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Research Paper

Mechanistic modeling of a capsule filling process

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A R T I C L E I N F O

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A B S T R A C T

Filling a dosator nozzle moving into a powder bed was investigated using the Discrete Element Method (DEM). Various particle diameters and contact properties were modeled. The simulations qualitatively showed the influence of powder properties on the amount of dosed powder. Two factors that influence the dosed mass were observed. First, the ratio between the particle and dosator diameters affects the packing of particles inside the dosator chamber. Second, the flow behavior of the powder significantly modifies its filling and compression behavior. Cohesive powders pack less densely inside the powder bed, which could lead to a lower amount of dosed powder. In contrast, cohesive powders are compressed more during dosing and the density inside the dosator chamber increases during the dosing process. Since the simulation of fine cohesive powders is numerically impossible due to a high number of particles and small simulation time steps, we applied a simple method for particle scaling to acquire a qualitative understanding of the filling behavior of coarse and fine powders.

1. Introduction

Hard capsules are next to tablets one of the most commonly used and prescribed oral dosage forms and were first introduced in the 19th century. The capsule is filled with powder or with pellets made by extrusion and spheronization. Capsules offer several advantages, including a reduction of excipients needed to achieve a designed pharmacokinetic profile. According to regulatory requirements, based on the needs and safety of patients, the content of capsules, i.e., the fill weight, needs to be constant within a certain narrow tolerance region. Moreover, content uniformity has to be ensured, i.e., segregation prior to the capsule filling step needs to be excluded. Fill weight variability and content uniformity are therefore considered critical quality attributes (CQAs) within the Quality-by-Design (QbD) framework. (Faulhammer et al., 2014b)

In the industry, several capsule filling techniques have been used over the last decades. These include tamping and dosator systems for hard-gelatin capsules (Podczeck et al., 1999). In addition, for low-dose capsules vacuum-roll techniques and vibration-based pepper-shaker systems are being used (Pinzon, 2012; Besenhard et al., 2015, 2016). In this study, dosator systems are considered. In a typical filling cycle, first a cylindrical (hollow) dosator nozzle plunges into an uncompacted powder bed stored in a rotating bowl (which is periodically refilled). The nozzle vertically dips into the powder bed until it reaches a prescribed minimum distance from the bottom. During this step, the powder enters the nozzle and is compressed to a predefined degree. Subsequently, the filled nozzle is lifted and removed from the powder bed. The nozzle is then placed on top of an empty capsule body and the powder is ejected into the capsule, after which the cap is placed onto the capsule body. A detailed review of the process is provided in (Jones, 2001). To prevent powder dropping from the nozzle before the powder is ejected into the capsule, a minimum stability of the powder plug inside the dosator chamber is required. Thus, the powder needs to be (lightly) compressed during the dipping step. In order to be able to control compression a moveable piston inside the dosator nozzle can enhance compression. The minimal compression stress is investigated in (Tan and Newton, 1990). However, the powder plug needs to be loose enough to allow rapid disintegration upon delivery, e.g., in case of capsules made for dry powder inhalers (DPIs) (Faulhammer et al., 2014a).

The filling volume of the nozzle is defined by its inner diameter and an adjustable piston, which defines the length of the dosator chamber. Since the volume of the chamber is exactly defined, this method is a volumetric dosing method. However, the critical quality attributes (CQA) of capsules are fill weight and fill weight variability. Thus, a constant fill weight is only achieved if the powder density is known and constant. Unfortunately, the density of a powder is highly variable and a strong function of many effects, including processing history, material properties, environmental conditions (such as humidity and vibrations) and the process parameters during compression. Even the surface texture of the dosator tools has to be considered as it is shown in (Jolliffe and Newton, 1983). Hence, controlling the final dosage mass is one of

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the biggest challenges associated with capsule filling processes, including dosator filling.

The influence of powder properties and process parameters on the capsule fill weight has been investigated experimentally by many groups (Patel and Podczeck, 1996; Podczeck and Newton, 1999, 2000; Pinzon, 2012; Llusa et al., 2013; Faulhammer et al., 2014b). Evidently, the densification of powder during the dipping step increases with powder compressibility and poorer flowability (leading to higher Hausner ratios). Moreover, the plug density is increased by the precompression ratio. The precompression ratio is defined as the ratio between the powder bed height and the dosator chamber length. The influence of the dosing speed is rather complex, since an increasing dosing speed leads to a higher rotational speed of the dosator machine, causing densification of the powder bed due to machine vibrations and other forces. In addition, the dosator nozzle dipping speed increases, and it is unclear, whether the influence of dosing speed is due to the densification of the powder bed or to the increased dipping speed of the nozzle. Likely, for different powders different effects are dominating. This example shows how difficult it is to acquire a full mechanistic understanding of the process via experiments alone. Lastly, the state of the powder bed in the bowl is unknown during industrial capsule filling. Depending on the capsule filling speed a few hundred to a several hundred thousand dipping events occur per hour, affecting the consistency of the powder bed. Although there are measures taken in a capsule filling machine to homogenize the powder and to sample from non-identical locations, the powder cannot *a priori* be assumed to be homogeneous. A homogeneous state of the powder in the bowl may be achieved only for materials with very good flowability (which in turn show a tendency to segregate). Nevertheless, no standard process-analytical tools are available to analyze the state of the powder in the bowl. (Pinzon, 2012)

Numerous experimental studies focused on linking material properties and process parameters to the critical quality attributes of capsules, i.e., average fill weight and fill weight variability, as for example (Faulhammer et al., 2014b). In contrast, modeling and simulation studies of the dosator capsule-filling process are rare. However, there are numerous groups working with simulation tools to describe other powder-based processes. For example, there are numerously simulation studies published dealing with die filling prior to compaction of tablets or the production of green bodies (Bierwisch et al., 2009; Tsunazawa et al., 2015; Guo and Wu, 2016). Similar to the dosator process, during die filling a fixed volume is filled with particles. Particles fall into the cavity due to gravity during die filling, and therefore, it is not directly comparable to the dosator process. Nevertheless, a constant filling mass is crucial for both processes. Another related process is the coil feeding process which can also be used for dosing. A coil feeder with cohesive powder was investigated with the discrete element method by (Imole et al., 2016).

As mentioned above, a mechanistic modeling of the dosator process itself has not been reported so far. However, a theoretical consideration of the dosator process can be found in (Jolliffe et al., 1980). This work deals with the retention of the powder inside the nozzle. It shows, that the interaction of the powder and the wall material is important for the capsule filling ability of powders. A phenomenological model proposed by (Khawam, 2011) takes precompression densification and compression density into account. However, a deeper mechanistic understanding of the process is required. (Rowe et al., 2005) simulated the packing behavior of various pellet shapes inside a hard capsule using a Monte Carlo method. This study was enhanced by (Ali et al., 2009). Although the results are not directly applicable to the dosing process, as they do not involve the movement of piston inside a powder, they describe how particle size and shape influence packing inside a closed chamber.

In the current study, the dosator capsule-filling process is studied using a mechanistic modeling tool. Specifically, the Discrete Element Method (DEM) is applied in this work. This method offers the opportunity to freely modify powder properties and to observe quantities that are not measurable experimentally. As such, it is a great complementary tool to experiments. Nevertheless, many simplifications are required to set up a simulation that can be run within a reasonable time and thus, modeling of the filling process is only a first step towards the rational design of capsule filling processes.

2. Methods

In our study, the discrete element method DEM introduced by Cundall and Strack (Cundall and Strack, 1979) was used to investigate the filling of a dosator nozzle. This method relies on the soft-sphere approach, with particles represented as (overlapping) spheres. The contact forces between two particles in the normal and tangential directions are computed as a function of the particle overlap. The contact law comprises the functional relationship between the particle overlap and the contact force and is the core of the DEM model. The particle position and velocity are computed at every simulation time step by solving Newton's second law. Since particle rotation in dense packed beds considered here is of minor importance the particle rotation is not considered in the simulation. This way, the position of every particle in the powder is tracked during the entire simulation. The open source DEM software LIGGGHTS® (Kloss et al., 2012) was used for that purpose.

2.1. Geometric setup

To simulate the dosator filling process, particles with nominal diameters of 500, 300, 200, 100 and 75 μm were allowed to settle on a fixed base in order to create a powder bed height of 8 mm. Since in DEM no ambient air is considered and particles could accelerate indefinitely, a viscous damping force is applied to get a terminal velocity of 0.1 m/s. Thus, compaction of the powder bed due to unrealistic high impact velocities can be avoided. To limit the computational effort, we only considered a section of the powder bed with a width of 12 mm both in the x- and y-directions (see Fig. 1). To compensate for the limited size of the powder bed, the boundaries of the domain were set to be periodic, meaning that a particle leaving one side of the boundary was inserted at the opposite side. This geometrical setup allowed to simulate approximately 3.5 million particles with a nominal diameter of 75 μm. To avoid modeling artefacts due to monodisperse particles a mass-based particle size distribution is used (see Fig. 2). A rather narrow distribution is used to avoid additional computational costs due to a high number of small particles. The diameter of the dosator nozzle was chosen to be 3.4 mm, which is a standard diameter also used in the

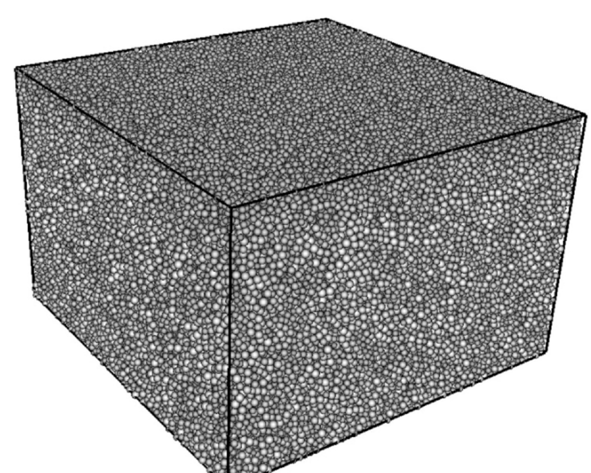

Fig. 1. Initial powder bed in the dosator filling simulation. Periodic boundary conditions are used in both horizontal directions.