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Original Research Paper

Simulation of particle size segregation in a pharmaceutical tablet press lab-scale gravity feeder

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ABSTRACT

The die filing process within a lab-scale rotary tablet press is simulated using the Discrete Element Method (DEM). Powder is transferred from a gravity feeder (comprising of a cylindrical pipe, an inclined chute, and a rectangular box) into rotating dies. Spherical shape micro-crystalline cellulose particles serve as an experimental pendant to measure the particle size distribution (PSD) and to calibrate the micro-mechanical material properties entering in the DEM calculations. At first, the die filling process of the particles having poly-dispersity in size is explored by analyzing the basic metrics such as tablet mass, tablet mass variation, and mass flow rate. Particle size segregation is investigated by computing the PSD development in different locations of the feeding system and in the filled dies. In addition, particles' velocity and coloring analysis (both qualitative and quantitative) are performed. Results show that different zones of the system are involved in various powder flow phenomena constituting varying particle size segregation causes. Next, the micro-mechanical properties, namely inter-particle cohesion, particle-particle and particle-wall friction, are varied one at a time to shed light on their influence on the particle size segregation and tablet quality. Finally, the influence of different material properties on various metrics are compared with each other providing a guide towards formulation optimization resulting in optimal tableting process performance.

1. Introduction

Today solid dosage formulations constitute the most frequent administration route of drug substances arising from outstanding advantages of tablets as dosage forms. Some of them are for instance the ease of handling, high production rates at low cost, and self-administration providing patient compliance [1]. Tablets are produced in industrial scale on high speed rotary tablet presses with a productivity of e.g. max. 1.6 million tablets per hour [2]. The production process can be divided into three distinct stages comprising die filling, compaction, and ejection. Each of them represents various challenges when it comes to tablet product quality according to the Ph. Eur. [3]. Those requirements are the "friability of uncoated tablets" [2.9.7], the "resistance to crushing of tablets" [2.9.8], the "disintegration of tablets and capsules" [2.9.1], the "uniformity of dosage units" [2.9.40], and eventually the "dissolution test for solid dosage forms" [2.9.3] [3]. However, all of the distinct process stages are intertwined with each other as well as with the product quality requirements. Hence in 2009 the International Council for Harmonisation (ICH) adopted the Quality by Design (QbD) paradigm for process development by introducing the ICH guideline Q8 to "build quality into products by design" using pharmaceutical development [4]. There are several options on how to implement the QbD approach into science-based manufacturing of pharmaceuticals such as process analytical tools, design of experiments, and implementation of risk management strategies but also process modeling and control via numerical simulations, see also [5].

As the die filling stage during manufacturing defines the accurate mass as well as content and content uniformity of the active pharmaceutical ingredient (API) it has been focused by experimental [6] and more recently by numerical research. In 2003 the first experimental system was mentioned to describe die filling in a model setup [7]. This system contained a stationary die and a moving delivery system (shoe) providing the opportunity to determine flowability and the amount of powder collected in the die as a function of the shoe velocity [7]. It has also been used by others supporting process understanding of powder delivery into a confined space with respect to the influence of particle size and

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density, of air and vacuum, and of gravity and suction filling [7–14]. In parallel to experimental studies the same system or adapted versions have been used as a framework for numerical simulations [11,15,13,16–23]. The geometry of these systems rather resembles an eccentric feed press [24] limiting its transfer to the pharmaceutical process. In high speed tableting the dies are moving underneath the delivery system which can be either shoe, hopper, or feed frame [25]. This shortcoming has been eliminated by [26,27] in which the powder is delivered in either a translating [26] or rotating [27] die. Recently much more complex systems found in rotary tablet presses with a closed feed frame system consisting of one or more paddle wheels which force incoming powder to pass into the dies of the rotating turret were developed [28–31].

Besides the limitations of the geometrical configurations, the numerical setups constitute additional restrictions that impede process understanding. Those include the much larger particle size (e.g. [27–31]) and the significantly differing material properties [28] considered compared to pharmaceutical powders. In addition, the powder stress level in some of the studies is either not including the normal stress exerted by powder mass in the feeding hopper (e.g. [26]) or lacks the re-filling of particles as mass is being discharged into the dies (e.g. [29,30]).

Even though the poly-disperse particle size nature of pharmaceutical powders significantly affects the product quality [32,33] it has only been taken into account by very few numerical studies [23,26,29–31] due to high computational effort. For the model-die filling system proposed by Wu et al. [11] Guo et al. [19] showed that the mass flow rate is higher in case of poly-disperse particles compared to mono-disperse particles. In addition, different fines concentrations were identified along the die width and height [20]. In a similar geometrical setup, Furukawa et al. [26] showed that the percolation of small particles which progressed in the feed shoe before particles were discharged into the die influenced segregation to a greater extent than die velocity. Mateo-Ortiz et al. [29] detected particle size segregation at low paddle wheel speeds in the feed frame of a Manesty Beta Press.

Particle segregation, e.g. defined as the "unintentional demixing of one or more components in a mixture of particulates" [34], could be triggered by different physical mechanisms that can be classified by the physical particle properties [35] as well as the energy input [36]. For the former absolute particle size, particle size ratio, particle size distribution, fine particle concentration, particle shape, particle density, and particle flowability can be named [37]. Furthermore different means to avoid, or control/limit segregation, e.g. choosing an optimal interparticle cohesion, have been suggested [38]. However, only very little is known about particle size segregation during the tableting process impairing API content and uniformity [39].

Numerical simulation of powder flow from a gravity feeder to the dies within a lab-scale rotary tablet press [27] provided a comprehensive insight into the impact of process and material attributes on the performance of the die filling process. The micro-mechanical material properties such as cohesion, friction, and the coefficient of restitution were systematically investigated and their influence on different performance parameters analyzed. Even though this work emphasized the importance of understanding the effect of material and process attributes, the particles considered were still equal sized granules. Reference is missing when it comes to the awareness of particle size segregation of materials having a poly-disperse particle size distribution under differing material properties. Consequently, the objectives of this work using three-dimensional discrete element method (DEM) simulations include a detailed investigation of particle size distribution in the system of Gopireddy et al. [27]. Moreover this study is the first of its kind investigating comprehensively the influence of particle properties on size segregation within an actual pharmaceutical application system.

2. Methodology

This section presents the details about the mathematical approach, geometrical configuration as well as the numerical simulations performed.

2.1. Discrete element method

After the introduction of the DEM in 1979 [40] it has evolved over almost 40 years to a well-known approach in particle technology and it is being used for different applications. This numerical model captures the trajectories of each and every particle in the system through Newton's equation of motion offering the main advantage, compared to the continuum approach, of high resolution in particulate flows. The details about the theory and algorithms are not the scope of this work but are well described in literature [41–43].

All computations in this study were performed using the open source DEM software known as LIGGGHTS [44], version 3.2.1. The normal and tangential forces were modeled by the Hertz and the Mindlin & Deresiewicz theories, respectively [45]. The non-contact inter-particle force other than gravity was included through the simplified Johnson-Kendall-Roberts (JKR) model [46]. All the force models as well as their implementation in LIGGGHTS are given by Kloss et al. [47] and the same models given by Gopireddy et al. [27] were used in this study.

The impact of air on the particles was assumed to be negligible due to the dense particle packing and the closed system (tableting machine). This assumption was shown to be valid in the earlier studies [21,27].

2.2. Geometrical setup

The geometrical configuration consisted of a rectangular shoe, which was connected to a feeding system similar to actual tablet presses, and a rotating die table. This system is shown in Fig. 1, and it is identical to Gopireddy et al. [27], so detailed dimensions can be found in the same. The geometry was constructed with the open source finite element mesh tool known as Gmsh [48] and later imported as physical boundaries into LIGGGHTS.

2.3. Material properties

As mentioned in the introduction, powder flow of a poly-disperse particle size distribution (PSD) was simulated. The PSD of VIVAPUR MCC Spheres 500 (JRS Pharma GmbH & Co. KG, Rosenberg, Germany), spherical particles of purely microcrystalline cellulose, was measured by laser diffraction (HELOS, Sympatec GmbH, Clausthal-Zellerfeld, Germany). The sizes and their corresponding density distribution (q_3) of the VIVAPUR MCC Spheres 500 were used to obtain the PSD in the simulation, as illustrated in Fig. 2. In total six different particle size fractions were modeled ranging from 167.5 to 402.5 μm out of which one particle size fraction (200–237.5 μm) with a proportion of 8.5% (w/w) served as the model "API", confer Section 3.1.2.4. The micro-mechanical properties (Table 1) as well as the particle density (1.6 g/cm^3) were set constant for all particle sizes. No individual value for different particle sizes have been set, rather the total bulk property was considered that is usually also assessed in powder flowability experiments. This implies that a given particle property, i.e. the cohesion energy density in which the contact area is a function

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