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Continuous low-dose capsule filling of pharmaceutical inhalation powders

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Statutory Declaration

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Abstract

Pulmonary local and systemic applications of dry powder inhalers (DPIs) are increasing and the need for low-dose capsules for the respiratory drug delivery route is becoming of major importance. Therefore this study deals with the low-dose dosator capsule filling process and its optimization using the Quality by Design (QbD)-based approach. First of all twelve inhalation powders, ten lactoses, mannitol and an active pharmaceutical ingredient (API), were thoroughly characterized and categorized into two powder families based on particle size and density as the powders cover a broad spectrum. The capsule filling process itself was subjected to a Risk Assessment (RA) to take actions and minimize the impact of process-related steps or from environmental conditions on the quality of the filled capsules. Further on an experimental plan with a screening Design of Experiments (DoE) (D-Optimal with design statistics G-Efficiency) for each powder family was established to identify and assess the impact of critical material attributes (CMAs) and critical process parameters (CPPs) on the capsule fill weight and weight variability, considered as the critical quality attributes (CQAs). The capsule experimental data combined with the values of the material attributes, were analyzed with multivariate data analysis (MVDA) and yielded coefficients (between 0 and ±1; ± 1 being high and 0 no influence) for both, CMAs and CPPs, of the capsule filling process for low doses. This was performed with a partial least square (PLS) regression to fit the model by simultaneously representing the variation of all responses (CQAs) with the variation of factors (CMAs and CPPs). According to the influencing parameters from both DoEs the capsule filling process could be optimized and the linear models, developed with the results of the screening DoE, were validated to predict the fill weight and weight variation of filled capsules within the designated Design Space to reliably produce high quality capsules for inhalation purposes.

Kurzfassung

In Anbetracht der steigenden Prävalenz von chronisch obstruktiven Lungenerkrankungen und den zahlreichen neuen Wirkstoffen aus dem Bereich der Biologicals, gewinnt der pulmonale Applikationsweg für lokale und systemische Anwendung immer mehr an Bedeutung. Zusätzlich werden dabei nur sehr geringe Dosen benötigt, die in dieser Arbeit anhand von einem automatisierten, kontinuierlichen Dosierstempel-Kapselfüllprozess mittels „Quality by Design"-Ansatz studiert und optimiert wurden. Die zwölf verwendeten Inhalationspulver, mit einem breiten Partikelgrößen-Spektrum, wurden in zwei Pulverfamilien eingeteilt und dafür zwei verschiedene „Screening-Design of Experiments" erstellt und durchgeführt. Mittels den daraus erhaltenen experimentellen Daten wurde eine multivariate Datenanalyse durchgeführt, die statistisch signifikante Einflussfaktoren, sowohl Pulvereigenschaften als auch Prozessparameter, aufzeigte. Anhand dieser Einflussfaktoren ist es möglich den Kapselfüllprozess dahingehend zu optimieren und zu validieren, um eine Aussage über das zu erwartende Gewicht und die Gewichtsabweichung der befüllten Kapseln im Voraus zu treffen. Durch die Einteilung in zwei Pulverfamilien kann man nach der Partikelgröße und der Dichte der Pulver die Pulvercharakterisierung auf die Einflussfaktoren des jeweiligen Design of Experiment eingrenzen und Kapseln in dem dazugehörigen Design Space produzieren. Eine zusätzliche Risikoanalyse zeigt etwaige Risiken im Umfeld und im Prozess auf und trägt dazu bei, diese Risiken zu minimieren um ein hoch qualitives Produkt innerhalb des designierten Design Space herzustellen.

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Abbreviations

AIF	Angle of internal friction
API	Active pharmaceutical ingredient
BFE	Basic flowability energy
C	Cohesion
cha	Dosing chamber
cha*lay	Interaction of dosing chamber and powder layer height
CI	Carr Index
CMA	Critical material attribute
cph	Capsules per hour (machine speed)
cps	Capsules
CPL	Compressibility Index
CPP	Critical process parameter
CQA	Critical quality attribute
DC	Dosing chamber
Det	Detectability
dia	Dosator diameter
dia*cha	Interaction of dosator diameter and dosing chamber
DoE	Design of experiments
DPI	Dry powder inhaler
FFC	Flow function
FMEA	Failure mode and effects analysis
GSK	Glaxo Smith Kline
IH 230	Inhalac 230
Layer	Powder layer height
LH_GSK	Lactohale formulated by GSK
LH100	Lactohale 100
LH300	Lactohale 300
MgSt	Magnesium stearate
MG2	MG2 Italy
ML001	Respitose ML001
ML006	Respitose ML006
M_MG2	Mannitol (spray-dried) produced by MG2 Italy

n. a.	Non available
Occ.	Occurance
P-FMEA	Process-failure mode and effects analysis
pbh	Powder bed height
PD	Pressure Drop across powder bed, measured by the Air Permeability Test on FT4
PLS	Partial Least Square Regression
QbD	Quality by Design
Ra	Roughness
r. H.	Relative humidity
RPN	Risk priority number
RSD	Relative standard deviation
S400	Sorbolac 400
Sev.	Severity
SL	Spheronized Lactose formulated by GSK
SOP	Standard Operating Procedure
Spe	Speed (cph)
Stdv.	Standard deviation
SV003	Respitose SV003
SV010	Respitose SV010
True	True Density
VMD	Volume mean diameter
WFA	Wall friction angle
X50	Particle size distribution, where 50% of all particles are below this size

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1. Goals and Motivation

The motivation of this thesis is to achieve a greater insight into the low-dose capsule filling process using a Quality by Design (QbD)-based approach to gain a design space for low fill weights concerned with high quality inhalation products.

A special focus is put on capsule-based dry powder inhalers (DPIs) as almost half of all marketed DPIs belong to this category as DPIs offer a wide range of advantages like better patient compliance, formulation stability and environmental sustainability, only to name a few (Newman and Busse, 2002; Ashurst et al., 2000; Smith and Parry-Billings, 2003). In general DPIs can be categorized into two types (Eskandar et al., 2011; Islam and Cleary, 2012): single-unit dose (capsules or disposable) and multiple-unit dose (pre-metered unit or reservoir). Pre-metered single-unit dose in capsules, is protected from environmental conditions until used, and ensures adequate control of dose uniformity (Daniher & Zhu, 2008). Examples for capsule-based devices are the Rotahaler™ (Glaxo Smith Kline), Handi-Haler™ (Boehringer-Ingelheim) as single unit-dose and the Flowcaps® (Hovione) as novel multiple pre-metered unit-dose technology, that comprises up to 20 capsules (Newman, 2004; Steckel et al., 2004; Islam and Gladki, 2008).

Pulmonary drug delivery is gaining grounds in the local treatment of respiratory diseases as well as in the targeted systemic application of highly potent, complex and low-dose active pharmaceutical ingredients (API). A high concentration of drug on the targeted site is achieved with relatively low doses and in addition reducing adverse drug effects. These advantages can be attributed to the high absorption area in the alveolar region of the lungs and the circumvention of the first pass effect of the oral administration route (Daniher and Zhu, 2008; Stegemann et al., 2013). Other key features of the respiratory drug delivery are the direct targeting of the drug; rapid and predictable onset of action; degradation within the gastrointestinal tract is avoided hence lower applied dosages minimize unwanted side effects and drug interactions (Timsina et al., 1994).

DPI as a dosage form consists of a powder formulation in a device, which is designed to deliver an active ingredient to the respiratory tract. The dry powder aerosol technology is intended, not only for local, but also for systemic treatment (Kou et al., 2012).

A lot of effort is put into research and development for novel DPI formulations and devices, searching ways to improve the efficiency of drug delivery (Islam and Cleary, 2012). Especially with the increased recognition of the potential role of DPI systems for other therapies in the field of low dosage medication, DPIs could become the device category of choice for local and systemic drug delivery (Newman, 2004).

The challenge for the successful development of low-dose DPI products is, however, to correlate the critical material attributes (CMAs) of the bulk solids to critical process parameters (CPPs) of the manufacturing process to the quality parameter of interest, in our case fill weight and weight variability. At the same time to ensure efficacious dose delivery according to inspiratory force of the patient (Eskandar et al., 2011; Marriott and Frijlink, 2012).

As most of the existing low-dose applications for filling capsules are based on the direct filling principle with gravimetric techniques, this research is motivated by an indirect filling principle based on one of the most common volumetric techniques in standard doses, the dosator nozzle principle. Yet it is the first scientific qualification and investigation of low-dose dosator nozzle capsule filling performance with much smaller dosator nozzles, compared to standard nozzles, and other special adjustments for the experimental procedure (provided by MG2).

The goal of this study is to carry out low-dose capsule filling experiments with a low-dose dosator nozzle capsule filling machine based on Design of Experiments (DoE) to gain process understanding of the influencing process parameters and to correlate them to previously obtained material attributes of 12 different inhalation powders. DoE is a tool attributed to QbD and it was performed with ten different grades of lactose, mannitol and an API. This is done to acquire statistically significant experimental data by analyzing information with multi-variate data analysis (MVDA) and to gain a design space ascribed CPPs and CMAs leading to desired responses concerned with critical quality attributes (CQAs), namely capsule fill weight and weight variability.

All DoE experiments are carried out with a lab-scale nozzle dosator machine ‘Labby’ with recently developed special low-dose adjustments from MG2 (MG2, 2011a, 2012).

Finally MVDA will be performed with MODDE 9.1 (Umetrics, Sweden) to identify influencing material attributes and process parameters on the final low-dose capsule quality within the largest possible design space for inhalation products.

Summary of goals of the present work:

1. Implementation of a QbD-based approach with DoE, MVDA and Risk Assessment (RA)
2. RA of the complete low-dose dosator capsule filling process
3. Completion of the screening DoE designed by MODDE 9.1

4. Data analyses of all experimental data sets aligned with material attributes in MODDE 9.1
5. Optimization of the capsule filling process of MG2 ‘Labby’ with gained process understanding (RA, DoE, MVDA)
6. Creating a design space for low-dose capsule filling with inhalation powders

2. Process Description

2.1. Capsule Filling Technologies – State of the Art

Capsule filling machines are available in various forms with quite a few different dosing systems, especially in low-dose capsule filling, with either volumetric or gravimetric operating principle. These are for volumetric principle the nozzle dosator, vacuum drum filler, vacuum dosator and tamp filler and various gravimetric techniques for micro dosing. Comparing all available low-dose capsule fillers, dosing less than 45 mg, quite a few can be operated on volumetric basis and only for very low-doses the gravimetric principle is applied. Common standard capsule filling methods are widely described in literature (Armstrong, 2008; Cole, 1999; Edwards, 2010; Florence and Siepmann, 2009; Jones, 2001; Keck and Müller, 2009; Podczeck and Jones, 2004a).

2.1.1. Direct Filling Methods

In the following section two principles of direct capsule filling are outlined and discussed taking standard- and low-doses into account. Especially for low- and micro-doses the gravimetric, vibration-assisted method is commonly used.

2.1.1.1. Auger-filling principle

This principle is based on semi-automatic equipment, where the powder is filled into the capsules by a rotating auger. The empty capsule bodies are provided beneath the auger by a filling ring rotating on a turntable. This filling principle is primarily volumetric as the fill weight is governed by the speed and the twist angle of the auger how much powder fits into an empty capsule body. Over time the powder in the auger reaches its tapped density compared to the bulk density at start, which affects the actual fill weight over time (Florence and Siepmann, 2009; Keck and Müller, 2009; Podczeck and Jones, 2004a).

2.1.1.2. Vibration-assisted filling principle

Capsules are positioned underneath a powder bowl with a mesh floor by a rotating turntable, similar to the auger-filling principle. The mesh floor is connected to a vibration plate, whereby the vibration tends to fluidize the powder bed and passes the powder through the mesh and assists de-agglomeration and flow. An intended overfill during the feeding step is then compressed to a plug and the excess powder is scraped off before

closing. With this volumetric technique fill weight is adjusted by the rotation speed and the extent of vibration as well as by compression settings and the actual plug length after scraping step (Florence and Siepmann, 2009; Podczeck and Jones, 2004a).

Direct filling at micro-dose level is usually a vibration-assisted gravimetric technique, where the powder dispensing head is equipped with a sieve of defined mesh size. The mesh size has to match the powder to allow arching. With the mechanical tapping (variable frequency) of the dispensing head the arches above the mesh collapse and allow a small dose being dispensed into the capsule body. In addition the equipment includes a microbalance or a weigh cell, weighing each capsule after dispensing of the powder (3 P Innovation, 2013a, 2013b; Bailey and Seaward, 2012; Bryant et al., n.d.; Chen et al., 2011, 2012; Edwards, 2010; GSK and MG2, 2010; MG2, 2011a, 2011b; Podczeck and Jones, 2004a).

2.1.2. Indirect Filling Methods

Indirect filling at low-dose level, especially for inhalation purposes, is impossible for tamp-filling machines due to compression and quite difficult for standard dosator nozzle machines to dose at such a low range. However with the dosator principle the compaction/compression step can be disabled and still produce filled capsules. But since the powder must be retained in the nozzle during transfer a free-flowing powder only exposed to pre-compression is not necessarily advantageous due to the inability to form an arch (Jones, 2001; Podczeck and Jones, 2004b). Moreover cohesive powders are retained easily by arching at slight pre-compression, however challenging in maintaining a uniform powder bed height due to extremely reduced flowability. In fact powder characteristics have an impact on reproducible fill weights and weight variation for indirect filling methods (Armstrong, 2008; Jones, 2001; Khawam, 2012; Newton, 2012; Podczeck and Jones, 2004b; Tan and Newton, 1990).

2.1.2.1. Tamp-filling principle

Tamp filling is usually referred to as dosing-disc-filling principle. The dosing-disc is the base of the filling chamber, with numerous holes bored through it. A so-called tamping ring prevents powder being pushed through the dosing bores by sliding along the bottom. Powder feed into the dosing holes is maintained at a relatively constant level. Sets of tamping pins, usually arranged in a circle, are aligned in a way that each plug is

compressed five times per cycle before being ejected into empty capsule bodies. The fill weight can be controlled by the thickness of the dosing-disc, the powder bed depth and the tamping pressure, which reaches compression forces in the range of 50-150 N (Armstrong, 2008; Florence and Siepmann, 2009; Jones, 2001; Keck and Müller, 2009; Podczeck and Jones, 2004a; Podczeck and Newton, 1999).

2.1.2.2. Dosator nozzle principle

Capsule filling using dosator nozzle principle has been widely investigated and it is one of the main technologies used by pharmaceutical industry today (Armstrong, 2004; Florence and Siepmann, 2009; Jones, 2001; Keck and Müller, 2009; Newton, 2012; Podczeck and Jones, 2004a). This section provides a detailed description of this principle.

Dosator nozzle capsule filling machines can be operated in two principles, either in intermittent motion or in continuous motion during operation. The intermittent principle needs two dosators whereas the continuous principle only needs one dosator in rotating movement within one working cycle at lab-scale (MG2, 2011a). At industrial scale up to 32 dosators can be aligned in series depending on production speed and capacity i.e. Planeta 100, MG2 (MG2, 2011c). The dosator nozzle itself consists of a hollow dosing tube, cylindrical inside whilst outside conical, and a corresponding piston inside. Initial position of the piston is determined by the set dosing chamber height, defining volume and consequently weight of the powder plug formed. For the retention of the powder in the nozzle during transfer the powder must be able to form an arch (see section 2.1.2.). Fill weight of capsules is variable by adjusting the dosing chamber as well as varying the powder bed height. At constant dosing chamber and increase in height of the powder layer the fill weight increases as more powder is compacted and densified by the piston movement while dosator is lowered into the powder. The powder in the rotary container is fed from a supply hopper and rotates in the same direction as the turret, where the dosator nozzle is fixed with a rotation diameter slightly smaller and off-centre. Therefore within a rotation cycle the dosator is shifted to the ejection position outside of the rotary container to release the powder into the capsule body (Armstrong, 2008; Florence and Siepmann, 2009; Jolliffe et al., 1980; Jones, 2001; Keck and Müller, 2009; Podczeck and Jones, 2004a, 2004b).

2.1.3. Comparison of low-dose capsule filling machines

Tables 2-1 and 2-2 show a comparison of technologies currently marketed for low-dose and micro-dose capsule filling. Three volumetric systems are based on a nozzle dosator and another three are operated vacuum-assisted (dosator, cavity-based drum or membrane filler). The volumetric systems are based on indirect filling whereas all gravimetric systems are direct filling methods. Along with the comparison of technologies, also results of the different dosing technologies in literature with various powders were examined and compiled in a table, which can be seen in appendix A.1 (3 P Innovation, 2009a, 2009b, 2013a, 2013b, 2013c; Bailey and Seaward, 2012; Bosch GmbH, 2013a, 2013b, 2013c; Bryant et al., n.d.; Capsugel, 2007, 2013; Edwards, 2008, 2010; Eskandar et al., 2011; GSK and MG2, 2010, 2013; Harro Höfliger, 2011; MG2, 2011a, 2011b, 2011c, 2011d; Podczeck and Jones, 2004a; Seyfang and Steckel, 2013).

Table 2-1 presents the low-dose nozzle dosator MG2 ‘Labby’ compared to MG2 ‘Planeta’ and other low-dose principles from various providers. Subsequently, in table 2-2 the gravimetric MG2 ‘Micro-Dose’ system is compared to other fully automated or manual-operated devices.

Comparison of technologies	MG2 Labby	MG2 Planeta	3 PI - Fill2Weight	Harro Höfliger Omnidose	3 PI - LabDosator
System	Low-dose Lab-scale	Low-dose Industrial-scale	Low-dose Lab-scale	Low-dose Lab-scale to small Industrial-scale	Low-dose Lab-scale
Method	volumetric	volumetric	gravimetric	volumetric	volumetric
Dosing Principle	dosator	dosator	powder dispensing	dosator, drum filler, membranfiller	dosator
Capsule sizes	all available sizes	all available sizes	5-00	n.a.	4-00
Weight [mg]	1-500mg	fully adjustable to target weight	2.5-500mg standard; 1-20000mg optional	0,5-500mg; dependent on specific dosing system	up to 600mg; powder consistency/ properties dependent
RSD [%]	1-10mg: 4 -19% [DoE_II] 10-50mg: 0,6-11,4% [DoE_I]	typically ~ 5%	typically < 3%	typically < 2%	typically < 5%
Speed [cph]	2500cph	100000cph	~750cph (5 seconds (5-50mg) dosing time); 1000cph with fill2weight robot	n.a.	450cph
Capacitance Sensor	none	NETT weight system	Fill2Weight dispensing	n.a.	weigh cell
Humidity control	laboratory environment	control unit installed	control unit installed	n.a.	laboratory environment
Temperature control	laboratory environment	control unit installed	control unit installed	n.a.	laboratory environment

Table 2-1: Comparison of low-dose capsule filling machines

Comparison of technologies	MG2 Microdose	Harro Höfliger Omnidose TT	Capsugel Xcelodose S	Bosch GKF 702	Bosch GKF 2500
System	Micro-dose Lab-scale to Industrial-scale	Micro-dose Lab-scale	Micro-dose Lab-scale	Micro-dose Lab-scale to Industrial-scale	Micro-dose Lab-scale to Industrial-scale
Method	gravimetric	volumetric	gravimetric	volumetric	volumetric
Dosing Principle	vibration dispensing: stand-alone or integrated unit (Labby, Planeta)	cavity-based-drum filler	vibration dispensing (pepper shaker)	vacuum dosing system: micro-dosing station	versatility of fill options: micro-dosing station
Capsule sizes	5-000	n.a.	5-000	5-00	5-00
Weight [mg]	0,5-40mg ± 0.2 mg of the net weight (depending on target weight and product characteristics)	1-50mg	0.1-several 100mg	n.a.	n.a.
RSD [%]	5mg: 1,5-2,5%; 25mg: 0,2-0,6%; 50mg: 0,1-0,8% [GSK/MG2]	~1-3%	depending on weight: ~ 2-3%; the lower the weight the harder to achieve	< 2,5%	< 2,5 %
Speed [cph]	manual operation (stand alone unit), 500-100000cph (integrated unit)	manual operation: 30-60cph	120-600cph	43000cph	150000cph
Capacitance Sensor	NETT weight system	n.a.	microbalance	n.a.	online weight control
Humidity control	laboratory environment	n.a.	control unit installed	laboratory environment	n.a.
Temperature control	laboratory environment	n.a.	control unit installed	laboratory environment	n.a.

Table 2-2: Comparison of micro-dose capsule filling machines

From the comparison it can be observed that most of the low-dose systems are operated on volumetric basis, except for the 'Fill2Weight' system of 3 P Innovations, whereas for micro-dose vibration-assisted gravimetric filling and vacuum-assisted volumetric filling are in place.

2.1.4. MG2 – ‘Labby’ with low-dose dosator nozzle adjustments

A lab scale continuous dosator nozzle machine (MG2 ‘Labby’, Bologna) was used for capsule filling experiments. Low-dosage filling on a continuous principle is made possible by MG2’s special adjustments of the standard capsule-filling set-up at lab scale. These are smaller nozzles, layer adjustment blades (figure 2-1-A), to keep a constant powder layer height even with micronized particles and a cleaning unit (figure 2-1-B) to remove excess powder from the dosator nozzle between the dosing and the ejection step to reduce fill weight variations. In this way it is possible to take advantage of the proven features available for the continuous standard dose dosator (MG2, 2011a, 2012; Podczeck and Jones, 2004a).

This study is the first scientific approach for filling low-doses with the dosator nozzle principle (MG2 ‘Labby’).

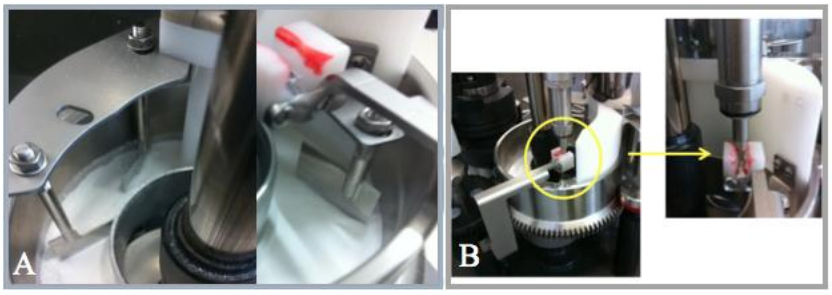

Figure 2-1: Low-dose adjustments for MG2 ‘Labby’: A-Layer adjustment blades; B-Cleaning unit with two-side scraper (MG2, 2012)

2.2. Capsule Handling

The section about capsule handling deals with capsules in general, their properties, specifications and handling before and during production.

2.2.1. Hard gelatin capsules

Capsules are described in the European Pharmacopoeia (Eur. Ph. 5.0) as ‘solid preparations with hard or soft shells of various shapes and capacities, usually containing a single dose of active substance.’ It also includes the description of hard capsules: ‘Hard capsules have shells consisting of two prefabricated cylindrical sections, one end of which is rounded and closed, the other being open. The active ingredient or ingredients usually in solid form (powder or granules) are filled into one of the sections, which are then closed by slipping the other section over it. The security of the closure may be strengthened by suitable means (Council of Europe, 2005).’

The manufacture of hard-gelatin capsules is a dipping process, where stainless steel mold pins are dipped into gelatin solution and the shells are formed by gelation and drying on the pins. Gelatin is gained from the hydrolysis of collagen obtained from animal connective tissue, bones and skin (Florence and Siepmann, 2009; Keck and Müller, 2009; Podczeck and Jones, 2004c).

Capsules are produced in sizes from 000, being the largest, down to 5, being the smallest size for human use. In the pharmaceutical industry capsules are widely used for development and production of new 'drug delivery systems' also including powder filled into capsules for inhalation. Capsule-based inhalers usually contain filled capsules of size 3 or smaller, depending on the device. A table of all capsule sizes is presented below, size 3 are marked as they are used in our experiments (Capsugel, 2013; Keck and Müller, 2009; Stegemann S., 2002).

2.2.2. Capsule handling before production

Hard gelatin capsules are quite vulnerable to change in weight with a change in humidity. Therefore a special focus is put on the handling of the capsules before production. This includes the storage (before and after weighing) of the capsules as well as additional precautions (gloves) during weighing and filling capsules into the hopper.

2.2.2.1. Pre-weighing and identification of capsules

This specific process step was necessary to be included, as the capsules (Coni-Snap®, Capsugel®) size 3, are approximately 48 mg ± 3 mg and therefore much heavier than the powder content (Capsugel, 2013). The variability in the weight of the empty capsules (± 3 mg) is approximately the same as the lower limits of the low-dose powder content (1 mg - 45 mg). Therefore, the weight of the empty body must be known before filling capsules. The weight of all used capsules was recorded by the Denver SI-234A Analytical Balance (readability: 0.0001 g; reproducibility: 0.1 mg) to achieve high precision in low-dose weighing measurements. In order to accurately measure capsule content in the low-dose range, it is necessary to have the adequate scale and know exactly the weight of every empty capsule body. Unnumbered hard gelatin capsules, size 3, are consecutively numbered and the weight of every single capsule is recorded automatically by the analytical scale into and excel-sheet for further use. During production numbered capsules are randomly filled and weighed again with the Denver SI-234A analytical scale. The

weight of the empty numbered capsule is then subtracted from the gross weight to gain the actual net weight of the numbered and filled capsule. Details of the complete numbering process can be seen in the Standard Operating Procedure (SOP) (see appendix A.6).

Size	000	00el	00	0el	0el*	0	1 el	1	2 el	2	3	4	5
Weight													
Mg	163	130	118	107	110	96	81	76	66	61	48	38	28
Tolerance Mg	±10	±10	±7	±7	±7	±6	±5	±5	±5	±4	±3	±3	±2
Capacity													
Capsule volume ml	1.37	1.02	0.91	0.78	0.78	0.68	0.54	0.50	0.41	0.37	0.30	0.21	0.13
Powder Density	**Capsule capacity mg**												
0.6 g/ml	822	612	546	468	468	408	324	300	246	222	180	126	78
0.8 g/ml	1096	816	728	624	624	544	432	400	328	296	240	168	104
1 g/ml	1370	1020	910	780	780	680	540	500	410	370	300	210	130
1.2 g/ml	1644	1224	1092	936	936	816	648	600	492	444	360	252	156

Table 2-3: Capsule sizes of Coni-Snap ® showing weight (±tolerance) and the capacity (Capsugel, 2013)

Figure 2-2: Coni-Snap ® capsules, size 3, A – Unnumbered capsules; B – Numbered capsules; C- Numbered and filled capsules with sample

2.2.2.2. Storage of capsules and pre-weighed capsules

General storage conditions should be between 15 and 25°C and the relative humidity (r.H.) should not exceed 35-65% (Keck and Müller, 2009). To keep temperature and r.H. stable for the pre-weighed capsules a dehumidifier was installed in the lab and capsules stored as batches in sealed containers until further use.

2.2.2.3. Filling capsules into capsule hopper

The influence of humidity in low-dose experiments has to be kept in mind during the whole process. Especially in the filling step it is necessary to work with gloves. Before using the numbered capsule batch a sample of 5 empty, numbered capsules is taken for weighing and comparing the weight with the weight from the excel table to identify weight differences due to humidity. Then numbered capsules can be filled in the hopper to run production experiments for representative sampling.

2.2.3. Capsule handling during production

In automated capsule filling, capsules follow a set route from a supply of empty capsules to the outlet of the production. Before capsules can be filled they have to pass through rectification, opening and separation and the capsule body is carried in a conveyor belt until the dosing area. After completed dosing filled capsule bodies are reassembled with the prior separated lids and mechanically closed for ejection of the product (MG2, 2011a; Podczeck and Jones, 2004a).

2.2.3.1. Capsule feeding, orientation and opening

Capsules, unnumbered or numbered, are fed, with lid and body assembled but not closed, into the designated hopper and drop randomly into the feeding tube to be positioned vertically by a rectification mechanism (Phase 1-5 in figure 2-3). For the right orientation, a rectification pin always touches the lid independent of the capsule orientation in the feeding tube (Phase 6 in figure 2-3). When this pin is pushed forward the capsule is aligned horizontally and the body positioned at the end of the orientation unit is pushed downwards by the sorting pin, aligning capsules vertically (Phase 7 and 8 in figure 2-3). Opening is usually vacuum-assisted (Phase 9 in figure 2-3) (MG2, 2011a, 2011c, 2011d; Podczeck and Jones, 2004a).

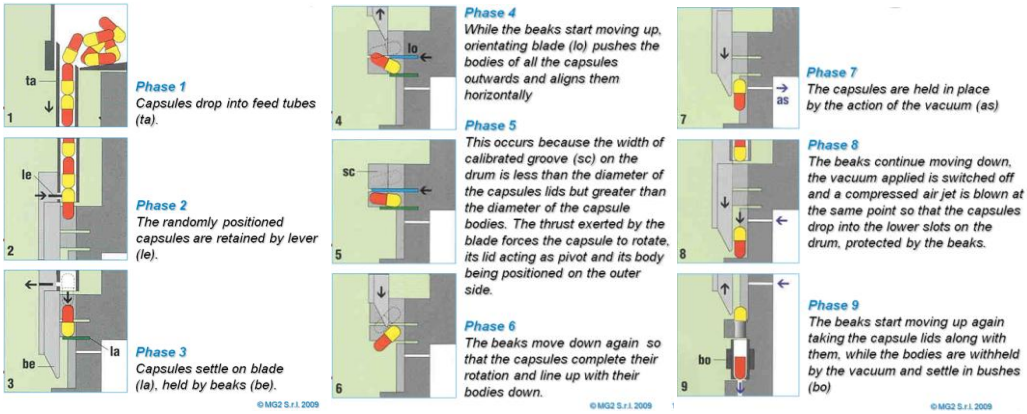

Figure 2-3: Process steps of feeding, orientation and opening divided into phase 1-9

2.2.3.2. Seperation and lid transfer

Subsequently to orientation capsules are positioned in the ‘bushes’ and with applied vacuum the lid and the body are separated (Phase 10-12 in figure 2-4). The lids are transferred in the machine in a separate process to the capsule bodies and they are rejoined at the closing unit (Phase 1-5 in figure 2-4) (MG2, 2011a, 2011c, 2011d; Podczeck and Jones, 2004a).

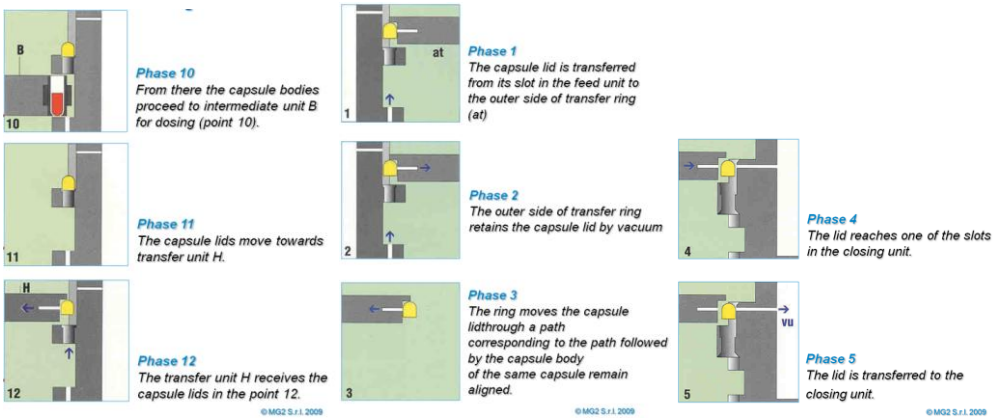

Figure 2-4: Process steps of seperation (phase10-12) and lid transfer (phase 1-5)

2.2.3.3. Filling of the open capsules

Meanwhile the capsule body is positioned in the bush of the carrier belt exactly under the ejection position of the dosator in such a way that the corresponding capsule body can take up the collected/dosed powder content. The down-stroke of the piston ejects and fills product into the open capsule body (Phase 8 and 9 in figure 2-5) (MG2, 2011a, 2011c, 2011d; Podczeck and Jones, 2004a).

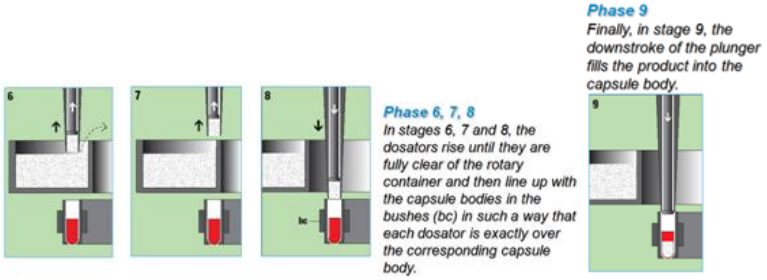

Figure 2-5: Process steps of the filling procedure (phase 6-9)

2.2.3.4. Rejoining, closing and ejection

For concluding the capsule handling process, capsules are rejoined by being positioned on top of each other after completed capsule filling. The pushers of the closing unit mechanically close lid and body after which the pushers rise up to eject the filled and closed capsule (Phase 1-5 in figure 2-6) (MG2, 2011a, 2011c, 2011d; Podczeck and Jones, 2004a).

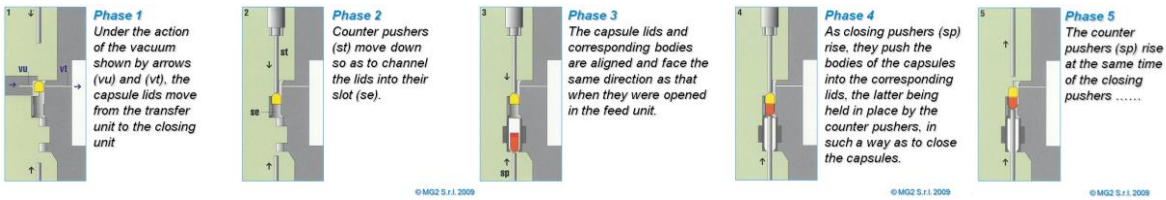

Figure 2-6: Process steps for caspule rejoining, closing and ejection

2.3. Layer Adjustment

Layer adjustment is a very critical process step for capsule filling performance. Therefore the adjustment and creation of an even powder layer in the rotary container has to follow a precise procedure. This is defined in the SOP for a low-dose capsule filling process on MG2 ‘Labby’ (see appendix A.6). A short outline, of the most important process steps, is stated below, which have to be fulfilled before every single run of the DoE.

First of all the powder hopper is aligned in the right position and the rotating blade has to be mounted inside the hopper to keep up right powder flow (MG2, 2011c). This is important to prevent ‘rat-holing’ for poor flowing powders and feeding of big agglomerates (snowballs) of micronized product (see figures 2-7-A and 2-7-B).

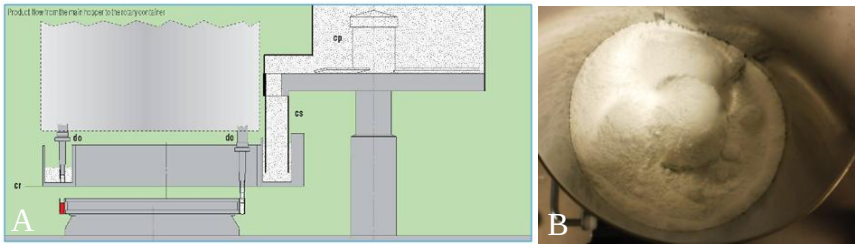

Figure 2-7: Powder hopper: A-Powder feed scheme with rotating blade (MG2, 2011c); B-Agglomerates of micronized powder above rotating blade.

The right adjustment for each experimental run has to be identified beforehand and the correct layer height has to be set on the graduated scale (see figure 2-8-A-2) and add 3 mm to the desired powder bed height (pbh) by turning the lock ring (see figure 2-8-A-1) on the feeding column. Put the product manually in the hopper of the powder-feeding unit and open the feeder orifice.

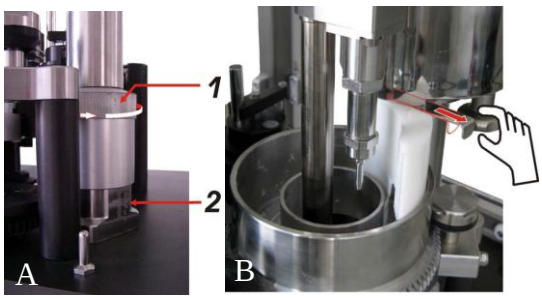

Figure 2-8: Powder bed height adjustment: A-Lock ring (1) and graduated scale (2); B-Opening of the feeder orifice (MG2, 2011d).

For the selected run the appropriate speed has to be set on the machine ahead of the layer creation process. This is varied according to the run order as machine speed has an impact on the state of the layer. Low-dose filling is limited to the maximum filling speed of 2500

cph, as the machine cannot produce filled capsules at 3000 cph, which would be being the maximum production speed in the specifications.

Preloading the product into the rotary container needs to be accomplished by pressing the assigned control button until a uniform layer of the powder is formed. The right height is measured with a vernier caliper. After the initial filling of the rotary container plain capsules are filled until the layer is in a good, uniform condition for the experimental run. This state is controlled visually, which can be seen in figure 2-10, to avoid holes in the layer (too less powder feed) and excessive powder falling back onto the conditioned layer (too much powder feed). The feed (powder loading settings: 'Time On'[s] and 'Time Off'[s]) is adjusted until the settings can be pre-set right and be recorded for each individual experiment (see figure 2-9). To maintain a uniform layer in low-dose capsule filling, special adjustments of the standard filling equipment of 'Labby' are necessary. These are layer adjustment blades to keep a constant powder layer height even with micronized particles and a cleaning unit between the dosing and the ejection step to reduce fill-weight variations (as seen above in figure 2-1).

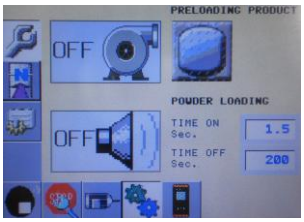

Figure 2-9: Feed adjustment display

Figure 2-10: Layer conditions: A-Holes in layer; B-Excess powder on the layer; C-Uniform, even powder layer.

2.4. Capsule Filling Procedure

Automated capsule filling is a sophisticated and interesting technique for industry, yet still influenced by a lot of factors for continuous reliable filling performance (Stegemann et al., 2013).

The actual capsule filling process on MG2 ‘Labby’ is split in 10 phases which are illustrated below in figure 2-11 In detail for low-dose capsule filling experiments phase 4, the compression step, is disabled as for inhalation purposes capsules have to be filled with loose powder. Another special feature of the low dose set-up is the dosator scraper as a cleaning unit between phase 7 and 8. This is needed for the removal of adhered powder to the dosator to reduce fill weight variations at low doses.

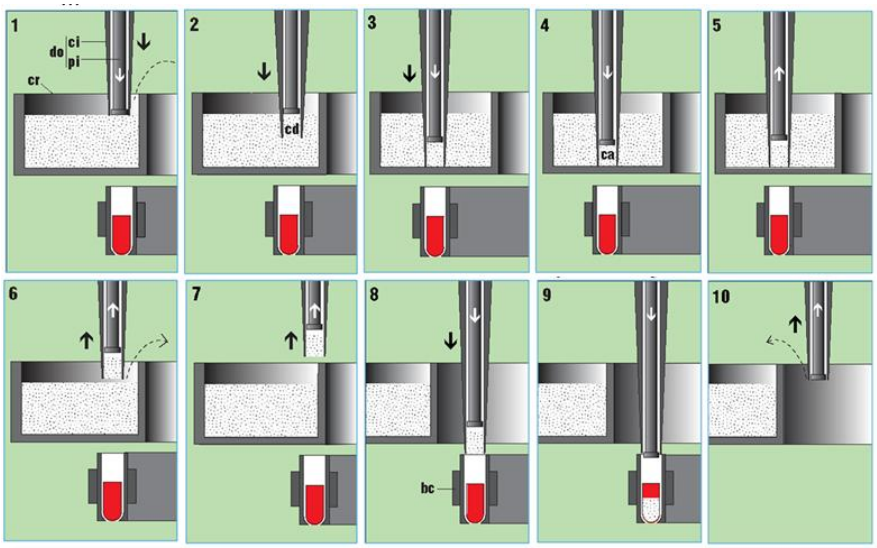

Figure 2-11: Ten phases of a capsule filling operation cycle (MG2, 2011c)

Before the actual working cycle of the machine with the mounted dosator can start the dose filling into capsules, some adjustments have to be made. First of all the right run of the DoE has to be identified and the other critical process parameters have to be set on the machine. These include speed, powder layer height, dosing chamber and the according low-dose dosator diameter.

2.4.1. Dosing chamber settings

The correct height of the dosing chamber has to be set on a graduated scale (2) on top of the dosator fixation turret. This is done by loosening the counternut (1) and adjusting the chamber using the graduated scale (2) (see figure 2-12-A). As it is not infinitely variable, adjustment gauges (figure 2-12-B) are necessary to avoid user-dependence. These gauges

are metal parts with heights of 2.5, 3.75 and 5 mm as they were needed for the experimental procedure of this study. The required adjustment gauge has to be fit into the free space of the scale for the required dosing chamber from the DoE run order. At correct height of the dosing chamber the counternut (1) has to be fixed tightly (MG2, 2011d).

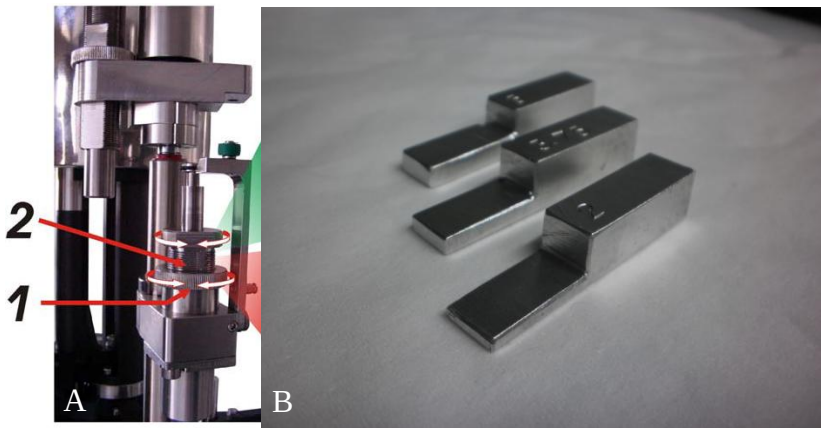

Figure 2-12: Dosing chamber adjustment: A-Graduated scale (2) and counternut (1) of dosing chamber; B-Adjustment gauges for user-independent height setting.

2.4.2. Dosator assembly

In particular the procedure of the low-dose dosator mounting is critical for the performance of the capsule filling process, as it is vulnerable to ruin machine equipment, if not mounted correctly. To start off with the dosator fixation unit, the turret has to be in the highest position of the working cycle to ease the assembly. The low-dose dosator consists of five separate parts, whereas the piston with the spring is fixed in a guiding tube, which is mounted first to the dosator fixation unit, as can be seen in figure 2-13 and 2-14. This mounting is tightened with a 24 mm wrench and at the lower end of the guiding tube the actual dosator nozzle is mounted with a screw for fixation needing a 19mm wrench for tightening. Next step after mounting the dosator is one manual operation cycle to ensure all parts of the dosator are aligned correctly before starting production. Then the machine is run with dosator and capsules until the first preset feeding occurs (MG2, 2011a, 2011d).

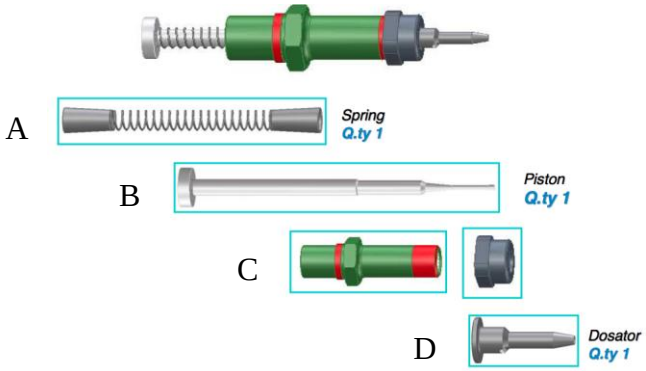

Figure 2-13: Low-dose dosator (MG2, 2011a): A-Spring; B-Piston; C-Guiding tube and special screw for dosator fixation; D-Dosator

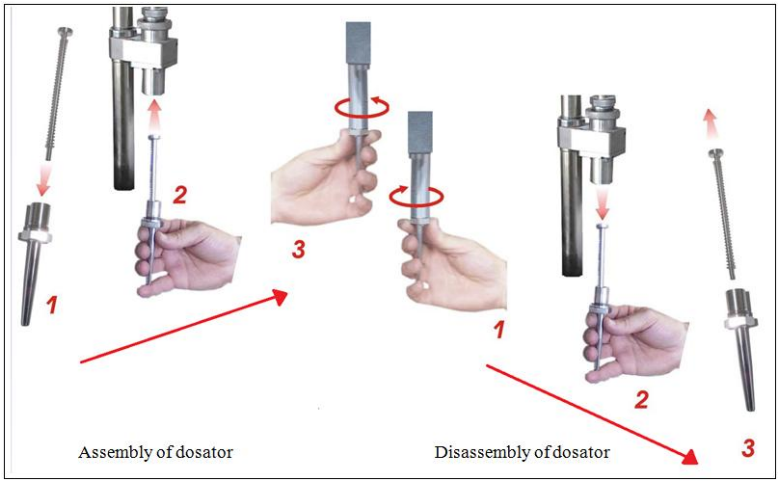

Figure 2-14: Dosator assembly and dissassembly (MG2, 2011d)

3. Experimental Procedure

The experimental procedure chapter deals with all experimental phases needed for a proper QbD-based approach towards the capsule filling technique in place. With the powder characterization and the ranking of the powders, CMAs were identified. Design of Experiments deals with the CPPs and compiling a set of experiments to statistically cover an area for process responses. Risk assessment was performed before data collection of the experiments to ensure stable conditions with minimized risks of all process steps. Finally MVDA showed the statistical influence of CMAs and CPPs on the desired CQAs.

3.1. Powder Characterization – Powder Ranking

The complete powder characterization of all twelve inhalation powders was performed by Mag. pharm. Eva Faulhammer ahead of my experimental work. This included measurements on the FT4 (Freeman Technology, United Kingdom), Pharmatest PT-TD200 (Pharmatest, Germany), Accupyc II 1340 (Micromeritics, USA), and QicPic and Helos (Sympatec, Germany). Detailed information on the characterization measurements is outlined in section 4.2.1.

According to the needs of the partners a powder ranking was established to identify the borderline properties of different inhalation grade powders. With lower (>) and upper (<) limits the powder properties were divided into two powder groups, named DoE I and DoE II. This was in concordance with the experimental results as seen in section 3.4.

Powder Properties DoE I	>	<	Units	Powders DoE2
VMD	23,07	160,02	[µm]	/
x50	18,16	155,24	[µm]	/
WFA	7,70	29,70	[degree]	SL: 11,20
BFE	510,67	2393,33	[mJ]	S400: 606,33 M_MG2: 643,67 API: 746,33 LH300: 1171,33
Tapped Density	0,8275	1,0456	[g/ml]	/
Bulk Density	0,4701	0,736	[g/ml]	/
True Density	1,5387	1,5541	[g/cm³]	LH300: 1,5535 S400: 1,5545
Hausner Ratio	1,187	1,8293	[dimensionless]	LH300: 1,4290 M_MG2: 1,4911 API: 1,5 SL: 1,6380 S400: 1,9080
Carr Index	15,7333	45,3333	[dimensionless]	LH300: 30,0 M_MG2: 32,9333 API: 33,3300 SL: 38,933 S400: 47,6000
Compressibility Index	1,043	1,266	[dimensionless]	M_MG2: 1,2133
Air Permeability	1,05	27,10	pressure drop over powder bed [mbar]	LH300: 6,17
AIF	17,533	31,267	[degree]	/
FFc	2,563	8,097	[dimensionless]	M_MG2: 2,897
Cohesion	0,189	0,574	[N]	M_MG2: 0,517
Adhesion	0,43	1,54	[dimensionless]	SL: 0,56

Table 3-1: Powder ranking with marginal values for powders of DoE I

Powder Properties DoE II	>	<	Units	Powders DoE1
VMD	1,68	8,71	[µm]	/
x50	1,43	7,61	[µm]	/
WFA	11,20	35,67	[degree]	ML006: 29,70 ML001: 12,57
BFE	424,0	746,33	[mJ]	/
Tapped Density	0,248	0,7597	[g/ml]	/
Bulk Density	0,151	0,4019	[g/ml]	/
True Density	1,3061	15,5545	[g/cm³]	LH100: 1,5385 LH_GSK: 1,5387 SV010: 1,5388 SV003: 1,5396 IH230: 1,547 ML001: 1,5533 ML006: 1,5541
Hausner Ratio	1,429	1,908	[dimensionless]	LH_GSK: 1,5122 IH230: 1,5890 ML001: 1,5890 ML006: 1,8293
Carr Index	30,00	47,60	[dimensionless]	LH_GSK: 33,8667 ML001: 37,0667 IH230: 37,0670 ML006: 45,333
Compressibility Index	1,2133	1,7433	[dimensionless]	ML006: 1,2766
Air Permeability	6,1733	40,466	pressure drop over powder bed [mbar]	LH_GSK: 13,233 ML001: 20,166 ML006: 27,1
AIF	31,833	36,333	[degree]	/
FFc	1,617	2,897	[dimensionless]	ML006: 2,563
Cohesion	0,517	0,966	[N]	ML006: 0,574
Adhesion	0,56	2,11	[dimensionless]	ML006: 1,54

Table 3-2: Powder ranking with marginal values for powders of DoE II

Previously acquired data for various powder characteristics are listed in appendix A.4. The diagrams below for each characteristic material attribute show the two DoEs, DoE I marked in red and DoE II in green. Respitose ML006 is marked in grey as its properties and the exact classification to one specific powder family is difficult. Seen from the perspective of the properties this powder would belong to DoE II, whereas the filling behavior has definitely to be attributed towards DoE I. This became apparent at capsule filling, where DoE II – experimental runs could not be filled with a 1:1 ratio as complete powder loss occurred during transfer. Therefore Respitose ML006 had to be assigned to DoE I.

15 powder properties of 12 inhalation powders are ranked in the diagrams below (see figures 3-1 until 3-15). As mentioned above the two DoEs are marked in different colors as well as Respitose ML006 (ML006). Due to its behavior varying between the two powder families and to make its characteristics obvious, it was colored in grey. Sometimes spheronized lactose (SL) i.e. WFA showed the opposite behavior due to its high magnesium stearate (MgSt) content.

Concerning particle size volume mean diameter (VMD) and x50 show ML006 is positioned at the border between the two families.

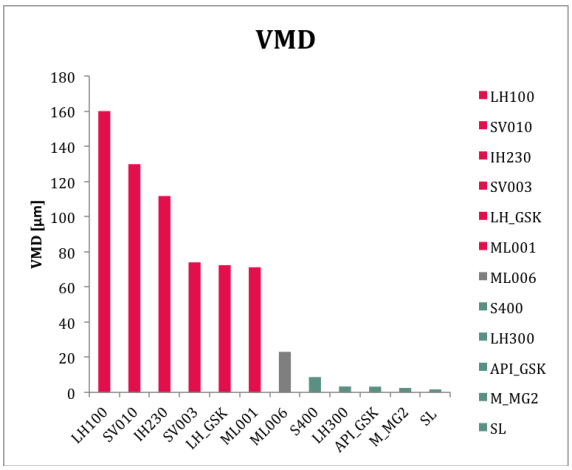

Figure 3-1: VMD ranking

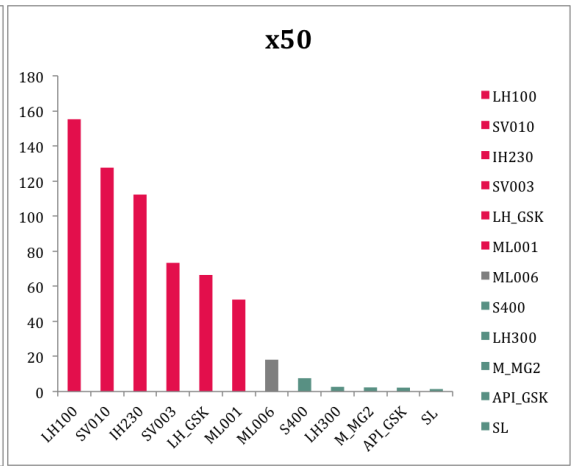

Figure 3-2: x50 ranking

This cannot be seen as clear at the wall friction angle (WFA) results (figure 3-3), where a much higher value than SL is indicated. In that case SL could be attributed to DoE I and ML006 to DoE II. For Basic Flowability Energy (BFE) (figure 3-4) it is Lactohale 300 (LH300), which would belong to powder group I and again ML006 has a value more suitable for powder group II.

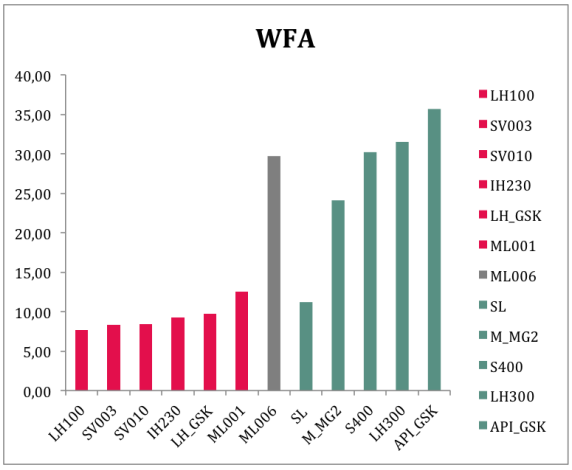

Figure 3-3: WFA ranking

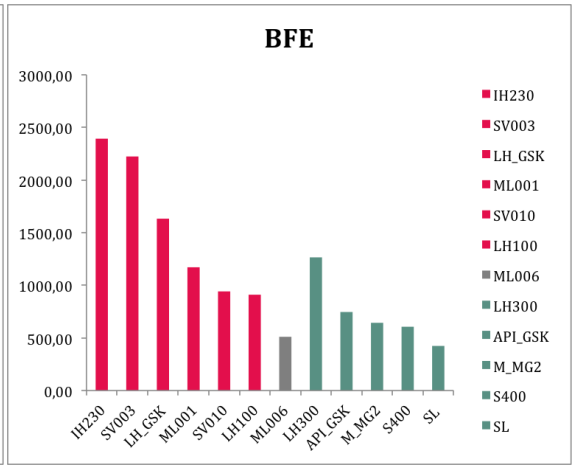

Figure 3-4: BFE ranking

The behavior of density measurements exhibit that ML006 for the tapped density (figure 3-5) definitely can be attributed to DoE I, whereas for the bulk density (figure 3-6) it is again situated between both DoEs.

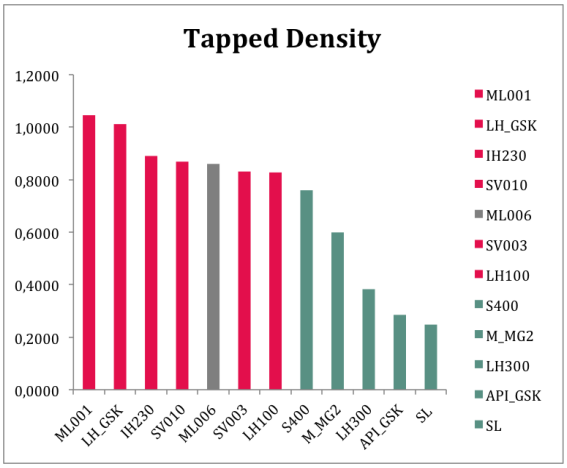

Figure 3-5: Tapped Density ranking

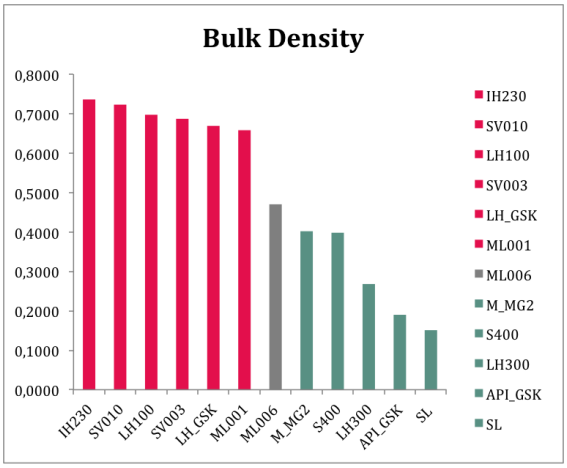

Figure 3-6: Bulk Density ranking

In figure 3-7 for true density can be observed that all lactoses are more or less the same except for the modified lactose with high MgSt content (SL), mannitol (M_MG2) and API (API_GSK) as they have a different chemical configuration and formula.

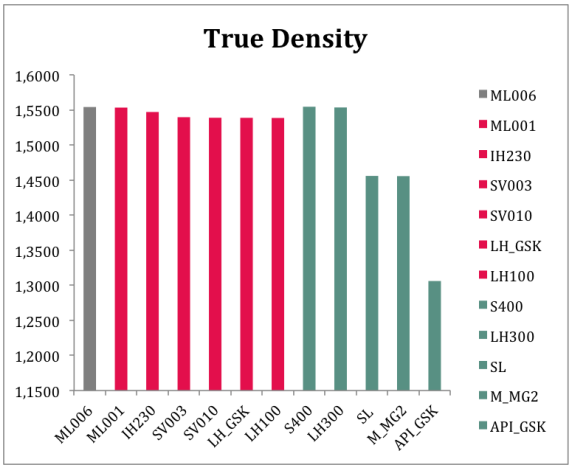

Figure 3-7: True Density ranking

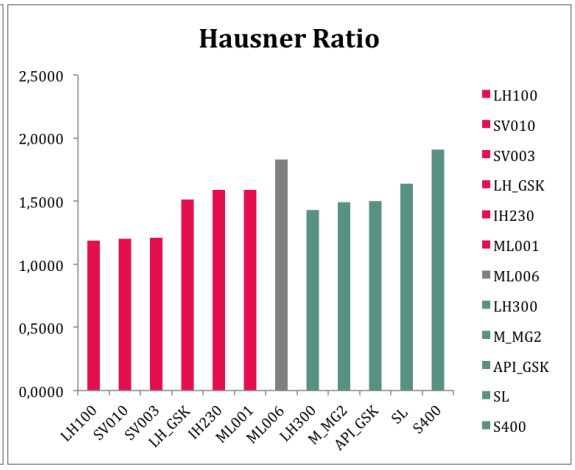

Figure 3-8: Hausner Ratio ranking

The flow properties expressed in Hausner Ratio (figure 3-8) and Carr Index (figure 3-9) definitely show that flow of ML006 is more of the cohesive nature of powders. However, for the compressibility index (CI) (figure 3-10) ML006 again ranges between the DoEs.

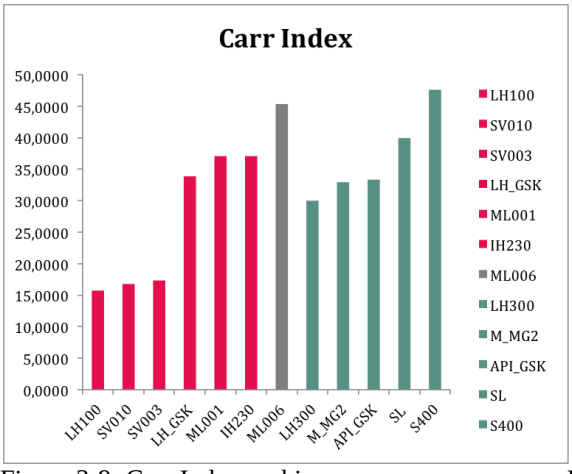

Figure 3-9: Carr Index ranking

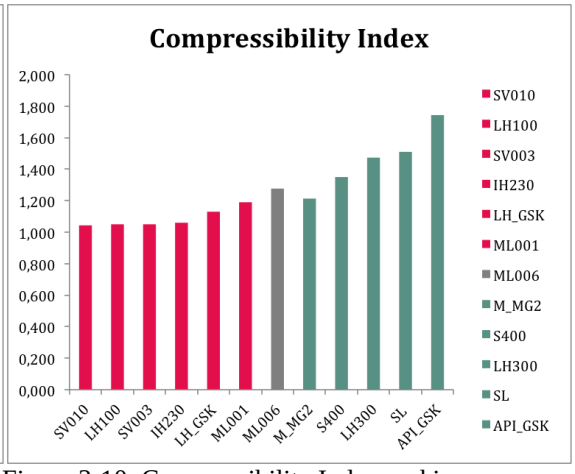

Figure 3-10: Compressibility Index ranking

The air permeability measurement (figure 3-11) represents the pressure drop across the powder bed, in general higher for very cohesive powders with small particle size. Even though Lactohale 300 has a very small particle size, it showed extremely low pressure drop as the powders from DoE I. Besides that ML006 could be attributed to DoE II from its air permeability behavior. For the angle of internal friction (AIF) (figure 3-12) no abnormal behavior of powders can be observed in the ranking.

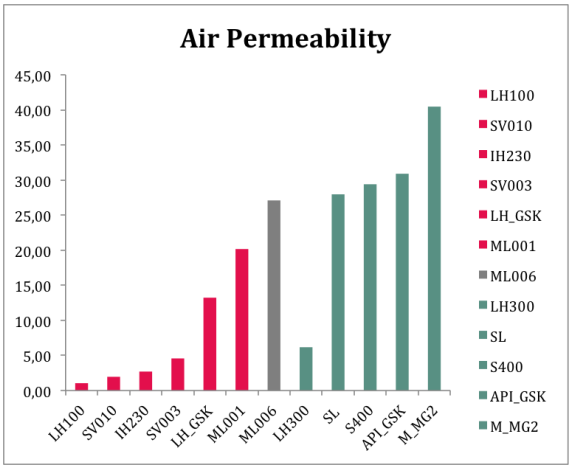

Figure 3-11: Air Permeability ranking

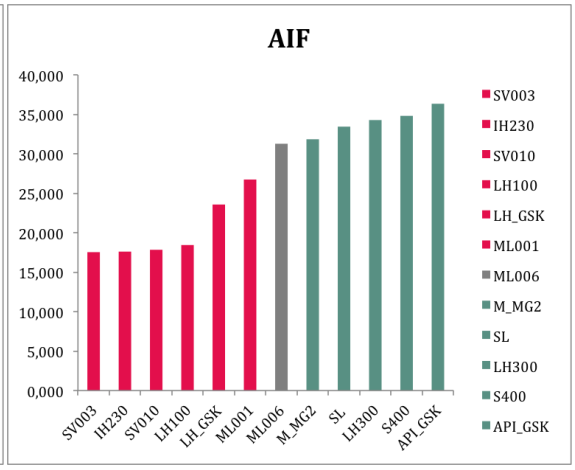

Figure 3-12: AIF ranking

As seen above (figure 3-8 and 3-9) the flow function (FFc) (figure 3-13) and cohesion values (figure 3-14) of ML006 are more like the ones of the challenging and cohesive DoE II powders. This is the same for the adhesion values (figure 3-15), which are in concordance with the actual filling performance of ML006, whereas SL shows the exact opposite behavior and could be attributed to DoE I.

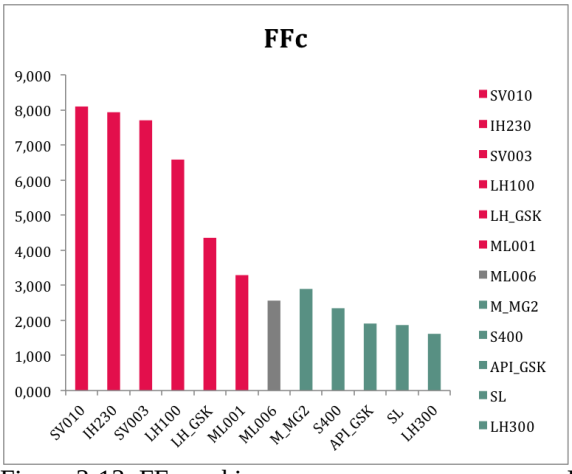

Figure 3-13: FFc ranking

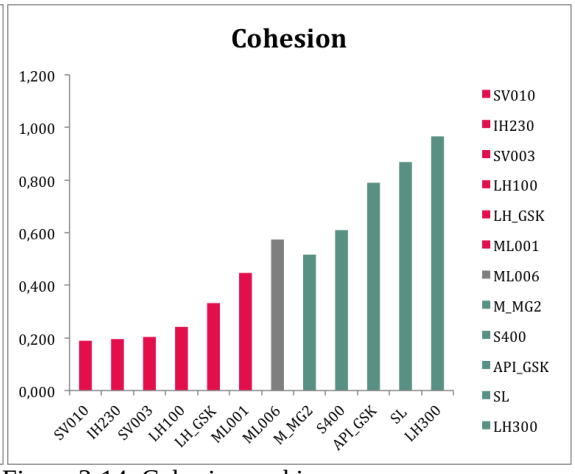

Figure 3-14: Cohesion ranking

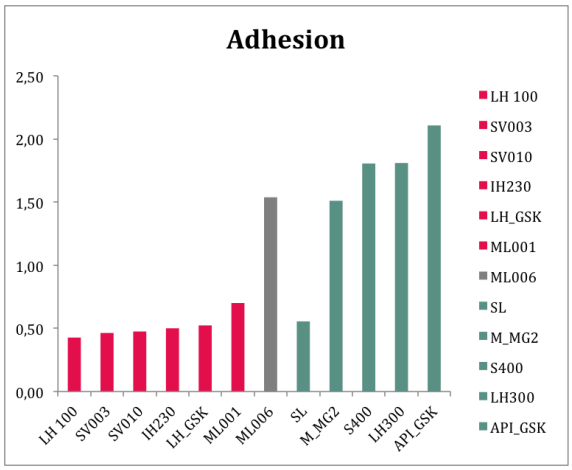

Figure 3-15: Adhesion ranking

In a quick summary these figures show all variable material attributes from twelve inhalation grade powders. It can be observed that every single powder has different behaviors that make them unique and cause diverse capsule filling results. Therefore it was necessary, as mentioned above, to divide the powders in two families and investigate their filling behavior with two different DoEs to get the largest possible Design Space for this broad spectrum of powders.

3.2. Design of Experiments-DoE

After a complete characterization of the powder properties, considered as CMAs, a DoE was compiled by MODDE 9.1 (Umetrics, Sweden). For the purpose of the capsule filling process a screening DoE (D-optimal with Design statistics G-efficiency) was generated including four factors (CPPs) and two responses (CQAs), two interactions (dosing chamber: powder layer and dosator diameter: powder layer) and two constraints (ratio between dosing chamber and powder layer).

3.2.1. Initial capsule filling experiment according to powder properties

As the powder characteristics of all 12 inhalation powders used in this study cover a broad range of particle size and therefore also in densities, some filling experiments were made ahead of the compilation of the DoE. The test procedure without an actual DoE included two of the more challenging powders at the lower particle size range with different powder characteristics (e.g. WFA and BFE) compared to the rest of the powders (see figures above from 3-1 until 3-15). These were namely spheronized lactose (SL) and Lactohale 300 (LH300). All process parameters were tested out with varying dosator diameters, machine speed, dosing chamber and powder layer height as well as the ratio between the latter. 10 mm powder layer height was the highest possible layer for successful filling. Additionally it became apparent that with SL bigger dosator diameters i.e. 2.8 and 3.4 mm failed at high ratios of 1:4 and 1:5 at low machine speed (see tables 3-3) whereas for LH300 capsules were hard to fill, only with extended initial running time, and could not be filled with a ratio of 1:5 (see table 3-4). This performance was frequently caused by plugs being stuck inside the nozzle or ejecting plugs too late. Screening experiments were continued with all other challenging powders except for the API from GSK (API_GSK). These experiments made clear that one single DoE for all inhalation powders is impossible to achieve considering all varying process parameters. Hence two DoEs were created by MODDE 9.1 to account for the two identified powder families from the powder ranking. (+) indicates normal performance of the process, (~) stands for normal performance after prolonged initial running time and at (-) the experimental settings failed to fill capsules.

Spheronized Lactose	*1.9/2.2*	*1.9/2.2*	*1.9/2.2*	*1.9/2.2*	*1.9/2.2*	*1.9/2.2*	*1.9/2.2*	*1.9/2.2*	*2.8/3.4*	*2.8/3.4*	*2.8/3.4*	*2.8/3.4*	*2.8/3.4*	*2.8/3.4*	*2.8/3.4*
DC	5	4	2,5	5	4	2,5	2,5	2,5	5	4	2,5	4	2,5	2,5	2,5
Layer	5	6	5	10	10	7,5	10	12,5	5	6	5	10	7,5	10	12,5
Ratio	1:1	1:1,5	1:2	1:2	1:2,5	1:3	1:4	1:5	1:1	1:1,5	1:2	1:2,5	1:3	1:4	1:5
RESULTS															
2500 cph	+/+	+/+	+/+	+/+	+/+	+/+	~/~	-/-	+/+	+/+	+/+	-/-	+/+	-/-	-/-
1500 cph	+/+	+/+	~/+	+/+	+/+	+/+	-/-	-/-	+/+	+/+	+/+	-/-	~/~	-/-	-/-
500 cph	~/+	~/+	~/~	+/+	+/+	~/+	-/-	-/-	+/+	+/+	~/+	-/~	-/-	-/-	-/-

Table 3-3: Initial screening experiments of spheronized lactose

Lactohale 300	*1.9/2.2*	*1.9/2.2*	*1.9/2.2*	*1.9/2.2*	*1.9/2.2*	*1.9/2.2*	*1.9/2.2*	*1.9/2.2*	*2.8/3.4*	*2.8/3.4*	*2.8/3.4*	*2.8/3.4*	*2.8/3.4*	*2.8/3.4*	*2.8/3.4*
DC	5	4	2,5	5	4	2,5	2,5	2,5	5	4	2,5	4	2,5	2,5	2,5
Layer	5	6	5	10	10	7,5	10	12,5	5	6	5	10	7,5	10	12,5
Ratio	1:1	1:1,5	1:2	1:2	1:2,5	1:3	1:4	1:5	1:1	1:1,5	1:2	1:2,5	1:3	1:4	1:5
RESULTS															
2500 cph	+/+	+/+	+/+	+/+	+/+	+/+	~/-	~/-	+/+	+/+	+/+	-/-	+/+	+/+	+/+
1500 cph	+/+	+/+	+/+	+/+	+/+	+/+	-/-	~/-	+/+	+/+	+/+	-/-	~/-	~/-	-/-
500 cph	+/+	+/~	+/-	+/+	+/+	+/+	-/-	~/~	+/+	+/+	~/+	~/-	-/-	~/-	-/-

Table 3-4: Initial screening experiments of Lactohale 300

3.2.2. Overview of the CPPs and CQAs for both DoEs:

To see the most important differences between the two compiled DoEs at one glance all CPPs (including factors, interactions and constraints) are listed below.

DoE I:

Four process parameters → factors (CPPs)

1 – Speed (500, 1500, 2500 capsules per hour = cph)

2 – Dosator diameter (1.9mm, 2.8mm, 3.4mm)

3 – Powder layer depth (5mm, 10mm, 12.5mm)

4 – Size of dosing chamber (2.5mm, 3.75mm, 5mm)

Two interactions:

1 – Size of dosing chamber and powder layer depth (cha*lay)

2 – Diameter of the nozzle and size of the dosing chamber (dia*cha)

Two constraints for the ratio between the size of dosing chamber and powder layer:

1 – Never smaller than 1:2

→ Perceived knowledge from literature (Tagaki et al., 1969 cited in Jones, 2001) and partner's experience considered as optimal ratio.

2 – Never larger than 1:5

Responses from the process (CQAs):

1 – Capsule fill weight

2 – Weight variability

	1	2	3	4	5	6	7	8	9	10
1	Exp No	Exp Name	Run Order	Incl/Excl	speed	diameter dosater	chamber	powder layer	weight	weight variability
2	2	N2	1	Incl	2500	1,9	2,5	5		
3	14	N14	2	Incl	1500	2,8	3,75	10		
4	7	N7	3	Incl	2500	3,4	2,5	12,5		
5	3	N3	4	Incl	500	3,4	2,5	5		
6	6	N6	5	Incl	500	3,4	2,5	12,5		
7	8	N8	6	Incl	500	1,9	5	12,5		
8	5	N5	7	Incl	2500	1,9	2,5	12,5		
9	9	N9	8	Incl	2500	3,4	5	12,5		
10	10	N10	9	Incl	2500	1,9	5	10		
11	12	N12	10	Incl	1500	2,8	3,75	10		
12	13	N13	11	Incl	1500	2,8	3,75	10		
13	4	N4	12	Incl	2500	3,4	2,5	5		
14	1	N1	13	Incl	500	1,9	2,5	5		
15	11	N11	14	Incl	500	3,4	5	10		

Table 3-5: DoE I worksheet

DoE II:

Four process parameters → factors (CPPs)

1 – Speed (500, 1500, 2500 capsules per hour = cph)

2 – Dosator diameter (1.9mm, 2.2mm, 2.8mm)

3 – Powder layer depth (5mm, 7.5mm, 10mm)

4 – Size of dosing chamber (2.5mm, 3.75mm, 5mm)

Two interactions:

1 – Size of dosing chamber and powder layer depth (cha*lay)

2 – Diameter of the nozzle and size of the dosing chamber (dia*cha)

Two constraints for the ratio between the size of dosing chamber and layer:

1 – Never smaller than 1:1

2 – Never larger than 1:4

Responses from the process (CQAs):

1 – Capsule fill weight

2 – Weight variability

	1	2	3	4	5	6	7	8	9	10
1	Exp No	Exp Name	Run Order	Incl/Excl	speed	diameter	dosing chamber	layer	weight	RSD
2	2	N2	1	Incl	500	2,8	2,5	5		
3	7	N7	2	Incl	500	1,9	2,5	10		
4	11	N11	3	Incl	500	2,8	5	10		
5	4	N4	4	Incl	500	1,9	5	5		
6	12	N12	5	Incl	2500	2,8	5	10		
7	9	N9	6	Incl	2500	2,8	2,5	10		
8	5	N5	7	Incl	2500	1,9	5	5		
9	3	N3	8	Incl	2500	2,8	2,5	5		
10	10	N10	9	Incl	2500	1,9	5	10		
11	14	N14	10	Incl	1500	2,2	3,75	7,5		
12	6	N6	11	Incl	2500	2,8	5	5		
13	13	N13	12	Incl	1500	2,2	3,75	7,5		
14	1	N1	13	Incl	2500	1,9	2,5	5		
15	15	N15	14	Incl	1500	2,2	3,75	7,5		
16	8	N8	15	Incl	2500	1,9	2,5	10		

Table 3-6: DoE II worksheet

Finally DoE I and DoE II were compiled of 14 and 15 different combinations of CPPs, meaning 14 or 15 experimental runs for each powder from the according family, respectively. For each run of both DoEs two sets of capsules (25-30 capsules each) were collected with a time interval of 5 minutes to allow the process to run under steady state conditions. Randomly sampled and weighed capsules presented the according responses, considered as CQAs, for every powder (see table 3-8 and 3-9 in experimental procedure section 3.4.2 and 3.4.3).

The experimental plan with the exact run order of the compiled DoE was carried out starting with the coarser milled and sieved lactoses followed by the more challenging fine powders.

3.3. Risk Assessment

As part of the quality risk management strategy a risk assessment with a Process Failure Mode and Effects Analysis (P-FMEA) of the process was conducted. The goal of the P-FMEA is to uncover potential failure modes based on the process steps, CPPs, CMAs, environmental parameters and equipment design parameters. It is a step-by-step approach to find out the failures that occur when the process does not work as specified (e.g. too high/low temperature, impurities in the raw material).

First of all a complete process description is elaborated, where all branches from the fishbone-diagram come into account. All individual process steps, attributed to process categories, are evaluated and ranked according to an assigned P-FMEA 5 level scale (with permission to use the copyright template for P-FMEA provided by RCPE) on severity (Sev), occurrence (Occ) and detectability (Det).

3.3.1. Fishbone Diagram

The Ishikawa or fishbone diagram is a very helpful method to structure the process and to overview the process factor that potentially can affect the final quality product (Eriksson et al., 2008). As seen in the figure 3-16 below all possibly influential factors to the capsule quality are listed according to the affecting area.

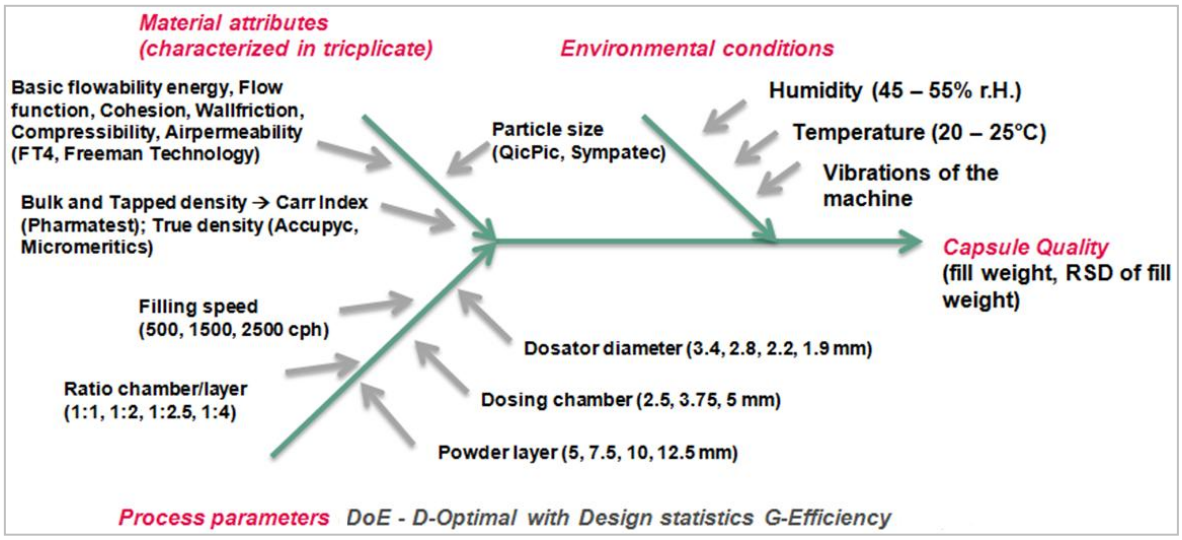

Figure 3-16: Fishbone-Diagram of capsule filling process for MG2-Labby

3.3.2. Process – Failure Mode and Effects Analysis on 5 Level Scale

Failures of the process are prioritized according to a scale how serious their consequences are (Sev), how frequently they occur (Occ) and how easily they can be detected (Det).
The ranking generates the risk priority numbers (RPN) of each process step to help eliminate or reduce failures of highest priority (see appendices A.3, A.4, A.5). The RPN is calculated by multiplying Sev*Occ*Det, aiming at defining risk areas and possibilities for reducing the impact, hence improving process robustness and enhancing the CQAs (Eriksson et al., 2008).
The five level scale classification is useful for well-known processes and product profile, but one do not need an expert because it is easy to decide in which class the failure fits. Nevertheless, the ranking clearly shows the importance of the failure because of the large evaluation scale. The definitions of the categories must be individually adapted to the considered product or process (Thanks to RCPE for permission to use the copyright P-FMEA template in figure 3-7 and appendix A.3, A.4, A.5).

Severity		
Ranking	Description	Definition
1	Very low or None	No effect on quality and human, effect not noticed
3	Low or Minor	Effect noticed but easy to repair
5	Moderate or Significant	Effect leads to highly unsatisfied customer
7	High	Great effect on quality and process, leads to restriction
9	Very high or Catastrophic	Catastrophic effect on humans safety and product quality

Occurrence		
Ranking	Description	Definition
1	Rare or Never	Unusual, not expected to occure
3	Seldom	Can happen in some cases, Error in <1%
5	Sometimes	Occurs now and then, Error in 1-5%
7	Frequently	Moderate possibility of occurrence, Error in 10-20%
9	Very often or Always	Can happen any time, expected to occure every day

Detectability		
Ranking	Description	Definition
1	Very high	Obvious failure, electronic monitoring
3	Easy to detect	Regular control not continuous, mostly detected
5	Moderate	Few methods to detect failure, sometimes overseen
7	Difficult to detect	Spot check, might be overseen
9	Hardly or not detectable	No method to detect failure, easy to overlook

Table 3-7: P-FMEA 5 level scale (©RCPE)

3.3.3. Re-Assessment with risk minimization suggestions

During production failures and effects were evaluated and compiled in a re-assessment of the process, which brought about risk minimization suggestions for almost all process steps at re-assessment. There is still a lot of space for improvements in the capsule filling process itself, whereas the other two branches could be regulated in a sufficient satisfactory way. All data of the RA and the minimization suggestions can be found in detail in the appendix A. 3, A. 4 and A. 5 for the process steps.

Risk minimization suggestions:

- Capsule Handling:
  - Dehumidifier
  - Gloves
  - Weighing software from the Denver SI 234A analytical balance
- Layer Adjustments:
  - 4-eye-principle
  - Venier-caliper
  - Three layer adjustment blades (implemented by MG2)
  - Breaking initial agglomerates
- Capsule Filling:
  - Dosing chamber adjustment gauges
  - Nozzle cleaning after each experimental run
  - Layer creation after each experimental run
  - Optimization of the feed

These suggestions were implemented on all DoE – experiments for data collection and yielded in suggestions for improvement of MG2's 'Labby'. These were:

- Environmental control inside the machine
- Optimization of the powder feeder: more precise feeder blade and better orifice closure
- Capacitance system for direct weight recording
- Laser measurement of the layer height linked to automated feed
- Spanker to break agglomerates and snowball behind layer adjustment blades
- Continuously adjustable dosing chamber with better fixation
- 4-side cleaning unit with integrated vacuum suction
- Improvement of the ejection mode of the piston

3.4. Experimental DoE - Data Collection

3.4.1. Production of capsule samples

Unnumbered capsules are filled in the capsule hopper to produce capsules for five minutes. Before starting the sampling procedure the filling behavior of the powder has to be checked, if any problems occur. Problems could be excess powder sticking to the dosator, not scraped off completely by the cleaning unit or dosator does not eject all of the powder above the empty capsule body in the ejection unit.

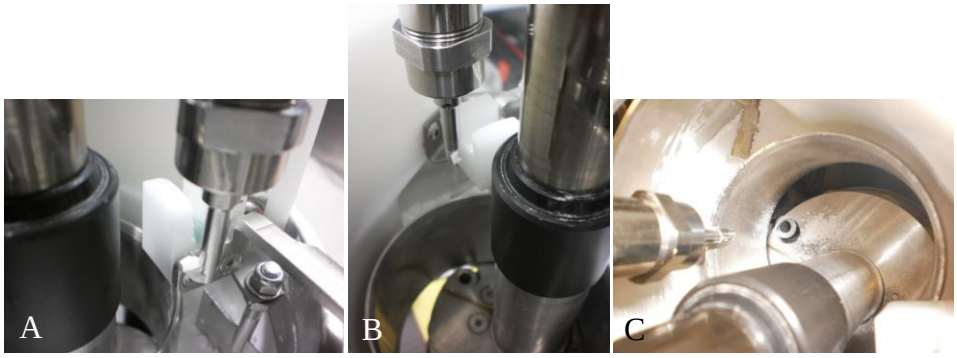

Figure 3-17: Problems during production: A-Powder adhering to nozzle before cleaning unit; B-Powder not scraped off by the cleaning unit; C-Powder loss before ejection unit

After the five minutes the unnumbered capsules are removed from the capsule hopper and numbered capsules are filled into the hopper for starting the first sampling run. The first sample consists of 25-30 collected capsules, where 20 are weighed randomly to calculate the actual net weight of the filled powder. Another set of 25-30 sample capsules is collected after the capsule filling process is continued for five minutes in steady state conditions. Again 20 capsules are weighed for determining the net weight.

From the results of both samplings the overall mean net weight, standard deviation and relative standard deviation is calculated and is recorded as the responses of the fixed process parameters (factors) of the experimental run.

Eur. Ph. 5, 2.9.5: Criteria for weight uniformity

'Weigh individually 20 units taken at random or, for single-dose preparations presented in individual containers, the contents of 20 units, and determine the average mass. Not more than 2 of the individual masses deviate from the average mass by more than the percentage deviation (see below) and none deviates by more than twice that percentage' (Council of Europe, 2005).

Capsules, granules (uncoated, single-dose) and powders (single-dose):

- *Less than 300 mg 10%*
- *300 mg or more 7.5%*

Changeover-procedure after every experimental run of the DoE includes that machine set-up has to be disassembled, cleaned and the new experimental settings have to be adjusted before starting production of new capsule samples. Details are stated in the capsule filling section (see 2.5).

3.4.2. Results DoE I

The results of DoE I experiments are compiled in the table below and graphically presented in diagrams of the responses (figures 3-8). All seven powders could be filled with DoE I reaching mean target fill weights between 5 and 45 mg (figure 3-18). The targeted RSD values (figure 3-19) below 5% could be accomplished except for ML001 and ML006 at mean weights dosed below 20 mg. Further discussion of the results is compiled in chapter 4.

					RESPITOSE ML001		RESPITOSE ML006		RESPITOSE SV010		RESPITOSE SV003		LACTOHALE 100		INHALAC 230		LACTOHALE GSK	
RUN	speed	diameter dosator	dosing chamber	powder layer	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	5,25	6,73	4,19	10,70	6,11	4,80	5,96	7,13	6,04	5,72	6,04	5,04	6,24	4,85
2	1500	2,8	3,75	10	23,77	2,71	14,77	10,43	19,97	1,87	19,11	1,78	19,01	2,10	18,97	2,42	23,14	1,77
3	2500	3,4	2,5	12,5	45,49	1,07	23,04	2,06	22,44	2,48	21,45	3,56	21,32	1,48	21,75	1,84	24,79	1,65
4	500	3,4	2,5	5	21,27	7,75	18,26	4,54	19,78	1,92	19,49	2,67	19,82	3,74	19,63	2,67	21,77	2,94
5	500	3,4	2,5	12,5	26,64	2,30	24,72	1,59	21,20	2,63	20,59	1,87	20,86	3,13	20,83	1,89	24,38	2,61
6	500	1,9	5	12,5	11,39	5,48	10,14	5,82	11,04	3,20	11,53	3,09	10,57	3,36	11,04	4,42	11,99	2,40
7	2500	1,9	2,5	12,5	7,28	5,30	6,93	5,02	6,82	3,93	6,66	6,81	6,30	4,02	6,36	4,87	7,60	3,37
8	2500	3,4	5	12,5	45,65	1,95	35,85	4,42	38,72	1,26	37,11	1,13	37,28	1,06	38,97	1,12	43,66	0,62
9	2500	1,9	5	10	10,68	11,44	7,35	9,20	11,21	4,25	10,63	4,75	10,43	3,23	11,19	2,50	10,99	3,67
10	1500	2,8	3,75	10	23,06	2,11	14,87	9,37	19,87	1,77	19,22	2,82	19,02	2,13	19,93	1,72	22,83	1,24
11	1500	2,8	3,75	10	22,32	3,66	11,85	8,79	19,73	2,54	19,12	2,62	18,49	2,25	19,65	3,04	22,56	1,67
12	2500	3,4	2,5	5	19,60	7,21	14,10	5,00	20,96	2,02	19,81	3,43	19,91	1,84	20,60	2,86	20,41	2,27
13	500	1,9	2,5	5	6,43	4,84	4,77	5,72	6,10	4,54	6,33	6,80	5,74	4,80	5,91	4,74	6,10	5,46
14	500	3,4	5	10	43,38	3,37	33,59	3,77	37,36	1,55	36,27	1,43	35,60	1,59	37,53	1,46	42,75	1,45
				Factors	dia/cha	dia/lay	dia/cha / lay	dia	dia/cha	dia/cha	dia/cha	dia	dia/cha	spe/dia /cha	dia/cha	dia/cha	dia/cha	dia/lay

Table 3-8: Results DoE I

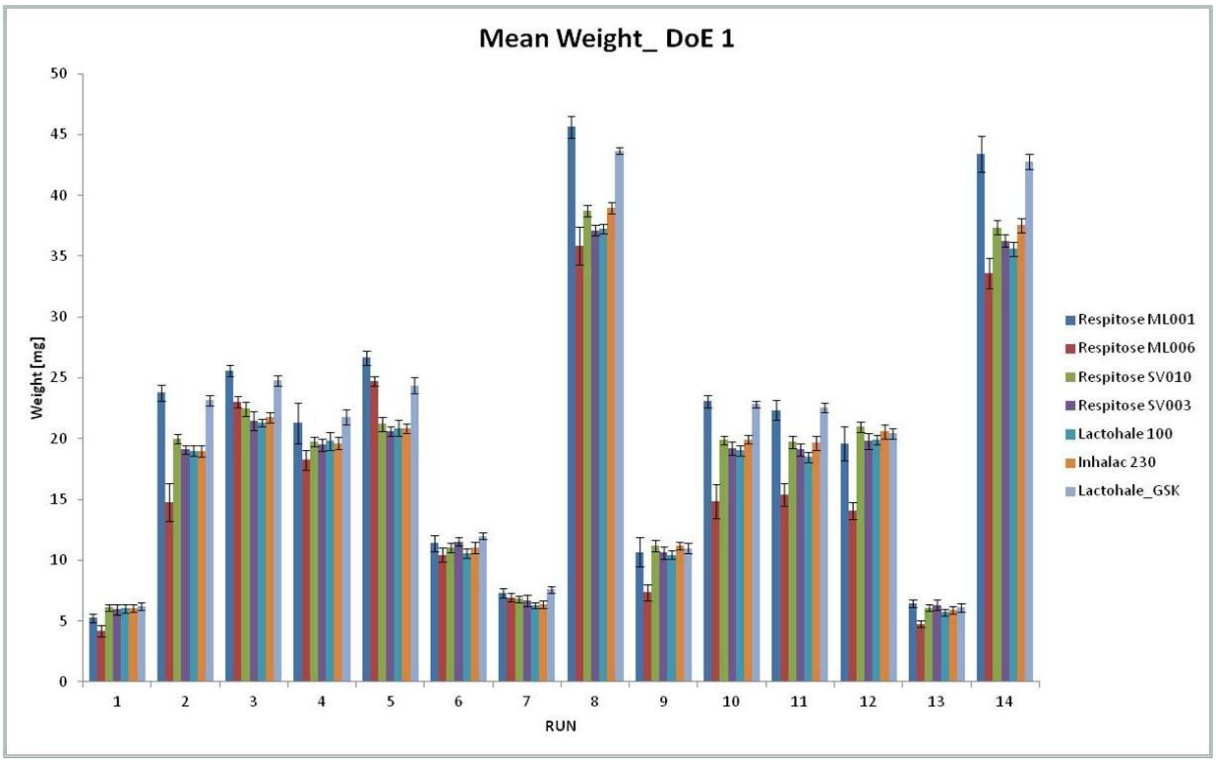

Figure 3-18: DoE I – Mean Weight

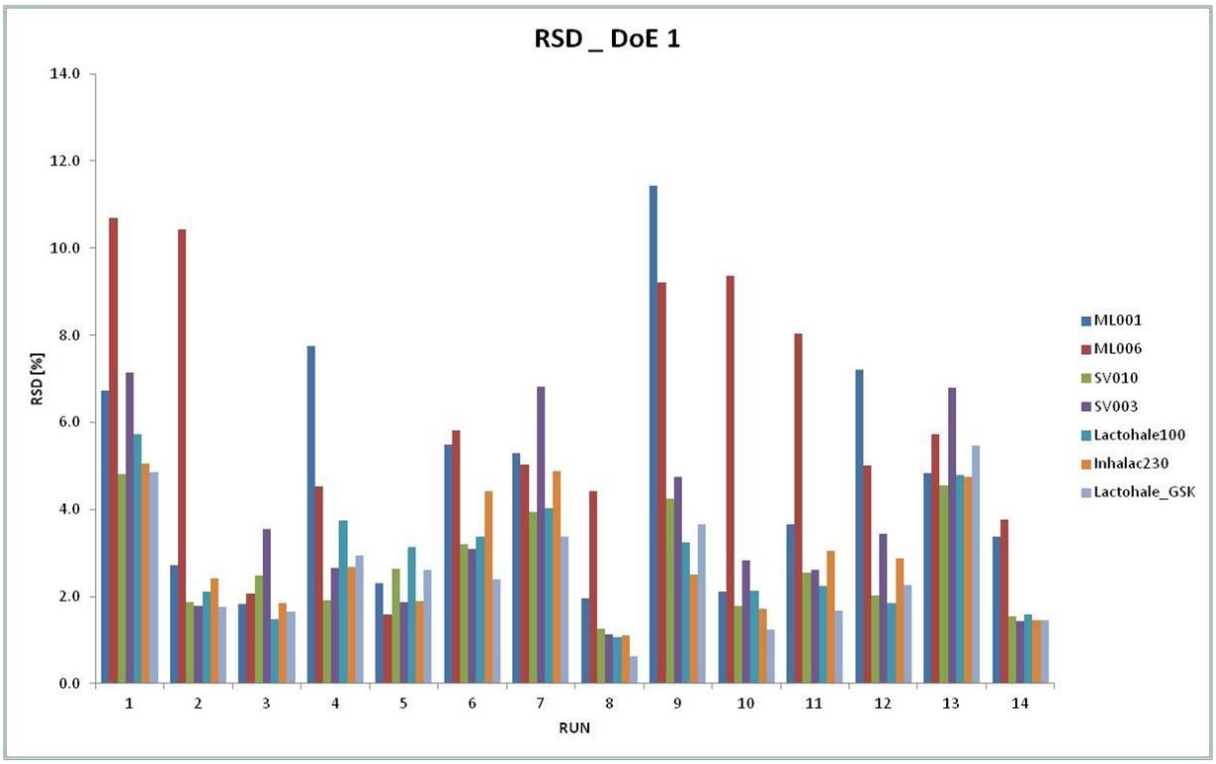

Figure 3-19: DoE I – RSD

In general the performance of DoE I was as expected, without any major problems during experimental procedure and without extremely high variations, as the powders were easy to handle and more or less free flowing.

3.4.3. Results DoE II

Compared to DoE I the finer lactose grade powders were far more challenging as they caused problems like powder adhesion on the dosator nozzle, uneven layer conditions due to agglomeration of snowballs and two runs of spheronized lactose could not be filled due to humidity, MgSt content and very low density (see section 3.5). Except for those two runs all experiments could be completed with mean target fill weights between 5 and 25 mg (figure 3-20), some even as low as 1.5 mg, and highly diverging RSD values (figure 3-21) compared to the targeted 10% according to Eur. Ph. 5, 2.9.5. (see section 3.4). Even though the targeted RSD was higher than the one of DoE I some experimental runs could not reach lower weight variation, due to very fine particles and cohesive nature of those powders. Further discussion of the results can be found in chapter 4.

					MANNITOL_MG2		LACTOHALE 300		SPHERONIZED LACTOSE_GSK		SORBOLAC 400		API_GSK	
RUN	speed	diameter dosator	dosing chamber	powder layer	Weight [mg]	RSD [%]	Weight [mg]	RSD [%]	Weight [mg]	RSD [%]	Weight [mg]	RSD [%]	Weight [mg]	RSD [%]
1	500	2,8	2,5	5	11,21	4,25	7,10	13,43	4,54	12,75	10,29	15,42	6,7	15,89
2	500	1,9	2,5	10	5,79	7,14	5,87	11,80	n.a.	n.a.	5,55	7,12	4,96	13,53
3	500	2,8	5	10	21,14	5,59	14,60	8,60	7,25	7,62	18,40	7,72	13,44	9,85
4	500	1,9	5	5	4,91	12,02	4,12	14,37	1,65	19,47	4,64	12,45	3,95	12,41
5	2500	2,8	5	10	18,58	4,74	15,32	7,37	7,16	6,50	18,88	5,92	12,99	10,08
6	2500	2,8	2,5	10	13,11	4,56	12,33	6,67	6,35	7,56	14,04	4,36	10,39	4,14
7	2500	1,9	5	5	5,13	8,93	5,60	11,49	1,84	17,76	5,48	8,20	4,16	11,91
8	2500	2,8	2,5	5	11,32	6,18	8,70	11,03	3,57	8,00	10,60	7,06	7,511	9,21
9	2500	1,9	5	10	8,04	9,70	7,05	8,57	2,74	10,21	7,75	9,43	5,50	7,04
10	1500	2,2	3,75	7,5	8,99	8,30	6,17	13,15	3,42	11,65	8,85	7,23	6,51	15,79
11	2500	2,8	5	5	12,66	5,71	10,29	8,68	3,39	15,35	11,33	5,84	6,14	8,40
12	1500	2,2	3,75	7,5	10,44	10,97	7,70	8,98	3,23	14,60	8,98	7,15	6,61	12,16
13	2500	1,9	2,5	5	4,12	13,88	5,31	16,45	1,52	16,68	4,62	9,03	3,15	11,74
14	1500	2,2	3,75	7,5	9,15	7,98	7,39	10,17	2,92	12,84	8,86	6,60	6,91	11,02
15	2500	1,9	2,5	10	6,03	9,82	5,22	8,29	n.a.	n.a.	6,07	5,53	3,84	9,37
				Factors	dia/lay	dia	dia/dc/lay	dia/lay/ spe	spe/dia/ lay	dia/lay	dia/dc/lay /cha*lay	spe/dia/la y/cha*lay	dia/dc/lay	spe/lay

Table 3-9: Results DoE II

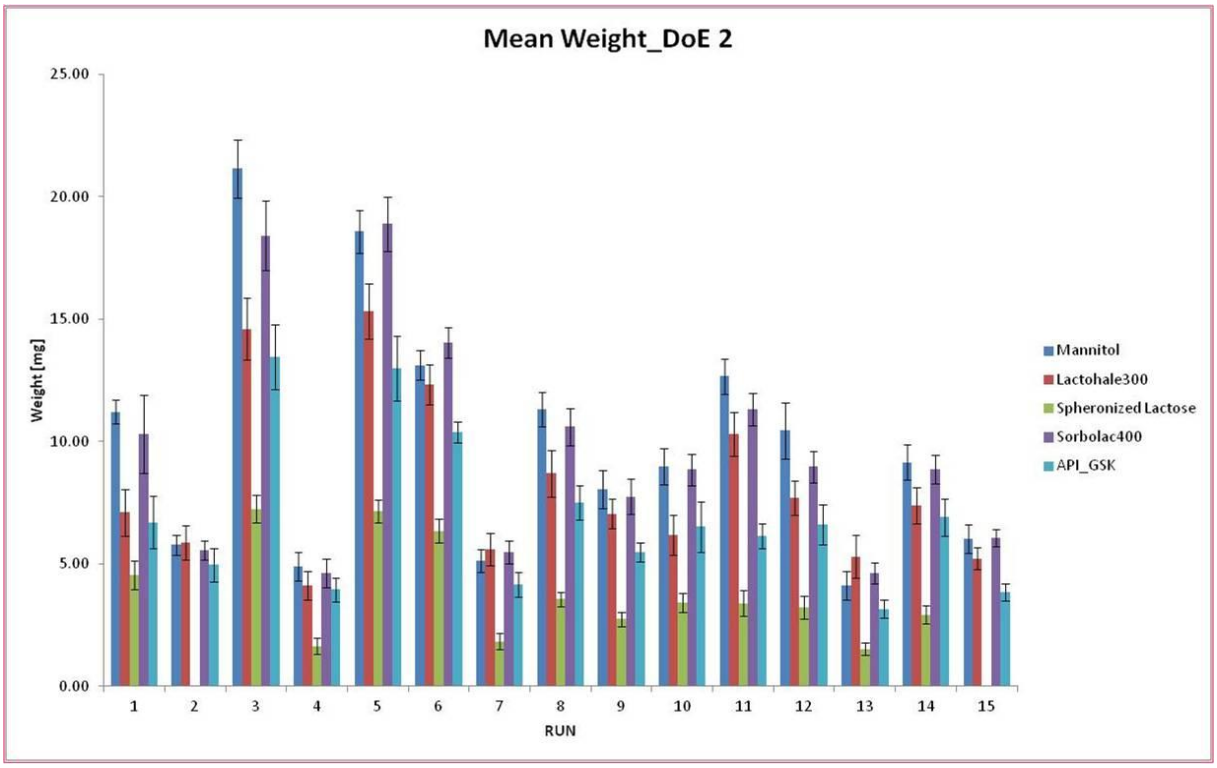

Figure 3-20: DoE II – Mean Weight

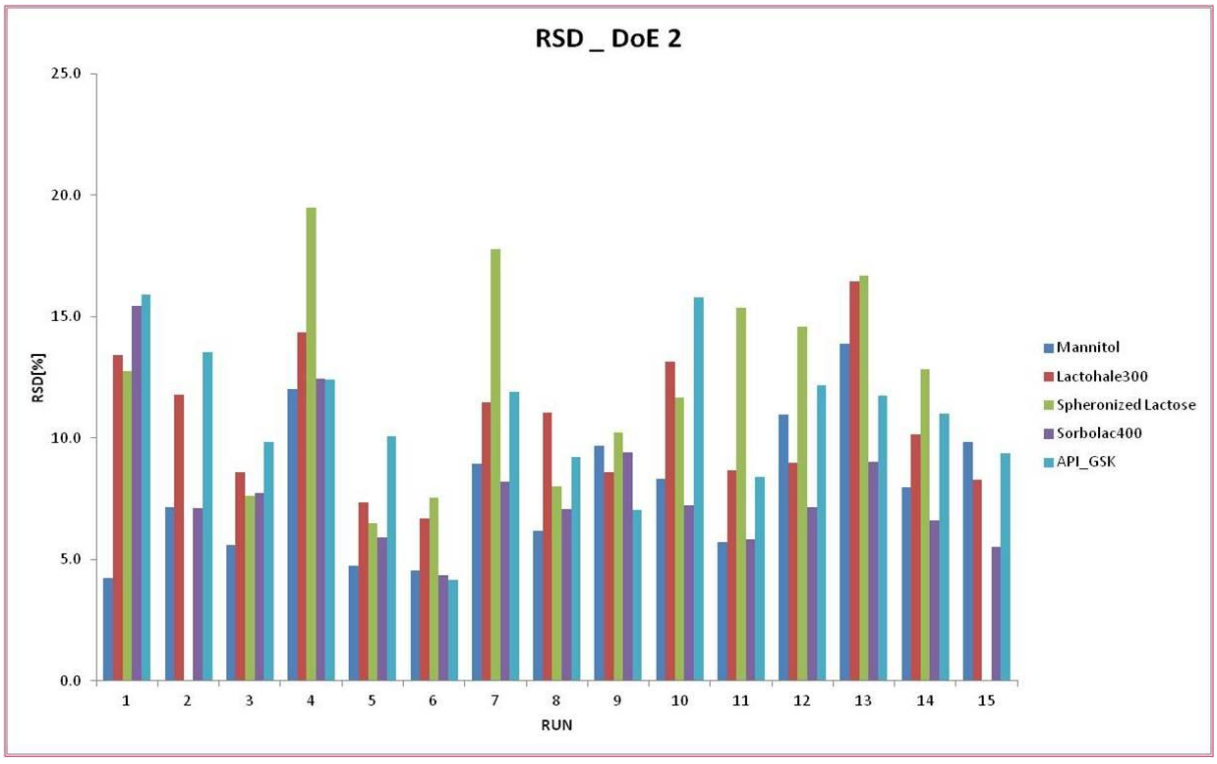

Figure 3-21: DoE II – RSD

The responses of the DoE II were deviating more to the initial set target fill weights and RSD values, as their performance was problematic and diverse according to their diverse properties, due to manufacturing, and their cohesive and adhesive behavior during the filling process.

3.5. Humidity Studies

The humidity studies were carried out with spheronized lactose within a relative humidity range from 55% up to 69%. This was done to justify the findings with 2.8 mm dosator and settings for 1:4 ratio of the DoE II, which failed at lower humidity (41% - 51%) as can be seen in table 3-10 and worked at humidities above 60% (see table 3-11). As seen in tables below red indicates experiments at low and green at higher humidity with all available low-dose dosators at different process settings as in the initial DoE experiments (see section 3.2.1.). Again (+) indicates normal performance of the process, (~) stands for normal performance after prolonged initial running time and at (-) the experimental settings failed to fill capsules. Even with higher humidity, experiments of the bigger dosator diameters and high ratios were hard to fill, which is in accordance with findings from the initial experiments due to too low ejection force of the machine.

Spheronized Lactose	*1.9/2.2*	*1.9/2.2*	*1.9/2.2*	*1.9/2.2*	*1.9/2.2*	*1.9/2.2*	*1.9/2.2*	*1.9/2.2*	*2.8/3.4*	*2.8/3.4*	*2.8/3.4*	*2.8/3.4*	*2.8/3.4*	*2.8/3.4*	*2.8/3.4*
DC	5	4	2,5	5	4	2,5	2,5	2,5	5	4	2,5	4	2,5	2,5	2,5
Layer	5	6	5	10	10	7,5	10	12,5	5	6	5	10	7,5	10	12,5
Ratio	1:1	1:1,5	1:2	1:2	1:2,5	1:3	1:4	1:5	1:1	1:1,5	1:2	1:2,5	1:3	1:4	1:5
RESULTS															
2500 cph	+/+	+/+	+/+	+/+	+/+	+/+	~/~	-/-	+/+	+/+	+/+	-/-	+/+	-/-	-/-
1500 cph	+/+	+/+	~/+	+/+	+/+	+/+	-/-	-/-	+/+	+/+	+/+	-/-	~/~	-/-	-/-
500 cph	~/+	~/+	~/~	+/+	+/+	~/+	-/-	-/-	+/+	+/+	~/+	-/~	-/-	-/-	-/-

Table 3-10: Humidity study of spheronized lactose at r. H. 41%-51%

Spheronized Lactose	*1.9/2.2*	*1.9/2.2*	*1.9/2.2*	*1.9/2.2*	*1.9/2.2*	*1.9/2.2*	*1.9/2.2*	*1.9/2.2*	*2.8/3.4*	*2.8/3.4*	*2.8/3.4*	*2.8/3.4*	*2.8/3.4*	*2.8/3.4*	*2.8/3.4*
DC	5	4	2,5	5	4	2,5	2,5	2,5	5	4	2,5	4	2,5	2,5	2,5
Layer	5	6	5	10	10	7,5	10	12,5	5	6	5	10	7,5	10	12,5
Ratio	1:1	1:1,5	1:2	1:2	1:2,5	1:3	1:4	1:5	1:1	1:1,5	1:2	1:2,5	1:3	1:4	1:5
RESULTS															
2500 cph	+/+	+/+	+/+	+/+	+/+	+/+	45/100 cps	+/+	+/+	+/+	+/+	+/+	+/+	+/+	18/63 cps
1500 cph	+/+	+/+	~/+	+/+	+/+	+/+	30/16 cps	-/-	+/+	+/+	+/+	-/+	+/+	+/-	-/-
500 cph	~/+	~/+	~/~	+/+	+/+	~/+	8/5 cps	-/-	+/+	+/+	~/+	-/+	+/+	-/-	-/-

Table 3-11: Humidity study of spheronized lactose at r. H. > 60%

Results of these studies showed that the most influencing factors of the filling performance for spheronized lactose were relative humidity and diameter of the dosator.

The effect of ratio between dosing chamber and powder layer on the filling of spheronized lactose helped to identify the borderline filling conditions between the two DoEs. For DoE I a 1:4 ratio and for DoE II a 1:3 ratio is the limiting factor for successful filling of inhalation products. Beyond these ratios (i.e.: 1:5 or 1:4) too much pre-compression is applied by the piston at dipping into the powder bed. Additionally with higher humidity the plug weight may increase due to water sorption and therefore can be ejected more easily. In detail for spheronized lactose the successful filling was hindered by too much compaction, due to high MgSt content, and too less ejection force of the machine.

3.6. Multivariate Data Analysis - Design Space

Multivariate data analysis was performed with MODDE 9.1 after completing all experiments for twelve inhalation grade powders. All acquired responses were combined in MODDE 9.1 with CMAs for statistical analysis and modeling. For this purpose linear models with underlying partial least square (PLS) regression were the basis for the MVDA. The data set for analysis contains uncontrolled variables (material attributes) and the controlled variables (process parameters) and the average values of the responses (fill weight and weight variability) from the process. The PLS regression helped to study the correlations between CMAs, CPPs and their responses of the process. As several responses were measured PLS is useful to fit a model simultaneously representing the variation of all responses to the variation of the factors, by taking their co-variances into account (Eriksson et al., 2008; Wold et al., 2004). This common data analytical tool has variable implementations such as several correlated responses, experimental design has 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 version, which relates two data matrices, X (factors) and Y (responses), where Y-data are modeled by the X-data, via a linear multivariate model (Wold et al., 2004). Models can be used to support design spaces across multiple scales and equipment (ICH, 2012) Modeling of the data sets generated coefficient – plots for both DoEs one for fill weight and weight variability (as seen in the figures 3-15 and 3-16 below).

3.6.1. Coefficient – Plots DoE I

Statistically significant coefficients for weight are, concerning CPPs, dosator diameter, dosing chamber and powder layer and concerning CMAs tapped and bulk density. Weight variability coefficients include the same CPPs as for weight and actually differ only in the CMA of the true density, of course with different statistical weighting.

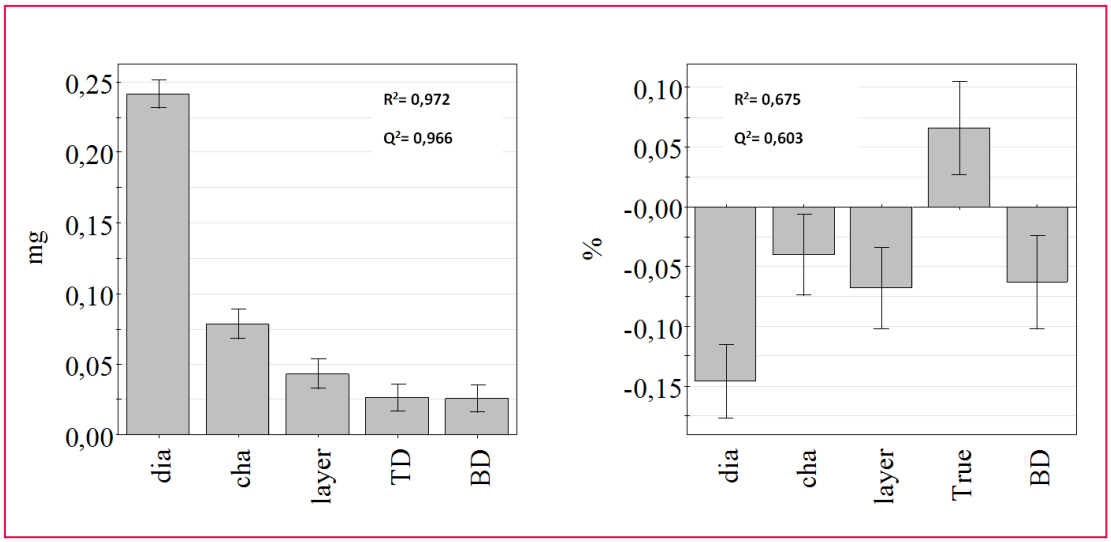

Figure 3-22: Coefficient – plots for fill weight and weight variability of DoE I

3.6.2. Coefficient – Plots DoE II

Data sets gave back information on the significant coefficients for fill weight, concerning CPPs, the same coefficients with diverging weighting as well as CMAs namely WFA and BFE and bulk density. For weight variability speed as a significant coefficient confirmed our experimental findings with the second powder family in the initial screening and the humidity studies with SL. Besides that dosator diameter, powder layer as CPPs and bulk density as CMA turned out to be statistically significant.

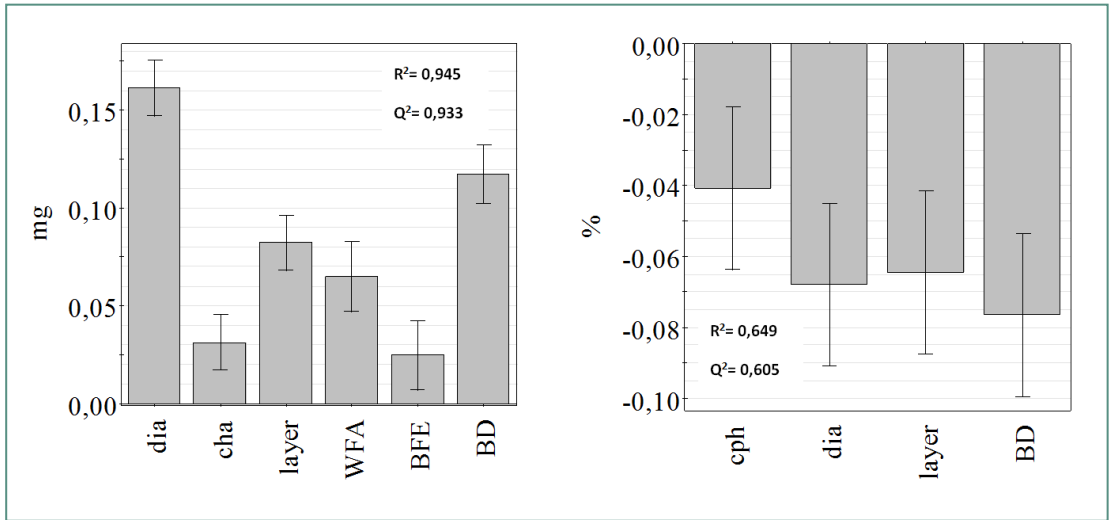

Figure 3-23: Coefficient – plots for fill weight and weight variability of DoE II

The modeling was the basis of a preliminary design space of low-dose capsule filling. Further discussion of the results from MVDA is assigned to chapter 4.

3.6.3. Design Space

The preliminary design space achieved for low-dose capsule filling, resulting from linear PLS regression models of the MVDA, includes the ranges of the values for CMAs and CPPs. Within these established ranges for both DoEs (see below), capsule filling can be performed confidently in the set design space.

DoE I design space:

- CPPs:
  - Dosator diameter: 1.9-3.4 mm
  - Dosing chamber: 2.5-5 mm
  - Powder layer: 5-12.5 mm
- CMAs:
  - Bulk density: 0.5-0.75 g/ml
  - Tapped density: 0.8-1.05 g/ml
  - True density 1.54-1.55 g/cm^3
- Responses:
  - Capsule fill weights: 6 - 46 mg
  - Weight variability: < 5 %

DoE II design space:

- CPPs:
  - Speed: 500-2500 cph
  - Dosator diameter: 1.9-2.8 mm
  - Dosing chamber: 2.5-5 mm
  - Powder layer: 5-10 mm
- CMAs:
  - Bulk density: 0.1-0.5 g/ml
  - Wall friction angle: 20-36°
  - Basic flowability energy: 400-1300 mJ
- Responses:
  - Capsule fill weights: 1.5 - 20 mg
  - Weight variability: < 15 %

3.7. Model Validation

The screening DoE (using PLS regression) was performed for identifying CPPs and previously characterized CMAs. Many factors were explored in order to reveal their influences on responses and to identify their appropriate ranges. The validation was conducted to ascertain that the method is robust to small fluctuations in the factor levels within the established design space (Eriksson et al., 2008).

Validation experiments were carried out after the final MVDA providing information on the influencing variables on the process. Two comparable powders were chosen for each DoE together with a prediction list including all influencing parameters on the responses. These were Inhalac 250 (Meggle) for DoE I and Lactochem microfine (DFE-Pharma) for DoE II.

For the validation experiments influencing powder material attributes for fill weight and weight variability were determined in triplicates and aligned with the process parameters. MODDE 9.1 generated a prediction list with values for the experimental responses and according upper and lower limits for the 95% confidence interval.

Experimental runs from the prediction list were performed as listed in the tables below (3-12, 3-13, 3-14) with a machine speed of 2500 cph. Three experimental runs, written in pink, were added as new process settings to test fluctuations in the factors and process robustness.

3.7.1. Inhalac 250

The characterized influencing material attributes (CMAs) for DoE I were:

- Bulk density: 0,5871 [g/ml]
- Tapped density: 0,9480 [g/ml]
- True density: 1,54 [g/cm³]

Speed	Dosator diameter	Dosing chamber	Powder layer	True density	Tapped density	Bulk density	Weight	Lower	Upper	Experimental results	Weight variability	Lower	Upper	Experimental results
2500	1,9	2,5	10	1,54	0,95	0,59	6,60	6,28	6,94	**6,63**	5,12	4,22	6,21	**2,84**
2500	1,9	5	10	1,54	0,95	0,59	10,02	9,53	10,55	**10,64**	4,14	3,41	5,03	**2,47**
2500	2,8	3,75	5	1,54	0,95	0,59	14,63	13,92	15,39	**14,39**	3,79	3,12	4,59	**2,74**
2500	3,4	2,5	5	1,54	0,95	0,59	19,60	18,63	20,63	**20,01**	3,11	2,56	3,78	**2,88**
2500	3,4	2,5	12,5	1,54	0,95	0,59	25,08	23,80	26,43	**23,44**	2,11	1,73	2,58	**1,78**
2500	3,4	3,75	10	1,54	0,95	0,59	28,47	27,39	29,59	**29,76**	2,16	1,83	2,54	**1,32**
2500	3,4	5	10	1,54	0,95	0,59	35,07	33,32	36,92	**39,17**	1,94	1,59	2,36	**1,62**

Table 3-12: Validation DoE I – prediction list for Inhalac 250

3.7.2. Lactochem microfine

The characterized influencing material attributes (CMAs) for DoE II were:

- Bulk density: 0,34 [g/ml]
- BFE: 529 [mJ]
- WFA: 33,9 [degree]

Speed	Dosator diameter	Dosing chamber	Powder layer	Bulk density	BFE	WFA 3kPa 0.2	Weight	Lower	Upper	Experimental results	Weight variability	Lower	Upper	Experimental results
2500	1,9	5	5	0,34	529	33,9	5,02	4,59	5,49	**5,60**	10,79	9,68	12,03	**11,35**
2500	1,9	2,5	7,5	0,34	529	33,9	5,27	4,86	5,72	**5,46**	9,15	8,33	10,04	**7,64**
2500	2,2	5	10	0,34	529	33,9	10,05	9,24	10,92	**9,44**	6,91	6,27	7,62	**5,29**
2500	2,2	3,75	7,5	0,34	529	33,9	7,50	7,02	8,02	**7,04**	8,16	7,55	8,80	**5,58**
2500	2,8	2,5	5	0,34	529	33,9	9,66	8,82	10,59	**10,33**	7,65	6,83	8,58	**5,78**
2500	2,8	5	8,5	0,34	529	33,9	15,26	14,00	16,63	**16,35**	6,07	5,50	6,70	**7,59**

Table 3-13: Validation DoE II – prediction list for Lactochem microfine.

Colored values indicate the scale for experimental results with 95% confidence interval. Green – in the predicted range between the limits, yellow – deviation under 5% and red – deviation over 5% from upper and lower limits.

With the information from the characterized CMAs model validation experiments were carried out with selected powders. The experimental results for both DoEs were predicted good for weight within the upper and lower limits except for four runs and worse for weight variability as many runs performed outside the 95% confidence interval, even though weight variability values were over-predicted and experiments gave lower percentage values of the RSD.

4. Results and Discussion

A QbD-based approach for low-dose capsule filling of inhalation products Part I: Screening of critical material attributes and process parameters

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Abstract

The aim of the present work is to use a screening Design of Experiment (DoE), in the frame of the Quality by Design (QbD) initiative for pharmaceuticals, to identify the material attributes and process parameters of a dosator nozzle machine that are critical to the fill weight and weight variability of hard gelatin capsules. This DoE also studies the criticality of interactions between process parameters to the fill weight and weight variability of these capsules. Twelve different powders, mostly inhalation carriers and one active pharmaceutical ingredient (API), were amply characterized and filled into size 3 capsules. Due to the need of using different process conditions to fill capsules with powders with large differences in material attributes, the powders were grouped into two different families. A DoE, which is based exclusively on process parameters, was developed for each family. In this manner, we are able to identify the critical material attributes and process parameters and at the same time, explore the largest Design Space for each family of powders. Multivariate data analysis (MVDA) allows the identification of the critical material attributes and process parameters to capsule fill weight and weight variability for each powder family. For fill weight, there is a significant correlation with the nozzle diameter, dosing chamber, powder layer thickness and the powder densities. Among material attributes, we identified wall friction angle and basic flowability energy as significant. This study is the first scientific qualification of dosator nozzles for low fill weight (1-45 mg) capsule filling.

4.1. Introduction

Dry powder inhalers (DPIs) are commonly used breath actuated inhalation devices for the treatment of respiratory diseases (Daniher and Zhu, 2008). A lot of effort is put into research and development for novel DPI formulations and devices, searching ways to improve the efficiency of drug delivery (Islam and Cleary, 2012). Especially with the increased recognition of the potential role of DPI systems for other therapies in the field of low dosage medication, DPIs could become the device category of choice for local and systemic drug delivery (Newman, 2004). Almost half of all marketed DPIs are single unit-dose devices with the powder formulation in individual hard-gelatin capsules. Examples for capsule based devices are the Rotahaler™ (Glaxo Smith Kline), Handi-Haler™ (Boehringer-Ingelheim) as single unit-dose and the Flowcaps® (Hovione) as novel multiple pre-metered unit-dose technology, that comprises up to 20 capsules (Newman, 2004; Steckel et al., 2004; Islam and Gladki, 2008).

As low-doses are typically needed for the oral inhalation of drugs (Kou et al., 2012), the challenge for the successful development of low-dose DPI products is the dose uniformity. To optimize the device design and the formulation of the drug a Quality by Design (QbD) - based approach. QbD is according to ICH Guideline Q8 (R2) "a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management (FDA/ICH 2009)." This approach is needed (Islam and Cleary, 2012) to take into account all the physico-chemical properties of the drug formulation, as well as the process parameters of the capsule filling technique in place.

Several low-dose capsule fillers are available with either volumetric or gravimetric operating principle. These are for volumetric principle the dosator nozzles (ND), vacuum drum filler, vacuum dosator and tamp filler and various gravimetric techniques for micro dosing (not further illustrated here). Capsule filling using nozzle dosators has been widely investigated (Jones, 2001; Newton, 2012; Podczeck and Jones, 2004a) and it is one of the main technologies used by pharmaceutical industry today. A lab scale low-dose dosator nozzle capsule filling machine (Labby, MG2, Bologna) was used in this study. MG2 adopted the standard dose Labby with special low-dose equipment: (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. These adjustments have been made to take advantage of the features already available for the standard dose dosator, especially

for a large output. However, this requires understanding the design space for nozzles of smaller diameter and re-examining the effects of process parameters and material attributes on the quality of filled capsules. Therefore, the objective of the current study is to identify and understand the complex relationship between the material attributes, process parameters, capsule fill weight and weight variability.

Because lactose is a well-known and widely used carrier for DPI applications (Kou et al., 2012), 10 different types of well-characterized α-lactose monohydrate were used in our experiments. In addition, mannitol and an active pharmaceutical ingredient (API) were also used in the present work.

The current study uses a screening Design of Experiments (DoE) as part of QbD approach to understand and to correlate the effects of process parameters and material attributes on fill weight and weight variability of capsules with low fill weight. Therefore different process parameters and material attributes as factors, for the desired responses (weight and weight variability) were studied.

Finally multivariate data analysis (MVDA) using the entire data set was performed and the critical material attributes and critical process parameters, which correlate with the quality of filled capsules were identified. Moreover, the design space for low-dose capsule filling with a dosator nozzle machine was established. This study is the first scientific qualification dosator nozzles for low fill weight (1-45 mg) capsule filling.

4.2. Materials and Methods

Ten different grades of lactose monohydrate excipients, mannitol and an API are used in this study (Table 1). All materials were used as received and each test was carried out in triplicate.

Many researchers state that different types and qualities of lactose may influence the performance of a DPI, and the Lactose quality needs to be carefully selected (Steckel et al., 2006; Hickey et al., 2007; Edge et al., 2008; Kou et al., 2012). For that reason ten different types of lactose were included in this study, with average particle sizes in the range of 1.5 to 160 µm. Two DoEs were developed according to capsule filling feasibility of the different powders. One DoE was necessary for powders with an x_{50} larger than 10 µm and a bulk density greater than 0,5g/ml (powder group I). The second DoE was required for more challenging powders (powder group II) with a mean particle size less than 10 µm and a bulk density less than 0,5g/ml.

Powder group	Powders for inhalation	Manufacturing Characteristics	Supplier
I	Lactohale 100	sieved	DFE Pharma, Goch, Germany
I	Lactohale_GSK	blend	GSK, Harlow, UK
I	Respitose ML001	milled	DFE Pharma, Goch, Germany
I	Respitose ML006	milled	DFE Pharma, Goch, Germany
I	Respitose SV003	sieved	DFE Pharma, Goch, Germany
I	Respitose SV010	coarse sieved	DFE Pharma, Goch, Germany
I	Inhalac 230	sieved	Meggle, Wasserburg, Germany
II	Sorbolac 400	milled	Meggle, Wasserburg, Germany
II	Spheronized Lactose	spheronized (10% MgSt)	GSK, Harlow, UK
II	Mannitol	spray-dried	MG2, Bologna, Italy
II	Lactohale 300	micronized	DFE Pharma, Goch, Germany
II	API_GSK	micronized	GSK, Harlow, UK

Table 4-1: Powder Selection

4.2.1. Powder characterization

The screening included a vast number of material attributes, which were characterized in triplicate: particle size (Qicpic OASIS/L wet and dry dispersing system Sympatec, Germany), bulk (BD) and tapped density (TD) (Pharmatest PT-TD200), true density (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 shearcell module at a maximum pressure of 3kPa. FFC is the ratio of consolidation stress, $\sigma 1$, to unconfined yield strength, σc. 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. The test starts applying 0.5kPa and increases the pressure by 2kPa with each step to 15kPa in the last step to obtain the ratio between the density at each compaction step and bulk density. WFA is a term that describes the interaction between a bulk solid and the surface of a material. To investigate the WFA, a stainless steel plate with a nominal roughness

(Ra) 0.2 µm was used, which is the material typically used for 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 elsewhere (Freeman, 2007; Freeman and Fu, 2008).

4.2.2. Design of experiments (DoE)

A DoE is developed around factors that are controlled, quantitative and manipulable. These factors are the process parameters. Each of these DoEs includes four process parameters of the capsule-filling machine. In addition, the DOE studies the interactions between size of dosing chamber and powder layer depth and the interaction between dosator diameter and size of the dosing chamber. In order to get most information with the smallest number of experiments, a D-optimal model was selected.

However, some experiments in the DoE could not be performed for some powders. For example, some powders could not be filled with a ratio of 1:5 and a dosator size of 3.4mm (i.e. piston blocking occurred immediately), which lead to the creation of a DoE for this particular group of powders. Therefore, for these powders a DoE using the same the process parameters and interactions but different values for their levels was built. These powders constitute the powder group II indicated in Table 1.

The parameter values for the two DoEs can be read in the first four columns of Table 6 (DoE for powder group I) and Table 7 (DoE for powder group II).

Based on that knowledge, we selected a screening DoE as experimental objective to find out which factors have a critical impact on the critical quality attribute. A DoE was created for each group with MODDE 9.1 (Umetrics) to study the effect of process parameters on capsule net weight and weight variability in low-dose capsule filling. Each of these DoE`s (D-Optimal with Design statistics G-Efficiency) includes four process parameters (controlled variables) of the capsule filling machine. Operation speed (500, 1500 and 2500 capsules per hour), dosator diameter (1.9 mm, 2.8 mm, 2.2mm and 3.4 mm), powder layer (5mm, 10mm and 12.5 mm) and dosing chamber (2.5mm, 3.75 mm and 5 mm).

The DoE has two constraints for the ratio between size of dosing chamber and layer (interaction 1): never smaller than 1:1 (DoE II)/1:2 (DoE I) and never larger than 1:4 (DoE II)/1:5 (DoE I).

4.2.3. Risk assessment - Process failure mode and effects analysis (P-FMEA)

FMEA is a fundamental step of the Quality by Design approach. FMEA identifies the potential failure modes of a product during its life cycle, the effects of these failures and the criticality of the latter in production functionality (Teng and Ho 1996). The aim in performing FMEA is to develop an effective quality control system, to improve the current production process and to ensure high quality and reliability of a product.

A P-FMEA begins with a process flowchart, which provides an overview of the complete production process for the manufacturing of the filled capsules. It identifies the potential process failures and determines the possible causes in manufacturing (Teng and Ho 1996). We divided the whole process in three sub processes: (1) the handling of empty capsules, (2) the feeding and layer creation in the bowl of the capsule filling machine and (3) the capsule filling itself. For each of these steps a detailed process flow was made. Then the possible failures and their effects were identified. Subsequent critical analysis to determine the severity, occurrence and detectability of the failure modes was performed. The last step was to evaluate and rank the criticality of each failure to get the risk priority number (RPN). This is done by multiplying severity, occurrence and detectability. Based on this RPN actions for risk minimization were taken to reduce or eliminate the failure causes. In our process, the three largest RPNs to fill weight and weight variability are: 1- Powder loss during transfer of the dosator, 2- Powder collection from the bowl, during nozzle dipping into the powder bed, 3- exposure of capsules to humidity during capsule handling and filling. We minimize the exposure of capsules to humidity by wearing gloves and using special films to seal the beakers in which the capsules were stored. Moreover a dehumidifier was put into the lab and the relative humidity was controlled.

4.2.4. Capsule filling experiments

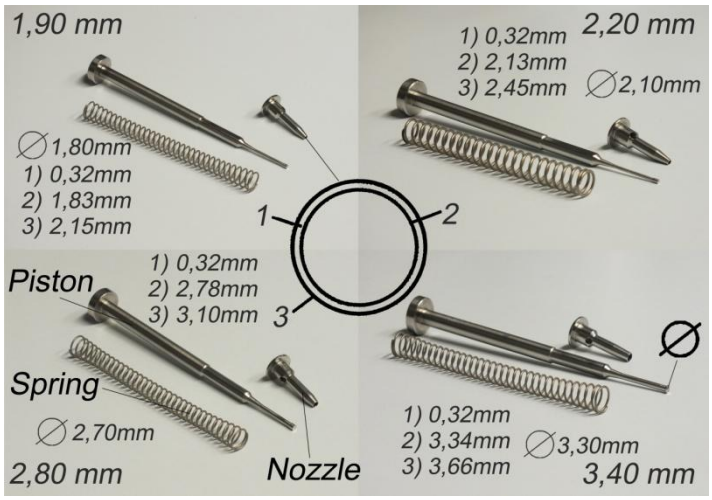

Figure 4-1: Schematic presentation of the low dose dosators

Figure 4-2: Screw for dosator fixation

Powders were filled into Coni-Snap® hard gelatin capsules of size 3 with a lab-scale dosator nozzle capsule-filling machine (Labby) using the process parameters described in Tables 5 and 6. Figure 1 shows a picture of the used low dose dosator nozzles. The diameter is much smaller than the one for standard doses and a special screw (Figure 2) is needed for nozzle mounting and fixation. Each capsule filling experiment followed a standard operating procedure (SOP) to minimize the effect of different factors, e.g. operator dependence on the quality for the product. The actions taken, according to the risk assessment, were repeated before and after each run: First action was the measurement of the exact height of the powder bed with a venier caliper, as the layer is recreated after every experimental run (rows in Table 5 and 6). Second the control of the exact dosing chamber height was performed with adjustment gauges. Third action was the visual inspection of the inside dosator nozzle wall and the piston before and after cleaning, to make sure that the walls were not coated with powder. After mounting the dosator one manual operation cycle was carried out to ensure the right position. More importantly, the whole study was performed under humidity-controlled conditions (45-55% relative humidity). It is widely accepted that the relative humidity can affect inter-particulate forces

through capillary condensation which could further lead to the formation of liquid bridges (Pilcer et al., 2012; Podczeck et al., 1997; Price et al., 2002).

Due to relative high weight of the empty capsule and its variability as compared to the fill weight, it is necessary to have the adequate scale and know exactly the weight of every empty capsule body. In order to accurately measure low-dose capsule content, hence on each single capsule body an assigned number was written and subsequent the weight was recorded with the Denver SI-234A (reproducibility 0.1 mg) analytical scale and saved in an Excel-sheet for further use.

After setting all process parameters, the powder layer was created and feeding of the powder to the bowl was optimized, which takes around half an hour for each run. In order to keep a smooth layer, the feeding must match the amount of powder collected by the nozzle. Then a group of 25-30 capsules was collected and another set of 25-30 capsules is collected after five minutes to check if the filling operation runs in a steady state condition. If the weight or RSD values of the two groups deviated more than 10% from each other the experiments were repeated.

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

4.2.5. Multivariate data analysis – Partial least squares regression

Finally, multivariate data analysis using the entire data set was performed with MODDE 9.1 (Umetrics). The data set contains the average value (of three measurements) for each powder property (uncontrolled variables), the value for each process parameter (controlled variables), which were the factors of the model and the average value for capsule weight and weight variability (RSD) as model responses. A partial least square (PLS) method was performed to study the correlations between material attributes and process parameters and capsule fill weight and weight variability. As several responses were measured PLS is useful to fit a model simultaneously representing the variation of all responses to the variation of the factors, by taking their co-variances into account (Wold et al., 2004). PLS is a common chemometric data analytical tool, which has various implementations such as several correlated responses, experimental design has 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 version, which 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)(FDA/ICH, 2012).

4.3. Results and Discussion

4.3.1. Powder characterization

Table 4-2 presents the particle size and densities of the different powders used in this research. According to the powder fineness classification in the USP 2011 <811>, Lactohale 100 and Respitose SV010 are fine powders. The rest of the studied powders can be classified as very fine in terms of particle size. In our studies we used powders with a broad range of densities.

According to Podczeck and Jones (2004) particles with a median size larger than 150 μm will usually be hard to fill on a dosator nozzle machine, whereas the ideal median particle size range is between 50 and 100 μm. Below 50 μm an increased tendency of powder adhesion to metal parts is observed alongside with an extremely reduced flowability. These are reflected in an increase of weight variability. Median particle sizes below 20 μm can usually not be filled successfully due to excessive adhesion, friction and poor powder flow (Podczeck and Jones, 2004). Working with these powders and nozzles of small diameter (Figure 4-1) was possible thanks to special features of the equipment, like nozzle cleaning unit and stabilizing blades for the powder bed (Figure 4-3).

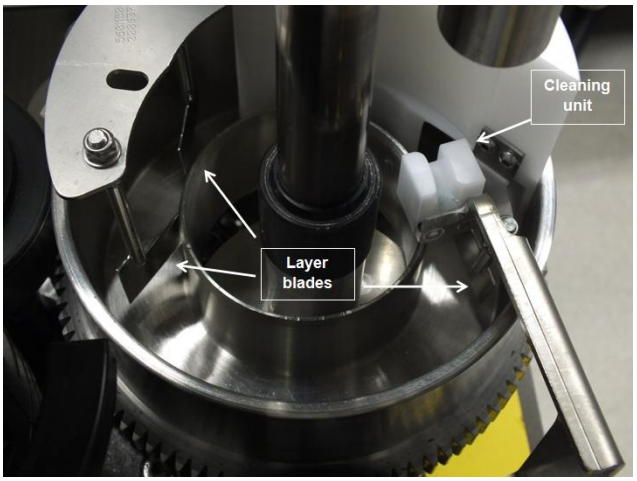

Figure 4-3: Low dose equipment

	VMD (µm)	BD (g/ml)	Stdv (+/-)	TD (g/ml)	Stdv (+/-)	True density (g/cm^3)	Stdv (+/-)
Spheronized Lactose	1.68	0.151	0.004	0.248	0.005	1.456	0.012
Mannitol	2.52	0.402	0.005	0.599	0.003	1.456	0.004
API_GSK	3.28	0.190	0.000	0.285	0.005	1.306	0.006
Lactohale 300	3.37	0.268	0.003	0.383	0.010	1.554	0.014
Sorbolac 400	8.71	0.398	0.001	0.760	0.005	1.555	0.007
Respitose ML006	23.07	0.470	0.002	0.860	0.004	1.554	0.009
Respitose ML001	71.17	0.658	0.003	1.046	0.004	1.553	0.006
Lactohale_GSK	72.36	0.669	0.001	1.012	0.007	1.539	0.005
Respitose SV003	73.99	0.687	0.000	0.831	0.002	1.540	0.003
Inhalac 230	111.71	0.736	0.004	0.890	0.002	1.547	0.005
Respitose SV010	129.82	0.723	0.012	0.869	0.004	1.539	0.001
Lactohale 100	160.02	0.697	0.004	0.828	0.013	1.539	0.003

Table 4-2: Particle size and Densities

Powder flowability is known to affect the weight variability of capsules filled using standard nozzles (Tan and Newton 1990; Podczeck and Miah 1996; Prescott and Barnum, 2000; Schulze 2011). In order to test if flow properties affect the weight variability of low fill weight products, a big effort was made to characterize this powder property using different techniques. The different flow indexes for the powders are summarized in Table 4-3. The successful and accurate dosing of low powder masses is challenging due to the limitations of volumetric dosing technologies, which rely on good flowing powders (Eskandar et al., 2011). According FFC and CI, the sieved Respitose showed the best powder flow. Lactohale 300 had the worst flow behavior (greatly cohesive), which is reflected by the lowest FFC value, whereas the CI classifies it only as poor flowing. This is not entirely surprising, as also other researchers, noted conflicting classifications obtained with different measurement techniques. Krantz et al. state that flow properties are dependent upon the stress state and that no single technique is suitable for fully characterizing a powder (Krantz et al., 2000). Guerin et al. could also see variable findings with different measurement techniques (Guerin et al., 1999).

	FFC	stdv (+/-)	C	stdv (+/-)	BFE (mJ)	stdv (+/-)	CI	stdv (+/-)
Spheronized Lactose	1.87	0.28	0.87	0.20	424.00	6.25	38.93	1.73
Mannitol	2.90	0.48	0.52	0.11	643.67	36.83	32.93	0.61
API_GSK	1.91	0.03	0.79	0.03	746.33	114.69	47.60	0.40
Lactohale 300	1.62	0.15	0.97	0.16	1265.33	96.50	30.00	1.00

Sorbolac 400	2.35	0.13	0.61	0.03	606.33	21.46	33.33	1.16
Respitose ML006	2.56	0.06	0.57	0.01	510.67	16.17	45.33	0.23
Respitose ML001	3.29	0.10	0.45	0.02	1171.33	83.68	37.07	0.46
Lactohale_GSK	4.35	0.09	0.33	0.00	1633.00	48.51	33.87	0.61
Respitose SV003	8.10	0.33	0.20	0.01	2393.33	74.27	17.33	0.23
Inhalac 230	7.93	0.57	0.20	0.01	2224.00	64.09	37.07	0.42
Respitose SV010	7.70	0.29	0.19	0.02	942.00	59.86	16.78	1.63
Lactohale 100	6.58	0.20	0.24	0.02	910.67	43.00	15.73	1.67

Table 4-3: Flow Properties

Table 4-4 shows the friction, compressibility and air permeability of the tested powders. The powder rheometer measurements showed that the more cohesive the powder, the greater the CPL. Fu et al. observed the same in their studies (Fu et al., 2012). The particle size correlates with the PD and therefore with air permeability. Except for LH 300, we see that 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 API and the sieved Lactoses show the lowest friction behavior. Furthermore, we observed a correlation between WFA and AIF.

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

Table 4-4: Friction, Compressibility and Permeability

4.3.2. Capsule filling

Table 5 presents the DoE for the first group of powders and shows the values for the four process parameters, the fill weight and weight variability (RSD) for each of the seven

powders tested. Weights between 4 and 45 mg and RSDs less than 5% were obtained for most of the experiments.

Lactohale_GSK showed the most uniform filling behavior (smallest RSD), although the powder layer creation took longer. All powders of group I were easy to handle during the entire process, except the milled Lactoses (Respitose ML001 and ML006). During the experiments with Respitose ML006 we faced some challenges, due to powder sticking inside- and on the outer wall of the nozzle. It can also be observed in Table 4-5 that the sieved Lactoses have more uniform fill weights than the milled ones. This effect could be explained due to the higher fine fraction of milled lactoses (Steckel et al., 2006). Fines tend to adhere on the outer wall of the nozzle; hence the dosing is not that accurate and are a key factor in the filling variability (Eskandar et al., 2011).

Plugs were never formed, not even for the largest ratio (1:4) between chamber and layer. This can be explained by the low powder cohesiveness and that no piston compaction was applied during filling. While investigating lactose powders, Jolliffe and Newton determined that the freer flowing the powder, the greater are the compressive stresses required for plug formation (Jolliffe and Newton, 1983; Jones, 2001).

DoE I					*ML001*		*ML006*		*SV010*		*SV003*		*Lactohale100*		*Inhalac230*		*Lactohale_GSK*	
	speed	diameter	chamber	layer	weight	RSD	weight	RSD	weight	RSD	weight	RSD	weight	RSD	weight	RSD	weight	RSD
RUN	[cph]	[mm]	[mm]	[mm]	[mg]	[%]	[mg]	[%]	[mg]	[%]	[mg]	[%]	[mg]	[%]	[mg]	[%]	[mg]	[%]
1	2500	1.9	2.5	5	5.25	6.73	4.19	10.70	6.11	4.80	5.96	7.13	6.04	5.72	6.04	5.04	6.24	4.85
2	1500	2.8	3.75	10	23.77	2.71	14.77	10.43	19.97	1.87	19.11	1.78	19.01	2.10	18.97	2.42	23.14	1.77
3	2500	3.4	2.5	12.5	45.62	1.82	23.04	2.06	22.44	2.48	21.45	3.56	21.32	1.48	21.75	1.84	24.79	1.65
4	500	3.4	2.5	5	21.27	7.75	18.26	4.54	19.78	1.92	19.49	2.67	19.82	3.74	19.63	2.67	21.77	2.94
5	500	3.4	2.5	12.5	26.64	2.30	24.72	1.59	21.20	2.63	20.59	1.87	20.86	3.13	20.83	1.89	24.38	2.61
6	500	1.9	5	12.5	11.39	5.48	10.14	5.82	11.04	3.20	11.53	3.09	10.57	3.36	11.04	4.42	11.99	2.40
7	2500	1.9	2.5	12.5	7.28	5.30	6.93	5.02	6.82	3.93	6.66	6.81	6.30	4.02	6.36	4.87	7.60	3.37
8	2500	3.4	5	12.5	45.65	1.95	35.85	4.42	38.72	1.26	37.11	1.13	37.28	1.06	38.97	1.12	43.66	0.62
9	2500	1.9	5	10	10.68	11.44	7.35	9.20	11.21	4.25	10.63	4.75	10.43	3.23	11.19	2.50	10.99	3.67
10	1500	2.8	3.75	10	23.06	2.11	14.87	9.37	19.87	1.77	19.22	2.82	19.02	2.13	19.93	1.72	22.83	1.24
11	1500	2.8	3.75	10	22.32	3.66	11.85	8.79	19.73	2.54	19.12	2.62	18.49	2.25	19.65	3.04	22.56	1.67
12	2500	3.4	2.5	5	19.60	7.21	14.10	5.00	20.96	2.02	19.81	3.43	19.91	1.84	20.60	2.86	20.41	2.27
13	500	1.9	2.5	5	6.43	4.84	4.77	5.72	6.10	4.54	6.33	6.80	5.74	4.80	5.91	4.74	6.10	5.46
14	500	3.4	5	10	43.38	3.37	33.59	3.77	37.36	1.55	36.27	1.43	35.60	1.59	37.53	1.46	42.75	1.45

Table 4-5: Low-dose capsule filling study - DoE I

Table 4-6 presents the DoE for the second group of powders. Again the weight and RSD for every experimental run are shown. Weights between 1.5 and 21 mg were obtained for these powders and process conditions. The weight variation (RSD) with values between 5% and 15 % was much higher than for powder group I. Some experiments with mannitol showed RSD values below 5%, which are the lowest values in this data set. With

spheronized lactose powder we could not fill capsules with the smallest dosator and 1:4 ratio between chamber and layer due to dosator/piston blocking and ejection failure.

Powder group II was much more challenging during production than the first group. The layer creation and the adjustment of machine parameters took much longer compared to powders in group I. Furthermore, all powder layers were more uneven, brittle and agglomerate formation occurred. The cleaning unit was covered with powder and the powders adhered inside and outside of the dosator nozzle. Therefore powder is carried over towards the ejection unit, which causes a higher weight variation.

The visual examination of the filled capsules revealed that all the powders formed weak plugs in all experiments with a 1:4 ratio and with a 1:2 ratio at low filling speed. This could be explained because at low filling speed the powder has the time to distribute the upcoming stresses, which is needed for proper arch and plug formation. However, plugs are soft and break easily when the capsules are manipulated. No plug was formed when filling was performed with high speed and a 1:2 ratio and for all 1:1 ratios. The weight variation was smaller for the experimental runs where plugs were formed, which could be explained because no powder was lost during transfer.

DoE II					*Mannitol*		*Sorbolac*		*Lactohale 300*		*Sph. Lactose*		*API_GSK*	
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	11.21	4.25	10.29	15.42	7.10	13.43	4.54	12.75	6.70	15.89
2	500	1,9	2,5	10	5.79	7.14	5.55	7.12	5.87	11.80	n.a.	n.a.	4.96	13.53
3	500	2,8	5	10	21.14	5.59	18.40	7.72	14.60	8.60	7.25	7.62	13.44	9.85
4	500	1,9	5	5	4.91	12.02	4.64	12.45	4.12	14.37	1.65	19.47	3.95	12.41
5	2500	2,8	5	10	18.58	4.74	18.88	5.92	15.32	7.37	7.16	6.50	12.99	10.08
6	2500	2,8	2,5	10	13.11	4.56	14.04	4.36	12.33	6.67	6.35	7.56	10.39	4.14
7	2500	1,9	5	5	5.13	8.93	5.48	8.20	5.60	11.49	1.84	17.76	4.16	11.91
8	2500	2,8	2,5	5	11.32	6.18	10.60	7.06	8.70	11.03	3.57	8.00	7.51	9.21
9	2500	1,9	5	10	8.04	9.70	7.75	9.43	7.05	8.57	2.74	10.21	5.50	7.04
10	1500	2,2	3,75	7,5	8.99	8.30	8.85	7.23	6.17	13.15	3.42	11.65	6.51	15.79
11	2500	2,8	5	5	12.66	5.71	11.33	5.84	10.29	8.68	3.39	15.35	6.14	8.40
12	1500	2,2	3,75	7,5	10.44	10.97	8.98	7.15	7.70	8.98	3.23	14.60	6.61	12.16
13	2500	1,9	2,5	5	4.12	13.88	4.62	9.03	5.31	16.45	1.52	16.68	3.15	11.74
14	1500	2,2	3,75	7,5	9.15	7.98	8.86	6.60	7.39	10.17	2.92	12.84	6.91	11.02
15	2500	1,9	2,5	10	6.03	9.82	6.07	5.53	5.22	8.29	n.a.	n.a.	3.84	9.37

Table 4-6: Low-dose capsule filling study - DoE II

4.3.3. MVDA

The screening model analyzes the regression between factors (X) and responses (Y). Figure 4-4 shows such an analysis - a significant PLS regression coefficients for the mean weight of capsules and their corresponding RSD for the DoE I. The error bars represent a 95% confidence interval. The coefficient plot summarizes the correlation between the capsule weight and RSD (y-axis) and process parameters and material attributes (x-axis).

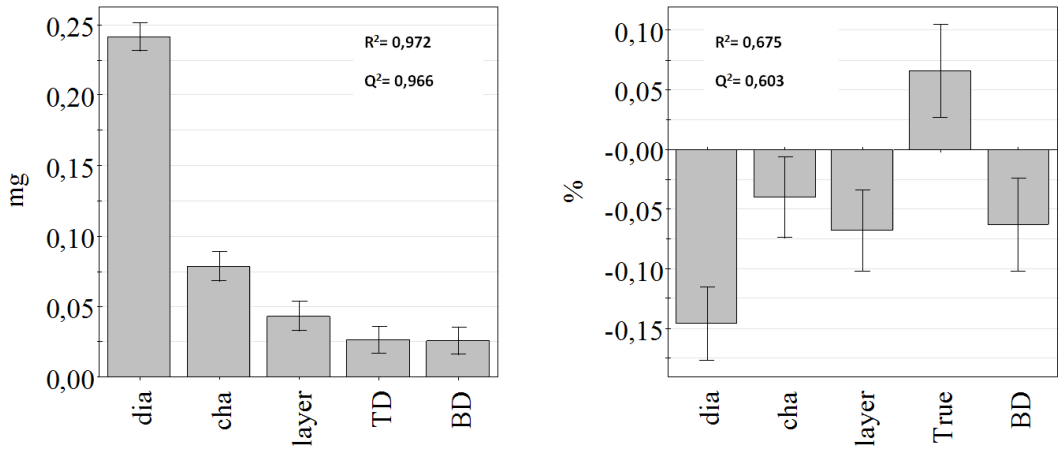

Figure 4-4: Coefficient plots for weight (mg) and RSD (%) – DoE I

The fill weight for the first group of powders (Figure 4) is affected by the diameter of the nozzle, the size of the dosing chamber and the densities (bulk and tapped). Diameter and size of the chamber are the two parameters that define the volume of the nozzle chamber. The larger the BD and TD, the higher the fill weight is. If all process parameters are kept constant and only the dosing chamber height gets doubled, the fill weight is nearly doubled (compare Run 5/8 and 12/14 in Table 4-5). Hence, filling is performed on volumetric basis for this group of powders. This is not the case for powder group II (compare Run 2/9 and 7/13 in Table 4-6). The diameter is the most influential factor for weight as the powder retention inside the dosator is governed by the size of its orifice. The ability of a powder to form an arch or a plug is related to attractive forces acting between the particles. The orifice of the diameter must match the powder characteristics for arch formation (Podczeck and Jones, 2004). This is difficult to achieve for many powders and that is the reason why diameter affects both, weight and weight variability most.

Figure 4-5 presents the PLS regression coefficients for the mean weight of capsules and their corresponding RSD for the second and more challenging group of powders. Dosator diameter and dosing chamber are the process parameters which again affect the capsule weight. Furthermore the WFA, BFE and BD have a significant correlation with fill weight. The weight variability is affected by the capsule filling speed, the dosator diameter, the powder layer and the bulk density. For this powder group the dosing chamber is not affecting fill weight. This could be explained because the friction, which is a significant parameter for weight, prevents the powder from filling the entire volume of the dosing chamber.

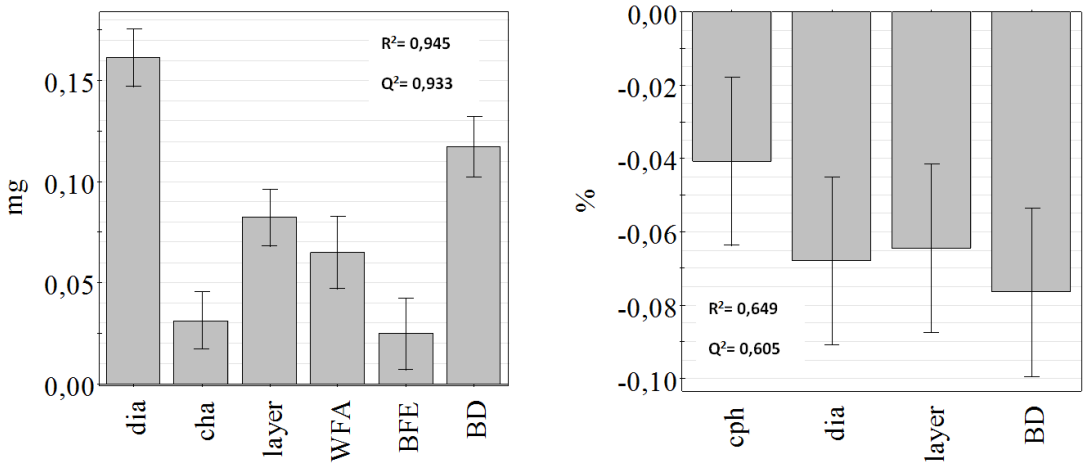

Figure 4-5: Coefficient plots for weight (mg) and RSD (%) – DoE II

As seen above in DoE I still diameter is one of the most influential factors for accurate filling next to the layer, which was challenging to keep stable. Due to the very low particle size powder characteristics had influence as these powders are of highly adhesive nature, poor flowability (BFE) and exert excessive friction (WFA) to the process which is in agreement with the findings of Podczeck and Jones (Podczeck and Jones, 2004). Moreover the speed is affecting the RSD of the filled capsule weight. At low production speed more powder adhered on the nozzle, especially for powders with low densities and was transferred into the empty capsule body with the powder plugs, causing higher fill weights.

4.4. Conclusions

In order to manufacture solid dosage capsule products with low fill weight (1-45 mg), the nozzles of the capsule filling machine are required to have diameters much smaller than the nozzles for standard capsules products. This paper presents the first scientific qualification of the performance of these low dose nozzles for a group of powders with very diverse material attributes. Special focus was placed on assessing material attributes that are known to affect the fill weight and weight variability of standard capsule products.

The principles of Quality by Design were implemented and a screening Design of Experiment (DoE) was the tool that allowed us to identify the critical material attributes and process parameters out of a large number of attributes and process parameters. At the same time, we established the largest possible design space for low fill weight capsule products. Depending on powder properties, different process parameters were required to perform capsule filling experiments. Therefore, we resorted to divide the powders into two groups or families, and a DoE with different values for process parameters was developed for each powder family.

This research makes two contributions to understand this process. First, it established the critical process parameters and material attributes for each powder family. The fill weight for both powder groups was affected by the same process parameters but different material attributes. The first group of powder with bigger particles and higher densities showed volumetric filling behavior, while the second group could not be categorized as filled per volume. The RSD for both groups was affected from the powder density and different process parameters. As particle and dose size decrease more factors are influencing the quality of the product. Second, the design space for low fill weight products is established as a function of process parameters and material attributes.

The results of the work will support the improvement of the current design of capsule filling equipment, particle engineering for inhalation and ultimately will allow the manufacturing of inhalation products with desired quality attributes.

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5. Conclusions

Every powder used in pharmaceutical industry, not specifically for inhalation, has its very own characteristics still not understood to full extent. Therefore the pharmaceutical industry puts a lot of effort in understanding the effects of material properties underlying nature of specific materials used for manufacturing various dosage forms.

In particular in this thesis the capsule filling performance of inhalation powders was studied on a continuous, automated MG2-'Labby', a dosator nozzle capsule filling machine. The studies included RA and the identification of process-related risks, where the highest risk is powder loss during transfer from the nozzle to the body of the capsule. Influenced mainly by material attributes, dosator diameter and machine speed, which could not be minimized at re-assessment due to the broad powder spectrum and low-dose machine settings for the DoE. The experimental fill weight and weight variation data showed that the free-flowing powders were easier and more consistently filled, but powder loss occurred with low pre-compression in the nozzle. On the other hand, powders of cohesive nature adhered to the metal parts, made filling hard to achieve and the very low fill weights gave high weight variation as single particles of adhered powder fell into capsule body. Cohesive powders yielded soft plugs, which were formed with slight pre-compression forces.

Not every powder could be filled with every experimental set-up due to its specific characteristics. According to this, a division into two powder groups with two different DoEs had to be established for this process. Using MVDA different critical material attributes (CMAs) were identified for each powder group. Alongside the CMAs, machine specific critical process parameters (CPPs) were identified with their weighting coefficients. The statistical analysis of the process from experimental data gave insight into this particular low fill weight capsule filling process, which was of particular interest for our partners for improving their products.

It is hard or almost impossible to achieve a universal design-space for all pharmaceutical inhalation powders used here. Still a lot of valuable data was gained by categorizing future inhalation powders and therefore choosing the appropriate DoE. With the known CMAs in alignment with critical process parameters, the desired responses, fill weight and weight variation, of the capsule filling process can be predicted within the corresponding powder group.

Still this categorization is not universal, due to the diversity of the powder characteristics. However it can be used as a guideline towards future experiments and scale-up. Combined with prior knowledge the new quality-oriented QbD-approach will lead to growing insight, understanding and improvement of the nozzle dosator-based capsule filling process at lab-scale and industrial scale, respectively.

Summary of achievements according to the goal:

For initial goals refer to chapter 1.

1. Due to the very different capsule filling performances of the twelve inhalation grade powders two different DoEs needed to be developed for each family of powders. One for powders with granulometry smaller than 10 μm and another for powders with granulometry larger than 20 μm.
2. The screening DoE yielded the CMAs for fill weight of DoE I (tapped- and bulk density) and of DoE II (wall friction angle, basic flowability energy and bulk density). As well as for the corresponding weight variation of DoE I (true- and bulk density) and only bulk density for DoE II. The yielded CPPs for fill weight of DoE I were dosator diameter, dosing chamber and powder layer which were the same for DoE II. As well as for the corresponding weight variation of DoE I dosator diameter, dosing chamber and powder layer and for DoE II speed, dosator diameter and powder layer were identified.
3. After an ample characterization of the powders, including 15 properties – namely particle size, density, powder flowability and compressibility, air permeability, cohesion and adhesion measurements using various techniques – the CMAs were included into the analysis. Every property was assessed, in triplicates for statistical significance, beforehand.
4. The optimization with gained process understanding was supported by RA as well as the re-assessment of the RA by identifying risks and the evaluation of risk minimization suggestions. These supported DoE with the identified CMAs and CPPs and the experimental procedure by incorporating RA results into best practice to gain best possible capsule quality. MVDA finally identified the critical coefficients to the process and setting a design space within optimized ranges.

5. The ranges of the values for CMAs and CPPs, identified in goal achievements number 2, where capsule filling can be performed confidently, are established, setting the design space.

   DoE I design space ranges are dosator diameters 1.9-3.4 mm, dosing chambers 2.5-5 mm, powder layers 5-12.5 mm, bulk densities 0,5-0.75 g/ml, tapped densities 0.8-1.05 g/ml, true densities 1.54-1.55 g/cm^3 yielding fill weights between 6 and 46 mg with weight variability lower than 5 %.

   DoE II design space spreads across speeds of 500-2500 cph, dosator diameters between 1.9-2.8 mm, dosing chamber heights from 2.5-5 mm, powder layer heights limited between 5-10 mm, for CMAs bulk densities of 0.1-0.5 g/ml, wall friction angles in the range of 20-36° and basic flowability energies of 400-1300 mJ yielding fill weights between 1.5 and 20 mg and weight variability below 15 %.

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Appendix

A.1. – Comparison of Technologies – Powders for Inhalation

Powder comparison	MG2 Labby	Capsugel Xcelodose S	Harro Höfliger Omnidose	3 PI - LabDosator	3 PI - Fill2Weight	MG2 Planeta (Low-dose)	MG2 Microdose	Conclusions/Additional Information
Respitose ML001								
Powder characterization:	TD:1,0456[±0,0044]; BD:0,6580[±0,0028] ; Hausner Ratio: 1,5890[±0,0117]; Carr Index:37,0667	n.a.	n.a.	n.a.	n.a.	n.a.	TD:0,88; BD:0,57; Hausner Ratio:1,54; Carr Index:35	
RSD [%]	4,8-6,7% (~5mg fill weights); 1,8-11,4% depending on experimental	n.a.	2,8%(5mg target fill weight)	n.a.	2-3%	n.a.	5mg: 1,5%; 25mg: 0,6%; 50mg: 0,8%; [GSK/MG2,2010]	Labby results from 1,9 diameter; Omnidose TT: 6,25mm³
weights [mg]	5,2-26,6mg	n.a.	5mg target fill weight	n.a.	5mg target fill weight	n.a.	1, 5, 25 & 50mg target fill	
Respitose ML006								
Powder characterization:	TD:0,8600[±0,0041]; BD:0,4701[±0,0017] ; Hausner Ratio: 1,8293[±0,0077]; Carr Index:45,3333 [± 0,2309]	n.a.	n.a.	n.a.	n.a.	n.a.	TD:0,75; BD:0,43; Hausner Ratio:1,7742; Carr Index:43	
RSD [%]	5-10,7% (~5mg fill weights); 1,6-10,7% depending on experimental	n.a.	n.a.	n.a.	n.a.	n.a.	5mg:1,9%; 25mg:0,6%; [GSK/MG2,2010]	
weights [mg]	4,1-35,9mg	n.a.	n.a.	n.a.	n.a.	n.a.	5 & 25mg target fill weight	
Respitose SV003								
Powder characterization:	TD:0,8310[±0,0019]; BD:0,6869[±0,0004] ; Hausner Ratio: 1,2097[±0,0034]; Carr Index: 17,3333 [± 0,2309]	n.a.	TD:0,81; BD:0,67; Hausner Ratio: 1,21	n.a.	n.a.	n.a.	TD: 0,78; BD: 0,63; Hausner Ratio: 1,24; Carr Index: 19	due to variation in fill weights --> 2 powder groups according density [Astra Zeneca]
RSD [%]	4,8-7,9% (<10mg fill weights); 1,4-7,9% depending on experimental	n.a.	2,7% (<10mg)	n.a.	n.a.	n.a.	5mg: n.a. 25mg: 0,2%; 50mg: 0,2% [GSK/MG2, 2010]	
weights [mg]	6-37mg	n.a.	6,2mg	n.a.	n.a.	n.a.	1, 5, 25 & 50mg target fill	

Powder comparison	MG2 Labby	Capsugel Xcelodose S	Harro Höfliger Omnidose	3 PI - LabDosator	3 PI - Fill2Weight	MG2 Planeta (Low-dose)	MG2 Microdose	Conclusions/Additional Information
Respitose SV010								
Powder characterization:	TD:0,8686[±0,0039]; BD:0,7229[±0,0120] ; Hausner Ratio: 1,2019[±0,0235]; Carr Index: 16,7798 [± 1,6304]	n.a.	n.a.	n.a.	n.a.	n.a.	TD:0,83; BD:0,69; Hausner Ratio:1,2028; Carr Index: 17	
RSD [%]	3,9-4,8% (~6-7mg fill weights); 1,3-4,8% depending on experimental condition	n.a.	n.a.	n.a.	n.a.	n.a.	25mg:0,2%; 50mg:0,1%; [GSK/MG2,2010]	
weights [mg]	6,1-37,4mg	n.a.	n.a.	n.a.	n.a.	n.a.	25 & 50mg target fill	
Inhalac 230								
Powder characterization:	TD:0,8903[±0,0017]; BD:0,7360[±0,0041] ; Hausner Ratio: 1,589[±0,0117]	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	
RSD [%]	1,1-5% depending on experimental condition	n.a.	n.a.	n.a.	10mg:0,6-1%; 25mg:0,5-1,5%; 50mg:0,4-2,3%; [Fill2Weights_3PI, Article 2012]	n.a.	n.a.	3PI -->Fill2Weights dispensing system uses adjustable dispensing time, for RSD reduction
weights [mg]	5,9-38,9mg	n.a.	n.a.	n.a.	10, 25 & 50mg target fill weight	n.a.	n.a.	
Sorbolac 400								
Powder characterization:	TD:0,7597[±0,0051]; BD:0,3981[±0,0014] ; Hausner Ratio: 1,9080[±0,0146]	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	
RSD [%]	7-9% (~5mg fill weights); 4,4-15,4% depending on experimental condition	n.a.	7,2% (5mg target fill weight)[Novartis; F. Eskandar, Paper+DDL Abstract]; > 8% [Astra Zeneca, DDL Abstract]	n.a.	5mg:3,57% [3PI,GSK 2008]; 10mg:1,3-2,8%; 25mg:2,1-2,7%; 50mg:1,4-3,2%; [Fill2Weights _3PI, Article 2012]	n.a.	n.a.	3PI -->Fill2Weights dispensing system uses adjustable dispensing time, for RSD reduction; Labby results from 1,9 diameter; Omnidose TT: 6,25mm³
weights [mg]	4,6-19mg	n.a.	5mg target fill weight	n.a.	5, 10, 25 & 50mg target fill weight	n.a.	n.a.	

Powder comparison	MG2 Labby	Capsugel Xcelodose S	Harro Höfliger Omnidose	3 PI - LabDosator	3 PI - Fill2Weight	MG2 Planeta (Low-dose)	MG2 Microdose	Conclusions/Additional Information
Micronized Lactose	***Spheronized Lactose [GSK]***	***n.a.***	***Micronized Lactose [Astra***	***n.a.***	***Spheronized Lactose [GSK]***	***n.a.***	***n.a.***	
Powder characterization:	TD:0,248[±0,005]; BD:0,151[±0,004]; Hausner Ratio: 1,638[±0,012]	n.a.	TD:0,34; BD:0,24; Hausner Ratio: 1,42	n.a.	TD:0,248[±0,005]; BD:0,151[±0,004]; Hausner Ratio: 1,638[±0,012]	n.a.	n.a.	due to variation in fill weights --> 2 powder groups according density [Astra Zeneca]
RSD [%]	very high RSD values:6,5% -18%; 2 experiments could not be performed	n.a.	trials with pure micronized lactose were terminated due to uneven filling of the drum	n.a.	4,7-5,9%	n.a.	n.a.	
weights [mg]	1,5-7,3mg	n.a.		n.a.	~5mg	n.a.	n.a.	
Denagliptin								
Powder characterization:	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	
RSD [%]	n.a.	n.a.	n.a.	n.a.	1mg: 11,9%; 10mg: 2,96-4,45%; 100mg: 3,3%; [3PI,GSK 2008]	n.a.	n.a.	
weights [mg]	n.a.	n.a.	n.a.	n.a.	1,10,100mg [3PI,GSK 2008]	n.a.	n.a.	
GSK 1144814C								
Powder characterization:	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	
RSD [%]	n.a.	n.a.	n.a.	n.a.	1mg: 34%; 10mg: 4,9%; 100mg: n.a.%; [3PI,GSK 2008]	n.a.	n.a.	conditions: end-of day and time-limited--> no optimization-RSD values should not be regarded as typical; unsieved material [3PI,GSK 2008]
weights [mg]	n.a.	n.a.	n.a.	n.a.	1,10,100mg [3PI,GSK 2008]	n.a.	n.a.	

A.2 – Values of Powder Characterization

Powder Properties DoE I	VMD		x50		WFA		BFE		Tapped Density	
1	LH100	160,02	LH100	155,24	LH100	7,70	IH230	2393,33	ML001	1,0456
2	SV010	129,82	SV010	127,64	SV003	8,36	SV003	2224,00	LH_GSK	1,0116
3	IH230	111,71	IH230	112,3	SV010	8,42	LH_GSK	1633,00	IH230	0,8903
4	SV003	73,99	SV003	73,37	IH230	9,25	ML001	1171,33	SV010	0,8686
5	LH_GSK	72,36	LH_GSK	66,47	LH_GSK	9,73	SV010	942,00	ML006	0,8600
6	ML001	71,17	ML001	52,43	ML001	12,57	LH100	910,67	SV003	0,8310
7	ML006	23,07	ML006	18,16	ML006	29,70	ML006	510,67	LH100	0,8275

Powder Properties DoE I	Bulk Density		True Density		Hausner Ratio		Carr Index		Compressibility Index	
1	IH230	0,7360	ML006	1,5541	LH100	1,1870	LH100	15,7333	SV010	1,043
2	SV010	0,7229	ML001	1,5533	SV010	1,2019	SV010	16,7798	LH100	1,050
3	LH100	0,6972	IH230	1,547	SV003	1,2097	SV003	17,3333	SV003	1,050
4	SV003	0,6869	SV003	1,5396	LH_GSK	1,5122	LH_GSK	33,8667	IH230	1,060
5	LH_GSK	0,6690	SV010	1,5388	IH230	1,5890	ML001	37,0667	LH_GSK	1,13
6	ML001	0,6580	LH_GSK	1,5387	ML001	1,5890	IH230	37,0670	ML001	1,190
7	ML006	0,4701	LH100	1,5385	ML006	1,8293	ML006	45,3333	ML006	1,277

Powder Properties DoE I	Air Permeability		AIF		FFc		Cohesion		Adhesion	
1	LH100	1,05	SV003	17,533	SV010	8,097	SV010	0,189	LH 100	0,43
2	SV010	1,96	IH230	17,600	IH230	7,933	IH230	0,196	SV003	0,46
3	IH230	2,71	SV010	17,833	SV003	7,703	SV003	0,204	SV010	0,48
4	SV003	4,58	LH100	18,433	LH100	6,583	LH100	0,242	IH230	0,50
5	LH_GSK	13,23	LH_GSK	23,567	LH_GSK	4,353	LH_GSK	0,332	LH_GSK	0,52
6	ML001	20,17	ML001	26,733	ML001	3,290	ML001	0,447	ML001	0,70
7	ML006	27,10	ML006	31,267	ML006	2,563	ML006	0,574	ML006	1,54

Powder Properties DoE II	VMD		x50		WFA		BFE		Tapped Density	
1	S400	8,71	S400	7,61	SL	11,20	LH300	1265,33	S400	0,7597
2	LH300	3,37	LH300	2,69	M_MG2	24,10	API_GSK	746,33	M_MG2	0,5992
3	API_GSK	3,28	M_MG2	2,37	S400	30,20	M_MG2	643,67	LH300	0,3829
4	M_MG2	2,52	API_GSK	2,24	LH300	31,50	S400	606,33	API_GSK	0,2851
5	SL	1,68	SL	1,43	API_GSK	35,67	SL	424,00	SL	0,2480

Powder Properties DoE II	Bulk Density		True Density		Hausner Ratio		Carr Index		Compressibility Index	
1	M_MG2	0,4019	S400	1,5545	LH300	1,429	LH300	30,000	M_MG2	1,213
2	S400	0,3981	LH300	1,5535	M_MG2	1,4911	M_MG2	32,9333	S400	1,350
3	LH300	0,268	SL	1,4559	API_GSK	1,5000	API_GSK	33,3330	LH300	1,473
4	API_GSK	0,1900	M_MG2	1,4556	SL	1,6380	SL	39,9330	SL	1,51
5	SL	0,1510	API_GSK	1,3061	S400	1,9080	S400	47,6000	API_GSK	1,743

Powder Properties DoE II	Air Permeability		AIF		FFc		Cohesion		Adhesion	
1	LH300	6,17	M_MG2	31,833	M_MG2	2,897	M_MG2	0,517	SL	0,56
2	SL	27,97	SL	33,433	S400	2,347	S400	0,610	M_MG2	1,51
3	S400	29,40	LH300	34,267	API_GSK	1,910	API_GSK	0,790	S400	1,81
4	API_GSK	30,90	S400	34,800	SL	1,867	SL	0,868	LH300	1,81
5	M_MG2	40,47	API_GSK	36,333	LH300	1,617	LH300	0,966	API_GSK	2,11

A.3 – P-FMEA – Capsule Handling

Risk Assessment – P-FMEA – Capsule Handling

Process Failure Mode and Effect Analysis (PFMEA)

System: Labby
Subsystem: Low dose capsule filling
Team: Material Science
Leader: Marcos Llusa

Date: 25.06.2013
Assessment number: 1
Page:

Process Phase	Process Parameter	Potential Failure Mode	Operating Range [unit]	Potential Failure Effect	S e v	O c c	Current Design Controls	D e t	R P N	Action	Re-Assessment: Risk Minimization Suggestion	S e v	O c c	D e t	R P N
Capsule Handling	1	Humidity	43-55% r.H.	weight variation	9	3	Hygrometer	3	81	dehumidifier; gloves	Humidity control	9	1	3	27
	1	error of the scale	1-45 mg	weight variation	1	1	Calibrated scale	1	1			1	1	1	1
	1	human error		weight variation	5	1	4-eye-principle	3	15	software		5	1	1	5
	2	Humidity	43-55% r.H.	weight variation	9	3	Hygrometer	3	81	dehumidifier; gloves	Humidity control	9	1	3	27
	3	pressured air	6 bar	no production	1	1	Barometer	1	1		regular value examination	1	1	1	1
	3 A 1	pressured air	6 bar	no production	1	1	Barometer	1	1		regular value examination	1	1	1	1
	3 A 1	capsule stuck in feeding tube		no production	1	1	Lid-Sensor	1	1			1	1	1	1
	3 A 2	damaged capsules		no production	1	3	Lid-Sensor	1	3			1	3	1	3
	3 A 3	damaged capsules		no production	1	3	Lid-Sensor	1	3			1	3	1	3
	3 F	lid loss/open capsules		weight variation	3	3	Lid-Sensor	1	9			3	3	1	9
	3 E 1	lid loss/open capsules		weight variation	3	3	Lid-Sensor	1	9			3	3	1	9
	3 E 2	no capsule ejection		no production	1	3		1	3			1	3	1	3
	4	humdity	43-55% r.H.	weight variation	9	3	Hygrometer	3	81	dehumidifier; gloves	Humidity control	9	1	3	27
	5	humidity	43-55% r.H.	weight variation	9	3	Hygrometer	3	81	dehumidifier; gloves	Humidity control	9	1	3	27
	5	error of the scale	1 - 45 mg	weight variation	1	1	Calibrated scale	1	1		Capacitance System	1	1	1	1
	5	human error		weight variation	5	1	4-eye-principle	3	15	software	Capacitance System	5	1	3	15

A.4 – P-FMEA – Layer Creation

Risk Assessment – P-FMEA – Layer Creation

Process Failure Mode and Effect Analysis (PFMEA)

System: Labby
Subsystem: Low dose capsule filling
Team: Material Science
Leader: Marcos Llusa

Date: 25.06.2013
Assessment number: 1
Page:

Process Phase	Process Parameter	Potential Failure Mode	Operating Range [unit]	Potential Failure Effect	Sev	Occ	Current Design Controls	Det	RPN	Action	Re-Assessment: Risk Minimization Suggestion	Sev	Occ	Det	RPN
Layer creation	6	blade not fixed properly	no feeding	weight variation	3	1	visual and manual examination	1	3		Vibration feeder	3	1	1	3
	7	agglomerates	feed: 0,5-1,5 s; feed waiting: 50-500 s	feeder blocking	3	3	visual examination	3	27	stirr powder with spoon	Vibration feeder	3	1	3	9
	8	user dependent	5; 7,5; 10; 12,5 mm	weight variation	5	1	graduated scale; caliper	5	25	check with 4 eye principle	Laser measurement of layer height; automated feeding	5	1	3	15
	9	feeder opening bar	feed: 0,5-1,5 s; feed waiting: 50-500 s	weight variation	1	9		1	9			1	9	1	9
	10	feeder blocking	feed: 0,5-1,5 s; feed waiting: 50-500 s	weight variation	3	1		3	9		Vibration feeder	3	1	3	9
	11	uneven layer/ layerheight	5; 7,5; 10; 12,5 mm	weight variation	5	5	visual examination; caliper	3	75	check height with caliper	Laser measurement of layer height; automated feeding	5	3	1	15
	12	segregation		weight variation	1	1	visual examination	3	3		Vibration feeder; spanker	1	1	3	3
	13	wrong feed	feed: 0,5-1,5 s; feed waiting: 50-500 s	weight variation	3	3		5	45	check after a few runs	Laser measurement of layer height; automated feeding	3	1	5	15

A.5 – P-FMEA – Capsule Filling

Risk Assessment – P-FMEA – Capsule Filling

Process Failure Mode and Effect Analysis (PFMEA)

System: Labby
Subsystem: Low dose capsule filling
Team: Material Science
Leader: Marcos Llusa

Date: 25.06.2013
Assessment number: 1
Page:

Process Phase	Process Parameter	Potential Failure Mode	Operating Range [unit]	Potential Failure Effect	Sev	Occ	Current Design Controls	Det	RPN	Action	Re-Assessment: Risk Minimization Suggestion	Sev	Occ	Det	RPN
Capsule Filling	14	user dependent	2,5; 3,75; 5 mm	weight variation	5	3	adjustment gauges	1	15	gauges	Steplessly adjustable dosing chamber; better fixation	5	1	1	5
	14	loose dosing chamber	2,5; 3,75; 5 mm	weight variation	5	5	visual and manual examination	1	25	check after a few runs; fix	Steplessly adjustable dosing chamber; better fixation	5	1	1	5
	15	dosator not fixed appropriate	ø 1,9; 2,2; 2,8; 3,4 mm	weight variation	1	1	Manual round with handwheel	1	1		Steplessly adjustable dosing chamber; better fixation	1	1	1	1
	16 A	setting speed	500; 1500; 2500 cph	no production	1	1		1	1			1	1	1	1
	16 B	open capsule cam		no production	1	1	visual examination	1	1			1	1	1	1
	16 C	sensor		no production	1	1	machine sensor	1	1			1	1	1	1
	17 A	autocompactation	ratios layer:dc 1:1;1:2;1:3; 1:4;1:5	weight variation	7	7		3	147	set lower ratio between chamber and layer		7	3	3	63
	17 A	holes in layer	feed: 0,5-1,5 s; feed waiting: 50-500 s	weight variation	7	5	visual examination	7	245	optimize feed	Laser measurement of layer height; automated feeding	5	3	5	75
	17 B	powderloss	speed; ø	weight variation	7	7		7	343			7	7	7	343
	18 A	powder on scraper		weight variation	5	7	visual examination	1	35	clean scraper manually	vacuum cleaning unit	5	3	1	15
	18 B	only two side cleaning		weight variation	5	9	visual examination	1	45	clean scraper manually	vacuum cleaning unit	5	5	1	25
	19	no proper plug ejection	force [N]	weight variation	9	3	empty capsules; visual examination	1	27		ejection phase improvement; higher ejection force	9	3	1	27

A.6 – SOP – Labby, MG2

Standard Operating Procedure (SOP)
MG2–LABBY low dose capsule production

research center pharmaceutical engineering

Instructions for MG2–LABBY low dose capsule production

Prepared on: 26th of March 2013
This SOP replaces: N/A
Field of Application: Laboratory

Written by: Mag. Pharm. Marlies Fink (Diploma Student)

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(Signature) (Date)

Revised by: Mag. Pharm. Eva Faulhammer (PhD Student)

---------- ----------
(Signature) (Date)

Approved by: Marcos Llusa, PhD (Team Leader, Material Science)

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(Signature) (Date)

Acknowledgements

We would like to address our acknowledgements to MG2 and especially to Stefano Biserni for supporting our experiments and for his advice and revision in creating this SOP during his stay at the beginning of March 2013.

This document was prepared after the submission of the 1st quarterly report and it is not listed in page 15 of this report.

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Standard Operating Procedure (SOP)
MG2–LABBY low dose capsule production

research center pharmaceutical engineering

Table of Contents

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Standard Operating Procedure (SOP)
MG2–LABBY low dose capsule production

research center pharmaceutical engineering

1. Goal

The goal of this SOP is to describe the main procedure of the production of low dose capsules for inhalation on the 'MG2 – Labby' capsule filling machine. Low dose is defined in this project as capsules having at least 5 mg powder content.

2. Scope

The SOP is only valid for the use of the 'MG2 – Labby' capsule filling machine with the low dose set-up.

3. Abbreviations

SOP = Standard Operation Procedure

DoE = Design of Experiments

RSD = Relative Standard Deviation

PBH = Powder Bed Height

DC = Dosing chamber

4. Responsibility

Marcos Llusa, PhD (Group Leader)

Mag. Pharm. Eva Faulhammer (PhD - Student)

Mag. Pharm. Marlies Fink (Diploma - Student)

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5. Achieving high precision in low dose weighing measurements

In order to accurately measure capsule content in the range of 5 mg, it is necessary to have the adequate scale and know exactly the weight of every empty capsule body.

a. Details of high precision scale

Analytical balance DENVER SI-234

- Capacity: 230 g
- Readability: 0.0001 g
- Pan size: ø 90 mm
- Linearity: 0.2 mg
- Reproducibility: 0.1 mg
- Measurement time: 2.5 sec
- Calibration: internal

b. Pre-weighing and identification of the empty capsules

The capsules, size 3, are approximately 48 mg ± 3 mg and therefore much heavier than the powder content. The variability in the weight of the empty capsules (± 3 mg) is almost as large as the content (5 mg). Therefore, the weight of the empty body must be known before filling capsules.

- Unnumbered hard gelatine capsules, size 3.

- Numbered capsules, size 3.

  - Weighed after writing the assigned number on the capsule with the Denver SI-234A analytical scale and each capsule weight is saved in an Excel-sheet for further use.

- Numbered and filled capsules, size 3.

  - Filled and numbered capsules are weighed again with the Denver SI-234A analytical scale and the weight of the empty, numbered capsule is subtracted from the gross weight to gain the net weight of the filled capsule.

Criteria for weight uniformity

PH. EUR. 5, 2.9.5:

Weigh individually 20 units taken at random or, for single-dose preparations presented in individual containers, the contents of 20 units, and determine the average mass.
Not more than 2 of the individual masses deviate from the average mass by more than the percentage deviation shown in Table 2.9.5.-1 and none deviates by more than twice that percentage.

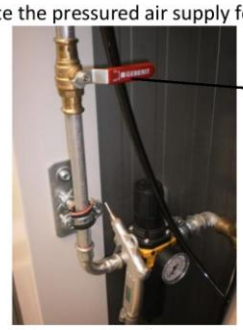
Capsules, granules (uncoated, single-dose) and powders (single-dose)	▪ Less than 300 mg 10% ▪ 300 mg or more 7.5%

c. Configuration of MG2 – Labby capsule filling machine

Start Up Procedure

- Turn the main switch from 0 to 1 to turn the machine on.

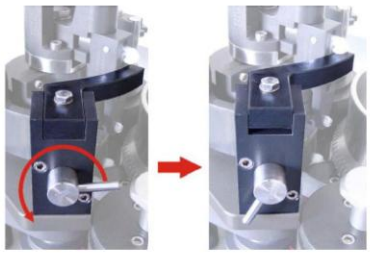
- Activate the pressured air supply for the machine in the lab and check the pressure of 6 bar.



- Check, if the machine is properly cleaned for starting the next run. For cleaning instructions refer to the 'cleaning instructions'.

Check of Capsule Flow

- Feed capsules manually into the capsule hopper.
- Open the capsule feeding cam for capsule turning procedure to fill the capsule carousel.



Closed position Open Position

- At that time, operation runs without powder. Therefore the powder dosing unit needs to be closed.
- Enable the lid presence sensor and set it to stop the machine after 3 missing capsules. This will help to ensure that capsules are feeded permanently.

- Make sure the capsules are feeded, orientated, and ejected correctly for a couple of minutes.

Creating the Powder Layer

- Check the correct run order of the DoE for needed adjustments during the creation of the powder layer before every test.
  This includes: Machine speed, diameter of the dosator, dosing chamber and height of the powder layer.
- Align the powder hopper in the right position and make sure that the rotating blade is mounted inside the hopper to keep up a right flow.
- Put the product manually in the hopper of the dosing unit.

Standard Operating Procedure (SOP)
MG2–LABBY low dose capsule production

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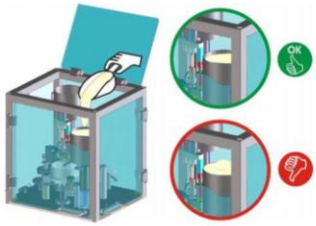
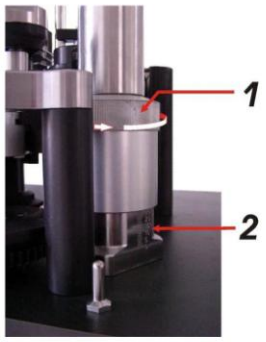
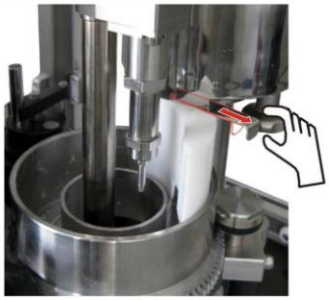


- Set the layer height on the graduated scale (2) and add 3 mm to the desired powder bed height (pbh) by turning the lock ring (1) on the column.



- Open the powder dosing unit.



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- Start feeding the powder manually into the rotary container.
  - Press the button two times to start the feed.

Manual Feeding Button

  - Powder feed until a uniform layer of the powder is formed in the rotary container.

- Check the right height of the powder layer with a vernier caliper.
- Run the machine WITHOUT dosator unit and capsules until the first preset feeding time after the preset feed waiting time.

Feeding Time (Time On, Sec.)

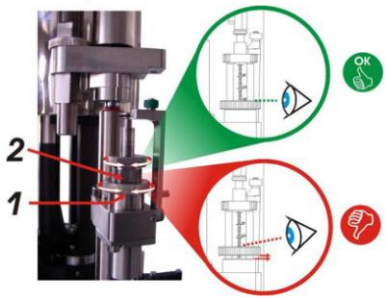
Feed Waiting Time (Time Off, Sec.)

- Set the correct height of the dosing chamber.
  - Dosing chamber adjustment gauge (metal pieces of 2.5, 3.75 and 5mm).

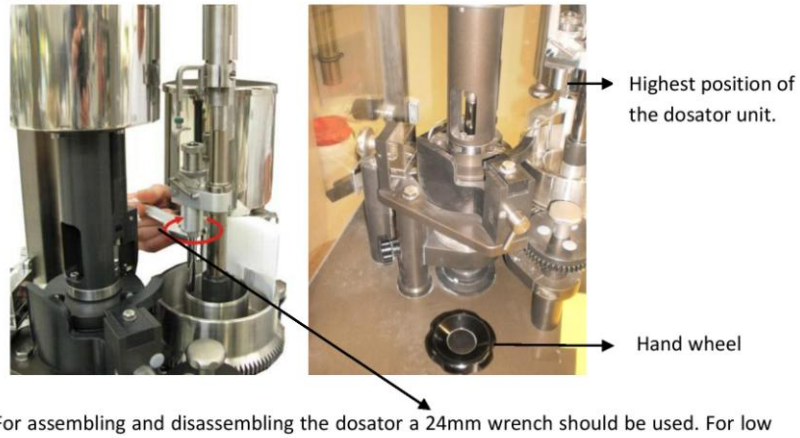
  - Check, if it is closed correctly.

Instructions for dosing chamber adjustment:

- Loosen the counternut (1) and adjust the chamber using the graduated scale (2) on top of the dosator unit.
- Tighten the counternut (1) as the reading must be taken on the flat top of the counternut.
- Fit the required adjustment gauge for the required dosing chamber, from the run order of the DoE, into the free space of the graduated scale to make sure the adjustments are user independent.

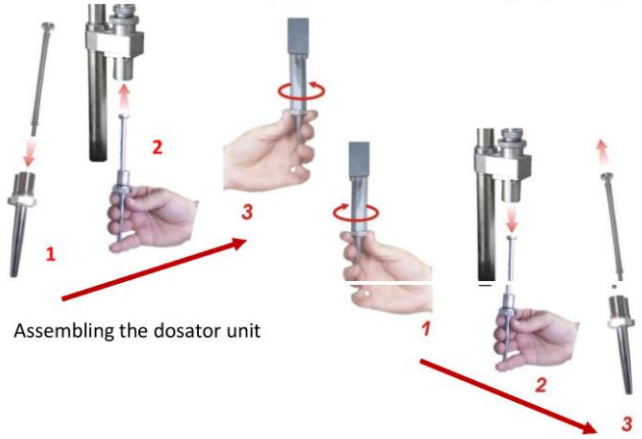


- Mount the dosator and the piston on the machine.
  - Turn the hand wheel until the dosator unit reaches its highest position to ease its dismantling.



  - For assembling and disassembling the dosator a 24mm wrench should be used. For low dose experiments a second 19mm wrench is needed.
  - 'Righty = Tighty and Lefty = Loosely'!

- For the final adjustment of the piston and dosator in the right position, hear the 'click'.



Assembling the dosator unit

Dissassembling the dosator unit

- Run the machine with the hand wheel for one round with open capsule releasing cam.

- Run the machine WITH dosator unit and capsules until the first preset feeding after the preset feed waiting time.
- Cleaning unit:
  Only part of the low dose set up, for low dose capsule experiments.

- Check for excess powder sticking to the dosator unit after passing the cleaning unit.

- Check the condition of the layer. Avoid:
  - Holes (too less powder feed).

  - Powder falling back on the layer (too much powder feed).

Adjust the feed until a good, uniform layer is built and record the settings for each experiment.

d. Operation of MG2 – Labby capsule filling machine

Production of capsules for DoE

- Unnumbered capsules are filled in the capsule hopper to produce unnumbered capsules for 5 minutes.
  Check, if any problems occur before starting the sampling procedure.
  - Excess powder sticking to the dosator, not cleaned properly by the cleaning unit.

Before cleaning unit

After cleaning unit

  - Dosing chamber does not eject all of the powder over the capsule.

- Stop the machine and remove unnumbered capsules.
  ALWAYS WORK WITH GLOVES!
- Before using the numbered capsule batch take a sample of 5 empty numbered capsules for weighing and comparing the weight with the weight in the table.
  - Confirmation of the right capsule batch and the according tables from the Excel sheet!
  - Check for weight differences due to humidity.

- Numbered and previously weighed capsules are filled in the capsule hopper to produce random capsule samples for each DoE experiment.

Sampling

- Collection of the first sample of 25 to 30 numbered capsules.
- Change from numbered to unnumbered capsules again and let the machine run for another 5 minutes.
- Change from unnumbered to numbered capsules in the hopper again.
- Collection of the second sample of 25 to 30 numbered capsules.
- 20 capsules of each sampling run are weighed straight after collection.
- Acquired data is put together in an Excel sheet.

Troubleshooting during collection:

- STOP during the collection of the sample, due to missing capsule warning:
  - Within the first 10 numbered capsules → complete restart of sampling
  - After the first 10 numbered capsules → throw away the first five capsules after restart, to ensure that the samples are not damaged.

  This procedure is the same for both sample collections.

- OPEN capsule in the sample → clean all other capsules from powder before weighing.
- STUCK capsule at the output slide → adjust the pipe or the strength of airflow for smooth ejection, especially at low speed.
- Straight after collection of the samples, check that the dosing chamber has not changed.
  If a change occurs → repeat the sample, after weighing the previous samples, by keeping to common sense.

Changeover Procedure

- This procedure needs to be done after every run of the run order of the DoE. Especially for repeating tests in the run order.
- Remove dosator and piston at the highest position as seen in the section 'Configuration', 'Creating a Powder Layer'.
  - Always check for powder build-up within the dosator sticking to the piston.

Standard Operating Procedure (SOP)
MG2–LABBY low dose capsule production

research center pharmaceutical engineering

- Clean the dosator and the piston with hot water and dry it with pressured air for re-use.
- The layer should be loosened up by mixing the powder in the rotary container after the completion of a test-run.
- The change of the layer can be accomplished by changing the height:
  - Lower layer: taking out and mixing of the powder for reassembling a uniform layer.
  - Higher layer: mixing of the pre-used powder and feeding powder from the hopper.

Criteria for repeating an experiment of the DoE

- If the mean net weight of the low dose capsules from the starting sample and the sample after 5 minutes continuous run differ by 10% the experiment should be repeated according to the DoE.
- For very low dosages of less than 5 mg a criteria still must be found, but it can be higher than 10% due to the very low filling weight.

- Criteria gained from PH. EUR. 5, 2.9.5:

  Weigh individually 20 units taken at random or, for single-dose preparations presented in individual containers, the contents of 20 units, and determine the average mass.
  Not more than 2 of the individual masses deviate from the average mass by more than the percentage deviation shown in Table (see below) and none deviates by more than twice that percentage.

Capsules, granules (uncoated, single-dose)and powders (single-dose)	Less than 300 mg 10% 300 mg or more 7.5%

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6. Cleaning Instructions

Refer to MG2 Instruction Manual LABBY – s/n 7604, RCPE – Austria (Ver. 1.0)

7. Environment- and Safety Information

Refer to MG2 Instruction Manual LABBY – s/n 7604, RCPE – Austria (Ver. 1.0)

8. Appendix

a. Reference Documents

- Capsugel, capsule size details
  http://capsugel.com/media/library/Capsugel_ConiSnap_Sizing_Information_1.pdf
- Refer to MG2 Instruction Manual LABBY – s/n 7604, RCPE – Austria (Ver. 1.0)
- Ph. Eur. 5, 2.9.5