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Research paper

A statistical approach to evaluate the potential use of compression parameters for classification of pharmaceutical powder materials

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ABSTRACT

The current work aims to investigate whether a multivariate statistical approach could reveal latent structures in compression data and group powders with respect to their compression behavior in a way that is consistent with an earlier proposed classification system. Seventeen pharmaceutically relevant materials, exhibiting a wide range of mechanical properties, were used as supplied, compressed, and parameters from three commonly used powder compression models (Kawakita parameters a and b^{-1}, the rearrangement index ab, the Shapiro f parameter and Heckel P_y) were retrieved. Multivariate analysis of the compression parameters was done with a Principal Component Analysis (PCA). It was found that the latent structures could be divided into three main parts; the most variation was found in the direction associated with particle rearrangement, second largest variation was found in the direction described by the particle fragmentation propensity, and the least variation was found in the direction associated with the plasticity of the particles. This work demonstrates that a combination of the selected compression parameters could be utilized to find relevant differences in compression behavior for a wide range of materials, and that this information can be presented in an efficient way by applying multivariate data analysis techniques.

1. Introduction

The preferred physical form of a pharmaceutical product is often the solid form, *e.g.* granules, capsules, tablets and powders for reconstitution into different dosage forms. During the manufacturing of a solid product, drugs and excipients are subjected to mechanical stresses, *e.g.* during charging and discharging, grinding, mixing, extrusion, fluidization, dispensing, compression and coating. It is thus the concern of the formulation and manufacturing scientists to understand the response of solids to mechanical stresses during the development of a product and in the production line. Two aspects of such a response have been subjects of considerable interest in powder and pharmaceutical science for some time: the mechanics [1] and the mechanical activation [2] of particles during mechanical straining. Understanding, characterizing and predicting material properties are important aspects in the current evolution of the conceptual view of the pharmaceutical development and manufacturing, reflected in several initiatives such as formulation by Quality by Design (QbD) [3], manufacturing with improved Process Analytical Technology (PAT) [4] and the testing of Functionality-Related Characteristics (FRC) [5].

A variety of methods and procedures are used to assess the mechanical properties of drugs and excipients. Mechanical testing of small particles is not trivial, and the use of compression parameters derived from powder compression curves, *i.e.* relationships between the volume of the powder bed and the applied pressure, is an attractive approach of both experimental and statistical reasons [6]. The problem with this approach is the question whether the derived compression parameters indicate a physically defined mechanical property, *i.e.* whether the parameters can represent indications of the plasticity and brittleness of the particles. In order to enable the use of compression parameters as descriptors of mechanical properties of powders, our understanding of their physical interpretation needs to be improved.

In previous work, the Kawakita compression parameters [7], often denoted a and b, were studied and it was found that powders expressing significant particle rearrangement at low compression pressures showed low values of parameter b^{-1} and high values of parameter a. It was suggested that the product of these parameters can be used as an indication of the overall contribution of particle rearrangement to the powder compression profile [8]. The powders studied were divided into two classes, characterized by high and low values of the ab index reflecting high (Class I) and low (Class II) incidence of particle rearrangement during the initial compression phase, respectively. For powders with limited initial particle rearrangement (Class II powders), the change in particle

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diameter due to particle fragmentation controlled the initial bending of a Shapiro–Konopicky–Heckel (SKH) profile [9,10], a compression profile most commonly referred to in pharmaceutical literature as the Heckel profile. Consequently, powders with limited initial particle rearrangement can be further sub-divided into two categories (denoted A and B), with particles showing low and high degree of fragmentation, respectively, during compression, *i.e.* ductile (IIA) and brittle (IIB) particles. In addition, an indication of particle plasticity (in terms of a yield pressure P_y) from the linear part of a Heckel profile could be derived for both Class I and II A and B powders. Hence, the Heckel profile seems to be an experimental tool to describe powder compression behavior in terms of particle fragmentation (f) and particle deformation (P_y) from one single compression analysis [11]. A simplified schematic summary of the different powder compression phases, and the parameters evaluated above, is found in Fig. 1.

By using a statistical multivariate data analysis, *e.g.* Principal Component Analysis (PCA), on a set of experimental data, it is possible to reveal intrinsic structures and to group observations in the data, which might be difficult to do by traditional univariate data analysis [12]. A multivariate approach has recently been used to study the compression of pharmaceutical powders [13]. In this paper, the aim was to investigate whether a multivariate approach would be able to reveal latent structures in compression data and group powders with respect to their compression behavior in a way that is consistent with the earlier proposed classification. A set of 17 pharmaceutical powders (objects, n) considered to represent a wide span of compression properties were selected, and from the powder compression *vs.* applied pressure relationships, five compression parameters (variables, p) were derived. The results were thereafter evaluated by a PCA.

2. Materials and methods

2.1. Materials

In this work, 17 common pharmaceutical materials were used as objects. The powder materials (Table 1) were chosen based on their assumed compression mechanics in order to create a wide span of mechanical properties and were divided into four groups based on their assumed hardness [14]. The following materials were used in the study: Aspirin (Sigma–Aldrich, Stockholm, Sweden); Dicalcium phosphate (Sigma–Aldrich, Stockholm, Sweden); Maize starch (Sigma–Aldrich, Stockholm, Sweden); Mannitol (Sigma–Aldrich, Stockholm, Sweden); Paracetamol (Sigma–Aldrich, Stockholm, Sweden); Sodium bicarbonate (Sigma–Aldrich, Stockholm, Sweden); Sodium chloride (Sigma–Aldrich, Stockholm, Sweden); Talc (Sigma–Aldrich, Stockholm, Sweden); α-monohydrate lactose (Pharmatose 90 M, donated by DMV-Fonterra Excipients, Goch, Germany); Polyethylene glycol 6000 (PEG 6000, Sigma–Aldrich, Steinheim, Germany); Polyvinylpyrrolindone (PVP 17PF, BASF, Limburgerhof, Germany); FlowLac® 100 (spray-dried α-monohydrate lactose, donated by Meggle, Wasserburg, Germany); MicroceLac® (spray-dried mixture of 75% Lactose monohydrate and 25% Microcrystalline cellulose, donated by Meggle, Wasserburg, Germany); StarLac® (spray-dried mixture of 85% Lactose monohydrate and 15% Maize starch, donated by Meggle, Wasserburg, Germany); Avicel® HFE-102 (Microcrystalline cellulose and Mannitol, donated by FMC BioPolymer, Leeds, England); Avicel® PH-102 (Microcrystalline cellulose, MCC, donated by FMC BioPolymer, Leeds, England); Starch 1500® (partially pregelatinized Maize starch, Colorcon, Dartford, England).

2.2. Conditioning of powders

The powders were used as supplied by the manufacturers, *i.e.* no particle size separation was done prior to the experiments. All powder materials were however 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 7 days prior to further powder characterization and compression. This temperature and humidity corresponded reasonably to the conditions of the laboratory. The spray-dried lactose (FlowLac100) was kept in a closed container over a silica gel, corresponding to a relative humidity of about 25%, in order to prevent crystallization of the amorphous particles.

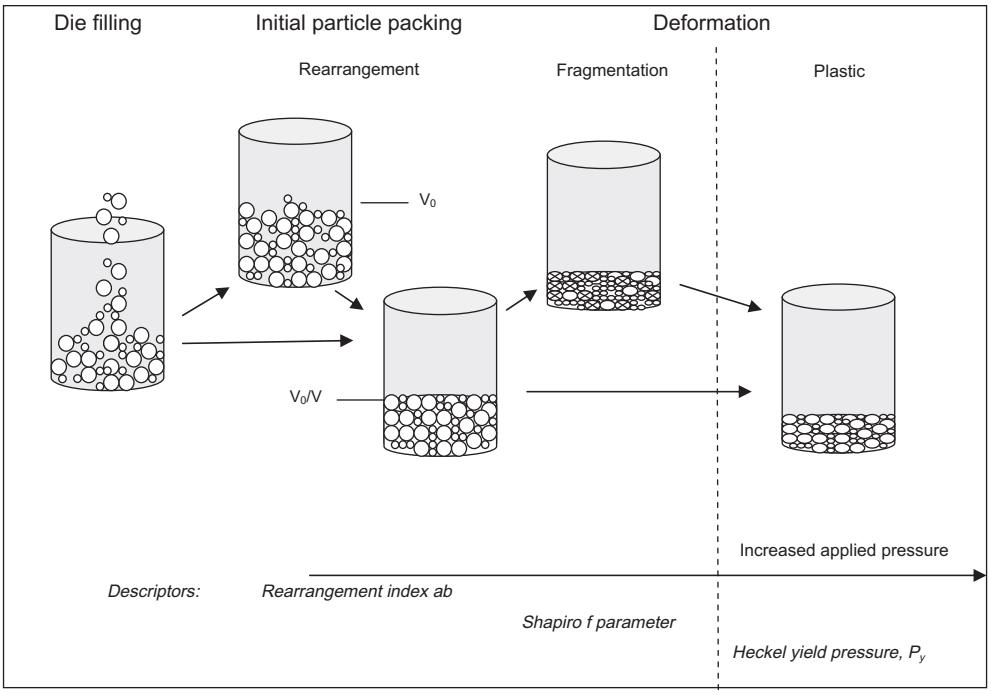


Fig. 1. Schematic illustration of the die filling, particle rearrangement and deformation of powder particles under load in a die.

Table 1
Materials included in the study and their expected dominating mechanical properties.

Material	
Primary particles	
Sodium bicarbonate	Hard, brittle[a]
Dicalcium phosphate	Hard, brittle[a]
Talc	Hard[a]
α-Lactose	Moderately hard, brittle, ductile[a]
Paracetamol	Moderately hard, brittle[a]
Mannitol	Moderately hard, ductile[a]
Sodium chloride	Soft, ductile[a]
Maize starch	Soft, ductile[a]
PEG 6000	Very soft, ductile[b]
PVP	Very soft, ductile[b]
Aspirin	Very soft, ductile[a]
Complex particles	
Avicel PH-102	Soft, ductile[a]
MicroceLac	Soft-moderately hard[b]
StarLac	Soft-moderately hard[b]
Starch 1500	Soft[b]
Avicel HFE	Soft-moderately hard[b]
FlowLac100	Soft-moderately hard[b]

[a] As given by Roberts and Rowe [14].
[b] *A priori* expected mechanical property.

2.3. Particle and powder characterization

Visual inspection of the powders was done by optical light microscopy (model Vanox, Olympus, Tokyo, Japan), and scanning electron microscopy (SEM) images of the powder samples were taken. The powder samples were mounted on an aluminium base with adhesive carbon tape and sputtered with gold and platinum under vacuum for 90 s prior to SEM-picture taking (JSM-6300 SEM, Japan Electron Optics Laboratory, Ltd., Tokyo, Japan).

The apparent particle density (ρ_{app}) was determined with a helium gas pycnometer (AccuPyc 1330, Micrometrics, Norcross, USA). Reported results are the mean of two separate experiments with 10 cycles for each experiment.

As a means to characterize powder flowability, the bulk densities before and after controlled tapping were determined for all powders. The unsettled bulk density of the powders (ρ_{bulk}) was measured by gentle pouring of powder samples (15–58 g) into a graduated 50-ml cylinder with a diameter of ~23 mm. The height of the powder bed was thereafter determined visually. The tap density (ρ_{tapped}) was obtained by tapping the same 50-ml cylinder up to 1250 times by the use of a tap density testing apparatus (PharmaTest, PT-TD, Hainburg, Germany) and thereafter visually determining the height of the powder bed. From the tapping data, the Hausner ratios, *HR* [15], were calculated as

$$HR = \rho_{tapped}/\rho_{bulk} \quad (1)$$

Reported results are the mean of three separate experiments.

In order to get an estimate of the height of the powder after filling the powders into the die used for the powder compression experiments described below, another measure of the unsettled bulk density of the powders (ρ_{poured}) was determined in a glass cylinder with a diameter of 11.47 mm. Powder samples (0.9–3.3 g) were gently poured into the cylinder, and the height of the powder beds were measured with a digital height gauge (Mitutoyo Digimatic, ID-C, Tokyo, Japan). Reported results are the mean of three separate experiments.

The volume-specific surface area (S_0) of the fine powders, *viz.* materials estimated as of sub-sieve size (<50 μm), was determined using a transient (Blaine) air permeability apparatus [16]. S_0 was calculated using a slip flow corrected Kozeny–Carman equation [17], and the reported results are the mean of five separate experiments with three recordings of flow time for each experiment. 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 [16,18] as described in previous work [8]. Reported results are the mean of three separate experiments with three recordings of flow rate and pressure for each experiment.

2.4. Collection of powder compression data

Confined compression of the powders was performed using a materials testing machine (Zwick Z100, Zwick/Roell GmbH & Co. KG, Ulm, Germany), equipped with 11.3-mm-diameter flat-faced punches, up to a maximal applied pressure of 300 MPa. The lower punch was stationary during the compression and the upper punch moved at a speed of 10 mm/min. All powder compression data were corrected for the determined elastic deformation of the punches according to a procedure described in previous work [19]. The die and punch faces were lubricated with a 1% magnesium stearate suspension in ethanol prior to the compression. The material for each tablet was weighed (about 500 mg) on an analytical balance and poured by hand into the die. Reported results are the mean of five separate compression cycles.

2.5. Analysis of the powder compression data

The compression data were thereafter adapted to the linear form of the Kawakita equation;

$$\frac{P}{C} = \frac{1}{ab} + \frac{P}{a} \quad (2)$$

where P is the applied compression pressure and C is the engineering strain of the powder

$$C = \frac{V_0 - V}{V_0} \quad (3)$$

where V_0 is the initial powder volume and V is the volume of the powder column at pressure P. V_0 was set from the unsettled bulk density (ρ_{poured}) transformed into a corresponding height in die. The Kawakita compression parameters a and b^{-1} were obtained by linear regression in the pressure range from 25 MPa to 250 MPa and $R^2 > 0.999$ in all cases. The product ab was finally calculated.

Furthermore, the compression data were adapted to the Shapiro–Konopicky–Heckel equation [9]:

$$\ln\frac{1}{E} = kP + A \quad (4)$$

where E is the porosity of the powder bed, P *is* the applied compression pressure, and k and A are constants. The reported yield pressures, P_y, are the reciprocal of the slope k, which was calculated using linear regression in a pressure range determined separately for each material. The range was determined by finding the minimum value of the first derivative of the Heckel profile and setting the endpoints used in the linear regression as ±25% of this value. Hence, correlation coefficients obtained by linear regression were for all materials approximately 1 (R^2-values > 0.999) except for Talc, for which this method was not applicable since a linear region of the Heckel profile was not obtained.

As a descriptor of the powder compression process in region I of a SKH-compression profile, the Shapiro compression parameter, here denoted f, was derived from the Shapiro General Compaction Equation (GCE) [10]:

$$\ln(E) = \ln E_0 - kP - fP^{0.5} \quad (5)$$

where E is the porosity of the powder bed, E_0 is the initial porosity of the powder bed, P *is* the applied compression pressure and k and f

are constants. Curve-fitting of the experimental data was done by the least squares method in the pressure range up to an applied pressure of 50 MPa, except for Aspirin where the upper pressure limit was 25 MPa.

2.6. Multivariate data analysis

Principal Component Analysis (PCA) (The Unscrambler® 9.7, CAMO AS, Norway) was performed to reveal latent structures in the data set and to identify grouping of the materials. The data matrix included the previously described set of materials (objects, $n = 17$), each characterized by the obtained compression parameters (variables, $p = 5$). Modeling was done using systematic cross-validation; data were centered and scaled using a common normalization method (1/SDev) [12]. A systematical approach was applied; first, including all materials and parameters into the model, followed by identification of extremes or potential outliers. Extreme samples were then left out in order to analyze remaining materials in further detail.

3. Results

3.1. Particle and powder properties

SEM images of all materials are given in the Appendix A and in Table 2 some particle and powder properties are presented. In terms of general appearance and particle structure, the images showed that the particles were of two types, *i.e.* primary particles and complex particles. The primary particles consisted of a single solid phase while the complex particles consisted of two or more phases, *i.e.* agglomerated, porous particles or particles composed of blends of two materials. The following 11 materials were categorized as primary particles: Aspirin, Dicalcium phosphate, Maize starch, Mannitol, Paracetamol, Sodium bicarbonate, Sodium chloride, Talc, α-monohydrate lactose, Polyethylene glycol and Polyvinylpyrrolindone. The remaining six materials were categorized as complex particles, *i.e.* FlowLac® 100, MicroceLac®, StarLac®, Avicel® HFE-102, Avicel® PH-102 and Starch 1500®. The two drug substances (Aspirin and Paracetamol) were, as all the materials, chosen primarily on the basis of their mechanical properties, but they could also be seen as representatives of drug substances that appear in high proportions in tablets, *i.e.* high-dose drugs for which the compression properties are important for the manufacturability of the formulation.

Table 2
Some characteristics of powders. The relative standard derivations are given in parentheses.

Powder	ρ_{app}[a] (g/cm^3)	ρ_{poured}[b] (g/cm^3)	ρ_{bulk}[c] (g/cm^3)	HR[d] (–)	S_0[e] (cm^{-1})
Aspirin	1.398 (0.001)	0.78 (0.01)	0.79 (0.01)	1.10	129 (0.02)
Avicel HFE	1.647 (0.0002)	0.38 (0.02)	0.42 (0.02)	1.35	1697 (0.07)
Avicel PH-102	1.584 (0.001)	0.34 (0.03)	0.36 (0.004)	1.33	2690 (0.02)
Dicalcium phosphate	2.358 (0.001)	0.50 (0.03)	0.59 (0.01)	1.72	21,865 (0.03)
FlowLac100	1.565 (0.001)	0.60 (0.03)	0.62 (0.001)	1.15	1028 (0.05)
Lactose	1.551 (0.001)	0.72 (0.01)	0.74 (0.001)	1.21	818 (0.02)
Mannitol	1.494 (0.0003)	0.50 (0.02)	0.57 (0.01)	1.37	2566 (0.01)
Maize starch	1.506 (0.001)	0.45 (0.04)	0.58 (0.01)	1.36	5795 (0.03)
Paracetamol	1.293 (0.0004)	0.24 (0.08)	0.32 (0.02)	1.88	2611 (0.02)
PEG 6000	1.245 (0.006)	0.47 (0.03)	0.51 (0.004)	1.16	128 (0.04)
PVP	1.195 (0.0003)	0.36 (0.01)	0.34 (0.002)	1.42	3088 (0.05)
MicroceLac	1.572 (0.0002)	0.48 (0.02)	0.49 (0.003)	1.22	1283 (0.09)
Sodium bicarbonate	2.227 (0.001)	0.81 (0.03)	0.91 (0.01)	1.39	1181 (0.01)
Sodium chloride	2.146 (0.001)	1.16 (0.03)	1.17 (0.004)	1.15	235 (0.01)
Starch 1500	1.503 (0.0002)	0.58 (0.001)	0.61 (0.01)	1.32	819 (0.03)
StarLac	1.553 (0.0002)	0.57 (0.02)	0.60 (0.001)	1.18	712 (0.07)
Talc	2.837 (0.004)	0.42 (0.03)	0.47 (0.001)	1.95	28,106 (0.09)

[a] Apparent particle density, $n = 2$.
[b] Unsettled bulk density (*in-die* start value), $n = 3$.
[c] Unsettled bulk density, $n = 3$.
[d] Hausner ratio.
[e] Powder volume-specific surface area, $n = 3$.

In terms of particle size and shape, a wide variation was also obtained between the powders used (Appendix A). The powders ranged from fine-particulate, such as Talc and Dicalcium phosphate, to coarse-particulate powders, such as Sodium chloride and Aspirin. The particle shape varied from flaky to regular. Consequently, a wide range of powder surface areas, S_0, was also obtained, from 128 cm^{-1} to 28,106 cm^{-1} for PEG and Talc respectively. The particle density, ρ_{app}, varied from 1.195 g/cm^3 for PVP to 2.837 g/cm^3 for Talc.

Due to the large variation in size, shape and surface area, the powders used also differed considerably in packing properties, having bulk densities ranging from the very lightly packed Paracetamol powder ($\rho_{poured} = 0.24$ g/cm^3 and $\rho_{bulk} = 0.32$ g/cm^3) to the dense packed Sodium chloride powder ($\rho_{poured} = 1.16$ g/cm^3 and $\rho_{bulk} = 1.17$ g/cm^3). The two values of unsettled powder densities, ρ_{poured} and ρ_{bulk}, correlated reasonably but the filling of the smaller cylinder gave mostly a lower powder density.

Particle shape and size are commonly recognized as important particulate properties for powder packing and flow and the powders used gave as expected a large variation in Hausner Ratio (HR). According to the scale of flowability in Eur. Ph. [20], adapted from Carr [21], commonly used as a means to classify powder flow, the powders varied in flowability from very very poor (Paracetamol ($HR = 1.88$), Dicalcium phosphate ($HR = 1.72$) and Talc ($HR = 1.95$)) to excellent (Aspirin with a $HR = 1.10$).

3.2. Compression parameters

In this study, the compression parameters and the derived compression index used, presented in Table 3, have been selected based on the assumption that they represent indications of the behavior of the particles in different stages of the powder compression process, as illustrated in Fig. 1. In terms of a Heckel profile, the relationship is often divided into two regions, I and II, where region I is non-linear followed by a nearly linear region II.

The Kawakita parameter a represents the maximal engineering strain, C_∞, of the powder bed and ranged from 0.456 (Aspirin) to 0.844 (Talc). Mathematically the parameter b^{-1} is equal to the pressure when the value of C reaches one-half of the limiting value ($C = C_\infty/2$) [22], and for the selected materials the b^{-1} parameter range from 1.19 MPa (Talc) to 28.3 MPa (Sodium chloride). It is earlier suggested [8] that the combination of the Kawakita parameters into a single index, ab, can be used as an indication of the incidence of particle rearrangement (powder flow) during powder compression and a high ab value corresponds to high degree of particle rearrangement, *i.e.* a powder characterized by a high value of the a parameter combined with a low b^{-1}. Talc showed a high value for the ab index (0.71), whereas Sodium chloride had a low index (0.02), meaning that the latter showed nearly no initial particle rearrangement and vice versa.

The compression parameter referred to as the Shapiro f parameter describes the bending of the Heckel profile in region I, here defined as a range of compression pressures up to 50 MPa. It has earlier been suggested [11] that this parameter indicates particle fragmentation if the incidence of particle rearrangement is low or in other cases indicates a combined effect of particle rearrangement and particle fragmentation. The Shapiro f parameter varied substantially for the powders used, from 0.52 (Aspirin) to 0.02 (Maize Starch), indicating a large variation in compression behavior between the powders in region I of a Heckel profile.

The Heckel yield pressure, P_y, representing the compressibility of the powder in region II, varied from 15.2 MPa to 473 MPa, *i.e.*

Table 3
The Kawakita, Heckel and Shapiro compression parameters and suggested classification of the powders. The relative standard derivations are given in parentheses.

Powder	a[a] (–)	b^{-1}[b] (MPa)	ab[c] (–)	P_y[d] (MPa)	f[e] (–)	Class[f]	Heckel type[g]
AvicelHFE	0.776 (0.002)	6.1 (0.03)	0.13 (0.03)	251 (0.16)	0.09 (0.02)	I	1
Avicel PH-102	0.799 (0.001)	6.7 (0.02)	0.12 (0.02)	91.3 (0.02)	0.07 (0.05)	I	1
Dicalcium phosphate	0.749 (0.004)	4.6 (0.04)	0.16 (0.04)	473 (0.09)	0.11 (0.07)	I	1
Mannitol	0.660 (0.007)	5.6 (0.04)	0.12 (0.04)	169 (0.21)	0.22 (0.03)	I	1
Paracetamol	0.754 (0.002)	3.0 (0.02)	0.25 (0.02)	117 (0.11)	0.27 (0.05)	I	1
PEG 6000	0.637 (0.001)	2.9 (0.04)	0.22 (0.04)	36.2 (0.06)	0.24 (0.02)	I	1
Talc	0.844 (0.003)	1.19 (0.02)	0.71 (0.02)	–	0.38 (0.05)	I	1
Maize starch	0.732 (0.006)	9.6 (0.03)	0.08 (0.02)	83.8 (0.03)	0.02 (0.28)	IIA	3
PVP	0.739 (0.007)	9.3 (0.02)	0.08 (0.02)	54.3 (0.03)	0.04 (0.13)	IIA	3
Sodium chloride	0.501 (0.01)	28.3 (0.04)	0.02 (0.05)	89.8 (0.24)	0.07 (0.06)	IIA	3
Starch 1500	0.648 (0.001)	14.6 (0.01)	0.04 (0.01)	67.9 (0.01)	0.07 (0.01)	IIA	3
Aspirin	0.456 (0.02)	4.5 (0.02)	0.10 (0.04)	15.2 (0.32)	0.52 (0.06)	IIB	2
FlowLac100	0.611 (0.002)	13.6 (0.04)	0.05 (0.04)	168 (0.02)	0.12 (0.08)	IIB	2
Lactose	0.524 (0.02)	12.8 (0.03)	0.04 (0.05)	208 (0.29)	0.14 (0.02)	IIB	2
MicroceLac	0.692 (0.009)	10.0 (0.02)	0.07 (0.02)	170 (0.29)	0.14 (0.01)	IIB	2
Sodium bicarbonate	0.609 (0.004)	9.05 (0.02)	0.07 (0.02)	284 (0.08)	0.12 (0.06)	IIB	2
StarLac	0.633 (0.001)	10.9 (0.01)	0.06 (0.01)	142 (0.01)	0.15 (0.01)	IIB	2

[a] Kawakita a, $n = 5$.
[b] Kawakita b^{-1}, $n = 5$.
[c] Kawakita ab, $n = 5$.
[d] Yield pressure, $n = 5$.
[e] Shapiro f, $n = 5$.
[f] Classification based on initial particle rearrangement [8].
[g] Classification based on region I in a Heckel profile [11].

a 30-fold variation. Since the Heckel yield pressure is often used as an indication of the plasticity of particles, the powders used represented particles that were very soft (*e.g.* Aspirin, $P_y = 15.2$), soft (*e.g.* Starch 1500, $P_y = 67.9$), moderately hard (*e.g.* Lactose, $P_y = 208$) and hard (Dicalcium phosphate, $P_y = 473$), as categorized by Roberts and Rowe [14]. For the Talc powder, no linear part of the Heckel profile could be identified with the procedure used and hence, no value for the yield pressure was derived. An explanation for this might be that plastic deformation of Talc particles was not a rate controlling compression mechanism in any part of the pressure range used in this study.

3.3. Principal Component Analysis of compression data

A Principal Component Analysis (PCA) was performed with the five variables derived from the compression analysis, *i.e.* Kawakita parameters a and b^{-1}, the rearrangement index ab, the Shapiro f parameter and the Heckel yield pressure, P_y. In general, a PCA is decomposing a data matrix in such a way that the first principal component (PC) lies along the direction with the largest variation in the data set, PC2 orthogonally to PC1 along the direction of second largest variation etcetera. Objects on the same side of a PC are positively correlated, opposite ones are negatively correlated. Objects close to each other or clustered in groups have similar features, in contrary to objects situated far away from each other which are dissimilar. Very distinguished groups should be analyzed separately, and isolated objects may be considered outliers, especially if they show both high leverage and residual values [23].

The PCA plots of the compression variables of all materials used are given in Fig. 2. As shown in the loading plot (Fig. 2b), the compression variables associated with PC1 were mainly the rearrangement index ab and the Kawakita parameter b^{-1}, oppositely correlated with each other. The PC2 in the loading plot was associated with the three other compression variables, *i.e.* the a parameter and P_y, located close to each other, and the f parameter, located opposite to the other two variables. The model built on all powders explained totally 75% (47% and 28% for PC1 and PC2 respectively) of the variation in the data.

The 17 powders were distributed in all quartiles of the score plot (Fig. 2a). However, three powders were clearly separated from the other 14, *i.e.* Sodium chloride and Talc, which were inversely correlated along PC1, and Aspirin which was located in the lower part along PC2. In Fig. 3, stress–strain profiles for these three powders are shown together with two arbitrarily chosen reference powders, *i.e.* Lactose and Mannitol. The three clearly separated powders in the score plot were characterized by a high compressibility (Talc) or a low compressibility (Aspirin and Sodium chloride) with corresponding high and low a parameters (Table 3).

Based on the PCA in Fig. 2, Talc, Sodium chloride and Aspirin were categorized as extreme objects and they were eliminated from the data set and a new PCA model was built without these powders, as a means to better describe the distribution of the 14 remaining powders that were apparently clustered in Fig. 2a. The PCA plots of the compression variables of these 14 powders are given in Fig. 4.

The powders spread out relatively homogeneously into four quartiles of the score plot (Fig. 4a). Also in this reduced PCA model, the compression variables associated with PC1 were the rearrangement index ab and the Kawakita parameter b^{-1}, oppositely correlated with each other (Fig. 4b) whereas PC2 was associated with only two compression variables, the f parameter and the a parameter, located opposite to each other along PC2. The Heckel yield pressure (P_y) was located close to the center of the loading plot and represented by itself a third PC (Fig. 5). The model presented in Figs. 4 and 5 explained a total of 96% of the variation on the data set over three principal components (PC1: 51%; PC2: 25%; PC3: 20%).

4. Discussion

In this paper, a set of 17 pharmaceutical powders were investigated in terms of their particle and powder properties and their compression properties. The characterization of the powders showed that they represented a wide range of properties in terms of structure and dimension with a subsequent variation also in packing density and flowability. The compression parameters derived indicated further that the powders represented a great variation of compression behavior in terms of the incidence of particle rearrangement and fragmentation and the particle plasticity. Since the powders were selected based on diversity in compression

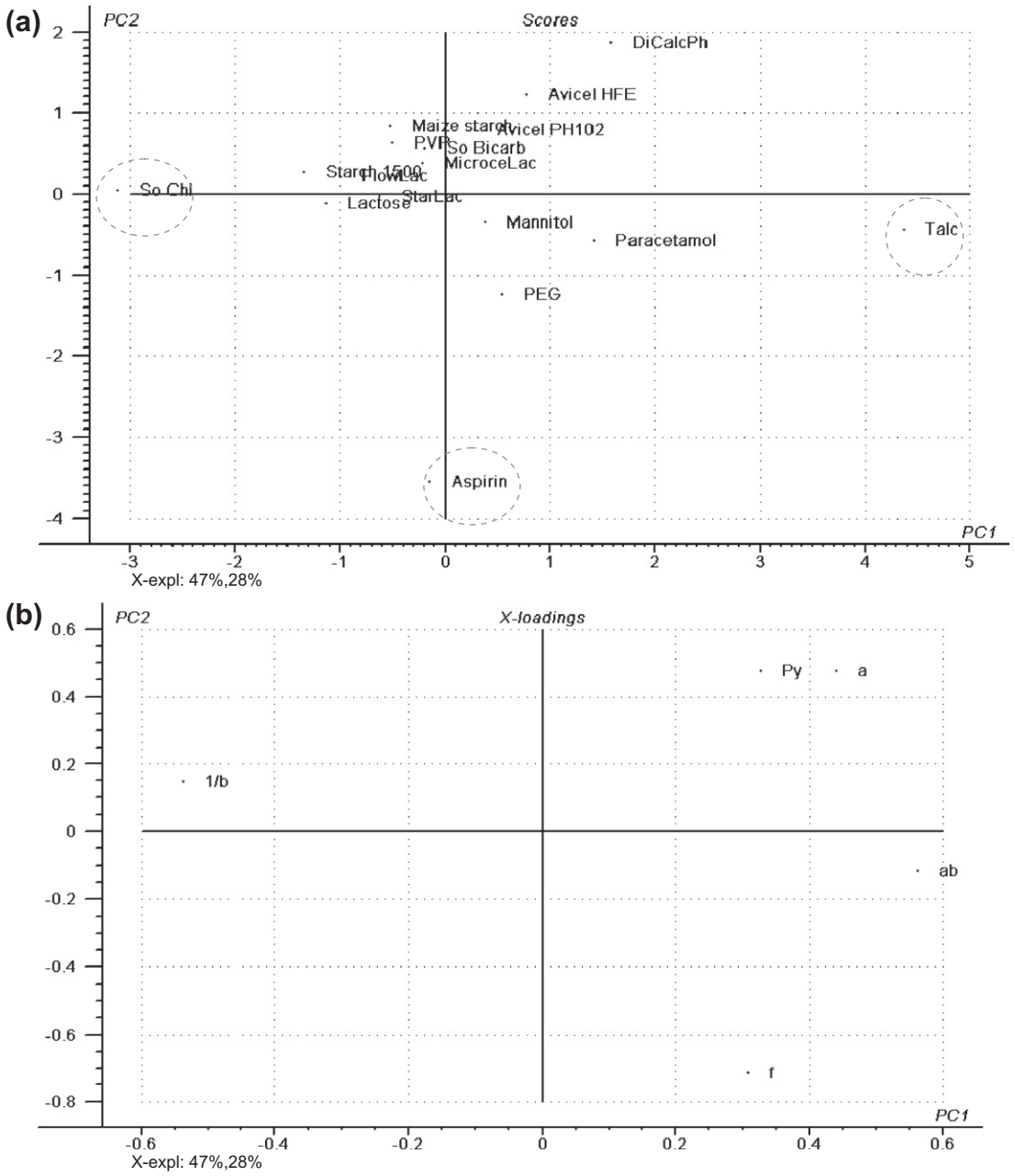


Fig. 2. (a) Score plot and (b) loading plot from PCA of compression parameters showing the extreme materials (outliers) in circles. The two displayed PCs explain totally 75% (47% and 28% respectively) of the variation in the data.

properties, the results of the characterization of compression properties were in general terms consistent with *a priori* expectations.

The compression parameters and the index derived from the compression analysis were subsequently subjected to a multivariate analysis in terms of a PCA. The objective was to explain the relative importance of different compression mechanisms for the compression process and the obtained variation in compression variables.

The PCA score plots for the original 17 powders (Fig. 2) and for the 14 powders remaining after exclusion of three powders (Fig. 4) indicated that the largest variation in the data set was related to two of the variables, the *ab* index and the b^{-1} parameter, and they were in both cases oppositely correlated with each other. The powders showing a high *ab* index and a low b^{-1} parameter were located to the right-hand side of the score plots. It is earlier suggested [8] that such a combination of these two variables is characteristic for powders showing a high degree of particle rearrangement during the initial compression phase. Hence, the materials situated in this part of the plot are materials that probably showed extensive particle rearrangement during compression, and they are thus classified as Class I powders (Table 3). Inversely, the materials situated in the left part of the score plots showed low *ab* and high b^{-1} values. Thus, the materials situated in this part of the plot are suggested to be characterized by showing limited particle rearrangement during compression and are thus categorized as Class II powders (Table 3). As these two variables are the main variables defining PC1, and hence represent the data structure with the most variation in the data matrix, it is concluded that the compression mechanism particle rearrangement had the most significant effect for the overall compression profile.

The PCA plots based on the 17 and the 14 powders had the common denominator that the PC2 was related to both the *f* parameter and the *a* parameter (oppositely correlated). For the model built on the 14 powders without the extreme objects, the Heckel yield pres-

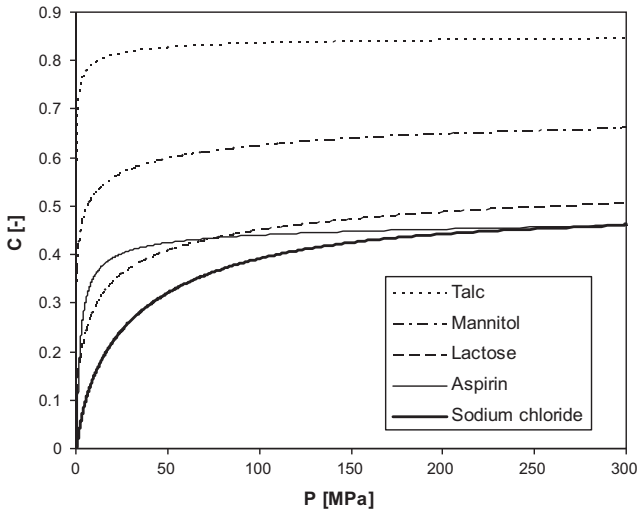


Fig. 3. Examples of stress–strain profiles for five materials exhibiting different volume-reduction profiles; Talc, Mannitol, Lactose, Aspirin and Sodium chloride.

sure had no significance for PC2. The *f* parameter is an indication of the degree of curvature in region I of the SKH profile and the bending may depend on two compression mechanisms, *i.e.* particle rearrangement and particle fragmentation [11].

The *a* parameter represents infinite degree of compression under the compression conditions used and the parameter is thus complex and depend on all three dominating compression mechanisms, *i.e.* particle rearrangement, particle fragmentation and particle deformation. By considering the distribution of powders along PC2 in the score plots (Figs. 2a and 4a), there was a tendency that materials that was expected to show limited fragmentation (*e.g.* Avicel, Maize starch and PVP) were located in the upper part of the plots whereas materials expected to show extensive fragmentation (*e.g.* Lactose, Mannitol, Paracetamol) were located in the lower part of the plots. A significant example is the comparison between two of the powders in Fig. 4a (Maize starch and Lactose) that gave low values of the *ab* index, *i.e.* powders suggested to show limited particle rearrangement. Maize starch, often considered to show limited fragmentation during compression [24], was located in the upper part of the score plot whereas Lactose, often consid-

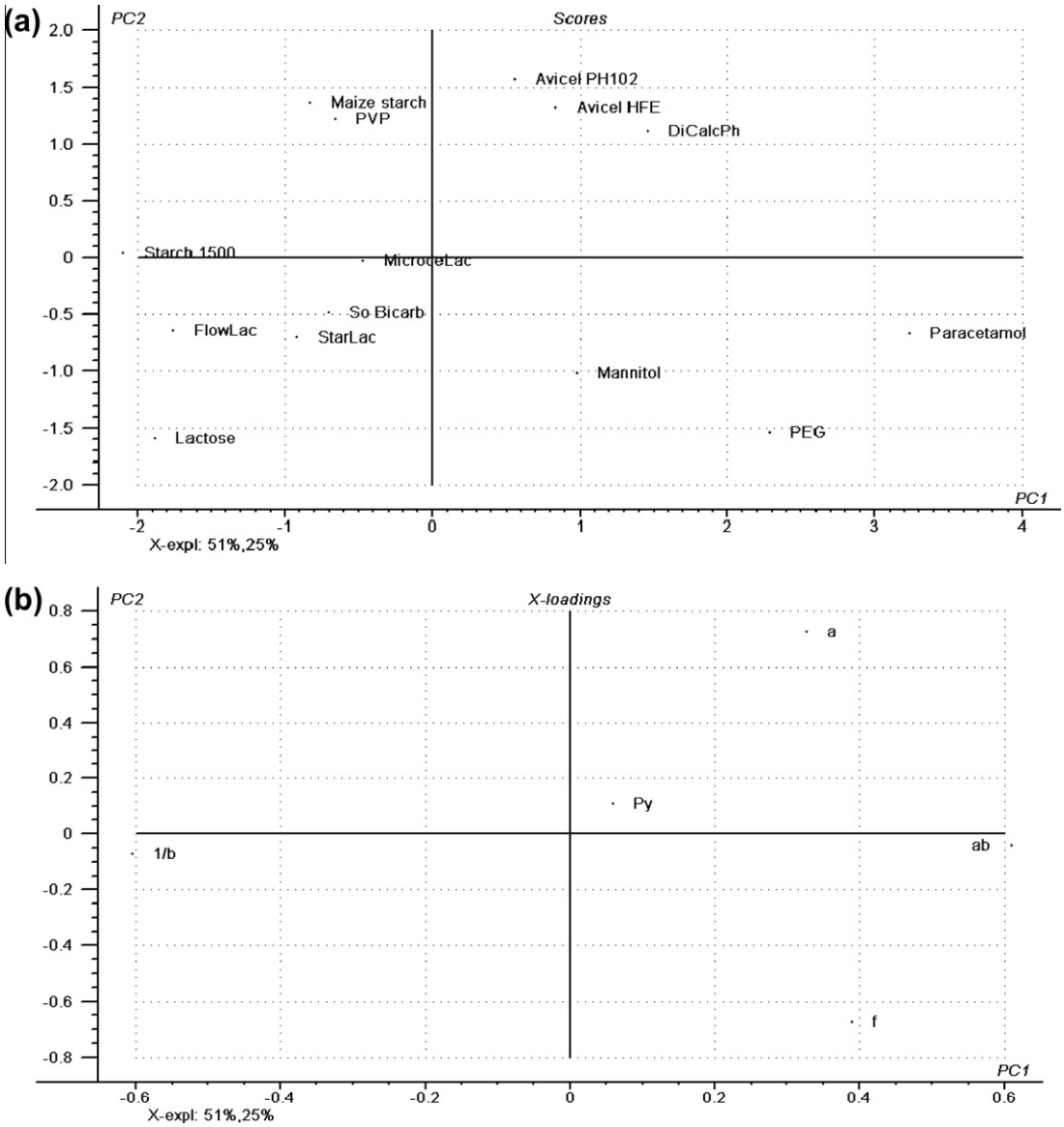


Fig. 4. (a) Score plot and (b) loading plot from PCA of compression parameters where the outliers (from Fig. 2) are excluded. The two displayed PCs explain totally 76% (51% and 25% respectively) of the variation in the data.

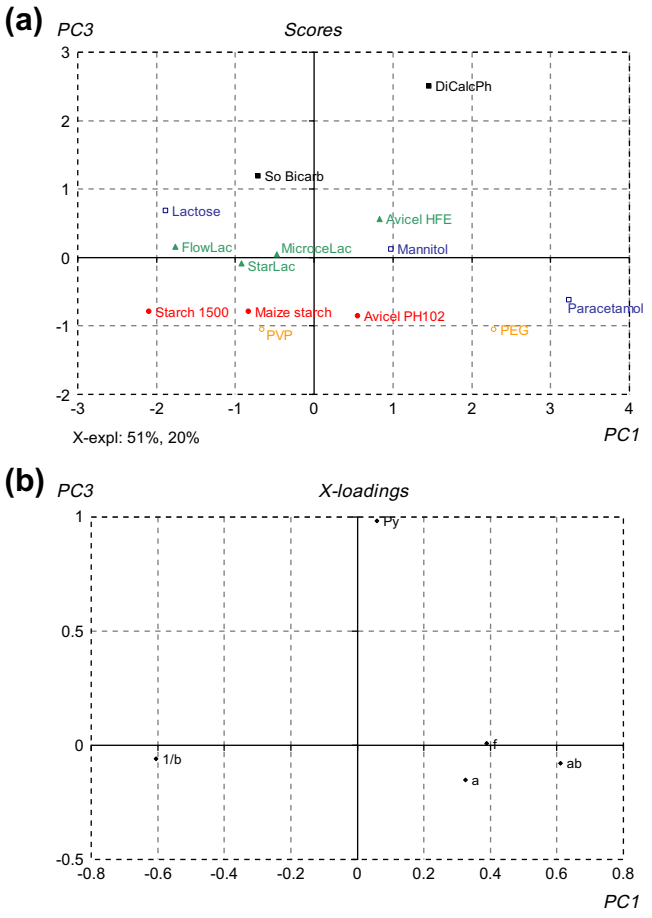


Fig. 5. (a) Score plot and (b) loading plot of PC1 vs. PC3. Classification according to Table 1 added as a category variable, see special symbols in plot (■ (black) hard, □ (blue) moderately hard, ▲ (green) soft – moderately hard, ● (red) soft, ○ (orange) very soft). PC3 explaining an additional 20% of the variation in the data (totally 96% on 3 PCs). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

ered to fragment to a high degree during compression [25], was located in the lower part of the score plot.

We thus conclude that particle fragmentation was a significant mechanism explaining the distribution of powders along the PC2, especially for the Class II powders, *i.e.* powders showing limited particle rearrangement. For the Class II powders it is suggested that the compression mechanism particle fragmentation had the second most significant effect for the variation in the compression data and in Table 3, Class II powders are further sub-divided into category A and B, representing low and high degree of fragmentation, respectively.

In the model of the 14 powders, the compression variable Heckel yield pressure, P_y, was located in the center of the loading plot (Fig. 4b) and could not be explained by PC1 or PC2 but rather represented a third property described by PC3 (shown in Fig. 5). Thus, the yield pressure represents an important characteristic of the compression process of a powder that in itself, and therefore in a defined way, explains differences in compression behavior between materials. The powders spread out relatively homogeneously along the PC3 (Fig. 5a), ranging from very soft (PEG, $P_y = 36.2$) to hard (Dicalcium phosphate, $P_y = 473$). The values of the Heckel yield pressure represented a means to characterize compression behavior of powders in a relatively fine tuned way (Table 3).

The yield pressure is often considered to represent plastic or permanent deformation of particles during compression. In Fig. 6, examples of Heckel profiles are presented for three of the materials used, representing materials with different plasticity, as assessed by the P_y. A classification of Heckel profiles in three types has earlier been proposed [11] and in Table 3, a categorization of powders in the respective type of Heckel profile is given. This categorization is based on the behavior of powder in the first stage of a Heckel profile and on the classification of powders as Class I, IIA and IIB in Table 3.

5. Summary and conclusions

In the study reported in this paper, some compression parameters and a particle rearrangement index were derived from powder compression data for 17 pharmaceutical powders by the use of the Kawakita compression equation, the Shapiro General Compaction Equation and the Shapiro–Konopicky–Heckel equation. In terms of compression mechanisms, the largest variation in the data set was suggested to be explained by particle rearrangement. Thereafter, particle fragmentation was considered to be the compression mechanism with the second most significant effect for the variation in the data set. Finally, the direction with the least variation was described by the Heckel yield pressure, *i.e.* can be explained by the deformation of the particles.

The statistical analysis of the compression parameters indicates that in the analysis and interpretation of compression data, a sequential handling of the parameters is important. In the first step, the powders can be grouped with respect to the incidence of particle rearrangement during compression and in the second step; the powders can be further sub-categorized with respect to their fragmentation propensity. Finally, the Heckel yield pressure can be used as a means to describe particle permanent deformation in a relatively fine tuned way independent of particle rearrangement and particle fragmentation. This sequence in data handling is consistent with a previously suggested approach [8,11] to classify powders based on their compression properties. It is thus concluded that this paper represents a statistical support for the use of a classification system for powders in the assessment of particle mechanics from powder compression data. It is further concluded

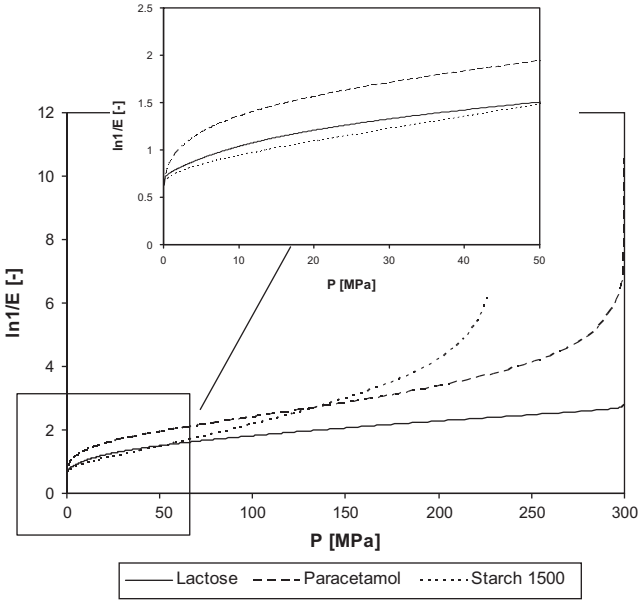


Fig. 6. SKH-profiles for Paracetamol, Lactose and Starch 1500, typical examples of Type 1–3 materials respectively.

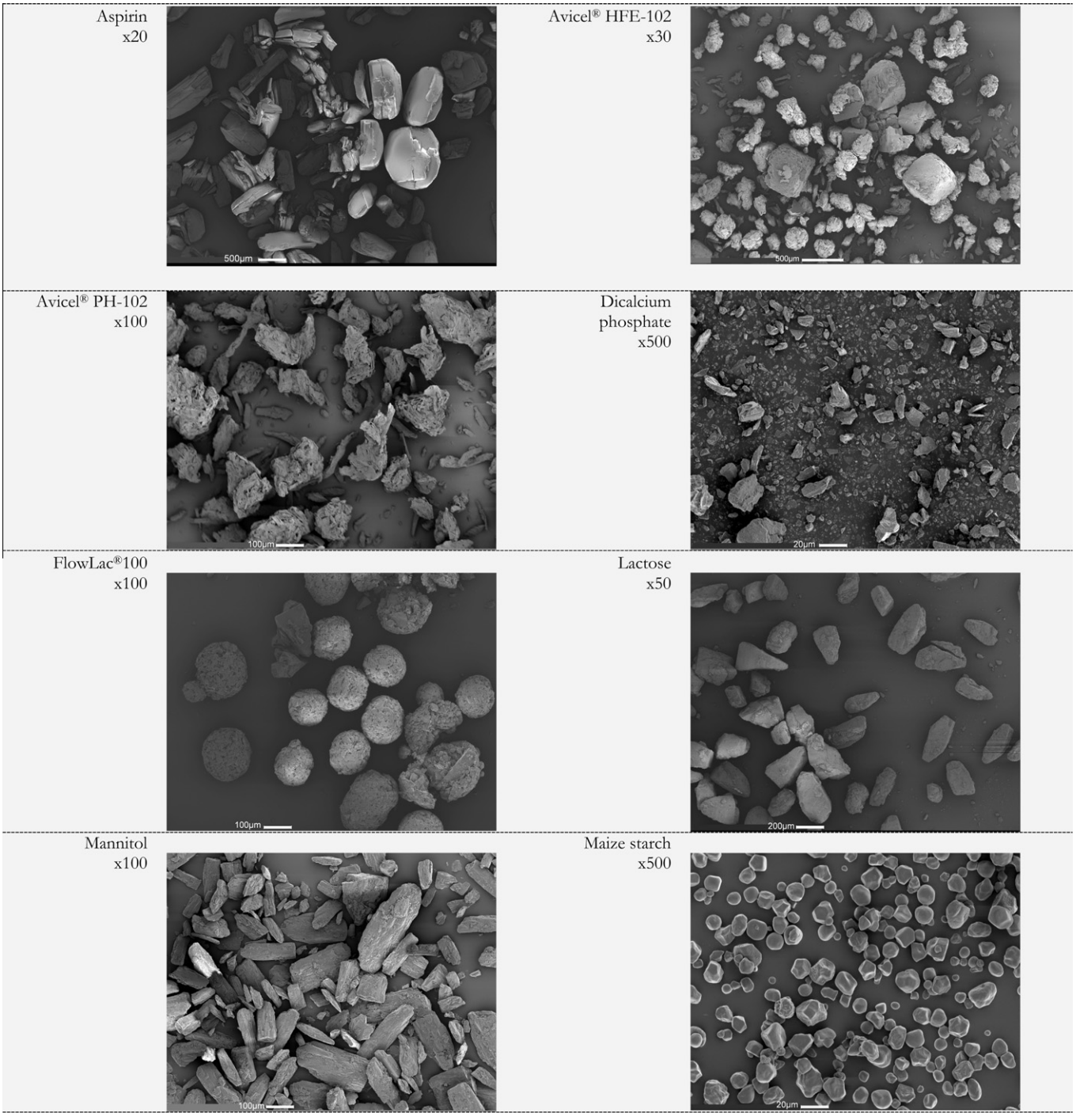
that a multivariate approach may be a valuable tool to group powders with respect to their compression behavior.

Acknowledgements

The authors would like to thank Merete Skar (Department of Pharmacy, University of Tromsø) for a helping hand during SEM-picture taking, Tom-Ivar Eilertsen (Faculty of Health Science, University of Tromsø) for taking the SEM pictures and Camilla Olsson (Department of Pharmacy, Uppsala University) for measuring the powder surface areas of fine powders.

Appendix A

A.1. Scanning electron microscopy (SEM) images of powder samples



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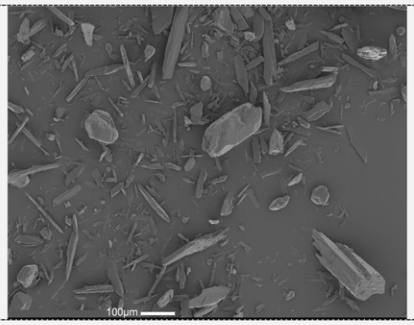
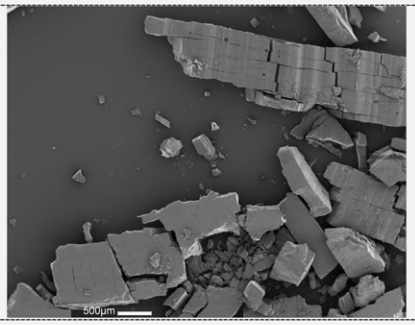
Appendix A.1 (*continued*)

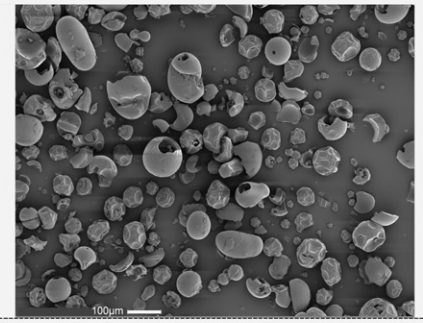
Paracetamol x100



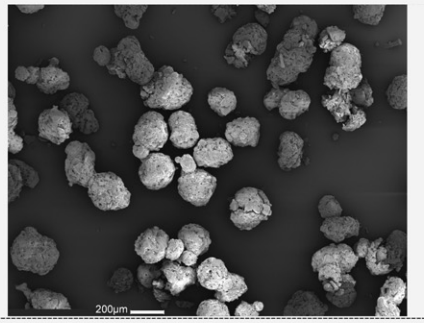
PEG 6000 x20



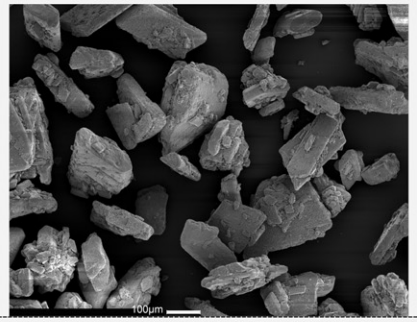
PVP x100



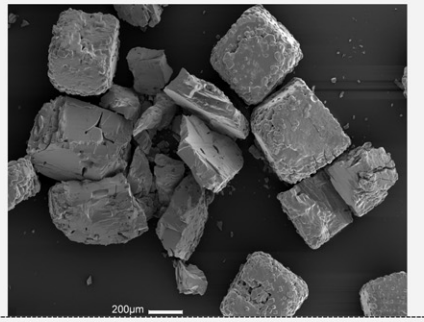
MicroceLac® x50



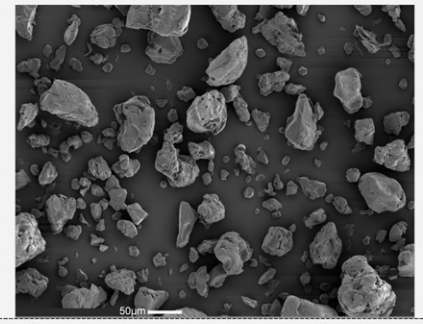
Sodium bicarbonate x100



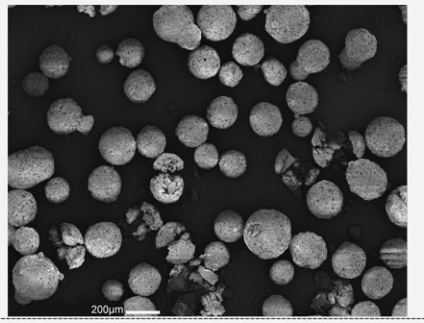
Sodium chloride x50



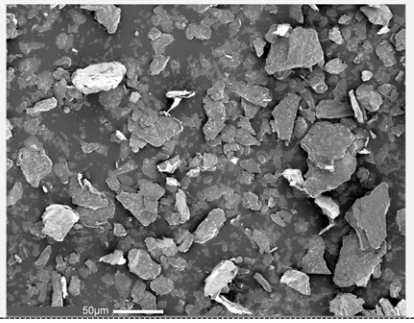
Starch 1500® x200



StarLac® x50



Talc x300



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