This is the accepted version of a paper published in Powder Technology. This paper has been peer-reviewed but does not include the final publisher proof-corrections or journal pagination.

Citation for the original published paper (version of record):

Investigations of single microcrystalline cellulose-based granules subjected to confined triaxial compression
Powder Technology, 289: 79-87
https://doi.org/10.1016/j.powtec.2015.11.051

Access to the published version may require subscription.

N.B. When citing this work, cite the original published paper.

Permanent link to this version:
http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-280895
Investigations of single microcrystalline cellulose-based granules subjected to confined triaxial compression

Henrik Jonsson and Göran Frenning*

Uppsala University, Department of Pharmacy, Uppsala Biomedical Centre, P.O. Box 580, SE-751 23 Uppsala, Sweden

*Corresponding author:
E-mail: Goran.Frenning@farmaci.uu.se, Fax +46 18-471 42 23, Phone +46 18-471 43 75

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.

Keywords: Compression; Triaxial; Hydrostatic; Single granules; Confined conditions; Contact mechanics
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 [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 ($E/\sigma_y$ 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.

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 Figure 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 Figure 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 (200M, 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 minutes. 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 minutes at a rate of 500 rpm, except for the MCC HP batch, which was agitated for 3 minutes 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 minutes 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 K₂CO₃ 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 minutes 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

\[
d = \sqrt{\frac{4a_p}{\pi}}
\]

(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

\[ \text{Circ} = \frac{4\pi a}{\psi^2} \]  

(2)

where \( \psi \) is the perimeter of the projection of each granule.

### 2.2.2 Intrgranular porosity

The densities of the granules were measured employing mercury intrusion pycnometry (number of independent measurements \( n = 2 \) for each granule type) at atmospheric pressure. Measurements were performed by Particle Analytical ApS (Hørsholm, Denmark).

The intragranular porosity \( \phi_0 \) was then calculated through

\[ \phi_0 = 1 - \frac{\rho_{\text{eff}}}{\rho_{\text{app}}} \]  

(3)

where \( \rho_{\text{eff}} \) is the experimentally measured effective density, and \( \rho_{\text{app}} \) is the apparent density. In the case of two-component granules, \( \rho_{\text{app}} \) was calculated from

\[ \rho_{\text{app}} = \frac{w_1 + w_2}{w_1/\rho_{\text{app},1} + w_2/\rho_{\text{app},2}} \]  

(4)

where \( w_1, w_2, \rho_{\text{app},1} \) and \( \rho_{\text{app},2} \) are the weight fractions and the apparent densities, respectively, of the two components.

### 2.3 Single granule compression experiments

#### 2.3.1 Confined triaxial compression

50 granules in the size range of 1.7-2.0 mm were separated from each batch by hand, after individual granule measurements using a dial indicator gauge (Mitutoyo No.3052, Mitutoyo, Kawasaki, Japan).

Each granule was placed in the triaxial testing apparatus and compressed hydrostatically at a rate of 1.2 mm/min. The data was collected using in-house LabVIEW software. Average compression curves were calculated using the measured compression forces along each axis from each run; hence, all in all 150 compression curves for each granule type. Intrinsic machine deformation (about 0.4 \( \mu \)m/N) was compensated for in accordance with Jonsson et al. [36].

After triaxial compression, particles were collected and visually analysed through a light microscope (Zeiss AxioCam ICC 5, Carl Zeiss AB, Sweden) at 20 times magnification.
2.3.2 Unconfined uniaxial compression

Unconfined uniaxial compression of the individual granules was performed using a TA.HDi texture analyser (Stable Micro Systems, Haslemer, UK) equipped with a 5 kg load cell. This was repeated 50 times for each granule type. The compression was effectuated by a circular (diameter 6 mm), flat faced steel probe, compressing at a rate of 3 mm/min. The obtained data was compensated for intrinsic machine deformation.

2.3.3 Mechanical analysis

Confined triaxial compression data were analysed by using an extension of the truncated-sphere model described in [27]. This model utilises an equivalent radius \( R_{eq} \) to account for volumetric particle deformation. The distance from the particle centre to the contact point is denoted by \( r \), the contact area by \( S \) and the contact force by \( F \). These variables are scaled by the equivalent radius \( R_{eq} \) to produce the quantities \( \tilde{r} = r / R_{eq} \), \( \tilde{S} = S / R_{eq}^2 \) and \( \tilde{F} = F / R_{eq}^2 \). In the model in its original form, in which plastic deformation was assumed to be volume-preserving, the equivalent radius was determined self-consistently as

\[
R_{eq} = R_{p0} \left(1 - \frac{3\tilde{F}^2}{2\pi\kappa}\right)^{1/3}, \tag{5}
\]

where \( R_{p0} \) is the initial particle radius and \( \kappa \) is the bulk modulus of the particle. In order to generalise the model to porous granules that densify plastically, the definition of the equivalent radius is here modified to read

\[
R_{eq} = \left[ R_{ps} + (R_{p0} - R_{ps}) \left(\frac{\tilde{r} - \tilde{r}_2}{1 - \tilde{r}_2}\right)^{\alpha} \right] \left(1 - \frac{3\tilde{F}^2}{2\pi\kappa}\right)^{1/3}, \tag{6}
\]

where \( R_{ps} = (1 - \phi_0)^{1/3} R_{p0} \) and \( \alpha \) is an empirical exponent (as before, \( \phi_0 \) denotes the initial porosity of the granule). In effect, the quantity within square brackets provides an interpolation between \( R_{p0} \) (obtained initially, i.e. when \( \tilde{r} = 1 \)) and \( R_{ps} = (1 - \phi_0)^{1/3} R_{p0} \) (obtained in the final stage when the initially porous particle has been transformed to a nonporous cube, i.e. when \( \tilde{r} = \tilde{r}_2 = (\pi/6)^{1/3} \approx 0.806 \)).
The particle is described as a truncated sphere for \( \bar{r} > \bar{r}_1 \) and as a cube with rounded corners for \( \bar{r} < \bar{r}_1 \). Hence, each contact surface is circular for \( \bar{r} > \bar{r}_1 \) and rectangular with rounded corners for \( \bar{r} < \bar{r}_1 \). The scaled radius of the truncated sphere is denoted by \( \bar{R} \) and calculated as

\[
\bar{R} = A \left( 2 \cos \left[ \frac{\arccos (B/A^3 - 1) + \pi}{3} \right] + 1 \right),
\]

where \( A = 3 \bar{r}/4 \) and \( B = 3 \bar{r}^3/8 + 1/4 \). Similarly, for the cube with rounded corners, the scaled half-length of the straight segment of the contact boundary is denoted by \( \bar{s} \) and determined as

\[
\bar{s} = \bar{r} - \bar{r}_1 \left( \frac{r^3 - r_1^3}{r_1^3 - r_2^3} \right)^{1/3}.
\]

The scaled contact area is expressed as

\[
\bar{S} = \begin{cases} 
\beta^2 \pi (\bar{R}^2 - \bar{r}^2) & \text{if } \bar{r} > \bar{r}_1 \\
(4 \bar{r}^2 - (4 - \beta^2 \pi) (\bar{r} - \bar{s})^2) & \text{if } \bar{r} < \bar{r}_1 
\end{cases}
\]

where \( \beta = 0.96 \) is a non-ideality factor [27]. The contact pressure is obtained as

\[
P = \begin{cases} 
\frac{2}{3} \sigma_y \left[ \ln \left( \frac{r^3 - r_1^3}{r^3 - r_2^3} \right) + \frac{r^3 - r_0^3}{r_0^3 - r_2^3} \right] + H & \text{if } \bar{r} > \bar{r}_0 \\
\frac{H}{2} & \text{if } \bar{r} < \bar{r}_0 
\end{cases}
\]

where \( H = 1.94 \sigma_y \) and \( \bar{r}_0 = \bar{r}_1 / \beta \approx 0.85 \) [27]. The contact force is finally found as

\[
F = R_{\text{eq}}^2 \bar{P} = R_{\text{eq}}^2 \bar{P} \bar{S}
\]

whereas the distance from the particle centre to the contact point becomes

\[
r = R_{\text{eq}} \bar{r}.
\]

Equations (11) and (12) provide a parametric representation of \( F \) as a function of \( r \).

The yield pressure of the individual granules (\( p_y \)) was determined from the slopes of the average uniaxial and triaxial compression curves in the linear plastic region \( 0.005 < \varepsilon < 0.035 \) (\( \varepsilon \) being the engineering strain, calculated as the ratio between the punch displacement and the initial particle size) to the force-displacement relationship, as described by Thornton and Ning [22],

\[
p_y = \frac{4}{\pi a} \frac{\partial F}{\partial \delta}
\]

where \( a \) is the particle radius.
where $\partial F/\partial \delta$ is the contact force increment with respect to normal contact displacement. An estimation based on the average rather than the individual curves was considered sufficient because of the complications resulting from deviations from a perfectly spherical shape for the triaxial experiments (see Sec. 3.3).

The nominal fracture strength ($\sigma_0$) of granules subjected to unconfined uniaxial compression was determined from the force at fracture ($F_{\text{frac}}$) in accordance with Adams et al. [38],

$$\sigma_0 = \frac{4F_{\text{frac}}}{\pi d^2}$$  \hspace{1cm} (14)

### 2.4 Confined bulk compression

Confined die compression of powder beds was made using a Zwick Z100 materials tester (Zwick/Roell GmbH & Co. KG, Ulm, Germany) equipped with a 100 kN load cell and circular flat faced punches with a diameter of 11.3 mm. Before each compression experiment, the die and the punches were lubricated with 1% magnesium stearate in ethanol. Thereafter, 0.75 g of granules was poured into the die, after which compression at a rate of 25 mm/min was allowed to proceed up to a pressure of 500 MPa. The experiment was repeated 3 times for each granule type. The collected data was adjusted to account for the intrinsic machine deformation, using the procedure described by Nordström et al. [30]. The engineering strain was calculated as the ratio between the punch displacement and the initial height of the powder bed. The latter was determined as the height of the bed at an applied pressure of 0.5 MPa.

### 3. Results and discussion

#### 3.1 Granule characteristics

Structural characteristics of the granules are provided in Table 2. The intragranular porosities were in the same range (10-14%) for all granule types, except for the MCC HP granules, which had a significantly higher porosity, as expected from prior experience of similarly prepared granules. Likewise, the circularity of the MCC HP granules was lower than for the other granule types.
However, judging from visual examination of the granules (see below), the low circularity rather reflected a rougher surface (originating from the higher porosity) than a more oblong granule shape compared to the other granule types.

### 3.2 Single granule compression experiments

#### 3.2.1 Confined triaxial compression

Results from triaxial compression experiments are shown in Figure 2, in which each curve represents averages formed over experimental runs and spatial directions. Considerable variations in contact force development were observed between granule types, depending on the material characteristics. For the ductile granules, the curve shapes were similar although different in terms of contact stiffness. MCC HP showed a consistently softer response than the other granule types throughout the whole compression. MCC LP and MCC PEG showed approximately equal responses in terms of contact force at low strains, with MCC LP exhibiting a slightly stiffer response than MCC PEG at higher strains. The rank order of granule hardness in terms of measured contact force (MCC LP > MCC PEG > MCC HP) is consistent with that reported in earlier bulk compression studies [30]. It has also previously been reported that PEG acts as a cushioning agent under compression [28], hence facilitating deformation without reduction in porosity, making the MCC PEG granules slightly softer than the MCC LP granules.

For the ductile-brittle MCC LAC granules, the development of contact force with increasing strain differed from those of the ductile particles. Initially, the MCC LAC granules showed a response similar to that of the ductile granule types, followed by a comparably rapid increase at higher strains (from about $\varepsilon = 0.07$). The reason for this is most likely emerging from the higher energy required for plastic flow within these granules, forcing them to deform by cracking.

Figure 3 displays fits (solid lines) of the extended truncated sphere model presented in Sec. 2.3.3 to the experimental data (symbols) from which values of the yield stress ($\sigma_y$) were extracted (Table 3).
The experimental particle radius and porosity were used as input in the model calculations and constant values of $\kappa = 6.25$ GPa and $\alpha = 4$ were assumed. The contact forces were found to be only weakly dependent on the bulk modulus $\kappa$ and hence a representative value for MCC was used [10]. The selected exponent $\alpha$ provided a good overall agreement between experimental results and model calculations. Since the model was developed for ductile particles, the agreement between the extended truncated sphere model and the experimental data for the ductile-brittle MCC LAC granules is not perfect and cannot be significantly improved by letting $\kappa$ vary within reasonable limits (data not shown). This observation fortifies the hypothesis of the different mode of deformation in the case of granules undergoing cracking under densification. As a consequence of the definition embodied in Eq. (6), the values of the yield stress $\sigma_y$ presented in Table 3 correspond to nonporous particles. It is therefore not surprising that comparable values are obtained for the LP and HP pellets although their contact stiffness differs considerably as seen in Fig. 2.

For further comparison, the strain $\varepsilon_{\text{max}}$ corresponding to zero porosity was calculated for each granule type. At this strain, the contact force should increase rapidly upon further compression, because elastic volume reduction is the only deformation mode possible. The granule can be approximated as a sphere with diameter $d_0$ and porosity $\phi_0$ initially and as a solid cube with side length $l_f$ once porosity has been exhausted. Hence

$$l_f^3 = \frac{\pi d_0^2}{6} (1 - \phi_0)$$  \hspace{1cm} (15)

implying that

$$\varepsilon_{\text{max}} = \frac{d_0 - l_f}{d_0} = 1 - \left(\frac{\pi}{6}\right)^{1/3} (1 - \phi_0)^{1/3}.$$  \hspace{1cm} (16)

The theoretical asymptotes corresponding to the calculated values of $\varepsilon_{\text{max}}$ can be seen in Figure 3 (dashed vertical lines). As a further reference, the strain corresponding to zero voidage for a particle that retains its initial volume during deformation was calculated, putting $\phi_0 = 0$ in Eq. (8), and also indicated in in Figure 3 (dotted vertical lines). As expected, spatial confinement is manifested by a
rapid increase in contact force once the strain approaches $\varepsilon_{\text{max}}$, thus explaining the effect of porosity on the contact force development.

Overall, the contact force response from triaxial compression exhibit the same features as in our previous experimental study [36] and in prior simulations [17, 26]. These include an initial linear region of predominantly plastic deformation that bends upwards as contact surfaces start to interact and the confinement increases.

3.3 Unconfined uniaxial compression

Figure 4 shows typical results from uniaxial compression experiments, and the mechanical characteristics calculated from these experiments are summarised in Table 3. First, it can be noted that all the granules, contrary to what was observed for the triaxial compression experiments, fractured at a certain point during the compression procedure. This is associated with the rapid decrease in contact force seen in all the curves in Figure 4 (indicated by arrows).

Due to the irregular shape of granules, the axes will make contact with the tested specimen at different temporal instances under hydrostatic triaxial compression, which will lead to lower observed average contact force at small strains than observed when compressing the same granule uniaxially. Therefore, both the overall triaxial average curves and the average from the axis that first made contact with the granule in each triaxial run, referred to as the primary axis, were included when comparing contact force development under these loadings, as seen in Figure 5. The uniaxial averages are only included up to the strain where the granules started to fragment; these curves are, consequently, shorter than the triaxial averages.

As anticipated, a high resemblance was observed between the primary axis averages and the uniaxial curves for all the granule types. Furthermore, the difference between the overall triaxial average and the uniaxial average was more pronounced for the harder granule types, which should also be expected. Generally, similar values of $p_y$ were obtained for the primary axis and the unconfined uniaxial compression, comprising the rank order otherwise observed in terms of contact stiffness.
3.4 Confined bulk compression

Confined bulk compression differs from confined hydrostatic triaxial compression in terms of the ratio between the axial and the lateral loadings. In the former, lateral forces emerge from the constraint provided by the immobile die wall, and are consequently lower than the normal force. In the confined triaxial case, the contact force will be equal in the normal and the lateral directions. However, as reported in numerical studies, the difference in contact force development can be explained by the evolution in coordination number during the compression procedure [17] (nominally constant = 6 under hydrostatic single particle compression, gradually increasing under confined bulk compression). For finer particles, bulk compression is also associated with a high degree of rearrangement. For granules in the mm-scale, however, this phenomenon has been shown to be practically negligible [39].

Figure 6 shows average compression curves from confined bulk compression experiments. All curves exhibit an initial relatively linear increase in pressure with increasing strain that is followed by a more rapid increase in pressure at larger strains. The former is generally attributed to plastic particle deformation and the latter may, in a broad sense, be interpreted as a crossover between a predominantly plastic and a predominantly elastic deformation stage [10]. As in the triaxial compression experiments, the ductile granule types showed the same rank order in terms of hardness from contact force response (MCC LP > MCC PEG > MCC HP, with MCC HP being considerably softer than the other ones), even though this was less pronounced in the bulk experiments. Furthermore, the trend of the ductile-brittle MCC LAC granules also follows that from the confined triaxial experiments: its compression curve involves an initially softer response than the ductile MCC LP granules, followed by a sharper increase of the MCC LAC curve at higher strains, all of which can be seen in the inset in Figure 6.

3.5 Morphological analysis
The compressed granules all showed a rigid texture and had no tendency to fragment during handling or visual post-compression analysis at any investigated strain. As seen in Figure 7, cracks can be observed at the particle surfaces of all granule types except the MCC HP granules. These are to some extent observable at the contact surfaces, but were predominantly present in the boundary regions between the contact zones. The locations of the cracks most likely have its explanation in the forced expansion of the granules in those directions when transitioning from a spherical to a cubical shape. It is therefore probable that relocation of primary particles through local fragmentation occurs at several instances during the compression process. However, none of the cracks sustained to the degree that complete fragmentation occurred during any of the runs. This phenomenon is consistent with earlier bulk compression studies, where granules compressed to high strains tended to keep their integrity [5, 33-35].

The MCC HP granules showed no observable cracks at the surface at any investigated strain. This is an expected behaviour that can be attributed to the more loosely connected network of primary particles within the granule, as compared to the other granule types. Thus, plastic deformation through relocation of primary particles, as opposed to local crack formation, is more energetically favourable for the MCC HP granules than for the other granule types. This can be directly associated to the observed softer contact force response for MCC HP, seen in the compression curves in Figures 2-6.

4. Conclusions

In this study, the contact force development when subjecting single granules to confined triaxial compression has been investigated experimentally for four different pharmaceutical materials. The analysed compression curves were well reproduced by the extended truncated sphere model and inherited the same features as results from earlier experiments and simulations of confined compression of single particles.
The intragranular porosity was shown to be an important parameter under these conditions, largely governing the rate at which the granule under load approached the plastic incompressibility associated with confined compression.

Compression curves from unconfined uniaxial compression were initially very similar to the confined triaxial compression curves in terms of contact force. However, at larger deformations, granule fracture was observed only in the uniaxial case, demonstrating a critical difference between confined and unconfined conditions.

Furthermore, clear correspondence could be noted in terms of hardness (and hence position of the elastic asymptote on the strain axis) between bulk compression and confined triaxial compression. Such a consistency will, in the long run, substantially simplify the establishment of a connection between the individual granule and the bulk powder under compression.

Finally, visual investigations lent support to our deductions from the confined triaxial compression curves. The granules deformed but maintained their integrity when compressed under confined triaxial conditions. This phenomenon has earlier been shown to manifest itself for individual granules under confined bulk compression, and has now been verified to occur also under confined triaxial compression of single granules.

**Acknowledgements**

This study was supported by a grant provided by the Swedish Research Council (No. 621-2011-4049).
References

Figure captions

**Figure 1** - The compression mechanism employed by the triaxial apparatus. In the default position (a), six flat-faced punches with square cross sections are aligned so that their faces bound a cubical cavity with 2 mm side length. Upon compression (b), the punches are allowed to slide past each other, effectuating the confined compression procedure by shrinking the space contained between them. The dashed squares represent punches perpendicular to the plane.

**Figure 2** – Average curves from triaxial experiments for the different granule types.
Figure 3 – Average contact forces from triaxial experiments (symbols) along with fits of the analytical extended truncated-sphere model (solid lines), reported separately for each granule type. The dashed vertical lines indicate the strain corresponding to zero porosity and the dotted vertical lines indicate zero voidage for a particle that retains its volume during compression. Error bars represent the standard error of the mean.

Figure 4 - Typical curves from unconfined uniaxial experiments. Arrows indicate failure.
Figure 5 - Average curves from unconfined uniaxial and confined triaxial experiments at small strains, as well as average compression curves for the axis that made first contact in confined triaxial experiments (denominated the primary axis).

Figure 6 – Average curves from confined bulk compression experiments. The inset highlights the compression pressure evolution of the ductile-brittle MCC LAC granules in comparison to the ductile granule types.
Figure 7 - Granules at 30 times magnification before compression and at certain triaxial strains (indicated to the right). The columns depict MCC LP (a), MCC HP (b), MCC PEG (c), and MCC LAC (d), respectively. The lowermost row comprises magnifications of the areas indicated by frames in the pictures at $\varepsilon = 0.25$. 
Tables

Table 1 - Compositions of the investigated granules.

<table>
<thead>
<tr>
<th>Particle type</th>
<th>Amount of MCC/PEG/Lactose (g)</th>
<th>Amount of granulation liquid (g)</th>
<th>Proportion water:ethanol in granulation liquid (w%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCC LP</td>
<td>400/0/0</td>
<td>440</td>
<td>100:0</td>
</tr>
<tr>
<td>MCC HP</td>
<td>400/0/0</td>
<td>440</td>
<td>30:70</td>
</tr>
<tr>
<td>MCC PEG</td>
<td>380/20/0</td>
<td>440</td>
<td>100:0</td>
</tr>
<tr>
<td>MCC LAC</td>
<td>200/0/200</td>
<td>200</td>
<td>100:0</td>
</tr>
</tbody>
</table>

Table 2 - Characteristics of the investigated granules (mean values with standard errors of the mean within brackets, except where indicated otherwise).

<table>
<thead>
<tr>
<th>Granule type</th>
<th>Diameter (mm)*</th>
<th>Porosity (%)</th>
<th>Circularity (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCC LP</td>
<td>1.63 (0.16)b</td>
<td>13.7 (1.1)</td>
<td>0.881 (0.0007)</td>
</tr>
<tr>
<td>MCC HP</td>
<td>1.82 (0.22)b</td>
<td>37.1 (0.86)</td>
<td>0.752 (0.0023)</td>
</tr>
<tr>
<td>MCC PEG</td>
<td>1.75 (0.20)b</td>
<td>12.6 (0.40)</td>
<td>0.864 (0.0007)</td>
</tr>
<tr>
<td>MCC LAC</td>
<td>1.84 (0.23)b</td>
<td>10.3 (0.37)</td>
<td>0.858 (0.0007)</td>
</tr>
</tbody>
</table>

* Median value
b Interquartile range

Table 3 - Nominal fracture strengths ($\sigma_0$), yield pressures ($p_y$) and yield stresses ($\sigma_y$) extracted from uniaxial and triaxial single granule experiments. The squared regression coefficient ($R^2$) is provided within brackets, except where indicated otherwise.

<table>
<thead>
<tr>
<th>Granule type</th>
<th>$\sigma_0$ (MPa, uniaxial)</th>
<th>$p_y$ (MPa, uniaxial)</th>
<th>$p_y$ (MPa, triaxial)</th>
<th>$p_y$ (MPa, triaxial, primary axis)</th>
<th>$\sigma_y$ (MPa, triaxial)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCC LP</td>
<td>17.3 (2.66)a</td>
<td>516 (0.999)</td>
<td>285 (0.997)</td>
<td>477 (0.999)</td>
<td>84.7 (-)</td>
</tr>
<tr>
<td>MCC HP</td>
<td>8.24 (1.74)a</td>
<td>133 (0.995)</td>
<td>134 (0.998)</td>
<td>159 (0.999)</td>
<td>95.8 (-)</td>
</tr>
<tr>
<td>MCC PEG</td>
<td>13.7 (3.39)a</td>
<td>467 (0.997)</td>
<td>250 (0.998)</td>
<td>377 (0.999)</td>
<td>69.1 (-)</td>
</tr>
<tr>
<td>MCC LAC</td>
<td>16.8 (2.95)a</td>
<td>614 (0.990)</td>
<td>298 (0.995)</td>
<td>547 (0.999)</td>
<td>92.6 (-)</td>
</tr>
</tbody>
</table>

a Standard error of the mean