

**Compression Analysis of Pharmaceutical Powders:
Assessment of Mechanical Properties and Tablet
Manufacturability Prediction**

Til familien

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ABSTRACT

Although the tablet has been produced in large quantities for a long time, there is a need for better understanding of the manufacturing process. Through the Process Analytical Technology –initiative (in 2004), the pharmaceutical industry has been encouraged to build rather than test quality into the products. This thesis deals with compression analysis for assessment of mechanical properties of pharmaceutical materials and tablet manufacturability prediction. The goal was to increase the understanding of the response in the powder material during the tableting process.

For this purpose, compression testing of powder material was conducted. This method allows for poorly compacted materials to be studied and could quite rapidly provide large (and accurate) datasets. The critical point was the physical interpretation of the compression parameters derived. Therefore, the first part of the thesis deals with investigation of the physical interpretation of parameters from the Kawakita and Shapiro- model, by the use of simple model materials. It was found that a combination of the Kawakita a and b^{-1} parameters into an ab - index could reflect the incidence of particle rearrangement at low pressures, and that materials can be divided into Class I and II based on the values of the index. Furthermore, it was found that for materials showing low degree of particle rearrangement, the initial curvature in a Heckel profile was a reflection of the degree of particle fragmentation. The curvature can be described mathematically by the Shapiro f parameter, and accordingly, the Class II materials can be further sub-divided according to low (A) and high (B) degree of particle rearrangement by this parameter. In addition, the deformability of the particles could be assessed by the Heckel yield pressure. These three descriptors were combined into a classification system which was challenged by compression analysis of a large set of pharmaceutically relevant materials, chosen on the basis of their expected different material properties. The obtained data was evaluated by multivariate data analysis, and the relative importance of the different compression parameters was found. The analysis indicated that a sequential approach was effective for comprehensive assessment of mechanical properties and a systematical description of this in the form of a protocol was suggested. Furthermore, the tableting relevant information found in compression data was evaluated by multivariate calibration. The Kawakita a parameter was the only compression parameter able to point towards the resulting tablet strength for the materials used at different maximum applied pressures. The results further indicated that the Kawakita b^{-1} parameter corresponded to the pressure needed to initiate deformation of the bulk and hence needed to produce a coherent tablet.

This thesis presents a protocol for the assessment of mechanical properties of pharmaceutical powders, and evaluates the tableting relevant information brought forward by compression data. This could be useful in a formulation development phase, enhance process understanding and possible also applicable for monitoring of the tableting process.

ABBREVIATIONS AND SYMBOLS

<i>A</i>	Area of tablet
<i>A</i>	Heckel compression parameter
<i>a</i>	Kawakita compression parameter
<i>ab</i>	Product of Kawakita parameters
<i>b⁻¹</i>	Kawakita compression parameter
<i>C</i>	Engineering strain of powder (also degree of compression)
<i>C_A</i>	Effective deformation parameter
<i>C_{max}</i>	Maximal degree of powder bed compression
<i>c.n.</i>	Coordination number
<i>d₅₀</i>	Estimate of particle size from surface area measurements
<i>d_t</i>	Tablet diameter
<i>E</i>	Powder bed porosity
<i>E₀</i>	Initial powder bed porosity
ER	Elastic recovery
F	Force
FDA	Food and Drug Administration
<i>f</i>	Shapiro compression parameter
GCE	General Compression Equation
HR	Hausner Ratio
<i>h_t</i>	Tablet height
<i>k</i>	Heckel compression parameter
L	Length of powder plug
M	Mesh
MPa	Mega Pascal
MVDA	Multivariate Data Analysis
N	Tapping number
<i>n</i>	Number of experiments
<i>P</i>	Applied compression pressure
<i>P₀</i>	Critical deformation pressure
<i>P_y</i>	Yield pressure
PAT	Process Analytical Technology
PCA	Principal Component Analysis
PLS	Partial Least Squares
RH	Relative Humidity
SDEV	Standard Deviation (also SD)
SEM	Scanning Electron Microscopy
<i>S₀</i>	Volume specific surface area of powder
<i>S_T</i>	Volume specific surface area of tablet
<i>t</i>	Time
<i>V</i>	Volume of powder plug
<i>V₀</i>	Initial volume of powder
<i>w_t</i>	Tablet weight

Δd	Change in particle size
Δ_p	Elastic deformation of punches
ε	Void ratio
η	Viscosity
ρ_{app}	Apparent particle density
ρ_{bulk}	Poured powder bulk density (also BD)
ρ_{poured}	Poured powder bulk density
ρ_{tapped}	Tapped powder bulk density
σ_0	Yield stress
σ_{max}	Maximal tablet tensile strength
σ_t	Tablet tensile strength

LIST OF PAPERS

The thesis is based on the following research papers, which will hereafter be referred to in the text by the Roman numerals assigned below:

- I. Nordström, J., I. Klevan and G. Alderborn (2009) "**A particle rearrangement index based on the Kawakita powder compression equation**", *Journal of Pharmaceutical Sciences* 98(3): 1053-1063.
- II. Klevan, I., J. Nordström, A. Bauer-Brandl, and G. Alderborn (2009) "**On the physical interpretation of the initial bending of a Shapiro-Konopicky-Heckel compression profile**", *European Journal of Pharmaceutics and Biopharmaceutics* 71(2): 395-401.
- III. Klevan, I., J. Nordström, I. Tho and G. Alderborn (2010) "**A statistical approach to evaluate the potential use of compression parameters for classification of pharmaceutical powder materials**", *European Journal of Pharmaceutics and Biopharmaceutics* 75(3): 425-435.
- IV. Nordström, J., Klevan, I. and G. Alderborn (2011) "**A protocol for the classification of powder compression characteristics**", *submitted to European Journal of Pharmaceutics and Biopharmaceutic*, may 2011, in progress.
- V. Klevan, I, Alderborn, G and A. Bauer-Brandl (2011) "**Prediction of tablet manufacturability from compression parameters: a basic study using simple model materials**", *in manuscript*

My contribution to the above listed papers was as follows:

I.-V.: Involved in all parts, except for in Paper III where the SEM-images were taken by others.

I. and II.: The results were partly obtained during my Master project (2004-2005).

Reprints of Papers I.-III. were made with permission from the respective publishers.

1 INTRODUCTION

EARLY HISTORY OF COMPOUNDING MEDICINE

The first collection of pharmaceutical records (the Papyrus Ebers, 1500 B.C) describes the process of compounding medicines in an Egyptian pharmacy, where the roles were divided into gatherers and preparers under supervision of a “head pharmacist”. In the Middle ages the profession of a pharmacist was mainly executed by monks in monasteries, where healing herbs were cultivated, preserved and formulated into tinctures. Besides, essential work was done on documenting relevant observations through the written word. Around 1540 in Italy, the first standardised methods for compounding and characterisation of different constituents, the precursor to what we now refer to as “the Pharmacopoeias”, were formalised. The dosage forms described varied from topical formulations (e.g. ointments and cerates), medicinal “mush” containing up to 70 (!) ingredients and medicinal patches [1, 2].

THE TABLET

Today, the tablet* (whose manufacturing through compression was patented by William Brockedon in 1843 [3]) is considered to be the preferred dosage form both in an administration and manufacturing perspective. The tablet formulation comprises several components with different properties and functions, in most cases divided in active ingredient(s) and excipients, e.g. fillers, disintegrants and antiadherents. The filler, which often constitute a large proportion of the excipients, should ideally be inert, pure, non-hygroscopic, have acceptable taste and be inexpensive [4]. The powder materials could be granulated to improve manufacturability or directly compressed into tablets. The chemical and physical quality of the raw material is characterised in the pre-formulation phase according to specified assays in the Pharmacopoeias. Throughout the process samples are collected and laboratory tested, and in the end the final product quality is assured by an end-point control. Specifications regarding the final tablet quality typically treat mechanical strength, uniformity of dose and dissolution profile. The tablet should be sufficiently hard to withstand attrition during handling but possible to be divided by hand. The tablet strength also subsequently influences the drug dissolution profile, which affects how fast (or slow) the effect of the drug is inserted in the patient.

JUST A WHITE ODORLESS POWDER?

Recently, and also with increased competition through generic manufacturing, more advanced tablet formulations exhibiting e.g. prolonged, extended, delayed or immediate release profiles have emerged. Consequently, there has been a shift from seeing the excipients merely as an inert vehicle towards an increased interest in what they do in a formulation and how they affect the final product, their Functionality Related Characteristics (FRC) [5-7]. To meet these demands, new and more complex

** Tablets are often wrongly referred to as “pills”. But while pills are made of a paste containing the active ingredient rolled into small spherical units, a tablet is compressed into a coherent mass from a dry powder. This linguistical mistake was also made by the entrepreneurs building the facility holding the Institute of Pharmacy in Tromsø, as they referred to the large auditorium on ground floor as “Pillen” (the Pill) instead of the correct “Tabletten” (the Tablet).*

excipients are produced [8, 9]. One essential FR-characteristic of a powder material intended for tableting is its mechanical properties, or how the solid particles respond to mechanical stresses during handling and compression. Three main approaches for mechanical properties testing are found in the literature: confined compression of the powder, testing of the finished compact and testing of single particles [10-15]. Compression analysis is the method of applying pressure to a powder bed in a confined die, while data for the punch movement and applied forces is sampled [16]. The method is attractive for many reasons: small amounts of material are needed, fine and poorly compactable materials can be tested, the data acquisition is often very accurate and large datasets are assembled. The data material is transformed into volume-pressure or porosity-pressure –relationships [17], more commonly known as compression models, from which compression parameters can be retrieved. Preferably, the models should be based on good understanding of the process described and the parameters should reflect a physical property of the material. Unfortunately, historically many compression models have been rather empirical, and their meaning needs to be improved.

CURRENT DEVELOPMENT WITHIN THE PHARMACEUTICAL INDUSTRY

Empiricism is not only limited to interpretation of the compression process, but the entire field of pharmaceutical powder technology has been considered to be more “an art than a science” [18]. In the Wall Street Journal article “New Prescription for Drug Makers” from 2003, it was stated that “the manufacturing techniques of the pharmaceutical industry lag behind those of the potato-chip makers”, a statement that was founded on the Sigma values for the two respective businesses. The Sigma value reflects the amount of deficient samples during a production line, and for the two they corresponded to a yield of approximately 70% (Not capable) for Pharma and > 99.999% (World class) for Potato chips respectively [19]. This led to the proposal of an initiative to encourage a shift towards a more scientifically based technology by the American Food and Drug Administration (FDA) in 2004: the Process Analytical Technology (PAT) –initiative [20]. The goal was to stimulate the pharmaceutical industry to “design and develop processes that can consistently ensure a predefined quality at the end of the manufacturing process”. The theory was that by identifying all sources of variation of importance for the product performance and quality, and by increased process understanding and continuous monitoring, quality could be built rather than tested into the product. The economic incentives for the industry were more efficient production lines, fewer discarded products and a more flexible regulatory process [20, 21]. The benefit for the patient should be safer medicine faster, but also allow for increased individualised therapy through a more easily adjustable production.


THIS THESIS IN THIS CONTEXT


In summary, and seen in the light of these new movements within the tablet manufacturing area, it appears obvious that there is a need for new knowledge to fund a base for a mechanistical understanding of the tableting process [22, 23]. This thesis aims to contribute in this large context by proposing a “toolbox” for the formulation scientist to comprehensively assess material mechanical properties in an early development phase. This is done stepwise by first increasing our physical understanding of some commonly used compression models and parameters (the “tools”). It is regarded as unlikely that one model could describe the entire compression cycle. Hence, an approach based on combining information from several compression models is proposed. This systematical approach is summarised and presented in the form of a Protocol (the “toolbox”). Finally, the tablet performance relevant information retrieved from compression data is evaluated in terms of predictability of tabletability.


2 AIMS OF THE THESIS


The main objectives of this thesis were to establish a system for assessment of mechanical properties of pharmaceutical materials through compression analysis and to evaluate the tableting relevant information provided by this system.


The specific aims were:

 *To investigate the effect of original particle size on the Kawakita parameters a and b^{-1}*

 *To evaluate the physical interpretation of the first bended region in a Shapiro-Konopicky-Heckel -profile*

 *To establish a classification system based on global compression parameters*

 *To evaluate the classification system with an extensive set of pharmaceutically relevant materials*

 *To suggest a protocol for classification of compression mechanics of pharmaceutical materials*

 *To evaluate the tableting relevant information found in compression data*

3 THEORETICAL ASPECTS

This section contains a brief overview of the theoretical prerequisites on which this thesis is based.

3.1 Powder compression

A powder could be seen as a special case of a disperse system, where particles (the solid phase) are dispersed in air (the gas phase). The term powder compression describes the volume reduction of a powder bed in a confined space caused by the application of a force. Hence, the compressibility describes the ability of a powder to decrease in volume. When a powder is compressed, the gas-phase is reduced and the particles are brought closer together. The interparticular bonds become increasingly stronger and finally the bulk powder transforms into a coherent mass or a compact [24]. This phenomenon is denominated compaction, and the ability of a powder to form a compact of specified strength the compactability [25]. Also, the term tabletability is used in this thesis, to describe the capacity of a powder to be transformed into a tablet in a broader manufacturing perspective. The compactability will be described in further detail in chapter 3.3, but first a more thorough description of the compression cycle of a powder (illustrated in Figure 1):

There are several different views regarding the mechanistic conception of the powder compression process, but the description of it as a process occurring in a sequence of consecutive, albeit overlapping stages is considered the most common [26, 27]. Each stage represents a certain part of the pressure range used, and is associated with one or more dominating compression mechanisms. Also, a wide spread of interpretation regarding this sequential perception exist in the literature, both in terms of number of stages or regions represented and regarding which physical processes that are dominating each region. However, the following discussion will be based on a four-stage model comprising initial particle rearrangement, particle fragmentation, particle plastic deformation and finally elastic deformation of the compact [28]. Initially, at low compression pressures the particles are brought closer together and the powder bed porosity and volume is reduced. At a certain applied pressure, the particles reach a maximum attainable packing structure and any further particle movement becomes impossible. The following volume reduction is therefore associated with changes in the dimensions of the particles. These changes might occur both temporarily by elastic deformation and permanently by plastic deformation. The particles dimension could also change by brittle fracture into smaller particles, which subsequently undergo a secondary particle rearrangement followed by plastic and /or elastic deformation. Thus, one particle may undergo this cycle of events several times. As a particle successively is reduced in size, a transition from brittle to ductile behaviour may occur [29-31]. In the decompression phase, i.e. when the applied pressure is removed, the particles (or the compact) may expand due to elastic recovery. All above mentioned physical processes occur to a different extent in different pressure regions dependent on the properties of the material(s). Furthermore, not all materials possess

dominating compression mechanics expressed in all regions, while other materials possess several mechanical properties. In addition, the loading conditions (e.g. temperature, applied pressure, punch velocity and total duration time for the compression cycle) affect the degree of fragmentation, plastic and elastic deformation [32, 33]. When punch speed and loading time affect the deformation, the behaviour of the materials is referred to as viscoelastic and/or viscous (strain-rate-sensitive) deformation, a behaviour often observed for pharmaceutical materials [34-36].

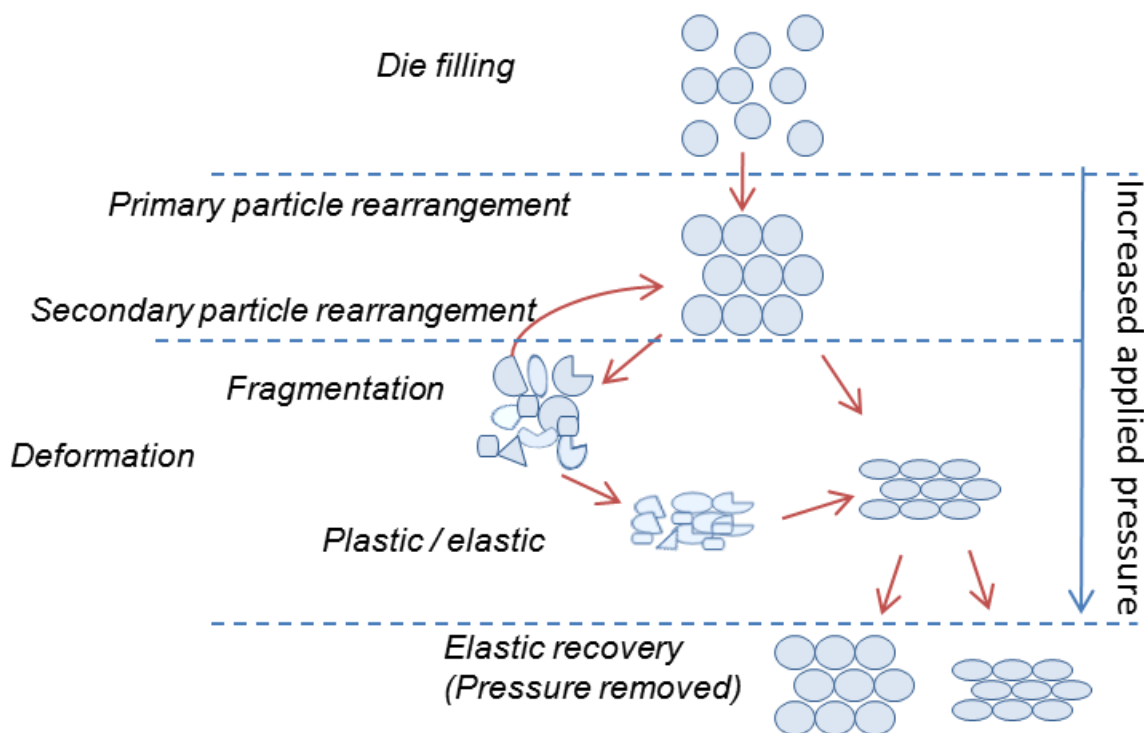


Figure 1. Schematic illustration of the powder compression cycle.

3.2 Powder compression models

As reflected in the literature, numerous attempts have been made to develop a compression model that is founded on the physical understanding of the powder compression process [37-41], and from which compression parameters reflecting an actual property of the material can be retrieved. The dominating approach has been to take the whole powder bed or tablet into consideration during modelling (so called global models), by relating either the powder porosity or the powder volume to the applied pressure [17]. Logarithmic transformations of both the porosity or volume terms and the pressure term are common. The first reported such relationship was proposed by Walker in 1923 [42]. More recently and with more advanced computational techniques models regarding each involved particle (discrete element methods (DEM)) [43], models based on the tablet as a continuous medium (finite element method (FEM)) [38], or an effective-medium approach [44] have been proposed. Nevertheless, a generally valid mathematical equation has not yet been

developed nor adapted over a broad range of different scientifically areas. However, for the area of pharmaceutical powder technology, the global models of Heckel and Kawakita have typically been the most frequently used. The reason for this could be their quite simple mathematical form, and also the fact that substantial knowledge already has been built on the basis of information retrieved from them. Or more importantly, that they are regarded to be attractive in terms of physical significance of the compression parameters.

3.2.1 The Heckel equation

Already in the 1940`s, Shapiro and Konopicky published data based on powder compression, where the natural logarithm of the tablet porosity as a function of the applied pressure was used to describe the process [45, 46]. However, the Heckel equation (Eq. 1) from 1961 became the most well-known and most commonly used [47, 48]. Accordingly, in paper III the relationship is referred to as the Shapiro-Konopicky-Heckel equation, but for the sake of simplicity it will be referred to as the Heckel equation in the following discussion. The equation is based on the assumption that compression of powders is analogous to a first-order chemical reaction, the pores being the reactant and densification of the bulk being the product. The equation was first developed and applied on compression of metals, materials known to deform predominately plastically.

$$\ln \frac{1}{E} = kP + A \quad \text{Equation 1}$$

where E is the porosity of the powder bed and P the applied compression pressure, A and k are parameters.

A Heckel profile is normally distinguished by three different regions, an initial non-linear part (Region I), followed by a linear part where the data obey the expression (Region II), and finally a non-linear region (Region III) (Figure 2). The expression of these three different regions is normally explained with the underlying rate controlling compression mechanisms that dominate the respective regions. For region I, two main explanations could be seen in the literature; firstly that the curvature is regarded to be dependent on particle rearrangement during compression [47, 49], and secondly that the curvature is due to particle fragmentation [50]. Regarding the second region, it is generally widely accepted that particle deformation, either plastic or elastic, is the controlling mechanism. And for region III it is argued that elastic deformation of the compact controls the process [51].

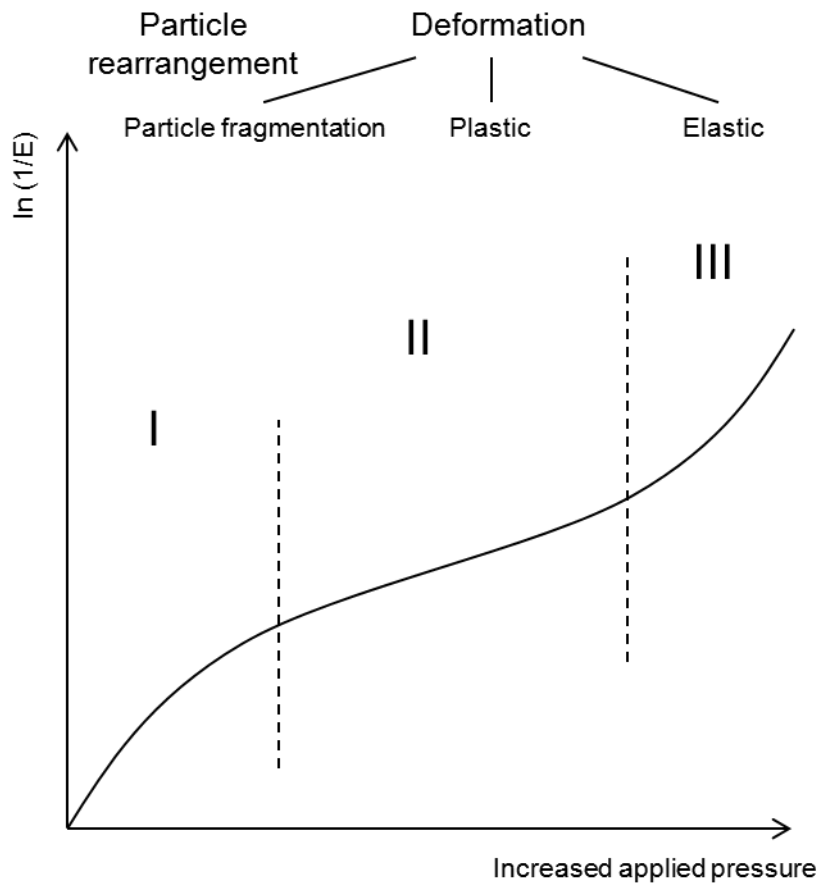


Figure 2. Schematic illustration of the three different regions dominating the Heckel profile.

The parameter A in the Heckel equation is said to reflect low pressure densification by interparticulate motion. From the linear region, the inverse of the slope (parameter k) is calculated. This is referred to as the Heckel parameter or the yield pressure, P_y , and is commonly used as an indication of the plasticity or hardness of a particle. This assumption originated from an empirical relationship between the parameter k and the yield strength (σ_0) (Eq. 2) [48]. The relationship has been further established through studies done on single particles [52], or derived from bulk compression [43]. The latter provided that a critical ratio between Young's modulus of elasticity and yield stress is exceeded, a criterion that is met for many pharmaceutical materials, but nevertheless indicating that a Heckel analysis does not have general validity.

$$\frac{1}{k} = P_y = 3\sigma_0 \quad \text{Equation 2}$$

Differences between reported values for the Heckel parameters are observed in the literature, and might be due to how the linear region is determined, deviations in the measured true densities or in the accuracy of the data acquisitions. Negative porosities in the upper pressure part of the profile have also been reported, which could lead to substantially lower retrieved yield pressures, and might contradict the assumption that the particle density is constant during compression [51, 53, 54]. Finally, and most

importantly, experimental conditions affect the result of the Heckel parameter, e.g. maximum applied pressure, punch velocity or the punch diameter [55, 56].

3.2.2 The Shapiro General Compression Equation

The Shapiro General Compression Equation (GCE) (Eq. 2) [57] can be seen as a refined Heckel equation, where an exponential term is added to describe the first curved part of the compression profile.

$$\ln(E) = \ln E_0 - kP - fP^{0.5} \quad \text{Equation 3}$$

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 are parameters.

The k parameter is in theory equal to the Heckel parameter, and the f parameter is an indication of the initial curvature in Region I. Accordingly, the GCE possess the potential to describe both Regions I and II in one single equation, and two compression parameters could be derived, which can be used as indicators of the dominating compression mechanism in the two respective regions.

3.2.3 The Kawakita equation

Another way of representing compression data is to relate the volume reduction (engineering strain) of a powder bed to the applied pressure, and the most familiar expression in this class is the Kawakita equation [58, 59].

$$\frac{P}{C} = \frac{1}{ab} + \frac{P}{a} \quad \text{Equation 4}$$

Where C is the degree of volume reduction, ($C = \frac{V_0 - V}{V_0}$, where V_0 is the initial volume of the powder bed and V is the volume under applied pressure), P is the applied pressure, and a and b are parameters.

The linear relationship between $\frac{P}{C}$ and P makes it possible to derive values of the parameters a and b . The parameter a represents the maximal engineering strain, C_{max} of the powder bed, and mathematically the parameter b is equal to the reciprocal of the pressure when the value, C , reaches one-half of the limiting value ($C = C_{max}/2$), as illustrated in Figure 3.

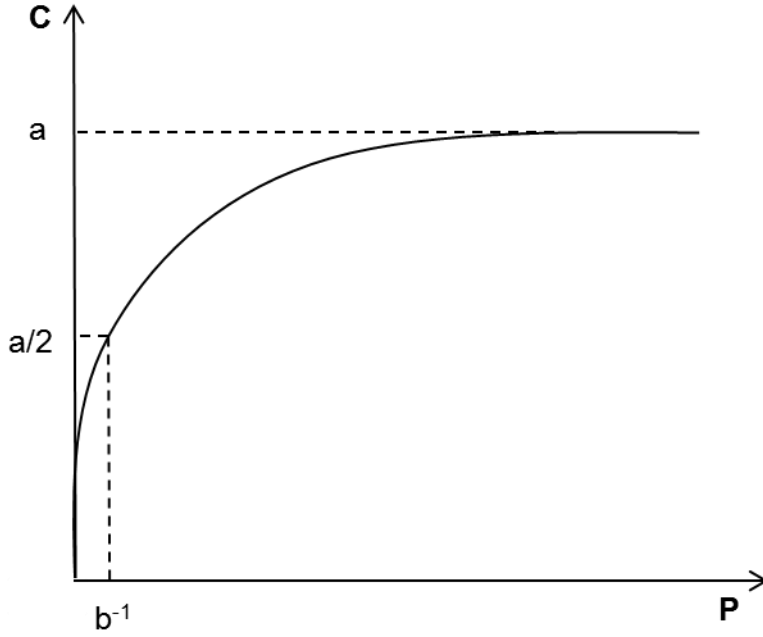


Figure 3. Schematic illustration of a typical engineering strain – pressure –curve and mathematical interpretation of the Kawakita parameters.

The Kawakita equation is often considered to be best suited for analysis of soft, fluffy powders compressed under low pressures [28]. However, setting the start volume for the calculations is a critical point that should be carefully considered, as this influence the outcome of the parameters retrieved to a large extend [53, 58]. The physical interpretation of the Kawakita parameters has been discussed in the literature, and the inverted b -parameter is claimed to reflect the agglomerate strength [60], fracture strength of single particles [52] or the plasticity of a granule [61]. The physical interpretation of the b -parameter in terms of bulk powders have been more complicated to address, represent a resistant towards compression.

The Kawakita equation may also be applied to tapping of bulk powders, as a measure of fluidity and cohesion, replacing the pressure term (P) in Eq.4 by N – the tapping number [62, 63]. Regarding the physical significance of the Kawakita parameters, the parameter a still represents the maximum degree of volume reduction now at infinite tapping and is considered to correspond to fluidity. The b parameter represents the tapping ability and hence, the inverted b parameter is considered to be related to interparticulate cohesion.

3.3 Powder compaction

During the powder compression process the particle surfaces are brought closer together and interparticulate attraction occurs. This enables bonding between particles. Bond formation during compression is critical for the formation of a tablet of sufficient mechanical strength, and the total tablet strength is reflected in the sum of number of bonds and the strength of each bond. For compaction of dry powders, the bonding mechanisms may roughly be divided into three main types: solid bridges,

attraction forces and mechanical interlocking [64]. Particle fragmentation increases the number of surfaces available for bonding, while particle plastic deformation contributes mainly to the bonding force. Thus, these two particle deformation mechanisms are bond producing and have a positive effect on tablet strength. Particle elastic deformation can lead to breakage of bonds after removal of the applied pressure as the tablet recovers in height. Thus, particle elastic deformation has a negative effect on tablet strength [27, 65]. Regarding particle size and shape, it is generally recognised that small particles form harder compacts (due to large surface areas available for bonding), while the effect of particle shape is most prominent for ductile materials, i.e. large increase in compactability going from regular to irregular particles [66, 67]. In addition, processing conditions affect the resulting tablet strength: as previously remarked the tableting speed is of importance for strain-rate-sensitive materials [35, 68]. Tablet formulations mostly comprise several components and prediction of tablet strength is difficult due to the complex nature of the process itself, and is further complicated through interactions between the different components in the formulation [69].

3.4 Multivariate data analysis

Multivariate Data Analysis (MVDA) techniques are listed in the PAT-initiative as one of four important means to efficiently provide information about the process of interest [20, 70]. MVDA aid the possibility to study multiple variables for several observations simultaneously, and has enabled prediction and monitoring of the tableting process through e.g. spectroscopic methods [71]. The techniques have also most recently been shown effective for the evaluation of compression behaviour of pharmaceutical materials and in tablet performance prediction [72-74]. In this thesis, MVDA is used to statistically evaluate the relative importance of different compression parameters and for evaluation of the information brought forward by compression analysis relevant for tablet manufacturing. This was done by pattern recognition in relatively large data sets of compression parameters by Principal Component Analysis (PCA) and by quantification of the relationships between parameters and response by a Partial Least Squares (PLS) –method. In MVDA each observation comprises a separate row in a data matrix (X), and each observation can be described by as many variables as one may wish (or as is possible), organised into columns. In this thesis typically the observations corresponded to the respective powder samples while the variables corresponded either to compression parameters or compactability descriptors. Tablet tensile strength was used as a response variable. In the MVDA-method Principal Component Analysis (PCA), the data matrix is decomposed into new dimensions, where each object in the data matrix is assigned a score and a loading (and an error) in variable space. The decomposition is based on variance analysis, and the new dimensions are found within the swarm of points along the directions represented by decreasing degree of variance: the first principal component (PC) lies along the direction with the largest variation in the data set, PC 2 orthogonally to PC1 along the direction of second largest variation etcetera. These directions are also referred to as the latent variables in the X -matrix which (hopefully)

reveal “hidden structures” in the data set. Identification of groups, trends and outliers can be done by examining the scores, while the influence of variables may be examined in the corresponding loading plot. Hence, the two plots complement each other when interpreting the results. Objects on the same side of a PC are positively correlated and 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 regarded dissimilar. For prediction and to identify the variables influencing the response to statistical significance, the MVDA-method Partial Least Squares (PLS) regression can be used. PLS is a continuation of a PCA-analysis where the latent variables act as a basis for quantification of the relationship to one or several response variables (Y) [75-77].

4 EXPERIMENTAL SECTION

4.1 Materials

The experimental work was conducted on powder materials, which can be divided into simple model materials (paper I, II, V) and more pharmaceutically relevant materials (paper III and IV) respectively. However, the cross-over between the groups is evident. The model materials used in Paper I, II and V, were chosen on the basis of their *a priori* expected mechanical properties [27, 78, 79]. These materials, with the exception of sucrose, were also included in Paper III, where a broad selection of 17 different materials was represented. The set of materials was chosen based on their expected mechanical properties in order to spread out the design space, ranging from very soft to hard [80, 81]. Among the 17 materials there were two drug substances (aspirin and paracetamol) chosen also primarily on the basis of their mechanical properties [82]. In addition they can be regarded as representatives of drugs that appear in high proportions in tablets, and hence are of importance for the total manufacturability of the tablet formulation. In Paper IV, two bulk materials, namely sodium chloride and mannitol, representing two different dominating compression mechanisms found in the previous work (Paper III), were refined into both coarse particulate and milled samples. All materials investigated, supplier information, expected dominating mechanical properties and which studies they were used in, are listed in Table 1.

4.1.1 Sample preparation

To fractionate the coarse particles (250-300 μm and 125-180 μm) of the powder materials used in paper I, II, IV and V, dry sieving was performed on a mechanical shake-sieve (Retsch, type RV, Haan, Germany). The finer fractions (63-90 μm) (Paper V) were prepared by gentle milling of the coarse raw material (sodium chloride) followed by dry sieving or respectively, just sieving of a finer grade of raw material (lactose, Pharmatose[®] 125M). The fine fractions (< 100 μm , < 50 μm) (Paper I and II) were prepared either by milling in an electrical mortar grinder (Retsch Grindomat, KM1) followed by air-jet sieving (Alpine 100MZR, Alpine AG, Augsburg, Germany), or by milling in a pin-disk mill (Alpine 63C Contraplex Labormühle, Alpine AG). The latter method was also used for preparation of the milled samples in Paper IV. After sieving and milling, the powders were inspected visually in an optical microscope (model Vanox, Olympus, Tokyo, Japan). In Paper III the powders were used as supplied from the manufacturer, that is, the samples were taken directly from the bulk containers without any particle size separation. For all studies, the materials were conditioned over a saturated K_2CO_3 -slurry (corresponding to a relative humidity of 40 %) in sealed containers for at least 7 days (at approx. 20°C) before any characterization or further experiments were conducted. These conditions corresponded roughly to the conditions of the laboratory. The amorphous FlowLac[®] (Paper III) was kept in a closed container over a silica gel (corresponding to a relative humidity of 25%) in order to prevent crystallization.

Table 1. List of materials included in the different studies.

Brand name	Material	Supplier	Expected mechanical properties	Paper
Paracetamol	Acetaminophen	Sigma-Aldrich	Moderately hard, brittle	III
Aspirin	Acetyl salicylic acid	Sigma-Aldrich	Very soft, brittle and ductile	III
Pharmatose [®] 50M	α -monohydrate lactose	DMV Fonterra-Excipients	Moderately hard, brittle, ductile	I, II, V
Pharmatose [®] 90M	α -monohydrate lactose	DMV Fonterra-Excipients		I, II, III
Pharmatose [®] 100M	α -monohydrate lactose	DMV Fonterra-Excipients		V
Pharmatose [®] 125M	α -monohydrate lactose	DMV Fonterra-Excipients		I, II, V
FlowLac [®] 100 *	α -monohydrate lactose	Meggle	Soft-moderately hard	III
MicroceLac [®] 100 *	α -monohydrate lactose (75 %) and microcrystalline cellulose (25 %)	Meggle	Soft-moderately hard	III
StarLac [®] *	α -monohydrate lactose (85 %) and maize starch (15 %)	Meggle	Soft-moderately hard	III
Dicalcium phosphate	Dicalcium phosphate	Sigma-Aldrich	Hard, brittle	III
Mannitol	d- mannitol	Sigma-Aldrich	Moderately hard, ductile	III, IV
Maize starch	Maize starch	Sigma-Aldrich	Soft, ductile	III
Starch 1500 [®] **	Maize starch	Colorcon	Soft	III
Avicel [®] PH-102	Microcrystalline cellulose (MCC)	FMC BioPolymer	Soft, ductile	III
Avicel [®] HFE-102 ***	Microcrystalline cellulose and mannitol	FMC BioPolymer	Soft, moderately hard	III
Sodium bicarbonate	Sodium bicarbonate	Fluka	Hard, brittle	I, II
Sodium bicarbonate	Sodium bicarbonate	Sigma-Aldrich		III
Sodium chloride	Sodium chloride	Fluka	Soft ductile	I, II
Sodium chloride	Sodium chloride	Sigma-Aldrich		III, IV
Sodium chloride	Sodium chloride	NMD		V
PEG 6000	Polyethylene glycol 6000	Sigma-Aldrich	Very soft, ductile	III
Kollidon [®] 17PF *	Polyvinylpyrrolidone (PVP)	BASF	Very soft, ductile	III
Sucrose	Sucrose	Fluka	Moderately hard, brittle	I, II
Talc	Talc	Sigma-Aldrich	Hard	III

* *Spray dried*

** *Partially gelatinised*

*** *Blend*

4.2 Characterisation of powder materials

The apparent particle density, ρ_{app} , also referred to as the true density of the particles, was determined in a helium gas pycnometer (AccuPyc 1330, Micrometrics, Norcross, GA). In general, 10 cycles of gas filling was conducted for each experiment ($n=2$ (Paper III and IV) or $n=3$ (Paper I, II and V)).

The unsettled bulk density was assessed by two different methods ($n=3$ in both cases). The powder was either poured gently into a cylinder of known volume (10 ml (Paper I and II) or 50 ml (Paper III)) and the height or volume of the powder was determined visually. These measurements were denoted ρ_{bulk} . Alternatively, the powder was poured gently into a cylinder of known diameter (~11 mm) and the height was determined with a digital gauge measurement (Mitutoyo Digimatic, ID-C, Tokyo, Japan) (Paper III, IV and V). The latter measurements were denoted ρ_{poured} . These bulk density values were transformed into a corresponding powder height in the die and used to set a sound starting point for the compression cycle in further data modelling. The ratio between the unsettled density (ρ_{bulk}) and the density after tapping (ρ_{tapped}) of the same cylinder 1000 (Paper I) or 1250 (Paper III) times on a tap density testing apparatus (PharmaTest, PT-TD, Hainburg) was determined (Eq. 5). This relationship is known as the Hausner Ratio [83].

$$HR = \rho_{tapped}/\rho_{bulk} \quad \text{Equation 5}$$

In order to get another indication of the packing density of the particles, a mean coordination number (*c.n.*) was calculated according to a model proposed by Chang et al. [84] (Eq. 6).

$$c.n. = 13.28 - 8\varepsilon \quad \text{Equation 6}$$

where ε is the void ratio of the powder bed and was calculated from the powder bed porosity of the poured and tapped powders.

The volume specific surface areas, S_0 , were calculated according to the Kozeny-Carman equation [85, 86] (Eq. 7). Two different air permeametry methods were used: for the coarse particulate powders, i.e. material estimated to consist of particles $> 100 \mu\text{m}$, steady-state air permeametry (after the Nicklasson-method, home built equipment) was used [87, 88], while for the fine particulate powders, a transient permeametry method (Blaine) was used [86]. For the latter, the surface area was corrected for slip flow between the fine particles in the calculations [89].

$$S_0 = \frac{\Delta P t A E^3}{c L V \eta (1-E)^2} \quad \text{Equation 7}$$

where ΔP is the change in pressure, t is the elapsed time, E is the porosity, L is the length-, V is the volume-, and A is the area of the powder plug, c is an empirical

correlation (shape and cross-section) constant equal to 5 and η is the viscosity of the fluid.

For the materials used in paper III, Scanning Electron Microscopy images (SEM) (JSM-6300 SEM, Japan Electron Optics Laboratory, Ltd., Tokyo, Japan) were taken. The powder samples were mounted on an aluminium base with adhesive carbon tape and sputtered with gold and platinum under vacuum for 90s prior to SEM-picture taking.

To obtain particle size distributions for the bulk material (Paper IV), small samples (approx. 5 g) were prepared 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. The samples were dry sieved on a set of precision sieves with a standard series of aperture size (Veco, Eerbeek-Holland) mounted on a mechanical sieve shaker (Retsch, type RV, Haan, Germany) and finally weighed on an analytical balance (n=3). End point determination for the particle size analysis was done according to the European Pharmacopoeia [90].

4.3 Compression analysis

Compression of the powder material was performed in a material testing machine (Zwick Z100, Zwick/Roell Zwick GmbH & Co. KG, Ulm, Germany), equipped with 11.3 mm diameter flat-faced punches (n=3 in Paper I and II, n=5 in Paper III, IV and V). The lower punch was stationary during the experiments, while the upper punch moved with a slow and constant speed (1 mm/min (Paper I and II) or 10 mm/min (Paper III, IV and V)). The punches and die were lubricated with a 1% magnesium stearate suspension in ethanol prior to each experiment. The maximum applied pressures varied in the different studies, see Table 2 for a more detailed description of the different experimental set-ups.

In addition, in Paper II, tablets (n=5) were made in an instrumented single-punch tablet press (Korsch EK0, Berlin, Germany) equipped with 11.3 diameter flat-faced punches. The machine was operated manually by hand up to an applied pressure of 50 MPa.

4.3.1 Correcting compression data

The instrumentation in the materials testing machine allowed for sampling of accurate force-displacement data. Prior to any further data analysis, all data collected were corrected for the deformation of the machine and punches. The elastic deformation of the punches (Δ_p) was estimated from recordings of punch-to-punch compression (n=3, $P_{\max}= 500$ MPa) through the expression:

$$\Delta_p = k_a P + l_a + l_b e^{(-k_b P)} \quad \text{Equation 8}$$

The exponential term describes the first non-linear part of the force-displacement data at low pressures. Values for k_a , k_b , l_a and l_b were found by curve-fitting, and the raw data were corrected for this system deformation error (approximately 0.5 $\mu\text{m}/\text{MPa}$), to find the correct powder bed height.

4.3.2 Modelling compression data

The corrected raw data was subsequently subjected to further transformation according to different compression models, and from these relationships compression parameters were retrieved. Firstly stress-strain profiles were created for all powder materials. The compression data was thereafter adapted to the linear form of the Kawakita equation and the compression parameters a and b^{-1} were obtained by linear regression. The compression data was then adapted to the Heckel-equation and the yield pressures, P_y , were calculated as the reciprocal of the slope k using linear regression. The Shapiro compression parameter f was derived from the Shapiro General Compaction Equation by curve-fitting of the experimental data by the least squares method in the pressure range up to an applied pressure of 50 MPa. The different settings for the different regression analyses are listed in Table 2.

Table 2. The parameters calculated in the different studies and chosen settings for the regression analyses

Model	Parameter	Maximum Applied Pressure (MPa)	Pressure Interval (MPa)	Paper
Kawakita	a b^{-1}	500	1-500	I
		300	25-250	III and IV
		100, 150, 200, 300, 400 and 500	25 -85 % of P_{\max}	V
Shapiro	f	500	$\ln E_{0_{BD}}-50$, 0.3-50 and 1-50	II
		300	$\ln E_{0_{BD}}-50$	III and IV
		100, 150, 200, 300, 400 and 500	$\ln E_{0_{BD}}-50$	V
Heckel	P_y	500	50-150	I and II
		300	Different due to best linear fit ($r^2 > 0.999$)	III and IV
		100, 150, 200, 300, 400 and 500	Different due to best linear fit ($r^2 > 0.999$)	V

4.4 Characterisation of tablets

For all tablets, the dimensions (h_i , d_i) were determined immediately after compression with a micrometer gauge (Mitutoyo, Japan), and the tablets were weighed (w_i) on an analytical balance (Mettler Toledo, AB204, Switzerland).

4.4.1 Volume specific surface area

The tablets compressed in the single punch tablet press (Paper II), were directly after ejection mounted in a special flow cell on a transient air permeability apparatus (Blaine) for determination of the tablet surface area (S_T). The calculations were done according to the before mentioned slip-flow corrected Kozeny-Carman relationship (Eq.7) [78, 89]. From the relationship between the powder surface area (S_0) and the tablet surface area (S_T), an estimate of the change in particle diameter (Δd) during compression (up to 50 MPa) was calculated (Eq.9). A constant surface to volume shape factor of 10 was used in the calculations.

$$\Delta d = 10 * \left(\frac{1}{S_0} - \frac{1}{S_T} \right) \quad \text{Equation 9}$$

4.4.2 Elastic recovery

The immediate axial elastic recovery of the tablet in die was assessed through the difference between the tablet height at maximum load ($h_{P_{\max}}$) and the last measurable height before the upper punch loses contact with the tablet in the decompression phase (h_{end}) (Paper V) [65].

$$ER_{\text{in-die}} \% = (h_{\text{end}} - h_{P_{\max}} / h_{P_{\max}}) * 100 \quad \text{Equation 10}$$

The tablet porosity, E_t , was determined from in-die data at the last measurable height in the decompression phase (Paper V).

4.4.3 Tensile strength

The force (F_t) needed to crush tablets along their diameter was recorded in a diametric tablet testing machine (Holland, UK) at a constant speed of 1 mm/min (Paper V). The tablet tensile strength (σ_t) was calculated according to the expression of Fell and Newton [91] taking the tablet dimensions into account.

$$\sigma_t = \frac{2F_t}{\pi h_t d_t} \quad \text{Equation 11}$$

4.4.4 Other descriptors of compactability

From the applied pressure vs. tablet tensile strength -relationship several compactability descriptors were retrieved (Paper V), i.e. the slope from the linear region (25-200MPa), the critical formation pressure, P_0 and the maximum attained tensile strength, σ_{\max} . The relative tablet tensile strength, σ_{rel} , was calculated as the ratio between the tablet tensile strength at a certain pressure and the tablet tensile strength at the pressure needed to attain the maximum tensile strength. From the

relationship between the relative tablet tensile strength and the effective pressure (P_{eff} , calculated as $P_{\text{app}} - P_0$), the inverted slope, C_A , was calculated in a pressure range up to 200MPa [92].

4.5 Multivariate data analysis

In paper III, Principal Component Analysis (The Unscrambler 9.8 / X 10.1, CAMO, Norway) was utilised to find latent structures in the compression data, in Paper IV to visualise the results and in Paper V for elucidation of inter-variable relationships between compression parameters and the compactability descriptors. Partial Least Square regression (PLS-1) was used for multivariate calibration to find the parameters significant for the response and to build prediction models (Paper V). Before any data modelling, all variables were standardised with their standard deviation (1/SDEV) to give each variable equal weight [77]. Full cross validation and jack-knifing was used to validate and assess the stability of the models [93].

5 RESULTS AND DISCUSSION

This section points out the most important findings from the different studies, and discusses these in a broader perspective.

5.1 Primary characteristics of the materials

All materials were characterised with respect to their bulk properties prior to the compression experiments: see Table 3 for an overview. For the detailed primary characteristics of all materials the reader is referred to the respective papers.

The apparent particle density (ρ_{app}) is a physical material characteristic and a prerequisite for porosity calculations, and accordingly is an input variable in the porosity-pressure –relationships. In addition, the particle densities served as a quality check of the raw or sieved material. The obtained results could easily be compared to literature values [94] and were in general consistent with the expected.

The volume specific surface areas confirmed successful particle size separation into the different powder fractions. In addition, the surface areas were used as a characteristic of the bulk powder, i.e. to indicate if the bulk consisted of fine-particulate- (e.g. talc, S_0 : 28106 cm²/cm³) or coarse particulate materials (e.g. aspirin, S_0 : 129 cm²/cm³, sodium chloride S_0 : 235 cm²/cm³).

The packing properties of the bulk powder were characterised by measurement of the unsettled powder volume (ρ_{bulk}), the volume after tapping (ρ_{tapped}), and the relationship between the two, expressed as the Hausner Ratio, which is commonly used as a measure of powder compressibility and/or flowability [95-98]. The HR varied from 1.12 to 1.93 for particle size fractionated materials and from 1.10 to 1.95 for bulk materials. A ratio of 1.25 is commonly used as a limiting value between a free flowing and a poorly flowing material [97], the latter a characteristic often associated with poor manufacturability. For the model materials, a general trend of decreasing bulk densities (ρ_{bulk}) with increasing surface areas (S_0) was seen, hence as the original particle size decreased, the particles packed more loosely. This could even be expected to represent the disposition of the particles in the die during compression analysis. The unsettled bulk powder density (ρ_{poured}) was also estimated by a method using a cylinder of approximately the same dimensions as the die (i.e. ~ 11 mm), in order to mimic the flow behaviour of powders during die-filling. The bulk density values (ρ_{bulk} or ρ_{poured}) were converted into corresponding start volumes (V_0) or initial heights (h_0) of the powder in the die, to set a reasonable starting point for further data analysis.

Since the apparent particle densities differed between the model materials and the packing distribution of the particles were interesting, a better representation was estimated by the coordination number. The coordination number describes the number of particles in contact with any given other particle. For irregular particles with a

widespread particle size distribution, the coordination number is difficult to calculate precisely. However, an over-simplified estimation was done on the basis of the powder porosity under the assumption that the particles were mono-sized spheres [84, 99, 100]. The coordination numbers obtained generally decreased with increasing surface areas, also indicating that the fine materials packed less densely.

Table 3. Some primary characteristics of the solid particles a) Paper I and II and b) Paper III. (For primary characteristics for the materials used in Paper IV and V, it is referred to the respective papers.)

a) Powder	d^a (μm)	ρ_{app}^b (g/cm^3)	ρ_{bulk}^c (g/cm^3)	HR^d (-)	S_0^e (cm^{-1})	$c.n.^f$ (-)
Sodium chloride	250-300	2.152 (0.002)	1.02 (0.03)	1.26	313 (0.01)	9.1
	125-180		0.80 (0.04)	1.43	587 (0.04)	8.3
	Milled*		0.70 (0.05)	1.62	1764 (0.03)	7.9
	Milled		0.48 (0.01)	1.89	2307 (0.03)	7.1
Sucrose	250-300	1.586 (0.000)	0.99 (0.02)	-	406 (0.06)	10.1
	125-180		0.64 (0.01)	1.22	676 (0.03)	8.5
	Milled*		0.63 (0.06)	1.32	975 (0.08)	8.5
	Milled		0.43 (0.01)	1.65	2020 (0.02)	7.4
Sodium bicarbonate	250-300	2.216 (0.001)	0.93 (0.01)	1.12	454 (0.03)	8.6
	125-180		0.88 (0.01)	1.29	756 (0.01)	8.5
	Milled*		0.71 (0.01)	1.45	1592 (0.01)	7.8
	Milled		0.61 (0.06)	1.69	2235 (0.07)	7.5
Lactose	250-300	1.540 (0.001)	0.70 (0.01)	1.13	330 (0.21)	8.9
	125-180		0.72 (0.01)	1.17	655 (0.04)	9.0
	Milled*		0.66 (0.02)	1.27	1406 (0.05)	8.7
	Milled		0.38 (0.05)	1.93	3234 (0.21)	7.3

b) Powder	ρ_{app}^b (g/cm^3)	ρ_{poured}^g (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 PH102	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)
MicrocelLac	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	28106 (0.09)

* Milled and air jet classified

Mean values ($n=3$). The relative standard deviations are given in parentheses.

a) Particle size range

b) Apparent particle density

c) Poured bulk density

d) Hausner ratio

e) Powder surface areas

f) Coordination number

g) Poured bulk density

The particle size distributions for the bulk materials used in Paper IV are compared in Figure 4. Both materials could be described as coarse particulate materials. Mannitol had the smaller particle size, with a median particle size of approximately 100 μm , while sodium chloride had a median particle size of approximately 450 μm .

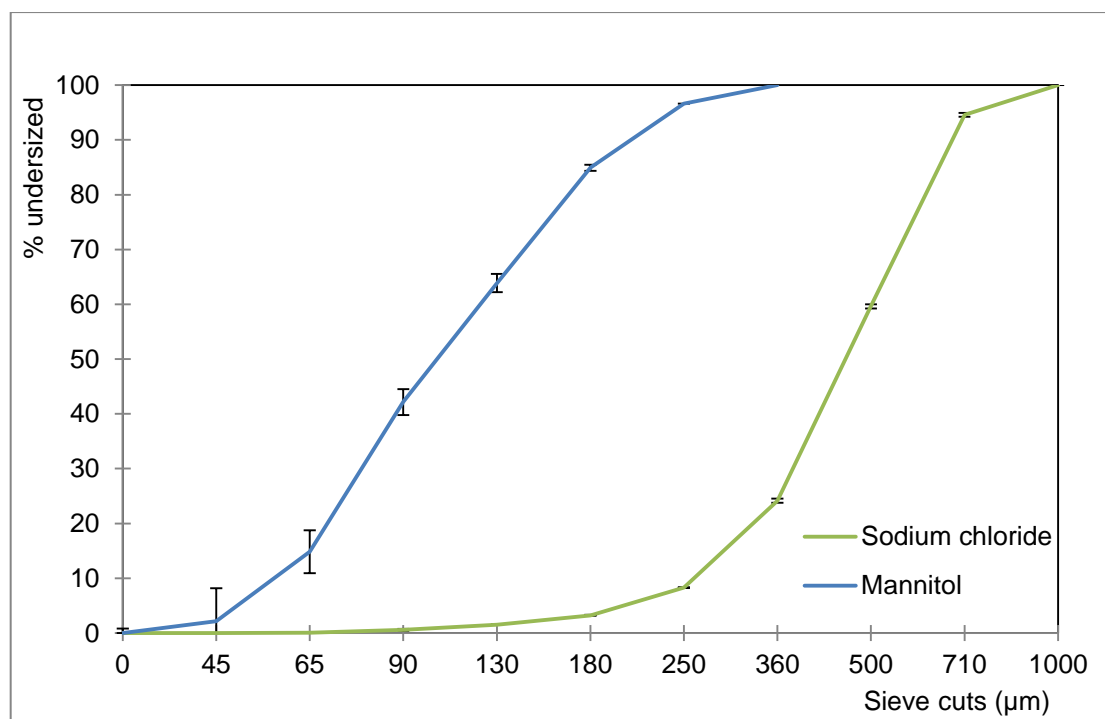
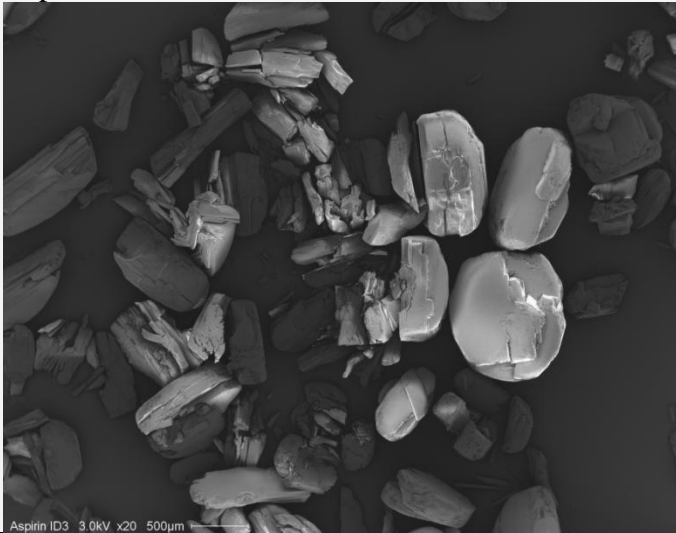


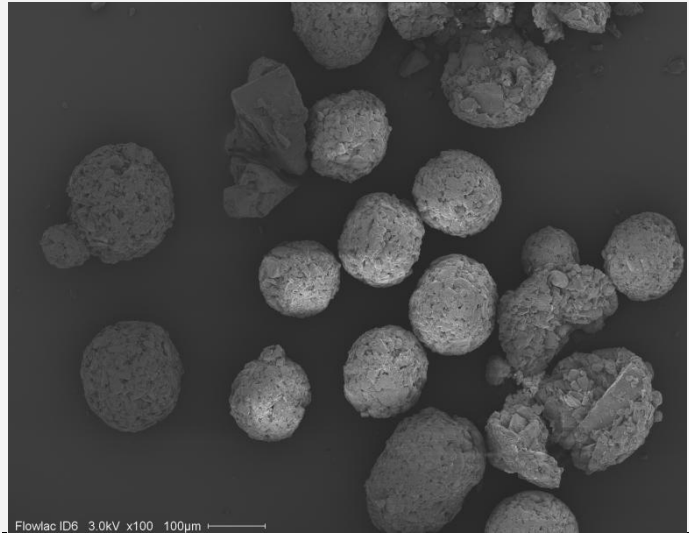
Figure 4. Particle size distribution of the two bulk materials measured by sieve analysis. Standard deviation indicated with bars, n=3.

The SEM-images indicated the difference in particle morphology between the materials, and confirmed that they can be divided into primary particles and complex particles. The primary particles typically consisted of a single solid phase, e.g. sodium chloride, sodium bicarbonate, mannitol and lactose, while the complex particles consisted of two or more phases, i.e. porous or agglomerated particles, and co-processed particles consisting of blends or spray dried mixtures of two materials. Typical examples of the latter group are StarLac[®], FlowLac[®] and MicroceLac[®]. The images also confirmed the observations from the volume specific surface areas concerning particle size: aspirin was a coarse particulate material, while maize starch consisted of fine particles. Information about particle shape as another dimension in the powder characteristics was added. Talc clearly consisted of small, flaky particles, whereas the sodium chloride particles were large cubic crystals. The processed materials, e.g. FlowLac[®] and MicroceLac[®], were composed of homogenous, spherical particles, while PVP had the typical hollow, spherical shape of a sprayed dried material (Figure 5).

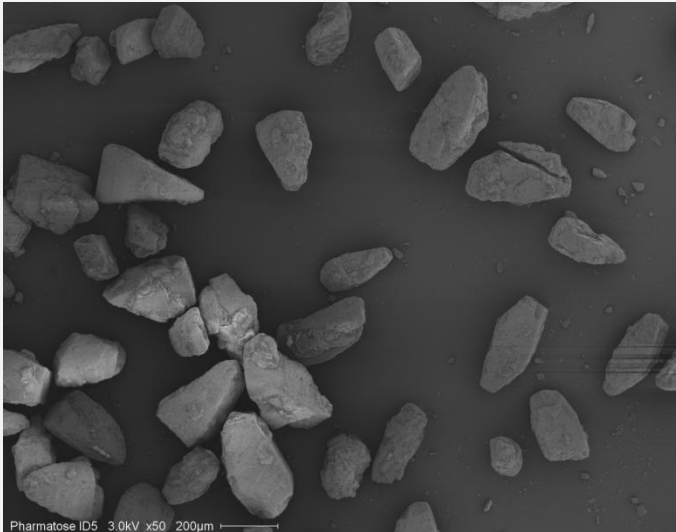
Aspirin



FlowLac® 100



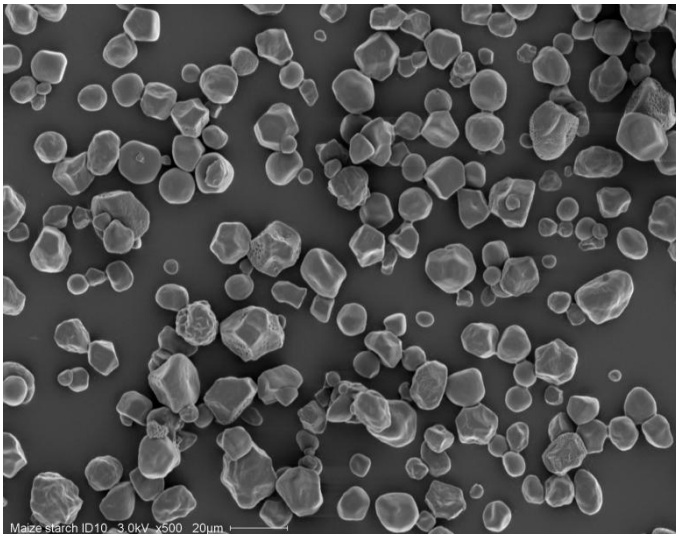
Lactose



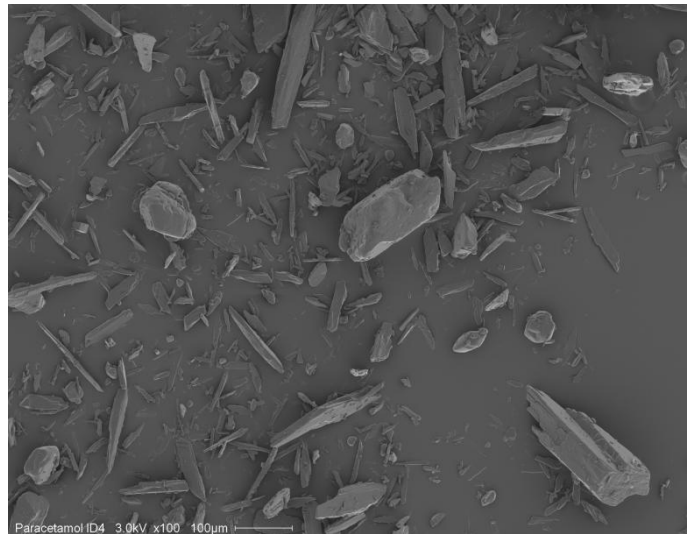
Mannitol



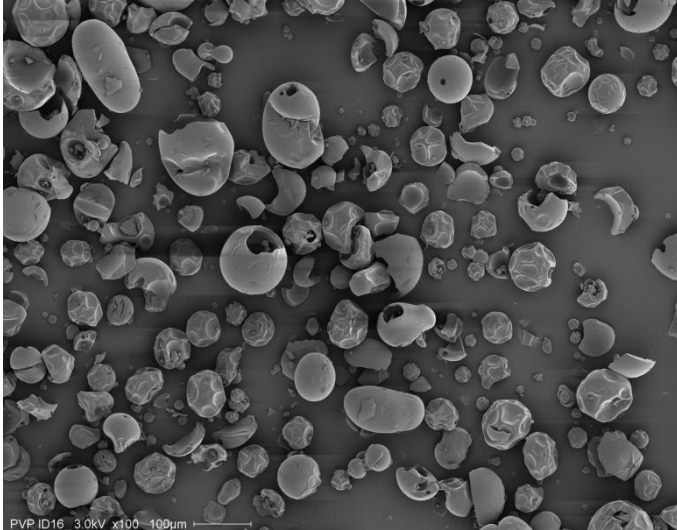
Maize Starch



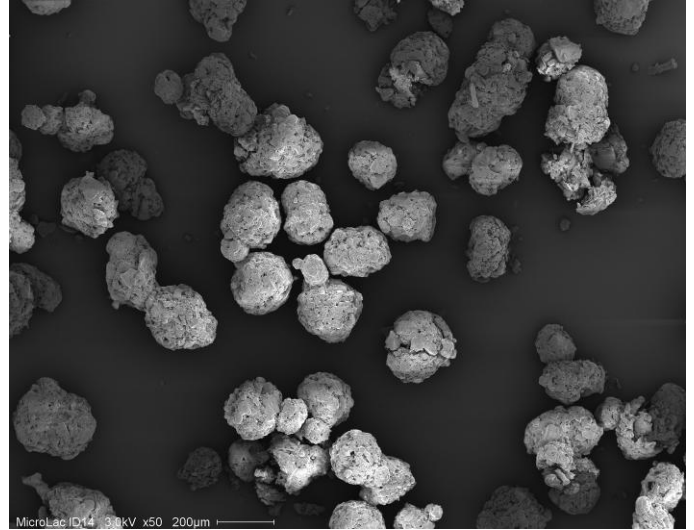
Paracetamol



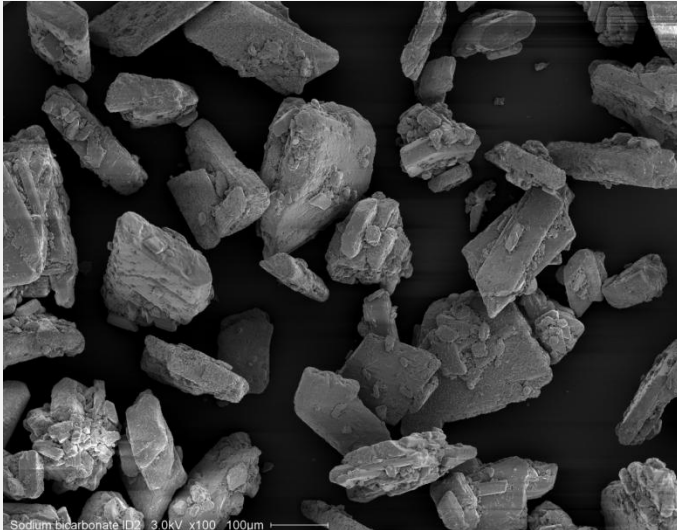
PVP



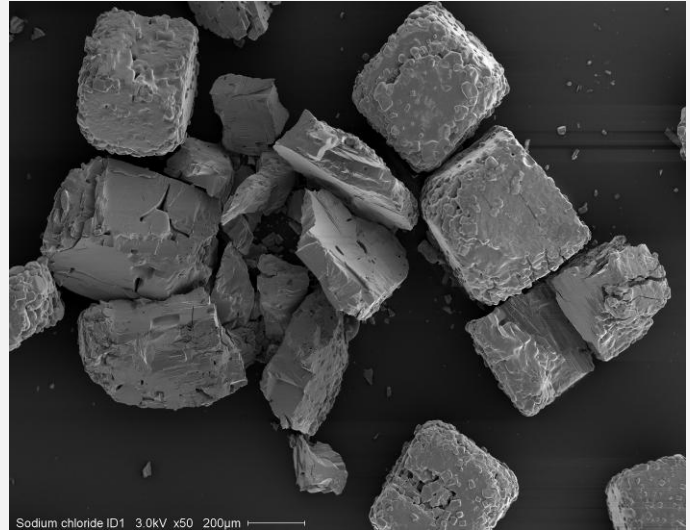
MicroceLac®



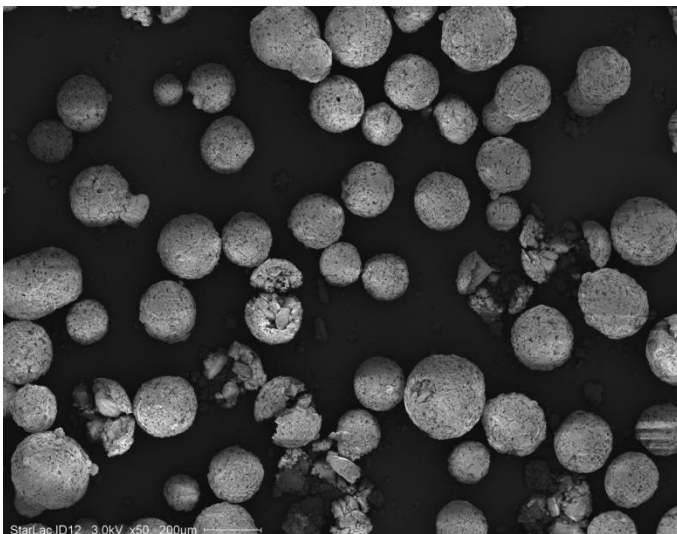
Sodium bicarbonate



Sodium chloride



StarLac®



Talc

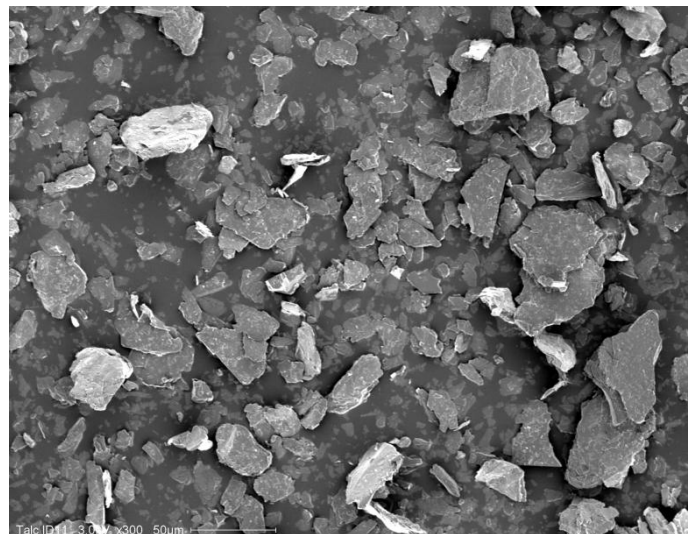


Figure 5. Scanning Electron Microscopy (SEM) –images (for all materials, see Paper III)

5.2 Part 1. Finding good descriptors – “The tools” (Paper I and II)

5.2.1 Compression properties of model materials

In order to investigate whether the Kawakita- and Shapiro compression parameters may allow for physical interpretation in terms of effect of mechanical properties and particle size, a simple experimental set-up was built. Four well-known model materials (i.e. lactose, sucrose, sodium bicarbonate and sodium chloride) were studied in four particle size fractions each (250-300 μm , 125-180 μm , approx. 100 μm and $\ll 50 \mu\text{m}$). Sucrose and lactose have been described as moderately hard materials that show marked fragmentation and limited deformation during compression, sodium chloride is a soft material that shows limited fragmentation but high degree of plastic deformation during compression, whereas sodium bicarbonate is considered being a hard material that shows limited fragmentation and deformation during compression [80]. The stress-strain-profiles of the materials and all size fractions are depicted in Figure 6.

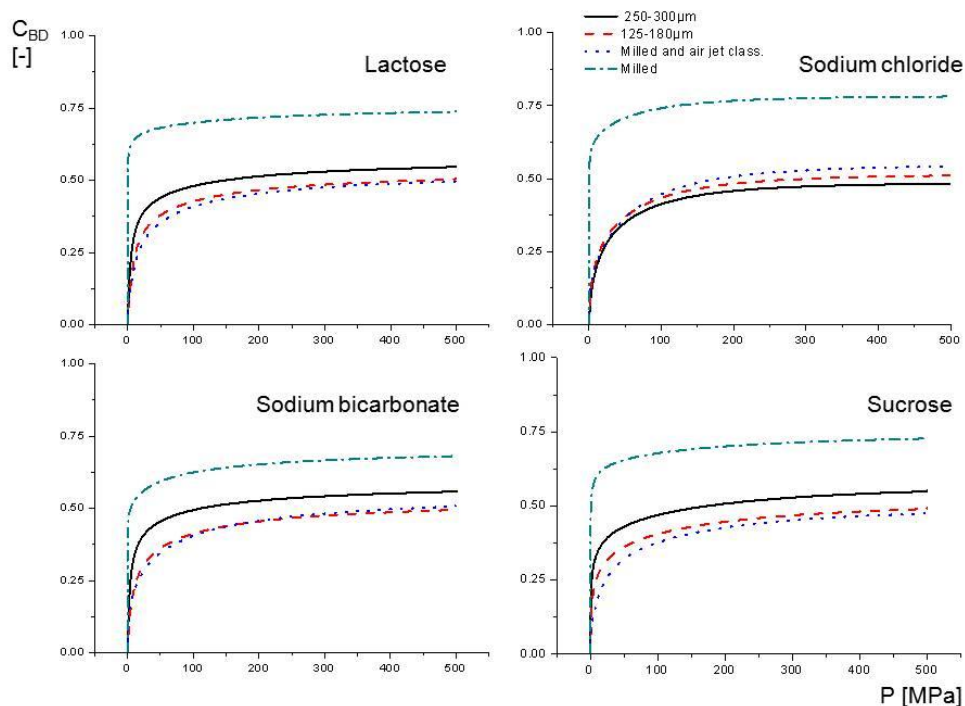


Figure 6. Compression profiles for the model materials a) lactose, b) sodium chloride, c) sodium bicarbonate and d) sucrose, and all four size fractions in the pressure range 0-500 MPa.

It was observed that all the powders showed a fast initial compression, and that a plateau (C_{BDmax}) was reached for most materials. Since the initial volume reduction was so marked, the C-values were calculated both using the starting volume V_0 at a set applied force of approx. 34 N ($\pm 3\text{N}$), and alternatively from a V_0 estimated from the bulk density. The two approaches resulted in different relative changes in volumes,

and consequently gave two sets of Kawakita parameters: for the three coarsest fractions the computation of the initial volume had little effect on the obtained C -values and hence the Kawakita a -parameter. However, when the bulk volume was used for V_0 , notably higher maximum compression was obtained for the finest powders compared to when the set force V_0 was used. This indicated that a large proportion of the compression was obtained already at compression forces below the lowest recordable (and consecutively increasing) applied force. The effect was most pronounced for the very fine particulate materials. It was therefore concluded that a V_0 transformed from bulk density was the optimum method for a good representation of the compression profiles and the total degree of compression, and only this method will be used in the following discussion.

Table 4. Kawakita parameters a , b^{-1} and their product ab derived from compression data.

		V_0 set from force (34 ± 3 N)			V_0 set from bulk density		
		a_F^a (-)	$b_F^{-1} b$ (MPa)	ab_F^c (-)	a_{BD}^d (-)	$b_{BD}^{-1} e$ (MPa)	ab_{BD}^f (-)
Sodium chloride	250-300 μm	0.50 (0.01)	18.40 (0.01)	0.03 (0.01)	0.50 (0.01)	18.40 (0.01)	0.03 (0.01)
	125-180 μm	0.53 (0.01)	17.67 (0.03)	0.03 (0.04)	0.56 (0.08)	14.50 (0.26)	0.04 (0.38)
	Milled*	0.55 (0.01)	27.06 (0.04)	0.02 (0.04)	0.55 (0.02)	25.15 (0.11)	0.02 (0.13)
	Milled	0.55 (0.02)	14.09 (0.03)	0.04 (0.02)	0.77 (0.02)	3.48 (0.01)	0.22 (0.02)
Sucrose	250-300 μm	0.52 (0.01)	13.98 (0.03)	0.04 (0.04)	0.58 (0.04)	9.92 (0.13)	0.06 (0.16)
	125-180 μm	0.51 (0.03)	14.28 (0.08)	0.04 (0.12)	0.51 (0.03)	14.28 (0.08)	0.04 (0.12)
	Milled*	0.48 (0.02)	24.06 (0.07)	0.02 (0.08)	0.48 (0.02)	22.97 (0.03)	0.01 (0.05)
	Milled	0.54 (0.03)	14.61 (0.07)	0.04 (0.05)	0.72 (0.01)	5.19 (0.14)	0.14 (0.15)
Sodium bicarbonate	250-300 μm	0.56 (0.01)	9.80 (0.05)	0.06 (0.06)	0.56 (0.01)	9.59 (0.02)	0.06 (0.01)
	125-180 μm	0.50 (0.01)	16.48 (0.02)	0.03 (0.01)	0.51 (0.01)	15.40 (0.08)	0.03 (0.09)
	Milled*	0.52 (0.01)	20.02 (0.04)	0.03 (0.06)	0.52 (0.01)	20.02 (0.04)	0.03 (0.06)
	Milled	0.48 (0.01)	19.64 (0.06)	0.02 (0.06)	0.69 (0.02)	5.56 (0.03)	0.12 (0.03)
Lactose	250-300 μm	0.55 (0.01)	10.83 (0.01)	0.05 (0.01)	0.55 (0.01)	10.83 (0.01)	0.05 (0.01)
	125-180 μm	0.51 (0.01)	15.96 (0.02)	0.03 (0.02)	0.52 (0.01)	15.69 (0.02)	0.03 (0.02)
	Milled*	0.51 (0.01)	19.98 (0.01)	0.03 (0.02)	0.52 (0.01)	18.82 (0.04)	0.03 (0.05)
	Milled	0.44 (0.03)	18.64 (0.06)	0.02 (0.04)	0.74 (0.02)	3.45 (0.07)	0.22 (0.08)

Mean values ($n=3$). Relative standard deviations are given in parentheses.

* Milled and air jet classified

a) Kawakita parameter, recorded V_0

b) Kawakita parameter, recorded V_0

c) The product of the Kawakita parameters, recorded V_0

d) Kawakita parameter, transformed V_0

e) Kawakita parameter, transformed V_0

f) The product of the Kawakita parameters, transformed V_0

The differences in compaction mechanisms were reflected in the overall shape of the Heckel profiles, as shown in Figure 7. At low pressures most materials and particle size fractions displayed curved profiles. The coarse particulate material of lactose, sucrose and sodium bicarbonate depicted the sharpest initial curvature associated with region I, while the sodium chloride fractions were approximately linear already at low

pressures. It was also observed that the finest fractions for all materials displayed a sharp initial curvature. With increasing compression pressure, all the profiles become nearly linear (region II). The Heckel parameters and yield pressures were derived as the reciprocal of the slope in this region, and the yield pressures (Table 5) indicated that sodium chloride deformed at the lowest pressures, lactose and sucrose at intermediate pressures and sodium bicarbonate at high pressures. The bending in the upper pressure region (seen for the three coarsest fractions for sodium chloride, lactose and sucrose), is typical for region III, and is associated with elastic deformation of the tablet. The transition pressure between these three regions differ for all materials used in the study, but for simplicity, the same transition pressures were used in the following discussion, i.e. 50 MPa between region I and II, and 150MPa between region II and III.

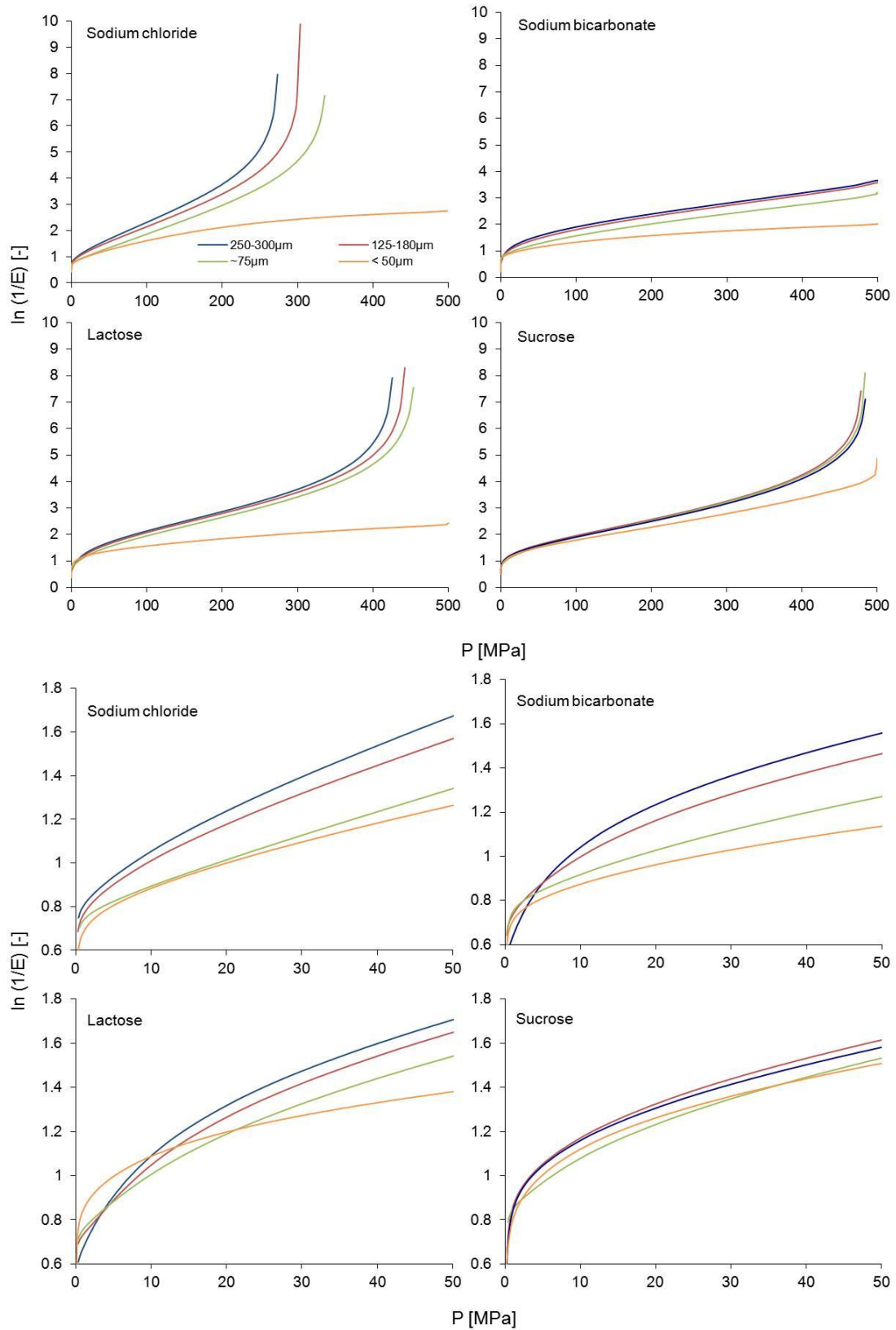


Figure 7. Heckel compression profiles for all materials and size fractions in the pressure range 0-500 MPa (upper) and 0-50MPa (lower). The four powder finesses are distinguished as follows; 250-300 μm (blue), 125-180 μm (red), $\sim 75 \mu\text{m}$ (green) and $< 50 \mu\text{m}$ (orange).

5.2.2 Physical interpretation of Kawakita parameters

For all materials studied, the finest milled powders generally showed the highest final engineering strain and the fastest initial compression. Accordingly, they also gave the highest values of Kawakita parameter a and the lowest values of Kawakita parameter b^{-1} (Table 4). For the three coarser powder fractions, the effect of initial particle size for the overall compression profiles was smaller and not generally consistent. In terms of the Kawakita parameters, a trend regarding the effect of original particle size on the a parameters could be identified with the exception for the sodium chloride powders: a decreased original particle size decreased the value of the parameter, that is, reduced the ability of the powder to reduce in volume. Considering the Kawakita parameter b^{-1} , a larger spread in values was obtained for the three coarsest fractions and the trend was that a decreased original particle size increased the value of the parameter. In mechanical terms, the powders became more resistant to compression at the lower pressure range. The compression profiles also indicated that a reduced particle size tended to reduce the ability of the powders to compress except for the finest powders for which compression was facilitated and the final degree of compression increased. In summary, except for the finest powders for all materials, a reduction in original particle size tended to make the powders more resistant to compression. This may reflect that a decrease in particle size resulted in particles less prone to deform. Further, it indicated that particle deformation was a mechanism of importance for the Kawakita parameters. The trend regarding the effect of original particle size was broken for the finest powders which generally showed a significantly different compression behaviour characterised by a reduced resistance to compression. Hence, it seems that at a critical particle size, the compression behaviour of the powders changed markedly.

5.2.2.1 *The particle rearrangement index*

From bulk densities, Hausner ratios, and calculated coordination numbers it was concluded that the fine particles packed more loosely after deposition in the die and that they were more compressible. Hence, it was regarded plausible that they were more prone to rearrange during compression. It was proposed that below a certain critical particle size, particle rearrangement became a significant compression mechanism. The expression of particle rearrangement affected both of the Kawakita parameters simultaneously, that is, the finest powders generally showed the lowest values of parameter b^{-1} and the highest values of parameter a . It was therefore hypothesised that the combination of the Kawakita parameters a and b^{-1} into a single value, may be used as an indicator of the extent of particle rearrangement during compression. The product ab was derived for all powders. For the three coarsest fractions, a range of indices between 0.01 and 0.06 (Table 4) was obtained with a trend that the index decreased with a reduced original particle size. For the fine fractions, considerably higher index values were generally obtained (0.12–0.22) with the two highest values for the powders with the largest volume specific surface areas (sodium chloride and lactose). There was, accordingly, a clear difference in the ab -values between the finest powder fractions relative to the all other powders (about a fivefold difference). As a consequence of the interpretation regarding the effect of original particle size on the Kawakita parameters it was proposed that the product

ab_{BD} may be used as an indication of the overall contribution of particle rearrangement to the compression profile. In Figure 8, the relationship between the ab_{BD} values and estimates of the original particle size from surface area measurements (d_{S0}) is shown for all powders. The sudden increase in ab_{BD} values coincided with a d_{S0} of about 40 μm . It was therefore suggested that a particle size of about 40 μm represented a threshold or a critical particle size below which the particle rearrangement was expressed to a substantial degree. The materials showing high degree of particle rearrangement all had coordination numbers below 7.5, and this may thus represent another threshold value. After tapping the coordination numbers increased above 8.7 (Table 1, Paper I), indicating that these materials possessed the potential to increase their packing density above the threshold value by particle rearrangement.

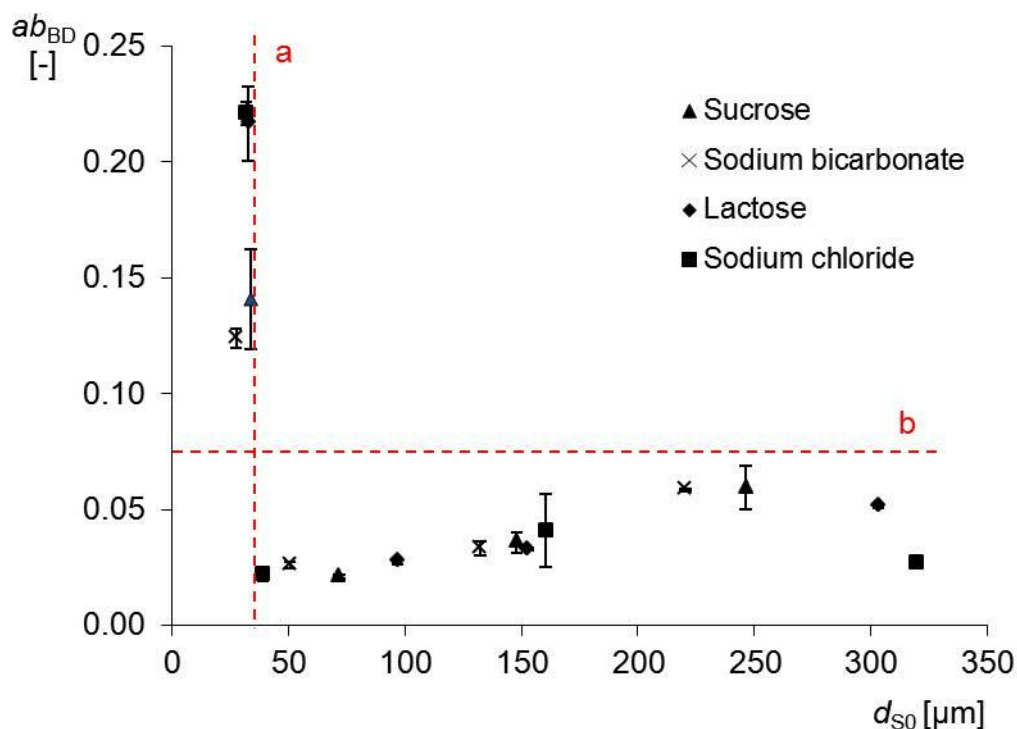


Figure 8. The rearrangement index ab estimated from the Kawakita model and the particle size estimated from the powder surface areas. The error bars indicate the standard deviations. The dotted lines indicate: a) a suggested particle size threshold value ($<40 \mu\text{m}$) below which the rearrangement index, ab , raises above another threshold value b) (> 0.075) indicating extended particle rearrangement.

5.2.3 Physical interpretation of the initial curvature in a Heckel profile

The Shapiro f parameter describes the initial curvature in the Heckel profile mathematically, a curvature that was after the previously discussed results hypothesised to be due to particle rearrangement and /or particle fragmentation. No general relationship between the rearrangement index ab and the f parameter was obtained. Thus, and in accordance with previously presented theories [47, 50, 57] it was assumed that particle rearrangement was not the only process controlling the initial curvature, more precisely that particle fragmentation also was of importance.

To be able to assess the particle fragmentation propensity, permeametry surface areas of tablets made at a compression pressure of 50 MPa were evaluated (Table 5). These results were compared to the surface areas of the powder, and a difference in mean particle size before and after compression was estimated. The data obviously and expected showed a trend to smaller quantitative size reduction (expressed in μm) for the smaller particles. This can also be expressed as an expected trend of decreased reduction in particle dimensions with increasing original powder surface area. According to the results, the lactose particles fragmented to the highest degree (an estimated change of $\sim 250 \mu\text{m}$ for the coarsest fraction), while sucrose and sodium bicarbonate exhibited an intermediate behaviour, and the sodium chloride particles showed limited particle fragmentation ($\sim 33 \mu\text{m}$ for the coarsest fraction). Since the bending of the compression profile in region I generally was consistent with the ranking of the fragmentation tendency of the materials, it was concluded that particle fragmentation in addition to rearrangement most probably was a process of importance for the initial bending of the Heckel profile.

Table 5. Permeametry results and compression parameters derived from linear regression analysis of Heckel profiles in the pressure interval 50-150 MPa.

		S_T^a (cm^{-1})	Δd^b (μm)	P_y^c (MPa)	f^d (-)
Sodium chloride	250-300 μm	349 (0.20)	33	69.91 (0.08)	0.09 (0.01)
	125-180 μm	826 (0.04)	49	86.75 (0.03)	0.10 (0.03)
	Milled and air jet classified	2986 (0.07)	6	94.94 (0.01)	0.04 (0.03)
	Milled	4066 (0.05)	8	137.04 (0.26)	0.16 (0.69)
Sucrose	250-300 μm	2940 (-)*	213*	161.29 (0.01)	0.14 (0.003)
	125-180 μm	2550 (0.05)	109	153.85 (0.01)	0.17 (0.02)
	Milled and air jet classified	2667 (0.02)	34	142.92 (0.03)	0.09 (0.20)
	Milled	6417 (0.05)	18	196.49 (0.12)	0.35 (0.15)
Sodium bicarbonate	250-300 μm	4567 (0.05)	198	163.93 (0.01)	0.23 (0.02)
	125-180 μm	2165 (0.05)	86	165.76 (0.01)	0.13 (0.01)
	Milled and air jet classified	3316 (0.24)	21	184.06 (0.01)	0.08 (0.003)
	Milled	5666 (0.08)	10	280.35 (0.11)	0.21 (0.04)
Lactose	250-300 μm	2037 (0.01)	254	124.49 (0.01)	0.22 (0.01)
	125-180 μm	2875 (0.02)	118	126.05 (0.01)	0.16 (0.01)
	Milled and air jet classified	3306 (0.03)	67	130.44 (0.01)	0.11 (0.005)
	Milled	14046 (0.07)	26	237.87 (0.27)	0.33 (0.06)

Mean values ($n=3$). Relative standard deviations are denoted in parentheses.

* Single value

a) Volume specific tablet surface area at 50 MPa

b) Estimated change in particle size

c) Heckel yield pressure

d) Shapiro-parameter f estimated in the range ($\ln E_{0BD} - 50$) MPa

5.2.3.1 The fragmentation (f) -parameter

Likewise, the obtained f parameters tended to decrease with an increase in original powder surface areas for the three coarsest fractions. This trend was inverted with markedly increased values of the f parameter for the finest fractions. These fractions showed high degrees of initial particle rearrangement expressed by high ab -values,

and also initial curvature in the first region of the Heckel profiles. For the materials exhibiting low degree of particle rearrangement during compression, the relationship between the f parameter and the estimated change in particle diameter during compaction is depicted in Figure 9. It appears that all the fractions of all studied materials followed a single non-linear relationship, and it was thus concluded that for powders without significant initial particle rearrangement, the change in particle diameter due to particle fragmentation controls the bending in region I of a Heckel profile. The importance of particle fragmentation for the bending of the compression profile may be explained in two ways: firstly, the fracturing of a particle into smaller units may result in a rearrangement of the formed particles, i.e. a secondary particle rearrangement. Such rearrangement may facilitate compression at low applied pressures. Secondly, the reduction in particle diameter due to particle fragmentation will progressively increase the hardness (reduce the plasticity) of the particles, corresponding to an increased yield pressure [101]. The resistance towards compression will consequently be controlled by a changing yield pressure until particle fragmentation ceases to occur, i.e. a brittle to ductile transition [31]. From this point on, the yield pressure will be approximately constant and the rate of compression will obey the model, i.e. the Heckel profile will become linear.

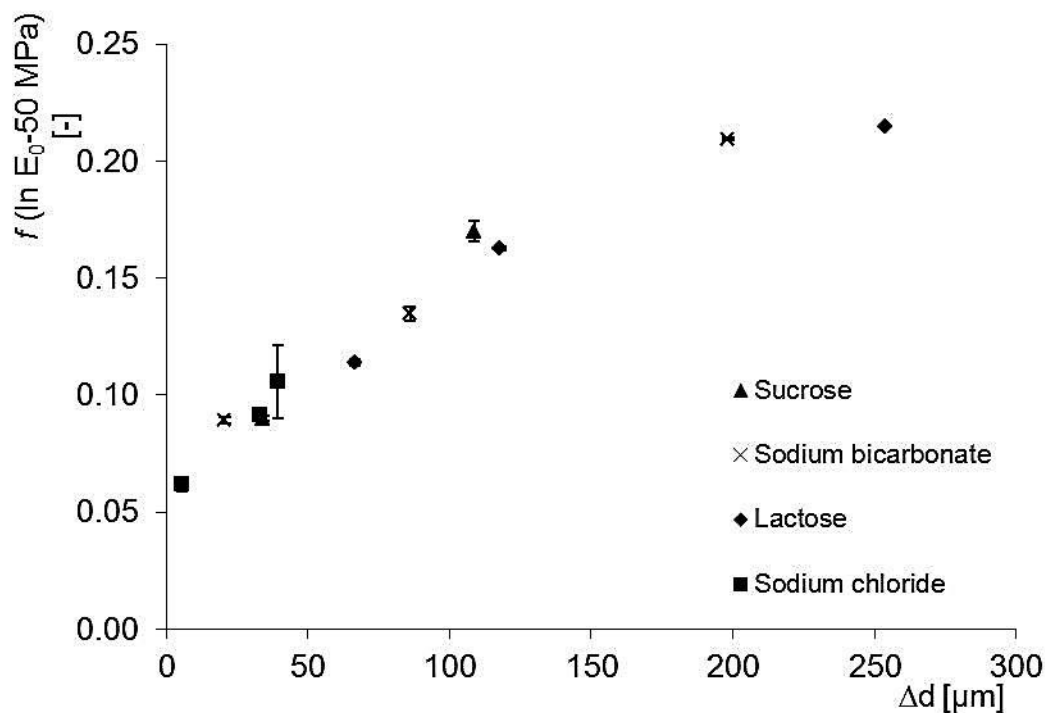


Figure 9. Relationship between the estimated change in particle size, Δd , and the compression parameter f from the Shapiro General Compaction Equation. Mean values $n=3$, the error bars indicate the standard deviations.

5.2.4 A proposed classification system

To summarize, the findings of the above discussed studies could be combined into a simple classification system according to material mechanical properties during compression. In Figure 10 a schematic overview the classification system, with the different classes and types depicted, is shown.

- The product of the Kawakita a and b^{-1} parameters could be used as an indication of the overall contribution of particle rearrangement to the powder compression profile. Powders could accordingly be divided into two classes, characterised by high (Class I) and low (Class II) values of the ab index, reflecting high and low incidence of particle rearrangement during the initial compression phase respectively.
- For powders with limited initial particle rearrangement (Class II powders), the initial bending of a Heckel profile is controlled by the change in particle diameter due to particle fragmentation. Powders with limited initial particle rearrangement could further be subdivided into two categories (denoted A and B), with particles showing low and high degree of fragmentation respectively during compression.
- An indication of particle plasticity (in terms of a yield pressure P_y) from the linear part of a Heckel profile can be derived for both Class I and Class II A and B powders.
- The Heckel profiles can be categorised into three types, dependent on the bending of the profile in region I with associated mechanistic explanation. Type 1, is characterised by a sharp bending of region I due to significant particle rearrangement possible in combination with particle fragmentation. Type 2, is characterised by a smoother and more extended bending of region I due to significant particle fragmentation without primary particle rearrangement. Type 3, is characterised by a nearly linear region I due to limited particle rearrangement and limited fragmentation. For all three types, region II is approximately linear with particle deformation as rate controlling compression mechanism. Region III is associated with elastic deformation of the stiff tablet formed in the die and may appear dependent on the range of compression pressures used.

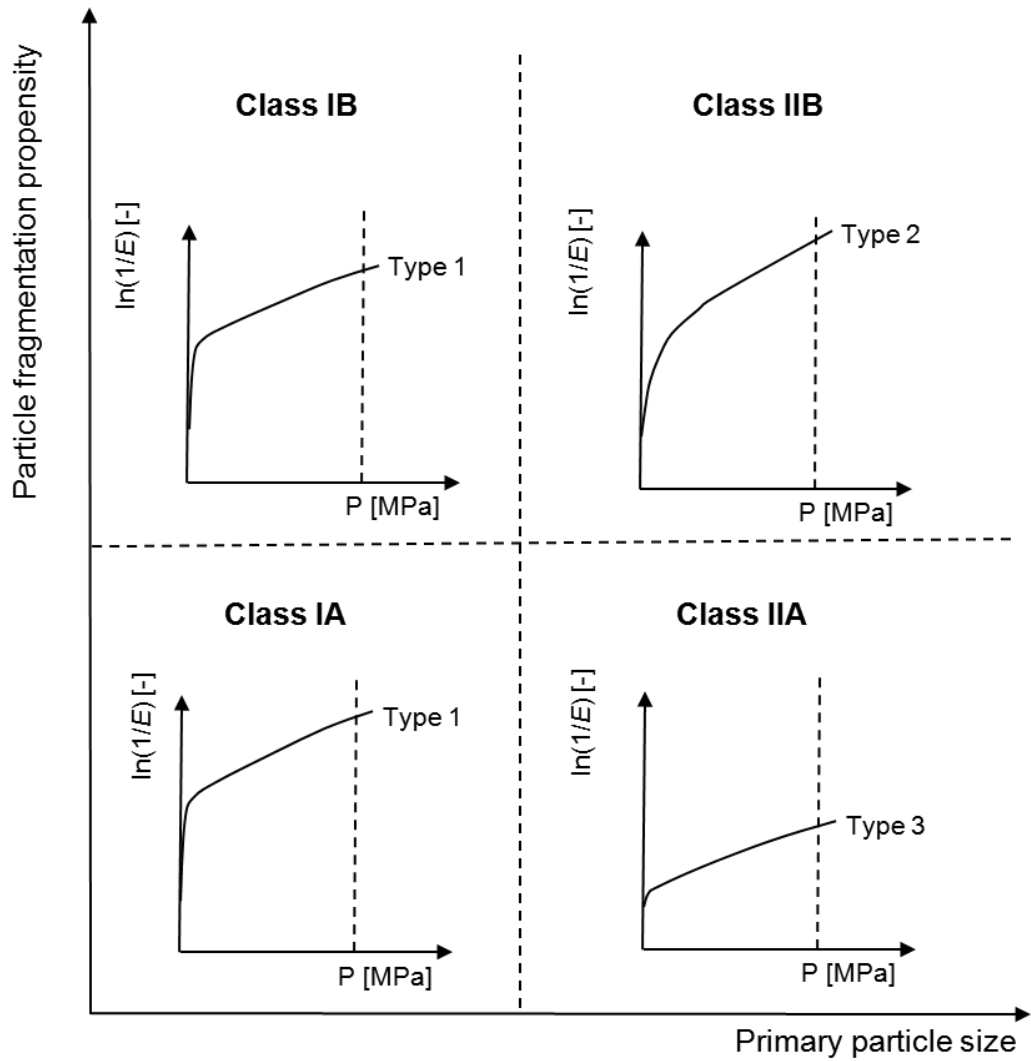


Figure 10. Schematic illustration of the proposed powder classification system and the three different types of Heckel profiles. The dotted lines in the profiles indicate the end of the initial low pressure region.

5.3 Part 2. “Testing the tools” (Paper III)

The classification system proposed above was based on parameters from global compression equations. The system was evaluated by simple model materials that were particle size fractionated. In the following section, a description of how the classification system was challenged by more complex materials is presented.

5.3.1 Important latent structures in compression data

Five compression parameters (Kawakita a , b^{-1} , rearrangement index ab , Heckel P_y and Shapiro f) were retrieved from compression analysis of 17 pharmaceutically relevant materials representing a broad span of compression properties. The compression parameters confirmed that the selected powders represented a wide range of compression behaviour in terms of the incidence of particle rearrangement, fragmentation and particle plasticity (see Table 3 in Paper III for a complete overview). The Kawakita a parameter, representing the maximum powder compression, ranged from 0.456 for aspirin, to 0.844 for talc. The Kawakita b^{-1} parameter ranged from 1.19 MPa for talc to 28.3 MPa for sodium chloride. A combination of these two parameters into the rearrangement index, ab , consequently also demonstrated a wide span of obtained values, from 0.71 for talc to 0.02 for sodium chloride. The Shapiro f parameter varied from 0.52 for aspirin to 0.02 for maize starch, and the Heckel yield pressure (P_y) also varied substantially from 15.2 MPa to 473 MPa for aspirin and dicalcium phosphate respectively. In order to identify groups and to evaluate the relative importance of the parameters in terms of explaining the variation in compression behaviour, the compression data was subjected to a Principal Component Analysis. In the PCA bi-plot of all materials (Figure 11) the scores (depicted in blue) and the loadings (red) are shown. Three materials that can be described as extreme objects were singled out, *i.e.* sodium chloride and talc, which were extreme but inversely correlated along PC1, and aspirin located far down in the vertical direction in the plot, described by PC2. With regard to the loads, the first component was associated with ab and b^{-1} , while the second component was associated with the f parameter, P_y and the a parameter (oppositely correlated). Thus, it was suggested that talc rearranged to a large degree during compression while sodium chloride showed limited particle rearrangement. Aspirin seemed to be characterised by intermediate particle rearrangement and/or high particle fragmentation in combination with high deformation (low P_y -value indicating a very soft material).



Figure 11. Bi-plot from PCA of compression parameters. The two displayed PCs explain totally 75 % (47% and 28% respectively) of the variation in the data.

In order to further investigate the distribution of the 14 clustered materials (marked by a circle) in Figure 11, a model was built excluding the three materials former identified as extremes. The remaining materials spread out relatively homogeneously into four quartiles (Figure 12), further supporting that they represented a wide range of compression behaviours. The Kawakita parameters (a , b^{-1}), the ab -index and the Shapiro f parameter remained the most important variables that described and spread out the materials in the PCA score plot (the two first components of the PCA described 76% of the variation in data). The yield pressure (P_y) was not any longer among the most important variables, being located close to the origin of the two first PCs. This compression parameter was mainly described by PC3, which explains an additional 20 % of the variance, (totally 96 % explained variance on 3 PCs) (Figure 13).

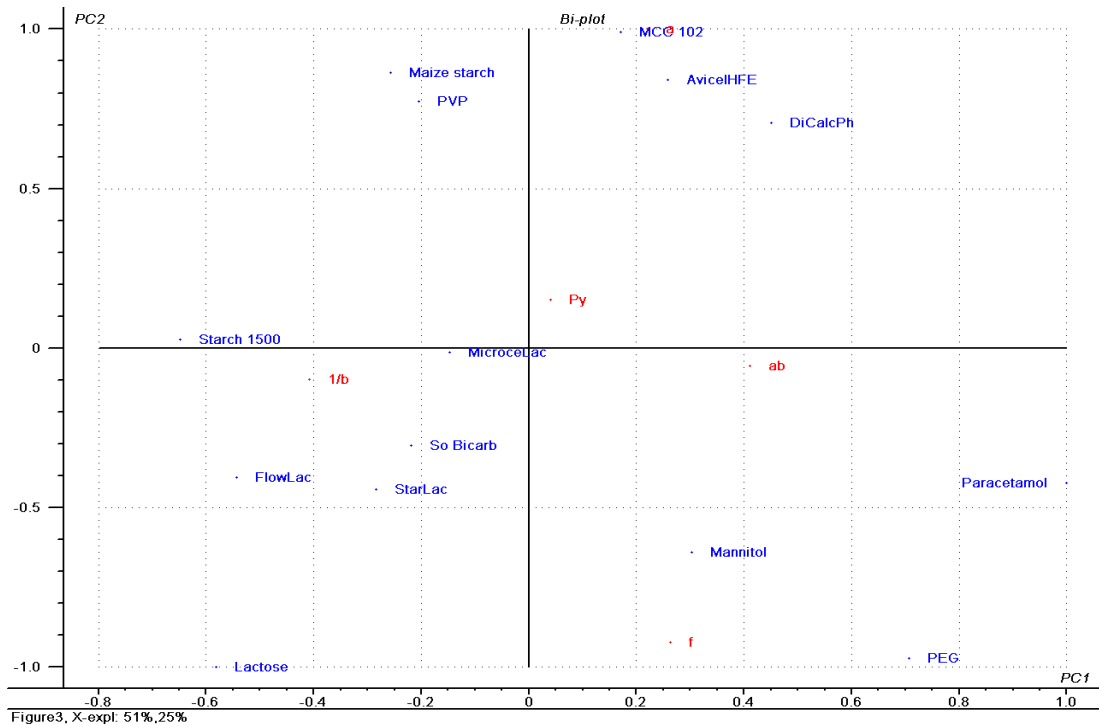


Figure 12. Bi-plot from PCA of compression parameters where the extreme materials (i.e. sodium chloride, talc and aspirin) are excluded. The two displayed PCs explain totally 76% (51% and 25% respectively) of the variation in the data.

The first principal component (PC1) represented the dimension explaining the largest variation in the data set and was associated mainly with the ab index and the b^{-1} parameter. On the right hand side, powders showing a high ab index and a low b^{-1} parameter were located. Hence, the materials situated in this part of the plot were materials that were assumed to show extensive particle rearrangement during compression. Oppositely, the materials situated in the left part of the score plot showed low ab and high b^{-1} values. Thus, the materials situated in this part of the plot were characterised by limited particle rearrangement during compression. As these two variables were the main descriptors defining PC1, and by definition represent the data structure with the most variation in the data matrix, it was concluded that the compression mechanism particle rearrangement had the most significant effect for the overall compression profile.

The second principal component (PC2) representing the second largest variation in the data set, was associated mainly with the Kawakita a parameter and the Shapiro compression parameter f , oppositely correlated. Particle fragmentation was thus suggested to be another significant compression mechanism that explained the obtained variation in the data set and it seemed that fragmentation affected the distribution of the materials in the vertical direction of the score plot. However, since the f parameter and possibly also the a parameter were affected by particle rearrangement during compression, the distribution along the PC2 was probably related to both particle fragmentation and particle rearrangement. One can, however, note that two of the powders that gave low values of the ab index, i.e. powders suggested to show limited particle rearrangement, were located in opposite directions

along the PC2, *i.e.* maize starch and lactose. Maize starch, frequently considered to show limited fragmentation during compression [102], was located in the upper part of the score plot while lactose, often considered to fragment to a high degree during compression [82], was located in the lower part of the score plot. Materials located close to zero value of PC2 could consequently most likely be characterised by an intermediate fragmentation propensity, but further conclusions regarding the discriminating capacity of this parameter could not be made.

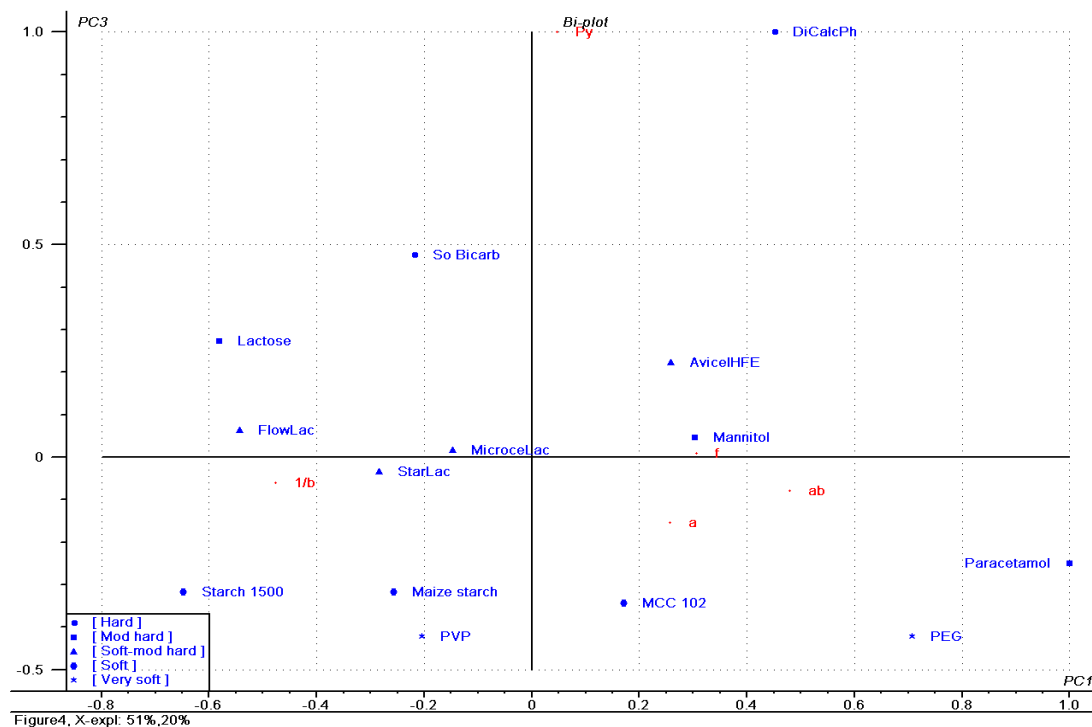


Figure 13. Bi-plot of PC1 vs. PC3. Classification according to expected particle hardness added as a category variable, see special symbols in plot. PC3 explaining an additional 20% of the variation in the data (totally 96 % on 3 PCs).

In Figure 13, the third principal component (PC3), explaining an additional 20 % of the variation in the data, is displayed versus PC1. Regarding the loadings, PC3 was mainly associated with the yield pressure, P_y , and plastic deformation thus represented another compression mechanism of importance for a compression profile. By adding the expected particle hardness as a category variable, it was observed that the materials spread out relatively homogeneously along the PC3 in the vertical direction, ranging from very soft (PEG, $P_y = 36.2$) to hard (dicalcium phosphate, $P_y = 472$). This indicated that the yield pressure was a compression parameter that in itself explained variation in compression behaviour between materials.

In summary, multivariate analysis grouped the materials according to similar features and identified the main descriptors of compression. The incidence of particle rearrangement explained the largest variation in compression data, particle fragmentation the second largest variation, and finally, particle plastic deformation explained the least variation. A sequential handling of compression data was therefore proposed; firstly the materials are characterised regarding their incidence of particle rearrangement, followed by a sub-categorization with respect to their fragmentation

propensity. Finally, the materials are described in terms of their plasticity in a more fine-tuned way using the Heckel yield pressure. From the compression data, examples of the three different types of Heckel profiles were also distinguished (Figure 14). Dicalcium phosphate displayed a sharp bending at very low pressures (typical Type 1 profile), followed by a part with a slight curvature. The sodium bicarbonate curve was bended over the whole low-pressure region (Type 2), while the maize starch curve was approximately linear already at low pressures (Type 3).

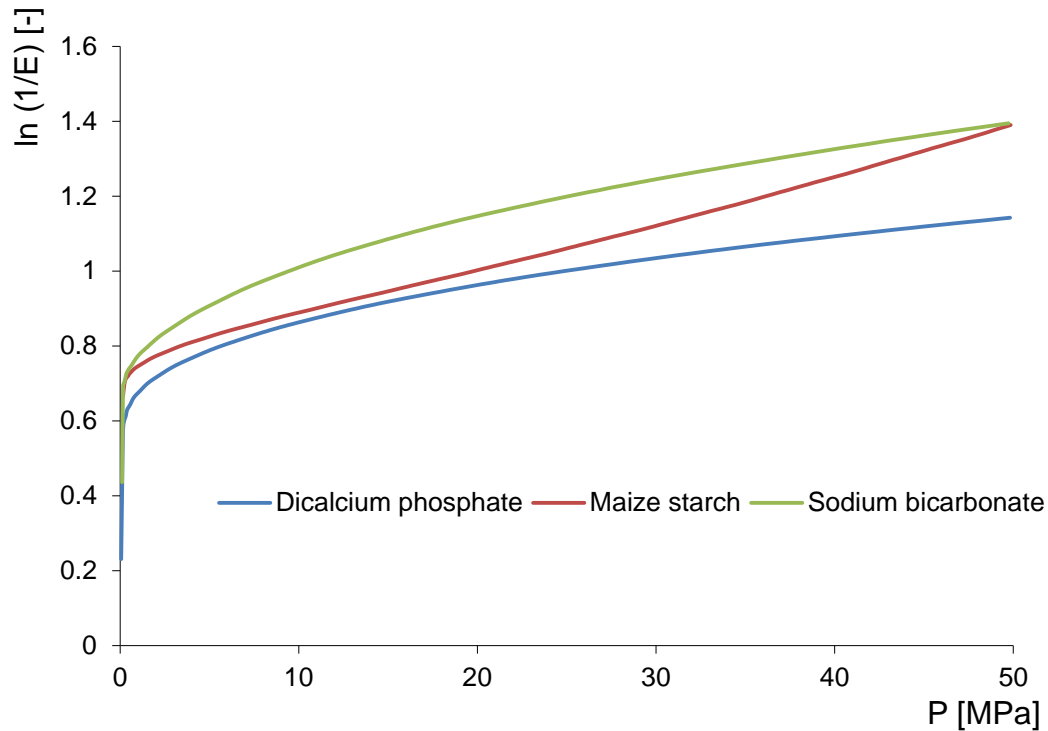


Figure 14. Examples of three different types of Heckel profiles as distinguished in Region I: dicalcium phosphate representing Type 1, sodium bicarbonate representing Type 2 and maize starch representing Type 3 profiles respectively.

5.4 Part 3. A classification protocol – “The toolbox” (Paper IV)

A classification system based on global compression models has been introduced. The discriminating capability of the system was challenged, and the relative importance of the different compression parameters was evaluated by a multivariate statistical approach. The results indicated that a sequential handling of compression data enhanced comprehensive assessment of particle deformation mechanisms. In the following part this classification system is presented in the form of a protocol.

5.4.1 Assessment of mechanical properties

The practical data handling was suggested to be a stepwise approach, as illustrated in Figure 15 :

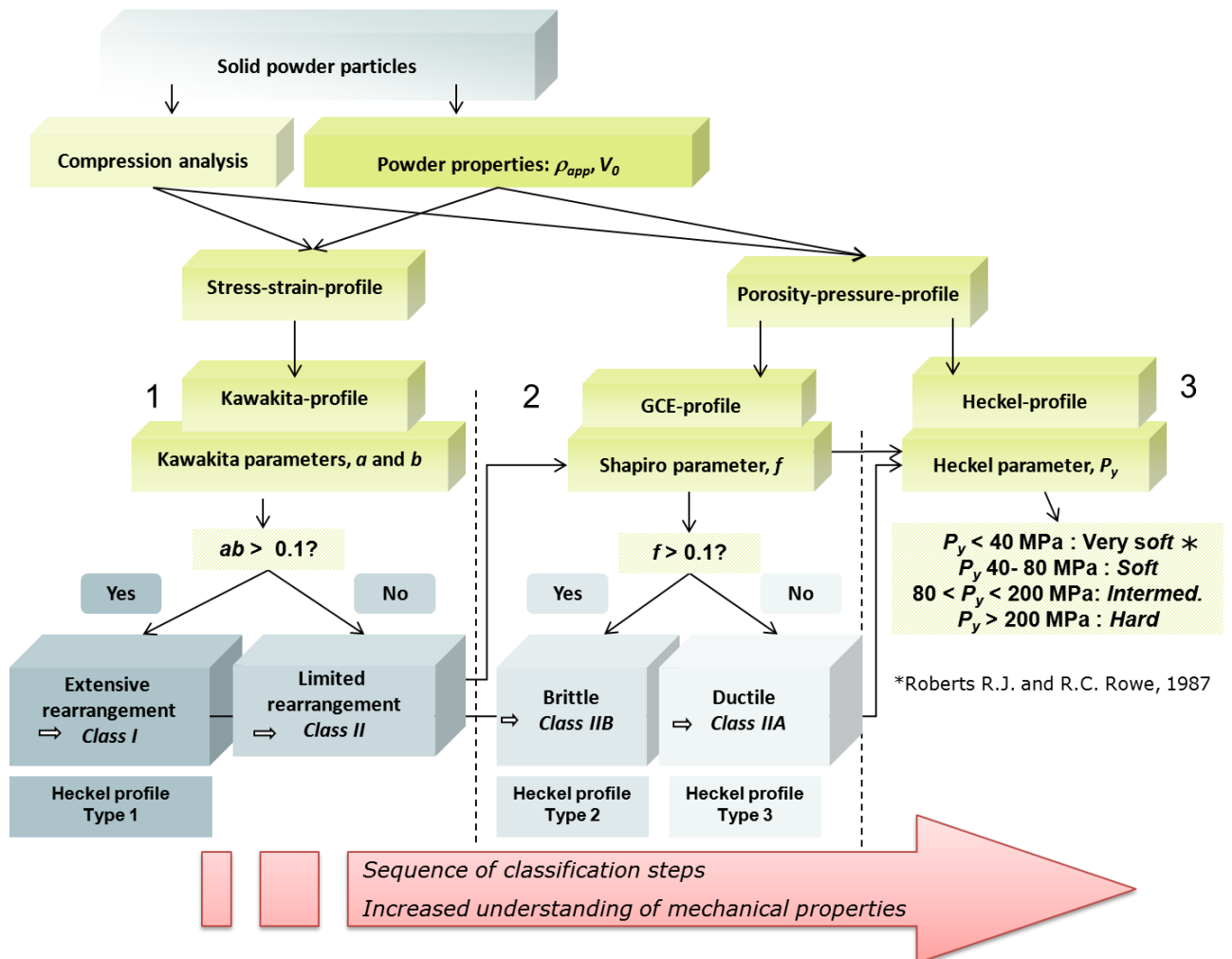


Figure 15. A schematic overview of the suggested protocol for the assessment of compression characteristics of powders (the “characterization and classification route”)

Step 1: The compression profile is described in terms of the Kawakita equation by which two compression parameters are derived, denoted a and b^{-1} . With the product of

these, the ab index, a powder is classified as Class I or II dependent on the incidence of particle rearrangement. A limiting value of 0.1 is suggested.

Step 2: The compression profile is thereafter described in terms the Shapiro general compression equation. By this relationship, the f -parameter is derived. The Class II powders are further sub-classified dependent on the incidence of particle fragmentation during compression (Type A or B powder). A limiting value of 0.1 is suggested.

Step 3: The compression profile is described in terms of the Heckel equation, and the yield stress, P_y , is derived. With this parameter, a powder is classified in one of four groups regarding particle plasticity, ranging from very soft to hard, with the limiting values adopted from Roberts and Rowe [80].

5.4.2 Influence of calculation settings

The importance of specifying how the data modelling is done in both a comparative and reproducibility perspective cannot be stressed enough. As an additional part of the suggested protocol, specifications regarding modelling of the compression data are listed below (Table 6).

Table 6. Specifications of procedures used to calculate the different compression parameters.

Equation	Starting point	Pressure range	Curve fitting	Fitting requirement	Compression parameters
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_{OBD}	Constant = ~0-50 MPa	Non-linear curve fitting	Convergence criterion = relative χ^2 change ≤ 0.00001	f
Heckel	Pressure corresponding to E_{OBD} (not relevant)	Variable	Linear regression	+ 25 % of minimum derivative of profile	P_y

E_{OBD} is the powder bulk porosity calculated from the measured powder bulk density.

5.4.3 Illustration of concept

It was hypothesised that alteration of the bulk material would affect the outcome of the resulting classification. Therefore, three different samples of each material chosen to represent materials from two different classes found *a posteriori* in the previous study were prepared: a bulk sample (similar to the ones used in Paper III), a milled sample and a sieved sample of same range of the median particle size for the respective materials (Table 7).

Table 7. Compression parameters and proposed classification of powders

Powder	a^a (-)	b^{-1b} (MPa)	ab^c (-)	f^d (-)	P_y^e (MPa)	Class ^f	Heckel type ^g
Sodium chloride (bulk)	0.51 (0.01)	27.2 (0.01)	0.02 (0.01)	0.06 (0.02)	70.5 (0.01)	IIA	3
Sodium chloride (sieved, 425-500 μm)	0.50 (0.01)	34.9 (0.01)	0.01 (0.01)	0.05 (0.02)	69.8 (0.01)	IIA	3
Sodium chloride (milled)	0.77 (0.01)	4.8 (0.01)	0.16 (0.01)	0.08 (0.03)	86.2 (0.02)	I	1
Mannitol (bulk)	0.65 (0.01)	5.4 (0.04)	0.12 (0.05)	0.23 (0.04)	133 (0.04)	I	1
Mannitol (sieved, 125-180 μm)	0.60 (0.01)	6.4 (0.07)	0.09 (0.07)	0.29 (0.03)	132 (0.01)	IIB	2
Mannitol (milled)	0.74 (0.01)	3.8 (0.03)	0.19 (0.03)	0.17 (0.03)	135 (0.03)	I	1

Mean values ($n=5$). Relative standard deviations denoted in parentheses

a) Kawakita parameter a

b) Kawakita parameter b^{-1}

c) ab -index

d) Shapiro parameter f

e) Heckel parameter P_y

f) Classification of powders in terms of classification system

g) Categorisation of powders in terms of type of Heckel profile

Principal component analysis of the compression data was performed merely to elucidate the changes in compression characteristics accomplished by the preparation procedures used. In the combined scores (blue) - and loading (red) plot (Figure 16), the first two PCs accounted for 98 % of the variation in the data set (76 % and 22 % respectively). Regarding the scores, 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. Regarding the loadings, 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, as expected, different between the bulk powders for both materials, and the sieving tended to increase the differences in compression behaviour. 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 changed the compression characteristics towards more similarity regardless of the different inherent mechanical properties of the materials. The milling changed the location in the PCA plot primarily due to a change in the Kawakita b^{-1} -parameter but also by a change in the other four variables. 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. The change due to milling could be explained by the same variables but in the opposite direction along the PC2.

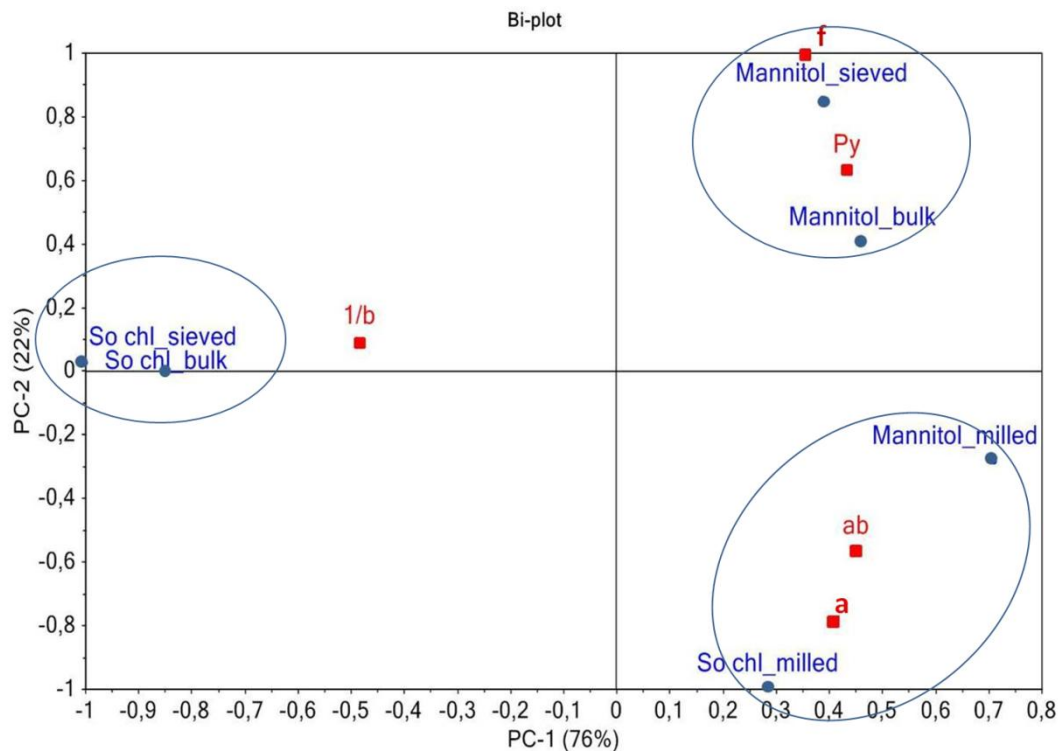


Figure 16. PCA bi-plot of the six materials. PC1 and PC2 describing totally 76% and 22% of the variation in the data respectively.

In classification terms, sieving of a Class I material (exemplified by the mannitol bulk sample) led to a shift in classification into Class II, and other deformation properties of the material could be identified. Milling of a Class II material (exemplified by the sodium chloride bulk sample) induced a shift in classification into a Class I material. In mechanistic terms, for mannitol sieving gave particles showing less rearrangement and more fragmentation than the bulk powder. For both powders, milling induced significant particle rearrangement and gave particles less prone to deform during compression.

5.5 Part 4. Tableting relevant information in “the toolbox” (Paper V)

To open the possibility to predict tablet performance from compression data, a simple experimental design based on two model materials, was built. By utilizing multivariate data analysis techniques, the relative importance of the different compression parameters on the tablet strength was found. In addition, other information from the compression data relevant for tablet manufacturing was evaluated.

5.5.1 Evolution in tablet strength

The two model materials (sodium chloride and lactose) were chosen according to their rather different and well-characterised material properties. The materials were separated into different particle sizes to further affect these properties. Compression parameters were obtained for both materials and all particle size fractions at six different maximum pressures, and the results confirmed the expectations in terms of plasticity and brittleness. In Figure 17, the scores and loadings from the PLS-1 modelling are depicted. The score plot clearly separated the two materials, with the sodium chloride samples to the right and the lactose samples to the left. Regarding particle size, in general for the sodium chloride samples the coarse fractions were found in the lower part of the plot, and the fine in the upper. For the lactose samples the intermediate fractions were found in the lower part of the plot. Furthermore, all materials spread out from left to the right with increasing applied pressure. However, the lactose fractions spread out over a relatively larger area than the sodium chloride fractions. For the latter, clusters of samples compressed at the highest pressures were observed. This pressure effect attenuation seems to reach a maximum for the sodium chloride samples as the pressure exceeds 200 MPa, i.e. these samples cluster to the right in the plot while the lactose samples continues to spread out with increasing pressure, although a slight attenuation of this effect may be seen at 500 MPa. In the loading plot (Figure 17 lower part), the response variable tensile strength (denoted TS) is found located in the upper right quartile, and consequently the disposition of the sodium chloride samples indicated that they in general yield tablets with higher strengths than lactose. The results further indicated that compression of fine particles resulted in stronger compacts than coarser particles, which was expected due to the larger amount of contact points available for interparticulate bonding. Values for the obtained compactability descriptors are listed in Table 3 in Paper V. The compression parameter, C_A , also clearly separates the two materials and has earlier been suggested to indicate the effective deformability of the particles [92]. The higher values for the lactose fractions are expected as this is known to be a harder material than the soft and ductile sodium chloride. The parameter $(\sigma_t - P_{app})$ slope confirmed the observations from the PLS-plot. The increase in tablet tensile strength with the compaction pressure was markedly faster for the sodium chloride fractions compared to the respective lactose fractions. For both materials the same trend of increasing differences with decreasing particle sizes was found. The critical formation pressure (P_0), i.e. the lowest pressure needed to create a coherent mass or a tablet, was highest

for the coarse sodium chloride fraction and lowest for the coarse lactose fraction. Here opposite trends were seen for the two materials, i.e. an increase in critical formation pressure with decreasing particle size for the lactose fractions, and decreasing for the sodium chloride fractions.

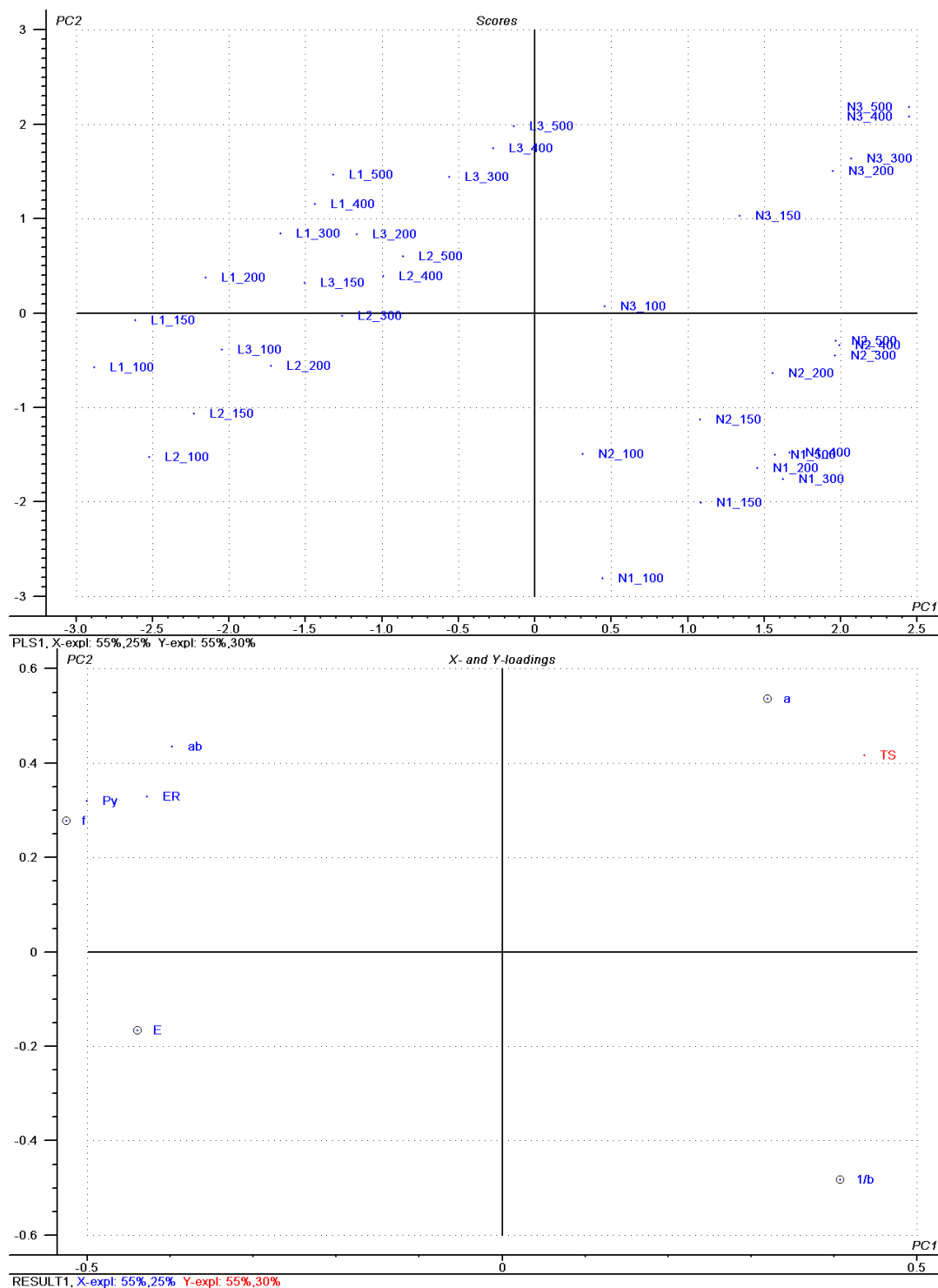


Figure 17. PLS-1 of both materials; a) score plot; b) loading plot. Object annotations: L=Lactose, N= Sodium chloride, 1=coarse, 2= intermediate, 3=fine fraction.

In conclusion, the expected effects of particle size and applied pressure on the evolution in tablet tensile strength were confirmed, and found to be most prominent

for the non-fragmenting, ductile material. Sodium chloride yielded harder tablets faster but also required a higher pressure before a tablet was formed. When this threshold was reached, the tablet formation was faster. A slower rate of densification was observed for lactose, but the critical formation pressure was also lower which means that the densification started at lower pressures and the evolution in tablet strength was slow, i.e. higher pressures needed to attain hard tablets.

5.5.2 Demonstration of compression and compaction parameters

An overview over a PCA based on all compression parameters (Kawakita a , b^{-1} ($1/b$ in the plot), the rearrangement index ab , Heckel P_y , Shapiro f) and the Elastic Recovery (ER), and the compactability descriptors (TS_{max} , TS , $slope$, C_A and P_0) is depicted in Figure 18. Regarding the scores (red), the two materials were separated along PC1, describing 55 % of the variation in the data. The particle sizes were separated along PC2 (describing 35 % of the variation on the data). The loadings (blue) showed that the first PC was mainly influenced by the Kawakita b^{-1} parameter and the critical formation pressure, P_0 , oppositely correlated to the rearrangement index, ab , C_A , f , P_y and ER . Hence, this latent structure in the data seemed to describe the deformation properties of the material. The Kawakita b^{-1} parameter has been shown to reflect particle deformability of single granules [61], but also to reflect the resistance of single particles against deformation [60], hence expected to be negatively correlated to Heckel P_y . Interestingly, the bulk effect on Kawakita b^{-1} has been more complex to interpret. The relationships between the Kawakita b^{-1} parameter and the Heckel yield pressure, P_y and the critical deformation pressure, P_0 , respectively are found in Figure 19. The first plot gave no clear relationship between the two parameters for both materials together, but if the materials were treated separately the relationship became clearer. The relationship between the Kawakita b^{-1} and P_0 also appears clearer, and was further supported by the strong correlation between these two parameters in the PCA-plot. In addition, the Kawakita b^{-1} and the P_0 -values were in the same range. Hence, the Kawakita b^{-1} parameter seemed to indicate at which pressure the deformation of the bulk powder started. The value of this compression parameter in a predictive perspective could be as an indicator of the minimum applied pressure necessary to produce a coherent tablet (although of low tensile strength).

According to the PCA and expected from previously published results [92], P_y was strongly correlated to the effective deformation parameter, C_A . The relationship can be seen as a constrain factor relating the hardness and the yield strength of materials to each other (factor approx. 3). The compression parameter corresponded to a fast evolution in tablet tensile strength and represents the pressure range in which the tablet tensile strength increases when compression pressures are increased. The second PC was mainly composed of Kawakita a , TS_{max} and TS , hence, was associated with the mechanical properties of the tablet. The Kawakita a parameter is mathematically equal to the maximum degree of compression and would be expected to be highly influenced by particle size. The Kawakita a parameter has been shown to be a promising process indicator during tablet manufacturing for granulated materials [103] and a relationship between the compressibility and compactability has also been reported [104].

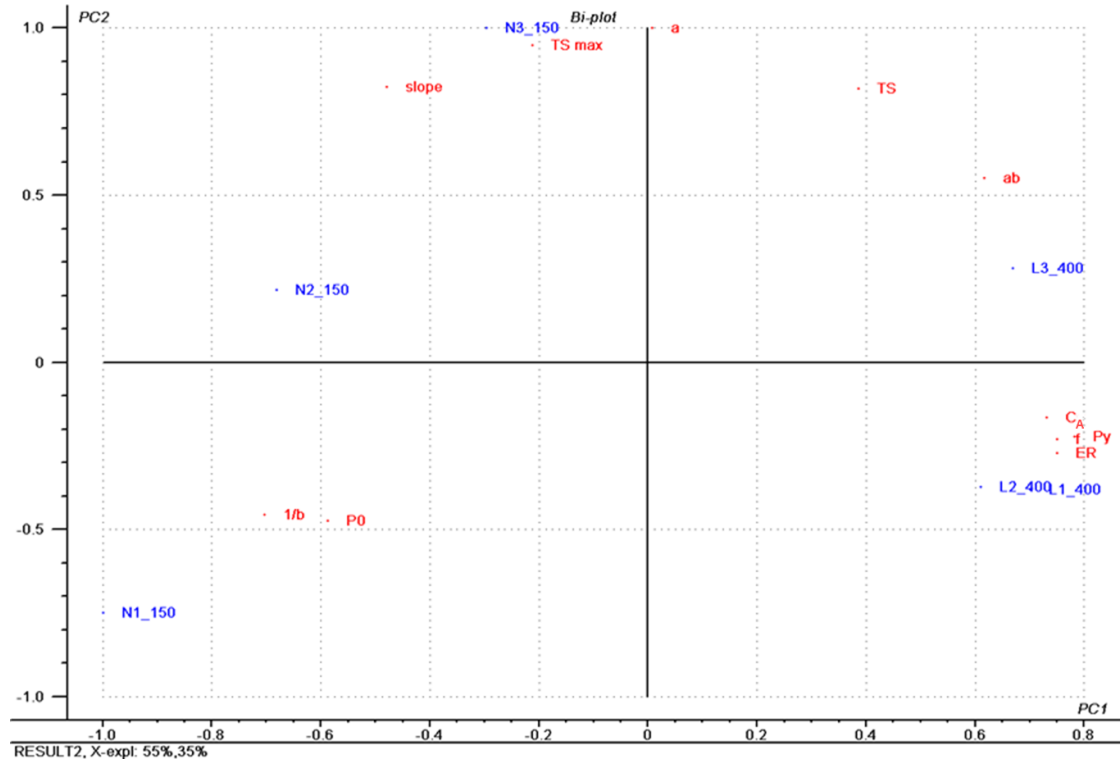


Figure 18. PCA bi-plot of both compression parameters (derived an approximate tablet porosity of 0.05) and the compactability descriptors.

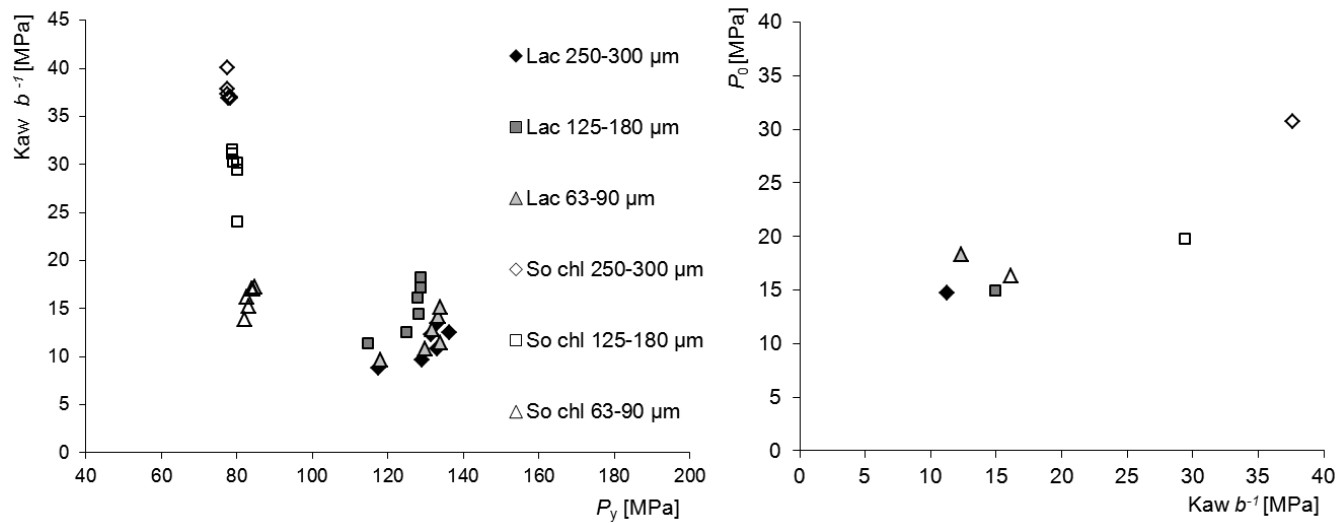


Figure 19. Relationships between Kawakita b^{-1} parameter and the yield pressure, P_y , and the critical formation pressure, P_0 , to the left and right respectively.

In summary, the compression parameters retrieved bring forward valuable information about the tableability of the powders and could possibly contribute in the formulation development phase. The Kawakita b^{-1} parameter seemed to indicate at which pressure the deformation of the bulk powder starts, hence in a predictive perspective - the minimum pressure needed to produce a tablet of low tensile strength. The b^{-1} parameter reflected not only the material deformation property, but also the deformation on the bulk affected by e.g. particle size. The rearrangement index ab , the

Shapiro f parameter, and the Heckel yield pressure, P_y , were most valuable as indicators of the material mechanical properties. Additionally, the yield pressure can be an indicator of the pressure interval at which the material deforms most effectively.

5.5.3 Prediction of tablet strength

Significance of the different parameters for the response was found from the PLS-modelling. Analysis of both materials together (Figure 17) and each material separately was done (summarised in Table 8). It was observed that there was a shift in which variables that became significant in the different models. The Kawakita b^{-1} was significant in the negative direction in the model for both materials, but non-significant for sodium chloride and significant in the positive direction for lactose. The f parameter was significant in the negative direction for both materials, in the positive direction for sodium chloride and negative direction for lactose. The f parameter was higher for the fragmenting material (as expected), but the effect of decreasing particle size on fragmentation give opposite pictures for the two. A similar trend was observed for the ab -index, and a possible link between the two is not unlikely. This has although been most prominent for materials having large ab -indices. The elastic recovery, ER , was non-significant for both materials together and sodium chloride but significant in the positive direction for lactose. The elastic recovery was in general much higher for the lactose samples compared to sodium chloride. In addition this is a parameter that is highly influenced by the applied pressure, as the increase in TS and could thus be an effect of the applied pressure in the model. The Heckel yield pressure, P_y , was non-significant in all models. The only two parameters valuable for predicting tablet tensile strength for both materials and for a series of maximum applied pressures were the Kawakita a parameter and the tablet porosity, E . These two parameters were found to be statistically significant and oppositely correlated in all three models. In spite of the non-complex nature of the materials and the simple experimental design, a generalised conclusion based on mechanistic understanding of the processes or prediction of tablet tensile strength from compression parameters could not be derived.

Table 8. Effect of the different compression parameters on the response variable TS obtained by PLS-1 modelling of both materials and sodium chloride and lactose separately.

Compression parameter	Both	Both (reduced)	Sodium chloride	Sodium chloride (reduced)	Lactose	Lactose (reduced)
Kawakita a	++	++	+	+	++	++
Kawakita b^{-1}	-	-	ns		+	+
ab -index	ns		-	ns	ns	
Shapiro f	-		++	++	-	--
Heckel P_y	ns		ns		ns	
Tablet porosity	--	--	-	-	-	--
Elastic recovery	ns		ns		+	+

+ Significant effect in positive direction

- Significant effect in negative direction

ns non-significant effect (error bars passing through origin)

The significance of the regression coefficients were determined by Jack-knifing and corresponds to $p=0.05$.

6 SUMMARY AND CONCLUDING REMARKS

The main goals of this thesis were to establish a system for classification of pharmaceutical materials according to mechanical properties and to evaluate the tableting relevant information provided by this system. The physical understanding of some commonly used compression parameters was addressed. The parameters evaluated were shown to be able to describe three main volume-reduction mechanisms during compression of powder particles. These findings were combined into a classification system, which was tested and found able to group materials according to their mechanical properties. The results indicated that a sequential data handling procedure increased the amount of information retrieved, and a systematical approach was summarised and presented in the form of a Protocol. The Protocol can be valuable for a formulation scientist in the product development phase, for comprehensive assessment of mechanical properties of pharmaceutical materials. Parameters derived from compression analysis were also shown to be useful for tableting prediction, both with respect to the pressure response in the material, and the resulting tablet strength. Compression analysis thus enhances process understanding and can possibly also be applicable for continuous monitoring of the tableting process.

More specifically the findings were:

- The effect of particle size on the Kawakita parameters was studied. Powders showing significant particle rearrangement in the first compression phase were found to show high values of the Kawakita parameter a and a low values of the Kawakita parameter b^{-1} . It was thus suggested that a combination of the two parameters into an index ab may be useful as an indication of the overall contribution of particle rearrangement to the compression profile. It was further suggested that powder materials could be divided into two classes dependent on high or low values of the rearrangement index.
- The physical interpretation of the first bending of a (Shapiro-Konopicky-) Heckel profile suggested being a combination of the incidence of particle rearrangement and particle fragmentation. For materials showing low degree of initial particle rearrangement, the change in particle diameter controls the bending in this region. As the Shapiro f parameter describes this first curves region mathematically, further sub-classification of materials according to fragmentation could be done based on this parameter.
- It was proposed to combine the previous findings into a classification system. Firstly, the Kawakita rearrangement index was used to classify materials into Class I or II reflecting high or low degree of particle rearrangement respectively. Secondly, sub-categorization into Class IIA and B

was suggested on the basis on the Shapiro fragmentation (f)-parameter. The Heckel yield pressure describes materials in terms of deformability and three different types of Heckel profiles were distinguished; Type 1 representing powders undergoing significant initial particle rearrangement, Type 2 representing fragmenting material, and finally, Type 3 representing plastically deforming materials.

○ The discriminating capability of the classification system was challenged by a set of 17 pharmaceutically relevant materials and the respective relative importance of the different compression parameters was evaluated by a multivariate statistical approach. The statistical analysis indicated that a sequential handling of compression data and the different parameters was of importance for the total information retrieved. Division of the materials into groups based on their underlying compression mechanisms was visualised by a PCA.

○ A structured protocol for classification of powder compression characteristics was presented and illustrated by alteration of bulk powder properties. The classification protocol appears valuable in a formulation development aspect, to comprehensively assess mechanical properties of pharmaceutical materials.

○ By a simple experimental design based on model materials, the compression parameters having statistically significant effect on the tablet tensile strength were identified. In addition, tablet performance relevant information from compression and compaction data was evaluated. The Kawakita a parameter was the only compression parameter able to point towards the resulting tablet strength for the materials used and at different maximum applied pressures. The Kawakita b^{-1} parameter might indicate the pressure needed to initiate deformation of the bulk and hence to produce a coherent tablet, while the yield pressure point towards the pressure interval at which the material deforms most effectively.

7 FUTURE PERSPECTIVES

The suggested protocol could be valuable in a product development phase to assess mechanical properties of drugs and excipients. The form of the protocol allows for further expansion to make an even more comprehensive procedure. For this purpose, both the fragmentation propensity and the plastic and elastic deformation of the powders could be evaluated in more detail, potentially using alternative approaches. More specifically:

- A good descriptor regarding the particle elasticity should be evaluated and included, to enable differentiation between plastic and elastic deformation. The latter is of particular interest with respect to prediction of compactability.
- The physical interpretation of the Heckel parameter and the Kawakita b^{-1} parameter is still a subject of discussion and should therefore be evaluated in more detail, particularly in terms of experimental conditions.
- Further discriminating capacity of the f parameter, or other possible descriptors for particle fragmentation, should be tested.

Regarding prediction of tableability from compression analysis data, there are several possible ways to go. All compression experiments in this thesis were collected during slow and constant speed, and the effect of this must be included to make it applicable to real-life systems. Further, a designed experimental set-up is an attractive approach: materials could be chosen on the basis of high and low degree of rearrangement, fragmentation, deformability (established through the classification system) and elastic properties. Hereby, the effect on the resulting tablet properties could be evaluated in a more systematical way. Later expansion with binary mixes is a natural step forward.

8 POPULÆRVITENSKAPELIG SAMMENFATNING

Tabletten er ofte ansett som den foretrukne legemiddelformen, mye fordi den er lett å dosere, svelge og handtere, men også fordi den er relativt enkel å produsere i stor skala. Tabletter produseres vanligvis ved komprimering av en pulverblanding i en matrise, og består av legemiddelet (-ene) og ulike hjelpestoffer. De krav man tradisjonelt har stilt til kvaliteten av hjelpestoffene er blandt annet at de skal være kjemisk- og mikrobiologisk rene, inerte og billige. Kvaliteten av tabletten blir både kontrollert ved prøvetaking underveis i prosessen og på slutten ved f.eks. test av bruddstyrke, om dosen av legemidlet er jevnt fordelt og hvor fort de løses opp. En tablett skal ha nok mekanisk styrke til motstå slitasje under handtering og pakking, men skal kunne deles for hånd av pasienten. Styrken av tabletten påvirker også hvor fort den løses opp i magen og dermed hvor fort eller sent pasienten får effekt av legemidlet. Utviklingen har gitt oss mer avanserte tabletter: de kan ha en forlenget, umiddelbar eller fordrøyd frigjøring av legemidlet, noe som blant annet gjør det mulig at pasienten tar en tablett daglig men får effekt gjennom hele døgnet. Nye tablettformer fører også med seg økte krav til at hjelpestoffene ikke bare skal være en inert transportør av legemidlet, men snarere at de skal ha en funksjon i forhold til det ferdige produktets effekt eller ytelse. For hjelpestoffer som inngår i en tablett, er derfor de mekaniske egenskapene, eller hvordan materialet responderer ved påføring av f.eks. trykk, av interesse. Denne responsen kan være kompleks både å måle og å forutse, og består ofte av flere ulike responser ved ulike trykk underveis i komprimeringsprosessen. Først, ved lave trykk, er partiklene i matrisen løst pakket. Ettersom trykket øker føres partiklene nærmere hverandre inntil man når et punkt der videre omposisjonering ikke lar seg gjøre. Da vil partiklene deformeres, enten ved at de brytes istykker til mindre biter (fragmenterer) eller ved permanent (plastisk) eller midlertidig (elastisk) deformasjon. Under denne prosessen skapes det bindinger mellom partiklene som tilslutt vil utgjøre en ferdig tablett med en definert styrke. Både graden av fragmentering og deformasjon vil påvirke hvilken mekanisk styrke den ferdige tabletten får.

Til tross for at tabletter har vært produsert i store mengder i mange år anses området fortsatt å være basert mer på håndverk og tradisjon enn vitenskap og forståelse. Men utviklingen de siste årene, bla. gjennom et initiativ fra det amerikanske legemiddelverket (FDA) i 2004, har vært preget av at den farmasøytiske industrien i økende grad oppfordres til å forstå fremstillingsprosessene bedre og dermed sikre både bedre produktkvalitet og høyere utbytte i produksjonen. Ved å identifisere alle faktorer som kan ha betydelse for sluttproduktet, kan man bygge kvalitet inn i produktet under fremstillingen i stedet for å teste det. For tablettindustrien kan man for eksempel tenke seg at man slipper tablettene rett ut på markedet når de er ferdigprodusert, istedet for at de må gjennom en rad sluttkontroller.

Denne avhandlingen handler om økt forståelse og bruk av komprimeringsparametere for mekanisk analyse av farmasøytiske pulvere. Videre viser den hvordan man kan bruke disse parameterene for å forutse hvor godt et material lar seg komprimere til en

tablett. For å studere tabletteringsprosessen og det som skjer med materialet underveis gjør man komprimeringsanalyse i instrumenterte tablettssimulatorer eller materialtestere. Metoden gjør det mulig å teste material som vanligvis ikke lar seg komprimere til en sammenhengende tablett, og gjennom disse testene genererer man raskt store datasett. Det kritiske punktet er tolkningen av de utledede komprimeringsparameterene. Derfor handler første del av avhandlingen om å forbedre forståelsen av noen vanlig brukte parametere. For å gjøre dette ble enkle modellmaterialer testet ved komprimeringsanalyse. Resultatene viste at man fra en komprimeringstest kunne få ut informasjon om materialets deformerbarhet og graden av fragmentering. En forutsetning for å kunne bestemme dette, var at graden av omposisjonering av partikler i starten av komprimeringsforløpet var liten. Et uttrykk for å avgjøre grad av omposisjonering av partiklene ble derfor også utviklet og evaluert. Disse funnene kunne dermed la seg kombinere til et klassifiseringssystem med en omposisjoneringindeks, en fragmenteringsparameter og en deskriptor for deformasjon. Systemet ble utfordret ved komprimeringsanalyse av en større gruppe farmasøytisk relevante material. Disse ble valgt på grunnlag av forventet ulike mekaniske egenskaper og fordi de ofte inngår i tablettformuleringer. Resultatene ble evaluert med multivariat statistisk analysemetode og den viste at pulvrene kunne grupperes i forhold til lignende egenskaper. Det ble også bekreftet at rekkefølgen for dataanalysen og hvordan man utførte den var viktig for hvor mye informasjon man fikk ut. Alt dette ble oppsummert i en protokoll for analyse av mekaniske egenskaper hos pulvermaterial. Muligheten for å bruke komprimeringsdata for å forutse evnen et pulvermaterial har til å danne en tablett ble også evaluert, og resultatene viste at graden av volumreduksjon kan peke mot hvilken endelig bruddstyrke tablettten får. Videre kan man få informasjon om det minimale trykk man må påføre pulveret for å få en sammenhengende (men svak) tablett, samt i hvilket trykkintervall materialet deformerer mest effektivt.

For å oppsummere kan man si at avhandlingen presenterer en systematisk framgangsmåte for å finne de mekaniske egenskapene hos farmasøytiske hjelpestoffer. Videre ble den informasjonen man får fra en komprimeringsanalyse evaluert i forhold til hva som er relevant for tablettens egenskaper. Dette kan være nyttig i en formuleringsfase, for å øke forståelsen av hva som skjer med materialet under trykk og muligens også for kontinuerlig kontroll underveis i tabletteringsprosessen.

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Ingrid

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