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Size-induced segregation during pharmaceutical particle die filling assessed by response surface methodology using discrete element method

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ABSTRACT

Discrete element method (DEM) combined with response surface methodology (RSM) was carried out for investigating the segregation behaviour of binary particles during die filling of the pharmaceutical tableting machine, which comprised a horizontally moving die equipped with a vertically moving bottom punch. To achieve accurate particle flow simulations, parameters of the pharmaceutical spherical granules were calibrated using experimental bounced height, rolling distance and angle of repose. These parameters were implemented in the DEM simulations and compared with experimental high-speed camera observations and measurements of the filling ratio. Simulations and experimental results showed reasonable qualitative and quantitative agreement, validating the simulation model. The validated model was employed to evaluate the segregation of binary particle mixtures and RSM was used for analysing the DEM results of the segregation. The RSM revealed that, unlike the die velocity, small particle size, horizontal position and vertical position affected the segregation index significantly. The segregation resulted from percolation of small particles between large particles in the feed shoe and bottom back corner of the die. DEM combined with RSM approach will become significantly efficient method to understand the process for implementing the quality by design approach.

1. Introduction

Tablets are a popular dosage form in the pharmaceutical industry. Their fabrication typically involves die filling, compaction and ejection steps conducted in a rotary tableting machine. During die filling, pharmaceutical powders consisting of active pharmaceutical ingredients (APIs), diluents, binders, disintegrants, lubricants and other substances are transferred from a hopper to the die via a feed shoe in a system equipped with a bottom punch that moves down. The tableting of these powders may be associated with segregation, which can severely affect the quality attributes of tablets, such as content uniformity, appearance, hardness and dissolution. Therefore, this manufacturing process needs to be accurately controlled. According to Virtanen et al. [1] and Lakio et al. [2,3], the particle size distribution in the tablet continuously changed during the tableting process, and segregation arose from the wide size distribution. Xie et al. [4] examined the segregation tendency between aspirin (ASP) and microcrystalline cellulose (MCC) using the ASTM D 6940-04 segregation tester. They concluded that segregation tendency increased as the particle size ratio between ASP and MCC increased by the analysis of variance (ANOVA) and principal component regression (PCR). In addition, the granulation process and the API properties result in inhomogeneous drug content in different granule size fractions [5–7]. This inhomogeneity significantly influences the uniformity of the tablet because granules with relatively high or low drug content undergo a size-induced segregation. In general, particle size affects cohesive forces between particles related to electrostatic, van der Waals and hydrophilic interactions as well as powder compactibility [8],

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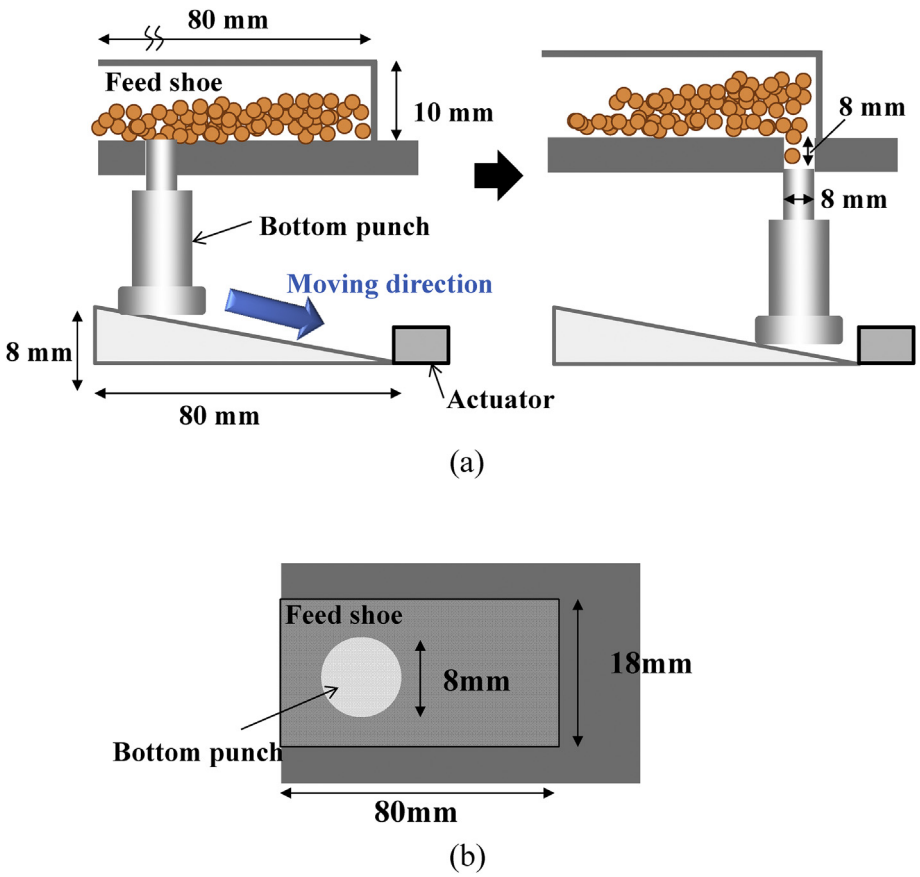

Fig. 1. Schematic representation of the simulation setup. (a) Side view and (b) top view.

leading to tableting issues such as sticking and capping. Several experimental studies have been conducted to quantify the segregation. However, a robust tableting process still requires in-depth understanding of particle flow mechanisms during die filling.

Several experiments have been performed to investigate powder flow behaviour between hopper and die [9–13]. Jackson et al. [9] and Sinka et al. [10] developed a fundamental understanding of pharmaceutical powder particle flow using a suction filling system. They also demonstrated that process parameters, such as shoe velocity and bottom punch motion, played an important role in enhancing tablet weight uniformity and productivity because suction filling efficiently delivered the powder in the die. Mills and Sinka [11] investigated the powder flow behaviour by gravity and suction filling using microcrystalline cellulose with different particle size and density and found that the critical shoe velocity was more significantly increased by suction than by gravity filling. Furthermore, their experimental evaluation of powder flow during die filling supported the parameter optimisation of rotary tableting. These experimental observations provide useful information on die filling. However, the analysis of single particle behaviour is necessary to understand segregation-related phenomena in more detail.

Discrete and finite element methods (DEM and FEM, respectively) are useful and reliable for analysing manufacturing processes because they determine individual particle movement and powder bed deformation, respectively. These methods have been exploited to model various pharmaceutical manufacturing processes, such as milling, granulation, blending, tableting and coating [14,15]. The DEM approach is attractive as it may find use in the optimisation of process design and parameters needed to establish a robust manufacturing process, as recommended by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Q8(R2) guidelines [16]. Moreover, it has proven valuable for assessing the particle flow and segregation during die filling. Its combination with computational fluid dynamics (CFD) has provided insight into the effect of particle density, particle charge and air on the powder filling behaviour of metal and pharmaceutical particles [17–22]. Mateo-Ortiz et al. [23] investigated the particle size segregation inside a feed frame fitted with two paddle wheels by DEM. Their results revealed that the paddle wheel speed contributed the most to the percolation-induced size segregation. Wu et al. [24] conducted a die filling simulation using a fixed bottom punch for pharmaceutical tableting. The effects of particle shape and size distribution on the size-induced segregation during container filling have been analysed by DEM and a percolation process has been evaluated using a screening model [25]. Although previous studies help us to understand the fundamental knowledge for some filling processes, the characteristic rotary tableting system consisting of moving bottom punch and fixed feed shoe does not fully understand.

This study aimed to establish a fundamental understanding of particle flow during die filling by combining moving bottom punch and fixed feed shoe and the segregation of binary particle mixtures during a simple filling process. The effect of die velocity on the filling behaviour and segregation of different sized particles was assessed by simulating the filling process of spherical purified sucrose granules, which have been widely used as core particles for pellets coated with functional films [26–28]. DEM parameters were determined through laboratory experiments, and simulation results were validated by comparison with filling experiments. The filling behaviour of monodisperse particles was evaluated. The segregation of binary particle mixtures was assessed by DEM simulations using the validated DEM parameters and the resulting