European Journal of Pharmaceutics and Biopharmaceutics xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research Paper

# Accuracy of micro powder dosing via a vibratory sieve–chute system

M.O. Besenhard [a,b,1], E. Faulhammer [a,b,1], S. Fathollahi [a], G. Reif [b], V. Calzolari [c], S. Biserni [c], A. Ferrari [c], S.M. Lawrence [d], M. Llusa [a], J.G. Khinast [a,b,*]

[a] Research Center Pharmaceutical Engineering (RCPE) GmbH, 8010 Graz, Austria
[b] Graz University of Technology, Institute of Process and Particle Engineering, 8010 Graz, Austria
[c] MG2, Via del Savena 18, I-40065 Pian di Macina di Pianoro, Bologna, Italy
[d] GlaxoSmithKline (GSK), New Frontiers Science Park, Harlow, Essex CM19 5AW, UK

ARTICLE INFO

*Article history:*
Received 24 February 2015
Revised 23 April 2015
Accepted in revised form 29 April 2015
Available online xxxx

*Keywords:*
Micro dosing
Micro feeding
Capsule filling
Vibratory sieve
Online scale
Lactose

ABSTRACT

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



## 1. Introduction

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

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

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

For accurate low-(or micro-) dosing, gravimetric techniques are better suited. Micro-dosing via vibrating capillaries or rods [31–33] (also in the ultrasonic regime [9,34,35]) is a promising low-dosing and feeding technique, which is currently investigated for solid-dosing applications. For example, it was reported that highly accurate low dosing (relative standard deviation of fill weight below 5%) can be performed via the "pepper-shaker" principle (MG2 Microdose, Capsugel Xcelodose®S or 3P Innovation Fill2weight) for capsule filling [36,37]. Furthermore, micro-feeding (<1 mg/s) has successfully been performed via auger methods [38,39] and vibratory channels [9,40,41] and vibrating spatulas [42].

* Corresponding author at: Graz University of Technology, Institute of Process and Particle Engineering, 8010 Graz, Austria. Tel.: +43 (316) 873 30400; fax: +43 (0) 316 873 30402.
*E-mail address:* khinast@tugraz.at (J.G. Khinast).
[1] First authorship equally shared.

http://dx.doi.org/10.1016/j.ejpb.2015.04.037
0939-6411/

**Nomenclature**

*Abbreviations*

| | |
|---|---|
| $A$ | amplitude |
| API | active pharmaceutical ingredient |
| BD | bulk density |
| CI | Carr index |
| DPI | dry powder inhaler |
| $F$ | frequency |
| FFC | flow function |
| PID | proportional integrative derivative |
| PSD | particle size distribution |
| RSD | relative standard deviation |
| RH | relative humidity |
| SV | sieved |
| TD | tapped density |

*Symbols*

| | |
|---|---|
| $C_{filled}$ | filled capsule |
| $C_{empty}$ | empty capsule |
| $\varepsilon$ | difference between target weight and fill weight |
| $fw$ | fill weight |
| $fw_{target}$ | target fill weight |
| $k_{cal}$ | calibration factor of the capacitive scale |
| $K_d$ | DERIVATIVE constant of PID control |
| $K_i$ | integrative constant of PID control |
| $K_p$ | proportional constant of PID control |
| $\sigma_1$ | consolidation stress |
| $\sigma_c$ | unconfined yield strength |
| $t_i$ | $i$th time step |
| $x_{10}, x_{50}, x_{90}$ | 10%, 50% and 90% of the PSD reside below the particle size $x$ |

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

## 2. Materials and methods

### 2.1. Materials

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

### 2.2. Material characterization

Particle size, density and flow behavior were investigated and each measurement was done in triplicate ($n = 3$).

#### 2.2.1. Particle size characterization

Particle size distribution was determined using laser light diffraction technique (HELOS/KR, Sympatec GmbH, Clausthal-Zellerfeld, Germany). A dry dispersing system (Rodos = L, Sympatec) and a vibrating chute (Vibri, Sympatec) were used for powder dispersion. A dispersion pressure of 2.5 bar was applied. The typical sampling time was 30 s. Evaluation of the data was performed using the software Windox 5 (Sympatec).

#### 2.2.2. Bulk density and tapped density

The bulk (BD) and tapped densities (TD) were analyzed (Pharmatest PT-TD200) via a standardized method described in the United States Pharmacopeia (USP 2011, ⟨616⟩). A certain mass of powder was filled into the cylinder and the level was recorded. The tapped density was attained after mechanically tapping the powder sample. Carr's Compressibility Index (CI) is a density-based index assessed out of TD and BD and indicates how a powder changes its density upon tapping. Large changes indicate poor flowability.

#### 2.2.3. Powder flow measurements

The flow function (FFC) was measured using the FT4 Powder Rheometer (Freeman Technology, UK) adjusted with a 1 ml shear cell module at a maximum pressure of 3 kPa. FFC is the ratio of consolidation stress, $\sigma_1$, to unconfined yield strength, $\sigma_c$. A high FFC value indicates that the powder should flow well.

Respitose SV003 is a sieved carrier (for inhalation APIs) and SV010 is a coarse sieved carrier. Both have a narrow particle size distribution (PSD). InhaLac 230 (Meggle, Germany) is a sieved carrier with the lowest PSD of the investigated samples. The three carrier systems had similar values of bulk and tapped densities. An overview of the particle sizes and powder flow attributes of these materials is provided in Table 1 [29]. As can be seen Respitose SV010 had a slightly better flowability than the other powders. All three powders were in a range of "close to good" flowability, with CI < 15 indicating good flowability and CI > 25 indicating poor powder flow behavior. The FFC of the powders indicates good flowability in all cases, with Respitose SV003 having the best value.

### 2.3. Process and equipment

#### 2.3.1. Vibratory sieve chute system

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

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



Please cite this article in press as: M.O. Besenhard et al., Accuracy of micro powder dosing via a vibratory sieve–chute system, Eur. J. Pharm. Biopharm. (2015), http://dx.doi.org/10.1016/j.ejpb.2015.04.037