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Research paper

A protocol for the classification of powder compression characteristics

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ABSTRACT

In this paper, a structured protocol for powder compression analysis as a test to assess the mechanical properties of particles in a formulation development programme is presented. First, the sequence of classification steps of the protocol is described, and secondly, the protocol is illustrated using compression data of six powders of two model substances, sodium chloride and mannitol. From powder compression data, a set of compression variables are derived, and by using critical values of these variables, the stages expressed during the compression of the powders are identified and the powders are classified into groups with respect to the expression of particle rearrangement, particle fragmentation and particle plastic deformation during compression. It is concluded that the proposed protocol could, in a satisfactorily way, describe and distinguish between the powders regarding their compression behaviour. Hence, the protocol could be a valuable tool for the formulation scientist to comprehensively assess important functionality-related characteristics of drugs and excipients.

1. Introduction

In order to effectively and rationally develop pharmaceutical dosage forms, an understanding of the properties of pharmaceutical materials, and how material properties can be changed or modulated to improve their functionality during manufacturing and use, is critical. As a consequence, the development scientist needs access to several methods of analysis during the formulation work to comprehensively assess important functionality-related characteristics of drugs and excipients [1,2].

The mechanics of a solid is a physical characteristic of relevance for the behaviour of particles during processing and for the quality and properties of formulated products [3]. Methods or procedures by which mechanical properties of particles can be characterized have, compared to the characterization of other functional properties, hitherto attended more limited interest in pharmaceutical science. In the literature, three approaches are reported by which mechanical properties of particulate matter are characterized: Uniaxial confined compression of a powder, testing of compacts (e.g. indentation and bending tests) and testing of single particles (e.g. compression loading and nanoindentation). An example is the use of nanoindentation as a means to characterize single-particle properties, which was suggested to be a valuable method in the early development phase [4]. One of the few comprehensive procedures to characterize and classify mechanical properties has been suggested by Roberts and Rowe [5], a procedure in which two of the approaches were combined, i.e. compact testing and powder compression. Another pertinent example of a comprehensive procedure has been developed by Hiestand and Smith [6], using compact testing as a means to derive a series of indices of tableting performance.

Powder compression is an attractive method of analysis from both a statistical and a material consumption perspective, i.e. a large number of particles are used in the test but the total amount of material required is low compared to mechanical characterization by compact testing. Furthermore, by powder compression, great variations in properties of the particles with respect to their size, shape and ability to form compacts can easily be handled. It is, however, important to recognize that variations in loading condition during compression [7–10] as well as in the data handling procedure, e.g. the importance of setting a valid starting point for the compression [11], may affect the value of the derived compression parameters. Thus, the standardization of experimental variables and data handling procedure is critical for the reproducibility of powder compression data. In addition, using compression equations based on tablet porosity data represents a special problem when analysing the compression properties of granulated particles [12].

In some earlier papers [13–15], a classification system for describing compression properties of powders, based on the use of some common compression parameters, was suggested. In this study, we bring together conclusions and considerations from these studies into a structured protocol which may enable the use of powder compression as a test to identify the

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functionality-related characteristics of particles in a formulation development programme. The intention with this paper was thus firstly to present such a protocol and, secondly, to illustrate the sequence of classification steps of the protocol using compression data of six powders of two model substances, sodium chloride and mannitol.

2. Theoretical considerations and overview of protocol

2.1. Stage models of powder compression

The possibility to rationally use compression data as a means to characterize material properties must be based on a mechanistic conception of the compression process. It is commonly assumed in the literature that powder compression, i.e. the compression of a powder up to maximum applied pressure ignoring densification and elastic recovery with reduced pressure (unloading), involves processes that occur in distinct stages [16,17]. This conception is based on the hypothesis that within a certain range of compression pressure, one specific physical process is controlling the rate of compression (i.e. the rate of change in compact density or porosity with pressure). Powder compression is thus viewed as a process occurring in a sequence of consecutive stages, each stage representing a certain part of the total pressure range used. The physical processes involved in the different stages are normally described on the particulate scale with the underlying objective that the analysis of the compression process gives an opportunity to extract information about the mechanical properties of the material (i.e. the particle). However, several interpretations of this sequence model exist in the literature in terms of the number of regions involved in the compression process as well as the sequence of physical processes. The variation in number of regions is probably the result of, firstly, the great variation in materials used in different industrial branches and, secondly, different opinions regarding to what extent a mechanistic model can be refined in terms of the number of identifiable stages.

A complete survey of the literature is not given here but important examples of formulations of the sequence model follow. Heckel [18] identified two stages, i.e. particle rearrangement followed by particle deformation, and he concluded that they corresponded to the stages suggested earlier by Seelig and Wulff [19], who were the first to suggest that the compression process comprises distinct stages with associated mechanisms [20]. James [16], also using metal powders, suggested three stages, i.e. interparticle movement, particle elastic and plastic deformation and finally compact contraction due to elastic deformation. Sun and Grant [21] suggested principally the same three regions for pharmaceutical powders, i.e. particle rearrangement (low-pressure region), particle plastic deformation (medium pressure region) and tablet elastic deformation (high-pressure region), while Duberg and Nyström [22] suggested two regions in sequence in the powder densification process, i.e. particle fragmentation followed by particle elastic and plastic deformation. Johansson and Alderborn [12] presented a sequence of three stages during the compression of granulated particles, i.e. granule repositioning, local granule deformation and finally bulk granule deformation and densification. This sequence of regions was later modified by Nordström et al. [23] by adding granule cracking as a rate-controlling mechanism in the low-pressure region, giving the following sequence of stages: granule rearrangement, granule cracking and finally, granule plastic deformation and densification.

Alternative views to a sequence model are also presented in the literature. It has been suggested that the compression process cannot be resolved into a sequence of distinct stages, each controlled by a single mechanism, but should be conceptually understood as a process where different mechanisms are active simultaneously and the sum effect of the mechanisms controls the rate of compression [24]. Sonnergaard described two mechanisms operating simultaneously, particle fragmentation and particle plastic deformation. Morris and Schwartz [25] discussed also a single compression region from punch-to-powder contact to maximum pressure in which several mechanisms could be expressed. Another alternative view was presented by Holman [26], who discussed regions of the compression process in terms of the structure of the formed compact rather than the mechanism of response of the powder that caused densification. Based on this percolation approach, Holman divided the compression process in up to four stages denoted as powder, flexible coherent particulate compact, rigid coherent particulate compact and continuum solid body.

It is concluded here that the sequence model is a dominant conception in the literature and the following is an attempt to summarize the literature: The powder compression process starts with a particle rearrangement process and ends with a stiff body. Particle plastic deformation is a dominant mechanism over a wide range of compression pressures, and this mechanism has also been in focus of modelling ambitions, e.g. Frenning et al. [27]. For granular solids, densification may occur in parallel with the granule plastic deformation. Finally, particles may crack and fragment into smaller particles, a process that often occurs initially in the compression process and precedes plastic deformation. This summary represents thus an up to four-stage model, which is consistent with the summary proposed earlier by Denny [28]: Particle rearrangement, particle fragmentation, particle plastic deformation and finally, elastic deformation of a stiff compact. Important to add is that the number of mechanisms and thus stages that in practice is expressed by a given powder varies between powders and depends on particulate and mechanical properties of particles and the pressure range (i.e. the degree of powder densification) used [23]. The four-stage model is from a system perspective characterized by two transition points. The first is the transition from a flowing (rearranging) into a cohesive powder with locked particles, i.e. the powder jamming transition [29,30]. The second is the transition from a plastically deforming compact into an elastically deforming compact.

2.2. Selection of compression parameters

In order to use powder compression as a test method, a procedure must be used that enables firstly the identification of the number of stages that is expressed during loading and, secondly, the derivation of measures of to what extent the underlying mechanisms of compression are expressed. An important aspect of such measures is that they should provide information about the fundamental mechanical characteristics of particles, i.e. to what extent the particles are prone to fracture and deform plastically while loaded. In a series of papers [13–15], a strategy for such a procedure has been outlined that can potentially satisfy these requirements. This strategy is based on the use of compression parameters as indicators of compression mechanisms followed by the identification of stages of compression in terms of their relative importance for the overall appearance of a compression profile.

The protocol suggested in this paper is based on, albeit not restricted to, three compression equations. These three equations have been selected since it has been reported that they include parameters that are considered to be defined in terms of physical significance, i.e. the equations often denoted the Kawakita and Lüdde [31], the Heckel [18,32] and the Shapiro general compression equation [33]. Regarding the Heckel equation, it seems to be a widespread opinion that the Heckel parameter (often denoted the yield stress or yield pressure) is an indication of the plasticity or hardness of the particles. This assumption originates from the work of Heckel but is also supported by modelling works by Hassanpour and Ghadiri [34] who states that information of the particle plasticity can be derived from bulk compression behaviour provided that a critical ratio between Young's modulus and yield stress is exceeded. The authors report further that this criterion is met for many pharmaceutical materials. More on, Yap et al. [3] determined the values of the Heckel yield stresses in the same order of magnitude as the yield stresses of single particles, derived from diametral compression. Finally, it has been shown [35] that the evolution in tensile strength with compression pressure is related to the Heckel yield stress. Since a Heckel profile often deviates from linearity at low compression pressures, a third equation, also a porosity–pressure equation, referred to as the Shapiro general compression equation (GCE) [33] was used by Klevan et al. [14] to describe the non-linear part of a Heckel profile.

2.3. Suggested protocol

As a means to describe typical or dominating features of a powder while compressed in terms of stages of compression, a simple classification system has been introduced [13–15]. In the classification, a powder is firstly classified depending on the incidence of particle rearrangement (Class I or II powder) and thereafter further sub-classified depending on the incidence of particle fragmentation during compression (Type A or B powder). Finally, the particles are classified in terms of plasticity into four groups, adopted from Roberts and Rowe [5]. The indicators guiding the classification are compression parameters derived from the compression equations discussed above. To perform the classification, a sequential data treatment should be done, which is illustrated in Fig. 1, as follows:

Step 1: The compression profile is described in terms of a pressure–engineering strain relationship, using the Kawakita equation by which two compression parameters are derived, denoted a and b^{-1}. The product of these represents an index of compression behaviour, denoted ab_I. With this index, a powder is classified as Class I or II depending on the incidence of particle rearrangement [13].

Step 2: The compression profile is described in terms of a porosity–pressure relationship, using the Shapiro general compression equation. By this relationship, a compression parameter denoted the f-parameter is derived. With this parameter, a Class II powder is classified as Type A or B, i.e. if the particle fragments to a low or high degree during compression (ductile or brittle particles) [14].

Step 3: The compression profile is described in terms of another porosity–pressure relationship, i.e. the Heckel equation, and a compression parameter often denoted the Heckel parameter or the yield stress is derived. With this parameter, a powder is classified into one of four groups regarding particle plasticity, ranging from very soft to hard [5].

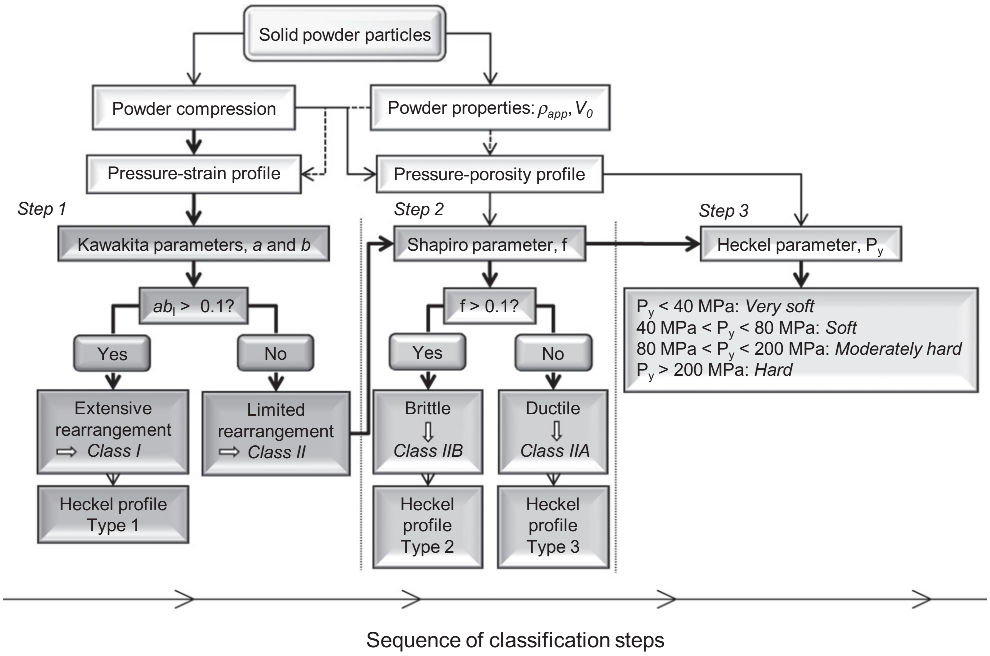

Fig. 1. A schematic overview of the suggested protocol for the assessment of compression characteristics of powders (the "characterization and classification route").

Table 1
Specifications of procedures used to calculate compression parameters.

Equation	Starting point	Pressure range for curve fitting	Curve fitting	Fitting requirement	Compression parameters derived
Kawakita	Extrapolated from bulk density to a start volume (V_0)	Constant = 25–250 MPa	Linear regression	Correlation coefficient $R^2 > 0.999$	a and b^{-1}
Shapiro GCE	Pressure corresponding to E_{0BD}	Constant = 0–50 MPa	Non-linear curve fitting	Convergence criterion = relative χ^2 change $\leqslant 0.00001$	f
Heckel	Pressure corresponding to E_{0BD}	Variable	Linear regression	+25% of minimum derivative of profile	P_y

E_{0BD} is the powder bulk porosity transformed from the measured powder bulk density.

Details of the procedure used are described below in the experimental section, and the procedures used to calculate the parameters are summarized in Table 1.

3. Materials and methods

3.1. Preparation of powders

Mannitol and sodium chloride (Sigma–Aldrich, Stockholm, Sweden) were used as test materials. In addition to the bulk powders, two size fractions were prepared for each of the two substances. A coarse fraction (125–180 μm for mannitol and 425–500 μm for sodium chloride) was prepared by simple dry sieving by hand (Retsch, type RV, Haan, Germany), and a fine fraction was prepared by milling the bulk powder in a pin disk mill (Alpine 63C Contraplex Labormühle, Alpine AG, Augsburg, Germany).

All six powders were conditioned in closed containers over a saturated K_2CO_3 solution, corresponding to a relative humidity of about 40%, and kept at room temperature (about 20 °C) for at least 5 days prior to further powder characterization and compression. This temperature and humidity corresponded roughly to the conditions of the laboratory.

3.2. Characterization of powders

Visual inspection of the particles was done by optical light microscopy (model Vanox, Olympus, Tokyo, Japan).

The apparent particle density, ρ_{app}, was determined using a helium gas pycnometer (AccuPyc 1330, Micrometrics, Norcross, USA), $n = 2$. The values reported in Table 2 are mean values of measures for all three powders of the respective substance, hence overall $n = 6$.

The volume-specific surface area (S_0) of the coarser powders was determined using a steady-state air permeability apparatus and calculated with the Kozeny–Carman equation [36,37], $n = 3$, whereas the volume-specific surface area (S_0) of the finer size fractions was determined using a transient (Blaine) air permeability apparatus, $n = 3$. For the latter powders, S_0 was calculated using a slip flow-corrected Kozeny–Carman equation, as described in previous work [13].

The poured (unsettled) bulk densities of the powders (ρ_{poured}) were measured by gentle pouring of powder samples into a graduated 5-ml cylinder with a diameter of 11.47 mm. The height of the powder bed was measured with a digital height measure (Mitutoyo Digimatic, ID-C, Tokyo, Japan), $n = 3$, see Table 2.

Small samples (approx. 5 g, $n = 3$) were prepared from the bulk powder using an eight-way split spinning riffler (Retsch, Haan, Germany). The powder was poured by hand into the apparatus and fed out into the different vessels through the influence of rotational gravity. Particle size distributions were obtained from these samples by dry sieving on a set of precision sieves (Veco, Eerbeek-Holland) with a standard series of aperture size mounted on a mechanical sieve shaker (Retsch, type RV, Haan, Germany) and finally weighed on an analytical balance. End point determination for the analysis was done according to the European Pharmacopoeia [38].

3.3. Compression of powders

Powders were compressed using a materials testing machine (Zwick Z100, Zwick/Roell Zwick GmbH & Co. KG, Ulm, Germany), equipped with 11.3-mm-diameter flat-faced punches. The die and punch faces were lubricated prior to the compression, using a suspension of 1% magnesium stearate in ethanol. The powder was weighed (about 500 mg) on an analytical balance and poured by hand into the die. The lower punch was stationary during the compaction cycle and the upper punch moved at a speed of 10 mm/min up to a maximal applied pressure of 300 MPa, $n = 5$. A sampling interval of 10 N was used.

In order to estimate the elastic deformation of the punches and the punch holder, system deformation curves were recorded by pressing the punches against each other at the same compression speed used in the compression experiments ($n = 3$, $P_{max} = 300$ MPa). These pressure (P)–displacement (Δ_p) relationships showed an initial curvature followed by a linear part. A system deformation expression $\Delta_p = k_aP + l_a + l_be^{(-k_bP)}$ was fitted to the system deformation curves, and values for k_a, k_b, l_a and l_b were thus obtained. In order to estimate the height of the powder bed in die, the powder compression profiles were corrected for the system deformation by this system deformation expression. The order of magnitude of the system deformation was approximately 0.5 μm/MPa.

3.4. Compression parameters

Step 1: The compression profiles were firstly adapted to the linear form of the Kawakita equation: $\frac{P}{C} = \frac{1}{ab} + \frac{P}{a}$, where P is the applied compression pressure and C is the engineering strain, calculated as $C = \frac{V_0 - V}{V_0}$, where V_0 is the initial powder volume

Table 2

Powder characteristics (relative standard deviations within brackets).

Substance	ρ_{app} [a] (g/cm^3)	Powder	ρ_{poured} [b] (g/cm^3)	S_0 [c] (cm^{-1})
Sodium chloride		Bulk	1.167 (0.004)	219 (0.04)
Sodium chloride	2.149 (0.004)	Sieved (425–500 μm)	1.207 (0.008)	151 (0.01)
Sodium chloride		Milled	0.507 (0.053)	2424 (0.03)
Mannitol		Bulk	0.518 (0.024)	2408 (0.03)
Mannitol	1.491 (0.002)	Sieved (125–180 μm)	0.562 (0.013)	732 (0.01)
Mannitol		Milled	0.380 (0.041)	7158 (0.02)

[a] Apparent particle density, (AccuPyc 1330, Micrometrics, Norcross, USA), $n = 6$.

[b] Unsettled bulk density of powders (used in estimation of V_0), $n = 3$.

[c] Volume-specific surface area of powders, $n = 3$.

and V is the volume of the powder column at pressure P. The volume of the powder bed in the die before compression, V_0, was estimated by transforming the unsettled powder bulk density into the corresponding height of the powder in the die [13]. The Kawakita compression parameters a and b^{-1} were obtained by linear regression of the profiles in the pressure range of 25–250 MPa. Experimental data tend to fit the Kawakita equation well over a wide pressure range and high correlation coefficients ($R^2 > 0.999$) for the linear regression should be expected.

In physical terms, the Kawakita parameter a represents the engineering strain at infinite pressure, while the inverted b-parameter represents the applied pressure needed to achieve an engineering strain of $a/2$. Powders for which particle rearrangement will have a significant influence on the overall compression process are associated with low values of parameter b^{-1} and high values of parameter a. The product ab_{I} was hence calculated and used as an index (ab_{I}) by which a powder can be classified as Class I ($ab_{\mathrm{I}} > 0.1$) or Class II ($ab_{\mathrm{I}} \leqslant 0.1$). A combination of $ab_{\mathrm{I}} > 0.1$, $a > 0.6$ and $b^{-1} < 7$ are thus typical features for a Class I powder.

Step 2: The compression profiles were thereafter adapted to the Shapiro general compression equation [33]: $\ln(E) = \ln E_0 - kp - fP^{0,5}$ where E is the porosity of the powder bed, E_0 the initial porosity of the powder bed, P the applied compression pressure and k and f constants. The Shapiro parameter f is preferably calculated using the bulk porosity transformed from the measured bulk density, as done for V_0. The f-parameter describes the initial curvature of a porosity–pressure profile in the low-pressure region, and the f-parameter was determined by non-linear curve fitting of the Shapiro equation to the compression data by a least-squares method in Excel (convergence criterion = relative χ^2-change $\leqslant 0.00001$). The curve fitting was carried out in the same pressure range for profile for all powders, i.e. 0–50 MPa. For Class I powders, both particle rearrangement and particle fragmentation that may occur simultaneously in stage 1 are reflected in the f-parameter, while for a Class II powder, the f-parameter is used as an indication of the degree of particle fragmentation that occurs during compression, i.e. the particles can be classified as brittle or ductile.

Step 3: The compression profiles were finally adapted to the Heckel equation [18,32]: $\ln(1/E) = kP + intercept$, where E is the porosity of the compressed powder bed at an applied pressure P. The ratio $\ln(1/E)$ is often referred to as the Heckel number. The slope k of the plot of Heckel number vs. pressure was obtained using linear regression, and the yield pressure, P_y, was calculated as the reciprocal of the slope k. The yield pressure P_y gives an indication of the plasticity of the material and thus can be used to categorize materials from very soft to hard.

In many cases, only a part of a Heckel profile is linear and the pressure range that can be described by the equation may vary markedly between powders. Thus, a procedure by which "the true" linear region is identified was used. The first derivatives of the profiles, defined as the slope of seven consecutive data points, were calculated and the minimum value of the first derivative was selected. The start point and end point of the linear region of the Heckel profile were thereafter defined as +25% of the minimum value of the derivative. This definition gave generally a R^2-value >0.999 of the linear region of the Heckel profile.

3.5. Multivariate data analysis

A principal component analysis, PCA (The Unscrambler X 10.1, CAMO, Norway), of the compression data was used to visualize or illustrate the change in compression characteristics accomplished by the preparation procedures used. All data were centred and standardized by their standard deviation (1/SDEV) [39] to give each variable equal weight prior to the analysis.

4. Results and discussion

The bulk powders could for both substances be described as coarse particulate powders (Fig. 2) with relatively low specific powder surface areas (Table 2). The particle size was lower for mannitol, having a median particle size of ~110 μm, than for sodium chloride, having a median particle size of ~470 μm. Mannitol had a 10-fold higher specific powder surface area than sodium chloride, which could be explained not only by the lower particle size but also by a more irregular particle shape.

When preparing new powder samples, the sieve cuts were chosen to give particles of a narrow spread in size and of a diameter in the same order of magnitude as the median particle size for the respective substance (Fig. 2). The preparation gave a reduction in specific powder surface area for the sieve cuts compared with the bulk powders. Milling was used to markedly reduce the size of the particles, and the milled powders showed consequently a considerably larger specific surface area than the other powders. The volume-specific surface areas of the milled powders corresponded to a particle size of ~15 μm for mannitol and of ~40 μm for sodium chloride, as calculated using an arbitrary value of the Heywood surface to volume shape coefficient of 10. For the respective substance, a decreased particle size corresponded to a decreased unsettled bulk density of the powders (Table 2).

For both substances, the bulk powders showed values of the Kawakita a-parameter and the Kawakita b^{-1}-parameter as well as the ab-index similar to earlier results [15]. The values indicate that mannitol exhibits a higher compressibility than sodium chloride. For both substances, the sieved powders tended to be less compressible than the bulk powders, as indicated by a decreased Kawakita a-parameter and an increased Kawakita b^{-1}-parameter. The consequence of the changes in Kawakita parameters was that the calculated ab-index became slightly lower. The milled powders finally gave the highest value of the Kawakita a-parameter and the lowest values of the Kawakita b^{-1}-parameter and the ab-index increased compared with the bulk and the sieved powders to values above 0.1. Thus, milling gave powders of increased compressibility compared with the bulk powders.

It has earlier been suggested that the ab-index could be used as an indication of the incidence of particle rearrangement during compression, i.e. if the low-pressure region of a compression profile could be attributed to particle rearrangement or to another

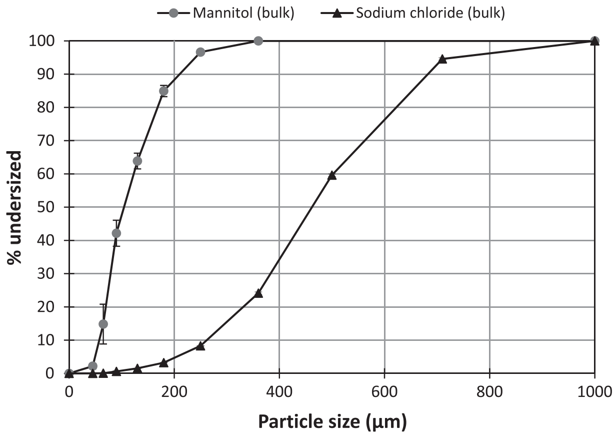

Fig. 2. Particle size distribution obtained from dry sieving of bulk powders.

Table 3
Compression parameters and proposed classification of powders (relative standard deviations within brackets).

Powder	a[a] (–)	b^{-1} [b] (MPa)	ab_{I} [c] (–)	f [d] (–)	P_y [e] (MPa)	Class [f]	Heckel type [g]
Sodium chloride (bulk)	0.508 (0.001)	27.2 (0.003)	0.019 (0.003)	0.06 (0.02)	70.5 (0.01)	IIA	3
Sodium chloride (sieved 425–500 μm)	0.504 (0.002)	34.9 (0.009)	0.014 (0.008)	0.05 (0.02)	69.8 (0.01)	IIA	3
Sodium chloride (milled)	0.772 (0.001)	4.8 (0.01)	0.16 (0.01)	0.08 (0.03)	86.2 (0.02)	I	1
Mannitol (bulk)	0.650 (0.001)	5.4 (0.04)	0.12 (0.05)	0.23 (0.04)	133 (0.04)	I	1
Mannitol (sieved 125–180 μm)	0.602 (0.001)	6.4 (0.07)	0.094 (0.07)	0.29 (0.03)	132 (0.01)	IIB	2
Mannitol (milled)	0.742 (0.001)	3.8 (0.03)	0.19 (0.03)	0.17 (0.03)	135 (0.03)	I	1

[a] Kawakita parameter a, $n = 5$.
[b] Kawakita parameter b^{-1}, $n = 5$.
[c] ab-index, $n = 5$.
[d] Shapiro parameter f, $n = 5$.
[e] Yield stress (Heckel parameter) P_y, $n = 5$.
[f] Classification of powders in terms of classification system.
[g] Categorization of powders in terms of type of Heckel profile.

mechanism. A threshold value of 0.1 has been suggested [13] to guide the classification of the powders, i.e. an ab-index >0.1 is indicative of a powder expressing significant particle rearrangement, while the converse applies for an ab-index ⩽0.1. The consequence is that for sodium chloride, only the milled powder was classified as a Class I powder, while for mannitol, both the bulk and the milled powders were classified as Class I powders.

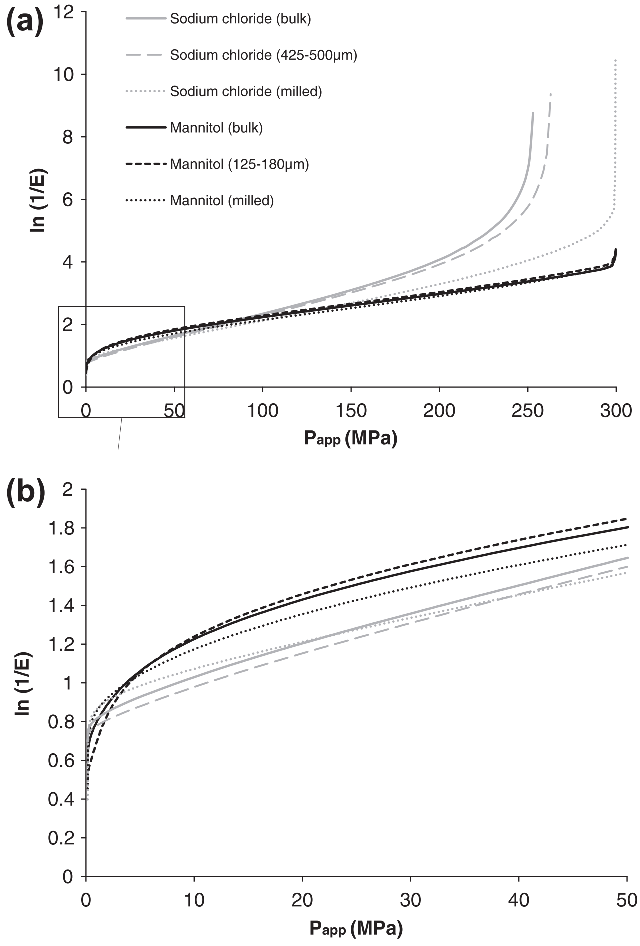

Fig. 3. Heckel profiles for the six materials up to an applied pressure of 300 MPa (a) and 50 MPa (b), respectively.

The bending of a Heckel profile in the low-pressure region, here defined as a pressure range up to 50 MPa, has earlier been suggested [14] to be caused by particle rearrangement or particle fragmentation or a combination thereof. The bending can be assessed by one of the compression parameters, the f-parameter, of the Shapiro general compression equation [33]. For both substances, the bulk powders showed values of the f-parameter similar to earlier results [14]. Mannitol showed generally higher values of the f-parameter than sodium chloride. For sodium chloride, the f-parameter was similar between all three powders, while for mannitol, the f-parameter reduced in the order sieved powder, bulk powder and milled powder.

Based on a statistical analysis, it was earlier suggested [15] that for Class II powders, i.e. powders showing limited degree of particle rearrangement during compression, particle fragmentation affected the degree of curvature of a Heckel plot in the low-pressure region. The statistical analysis gave no support that the f-parameter can be used as a fine-tuned approach to determine particle fragmentation but is thus suggested to be used as a means to make a rough distinction between particles with respect to their fragmentation propensity. This distinction was based on the value of the f-parameter of 0.1, i.e. a f-parameter ⩽0.1 is indicative of a powder expressing a low degree of particle fragmentation (Class IIA), while a f-parameter >0.1 is indicative of a powder expressing a high degree of particle fragmentation (Class IIB). Based on the parallel set of values of the ab-index and the f-parameter, bulk and sieved powders of sodium chloride and sieved powder of mannitol could be further sub-categorized as low-fragmenting (ductile) and high-fragmenting (brittle) powders, respectively. Based on the classification of powders as Class I, Class IIA and Class IIB, the powders were also categorized in terms of type of Heckel profile (Fig. 1 and Table 3). Heckel profiles for all powders used are given in Fig. 3.

The sodium chloride powders gave as expected generally lower yield stresses (P_y) than the mannitol powders, i.e. sodium chloride was softer than mannitol. The P_y was similar for all three mannitol

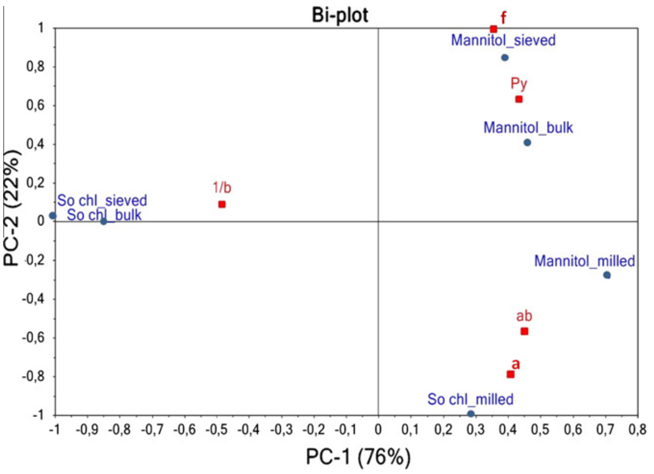

Fig. 4. Combined score (blue circles) and loading (red squares) plot from PCA of powder samples and compression variables. 76% and 22% of the variation in the data explained on PC 1 and PC 2, respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

powders, while for sodium chloride, the milled particles gave a higher P_y, indicating that for sodium chloride, the milling gave slightly harder particles. Compared with the *ab*-index and the *f*-parameter, the P_y can be used as a more fine-tuned distinction between powders in terms of compression characteristics [15]. As suggested by Roberts and Rowe [5], the P_y can be used to classify powders into four groups describing their plasticity. This classification is adopted also here (Fig. 1). Accordingly, sodium chloride can be described as a soft material and mannitol as a moderately hard material.

A principal component analysis (PCA) of the compression data was performed to elucidate the change in compression characteristics accomplished by the preparation procedures used. In the combined scores (blue) and loading (red) plot (Fig. 4), the first two PCs accounted for 98% of the variation in the data set (76% and 22%, respectively). The six powders spread out into three groups, i.e. the powders grouped in pairs due to their similar compression characteristics. The bulk and sieved sodium chloride powders were located close to each other to the left along PC1, the bulk and sieved mannitol powders in the upper right quartile and the milled powders for both materials in the lower right quartile.

The compression variable Kawakita b^{-1} was significant only to PC1, while the other four variables were significant to both principal components. These latter variables grouped in pairs, i.e. the *f*-parameter and P_y located in the upper right quartile and the *a*-parameter and the *ab*-index located in the lower right quartile.

The compression behaviour was different between the bulk powders for both materials, and the sieving tended to increase the differences in compression behaviour. Thus, for these four powders, the inherent mechanical properties of the two materials respectively controlled the observed difference in compression characteristics. The two milled powders, one for each material, grouped, however, more close to each other, i.e. milling changes the compression characteristics towards more similarity regardless of the different inherent mechanical properties of the materials.

For the sodium chloride powders, the bulk and sieved powders were located close to each other in the PCA plot and showed similar compression characteristics. The milling of the bulk powder changed the location in the PCA plot primarily due to not only a change in the Kawakita b^{-1}-parameter but also a change in the other four variables. In mechanistic terms, the milling induced significant particle rearrangement and gave particles less prone to deform.

For the mannitol powders, both sieving and milling changed the position of the powders in the PCA plot. The change due to sieving could be explained by changes in mainly the *a*-parameter, the *ab*-index, the *f*-parameter and P_y, while the Kawakita b^{-1}-parameter did not explain the obtained change. In mechanistic terms, sieving gave particles showing less rearrangement and more fragmentation than the bulk powder. The change due to milling could be explained by the same variables but in the opposite direction along the PC2. In mechanistic terms, milling gave particles showing more particle rearrangement during compression.

The outcome of the protocol described in this paper for the assessment of compression characteristics of the powders is finally summarized in Table 4 in terms of stages expressed during the compression process and dominant mechanical properties of the particles, i.e. their fragmentation propensity and plasticity.

The protocol represents a standardized approach to powder compression analysis with the ambitions to categorize powders with respect to their compression behaviour. Within this frame, the protocol suggested here can be further developed in different ways into a more comprehensive procedure. The most fine-tuned descriptor of the compression behaviour is based on the use of the Heckel parameter, and we have earlier pointed out [15] that this parameter is a strong descriptor of the compression behaviour of a powder. There is, however, still a need to forward our understanding of the physical significance of the Heckel parameter and new equations with parameters describing particle plasticity may also be included in the protocol, e.g. the equation developed by Frenning et al. [27]. In order to assess the fragmentation propensity of particles in a more fine-tuned way, it seems that another approach than powder compression analysis is needed. Possible approaches may be the measurement of tablet surface area as a function of compression pressure [40] or the measurement of the mechanical strength of single particles [41]. Finally, the elasticity of particles may be of importance of the compactibility of a

Table 4
Overview of the compression behaviour of the powders in terms of stages expressed during the compression process and description of particle mechanics.

Powder	Stage 1: particle rearrangement	Stage 2: particle fragmentation	Stage 3: particle plastic deformation	Stage 4: elastic deformation of stiff compact	Particle mechanics
Sodium chloride (bulk)	No	No	Yes	Yes	Ductile, soft
Sodium chloride (sieved 425–500 μm)	No	No	Yes	Yes	Ductile, soft
Sodium chloride (milled)	Yes	No	Yes	Yes	Ductile, soft
Mannitol (bulk)	Yes	Yes	Yes	Yes	Brittle, moderately hard
Mannitol (sieved 125–180 μm)	No	Yes	Yes	Yes	Brittle, moderately hard
Mannitol (milled)	Yes	Yes	Yes	Yes	Brittle, moderately hard

powder, and a simple compression test for assessing the stiffness of particles seems a valuable asset.

5. Summary and conclusions

In this paper, a standardized protocol for powder compression analysis has been presented. From powder compression data, a set of compression variables were derived, and by using critical values of these variables, the stages expressed during the compression of the powders could be identified and the powders could be classified into groups with respect to the expression of particle rearrangement, particle fragmentation and particle plastic deformation during compression. It is concluded that the proposed protocol could, in a satisfactorily way, describe and distinguish between the powders regarding their compression behaviour. Hence, the protocol could be a valuable asset in a formulation development programme to assess compression characteristics of powders and particle mechanical properties. Within the suggested structure of the approach, the protocol could be further developed to refine the analysis.

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