Powder Technology 289 (2016) 79–87

Contents lists available at ScienceDirect

Powder Technology

journal homepage: www.elsevier.com/locate/powtec

Investigations of single microcrystalline cellulose-based granules subjected to confined triaxial compression

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ARTICLE INFO

Article history:
Received 2 September 2015
Received in revised form 20 November 2015
Accepted 21 November 2015
Available online 22 November 2015

Keywords:
Compression
Triaxial
Hydrostatic
Single granules
Confined conditions
Contact mechanics

ABSTRACT

Confined triaxial compression of single granules was performed in order to assess the contact force development and modes of granule deformation under these conditions. In the study, four microcrystalline cellulose-based granule types of different characteristics were investigated. Results from triaxial single-granule compression experiments were evaluated using an analytical model as well as by comparison to unconfined single-granule compression and to confined bulk compression experiments. It was observed that single granules deform and densify, but tend to keep their integrity during confined triaxial compression, as evident from both compression data and from morphological analysis. Results from confined single granule compression were well represented by the analytical model. These results also largely reflected those from bulk compression experiments, including features of the force–displacement curves as well as rank order between the granule types in terms of contact stiffness. Furthermore, it was shown that intragranular porosity to a high extent governs the onset of plastic incompressibility.

1. Introduction

When designing an efficient manufacturing process for pharmaceutical compacts, the ability to predict and monitor the performance of the process is important. This has for instance led to the Process Analytical Technology (PAT) initiative being introduced in the US by the FDA under the Quality by Design (QbD) umbrella [1,2]. The purpose of such initiatives is to assure a high quality of the end product, using in-process control measures. Its implementation hence demands a deep understanding of the processes involved in tablet manufacturing. Validated models with clearly defined critical key parameters that can easily be monitored may serve as a means for obtaining the desired product quality. It is essential to connect the mechanical behaviour of the single particle to the bulk deformation and tablet forming ability of the powder. However, the character of this link has not yet been fully established, even though it has been a subject of interest for a long period of time [3–10]. One reason for this is the difficulty to emulate and investigate the nature of the multiple contacts emerging on an individual particle in a powder bed during tableting.

Several attempts have been made to connect the behaviour of a powder bed under confined compression to single particle characteristics utilising largely empirical equations derived from bulk compression experiments. For example, parameters from the Heckel [11] and Kawakita and Lüdde [12] equations are often analysed. However, despite numerous attempts to relate the parameters inferred from these relationships to single particle characteristics, they cannot be interpreted unambiguously and often have to be determined from case to case. One reason appears to be that the validity of the models to some extent is conditioned by inherent material parameters. For example, Hassanpour et al. reported that the Heckel parameter is valid only for certain ratios between the Young's modulus and the yield stress (E/σ_y ratios) [7,13]. Furthermore, for a more complete mapping of the compaction procedure, studies have shown that it is necessary to extract parameters from several bulk compression models [14].

The behaviour of individual particles and granular materials under confined compression has also been studied extensively using numerical methods, which is as close to empirical investigations as is possible without employing experimental methods. Gethin et al. [15] made an early effort using a combination of the finite (FEM), and the discrete (DEM) element methods (referred to as multi-particle finite method (MPFEM) or meshed discrete element method (MDEM)) in two dimensions, a procedure also employed by Procopio and Zavaliangos [16]. Harthong et al. [17] as well as Frenning [18] extended the MDEM to three dimensions. The main drawback of the otherwise high-performing MDEM is that it demands vast computational power, and is hence at present primarily used for extraction of parameters for implementation in the DEM. Thanks to its ability to handle powder beds of high enough numbers of particles, the DEM has to be regarded the most promising method for simulations of powder compression. However, most DEM procedures of today are still rather poor in the reproduction of powder beds at large strains, due to the lack of appropriate contact models and the inherent assumption of independent contacts.

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http://dx.doi.org/10.1016/j.powtec.2015.11.051
0032-5910/

At a micromechanical level of investigation, well-established models often emanate from evaluations of isolated two-body contacts. The fully elastic Hertzian model [19] is for instance sufficient at small strains, where the deformation is purely elastic. For the ensuing plastic stage, solutions have for example been proposed by Fleck [20], by Storåkers et al. [21], and by Thornton and Ning [22]. However, Mesarovic and Fleck [6], who specifically investigated the Storåkers model, reported that two-body models are accurate only when the particle–particle overlap is significantly smaller than the particle radius, and when the contacts can be described as fully independent of each other. Contact dependence was reported to occur at a relative density of the powder bed of about 0.82 [6]. More recently, Harthong et al. [17,23] reported that contact dependence becomes relevant from relative densities as low as 0.70. As a reference, it can be mentioned that in order to form coherent compacts, approaching relative densities of about 0.95 is often required.

Apart from contact impingement, compression at high relative densities is associated with the exhaustion of the voidage contained within and in-between the individual particles. Under plastic deformation, the displaced material can expand to fill out this empty space. However, as the porosity approaches zero, plastic incompressibility manifests itself and the contact forces increase rapidly [24]. To capture this transition, Arzt [25] utilised an extrusion procedure involving truncation of spheres by Voronoi cells. This method has since been adapted and further developed by several authors [17,26,27] and recently used to simulate compression of granule beds [10]. In a similar vein, a semi-empirical model that utilises the local relative density as inferred from Voronoi cells to enforce the plastic incompressibility constraint has been proposed and used to simulate compression of particle beds by Harthong et al. [17,23].

In this work, we address the deformation behaviour of single pharmaceutical agglomerates under confined triaxial compression. The purpose is, firstly, to experimentally investigate how the mode of deformation (confined triaxial vs. unconfined uniaxial) affects the single particle-responses, secondly, to investigate how well confined triaxial experiments can be captured using an analytical model for hydrostatic compression, and, thirdly, to assess to what extent data obtained from confined single-particle experiments can be used to predict bulk compression behaviour. Four types of agglomerates (henceforth referred to as granules), all based on the common pharmaceutical excipient microcrystalline cellulose (MCC) are the subject of this study. To investigate the influence of hardness and modes of deformation (ductile and ductile-brittle, respectively), granules containing the softening agent polyethylene glycol (PEG) [28] and the hard and brittle material lactose monohydrate (LAC) [29] were prepared. To estimate the influence of intragranular porosity, granules of high and low porosity were prepared using different proportions of water and ethanol in the agglomeration liquid [30,31].

Under impact or unconfined compression, the force required for granules to fracture is rather low, due to their porous nature [32]. However, when compressed under confined conditions, e.g. in a conventional tablet press, the propagation of cracks has been shown be impeded as the compaction proceeds. Rather, due to the rearrangement of primary particles within the agglomerate, new bonds are formed between primary particles [5,33–35]. Visual post-compaction investigations of individual agglomerates after die compression have though only been possible at relatively low final compaction pressures. At high compaction pressures, the agglomerates lose their integrity and cannot be studied out-of-die as distinct bodies [33,34]. An experimental method, such as the one employed in this study, involving single deforming agglomerates under confined conditions, could therefore extend the knowledge of the morphological transformation of granules during a compaction process.

2. Materials and methods

For the triaxial compression experiments, an apparatus for confined triaxial compression of single particles was used. This apparatus was earlier constructed and evaluated for nominally ideal elastic–plastic particles [36]. The apparatus employs a mechanism first introduced by Hambly [37] for triaxial testing of soil specimens, and is to our knowledge the first to employ this mechanism to study single particles in the mm-scale. Six rigid boundaries (punches) of stainless steel with a side length of 2 mm are arranged as shown in Fig. 1a, allowing for the insertion of a particle. Compression is effectuated by three linear actuators, one along each spatial direction. Through this configuration, the punches are allowed to move independently, sliding with negligible friction past each other and narrowing the rectangular box contained between them (see Fig. 1b). A detailed description of the apparatus can be found in the work by Jonsson et al. [36].

2.1. Granule preparation

Four granule types, with the compositions specified in Table 1, were produced through an extrusion-spheronisation procedure using deionised water and ethanol (95% Analytical Grade, Solveco, Rosersberg, Sweden) as agglomeration liquids. In the preparation of the MCC PEG batch, PEG 6000 (Fluka Chemie GmbH, Buchs, Germany) was dissolved in the agglomeration liquid. The granulation process was initiated by adding MCC (Avicel PH101, FMC Biopolymer, Philadelphia, USA) and/or lactose monohydrate (200 M, Pharmatose, DMV International, Veghel, Netherlands) to a high shear mixer (QMM-II, Donsmark Process Technology, Copenhagen, Denmark) in the amounts stated in Table 1, after which mixing under dry conditions at 500 rpm was conducted for 3 min. The agglomeration liquid was then added at a rate of 100 ml/min under continuous agitation. The agitation was allowed to proceed for another 3 min at a rate of 500 rpm, except for the MCC HP batch, which was agitated for 3 min at a rate of 300 rpm. The wet mass was extruded through a screen with holes of a diameter of 2 mm and a thickness of 1 mm, mounted on a NICA System AB model E140 (Mölndal, Sweden) and spheronised on a friction plate (diameter 32 cm) (model S320-450, NICA System AB, Mölndal, Sweden) for 3 min at a rate of 850 rpm. The granules were dried on trays for three days at ambient conditions, after which they were placed in a desiccator over a saturated K_2CO_3 solution (at a relative humidity of about 40%) for at least five days before conduction of any experiments. Granules in the size range of 1.4–2.0 mm were then separated through sieving for 20 min in a Retsch AS 300 vibratory sieve shaker (Retsch GmbH, Haan, Germany).

2.2. Granule characterisation

2.2.1. Granule shape

A minimum of 1000 particles were separated from each of the four batches. Images (1600 dpi resolution) of these were captured using a flatbed scanner (Epson Perfection 1640SU Scanner, Seiko Epson Corp., Japan). The obtained images were analysed using the ImageJ software. Individual granule diameters (d) were calculated with the equation

$$d = \sqrt{\frac{4a_p}{\pi}} \tag{1}$$

where a_p is the projected granule area, as approximated by the software. The median diameter for each granule type was selected for further calculations.

The mean circularity of the particles was determined from the projected area, using the formula

$$\mathrm{Circ} = \frac{4\pi a_p}{\psi^2} \tag{2}$$

where ψ is the perimeter of the projection of each granule.