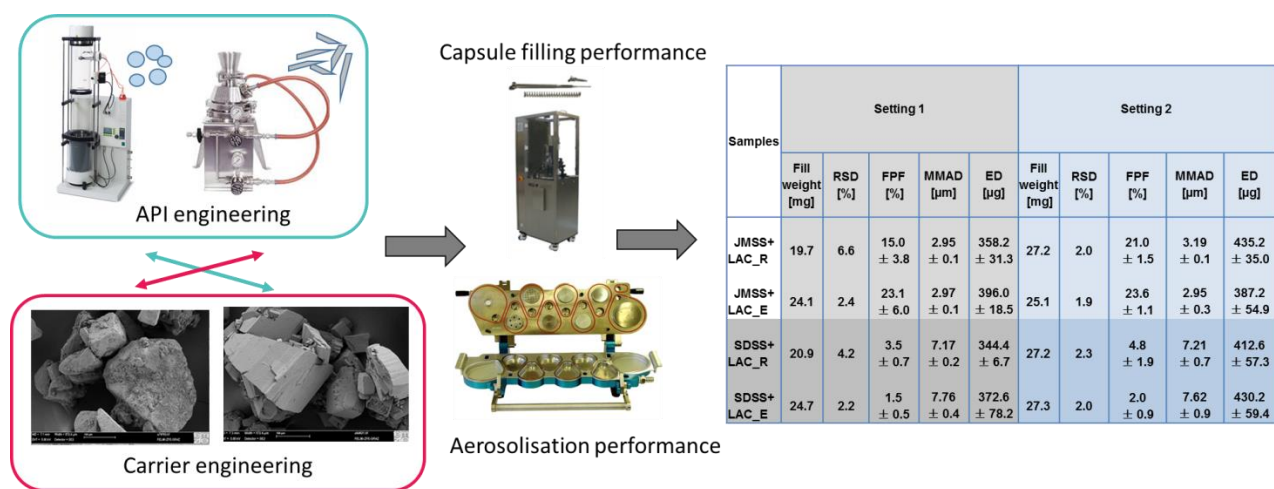
Performance indicators for carrier-based DPIs: Carrier surface properties for capsule filling and API properties for *in vitro* aerosolisation

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ABSTRACT

This study investigates engineered carrier, as well as engineered API particles, and shows that there are distinct performance indicators of particle engineering for carrier-based DPIs. Spray dried (SDSS) and jet-milled (JMSS) salbutamol sulphate (SS) was blended with untreated α-lactose monohydrate (LAC_R) and α-lactose monohydrate engineered (LAC_E). Subsequent capsule filling was performed with different process settings on a dosator nozzle capsule filling machine in order to reach a target fill weight of 20 to 25 mg. To evaluate the performance of the different mixtures, in vitro lung deposition experiments were carried out with a next generation impactor, the emitted dose (ED) and fine particle fraction (FPF) were calculated based on the specification of the European pharmacopoeia. The FPF of micronised powder blends is significantly higher (20%) compared to the FPF of spray dried blends (5%). Compared to API engineering, carrier engineering had a positive effect on the capsule filling performance (weight variability and mean fill weight) at lower compression ratios (setting 1). Results further showed that higher compression ratios appear to be beneficial in terms of capsule filling performance (higher fill weight and less fill weight variation). Concluding, it can be stated that the carrier engineering, or generally carrier properties, govern downstream processing, whereas the API engineering and API properties govern the aerosolisation performance and thereby significantly affect the dose delivery to the lungs.

Keywords: Salbutamol sulphate Surface modification Particle engineering Capsule filling Dry powder inhalation

+ Both authors contributed equally to this work

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6.1 Introduction

Dry powder inhalers (DPIs) are important devices for pulmonary drug delivery. They are a keystone in the treatment of asthma and chronically obstructive pulmonary diseases (COPD) (Yang et al., 2016). Compared to nebulisers and metered dose inhalers (MDIs), DPIs have several advantages, such as absence of propellants, no need for co-ordination of inhalation step and dose discharge, low costs and superior stability (Alagusundaram et al., 2010; Rahimpour and Hamishehkar, 2012). DPIs usually have unit doses of their drug in either a reservoir, a blister pack or a capsule. Capsule-based devices allow flexibility, as they can deliver either high or low doses, depending on the capsule size used. Moreover, patient compliance can be improved due to a feedback mechanism, such as a rattling sound when the correct dosage delivery flow rate is achieved. Additionally, the patient can easily check visually if the capsule is empty after inhalation and if the dose has been successfully administered (Saleem et al., 2015; Smith et al., 2010).

Nevertheless, formulation development for dry powder inhalers is challenging, as active pharmaceutical ingredient (API) particles must exhibit an aerodynamic diameter of 1 µm – 5 µm in order to reach the deep lung. Particles in this size range are inherently cohesive, showing agglomeration and poor flowability. This is problematic for powder handling, processing, and especially, during the (gravimetric or volumetric) capsule filling process (Besenhard et al., 2016, 2015; Faulhammer et al., 2014b). Consequently, well-flowing powders are required to guarantee uniform doses, for example during capsule filling or dose metering within a reservoir inhaler. This is usually achieved by blending the small API particles with larger carrier particles (usually 50 µm – 200 µm) which have adequate flowability. This is called a carrier-based formulation. A crucial step during inhalation of carrier-based DPI is the detachment of the API from the carrier, following device discharge. Particles which do not detach from the carrier usually impact together with the carrier in the mouth or throat. They are then swallowed and are not available for the delivery via the lungs. Only detached API particles are able to reach the therapeutic target at or through the lung (local vs systemic).

Carrier and API properties influence the drug detachment process. Various studies have focused on carrier engineering in order to tailor drug detachment from the carrier (Chow et al., 2007). Carrier engineering techniques that have been explored include, for example, spray drying (Amaro et al., 2011; Chow et al., 2007; Y. W. Lin et al., 2015; Littringer et al., 2012; Maas et al., 2011; Wu et al., 2014), crystallisation (Rahimpour and Hamishehkar, 2012; Zeng et al., 2001,

2000) novel innovative strategies like Pulmospheres[TN] (large porous hollow particles comprising of phosphatidylcholine (Rahimpour et al., 2014)) or Technospheres® (self-assembled fumaryl diketopiperazine (FDKP) carrier particles with a high surface area for absorption of large active molecules (de Boer et al., 2017)) and different solvent treatment techniques like wet decantation (Boshhiha and Urbanetz, 2009a; Faulhammer et al., 2015; Islam et al., 2004). Wet decantation is reported to remove fine particles adhering to the raw carrier material and to overall smoothen carrier particles, which in turn result in poorer aeroslisation performance (Boshhiha and Urbanetz, 2009a; Faulhammer et al., 2015). Fine lactose particles, and especially the ratio of fines and drug particles, play a key role in controlling drug detachment and the volume of particles transported to the lung (Islam et al., 2004). Moreover, fine lactose particles are reported to cover or saturate so called active sites (which can otherwise irreversibly adhere to API particles) on the carrier surface and facilitate efficient detachment of the API particles (Peng et al., 2016; Zhou and Morton, 2012). Furthermore, fine lactose particles may help in breaking up drug particle agglomerates, by forming mixed agglomerates with the drug particles (Islam et al., 2004; Louey et al., 2003).

The impact of API particle engineering on the aerosolisation performance of carrier-based DPI is far less studied. For example, Dhumal et al. investigated salbutamol sulphate particles of different shapes, generated via sono-crystallisation, spray drying and jet-milling. They found that the elongated sono-crystallised particles showed highest lung deposition, due to a reduction of the effective contact area, between the crystals and the carrier surface and thus the adhesive forces (Dhumal et al., 2009). Further, Shur et al. compared jet-milled and sono-crystallised Budesonide in blends with lactose and found that the engineered sono-crystallised material showed less surface disorders and better aerosolisation performance (Shur et al., 2013). Another recently published study by Moura et al. reported the effect of jet-milling and wet polishing on inhalation API properties. Both techniques supported the production of particles with similar sizes, but with distinct physico-chemical properties, such as surface area, rugosity, density, porosity and moisture content (Moura et al., 2016).

The interplay between particle engineering, particle properties, their downstream processability and aerodynamic performance is complex. Understanding these factors is crucial in DPI formulation development. Primarily, the effect of particle engineering on aerodynamic performance, the effect of particle engineering on processability, as well as the impact of the latter on aerodynamic performance, must not be neglected. Therefore, the present study evaluates the effect of API and carrier particle engineering on processability during blending / capsule

filling, as well as on aerodynamic performance. For carrier particle engineering, wet decantation was chosen to compare raw inhalation grade carrier material and engineered smooth fines free carrier particles. This supports investigation of the impact of surface topography and the effect of carrier fines. The model API was engineered to obtain the inhalable size via jet-milling and spray drying. Spray drying offers the possibility of tailoring particle properties like size, shape and solid-state. Compared with jet-milling, spray drying generates spherical particles with a narrow particle size distribution (Littringer et al., 2013). The use of these two techniques allows studying the impact of different API characteristics during processing and aerodynamic performance.

This study is a follow up on our work by Faulhammer et al. where the influence of carrier surface processing on capsule filling performance and aerosolisation performance was also analysed (Faulhammer et al., 2015). Nevertheless, the present study includes a different carrier engineering technique, as well as uses two differently processed/engineered API particles. The carrier engineering technique applied is a special wet decantation method, described in materials and methods section (6.2.2.1.), and API engineering was done via spray drying and jet-milling. With this, it was possible to study not only the impact of carrier particle engineering, but also the impact of API particle engineering on downstream processability and aerodynamic performance of DPI formulations. The outcome of the present work highlights the importance of assessing downstream processability of spray dried amorphous API particles for inhalation and impact on the aerosolisation performance. Despite the increasing strides towards engineering inhaled API particle via spray drying, this is among first of few studies where the impact of the process like capsule filling on emitted and fine particle fractions from the carrier based DPI of spray dried particles is compared and contrasted with that of traditionally milled API particles. The obtained data expand the understanding of the interplay between carrier and API morphology, drug detachment and capsule filling efficiency. The final goal is to analyse combinations of the same API and carrier particles as DPI blends that are differently engineered. This leads to a detailed understanding of how different engineering techniques affect particle characteristics, enhancing capsule filling and aerodynamic performance. We found two distinct performance indicating properties of carrier and API in terms of capsule filling and in vitro aerosolisation performance for the investigated system. More precisely, smoothening of surface and fines removal from lactose surface via wet decantation improved flowability and thus resulted into better capsule filling performance (fill weight and weight variability), while improvement of flowability of API particles via spray drying has no particular impact on capsule filling. Despite comparable emitted

dose, fine particle fraction of spray dried amorphous API was lower compared to that of jet-milled crystalline API and irrespective of carrier particle types. Therefore, the performance indicator for aerosolisation of the selected system appeared to be the solid-states of API rather than micromeritics and flow properties of API and carrier. Ideally, this specific knowledge base should allow the pre-selection of suitable API carrier combinations, in terms of their engineering routes and downstream process parameters based on particle characteristics.

6.2 Materials and methods

6.2.1   Materials

Alpha lactose monohydrate (modified Inhalac 70, Meggle, Germany), a standard inhalation carrier material was used as received and after wet surface treatment as model carrier. Salbutamol sulphate was purchased from Selectchemie (Zuerich, Switzerland) and used as model drug. Isopropanol and absolute ethanol were used for the wet surface treatment and obtained from Lactan Chemikalien and Laborgeraete Vertriebsgesellschaft m.b.H & Co. KG (Graz, Austria). To test the aerodynamic performance, size 3 gelatin capsules were used and supplied by Capsugel® (Bornem, Belgium).

6.2.2   Particle engineering

6.2.2.1 Engineering of carrier particles via wet decantation

A wet surface treatment was chosen in order to generate surface engineered carrier particles. To achieve that, 200 ml of absolute ethanol and 60 g of lactose were transferred to a beaker and mixed. The mixture was vigorously stirred to form a homogenous suspension. The latter was allowed to settle for 10 minutes and the supernatant was removed. Another 200 ml of fresh ethanol were added and the procedure repeated for a total of 5 times. In a final step, propan-2-ol, in which lactose is insignificantly soluble, was added and after a settling time of 10 minutes the supernatant was again removed (Boshhiha and Urbanetz, 2009a). Special care was taken to ensure minimal disturbance of the lower layer of the suspension when removing the supernatant. Sedimentation time (Eq.1) was calculated using the Stokes equation (Eq.2).

$$t = \frac{h}{v_s}$$

Equation 1: Sedimentation time; t is the time (min), h is the height of the beaker (m) and v_s is the particle's settling velocity (m/s).

$$v_s = \frac{2}{9} * \frac{\rho_p - \rho_f}{\mu} * g * R^2$$

Equation 2: Stokes equation; v_s is the particle's settling velocity (m/s), g is the gravitational acceleration (m/s^2) ρ_p is the mass density of the particles (kg/m^3), ρ_f is the mass density of the fluid (kg/m^3) and µ is the dynamic viscosity (kg/m*s), R is the thermal velocity.

The cloudy supernatant suspension was decanted and replaced with fresh ethanol. During the removal of the supernatant, special care was taken to ensure minimum disturbance of the lower layer of the suspension. At the end of the decantation process, the powder sample was left to dry for 2–4 days under a fume hood and stored afterwards in desiccators containing silica (Faulhammer et al., 2015).

6.2.2.2 Engineering of API particles

In order to generate inhalable sized particles (1 µm – 5 µm) spray drying and air jet-milling were chosen. Spray drying was performed with a Buchi Nano spray dryer B-90 (Flawil, Switzerland) using a spray head mesh of 7 µm, a feed concentration of 7.5% (w/w) salbutamol sulphate in purified water, a flow rate was set to 110 L/min and a spraying intensity of 30%. Process conditions were chosen based on our previous work and are described in more detail elsewhere (Faulhammer et al., 2015; Littringer et al., 2013). Micronisation was performed with an air jet-mill (Spiral Jet Mill 50 AS, Hosokawa Alpine AG, Augsburg, Germany). An injection pressure of 6 bar and a milling pressure of 3 bar were set. Powder was fed manually at an estimated rate of 30 g/h and one milling cycle was sufficient in order to generate inhalable sized particles.

6.2.3 Characterisation of engineered particles

6.2.3.1 Scanning electron microscopy (SEM)

The surface morphology of raw and engineered carrier and API particles, as well as the quality of the adhesive mixtures, were examined using scanning electron microscopy (SEM) (Zeiss Ultra 55, Zeiss, Oberkochen, Germany) operating at 5 kV. All samples were gold-palladium sputtered prior to analysis.

6.2.3.2 Particle size characterisation

The dynamic image analysis system QICPIC (OASIS/L wet and dry dispersing system, Sympatec GmbH, Clausthal-Zellerfeld, Germany) was used for particle size characterisation of the carriers and the API-carrier mixtures, using dry dispersion mode. A dispersion pressure of 0.5 bar was applied. In each measurement (n=3), approximately 4 g powder were used. The images of the investigated particles were captured by the camera and evaluated using the software Window 5.6.0.0. Particle size distribution, the volumetric mean diameter (VMD) and the median particle size (x_{50}) were determined based on the diameter of a circle of equal projection area (EQPC). The median of the particle size distribution (x_{50}) describes a particle diameter corresponding to 50% of the cumulative undersize distribution. The width of the particle size distribution, measured by the laser diffraction, was expressed as span = $(x_{90}-x_{10})/x_{50}$. Here, the x_z value is the diameter where z% of the sample has a smaller particle size.

The particle size and distribution of the API was measured using the laser diffraction technique (HELOS/KR, Sympatec GmbH, Clausthal-Zellerfeld, Germany). A dry dispersing system (Rodos/L, Sympatec) and a vibrating chute (Vibri, Sympatec) were used for powder dispersion. A dispersion pressure of 2.0 bar was applied. Measurements were made in triplicate (n=3), with a typical sampling time of 30 seconds. Data evaluation was performed using the software Window 5.6.0.0 (Sympatec, Clausthal-Zellerfeld, Germany).

6.2.3.3 Bulk density and tapped density

The bulk and tapped density (BD/TD) were measured via the Pharmatester (PT-TD200) and according to the standardised method described in the United States Pharmacopeia (USP 2015) in triplicate. The definite volume of powder was filled into a cylinder (250 ml) after which the level

and mass were recorded. After the mechanical tapping of the cylinder, the new volume yielded the tapped density of the sample.

6.2.3.4 Powder rheometry

The FT4 powder rheometer (Freeman Technology, Malvern, United Kingdom) was used to determine different indices of powder flow, such as flow function coefficient (FFC), basic flowability (BFE) and associated derived properties.

FFC and Cohesion (C) were measured using the 1 ml shear-cell module, at a normal pressure of 3 kPa. FFC defines the ratio of consolidated stress to unconfined yield strength. Typically, a high FFC value (>4 – 10) represents powder with good flowability. FFC greater than 10 indicates a free flowing powder. C is an important parameter to provide information about the inter-particle interactions due to electrostatic, capillary or van der Waals forces. The angle of internal friction (AIF) for a given powder is the angle on the graph in Mohr's Circle (shear stress vs. normal stress) at which shear failure occurs. Details of these methodologies can be found in the literature (Freeman, 2007b, 2011; Fu et al., 2012b).

The BFE defines the energy required to establish a particular flow pattern in a conditioned, precise volume of powder. To measure BFE and aerated energy (AE), an air conditioning unit providing pressured dry air (2 mm/s air velocity) was applied. Air permeability (PM) was determined by transmitting air through a bulk powder bed and measuring the air pressure drop (PD) across the powder bed. The higher the air permeability of a bulk powder bed, the lower the resistance to air flow and the pressure drop. All measurements were done in triplicate.

6.2.4   Preparation of adhesive mixtures

Adhesive mixtures of raw and engineered carrier, and both spray dried and jet-milled API, were prepared in a tumble blender TC2 (Willy A. Bachofen Maschinenfabrik, Muttenz, Switzerland). The API loading was 2% w/w and a standard mixing procedure was used, where half of the carrier was layered in a plastic vessel followed by a layer of API in the middle and the second half of the carrier layered on the top (filling volume approximately 40%). The batch size was 150 g and the mixing time was set to 60 min at 62 rpm (Faulhammer et al., 2015). The blends were stored in a desiccator over silica gel before further analysis. The homogeneity of the blends was expressed as the coefficient of variation of the mean drug content, of n=10 sample, determined

via a validated HPLC method. A mixing homogeneity of below 5% deviation from the mean drug content of the sample was regarded as acceptable.

6.2.5 Capsule filling

In the present study all four blends were filled using a lab scale dosator nozzle capsule filler, with special low powder dosing adjustment (Labby, MG2), into Coni-Snap hard gelatine capsules of size 3 (0.3 ml, provided by Capsugel). The target fill weight was approximately 20–25 mg, in order to reach a dose of 400 µg. Filling parameters were set at an output rate of 2500 capsules per hour (cph), a powder bed height of 5 mm and 10 mm, a dosing chamber length of 2.5 mm and a 3.4 mm dosator nozzle was used. This resulted in two pre-compression ratios of powder bed height versus dosing chamber length of 1:2 and 1:4. Before mounting and feeding the powder, a smooth powder layer was created by running the machine without capsule filling. A vernier caliper was used to measure the powder layer height. Capsule filling took place under humidity- and temperature-controlled conditions (humidity frame of 40% to 55% relative humidity (%RH)) to avoid moisture uptake. For each setting a runtime of 15 minutes was chosen and resulted in 625 capsules per batch using a production speed of 2500 cph.

Table 1: Capsule filling process parameters

	Capsules per hour [cph]	Dosing chamber length [mm]	Dosator diameter [mm]	Dosing volume [mm³]	Powder bed height [mm]
Setting 1	2500	2.5	3.4	22.7	5
Setting 2	2500	2.5	3.4	22.7	10

6.2.6 Pre-weighing and identification of capsules

Empty capsule shells have a relatively high weight variability compared to the low fill weight used for inhalation applications. Therefore, an analytical scale (Denver SI- 234A, Denver Instrument GmbH, Göttingen, Germany) was used to measure the exact weight of every empty capsule body, which were then assigned with an individual number. Each filled and numbered

capsule was weighed again. The weight of the empty, numbered capsules was subtracted from the gross weight to obtain the precise fill weight (Faulhammer et al., 2014a). For determining the mean fill weight and weight variability 20 capsules were taken. Also, a visual check of the capsule content was conducted to ensure that no strong powder plugs were build and that the capsule is intact. The capsules were preserved in a desiccator over silica gel, prior to further analysis.

6.2.7 Blend uniformity during filling

Initial blend uniformity was determined and blends showed acceptable distribution of the API within the blends (RSD of mean drug content < 5%). In order to investigate the effect of powder handling and processing on blend uniformity the latter was determined during capsule filling inside the rotary container by sampling the filled capsules and quantifying the salbutamol sulphate content using a validated HPLC method (Faulhammer et al., 2015). Therefore, 25 capsules were collected after 5 and 10 minutes from the beginning of capsule filling and 10 capsules taken for determining the mixing homogeneity. The homogeneity of the blends was expressed as the coefficient of variation of the mean drug content, of n=10 samples. Therefore, the content of the capsules was dissolved in 20 ml of buffer (water adjusted by acetic acid to pH 3) and the salbutamol sulphate content in each sample was determined via a validated HPLC method (Faulhammer et al., 2015). A mixing homogeneity of below 5% deviation from the mean drug content of the sample was regarded as acceptable.

6.2.8 Aerodynamic assessment of particles

The aerodynamic performance of the different lactose salbutamol sulphate mixtures was tested with an Aerolizer® device, coupled with a next generation impactor (NGI) (Copley Scientific, Nottingham, UK) using an air flow rate of 100 l/min. For each adhesive mixture four capsules were discharged into the impactor in a direct sequence. Experiments were performed according to the European Pharmacopoeia and have been described in detail in a previous articles published by the authors (Faulhammer et al., 2015). From these experiments, the emitted dose (ED), the fine particle dose (FPD), the fine particle fraction (FPF) and the mass median aerodynamic diameter (MMAD) were calculated for the different formulations and compared among each other. The ED gives the amount of API found in the whole impactor (mouthpiece adaptor, introduction port, preseparator, impaction stages) in µg, the FPD gives the amount of API exhibiting an aerodynamic diameter of < 5 µm in µg and the FPF gives the % of API < 5 µm

149

related to the ED. The MMAD gives the average size of particles constituting the dose which reach the impactor, excluding particles deposited in the throat (Traini, 2013). This governs the respirable fraction and represents the particle deposition pattern in the lung. All experiments were performed in triplicate.

6.2.9   HPLC Method

The salbutamol sulphate content from mixing homogeneity as well as NGI experiments was assessed via HPLC using a mobile phase of A – 5 mM hexanesulfonic acid sodium salt in water + 1% acetic acid and B – methanol (A:B 60%:40%), at a flow rate of 1 ml/min. The system consists of a pump (Waters 2695, Milford, USA), an autosampler, a Waters 2996 photodiode array detector and, as stationary phase, a Phenomenex Luna C18 5 µm 100 Å column (150 x 4.6 mm, 5 µm). The column temperature was set to 30 °C and the injection volume was 50 µl. Seven calibration standards were prepared with salbutamol sulphate concentrations between 2.6 µg/ml and 70.5 µg/ml. To overcome the limit of detection for each experiment, three capsules were discharged into the NGI via the Aerolizer® directly after each other.

6.3 Results and discussion

In the following section, the untreated lactose will be called LAC_R (R representing raw material) and the decanted engineered lactose, LAC_E (E representing engineered). The jet-milled salbutamol sulphate will be called JMSS, and the spray dried salbutamol sulphate SDSS.

6.3.1   Characterisation of engineered API particles

API processing can significantly affect the final product characteristics. SEM images in Figure 1 show that spray drying results in smooth and spherical particles, whereas jet-milling preserves the stick- or needle-shaped crystalline particles from the precursor. Although salbutamol sulphate particles prepared by two different techniques were in the inhalable size range, SDSS particles were larger in comparison to the JMSS particles (Table 2). Furthermore, spray drying resulted in a more narrow particle size distribution (PSD), or more precisely, in monodisperse particles, indicated by a smaller span value below 2.

Previous studies from our working group showed that SDSS particles are amorphous, while JMSS particles are predominantly crystalline when solid-state is analyzed using DSC and

SWAXS (Faulhammer et al., 2015; J.T. Pinto, S.Radivojev, S. Zellnitz, E. Roblegg, 2017; Littringer et al., 2013).
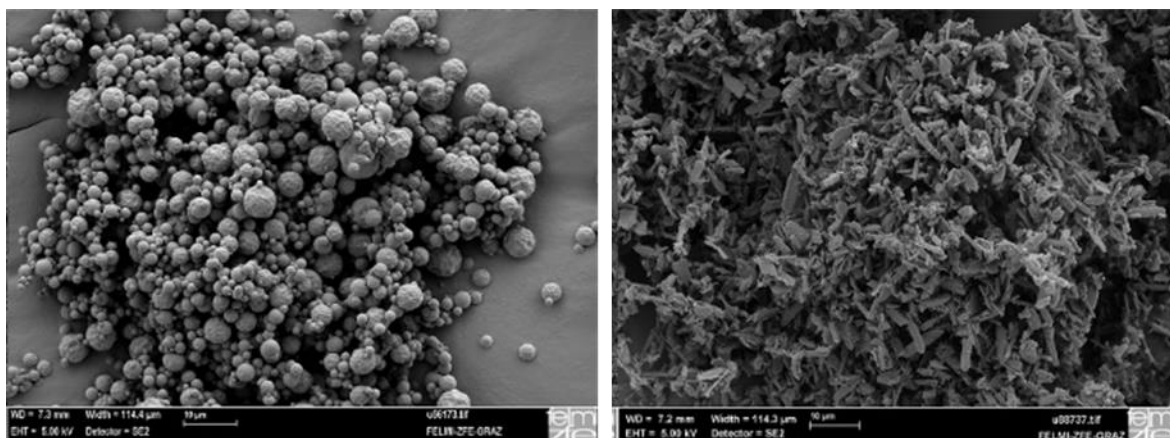
Figure 1: SEM images of SDSS (left) and JMSS (right) particles (Image width 114.3 μm).

Table 2: Particle size and distribution of JMSS and SDSS (±stdv) – Helos dry dispersion (2.0 bar dispersion pressure).

	x_{10} [μm]	± stdv	x_{50} [μm]	± stdv	x_{90} [μm]	± stdv	Span $[(x_{90}-x_{10})/x_{50}]$
JMSS	0.52	0.01	1.99	0.0	4.97	0.09	2.23
SDSS	0.50	0.01	3.0	0.13	5.67	0.24	1.72

6.3.2 Characterisation of engineered carrier particles

SEM images in Figure 2 show the difference in the surface morphology of lactose particles before (left) and after (right) decantation. It appears that carrier engineering via wet surface processing results in smoother particles, with less fine lactose attached, compared to the raw material. Overall, the shape of the particles was not changed. Lactose particles remain tomahawk shaped, but shallow steps were introduced on the surface after decantation.
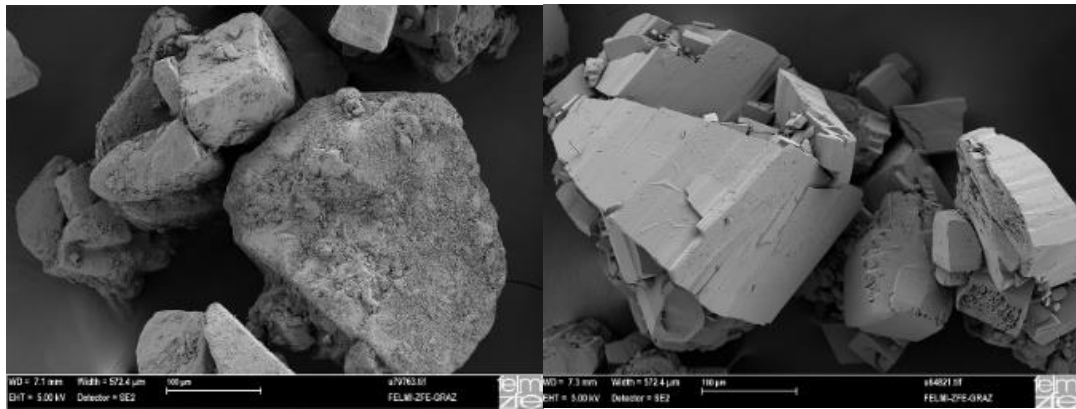
Figure 2: SEM images of lactose carrier particles before (left) and after (right) decantation (Image width 572.4 µm).

Table 3 presents the particle size and particle size distribution of the carrier particles, before and after decantation. An overall decrease in particle size could be observed after decantation. These findings are in agreement with the SEM observations. The differences can be explained by the removal of fine lactose particles and particle smoothing. Figure 4 schematically explains the reduction in mean particle size of coarse lactose particles, via removal of surface fines during decantation. Additionally the decrease in particle size can partly be related to the breakage of aggregates during decantation.

Figure 3: Scheme - Schematic depiction of the removal of surface fines and reduction of the particle size through wet decantation.

6.3.3 Characterisation of powder blends

Figure 4 shows representative SEM images of adhesive mixtures containing engineered lactose and SDSS particles (right), or JMSS particles (left). After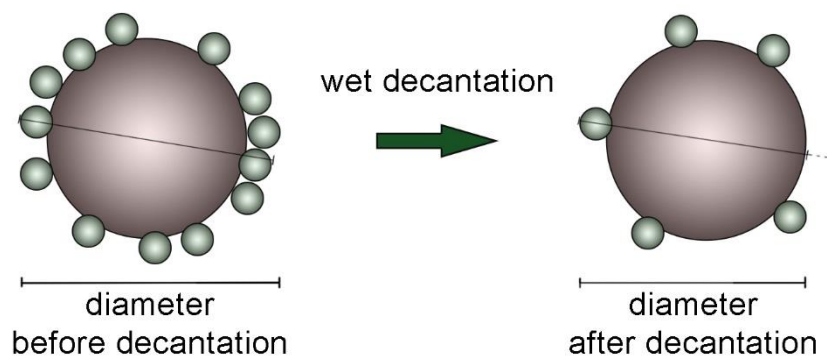 blending, API particles appear to be distributed homogenously over the carrier surface. The free pits/steps that were generated during decantation seemed to be filled up with API particles upon blending. SEM images show no visual differences in API distribution on the carrier surface when using API particles that were engineered via two different means, generating two distinct solid-states (i.e., amorphous SDSS versus crystalline JMSS particles). This was further confirmed by the mixing homogeneity results; for both samples the RSD of the mean drug content was below 5%. However, the inter-particle interaction with carriers appeared to be significantly different. This in fact is reflected by their NGI performance (see results below).
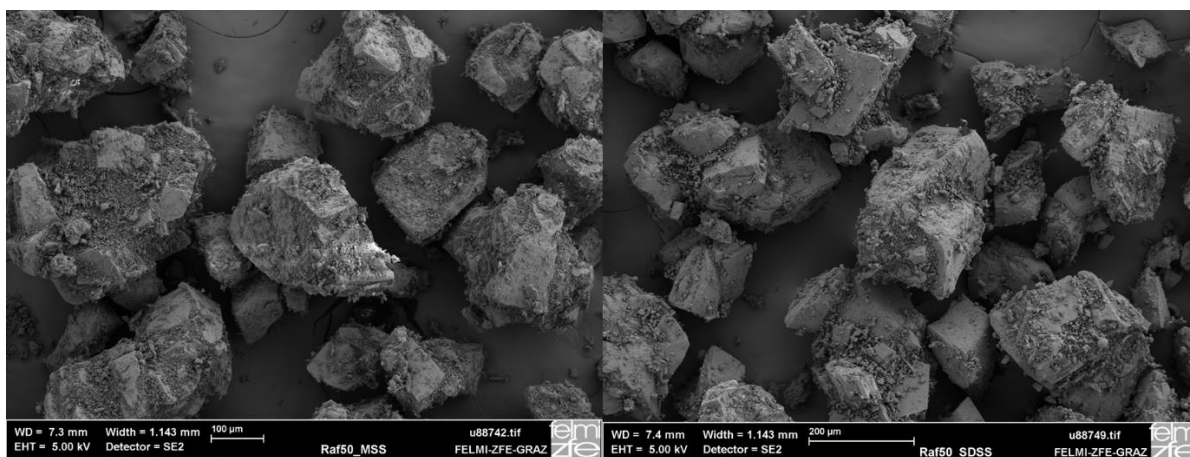
Figure 4: SEM images of adhesive mixtures of decanted lactose with JMSS (left) and SDSS (right) particles (Image width 1.143 mm).

PSD results in Table 3 suggest that for both blends with engineered carrier, the x_{50}-values were slightly lower, compared to that of the blends with untreated lactose. This can again be explained by the decrease in particle size of the lactose particles, due to the removal of fine lactose particles (Figure 4) and some abrasion of the carriers during decantation. When comparing the raw material and blends of raw material, the latter show relatively lower mean particle size (Table 3). This could again possibly be due to some particle abrasion, in this case due to the forces acting on the material during the mixing process, in the tumble blender. The spans of the PSD were in the

same range for all powder blends and were not affected by the use of either engineered carrier or engineered API particles.

Table 3: Particle size and distribution of raw and engineered carrier material as well as of the drug-carrier blends before and after decantation (n=3 ± stdv) – Qicpic (0.5 bar dispersion pressure).

	$x_{10}[\mu m]$	± stdv	$x_{50}[\mu m]$	± stdv	$x_{90}[\mu m]$	± stdv	Span $[(x_{90}\text{-}x_{10})/x_{50}]$
LAC_R	95.27	3.74	216.03	5.60	354.70	8.53	1.20
LAC_E	71.74	3.67	179.04	6.39	313.93	5.33	1.35
JMSS+LAC_R	95.58	2.08	183.26	7.33	287.42	1.21	1.05
JMSS+LAC_E	95.76	0.38	173.45	0.70	279.54	1.08	1.06
SDSS+LAC_R	99.62	1.38	193.11	4.29	310.2	23.14	1.09
SDSS+LAC_E	99.57	0.44	185.48	0.94	291.98	1.52	1.04

6.3.4 Bulk powder and flowability properties of the blends

Fu et al. reported a significant effect of the particle size and shape on the bulk and shear characteristics of lactose powders (Fu et al., 2012b). Thus, it can be expected that the decrease of the PSD will lead to a change of the powder flow behaviour. As a measure for the flowability of the different adhesive mixtures, the bulk density (BD) and tapped density (TD) were measured and the values of Carr's index (CI) were calculated. Wet decantation resulted in an increase of BD and TD for the carrier materials, possibly through the exposure of surface asperities and the consequently improved powder packing and flowability. Furthermore, results show that carrier engineering lowered the CI from 26.9 (LAC_R + SDSS) and 26.6 (LAC_R + JMSS) to 21.7 (LAC_E + SDSS) and 23.2 (LAC_E + JMSS) respectively, indicating better flowability of the mixtures with engineered carrier material. This is true for mixtures of engineered carrier and both spray dried and jet-milled API. The use of engineered API in the blend preparation appeared not to affect the flowability of the mixtures. This is most likely due to the small amount of API present in the mixtures and predominance of carrier that can describe blends properties.

To obtain a deeper insight into the flowability and aeration behaviour of the DPI blends, shear-based powder flow measurements were carried out using the FT4 powder rheometer (Table 4). As previously described, the FFC is defined as the ratio of consolidation stress to unconfined

yield strength and also a parameter to describe powder flowability. Blends containing engineered lactose carrier particles show higher FFC values, as an indication of the improved flowability. A significant improvement of flowability to 9, near to the free-flowing limit of 10, could be observed for adhesive mixtures when engineered lactose and JMSS are used, instead of raw lactose. The flowability of the API-carrier mixtures of lactose and SDSS improved from 5.43 to 7.86 when engineered lactose is used. These results agree well with the CI and HR. This further supports our findings that powder flowability is governed by carrier properties and that wet decantation of the carrier improved the flowability of the adhesive mixtures.

Regarding the AIF, a different behaviour could be noticed for the two different API-carrier mixtures. The AIF for the blend with SDSS decreased after decantation, the AIF for the blend with the JMSS remained almost unaltered. This might be explained by the higher rolling ability of the spherical spray dried API particles, on the smoother decanted lactose surface, after decantation. As the amount of fine lactose particles is reduced and the surface is smoothed, less internal friction was measured. This effect could not be observed for needle shaped API particles.

Table 4: Shear cell measurements (n=3) of API-carrier mixtures.

	FFC	± stdv	AIF [°]	± stdv	Cohesion (C) [kPa]	± stdv
JMSS+LAC_R	5.43	0.93	33.67	0.74	0.29	0.07
JMSS+LAC_E	7.87	1.53	33.37	0.95	0.17	0.07
SDSS+LAC_R	6.35	1.1	37.00	1.21	0.19	0.09
SDSS+LAC_E	9.00	4.5	32.97	0.51	0.23	0.05

Table 5 shows the basic flowability energy (BFE), aerated energy (AE) and permeability (PM) of the four blends. Depending on API engineering, the decantation of the carrier has different consequences on the BFE. An increase of the BFE could be observed after decantation for the blend with the JMSS, while the BFE of the blend with the SDSS remained statistically the same. Since other flowability indicators showed an improvement of the flow properties through wet decantation, it may be assumed that some unaccountable parameters (like electrostatic forces) could have led to the contradicting trends of the obtained BFE values.

The AE, which also is a parameter to assess the flowability, is governed by permeability and compressibility. Here again, a different behaviour of the two adhesive mixtures could be observed. The AE of the mixture of lactose with JMSS decreased after decantation, whereas this parameter slightly increased for the mixture with the spray dried API. These results indicate that powders tend to be more cohesive when JMSS particles are used and that the combination of engineered carrier and jet-milled API lowers the cohesion. This is further supported by the cohesion measurements presented in Table 4 (0.29 for JMSS+LAC_R versus 0.17 for JMSS+LAC_E). Nevertheless, the cohesion values do not support the findings that adhesive mixtures with jet-milled API particles show generally higher cohesion. These different observation could be due to the different measuring principles and set up; the sample volume in the shear cell is much less than the volume needed for AE measurements.

The results of the permeability (PM) measurements again support the idea of a different impact on the flowability after decantation of mixtures with JMSS and SDSS. First, adhesive mixtures with JMSS overall showed higher permeability values, compared to adhesive mixtures with SDSS particles. A closer look at the mixture with JMSS showed a slight increase in PM after decantation. SDSS displayed a slight decrease. This increase of PM, for the JMSS mixture, means that the decanted jet-milled powder blend has a slightly higher capacity to remove air during compaction, and therefore, should be easier to handle during capsule filling or tabletting. As the PM value of the spray dried blend decreased after the decantation, it can be expected that for this blend the air cannot be removed as fast as before this process step, resulting in somewhat less effective compaction. Hence, with respect to the initial situation of SDSS and JMSS, it is hypothesised that the jet-milled blend will show a better capsule filling performance.

Generally, in literature it is reported that permeability increases with decreased fine particle amounts in the blends (e.g. due to decantation) (Cordts and Steckel, 2012; Shur et al., 2008). In our work, this trend can only be observed when jet-milled API is used. The contrasting findings for spray dried API blends could possibly be explained by the different solid-state. In presence of carrier fines, they might intervene with amorphous SDSS particles pressing them against coarse lactose particles and forming bridges (to facilitate airflow). These results imply that permeability and (carrier) fines relation for the powder mixture with heterogeneous solid-state could not be interpreted in the same way as crystal-crystal mixtures.

Table 5: FT4 powder rheometer measurements with the air conditioning unit (n=3) of API-carrier mixtures.

	Basic Flow Energy [mJ]	± stdv	Aeration Energy [mJ]	± stdv	Permeabiliity [mBar] at 1 to 15 kPa	± stdv
JMSS+LAC_R	337.67	12.58	54.40	10.69	1.84	0.04
JMSS+LAC_E	388.17	23.93	34.00	5.30	1.90	0.04
SDSS+LAC_R	326.98	20.78	27.77	0.51	1.62	0.07
SDSS+LAC_E	324.33	11.93	31.60	2.11	1.29	0.08

6.3.5 Impact of particle engineering on processability – capsule filling performance

The target fill weight was 20–25 mg, in order to reach a salbutamol sulphate dose of 400 µg. This is a common fill weight in capsules for dry powder inhalers (DPI), as used for example in the marketed product Salbutamol 400 Cyclocaps® (PB Pharma GmbH, Germany). In these capsules 400 µg Salbutamol is blended with lactose monohydrate. Each capsule contains 20 mg of the 2%-API blend.

In order to evaluate the impact of particle (carrier and API) engineering on downstream processing (blending / capsule filling), (1) the blend uniformity during filling was evaluated between 5 and 10 minutes, as well as between 10 and 15 minutes, of process runtime (2). Fill weight and fill weight variability, expressed by the relative standard deviation (RSD), were compared for the different adhesive mixtures. A decrease in blend uniformity values represents a more homogenous distribution of API within the mixture.

Overall results in Table 6 show that the blend uniformity is good and within the acceptable range of below 5% for all formulations independent of the carrier, API combination and process settings. When further investigating the values it can be detected that, for the process setting with a higher compression ratio, the blend uniformity drastically improves with increasing capsule filling time. After 15 minutes, the API is distributed more homogenously in all blends. This is possibly due to start up effects (Stranzinger et al., 2017). This effect is negligible at a lower

compression ratio. Nevertheless, neither carrier nor API engineering had a significant effect on blend uniformity during capsule filling.

Table 6: Mixture homogeneity during the filling process at different powder bed heights. Samples were taken from 5 to 10 minutes and from 10 to 15 minutes (n=10, RSD from mean drug content).

	Mixture Homogeneity at Process Setting 1 [%]		Mixture Homogeneity at Process Setting 2 [%]	
	Min 5-10	Min 10-15	Min 5-10	Min 10-15
JMSS+LAC_R	1.44	0.98	2.96	1.35
JMSS+LAC_E	1.75	1.62	3.80	0.93
SDSS+LAC_R	2.11	1.33	3.90	1.81
SDSS+LAC_E	1.07	0.66	3.32	1.48

Two different process parameters for capsule filling, resulting in different compression ratios (1:2 and 1:4), were chosen in order to evaluate the optimum process settings in terms of filling, as well as aerodynamic performance. For both compression settings, no powder plug was created, which is desirable for inhalation dosage forms. Furthermore, the effect of particle engineering on capsule filling performance was evaluated. Results in Table 7 show that the intended fill weight of 20–25 mg per capsule was achieved for all blends (Yin, 2007). However, when studying the values in more detail, it can be observed that carrier engineering had a positive effect on weight variability at a lower compression ratio (setting 1), represented by lower RSD values (significant different, $p<0.001$, F-test of equality of variances). Moreover, the use of engineered carriers in combination with process setting 1 led to higher fill weight, compared to raw lactose carriers. The positive effect of engineered lactose on the capsule filling performance can be related to the increased flowability of adhesive mixtures containing engineered lactose particles. However, the LAC_E is far less compressible than the raw material. Comparing the capsule fill weight of setting 1 and 2, it can be seen that the capsules filled with blends containing LAC_R as carrier show an increase in fill weight of approximately 30%, independent of what kind of engineered API was used. In contrast the blends with LAC_E only have little higher fill weight when processed at setting 2.

Table 7: Capsule filling performance - fill weight and weight variability represented by the RSD (n=20 (±stdv) - and in vitro performance - fine particle fraction (FPF), emitted dose (ED) per capsule and mass median aerodynamic diameter (MMAD) (n=3 (±stdv − for the different adhesive mixtures) and the mean loaded dose determined from the mixing homogeneity experiments (n=10 (±stdv)

Samples	Setting 1						Setting 2					
	Fill weight [mg]	RSD [%]	Loaded dose [%]	FPF [%]	MMAD [µm]	ED [µg]	Fill weight [mg]	RSD [%]	Loaded dose [%]	FPF [%]	MMAD [µm]	ED [µg]
JMSS+ LAC_R	19.7	6.6	2.02 ± 0.02	15.0 ± 3.8	2.95 ± 0.1	358.2 ± 31.3	27.2	2.0	2.09 ± 0.03	21.0 ± 1.5	3.19 ± 0.1	435.2 ± 35.0
JMSS+ LAC_E	24.1	2.4	2.06 ± 0.03	23.1 ± 6.0	2.97 ± 0.1	396.0 ± 18.5	25.1	1.9	2.05 ± 0.02	23.6 ± 1.1	2.95 ± 0.3	387.2 ± 54.9
SDSS+ LAC_R	20.9	4.2	1.96 ± 0.02	3.5 ± 0.7	7.17 ± 0.2	344.4 ± 6.7	27.2	2.3	2.01 ± 0.03	4.8 ± 1.9	7.21 ± 0.7	412.6 ± 57.3
SDSS+ LAC_E	24.7	2.2	1.89 ± 0.02	1.5 ± 0.5	7.76 ± 0.4	372.6 ± 78.2	27.3	2.0	1.86 ± 0.03	2.0 ± 0.9	7.62 ± 0.9	430.2 ± 59.4

Compared to carrier engineering, API engineering seemed not to affect the capsule filling performance. A possible explanation, therefore, could be the amount of API, which is 2% and relatively small in the mixtures. Although from powder rheometry, it was expected that the JMSS blend will show a better capsule filling performance. This effect was not pronounced during capsule filling experiments.

Furthermore, capsule fill weight and weight variability values indicate that a higher compression ratio (setting 2) lead to more constant capsule filling results. Compared to a lower compression ratio, where carrier engineering positively affected weight variability and mean fill weight, these parameters are independent of the carrier and API material used at a compression ratio of 1:4.

6.3.6 Impact of particle engineering on the in vitro aerodynamic performance

Fine particle fraction (FPF), the emitted dose (ED) and the mass median aerodynamic diameter (MMAD) were chosen for evaluating the impact of particle engineering on the performance of the different adhesive mixtures. Further, the loaded dose per capsule was determined from the mixing homogeneity experiments. Results show that the loaded doses are in the range of the target dose (2% API). This is true for all adhesive mixtures however, the drug load is overall slightly lower when SDSS is used (Table 7). Irrespective of carrier modifications or capsule filling process parameters, the blends comprised of SDSS show considerably lower FPFs (2 to 5%), compared to those containing JMSS particles (15 to 24%) (Table 7) (significant different, $p<0.001$, 2-tail t-test for unequal variances). This is linked to and can most likely be explained by the large MMAD values returned from the blends with SDSS particles (around 7.5 µm), compared to those from JMSS based blends (3 µm). The MMAD of JMSS particles is within the range of the mean particle size (x_{50}) measured via laser diffraction. By contrast, for SDSS particles the MMAD is about double the diameter of the mean particle size, measured via laser diffraction. The differences in MMAD might be explained by the different physico-chemical properties of spray dried and jet milled material. It is evidently expected that amorphous SDSS possesses higher surface energy (and also cohesivity), as well as higher hygroscopicity (thus a higher tendency to form solid-bridging), when compared to dominantly crystalline JMSS. Therefore, fine SDSS particles tend to form irreversible agglomerates over time or during blending (Pinto et al., 2017).

The fact that the ED is about the same, regardless of whichever spray dried or jet-milled API is used and that the FPF is significantly affected by the API used, supports the hypothesis that spray dried salbutamol sulphate particles form agglomerates that are able to leave the inhaler but cannot be dispersed during inhalation (Pinto et al., 2017). A poor deaggregation and aerosolisation efficiency for spray dried particles was described before for Budesonide. To reduce the spray dried particle-particle cohesivity and to prevent the micronised particle aggregation, surface coating with polymers and surfactants has shown to be a successful approach (Buttini et al., 2008; Tuli et al., 2012). Another explanation could be the mechanical forces during mixing that could lead to inefficient detachment of spray dried particles from the carrier. Selvam et al. showed that drug particle physico-chemical properties might be responsible for differences in the effects of the press on forces during mixing on drug detachment of different drug materials (Selvam and Smyth, 2011). Furthermore, no correlation between the ED and the different process settings, or

the use of engineered particles, can be found. However, the ED can be correlated with the capsule fill weight. Higher capsule fill weights resulted in higher EDs, indicating that the dose was properly released from the capsule shell.

Thus, API engineering has a larger effect on the aerodynamic performance than carrier engineering. Taking the standard deviations into account, the use of engineered lactose particles did not significantly change the FPF when jet-milled API particles were used. By contrast, when spray dried API is used, the FPF decreases for the engineered carrier material at high and low compression ratios. This is in agreement with previous studies and can be explained by the absence of fine lactose particles (Boshhiha and Urbanetz, 2009b; Faulhammer et al., 2015). The highest FPFs were obtained for jet-milled API in combination with engineered lactose particles, at either low or high compression ratios.

Concerning the impact of powder properties on the aerodynamic performance, a correlation between the air permeability (Table 5) and the FPF could be observed. The higher the air permeability of the adhesive mixture, the higher the FPF. Moreover the permeability as well as the FPF is drastically reduced when spray dried API was used. Cordts and Steckel investigated permeability and aeration of ternary mixtures and no correlations between these two parameters and the FPF could be found. However, a relationship between the amount of fines and DPI performance was shown, the higher the amount of fines, the lower the permeability value (Cordts and Steckel, 2012). Further, Le et al. reported a correlation between the air permeability and the quantity of free particle fraction in the interparticular spaces of a powder bed that leads to the fine particle fraction during fluidization in the airflow (Le et al., 2010). Recently, Hertel et al. reported a correlation between permeability, amount of fines in ternary mixtures and the aerodynamic performance. Air permeability in relation to fluidization energy was introduced as a tool in order to predict the optimum amount of fines for good inhalation performance (Hertel et al., 2018). Nevertheless, more fundamental research is needed to elucidate the aerodynamic dispersion of powders linking with their bulk properties.

Future work will focus on understanding the agglomeration behaviour and tendency of SDSS particles, in order to explain the superior in vitro performance of JMSS versus SDSS particles. Besides, the interplay between carrier and API properties, drug detachment and capsule filling efficiency will be studied for additional carrier API combinations.

6.4 Conclusion

Particle engineering has been intensively explored in carrier-based DPI formulation development. This study investigates engineered carrier, as well as engineered API particles, and shows that there are distinct performance indicators of particle engineering for carrier-based DPIs. Compared to API engineering, carrier engineering has a positive effect on the capsule filling performance (fill weight variability) at a lower compression ratio (setting 1). Whereas API engineering seems to have no effect on capsule filling performance. Carrier engineering significantly improves the flowability of the formulation, which in turn positively affected capsule filling. Results further showed that a higher compression ratio during capsule filling appears to be beneficial in terms of capsule filling performance. The mean fill weight and fill weight variability is not affected by the use of differently engineered carrier materials and higher overall fill weight can be achieved.

By contrast, drug detachment and aerodynamic performance is rather governed by the API particles used, and thus, by API engineering. The use of SDSS particles, compared to JMSS particles, decreased the FPF. This could be explained by particle characteristics that were more distinct for the differently prepared API particles, than for raw and engineered carrier particles. API engineering resulted in particles with different size, shape and solid-state properties, whereas carrier engineering mainly changed surface topography. Spray dried amorphous particles tend to form irreversible agglomerates over time, due to amorphous bridging which leads to poor in vitro aerosolisation. Overall carrier engineering did not have a significantly positive effect on the aerosolisation performance. The highest FPF (≈23%) was obtained for jet-milled API in combination with engineered lactose carrier particles.

Thus, it can be concluded that in carrier based formulations using lactose and salbutamol sulphate, the carrier engineering, or generally carrier properties, govern downstream processing, whereas the API engineering and API properties significantly affect the dose delivery to the lung, and thereby, govern aerosolisation performance. More precisely, flowability of carrier (tunable by altering surface fine and smoothness) acts as a performance indicator for capsule filling irrespective of solid-state and shape of the same API used in the blend. On the other hand, solid-states of API (amorphous versus crystalline and thus the possible difference in mechanical properties e.g. press on force) represent in vitro aerosolisation performance indicator irrespective of the surface properties of the same carrier. However, for establishing this as a general predictive

knowledge requires further investigations including other APIs and/or carriers with varying physico-chemical properties.

The obtained data are useful, to improve the understanding of the relationship between particle engineering on capsule filling efficiency and aerosolisation performance in carrier-based DPI formulations. Moreover, this should allow knowledge-based preselection of suitable API carrier combinations, their engineering routes and downstream process parameters based on particle characteristics.

6.5 Acknowledgements

6.6 References

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7. Summary and conclusion

The introductory chapter 1 provides an overview of capsule filling systems used for filling of granular material into capsules, with the main focus on the dosator capsule filling system in particular for low-doses. Since in this filling system the powder condition in the container from where the powder is taken and transferred into a capsule is known to be critical, process analytical technology (PAT) as a promising tool to optimize filling performance is introduced, whereas the terahertz technology as one of the most promising ones for this purpose is described in detail.

In chapter 2 a low-dose dosator nozzle capsule filling machine (Labby, MG2, Bologna) with special low-dose equipment adaptations (i.e., smaller nozzles, a cleaning unit for the removal of excess powder from the dosator, special blades to create the powder layer) was used to investigate the filling performance of three grades of lactose excipient, with a special focus on the powder layer uniformity. Prior to capsule filling, powders were extensively characterized using standard and advanced measurement techniques. The fill weight of the coarse carrier remained almost the same, regardless of the process parameters throughout the capsule filling run time, whereas for the cohesive powder the bed inhomogeneity was a critical factor, resulting in an increase in fill weight. In terms of combination of process parameters, for the latter a high dosing chamber volume requires a low filling speed in order for the powder to completely fill the dosator nozzle. Moreover, it was established that a dosing chamber length of 2.5 mm and a powder bed height of 10 mm were required due to the powder's high fill weight variability over time, while the dosator size had no effect on it. The results indicate that Lactohale 220 requires special attention during low-dose capsule filling.

Because several process parameters can affect the fill weight and weight variability of the final capsule, chapter 3 investigated some of them in more detail by decoupling the capsule filling process in dynamic and static mode tests. Dynamic tests refer to filling of capsules in a regular lab-scale dosator capsule filling machine (Labby, MG2, Bologna) with special low-dose equipment adaptations. Static tests were conducted using a novel filling system developed by us. The findings of this study suggest that for low-dose dosator capsule filling it is strongly recommended to continuously control instrumental settings, i.e., gaps between the lowest point of the dosator and the bottom of the box, as well as factors which mimic environmental conditions, i.e. mechanical vibrations. Both parameters clearly affect the fill weight and weight variability.

Investigations on the effect of certain process parameters of various powder materials on the filling performance provide valuable insights into a dosator nozzle filling process, step by step. Our results could help formulation and process developers to rapidly screen the required process parameters based on the specific properties of the powders used.

Based on the previous studies, where we found that the powder layer inhomogeneity is one of the main challenges during low-dose capsule filling, we placed the strategic focus on the latter to optimize the filling process as described in chapter 4. The most promising analytical technology capable to continuously measure the layer uniformity of the powder bed was evaluated for its applicability for a low-dose capsule filling process. We present a novel approach to quantify density variations in a moving powder bed by means of terahertz technology as well as the sensitivity of the method. Powder samples of model excipients (lactose and microcrystalline cellulose (MCC) of varying density and particle size) were systematically investigated in reflection in a moving powder bed. Each powder was compacted to several different relative densities and the measured refractive index obtained from in-line terahertz measurements was correlated to the powder state inside the moving powder bed. The coefficient of determination (R^2) was larger than 0.962 (Lactohale 100) for all six powders, with the highest coefficients for Lactohale 220 ($R^2 = 0.996$) and SMCC 50 LD ($R^2 = 0.995$). The results suggest that the proposed method can resolve relative density variations that are as small as 0.3% (Lactohale 100). Furthermore, the novel approach allows a precise resolution of the spatial distribution of relative density, which facilitates an in-depth analysis of powder behavior upon compaction.

In chapter 5 we utilized the developed method (see chapter 4) to investigate the correlation of the measured powder density with the fill weight in a capsule of three grades of lactose excipients at two different terahertz probe positions, i.e. from the side (terahertz probe position 1) and the bottom (terahertz probe position 2) of the rotary container. Small quantities were drawn from the powder bed using a novel sampling system that mimics the capsule filling process. We further analyzed the effect of sampling on the density of the powder bed for the different materials. The predictions and the measured weights of the powder in the capsules were in excellent agreement, where the relative density measurements of Lactohale 200 ($R^2 = 0.995$) showed the strongest correlation with the respective fill weight. We also studied how the uniformity of the powder bed is impacted by the dosing and the subsequently filling of the holes which were introduced in the powder bed after the dosing. Even though the holes seemed to be filled with new powder (by visual inspection), the relative density in these specific segments clearly differ from the powder

bed state prior to dosing. The study provides a new perspective of the terahertz technology to be used as an in-line monitoring tool for manufacturing processes where powder bed variations are directly linked to the quality of final products, e.g. feeder, rotary container used in a dosator or tamping pin capsule filling process.

Since the final targeted product, in our case a DPI product formulated as dry powders of API in the presence of excipient particles – the carrier, in chapter 6 we studied performance indicators of carrier-based DPIs filled with a lab-scale dosator capsule filling machine (Labby, MG2, Bologna) with special low-dose equipment adaptations. In vitro lung deposition experiments were carried out with a next generation impactor. We found two distinct performance indicating properties of carrier and API in terms of capsule filling and in vitro aerosolization performance for the investigated system, i.e. carrier surface properties for capsule filling and API properties for in vitro aerosolization. Ideally, this specific knowledge base should allow the pre-selection of suitable API carrier combinations, in terms of their engineering routes and downstream process parameters based on particle characteristics. The study provides valuable data for improving the understanding of the relationship between particle engineering, capsule filling efficiency and aerosolization performance of carrier-based DPI formulations.

8. Outlook

The precise dose filling of capsules in the lower mg-range, which is required for inhalation therapies, needs a sound understanding of the process in order to successfully manufacture high-quality products. One of the biggest problems in the manufacturing of high-quality, low-dose inhalation products, is dose uniformity, related to safety and efficacy of the drug products. Up to now, the main challenge is the powder layer inhomogeneity of very fine powders with low density particles, i.e., particle sizes smaller than 10 μm, exhibiting poor flowability and high cohesivity. Currently, no systematic understanding exists of how the evolution of the powder layer during the capsule filling contributes to such critical quality attributes as the fill weight and the weight variability.

In the course of this thesis several critical process parameters and material attributes that affect the filling performance could be identified. Using the developed stand-alone static test tool we found two critical instrumental settings, i.e., gaps between the lowest point of the dosator and the bottom of the box, as well as mechanical vibrations that clearly affect the fill weight and weight variability. As a first step our results could help formulation and process developers to rapidly screen the required process parameters based on the specific properties of the powders used. For the future, we suggest the novel test tool to be used for preliminary tests to evaluate the performance of new dosators and to ascertain optimal process settings for new formulations without needing an excessive amount of material. In the end, a stepwise mechanistic process understanding could be developed, with the ultimate goal of creating a platform indicating the required instrumental settings for a range of various materials.

Furthermore, in terms of powder layer uniformity we strongly recommend to implement the developed novel approach, i.e. terahertz in-line sensing, for continuously monitoring the powder bed density variations. This is supported by the findings of our study about how the uniformity of the powder bed is impacted by the dosing and the subsequently filling of the holes which were introduced in the powder bed after the dosing. Even though the holes seemed to be filled with new powder (by visual inspection), the relative density in these specific segments clearly differ from the powder bed state prior to dosing. The knowledge about the state of the powder bed throughout the process will help in designing production machines, e.g. introduction of tools to stabilize the powder bed condition, which are capable to maintain a constant powder bed density and thus reduce process induced variability of final products.

Moreover, as stated in chapter 6, instrumental settings notably affect the blend uniformity over time. In particular, a more homogenously distribution of the API was detected for a higher compression ratio after 15 min compared to the samples drawn at the beginning of the capsule filling process. However, blend uniformity results must be interpreted carefully due the the small sample size and the well-known off-line sampling issues. Therefore, for future research it is recommended to determine the blend uniformity continuously throughout the process using in-line analytical tools. For this, we did preliminary tests using RAMAN spectroscopy for continuously monitoring the blend uniformity of the powder bed in the rotary container. The developed RAMAN spectroscopy model for blend uniformity measurements has high potential to be implemented as an in-line PAT tool. Therefore, the introduced model which was tested at lab-scale should be further developed to be applied at industrial scale as well. In a further step, this model may be used to evaluate the performance of existing solutions to stabilize the powder layer, e.g. scrapers, hockey sticks, as well as new adaped respective versions, an in turn improve the distribution of the API in the rotary container to have in the end the same API content in each filled capsule.

As discussed in chapter 6, API and carrier particle properties inherited from engineering can notably affect downstream processability (i.e. capsule filling) and aerodynamic performance of DPI products. Therefore, future work needs to be done to get a detailed mechanistic understanding of the interplay of material properties, carrier modification, and downstream processability of carrier-based DPI products. Moreover, the emergence of new therapies in pulmonary drug delivery which necessitate that higher drug loads are delivered to or through the lung, pose a new challenge. This higher drug loads and in consequence the increased importance of drug physicochemical characteristics requires a sound understanding of how drug particle properties effects the blending and capsule filling process and the aerodynamic performance of the respective produced inhalation products under specific process conditions.

Moreover, we strongly recommend to further investigate the dosator dipping step in more detail via simulation studies using the implemented DEM model (for details see (Loidolt et al., 2017 and Loidolt et al., 2018)) supported by experimental data derived from our in-house developed stand-alone static tool. In particular, not only the movement of the dosator into the powder bed, but also the movement out of the bed should be considered to establish if the powder plug inside the dosator nozzle is kept during the transfer into the capsule or if powder is lost, resulting in inconsistent dose units. Furthermore, a greater focus should be placed on the variability of the

dosed mass as a function of powder bed inhomogeneity, another critical quality indicator of filled pharmaceutical capsules. Especially highly cohesive powders which are known to be challenging in term of powder layer inhomogeneity, e.g. due to holes, channels, compacted, loosened, or segregated areas within the powder mass, need to be investigated in more detail.

Based on the findings of the applicability of the developed novel approach to quantify density variations in a moving powder bed by means of terahertz technology and its ability to predict capsule fill weight, the combination of the former with simulation studies could be a fruitful area of future work. In particular, the quantified density variations via terahertz in-line sensing should be validated via simulation studies to (1) find the optimal terahertz probe position (e.g. horizontal or vertical to the rotary container) for a dosator nozzle capsule filling process and to (2) validate the terahertz in-line measurments in terms of "Can the detected density variations of the powder bed be deduced to the entire powder bed height.

The ultimate goal of all proposed further research work should be the determination of material and process parmameters (i.e., a comprehensive design space) that should finally ensure a stable capsule filling process with low variation in the dosed mass.

9. Appendix

Curriculum vitae   *Sandra Stranzinger*

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Email: s.stranzinger@gmx.net   Nationality: Austrian

Education

2015–2018   **Doctor of Philosophy – Chemical and Process Engineering,** *Graz University of Technology*, Austria
- **Title** – "Optimization of an industrial scale low-dose dosator capsule filling process for inhalation products"

2011–2014   **Master of Science – Technical Chemistry – Biotechnology and Bioanalytics,** *Vienna University of Technology, Austria*
- **Title** – "Development of a quantitative proteomics method to study the adaption of fungi to extreme environments"

2007–2011   **Bachelor of Science – Nutritional Sciences,** *University of Vienna, Austria*

Research experience

2014–   **Research Center Pharmaceutical Engineering (RCPE),** Graz
- **Lead of analytical team** – Plan, perform and interpret analytical activities including method development & characterization of materials; communication with client; compilation of method development & analytical technical reports
- **Scientific project lead** of two projects with industrial partners –
  1st Project: Evaluation of a new method for accelerated chemical stability assessment of solid-state pharmaceuticals. In the course of the project proof-of-concept data was generated for establishing the proposed method.
  2nd Project: Implementation and evaluation of the previously established (solid-state mechano-chemical catalysis) method for rapidly assessing a known drug-excipient interaction under reduced time and experimental efforts.
- **Supervision of Master thesis** – Guide the design and execution of experiments and proof-reading of thesis
- **Researcher in the analytical laboratory** – HPLC method development for industrial partners and for scientific purpose (co-author of publications)

SS2013   **Institute of Chemical Technologies and Analytics,** Vienna
- **Tutor (Internship Bioprocess Technologies and Analytics)** –
  The aim of the exercise was the elaboration of an integrated bioprocess (red biotechnology) and the implementation of crosslinked protein analysis.

08/2011–08/2012   **Avir Green Hills Biotechnology AG,** Vienna
- **Research Assistant in the field of bioanalysis –**
  Implementation of DNA- and protein detection methods; project "Optimization of quantitative and qualitative analysis methods of host cell DNA in influenza virus samples"

Key research skills

Experimental and theoretical techniques

- Terahertz Spectroscopy (THz-TDS, Terahertz Imaging)
- Raman Spectroscopy – Raman Microscopy
- UV-Visible-NIR Spectroscopy
- Chromatography (Liquid, High Performance Liquid)
- Mass Spectroscopy (MALDI-TOF, ESI)
- GraphPad Prism (Statistics)
- MATLAB® basics
- Chromatography Data Analysis: Empower 3 Chromatography Data Software, Mass Lynx Mass Spectrometry (Waters)

Additional skills and languages

Collaboration/ networking

Developed research network between scientific and industrial partners; facilitated links between RCPE and scientific partners (University of Cambridge, University of Ljubljana)

Languages/IT

German; English; basic French;
Regular use of MS Word, Excel, Powerpoint and Outlook; Photoshop; Adobe Illustrator

Publications

First author publications

- "The effect of material attributes and process parameters on the powder bed uniformity during a low-dose dosator capsule filling process" – Int. J. Pharm. 516 (2017) 9–20
- "Study of a Low-dose capsule filling process by dynamic and static tests for advanced process understanding" – Int. J. Pharm. 540 (2018) 22–30
- "Measuring bulk density variations of a moving powder bed via terahertz in-line sensing – submitted to the Powder Technology Journal (2018)
- „ Predicting capsule fill weight from in-situ powder density measurements using terahertz reflection technology "– submitted to the Int. J. Pharm. (2018)
- Insights into the processability and performance of adhesive blends of inhalable jet-milled and spray dried salbutamol sulphate at different drug loads – submitted to the Int. J. Pharm. (2018)
- Patent: "1710246.8 Device and Method for measuring a density of provided granular matter"

Presentations

Contributed talks and posters

- Talk at the AIChE annual meeting 2017, Minneapolis
- Talk at the PSSRC annual meeting 2017, Graz
- Talk at the AIChE annual meeting 2016, San Francisco
- Poster at the ICPE 2016, Graz
- Talk at the PSSRC annual meeting 2016, Copenhagen
- Talk at the Austrian Particle Forum 2016, Graz
- Talk at the International Forum-Competition 2013, St. Petersburg

Referees

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Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde
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List of publications

Research papers

S. Stranzinger, E. Faulhammer, J. Li, R. Dong, J.A. Zeitler, S. Biserni, V. Calzolari, J.G. Khinast, D. Markl, Predicting capsule fill weight from in-situ powder density measurements using terahertz reflection technology, submitted to the Int. J. Pharm. (2018).

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J.T. Pinto, S. Stranzinger, A. Kruschitz, E. Faulhammer, S. Stegemann, E. Roblegg, A. Paudel, Insights into the processability and performance of adhesive blends of inhalable jet-milled and spray dried salbutamol sulphate at different drug loads, submitted to the Int. J. Pharm. (2018).

V. Demiri, S. Stranzinger, M. Piller, S. Sacher, J. Lingitz, J.G. Khinast, S. Salar-Behzadi, Gluing Pills Technology: A novel route to multilayer tablet manufacturing, Int. J. Pharm. 548 (2018) 672–681.

S. Stranzinger, E. Faulhammer, O. Scheibelhofer, V. Calzolari, S. Biserni, A. Paudel, J.G. Khinast, Study of a low-dose capsule filling process by dynamic and static tests for advanced process understanding, Int. J. Pharm. 540 (2018) 22–30.

E. Faulhammer, S. Zellnitz, T. Wutscher, S. Stranzinger, A. Zimmer, A. Paudel, Performance indicators for carrier based DPIs: Carrier surface properties for capsule filling and API properties for in vitro aerosolisation, Int. J. Pharm. 536 (2017) 326–335.

S. Stranzinger, E. Faulhammer, V. Calzolari, S. Biserni, R. Dreu, R. Š, A. Paudel, J.G. Khinast, The effect of material attributes and process parameters on the powder bed uniformity during a low-dose dosator capsule filling process, Int. J. Pharm. 516 (2017) 9–20.

C. Meindl, S. Stranzinger, N. Dzidic, S. Salar-Behzadi, S. Mohr, A. Zimmer, E. Fröhlich, Permeation of therapeutic drugs in different formulations across the airway epithelium in vitro, PLoS One. 10 (2015) e0135690.

Talks

S. Stranzinger, E. Faulhammer, O. Scheibelhofer, V. Calzolari; S. Biserni, A. Paudel, J.G. Khinast, Optimization of a low-dose dosator capsule filling process for dry powder inhalation (DPI) applications using in-line PAT approaches – in: AIChE Annual Meeting, Minneapolis (US), 2017.

S. Stranzinger, E. Faulhammer, O. Scheibelhofer, S. Biserni, V. Calzolari, A. Paudel, J.G. Khinast, Strategies for Optimizing a low-dose dosator capsule filling process for inhalation application products – in: PSSRC-Meeting, Graz (AT), 2017.

E. Faulhammer, S. Stranzinger, P.Loidolt, V. Calzolari, S. Biserni, S. Srčič, R. Dreu, A. Paudel, J.G. Khinast, Decoupling of a low-dose dosator capsule filling process in dynamic and static mode tests to understand the extend of the effect of powder and process parameters on capsule quality attributes – in: AIChE Annual Meeting, San Francisco (US), 2016.

S. Stranzinger, E. Faulhammer, S. Srčič, R. Dreu, S. Biserni, V. Calzolari, A. Paudel, J.G. Khinast, The effect of material attributes and process parameters on the powder bed uniformity during a low-dose dosator capsule filling process – in: PSSRC-Meeting, Copenhagen (DK), 2016.

S. Stranzinger, E. Faulhammer, S. Srčič, R. Dreu, S. Biserni, V. Calzolari, A. Paudel, J.G. Khinast, Decoupling of a low-dose dosator capsule filling process in dynamic and static mode tests – in: Austrian Particle Forum (APF), Graz (AT), 2016.

Posters

S. Stranzinger, E. Faulhammer, S. Biserni, A. Mercandelli, J.G. Khinast, Combinational investigation of dosator nozzles for low fill weight (< 50 mg) capsule filling – in: MG2 site, Bologna (IT), 2018.

E. Faulhammer, S. Stranzinger, A. Mercandelli, S. Biserni, A. Paudel, J.G. Khinast, Combinational approach for advanced understanding of a low-dose capsule filling process for DPI products – in: Worldmeeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology (PBP), Granada (ES), 2018.

E. Faulhammer, S. Stranzinger, V. Calzolari, S. Biserni, P. Loidolt, A. Paudel, J.G. Khinast, Combinational approach for advanced understanding of a low-dose capsule filling process for inhalation application – in: Drug Delivery to the Lungs (DDL), Edinburgh, 2017.

S. Stranzinger, E. Faulhammer, S. Srčič, R. Dreu, S. Biserni, V. Calzolari, A. Paudel, J.G. Khinast, Optimization of an industrial scale low-dose dosator capsule filling process for inhalation products – in: Interpack Processing & Packaging, Düsseldorf (DE), 2017.

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Website contribution

S. Stranzinger, Novel stand-alone test tool for scientific analysis of a dosator capsule filling process in: http://www.pssrc.org, 2018.

Supervised Master Students

Maria Chiara Moriconi (graduation, 2018)

Andreas Kruschitz (graduation, 2017)

Valjon Demiri (graduation, 2017)

Thomas Wutscher (graduation, 2017)

British patent application

J.G. Khinast, T. Klein, M. Bresciani, E. Faulhammer, S. Stranzinger, D. Markl, J.A. Zeitler: 1710246.8 Device and Method for measuring a density of provided granular matter (date of filing 27.06.2018).