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Process understanding and optimization of dosing and filling systems for the production of pharmaceutical hard capsules

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Dissertation

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“A scientist in his laboratory is not a mere technician: he is also a child confronting natural phenomena that impress him as though they were fairy tales.”

Marie Curie

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Abstract

Dosator nozzle machines are widely used in pharmaceutical industry to dose granular material volumetrically into hard capsules for oral- or inhalation application. This technology has been used for over forty years now and was constantly optimized over time. However, there are still challenges, especially the accurate and reliable dosing of low-fill weight for inhalation application. This can be attributed to the lack of understanding how these formulations behave during filling process.

The goal of this thesis is to identify and understand the complex relationship between the material attributes and process parameters affecting fill weight and weight variability of capsules filled with a dosator nozzle machine for standard doses (30-150mg) and low-doses (5-45mg). Therefore, different excipients, mostly inhalation carriers, some fines and one proprietary active pharmaceutical ingredient (API), were carefully characterized and filled into hard gelatin capsules on a labscale dosator capsule filler (Labby, MG2) at different combinations of process settings. Larger fill weights were more affected by density, while lower fill weights more by flow and friction characteristics. No correlation was found between the material attributes and the weight variability for standard doses. For low-fill weight, the density was the only critical material attribute influencing weight variability. It was observed that the process parameters have the major effect on weight variability. Moreover, it could be shown that for powders with a small particle size (<10 µm) dosator filling was not volumetric anymore.

Based on the generated experimental data a predictive statistical model was developed via the quality by design (QbD) approach. The model was validated, a design space for the performance of different types of inhalation grade lactose on low-fill weight capsule filling was established based on the critical material attributes (CMA) and critical process parameters (CPP) and successfully used to predict fill weight of powders that were not included in the development set. The model predicted accurately the fill weight and provided a good approximation of the weight variability.

In the end of the study a vibrational gravimetric system (Microdose system, MG2) was used to evaluate its potential for filling and feeding highly potent APIs with doses under 5mg into

hard gelatin capsules. It could be demonstrated that accurate and fast dosing, as well as feeding of very low amounts of powder is possible if the material behavior is properly understood and the process settings are varied accordingly.

Kurzfassung

Dosierstempel sind in der pharmazeutischen Industrie eine weit verbreitete Methode um körniges Material zur oralen oder inhalativen Anwendung volumetrisch in Hartkapseln zu dosieren. Diese Technologie wird seit über vierzig Jahren verwendet und wurde mit der Zeit kontinuierlich verbessert. Es gibt jedoch noch immer einige Herausforderungen an dieser Füllmethode. Vor allem die genaue und zuverlässige Dosierung von sehr geringen Dosen, welche üblicherweise in Inhalationsapplikationen benötigt werden, stellt noch einige Schwierigkeiten dar. Letzteres ist auf das mangelnde Verständnis, über das Verhalten dieser speziellen Formulierungen während des Füllprozesses zurückzuführen.

Das Ziel dieser Arbeit ist es, die komplexe Beziehung zwischen den Materialeigenschaften und Prozessparameter, welche Füllgewicht und Füllgewichtsschwankungen von Kapseln, die mit einem Dosierstempel gefüllt wurden zu identifizieren und zu verstehen.

Hierzu wurden verschiedene Hilfsstoffe, überwiegend Inhalationsträger, einige Feinmaterialien und ein neuer pharmazeutischer Wirkstoff, sorgfältig charakterisiert und auf einem Labormaßstab-Kapselfüllgerät (Labby, MG2) bei verschiedenen Kombinationen von Prozesseinstellungen in Hartgelatinekapseln gefüllt. Somit wurden Standard-Dosen (30-150mg) und Niedrig-Dosen (5-45mg) produziert. Standard Füllgewichte wurden überwiegend durch die Dichte der einzelnen Materialien (grobkörniger) beeinflusst, während niedrigere Füllgewichte (feinkörnige Materialien) von Fließfähigkeits- und Reibungseigenschaften abhängig waren. Es wurde keine Korrelation zwischen den Materialeigenschaften und den Füllgewichtsschwankungen für Standard-Dosen gefunden. Für Niedrig-Füllgewicht, war die Pulverdichte die einzige kritische Materialeigenschaft die die Gewichtsschwankungen beeinflusst. Es wurde beobachtet, dass die Prozessparameter einen bedeutenden Effekt auf die Füllgewichtsschwankungen haben. Außerdem konnte gezeigt werden, dass für Pulver mit einer kleinen Partikelgröße (<10 um) die Dosierstempel Füllung nicht mehr volumetrisch verläuft.

Basierend auf den experimentellen Daten wurde ein vorhersagendes statistisches Modell über den Quality by Design (QbD) Ansatz entwickelt. Das Model wurde validiert und basierend auf den entsprechenden kritischen Material- und Prozessparameters verwendet,

um das Füllgewicht diverser Pulver vorherzusagen. Über die Füllgewichtsschwankungen konnte mittels dem Model eine gute Annäherung gegeben werden.

Am Ende der Studie wurde ein gravimetrisch arbeitendes System (Microdose System, MG2) verwendet, um das Potential des Füllens und Zuführens hochwirksamen Wirkstoffen mit Dosen unter 5 mg in Hartgelatinekapseln zu bewerten. Es konnte gezeigt werden, dass genaue und schnelle Dosierung, sowie Zuführung von Niedrigsdosierungen möglich ist, ferner das Materialverhalten vollständig verstanden und die Prozesseinstellungen entsprechend variiert werden.

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Abbreviations

A: Amplitude [E]

AIF: Angle of internal friction

AMYP: Apparent mean yield pressure

AOR: Angle of repose

API: Active pharmaceutical ingredient

AR: Aspect ratio

BD: Bulk density

BFE: Basic flowability energy

C: Cohesion

CCF: Central composite face centered design

CI: Carr`s compressibility index

CMA: Critical material attribute

CP: Compressibility

CPH: Capsules per hour (Filling speed)

CPL: Compressibility

CPP: Critical process parameter

CQA: Critical quality attribute (Capsule fill weight and weight variability)

DC: Volume of the dosing chamber / dosing chamber

DOE: Design of experiments

DPI: Dry powder inhaler

ED: Emitted dose

Eq: Equation

F: Frequency [Hz]

F: Ratio between powder bed hight and dosing chamber length

FDA: Food and drug administration

FFC: Flow function

FFT: Fast Fourier Transormation

FPF: Fine particle fraction

FW: Fill weight

ICH: International conference on harmonization

$K_{D:}$ Derivative

K_I: Integrative

K_P: Proportional

L: Pressure modulus

LH: Lactohale

LVD: Laser Doppler Vibrometry

MCC: Multi crystalline cellulose

MgSt: Magnesium stearate

ML: Milled

MVDA: Multivariate data analysis

PBD: Powder bed depth

PBH: Powder bed hight

PD: Pressure drop

PID: Proportional integrative derivative

PLS: Partial least squares

PSD: Particle size distribution

Q^2: Model predictability

QBD: Quality by design

R^2: Model fit

Ra: Roughness

R.H. / RH: Relative humidity

Rep.: Reproducibility

RMS: Root Mean Square

RSD: Relative standard deviation (weight variability)

RSM: Response surface methodology

SMCC: Silicified microcrystaliine cellulose

SOP: Standard operating procedure

SV: Sieved

TD: Tapped density

VMD: Volumetric mean diameter

W: Walker compressibility

WFA: Wall friction angle

„Nothing in life is to be feared, it is only to be understood.“

Marie Curie

1. Introduction and Motivation

Pharmaceutical capsules are the second most used dosage form after tablets. This can be related to some benefits , e.g. they are tasteless, odorless, easy to swallow and some patients state that capsules are attractive in their visual presentation, hence capsules exhibit a high patient compliance [1]. They may offer an even better solid dosage form than tablets for powders with low compressibility and slow dissolution behavior and they are also used in clinical studies for blinding purpose. Capsules mask unpleasant taste and odor and they can also provide protection of sensitive APIs against the environment. Capsules can be used for either combining dry, powdered ingredients, granules, small pellets, mini-tablets and pastes or various combinations of different materials as multiple units [2] or to separate incompatible products to achieve specific goals in terms of stability and modified release. Moreover, in comparison to tablets, hard capsules are simpler to produce because they are more flexible in formulation and therefore faster in development. Especially, during formulation development in early stages of a clinical trial of a new drug, capsules require much less excipients than tablets, or only the API (Active Pharmaceutical Ingredient) itself. Moreover, a capsule filling process uses less unit operation steps than a tabletting process. Steps that are always present in tableting, such as granulation, drying, sieving, lubrication and compression can be avoided in a capsule filling process. Figure 1 shows a representative sequence of unit operations involved in tabletting and capsule filling.

However, there are also some limitations for the usage of capsules as a dosage form. The filling material must be compatible with the shell, and therefore, no deliquescent or hygroscopic materials can be used. Some other disadvantages are, that the manufacturing process of capsules is more expensive than the tableting. Moreover, some API’s are unsuitable for capsule filling due to physical properties. There is also the problem of working in a non controlled environment, as the moisture content of the powder or environmental conditions during production or storage can heavily affect the capsule shell.

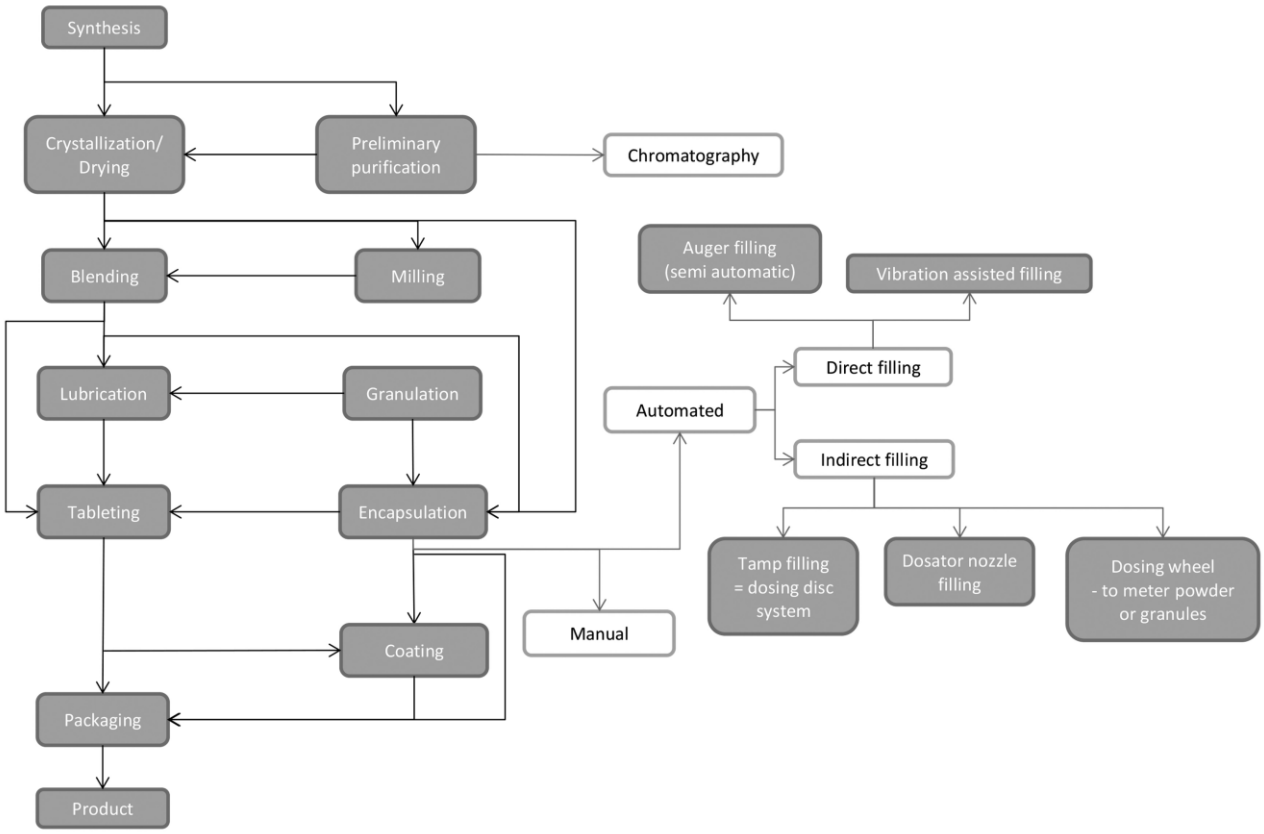

Figure 1: Typical flowsheet of tablet and capsule manufacturing.

Hard-shell capsules, which are typically made using gelatin (non-animal sources do exist as well) consist of two halves: a lower-diameter body that is filled and then sealed using a higher-diameter cap [1]. Hard capsules can be filled in several ways from manual preparation in the lab or in the pharmacy to fully automated industrial production. Although capsule-filling machines may vary widely in their engineering design the major difference between them is the dosing technique. The most common classification is: (1) direct (Auger filling, vibration assisted gravimetric filling) and (2) indirect filing methods (tamp or dosing disc filling, dosator nozzle filling, vacuum drum filling and vacuum dosator) [3]. Filling of hard-shell capsules via a dosator nozzle system is the focus of this thesis. Soft-gel capsules, which often contain liquids, are not discussed here.

Depending on the powder density, different fill weights can be obtained. Capsule sizes range from 5 (smallest) to 000 (largest) and maximum fill volume ranges from 0.1 ml to 1.37 ml. Thus, up to 1.5 g of powder or pellets can be filled in capsules. However, an important current trend is to manufacture small doses (< 50mg) of pure API for early research clinical trials using the so-called “drug-in-capsule” approach and for inhalation purpose (dry-powder

inhalers, DPI) for the treatment of respiratory disease or if the API is not readily absorbed orally [4].

Formulations relevant for capsule filling typically involve a combination of materials to achieve accurate dosing, good bioavailability, ease of filling and production, product stability and also elegance for the patient. They must provide good flowability, be non-adhesive but compressible enough to form plugs if required. To enhance the powder flow properties lubricants or glidants are added. Disintegrants are used to assist the break up and disintegration of the capsule content in the stomach. For highly potent APIs, which are administered in very low doses, the bulk volume has to be increased to allow accurate filling. For this, fillers or diluents are included in the formulation. Colouring and taste masking is performed to enhance safety and the patient compliance [5].

Beside the oral delivery of drugs, the capsule filling industry focuses nowadays on dry inhaled powders for pulmonary application. This places different requirements on the formulation as well as on the filling equipment. In order to reach the deep lung, API particles have to exhibit an aerodynamic diameter of 1µm to 5µm. Particles of this size however are rather cohesive and have poor flow properties. This challenges reproducible dosing for dry powder inhalers (DPIs), which is carried out volumetrically. Especially with the increased recognition of the potential role of DPI systems for other low dose medications, DPIs could become the device category of choice for local and systemic drug delivery [6]. Several low-dose capsule filling systems are currently available. Specifically in DPI filling the dosator filling principle plays an important role, as the doses need a controlled degree of compaction, to ensure the DPI can reliably turn the plug back into a powder for efficient dose delivery. Moreover pulmonary delivered powders normally need smaller quantities for the drug and variations in low-fill weight will affect patients health [7]. To ensure final low-dose product quality, much smaller dosators and several special low-dose equipment adaptions as well control mechanism have to be applied to the dosator filling system.

One more trend in pharmaceutical industry is to eliminate the carrier systems in inhalation formulations and manufacture small doses of pure API to be supplied by respiratory tract. High cohesiveness, poor flow as well as eloctrostatic charging are some of the properties of inhalation powders, hence the accurate filling of low-doses is a pretty challenging task.

The manufacturing of personalized medicine is another important issue where capsules could be the dosage form of choice. It is possible to fill combinations of serveral drug products even in micordoses into capsules. Therefore, tailoring medications for specific patients or groups can be done.

All these trends show that there is a need for an improved understanding of (1) the pharmaceutical material science principles and (2) to be able to apply them to the manufacturing process in an efficient and scientifically rigorous way [8].

In the scope of this thesis, a dosator nozzle capsule filling process was studied and a variety of pharmaceutical powders for oral as well as inhalation application were completely characterized and filled into hard capsules to see which material attributes, process parameters, environmental conditions or combinations thereof affect the quality of the final product. As a first approach, the objective was to understand the operating principle of a lab scale dosator nozzle machine and the material behavior of powders during standard dose filling. Second the challenging task of accurate low-dose filling for inhalation products was investigated and a model for the prediction of their behaviour during dosator nozzle capsule filling was established. Finally, the accurate dosing via a microdose capsule filling system was studied to evaluate its potential for filling highly potent APIs with doses under 5mg into hard capsules.

1.1. Powders

Particulate systems, such as powders and bulk solids have to be handled or stored in several industrial disciplines, such as pharmaceutics, agriculture, mining, food and cosmetic production, chemical processing and environment. Their importance derives from the fact that most of the raw materials used by industries to manufacture final products, are granular materials. All these materials have to be transported, conveyed, stored, dosed or handled, which may result in several problems, e.g. vibrations, segregation, flow obstruction or unsteady flow. Granular material consists of discrete solid, macroscopic particles, most frequently in large numbers. Sand, coffee, rice, coals, grains in silos, are some examples of granular materials, differing in their particle size, shape and amount. Powders are a special category of granular material, in terms of their cohesive behavior due to smaller particle sizes. The before mentioned wide range of applications of granular material makes the study of their natur an important and challenging matter of research, because it displays different performance depending on the application and their material attributes, making an establishment of general rules difficult [9]-[11].

In pharmaceutics, powders are the simplest dosage forms and mostly used as intermediate for further processing, like compaction to tablets and capsule filling. Powders are composed

of a large number of solid particles with dimensions ranging from 0.5 to 1000µm. According to the European Pharmacopoeia, powders as dosage forms are made of solid, dry, free, and more or less fine particles, which contain one or more active pharmaceutical ingredients (API) with or without excipients, coloring or flavoring substances [12]. Moreover, powders can be physically described as a disperse system consisting of discrete solid particles, which are surrounded by air or dispersed in air. However, the particles are normally in contact with each other and surrounding voids. Thus the micromechanical behavior of powders is determined by (1) how the particles are arranged in space and (2) by interactions operating among the particles [13]–[16].

The final product performance is determined by material attributes, which are determined by its strucuture [17] – more detailed by molecular, particulate and surface properties. There is a lack of research on micromechnical behavior within granular materials and inter-dependent relationship between structure-properties-performance-processing which often leads to poor manufacturability of the final product. Hence, it is crucial to characterize and understand the critical particle, powder and compact properties of granular materials that will influence product development and performance. The physics of granular material, which is surrounded by gas (air) is driven by interparticle forces, geometry of particle position and geometry of particle contacts. For very fine powders (micron size) interparticulate attractive forces are much higher than particle weight and they tend to agglomerate. Figure 1 and 2 provide an overview about forces acting on and between single particles.

With a sound understanding of these properties, formulation development, as well as processing of powders the manufacturing of the dosage form can proceed most efficiently and scientifically [9][17].

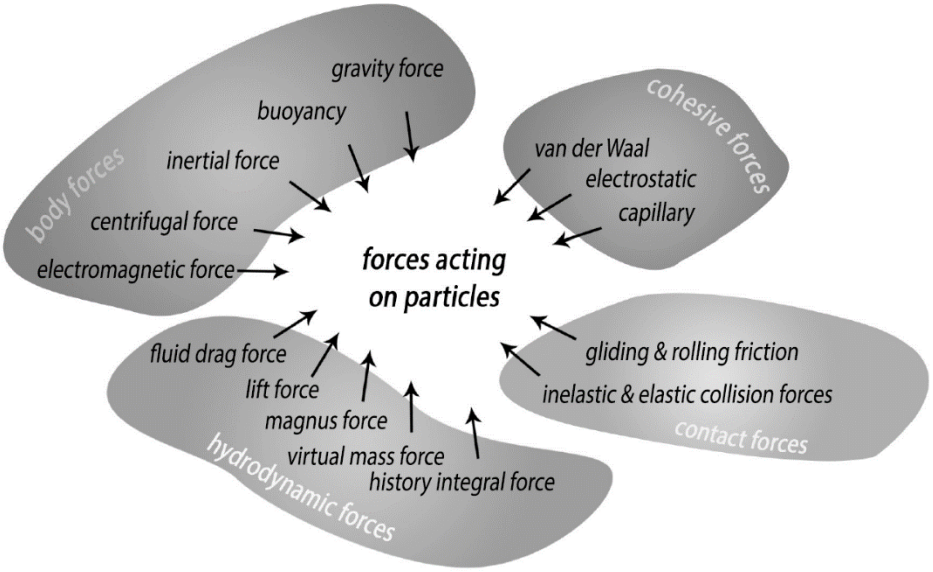

Figure 2: Forces acting on a particle

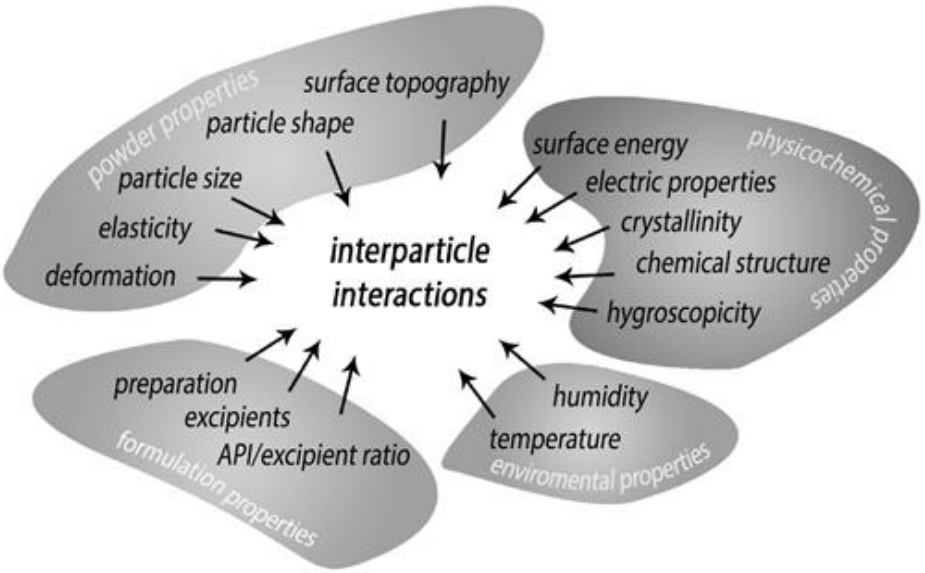

Figure 3: Interparticulate interaction

1.2. Dry Filling of Hard Capsules [1]

In the pharmaceutical industry, a wide range of capsule filling systems, which employ different technologies and principles are in use today. Capsule filling is sometimes also referred to as "encapsulation". Hard capsules can be filled in several ways from manual preparation in the lab or in the pharmacy to fully automated industrial production. Although capsule-filling machines may vary widely in their engineering design the major difference between them is the dosing technique. The most common classification is: (1) direct and (2) indirect filling methods. Principles that dose directly into the capsule are direct methods and machines that implement dosing techniques outside the capsule before filling are considered indirect methods. The major challenge for indirect systems is that although doses need to be specified by weight these filling systems work on a volumetric basis [3].

1.2.1. Filling Principles

1.2.1.1. Direct Filling

Auger filling: This principle is based on the semi-automatic and automatic equipment, where the powder in a hopper is filled into capsules continuously by a rotating auger in conjunction with a stirrer. This principle is shown in Figure 4. The empty capsule bodies are placed below the auger into a rotating turntable. The dosed weight is dependent on auger speed, the twist angle of the auger and the time the capsule body spends under the hopper outlet. Fill weight is also dependent on the powder density, which evolves from initial bulk density in the auger until reaching steady state [3]. Thus, fill weight may vary over the course of the filling process. For example, Mettler Toledo is producing the Quantos MicroDosing System™, which uses the above described Auger filling principle.

[1] This chapter is based on: J.G. Khinast and S. Sacher, „An overview of Pharmaceutical Manufacturing for Solid Dosage Forms – Filling of Hard Capsules", M. Ierapetritou and S. Garcia-Munoz, Eds. To be published by Humana Press in 2015.

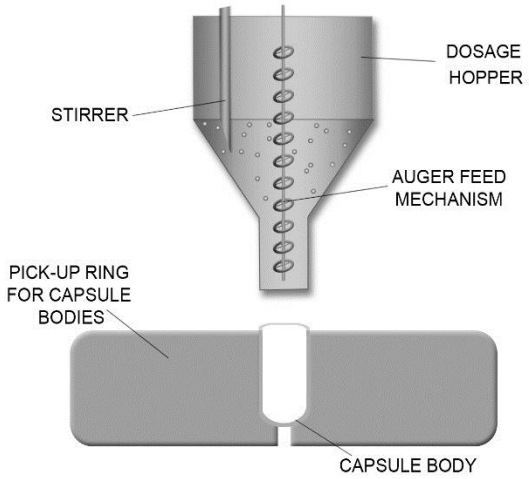

Figure 4: Auger filling mechanism

Vibration assisted filling: In this gravimetric dosing principle, the capsule body is filled directly through a mesh, which is connected to a vibration plate. This vibration assists powder flow and therefore dosing ("pepper shaker principle"). In addition, the equipment includes a microbalance, a load cell or a capacitance system to control fill weight, even for very low doses. Current systems on the markets include for example MG2's Microdose (1-40mg) or Capsugel's Xcelodose®S (0.1 – 100mg). These machines are of special interest for research purposes and clinical trials batches and allow the filling of several hundred capsules per hour with doses in the range between 0.1 mg up to about 100 milligrams.

1.2.1.2. Indirect filling

Tamp Filling: In dosing-discs or tamp-filling machines, the powder is in a cylindrical powder bowl that contains a removal dosing disk with six dosing holes (Figure 5)**.** The powder bowl rotates 360 degrees stopping at six stations with matching dosing holes. The material is fed from a hopper, to a dosing cone, which helps to distribute the powder horizontally into the powder bowl. As the dosing disk rotates, the first hole is partially filled with powder and then is tapped by a pin or tamping fingers. This process of partially filling and tamping is repeated until the last hole is reached. After excess powder is scraped off, the dosating disk positions the plug of powder over a capsule body and injects it into the capsule. The fill weight can be controlled by the thickness of the dosing-disc, the powder bed depth and the tamping pressure. The tamping pins are spring loaded in lab and medium scale or have a cushion of compressed air at industrial scale to minimize the tamping force to keep the plug density low [3], [18], [19]. Tamping machines such as the Bosch GKF 2500 (Figure 6)

adjusted with up to 18 tamping fingers (industrial scale) can produce up to 150.000 capsules per hour. Other manufacturers of industrial-scale tamping machines are IMA and Romaco (Itlay) and Harro Höfliger (Germany).

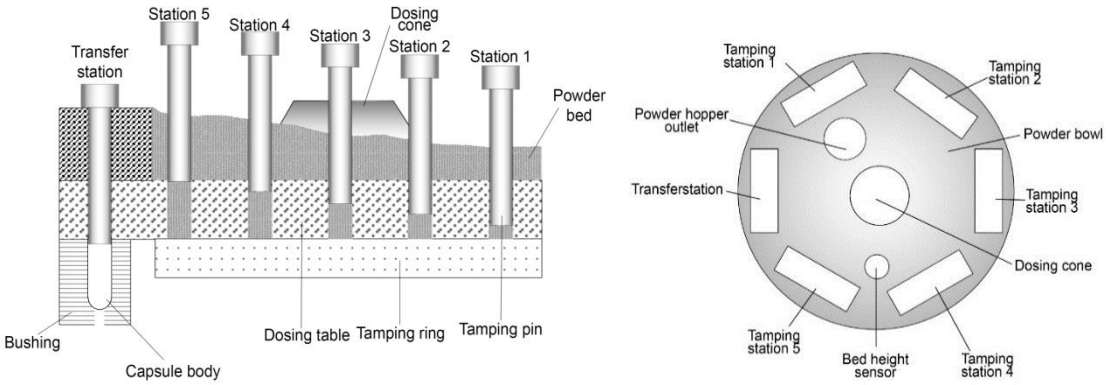

Figure 5: Schematic diagram of a dosing-disc and tamp-filling system

Figure 6: Bosch Packaging Technology – GKF 2500

Dosator-nozzle filling: In dosator-nozzle machines (MG2, Zanasi, IMA, Matic, Marcofar), the dosator (Fig. 7 & 8) moves into the powder bed and collects the desired volume of powder from the powder layer. During dosing, compaction is applied to form a stable plug.

For inhalation products, the capsules are filled with a controlled degree of compaction or even without compaction, to ensure that the plug is turned back into a powder for efficient drug delivery (plugs cannot be inhaled). The cylindrical volume (dosing chamber) is determined by the dosing chamber length (determined by a movable piston) and dosator diameter. After collecting the powder, the dosator nozzle is lifted from the powder bed and moves towards the empty capsule body into which the dose is ejected. The rotary product container and the dosators have different axes of rotation to enable the dosators first to sink into the product layer and then to discharge the product into the capsule bodies. 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. Hence, the requirements for powders and granules to be used in dosator-nozzle machines vary significantly from those used in tamping pin machines. Fill weight of capsules is controlled by adjusting the dosing chamber length, as well as varying the powder bed height in the bowl. Compared to tamp-filling, the dosator-nozzle system allows a wide range of fill weights by simple adjustment of the piston position for the choice of nozzle [3]. The instrumented continuous production machine G250 from MG2 can dose a variety of dosage forms accurately into capsules and can reach a maximum output of 200,000 capsules per hour.

A further development in dosator-nozzle design is the vacuum-operated system that implements a static piston with a porous plate at its product-touching end. The powder is sucked into the nozzle by vacuum and ejected into the capsule by reversal of the airflow. In that way, no compaction is performed, the nozzle does not contain any moving parts, resulting in less demand for lubrication and less densified powder plugs, and therefore, very small doses can be filled. Romaco produces the Macofar series and Harro Höfliger offers vacuum-assisted dosator nozzles, which are able to dose 10 – 600mg with a maximum output of 4500 capsules per hour [3].

Figure 7: Dosator filling mechanism: Industrial scale machine dosator (MG2, Italy)

Figure 8: Dosator filling mechanism: Lab scale machine dosator (MG2, Italy)

1.2.2. Low-dose Filling

As mentioned above, low-dose filling (< 50mg) of pure APIs is becoming of significant interest for various reasons. However, low-dose filling leads to challenges during manufacturing. Modern capsule-filling technologies [20]–[22] take into account these challenges and apply special adjustment to the machines for accurate dosing. For example, high-end continuous dosator machines like the Planeta 100 (Figure 9) with two dosing units and 16 dosators mounted (MG2) offers accurate capsule filling at an industrial output of up to 100,000 capsules per hour even for very low doses for inhalation purpose. Other systems exist as well, e.g., the GKF2500 (Bosch packaging technology) production machine with a microdosing-wheel adjusted can reach a maximum output of 150,000 capsules per hour. The Modu C (Harro Höfliger) uses a drum dosing system with vacuum and compaction free (Figure 10). It can reach an output up to 200,000 capsules per hour and achieves doses down to 1 mg depending on the formulation.

Figure 9: Industrial dosator capsule filler - Planeta 100 (MG2, Italy)

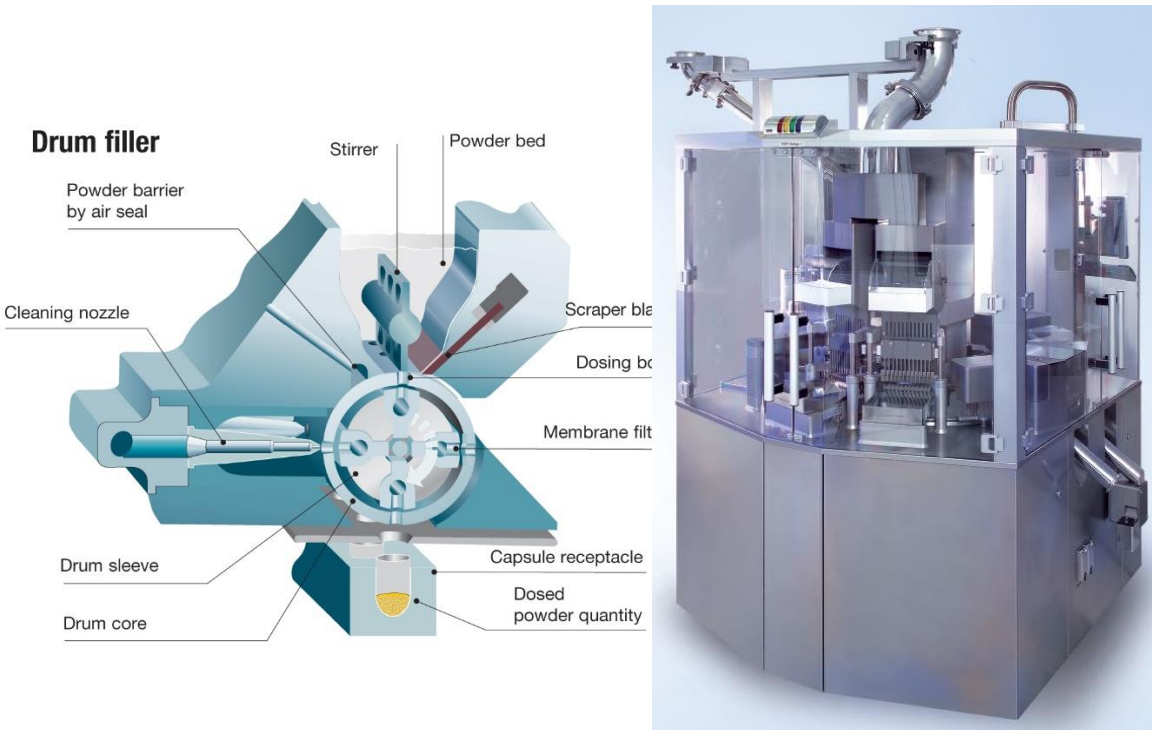

Figure 10: Drum filling principle and the Modu C high-speed machine (Harro Höfliger, Germany) with exchangeable dosing systems (tamping pin, dosator and vacuum drum).

Table 1: Overview about state of the art capsule filling systems

Manufacturer	***Machine Model***	***Motion***	***Max. Output (capsules per hour)***	***Operation principle***
Shionogi Qualicaps	F-40/80: LIQFIL ^{super}	---	40.000 – 80.000	Vibration and Tamping Pin
Capsugel	Xcelodose®S *	Manually and automatic	Up to 600	Vibration
3P Innovation	Fill2Weight and Lab dosator *	Automatic	Up to 1000	Gravimetric and Dosator
Harro Höfliger	Modu – C Low speed (LS)	Intermittent	25.000	Drum filling Tamp filling Vacuum Dosator
	Modu – C Mid speed (MS)	Intermittent	100.000	
	Modu – C High speed (HS)	Intermittent	200.000	
	Omnidose R+D *	Manual and automatic	---	
IMA	Zanasi 6, 12, 25, 40	Intermittent	6.000 – 40.000	Aspirating Bowl and Vacuum Dosator
	Zanasi Plus 16, 48, 70	Intermittent	16.000 – 70.000	
	Zanasi 70C	Intermittent	55.000	
	Adapta 100, 200	Intermittent	100.000 – 200.000	
	Practica	Intermittent	100.000	
	Imatic 100, 150	Continuous	100.000 – 150.000	
Romaco	Macofar CD 25, 40, 60	Intermittent	25.000 – 60.000	Vacuum Dosator and Tamping Pin
Bosch	GKF 702*, 705	Continuous	3000 – 42.000	Tamping Pin
	GKF 1400, Capsylon 1505	Continuous	84.000 – 92.000	
	GKF Hi Pro Tect	Continuous	100.000	
	GKF 2000, 2500*	Continuous	150.000	
	GKF 3000, Capsylon 3500	Continuous	175.000	
MG2	Microdose*	Manually and automatic	---	Vibration
	Labby* R+D / FlexaLab*	Continuous or intermittent	3000	Dosator Nozzle
	Suprema	Continuous	48.000	
	G 70, 100, 140, 250	Continuous	70.000 – 250.000	
	Alterna/Alternova	Intermittent	70.000 – 150.000	
	Planeta – 100*	Continuous	100.000	
	MultiFlexa 250	Continuous	250.000	
****) Indicates the possibility of low-dose filling.***				

1.2.3. Process Scale Up

The scale-up of a capsule filing process must consider the design and operating principle of the filling technology, like different powder handling and plug formation mechanism as well as the formulation requirements. Similar to tablets, capsule size does not change upon scale-up. However, the filling speed increases potentially, leading to different effects during the powder sampling. Most filling principles form plugs via pistons, compression or tamping fingers, equal to tableting, and then eject the plug into the capsule body. Capsule plugs are considerably different from compressed tablets. The plug height to diameter ratio is bigger and the compression forces are much lower than for tablets. Another difference to tableting is that the increased output of capsules is achieved by increasing the number of dosing units, whereas in tableting, the compaction tends to be faster and dwell and contact time tend to be shorter. Thus, scale-up of capsule filling is often a (more or less) straightforward process [1], [23]–[25].

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„Be less curious about people and more curious about ideas.“

Marie Curie

2. The effects of material attributes on capsule fill weight and weight variability in dosator nozzle machines

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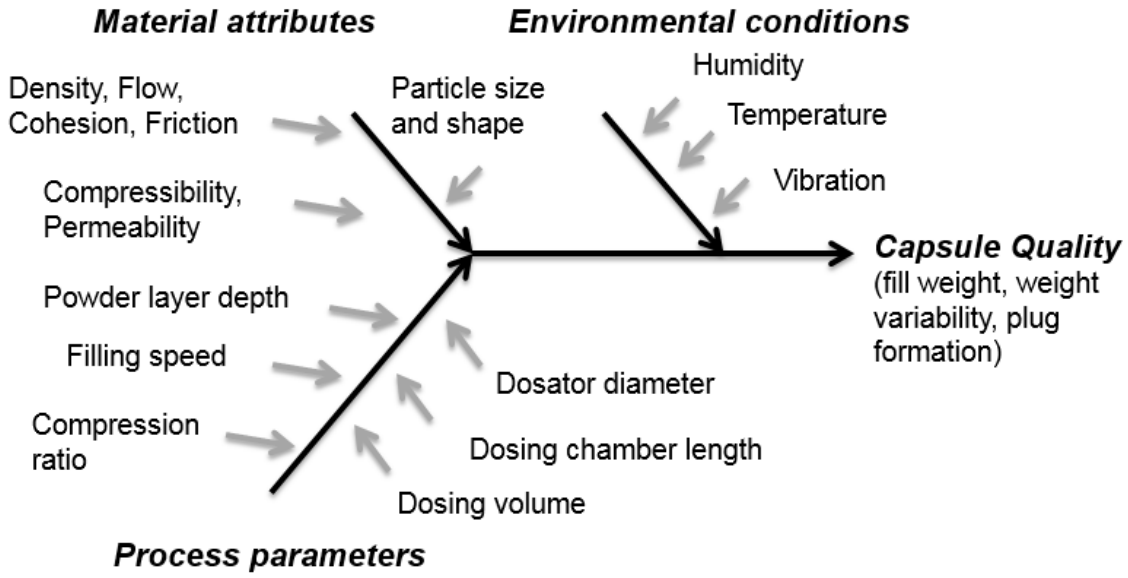
Graphical abstract



Keywords: microcrystalline cellulose; powder characterization; material attributes; capsule-filling; dosator nozzle machine; multivariate data analysis

The effects of material attributes on capsule fill weight and weight variability in dosator nozzle machines

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Abstract

The goal of this work is to identify and understand the complex relationship between the material attributes, capsule fill weight and weight variability of capsules filled with a dosator nozzle machine. Six powders were characterized and filled into size-3 capsules in three volumes of dosing chambers and at two filling speeds. Subsequent multivariate data analysis was used to identify the influence of the material attributes on the capsule fill weight and weight variability. We observed a clear correlation between the capsule fill weight and the particle size, the air permeability and the compressibility. As the fill weight decreases, more factors affect capsule fill weight. For example, the wall friction angle, the tapped density, and the particle shape proved to be important factors. Larger fill weights were more affected by density while lower fill weights by flow and friction characteristics. No correlation was found between the material attributes and the weight variability. Rather, we could also see the major effect of process parameters on capsule fill weight and weight variability.

Keywords: microcrystalline cellulose; powder characterization; material attributes; capsule-filling; dosator nozzle machine; multivariate data analysis

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2.1. Introduction

Hard-gelatin capsules are one of the most common pharmaceutical dosage forms. Compared to tablets, capsules are relatively easier to formulate and manufacture, which results in shorter development times (Augsburger, 2009). However, the quality of filled capsules is affected by a large number of powder and processing parameters and several researchers have undertaken the task of identifying and assessing these effects (Podczeck and Newton, 1990, 2000; Patel and Podczeck, 1995; Tan and Newton, 1990a). Numerous material and process parameters affect the quality attributes of filled capsules, such as the weight variability. Due to the large number of parameters to consider, a Design of Experiments (DOE) and multivariate data analysis (MVDA) (Hogan et. al, 1996) in framework of Quality by Design (QBD) is the best approach to obtain a deep process understanding.

The aim of this study was to identify and quantify the effect of critical material attributes (CMA) on the critical quality attributes (CQA), which in our work were the (1) fill weight and (2) weight variability (RSD) of capsules filled with a dosator nozzle (Labby, MG2, Bologna, Italy). Capsules were filled with six different microcrystalline cellulose (MCC) powders, and their material attributes were amply characterized. The MCC grades represent a wide range in terms of particle sizes, density, flow and several other material attributes. A dosator filling mechanism is the most conventional principle used in capsule-filling machines. It consists of a nozzle that dips into a powder bed, collects powder and transfers into an open capsule (Tan and Newton, 1990e; Podczeck and Jones, 2004).

A DOE was developed using process parameters of the capsule filling machine as controllable variables (dosator size, dosing chamber length, powder layer height and filling speed). The material attributes of the six types of MCC powders were the “uncontrollable” variables. Finally, a multivariate data analysis (MVDA) using the entire data set was performed. The data set contained the average value (of three measurements) for each material attribute and the average values of capsule fill weight and weight variability (of the contents of 100 capsules) for each experimental condition. A partial least square (PLS) method was applied to study the correlations between the CMAs and CQAs.

In summary, material attributes were assessed and their correlations to capsule fill weight and weight variability were investigated. Subsequently, these attributes were ranked according to

their effect on the capsule fill weight. These results can help scientists design formulations with the CMAs in order to obtain products amenable to capsule filling and with the desired weight variability.

2.2. Materials and methods

2.2.1. Materials

We selected six common pharmaceutical microcrystalline cellulose (MCC), which have been extensively characterized (Amidon and Houghton, 1995; Patel and Podczeck, 1996). We used Avicel® PH102, PH200, PH301, PH302 (FMC BioPolymer), Vivapur®12 (JRS Pharma GmbH) and Prosolv®_SMCC 90 (JRS Pharma GmbH), which is a silicified material. All materials were used as received and each test was carried out in triplicate. In order to minimize the number of material attributes to be investigated and to simplify our research, we only used MCC.

2.2.2. Methods

2.2.2.1. Particle size characterization

QICPIC (OASIS/L dry dispersing system Sympatec, Germany) was used to measure the size (volumetric mean diameter, VMD, and median particle size) and shape of millions of particles in each sample via dynamic image analysis. The two-dimensional images of a particle were described in terms of the minimum and maximum Feret diameters ($F_{min,}$ F_{max}).

The aspect ratio (AR) is the ratio between F_{min} and F_{max} and describes the shape of particles. Its value can be between 0 and 1, which reflects the elongation of a particle and deviation from a sphere. The higher the value, the more spherical the shape.

Since the particle size and shape are known to affect the bulk behavior of powders (Fu et al. 2012), they are critical to capsule filling. For example, the particle size of a powder significantly influences the flow properties and cohesion of bulk powder. Typically, the smaller the particle size, the more cohesive the powder (Jolliffe and Newton, 1982; Fu, 2012). Moreover, the particle shape affects the particle packing and therefore their flowability and internal friction (Podczeck and Miah, 1996, Yu et al. 2011, Fu et al., 2012). In addition, they influence how powders interact with walls and hence it has an impact on the wall friction coefficient (Jolliffe and Newton, 1982). Furthermore, particle size and shape have a considerable impact on the powder compressibility and permeability (Fu et al., 2012).

2.2.2.2. Bulk density, tap density and true density

The bulk (BD) and tapped densities (TD) were analyzed (Pharmatest PT-TD200) via a standardized method described in the United States Pharmacopeia (USP 2011, <616>). A certain mass of powder was filled into the cylinder and the level was recorded. The tapped density was attained after mechanically tapping the powder sample. These numbers were used to estimate the flow index (Carr`s compressibility index).
To obtain the true density, a helium pycnometer (AccuPyc II 1340, Micromeritics, Norcross, USA) was used after drying the powders.

2.2.2.3. Compressibility (CPL)

Compressibility is a measure of the volume change in a conditioned sample when it is slowly compressed under a specific normal force. Compressibility of a powder is important for dosator filling because powder is compacted by the piston to enhance powder retention inside the nozzle and to reduce its volume in order to accommodate the powder inside a capsule. Further, the powder undergoes pre-compression as the nozzle dips into the powder bed and in this study the powder bed height was higher than the dosing chamber length (see 2.2.8). In our study, compressibility was measured with the FT4 Powder Rheometer (Freeman Technology, Malvern, United Kingdom). The test starts at 0.5kPa, increases pressure stepwise until 15kPa and calculates the ratio between the density and bulk density for each compaction step.

2.2.2.4. Air permeability

Air permeability is a measure of how easily material can transmit air through its bulk and it is measured by the air pressure drop (PD) across a powder bed. A high pressure drop indicates low air permeability. Moreover, high air permeability is obtained for large particles as inter-particular spaces are large as well, reducing the pressure drop. It is expected to affect capsule filling because during powder pre-compression, and piston compaction the entrained air must escape the powder bulk (Freeman and Fu, 2008). The permeability test was performed with pressured dry air (2mm/s air velocity) with the FT4 powder rheometer. Details of these methodologies can be found in the literature (Freeman, 2007; Freeman and Fu, 2008).

2.2.2.5. Powder flow properties

The flowability of powders affects various capsule quality attributes, such as fill weight and content uniformity (Prescott and Barnum, 2000). Powder flow affects the weight variability of capsules e.g. in tamp-filling machines (Tan and Newton, 1990c; Podczeck and Miah, 1996; Schulze, 2011). In this study, we measured the following flow indexes:

- Carr`s Compressibility Index (CI) (Carr, 1965) is a density-based index assessed according to Pharmacopoeia 2011 (Method <616>). CI indicates how a powder changes its density upon tapping. Large changes indicate poor flowability.
- Flow function coefficient (FFC): A shear-cell based flow index determined in a 1 ml shear cell module with the FT4 Powder Rheometer. FFC is the ratio of consolidation stress, $\sigma 1$, to unconfined yield strength, σc. A high FFC value (> 4, or more strictly >10) indicates that the powder will flow well. Two parameters that are simultaneously measured with the shear cell are cohesion and angle of internal friction. Cohesion (C) describes the inter-particle interaction due to electrostatic, capillary or van der Waals forces. Cohesion affects the flowability of powders and thus the associated quality attributes of filled capsules. If a powder has low cohesivity, a plug might fail to form in the dosator nozzle and powder losses before its transfer to the capsule body may occur, resulting in inconsistent capsule fill weight due (Tan and Newton, 1990d; Stegemann, 2002). Angle of internal friction (AIF) measures the shear stress, τ, for various values of normal stress, σ, to describe the magnitude of the shear stress that a soil can sustain (Freeman, 2007).
- Basic Flowability Energy (BFE) is a FT4 parameter defined as the energy required for establishing a particular flow pattern in a conditioned, precise volume of powder. In our study, BFE was quantified with the FT4 (Freeman, 2007).
- Angle of Repose (AOR) was determined by using a glass funnel described in the pharmacopoeia (USP 2007, 1174).

2.2.2.6. Powder wall friction

The wall friction angle (WFA) describes the mechanical interaction between a bulk solid and a surface. During capsule filling, wall friction occurs between particles and the nozzle dosator's wall. Specifically, it is quantified by the slope of the line in the plot of the friction vs. normal forces for a powder sample sheared against a surface. To measure the WFA, a stainless steel

plate with a nominal roughness (Ra) 0.2 µm, which is typically the material in MG2 nozzles, was mounted in the FT4 equipment. Measurements were performed by increasing the pressure up to 3 kPa. Wall texture or rugosity of the dosator material has been long known to have an impact on the capsule filling operation (Tan and Newton, 1990b) by influencing the powder compaction and retention in the nozzle when it dips into and withdraws from the powder bed, respectively. Moreover, Jolliffe et al. (1980) showed that the WFA is important for determining the stress distribution inside the nozzle, and hence, for arching.

2.2.3. Design of Experiments

The DOE for this study was full-factorial, using process parameters of the capsule filling machine set at the desired values. The volume of the dosing chamber (DC), which is the space inside the nozzle to be filled by powder, is determined by the position of the piston. The piston was fixed at 3 mm, 6 mm and 12 mm dosing chamber length, in order to fill the capsules with different amounts of powder. The feeder maintained a constant powder bed height of 32 mm in the powder bowl. These settings result in three ratios, also called compression ratio, of the powder bed height and the dosing chamber length (2.7, 5.3, 10.7). Furthermore, one dosator nozzle (size 3) and two filling speeds (500 and 3000 capsules per hour) were selected to see if we observe changes in the dynamic friction between the material and the dosator nozzle surface. A key aspect of the experiments was to create a smooth powder layer. Feeding to the bowl was optimized to match the amount of powder collected by the nozzle. The powder layer height was corroborated with a venier caliper. To ensure that the filling operation runs in a steady state condition the first capsules were collected after 5 minutes. For every experiment of the DOE, about 400 capsules were produced. The full DOE set of experiments was performed for every powder.

2.2.4. Capsule filling

In our work transparent Coni-Snap hard gelatin capsules of size 3 (0.3 mL) supplied by Capsugel were filled with a dosator nozzle capsule filling machine (Labby, MG2, Bologna, Italy). This is a research and development machine based on the same principle as industrial capsule filling machines but has only one dosator nozzle and a maximum filling speed of 3000 capsules per hour (CPH). We selected small volumes of dosing chambers and a filling-mode without compaction to obtain low fill weights. Moreover, Tan and Newton have shown in their

studies that the optimal filling condition for most powders was without piston compaction (Tan and Newton, 1990a, d). A clean nozzle and piston set was used for each powder and no lubricant was added. After each experiment, the dosator and piston was visually examined and cleaned. The filled capsules were collected and stored in sealed plastic containers until their fill weight and weight variability was analyzed.

A single dosing event consists of multiple steps. First, the dosator is lowered into the rotary container to reach the top of the product layer. At this point of time, there are no imposed stresses in this layer, except due to gravitational forces. A spring inside the dosator nozzle pushes the piston up until the desired volume of the dosing chamber is achieved (volumetric principle). The volume of the dosing chamber is constant while sampling. Second, the dosator nozzle dips into the powder bed, inducing anisotropic stress, and the powder starts entering the volume of the dosing chamber (Figure 1, which is a snapshot of a discrete element simulation). The friction between powder and dosator wall causes pre-compression and induces horizontal stresses. Due to the stresses normal to the wall, and the resulting wall friction, particles form a plug and can be lifted by the nozzle to be filled into the capsule. As shown in Figure 2, the dosator first fills up. Yet, once the final filling (densification) level in the dosator has been reached, powder below the dosator is replaced, causing local densification of the powder in the area under and close to the tip. However, in the region adjacent to the dosator wall and close to the surface the powder bed is expanding and density decreases, introducing inhomogeneity in the powder bed.

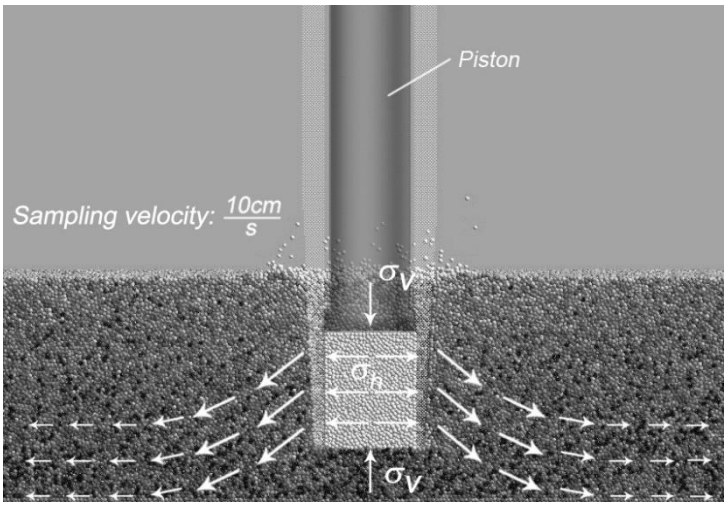

Figure 1: Stress profile - central cut through the dosator moving into a lactose powder bed containing particles with an x50 of 155µm. The nozzle is see-through, i.e., particles behind and inside the nozzle can be seen. The arrows inside the dosator correspond to wall stresses (□h, □v). The arrows outside of the dosator represent the stress, which is imparted by the dosator to the surrounding powder bed.

If additional compression inside the dosator nozzle is required to form a plug, compaction (vertical compressive stress) by the piston may be performed. Here the internal piston is moved downwards. This force should be low so that the subsequent ejection of the plug requires minimum effort (Joliffe et al., 1980). Third, the dosator nozzle is withdrawn from the powder bed, moved out of the bowl and lined up with the empty capsule body. The powder is retained in the dosator nozzle because of the formation of a stable arch at the outlet, which is dependent on powder properties and the vertical compressive stresses which are transmitted through the powder bed (Jolliffe et al., 1980). Many researchers showed that powder retention is dependent on the cohesiveness of a powder (Jolliffe and Newton 1983 a, b; Tagaki et al., 1969; Jones, 2001). For low-density and highly cohesive powders, arch formation occurs easily. However, for dense and free flowing powders, arch formation is problematic. Lastly, the down stroke of the piston ejects the powder or plug into the body of the capsule. Here the wall friction needs to be overcome. The dosator rises and a new capsule-filling cycle begins.

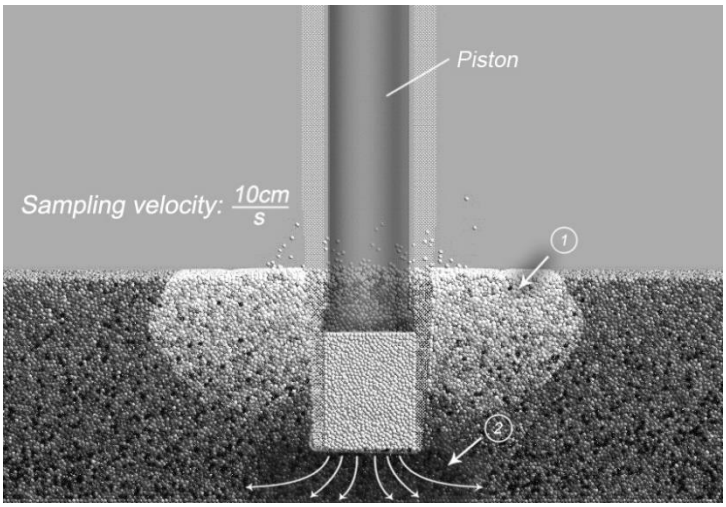

Figure 2: Velocity profile - cut through the dosator moving into a lactose powder bed containing particles with an x_{50} of 155µm. The nozzle is see-through, i.e., particles behind the nozzle can be seen. In the light grey area on the top of the powder layer (indicated by number 1), the powder density is low. Close to the dosator tip densification occurs (indicated by number 2). This is caused by volume reduction due to the immersing dosator with its fixed piston. The arrows represent the powder in motion, which is restricted by the bottom of the chamber.

2.2.5. Analysis of capsule fill weight and weight variability

The weight of 100 single capsules was measured with a Denver (SI-234A) scale and was electronically recorded using the software Denver Transmit. The average weight and standard deviation of 100 empty capsules were subsequently calculated. After filling about 400 capsules, 100 capsules were selected randomly and each weighed on the Denver (SI-234A) scale. To

calculate the capsule fill weight, the average weight of the empty capsule shell was subtracted from the total weight (capsule shell and powder) of the filled capsules. The variance of the empty capsule shells was subtracted from the variance of the capsule fill weight, and the standard deviation of the fill weight was calculated by applying the square root. The relative standard deviation (RSD) of the capsule fill weight was used as indicator for weight variability. A visual examination of the capsules showed if a powder plug was formed. We investigated the stability of the plugs via subjecting it to mechanical shocks (strongly shaken in hands).

2.2.6. Multivariate data analysis – partial least squares regression

Multivariate Data Analysis (MVDA) has proven to be a powerful tool for extracting relevant information from the measured data (Rajalahti and Kvalheim, 2011). Regression by means of projection to latent structures, also called partial least squares (PLS), is a common chemometric data analytical tool, which has various applications. Its most widespread form in science and technology is the two-block predictive PLS version, which relates two data matrices, X and Y via a linear multivariate model and models the structure of X and Y (Wold et al., 2004). In this study PLS was performed with the software SIMCA-P 13.0 (Umetrics, Sweden) to see the main factors affecting capsule fill weight and weight variability.

2.3. Results and discussion

2.3.1. Powder characterization

Table 1 presents the particle size and shape, as well as the friction coefficients of the various MCC products. According to the powder classification in the USP 2011 <811>, Avicel PH301 is a very fine powder, Avicel PH200 and Vivapur®12 are moderately fine powders, and the rest of the studied powders have a fine grade. All of the tested powders have a similar shape. Further, Table 1 shows the friction behavior of the tested powders. Avicel PH200 has by far the largest WFA and the lowest AIF and Vivapur®12 the lowest WFA and highest AIF.

	VMD [µm]	AR	AIF	WFA 3kPa 0.2 Ra
Avicel PH102	170.12	0.688	19.1	6.6
Avicel PH200	255.37	0.741	15.1	12.8
Avicel PH301	95.19	0.631	20.0	5.9

Avicel PH302	144.93	0.686	17.5	6.1
Prosolv®_SMCC 90	153.53	0.623	21.6	4.8
Vivapur® 12	194.1	0.658	21.4	4.8

Table 1: Particle size, shape and friction properties. VMD=volume-mean diameter, AR=aspect ratio, AIF=angle of internal friction, WFA=wall friction angle.

Table 2 shows the bulk properties of the powders. Avicel PH301 has the highest density and compressibility. Its air permeability is much lower than that of the other studied powders. Avicel PH200 has the lowest compressibility and highest air permeability.

	BD[g/ml]	TD[g/ml]	True density [g/ml]	CPL at 8kPa [Ratio ρ_{comp}/ρ_{BD}]	PD at 8kPa [mbar]
Avicel PH102	0.34	0.51	1.546	1.097	1.84
Avicel PH200	0.36	0.41	1.547	1.05	0.81
Avicel PH301	0.40	0.57	1.562	1.117	4.12
Avicel PH302	0.41	0.55	1.549	1.103	2.18
Prosolv®_SMCC 90	0.34	0.45	1.564	1.093	2.78
Vivapur® 12	0.33	0.46	1.549	1.107	1.68

Table 2: Bulk powder properties. BD=bulk density, TD=tapped density, CPL=compressibility, PD=pressure drop.

The powder flow properties are summarized in Table 3. In this study the FFC (FFC < 2: very cohesive; FFC = 2-4: cohesive; FFC = 4-10: easy-flowing; FFC > 10: free-flowing) was chosen as the indicator for flowability because many other material attributes measured with FT4 powder rheometer are also used in this study. All the powders are free flowing, with the exception of Vivapur®12 with easy flowing behavior.

	CI	AOR [°]	BFE [mJ]	FFC	C
Avicel PH102	32.9	35.9	502.7	19.1	0.23
Avicel PH200	12.3	26.9	532.3	14.6	0.36
Avicel PH301	28.3	34.7	661.7	11.3	0.38
Avicel PH302	24.9	34.7	628.7	10.4	0.42
Prosolv®_SMCC 90	24.3	33.7	748.0	11.9	0.38
Vivapur® 12	29.0	33.9	628.7	6.8	0.68

Table 3: Flow properties. CI= Carr`s Compressibility Index, AOR=angle of repose, BFE=basic flowability energy, FFC=flow function, C=cohesivity.

Table 4 presents the correlation matrix between single material attributes. A correlation coefficient of zero indicates no correlation and 1 and -1 represent perfect direct and indirect correlation, respectively.

	VMD	AR	WFA	AIF	FFC	C	TD	BD	CI	AOR	BFE	PD	CPL
VMD	1.00	**0.78**	0.72	-0.53	0.18	0.12	**-0.88**	-0.56	-0.64	-0.68	-0.72	**-0.94**	**-0.86**
AR		1.00	**0.86**	**-0.91**	0.42	-0.22	-0.42	-0.04	-0.59	-0.28	-0.74	**-0.82**	**-0.78**
WFA			1.00	**-0.89**	0.42	-0.32	-0.51	0.03	**-0.82**	**-0.89**	-0.42	-0.59	**-0.90**
AIF				1.00	-0.40	0.38	0.20	-0.33	0.70	0.03	0.41	0.54	0.73
FFC					1.00	**-0.91**	-0.08	-0.15	0.00	0.51	-0.32	-0.21	-0.40
C						1.00	-0.15	-0.19	0.04	0,00	-0.07	-0.09	0.27
TD							1.00	0.73	0.61	0.65	0.40	0.73	**0.79**
BD								1.00	-0.09	0.50	0.49	0.51	0.27
CI									1.00	**0.95**	0.04	0.47	**0.86**
AOR										1.00	0.46	0.56	**0.91**
BFE											1.00	0.63	0.45
PD												1.00	0.74
CPL													1.00

Table 4: Correlation Matrix - critical material attributes.

It can be seen in Table 4 that large, more spherical particles lead to lower inter-particulate friction. This is most likely due to the reduction in the interlocking effects in spherical particles. Furthermore a large VMD correlates with good flow properties, lower pressure drop (larger space between particles) and a lower tapped density. Thus, these powders show less compressibility.

For this particular set of powders, we observed a positive correlation between particle size and WFA. Avicel PH200, the biggest MCC of this study, has by far the highest angle of wall friction. Surface effects like rugosity could explain the extreme high value. The latter dominates the correlation of the total analysis and due to that, a high positive correlation between particle size and WFA, even if this is not the case for the other powders, and an unexpected high negative correlation between AIF and WFA was observed. Interestingly no significant correlation was found between BD, FFC, C and any other material attribute.

2.3.2. Effects of material attributes on fill weight

Table 5 presents the correlation of single material attributes with the fill weight and with the weight variability. For the latter see chapter 3.3. As can be seen, particle size, tapped density, compressibility and air permeability correlate with the capsule fill weight the most. Smaller particles and higher compressibility (and the air pressure drop, which is a derived property as depends on the consolidation ability of the material) resulted in heavier capsules. Furthermore, the effect of densities (BD and TD) decreases with smaller dosing volumes. Interestingly, correlation of compressibility remained stronger at lower volumes while density effects progressively weakened. This could be possibly the regimen where the effect of inter-particulate interactions on densification and thereby the fill weight dominate over the porosity of the bulk powder bed. This is also supported by the consistent correlation of PD across the dosing volumes. The latter are dominated by factors like the WFA, particle shape and flow indicators.

	DC with 12 mm length fill weight	DC with 12 mm length weight variability	DC with 6 mm length fill weight	DC with 6 mm length weight variability	DC with 3 mm length fill weight	DC with 3 mm length weight variability
VMD	-0.87	-0.39	-0.88	0.02	-0.76	0.17
AR	-0.66	-0.42	-0.82	-0.43	-0.8	-0.32
WFA	-0.67	-0.35	-0.83	-0.34	-0.8	-0.23
AIF	0.44	0.28	0.66	0.52	0.67	0.43
FFC	-0.51	-0.32	-0.54	-0.29	-0.65	-0.54
C	0.23	0.13	0.29	0.29	0.42	0.58
TD	0.84	0.26	0.75	-0.33	0.59	-0.43
BD	0.64	0.26	0.44	-0.43	0.35	-0.41
CI	0.5	0.09	0.62	0.05	0.51	-0.11
AOR	0.66	0.23	0.74	0.05	0.64	-0.13
BFE	0.56	0.49	0.67	0.50	0.74	0.48
PD	0.80	0.4	0.81	0.07	0.71	-0.06
CPL	0.84	0.32	0.91	0.07	0.82	0

Table 5: Correlation Matrix - critical quality attributes.

Figure 3 shows the significant PLS regression coefficients (R^2 value) for the capsule fill weight for each volume of dosing chamber with different dosing chamber length. The error bars represent a 95% confidence interval. The coefficient plot summarizes the relationship between the fill weight (Y) and all material attributes (X). It is apparent that the capsule fill weights of the different volumes of dosing chambers were significantly affected by similar material attributes. Correlations between the single-material attributes are not shown here.

The coefficient plot again shows that the capsule fill weight is most significantly influenced by the particle size (VMD), the wall friction angle (WFA), air permeability (PD), compressibility (CPL), tapped density (TD) and the basic flowability energy (BFE). Smaller doses are also affected by the flow function (FFC), aspect ratio (AR) and angle of internal friction (AIF). In general, the smaller the volume of the dosing chamber and the resulting fill weights are, the more factors seem to influence the capsule fill weight. Thus, for larger capsule fill weights and larger volumes of dosing chambers, less impact of the specific powder grades can be expected.

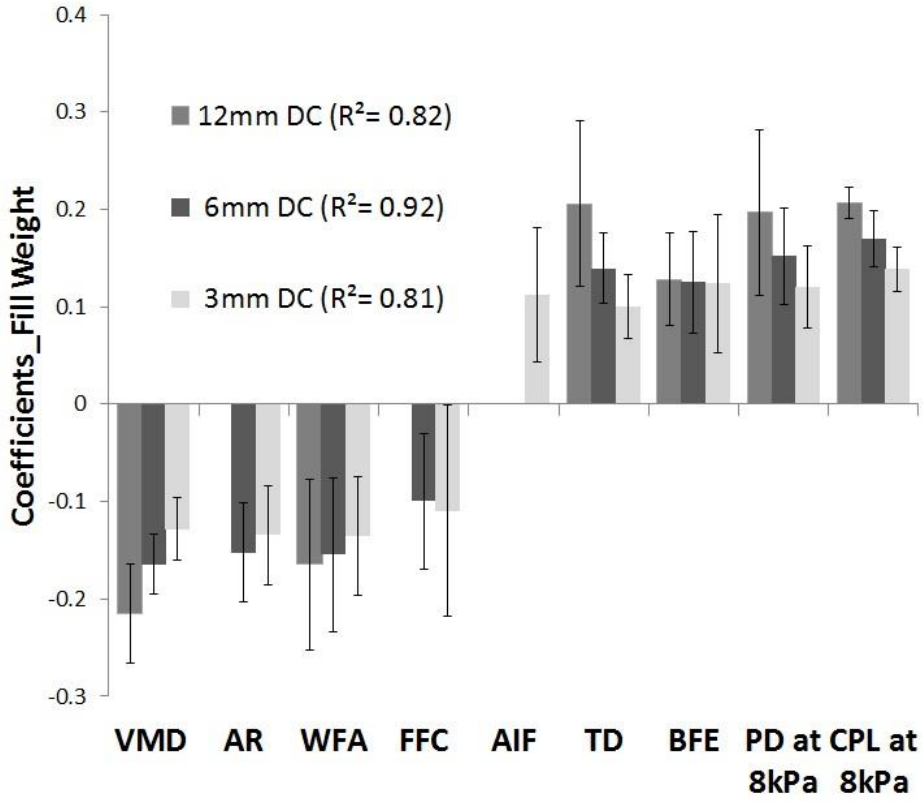

Figure 3: Coefficient Plot for three different volumes of dosing chambers.

Table 6 presents the capsule fill weight and the weight variability of capsule filling experiments for the six different MCCs.

As can be seen, the cellulose with the smallest particles, lowest air permeability, highest density and compressibility (Avicel PH301) had the highest fill weight. MCCs with larger particles, high air permeability and low densities and compressibility result in a lower capsule fill weight (Avicel PH200). This is expected as small particles are more cohesive, and therefore, display more significant volume reduction during pre-compaction than the other studied powders. Thus, the capsule fill weight also correlates well with the CI. The higher the CI, the higher the fill weight should be. Tables 3 and 6 confirm this trend to a certain extent. The main outliers are Avicel PH102 and Avicel PH302, which show an opposite trend, i.e., a lower fill weight for a higher CI. However, in these cases, also the tapped density must be taken into account. Avicel PH302 has a 10% higher tapped density than Avicel PH102, thus explaining the higher capsule fill weight.

The particle size and the compressibility were determined as major factors correlating with the capsule fill weight. Nevertheless, the capsule fill weight is not fully explained by CI, tapped density and particle size. Thus, other effects must be important in the filling process. A strong correlation of air permeability and WFA to the capsule fill weight was found as well. Furthermore, the flow indices FFC and BFE correlated with the capsule fill weight to certain extents.

In a study of lactose powders filling, Jolliffe and Newton determined that the more freely a powder flows, the greater are the compressive stresses required to form stable plugs (Jolliffe and Newton 1983c; Jones, 2001). Avicel PH200 is the freest flowing MCC in our study, which explains the observed lack of powder plug formation without piston compaction. Podczeck (2004) states, that an excellent powder flow is usually accompanied by an inability of a powder to form an arch (Podczeck and Jones 2004). Due to this effect, powder is not fully retained in the dosator nozzle and lost during transfer into the capsules and the fill weight is lower. Thus, the relatively lower fill weight for Avicel PH200 was explained.

The capsule fill weight also increases at higher filling speeds (Table 6). Due to machine vibrations during production, the powder bed gets denser and the capsules result in higher fill weights (Llusa et al., 2013).The capsule fill weight of Prosolv®_SMCC 90 and Avicel PH301 were the most and the least affected by filling speed respectively.

	DC 12mm length				**DC 6mm length**				**DC 3mm length**			
Filling Speed (CPH)	**500**		**3000**		**500**		**3000**		**500**		**3000**	
Material	Fill Weight (mg)	Weight Variability (%)	Fill Weight (mg)	Weight Variability (%)	Fill Weight (mg)	Weight Variability (%)	Fill Weight (mg)	Weight Variability (%)	Fill Weight (mg)	Weight Variability (%)	Fill Weight (mg)	Weight Variability (%)
Avicel PH102	111.2	1.8	113.7	1.7	59.5	3.6	64.0	3.3	37.7	4.9	42.4	4.2
Avicel PH200	97.1	2.2	98.8	1.9	46.2	4.5	51.0	4.4	31.5	8.8	35.4	5.1
Avicel PH301	141.4	5.1	146.6	2.1	79.2	7.1	79.1	2.9	53.9	6.2	53.8	5.1
Avicel PH302	131.4	3.4	143.4	1.5	71.6	5.5	75.6	3.5	49.3	7.3	53.2	4.4
Prosolv®_ SMCC 90	114.9	4.7	128.6	1.2	68.5	2.7	77.2	2.6	45.7	3.9	55.2	4.0
Vivapur® 12	122.0	4.1	124.9	1.4	68.9	2.9	71.9	2.5	47.7	4.1	53.9	3.7

Table 6: Capsule fill weight and weight variability.

2.3.3. Effects of material attributes on fill weight variability (RSD)

No major correlations between material attributes and the weight variability of the filled capsules were observed (Table 5). This implies two things: First, the weight variability is not strongly dependent on single material attributes, but is affected by all parameters to a certain small extent. Second, only process parameters (i.e., the filling speed, the volume of the dosing chamber and thus the absolute fill weight and the compression ratio) influence the weight variability of capsules filled with MCC.

In terms of weight variability, Jolliffe and Newton stated that fine fractions of lactose powders produced the most uniform fill weights (1982). However, in our study we could not confirm such trend for MCC powders. Instead, Vivapur®12 with a big VMD, and Avicel PH301, with the finest VMD, had the lowest and highest weight variability respectively. This could be explained because the powder layer of Avicel PH301 was not as uniform during capsule filling as for the other powders. Prosolv®_SMCC90, the silicified material, showed low weight variability as well. Felton et al. (2002) reported that capsules filled with silicified material on a

tamp filling machine resulted in lower weight variability than those containing MCC powders, due to its better flow. The low weight variability of Vivapur®12 and Prosolv®_SMCC90 is because of the stable plug formation and therefore no powder was lost during transfer. Furthermore, both materials showed smooth uniform powder layers during production. Avicel PH200, which has the best flow of the studied powders did not form strong plugs and powder loss occurred.

The process parameters, which have an impact on the weight variability of the filled capsules are the filling speed, compression ratio and volume of the dosing chamber. The highest weight variability was measured in the experiments with low filling speed and the smallest volume of dosing chamber (dosing chamber length of 3mm). Reier et al. also reported the filling speed of operation as variable affecting weight variability on a semi-automated capsule filler (Reier et al., 1968). Another important factor is compression ratio. Jones (2001) refers in his review to the research group Takagi et al., who obtained the most uniform capsule fill weights with a compression ratio of 1:2 (Takagi et al., 1969). In our experiments, the most uniform fill weights were achieved at a high filling speed with a 12mm dosing chamber length and a ratio between chamber length and powder layer height of 1:2.5.

2.4. Conclusion

In this work, material attributes of various MCC types were determined using previously-described techniques and correlated with the capsule fill weight and weight variability of a lab scale dosator nozzle system via the PLS regression tool of a multivariate data analysis. MVDA was useful for identifying the effect of the material attributes on the capsule fill weight. There was a clear correlation between the capsule fill weight and the particle size, the compressibility and air permeability. The WFA, tapped density and particle shape also displayed a major impact. Larger fill weights were more affected by density while lower fill weights by flow and friction characteristics. No significant correlation was found between the material attributes and the weight variability.

In summary, MCCs with smaller particles resulted in higher fill weights and stable powder plugs. Higher compressibility and air pressure drop correlate with higher capsule fill weights. However, many CMAs influence the capsule-filling process, hence the CQA and the analysis becomes increasingly challenging when the dose size decreases. In addition, we observed that the filling speed has a major effect on fill weight and weight variability.

Nomenclature

AIF: Angle of internal friction

AOR: Angle of repose

AR: Aspect ratio of 50% particle population of powder

BD: Bulk density

BFE: Basic flowability energy

C: Cohesion

CI: Carr`s compressibility index

CMA: Critical material attribute

CPH: Capsules per hour (Filling speed)

CPL: Compressibility

CQA: Critical quality attribute (Capsule fill weight and weight variability)

DC: Volume of the dosing chamber

DOE: Design of experiments

FFC: Flow function

MCC: Multi crystalline cellulose

MVDA: Multivariate data analysis

PD: Pressure drop

PLS: Partial least squares

QBD: Quality by design

RSD: Relative standard deviation (weight variability)

TD: Tapped density

VMD: Volumetric mean diameter

WFA: Wall friction angle

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„Scientist believe in things, not in persons.“

Marie Curie

3. Low-dose capsule filling of inhalation products: Critical material attributes and process parameters

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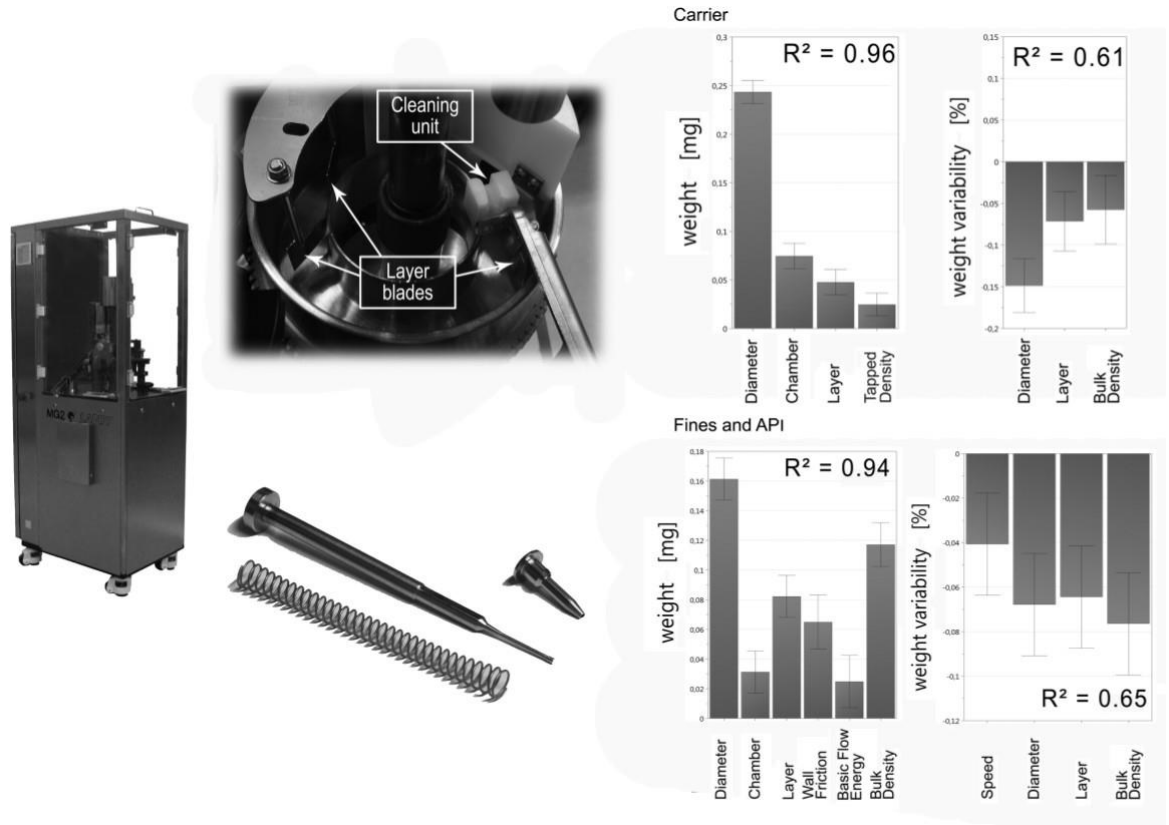
Graphical abstract



Keywords: inhalation powders; low-dose capsule filling; low-fill weight; dosator nozzle machine; critical material attributes; multivariate data analysis

Low-dose capsule filling of inhalation products: critical material attributes and process parameters

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Abstract

The aim of the present work was to identify the material attributes and process parameters of a dosator-nozzle capsule filling machine that are critical in low-fill weight capsule filling for inhalation therapies via hard-gelatin capsules. Twelve powders, mostly inhalation carriers, some fines and one proprietary active pharmaceutical ingredient (API), were carefully characterized and filled into size 3 capsules. Since different process conditions are required to fill capsules with powders that have very different material attributes, the powders were divided into two groups. A Design of Experiments (DOE) based exclusively on process parameters was developed for each group, to identify the critical material attributes (CMA) and critical process parameters (CPP). The fill weight (4 - 45mg) of the group I powders (larger particles, higher density, better flowability and less cohesion) correlated with the nozzle diameter (1.9 – 3.4mm), the dosing chamber length (2.5 – 5mm), the powder layer depth (5 – 12.5mm) and the powder density (bulk and tapped density). The RSDs were acceptable in most cases, even for very low doses. The fill weight (1.5 - 21mg) of group II powders (very fine and low dense particles with a particle size < 10□m, poor flowability and higher cohesion) depended also on the nozzle diameter (1.9 – 2.8mm), the dosing chamber length (2.5 – 5mm) and the powder layer depth (5 – 10mm), albeit in a different way, indicating that for these powders dosator filling was not volumetric. Moreover, frictional (wall friction angle) and powder-flow characteristics (bulk density and basic flowability energy) have an influence on the mass.

Thus, in summary, group I and group II powders can be filled successfully via dosator systems at low fill weights. However, the group II powders were more challenging to fill, especially

without automated process control. This study is the first scientific qualification of dosator nozzles for low-fill weight (1 - 45 mg) capsule filling.

Keywords: Inhalation powders, Low-dose capsule filling, Low-fill weight, Dosator nozzle machine, Critical quality attributes, Multivariate data analysis

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3.1. Introduction

Dry powder inhalers (DPIs) are commonly-used, breath-actuated inhalation devices for the treatment of respiratory and other diseases (Daniher and Zhu, 2008). Significant efforts have been devoted to the research and development of novel DPI formulations and devices, aiming at improving the efficiency of drug delivery (Islam and Cleary, 2012). As the potential for pulmonary delivery of low-dose medications becomes increasingly recognized, DPI systems may one day be the device category of choice - or at least a potential option - for local and systemic drug delivery (Newman, 2004). This delivery route is becoming even more interesting since large molecules can be delivered via the lung, potentially replacing injection-based drug products. The formulations used in DPIs typically consist of adhesive mixtures of the active pharmaceutical ingredient (API) attached to the surface of coarse carrier particles, so called binary formulations. In order to reach the tiny airways of the deep lung the API particles have to exhibit an aerodynamic diameter of 1–5 μm. Particles of this size are rather cohesive and show poor flow properties and dosing (Daniher and Zhu, 2008). Thus, to improve the flowability, dosing accuracy and minimizing dose variability of such powders carrier based formulations, are used. By adding a small amount of fine particles ("fines") to the coarse carrier and API, a ternary formulations are formed, which increase the performance of DPIs (Jones and Price, 2006). During inhalation, the API detaches from the carrier to reach its target site, the deep lung. Therefore an aerodynamic diameter of <5μm is required, to avoid impaction and sedimentation in the upper respiratory tract together with the coarse carrier particles (Alagusundaram et al., 2010).

Almost half of all marketed DPIs are single-unit dose devices with a powder formulation in individual hard-gelatin capsules. Capsule-based devices are, for example, single unit-dose RotahalerTM (Glaxo Smith Kline) and Handi-HalerTM (Boehringer-Ingelheim) and novel multiple pre-metered unit-dose Flowcaps® (Hovione) that contain up to 20 capsules (Newman, 2004; Steckel et al., 2004; Islam and Gladki, 2008). As inhalation therapies typically involve low doses in the mg-range (Kou et al., 2012), the challenge to the successful development of low-dose DPI products is the dose uniformity. Understanding and optimization of the capsule quality attributes and the drug formulation is a perquisite for a successful and widespread implementation of such devices and is also demanded by the Quality by Design (QBD) principles, according to the ICH Guidelines Q8 (R2). Under this approach, all the physico-

chemical properties of the drug formulation and the process parameters of the capsule filling technique have to be taken into account (Islam and Cleary, 2012).

Several low-dose capsule filling systems are currently available. Filling principles can be divided into volumetric (e.g., the dosator nozzles, vacuum drum filler, vacuum dosator and tamp filler) or gravimetric (e.g., micro-dosing, not further illustrated here) methods. Capsule filling by nozzle dosators has been broadly investigated (Jones, 2001; Podzeck and Jones, 2004a; Llusa et al., 2013, 2014; Newton, 2012) and is an important technology applied in the pharmaceutical industry today. Especially in DPI filling the dosator principle plays an important role, as the doses need a controlled degree of compaction, to ensure the DPI can reliably turn the plug back into a powder for efficient dose delivery.

However, the filling of capsules with low doses in the mg range poses significant problems. Thus, in the current study, a lab-scale, low-dose dosator nozzle capsule filling machine (Labby, MG2, Bologna) was studied. Essentially, this is a standard-dose Labby with the following special low-dose equipment adaptations: (1) smaller nozzles, (2) a cleaning unit to remove excess powder from the dosator and (3) special blades to keep a stable and uniform powder bed during production. Further no piston compaction is performed. These adjustments allow taking advantage of the features already available in a standard dose dosator. However, a precise understanding of the design space of small-diameter nozzles and a re-examination of the impact of process parameters and material attributes on fill weight and variations thereof are needed. Thus, the objective of the current work was to investigate the complex relationship between the critical material attributes (CMA), critical process parameters (CPP) and critical quality attributes (CQA), here capsule fill weight and weight variability. For details about previous (standard-dose) capsule filling studies with Labby see Llusa et al., 2013 and 2014 and Faulhammer et al., 2014.

Because lactose is a well-known and widely used carrier for DPI applications (Kou et al., 2012), ten types of well-characterized α-lactose monohydrate were used in our experiments and in addition mannitol and a proprietary active pharmaceutical ingredient (API). The current study used a screening Design of Experiments (DOE) to understand and correlate the effects of process parameters and material attributes on the fill weight and weight variability of capsules with low powder content. We investigated various process parameters and material attributes as factors impacting the responses (fill weight and weight variability).

Finally, multivariate data analysis (MVDA) with the entire data set was performed, identifying the CMAs and CPPs that correlate with the quality of filled capsules (CQA). To the best of our

knowledge, this study is the first scientific qualification of dosator nozzles for low fill weight (1 - 45 mg) capsule filling.

3.2. Materials and methods

Ten grades of α lactose monohydrate excipients (further called lactose), mannitol and an API were used as received (Table 1). It is well known that different types and qualities of lactose may influence the performance of a DPI. Thus, the lactose quality must be carefully selected (Steckel et al., 2006; Hickey et al., 2007; Edge et al., 2008; Kou et al., 2012). To that end, ten types of lactose were included in this study, with average particle sizes between 1.5 and 160 μm. Two DOEs were developed according to the capsule filling feasibility of different powders: one for powders with a particle size larger than 10 μm and a bulk density greater than 0.45g/ml (powder group I – coarse carriers) and the other for more challenging powders (powder group II – fine carriers and API) with a mean particle size under 10 μm and a bulk density under 0.45g/ml. It can be seen in Table 1 that the selected powders have different manufacturing characteristics. According to the suppliers DFE Pharma and Meggle the sieved lactose products show relatively narrow particle size distributions and a good flowability, whereas the milled ones do not flow as well but are very compressible due to their high surface area. Spray drying is used to produce spherical agglomerates which flow and compact well. Micronized lactose has extremely small particles and is used for pre-blending with the API to prevent segregation (DFE Pharma, Meggle 2014).

Name **Bacth no.**	**Powder group**	**Manufacturing characteristics**	**Supplier**
Lactohale 100 *601157*	I	sieved	DFE Pharma, Goch, Germany
Lactohale_GSK	I	blend	GSK, Harlow, UK
Respitose ML001 *10648940*	I	milled	DFE Pharma, Goch, Germany
Respitose ML006 *10683656*	I	milled	DFE Pharma, Goch, Germany
Respitose SV003 *10680001*	I	sieved	DFE Pharma, Goch, Germany
Respitose SV010	I	coarse sieved	DFE Pharma, Goch, Germany

10672704			
Inhalac 230 *1244*	I	sieved	Meggle, Wasserburg, Germany
Sorbolac 400 *1022*	II	milled	Meggle, Wasserburg, Germany
Spheronized Lactose	II	spheronized (10% MgSt*)	GSK, Harlow, UK
Mannitol	II	spray dried	MG2, Bologna, Italy
Lactohale 300 *601371*	II	micronized	DFE Pharma, Goch, Germany
API_GSK	II	micronized	GSK, Harlow, UK

Table 1: Powder selection; * the MgSt simulates the API attached to the lactose carrier. For the powders supplied by GSK and MG2 no batch number is shown.

3.2.1. Powder characterization

Characterization included a significant number of material attributes, where all measurements were done in triplicate: These include: particle size (via Qicpic – image analysis and Helos – laser diffraction, Sympatec, Germany), bulk (BD) and tapped density (TD) (via Pharmatest PT-TD200), true density (via AccuPyc II 1340, Micromeritics, Norcross, USA) and Carr index (CI). The basic flowability energy (BFE), flow function (FFC), cohesion (C), compressibility (CPL), wall friction angle (WFA) and air permeability (PD) were characterized with the FT4 powder rheometer (Freeman Technology, Malvern, United Kingdom). The BFE is defined as the energy required for establishing a particular flow pattern in a conditioned, precise volume of powder. FFC and C were analyzed with a 1ml shear-cell module at a maximum pressure of 3kPa. FFC is the ratio of consolidation stress, σ_1, to unconfined yield strength, σ_c. A high FFC value indicates that the powder should flow well. C describes the inter-particle interaction due to electrostatic, capillary or van der Waals forces. Compressibility is a measure of the volume change in a conditioned sample under slowly applied normal stress. In the beginning, the pressure 0.5kPa was applied and then increased by 2kPa at each step to 15kPa in the last step to obtain the ratio between the density at each compaction step and bulk density. The WFA describes the friction between a bulk solid and the surface of a material. In a typical measurement of the WFA, a stainless steel plate with a nominal roughness (Ra) 0.2 µm was used, which is the material of MG2 nozzles, and a maximum pressure of 9kPa was applied. Air

permeability is a measure of how easily material can transmit air through its bulk. It is determined by the air pressure drop (PD) across a powder bed. A high pressure drop indicates low air permeability. Details on the powder rheometer tests can be found in the literature (e.g., Freeman, 2007; Freeman and Fu, 2008).

3.2.2. Design of experiments (DOE)

The initial DOE in our study consists of four process parameters of the capsule filling machine. These are the (1) dosator diameter, (2) dosing chamber length, (3) powder layer depth and (4) capsule filling speed. In order to obtain the largest amount of information from the smallest number of experiments, a D-optimal model with design statistics G-efficiency with three replicates was selected.

However, some experiments in this initial DOE could not be performed for some very fine powders (group II), e.g., the ones that could not be filled at a dosing chamber length of 2.5mm and powder layer depth of 12.5mm (which gives a compression ratio between of 1:5). In this case the powder layer depth was 5 times the dosing chamber length and the powder densified extensively in the nozzle. These hard plugs, which are not applicable via inhalation route of administration, could not be ejected into the capsule body and the piston blocked (see Fig. 1).

Therefore, the powders were divided into two groups and a DOE was created for each group with MODDE 9.1 (Umetrics). Each of these DOEs included the four process parameters (controlled variables) of the capsule filling machine: filling speed (500, 1500 and 2500 capsules per hour - CPH), dosator diameter (1.9 mm, 2.8 mm, 2.2mm and 3.4 mm), powder layer depth (5mm, 10mm and 12.5 mm) and dosing chamber length (2.5mm, 3.75 mm and 5 mm). Based on the initial studies, we set constraints, i.e., that the ratio between dosing chamber length and powder layer depth, also called compression ratio is between 1:2 and 1:5 for the first group (14 experimental runs) and between 1:1 and 1:4 for the second (15 experimental runs). The parameter values for the two DOEs are provided in Table 5 (group I) and Table 6 (group II) below in the results section.

Fig. 1: Piston blocking of the 3.4 mm dosator: Extensive pre-compression of the powder occurred due to a 1:5 compression ratio between dosing chamber length and powder layer depth. A very hard plug was formed, which could not be ejected by the piston.

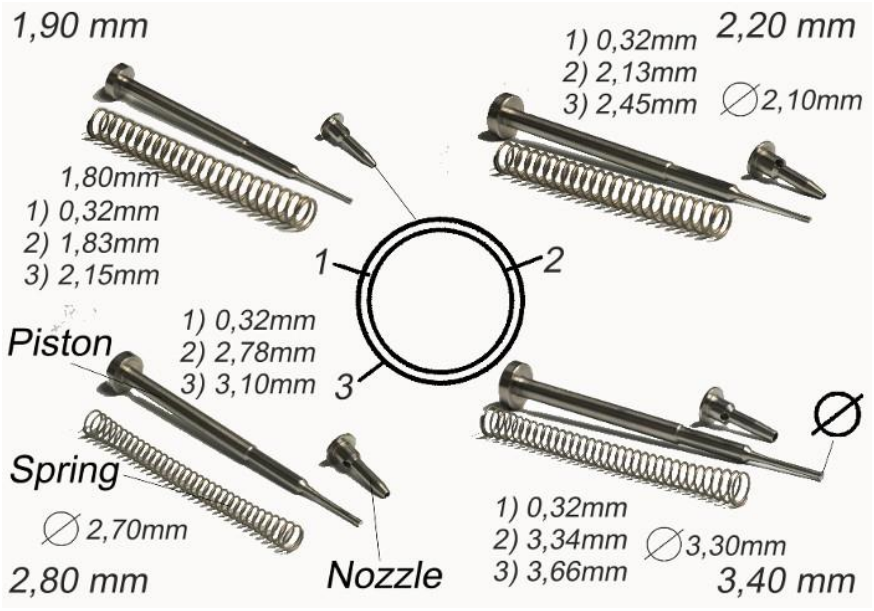

Fig. 2: Schematic presentation of the four low dose dosators (nominal 1.9mm, 2.2mm, 2.9mm and 3.4mm): 1 – thickness of the nozzle wall; 2- inner diameter of the nozzle; 3 – outer diameter of the nozzle; Ø – diameter of the piston.

3.2.3. Capsule filling experiments

Powders were filled into Coni-Snap hard gelatin size 3 capsules by a lab-scale dosator nozzle capsule filling machine (Labby), with the process parameters described in Tables 5 and 6. Fig. 2 shows the low-dose dosator nozzles, which have a much smaller diameter than those used for standard doses, and a special screw (Fig. 3) for nozzle mounting and fixation. Each capsule filling experiment followed a standard operating procedure (SOP) to minimize for example the dependence on the operator. First, we measured the exact height of the powder bed with a venier caliper, as the layer was recreated after every experimental run. Second, the exact dosing chamber length was established by adjusting the gauge (Fig. 4). Third, a visual inspection of the inside dosator nozzle wall and the piston before and after cleaning was performed to ensure that the walls were not coated with powder. After mounting the dosator, one manual operation cycle was carried out to ensure the right position. Most importantly, the entire study was performed under humidity-controlled conditions (45-55% relative humidity). It is well known that the relative humidity can affect inter-particulate forces through capillary condensation and due to increased van der Waals interactions (Pilcer et al., 2012; Podczeck et al., 1997; Price et al., 2002).

Fig. 3: Screw for dosator fixation

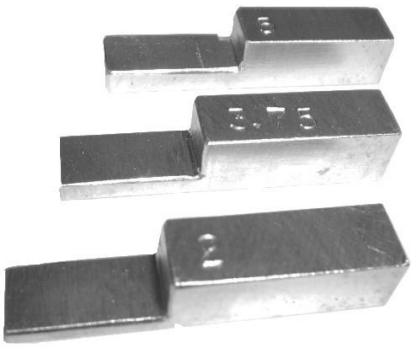

Fig. 4: Gauge to adjust the dosing chamber length

Due to a relatively high weight of empty capsules and their variability, a precise scale was used to determine the exact weight of every empty capsule body. Each capsule was assigned a number and, subsequently, the weight was recorded with the Denver SI-234A (reproducibility 0.1 mg) analytical scale.

After setting all process parameters, the powder layer was created and feeding of the powder to the bowl was optimized. In order to keep a smooth powder layer, the feeding had to match the amount of powder collected by the nozzle. Next, a set of 25-30 capsules was collected, followed by another set of 25-30 capsules after five minutes to determine, if the filling operation had reached a steady state. If the fill weight or RSD values of the two groups deviated more than 10% from each other, the experiments were repeated.

Each filled and numbered capsule was weighed again on a Denver SI-234A analytical scale and, to obtain the fill weight of capsules, the weight of the empty, numbered capsules was subtracted from the gross weight. The mean fill weight and RSD were obtained using both groups compounded in one data set.

3.2.4. Multivariate data analysis via PLS

PLS is a commonly-used chemometric data analysis technique, which has various implementations and allows an experimental design with a high condition number or small amounts of missing data in the response matrix. Its most widespread form in science and technology is the two-block predictive PLS that relates two data matrices, X (factors) and Y (responses), via a linear multivariate model and models the structure of X and Y (Wold et al., 2004). Models can be used to support design spaces across multiple scales and equipment (FDA/ICH, 2012).

In our study, multivariate data analysis using the entire data set was performed with MODDE 9.1 (Umetrics). It contained the average value (three measurements) for each powder property (uncontrolled variables) and the value for each process parameter (controlled variables), which were the model's factors as well as the average capsule fill weight and the weight variability (RSD), which were the model's responses. A partial least square (PLS) method was used to study the correlations between the material attributes and process parameters and the capsule fill weight and weight variability. As several responses were measured, PLS was applied to fit a model and to simultaneously represent the variation of all responses with regard to the variation of factors by taking their co-variances into account (Wold et al., 2004).

3.3. Results and discussion

3.3.1. Powder characterization

In our study we used powders with a broad range of sizes and densities (see Table 2). According to the powder fineness classification in the USP 2011 <811>, Lactohale 100 and Respitose SV010 are fine powders. The rest of the powders can be classified as very fine in terms of particle size.

Podczeck (2004) reported that particles with a median size larger than 150 μm were hard to fill with a dosator nozzle machine due to excellent flow properties and the associated inability to form plugs. The ideal median particle size ranged between 50 and 100 μm. Below 50 μm, an increased tendency of powder adhesion to metal parts and a significantly reduced flowability were observed, leading to an increase in weight variability. Further, it is reported that powders with a median particle sizes below 20 μm could not successfully be filled due to excessive adhesion, friction and poor powder flow properties (Podczeck and Jones, 2004b).

In our system, filling of these powders with smaller nozzles was made possible by introducing special features to the equipment (MG2), which can be seen in Fig. 5. The nozzle cleaning unit removes adhering powder from the outer wall or around the nozzle tip to minimize weight variability. Moreover, the stabilizing blades keep the powder layer as smooth and homogenous as possible (Fig. 5). Furthermore, no compaction step is performed in low-dose capsule filling to avoid the formation of hard powder plugs.

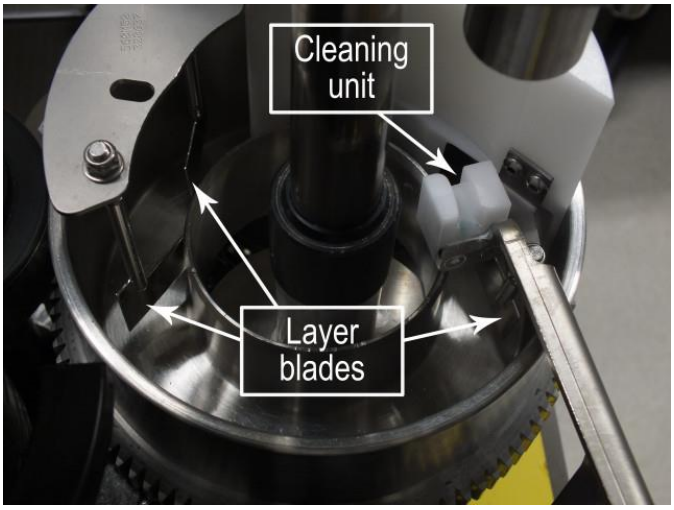

Fig. 5: Low dose equipment

Table 2 presents the particle size and density of the inhalation products investigated. A VMD ranging from 1.6 to 160 µm and a density range between 0.15 to 0.74g/ml demonstrates the significant variability in powder characteristics. Although Mannitol has a small VMD and true density (similar to spheronized lactose) its bulk density is relatively high. These differences could be explained by the contrasting manufacturing ways. Usually spray dried powders are spherical and hollow. However, the spray dried mannitol consists of a shell and a porous inside (Elversson and Millqvist-Fureby, 2005; Littringer et al., 2012) and therefore shows a higher density.

	VMD (µm)	*BD (g/ml)*	*stdv (+/-)*	*TD (g/ml)*	*stdv (+/-)*	*True density (g/cm^3)*	*stdv (+/-)*	*Powder group*
Spheronized Lactose	*1.68*	*0.15*	*0.004*	*0.25*	*0.005*	*1.46*	*0.012*	*II*
Mannitol	*2.52*	*0.40*	*0.005*	*0.56*	*0.003*	*1.46*	*0.004*	*II*
API_GSK	*3.28*	*0.19*	*0.000*	*0.29*	*0.005*	*1.31*	*0.006*	*II*
Lactohale 300	*3.37*	*0.27*	*0.003*	*0.38*	*0.010*	*1.55*	*0.014*	*II*
Sorbolac 400	*8.71*	*0.40*	*0.001*	*0.76*	*0.005*	*1.56*	*0.007*	*II*
Respitose ML006	*23.07*	*0.47*	*0.002*	*0.86*	*0.004*	*1.55*	*0.009*	*I*
Respitose ML001	*71.17*	*0.66*	*0.003*	*1.05*	*0.004*	*1.55*	*0.006*	*I*
Lactohale_GSK	*72.36*	*0.67*	*0.001*	*1.01*	*0.007*	*1.54*	*0.005*	*I*
Respitose SV003	*73.99*	*0.69*	*0.000*	*0.83*	*0.002*	*1.54*	*0.003*	*I*
Inhalac 230	*111.71*	*0.74*	*0.004*	*0.89*	*0.002*	*1.55*	*0.005*	*I*
Respitose SV010	*129.82*	*0.72*	*0.012*	*0.87*	*0.004*	*1.54*	*0.001*	*I*
Lactohale 100	*160.02*	*0.7*	*0.004*	*0.82*	*0.013*	*1.54*	*0.003*	*I*

Table 2: Particle size and Densities (BD = bulk density, TD = tapped density)

Powder flowability is known to affect the weight variability of capsules filled using standard nozzles (Freeman and Fu, 2008; Freeman, 2007; Podczeck and Miah, 1996; Prescott and Barnum, 2000; Schulze 2011). Moreover, Eskandar stated that successful and accurate dosing of low powder masses is challenging due to the limitations of volumetric dosing technologies that rely on the good flowability of powders (Eskandar et al., 2011). In order to determine if and to what extent flowability affects the weight variability of low fill weight products, much effort was made to characterize this powder property as shown in Table 3. According to the

parameters FFC and C, Respitose SV003 has the best flowability. The worst was observed for Lactohale 300 (very cohesive), which is reflected by the lowest FFC value and a high value for C. Also, the API and the spheronized lactose show poor flowability and very high cohesivity. Sorbolac 300, Respitose ML006 and Respitose ML001 are classified as cohesive with expected flowability issues. The other powders likely flow well.

	FFC	*stdv (+/-)*	*C*	*stdv (+/-)*	*BFE (mJ)*	*stdv (+/-)*	*CI*	*stdv (+/-)*	*Powder group*
Spheronized Lactose	*1.87*	*0.28*	*0.87*	*0.20*	*424.00*	*6.25*	*38.93*	*1.73*	*II*
Mannitol	*2.90*	*0.48*	*0.52*	*0.11*	*643.67*	*36.83*	*32.93*	*0.61*	*II*
API_GSK	*1.91*	*0.03*	*0.79*	*0.03*	*746.33*	*114.69*	*47.60*	*0.40*	*II*
Lactohale 300	*1.62*	*0.15*	*0.97*	*0.16*	*1265.33*	*96.50*	*30.00*	*1.00*	*II*
Sorbolac 400	*2.35*	*0.13*	*0.61*	*0.03*	*606.33*	*21.46*	*33.33*	*1.16*	*II*
Respitose ML006	*2.56*	*0.06*	*0.57*	*0.01*	*510.67*	*16.17*	*45.33*	*0.23*	*I*
Respitose ML001	*3.29*	*0.10*	*0.45*	*0.02*	*1171.33*	*83.68*	*37.07*	*0.46*	*I*
Lactohale_GSK	*4.35*	*0.09*	*0.33*	*0.00*	*1633.00*	*48.51*	*33.87*	*0.61*	*I*
Respitose SV003	*8.10*	*0.33*	*0.20*	*0.01*	*2393.33*	*74.27*	*17.33*	*0.23*	*I*
Inhalac 230	*7.93*	*0.57*	*0.20*	*0.01*	*2224.00*	*64.09*	*37.07*	*0.42*	*I*
Respitose SV010	*7.70*	*0.29*	*0.19*	*0.02*	*942.00*	*59.86*	*16.78*	*1.63*	*I*
Lactohale 100	*6.58*	*0.20*	*0.24*	*0.02*	*910.67*	*43.00*	*15.73*	*1.67*	*I*

Table 3: Flow properties of investigated powders (ffc < 2: very cohesive; ffc = 2-4: cohesive; ffc = 4-10: easy-flowing; ffc > 10: free-flowing; C=0: not cohesive; C=1: very cohesive; CI ≤ 10: excellent flow, CI= 11-15: good flow, CI= 16-20: fair flow, CI=21-25: passable flow, CI= 26-31: poor flow, CI= 32-37: very poor flow, CI ≥ 38: very, very poor flow).

Table 4 shows the friction (WFA and AIF) coefficients, compressibility (CPL) and air permeability (PD) of the tested powders. The more cohesive the powder is, the larger is the CPL, which is in agreement with the results reported by Fu et al. (2012). The particle size correlates with the PD and, therefore, with air permeability. With the exception of LH 300, bigger particles result in lower PDs and more cohesive powders generate a higher pressure drop (Fu et al., 2012). The powder with the highest WFA and AIF is the proprietary GSK API, and the sieved lactoses show the lowest friction coefficients. Furthermore, we observed a correlation between WFA and AIF. Contrary to this trend the spheronized lactose with the smallest VMD

has a small WFA. This can be explained by the 10% MgSt content in the spheronized Lactose which usually acts as a lubricant, and therefore, reduces friction.

	WFA 3kPa 0.2 Ra	*stdv (+/-)*	*AIF*	*stdv (+/-)*	*PD at 8kPa [mbar]*	*stdv (+/-)*	*CPL at 8kPa [Ratio ρ_{comp}/ρ_{BD}]*	*stdv (+/-)*	*Powder group*
Spheronized Lactose	*11.20*	*0.46*	*33.43*	*2.31*	*27.97*	*1.94*	*1.51*	*0.00*	*II*
Mannitol	*24.10*	*0.28*	*31.83*	*3.57*	*40.47*	*2.50*	*1.21*	*0.01*	*II*
API_GSK	*35.67*	*1.33*	*36.33*	*1.25*	*30.90*	*0.89*	*1.74*	*0.13*	*II*
Lactohale 300	*31.50*	*1.95*	*34.27*	*4.72*	*6.17*	*0.17*	*1.47*	*0.06*	*II*
Sorbolac 400	*30.20*	*0.60*	*34.80*	*2.36*	*29.40*	*0.98*	*1.35*	*0.06*	*II*
Respitose ML006	*29.70*	*0.87*	*31.27*	*1.01*	*27.10*	*0.80*	*1.28*	*0.01*	*I*
Respitose ML001	*12.57*	*0.67*	*26.73*	*0.91*	*20.17*	*0.06*	*1.19*	*0.02*	*I*
Lactohale_GSK	*9.73*	*0.19*	*23.57*	*0.35*	*13.23*	*0.21*	*1.13*	*0.01*	*I*
Respitose SV003	*8.36*	*0.45*	*17.53*	*0.38*	*4.58*	*0.06*	*1.05*	*0.00*	*I*
Inhalac 230	*9.25*	*0.31*	*17.60*	*0.60*	*2.71*	*0.05*	*1.06*	*0.00*	*I*
Respitose SV010	*8.42*	*0.79*	*17.83*	*1.32*	*1.96*	*0.01*	*1.04*	*0.01*	*I*
Lactohale 100	*7.70*	*0.02*	*18.43*	*0.49*	*1.05*	*0.02*	*1.05*	*0.00*	*I*

Table 4: Friction coefficients, WFA and AIF, air permeability (PD) and compressibility (CPL)

3.3.2. Capsule filling

Table 5 shows the DOE for the first group of seven powders, i.e., the values of the four process parameters, the fill weight and the corresponding weight variability (RSD). In most of the experiments, fill weights between 4 and 45 mg and RSDs less than 5% were obtained.

DOE I					***RESPITOSE ML006***		***RESPITOSE ML001***		***LACTOHALE GSK***		***RESPITOSE SV003***		***INHALAC 230***		***RESPITOSE SV010***		***LACTOHALE 100***	
RUN	**Speed [cph]**	**Diameter [mm]**	**Chamber [mm]**	**Layer [mm]**	**Weight [mg]**	**RSD [%]**	**Weight [mg]**	**RSD [%]**	**Weight [mg]**	**RSD [%]**	**Weight [mg]**	**RSD [%]**	**Weight [mg]**	**RSD [%]**	**Weight [mg]**	**RSD [%]**	**Weight [mg]**	**RSD [%]**
1	*2500*	*1.9*	*2.5*	*5.0*	*4.2*	*10.7*	*5.3*	*6.7*	*6.2*	*4.9*	*6.0*	*7.1*	*6.0*	*5.0*	*6.1*	*4.8*	*6.0*	*5.7*
2	*1500*	*2.8*	*3.75*	*10*	*14.8*	*10.4*	*23.8*	*2.7*	*23.1*	*1.8*	*19.1*	*1.8*	*19.0*	*2.4*	*20.0*	*1.9*	*19.0*	*2.1*
3	*2500*	*3.4*	*2.5*	*12.5*	*23.0*	*2.1*	*25.6*	*1.8*	*24.8*	*1.7*	*21.5*	*3.6*	*21.8*	*1.8*	*22.4*	*2.5*	*21.3*	*1.5*
4	*500*	*3.4*	*2.5*	*5.0*	*18.3*	*4.5*	*21.3*	*7.8*	*21.8*	*2.9*	*19.5*	*2.7*	*19.6*	*2.7*	*19.8*	*1.9*	*19.8*	*3.7*
5	*500*	*3.4*	*2.5*	*12.5*	*24.7*	*1.6*	*26.6*	*2.3*	*24.4*	*2.6*	*20.6*	*1.9*	*20.8*	*1.9*	*21.2*	*2.6*	*20.9*	*3.1*

6	500	1.9	5.0	12.5	10.1	5.8	11.4	5.5	12.0	2.4	11.5	3.1	11.0	4.4	11.0	3.2	10.6	3.4
7	2500	1.9	2.5	12.5	6.9	5.0	7.3	5.3	7.6	3.4	6.7	6.8	6.4	4.9	6.8	3.9	6.3	4.0
8	2500	3.4	5.0	12.5	35.9	4.4	45.7	2.0	43.7	0.6	37.1	1.1	39.0	1.1	38.7	1.3	37.3	1.1
9	2500	1.9	5.0	10	7.4	9.2	10.7	11.4	11.0	3.7	10.6	4.8	11.2	2.5	11.2	4.3	10.4	3.2
10	1500	2.8	3.75	10	14.9	9.4	23.1	2.1	22.8	1.2	19.2	2.8	19.9	1.7	19.9	1.8	19.0	2.1
11	1500	2.8	3.75	10	11.9	8.8	22.3	3.7	22.6	1.7	19.1	2.6	19.7	3.0	19.7	2.5	18.5	2.3
12	2500	3.4	2.5	5.0	14.1	5.0	19.6	7.2	20.4	2.3	19.8	3.4	20.6	2.9	21.0	2.0	19.9	1.8
13	500	1.9	2.5	5.0	4.8	5.7	6.4	4.8	6.1	5.5	6.3	6.8	5.9	4.7	6.1	4.5	5.7	4.8
14	500	3.4	5.0	10	33.6	3.8	43.4	3.4	42.8	1.5	36.3	1.4	37.5	1.5	37.4	1.6	35.6	1.6

Table 5: Low-dose capsule filling study - DOE I: 14 experimental run with 3 repetition experiments (2, 10, and 11).

In most cases the lightest capsules were those filled with Respitose ML006. This is not surprising as this is the powder with the lowest density in this group. In most cases the heaviest capsules were produced with Respitose ML001 and Lactohale GSK. This can be explained by the high tapped density of these two powders. Lactohale_GSK had the most uniform filling behavior (lowest RSD), although it took a long time to create a smooth powder layer. Also Respitose SV010, SV003, Lactohale 100 and Inhalac 230 resulted in relatively low RSDs. All group I powders were easy to handle during the entire process, except for the milled lactose powders (Respitose ML001 and ML006). During the experiments with Respitose ML006 we faced some challenges associated with the powder sticking to the inside and the outer wall of the nozzle, resulting in significant higher RSDs. Reasons for sticky powders are according to Podczeck large adhesion forces caused by a fine particle size, the tendency to adsorb moisture and a value for the WFA over 10° (Podczeck and Jones, 2004b), which is the case for the milled lactose powders of group I.

Table 5 also shows that the sieved lactose powders had more uniform fill weights than the milled ones, which could be explained by a higher fine fraction in the latter (Steckel et al., 2006). Fines tend to adhere on the outer wall of the nozzle, causing filling variability (Eskandar et al., 2011). As desired, plugs were never formed, not even at the highest compression ratio of 1:4 between the dosing chamber length and powder layer depth. The reason may be low powder cohesiveness and the lack of piston compaction during the filling. This is also supported by literature (Jolliffe and Newton, 1983; Jones, 2001).

Table 6 presents the DOE for powder group II, showing the weight and RSD for every experimental run. As can be seen, weights between 1.5 and 21 mg were obtained for these powders under these process conditions. Due to dosator/piston blocking and ejection failure, we could not fill capsules with spheronized lactose powder using the smallest dosator and a 1:4

ratio between the chamber and layer. The filling behavior of this powder is strongly dependent on environmental conditions (relative humidity) and needs to be further investigated. Capsules filled with mannitol showed in most of the experiments the highest fill weight, whereas spheronized lactose showed the lowest capsule fill weight, which is in accordance with their density values.

DOE II					***SPHERONIZED LACTOSE***		***MANNITOL MG2***		***API GSK***		***LACTOHALE 300***		***SORBOLAC 400***	
RUN	**Speed [cph]**	**Diameter [mm]**	**Chamber [mm]**	**Layer [mm]**	**Weight [mg]**	**RSD [%]**	**Weight [mg]**	**RSD [%]**	**Weight [mg]**	**RSD [%]**	**Weight [mg]**	**RSD [%]**	**Weight [mg]**	**RSD [%]**
1	*500*	*2.8*	*2.5*	*5.0*	*4.5*	*12.8*	*11.2*	*4.3*	*6.7*	*15.9*	*7.1*	*13.4*	*10.3*	*15.4*
2	*500*	*1.9*	*2.5*	*10*	*n.a.*	*n.a.*	*5.8*	*7.1*	*5.0*	*13.5*	*5.9*	*11.8*	*5.6*	*7.1*
3	*500*	*2.8*	*5.0*	*10*	*7.3*	*7.6*	*21.1*	*5.6*	*13.4*	*9.9*	*14.6*	*8.6*	*18.4*	*7.7*
4	*500*	*1.9*	*5.0*	*5.0*	*1.7*	*19.5*	*4.9*	*12.0*	*4.0*	*12.4*	*4.1*	*14.4*	*4.6*	*12.5*
5	*2500*	*2.8*	*5.0*	*10*	*7.2*	*6.5*	*18.6*	*4.7*	*13.0*	*10.1*	*15.3*	*7.4*	*18.9*	*5.9*
6	*2500*	*2.8*	*2.5*	*10*	*6.4*	*7.6*	*13.1*	*4.6*	*10.4*	*4.1*	*12.3*	*6.7*	*14.0*	*4.4*
7	*2500*	*1.9*	*5.0*	*5.0*	*1.8*	*17.8*	*5.1*	*8.9*	*4.2*	*11.9*	*5.6*	*11.5*	*5.5*	*8.2*
8	*2500*	*2.8*	*2.5*	*5.0*	*3.6*	*8.0*	*11.3*	*6.2*	*7.5*	*9.2*	*8.7*	*11.0*	*10.6*	*7.1*
9	*2500*	*1.9*	*5.0*	*10*	*2.7*	*10.2*	*8.0*	*9.7*	*5.5*	*7.0*	*7.1*	*8.6*	*7.8*	*9.4*
10	*1500*	*2.2*	*3.75*	*7.5*	*3.4*	*11.7*	*9.0*	*8.3*	*6.5*	*15.8*	*6.2*	*13.2*	*8.9*	*7.2*
11	*2500*	*2.8*	*5.0*	*5.0*	*3.4*	*15.4*	*12.7*	*5.7*	*6.1*	*8.4*	*10.3*	*8.7*	*11.3*	*5.8*
12	*1500*	*2.2*	*3.75*	*7.5*	*3.2*	*14.6*	*10.4*	*11.0*	*6.6*	*12.2*	*7.7*	*9.0*	*9.0*	*7.2*
13	*2500*	*1.9*	*2.5*	*5.0*	*1.5*	*16.7*	*4.1*	*13.9*	*3.2*	*11.7*	*5.3*	*16.5*	*4.6*	*9.0*
14	*1500*	*2.2*	*3.75*	*7.5*	*2.9*	*12.8*	*9.2*	*8.0*	*6.9*	*11.0*	*7.4*	*10.2*	*8.9*	*6.6*
15	*2500*	*1.9*	*2.5*	*10*	*n.a.*	*n.a.*	*6.0*	*9.8*	*3.8*	*9.4*	*5.2*	*8.3*	*6.1*	*5.5*

Table 6: Low-dose capsule filling study - DOE II: 15 experimental run with 3 repetition experiments (10, 12, and 14).

Powder group II was much more challenging than group I. Compared to powder group I, creating the layer and adjusting machine parameters took significantly longer. Furthermore, all powder layers were more uneven, the surface appeared to crack easily, and agglomerate formation occurred. The poor flowability and high cohesion of these powders make the feeding of the bowl, as well as the powder-bed formation and the filling of holes generated by the nozzles more challenging. Powder bed inhomogeneities will introduce variability in a volumetric filling process as fill weight depends on the position in the powder bed where the nozzle collects the dose. Thus, the high cohesivity of the powders in this group will lead to an increase in fill-weight variability. Moreover, fine powders tend to dust (entrainment in air flow). For example, the cleaning unit was covered with powder, which adhered to the inside and outside of the dosator nozzle and was transported towards the ejection unit, causing a higher

weight variation. The weight variation (RSD) with typical values between 5% and 15% was much higher than for powder group I.

There are no quality tests dedicated to low-fill-weight capsules in the European Pharmacopoeia 8.2, and therefore, the standard test "uniformity of mass of single-dose preparations test" was used. According to the latter "for a capsule fill content smaller than 300mg not more than 2 out of the 20 samples may be outside +/- 10% of the average and all capsules must be within 20%". Sorbolac, which passed all the experimental settings, the API, which only failed one of the repetition runs and Mannitol, which only had a bad performance in Run 4, showed very promising results. With respect to the low fill weight and no automated process control Lactohale 300, which passed 12 out of 15 runs showed acceptable results too. Only the spheronized lactose could not be filled successfully.

A visual examination of the filled capsules indicated that all the powders formed weak plugs, in all experiments with 1:4 and 1:2 compression ratios at low filling speeds. These low speeds provide enough time for arching and plug formation. However, plugs were soft and broke easily when the capsules were manipulated. No plugs were formed when filling was performed at a high speed with a 1:2 compression ratio and for all cases (slow and fast) with 1:1 compression ratios, as compression was not sufficient. Interestingly, the weight variation was smaller in the experimental runs during which plugs were formed, possibly since no powder was lost during transfer.

3.3.3. MVDA

A MVDA (partial least square method) was used to analyze the regression between factors (X) and responses (Y). Fig. 6 shows such an analysis, i.e., the significant PLS regression coefficients for the mean fill weight of capsules and their corresponding RSD for the DOE I. The error bars represent a 95% confidence interval. The coefficient plots summarize the correlation between the capsule fill weight and RSD (y-axis) and the process parameters and material attributes (x-axis).

As expected, the fill weight for the first group of powders (Fig. 6) was mainly affected by the diameter of the dosator and the length of the dosing chamber. These are the parameters, which define the volume of the dosing cylinder. Thus, these parameters are obviously critical, as large diameter (square dependence) and greater chamber length lead to a higher volume to be filled. Fig. 7 shows a plot of the mean fill weight (for group I powders for each volume) as a function of the dosing volume (dosing cylinder). Clearly, powders of group I exhibit volumetric filling.

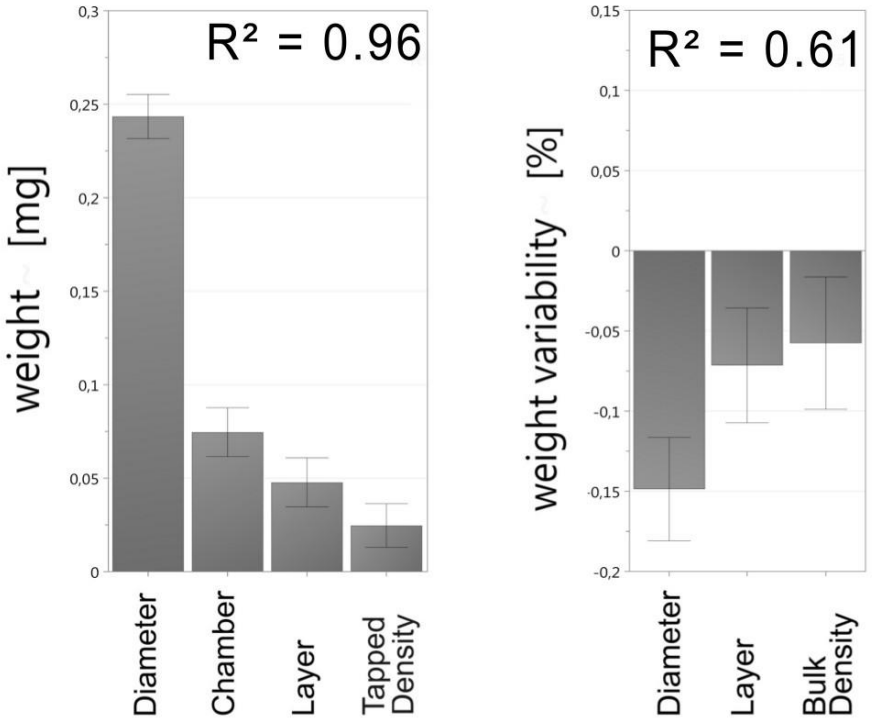

Fig. 6: Coefficient plots for (left) fill weight and (right) weight variability (RSD) – DOE I: R2 shows the model fit.

The RSD of powder group I was affected by dosator diameter, powder layer depth and the bulk density (Fig. 6). As expected, Fig. 8 shows that a decrease in dose leads to an increase in RSD. However, the correlations are not as significant (R^2=0.61) as for the fill weight. Moreover, we note that in powder group I the capsule fill weight and the RSD is significantly affected by the same process parameters (except dosing chamber length) and the density.

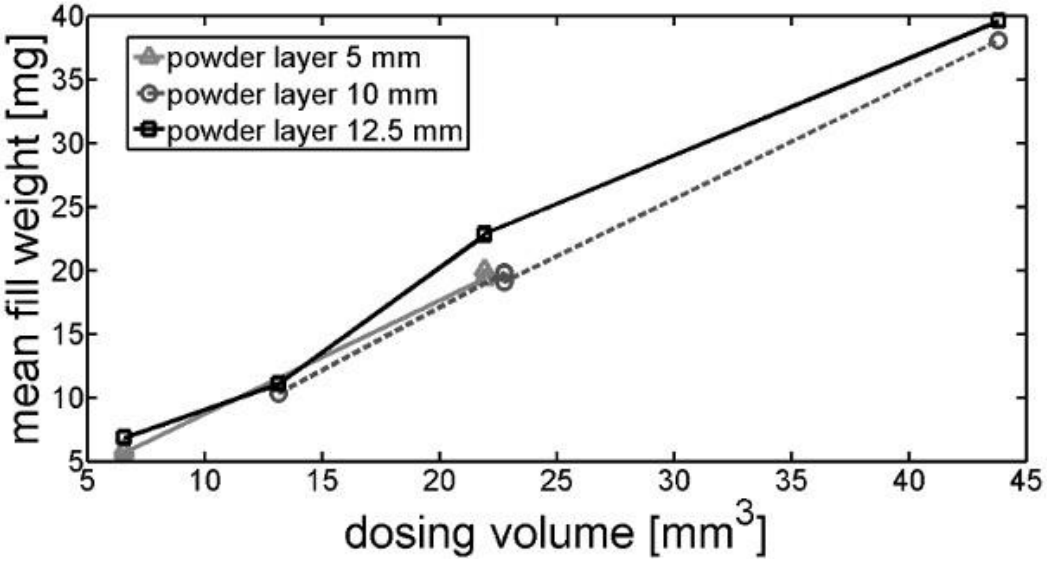

Fig. 7: Volumetric filling behaviour of powder group I – The mean fill weight is linearly increasing with increasing dosing volume.

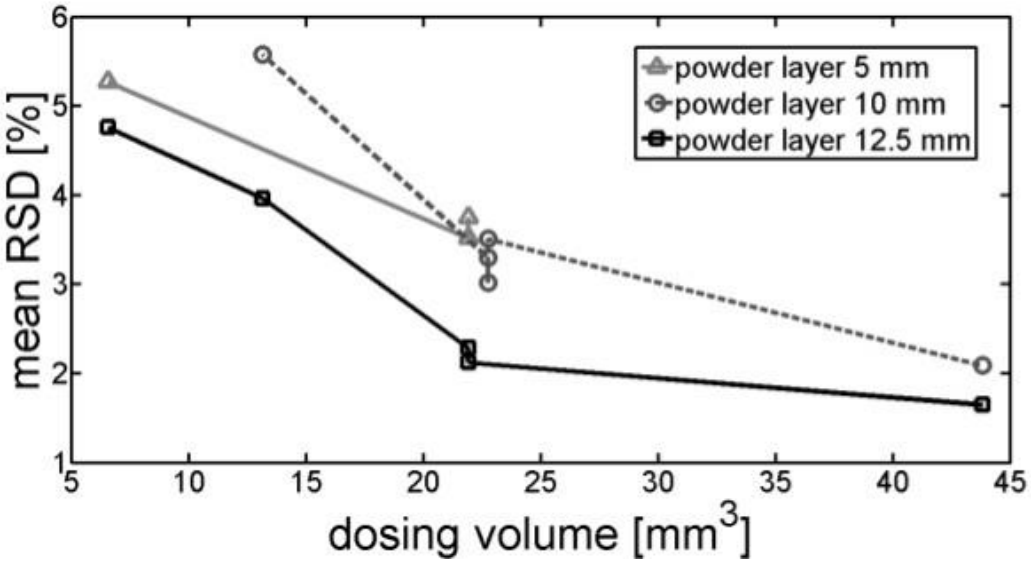

Fig. 8: The mean RSD is linearly decreasing with increasing dosing volume.

Filling speed did affect neither weight nor RSD. For standard doses filled with micro-crystalline cellulose (MCC) powders on the Labby we reported that high speed filling lead to denser powder beds, resulting in higher fill weights (Llusa et al., 2013). In the low-dose experiments, we observe an effect of speed only for powders with a VMD bigger than 100 µm (Lactohale 100, Respitose SV010 and Inhalac 230 – sieved lactose powders). The milled lactoses of this group (Respitose ML001 and ML006) show exactly the opposite behavior. This may be explained by the higher fines fraction of these materials. Due to the high capsule filling speed, vibrations occur and induce convective flow cells in the bowl (Ratkai, 1976). This, in turn, causes segregation of the fine particles to the bottom of the rotary container (Muzzio et al., 1997; Popplewell and Peleg, 1991; Julien et al., 1992; Rosato et al., 1991, 2002; Scheibelhofer et al., 2012; Staniforth, 1982). When the dosator dips into the powder bed, pre-compression occurs and bigger particles are sampled, which could cause a lower fill weight at high production speed for the milled powders. However, overall the group I was not significantly affected by capsule filling speed.

Fig. 9 presents the PLS regression coefficients for the mean fill weight of capsules and their corresponding RSD for the second and more challenging group of powders. Again, the dosator diameter was (obviously) the most influential factor with regard to fill weight. However, compared to group I powders, the chamber size was only of reduced importance.

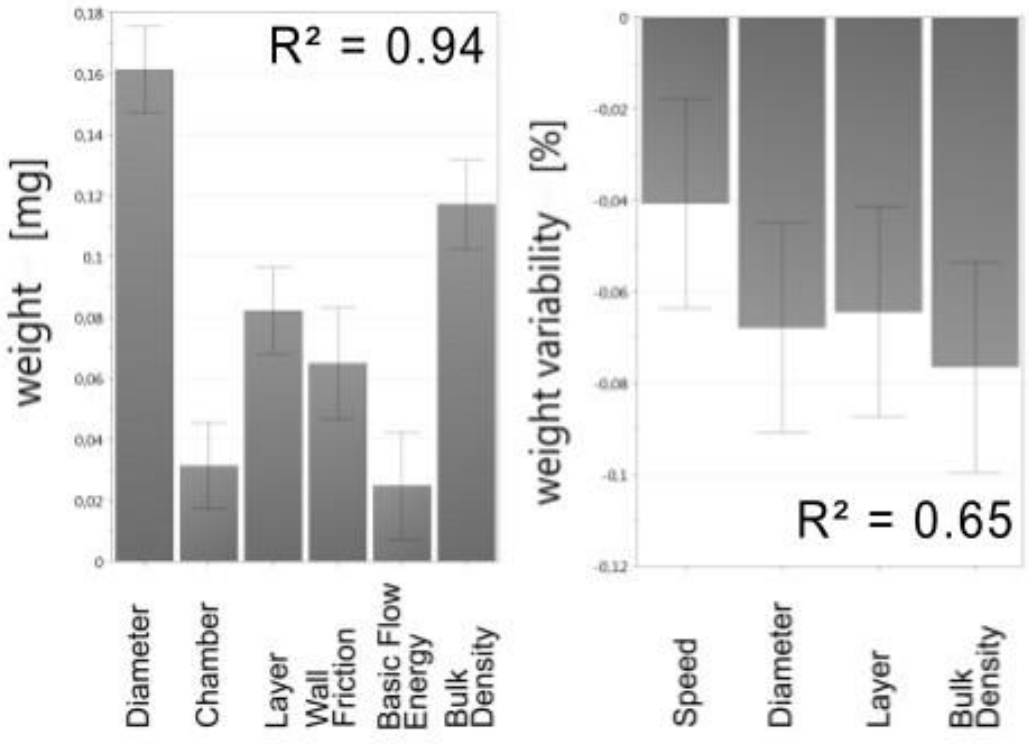

Fig. 9: Coefficient plots for (left) fill weight and (right) weight variability (RSD) – DOE II: R2 shows the model fit.

This indicates that for this powder group no volumetric filling behavior is obtained. This is also clearly visible in Fig. 10, which shows the fill weight as a function of chamber volume for all powders. In runs 13/7, 15/9, 8/11 and 5/6 all process parameters were kept constant and only the dosing volume (dosing cylinder) doubled. Thus, the weight should double. But this is not the case for the powders of group II.

Furthermore, the capsule fill weight of powder group II is more affected by the depth of powder layer (Fig. 9) than group I. In experiments with deeper powder layers, heavier capsules are produced, due to higher compression of the powder inside the dosing cylinder. Additional critical material attributes for powder group II are BD, WFA and BFE, which correlate significantly with the fill weight. High WFA induces arching and retention of powder in the nozzle, whereas a high BFE indicates a more cohesive, and therefore more compressible, powder which explains the positive correlation with the fill weight.

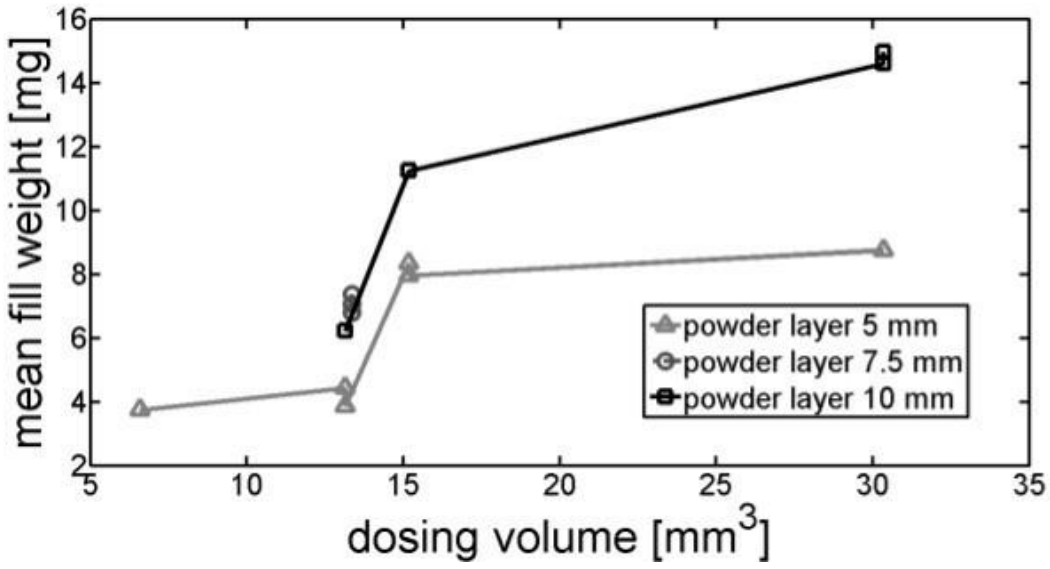

Fig. 10: Powder group II - no volumetric filling behavior is observed. The fill weight of group II powders is not linearly increasing with the volume.

The weight variability (RSD) is affected by the capsule filling speed, the dosator diameter, the powder layer depth and only the bulk density (Fig. 9). For all of these parameters, an inverse correlation was observed. The smaller these parameters are the higher is the RSD of the fill weight. In contrast to group I the RSD of the powders of group II show a filling speed dependence. Therefore, the RSD can not be correlated with the dosing volume as shown in Fig. 8, where the RSD values have been averaged over filling speed. Nevertheless, it is again to see (Table 6) that lower fill weight lead to higher values of the RSD. Regarding the effect of material attributes, we did not observe (as hypothesized) a significant correlation between any of the flow indices and fill weight variability. RSD values were generally high for this powder family (as this machine does not make any corrective actions during the filling operation) although several tools were used to homogenize the powder bed. Despite these tools, it was clear from visual inspection that the powder bed does not reach a final homogeneity and that advanced analytical techniques should be required to monitor its density and density distributions. Enhancing powder flowability (i.e., by adding glidants), in addition to inducing flow in the bowl via mechanical methods, may provide additional benefits, and therefore, minimize fill weight variability. The effect of dusting and powder adhesion was also visually evident. When filling capsules at low speed a lot of powder, especially for the low-density and sticky powders, adhered to the outer dosator wall. This powder was occasionally transferred into empty capsule bodies while dosing, thereby causing higher fill weight variations.

3.4. Conclusions

In order to manufacture solid dosage capsule products with a low fill weight (1- 45 mg), the nozzles of the capsule filling machine must have diameters that are much smaller than those used for standard capsules products. This paper is the first work studying the performance of low-dose nozzles for a group of powders with a broad range of material attributes. Special focus was on assessing material attributes that are known to affect the fill weight and weight variability of standard capsule products.

A screening (DOE) was used to select the most CMAs and CPPs. Powders were divided into two groups depending on their properties. For these two groups different sets of critical process parameters were required to perform capsule filling. Thus, two DOEs were performed. The results of our study can be summarized as follows:

First, we established the critical process parameters and material attributes for each powder group to perform successful powder filling. The fill weight of both powder groups was affected by the same process parameters but by different material attributes. While the first group of powders (bigger particles and higher densities) exhibited volumetric filling behavior, the second group (smaller particles and lower density) did not. For the latter the wall friction angle and the basic flowability energy were determined as additional critical material attributes.

The RSD for both groups was affected by the powder density as material attribute but the significant process parameters differ. While for powder group I dosator diameter and powder layer depth influenced the capsule filling performance, powder group II was also affected by the capsule filling speed.

The manufacturing of the powders has an effect on low dose dosator capsule filling performance. Sieved and spray dried powders show a better behavior during filling than the milled and micronized ones. The spheronized powder showed the worst results.

Depending on the process parameters and the material attributes, every desired fill weight in the classical low-dose range could be obtained. From a regulatory perspective, the RSD of group I powders was in most cases below the required threshold. For group II powders this was, however more challenging to achieve without the use of a process control system. Thus, for very fine powders low-dose filling with a dosator system is highly challenging and a process control would be required to achieve product specification compliance.

In future, the knowledge gained from the current experiments will be used to create a design space and a predictive process model as a function of process parameters and material attributes for low fill weight products.

Nomenclature

API Active pharmaceutical ingredient

AIF Angle of internal friction

BD Bulk density

BFE Basic flowability energy

C Cohesion

CI Carr's compressibility index

CMA Critical material attribute

CPH Capsules per hour (filling speed)

CPL Compressibility

CPP Critical process parameter

CQA Critical quality attribute (capsule fill weight and weight variability)

DOE Design of experiments

DPI Dry powder inhaler

FDA Food and drug administration

FFC Flow function

ICH International conference on harmonization

MgSt Magnesium stearate

MVDA Multivariate data analysis

PD Pressure drop (indicates air permeability)

PLS Partial least squares

QBD Quality by design

RSD Relative standard deviation (weight variability)

TD Tapped density

VMD Volumetric mean diameter

WFA Wall friction angle

Acknowledgments

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„I was taught that the way of progress
was neither swift nor easy.“

Marie Curie

4. Development of a design space and predictive statistical model for the capsule filling of low-fill weight inhalation products

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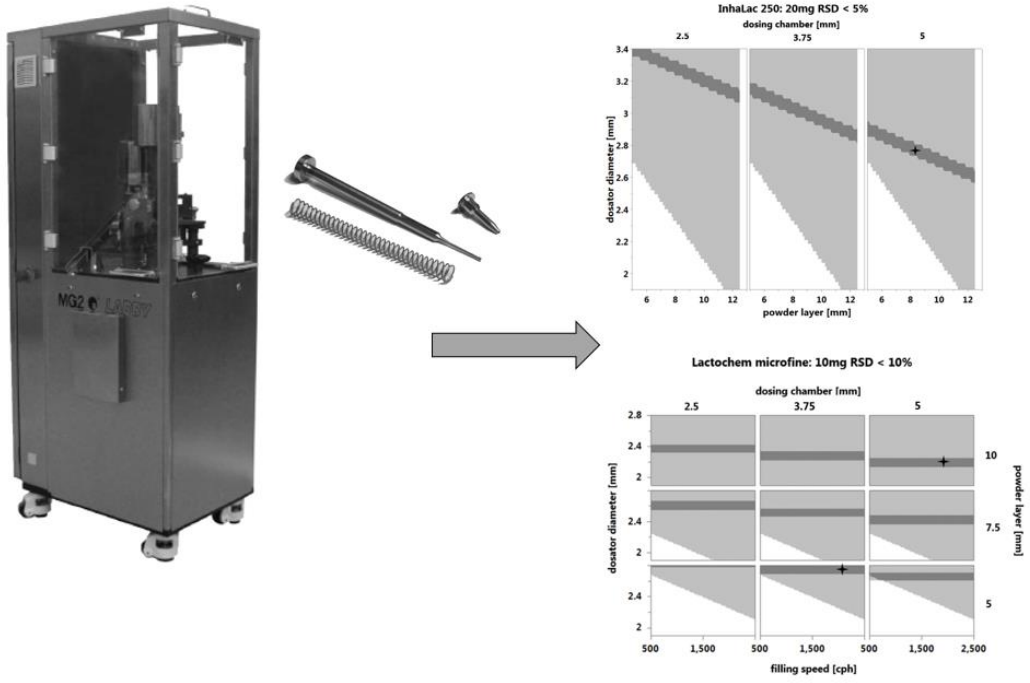
Graphical abstract



Keywords: dosator nozzle capsule filling, low-dose inhalation products, predictive statistical process model, multivariate data analysis, operating space, design space

Development of a design space and predictive statistical model for the capsule filling for low-fill weight inhalation products

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Abstract

The objectives of this study were to develop a predictive statistical model for low-fill-weight capsule filling of inhalation products with dosator nozzles via the quality by design (QbD) approach and, based on that, to create refined models that include quadratic terms for significant parameters. Various controllable process parameters and uncontrolled material attributes of 12 powders were initially screened using a linear model with partial least squares (PLS) regression to determine their effect on the critical quality attributes (CQA) (fill weight and weight variability). After identifying critical material attributes (CMAs) and critical process parameters (CPPs) that influenced the CQA, model refinement was performed to study if interactions or quadratic terms influence the model. Based on the assessment of the effects of the CPPs and CMAs on fill weight and weight variability for low-fill-weight inhalation products, we developed an excellent linear predictive model for fill weight (R^2= 0.96, Q^2= 0.96 for powders with good flow properties and R^2 = 0.94 , Q^2 = 0.93 for cohesive powders) and a model that provides a good approximation of the fill weight variability for each powder group. We validated the model, established a design space for the performance of different types of inhalation grade lactose on low-fill weight capsule filling and successfully used the CMAs and CPPs to predict fill weight of powders that were not included in the development set.

Keywords: dosator nozzle capsule filling, low-dose inhalation products, predictive statistical process model, multivariate data analysis, operating space, design space

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4.1. Introduction

Capsule filling of low fill weight formulations is a common unit operation that can be challenging, especially with regard to formulations involving difficult-to-handle active pharmaceutical ingredients (APIs) and/or excipient powders. This requires a thorough understanding of material attributes, process parameters and their interactions. Complex interactions between processes and material properties, and the limited amount of API in the early development phase, necessitate a well-designed experimental plan for minimizing the number of experiments, which is a key aspect of quality by design (QbD) [1–3]. Designed experiments in combination with multivariate data analysis techniques have been recommended for several research areas and are increasingly implemented in the pharmaceutical industry [4–7].

QbD is a nowadays a well-established tool for formulation and process optimization [2,8–11]. It defines potential critical quality attributes (CQAs) of the finished product specified in the quality target product profile (QTPP) that relate to safety and efficacy [2]. In addition, the successful development of low-fill-weight inhalation products requires a sound understanding of the interaction of critical material attributes (CMAs) of the API and excipients and the critical process parameters (CPPs) and their combined impact on the quality of the product [12–14]. For inhalation products, this is mainly fill weight and weight variability. At the same time, consistent dose delivery that is independent of the patient's inspiratory force needs to be ensured [15,16]. Thus, the first steps in the QbD-process are to establish the CQA (capsule fill weight and weight variability, i.e., RSD) and to link them to formulation and process factors.

To that end, a screening design of experiment (DoE) that relates CPPs and CMAs to the CQA of the inhalation products was developed. A D-optimal G-efficiency design was chosen and partial least square (PLS) regression was used to evaluate the model. In a subsequent step, a linear model that correlates CMAs and CPPs with the CQAs was created. Subsequently, the models were refined to include quadratic terms representing two-factor interactions, for which additional experiments were required. This sequential approach, which is used in several areas of pharmaceutical development [17–21] enabled us, first, to identify the main factors that influence the quality of capsules filled with an inhalation product and, second, to minimize the experiments used for developing a predictive model.

In the Q11 Guidelines, the International Conference on Harmonization (ICH) defined the design space 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." Design space can be developed based on prior knowledge, first principles and/or empirical understanding and regarded as a subset of the characterized space, sometimes termed knowledge space. When investigating new products, the developed models and design spaces can save time and material, i.e., costs, by predicting the CQA of a new product via a model that only includes CPPs and CMAs.

In this paper, we describe the development and refinement of a QbD-based model for capsule filling operations of low-fill-weight inhalation products. We used this model and the associated design space to predict the capsule filling performance of powders that were not part of the development set. Thus, the design space predicts the conditions under which low-dose capsule filling for various inhalation grade powders yields products of acceptable quality. These results can help to develop and manufacture low-dose inhalation products suitable for capsule filling of the desired quality.

4.2. Materials and Methods

4.2.1. Materials

Table 1 lists the various excipients, the API and the excipient blend used in the present work. Most of these materials were extensively characterized in our previous study [12]. Powders with appreciable flow properties were classified as group I possessing (volumetric mean diameter – VMD >10µm and a bulk density-BD> 0.45g/ml) and fine powders with poor flowability were classified as group II. The API in this study was a drug candidate from GSK. Two additional types of lactose were used to validate the models developed for each powder group. An overview of the investigated powders is provided below:

Table 1: Inhalation grade powders included, see also [12]

Name (Manufacturing characteristics/Batch no.)	Group	Supplier	VMD [µm]	Bulk density [g/cm³]	Tapped density [g/cm³]	WFA [°]	BFE [mJ]
Lactohale 100 (sieved/601157)	I	DFE Pharma, Germany	160.02	0.70	0.82	7.70	424.00
*Respitose SV010 (*coarse sieved/*10672704*)	I	DFE Pharma, Germany	129.82	0.72	0.87	8.42	643-67
InhaLac 230 (sieved/1244)	I	Meggle, Germany	111.71	0.74	0.89	9.25	746.33
Respitose SV003 (sieved/10680001)	I	DFE Pharma, Germany	73.99	0.69	0.83	8.36	1265.33
Lactose_GSK (blend)	I	GSK, UK	72.36	0.67	1.01	9.73	606.33
Respitose ML001 (milled/10648940)	I	DFE Pharma, Germany	71.17	0.66	1.05	12.57	510.67
Respitose ML006 (milled/10683656)	I	DFE Pharma, Germany	23.07	0.47	0.89	29.70	1171.33
Sorbolac 400 (milled/1022)	II	Meggle, Germany	8.71	0.40	0.76	30.20	1633.00
Lactohale 300 (micronized)	II	DFE Pharma, Germany	3.37	0.27	0.38	31.50	2393.33
API_GSK (micronized)	II	GSK, UK	3.28	0.19	0.29	35.67	2224.00
Mannitol (spray dried)	II	MG2, Italy	2.52	0.40	0.56	24.10	942.00
Spheronized Lactose (spheronized)	II	GSK, UK	1.68	0.15	0.25	11.20	910.67
Validation powders							
InhaLac 250 (sieved/129490)	I	Meggle, Germany	65.00	0.6	0.9	---	---
Lactochem microfine (micronized/601775)	II	DFE Pharma, Germany	6.0	0.34	---	33.9	529.00

4.2.2. Methods

4.2.2.1. Linear Model Development and Interpretation

In our previous study [12], a linear model for capsule filling of low-fill-weight inhalation products was developed for two groups of powders. The capsule filling machine used in our present work (MG2 Labby) has no process control capacity, i.e., no corrective actions with regard to process parameters were taken when the quality of the product was off target [22,23]. The linear models were a D-optimal models with the highest G-efficiency and included three replicates to assess reproducibility (Rep.). Each of these screening DoEs (see Appendix) included 13 measured material attributes (uncontrolled variables such as particle size, density, permeability, compressibility, friction- and flow behaviour) and 4 process parameters (controlled variables) of the capsule filling machine: the filling speed (500,

1500 and 2500 capsules per hour), the dosator diameter (1.9 mm, 2.2 mm, 2.8mm and 3.4 mm), the powder layer depth (5mm, 10mm and 12.5 mm) and the dosing chamber length (2.5mm, 3.75 mm and 5 mm)[12].

Based on our experience, the constraints for process variables were set as follows: the ratio between the dosing chamber length and the powder bed depth (pre-compression ratio) was between 1:2 and 1:5 for the first group and between 1:1 and 1:4 for the second one. This resulted in a DoE with 14 experimental runs (Table 5 in the Appendix) for powder group I (free-flowing powders) and a DoE with 15 runs (Table 7 in the Appendix) for powder group II (cohesive powders). All capsule-filling experiments were carried out under identical controlled operational, temperature and humidity conditions. Multivariate data analysis (MVDA) of the entire data set was performed, identifying the CMAs and CPPs that correlated with the nominated responses (i.e., capsule fill weight and weight variability). Furthermore, a linear predictive model for each powder group was developed using Partial Least Square (PLS) [24]. The quality of the models was evaluated by mean of (1) R^2, (2) Q^2, (3) validity and (4) reproducibility. Qualitative models are obtained if R^2 is above 0.8 and Q^2 is above 0.5 [25]. The following model specifications were defined in Eriksson et al. (2006) [26]: R^2 indicates the model fit, i.e., how well the response (weight and weight variability) of the training (calibration) set is mathematically reproducible. Q^2 is the prediction ability of the model, which measures how accurately the model can predict the data that were not previously used in the model training.

Model validity deals with the outliers, the correctness and transformation problems. Although a value of less than 0.25 indicates statistically significant differences between model and experimental data, some very good models ($Q^2 > 0.9$) may have low model validity if the Rep. is very high (close to 1.0) or even negative if the Rep. is 1.0. The Rep. of a response is close to 1.0, if the observed variability of replicate experiments is low, compared to the total variation of the response. A high Rep. is desireable, because the process is well controlled. A Rep. value greater than 0.5 is a minimum requirement. Therefore, if the Rep. is nearly 1.0, the differences between model and experimental data are attributed to model errors only, resulting in low validity of the model. Thus, a model with a low validity but very high Rep. can have a good predictive power.

4.2.2.2. Model Refinement

Model refinement was performed to obtain models that fit the data more accurately and offer better predictability of the CQAs of powders outside of the development set, especially the fill weight variability (RSD). Model refinement required a more extensive knowledge of CMAs and CPPs and, to that end, additional experiments. The response surface methodology (RSM) was used to develop a quadratic model capable of identifying the effect of all possible interactions and quadratic terms [27–31]. An optimization DoE was developed within the space of the screening DoE that produced the

most promising results [32]. To cover the entire range within the low- and high-factor levels of the initial experimental setup, we used a central composite face-centered (CCF) design.
The model was analyzed via PLS. Since according to the screening study the speed did not affect the quality of filled capsules for powder group I, this parameter was excluded from the DoE for model refinement and all experiments were carried out at 2500 capsules per hour (cph) (a high capsule output). The CCF design for powder group I consisted of 18 combinations of process parameters (see Table 6 in the Appendix), including 3 replicate runs (center points). For powder group II, the DoE had 27 runs (see Table 8 in the Appendix) and included the parameter "speed". MODDE 10 software (Umetrics, Umea, Sweden) was applied to generate the set of runs for all DoEs. The new DoEs were done with 3 out of 7 powders in group I (Respitose SV010, ML001 and InhaLac 230) and 2 out of 5 powders in group II (Sorbolac 400 and Lactohale 300) with the most dissimilar material attributes, i.e. particle size, density, friction and flow behaviour (see Tab. 1). The resulting data were combined with the data of the screening DoE for all powders.

4.2.2.3. Model Validation

According to Eriksson et al. (2006), the most comprehensive way of model validation is the external validation, which consists of making predictions for an independent set of data that was not included in the model calibration [26]. To that end, we validated the model for each powder group using the powders that were not included in the calibration set: InhaLac 250 (Meggle, Germany) and Lactochem Microfine® (DFE Pharma, Germany) for the powder group models I and II, respectively. For the validation experiments, only powder CMAs were assessed in triplicate and used in combination with process parameters to obtain specific target fill weights. A prediction list for the experimental responses (fill weight and weight variability) with upper and lower limits for the 95% confidence interval (CI) was generated using MODDE 10 (Umetrics, Umea, Sweden). This confidence interval does not include the uncertainty of the process or the analytical methods used to determine the CQAs. Subsequently, the validations experiments, with new combinations of process settings were carried out.

4.2.2.4. Design Space and Use of the Model

Our ultimate goal was to establish a design space (operating range or operation knowledge space) for each powder group. The design space is a mathematical model, in which the correlations between input and output are known and the output is within specifications.

Design space is likely to be established in small scale batches using DoE and prior knowledge depending on equipment, design principle and batch size [33]. Control space is the upper and lower limits of the process settings and material attributes, within which the attribute and parameter are routinely controlled during the production in order to ensure reproducibility and high product quality. Control space should be established within design space, where the CMAs and CPPs can individually be varied with the goal of achieving high product quality [34]. This means that specific low-dose fill weights with desired RSD can accurately be predicted by setting the process conditions for the inhalation powders that fit our powder classification system.

4.3. Results and Discussion

4.3.1. Comparison between the Linear and Quadratic Models

For powder group I, the CPPs and CMAs with a statistically significant effect on fill weight (Fig. 1) and RSD (Fig. 2) are the same for the linear and quadratic models and have almost identical coefficients. No significant effect of process parameters interactions is observed. The CPPs influencing the fill weight are the dosator diameter, the dosing chamber length and the powder layer depth and tapped density (TD) influenced the CMAs (Fig. 1). More importantly, both models for fill weight have excellent data (R^2 = 0.96) and reproducibility (Rep. = 0.99) fitting. Weight variability coefficients include the dosator diameter and the powder layer depth as the CPPs and the bulk density (BD) as the CMAs (Fig. 2). The model with quadratic terms only provides a marginal advantage over the linear model in terms of R^2 and reproducibility (R^2 = 0.61 and Rep. = 0.87 for the linear model and R^2 = 0.66 and Rep. = 0.91 for the quadratic model). As such, we proceeded to validate the linear model using an independent powder. The effects of the CMAs and CPP on the CQAs are extensively discussed for both models in [12].

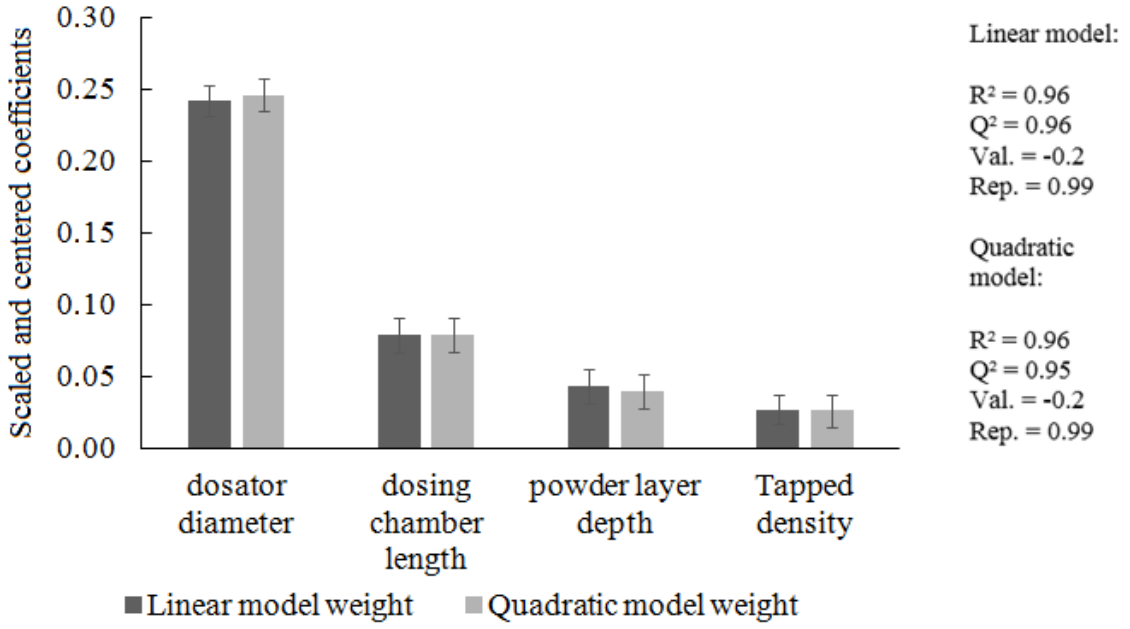

Figure 11: Linear and quadratic models for fill weight - group I

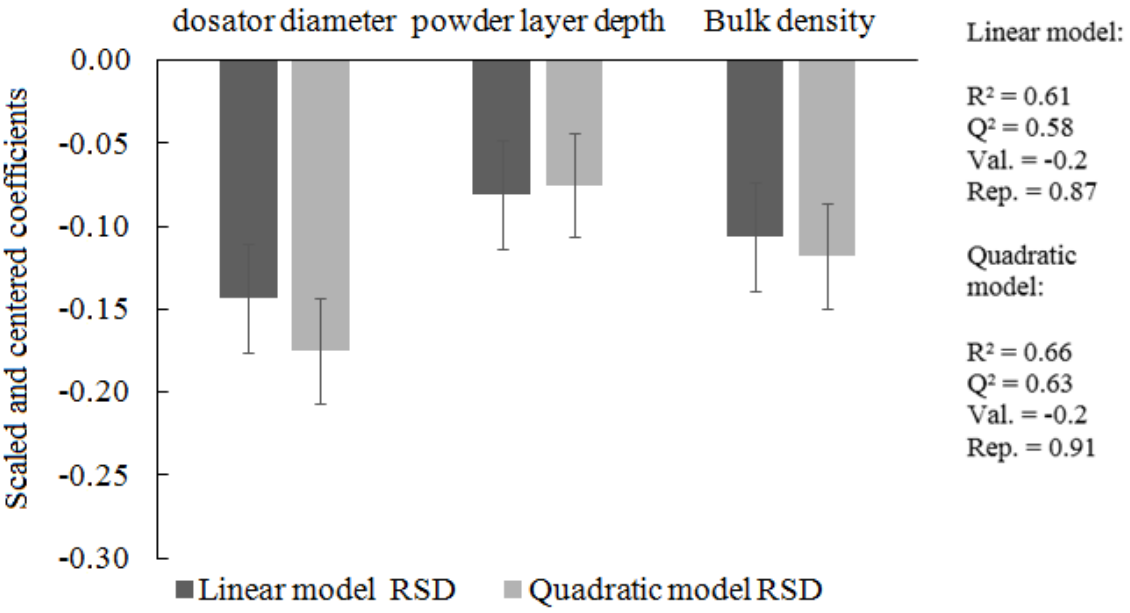

Figure 12: Linear and quadratic model for RSD - group I

For powder group II (see Figures 3 and 4), both models have the same CPPs and CMAs for fill weight but slightly different weighting coefficients. CMAs affecting the fill weight are the wall friction angle (WFA), basic flowability energy (BFE) and bulk density (BD). However, both models for fill weight are almost identical in terms of R2 and reproducibility (R2 = 0.94 and Rep. = 0.98 for the linear model and R2 = 0.93 and Rep. = 0.98 for the

quadratic model). With regard to weight variability (RSD), the filling speed proves to be a significant coefficient. The dosator diameter and the powder layer height as the CCPs and bulk density as the CMA are statistically significant. For this powder group, the model with quadratic terms performed slightly worse than the linear model in terms of R2 and reproducibility (R2 = 0.65 and Rep. = 0.83 for the linear model and R2 = 0.55 and Rep. = 0.84 for the quadratic model). Therefore, the initial linear model was chosen for further investigations.

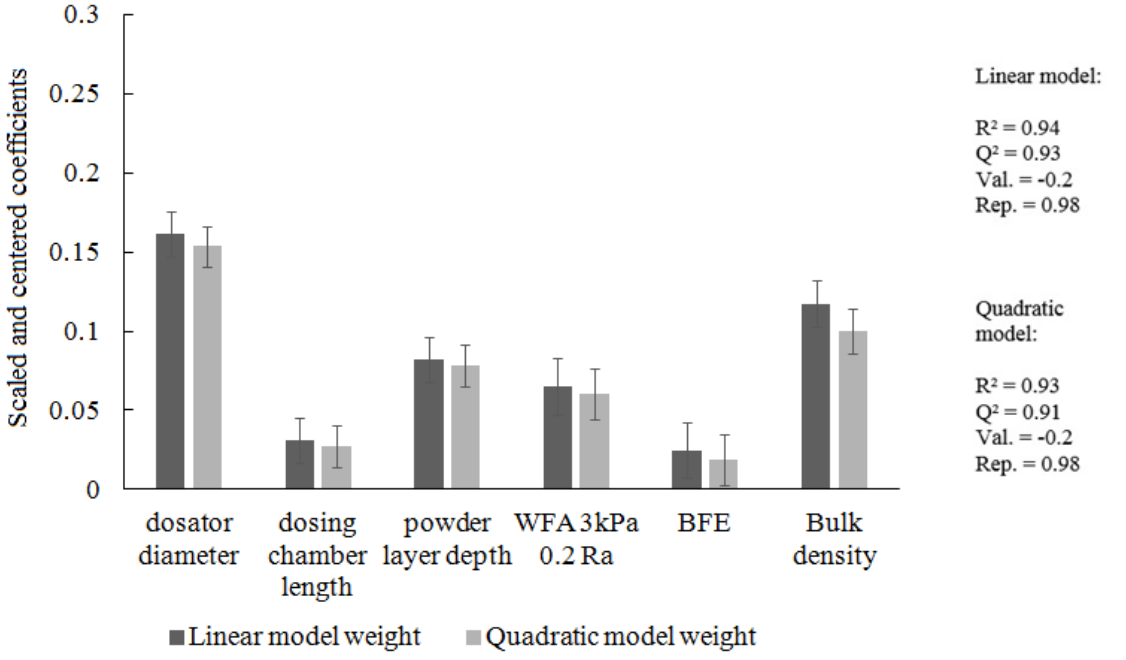

Figure 13: Linear and quadratic model for fill weight - group II

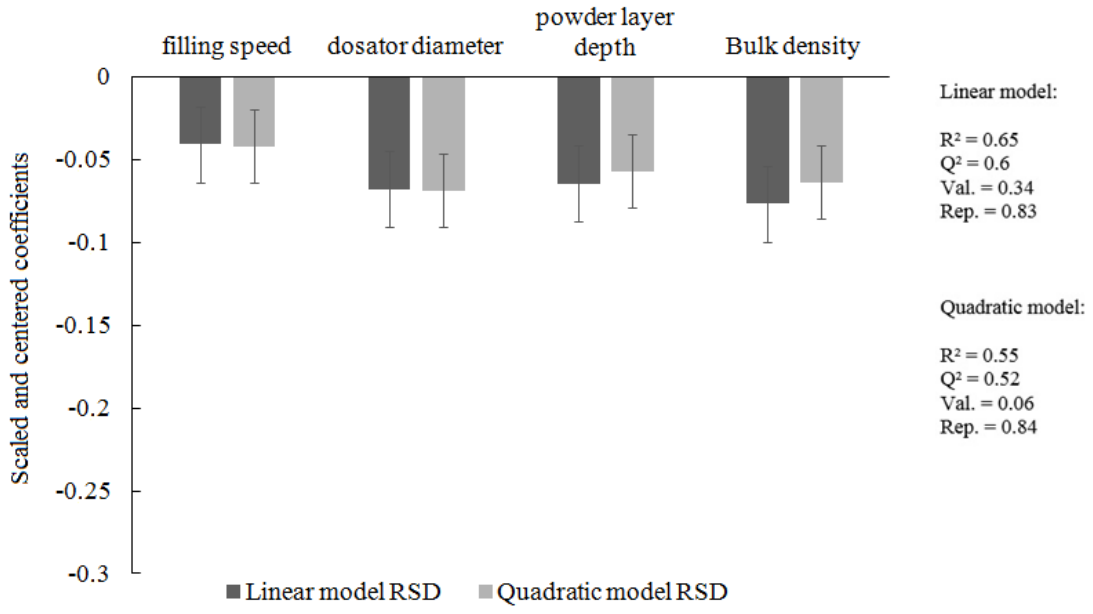

Figure 14: Linear and quadratic model for RSD - group II

4.3.2. Model Validation

We tested the performance of the model for group I using the target fill weights between 5mg and 30mg. The validation was performed using InhaLac 250. First, the CMAs which have an effect on the fill weight and RSD of group I powders, i.e., BD and TD, were determined. InhaLac 250 has a BD of 0.6 g/ml and TD of 0.9g/ml. Table 2 shows the combinations of CPPs for achieving the target fill weight, the values predicted by the linear model and the results of the actual filling experiments with this validation powder. Runs 3 and 6 were combinations of process parameters within the knowledge space that were not part of the DoE for development for the linear model. All capsules were filled at a speed of 2500cph. Except for run 5 the fill-weights of all combinations of process settings fall were within a 95% confidence interval (CI). The RSD values predicted by the model were on average 1.8 % higher than those obtained experimentally. One reason could be that the screening and optimization experiments of each powder were carried out over a range of several days, whereas the validation experiments were completed within 1 day. The RH was always below 50% during validation experiments.

Table 2: Model validation - group I

	Filling speed (cph)	*Dosator diameter (mm)*	*Dosing chamber length (mm)*	*Powder layer depth (mm)*	*Predicted weight (mg)*	*95% Limit (mg)*	*Experimental weight (mg)*	*Predicted weight variability (%)*	*95% Limit (%)*	*Experimental weight variability (%)*
Run 1	2500	1.9	2.5	10	6.7	6.4 – 7.1	6.6	5.6	4.8 – 6.4	2.8
Run 2	2500	1.9	5.0	10	10.2	9.7 – 10.7	10.6	5.6	4.8 – 6.4	2.5
Run 3	2500	2.8	3.75	5.0	14.9	14.2 – 15.7	14.4	4.9	4.2 – 5.6	2.7
Run 4	2500	3.4	2.5	5.0	20.0	19.0 – 21.0	20.0	3.6	3.0 – 4.3	2.9
Run 5	2500	3.4	2.5	12.5	25.6	24.2 – 27.0	23.4	2.3	2.0 – 2.6	1.8
Run 6	2500	3.4	3.75	10	29.0	28.0 – 30.0	29.8	2.7	2.3 – 3.0	1.3

For powder group II, Lactochem Microfine® was selected as a validation material, and its CMAs were determined, i.e., WFA (33.9 °), BFE (529 mJ) and BD (0.34 g/ml). The target fill weights for powder group II were set between 5 and 15 mg. The powders in group II were less dense and the fill weights were generally lower than in group I. In Table 3, runs 3 and 5 were combinations of process parameters that were not included in the DoE for the

development of the model. The model predicted the fill weight for all the conditions within the 95% CI. As all powders in group II, this validation powder did not follow volumetric filling. The model predicted higher RSD values than those experimentally obtained. However, the predictions for the RSD were very close to the experimentally obtained values with a mean deviation under 2%, especially when considering the low fill-weight.

Table 3: Model validation - group II

	Dosator diameter (mm)	*Dosing chamber length (mm)*	*Powder layer depth (mm)*	*Predicted weight (mg)*	*95% Limit (mg)*	*Experi-mental weight (mg)*	*Predicted weight variability (%)*	*95% Limit (%)*	*Experi-mental weight variability (%)*
Run 1	1.9	2.5	7.5	5.3	4.9 – 5.7	5.5	9.2	8.3 – 10.0	7.6
Run 2	2.2	3.75	7.5	7.5	7.0 – 8.0	7.0	8.2	7.6 – 8.8	5.6
Run 3	2.2	5.0	10	10.1	9.2 – 10.9	9.4	6.9	6.3 – 7.6	5.3
Run 4	2.8	2.5	5	9.7	8.8 –10.6	10.3	7.7	6.8 – 8.6	5.8
Run 5	2.8	5.0	8.5	15.3	14.0 – 16.4	16.4	6.1	5.5 – 6.7	7.6

In general, the fill weight predictions were more accurate for the lower fill weights in both powder groups and the overall predictability of the model was acceptable (maximum deviation under 5%). Although the linear model accurately predicted the fill weight (CI = 95%) of a powder that was not in the development set, RSD predictability was not within the 95% CI. At present. We do not have an explanation why a higher accuracy at low fill weight is obtained. We are currently working to understand these effects.

4.3.3. Creating the Process Window – Working Within the Design Space

Based on the above an operation knowledge space was created, representing the entire range of the CMAs and CPPs and their effects on the selected CQAs. The acceptable ranges were based on multivariate experimentation that took into account both the main effects and the interactions of input variables [35,36]. Table 4 shows the ranges for process parameters, material attributes and quality attributes for both powder groups, which constituted the border of the design space.

Table 4: Design space – operation knowledge space

	Design space group I (VMD > 10 µm)	**Design space group II (VMD < 10 µm)**
CPP		
Filling speed (cph)	**---**	**500 – 2500**
Dosator diameter (mm)	**1.9 – 3.4**	**1.9 – 2.8**
Dosing chamber length (mm)	**2.5 – 5.0**	**2.5 – 5.0**
Powder layer depth (mm)	**5.0 – 12.5**	**5.0 – 10**
CMA		
BD (g/ml)	**0.45 – 0.75**	**0.1 – 0.45**
TD (g/ml)	**0.8 – 1.05**	**---**
WFA (°)	**---**	**20 – 36**
BFE (mJ)	**---**	**400 – 1300**
CQA		
Fill weight [mg]	**5 - 50**	**4 - 20**
RSD [%]	**0 - 10**	**0 - 20**

Within this design space the selected CQA can be predicted for arbitrary process settings depending on the CMAs. However, first the new material has to be assigned to one of the groups according to the particle size and density. Powders with a particle size larger than 10 µm and a density of at least 0.45g/ml belong to group I. Other powders belong to group II. Based on the developed model, Figure 5 shows the sweet spot or the "process window" (indicated as dark grey area) for InhaLac 250 (group I powder) for an example target weight of 19.5– 20.5 mg and an RSD of less than 5%. This is a common fill-weight in capsules for dry powder inhalers (DPI) as used for example in the marketed product Cyclocaps® (PB Pharma GmbH, Germany), where 200µg Salbutamol are blended with lactose-monohydrate. Each capsule contains 20mg of the 1%-API blend. In the light grey area either target fill weight or target RSD were satisfied and in the white area none, respectively. The sweet spot is the superposition of several response contour plots, where the CQA criteria (i.e., fill weight and RSD in this case) are fulfilled.

The predicted process window was validated using a validation material, i.e., InhaLac 250. Here, the third process window in Fig. 5 (indicated by the black cross) was chosen, because this combination of CPPs never occurred in the screening, optimization or validation studies. InhaLac 250 was filled at 2500 cph, with a dosator diameter of 2.8mm, a dosing chamber of 5mm and a powder layer of 8 to 8.5mm. The results were a mean weight of 20.2mg with an RSD of 4.2%, which is in perfect agreement with the prediction of the model (20.16mg and 3.9% RSD). This indicates that InhaLac 250 can be successfully filled with the desired quality attributes in the narrow process window predicted by the model.

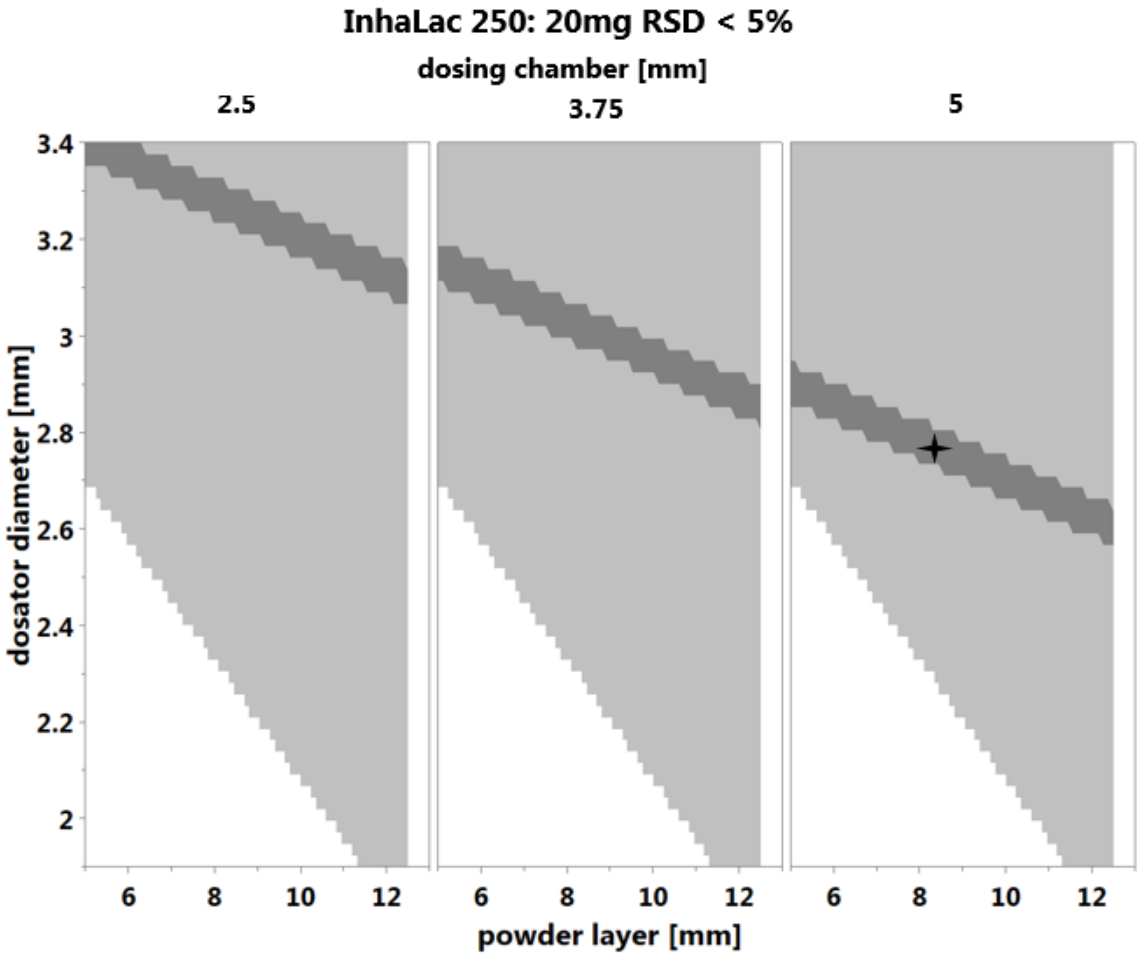

Figure 15: Process window for group I (InhaLac 250). In the light grey area either target fill weight, or target RSD and in the white area none of them are satisfied. The dark grey area represents the process window where target weight and RSD will be achieved.

Another example is given in Fig. 6, showing the process window for 15mg target weight and a RSD less than 5 %. A dosator diameter of 2.7mm a dosing chamber 3.75mm and a layer of 8.5mm would result in a fill weight of 15mg with a RSD of 4%.

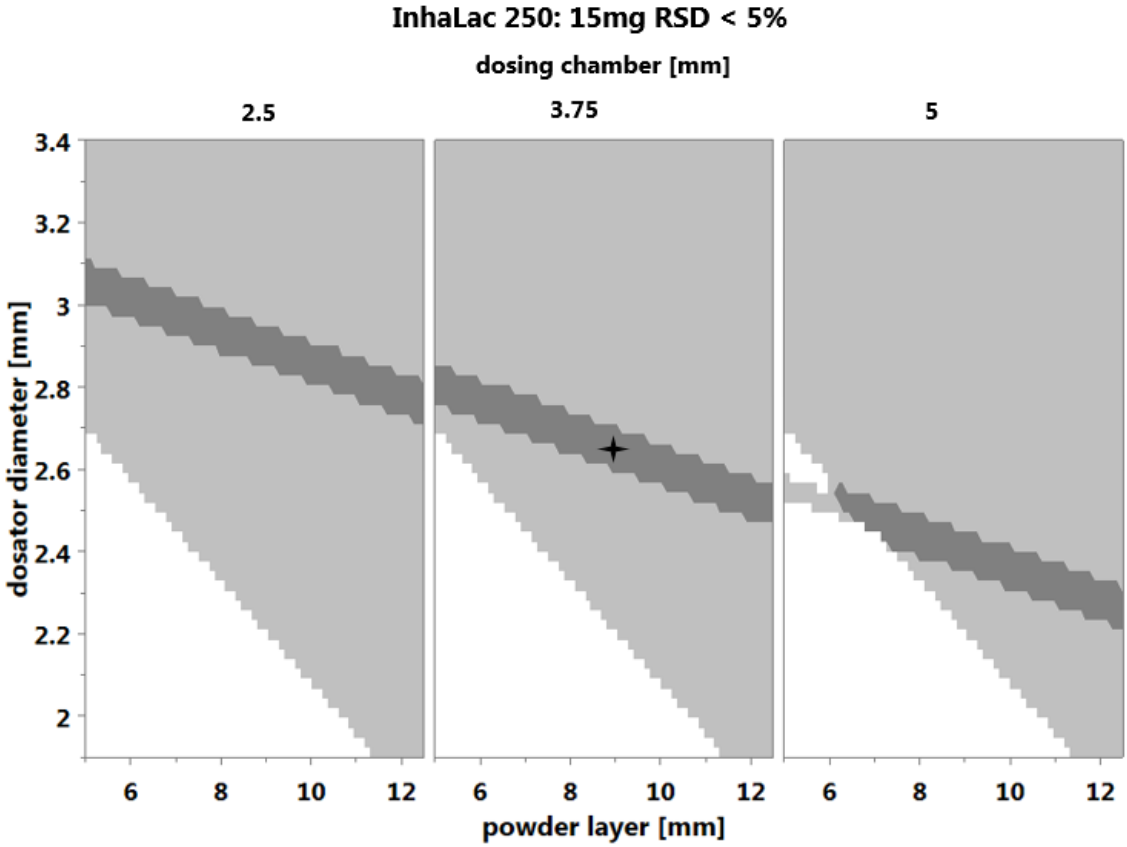

Figure 16: Process window for a target weight of 15mg and an RSD less than 5% for InhaLac 250 . In the light grey area, either target fill weight or target RSD, and in the white area none of them are satisfied. The dark grey area represents the process window where target weight and RSD will be achieved.

The CQAs were also predicted for Lactochem microfine® which represents powder group II. A target weight of 10mg with a weight variability (RSD) of less than 10 % was chosen and the values for WFA, BFE and BD were entered (Fig. 6).

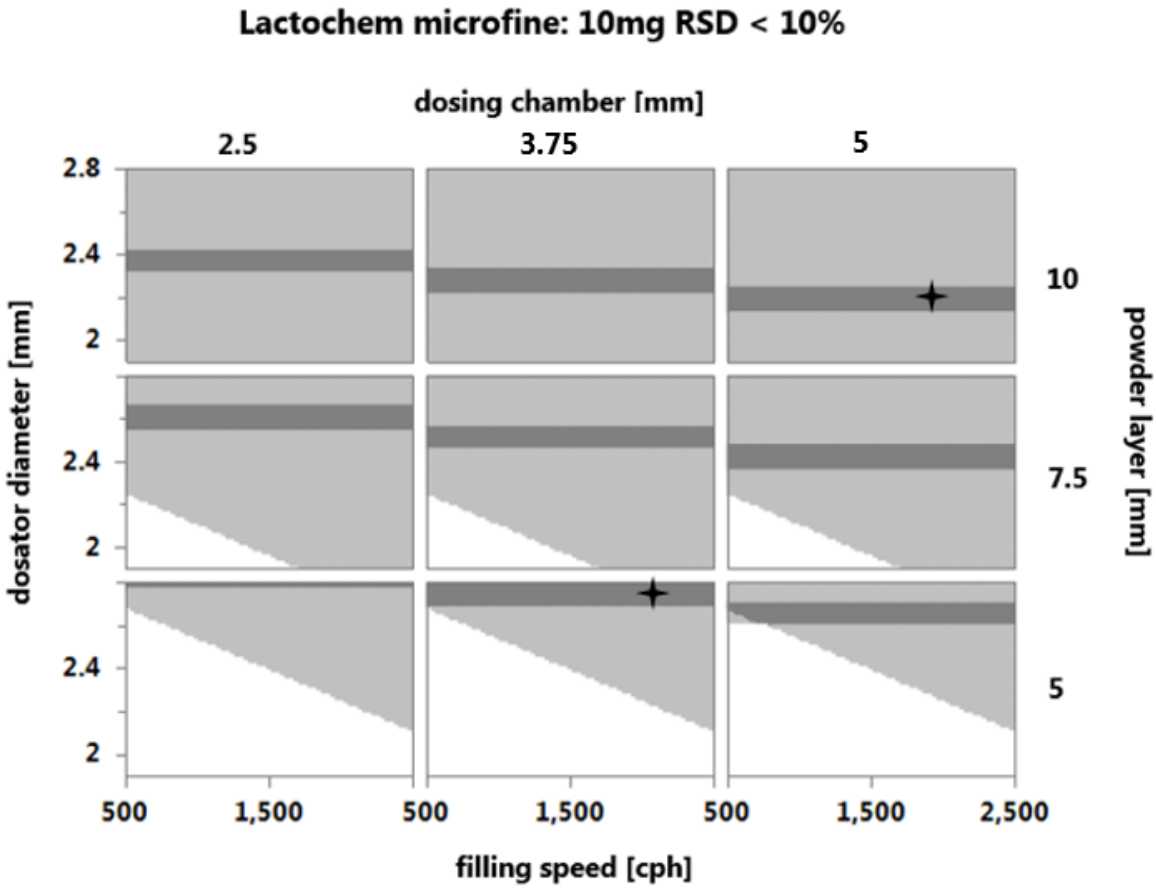

Figure 17: Process window for group II. In the light grey area either target fill weight or target RSD, and in the white area none of them are satisfied. The dark grey area represents the process window where target weight and RSD will be achieved.

For Lactochem microfine two process windows (black crosses in Fig. 6) with new combinations of CPPs were tested. A mean fill weight of 9.9mg with an RSD of 8.4% was achieved for capsules filled with a 2.2mm dosator, a 5mm dosing chamber a 10mm layer and a filling speed of 2000cph. Model predictions were 9.99mg and fill weight and 7.2% RSD. For the 2.8mm dosator with a 3.75mm chamber and a 5 mm layer a mean fill weight of 10.15 mg with and RSD of 4.1% was obtained experimentally. The model predicted for these settings and a filling speed of 2000cph a mean weight of 10.18mg and a RSD of 6.1%. Thus, both experiments resulted in CQAs in agreement with the predictions of the model. These results show that Lactochem microfine, a representative of group II powders can also be successfully filled with the desired quality attributes in the narrow process window predicted by the model.

4.4. Conclusions

In this study, a linear screening DoE was used to establish a design space and a predictive process model as a function of process parameters and material attributes for low-dose inhalation products. The performance of a refined quadratic model was not better than the linear one. A process window plot (sweet spot plot) in MODDE 10 was successfully used to determine which process settings are required for a specific powder to achieve a desired fill weight with a chosen RSD. Model validation via linear PLS proved that most of the predicted fill weights in the classical low-fill weight range could be obtained experimentally. Low-dose capsule filling was performed within the established design space. Powders with good flow properties (group I) and the cohesive powders (group II) behave completely different during processing. Thus, the operating ranges for the design space of the two groups, which predict the conditions under which low-dose capsule filling yields product of desired and acceptable quality, show major differences. Although the desired fill weight was accurately predicted for powders in both classes for the known CMAs and CPPs, the model's predictive performance was inadequate in terms of fill weight variability.

The developed model and the established design space could save time and material costs during the development of low fill-weight capsule filling for inhalation products. In future, the effect of the selected CMAs and CPPs of the inhalation-grade powders on aerosolization performance, fine particle fraction (FPF) and emitted dose (ED) will be investigated. Moreover, other relevant critical factors, such as surface properties and processing-induced pre-compression limits for a particular DPI, will be studied and related to the aerodynamic and *in vitro* inhalation performance. This will enable prediction of the *in vivo* fate of a product developed for particular processing conditions.

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Declarations of interest

The authors report no declarations of interest.

Appendices

Table 2: Linear D-optimal design group I [12]

					RESPITOSE ML006		RESPITOSE ML001		LACTOSE GSK		RESPITOSE SV003		INHALAC 230		RESPITOSE SV010		LACTOHALE 100	
run order	filling speed [cph]	dosator diameter [mm]	dosing chamber length [mm]	powder layer depth [mm]	fill weight [mg]	RSD [%]	fill weight [mg]	RSD [%]	fill weight [mg]	RSD [%]	fill weight [mg]	RSD [%]	fill weight [mg]	RSD [%]	fill weight [mg]	RSD [%]	fill weight [mg]	RSD [%]
1	2500	1.9	2.5	5.0	4.2	10.7	5.3	6.7	6.2	4.9	6.0	7.1	6.0	5.0	6.1	4.8	6.0	5.7
2	1500	2.8	3.75	10	14.8	10.4	23.8	2.7	23.1	1.8	19.1	1.8	19.0	2.4	20.0	1.9	19.0	2.1
3	2500	3.4	2.5	12.5	23.0	2.1	25.6	1.8	24.8	1.7	21.5	3.6	21.8	1.8	22.4	2.5	21.3	1.5
4	500	3.4	2.5	5.0	18.3	4.5	21.3	7.8	21.8	2.9	19.5	2.7	19.6	2.7	19.8	1.9	19.8	3.7
5	500	3.4	2.5	12.5	24.7	1.6	26.6	2.3	24.4	2.6	20.6	1.9	20.8	1.9	21.2	2.6	20.9	3.1
6	500	1.9	5.0	12.5	10.1	5.8	11.4	5.5	12.0	2.4	11.5	3.1	11.0	4.4	11.0	3.2	10.6	3.4
7	2500	1.9	2.5	12.5	6.9	5.0	7.3	5.3	7.6	3.4	6.7	6.8	6.4	4.9	6.8	3.9	6.3	4.0
8	2500	3.4	5.0	12.5	35.9	4.4	45.7	2.0	43.7	0.6	37.1	1.1	39.0	1.1	38.7	1.3	37.3	1.1
9	2500	1.9	5.0	10	7.4	9.2	10.7	11.4	11.0	3.7	10.6	4.8	11.2	2.5	11.2	4.3	10.4	3.2
10	1500	2.8	3.75	10	14.9	9.4	23.1	2.1	22.8	1.2	19.2	2.8	19.9	1.7	19.9	1.8	19.0	2.1
11	1500	2.8	3.75	10	11.9	8.8	22.3	3.7	22.6	1.7	19.1	2.6	19.7	3.0	19.7	2.5	18.5	2.3
12	2500	3.4	2.5	5.0	14.1	5.0	19.6	7.2	20.4	2.3	19.8	3.4	20.6	2.9	21.0	2.0	19.9	1.8
13	500	1.9	2.5	5.0	4.8	5.7	6.4	4.8	6.1	5.5	6.3	6.8	5.9	4.7	6.1	4.5	5.7	4.8
14	500	3.4	5.0	10	33.6	3.8	43.4	3.4	42.8	1.5	36.3	1.4	37.5	1.5	37.4	1.6	35.6	1.6

Table 3: CCF design group I

					RESPITOSE SV010		INHALAC 230		RESPITOSE ML001	
run order	filling speed [cph]	dosator diameter [mm]	dosing chamber length [mm]	powder layer depth [mm]	fill weight [mg]	RSD [%]	fill weight [mg]	RSD [%]	fill weight [mg]	RSD [%]
1	2500	3.4	2.5	12.5	22.44	2.48	21.75	1.84	45.49	1.07
2	2500	3.4	5.0	12.5	38.72	1.26	38.97	1.12	45.65	1.95
3	2500	1.9	5.0	12.5	12.03	3.79	12.19	3.17	12.27	6.31
4	2500	3.4	4.0	8.0	34.13	1.14	33.48	0.93	34.52	5.36
5	2500	3.4	3.8	10.0	33.46	1.02	30.21	1.14	37.89	2.14
6	2500	1.9	2.5	5.0	6.11	4.80	6.04	5.04	5.25	6.73
7	2500	3.4	2.5	5.0	20.96	2.02	20.60	2.86	19.60	7.21
8	2500	2.8	2.5	7.5	14.19	2.51	13.98	2.51	17.08	3.63
9	2500	1.9	2.5	10.0	6.24	4.57	11.97	2.97	7.51	5.06
10	2500	1.9	2.5	12.5	6.82	3.93	6.36	4.87	7.28	5.30
11	2500	1.9	5.0	10.0	11.21	4.25	11.19	2.50	10.68	11.44
12	2500	3.4	3.8	10.0	33.59	1.00	30.13	1.89	38.08	1.70
13	2500	3.4	2.5	10.0	21.26	1.74	21.46	1.85	26.09	1.52
14	2500	1.9	3.0	6.5	7.49	4.64	7.60	4.65	7.16	7.06
15	2500	3.4	3.8	10.0	33.40	0.89	30.31	1.21	37.72	2.69
16	2500	2.8	3.0	12.5	18.33	1.48	19.06	1.65	21.30	1.66
17	2500	2.8	5.0	10.0	27.87	1.28	27.63	1.29	23.76	6.18
18	2500	1.9	4.0	12.5	10.13	4.15	10.04	4.01	10.79	4.88

Table 4: Linear D-optimal design group II [12]

					SPHERONIZED LACTOSE		MANNITOL MG2		API GSK		LACTOHALE 300		SORBOLAC 400	
run order	filling speed [cph]	dosator diameter [mm]	dosing chamber length [mm]	powder layer depth [mm]	fill weight [mg]	RSD [%]	fill weight [mg]	RSD [%]	fill weight [mg]	RSD [%]	fill weight [mg]	RSD [%]	fill weight [mg]	RSD [%]
1	500	2.8	2.5	5.0	4.5	12.8	11.2	4.3	6.7	15.9	7.1	13.4	10.3	15.4
2	500	1.9	2.5	10	n.a.	n.a.	5.8	7.1	5.0	13.5	5.9	11.8	5.6	7.1
3	500	2.8	5.0	10	7.3	7.6	21.1	5.6	13.4	9.9	14.6	8.6	18.4	7.7
4	500	1.9	5.0	5.0	1.7	19.5	4.9	12.0	4.0	12.4	4.1	14.4	4.6	12.5
5	2500	2.8	5.0	10	7.2	6.5	18.6	4.7	13.0	10.1	15.3	7.4	18.9	5.9
6	2500	2.8	2.5	10	6.4	7.6	13.1	4.6	10.4	4.1	12.3	6.7	14.0	4.4
7	2500	1.9	5.0	5.0	1.8	17.8	5.1	8.9	4.2	11.9	5.6	11.5	5.5	8.2
8	2500	2.8	2.5	5.0	3.6	8.0	11.3	6.2	7.5	9.2	8.7	11.0	10.6	7.1
9	2500	1.9	5.0	10	2.7	10.2	8.0	9.7	5.5	7.0	7.1	8.6	7.8	9.4
10	1500	2.2	3.75	7.5	3.4	11.7	9.0	8.3	6.5	15.8	6.2	13.2	8.9	7.2
11	2500	2.8	5.0	5.0	3.4	15.4	12.7	5.7	6.1	8.4	10.3	8.7	11.3	5.8
12	1500	2.2	3.75	7.5	3.2	14.6	10.4	11.0	6.6	12.2	7.7	9.0	9.0	7.2
13	2500	1.9	2.5	5.0	1.5	16.7	4.1	13.9	3.2	11.7	5.3	16.5	4.6	9.0
14	1500	2.2	3.75	7.5	2.9	12.8	9.2	8.0	6.9	11.0	7.4	10.2	8.9	6.6
15	2500	1.9	2.5	10	n.a.	n.a.	6.0	9.8	3.8	9.4	5.2	8.3	6.1	5.5

Table 5: CCF design group II

					LACTOHALE 300		SORBOLAC 400	
run order	filling speed [cph]	dosator diameter [mm]	dosing chamber length [mm]	powder layer depth [mm]	fill weight [mg]	RSD [%]	fill weight [mg]	RSD [%]
1	500	1.9	2.5	5.0	4.03	10.09	3.74	13.79
2	500	2.8	2.5	5.0	7.10	13.43	10.29	15.42
3	1500	1.9	3.8	7.5	4.17	12.85	5.58	12.10
4	2500	2.2	3.8	7.5	6.77	7.62	8.81	5.36
5	500	2.2	3.8	7.5	6.91	9.65	7.80	9.19
6	1500	2.8	3.8	7.5	12.10	7.51	10.92	11.28
7	1500	2.2	3.8	7.5	6.17	13.15	8.85	7.23
8	500	1.9	5.0	10.0	6.02	12.64	6.76	14.44
9	500	2.8	2.5	10.0	12.11	7.23	13.79	3.50
10	2500	2.8	2.5	10.0	12.33	6.67	14.04	4.36
11	500	1.9	5.0	5.0	4.12	14.37	4.64	12.45
12	2500	2.8	2.5	5.0	8.70	11.03	10.60	7.06
13	500	1.9	2.5	10.0	5.87	11.80	5.55	7.12
14	2500	1.9	2.5	10.0	5.22	8.29	6.07	5.53
15	1500	2.2	3.8	5.0	5.28	9.71	5.26	7.92
16	1500	2.2	3.8	7.5	6.17	13.15	8.98	7.15
17	2500	2.8	5.0	5.0	10.29	8.68	11.33	5.84
18	2500	1.9	5.0	5.0	5.60	11.49	5.48	8.20
19	1500	2.2	5.0	7.5	7.67	13.22	6.20	11.98
20	2500	1.9	2.5	5.0	5.31	16.45	4.62	9.03

21	2500	2.8	5.0	10.0	15.32	7.37	18.88	5.92
22	1500	2.2	3.8	10.0	7.75	11.98	8.12	7.14
23	1500	2.2	2.5	7.5	6.20	7.64	5.82	11.83
24	500	2.8	5.0	10.0	14.60	8.60	18.40	7.72
25	1500	2.2	3.8	7.5	7.39	10.17	8.86	6.60
26	500	2.8	5.0	5.0	7.46	8.48	10.55	13.39
27	2500	1.9	5.0	10.0	7.05	8.57	7.75	9.43

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*„There are sadistic scientists who hurry
to hunt down errors instead of
establishing the truth.“*

Marie Curie

5. Accuracy of Micro Powder Dosing via a Vibratory Sieve-Chute System

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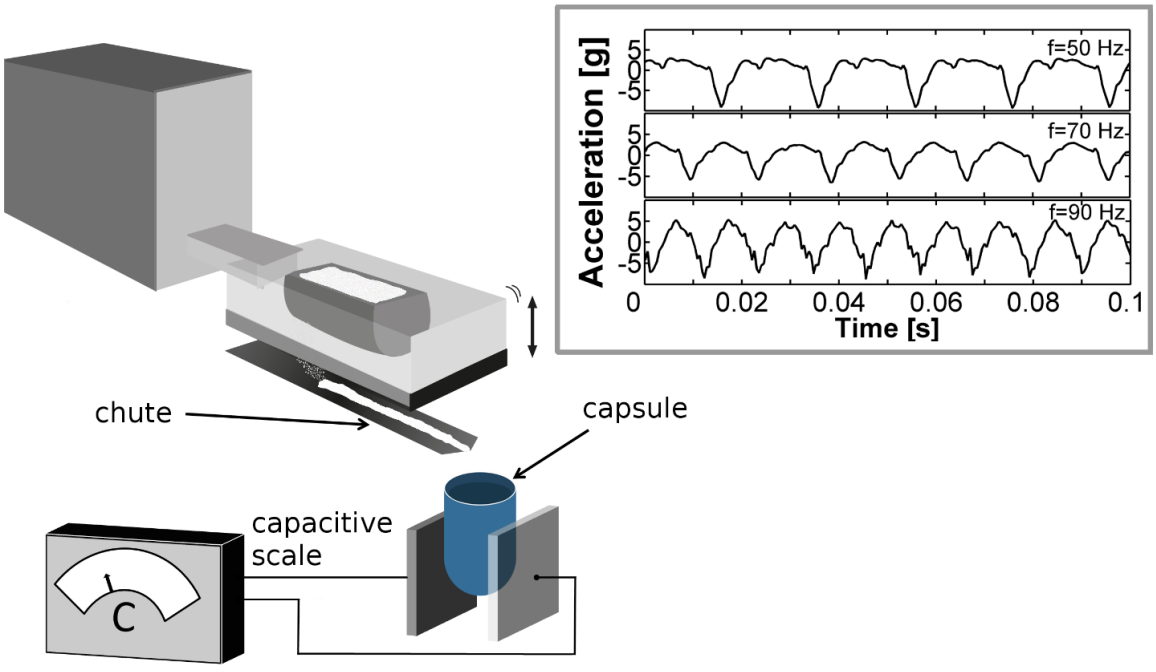
Graphical abstract:



Keywords: micro dosing, micro feeding, capsule filling, vibratory sieve, online scale, lactose

Accuracy of Micro Powder Dosing via a Vibratory Sieve Chute System

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Abstract

This paper describes a powder dosing system with a vibratory sieve mounted on a chute that doses particles into a capsule. Vertical vibration occurred with a broad range of frequencies and amplitudes. During dosing events, the fill weight was accurately recorded via a capacitance sensor, covering the capsules and making it possible to analyze filling characteristics, i.e., the fill rates and their robustness. The range of frequencies and amplitudes was screened for settings that facilitated reasonable (no blocking, no spilling) fill rates for three lactose powders. The filling characteristics were studied within this operating space. The results reveal similar operating spaces for all investigated powders. The fill rate robustness varied distinctly in the operating space, which is of prime importance for selecting the settings for continuous feeding applications. In addition, we present accurate dosing studies utilizing the knowledge about the filling characteristics of each powder.

Keywords: micro dosing; micro feeding; capsule filling; vibratory sieve; online scale; lactose

5.1. Introduction

Precise dosing of small powder quantities is required in many industrial operations and is a focus of intense research. In recent years, granular 3D printing (e.g., direct, selective or laser sintering [1],[2]) became state-of-the-art, introducing a multitude of applications ranging from rapid prototyping to tissue engineering [3]–[8]. The incorporation of functional gradients via multiple components requires low dosing of powders to accomplish high resolutions [9]. Hence, many recent developments in low dosing address free-forming methods (such as 3D printing).

In pharmaceutical development and manufacturing, precise powder filling remains a challenge [10], [11]. Regulatory requirements impose a high dose uniformity, especially when the therapeutic window is narrow [12], which is – for example - the case for dry powder inhalers (DPI) [13]–[15] that deliver small quantities of highly-potent active pharmaceutical ingredients (APIs). A current trend in oral solid dosage forms as well as in inhalation application is dosing small quantities of a pure API into a capsule, effectively avoiding fillers, binders, lubricants, flavoring agents, and the associated efforts and risks in formulation development. Furthermore, there is increasing interest in continuous processing, which demands robust low-dose feeders for APIs [16]–[18].

Most dosing techniques used in capsule filling [15][19] involve volumetric filling principles, such as dosator nozzles systems [20]–[23], vacuum or pneumatic dosators [24]–[26] and tamp fillers [27], [28]. All of them initially place powders into chambers of a fixed volume that define the final dosage. Since most volumetric techniques require powder beds, there is always some waste powder created [15]. Although volumetric dosing is generally faster, for precision dosing, other methods are preferred [5]. Nevertheless, low-dose filling (<10mg) with nozzle dosator systems [29] and drum dosing [30] have been studied recently.

For accurate low-(or micro-) dosing, gravimetric techniques are better suited. Micro-dosing via vibrating capillaries or rods [31]–[33] (also in the ultrasonic regime[34][35][9]) is a promising low-dosing and feeding technique, which is currently investigated for solid-dosing applications. For example, it was reported that highly accurate low dosing (relative standard deviation of fill weight below 5 %) can be performed via the “pepper-shaker” principle (MG2 Microdose, Capsugel Xcelodose®S or 3P Innovation Fill2weight) for capsule filling [36][37]. Furthermore, micro-feeding ($< 1\,mg/s$) has successfully been

performed via auger methods [38][39] and vibratory channels [40][41][9] and vibrating spatulas [42].

This study is an in-depth analysis of a gravimetric micro-dosing system for fine powders in the milligram range based on the "pepper-shaker" principle. Hard galantine capsules were filled directly via a sieve merged with a vibrating chute. The device (MG2 Microdose) was equipped with a capacitive scale, making it possible to analyze the effect of process settings on the filling characteristics. An operating space was created for three common excipients in inhalation products (i.e., lactose powders[43][44]) and the results were analyzed to establish the optimal settings for continuous micro-feeding. Furthermore, the limitations of the low-dose accuracy were addressed by performing dosing experiments with a target weight of 2.5 mg.

5.2. Material and Methods

5.2.1. Materials

Three grades of inhalation-grade α-lactose monohydrate (hereinafter referred to as lactose) excipients with different particle sizes and supplied by different manufacturers (DFE Pharma, Germany; Meggle, Germany) were used as received.

Respitose SV003 is a sieved carrier (for inhalation APIs) and SV010 is a coarse sieved carrier. Both have a narrow particle size distribution (PSD). InhaLac 230 (Meggle, Germany) is a sieved carrier with the lowest PSD of the investigated samples. The three carrier systems had similar values of bulk and tapped densities. An overview of the particle sizes and powder flow attributes of these materials is provided in Table 1 [29]. The listed values were obtained from the volumetric particle size distribution determined via laser diffraction (Helos, Sympatec, Germany). Powder samples were measured in the dry form after dispensing via compressed air (RODOS dispersion module). Bulk and tapped density were determined using Pharmatest PT-TD200. Besides Carr index (CI) the flow function (FFC) was determined as flow indicator with the FT4 Powder rheometer (Freeman Technology). All measurements were performed in triplicate. As can be seen Respitose SV010 had a slightly better flowability than the other powders. All three powders were in a range of "close to good" flowability, with CI<15 indicating good flowability and CI>25 indicating poor powder flow behavior. The ffc of the powders indicate good flowability in all cases, with Respitose SV003 having the best value.

Table 1: Powder properties of the three inhalation carriers [29]

Name (Manufacturing characteristics/Batch no.)	**Supplier**	**x_{10} [µm]**	**x_{50} [µm]**	**x_{90} [µm]**	**Span (x_{90}-x_{10}/x_{50})**	**BD [g/cm³]**	**TD [g/cm³]**	**CI [-]**	**FFC**
Respitose SV010 (coarse sieved/10672704)	DFE Pharma, Germany	80.83	127.64	181.45	0.79	0.72	0.87	16.8	7.7
InhaLac 230 (sieved/129490)	Meggle, Germany	78.36	112.3	141.23	0.56	0.74	0.89	17.3	7.9
Respitose SV003 (sieved/10680001)	DFE Pharma, Germany	49.59	73.37	98.63	0.67	0.67	0.83	17.3	8.1

5.2.2. Process and Equipment

5.2.2.1. Vibratory Sieve Chute System

We used the MG2 Microdose stand-alone unit, a dosing system with a vibratory sieve (oscillating vertically) mounted on top of a chute ($2.5\ cm$) to guide the powder into the capsule. Figure 1 shows the operating principle and parts of the set-up. The chute is tilted at a fixed angle of 5° and the sieve with 10 holes of 0.7mm in diameter is fixed on its top. The powder was discharged from the sieve into the chute and the capsule body using gravity. Every capsule was loaded manually.

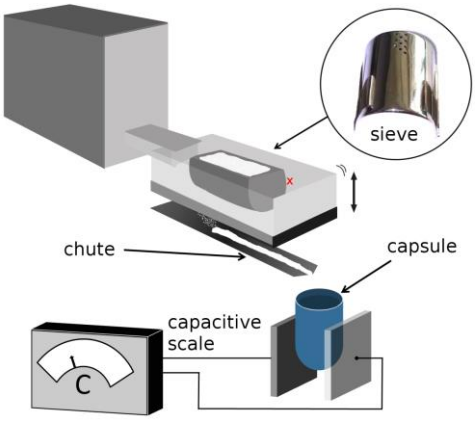

Figure 1: Principle of powder dosing via a vibratory sieve chute system. The inlet shows a photo of the sieve used, and the red x depicts the position of the acceleration probe.

The fill weight during the dosing events was recorded via a capacitance sensor, which had two parallel electrode plates encompassing the capsule body. The electrical field and the capacitance varied depending on of the powder quantity in the capsule. In order to correlate the capacity C_{filled} (relative to the capacity of an empty capsule C_{empty}) with the capsule fill weight fw, the sensor had to be calibrated (Equation 1). The calibration factor k_{cal} was determined based on the weight measurements performed on a SI-234A (Denver Instruments) scale. The calibration was executed for a given powder prior to the experimental studies. The accuracy of the capacitive scale was best ($< 0.1\,mg$ deviation from laboratory scale) if fw was in the range of the fill weight used for calibration. Hence the target fw was used to determine k_{cal}. If the fw deviated more than $2\,mg$ from the fill weight used to calibrate the capacitive scale, the deviation from laboratory scale were still $< 0.3\,mg$.

$fw = (C_{filled} - C_{empty})/k_{.cal}$	(1)

In addition to the target weight, the amplitude, the frequency and the acceptance range have to be set before dosing. Figure 2 illustrates the behavior of the vibratory system during a single dosing event. The amplitude setting does not refer to the actual displacement of the sieve-chute system but the driving force of the linear voice coil motor that is moving the system vertically. In the following this driving force will be quantified in entities E (see Figure 3 for sieve acceleration in dependence of E). The used Microdose system can be operated up to frequencies of 100 Hz and amplitudes of 100 E. The acceptance range signals the capacitive weight control when to stop dosing, avoiding a powder overshot. Thus, the vibrations are stopped after the fill weight exceeds the target weight minus the acceptance range.

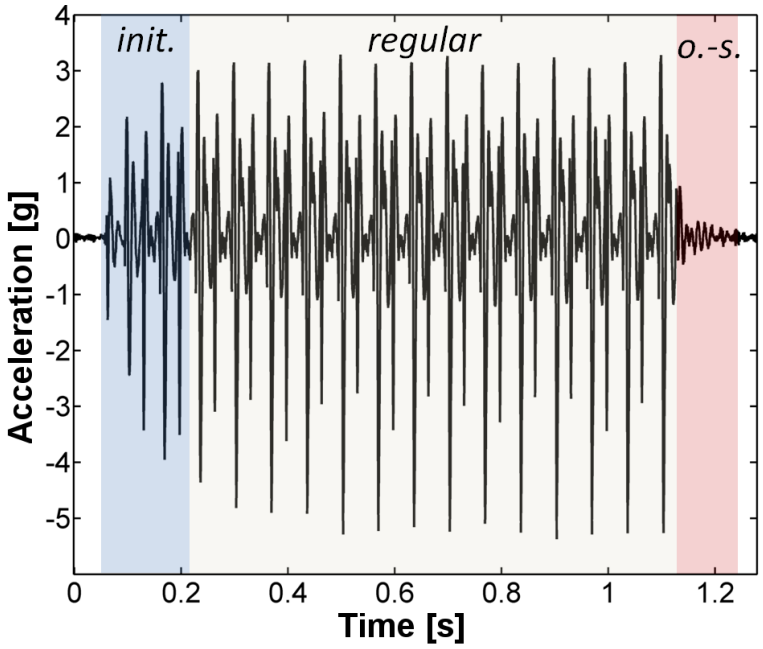

Figure 218: Acceleration during a **5 mg** capsule filling at a frequency of **15 Hz** and an amplitude of **75 E**. The highlighted zones denote the initial (onset of vibrating) and the regular and off-swing phases (after the motor that causes vibration was stopped).

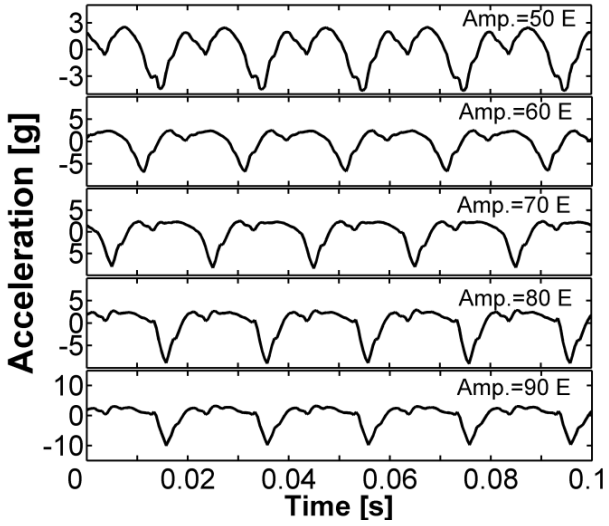

Figure 3: Acceleration profiles of the regular phase for varying amplitudes at a frequency of 50 Hz. The maximal acceleration values were $\mathbf{4.6}\ \boldsymbol{g}$ for Amp.= $\mathbf{50}\ \boldsymbol{E}$, $\mathbf{6.7}\ \boldsymbol{g}$ for Amp.= $\mathbf{60}\ \boldsymbol{E}$, $\mathbf{8.4}\ \boldsymbol{g}$ for Amp.= $\mathbf{70}\ \boldsymbol{E}$, $\mathbf{9.6}\ \boldsymbol{g}$ for Amp.= $\mathbf{80}\ \boldsymbol{E}$ and $\mathbf{10.0}\ \boldsymbol{g}$ for Amp.= **90** E.

Since the capacitive system records capsule fill weights 20 times per second, dosing is also possible using a (discrete) proportional-integral-derivative (PID) controller. The latter manipulates amplitude A for a subsequent time step t_{i+1} based on the difference ε between

the target and fill weights (Equations 2-3). Dosing with the aid of PID controller will be referred to as PID controlled dosing.

$\varepsilon(t_i) = fw_{target} - fw(t_i)$	(2)

$A(t_{i+1}) = K_P \cdot \varepsilon(t_i) + K_i \cdot \sum_{j=1}^{t_i} \varepsilon(t_j) + K_d \cdot \frac{\varepsilon(t_i) - \varepsilon(t_{i-1})}{\underbrace{\Delta t}_{=0.05\ \mathrm{s}}}$	(3)

5.2.2.2. Analysis of the Vibratory System

The vibration patterns of the dosing system were characterized using a dynamic accelerometer (Seika BDK 100), which contains a capacitive spring-mass accelerometer with integrated sensor electronics with a resolution $< \frac{1}{10}\ g$ and an output frequency of $2{,}000\ Hz$. Signal acquisition was performed using a NI-9234 high-accuracy analog input module, specifically designed for high-channel-count vibration applications and LabVIEW. The accelerometer was mounted beside the sieve, close to the edge of the vibrating arm (see red X in Figure 1). In addition, high-speed camera videos of the dosing procedure were recorded at 500 frames per second. The videos are accessible on the journal's website.

5.2.3. Powder Handling

The powders were stored at a relative humidity (R.H.) <55% and a room temperature <25°C. Prior to dosing studies, 90 % of the sieve's volume was filled with powder. This filling level was maintained throughout the studies to ensure identical conditions for every dosing event. If during experimentation the powder bed inside the sieve became inhomogeneous, a spoon was used to smooth its surface.

5.2.4. Operating Space Analysis

In order to determine the frequency and amplitude settings that yield constant and reproducible filling rates, the possible settings ($0 - 100\ Hz;\ 0 - 100\ E$) were screened for appropriate combinations. To that end, the filling characteristics were examined for ten frequencies and eight amplitudes, i.e., 80 combinations. Based on how steadily a powder

could be dosed from the sieve, which was reflected by the distribution of the powder in the chute, one of three attributes was assigned, as shown in Figure 4. These initial studies were performed to define an operating space, i.e., the range of applicable frequency and the amplitude settings, for each powder. The results are shown in Table 2.

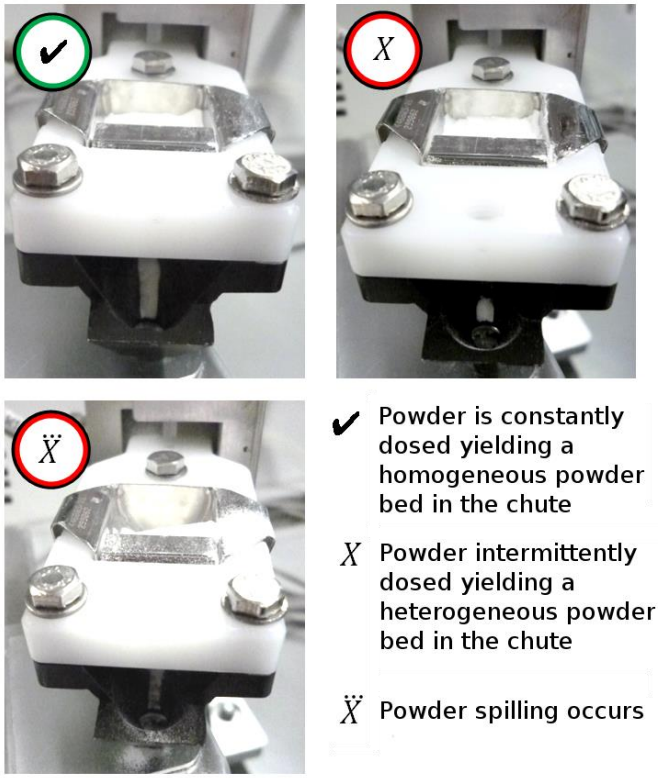

Figure 4: Characterization of powder filling process

Table 2: Initial studies to define the operating space (the symbols used are explained in Fig. 4)

Amplitude [E] → / **Frequency [Hz] ↓**	**30**	**40**	**50**	**60**	**70**	**80**	**90**	**100**
10	XXX	XXX	X✓X	✓✓X	✓✓✓	✓✓✓	✓✓✓	✓✓✓
20	XXX	XXX	X✓X	✓✓X	✓✓✓	✓✓✓	✓✓✓	✓✓✓
30	XXX	XXX	X✓X	X✓X	✓✓✓	✓✓✓	✓✓✓	✓✓✓
40	XXX	X✓✓	✓✓✓	✓✓✓	✓✓✓	ẌẌẌ	ẌẌẌ	ẌẌẌ
50	XXX	X✓✓	✓✓✓	✓✓✓	✓✓✓	✓✓✓	✓✓✓	ẌẌẌ
60	XXX	✓✓✓	✓✓✓	✓✓✓	✓✓✓	✓✓✓	✓✓✓	✓✓✓
70	XXX	X✓✓	✓✓✓	✓✓✓	✓✓✓	✓✓✓	✓✓✓	✓✓✓
80	XXX	X✓X	X✓X	X✓X	✓✓✓	✓✓✓	✓✓✓	✓✓✓

90	XXX	X✓X	X✓X	X✓X	✓✓✓	✓✓✓	✓✓✓	✓✓✓
100	XXX	X✓X	X✓X	X✓X	✓✓✓	✓✓✓	✓✓✓	✓✓✓
		Respitose SV003		**Respitose SV010**		**InhaLac 230**		

Further studies were performed for all feasible settings (check marks in Table 2), to characterize the filling properties. For each parameter setting, 35 capsules were filled with at least 5 mg while recording the capsule fill weight (fw). Examples of the filling profiles fw(t) are provided in Figure 5 for Respitose SV010.

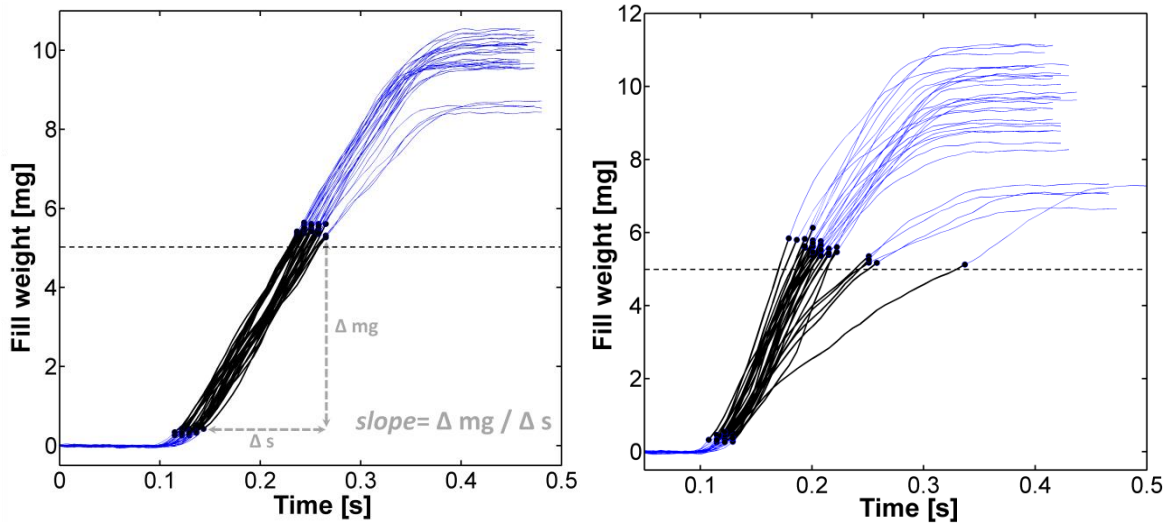

Figure 5: Capsule fill weight during dosing with Respitose SV010 at **(a)** an amplitude = 40 E and a frequency = 40 Hz (showing an example how the slope was determined) and **(b)** an amplitude = 40 E and a frequency= 70 Hz. The sections used to evaluate the slopes are marked black. The increase in fill weight after the motor inducing vibration was stopped (first time fill weight exceeded 5 mg; acceptance range= 0; fw recorded 20 times per second) is caused via filling during the off-swing phase (see Figure 2).

The filling rate was determined by averaging the slopes ($\Delta fw(t)/\Delta t$ $[mg/s]$) of 30 filling profiles (the first 5 fillings were excluded from the analysis). The slopes were evaluated between the first point in time at which the fill weight exceeded 0.25 mg and the first point in time after the vibration-causing engine was stopped (i.e., fw $> 5\ mg$). The higher the probabilities of an unsteady filling behavior (as shown in Figure 5 b) or fluctuations in the filling rate are, the higher is the standard deviation ([mg/s]) of the

evaluated slopes. Therefore, the latter can be used to characterize the robustness of the fill rate.

Since the settings in the operating space exhibited filling rates of $10 - 80\ mg/s$, accurate dosing of small powder quantities is difficult (see overdosing in Figure 5). Even for optimized settings of the acceptance range, accurate low-dosing ($< 10mg$) could not be achieved. Filling during the off-swing phase (see Figure 2) was already in the range of the target weights, causing systematic overdosing. Thus, five of the ten sieve holes were sealed to reduce the filling rate for the low dosing studies presented in Section 3.3.

5.3. Results and Discussion

5.3.1. Vibration Analysis

The acceleration of the vibrating arm was recorded. Since the accelerometer was positioned close to the sieve, the recorded accelerations reflect the vertical forces acting on the sieve with the powder. Oscillations shown in this section originate from the regular phase (Figure 2).

Figure shows acceleration profiles in various amplitude settings and at a fixed frequency during ≈ 5 oscillations. The results indicate that the vertical vibrations were not sinusoidal (sinusoidal displacements yield sinusoidal accelerations) and had the highest accelerations during the upward movement (negative acceleration causes upward motion). This is the phase where powder exits the sieve. The maximum (negative) acceleration increased with the amplitude settings as can be seen from the Figure 3.

Figure 6 shows the acceleration profiles at various frequencies and a fixed amplitude value. The results suggest that only above a certain critical frequency (above 30 Hz) a regular acceleration pattern is obtained. Moreover, the maximum accelerations are similar for the investigated frequencies. Clearly, the acceleration maximum appears more frequently via an increase in the frequency.

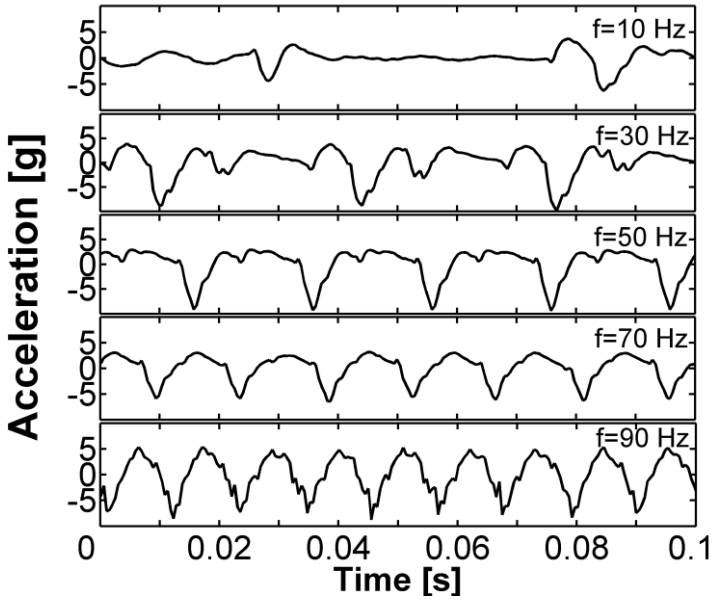

Figure 6: Acceleration profiles of the regular phase for varying frequencies at amplitude settings of 85 E. The maximal acceleration values were 6.3 g for f = 10 Hz, 9.9 g for f = 30 Hz, 9.4 g for f= 50 Hz, 6. 5 g for f= 70 Hz and 8.8 g for f = 90 Hz.

5.3.2. Powder Dosing

As shown in Table , none of the investigated powders could be dosed (or feed into the capsule) below an amplitude of 30 E since the introduced vibration energy was not sufficient to overcome the inter-particle forces and initiate powder flow. All powders could be dosed from the sieve above amplitudes of 70 E.

For some frequency and amplitude settings, powder dosing was not feasible since the powder spilled over from the sieve and the chute due to high accelerations during the upward movement of the sieve at frequencies of about 40 Hz and amplitudes higher than 80 E. Figure 3 makes it apparent that those settings (Figure 3 shows acceleration profiles at 50 Hz) yield an unsymmetrical acceleration pattern featuring accelerations up to 10 g in the negative direction (upward movement). A high-speed camera recording of a capsule-filling event with Respitose SV003 at a frequency of 45 Hz and an amplitude of 90 E showing the onset of spilling is provided on the journal's website (*RespitoseSV003_F45_A90.mp4*). Apparently, a resonance effect of the powder causes this behavior.

Figures 7 to 9 show the filling rates and their standard deviations (= error bars) in the operating space for Respitose SV003, Respitose SV010 and InhaLac 230 as defined in Table . Clearly, higher frequencies resulted in higher filling rates for all three powders. Vibrations

cause a temporal increase in the free volume, which facilitates the powder flow since an increase in the free volume breaks agglomerates and cohesive bonds by overcoming interparticular forces and provides free space for particle displacement that can also be described as activation energy [5]. Filling at higher frequencies overcomes this activation energy more frequently, yielding higher filling rates.

However, no monotone increase of the filling rate with either frequency or amplitude was observed, possibly due to different wave shapes, i.e., the vibrating arm displacement during oscillation. Figure 3 and 6 show that the wave shapes are not similar for different frequencies and amplitudes. The filling rate can thus vary distinctly with the wave shapes affecting the filling rate even if amplitudes and frequencies are identical [31][33][45].

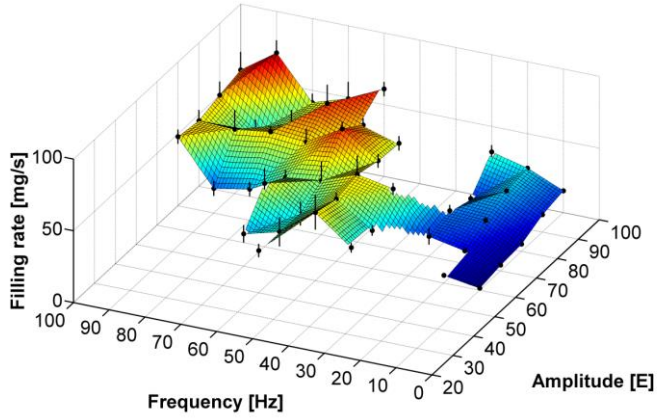

Figure 7: Filling rate and its standard deviations for Respitose SV003 in the amplitude and frequency settings of the operating space.

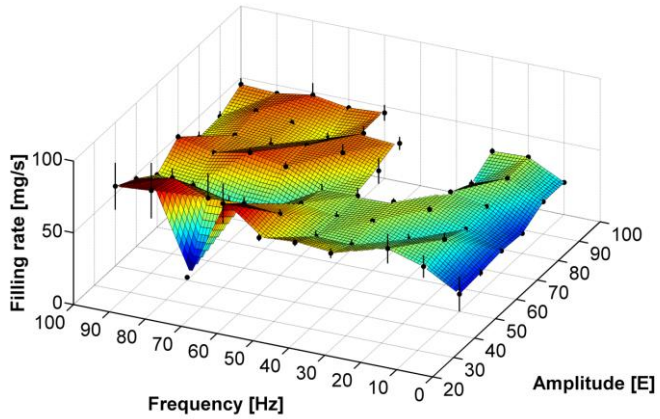

Figure 8: Filling rate and its standard deviations of Respitose SV010 in the amplitude and frequency settings of the operating space.

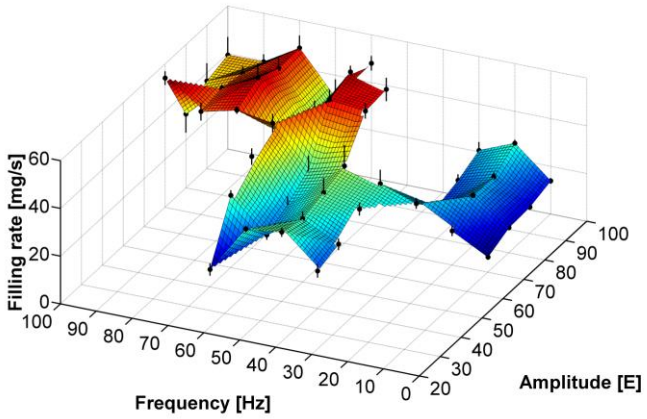

Figure 9: Filling rate and its standard deviations for InhaLac 230 in the amplitude and frequency settings of the operating space.

As can be seen from the Figures 7-9, for all powders dosing at high amplitude was possible, except for the "resonance region" causing powder spilling at intermediate frequencies. Below an E of approximately 60, dosing was possible only in at intermediate frequencies with a decreasing range for decreasing E. Below E=40 dosing could not be achieved. In general, low to intermediate frequencies had a broader parameter range of E for successful doing that higher frequencies.

Respitose SV010 provided the largest operating space (see Table). In contrast to Respitose SV003 and InhaLac 230, the powder was successfully dispensed into the chute at every frequency if the amplitude was higher than 40 E. Furthermore, dosing was possible at amplitudes of 40 E and frequencies above 40 Hz. Since Respitose SV010 has the lowest surface-to-volume ratio (largest particles) and hence the lowest cohesive force of attraction, the "activation energy" of the powder flow was the lowest. This is also indicated by the (slightly) lower Carr index than the other materials.

As expected, all powders had comparable filling rates for the same combinations of frequency and amplitude since they exhibit a similar flow behavior (see Three grades of inhalation-grade α-lactose monohydrate (hereinafter referred to as lactose) excipients with different particle sizes and supplied by different manufacturers (DFE Pharma, Germany; Meggle, Germany) were used as received.

Respitose SV003 is a sieved carrier (for inhalation APIs) and SV010 is a coarse sieved carrier. Both have a narrow particle size distribution (PSD). InhaLac 230 (Meggle, Germany) is a sieved carrier with the lowest PSD of the investigated samples. The three carrier systems

had similar values of bulk and tapped densities. An overview of the particle sizes and powder flow attributes of these materials is provided in Table 1 [29]. The listed values were obtained from the volumetric particle size distribution determined via laser diffraction (Helos, Sympatec, Germany). Powder samples were measured in the dry form after dispensing via compressed air (RODOS dispersion module). Bulk and tapped density were determined using Pharmatest PT-TD200. Besides Carr index (CI) the flow function (FFC) was determined as flow indicator with the FT4 Powder rheometer (Freeman Technology). All measurements were performed in triplicate. As can be seen Respitose SV010 had a slightly better flowability than the other powders. All three powders were in a range of "close to good" flowability, with CI<15 indicating good flowability and CI>25 indicating poor powder flow behavior. The ffc of the powders indicate good flowability in all cases, with Respitose SV003 having the best value.

Table) and the sieve hole diameter was approximately four times x_{90} of the powder with the largest particles (Respitose SV010).

Robust filling rates, i.e., those with low standard deviations (= error bars in Figure 7-9), were observed for settings away from the borders of the operating space. Therefore, the proposed vibratory sieve chute system is most suitable for continuous feeding applications when operated at settings that guarantee powder flow (amplitudes $> 55\,E$) but do not have a spilling-resonance tendency. The powder with the largest particles and the lowest Carr index (Respitose SV010) had the highest filling rate robustness, demonstrating the importance of powder properties in designing continuous feeders based on the proposed function principle.

5.3.3. Low Dosing

In order to test the low-dosing capability of the vibratory sieve-chute system, capsule filling was studied using a target weight of $2.5\,mg$. Low dosing was performed at $15\,Hz$, the frequency at which all powders showed a robust filling behavior. Different amplitudes were used since the powders had (slightly) different operating spaces. 30 capsules were filled via three different approached: (1) dosing at a fixed amplitude, (2) applying a PID controller to manipulate the amplitude within the operating space and (3) an *unrestricted* PID controller. The PID controller was operated using the default values of $K_P = 10, K_i = 0.05, K_d = 2$ (Equation 3). The results for the low- dose experiments are presented in Table 363.

Table 36: Results of the low-dose studies

Target weight 2.5 mg	***InhaLac 230***			***Respitose SV003***			***Respitose SV010***		
	Dosing via fixed settings (F 15, A 75, accept.range.=0.7 mg)	***Dosing via restricted PID control (F 15, A 70-100, accept.range =0.6 mg)***	***Dosing via PID control (F 15, accept.range =0.05 mg)***	***Dosing via fixed settings (F 15, Ampl 75, accept.range =1 mg)***	***Dosing via restricted PID control (F 15, A 70-100, accept.range =0.5 mg)***	***Dosing via PID control (F 15, accept.range =0.05 mg)***	***Dosing via fixed settings (F 15, A 55, accept.range. =1.2 mg)***	***Dosing via restricted PID control (F 15, A 55-100, accept.range =1.2 mg)***	***Dosing via PID control (F 15, accept.range =0.08 mg)***
Average dosing [mg]	***2.56***	***2.6***	***2.6***	***2.5***	***2.5***	***2.6***	***2.8***	***2.7***	***2.6***
RSD [%]	***6.3***	***4.6***	***9.2***	***4.6***	***4.6***	***6.4***	***12***	***8.5***	***7.5***
Max dosing [mg]	***2.85***	***2.82***	***3.34***	***2.8***	***2.7***	***3.23***	***3.23***	***3.11***	***3.11***
Min dosing [mg]	***2.28***	***2.39***	***2.41***	***2.3***	***2.3***	***2.44***	***1.94***	***2.35***	***2.35***
Filling time [s]	***0.86***	***0.79***	***4.1***	***0.98***	***0.66***	***4.4***	***0.72***	***0.65***	***4.3***
Filling time RSD [%]	***5.5***	***3.8***	***20.8***	***15.8***	***4.4***	***46.5***	***4.3***	***3.8***	***48.6***

The first columns for each powder presents the mean fill weight, the fill weight variability (=RSD), the maximum and minimum weights, the filling time and its RSD during dosing at a fixed amplitude. For InhaLac 230 and Respitose SV003, an amplitude $75E$was used, whereas Respitose SV010 was filled at an amplitude of $55E$. The best filling performance, i.e., the lowest fill weight variability, was achieved for Respitose SV003, with a mean target weight of exactly $2.5\,mg$ and a RSD of 4.6 %. For InhaLac 230, a mean fill weight of $2.56\,mg$ with 6.3 % RSD was obtained. For reasons discussed below, Respitose SV010 performed the worst, with a mean fill-weight of $2.8\,mg$ and 12 % RSD, although it has the best flowability.

Table 3 also presents results for the experiments using a PID controller with two different strategies: manipulating the amplitude was done at a fixed frequency of $15\,Hz$ and PID control was established either for all possible amplitudes (PID control) or for amplitudes within the operating space (restricted PID control). Respitose SV003 and InhaLac 230 had the lowest fill weight variability if dosed using constant settings or the restricted PID controller. The reason is that capsule filling using settings (i.e., E and frequency) in the operating space creates a homogeneous powder bed in the chute. In contrast, PID-controlled dosing without any restrictions applies amplitudes that yield no powder flow out of the sieve (see2). Hence, settings that violate the operating space yield inhomogeneities of the powder bed in the chute, which may cause overdosing. This overdosing can be seen in Figure 10 showing fill weights and amplitudes during PID controlled dosing. Inhomogeneities of the powder bed provoke overdosing for two reasons. i) Vacant sections on the chute yield an excessive increase of the Amplitude if the PID controller is used (see dosing 1-5 in Figure 10). ii) Temporarily high filling rates due to piles in the reserve powder in the cute. This is depicted in Figure 11. If the fill weight is close to the target weight (e.g., $fw_{target} = 2.5\,mg$, fw $= 2.4$ mg) it can happen that the remaining powder in the cute formed a pile. Hence the fill rate increases temporarily at the end of the dosing and overdosing cannot be avoided (see dosing 6 in Figure 10).

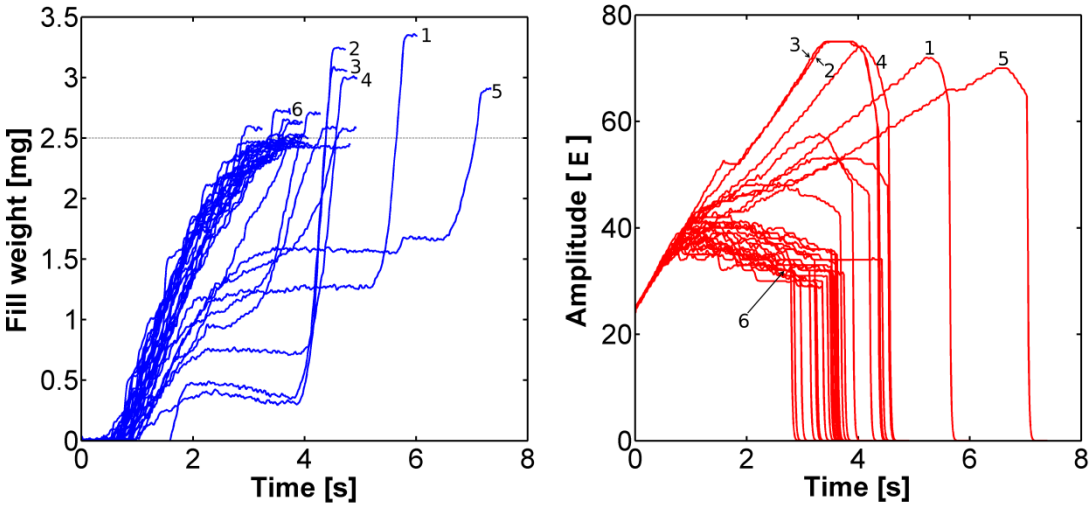

Figure **10:** Fill weights and amplitudes for InhaLac 230 dosing with a target weight of $\mathbf{2.5}\ \boldsymbol{mg}$ at a frequency of $\mathbf{15}\ \boldsymbol{Hz}$ during PID controlled dosing. The fill weight and amplitude profiles of the six most overdosed fillings are labeled.

Even though Respitose SV010 had robust filling rates at 15 Hz, the fill weight variability was comparatively high. In addition, dosing was the most accurate when using PID control only in the case of Respitose SV010 since the filling rate was too high ($\approx \frac{1}{2} \cdot 20\ mg/s$ at a frequency of 15 Hz and an amplitude of 55 E). Even an acceptance range of 1.2 mg was not sufficient to avoid overdosing (Respitose SV010 dosing in fixed settings had the highest average dosing). The filling rates of InhaLac 230 ($\approx \frac{1}{2} \cdot 13\ mg/s$ at a frequency of 15 Hz and an amplitude of 75 E) and Respitose SV003($\approx \frac{1}{2} \cdot 8\ mg/s$ at a frequency of 15 Hz and an amplitude of 75 E) were lower, suggesting that accurate dosing is possible using fixed settings. However, the acceptance ranges were already in the order of the target weight, indicating that lower filling times could not be achieved without an increase in the fill weight variability. The fastest dosing was accomplished using the restricted PID controller.

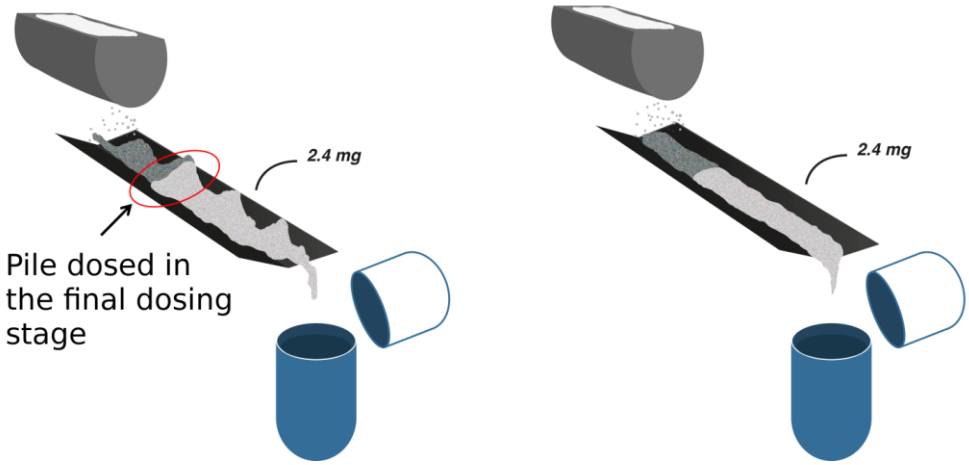

Figure 11: Powder bed in the chute during a PID controlled dosing (left) and dosing using constant settings (right).

5.4. Summary and Conclusions

In this work a vibratory sieve-chute system that can be operated at various frequencies and amplitudes is examined in terms of its applicability for continuous feeding applications and low- (or micro-) dose capsule filling. The analysis of the vertical vibrations revealed non-sinusoidal but recurring oscillations. The maximum accelerations were similar at various frequencies and increased with increasing amplitudes. The highest accelerations were observed during the upward movement, which caused powder spilling for some amplitude and frequency combinations due to resonance phenomena.

The operating space, i.e., settings that yield a steady flow of powder into the chute, was determined for three inhalation carriers. Further studies of the filling rates revealed that in the proposed settings feeding with a variability below $1\ mg/s$ was feasible for feed rates in the range of $30 - 40\ mg/s$. Hence, the described vibratory sieve chute system is suitable for continuous (micro-) feeding applications. However, no monotone increase of the filling rate was observed. For high-accuracy feeding, we recommend screening for amplitudes and frequencies that have low fill rate variations. The feed rate can subsequently be tuned by adjusting the number of holes in the sieve.

The performed low-dose studies show that capsules can be filled with $2.5\ mg$ and that a fill weight variability below 5 % can be achieved in less than one second. If filling time is not an issue, the proposed system can dose with almost any accuracy, limited only by the

accuracy of the integrated capacitive weight control. The slower the capsule is filled (e.g., by sealing sieve holes), the easier it is to stop the dosing in time. However, the key for accurate and fast dosing is a homogeneous powder distribution in the chute.

Supplementary Information

Three high-speed camera videos showing dosing procedures with different settings are accessible on the journal's website.

Acknowledgements

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„After all, science is essentially international,
and it is only through lack of the historical sense
that national qualities have been attributed to it.“

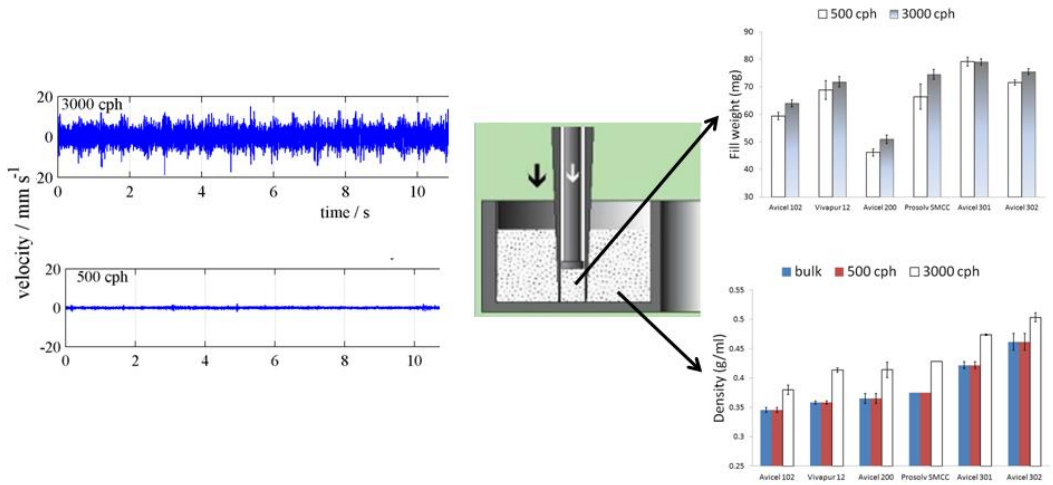
Marie Curie

6. The effect of capsule-filling machine vibrations on average fill weight of capsules

Marcos Llusa, Eva Faulhammer, Vittorio Calzolari, Stefano Biserni, Simon M. Lawrence, Massimo Bresciani, Johannes G. Khinast.

International Journal of Pharmaceutics, vol. 454, pp. 381-387, 2014.

Graphical abstract



Keywords: vibrations; powder density, fill weight

The Effect of Capsule-Filling Machine Vibrations on Average Fill Weight

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Abstract

The aim of this paper is to study the effect of the speed of capsule filling and the inherent machine vibrations on fill weight for a dosator-nozzle machine. The results show that increasing speed of capsule filling amplifies the vibration intensity (as measured by Laser Doppler Vibrometer) of the machine frame, which leads to powder densification. The mass of the powder (fill weight) collected via the nozzle is significantly larger at a higher capsule filling speed. Therefore, there is a correlation between powder densification under more intense vibrations and larger fill weights. Quality-by Design of powder based products should evaluate the effect of environmental vibrations on material attributes, which in turn may affect product quality.

Keywords: Vibration, powder density, fill weight

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6.1. Introduction

Process understanding has become a central element of Quality-by Design (QbD) for new drug applications. In this context, the use of Ishikawa diagrams to systematically account for all parameter and variables having impact on the product quality has become a standard operating procedure. Typically, operation variables (e.g., fill speed) and material properties (e.g., powder cohesivity), as well as the design parameters (e.g., machine size) are among the main parameters affecting quality (Fung and Ng, 2003). In addition, environmental conditions, such as temperature and relative humidity may influence the process. Among them, vibrations have attracted the least attention.

Vibration is an environmental condition that is always present during a manufacturing process. It is caused by the continuous operation of motors and occasional events triggered by personnel. The vibration frequency and intensity typically depend on the manufacturing conditions (i.e., high speed versus low operating speed). In the context of dosator nozzle capsule filling, the effect of the machine vibration on powder density has been assessed in-situ via either non-invasive methods (i.e., gamma and x-rays) or by sampling, which alters the powder bed condition (Woodhead, 1980, Woodhead and Newton, 1984, Woodhead et al., 1983). However, the effect of vibration on the quality of pharmaceutical capsules has not been the focus of detailed studies. Thus, in this study we investigate the impact of vibrations on powder density and fill weight of capsules.

Vibration is an important issue for dosator nozzle machines. These machines are equipped with a rotating bowl that contains a powder bed from which the nozzle collects a specific volume of powder. The bowl is subject to vibration as it rotates, and it is expected that the powder contained in it may densify and other powder properties may also be affected. MG2 industrial machines are equipped with a weight capacitance control system to keep fill weight within specifications. Capacitance sensors have been studied, and a recent publication described high-precision weighing of 75,000 capsules/hour (Burmen et al., 2009). Whenever capsules are out of specification, a control system changes the dimension of the dosing chamber in the nozzle to keep fill weight as close as possible to the target. It is important to mention that while the fill weight can be maintained on target thanks to the instrumentation, there is no possible corrective action for API segregation in the bowl, an event also triggered by vibration (Harwood, 1977). Hence, vibration assessment of a capsule filling machines is a critical issue when handling blends with segregation tendencies.

There are process parameters that significantly affect fill weight, such as piston compression setting ratio. In general, the larger the compression setting ratio, the smaller the fill weight for most powders (Tan and Newton, 1990a, 1990b; Jolliffe and Newton, 1982, 1983a). The study of the effect of compression ratio on fill weight is generally performed in combination with the study of the effect of particle size (compression must be applied to guarantee the retention of powder in the nozzle for large particle sizes). Fill weight is also affected by particle size (Jolliffe and Newton, 1982, 1983a). In the current research, no piston compression was applied, but the effect of particle size was studied. The dosator nozzle wall texture may also affect fill weight significantly and resurfaced nozzles have shown increased fill weights (Jolliffe and Newton, 1983b). In our study, we used a single dosator nozzle throughout all the experiments (i.e., same nozzle diameter and construction material). Regarding the effect of powder properties, most of the literature is focused on the effect of powder flowability on fill weight variability (Tan and Newton, 1990c; Freeman et al., 2011; Patel and Podczeck, 1996). However, flowability was also suggested to affect fill weight (Gohil et al., 2004). Powder flow properties for dosator nozzles should be average to moderately good, and excipients with enhanced flow properties, such as silicified MCC (SMCC), have been investigated for capsule filling operations. The benefit of using SMCC in capsule filling comes from their higher compactability at low forces (Guo et al., 2002; Guo and Augsburger, 2003) and we included this material in the current research.

This paper demonstrates that a six-fold increase in the operating speed (and vibration) of a research dosator nozzle machine (Labby, MG2) led to densification of the powder and to a larger fill weight collected via the nozzle. To our knowledge, the effect of vibration on fill weight has not yet been investigated. Understanding this effect will improve process development, scale-up and transfer.

6.2. Materials and Methods

6.2.1. Materials

Microcrystalline cellulose was selected for the current study since 1) it is a commonly used excipient in pharmaceutical formulations, 2) it has been amply characterized and discussed in the literature (e.g., Amidon and Houghton, 1995, Patel and Podczeck, 1996), and 3) it is a binder and hence tends to form good plugs that can easily be transferred from the nozzle into the

capsule. The powders used here are: four types of pharmaceutical microcrystalline Cellulose (Avicel PH-102, PH-200, PH.301, PH-302; FMC BioPolymer), one type of silicified microcrystalline cellulose (PROSOLV® SMCC 90; JRS PHARMA GmbH) and one type of microcrystalline cellulose from a different supplier (VIVAPUR® 12; JRS PHARMA GmbH). A laser diffraction instrument (Qicpic, dry dispersing system, Sympatec, Germany) was used to measure particle size via the principle of dynamic image analysis. Bulk and tap densities were measured (Pharmatest PT-TD200) in a dry, graduated, 100 mL cylinder (readable to 2 mL). A known mass of powder was filled into the cylinder, and the volume was recorded. The tapped density is calculated after tapping the powder sample 1250 times and reading the new volume. All particle size and density measurements were performed in triplicates. Table 1 presents the results of the particle size characterization. The powders were encapsulated in gelatin capsules (Capsugel) size 3.

	Avicel 301	**Avicel 302**	**Avicel 102**	**Avicel 200**	**Prosolv SMCC 90**	**Vivapur 12**
Volumetric mean diameter [µm]	95.2	144.9	170.1	255.4	153.5	194.1
x_{10} [µm]	48.2	60.8	68.4	114.4	67.8	73.5
x_{50} [µm]	89.6	135	156.9	248.6	142.7	188.9
x_{90} [µm]	148.7	242.3	291	400.7	251	322.1

Table 1: Results of the powder characterization.

6.2.2. Capsule Filling Equipment and Fill Weight Measurements

The research capsule filling machine used in this work (Labby, MG2, Italy) was a unit equipped with one single dosator nozzle and a rotating bowl designed for small powder quantities. It has three motors that caused vibration: an air compressor, a vacuum pump and a motor (1 kW) that drove the capsule filling system. Vacuum and compressed air are necessary to handle the empty capsules (transfer, open, etc) in the capsule filling machine. The vacuum pump and the air compressor operate in a single mode, and hence they contribute the same vibration at every speed of capsule filling. However, in order to avoid having to regularly clean air filters and

purge water, the air compressor was always off and the equipment was connected to an external compressed air line.

In order to study the effect of speed and vibrations, a condition of 500 capsules per hour (cph) and negligible vibrations is contrasted with a condition of 3000 cph (maximum speed of the machine) and the largest possible vibrations for this machine. The volume of the dosing chamber (DC), which is the space inside the nozzle to be filled by powder, is determined by the position of the piston. The piston was fixed at positions of 3 mm, 6 mm and 12 mm in order to fill the capsules with different amounts of powder. Hence, six different experimental conditions generated by the combination of two different speeds of operation (500 cph, 3000 cph) and three different volumes of the dosing chamber are studied. The nozzle used in all experiments was number 3 (diameter = 4.7 mm). The feeder maintained a constant powder bed depth of 32 mm in the bowl.

For each experimental condition, one hundred full capsules were collected and weighed. The capsules are collected after one minute of operation of the capsule filling machine, when the powder density is the bowl is expected to have reached steady state (as explained in more detail in the section for powder density at capsule filling operation conditions). One hundred empty capsules were also weighed with a Denver SI-234A scale (Readability: 0.0001 g; Reproducibility: 0.1 mg) and the average weight and the standard deviation were calculated. In order to obtain the fill weight, the average weight of 100 empty capsules was subtracted from the total weight of each full capsule. The variance of the weight of empty capsules was subtracted from the variance of the weight of filled capsules. Then, the standard deviation of the net powder weight is obtained by calculating the square root of the variance. The average and the standard deviation of the fill weight were calculated.

6.2.3. Laser Doppler Vibrometer (LDV)

The vibration frequency, intensity and direction are important considerations. In the rotating bowl, vibrations occurred along the axis of rotation (i.e., vertical) and in the radial direction. Although the rotating bowl may undergo more intense vibration than the static part of the frame, LDV measurements on the surface of the bowl was not entirely reliable because the bowl surface was not perfectly round and smooth. As the bowl rotates, the distance between the laser source and the surface of the bowl may change due to slight deviations from a perfect cylinder shape of the bowl (i.e., due to construction tolerances). Thus, a surface of the frame was used

to measure the vibrations along the radial direction of the bowl. Specifically, the laser focused on a mirror fixed to the surface of the capsule filling machine, as close to the bowl as possible (Figure 1). The mirror vibrated when the machine operated. Vibrations along the axial direction were not measured. Vibration is assessed while running an empty machine (without powder in the bowl). The vibration of the machine frame should not be affected by the mass of powder contained in the bowl, which is slightly different (total mass between 150g and 200g) for the powders tested because they have different density.

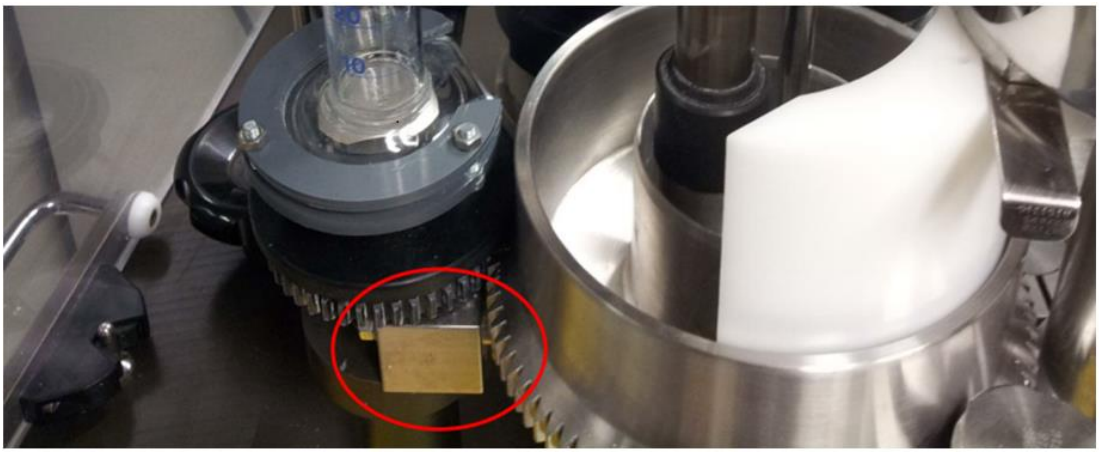

Figure 1: A section of the capsule filling machine. The gear teeth are the lower rim of the rotating bowl that contains the powder. The laser beam, which is denoted by a red line, is reflected from the surface of the mirror used for LDV measurements.

LDV is a non-contact method to assess the displacement, velocity and acceleration of a surface in the direction of a laser beam. The measurements were performed by a Laser-head equipped with a Helium-Neon laser driven interferometer, a vibrometer controller with a velocity decoder and an Analog/Digital converter. Due to the Doppler effect, there was a shift in the frequency of the light reflected by the mirror, which was a function of the velocity of the moving surface (mirror) and which was evaluated by an interferometer and converted into a voltage analog signal. The vibrometer controller sent the analog signal to the Analog/Digital converter. The digital signal was recorded by a laptop for 25 seconds, which provided enough data for the Fast Fourier Transformed (FFT) spectra. Most of the post-processing was performed using MATLAB v.7.9.0.529 (R2009b). The details and set-up of each piece of equipment are described below.

The laser head (Polytec OFV-503 Optical Head, serial no. 0120062) had a wavelength of 633 nm, a power of approximately 1 mW and a frequency of 40 MHz. The laser vibrometer

controller (Polytec OFV-5000-2G, serial no. 120061) had a velocity decoder card VD-04 (serial no. 001622). The practical limits and the accuracy of these two devices depend on the measured frequency. The frequency range was 0.5 Hz-250 kHz, the sensitivity of the LDV controller was 10 mm⁄s.V (highest value) and the sampling rate f_s was 2^{15} Hz.

The Analog/Digital converter (Brüel & Kjaer Type 3560-B-130, serial no. 2519484) was used at a constant sampling rate of 32,768 Hz, which allowed detection of frequencies of up to 16 kHz. A filter eliminated frequencies below 0.7 Hz, and therefore, the frequency of the rotation of the bowl (and motion of the nozzle) was not taken into account for most operating speeds of the machine (i.e., it was 0.69 Hz for 2500 cph).

In a seminal study Macrae et al. (1957) showed that the density (or porosity) of coal and zircon powders (of less than 300 B.S. sieve) in a graduated cylinder clamped to a platform that oscillates vertically in a simple harmonic fashion is a function of the acceleration and velocity of the mass of particles at the moment of interrupting the vibration (arrest). In their experiments, the motion of the cylinder is abruptly stopped at different points of the downward movement of the oscillation cycle. The stop positions are selected in order to attain a specific velocity of the cylinder (impact velocity). At the stop, the particles suffer a rapid deceleration, and a dissipation of energy occurs. Macrae et al. show that the porosity of these two materials, instead of being a function of the amplitude and frequency of the oscillation, is a function of the velocity at the moment of this abrupt interruption. Moreover, porosity reduces, reaches a minimum, and then at higher velocities, powder bed expands. Thus, due to the relevance of velocity and acceleration of a vibrating surface on porosity and density, we performed measurements of these variables in the radial direction of the bowl of our capsule filling machine.

6.2.4. Powder Density at Capsule Filling Operation Conditions

Powder density at capsule filling operation conditions was assessed using a graduated cylinder that was attached to the top of the rotating bowl's driver. Because of the close mechanical connection between the driver and the bowl (Figure 2), and their identical speeds of rotation, it may be expected that the powder in the graduated cylinder and in the bowl are exposed to the same vibration. Hence, the densification that occurs in the graduated cylinder is representative of the densification in the bowl. The initial powder bed depth in the glass cylinder (before operation of the machine) was the same as in the bowl (32 mm). Powder density in the cylinder was assessed after operating the capsule filling machine at a specific speed for ten minutes.

Most of the densification in the cylinder occurred in the first minute of machine operation, and subsequently a steady state for density was reached. Density was assessed in triplicates. Capsules for weight analysis are always collected after the first minute of operation, allowing for the powder to reach the steady state.

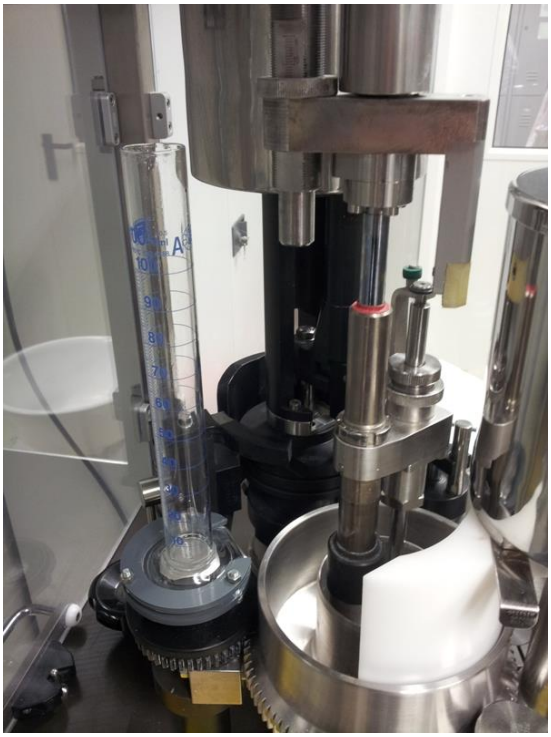

Figure 2: A graduated cylinder fixed with a clamp to the knob located on a rotating disc that is intermeshing with the teeth of the powder bowl.

6.3. Results

6.3.1. LDV Measurements

The measurements reported in this study were performed by LDV on a mirror that is placed as close as possible to the rotating bowl. The signal recorded (Figure 3) was the velocity of the motion of the mirror as a function of time. Increasing the operating speed of the equipment (500, 1500, 2500 and 3000 cph) amplified the vibration velocity of the surface of the equipment. Similar plots for the displacement and acceleration of this surface were obtained by simple integration or derivation of the velocity signal in Figure 3. These measurements indicate that the static parts of the framework reverberated when the moving parts (i.e., the bowl) of the equipment were operating.

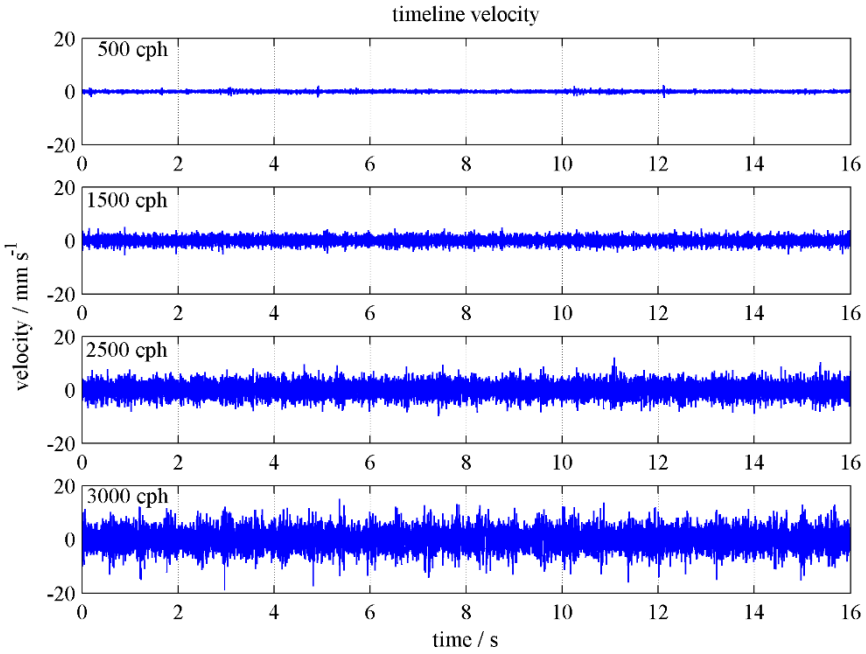

Figure 3: Velocity signal as a function of time at different operating speeds of 500 cph, 1500 cph, 2500 cph, 3000 cph.

The frequencies of the velocity signal were obtained by applying Fast Fourier transform (FFT) to the signal shown in Figure 3. Figure 4 shows the frequencies for the velocity signal, with a frequency resolution of 1 Hz (the spectra were scaled to frequency ranges where a signal was observed). In order to reduce random peaks in the FFT spectrum, this transformation was applied to 16 spectra, which were obtained by splitting Figure 3 in 16 consecutive sections (1 second each, no overlapping). It can be seen that the frequency of the velocity signal never exceeds 400 Hz. Moreover, as the speed of operation of the capsule filling machine increases from 500 cph to 3000 cph, the frequency spectra become more complex and different frequencies (especially at a low range) dominate the spectra. As the speed of capsule filling increases, the speed of the driving motor increases, and the upward and downward motion of the dosator nozzle is faster. On the other hand, the vacuum pump operates always at a constant speed. However, the complexity and the interactions among the many parts of the capsule filling machine make it difficult to identify exactly the mechanical events that trigger the frequencies observed in Figure 4.

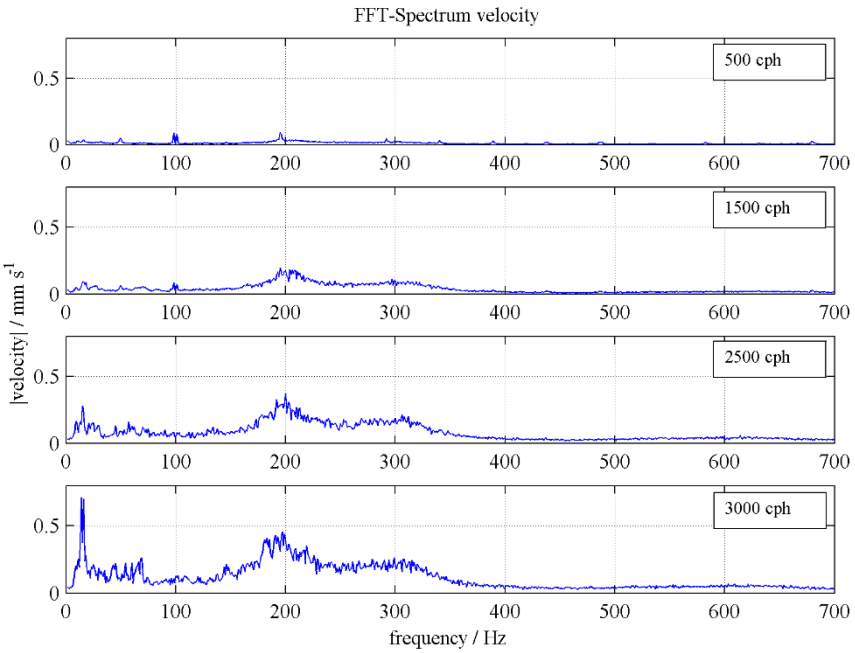

Figure 4: Frequencies of vibration obtained by average Fast Fourier Transform (FFT) of the velocity signal (Figure 3) for speeds of operation of 500 cph, 1500 cph, 2500 cph and 3000 cph.

The Root Mean Square (RMS) is an index typically used to quantify the magnitude of temporal signals. The RMS for velocity was calculated using discrete time series of the signal in Figure 3 and the following equation:

$$v_{RMS} = \sqrt{\frac{1}{T} \cdot \sum_{i=t_0}^{i=t_1} {v_i}^2 \cdot \Delta t}$$

where the time $T = t_1 - t_0$ is the period of time for data collection (16 seconds), Δt is the time between two sampling events and v_i in this case the velocity at a specific time t. The RMS for acceleration was calculated using the corresponding signals equivalent to Eq. 1. Results are shown in Figure 5, which shows that the RMS values for velocity and acceleration increase together with the operating speed of the capsule filling machine. At low speeds of capsule filling (500 cph), the velocity and acceleration of the vibrating surface are almost negligible. However, as the speed of capsule filling increases, velocity and acceleration significantly increase. The following section shows how the vibration at different speeds of operation affect the density of the powders.

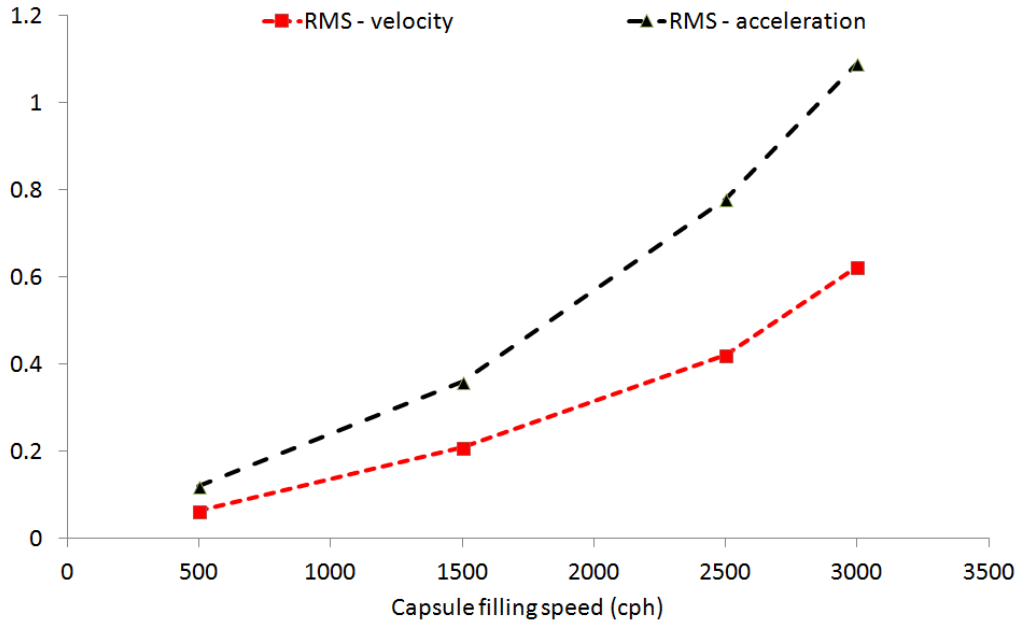

Figure 5: RMS values for velocity (mm/sec) and acceleration (m/sec^2) of the vibrating surface, averaged over a period of 16 seconds.

6.3.2. Effect of Vibration on Powder Density

The measurements performed in a glass cylinder attached to the driver indicate that the powder density was affected by the operating speed and hence by the vibration of the capsule filling machine. Figure 6 shows that powder density in the cylinder fixed on the machine operated at 500 cph was identical to the bulk density (as measured in the glass cylinder on a lab bench) for all powders. Thus, at 500 cph no densification occurred. Even though different amounts of powder are used in the bench test and in the glass cylinder attached to the capsule filling machine, the density measured in the bench test (bulk density) and in the capsule filling machine (before and after operation at 500 cph) are all identical. The glass cylinder in the capsule filling machine contains an amount of powder that has initially (before operation of the machine) the same height as the powder bed depth in the bowl (32 mm). The bench tests uses more powder (a volume of approximately 50 ml).

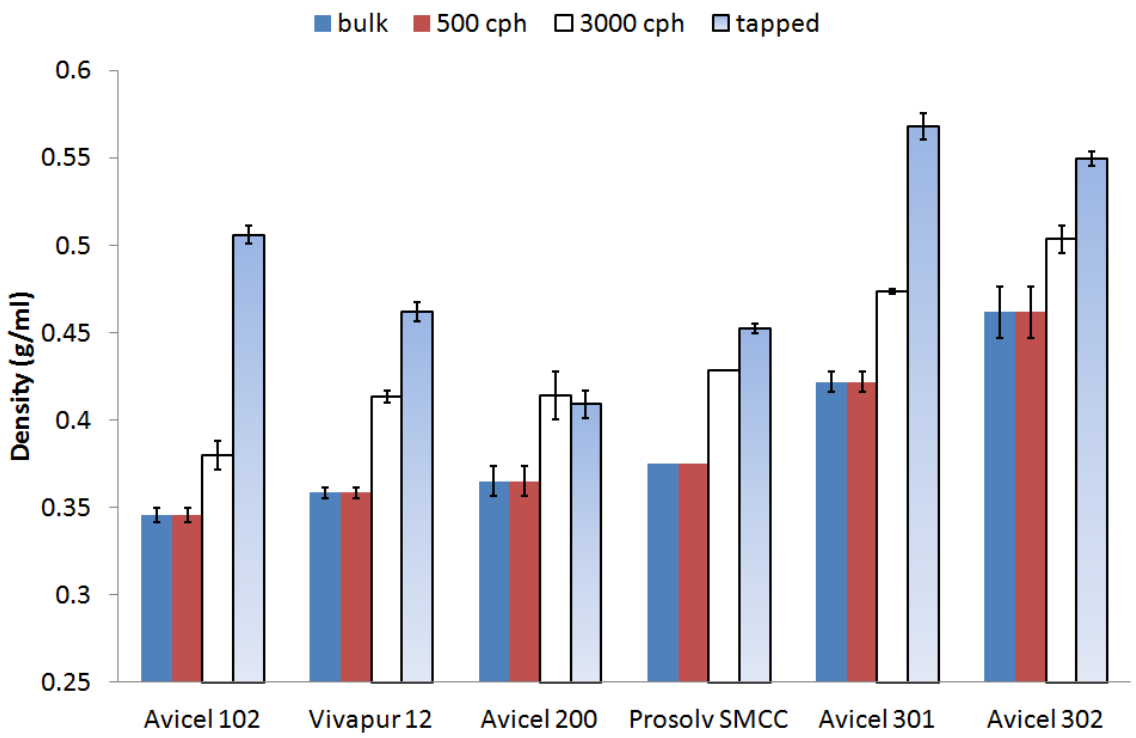

Figure 6: Bulk density and "in-process" density (± standard deviation of density) as a function of the speed (and hence vibration) of the research capsule filling machine (Labby, MG2).

At 3000 cph significant densification was observed for all the powders. For reference, tapped density is also displayed in Figure 6, and shows that most powders still have room for further densification under more intense vibrations. The only exception is Avicel 200 (the coarsest of all powders used here), which at 3000 cph reached a density equivalent to the tapped density for the bench test.

The effects of vibration on density are not trivial. In fact, simplified experimental set-ups that use specific vibration frequencies and intensities and also model materials, such as monodisperse spherical beads, show a wealth of effects. For example, the effect of vibration intensity on powder density may be reversible or irreversible. Under vibrations the bead packing evolves from an initial low-density configuration towards higher density. Experiments with monodisperse spherical beads have shown that ramping vibration repeatedly up and back down reveals the existence of both an irreversible and a reversible branch in the packing density (Nowak et al., 1997). Also, there a complex time evolution from an initial low density configuration toward a steady state for monodisperse spherical glass particles confined in a long, thin cylindrical tube (Knight et al., 1995). For this system, the density of the pile slowly reaches a final steady-state value about which the density fluctuates (Nowak et al., 1998).

Pharmaceutical powder formulations contain particles with a wide range of particle sizes and shapes, different true densities, different mechanical properties, etc. Moreover, the vibration profile of a manufacturing equipment is complex and presents many simultaneous frequencies. In order to get a more comprehensive characterization of the effects of vibration on density, dynamic density profiles are suggested for pharmaceutical products (Mohammadi and Harnby, 1997). Understanding the effects of vibration variables and powder variables on the densification of pharmaceutical formulations is a complex matter.

6.3.3. Effect of Vibration on Fill Weight

The dosator nozzle samples a specific volume of powder from the bowl, which is defined by the diameter of the nozzle and the length of its chamber (distance between the tip of the nozzle and the position of the piston inside the nozzle). When the size of dosing chamber is reduced, fill weight is reduced accordingly. The fill weight results for the various sizes of dosing chambers are reported in Figure 7 (DC=12mm), Figure 8 (DC=6mm) and Figure 9 (DC=3mm) for two different fill speeds (500 and 3000 cph, respectively) for six powders. These figures show the average fill weight of 100 capsules, with error bars that represent two standard deviations.

Figures 7, 8 and 9 show that for three different process conditions (i.e. size of the dosing chamber) the fill weight increases in the presence of strong vibrations: the fill weight is significantly higher at 3000 cph than at 500 cph. Because standard deviation bars offer the visual impression that the effect of speed and vibration on fill weight for Avicel 301 and Vivapur 12 was not always significant, we complemented the visual information of the Figures 7, 8 and 9 with the statistical parameter p. p values are used to evaluate the effect of speed and vibration on fill weight, and they are valuable in the current research because of the large number of samples available (one hundred fill weight samples per experimental condition). The p value was calculated for every powder and for every dosing chamber. This parameter indicates that the effect of speed was not significant only for three experimental cases: Avicel 200 (dosing chamber = 12 mm) and Avicel 301 (dosing chamber = 3 mm and 6 mm).

In fifteen out of eighteen cases, the effect of vibration on fill weight was significant, and higher vibration led to higher powder density and hence, to a larger amount of powder collected by the nozzles.

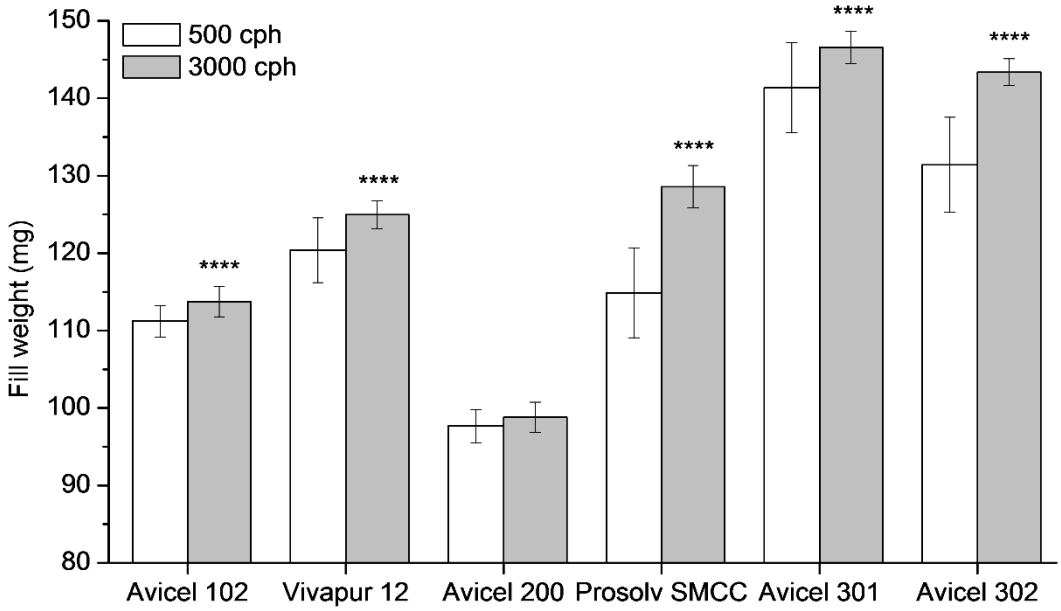

Figure 7: Effect of the vibration associated to two capsule filling speeds (500 and 3000cph) on capsule fill weight (± standard deviation of fill weight) for six powders. Dosing chamber: 12 mm. The four asterisks (****) indicate that the p-value were <0.0001. Hence, only the fill weights of Avicel 200 are not significantly different (p=0.53).

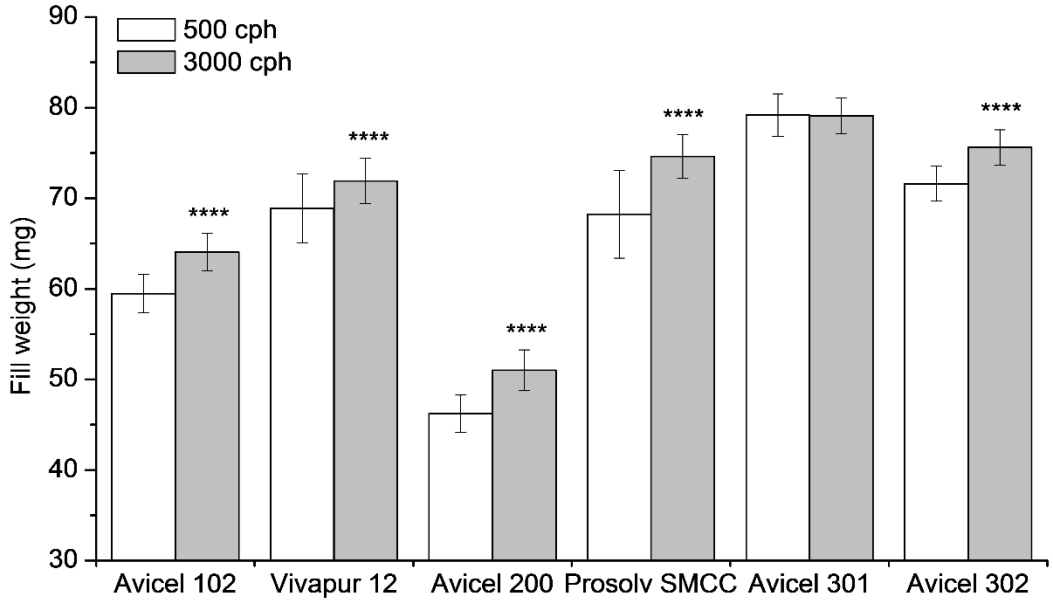

Figure 8: Effect of the vibration associated to two capsule filling speeds (500 and 3000cph) on capsule fill weight (± standard deviation of fill weight) for six powders. Dosing chamber: 6 mm. The four asterisks (****) indicate that the p-value were <0.0001. Only the fill weights of Avicel 301 are not significantly different (p>1).

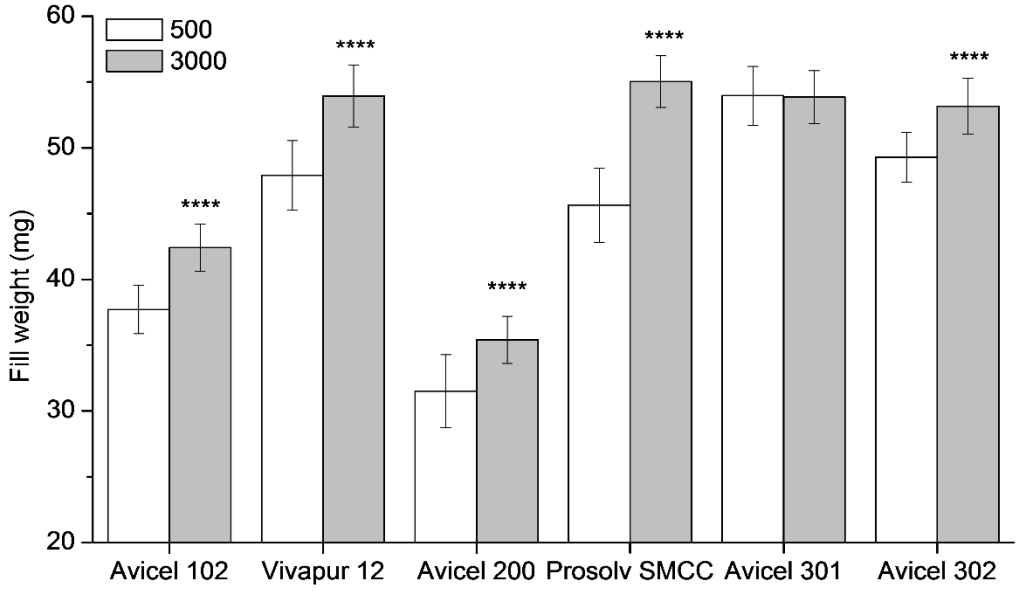

Figure 9: Effect of the vibration associated to two capsule filling speeds (500 and 3000cph) on capsule fill weight (± standard deviation of fill weight) for six powders. Dosing chamber: 3 mm. The four asterisks (****) indicate that the p-value were <0.0001. Only the fill weights of Avicel 301 are not significantly different (p>1).

6.4. Conclusions

This study shows that the vibrations of a capsule filling machine may affect the density of the powder used for encapsulation and, therefore, the fill weight of the capsules. The powders' density was not measurably affected by the process conditions at 500 cph (the lowest filling speed investigated) as vibrations were insignificant for this speed. At the highest speed (3000 cph), vibration and powder densification were significant. As a consequence, fill weight at 3000 cph is significantly larger.

Published research shows that powder properties such as flowability also have an effect on fill weight and weight variability. Many of these properties are also affected by the vibrations. For example, vibrations can reduce the shear strength and the unconfined yield strength of fine powders (Kollmann and Tomas, 2001). More specifically, vibration frequency, amplitude and energy input can reduce the flow function of powders, as measured with a Jenike shear cell (Roberts and Scott, 1978). Mechanistic models for the effect of vibration on particles interactions which can be implemented in the simulation of capsule filling processes have been proposed (Matchett, 1986).

Due to the fact that vibration affects a number of powder properties (i.e. density, flowability) that are known to affect fill weight and fill weight variability, it is advisable that "Quality by Design" approach for powder-based products considers the characterization of material attributes at process conditions. Following a "Quality by Design" approach which integrates environment variables into the experimental space leads to an improved understanding of the variables that affect the quality of capsules (i.e. fill weight). As a consequence, this may improve the development, scale-up and transfer of capsule filling processes.

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Disclosure Statement

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Roles of the Funding Sources

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„All my life through, the new sights of Nature made me rejoice like a child.“

Marie Curie

7. The effects of powder compressibility, speed of capsule filling and pre-compression on plug densification

Marcos Llusa, Eva Faulhammer, Georg Scharrer, Simon M. Lawrence, Stefano Biserni, Vittorio Calzolari, Johannes G. Khinast.

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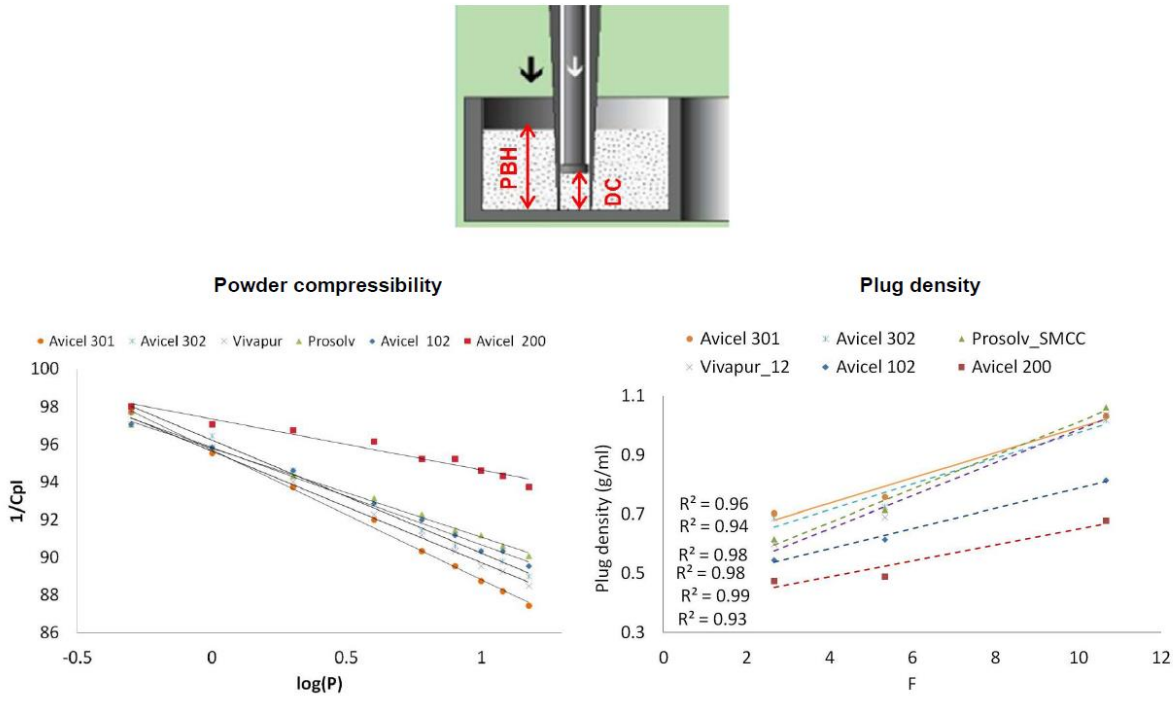
Graphical abstract:



Keywords: powder compressibility; plug density; capsules; dosator nozzle

The effects of powder compressibility, speed of capsule filling and pre-compression on plug densification

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Abstract

This paper describes the effect of powder compressibility and two process parameters of a dosator nozzle capsule filling machine on powder densification during plug formation. One process parameter was the ratio between the powder bed's depth and the length of the nozzle dosing chamber, hereinafter referred to as F. The other one was the speed of capsule filling. This paper demonstrates that powder densification during the capsule filling process is a function of the powder compressibility and the above process parameters (increasing them leads to higher plug density). The Walker model was used to characterize the compressibility of powders at low compression forces and the obtained compressibility coefficient W proved to be a good predictor of powder densification during the capsule filling process.

Keywords: Powder compressibility, plug density, capsules, dosator nozzle.

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7.1. Introduction

The effectiveness and quality of a capsule filling process with a dosator nozzle machine depends on several parameters, such as the powder properties, the speed of capsule filling, the size of the dosator nozzle, the roughness of the nozzle walls and the piston compression effects. The ratio between the powder bed depth (PBD) and the length of the dosing chamber (DC), hereinafter referred as F (Figure 1), determines the pre-compression of powder in nozzles. Although F is a frequently-manipulated process parameter, its effect on the quality attributes of the filled capsules has only recently been addressed (Khawam, 2011; Khawam and Schultz, 2011), for example, with regard to the fill weight and to calculate a powder flow factor (Khawam and Schultz, 2011). The objective of this work was to investigate the effect of F and powder compressibility on the plug density.

Figure 1 illustrates how F affects the plug density: as the nozzle dips into the bowl, the powder enters the chamber of the nozzle through the opening located in its lower section. The nozzle fills up entirely and, as it moves towards the bottom of the bowl, the powder undergoes pre-compression (Khawam, 2011 and Britten et al., 1995). As the powder in the dosing chamber becomes pre-compressed, more powder enters the dosing chamber. The higher the F value, the stronger the powder pre-compression. Fill weight and density increase simultaneously. Final compression may be achieved by an additional down-movement of the piston inside the dosator. A certain densification of the plugs is important to increase interaction with the walls, facilitate powder retention in the nozzle and avoid losses in the transfer of the plug from the bowl into the capsule body.

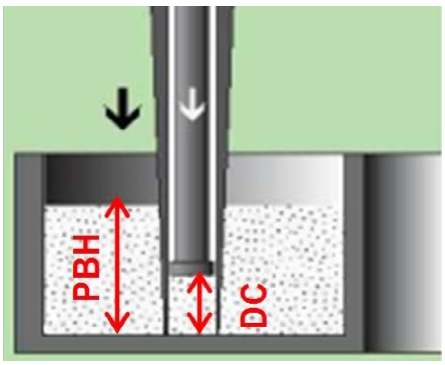

Figure 1: Process parameter F =powder bed depth (PBD)/length of dosing chamber (DC).

Powder is densified in the nozzle as a result of higher F values (pre-compression) and/or by applying force with the piston. Piston compression has received more attention in the literature

than the pre-compression. The dissolution of plugs is affected by the plug hardness, which is a function of the piston compression force and the magnesium stearate content of the formulation. Mehta and Augsburger (1981) reported that the content of magnesium stearate can be optimized to generate softer plugs that lead to enhanced dissolution. Piston compression has been shown to negatively affect the capsule fill weight variability (Tan and Newton, 1990a). Moreover, the effects of piston compression on the plug density are powder-dependent, as, for example, demonstrated by Tan and Newton (1990b). With regard to the physics of piston compaction, the equations developed for tableting apply to low-force compression with a piston as well (Heda et al., 1999).

The objective of this work was to study the effect of F and powder compressibility on powder densification during the pre-compression step of capsule filling process, which to date has not been investigated.

7.2. Material and Methods

7.2.1. Materials

As a model compound we selected Microcrystalline Cellulose (MCC), a pharmaceutical excipient that is typically used as filler, which densifies easily and forms plugs. We used five types of pharmaceutical grade MCC (Avicel PH-102, PH-200, PH.301, PH-302 by FMC BioPolymer and VIVAPUR® 12 by JRS PHARMA GmbH) and a silicified MCC containing 2% colloidal silicon dioxide (PROSOLV® SMCC 90 by JRS PHARMA GmbH). Gelatin capsules (Capsugel) size 3 were used.

We analyzed the following densification-related powder properties: compressibility (Cp), densities (true density, bulk and tapped density), particle size and shape. Powder compressibility is a measure of how density changes as a function of the applied normal stress. It is affected by several factors, such as the particle size distribution, particle shape, particle stiffness, particle surface texture, etc. In order to minimize the number of variables that affect powder compressibility and to simplify our research, we only used MCC (i.e., the same material stiffness). The powders used in our study differed significantly in terms of particle size (the median particle size of Avicel 301 is 95 µm and Avicel 200 is 255 µm), there were no significant variations in shape (S_{50} ranged from 0.84 to 0.89). The span of the particle size distribution was similar for all powders and ranged between 1.12 and 1.34. Particle surface texture was not

investigated in our work and, based on scientific evidence (Edge et al., 1999; Rojas and Kumar, 2011), we assumed that only silicified MCC had a different surface texture (enhancing its flowability).

7.2.2. Powder Compressibility (Cp) and Density

Cp was measured using the compressibility module of the FT4 equipment (Freeman Technologies). Here, normal stresses are applied in incremental steps (from 0.5 kPa to 15 kPa) via a vented piston. Before the compressibility test, the samples were pre-conditioned in the FT4 instrument to ensure that the bulk density (and initial test condition) did not depend on the operator and the loading procedure. The vented piston was constructed from a woven stainless steel mesh and allowed the air entrained in the powder to escape uniformly across the surface of the powder bed. Normal stress was applied for a defined time to allow the powder to settle (reach equilibrium). The distance travelled by the vented piston was measured for each applied normal stress, and the compressibility was automatically calculated as a percentage change in volume. The definition of compressibility is density after compression divided by conditioned bulk density.

Various compression models (i.e., Kawakita, Walker, Log-Exp) have successfully been used to characterize the compressibility of materials at low compression forces (Sørensen et al., 2005). In fact, a single-punch compaction simulator has been applied at very low compression forces to simulate the plug formation and to study the compression generated by the piston in a nozzle (Heda et al., 1999). However, at low compression forces the initial packing of particles may affect the results of the Kawakita compression model (Sheikh-Salem and Fell, 1981), indicating the importance of conditioning the powder before performing the compressibility test. We found that in our case the Walker model is the best option for interpreting the compressibility data obtained via FT4. Figure 2 presents the results of the compressibility test using the FT4 compressibility module, showing Cp along the Y-axis and normal compression stress applied to the sample along the x-axis.

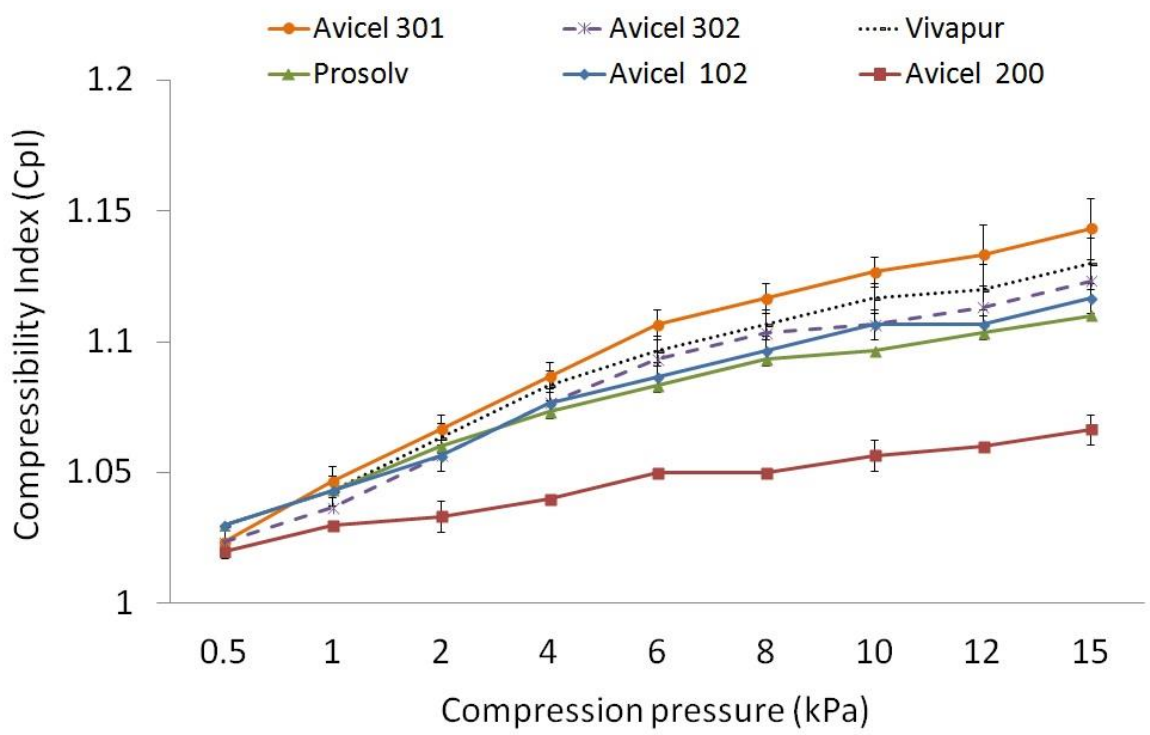

Figure 2: Compressibility (Cp) as a function of pressure measured using the compressibility module of the FT4.

The data in Figure 2 were fitted using the Walker equation, which is less sensitive to small errors in experimental conditions and has more discriminative powder than the Heckel analysis (Sonnergaard, 1999). The model is given by:

$$100 \times V = -W \times \log(P) + C \qquad \text{(Eq. 1)}$$

where V is the relative volume (inverse of the relative density of the compact), P is the pressure, W is the compressibility coefficient and C is a constant. W is considered a measure of the irreversible compressibility of the compact, which is relevant to the pharmaceutical product characterization. Equation 1 indicates a linear relationship between the relative volume and the logarithm of the pressure and can be used to fit the compressibility (Cp) data measured via the FT4. As such, Equation 1 can be rewritten as:

$$1/Cp \times 100 = -W \times \log(P) + C \qquad \text{(Eq. 2)}$$

Figure 3 shows the fitting of data in Figure 2 using Equation 2. A linear regression was used to calculate the compressibility coefficients W and showed an excellent fit for all materials: Avicel

200 (R^2 = 0.9611); Prosolv (R^2 = 0.9969); Avicel 102 (R^2 = 0.9923); Avicel 302 (R^2 = 0.9954); Vivapur (R^2 = 0.9956); Avicel 301 (R^2 = 0.9971). The W values which correspond to the slopes of the regression lines are summarized in Table 4.

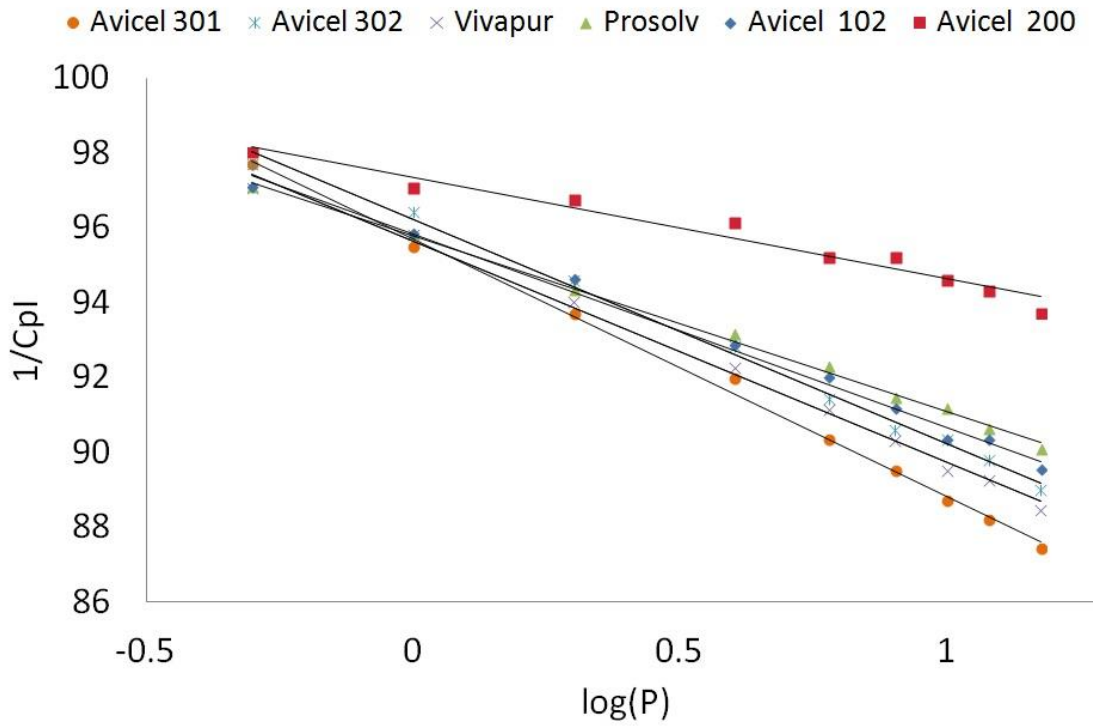

Figure 3: Regression analysis between the inverse of the compressibility (Cp) and pressure. The slope of the lines corresponds to the compressibility coefficient W in Equations 1 and 2.

	Avicel 301	Avicel 302	Vivapur 12	SMCC Prosolv 90	Avicel 102	Avicel 200
Compressibility Coefficient W	6.8811	5.9979	5.9144	4.7059	5.162	2.7
Densification coefficient in nozzles						
At 500 cph	0.0457	0.0408	0.0422	0.0413	0.0245	0.0189
At 3000 cph	0.0428	0.0435	0.056	0.0567	0.0341	0.0271

Table 1: Material attributes for the various MCC used in this research. Each measurement was performed in triplicate and the mean is shown here.

Bulk and tap densities were measured (Pharmatest PT-TD200) in a dry, graduated 100 mL cylinder (readable to 2 mL), following USP General Chapter <616> guidelines. To determine tap density, a certain amount of powder was placed into the cylinder, and the volume was recorded after tapping the powder sample 500 and 1250 times. As there is no change in tapped

density between 500 taps and 1250 taps, we report the density at 1250 taps. All measurements were performed in triplicates.

7.2.3. Particle Size Distribution and Particle Shape

Particle size distribution and shape are properties that affect the compressibility of powders. We used a dynamic image analysis instrument (QicPic, Sympatec, Germany) with dry dispersion sampling to measure the particle size and shape for the powder samples (Table 1). The range of the particle size distribution was assessed using the span parameter.

Particle size shows a correlation with the Walker compressibility coefficient W and other compressibility parameters related to W, such as the pressure modulus L. Therefore, in order to use W to analyze the compressibility of powders in the nozzle, this correlation must be confirmed. Sonnergaard (1999) and other authors indicated that there was a correlation between the pressure modulus L (which is a material parameter in an alternative version of the Walker equation) and particle size. L is inversely related to the W and has been proven to increase with the increasing particle size of sodium chloride, sucrose and quartz (Huffine and Bonilla, 1962), as well as spray-dried and crystalline lactose (Fell and Newton, 1971; York, 1978). Our results showed the same trend: Avicel 200 had the largest particle size and was the least compressible of all tested powders with the lowest W. Avicel 301 had the smallest particle size and was the most compressible of all tested powders with the highest W. The linear correlation between the volumetric mean diameter and W had an R^2= 0.74. Moreover, when the silicified MCC was removed from the data set (Figure 4), the linear correlation improved (R^2= 0.82).

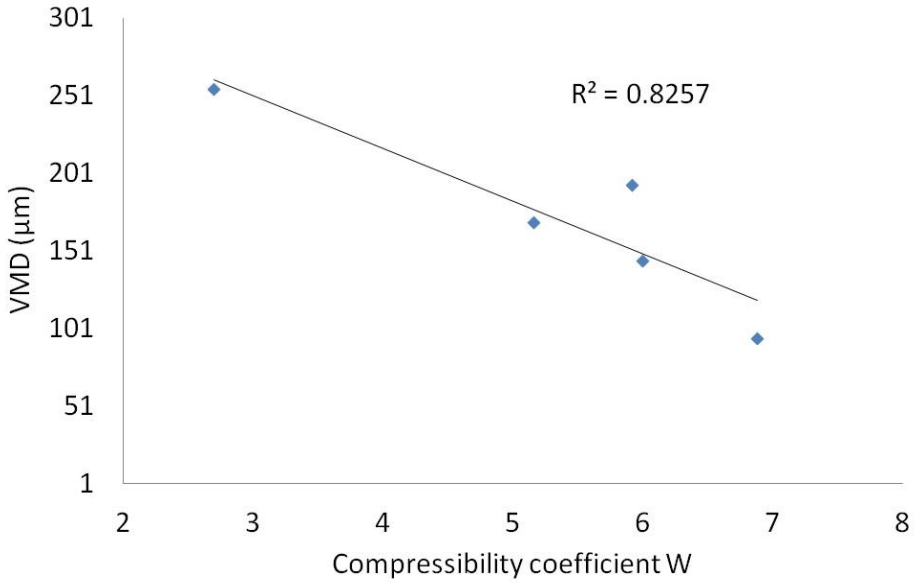

Figure 4: Linear correlation between the volumetric mean diameter and compressibility coefficient W. When data for the silicified MCC Prosolv (different surface texture) was included in the regression, the fitting was slightly less accurate ($R^2 = 0.74$).

We justify the separation of SMCC data from the correlation in Figure 4 (and also from correlations in Figures 9 and 10) on the basis of the different compressibility reported for SMCC. SMCC has a different surface texture than MCC due to the presence of silicon dioxide (Edge et al., 1999; Rojas and Kumar, 2011). Guo et al. (2002) showed that similar grades of MCC and SMCC have different compressibility characteristics. In fact, MCC and SMCC have different values for Apparent Mean Yield Pressure (AMYP), which is a measure of resistance to particle rearrangement and packing during the plug compression, and for Kawakita constant b, which is related to the forces resisting compression. Tobyn et al. (1998) have shown that the regular MCC (i.e., Emcocel 90M) and the SMCC (Prosolv SMCC90) used by Guo et al. (2002) have identical bulk chemical properties and polymorphism.

7.2.4. Capsule Filling

The capsule filling machine (Labby, MG2, Italy) used in our study is equipped with one dosator nozzle and a rotating bowl designed for small powder quantities. The selected speed of capsule filling was 500 and 3000 capsules per hour (cph), with 3000 cph being the maximum speed of the machine. The length of the DC is determined by the position of the piston. In order to fill the capsules with different amounts of powder, the piston was positioned at 3 mm, 6 mm and 12 mm from the edge of the nozzle. Although at DCs of 3mm and 6 mm size-3 capsules were not fully filled, these values were chosen to increase the pre-compression effect (effect of F) without needing to increase the powder bed depth. The feeder maintained the powder bed depth (PBD) at 32 mm in the bowl and is kept constant throughout all experimental conditions tested. Thus, the F values for the above piston positions (i.e., DCs) were 10.66, 5.33 and 2.66, respectively. The machine setup for each of the three F values is reported in Table 2. Six experimental conditions were generated by combining two speeds of operation (500 cph, 3000 cph) and three values of F. The nozzle used was number 3 (diameter = 4.7 mm).

Powder bed height (PBH)	32 mm	32 mm	32 mm
Dosing Chamber depth (DC)	3 mm	6 mm	12 mm
Ratio PBH/DC (F)	10.66	5.33	2.66
Volume dosing chamber (mm^3)	52 mm^3	104 mm^3	208 mm^3
Piston Compression (mm)	0 mm	0 mm	0 mm

Table 2: Parameter set-up of the capsule filling machine for each of the three F values.

The procedure followed in this study is a very important consideration because operators may introduce variability to the results. The machine was instrumented to minimize such effects. The dosing chamber in the nozzle was adjusted using the graduated scale attached to the top of the piston (Figure 5). The powder bed depth was set by means of a graduated scale located below the bowl (Figure 6) and was always corroborated by inserting a Vernier caliper in the powder bed. The rate of feeding to the bowl must always match the rate of powder removal by the nozzle. If powder quickly accumulated behind the blade used to distribute the powder in the bowl, then the rate of feeding was reduced and the excess of powder removed with a spatula. When the layer was stable and the process reached steady-state, fifty consecutively filled capsules were collected. The process was allowed to run for another five minutes before collecting another fifty filled capsules. If the difference between the mean fill weight for each set is significant (C.I. 95%), the root-cause was identified and the experiment repeated. If no difference in the mean fill weight was detected, the data was amalgamated into a single set and used for subsequent analysis.

Figure 5: Picture of the caliper used to fix the position of the piston in the nozzle (and hence the size of the dosing chamber).

Figure 6: Picture of the caliper used to fix the depth of powder bed in the bowl (located at the base of the shaft that controls the vertical position of the bowl).

In order to measure the fill weight, a Denver SI-234A scale (Readability: 0.0001 g; Reproducibility: 0.1 mg) was used. One hundred empty capsules were weighed and the average and the variance were calculated. The fill weight was subsequently calculated by subtracting the average weight of empty capsules from the weight of each full capsule. The plug density was calculated by dividing the fill weight by the volume of the dosing chamber. The variance of the fill weight (and plug density) was calculated using Equation 3:

$$\mathrm{Var}(\text{fill weight} + \text{capsules}) = \mathrm{Var}(\text{fill weight}) + \mathrm{Var}(\text{capsule}) + 2\,\mathrm{CoV}(\text{fill weight}, \text{capsules}) \quad \text{(Eq. 3)}$$

We assumed that the covariance of these two parameters is zero since they are not related and have no influence on each other. The standard deviation of the fill weight is the square root of the variance obtained in Eq. 3 and the relative standard deviation (RSD) of fill weight is the RSD divided by the average fill weight. The data for fill weight and RSD are presented in Table 3.

Speed	500 cph						3000 cph					
F value	10.67		5.33		2.67		10.67		5.33		2.67	
	Weight (mg)	RSD (%)	Weight (mg)	RSD (%)	Weight (mg)	RSD (%)	Weight (mg)	RSD (%)	Weight (mg)	RSD (%)	Weight (mg)	RSD (%)
Avicel 301	54.0	4.13	79.2	2.95	141.4	4.11	53.8	3.74	79.1	2.50	146.6	1.41
Avicel 302	49.3	3.86	71.6	2.68	131.4	4.67	53.2	4.01	75.6	2.57	143.4	1.20
Vivapur_12	47.7	7.33	68.9	5.53	122.0	3.43	53.9	4.36	71.9	3.46	125.0	1.47
Prosolv_SMCC	45.6	6.18	66.5	6.74	114.9	5.05	55.2	5.04	74.6	3.21	128.6	2.12
Avicel 102	37.7	4.86	59.46	3.56	111.2	1.84	42.4	4.21	64.0	3.25	113.7	1.71
Avicel 200	31.5	8.80	46.2	4.47	97.7	2.19	35.4	5.06	51.0	4.41	98.8	1.96

Table 3: Mean fill weight and RSD for groups of 100 capsules collected at 6 operation conditions (combination of F and speed).

7.3. Results

7.3.1. Effect of F and the Speed of Capsule Filling on Densification in the Nozzle

The effect of F on the plug density for filling speeds of 500cph and 3000cph is shown in Figures 7 and 8, respectively. For both speeds, when the nozzle travels through a deeper powder bed (larger F), additional pre-compression takes place and more material is allowed into the dosing chamber. As a result, heavier capsules are produced and the plug density increases. For the investigated range of F, the correlation between F and powder densification in the nozzle is linear and has a very good fit ($R^2 > 0.97$), except for Avicel 200 with a modest fit ($R^2 = 0.78$ at 500 cph and $R^2 = 0.93$ at 3000 cph). The effects of the pre-compression densification on fill weight has recently been investigated using a Zanasi dosator nozzle machine (Khawam, 2011; Khawam and Schultz, 2011), but the results are not comparable with ours due to differences in the design of the dosator nozzle. While in the Labby machine the position of the piston inside the nozzle is fixed in the pre-compression step, the displacement of the piston during pre-compression depends on the stiffness of the spring in the Zanasi dosator, which changes the size of the dosing chamber during pre-compression leading to a discrepancy between the measured and predicted values of the plug's size (Khawam and Schultz, 2011).

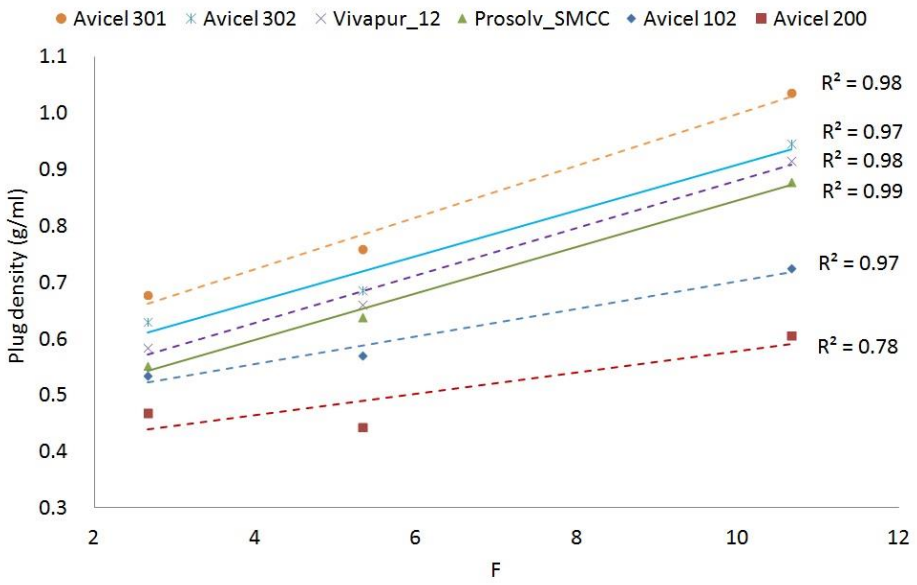

Figure 7: Effect of F on the plug density at a speed of 500 cph. The plug density had a strong linear correlation with F (R^2 was at least 97%, except for Avicel 200 with R^2 of 78%). Avicel 200 was the only material that did not form strong plugs.

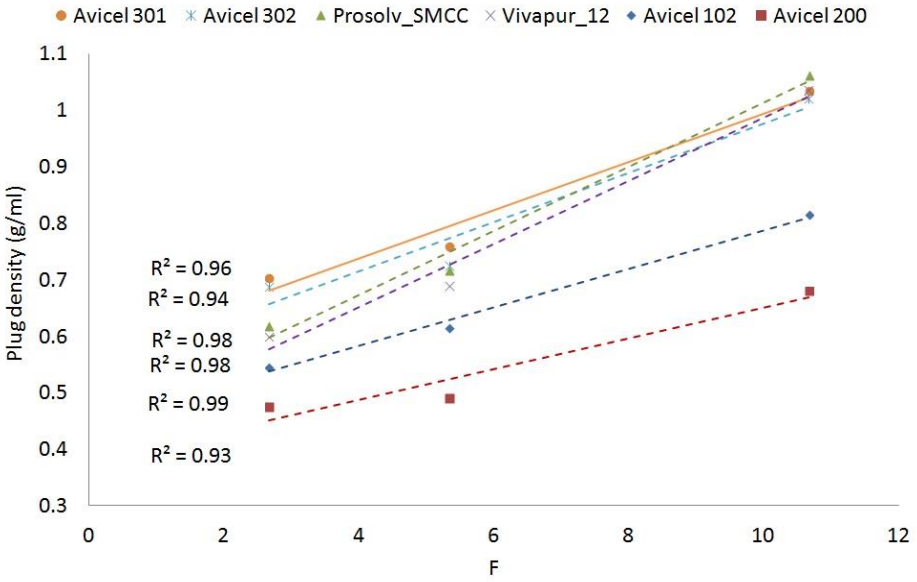

Figure 8: Effect of F on the plug density at a speed of 3000 cph. There is a strong linear correlation between the plug density and F (R^2 was at least 93%).

Although the effect of speed on the plug density is less pronounced than that of F, it is significant. The effect of speed on the plug density of the studied powders and therefore on the fill weight (factored by the volume of the dosing chamber of the nozzle) is associated with the vibrations of the capsule filling machine (Llusa et al., 2013). When the speed increases six-fold (from 500 cph to 3000 cph), the plug density increases in the range from 0% to 20% (depending on the type of MCC and on the F value). The effect of F on the plug density is much larger:

while F increases by a factor of approximately four (i.e., from F=2.66 to 10.66), the plug density almost doubles for the group of the six powders studied.

7.3.2. Effect of Powder Compressibility on Densification in the Nozzle

The Figures in the section above show that powder densification in the nozzle is affected by pre-compression caused by F. In this section, we investigate the effect of powder compressibility (W) on the densification of powder in the nozzle. To perform this analysis, we define a coefficient for densification of the powder in the nozzle as the slope of the linear regressions in Figures 7 and 8, which displays an appreciable fit for most powders ($R^2 > 0.97$) and a still acceptable fit for Avicel 200 ($R^2 = 0.93$ at 3000 cph and $R^2 = 0.78$ at 500 cph). The coefficient values (or slopes) are reported in Table 4.

	Avicel 301	Avicel 302	Vivapur 12	SMCC Prosolv 90	Avicel 102	Avicel 200
Compressibility Coefficient W	6.8811	5.9979	5.9144	4.7059	5.162	2.7
Densification coefficient in nozzles						
At 500 cph	0.0457	0.0408	0.0422	0.0413	0.0245	0.0189
At 3000 cph	0.0428	0.0435	0.056	0.0567	0.0341	0.0271

Table 4: Compressibility Coefficient W from the Walker equation and coefficient for the powder densification in the nozzle of capsule filling machine at 500 cph and 3000 cph.

The coefficient of densification in the nozzle depends on the speed of capsule filling, which agrees with the findings reported for the formation of plugs at low compression forces using a compaction simulator by Guo (2002), who observed that the dynamics of compression (speed) for low axial loads influenced the process of plug formation and the Kawakita compressibility index. Our results also indicate that the densification coefficient in the nozzle is affected by the speed of capsule filling (the nozzle dipping into the powder bed resulted in a different speed of pre-compression). Almost all materials, except Avicel 301 (i.e., the finest grade of MCC), densify further at higher speeds of sampling by the nozzle.

Correlations between W and the coefficients for densification in the nozzles during capsule filling are studied. At 500 cph, there is a modest linear correlation ($R^2 = 0.67$) between W and the coefficient for densification in the nozzle. However, when the SMCC (Prosolv) is removed from the data set, the linear correlation improves considerably ($R^2 = 0.82$ in Figure 9). At a high

speed of capsule filling (3000 cph), the correlation between the above two parameters is poor ($R^2 = 0.25$), and it also improves significantly when the silicified MCC (Prosolv) is removed from the data set ($R^2 = 0.54$ - Figure 10).

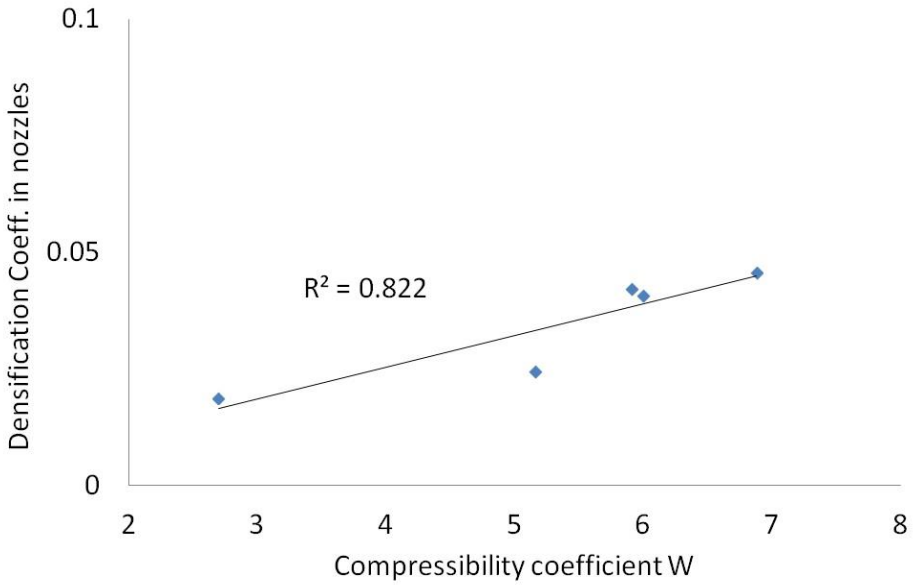

Figure 9: Correlation between the powder densification during the capsule filling process at 500 cph and the compressibility coefficient W from the Walker model.

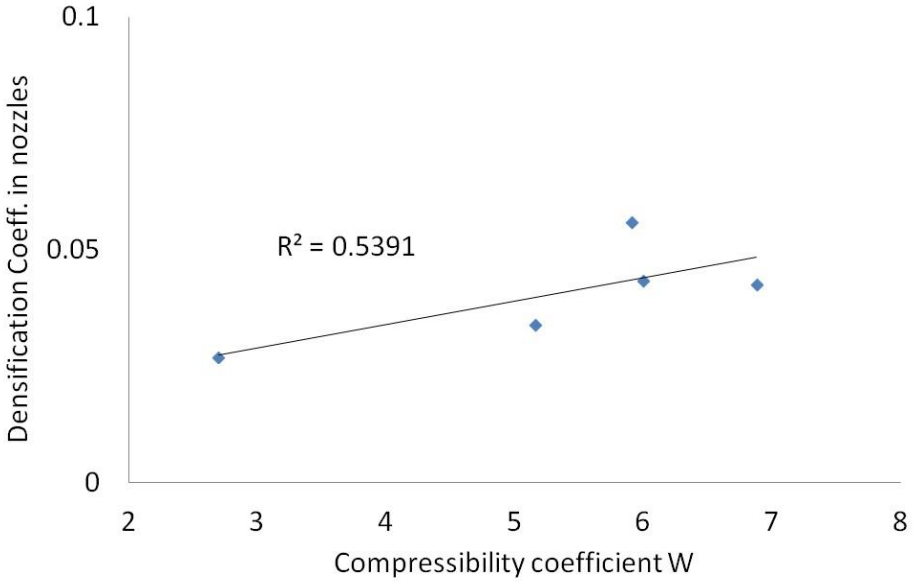

Figure 10: Correlation between the powder densification during the capsule filling process at 3000 cph and the compressibility coefficient W from the Walker model.

At both speeds of capsule filling, there is a correlation between the compressibility coefficient and the powder densification in the nozzles. Moreover, in both cases, excluding SMCC from the data set leads to a better fit between W and densification during the capsule filling process. Since the compressibility behavior of SMCC is different from the regular MCC and other

pharmaceutical excipients (Guo et al, 2002), we limit the current study to MCC powders with different particle sizes and similar surface properties.

7.4. Conclusions

In this study, we investigated the effects of powder compressibility, speed of capsule filling and ratio between the powder bed depth (PBD) and the length of the dosing chamber (DC) on powder densification in the nozzle of a capsule filling machine. This work provides an insight into modeling the powder compressibility data at low compression forces (measured using the module of the FT4) via the Walker equation for the pre-compression of powders in nozzles. A strong correlation between the Walker compressibility coefficient and particle size was observed, which supports utilization of this expression for modeling the compressibility data. Subsequently, W was successfully used to analyze powder densification in the nozzle during the capsule filling operation.

The effect of the ratio between the PBD and the length DC, i.e., F, on the powder densification was assessed at very low and high capsule filling speeds. As expected, higher F values led to denser plugs and the investigated types of MCC showed a strong linear correlation between the plug density and F. Although the parameter F is frequently manipulated, it has not been systematically investigated with regard to dosator nozzle capsule filling machines. Nozzles may have a different mechanism of controlling the size of the dosing chamber. For example, the displacement of the piston in the nozzle described by Khawan (2011) is regulated by a spring (and the stiffness of the spring) as the nozzle moves through the powder bed, as opposed to the nozzle used in the current research, in which the piston position was fixed before the nozzle entered the powder bed. Such details should be considered before extending or applying the conclusions of the current study to capsule filling operations that involve nozzle systems of various types.

Acknowledgements

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Disclosure Statement

The current study was commissioned to RCPE by MG2 (Bologna, Italy) and GlaxoSmithKline (GSK).

Role of the Funding Sources

We thank MG2 and GSK for funding this research and MG2 for providing the capsule filling equipment. The research was conducted exclusively at RCPE (Graz, Austria).

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„We must have perserverence and above all confidence in ourselves. We must believe that we are gifted for something.“

Marie Curie

8. Summary and Conclusion

Chapter 1 provides an overview of (1) the state of the art capsule filling systems using granular material, (2) the behaviour of those materials during processing and (3) the motivation to work in this research field.

In Chapter 2, a lab scale dosator nozzle process was investigated and was used to fill standard doses (30 - 150mg) of various MCC types into hard gelatin capsules. Material attributes were determined and correlated with the capsule fill weight and weight variability of a lab scale dosator nozzle system. There was a clear correlation between the capsule fill weight and the particle size, the compressibility and air permeability. The WFA, tapped density and particle shape also displayed a major impact. Larger fill weights were more affected by density, while lower fill weights by flow- and friction characteristics. However, no significant correlation was found between the material attributes and the weight variability for standard doses leading to the assumption that the weight variability for standard doses is more affected by process parameters. In summary, it was demonstrated that MCCs with smaller particles resulted in higher fill weights and formed stable powder plugs due to their higher compressibility and air pressure drop. However, many critical material attributes (CMAs) influence the capsule-filling process, hence the critical quality attributes (CQA) and the analysis becomes increasingly challenging when the dose size decreases.

Therefore Chapter 3 investigated the CMAs and critical process parameters (CPPs) affecting low-fill weight (1 - 45 mg) products. Thirteen inhalation powders were divided into two groups depending on their material attributes. For these two groups different sets of CPPs were required to perform capsule filling. The fill weight of both powder groups was affected by the same process parameters but by different material attributes. A key finding was that the first group of powders (bigger particles and higher densities) exhibited volumetric filling

behavior as expected, whereas the second group (smaller particles and lower density) did not. For the latter the wall friction angle and the basic flowability energy were determined as additional critical material attributes. The relative standard deviation (RSD) for both groups was affected by the powder density as CMA but the significant process parameters differ. Both powder groups behaved completely different during capsule filling. While for powder group I dosator diameter and powder layer depth influenced the capsule filling performance, powder group II was also affected by the capsule filling speed. Moreover, it could be demonstrated that the manufacturing of the powders has an effect on low dose dosator capsule filling performance. Sieved and spray dried powders show a better behavior during filling than the milled and micronized ones. The spheronized powder showed the worst results. The RSD of fill weight of group I powders was from a regulatory perspective in most cases below the required threshold. For group II powders this was, however more challenging to achieve without the use of a process control system. Thus, for very fine powders low-dose filling with a dosator system is highly challenging and a process control would be required to achieve product specification compliance. Finally it was demonstrated that very complex combinations of CMAs, CPPs and environmental conditions affect the fill weight variability.

Based on the research of chapter 3 the focus of chapter 4 was to validate and optimize the proposed model to create a design space and a predictive process model as a function of process parameters and material attributes for low-dose inhalation products. The model was successfully used to determine which process settings are required for a specific powder to achieve a desired fill weight with a chosen RSD. Low-dose capsule filling was performed within the established design space. The operating ranges for the design space of the two groups, which predict the conditions under which low-dose capsule filling yields product of desired and acceptable quality, show major differences. Although the desired fill weight was accurately predicted for powders in both classes for the known CMAs and CPPs, the model's predictive performance was inadequate in terms of fill weight variability. The developed model and the established design space could save time and material costs during the development of low fill-weight capsule filling for inhalation products.

In chapter 5 a vibratory sieve chute system (MG2 Microdose system) was investigated for filling capsules gravimetrically with fill weights under 5 mg. Different frequencies and

amplitudes as CPPs were investigated and an operating space was established for three inhalation grade lactoses. It could be shown that the system is suitable for the gravimetric feeding of very low doses. Moreover it was demonstrated that the system is capable to fill doses in the sub mg range fast and accurately when the powder is distributed homogenously inside the vibrating chute.

Because several process parameters can heavily affect the CQAs of the final capsule, Chapter 6 and 7 investigated some of them more detailed. The effect of machine vibrations, powder compressibility, speed of capsule filling and ratio between the powder bed depth and the length of the dosing chamber on powder densification in the nozzle of a capsule filling machine were studied. It could be shown that the vibrations of a capsule filling machine affect the density of the powder used for encapsulation and, therefore, the fill weight of the final product. As expected, higher compression ratios led to denser plugs and the investigated types of MCC showed a strong linear correlation between the plug density and and the bigger compression ratio. Comparing this fact with the investigations of chapter five where powder with a particle size smaller 10 µm could not be filled at higher ratios (dosator blocking) it can again be demsontrated how different and complex the powders behave during processing and that still more research is needed to fully understand the behaviour of granular material during processing.

„One never notices what has been done;
one can only see what remains to be
done.“

Marie Curie

9. Outlook

An accurate low fill weight is the key quality factor for the final product of a low-dose capsule filling process. The following effects are often encountered resulting in a negative influence on the filling, hence product quality. Segregation of the API in the hopper, as well as during the feed into the rotary container could lead to irregularities in the API distribution in the final products. As the filling of the rotary container is done automatically, variations in fill level can be encountered depending on material attributes such as cohesiveness, electrostatic properties, etc. Throughout the dosing process, some additional properties, so called in process parameters of the powder inside the rotary container might evolve, e.g. agglomeration, densification or electrostatic charging. In consequence changes is powder layer constitution can arise resulting in deviations of the final fill weight. Especially for inhalation powders, the fine cohesive API particles have a high tendency to agglomerate, resulting in a smaller effective number of larger particles, which can increase the statistical fluctuations in active content.

As could be demonstrated throughout this thesis the powder layer is a major issue concerning weight variability of capsules filled with dosator nozzles. Channels inside the powder layer, created during dosator dipping are sometimes only covered but not filled up and therefore not visible for the operator. Additionally compacted or loose areas of the powder layer have to be avoided to ensure consistent fill weight thus final product quality. Various scrapers and other systems are used to re-create a uniform bed. This is, however, not straightforward and it is especially critical when the physical properties of the powder make dosing difficult and the powder bed remains heterogeneous due to a lack of flowability. Optimization of the current solutions to prevent this effect should be performed to guarantee a smooth an even layer for all powders.

Moreover, the implementation of a suitable process analytical technology (PAT) strategy for monitoring the quality of the powder layer could help to establish an industrial scale low fill

weight process, which runs stable over a long time period. Therefore, on line measurement of the density distribution of the powder layer during capsule-filling process should be investigated in future studies.

Furthermore, it is well known that environmental conditions highly affect the product during processing and dosator blockage might be one of several problems that could be encountered in consequence. The interaction between API and carrier may also be affected due to scale-up, which can have a significant impact on the product drug delivery capabilities. In order to achieve the desired fill weight and minimize weight variability, powder must be retained in the nozzle during transfer from the powder bed to the capsule shell. Material losses can occur as powder enters the capsule body and particles are entrained by the air, that is displaced out of the capsule. Critical material attributes affecting the process are known on lab scale. However, profound knowledge of the critical material attributes, critical process parameters, environmental conditions and combinations thereof still have to be established for industrial scale.

Another important topic of current interest is the development of an environmentally controlled continuous capsule filling line. After raw material feeding and blending of i.e. excipient (s) with API (s) and an optional granulation step, the powderblend is dosed into the capsule (via direct or indirect methods). All these unit operations have to be mechanically integrated and adequate process monitoring tools and control strategies should be applied to minimize raw material, blend and final product waste. Some current challenges are, (1) to implement sensor concepts that monitor critical quality attributes such as fill weight and content uniformity; (2) the feeding of low doses might be the biggest obstacel since feeding rates of 100 g/h and lower might be required; (3) segregation or insufficient mixing in continous blenders might be another challenge to overcome during processing. Also an additional implementation of primary and secondary packaging could be implemented into the continuous capsule filling line.

This work highlightes a number of avenues that could be explored in order to enhance and progress with the interesting research field of standard and low-dose capsule filling of oral and inhalation products, especially on industrial scale.

10. Appendix

10.1. Curriculum vitae

Eva Christina Faulhammer

Born on May 25th 1984, Gnas, Austria

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EDUCATION

Since 05/2011	**Doctoral Program in Natural Science** University of Technology, Graz, Austria Reserach Center Pharmaceutical Engineering (RCPE) Thesis: Process understanding and optimization of dosing and filling systems for the production of pharmaceutical hard capsules Supervisor: Prof. Johannes G. Khinast
10/2010 – 10/2014	**Master Program Pharmaceutical Engineering** University of Technology Graz, Austria Reserach Center Pharmaceutical Engineering (RCPE) Thesis: Impact of carrier surface modification and dosator capsule filling process on DPI performance of adhesive mixtures Supervisor: Prof. Johannes G. Khinast
10/2003 – 09/2010	**Diploma study Pharmacy** University of Graz, Austria University Hospital Graz With distinction

	Thesis: Evaluierung und Beiträge zur Optimierung in der Behandlung mit Blutgerinnungsfaktoren am LKH Univ. klinikum Graz Supervisor: Prof. Reinhold Wintersteiger
09/1999 – 06/2003	**Bundesoberstufenrealgymnasium** **Monsbergergasse Graz**

PROFESSIONAL EXPERIENCE

Since 10/2010	**Research Center Pharmaceutical EngineeringGmbH** Researcher (Area II, Products and Formulations)
01/2009 – 07/2011	**Institut für Kind Jugend und Familie (IKJF), Dr. Streit** Social assistance and social care for children and teenagers
01/2005 – 06/2006	**Medical University of Graz** Part time worker in a student program
05/2009	**Christine Breitfuss** Internship gastronomy
06/2010	**Christine Breitfuss** Internship gastronomy

DISTINCTIONS

12/2013	Nominated for the Pat Burnell New investigator Award at Drug Delivery to the Lungs, Edinburgh, 2013.

10.2. Publications

Research Papers

M. O. Besenhard, E. Faulhammer, S. Fattholahi, M. Llusa, S. Biserni, V. Calzolari, S:M: Lawrence, J.G. Khinast: Accurate Powder Dosing via a Vibratory Sieve Chute System. Europ. J. Pharm., submitted Feb. 2015.

E. Faulhammer, M. Llusa, P.R. Wahl, A. Paudel, S. Biserni, V. Calzolari, S. M. Lawrence, J.G. Khinast: Development of a design space and predictive statistical model for the capsule filling of low- fill weight inhalation products. DDIP, accepted for publication, April 2014.

M. O. Besenhard, A. Thurnberger, R. Hohl, E. Faulhammer, J. Rattenberger, J. G. Khinast: Continuous API-Crystal Coating via Coacervation in a Tubular Reactor. Int. J. Pharm., vol. 475, pp. 198-207, 2014.

E. Faulhammer, M. Fink, M. Llusa, S. Biserni, V. Calzolari, S. M. Lawrence, J. G. Khinast: Low-dose capsule filling of inhalation products: Critical material attributes and process parameters. Int. J. Pharm., vol. 473, pp. 617-626, 2014.

E. Faulhammer, M. Llusa, O. Scheibelhofer, S. Biserni, V. Calzolari, S. M. Lawrence, J. G. Khinast: The effects of material attributes on capsule fill weight and weight variability in dosator nozzle machines. Int. J. Pharm., vol. 471, pp. 332-338, 2014.

M. Llusa, E. Faulhammer, S. Biserni, V. Calzolari, S. M. Lawrence, J. G. Khinast: The effects of powder compressibility, speed of capsule filling and pre-compression on plug densification. Int. J. Pharm., vol. 471, pp. 182-188, 2014.

M. Llusa, E. Faulhammer, S. Biserni, V. Calzolari, S. M: Lawrence, J.G. Khinast: The effect of capsule-filling machine vibrations on average fill weight of capsules. Int. J. Pharm., vol. 454, pp. 381-387, 2014.

Talks

E. Faulhammer, M. Besenhard, S. Fattholahi, M. Llusa, S. Biserni, V. Calzolari, S. M: Lawrence, J.G. Khinast: Microdosing / Microfeeding of Pharmaceutical Products into Capsules - in: AIChE Annual Meeting, Atlanta, 2014.

E. Faulhammer, D. Lopes, K. Becker, D. Haack, D. Lochmann, J.G. Khinast, A. Zimmer, S. Salar-Behzadi: Advanced structuring of lipids for controlled drug release - in: AIChE Annual Meeting, Atlanta, 2014.

E. Faulhammer, M. Llusa, S. Biserni, V. Calzolari, S. M: Lawrence, J.G. Khinast: Scale - Up / Process transfer of a low-dose capsule filling process for inhalation products - in: AIChE Annual Meeting, Atlanta, 2014.

S. Zellnitz, E. Faulhammer, V. Wahl, H. Schröttner, J. G. Khinast: Investigating the influence of carrier morphology and dosator capsule filling process on the performance of dry powder inhalers (DPIs) - in: AIChE Annual Meeting, Atlanta, 2014.

E. Faulhammer, M. Llusa, S. Biserni, V. Calzolari, S. M: Lawrence, J.G. Khinast: Scale - Up of a low-dose capsule filling process for inhalation products - in: PSSRC-Meeting, Ljubljana, 2014.

M. Llusa, E. Faulhammer, J. G. Khinast, M. Fink, S.M. Lawrence, S. Biserni, V. Calzolari: Manufacturing of Low-Fill Weight Capsules Using a Nozzle Dosator Capsule Filling Machine – in: AIChE Annual Meeting, San Francisco, 2013.

E. Faulhammer, M. Llusa, J.G. Khinast, M. Fink, S. M. Lawrence, S. Biserni, V. Calzolari: Effect of process parameters and powder properties on low dose dosator capsule filling - in: Drug Delivery to the Lungs, Edinburgh, 2013.

M. Llusa, E. Faulhammer, J. G. Khinast, S. Scharrer, S. M. Lawrence, S. Biserni, V. Calzolari: Capsule Filling Operations Using a Nozzle-Dosator – in: AIChE Annual Meeting, Pittsburgh, 2012.

Posters

E. Faulhammer, M. Besenhard, S. Fattholahi, M. Llusa, S. Biserni, V. Calzolari, S. M. Lawrence, J. G. Khinast: Microdosing / Microfeeding of Pharmaceutical Products into Capsules - in: AIChE Annual Meeting, Atlanta, 2014.

E. Faulhammer, M. Llusa, M. Fink, S. M. Lawrence, V. Calzolari, S. Biserni, J. G. Khinast: Creating a design space for low-dose capsule filling of products for inhalation - in: 9th Worldmeeting on Pharmaceutics, Biopharmaceuticsand Pharmaceutical Technology, Lissabon, 2014.

M. Llusa, E. Faulhammer, S. M. Lawrence, V. Calzolari, S. Biserni, J. G. Khinast: The effects of powder compressibility and precompression in nozzles on plug densification - in: 9th Worldmeeting on Pharmaceutics, Biopharmaceuticsand Pharmaceutical Technology, Lissabon, 2014.

E. Faulhammer, M. Llusa, J. G. Khinast; M. Fink, S. M. Lawrence, S. Biserni, V. Calzolari: Effect of process parameters and powder properties on low-dose dosator capsule filling - in: Drug Delivery to the Lungs, Edinburgh, 2013.

E. Faulhammer, M. Llusa, S. M. Lawrence, V. Calzolari, S. Biserni, J. G. Khinast: The Effect of Capsule-Filling Machine Vibrations on Average Fill Weight of Capsules - in: 9th Minisymposium Verfahrenstechnik, MU Leoben, 2013.

E. Faulhammer, M. Llusa, M. Bresciani, S. M. Lawrence, V. Calzolari, S. Biserni, J. G. Khinast: The Effect of the Ratio Between the Powder Bed's Height and the Length of the Dosing Chamber and the Speed of Capsule Filling on Plug Density and Capsule Weight Variability – in: AAPS Annual Conference, San Antonio, 2013.

E. Faulhammer, M. Llusa, S. M. Lawrence, V. Calzolari, S. Biserni, J. G. Khinast: The Correlations between Powder properties, nozzle material and capsule weight variability -in: 8th Minisymposium Verfahrenstechnik, JKU Linz, 2012.

E. Faulhammer, M. Llusa, J.G. Khinast, G. Scharrer, S. Biserni, S.: Understanding the effects of powder and wall material properties on weight variability during capsule filling - in: 8th Worldmeeting on Pharmaceutics, Biopharmaceuticsand Pharmaceutical Technology, Istanbul 2012.

Supervised Bachelor students

Thomas Pichler (graduation July 2013)

Supervised Master Students

Marlies Fink (graduation, Februar 2014)
Sigrid Pilz (graduation, October 2013)

European patent application

J.G. Khinast, T. Klein, E. Faulhammer, M. Bresciani: Continuous low dosing of an active ingredient (date of filing 09.09.2014).

„Life is not easy for any of us.
But what of that?
We must have perseverance
and above all confidence in ourselves.
We must believe that we are gifted for something
and that this thing must be attained.“

Marie Curie