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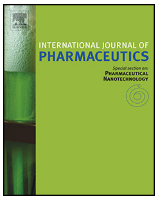

Continuous feeding of low-dose APIs via periodic micro dosing

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ABSTRACT

Precise and effective feeding of small powder quantities remains a challenge in many fields, including pharmaceutical development and production. This paper demonstrates that a simple feeding principle can be applied to accomplish stable micro feeding (<100 mg/s) and describes a gravimetric powder feeding system with a vibratory sieve mounted on a chute. Feeding was induced via vertical vibrations that can be adjusted within a broad range of frequencies and amplitudes. The feeding system was studied using different frequencies, amplitudes, sieves and powder properties. Feeding was characterized by means of a dynamic scale and high-speed camera recordings. The feeding system provided effective powder feeding even in a range of 1–2 mg/s. It was shown that powder properties require special attention when the vibratory sieve-chute system operates at higher feed rates (or feeding times >30 min), i.e., feeding at a higher throughput.

A combination of discrete element method (DEM) simulations and compartment population balance model (PBM) was used to incorporate the proposed micro feed system into a continuous powder mixer (Gerike GCM250; Gerike Holding LTD., Regensdorf, Switzerland). It illustrates how oscillating feeding rates (the latter is a characteristic of the studied micro feeding system) affect the content uniformity of low dose blends, i.e., powder mixtures with a relatively low fraction of active pharmaceutical ingredient.

1. Introduction

Handling small quantities of powder is a common practice in pharmaceutical development, which is currently gaining importance in the pharmaceutical production due to new operation procedures and manufacturing strategies, including accurate and robust strategies for micro feeding (<100 mg/s) of powders. Another aspect is the increasing fraction of high-potency active pharmaceutical ingredients (HPAPI) in the development pipelines with only a few mg of active substance in the formulation (Mehrotra, 2015). Direct dosing of API into capsules (Edwards, 2010; Faulhammer et al., 2014), generating low-dose blends for HPAPIs (Bi et al., 2011; Zheng, 2009) and creating seeding strategies for crystallization processes (Nagy and Braatz, 2012; Besenhard et al., 2015a) are just a few instances in which robust powder feeding at feed rates of several milligrams per second is required. In addition, in several flow chemistry applications, direct powder feeding into a fluid stream would eliminate sampling issues associated with feeding from a reservoir suspension (Timothy Noël and Yuanhai Su, 2015; Liedtke et al., 2015; Besenhard et al., 2014). Yet powder feeders that allow sufficiently low feed rates are unavailable, especially with feeding rates <5 mg/s. With regard to such small powder quantities, the influence of powder/wall interactions cannot be neglected due to a high surface-to-volume ratios, e.g., in small cavities, channels or tubing. Since gravitational forces are comparatively small, inter-particle forces become important. Overall, feeding strategies for micro feeders thus differ from those for common powder feeders (Levy and Kalman, 2001; Masuda et al., 2006; Vetter, 2001).

There is no strict distinction between powder dosing (i.e., dispensing discrete powder entities) and feeding (i.e., permanent outflow of powder). By increasing the dosing frequency (i.e., number of powder releases per time) and decreasing the amount of dispended powder, multiple powder dosing events may be considered feeding. Hence, micro-dosing systems can serve as micro feeders based on the feeding requirements. As discussed in (Besenhard et al., 2015b), dosing of small powder entities is relevant in the field of granular 3D printing that became state-of-

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Nomenclature

Abbreviations

A	Amplitude
AoR	Angle of repose
API	Active pharmaceutical ingredient
AR	Aspect ratio
BD	Bulk density
BDF	Backward differential formula
BU	Blend uniformity
CI	Carr index
CU	Content uniformity
DEM	Discrete element method
E	Entities (amplitude unit)
F	Frequency
HPAPI	High-Potency active pharmaceutical ingredients
PBM	Population balance model
PSD	Particle size distribution
RSD	Relative standard deviation
R.H.	Relative humidity
SV	Sieved
TD	Tapped density
USP	United States pharmacopeia

Symbols

x_{10}, x_{50}, x_{90}	10, 50 and 90% of the PSD reside below the particle size x
$F_{\min}$, $F_{\max}$	Minimum and maximum Feret diameters
d_{hole}	Sieve hole diameter (all hole are of the same size)
f	Number of particles
a	(vertical) acceleration of the sieve
t	Time
n	Component number ($n = 1 \equiv$ API; $n = 2 \equiv$ excipient)
x, y	Spatial coordinates in axial and radial directions respectively
$\dot{f}_{in}$	Rates of particles entering the mixer
$\dot{f}_{in}$	Rate of particles exiting the mixer
fr	Feeding rate
nfr	Net feeding rate (i.e., the relative amount of time powder actually exits the sieve)

the-art in the recent years (Yang and Evans, 2003; Yang and Evans, 2007). Several recent developments and micro dosing/feeding prototypes address free-forming method, such as 3D printing.

Table 1 provides an overview of micro feeders and their feeding principles. Many of them involve small capillaries that obstruct the powder flow via arching, plugging and blocking (Lu et al., 2006) in the absence of agitation. Vibration-assisted powder feeding through a narrow orifice is a well-established concept (Jasion et al., 2013). However, due to strict regulatory requirements with regard to the dose and content uniformity, pharmaceutical processes require highly accurate dispensing and feeding.

This paper describes micro feeding via a gravimetric powder feeding system with a vibratory sieve mounted on a chute. While our earlier work (Besenhard et al., 2015b) focused on micro dosing of capsules via a vibratory sieve-chute system, the current one addresses the micro feeding properties of such a system. The feeder was tested in terms of feasible feed rates, feed robustness and reproducibility. A compartment model that utilizes Discrete Element Method (DEM) simulation results was used to investigate how a micro feeder can be incorporated into a continuous powder mixer in order to generate a low-dose blend. The model predicts the content uniformity achieved during ideal micro feeding and in the presence of feed rate fluctuations, which are typical during vibration-assisted powder feeding.

2. Materials and methods

2.1. Materials

In this study, two powders (hereinafter referred to as powder I and powder II) of inhalation-grade α-lactose monohydrate with different particle sizes and supplied by different manufacturers (DFE Pharma, Goch, Germany and Meggle, Wasserburg am Inn, Germany), as received. The same powders were used in our previous work (Besenhard et al., 2015b), which contains a detailed description of the characterization procedures. Since new powder samples, i.e., new batches, were provided for this study, powder properties were characterized again (see Table 2, the results are in good agreement with Besenhard et al., 2015b). Properties not mentioned in (Besenhard et al., 2015b) were determined as described below.

2.1.1. Particle size characterization

QICPIC (OASIS/L dry dispersing system Sympatec, Clausthal-Zellerfeld, Germany) was employed to measure the size (volumetric mean diameter, VMD and median particle size) and shape of millions of particles in each sample via dynamic image analysis. Two-dimensional images of a particle were interpreted in terms of the minimum and maximum Feret diameters ($F_{\min}$, $F_{\max}$). Aspect ratio (AR) is the ratio between $F_{\min}$ and $F_{\max}$ that describes the shape of particles. Its value can be between 0 and 1. It reflects the deviation of its shape from a sphere. The higher the value is, the more spherical the shape is. Particle size distributions (PSDs) of powders I and II are shown in the Supplementary Information (SI 1: Particle Size Distribution of the Powders).

2.1.2. Density and flow characteristics

The bulk (BD) and tapped densities (TD) were analyzed (Pharmatest PT-TD200; Pharma Test, Hainburg, Germany) via a standardized method described in the United States Pharmacopeia (USP 2011, 616). The powder was filled into a cylinder and the level was recorded. The tapped density was attained after mechanically tapping the powder sample and recording the level again. The two levels were used to estimate the flow index (Carr's compressibility index). The Angle of Repose (AoR) was determined using a glass funnel described in the pharmacopoeia (USP 2007, 1174).

2.2. Vibratory sieve chute system

The study was performed using a feeder with a vibratory sieve (oscillating vertically) mounted on a chute (2.5 cm) and directing the powder into an orifice, i.e., the outlet as shown in Fig. 1. A feeding unit of the MG2 Microdose® (MG2; Bologna, Italy) stand-alone unit, i.e., a capsule filler, was used, with the chute tilted at a fixed angle of 5° and the sieve fixed on top. The sieve had six holes, all with a diameter of d_{hole} = 0.7 mm. Feeding was studied with a varying number of sieve holes (min. 1–max. 5).

The system allowed for vibrations within a broad range of amplitudes and frequencies that were set independently. The amplitude setting refers to the driving force of the linear voice coil motor moving the sieve-chute system vertically. In this work, the driving force was quantified by the entity*E*. A detailed description of the vibratory sieve chute system, including an analysis of the vertical accelerations profiles, is presented in (Besenhard et al.,