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Single and bulk compression of pharmaceutical excipients: Evaluation of mechanical properties

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Abstract

The compaction of powders into tablets is widely used in the pharmaceutical industry to convert drugs, in the form of small particles, into coherent and robust metered solid dosage forms. In order to produce robust tablets with the required properties, it is essential to understand the elastic, viscoelastic and plastic properties and rupture strength of the feed particles, which can be as small as a few microns in diameter. The objective of this work is to characterise the mechanical properties of single particles using a micromanipulation diametrical compression technique and relate the parameters to the compression behaviour of powders. Mechanical parameters, such as the Young's modulus, hardness and nominal rupture stress, were thus determined for each sample. The bulk compression data of the powders were analysed to calculate the parameters of the Heckel (Heckel, R.W., 1961a An analysis of powder compaction phenomena, Trans Metal Soc. AIME, 221, 1001–1008; Heckel, R.W., 1961b Density–pressure relationships in powder compaction, Trans Metal Soc. AIME 671–675), Kawakita (Kawakita, K. and Ludde, K.H., 1971 Some considerations on powder compression equations, Powder Technology, 4, 61–68) and Adams (Adams, M.J., Mullier, M.A. and Seville, J.P.K., 1994 Agglomerate strength measurement using a uniaxial confined compression test, Powder Technology, 78, 5–13.) models. These parameters will be compared with each other, and with the mechanical properties of the individual component particles. A correlation has been found between the nominal rupture stress of single particles and the apparent strength derived from the Kawakita and Adams models.

Keywords: Compaction; Mechanical properties; Young's modulus; Yield stress; Micromanipulation; Particles

1. Introduction

Generally, the packing of the feed powder is rearranged and the individual particles undergo deformation and possibly breakage during compaction. These events can occur sequentially or in parallel. Elastic and plastic deformations and also the rupture of particles during the consolidation of a powder bed contribute to the formation of a coherent mass in a tabletting process. The mechanical strength of a compact is strongly dependent on the mechanical properties of the individual feed particles and the particle–particle interactions within the compact [1]. Hence, it is important to understand the mechanical properties of such particles that are critical in controlling the overall behaviour of the assembly. In particular, the formulation of functional products often requires an understanding of the mechanical properties of single micro-particles and the prediction of their compaction behaviour. The deformation characteristics of single particles/granules may be elastic, viscoelastic or plastic and may involve fracture or a combination of these deformation mechanisms.

The Young's modulus and the yield stress are important material properties that are known to influence the compaction behaviour of powders [2–4]. They provide information about the particle deformation behaviour [5]. The Young's modulus has been measured using beam-bending methods [1,2]. The yield stress has been determined using indentation on compacts [4,6] and the uniaxial compression of particles with data analysed using Heckel analysis [1,7,8].

The compression of a single particle between two rigid platens, which is also known as diametrical compression, has

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been used to measure the mechanical properties of powders directly. Examples include agglomerates (>500 μm), prepared from quartz sand and polyvinylpyrrolidone as a binder [9], spherical polystyrene colloids binderless granules [10,11], melt and wet granules [11] and soft detergent based agglomerates (1–2 mm) [8]. A micromanipulation technique has been developed for characterising the mechanical properties of particulate materials on the micron scale, involving animal cells [12], plant cells, yeast, bacteria, latex aggregates, microcapsules [13,14] and microspheres [15]. It is also based on diametrical compression and has been used, for example, to measure the fracture force of calcium carbonate particles with a mean diameter of 52.5±1.4 μm [16].

The elastic deformation at spherical contacts was investigated by Hertz [17]. The force–displacement behaviour of a spherical elastic particle against a rigid plate can be expressed using the following equation:

$$F = \frac{4E\sqrt{R}}{3(1-\upsilon^2)}\delta^{\frac{3}{2}} \quad (1)$$

where R is the original particle radius, E is the Young's modulus of the particle and υ is the Poisson's ratio of the particle. In a diametrical compression test, δ is equivalent to half of the total compressive displacement. The hardness of a particle, H, can be obtained from the slope of the linear plastic region of the force–displacement curve at which it deviates from Hertzian behaviour using the following relationship [17]:

$$F = 2\pi HR\delta \quad (2)$$

However, at large strains in the so-called *finite deformation regime*, corresponding to $a/R\approx 0.2$ where a is the maximum contact radius, this relationship would increasingly underestimate the hardness [18].

In the case of pharmaceutical tablet compression, the ability of the feed powders to form a coherent mass is of prime importance. Numerous porosity–pressure functions are used to describe the change in bed density as a function of the applied stress [19]. For example, Samimi et al. [8] employed the Heckel and Kawakita equations together with an equation developed by Adams et al. [9]. In addition there has been considerable interest in relating the strength of single particles to the bulk properties as measured by uniaxial compression [9,10].

The Heckel [20] equation was initially derived using a first order differential equation as follows:

$$-\frac{de_{\mathrm{b}}}{d\sigma} = Ke_{\mathrm{b}} \quad (3)$$

where e_{b} is the bed porosity, σ is the applied stress and K is termed the Heckel parameter. Applying the boundary condition that e_{i} is the bed porosity at zero pressure, Eq. (3) becomes:

$$\ln\frac{1}{e} = \ln\frac{1}{e_{\mathrm{i}}} + K\sigma \quad (4)$$

Heckel [20] later modified the model for uniaxial compression of metallic particles by replacing the parameter e with $(1-\rho^*)$ where ρ^* is the relative density and assumed that the term $\ln(1/e_{\mathrm{i}})$ should be a constant parameter, C, thus:

$$\ln\frac{1}{1-\rho^*} = C + K\sigma \quad (5)$$

Eq. (5) is widely used in the literature. The slope and intercept of the linear relationship involving $\ln[1/(1-\rho^*)]$ as a function of applied stress σ may be used to determine the Heckel parameters K and C respectively. However, experimental data are commonly not linear [21] showing some curvature in the low and high-pressure regions and linearity is only observed in the middle pressure range.

Heckel [20] also related K to the uniaxial yield stress σ_o of individual metallic particles:

$$K = \frac{1}{3\sigma_{\mathrm{o}}} = \frac{1}{H} \quad (6)$$

Thus K is inversely related to the ability of the material to deform plastically [22] and the Heckel model can be employed mainly for materials that consolidate by plastic deformation. Roberts and Rowe [22] compared the yield stresses obtained from bulk compression tests, and the values of hardness and Young's moduli measured by indentation. They found a correlation between $1/K$ with the hardness and Young's modulus for a wide range of materials (metals, inorganic halides and polymers).

It is assumed that the yield stress is constant in deriving the Heckel equation. However, this might not be the case due to the constraining presence of neighbouring particles. Hence, Denny [21] proposed a pressure dependent term for characterising the yield stress, σ_{op}, as follows:

$$\sigma_{\mathrm{op}} = \sigma_{\mathrm{o}} + k_1\sigma_{\mathrm{ap}} \quad (7)$$

This is based on the assumption that the lateral pressure is proportional to the axial value,σ_{ap}, with a proportionality constant, k_1. Hence, Eq. (6) becomes $K=1/(3\sigma_{\mathrm{op}})$ and integrating Eq. (3) and using Eq. (7) leads to a different version of Heckel's equation:

$$\ln\frac{1}{e} = \ln\frac{1}{e_i} + \frac{1}{3k_1}\ln\left(1 + \frac{k_1\sigma_{\mathrm{ap}}}{\sigma_{\mathrm{o}}}\right) \quad (8)$$

Eq. (8) will revert to the original Heckel equation (*cf* Eq. (3)) at low pressures, where $k_1\sigma_{\mathrm{ap}} \ll \sigma_{\mathrm{o}}$. Therefore, the yield stress can be determined by linearly fitting data at low bed pressures. However, this region corresponds to the early stages of compression, which may be associated with rearrangement and sliding of the particles if the initial bed is not reasonably consolidated.

The Kawakita equation is another empirical model, which was proposed by Kawakita and Ludde [23] as follows:

$$\frac{\sigma}{\varepsilon} = \frac{1}{ab} + \frac{\sigma}{a} \quad (9)$$

where ε is the degree of volume reduction, which is equivalent to the uniaxial strain:

$$\varepsilon = \frac{h_{\mathrm{i}} - h_{\mathrm{p}}}{h_{\mathrm{i}}} \quad (10)$$