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Micro-dosing of Pharmaceutical Powders into Capsules via a vibratory sieve-chute system

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Abstract

A direct gravimetric powder dosing system based on vibratory sieve-chute system is used in this study to optimize the procedure of low-dosing of hard two-piece capsules. The system operates in a large range of amplitudes and frequencies based on vertical vibration principle. There is a close loop in this system to control the operation space to achieve accurate capsule dosing in the milligram range via a vibratory sieve-chute system. This close loop is used to avoid the over or under-dosing of capsules, but in this study it is not used to analyze the powder characteristics without manipulating them.

Recording the fill weight accurately during capsule dosing in this system was possible via a capacitance sensor, which cover the capsule body during the filling process. This makes it possible to analyze the filling characterisation of selected powders (fill rate, robustness, etc.). To find the best and reproducible settings for powder filling, screening tests were done for different possible combination of amplitude and frequency to study filling characteristics. Flow behaviour of powder is an important factor to describe the powder characteristic, thus powder flow has the highest influence on the filling performance for powders filled via vibratory sieve-chute systems. The selected operating settings (combination of amplitude and frequency) for all used powders were similar. Operating setting had an obvious effect on fill rate robustness of powders, thus selecting suitable settings is the most importance for continuous feeding applications and to achieve accurate dosing via this vibratory sieve-chute system. At the end with this knowledge about the filling characteristics of powders, the accurate low-dose studies for all powders were done.

Keywords:

Micro-dosing; micro-feeding; capsule filling; vibratory sieve; online scale; lactose

Kurzfassung

Ein direktes gravitmetrisches Pulver Dosiersystem basierend auf einer vibrierenden Sieb-Rampe wird verwendet, um die niedrige Dosierung in aus zwei Teilen bestehende Hartkapsel zu optimieren. Das System funktioniert in einem großen Bereich von Amplituden basierend auf dem vertikalen Vibrationsprinzip. In dem System ist ein geschlossener Regelungskreis, um den Funktionsbereich zu kontrollieren und somit ein akurates Befüllen der Kapseln im Bereich von Milligramm durch eine vibrierende Sieb-Rampe sicherzustellen. Diese Reglung wird verwendet, um zu verhindern, dass Kapsel zu viel oder zu wenig befüllt werden. Diese Reglung ist nicht in diese Studie verwendet, weil wir die Pulver-Charakteristika analysieren wollten. Es war durch einen Füllstandssensor, welcher die Kapsel während des Prozesses bedeckte, möglich, das Füllgewicht akkurat zu bestimmen. Dies ermöglicht eine Analyse der Füllcharakteristika von ausgewählten Pulvern (Füllrate, Robustheit, usw.). Um das beste und reproduzierbarste Pulverrüllen zu ermitteln, wurden Tests mit unterschiedlichen Kombinationen von Amplitude und Frequenz durchgeführt. In diesem Bereich konnten Füllcharakteristka untersucht werden. Die Fließfähigkeit eines Pulvers ist ein wichtiger Faktor, um die Pulvercharakteristika zu beschreiben. Die Fließeigenschaften verschiedener Pulver in einer vibrierenden Sieb-Rampe werden in dieser Studie untersucht. Der Funktionsbereich der Pulver hatte einen beträchtlichen Effekt auf die Füllrate, deswegen ist der wichtigste Parameter für die ununterbrochene Füllung (um eine genaue niedrige-dosis zu erreichen). Zum Schluss wurden mit den erworbenen Kenntnissen der Pulver genaue niedrige-dosier Versuche für alle Pulver durchgeführt.

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1. Introduction

Precise dosing of small powder quantities into a capsule body is a key technology in several fields of research and can be found in many industrial operations. In the recent years granular 3D printing (e.g., direct or selective or laser sintering [1], [2]) became state-of-the-art and enabled a multitude of applications, ranging from rapid prototyping to tissue engineering [3]–[8]. The incorporation of functional gradients via heterogeneous components requires low dosing of powders to accomplish high resolutions [9]. Hence, many recent developments in low dosing and feeding address solid free-forming methods. For applying the precise dosing of small powder quantities in pharmaceutical industry, there are several methods available. In these methods, the powder quantities can be measured by volumetric or gravimetric approaches, both having advantages and disadvantages [10].

However, precise powder filling or powder dosing in pharmaceutical development and manufacturing is still a challenge [11]–[13]. Powder behaviour should be fully understand to prevent under or over-dosing. The powder particle size, shape and distribution, as well as other physical and chemical characteristics, influence the powder dosing behaviour [14]. Regulatory requirements demand high dose uniformities, especially when the therapeutic window is narrow [15], which is the case for dry powder inhalers (DPI) [16]–[18], delivering small powder quantities of highly potent actives. Another current trend for oral solid dosage forms is dosing small quantities of pure active pharmaceutical ingredients (API) into a capsule. Hence, there is no need for a formulation with fillers, binders, lubricants, flavouring agents etc [19].

Most dosing techniques, for capsule filling [18][20], are based on volumetric filling principles. These include dosator nozzles systems [21]–[24], vacuum or pneumatic dosators [25]–[27] or tamp fillers [28], [29]. What they have in common is that powders are charged initially into chambers of a fixed volume, defining the final dosage. Thus, the final weight is a function of the fixed volume (constant) and the density of the powder (which may change).

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Thus, the fundamental disadvantage of volumetric dosing systems is that the dose weight is variable and depends on the densification level (and thus the processing history) of the powder. Moreover, since most volumetric techniques require powder beds, there is always some powder wasted since typically not all the powder from this reservoir can be used [18]. For example, low dose filling (<10mg) was recently investigated for nozzle dosator systems [30]. Although such volumetric dosing methods are generally faster, other methods (i.e., gravimetric ones) are preferred for precision (or micro-) dosing [5].

Micro-dosing via vibrating capillaries or rods [31]–[33] (also in the ultrasonic regime[34][10][9]) is a promising technique for low dosing and feeding and is currently investigated in terms of solid-free-forming applications. Recently, the "pepper-shaker" principle (MG2 Microdose, Capsugel Xcelodose®S, and 3P Innovation Fill2weight), as used for capsule filling [35][36], was shown to be capable for low dosing with high accuracies (relative standard deviation of the fill weight below 5 %). Another trend in pharmaceutical manufacturing is continuous processing. For this technology, continuous feeding of materials with a constant mass flow rate in kg/h is a prerequisite. While constant powder flow rates can be achieved with relative ease by loss-in-weight feeders for relatively high flow rates (> a few kg/h), low mass flow rates pose a significant problem, especially for powders with low and medium flowability. In almost every continuous manufacturing operation established today low-dose feeding of APIs has posed one of the main problems. Thus, there is a high demand for robust low-dose feeders that are capable of dosing APIs in the range of a few hundred grams per hour, with low dose-rate fluctuations. Screw-based feeders are typically not suitable for this task, as has been demonstrated repeatedly [37]–[39].

However, gravimetric (micro-)-dosing techniques via the pepper-shaker principle could – in theory – be applicable to continuously dose material to a continuous powder stream [33][14]. Furthermore, micro-feeding ($< 1 \, mg/s$) via auger methods [40][41] or vibratory channels [42][43][9] was reported. Vibratory channels can be applied to sticky and cohesive powders or powders sticking to surfaces effect of vibrations on pharmaceutical capsule

dosing is not been studied in much now [44][45]. Beside dry powder low dosing techniques direct printing of drug solutions or suspensions is possible [46]–[48].

In this thesis the gravimetric micro-dosing system for fine powders based on a vibration-assisted system in the milligram dosing range is studied.

2. State-of-the-art capsule filling

In this section the general background of capsules to filling machine technologies is reviewed.

2.1. Hard capsules

Capsules are divided into-two main groups, i.e., hard and soft capsules. Hard capsule contains a cap and a body [49][50]. The cap has a larger diameter, such that it fits on the body part of the capsule. Usually, after closing the capsule it is not possible to open it again. During formulation, the stability of the dosage form and the-release-characteristics are important factors, that should be considered when developing new dosage forms of medicines [50].

US Pharmacopeia (USP 24) describe capsules as solid dosage forms, in which the active ingredients and other substances are filled in hard or soft container. European Pharmacopoeia (Eur. Ph.) also describes capsules as: 'solid preparations with hard or soft shells of various shapes and capacities, usually containing a single dose of active substance.' In USP 24 also the substances in shells are mentioned. European Pharmacopoeia describe also hard capsules as following: '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' [50].

Capsule sizes range from 000 to 5. A list of capsule sizes and their volume and capacity in mg is listed in Table 1 [50].

Table 1: Hard capsule sizes, their volume and filling capacities [50].

Capsule size/Volume [ml] →	000	00el	00	0el	0	1	2	3	4	5
Capsule capacity [mg] powder density ↓	1.37 [ml]	1.02 [ml]	0.91 [ml]	0.78 [ml]	0.68 [ml]	0.50 [ml]	0.37 [ml]	0.30 [ml]	0.21 [ml]	0.10 [ml]
0.6 [g/ml]	822	612	546	468	408	300	222	180	126	78
0.8 [g/ml]	1096	816	728	624	544	400	296	240	168	104
1 [g/ml]	1370	1020	910	780	680	500	370	300	210	130

The filling process of two-piece hard capsules is impacted by many factors and depends strongly on the filling principle, the operating parameters of the filling system, the capsule size and the material properties, including the processing history. Among powder properties, the powder flowability is one of the most important factors and depends on the particle size distribution (PSD), shape, cohesivity, packing fraction, humidity, temperature and electrostatic charges [44]. This is described below in more detail.

Typically, in capsule filling, a target weight is selected and the weight should be within the "acceptance range". The "acceptance range" is the range of filled mass, based on the specific regulations. Typically, a fill weight variability of +/- 5% is acceptable.

Capsules are the preferred delivery system during clinical development due to the flexibility in delivering different doses during dose-finding studies. Also, the process development is easier compared to tableting, since processes such as wet granulation and drying are not necessary in many cases. Nevertheless, tablets are still the preferred oral solid dosage form for the final products, and the rule of the thumb is that capsules are developed only if the

development of tablets is infeasible (for whatever reason). This is mainly due to the higher (conceived) price of overall production costs for capsule. Thus, developing efficient and precise capsule filling processes is even more important. Hard capsules are in compare less cost and time-consuming, which avoid 15% addition of price to the overall cost of production [50].

2.2. Impact of powder properties

As stated above powder properties are very important for capsule filling. These properties can be divided in to primary properties and secondary (or derived) properties. Primary properties include the material type, the PSD, shape, the surface energetics, true density and level of densification. Secondary properties, which are a function of the primary properties (and are derived from them) include the flowability, fluidizability, the bulk density and the tendency to segregate/electrically charge. Although, the secondary properties are the ones which determine the ability to fill capsules (and the quality of the filling process), the primary properties need to be analyzed as well as they are the fundamental attributes that determine the derived properties [51].

In terms of bad powder flowability, often described as cohesivity, that cohesivity reduces powder segregation (which is the de-mixing of powders with different properties). One of the most dominant segregation mechanism is size segregation. Size segregation occurs if powders with different particle sizes are sheared or aerated. In the former case, large particles can be found in the top of the powder bed. In the latter case, finer particles are more effectively fluidized and can then be found on top of the powder bed. Both mechanisms can be effectively reduced by a certain level of cohesivity. Thus, moderate cohesivity is beneficial for many processes. Another way of avoiding segregation is by making sure that particle sizes in free-flowing powders do not differ by more than 30%. Addition of very small level of fluids (oils, water) can also suppress segregation due to the formation of capillary bridges and the intensification of surface contacts between neighboring particles.

Powder particle size distribution and shape are also important factors influencing the powder flowability. These factors also determine the bulk density of the powder in the mixture [51] and thus impact directly the fill weight. All steps of powder handling, such as particle mixing, packing and flow are influenced by the shape of powder particle size [49].

As mentioned above, the main difficulties in filling capsules are caused by the poor flowability of some powders. A possible solution to this problem (in case of fine powders) is granulation, i.e., the increase of particle size by gluing primary particles together. Granulation increases particle size, and thus, increases the flowability by reducing cohesion. Powder granulation is the most common method enhances the flowability problem of fine particles. However, flow aids are another effective way of enhancing powder flowability. In this method, a small amount of fine particles are blended with the original powder. These fine particles act as spacers between original particles, thus drastically reducing van-der-Waals forces which act only in a range of a few nm. For example, during manufacturing of hard capsules, colloidal silicon dioxide is used to improve flow characteristics and reduce cohesion [52][49].

Powder flowability is also influenced by shape of the powder particles. Clearly, elongated powder particle shapes, such as needle-shapes, are critical since interlocking of particles occurs, resulting in the blockage of the flow. Again granulation is a common method to solve problems, which are caused by this critical particle shape. Another method is adding excipients with roundish particle shape of similar particle size. As it is mentioned above, these excipients can affect the powder mixture properties [49].

Another common problem in machinery filling is the stickiness of powder to metal parts of the capsule filling machine. This problem is most of the times difficult to solve and leads to significant fill-weight variability, which is not desired. Adhesivity (i.e., interaction forces between different materials), partial melting of low-melting materials and air-moisture adsorption are the main reasons for stickiness problem. For hygroscopic powders addition of moisture-absorbing excipients (e.g., Cellulos), is a possible solution for stickiness problem. Also, operating parameters can be changed to minimize sticking. For example,

powder stickiness problem in the gap between dosing disk and tamping ring for tamp-filling machine can be solved by increasing the gap size (see section 2.3.3). Finally, electrostatic charging of powders may severely impact the capability for capsule filling. Measures to reduce tribo-charging are thus of highest importance [49].

Another factor, which is strongly affected by the flowability of the powder, is the consistency of the powder bed (from which the individual dose is taken to be placed into the capsule). Since most filling mechanisms are based on volumetric principles, variations in powder-bed density and height will automatically lead to variability in capsule fill weight. In tamping machines (see below) an inconsistent height will lead to a variable amount of powder tamped into the capsules. In dosator systems (see section 2.3.4) inconsistency in height of the powder bed will lead to a variable densification during plug formation, and thus, to variability in the fill weight. Thus, a smooth and homogenous powder bed is desirable. This is best achieved, if the powder freely flows into holes and cavities created by tamping pins or dosator nozzles. Moreover, enough powder should be filled from the hopper into the powder bowl [49].

To have a constant bed height and also powder bed structure not only flowability, but also the powder packing properties are important. Poor powder flowability also affects the powder bed shape. The powder bed behavior in the powder bowl of a tamp-filling machine is shown in Figure 1 as an example for good and bad bed structures, depending on the different powder flowability. Three different powders characteristics are shown in this figure as; (a) shows excellent flow properties which is indicated by a smooth and flat powder bed, (b) is an angled, smooth powder bed with different bed height that occur with well or moderately flowing powders and (c) is a rough surface, which is a sign of poor power flow [49].
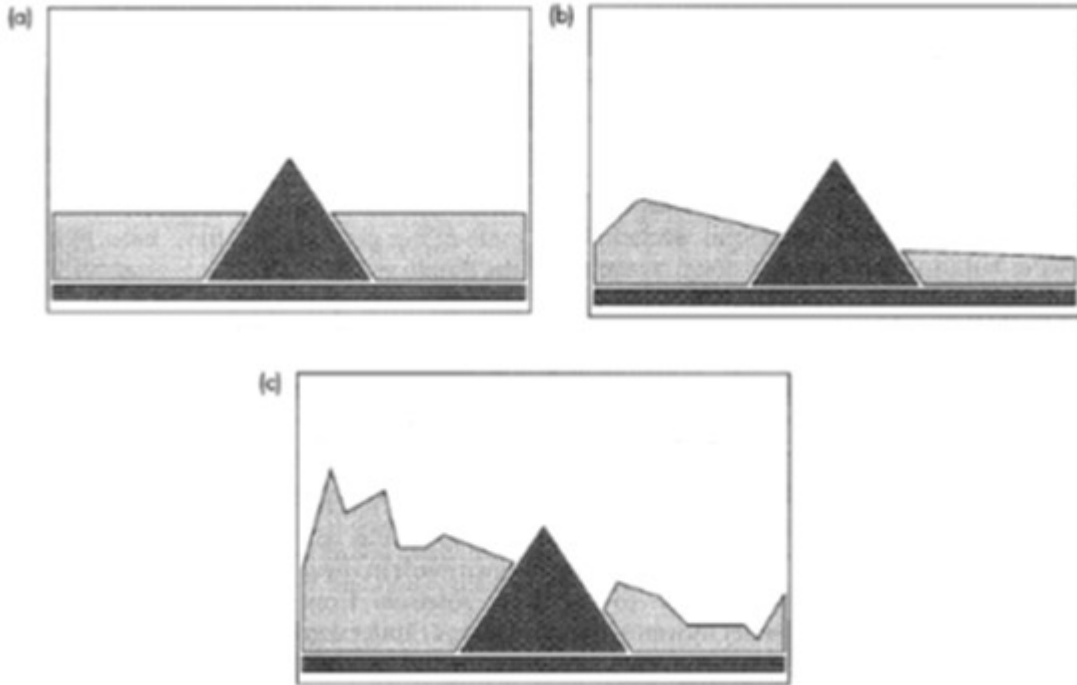
Figure 1: Effect of powder bed on flowability in the powder bowl of a tamp-filling machine. (a) Very good flow properties; (b) good or moderate powder flow; (C) poor power flow (with permission from [49]).

There are two packing state for powders, they are named "loose" and "tight" packing. In Figure 2 tight packing and loose packed powders are shown for both spherical and cubic particles. Loose packed powders have a maximum of air space between their particles and minimum contact points (Figure 2, left). For tight packing the air space between the particle sizes is minimum (Figure 2, right). For spherical shape particles the porosity can not be less than 26%. For cubic shape particles it can ideally reach porosity of 0% [49].

When powder is poured into a container, the so-called poured density is obtained, i.e., a case where the porosity is high. When the powder is compacted or vibrated, the density is increased. When the density is increased by tapping (repeated hits of the container) the so-called tapping density is obtained. Vibration is another method to increase density. The ratio between tapped and poured density is the Hausner ratio >1. The higher the ratio the poorer the flowability is. In practice the maximal achievable powder density (without compaction) is between 60 and 70% [49].
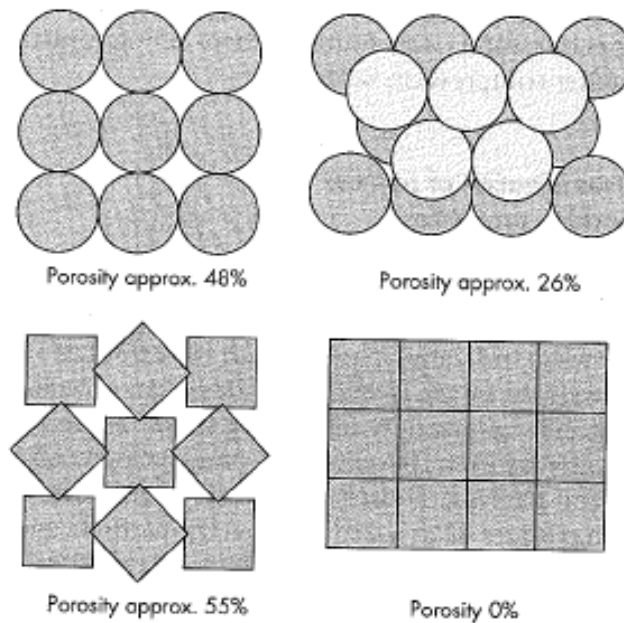
Figure 2: "Loose" and "tight" packing state for both spherical and cubic shape powder particles (with permission from [49]).

2.2.1. Powder characterization

In this section the definition and measuring principle of important powder properties will be described.

Particle size characterization

An optical system, Qicpic (Sympatec, Germany), was used to measure the size (volumetric mean diameter and median particle size by weight) and shape particles in a sample via dynamic image analysis (DIA). The system analyzes the two-dimensional shape of a particle, and the most important factor for describing the particle size, i.e., the minimum and maximum Feret diameters (Fmin, Fmax).

Several other parameters were measured as well: sphericity (S), aspect ratio (AR) and convexity, describing the shape of particles. As the particle size and shape affect the bulk behavior of powders they are critically important for capsule filling. For example, the particle size of a powder significantly influences the flow properties of bulk powder. Based on the measurements the following parameters were established:

Volume mean diameter (VMD)

One of important factors to define powder behavior is powder particle size. For example larger particles flow easier than smaller particles, but smaller particles dissolve faster in liquids. Information about size and shape of powder particles define particle properties [53][54].

For homogeneous spherical shape powders, their diameters define their particle size. Most of the powders do not have a homogeneous powder shape, for measuring size of these powder particles one or more dimensions can be defined. Usually particle diameter is determined by measuring a size dependent property and then relating it somehow to a single linear dimension (most of the time equivalent spherical diameters). Then the volume diameter is calculated by considering that volume of a spherical particle with diameter of 1.24 units is same as unite cube. Hence the diameter measurements depend on the measured property [54].

Span

The span is a factor that defined the width of the distribution, as shown in Eq. (1).

$$\text{Span} \; = \; (D_{V90} - D_{V10})/D_{V50} \qquad\qquad (1)$$

Median

Median is the most meaningful value (size in microns) in the particle distribution function diagram (D50 or X50 with following the certain ISO guideline) that half of the data are smaller than it and other half are bigger than this value. Median for the volume distribution is shown as D_{V50} [53].

Mode

In statistic the value that appears the most is mode. In powder particle distribution, peak of the frequency distribution is mode, which show the particle size that is the most commonly found in powder [53].

Mean

Mean (has similar concept to averaging) define the center of gravity in the powder particle distribution [53].

Bulk density and Tapped density

The bulk density (BD) and tapped density (TD) of all these powders are analysed via a standard method. The BD is the ratio of powder mass that is filled into cylinder to its volume. Preparation of the powder, storage and processing story have an effect on bulk properties. There are three methods to measure BD. The first method is to measure the volume of a known weight of powder which is filled through a sieve into a cylinder. The second method is measuring the mass of a known volume powder by passing it through a

volumeter into a cup and third method is measuring the mass of a known volume powder by passing it through a measuring vessel. The first and third methods are the most common ones. After mechanically tapping the powder sample, the TD is attained (TD is an increased BD) [55].

The Carr's Index (CI) is a density based index assessed out of TD and BD (see Eq. (2)) and is used to estimate powder flow and compressibility [50][56].

$$CI = [(TD - BD)/BD] * 100 \qquad\qquad (2)$$

A CI < 15 % is a sign for a very good flow properties, 16-26 % shows a good flowability, 27-35 % is fair and >35 % is for a poor flow. The reason is that poorly flowing powders do not fill-up small spaces and create many small holes in the powder bed, which are then eliminated during tapping [50].

Air permeability

Air permeability is a measure of how easily material can transmit a fluid, i.e., air. Air pressure drop (PD) across a powder bed is measured when air flows through the system. A high pressure drop indicates low air permeability. It is expected to affect capsule filling operations since, during powder compaction in the tamping and dosator system the air must escape. High permeability values are obtained for large particles as inter-particular spaces are larger, reducing the pressure loss [23].

Basic flowability energy

The Basic Flowability Energy (BFE) is a parameter defined as the energy required for establishing a particular flow pattern in a conditioned well-defined volume of powder. It is measured in a Freeman FT4 Powder Rheometer [23][57].

2.3. Capsule Filling Technologies

Hard capsules can be filled in several ways from manual preparation in the lab to fully automate industrial production. All of these methods follow the same process. Current dosing can be divided into two groups, i.e., dependent and independent dosing systems. The first systems use the capsule body directly to fix the powder mass. Uniformity of fill weight can thus only be achieved if the capsules are filled completely. A typical dependent approach is Auger filling [49].

In independent dosing systems the powder is measured independently of the body in a special measuring device. Weight uniformity does not dependent on filling the body completely. Thus, partial filling of capsules is possible. Dosator and tamping are two main types of independent machines [21].

Capsule filling common technologies that are used in filling capsules direct (Auger filling principle, Vibration-assisted filling principle) or indirect (Tamp filling machine, Dosator nozzle principle) are completely explained in this section. The operating principles of these technologies are based on either volumetric or gravimetric dosing.

2.3.1. Auger filling principle

The Auger-filling principle is a volumetric process and the oldest semi-automatic equipment, which is nowadays also fully automated. A schematic is shown in Figure 3.
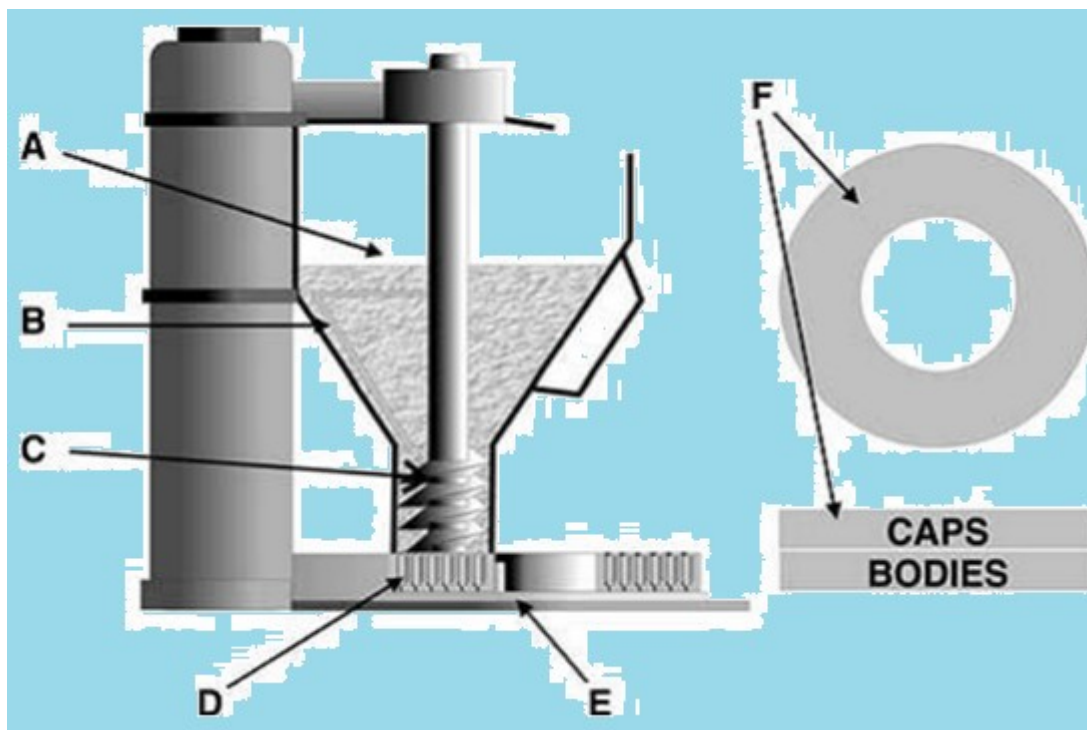
Figure 3: Auger filling principle. (A) powder hopper; (B) stirrer arm; (C) auger; (D) body ring holder; (E) turntable; and (F) capsule carrying rings. (redrawn from [58])

The auger principle is quite simple. The powder is stored in hopper and is continuously filled by rotation of an auger (screw) into the capsule bodies. Capsule bodies are positioned exactly under the hopper outlet on a 'pick-up ring' (which is a rotating turntable). The amount of powder that is filled into capsule depends on auger speed and the time that capsule stays under funnel. Decreasing the auger speed leads to increase of the powder filling weight, because the capsules stay longer under the hopper outlet. To control capsule weight the auger speed and turntable rotating rate are changed according to changes in bulk

density of powder in the hopper during time. Otherwise the desirable dosing amount may not be reached. Nevertheless, auger filling is a volumetric method [49].

2.3.2. Vibration-assisted filling principle

In this method, the powder is directly filled into capsule similar to auger filling principle. There is a rotating turntable that capsule bodies will be placed in it. This rotating turntable is under the powder bowl, which - through a mesh floor - is connected to the turntable vibrator. Powder flows through the mesh floor by help of vibration into capsules. Capsule bodies get filled until a maximum level is reached. Rotating of turntable change the positions of capsule bodies, such that a spring plunger presses the powder into the capsules to form a less hard plug. Then the capsule bodies are pushed up by joining block to cap of capsule and so get the capsule closed. The final filling weight in this method depends on speed of turntable rotation and compression setting of plunger. Again, this is a volumetric filling method [49].

2.3.3. Tamp-filling machines

In tamp-filling machines there is a rotating powder bowl. The filling process consists of rotational events, performing a cycle (six stations). The bottom of this powder bowl is a removable dosing disk that contains six sets of dosing bore holes. Depending on the machines there are different numbers of holes (typically 3-5). First the bowl is filled from a hopper into powder bowl with help of auger mechanism. There is a conductive sensor positioned in powder bowl to control the amount of powder that is filled into powder bowl, i.e., the powder level. The powder is distributed with help of a dosing cone that pushes the powder to the edge of the dosing disc. Here the sets of bore holes are located and at every station tamping pins push the powder into the bore hole. This process is repeated several

times (up to five) and at the last station the formed powder plug is pushed into the capsule body. Therefore, plugs are formed in a series of tamps and not in a single step. Dosing discs come in a range of thicknesses for each size of capsule. Thus, selection of the thickness of a disc is critical for determining fill weight. The latest developments on Bosch machines are dosing discs with adjustable thickness. Thus, a higher flexibility can be reached [49].

2.3.4. Dosator nozzle principle

There are dosator nozzle machines with both intermittent motion und continuous filling operations. In this method the powder is filled into a rotational dosing hopper. There is a metal plate in the dosing hopper, which control the powder bed height (i.e., a scaper). The dosator nozzle is a hollow dosing tube with a piston inside it. The first position of piston in the tube defines the last filling weight (the volume of the hollow dosing tube depends on the position of the piston and this will define the powder plug weight) [49].

A single dosing event consists of several steps. First, the dosator is entering the rotary container to reach the top of the powder bed. Then, the nozzle penetrated the powder bed. By doing so the nozzle is filled and powder is compacted lightly. Once the nozzle reaches the bottom of the bowl more compression is achieved, which is important to form a powder plus. Without the formation of a powder plug, powder would drop from the nozzle upon removal of the nozzle from the bed. If the "natural" compression is not sufficient, the piston inside the dosator nozzle can be lowered to compress the powder even more. Finally, the nozzle is removed and positioned above an empty capsule. Then the plug is ejected and a new filling cycle begins [49].

Critical process and design parameters are the size and depth of the nozzle, the penetration depth and possible piston compression force, the fill level of the bowl and the speed of capsule filling. Clearly, material properties are critical as well, favoring less cohesive

powders that shown a sufficient compressibility. The filling principle is based on a volumetric method [49].

2.4. Low-dose capsule filling machines

In the pharmaceutical industry there is increasingly a research focus on manufacturing of small doses of active pharmaceutical ingredients (APIs). However, low-dose manufacturing poses significant challenges. One opportunity to fill very low-doses (<45mg) is to use capsule fillers with vibration assisted gravimetric feeding, such as MG2 Microdose, Capsugel Xcelodose S and 3P Innovation fill2weight. Table 2 shows a comparison between common gravimetric low-dose filling systems.

Table 2: Comparison of gravimetric low filling machines.

Comparison	MG2 Microdose	Capsugel Xcelodose S	3 PI - Fill2Weight
System	Micro-dose Lab scale to industrial-scale	Micro-dose Lab-scale	Low-dose Lab-scale
Method	Gravimetric	Gravimetric	Gravimetric
Dosing Principle	Vibration dispensing, stand alone or integrated unit	Vibration dispensing (pepper shaker)	Powder dispensing
Capsule sizes	3	5-00	5-000
Weight [mg]	0-40mg±0.2mg	0-several 100mg	Standard: 2.5-500mg Optional: 1-20000mg
RSD [%]	0.1-2.5%, depending on weight The lower the weight, the harder to achieve	2-3%, depending on weight	Typically < 3%
Operation	Manual	Automate	Automate
Capacitance sensor	NETT weight system	Microbalance	Fill2weight dispensing
Temp./Humidity control	Laboratory environment	Control unit installed	Control unit installed

However, also standard machines (see section 2.3) can be used for low-dose filling, if certain modification have been be made. In Table 3 a comparison of volumetric low-dosing machines based on the dosator principle is shown. Most low-doses machines on market are based on volumetric filling method.

Table 3: Comparison of volumetric low filling machines.

Comparison	MG2 Labby	MG2 Planeta	3 PI - Labdosator
System	Low and Micro-dose Lab-scale	Low-dose Industrial-scale	Low-dose Lab-scale
Method	Volumetric	Volumetric	Volumetric
Dosing Principle	Dosator	Dosator	Dosator
Capsule sizes	000-5	000-5	000-5
Weight [mg]	1-500mg	Fully adjustable to target weight	Up to 600mg; powder consistency/properties depends
RSD [%]	0.6-19 %	Typically 5%	Typically < 5%
Operation	Automat	Automat	Automat
Capacitance sensor	None	NETT weight system	Weight cell
Temp./Humidity control	Laboratory environment	Control unit installed	Laboratory environment

The NETT weighing system on MG2 machines is a capacitance based system, where capsules are weighed before and after filling. The system calibrates the capacitive sensors by continuously testing/resetting them using precision balance each time a capsule is weighed.

In the next section the MG2 microdose system (which was the basis of the current work) is described in more detail.

2.5. MG2-Microdose System

The MG2 Microdose system was used as stand-alone unit (see Figure 4) which is connected to a computer to apply the dosing variables and saving dosing data. The dosing principle in this system is based on the 'pepper-shaker' principle, a vibratory sieve (oscillating vertically) which is positioned on top of a 2.5cm chute that guides the powder into a capsule. The operating principle of the MG2 Microdose system and parts of the set-up are shown in Figure 5. The chute is fixed in a 5° angle and different sieves can be fixed on top of it. The powder is filled into the capsule body directly through the sieve and the chute by help of vertical vibration and the gravitation force. In this method each capsule body can be placed and filled manually and a capacitance sensor makes it possible to record the fill weight during dosing process. In our work hard gelatin capsules of size 3 were placed exactly under the chute in this method and were filled up to the target weight (<=5mg) [56].

Figure 4: MG2 Microdose system, stand-alone unit.
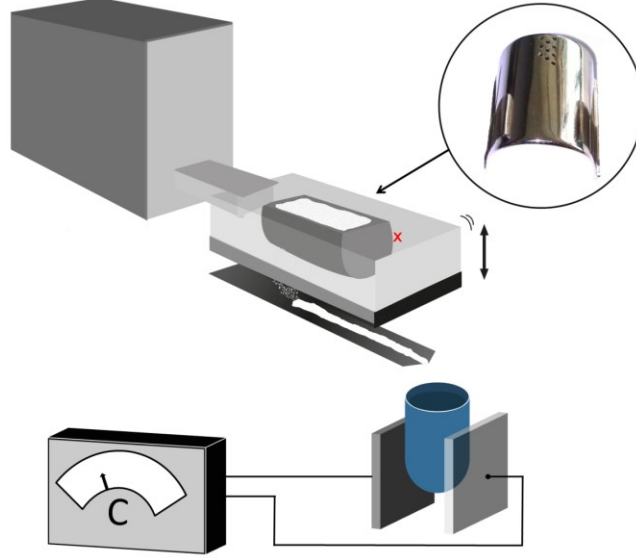
Figure 5: Principle of powder dosing via a MG2 Microdose system. The red x shows the position of the acceleration probe (with permission from [56]).

The operation principle of the Microdose systems' capacitance sensor -(that records the fill weight during dosing process in this study) and the control software will be described below. The sensor contains two parallel electrode plates which are holding the capsule body (see Figure 5). The powder quantity in the capsule body determine variation of the electrical field, and therefore, the capacitance (transmission of electrical field). The sensor needs to be calibrated to correlate the capacitance C_{filled} (relative to the capacitance of an empty capsule C_{empty}) with the capsule fill weight fw (see Eq. (3)). The calibration factor K_{cal} was determined by comparison of weight measurements performed on a SI-234A (Denver Instruments) high-precision scale. This calibration was done before staring the experimental study and was repeated every 2 hours to make sure that the sensor is working precisely. The target weight fw for the experimental study was also used to calibrate the system and every time with changing the target fw, the calibration is also redone [56].

$$fw = (C_{filled} - C_{empty})/K_{cal} \qquad (3)$$

The target weight, the amplitude, the vibration frequency and the acceptance range are the informations that have to be set before starting dosing by the MG2 Microdose system. The amplitude value is referring to the linear voice coil motor displacement that is moving the system vertically and this driving force is in the following called "E", Frequency refers to the oscillations per second. The MG2 Microdose system can operate up to 100 Hz in frequencies and up to 100 E in amplitudes. The acceptance range determines the range of accepted filling weight (target weight ± acceptance range) that the filling process should be achieving. If the target weight is reached within the accepted filling weight range, the filling process is stopped.

The engine causing vibrations will usually stop after the current filling weight achieves the target weight minus the acceptance range. Figure 6 shows the behavior of the vibratory system during a single dosing process. The highlighted periods in Figure 6 show the initial (onset of vibrating), the regular and the off-swing phase (after the engine causing the vibration was stopped). Because the capsule fill weights are recorded 20 times per second by the capacitive system, dosing is possible using a (discrete) proportional-integral-derivative (PID) controller. In this study the dosing with the aid of PID controller will be termed PID controlled dosing [56].
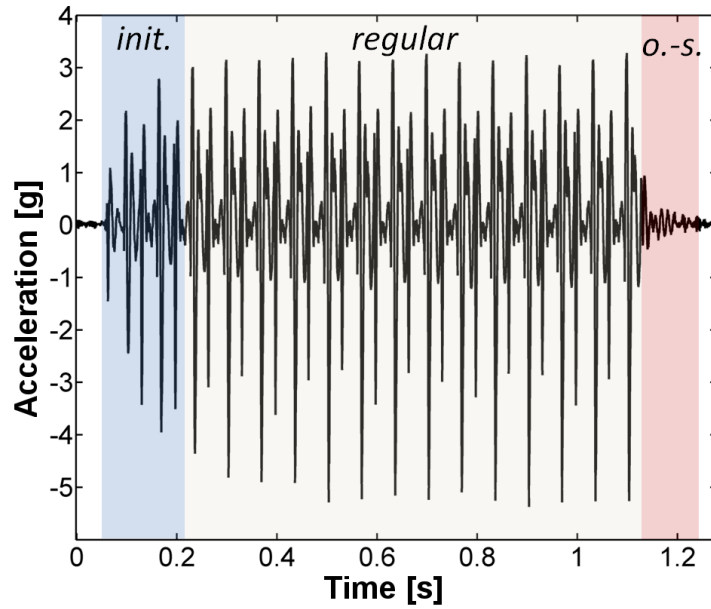
Figure 6: Acceleration during a 5 mg capsule filling with a frequency of 15 Hz and amplitude of 75 E (with permission from [56]).

The acceleration profiles of the regular phase for amplitudes of 50E, 60E, 70E, 80E and 90E with a frequency of 50 Hz are shown in Figure 7. The Figure demonstrate that sieve acceleration in dependent of E [56].
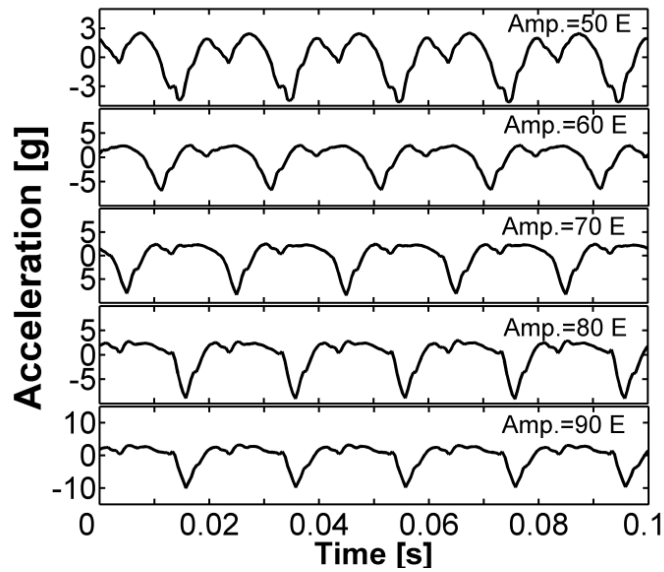
Figure 7:Acceleration profiles of the regular phase for varying amplitudes using a frequency of 50 Hz (with permission from [56]).

The maximum acceleration value for each of these amplitudes and also the maximum acceleration value for different frequencies with a fix amplitude of 85 E are listed in Table 4 [56].

Table 4: Maximum acceleration value.

Amplitude/Frequency	Maximum acceleration value	Amplitude/Frequency	Maximum acceleration value
Amplitude= 50 E , Frequency= 50 Hz	4.6 g	Amplitude= 85 E , Frequency= 10 Hz	6.3 g
Amplitude= 60 E , Frequency= 50 Hz	6.7 g	Amplitude= 85 E , Frequency= 30 Hz	9.9 g
Amplitude= 70 E , Frequency= 50 Hz	8.4 g	Amplitude= 85 E , Frequency= 50 Hz	9.4 g
Amplitude= 80 E , Frequency= 50 Hz	9.6 g	Amplitude= 85 E , Frequency= 70 Hz	6.5 g
Amplitude= 90 E , Frequency= 50 Hz	10.0 g	Amplitude= 85 E , Frequency= 90 Hz	8.8 g

2.5.1. Sieve study

The Microdose machine is compatible with different sieves, which are shown in Figure 8. The Size of holes (diameter) is of significant important in how much powder is filled through sieve. Sieve number 3 (in Figure 8 up, left side) has 10 holes with hole size of 0.73 mm and it is shown schematically in the inlet of Figure 5 as an example of how this sieve will be placed in Microdose system. Sieve number 4 (in Figure 8 up, right side) has 15 holes with hole size of 0.73 mm, sieve number 5 (in Figure 8 down, left side) has 10 holes with hole size of 1.03 mm and sieve number 6 (in Figure 8 down, right side) has 10 holes with hole size of 1.25 mm.

Figure 8:Comparing available sieves for Microdose system. Sieve number 3 with smallest holes' size and sieve number 6 with biggest. Sieve number 4 has the most holes.

2.5.2. PID controller

The amount of powder which is filled into capsules in the MG2 Microdose system is a function of different material attributes and process parameters. Vibration amplitude and frequency can be adjusted to reach the desire fill weight that is controlled in MG2 Microdose system by using a PID controller. The controlled variable is measured first as an electrical signal and then this measured value in is compared to the desired value and according to this comparison, any required control action can be taken. The controller will also calculate and output the manipulated variable [59].

PID controllers are the most common continuous-action controllers which combine the behavior of proportional controllers, integral-action controllers and differential-action controllers. The reset time is the period that the controller needs to reset the manipulated variable (for compensation of the remaining system deviation) [59].

2.5.2.1. Proportional controller (K_P)

The manipulated variable output is proportional to the system deviation. If there is no system deviation, the manipulated variable will not be changed. Because of this, a proportional controller is not able to achieve a system deviation of zero (no manipulated variable = no control) [59].

2.5.2.2. Integral-action controller (K_i)

This controller sums the system deviation over time. If the system deviation stays constant, the manipulate value increases because this controller adds the system deviation over time. This controller is used to avoid permanent system deviation and will continue processing till the system deviation reaches zero [59].

2.5.2.3. Differential- action controller (K_d)

This controller is differential of the system deviation. Its control action is proportional to the rate of change of the error. Thus, if the deviation increases quickly, the control action is more pronounced. Thus, this controller acts based on the rate of change in system deviation [59].

In the MG2 Microdose system the amplitude A (quantified in entities E) is manipulated by the PID controller for the subsequent time step t_{i+1} based on difference between fill and target weigh (ε). The calculation of the manipulated amplitude according to error in Eq. (4) is given by Eq. (5). [56]

$$\varepsilon(t_i) = fw_{target} - fw(t_i) \tag{4}$$

$$A(t_{i+1}) = K_P \cdot \varepsilon(t_i) + K_i \cdot \sum_{j=1}^{t_i} \varepsilon(t_j) + K_d \cdot \frac{\varepsilon(t_i) - \varepsilon(t_{i-1})}{\underbrace{\Delta t}_{=0.05 \text{ s}}} \tag{5}$$

3. Methods and Materials

3.1. Materials

The properties of the material to be filled into capsules have an important effect on capsule filling performance. According to the material properties, different filling strategies are taken.

Six different grades of inhalation grade α-lactose monohydrate excipients with different particle sizes, which are supplied by different manufacturers (DFE Pharma, Germany; Meggle, Germany), were used in this study as they were received. These powders are categorized in Table 5.

Table 5:Powder selection.

Powders for inhalation	Manufacturing Characteristics	Supplier
Custom-made Lactohale*	blend	GSK, Harlow, UK
Respitose ML001	milled	DFE Pharma, Goch, Germany
Respitose ML006	milled	DFE Pharma, Goch, Germany
Respitose SV003	sieved	DFE Pharma, Goch, Germany
Respitose SV010	coarse sieved	DFE Pharma, Goch, Germany
Inhalac 230	sieved	Meggle, Wasserburg, Germany

*Supplier: RCPE scientific partner.

The average particle size of these powders ranged from 23μm to 130μm. Thus, we expected to include cohesive and free-flowing powders in our work.

3.2. Material characterization

In this section particle size distribution (PSD), density and flowability behavior are described for all six powders.

3.2.1. Particle size characterization

In the following paragraphs, the material used in our study are described:

- Inhalac230 is a high-quality crystalline lactose product, designed for DPIs (Dry Powder Inhalers). Because of the good physical-chemical stability and excellent flowability, inhalac230 can be safely used in DPI formulations [60]. 10% of powder particles of Inhalac 230 are smaller than 78.36µm, 50% smaller than 112.3µm and 90% are smaller than 141.23µm.

- Respitose ML001 is a milled inhalation-grade lactose which has a relatively broad particle size distribution [61]. Particle size distribution of Respitose ML001 is as follow: 10% of powder particles are smaller than 4.61µm, 50% smaller than 52.43µm and 90% are smaller than 167.2µm.

- Respitose ML006 is a fine milled inhalation grade lactose which has a narrow particle size distribution [62]. 10% of powder particles of Respitose ML006 are smaller than 2.37µm, 50% smaller than 18.16µm and 90% are smaller than 49.64µm.

- Respitose SV003 is a sieved inhalation grade lactose which has a narrow particle size distribution [63]. The particle size versus cumulative undersize plot shows that 10% of powder particles of Respitose SV003 are smaller than 30µm, 50% smaller than 60µm and 90% are smaller than 100µm.

- Respitose SV010 is a coarse sieved inhalation grade lactose with a relatively broad particle size distribution [64]. 10% of powder particles are typically smaller than 80.83µm, 50% smaller than 127.64µm and 90% are smaller than 181.45µm.

- Custom-made Lactohale is a blend inhalation. In this powder 10% of particles are typically smaller than 9.26µm, 50% smaller than 66.47µm and 90% are smaller than 143.57µm.

For all the powders the particle size distribution was also determined by using laser light diffraction technique (Helos/KR, Sympatec GmbH, Clausthal-Zellerfeld, Germany). In this method a dry dispersing system and a vibrating chute were used for powder dispersion. The sampling time was 30 seconds and a dispersion pressure of 2.5 bar was applied. The performed data were similar to manufacturer particle size distribution. All measurements on the FT4 (Freeman Technology, United Kingdom), Pharmatest PT-TD200 (Pharmatest, Germany), Accupyc II 1340 (Micromeritics, USA), and QicPic and Helos (Sympatec, Germany) are done in triplicate by Dr. Mag. pharm. Eva Faulhammer.

3.2.2. Powder flowability measurement

The flow function coefficient (FFC) is the ratio of consolidation stress to unconfined yield stress, which was measured by FT4 Powder Rheometer (Freeman Technology, UK) with setting of 1ml shear cell module and a maximum pressure of 3 kPa. Higher value of FFC is a sign of good flow properties [56]. In Table 6 a summary of particle sizes and powder flow attributes of the used materials is provided.

Table 6:Powder properties of used materials [30].

Name (Manufacturing characteristics/Batch no.)	Supplier	x_{10} [μm]	x_{50} [μm]	x_{90} [μm]	Span (x_{90}-x_{10}/x_{50})	Bulk density [g/cm^3]	Tapped density [g/cm^3]
Respitose SV010 (coarse sieved/10672704)	DFE Pharma, Germany	80.83	127.64	181.45	0.79	0.72	0.87
InhaLac 230 (sieved/129490)	Meggle, Germany	78.36	112.3	141.23	0.56	0.74	0.89
Respitose SV003 (sieved/10680001)	DFE Pharma, Germany	49.59	73.37	98.63	0.67	0.67	0.83
Respitose ML001 (milled/10648940)	DFE Pharma, Germany	4.61	52.43	167.2	3.1	0.66	1.05
Respitose ML006 (milled/10683656)	DFE Pharma, Germany	2.37	18.16	49.64	2.6	0.47	0.86
Custom-made Lactohale (blend/*)	*	9.26	66.47	143.57	2.02	0.67	1.01

*For Lactohale supplied by RCPE scientific partner, no number is available.

Other important powder properties which are significantly different between materials are shown in Table 7.

Table 7:Powder properties [30].

Name	VMD [μm]	Air permeability [m$^3 \cdot$m^{-2}.min]	Carr Index [-]	FFC [-]	BFE [mJ]
Respitose SV010	129.82	1.96	16.8	7.7	942.0
InhaLac 230	111.71	2.71	17.3	7.9	2393.33
Respitose SV003	73.99	4.58	17.3	8.1	2224.0
Respitose ML001	71.17	20.17	37.1	3.3	1171.33
Respitose ML006	23.07	27.1	45.3	2.6	510.67
Custom-made Lactohale	72.36	13.23	33.9	4.4	1633

3.3. Process and equipment

3.3.1. Analysis of the vibratory system

In Besenhard et al. [56] the characterization of vibration patterns of the Microdose system was presented using a dynamic accelerometer (Seika BDK 100). This system contains a capacitive spring-mass accelerometer with integrated sensor electronics providing a resolution $< \frac{1}{10} g$ $(g = 9.82 \frac{m}{s^2})$ and an output frequency of $2000\ Hz$. A NI-9234 high-accuracy analogue-input module was used in Besenhard et al. [56] for signal acquisition, which is specifically designed for high-channel-count vibration applications and LabVIEW. The exact position of the accelerometer is shown in Figure 5 by a red X [56].

3.4. Powder and capsule handling

All of the powders were stored for the whole period of this study at a relative humidity (R.H.) <55% and a room temperature <25°C. To keep the condition of all experimental dosing studies same and to reduce the error, the sieves were filled with powder up to 90 % of its volume. This filling level was kept for all studies to guarantee equal conditions for every dosing event. It was taken care that the powder bed inside the sieve did not become inhomogeneous during the experiments. When the powder bed became inhomogeneous, a spoon was used to smooth its surface, without compressing the material [56].

Hard gelatin capsules are sensitive to changes in humidity or by addition of moisture. To avoid the changing in capsules weight by change of the humidity, a constant RH was

established in the room and gloves were used all the time to minimize transform of sweat. Because in the MG2 Microdosing system the capsule should be manually filled one by one, it was not necessary to number the capsules before weighing.

3.5. Experimental procedure

In first step of this study, the screening is done to select powders and sieves according to special design of Microdose machine.

3.5.1. Sieve Selection

The aim is to select the sieve that allows powder feeding in the broadest range of amplitude and frequency for each powder (steady powder flow and homogeneous powder bed in the chute are the qualitative evaluation criteria). Knowing that Microdose machine can operate in a broad range of amplitudes and frequencies guarantees the flexibility (when operated with the PID control) that is required to obtain accurate fill weights. The filling characteristics were tested ten different frequencies (10-100 Hz) and eight different amplitudes (30-100 E). This 80 combinations screening determine the best settings for each powder. The screen tables for each of the six different powders are prepared (Tables 5-10). In all these tables three different signs (✔, **X** and **X.**) based on how steady the powder flow through the sieve and distribution of the powder on the chute were assigned. This three attributed of filling characteristics is shown in Figure 9. In all of tables ✔ sign shows a constant powder flow, **X** sign shows interrupted powder flow or no flow at all, **X.** sign shows powder spilling over the rim of the sieve [56].

These initial studies were done to choice the powders with a larger operating space, in which the powder filling, with Microdose system and with the applicable amplitude and frequency settings, is possible. For these initial studies filling with each setting was repeated 10 times to make sure that a reproducible filling is possible. Then, one of the three signs of ✔, **X** and **X.** is assigned [56].
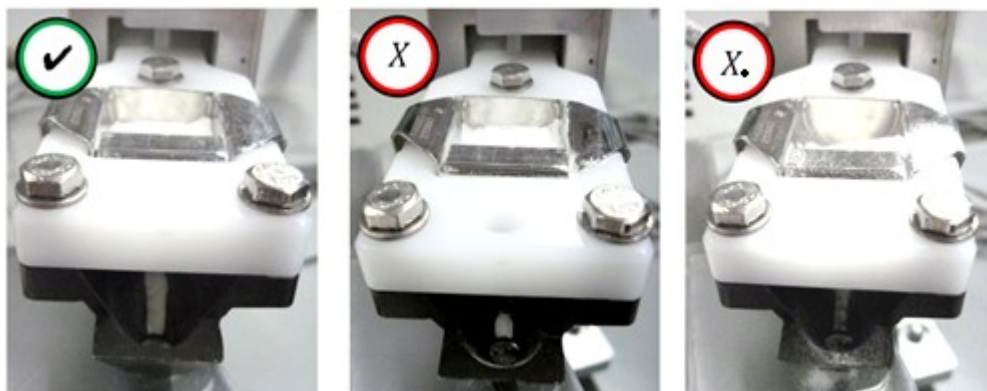
Figure 9:Assigned attributed of the filling characteristics (with permission from [56]).

In Table 8 screening for Respitose ML001 with sieve number 6, Sieve number 5, sieve number 4 and sieve number 3 is shown. In all the Tables, the sign for sieve number 6 is shown in black color, the sign for sieve number 5 is shown in red, the sign for sieve number 4 is shown in orange and for sieve number 3 it is shown in green.

Table 8:Operating space for Respitose ML001 with sieve6, sieve 5, sieve 4, sieve 3.

Amplitude [E] → Frequency [Hz] ↓	30	40	50	60	70	80	90	100
10	X X X X	X X X X	X X X X	X X X X	X X X X	X X X X	✔✔ ✔✔	✔✔ ✔✔
20	X X X X	X X X X	X X X X	X X X X	X X X X	X X X X	✔✔ ✔✔	✔✔ ✔✔
30	X X X X	X X X X	X X X X	X X X X	X X X X	X X X X	✔✔ ✔✔	✔✔ ✔✔
40	X X X X	X X X X	X X X X	✔X X X	X. X. X X	X. X. X X	X. X. X. X.	X. X. X. X.
50	X X X X	✔X X X	✔✔ X X	✔✔ X X	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	X. X. X. X.
60	X X X X	X X X X	✔X X X	✔X X X	✔X X X	✔X X X	✔✔ X X	✔✔ ✔✔
70	X X X X	X X X X	X X X X	X X X X	✔X X X	✔X X X	✔✔ X X	✔✔ ✔✔
80	X X X X	X X X X	X X X X	X X X X	✔X X X	✔X X X	✔✔ ✔✔	✔✔ ✔✔
90	X X X X	X X X X	X X X X	X X X X	✔X X X	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔
100	X X X X	X X X X	X X X X	X X X X	✔X X X	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔
	sieve6, **Sieve 5**, **sieve 4**, **sieve3**							

In Table 9 screenings for Respitose SV003 with sieve number 6, Sieve number 5, sieve number 4 and sieve number 3 are shown.

Table 9:Operating space for Respitose SV003 with sieve6, sieve 5, sieve 4, sieve 3.

Amplitude [E] → / Frequency [Hz] ↓	30	40	50	60	70	80	90	100
10	XXXX	X X X X	X X X X	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔
20	XXXX	X X X X	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔
30	XXXX	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔
40	XXX XX	✔✔ XX	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	X.X. X.X.	X.X. X.X.	X.X. X.X.
50	XXXX	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	X.X. X.X.
60	XXXX	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔
70	XXXX	✔✔ XX	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔
80	XXXX	XXXX	XXXX	XXXX	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔
90	XXXX	XXXX	XXXX	XXXX	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔
100	XXXX	XXXX	XXXX	XXXX	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔
sieve6, Sieve 5, sieve 4, sieve3								

In Table 10 screenings for Respitose SV010 with sieve number 6, Sieve number 5, sieve number 4 and sieve number 3 are shown.

Table 10:Operating space for Respitose SV010 with sieve6, sieve 5, sieve 4, sieve 3.

Amplitude [E] → Frequency [Hz] ↓	30	40	50	60	70	80	90	100
10	✗✗✗✗	✔✔ ✗✗	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔
20	✗✗✗✗	✔✔ ✗✗	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔
30	✗✗✗✗	✔✔ ✗✗	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔
40	✔✗✗✗	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	X.X. X.X.	X.X. X.X.	X.X. X.X.
50	✔✗✗✗	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	X.X. X.X.
60	✔✗✗✗	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔
70	✔✗✗✗	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔
80	✗✗✗✗	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔
90	✗✗✗✗	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔
100	✗✗✗✗	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔
sieve6, Sieve 5, sieve 4, sieve3								

In Table 11 screenings for Respitose ML006 with sieve number 6, Sieve number 5, sieve number 4 and sieve number 3 are shown.

Table 11:Operating space for Respitose ML006 with sieve6, sieve 5, sieve 4, sieve 3.

Amplitude [E] → Frequency [Hz] ↓	30	40	50	60	70	80	90	100
10	X X X X	X X X X	X X X X	X X X X	X X X X	X X X X	X X X X	X X X X
20	X X X X	X X X X	X X X X	X X X X	X X X X	X X X X	X X X X	X X X X
30	X X X X	X X X X	X X X X	X X X X	X X X X	X X X X	X X X X	X X X X
40	X X X X	X X X X	X X X X	X X X X	X X X X	X.X. X.X.	X.X. X.X.	X.X. X.X.
50	X X X X	X X X X	X X X X	X X X X	X X X X	X X X X	X.X. X. X.	✔ X X X
60	X X X X	X X X X	X X X X	X X X X	X X X X	X X X X	X X X X	X X X X
70	X X X X	X X X X	X X X X	X X X X	X X X X	X X X X	X X X X	X X X X
80	X X X X	X X X X	X X X X	X X X X	X X X X	X X X X	X X X X	X X X X
90	X X X X	X X X X	X X X X	X X X X	X X X X	X X X X	X X X X	X X X X
100	X X X X	X X X X	X X X X	X X X X	X X X X	X X X X	X X X X	X X X X
sieve6, Sieve 5, sieve 4, sieve3								

In Table 12 screenings for Custom-made Lactohale with sieve number 6, Sieve number 5, sieve number 4 and sieve number 3 are shown.

Table 12:Operating space for Custom-made Lactohale with sieve6, sieve 5, sieve 4, sieve 3.

Amplitude [E] → Frequency [Hz] ↓	30	40	50	60	70	80	90	100
10	XXXX	XXXX	XXXX	XXXX	XXXX	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔
20	XXXX	XXXX	XXXX	XXXX	XXXX	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔
30	XXXX	XXXX	XXXX	XXXX	XXXX	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔
40	XXXX	XXXX	✔XXX	✔XXX	✔✔ ✔✔	X.X. X.X.	X.X. X.X.	X.X. X.X.
50	XXXX	✔XXX	✔✔ ✔✔	✔✔ XX	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	X.X. X.X.
60	XXXX	✔XXX	✔✔ ✔✔	✔✔ XX	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔
70	XXXX	XXXX	XXXX	XXXX	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔
80	XXXX	XXXX	XXXX	XXXX	XXXX	✔✔ XX	✔✔ ✔✔	✔✔ ✔✔
90	XXXX	XXXX	XXXX	XXXX	XXXX	✔✔ XX	✔✔ ✔✔	✔✔ ✔✔
100	XXXX	XXXX	XXXX	XXXX	✔✔ XX	✔✔ XX	✔✔ ✔✔	✔✔ ✔✔
		sieve6, Sieve 5, sieve 4, sieve3						

In Table 13 screenings for Inhalac230 with sieve number 6, Sieve number 5, sieve number 4 and sieve number 3 are shown.

Table 13:Operating space for Inhalac230 with sieve6, sieve 5, sieve 4, sieve 3.

Amplitude [E] → / Frequency [Hz] ↓	30	40	50	60	70	80	90	100
10	XXXX	XXXX	✔✔ XX	✔✔ XX	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔
20	XXXX	✔X XX	✔✔ XX	✔✔ XX	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔
30	XXXX	✔✔ XX	✔✔ XX	✔✔ XX	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔
40	✔XXX	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	X.X. X.X.	X.X. X.X.	X.X. X.X.
50	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	X.X. X.X.
60	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔
70	✔XXX	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔
80	XXXX	✔✔ XX	✔✔ XX	✔✔ XX	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔
90	XXXX	✔✔ XX	✔✔ XX	✔✔ XX	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔
100	XXXX	✔✔ XX	✔✔ XX	✔✔ XX	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔	✔✔ ✔✔
	sieve6, Sieve 5, sieve 4, sieve3							

3.5.2. Detailed studying of the filling rate

Further studies were planned according to the screening results and limited to the three best powders and the best sieve. For all possible settings (shown with marks in the screening tables) 35 capsules were filled with 5mg. In all filling events the weight was recorded by the Microdose system. As an example the filling profiles for Respitose SV010 in Figure 10 are shown. In Figure 10a the amplitude is 40 E and the frequency is 40 Hz and in Figure 10b the amplitude is 40 E and the frequency is 70 Hz. Also the slope (i.e., the fill rate) can be calculated (see Eq. (6)) [56].

$$\text{Slope} = \Delta\, fw(t) / \Delta t \qquad\qquad (6)$$

The slope [mg/s] is an indicator of the powder flow through the sieve and can determine the flowability of the powder with current setting. Even more, the slope could be a standardized flowability measure for general studies of powder flowability, not limited to capsule filling. The slopes were evaluated between the first point after filling 0.25 mg in the capsule body and the first point after the motor stopped (after reaching the target weight, i.e., $fw = 5\ mg$). The black lines in Figure 10 show the parts that were evaluated to determine the slopes. The effect of the vibration phase during the filling is obvious in this figure. After stopping the motor (stopping vibration after reaching the target weight), filling weight increased significantly, due to filling during the off-vibration phase[56].

The flow rate was determined by averaging the 30 filling profiles slopes for each settings of powder. The first five fillings were not included in the calculation, to avoid the errors of first fillings (filled powder need some time to reach the end of 2.5cm chute) [56].
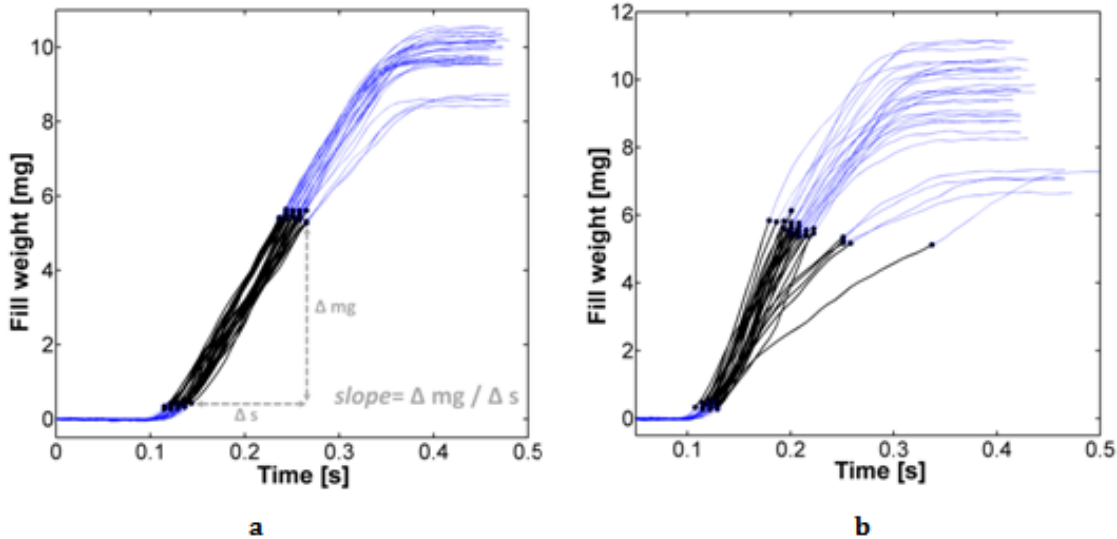

Figure 10: Capsule filling weight during dosing with Respitose SV010 with (a) amplitude = 40 E frequency = 40 Hz and (b) amplitude = 40 E frequency = 70 Hz (with permission from [56]).

The relative standard deviations (RSDs) of the evaluated slopes increase when the probabilities of unsteady filling behavior are higher (see Figure 10b for unsteady filling

behavior) or when the filling rates are not constant [56].

3.5.3. Operating space for modified sieve number 3

After the initial studies (screening involving all six powder and 4 sieves), the study was limited to the three best-flowing powders, i.e., Respitose SV003, Respitose SV010 and Inhalac 230, and the best sieve, which is sieve number 3.

Because the settings from the screened operation space (see section 3.5.1) show a relative high flow rate of 10-80 mg/s, dosing a small amount of powder accurate into a capsule body is difficult (see Figure 9 for overdosing). All the fillings are done without applying the PID control (to reach the goal of powder characterization). The optimized acceptance range was also applied to achieve accurate low-dose filling (<10mg), but the procedure was still unsuccessful and accurate micro-dosing remains yet a challenge in this study. The amount of powders that is filled into capsules during the off-vibration phases (see Figure 6) is already in the range of target weight, and thus, leads to systematic overdosing (see Figure 10). Because of this a modification of sieve number 3 was designed to reduce the fill rate. The goal of this section was to analyze, if modification of sieve number 3 can enhance dosing accuracy (providing a smaller RSD). Modification of sieve number 3 will be referred to as sieve 3* in the following part of the thesis. The modification consists of blocking half of the holes (five holes of ten holes) to obtain a lower filling rate, which is shown in Figure 11 [56].

Figure 11: Modified sieve 3 (referred to as sieve 3*).

In Table 14 screenings for all three best-flowing powder with sieve 3* are shown. The same symbols as described in section 3.5.1 were used in this section as well.

Table 14: Operating space for free flowed powders with sieve 3*.

Amplitude [E] → Frequency [Hz] ↓	30	40	50	60	70	80	90	100
10	XXX	XXX	X✔X	✔✔X	✔✔✔	✔✔✔	✔✔✔	✔✔✔
20	XXX	XXX	X✔X	✔✔X	✔✔✔	✔✔✔	✔✔✔	✔✔✔
30	XXX	XXX	X✔X	X✔X	✔✔✔	✔✔✔	✔✔✔	✔✔✔
40	XXX	X✔✔	✔✔✔	✔✔✔	✔✔✔	X.X.X.	X.X.X.	X.X.X.
50	XXX	X✔✔	✔✔✔	✔✔✔	✔✔✔	✔✔✔	✔✔✔	X.X.X.
60	XXX	✔✔✔	✔✔✔	✔✔✔	✔✔✔	✔✔✔	✔✔✔	✔✔✔
70	XXX	X✔✔	✔✔✔	✔✔✔	✔✔✔	✔✔✔	✔✔✔	✔✔✔
80	XXX	X✔X	X✔X	X✔X	✔✔✔	✔✔✔	✔✔✔	✔✔✔
90	XXX	X✔X	X✔X	X✔X	✔✔✔	✔✔✔	✔✔✔	✔✔✔
100	XXX	X✔X	X✔X	X✔X	✔✔✔	✔✔✔	✔✔✔	✔✔✔
	Respitose SV003		**Respitose SV010**		**Inhalac 230**			

4. Results

4.1. Vibration parameters

As described in Besenhard et al. [56] the acceleration of the vibrating arm in the Microdosing system (the accelerometer was attached close to the sieve, see Figure 5) reflects the vertical forces acting on the sieve with the powder.

4.1.1. Effect of sieve design and vibration parameters on flow rate and RSD

The flow rate versus amplitude, and RSD versus amplitude is plotted in Figure 12 for three different frequencies. Because in the Microdose system the amplitude is the process parameter that the machine adjusts in order to reach the target weight, it is important for development of control tools/algorithms to know the correlation between flow rate and RSD as a function of the amplitude. Figure 12 shows the flowrate-amplitude plots for the free-flowing powders for three different frequencies (60, 80, 100Hz). In this figure the lines are for dosing via sieve number 3 and the dot lines are for same dosing via sieve number 3*. Different powders are shown by different colors (Inhalac 230 is shown in blue, Respitose SV003 in black and Respitose SV010 in green).
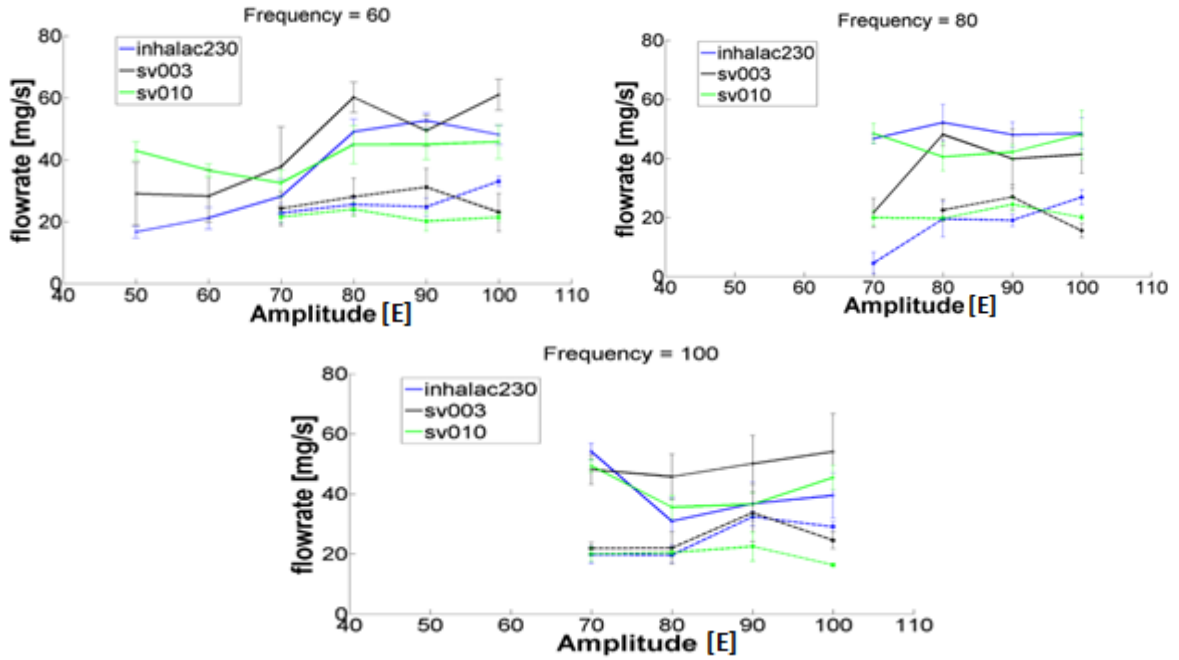
Figure 12: Changes of flow rate according to amplitudes for Inhalac 230, Respitose SV003 and Respitose SV010.

The relative standard deviation (RSD) was analyzed in this study according to Eqs. (7) and (8), which illustrate how the SD and RSD were calculated for the 30 filling events (after discarding the first five dosed capsules). In these equations, n denotes the number of measurements (n = 30), W_i is the dosed mass for the ith filling and W_{mean} is the mean of dosed mass [65].

$$SD = \sqrt{(1/(n-1)) \sum_{i=1}^{n} (W_i - W_{mean})^2} \qquad (7)$$

$$RSD = SD/W_{mean} \qquad (8)$$

Figure 13 shows the amplitude-RSD plots for the free-flowing powders for three different frequencies (60, 80, 100Hz).
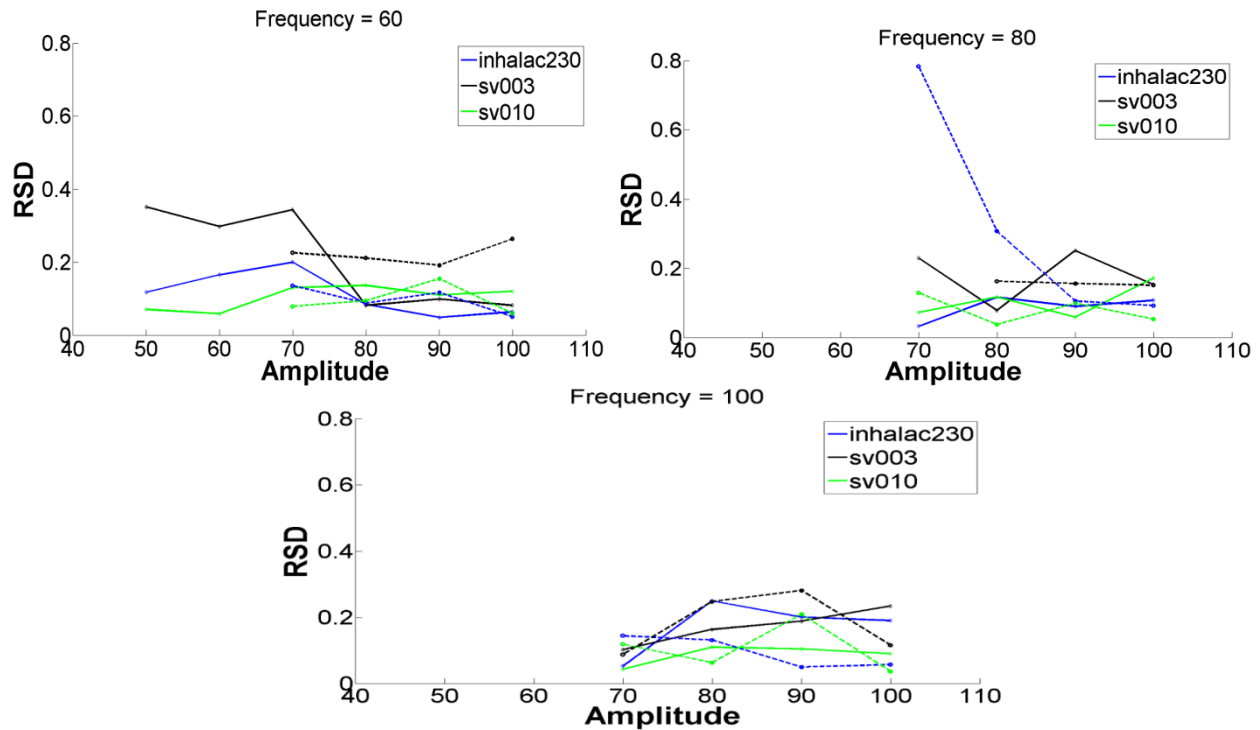

Figure 13: Changes of RSD according to amplitudes for Inhalac 230, Respitose SV003 and Respitose SV010.

Blocking half of the holes in the sieves (sieve number 3*) led to a significant reduction of the filling rate (dot lines). However, blocking half of the holes did not lead to a reduction of the filling rate by 50%, as would have been expected. Therefore, the relationship between fill rate and number of holes is not linear.

4.1.2. Effect of material attributes on flow rate and RSD

Here the goal was to analyze the effect of properties that differ significantly between the three powders (i.e., BFE, particle size, span of particle size distribution, air permeability).

The study was designed to elucidate the impact of powder properties on the flow rates and was done for both sieves (i.e., number 3 and 3*). Figure 14 shows the flow rate the corresponding relative standard deviation (RSD) as a function of the powders' BFE (basic flowability energy) for sieve number 3* with frequencies of 60, 80 and 100 Hz and different amplitudes (70, 80, 90, 100 E which are defined by different colors).
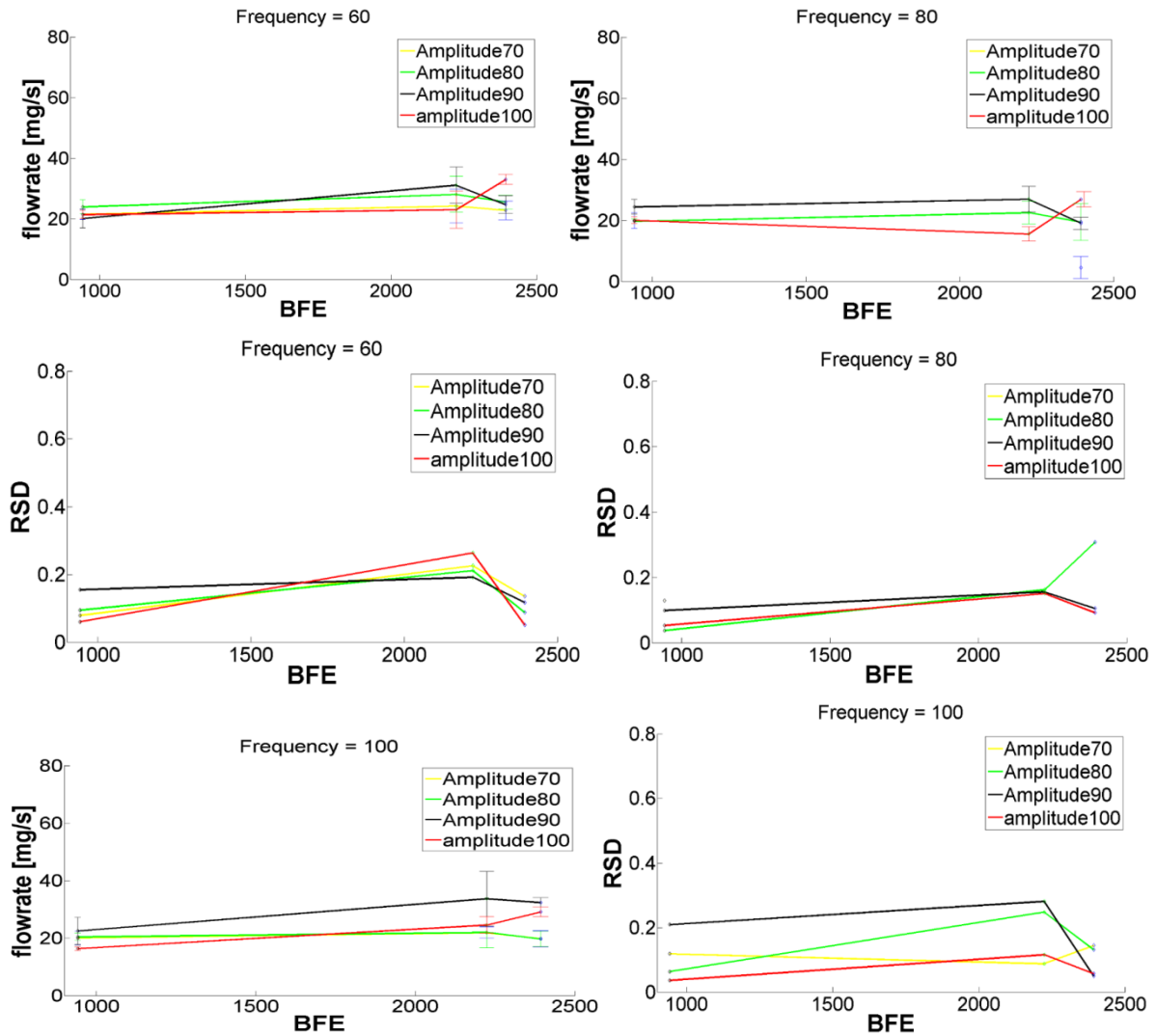

Figure 14: Effect of powder flowability on flow rate/RSD for sieve 3*.

Figure 15 shows the flow rate and RSD as a function of the BFE for sieve number 3 with frequencies of 60, 80 and 100 Hz and amplitudes of 70, 80, 90, 100 E.
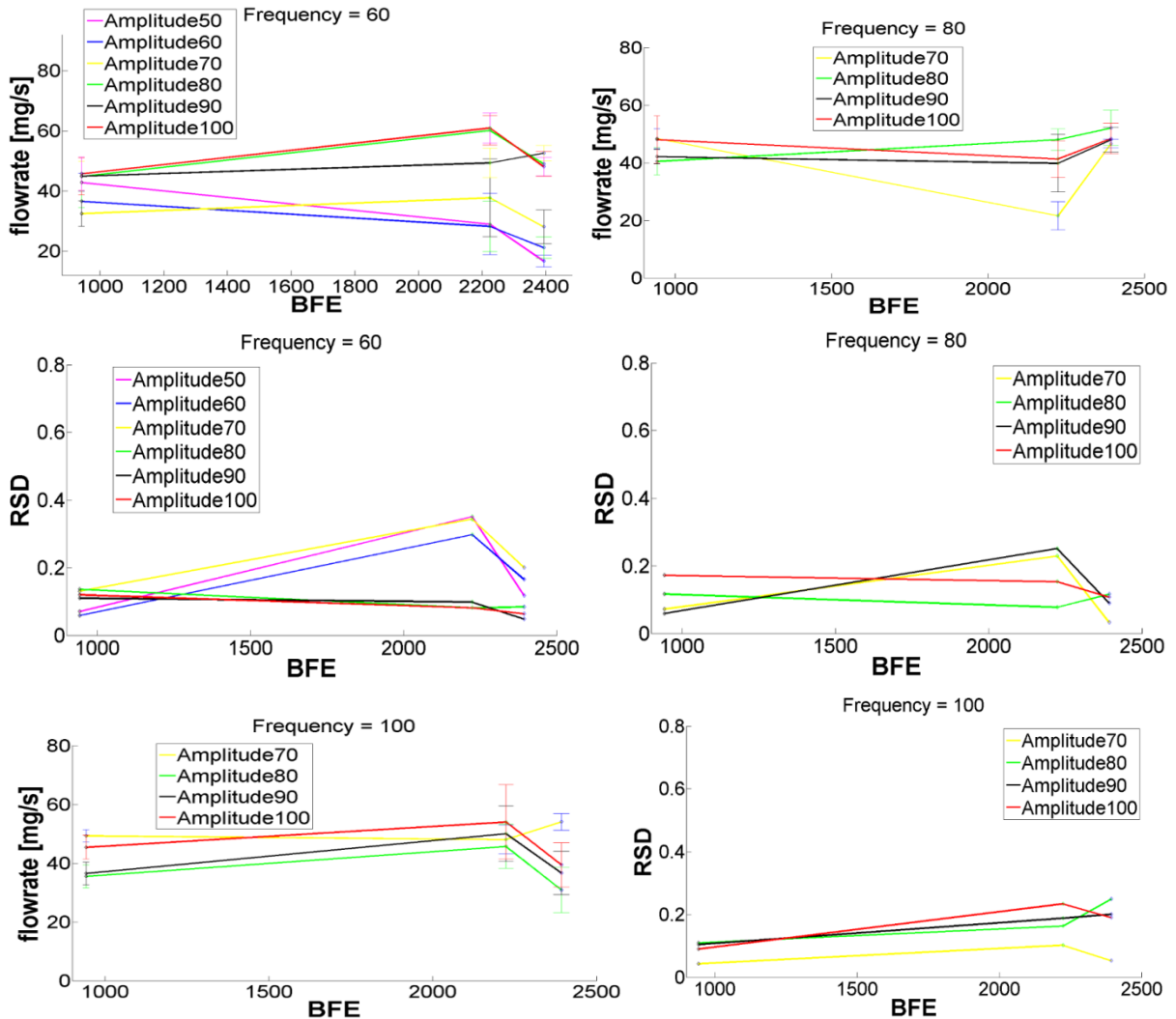

Figure 15: Effect of powder flowability on flow rate/RSD for sieve 3.

The same plots for other powder attributes that differed significantly between powders (i.e., VMD, span and air permeability) were also generated. However, the same conclusions were obtained and thus, the data are not presented in this work.

4.2. Filling rates and standard deviation

Filling rates and standard deviations (shown as error bars) of Respitose SV003, Respitose SV010 and Inhalac 230 in their operating space as defined in section 3.5.1 are shown in Figures 16-18. The empty spaces in these figures are the areas that no powder flow was possible or areas with powder spilling [56].

Figure 16: Filling rates and standard deviation of Respitose SV003 for different amplitudes and frequency settings in the operating space (with permission from [56]).
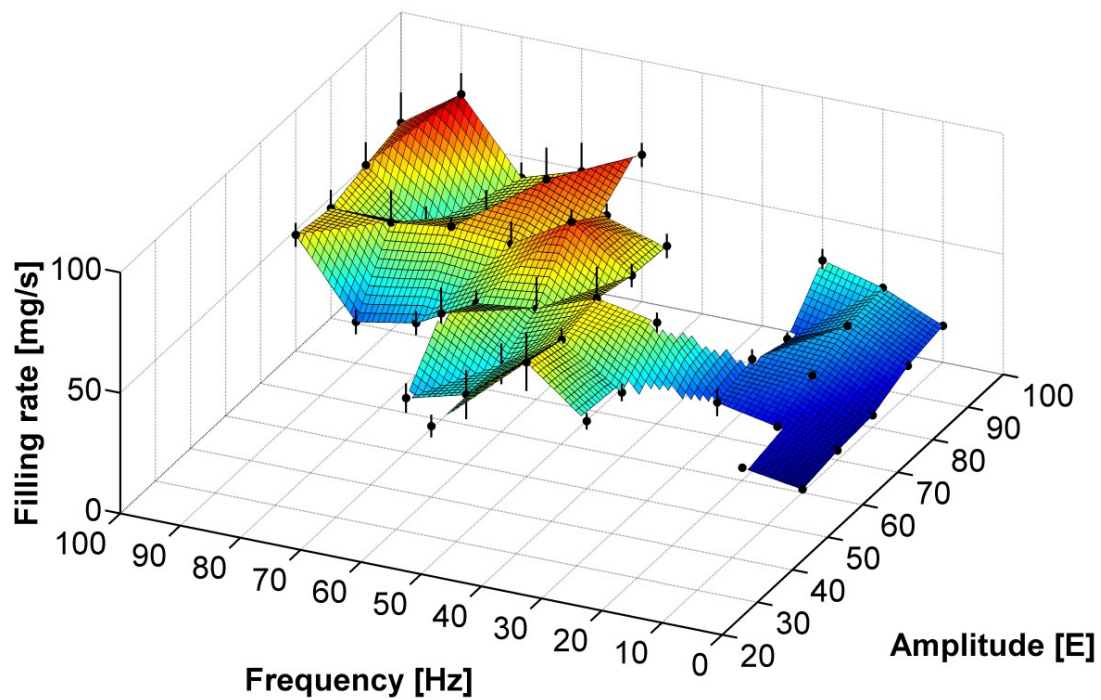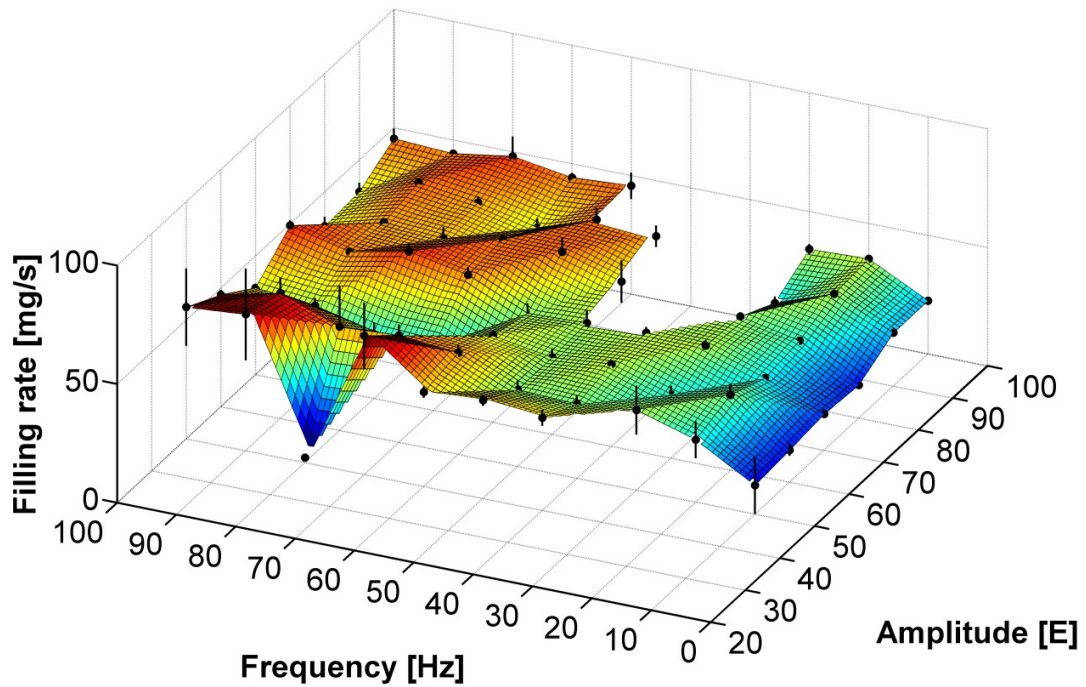
Figure 17: Filling rates and standard deviations for Respitose SV010 for different amplitudes and frequency settings in the operating space (with permission from [56]).
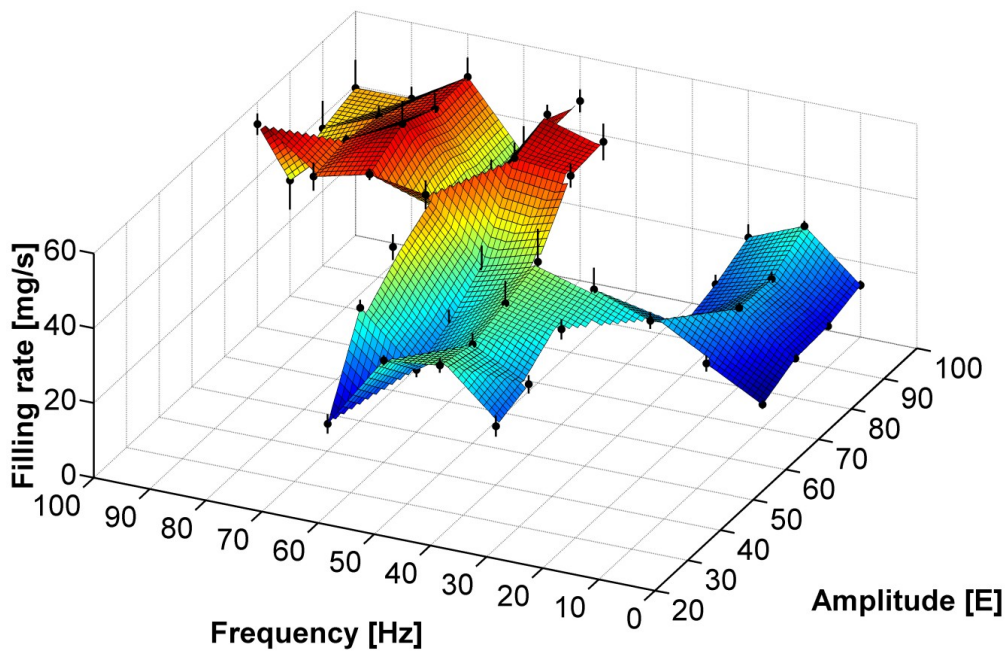

Figure 18: Filling rates and standard deviations for Inhalac 230 for different amplitudes and frequency settings in the operating space (with permission from [56]).

As it is shown in Figure 17 and in Table 14 Respitose SV010 had the largest operating space. Powder dosing was possible for Respitose SV010 with amplitude of 40 E and frequencies of higher than 40 Hz. In contrast to Respitose SV003 and Inhalac 230, powder could be dosed on the chute for every frequency in combination with amplitudes higher than 40 E [56].

4.3. Accuracy of low dosing using PID control

The purpose of this section is to highlight tests of the low-dosing capability of the Microdose sytem. To achieve this goal, within the operating space a capsule-filling study with target weight of 2.5 mg at the best settings for each powder was carried out to see if accure low dosing is possible with this system. Hence low dosing for all powders was performed at 15 Hz (frequency at which all powders had the best filling behavier, see Figure 16-18), but different amplitudes according to different operating space of powders. For Respitose SV003 and Inhalac 230 the same amplitude values of 75 E were applied and for Respitose SV010 an amplitude of 55 E was used [56].

Via three different methods 30 capsules were filled.

- In first method dosing was carried out at a fixed amplitude.
- In the second, second method filling was done by applying a PID controller to the amplitude.
- In the third method filling was performed with applying an unstricted PID control.

The parameters of the PID controller were as follow: $K_P = 10$, $K_i = 0.05$, $K_d = 2$ (see section 2.5.2.3, Eq. (5)). In Tables 15-17 the result of the low-dosing study for all three powders are shown. In these tables the information is presented separately for each powder. In the first column all information (the mean fill weight, its RSD, maximum and minimum weights, the filling time and filling time RSD) during dosing at the fix amplitude are presented (first method of low dosing study). The second column presents the same information for filling with restricted PID control (second method of low dosing study) and the third column for filling with unrestricted PID control (third method of low dosing study) [56].

In Figure 16-18 the results of the first method test are presented as follow: Respitose SV003 showed the best filling behaviour, i.e., the lowest fill weight variability with the mean target of exactly 2.5 mg and RSD of 4.6%. Inhalac 230 yielded an RSD of 6.3% and a mean filling weight of 2.56 mg. Thus, the difference to target weight is very low. Due to reasons discussed below, Respitose SV010 performed worst with a mean fill weight of 2.8mg and an RSD of 12%. Interestingly, this powder has the best flowability [56].

The other results shown in the tables are for experiments with restricted PID control, in which PID control was applied just to modulate the amplitudes within the operating space and for unrestricted PID control that PID control was applied to all possible amplitudes. The lowest fill weight variability was achieved for Respitose SV003 and Inhalac 230 when the restricted PID control was applied during the filling (using constant settings). This is because of homogeneous powder bed in chute that was created by capsule filling with settings (i.e., amplitudes and frequencies) in their optimal operating space [56].

Table 15: Results of the low dose studies for Inhalac 230 [56].

Target weight 2.5 mg	Dosing via fixed settings (Freq. 15, Ampl. 75, accept.range.=0.7 mg)	Dosing via restricted PID control (Freq. 15, Ampl. 70-100, accept.range =0.6 mg)	Dosing via PID control (Freq. 15, accept.range =0.05 mg)
Average dosing [mg]	2.56	2.6	2.6
RSD [%]	6.3	4.6	9.2
Max dosing [mg]	2.85	2.82	3.34
Min dosing [mg]	2.28	2.39	2.41
Filling time [s]	0.86	0.79	4.1
Filling time RSD [%]	5.5	3.8	20.8

Table 16: Results of the low dose studies for Respitose SV003 [56].

Target weight 2.5 mg	Dosing via fixed settings (Freq. 15, Ampl. 75, accept.range =1 mg)	Dosing via restricted PID control (Freq. 15, A70-100, accept.range =0.5 mg)	Dosing via PID control (Freq. 15,accept.range =0.05 mg)
Average dosing [mg]	2.5	2.5	2.6
RSD [%]	4.6	4.6	6.4
Max dosing [mg]	2.8	2.7	3.23
Min dosing [mg]	2.3	2.3	2.44
Filling time [s]	0.98	0.66	4.4
Filling time RSD [%]	15.8	4.4	46.5

Table 17: Results of the low dose studies for Respitose SV010 [56].

Target weight 2.5 mg	Dosing via fixed settings (Freq 15, Ampl 55, accept.range. =1.2 mg)	Dosing via restricted PID control (Freq. 15, A55-100, accept.range =1.2 mg)	Dosing via PID control (accept.range =0.08 mg)
Average dosing [mg]	2.8	2.7	2.6
RSD [%]	12	8.5	7.5
Max dosing [mg]	3.23	3.11	3.11
Min dosing [mg]	1.94	2.35	2.35
Filling time [s]	0.72	0.65	4.3
Filling time RSD [%]	4.3	3.8	48.6

Dosing with unrestricted PID control applies also amplitudes that were not in the operating space. Thus, situations were encountered that led to no powder flow from the sieve. As shown in Figure 19 (-left) for unrestricted PID control powder flows when the applied amplitude is in the operating space. In contrast, no powder flow occurs from the sieve on the chute when the applied amplitude is not in the operating space. Hence, the powder bed on the chute is not homogenous and this may cause overdosing. An example of this overdosing for Inhalac 230 is shown in Figure 20 by comparing the amplitude and fill weights during PID control filling [56].
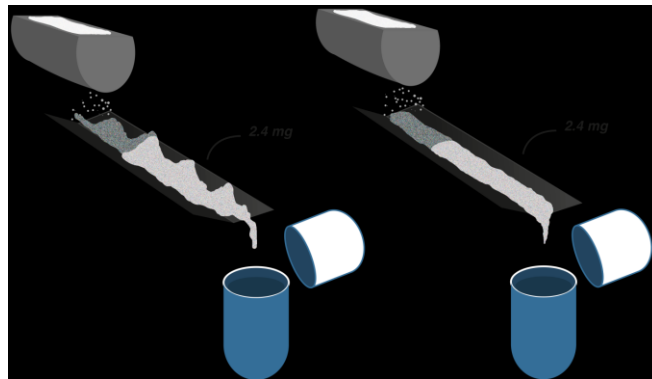

Figure 19: Left: dosing with PID control, Right: dosing without PID control (with permission from [56]).
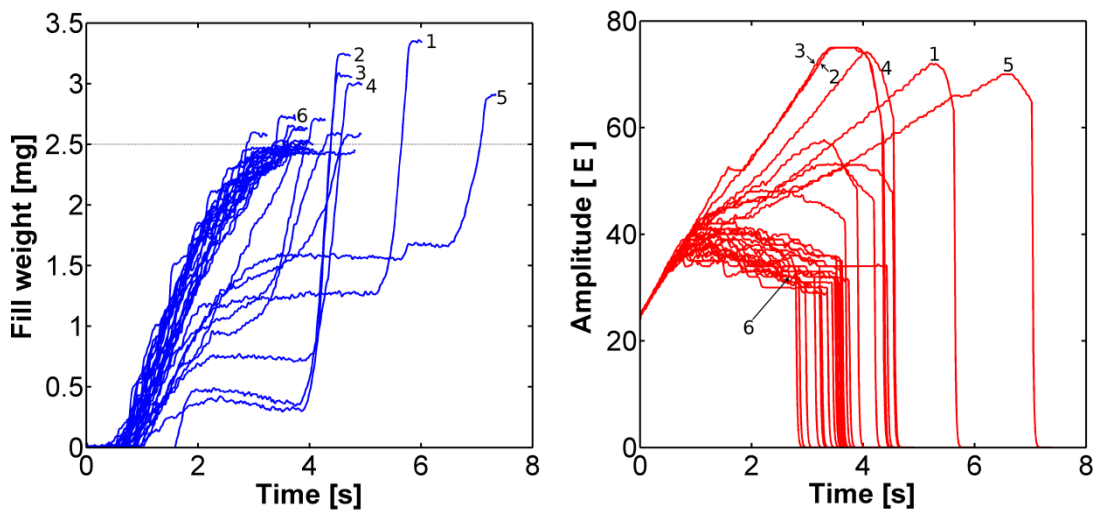

Figure 20: Fill weights and amplitudes plots, recorded during InhaLac 230 dosing with a target weight of 2.5 mg and a frequency of 15 Hz (with permission from [56]).

5. Discussion

5.1. Screening of sieves and Vibration parameters

Cohesive powders such as Respitose ML006 cannot be filled with the Microdose system. Screening tests for this powder showed just one possible setting for capsule filling with this system (see Table 11). Other high-cohesion powders, such as Respitose ML001 (see Table 8) and Custom-made Lactohale (see Table 12) which also showed a small operating space, were not used for further studies with the MG2 Microdose system. Instead, additional studies were limited to Respitose SV003, Respitose SV010 and Inhalac 230 (free-flowing powders). According to the screening tables (Tables 8-13) sieve number 3 offered the largest operating space (combination of vibration frequency and amplitude) for dosing of selected powders by MG2 Microdose system. Blocking half of the sieve holes (sieve number 3*) led to a reduction of filling rate, yet not a more accurate dosing, as it was expected.

Not only the amplitude and frequency and their interaction, but also the wave shape of vibration is important for the Microdose system's behavior [31]. The phase that powder flew out of the sieve can be explained by help of vibration wave shape and maximum of acceleration. As described by Besenhard et al. [56] the vertical vibrations were not sinusoidal (sinusoidal accelerations causes sinusoidal displacement) and negative acceleration leads to upward movement of the Microdose arm. The negative acceleration increased with increasing amplitude variable (see Table 4) and this maximum acceleration caused powder to spill from the sieve. [56] With sieve number 3* there were few settings in comparison with the original sieve number 3 (Tables 8-13) where no flow happened. Hence, the operating space stayed about the same.

The same acceleration study for various frequencies and a fixed amplitude value is described by Besenhard et al. [56]. The results show the frequency space in which no flow was achieved, or not enough flow (under 30 Hz) as shown in screening study tables in section 3.5.1. It is suggested that a regular acceleration pattern can be reached above a

critical frequency (above 30 Hz) in the MG2 Microdose system [56]. In summary there are sets of parameters where the powder does not flow (no dosing occurs).

5.2. Effects of process parameters and material properties on feeding rate

As result from the screening tables, all three selected powders could not be filled into the capsule bodies below amplitudes of 30 E. This is due to the vibration energy imparted to the system to overcome the inter-particle forces [1][31][56]. All powders filled through the sieves above amplitudes of 70 E. For amplitudes higher than 80 E and frequencies of about 40 Hz, the powder spilled over from the sieve and chute (see Figure 9) because of the high accelerations during the upward movement. The acceleration profiles shown by Besenhard et al. also show for these amplitudes and frequencies an unsymmetrical acceleration pattern featuring high negative-direction accelerations (upward movement) [56].

For all three powders higher filling rates resulted in higher frequencies. A temporal increase in the free volume is a result of vibrations (dilation of powder) which helps a static powder bed to flow by increasing the free volume on the sieve. Expansion of powders is a well-known prerequisite for granular systems to flow, as the expansion of volume overcomes inter-particular forces, allows particles to slip past each other, and breaks agglomerates and cohesive bonds. Thus, free space for particle displacement is provided that can also be described as activation energy in a molecular analog [5][56]. According to this explanation filling at higher frequency overcomes this activation energy more frequently and lead to higher filling rates [56].

As described by Besenhard et al. [56] the wave shapes are not similar for different frequencies and amplitudes in the Microdose system. This can be one of the reasons why the increase of the filling rate is not monotone with an increase of the amplitude and frequency.

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As mentioned by Chen et al. [31] the vibration wave shape variations can lead to filling performance variations (different filling rate) even if amplitudes and frequencies stay identical [56].

All powders at higher amplitude could be filled into capsule bodies (see Figure 16-18). An exception is the combination of operating parameters that causes powder spilling at intermediate frequency. For all powders below amplitude of 60 E dosing was only possible at intermediate frequencies. Below 40 E no dosing was achieved. As summary, low to intermediate frequencies yielded a broader range of the operating space (broader range of amplitude E) for successful dosing in comparison to higher frequencies [56].

Respitose SV010 has the largest particles amongst all powders, and thus, the lowest surface-to-volume ratio. Hence, the lowest cohesive force of attraction and the lowest activation energy for inducing powder flow can be observed for Respitose SV010. This can explain why this powder has the largest operating space (also with lower amplitude values). This result also correlated with the Carr index of the powders (Respitose SV010 has a lower CI than other powders) [56].

According to Table 14 the three powders show similar flowability characteristics. This is the reason why all powders showed comparable filling rates at the same settings (combination of amplitude and frequency). The most robust filling rates, i.e., the ones with small standard deviation (see error bars in Figures 16-18), were observed for settings away from the operation space borders. Therefore, the MG2 Microdosing system is most suitable for continuous filling applications when it is operated at settings that guarantee good powder flow (amplitudes > 55 E) without spilling of the powder. Respitose SV010, i.e., the powder with the largest particle size and lowest CI showed the best filling behaviour with the low SD. This fact highlights the importance of powder properties for designing a continuous filling system based on the proposed functional principles [56].

The effect of powder segregation on such vibratory sieve chute system has not been studied so far. There are two sources of segregation that are possible in such system. The first

source of segregation is the vibratory sieve and chute via the well-known sieving segregation mechanism. The second one is associated with air currents that levitate finer powder particles during feeding from the chute into the capsule bodies (fluidization segregation). The residence times on the chute are rather low in this system, hence the segregation in capsule body is not considered in this study and only segregation in the vibrating sieve is of interest here [56].

According to study of Besenhard et al. [56] the vertical acceleration during a capsule filling procedure is enough for generating voids (>1 g). "Void filling" beneath large particles which leads to a rise of the large particles, is the source of sieving segregation. Such a size-based segregation mechanism depends not only on powder properties, but also on the amplitude and frequency values and the geometry (i.e., downward currents of powders near the walls). A reverse size-based segregation can be observed where larger powder particles accumulate at the bottom of fluidized beds. This is termed fluidization segregation. Both mechanisms are likely to be observed in the system under investigation. However, vibrations increase the granular temperature of the powder (i.e., fluctuations of individual grains) and thus, dispersive mixing of particles is induced, effectively counter-acting segregation. The relative magnitude of segregation and mixing effects will determine if powders can be filled or of strong de-mixing occurs [56].

In conclusion, segregation is likely to happen in such systems and the magnitude of the effect strongly depends on both powder properties and the values of amplitudes and frequencies [56]. This, however, will be subject to further studies.

For low amplitudes and frequencies, it can happen that the powder particles accumulate in the range of the sieve holes' diameter. Hence, no filling through these holes is possible and this influences the flow rate directly [56].

Mixing of powders that are prone to segregation can cause problems in uniformity of the capsules' content. Such powders (free flowing, with differences in density, particle sizes or shapes and etc.) should be filled into capsule separately. For further studies, it is suggested

to observe the impact of size segregation on the filling rate for individual powders. This can be done by comparing the filling rate between capsules filled first and last or by sieving powder in a smaller range, that all particles will be in same range (i.e., 90-100 μm) [56].

5.3. Effects of process parameters and material properties on final fill weight

Overdosing is caused by inhomogeneous powder bed in this system for two reasons: first, the empty sections on the chute lead to extreme increase of amplitude (when PID control is applied, see Figure 20) and second, temporarily high filling rates because of piles on the chute (see Figure 19-left). When the fill weight is near to target weight, the remaining powder on the chute may form a pile. Because of this the fill rate increases at end of dosing temporarily and in this case an overdosing cannot be avoided (see dosing number 6 in Figure 20) [56].

The fill weight variability for Respitose SV010 was high in comparison with other powders (It had the most robust filling rate at 15 Hz). Dosing with PID control was the most accurate for Respitose SV010, because the filling rate was too high ($\approx \frac{1}{2} \cdot 20\,mg/s$ at frequency =15 Hz, amplitude=55 E). Although a high acceptance range (1.2 mg) was used for this powder, it was not enough to avoid overdosing. In InhaLac 230 ($\approx \frac{1}{2} \cdot 13\,mg/s$ at frequency =15 Hz, amplitude=75 E) and Respitose SV003 ($\approx \frac{1}{2} \cdot 8\,mg/s$ at frequency =15 Hz, amplitude=75 E) a lower filling rate was achieved, suggesting that with fix settings an accurate dosing is possible. Lower filling times in this study were observed only by increasing the fill weight variability (using acceptance ranges during dosing) and faster dosing by using the restricted PID controller [56].

6. Summary and Conclusion

Within this work a vibratory sieve chute system that can be operated at various frequencies and amplitudes is examined in terms of continuous feeding applications and its capability for low (or micro) dose capsule filling. The analysis of the vertical vibrations revealed irregular but recurring oscillations. The maximum accelerations were similar for various frequencies and increased with increasing in amplitudes. The highest accelerations were observed during the upward movement, which caused powder spilling for some amplitude and frequency combinations [56].

The operating space, i.e., settings that facilitate a steady flow of powder onto the chute, was determined for three inhalation carriers. Further studies of the filling rates revealed that via the described set-up feeding with variations below $1\, mg/s$ was feasible for feed rates in the range of $30 - 40\, mg/s$. Hence the described vibratory sieve chute system is suitable for continuous (micro) feeding applications. However, a monotone increase of the filling rate with either frequency or amplitude was not observed. In order to obtain a desired feeding with a high accuracy we recommend screening for amplitudes and frequencies that feature low fill rate variations. The feed rate can be tuned afterwards via the number of holes in the sieve [56].

The performed low-dose studies showed that capsules can be filled with $2.5\, mg$ and a fill weight variability below 5 % in less than one second. If filling time is of no interest, the presented system is capable of dosing with almost any accuracy, only limited by the accuracy of the integrated capacitive weight control. The slower the capsule is filled (e.g., by sealing sieve holes) the easier it is to stop the dosing on time. However, the key for accurate and fast dosing is a homogeneous powder distribution on the chute [56].

The results of this work are used as basis for the recently published paper by Besenhard et al. [56] and hopefully will induce interest in further studies.

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