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The effect of material attributes and process parameters on the powder bed uniformity during a low-dose dosator capsule filling process

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ABSTRACT

The objective of this work was to assess the effect of process parameters of a dosator nozzle machine on the powder bed uniformity of inhalation powders with various characteristics during a low-dose dosator capsule filling process. Three grades of lactose excipients were extensively characterized and filled into size 3 capsules using different dosing chamber lengths (2.5, 5 mm), nozzle diameters (1.9, 3.4 mm), powder bed heights (5, 10 mm) and filling speeds (500, 3000 capsules/h).

The fill weight and the weight variability of Lactohale 100 (large particles, good flowability, low cohesion) remained almost the same, regardless of the process parameters throughout the capsule filling run time. Moreover, for this powder an increase in the fill weight at a higher filling speed was observed in all cases. Fill weight variability was significantly higher for lower dosing chamber volumes at a filling speed of 3000 capsules per hour. Lactohale 220 (small particles, poor flowability, high cohesion) delivered entirely different results. After a certain run time, depending on instrumental settings, a 'steady-state' with constant fill weights and low weight variability was achieved. For this highly cohesive powder, a high dosing chamber volume requires a low filling speed in order for the powder to completely fill the dosator nozzle. Moreover, it was established that a dosing chamber length of 2.5 mm and a powder bed height of 10 mm were required due to the powder's high fill weight variability over time, while the dosator size had no effect on it.

In summary, the layer uniformity, the fill weight and the weight variability strongly depend on the powder characteristics and the instrumental settings. The results indicate that Lactohale 220 requires special attention during low-dose capsule filling. The study presents excellent insights into the effect of material attributes and process parameters on the layer uniformity and the quality of end product.

1. Introduction

Capsule filling is widely applied in the pharmaceutical industry. Different methods exist, including tamping systems and the nozzle-dosator technique, which is especially relevant for filling capsules for inhalation application (Faulhammer et al., 2014a). Precise dose filling in the lower *mg*-range, which is required for inhalation therapies (Kou et al., 2012), is essential for the successful manufacturing of high-quality products. One of the greatest challenges for effectively developing low-dose inhalation products is dose uniformity (Islam and Cleary, 2012). Although several studies have reported that many powder and processing parameters affect the quality of filled capsules (Faulhammer et al., 2014b; Nalluri et al., 2013; Podczeck and Newton, 1999, 2000; Patel and Podczeck, 1996; Tan and Newton, 1990a,b) little research has been performed with regard to low-dose dosator capsule filling processes. To the best of our knowledge, the studies of Faulhammer et al. (2014a) and Seyfang et al. (2014) were the first attempts to scientifically qualify dosator nozzles for low-fill-weight capsule filling. In these systems the powder is forming a layer in a rotating bowl from which periodically material is sampled via the dosator nozzle and filled into empty capsule bodies. The main challenge in

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Nomenclature

API	Active pharmaceutical ingredient
BD	Bulk density
CMA	Critical material attribute
CPH	Capsules per hour (filling speed)
CPP	Critical process parameter
CQA	Critical quality attribute (capsule fill weight and weight variability)
DCL	Dosing chamber length
DIA	Dosator diameter
DOE	Design of experiments
DPI	Dry powder inhaler
LH	Lactohale
PAT	Process analytical technology
PBH	Powder bed height
RSD	Relative standard deviation (weight variability)
TD	Tapped density
USP	United States Pharmacopeia
VMD	Volumetric mean diameter

their experiments was the powder layer inhomogeneity of very fine powders with low density particles, i.e., particle sizes smaller than 10 μm, exhibiting poor flowability and high cohesivity (Faulhammer et al., 2014a; Seyfang et al., 2014). Currently, no systematic understanding exists of how the evolution of the powder layer during the capsule filling contributes to such critical quality attributes as the fill weight and the weight variability.

The objective of this work was to assess the effect of process parameters of a dosator nozzle machine on the powder bed uniformity of powders with various characteristics during a low-dose dosator capsule filling process. A lab-scale, low-dose dosator nozzle capsule filling machine (Labby, MG2, Bologna) with special low-dose equipment adaptations (i.e., smaller nozzles, a cleaning unit for the removal of excess powder from the dosator, special blades to create the powder layer) was used in this study. The evolution of the powder bed for three grades of lactose and the combination of various process parameters was assessed by measuring the weight of filled capsules for a total run time of 30 min. The effect of combinations of various material attributes and process parameters was investigated with respect to fill weight and weight variability over time. Compared to previous studies in the field of assessing the capsule filling performance, a key strength of this study was the ability to demonstrate the changes in fill weight and weight variability not only depending on the instrumental settings, but also their changes over time.

This study provides new insights into the significance of powder layer monitoring during a low-dose dosator capsule filling process in order to achieve product-specification compliance.

2. Material and methods

Three grades of lactose excipients commonly used as carriers in inhalation therapies (Kou et al., 2012) were used as received from the supplier (DFE pharma). The sieved Lactohale 100 and two milled powders Lactohale 200 and Lactohale 220 were selected since for powders with different characteristics (such as compressibility) a certain combination of instrumental settings is required in order to successfully fill capsules with a dosator nozzle machine. A recent study by Faulhammer et al. (2014a) describes the processability of two groups of powders (group 1–coarse carriers; group 2–fine carriers and API). In our study the described classification of powders will be extended by introducing another group – 'intermediate group' – to enhance the process understanding. Each of the three used lactose excipients will act as a representative for one group. Table 1 shows the parameters which were used for grouping the powders. In order to minimize manufacturer and batch-to-batch variations, experiments were carried out using powders from one batch and one supplier (DFE pharma).

2.1. Powder characterization

All experiments were carried out under controlled environmental conditions (20–24 °C, 40–60% relative humidity). The following material attributes were established in triplicate: Particle size was measured via QICPIC (OASIS/L wet and dry dispersing system, Sympatec GmbH, Clausthal-Zellerfeld, Germany) and Helos KR (Sympatec GmbH, Clausthal-Zellerfeld, Germany). Dynamic image analysis of millions of particles in each sample was performed to determine the size distribution and the volumetric mean diameter (VMD) and median particle size.

The bulk (BD) and tapped densities (TD) were analyzed using the Pharmatester (PT-TD200) and the standardized method described in the United States Pharmacopeia (USP 2015). To this end, a certain mass of powder was filled into a cylinder and the level was recorded. After mechanically tapping the powder sample, the tapped density was determined. The true density was measured with a helium pycnometer (AccuPac II 1340, Micromeritics, Norcross, USA).

The compressibility, air permeability, flow function coefficient, cohesivity, angle of internal friction, basic flowability energy and wall friction angle were measured with the FT4 powder rheometer (Freeman Technology, Malvern, United Kingdom). Compressibility was determined by assessing the volume change of a conditioned sample when it was compressed under a specific normal force. For this purpose, the conditioned sample was compressed with normal forces starting at 0.5 kPa up to 15 kPa. The ratios between the density and bulk density of each compaction step were recorded. Air permeability was measured by transmitting air through a bulk and detecting the air pressure drop across the powder bed. Pressured dry air (2 mm/s air velocity) was used for the permeability test. In order to determine the flow function coefficient and cohesion, a 1 ml shear-cell module at a maximum pressure of 3 kPa was used. High flow function coefficient values (>4, or more strictly >10) represent powders with good flowability. The cohesivity C provides information about inter-particle interactions due to electrostatic, capillary or van der Waals forces. The angle of internal friction for a given soil is the angle on the graph in Mohr's Circle (shear stress vs. normal stress) at which shear failure occurs. The basic flowability energy indicates the

Table 1
Material classification.

Group	Representative powder	Particle size x_{50} [μm]	Bulk density [g/ml]
Small	Lactohale 220	<10	<45
Intermediate	Lactohale 200	10–150	45–65
Large	Lactohale 100	>150	>65