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Compression analysis as a tool for technical characterization and classification of pharmaceutical powders

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Abstract
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There are today strong incentives for an increased understanding of material properties and manufacturing processes to facilitate the development of new technologies in the pharmaceutical industry. The purpose of this thesis was to suggest methods requiring a low sample amount for characterization of technical properties of powders.

Compression analysis was used to evaluate the formulation relevance of some compression equations. Using the mechanics of single granules to estimate powder functionality was part of this work. It was concluded that the formability of granular solids and the plasticity of single granules could be determined with compression analysis by using the Kawakita model for single components and binary mixtures of ductile granules.

Further on, the fragmentation propensity of solid particles could be estimated from compression analysis by using the Shapiro equation, enabling indicators of both the fragmentation and the deformation propensity of particles to be derived in one single compression test.

The interpretations of the compression parameters were only valid if the influence of particle rearrangement was negligible for the overall compression profile. An index indicating the extent of particle rearrangement was developed and a classification system of powders into groups dependent on the incidence of particle rearrangement was suggested as tools to enable rational interpretations of compression parameters.

The application of compression analysis was demonstrated by investigating the relevance of the mechanics of granular solids for their tableting abilities. The plasticity of single gran-ules was suggested to influence both the rate of compactibility and the mode of deformation, and consequently the maximal tablet strength. The degree of granule bed deformation was shown to be a potential in line process indicator to describe the tableting forming ability.

This thesis contributes to a scheme, suitable in formulation work and process control, to describe manufacturability of powders for an enhanced tablet formulation technology.

Keywords: compaction, compression, granules, Kawakita, mechanical properties, particles, PAT, pharmaceutical powders, tablets

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“They say that the definition of madness is doing the same thing twice and expecting a different result”

List of papers

This thesis is based on the following papers, which will be referred to by the Roman numerals assigned below:

I. Nordström, J., Welch, K., Frenning, G. and Alderborn, G., On the physical interpretation of the Kawakita and Adams parameters derived from confined compression of granular solids, *Powder Technology 182 (2008) 424–435*
II. Frenning, G., Nordström, J. and Alderborn, G., Effective Kawakita parameters for binary mixtures, *Powder Technology (2008) doi: 10.1016/j.powtec.2008.04.016*
III. Nordström, J., Klevan, I. and Alderborn, G., A particle rearrangement index based on the Kawakita powder compression equation, *Journal of Pharmaceutical Sciences(2008) doi: 10.1002/jps.21488*
IV. Klevan, I., Nordström, J., Bauer-Brandl, A. and Alderborn, G., On the physical interpretation of the initial bending of a Shapiro-Konopicky-Heckel compression profile, *European Journal of Pharmaceutics and Biopharmaceutics, in progress*
V. Nordström, J., Welch, K., Frenning, G. and Alderborn, G., On the role of granule yield strength for the compactibility of granular solids, *Journal of Pharmaceutical Sciences (2008) doi: 10.1002/jps.21351*
VI. Nordström, J. and Alderborn, G., Degree of compression as a process indicator of tablet tensile strength, *in manuscript*

My contribution to the papers above was as follows:
Paper I and Paper III-VI: I was involved in all parts of the work, *i.e.* in the problem formulation, the experimental work and the analysis and interpretation of data. I have in conjunction with my co-authors, written the manuscripts.
Paper II: I was involved in the problem formulation, experimental work and data interpretation, and made a minor contribution during the writing process. I was not involved in the development of the mathematical model used.

Contents

Abbreviations and symbols

a	Kawakita parameter
b^{-1}	Kawakita parameter
c	Circularity of single pellets
C	Degree of powder bed compression
C_{max}	Maximal degree of compression of a powder bed
d	Projected area diameter of single pellets
d_{S0}	Particle size calculated from powder surface area
e	Deformation module for a bed of pellets
E	Powder bed porosity
E_0	Initial powder bed porosity
E_{mod}	Modulus of elasticity for single pellets
f	Shapiro parameter
HR	Hausner ratio
k	Heckel parameter
LAC	Lactose
MCC	Microcrystalline cellulose
$MCC\ HP$	Low porosity spherical granules of *MCC*
$MCC\ LAC$	Low porosity spherical granules of *MCC* and *LAC*
$MCC\ HP$	High porosity spherical granules of *MCC*
$MCC\ PEG$	Low porosity spherical granules of *MCC* and *PEG*
PEG	Polyethylene glycol 6000
P_n	Nominal compression pressure
P_y	Yield pressure
RH	Relative humidity
SA	External pellet surface area
S_0	Powder surface area
S_T	Tablet surface area
Δd	Change in particle size
ρ_{app}	Apparent particle density
ρ_{bulk}	Bulk density for the powders
ρ_{eff}	Effective pellet density
σ_0	Nominal fracture strength of single pellets
σ_{max}	Maximal tablet tensile strength
σ_t	Tablet tensile strength
σ_y	Yield pressure for single pellets
τ_0	Adams parameter

Introduction

In the science of Pharmaceutics, a drug is transformed into an appropriate delivery system which is both convenient and safe for the patient and suitable for large scale manufacture. In Swedish, the discipline has kept the name "Galenisk farmaci" after the Greek physician Claudius Galenos (131-201 A.D.), whose ideas dominated the western medicine for almost 1500 years [1].

The formulation of different dosage forms has been the core of the pharmacy practice since the era of the Egyptian pharaohs and in the ancient Rome a variety of dosage forms like ointments, oils, powders and pills were utilized. "Pill-making" soon became a popular activity because of the possibility of concealing awful tasting drugs by adding various excipients and evolved over time to be a vital part in the "art of pharmacy" [2]. The solid ingredients could be powdered in a mortar with a pestle and transformed into a firm mass, from which spherical pills were formed with a variety of facilitating equipments. Today, tablets formed by confined compression of dense or porous powder particles are the first-hand choice when developing drugs into medicines, hence representing a dominating dosage form on the world market. Thus, principles of design and manufacturing methods for different types of tables are well established knowledge.

The success of a tableting operation depends on the properties of the powder components and their response to the applied compression pressure determines important tablet characteristics such as tablet tensile strength, porosity and dissolution rate. An oral dosage form should have sufficient tensile strength to withstand the forces during production, packing and transportation, but still be possible for the patient to break. The active pharmaceutical ingredient is therefore often mixed with a number of excipients to form a final product with certain functionalities. In order to reassure a successful manufacture of tablets, an understanding and analysis of fundamental mechanical properties of the raw material is required to choose excipients and processing equipment with appropriate properties that match the properties of the drug.

The patent on a technique for solidifying a granulated powder under pressure into a solid mass in 1843 by William Brockedon (1787-1854) [3], opened up the possibility for a more large scale manufacture of tablets. A number of different tableting machines were developed during the end of the 18th century and in the 1950s the first instrumented tableting machines made their

appearance. The measurements of the upper punch displacement and applied compression force generated an improved understanding of the powder compression process and also, gave the option to describe it in mathematical terms. Numerous of more or less empirical compression models describing the relationship between force and displacement, have been presented in the literature during the years [4]. From these models, so called compression parameters can be derived as descriptors of powder functionality. However, the physical interpretation of the derived compression parameters is often unclear and has not been discussed in theoretical satisfactory way.

During the last years, the progress in drug design and combinatorial chemistry together with a methodological development in pharmacological screening of drug compounds have considerably affected the process of discovering new drug candidates. The formulation of drugs into drug delivery systems and the development and scaling up of production procedures for these delivery systems, might in the future constitute the bottleneck in the process of developing pharmaceutical formulations. In addition, the Process Analytical Technology (PAT) initiative of the American Food and Drug Administration (FDA) encourages the development and implementation of new technologies and procedures on how to characterize manufacturability of pharmaceutical powders [5, 6].

The purpose of the PAT guidelines is to increase the understanding and the control of different manufacturing processes to meet increased quality demands on pharmaceutical preparations in terms of efficacy, safety, cost and higher product reliability. The PAT guidelines are of course strong incentives for a "quality by design" approach in pharmaceutical research and development work, which requires an increased mechanistic understanding of critical raw material properties that determines product functionality. An increased understanding of the manufacturing processes and different process parameters that control the end product and how indicators of these can be monitored on line are also necessary in an adaptive tableting manufacture process. It is thus essential that knowledge which can be implemented to make the development phase more effective and less time consuming is generated in the area of pharmaceutical formulation technology.

In this thesis, some theoretical aspects of the field will first be discussed, followed by a short review of some current research. The experimental work will then be described, after which the main results of the six papers will be discussed. Finally, the conclusions of the thesis are summarized.

Theoretical aspects

The following section will discuss the concept of powder compression mechanics from a tableting perspective and give a short presentation of some equations used in the field of pharmaceutics to describe the compression behaviour of solid and porous particles.

Compressibility of solid and porous powder particles

A powder can in physical terms be considered as a heterogeneous two phase system composed of a dispersed solid phase and a continuous gas phase that both surrounds the particles and forms a porous network inside the particles. In a real physical system a particle is normally in contact with the neighbouring particles and subjected to various surface forces.

The compressibility of a powder is defined as its ability, when held within a confined space, to reduce in volume under an applied pressure, whereas the compactibility (which will be discussed later) of a powder is the ability to be compressed into a tablet of a specified tensile strength [7].

When a force is applied to a powder bed a number of different compression mechanisms will be active in the volume reduction process and the densification of a powder is traditionally described in terms of a model outlining a series of consecutive, but overlapping stages [8, 9]. It is assumed that in each region, a defined mechanism controls the compression behaviour. After the initial die filling, the rearrangement of particles to a closer packing structure is probably critical for the densification during the first compression region at low applied pressures. With increasing compression pressure, particle rearrangement becomes insignificant since the increased interparticular friction will prevent any further interparticular movement. Any further volume reduction is associated with changes in the dimensions of the particles due to plastic and elastic deformation. For viscous and viscoelastic materials the deformation is also time dependent. In parallel, brittle materials may also fragment into smaller units, which probably occurs directly after the initial rearrangement phase. These smaller secondary particles can subsequently rearrange and may when pressure is further increased, undergo deformation.

The compression mechanics of porous particles (*i.e.* agglomerates formed from a cluster of discrete primary particles) is even more complex since the

powder bed subjected to the pressure consists of both intergranular and intragranular pores. The compression of porous particles has been described according to a four step volume reduction sequence [10]; initial filling of interparticle voids, *i.e.* rearrangement of the secondary porous particles, followed by fragmentation and plastic deformation of the secondary porous particles, thereafter the rearrangement of primary particles leads to densification of the granulated particles, followed by fragmentation and plastic deformation of the primary particles.

This description of the compression behaviour of porous particles has however been modified over the years and it has been shown that ductile porous particles consisting of microcrystalline cellulose show different modes of deformation (*i.e.* ability to conform to the neighbouring particles); local deformation (surface flattening of the porous particles) and bulk deformation (change in dimensions of the porous particles) which occurs in parallel with densification of the porous particles and reduces the intergranular pore volume until a critical number of contact points is reached [11]. An overview of compression behaviour of porous particles and the different stages in the compression process is given in *Figure 1*.

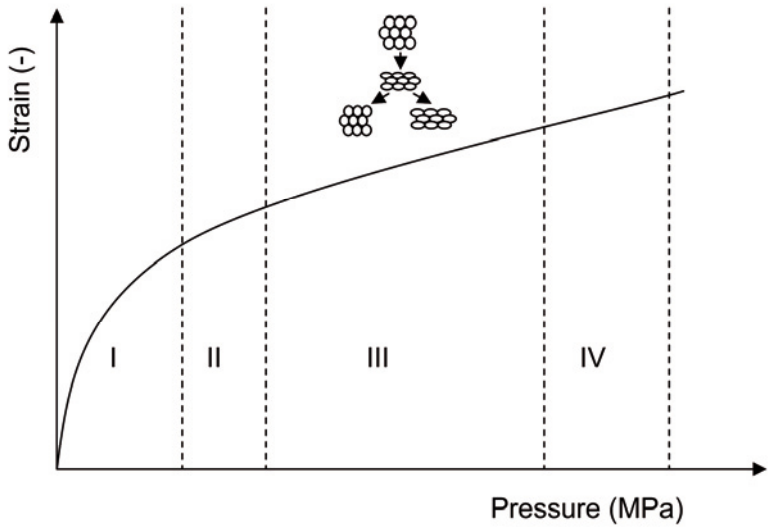

Figure 1. Overview of the different stages involved in the compression process of porous particles. I) rearrangement of granules, II) surface flattening of granules, III) bulk deformation and densification of granules and IV) elastic deformation of the tablet in the die.

Models describing the compression of powders

A compression equation should describe the densification process and preferable indicate changes in compression mechanisms the in the whole applied pressure range with sufficient accuracy, and the derive compression parameters should be related to physical relevant properties of the powder and consequently be sensitive to changes in formulation and differentiate between powders showing different compression mechanics.

Compression behaviour of solid particles

Since Walker described the relationship between applied pressure and powder volume held in the die in 1923 by relating the relative volume of the powder bed to the logarithm of pressure [12], a large number of expressions with the ambition to describe in a linear form the relationship between a tablet descriptor and the applied compression pressure can be found in literature [4, 10, 13-21]. The use of the natural logarithm of the tablet porosity as a function of applied pressure has evolved as a common means to describe the compression of a powder in several different fields of powder technology. Shapiro [22] and Konopicky [23] published powder compression data using this approach, but in the pharmaceutical field this type of profile is most commonly referred to as the Heckel equation [14]. The process of compression is described as a first-order chemical reaction, the pores being the reactant and densification of the bulk of the product. The kinetics of the process may then be described by the proportionality between the changes in density with pressure, and linearization gives the following expression:

$$\ln\left(\frac{1}{E}\right) = kP + A \qquad \textit{Equation 1}$$

where E is the porosity of the powder bed and P the applied compression pressure. The parameter A is said to relate to low pressure densification by interparticle motion while the parameter k indicates the ability of the compact to densify by plastic deformation after interparticle bonding, often referred to as the yield pressure P_y. In this thesis, the relationship between ln$E$ and P is referred to as a *SKH* (Shapiro-Konopicky-Heckel) compression profile, which can be described by the Shapiro General Compaction Equation:

$$\ln E = \ln E_0 - kP - fP^{0,5} \qquad \textit{Equation 2}$$

where E_0 the initial porosity of the powder bed. The Shapiro compression parameter f is an indication of the degree of curvature of region I (see *Figure 2 a*) of the compression profile and the compression parameter k is in theory equal to the Heckel compression parameter.

A common approach of interpreting a *SKH* profile is that the profile can be divided into three regions [9]: Firstly, an initial non-linear part with a falling derivative (here denoted region I), followed by a linear part (region II) and finally, a second non-linear part with an increasing derivative (region III). The physical explanation for these three regions of the profile is normally provided in terms of rate controlling compression mechanisms that vary between the different regions. For region II, it is argued that particle deformation is the controlling mechanism, either reversible or permanent [13], and for region III it is proposed that elastic deformation of the whole tablet controls the compression process [9]. For region I finally, several explanations have been proposed for the deviation of linearity often observed for different types of particulate solids [4]. Excluding one of the explanations concerning the problem of constructing a *SKH* profile for porous particles [20, 24, 25], two main reasons are discussed in the literature. The first, proposed by Shapiro and Heckel, is that the curvature is due to particle rearrangement during compression. This explanation seems to be preferred in the literature for a spectrum of materials exhibiting ductile to brittle behaviour [9, 13]. The other explanation is that particles fragment during compression and that this fragmentation causes a gradual change in the derivative of the curve until fragmentation ceases to occur [8, 26, 27].

The Heckel model has been shown to be useful for ranking powder materials consisting of dense particles in terms of plasticity and hardness. The yield pressure (P_y) can be related to the yield strength (σ_0) for a range of powder by the empirical relationship:

$$\frac{1}{k} = P_y = 3\sigma_0 \qquad \textit{Equation 3}$$

The shape of the *SKH*-profiles has been shown to depend on various powder properties, such as the particle size [19] and particle density [28]. The effect of several experimental parameters *(i.e.* mode of die filling, lubrication, punch velocity and dimensions) on the compression profiles has also been reported [29, 30].

Elastic deformation of the powder particles has been shown to cause deviations in the Heckel profile, generating a yield pressure significantly lower than the true value of the material tested [9]. Development of the Heckel model into a three-dimensional model including the viscoelastic properties of the materials by using force, displacement and time to characterize the volume reduction behaviour has been done, and by determining three compression parameters; the time plasticity *d*, the pressure plasticity *e* and the angle of torsion ω it was possible to disguise whether to compression behaviour of the powders was pressure or time dependent [31, 32]. Further on, the pressure plasticity has been shown to correlate with the microhardenss of tablets and the angle of torsion with Young's modulus of elasticity [33].

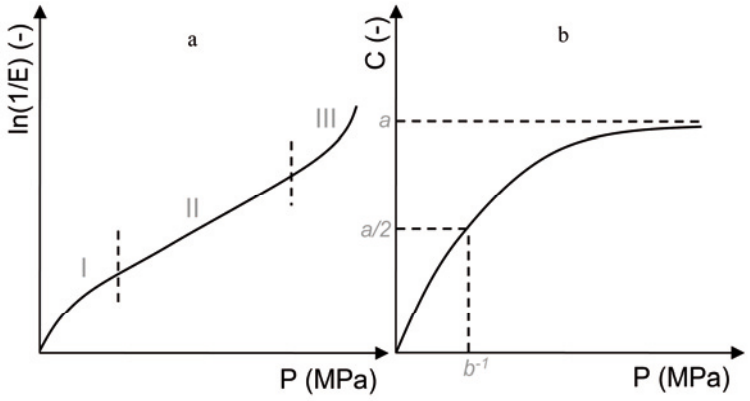

Figure 2. a) A schematic description of a Shapiro-Konopicky- Heckel compression profile with the three different regions. b) A schematic description of a typical compression-pressure curve and interpretation of the Kawakita parameters in mathematical terms.

Another basic representation of the compression process for a powder is the relationship between the degree of compression (engineering strain) of the powder bed and the applied compression pressure (*Figure 2 b*). The calculation of the engineering strain requires a value of the volume of the bed of powder held in the die before compression, *i.e.* the initial volume. The importance of the determination of the initial powder volume (V_0) in the die for the values of the derived compression parameters has previously been addressed in the literature [34]. The most common procedure used to determine the initial volume is to pour the powder into the die and make an estimate of the bed height by recording the bed height at a certain fixed applied pressure in the beginning of the compression phase, such as 1 MPa [17]. Alternative procedures are also reported, such as the transformation of bulk density of the powder, based on a separate determination, into a bed height [35] or the iteration of a pressure-volume relationship [36].

The Kawakita equation [19, 37] is a commonly used expression to linearize compression data, both from tapping and from continuous compression experiments. The basis for the Kawakita equation is the assumption that a powder held in a confined space and subjected to an applied force is a system in equilibrium at all stages of compression, so the product of the increased applied pressure and the volume reduction is constant:

$$C = \frac{V_0 - V}{V_0} = \frac{abP}{1 + bP} \rightarrow \frac{P}{C} = \frac{P}{a} + \frac{1}{ab} \qquad \textit{Equation 4}$$

where C is the engineering strain of the particle bed, V_0 and V the powder bed volume at zero pressure and the applied pressure, respectively.

The equation also includes two compression parameters, often referred to as a and b. The physical significance of these parameters during tapping compression as well as during continuous compression at high compression pressures has been discussed in the literature [38,39]. Mathematically, the parameter a represents the engineering strain (or degree of compression) at infinite pressure, while the inverted b-parameter represents the applied pressure needed to achieve an engineering strain of $a/2$ (see *Figure 2 b*). Thus, the Kawakita parameter a represents the total compressibility while the parameter b^{-1} may reflect the initial compressibility of the bed of particles.

The compression parameters mentioned above are invariably calculated from relationships between volume or relative density of a tablet and compression pressure. Ideally, a compression parameter should not only indicate a property of particles that is relevant for the evolution in tablet structure but also have implications for the tablet strength. A procedure to calculate a compression parameter from the relationship between tablet tensile strength and compression pressure as been suggested for this purpose [40]. It was concluded that this compression parameter represents an indication of the effective deformability of particles during compression and that the effective deformability of particles is critical for the increase in tablet tensile strength with compaction pressure in a pressure dependant region of a compactability profile.

Compression behaviour porous particles

The application of the Heckel model to the compression of granular solids has been questioned [20, 35, 41, 42] and it has been shown that the use of Heckel numbers based on total porosity data is inadequate to describe the compression mechanics of agglomerates, *i.e.* the derived yield strength values did not vary with agglomerate porosity [43].

The Kawakita model has been considered of special interest in the compression of granular solids and the significance of these parameters has also been discussed in terms of the physical properties of the porous particles [43], such as the fracture strength and the yield pressure [20, 44]. The parameter b^{-1} has been compared with a micromechanically derived compression parameter, called the Adams parameter.

Adams et al.[20, 45] proposed a theoretical model for confined uniaxial compression of agglomerates in order to estimate the fracture strength of single pellets from *in-die* compression data. In the model it is assumed that the elastic energy stored in the system is negligible and the energy input to the system is mostly consumed for failure. Based on the assumption of parallel columns for force transmission, the following equation for the relation between the applied pressure on the bed and natural strain was obtained:

$$\ln P = \ln \frac{\tau_0}{\alpha} + \alpha\varepsilon + \ln\left(1 - e^{(-\alpha\varepsilon)}\right) \qquad \textit{Equation 5}$$

where P is the applied pressure, α a friction coefficient, ε the natural strain of the powder bed and τ_0 the apparent single agglomerate fracture strength. At higher values of natural strain, the last term of the Adams equation becomes negligible, leaving a linear function.

Using the Adams or Kawakita equations, parameters have been derived which varied noticeably with porosity of the particles, and that also were related to the agglomerate composition. It has been suggested that both these parameters reflect the failure strength of the granulated particles where the failure was described as a crack opening mechanism. It was thus concluded that the characterization of agglomerates in terms of their compression shear strength, the Kawakita or Adams parameter, can be used as an indicator of tablet forming ability [43].

Compression behaviour of powder mixtures

A dosage form is usually a multi-component system consisting of the active substance and one or more excipients [46], but can also be a mixture of agglomerates with different properties [47, 48]. However, as a result of the complexity of the compression process, most fundamental work has been carried out on single component powders. Some work has however been done as an attempt to formulate general mixing laws for the compression behaviour of mixtures. Assuming that each component in the mixture behaves independently of the other(s), and using a mathematical approximation, it has been shown that the porosity E as well as the coefficients k and n in a porosity–pressure function of the form $E = k - n*\ln P$, could be determined by using a simple arithmetic additivity rule [49]. Although the assumption of independent behaviour of the components may be an oversimplification, it is of interest to know the expected behaviour in the ideal case when the components do not interact [50].

The Heckel equation has been used by a number of researchers to describe multi-component systems [51, 52]. However, no theoretically derived mixing laws for its parameters to have been reported.

Compactability of powders

When a powder is compressed the porosity of the power bed is reduced and the particles are brought closer to each other. A tablet can be seen as an aggregate of adhering particles, that still can be described as a disperse system, where the gas phase consists as a three-dimensional pore network. The

tensile strength of a tablet can in a simplified way be explained as the sum of all the bonding forces, *i.e.* the number of bonds and the respective bonding force, in the failure plane. The obtain mechanical strength is hence not a constant factor, *i.e.* the retrieved values will depend on the experimental conditions and method used [53, 54].

The compactibility of a powder is said to be governed by two main factors, the bonding mechanism and the total bonding area [55]. The bonding area is depended of several particle properties such as shape and size [56]. Large powder surface area [57] and an irregular shape [58] have been shown to promote the formation of a tablet for solid particles and increasing the tablet tensile strength. The compression mechanics of the particles will also affect the bonding area. Particle fragmentation and particle deformation are both bond forming mechanisms. Fragmentation will to a higher extent affect the number of bonds, while deformation will affect the bonding force. In the case of time-dependent deformation, the bonding force will depend on the contact time.

The tablet tensile strength has also been shown to increase with increasing fragmentation propensity of granulated particles, which can be affected by the granule composition as well as the granule shape and size [59, 60].

For ductile porous particles however, the compactibility has been shown to be independent on granule size [61]. This might be explained by the fact that a variation in granule size did not to a high extent influence the deformation behaviour, which has been shown to be critical for the evolution in tablet micro-structure during compression. Further on, the tensile strength of tablets has been shown to increase with increasing deformability of granulated particles [24, 35, 62]. If the granulated particles have a high capacity for permanent deformation, the total densification of the tablet structure will be high and intergranular pore structure in tablets is a controlling factor for the mechanical strength of the tablets.

The thesis in perspective of current research

The mechanical characteristics of a dosage form are interesting to determine in order to identify the properties critical for the tableting behaviour in terms of compressibility and compactibility. The testing of physical and mechanical properties of drugs and excipients hence represents an import activity during the formulation of solid pharmaceutical preparations [63].

The understanding of fundamental material properties of pharmaceutical powders critical for their tableting behaviour and parameters that reflects these properties can be described on different levels of scrutiny [64]. On the molecular level relationships between solid state properties, like crystal form, and different mechanical properties such as the Young's modulus, hardness, fracture strength and critical stress intensity factor have successfully been proposed [65, 66]. Different data models can then be used to describe the impact of the solid state properties on the manufacture properties. Such an understanding is valuable since it make it possible to modify the solid material in the early formulation work, in order to get certain mechanical properties during the production of the syntactical drug.

On a particle level the impact of particle shape, size, porosity and mechanics, on the response to an applied compression force and as a consequence the micro-structure of the tablet have been investigated [67, 68]. The tablet micro-structure and tablet strength during compression of powders can be affected by modifying these macro-structural properties of the particles. It has been proposed that variations in such properties will affect the degree of deformation that the particles undergo under compression and hence the structure of the formed tablets [69].

As discussed in the previous section, during tableting several mechanisms are involved in the compression process; initial packing, rearrangement, densification, plastic and elastic deformation, fragmentation and attrition. Because of the complex response of both dense and porous particles to an applied stress during confined compression it is probably difficult to mimic the compression behaviour by a single granule or a compact analysis process. The analysis of powder compression data therefore constitutes an interesting method for characterising the mechanics of powders [21, 43]. Compared to the testing of mechanical properties of compacts formed from a powder, which has been a common approach in the literature [65, 66], the analysis of the compression process [70] has two main advantages: the amount of powder required for the test is low and poorly compactable powders can be analyzed.

Although the fact that compression of a powder in a confined space is a well defined operation, the complexity of the response of the powder to the applied compression force has resulted in difficulties in relating the derived compression parameters to physically defined processes [28, 43].

Traditional powder compression models consider the whole tablet or powder bed and are based on the use of global descriptors, such as absolute or relative volume of the tablet held in the die (*Figure 3*), and how such a descriptor depend on the applied pressure during the compression [14, 37]. The use of process modelling and computational mechanics methods has increased in the recent years and is a part of all aspects of the discovery and development process in the pharmaceutical industry [71]. The tableting process is described by a number of equations that can be solved using a number of different techniques.

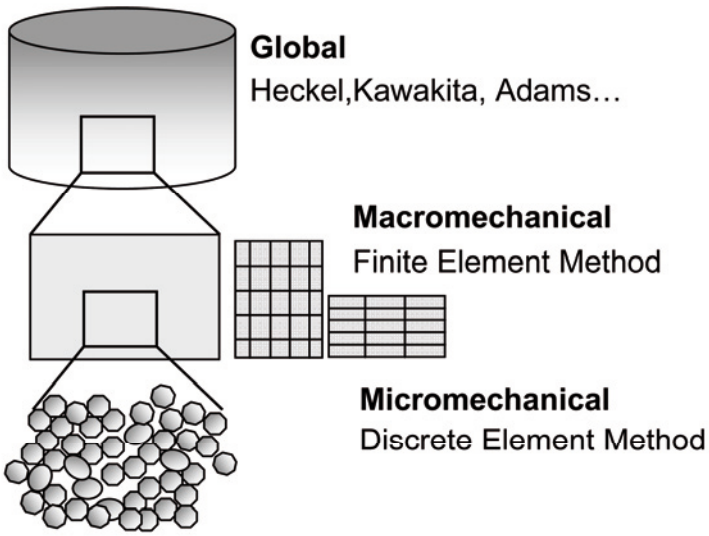

Figure 3. Both the resolution and the computational cost increase from global via macromechanical to micromechnical techniques.

The modelling techniques can broadly be classified as either macro-or micromechanical techniques, but combinations of the two are also possible [72]. Macromechnical techniques, *i.e.* large scale models, consider part of the tablet or powder bed as hypothetical continuous medium [18] and elastoplastic material models (like the Drucker-Prager Cap model) are employed and the finite element method (FEM) are used to solve the governing equations. In these types of models it is assumed that the system under investigation is large enough to be described by the average or the macroscopic effect of many particles. One of the advantages with FEM is that robust commercial software are available and may predict density and stress distributions in

tablets and indicate under which circumstances tableting fails due to capping [73]. These types of models do however need reliable in data in terms of Young's modulus, Poisson ratio etc.

Micromechnical techniques, *i.e.* small scale models, consider individual particles and apply Newton's laws to determine the movement of each single particle from the forces it experiences [74]. The interactions between different particles are usually treated with contact mechanics and this procedure is often referred to as the discrete element method (DEM). This type of techniques may provide very detail information, but they also require a lot of compute power and are sometimes difficult to validate which limits the practical applications.

Some models based on global descriptors are still considered be useful to increase the understanding of the underlying compression mechanics due to the simplicity in their application. If the physical significance of the compression parameters and how they relate to powder functionality can be established, this type of compression analysis can be in a part of "tool box" for the formulator scientist, and hopefully generating a more effective and science based development process of tablets and other solid dosage forms.

Aims of the thesis

The intention of this thesis was to contribute to the development of procedures suitable in preformulation and formulation work and during process control to characterize the manufacturability of pharmaceutical powders. The emphasis of the work was to clarify the formulation relevance of some global compression parameters and finally, to stipulate recommendations regarding the technical characterization and classifications of powders. More precise, this was done by achieving the following partial goals:

- To suggest methods for compression analysis of both dense and porous particles and enhance the mechanistic understanding of the different regions in a typical compression data profile, in order to evaluate the physical significance of some compression equations and to investigate the use of the derived parameters as descriptors of powder functionality (Paper I, II, III and IV).

- To contribute to a systematic technical classification system for powders based on their compression mechanics determined by compression analysis (Paper III and IV).

- To analyze the relevance of the mechanics of some granulated particles for their tableting forming behaviour and investigate the potential use of the degree of powder bed compression as a process indicator of tablet tensile strength (Paper V and VI).

Materials

In all the work included in the thesis common pharmaceutical excipients were used as model materials:

- Microcrystalline cellulose (Avicel PH101, FMC, Wellingstown, Ireland, later referred to as MCC, apparent density of 1.571 g/cm^3). The cellulose molecular unit consists of two glucose molecules [75]. MCC is widely used as a binder and filler in tablet production since it is appropriate for direct compression [76, 77].
- α-lactose monohydrate ($C_{12}H_{22}O_{11}$, crystalline α-monohydrate Pharmatose 200M, DMV, Veghel, The Netherlands, later referred to as LAC, apparent particle density of 1.542 g/ cm^3). LAC is a disaccharide consisting of galactose and glucose molecules. LAC is used as a filler or diluent in tablets and capsules [77, 78].
- Polyethylene glycol 6000 (Sigma-Aldrich, Steinheim, Germany, later referred to as PEG, apparent density of 1.221 g/ cm^3). PEG is a water soluble polymer composed of repeating monomers with the following chemical structure: HO-(CH_2-CH_2-O)$_n$-H. PEG is widely use in several types of pharmaceutical formulations as solvent, binder, lubricant and plasticizer [11].
- Sodium chloride (NaCl, crystalline, Fluka, Steinheim, Germany, apparent density of 2.152 g/ cm^3). NaCl is for instance used in capsules and direct compression tablet formulations as a lubricant and diluent.
- Sodium bicarbonate ($NaHCO_3$, crystalline, Fluka, Steinheim, Germany, apparent density of 2.216 g/ cm^3). $NaHCO_3$ is used in pharmaceutical formulations as a source of carbon dioxide in effervescent tablets and granules.
- Sucrose ($C_{12}H_{22}O_{11}$, crystalline, Fluka, Steinheim, Germany, apparent density of 1.586 g/ cm^3). Sucrose is a disaccharide consisting of one glucose and one fructose molecule and has several of functions when used as an excipient, such as granulating agent, sweetening agent and tablet and capsule diluents [78].
- Ethanol (95% w/w, Solveco Chemicals AB, Täby, Sweden, later referred to as E) and deionised water (later referred to as W) were used as granulation liquid.

Experimental section

In this section the experimental works of the different studies included in the thesis are briefly described.

Preparation of powders

Preparation of solid particles

In Paper III and IV four size fractions of the different powders materials used were prepared according to the following procedures: The coarser size fractions (250-300 µm and 125-180 µm) were obtained by dry sieving with a set of sieves with squared openings (Retsch, type RV, Haan, Germany). The size fraction of a particle size of ~ 70 µm was obtained by milling the raw material in an electrical mortar grinder (Retsch, Grindomat KM1, Haan, Germany) followed by particle separation in an air classifier (Alpine 100MZR, Alpine AG, Augsburg, Germany). Finally, the finest size fraction (< 50 µm) was prepared by milling the raw material in a pin disk mill minutes (Alpine 63C Contraplex Labormühle, Alpine AG, Augsburg, Germany).

All test materials were stored in desiccators (over a saturated K_2CO_3 solution) at ~ 40% relative humidity and room temperature (~ 20 °C) for at least 7 days prior to further characterization.

Preparation of porous particles

In Paper I, II, V and VI, 400 g of powder (single powder or binary mixture) was agitated in a high shear mixer (QMM-II, Donsmark Process Technology, Denmark) at 500 rpm for 1-3 min before the granulation liquid was added into the powder at a flow rate of 100 ml/min. Wet mixing was then continued for 3 min at 500 rpm. Different proportions of water and ethanol were used in the granulation liquid in order to produce granules of low and high porosities according to previous experiences [35, 79].

In some cases the wet granulated mass was then immediately extruded (model E140, NICA System, Sweden) trough holes 1.0 mm in diameter, and when producing pellets, spheronised (model S320-450, NICA System, Swe-

den) for 3 min on a 32 cm diameter friction plate with a radially designed grid at a rotation speed of 850 rpm.

All granulated powders were spread out in thin layer on plates and dried at ambient conditions for at least 3 days before different size fractions were prepared by dry sieving with a set of standard sieves with square openings (Retsch KG, 5657, Haan, Germany).

The porous particles were finally conditioned by storage in desiccators over a saturated K_2CO_3 solution (~ 40% RH) at room temperature (~ 20 °C) for at least 3 days before further investigations.

Characterization of the solid and porous particles

Powder surface area

For the two coarsest size fractions of solid particles (denoted 1 and 2 in Paper III and IV) and for the granulated porous particles (Paper I, II and V) the volume specific surface area (S_0) was assessed by steady-state air permeametry (n = 3). The powders were manually poured into a glass cylinder of 11.47 mm diameter. The weight and height of the powder bed were then measured and the container was connected to a pump. Air was pumped through the sample bed at a series of controlled flow rates (Brook flow meter, Brook Instruments B.V., The Netherlands) and the corresponding pressure was drop recorded by a digital differential manometer (P200 S, Digitron Instrumentation Ltd, UK). The permeametry surface area was calculated with the Kozeny-Carman equation as described in a previous work [80].

The surface area of finer powders of solid particles (denoted 3 and 4 in Paper III and IV) was measured with a Blaine air permeability apparatus (n = 2) and S_0 was calculated using a slip flow corrected Kozeny-Carman equation [81].

Appearance, size and shape

Visual inspection of the solid particle sizes (Paper III and IV) was done by optical light microscopy (model Vanox, Olympus, Tokyo, Japan). The S_0 was transformed into an estimate of the original particle size (d_{S0}) as the ratio between a surface to volume shape factor and S_0. Generally, a constant surface to volume shape factor of 10 was used in the calculation based on previous work [82,67].

For the porous particles (Paper I, II and V) a minimum of thirty granules of each granule type were randomly selected, and the size and shape of the granules were assessed by using a light microscope (Olympus Vanox, Japan) equipped with a CCD camera (Olympus DP50). Digital images with a pixel resolution of 1.8 μm/pixel were acquired at 5× magnification. The images

were analyzed by using the non-commercial software ImageJ. For each granule, the projected area (A), the perimeter length (p), the projected area diameter (d) and the circularity (c) were determined. A steel sphere with a diameter of 1000 μm (SKF, Sweden) with an assumed circularity of 1.00 was used as reference [80]. The circularity (a measure of the closeness of the projected area of the granule to the area of a circle with the same perimeter) is in this case calculated as $c = 4\pi A/p^2$ [83].

Scanning Electron Microscopy (SEM) images of single granules were prepared using a high resolution SEM (LEO 1550 FEG) or an ordinary SEM (LEO 440 or LEO 1530) (Paper I, V and VI).

Powder densities

The apparent particle densities (ρ_{app}) of the starting materials were determined using helium pycnometry (AccuPyc 1330, Micromeritics, USA) (n = 3). The apparent particle density of binary mixtures of powders was estimated from the apparent particle densities of the two components according to a model described in previous work [84].

The bulk densities (ρ_{bulk}) of the different powders were determined from the weight and height of the powders and of the dimensions of the glass cylinder described above. The tap density (ρ_{tapped}) was obtained by tapping the cylinder up to a 1000 taps by the use of a typical tap density testing apparatus (PharmaTest, PT-TD, Hainburg, Germany) (n=3). The height or volume of the powder bed was determined visually throughout the experiment. From the tapping data, the Hausner ratio (*HR)* [85] was calculated as $HR = \rho_{tapp}/\rho_{bulk}$.

The effective particle density of the porous particles was detemined by using mercury pycnometry (Autopore III 9420, Micromeritics, USA) according to a procedure described elsewhere [25]. Before performing the mercury intrusion measurements, the granules were stored in ~ 0 % RH for at least 3 days to facilitate the degassing step in the intrusion equipment. The intragranular porosity of the each granule type (Paper I and V) was calculated as one minus the ratio between the effective and the apparent particle densities ($n \geq 2$). In Paper II the packing fraction in the experiments was assumed to approach 0.628, and the porosity of the spherical granules (pellets) was estimated as $1 - \rho_{bulk}/(\text{packingfraction} * \rho_{app})$.

Mechanical properties

Granules ($n \geq 30$ of each type) were compressed individually at a loading rate of 0.05 mm/s using a Texture analyser, TA.HDi (Stable Micro Systems, Haslemer, UK), equipped with a 5-Kg load cell. The Texture analyser was calibrated prior to use. The peak force (F_{max}) was determined as the first significant drop in the force-displacement profile obtained when the granules

cracked and was later transformed into the nominal fracture strength σ_0 of the granules according to Adams et al.[45] (Paper I, II and V).

To calculate the yield pressure (σ_y) and the modulus of elasticity (E_{mod}) of the granules, the force-displacement data obtained below F_{max} were fitted to the model of elastic-perfectly plastic contact deformation and the Hertzian elastic relationship described by Thornton and Ning [86, 87].
The slopes were calculated by linear regression. The yield pressure was calculated in range of displacement of 20 to 96 μm corresponding to a strain of ~ 2 to 10 % and the modulus of elasticity in a range of displacement of 0 to 16 μm corresponding to a strain of ~ 0 to 1.6 %.

Characterization of compressibility

Confined continuous uniaxial compression studies were performed using a materials testing machine (Zwick Z100, Zwick/Roell Zwick GmbH & Co. KG, Ulm, Germany) equipped with a 100 kN load cell and circular flat faced punches (diameter 11.3 mm). Magnesium stearate ($C_{36}H_{70}MgO_4$, 1 % w/w suspension in ethanol, Ph. Eur., Kebo, Sweden) was used as a lubricant in all compression experiments to reduce the friction [88, 89]. The die was manually filled with a preweight amount of powder (single component or binary mixture), which then were compressed at a linear loading rate of 1 mm/min up to the maximal pressure by using a stationary lower punch and a movable upper punch. An external displacement gauge was used to record the upper punch position. To assess the elastic deformation of the punches and the punch holder, deformation curves were recorded by pressing the punches against each other. Except for an initial non-linear part at low pressures, the pressure (P) - displacement (Δ) curves of the system deformation were approximately linear. The equation $\Delta = l_a + k_aP + l_be^{(kbP)}$, where the exponential term accounts for the initial curvature, was fitted to the deformation data and values for k_a, k_b, l_a and l_b were obtained. The punch displacement data obtained from powder compression was corrected for the system deformation error, calculated with the above equation, to assess the granule bed height. The system deformation was in the order of magnitude of 0.5 μm/MPa.

The degree of compression of the bed of particles (C), corresponding to the engineering strain, was calculated as $C = (V_0 - V)/ V_0$, $(0 < C < 1)$, where V_0 is the initial bed volume in-die and V the bed volume at the applied pressure P. In Paper I the initial volume of the bed of granules was determined from the position of the upper punch at four different applied forces up to 100 N. The lowest applied force corresponded to the transition point at the force-displacement relationship at which contact between punch and powder was considered to have been established followed by three fixed applied

forces, *i.e.* 25, 50 and 100 N. The experiment was at least repeated three times for each material and aspect ratio.

In Paper III, C was calculated by using two different approaches to determine V_0: Firstly by recording the height of the powder column in the die by the displacement transducer at lowest possible consistent applied compression force, *i.e.* ~34 N for all powders, and, secondly, by transforming the bulk density (determined as described above) into the corresponding height of the powder in the die.

The initial compressibility (e) was calculated as the inverse of the slope of the initial linear part of the pressure-strain curve ($2 < P < 20$ MPa, $R^2 > 0.999$) (Paper I), and the maximal engineering strain (C_{max}) was calculated as the engineering strain at a compression pressure of 300 MPa (Paper II and VI) and 500 MPa (Paper I and IV).

Calculations of the compression parameters

Single component powders

The Kawakita parameters a and b^{-1} for the single component powders was generally obtained by linear regression in a constant compression pressure range from 1 MPa to 500 MPa ($R^2 > 0.9972$) in Paper III, and between 10 – 250 MPa in Paper I, II and VI.

In order to evaluate the potential influence of initial volume for the derived Kawakita parameters, the initial volume was determined from the position of the upper punch at four different applied forces up to 100 N, corresponding to 1 MPa (Paper I). Further on, the potential influence of the aspect ratio on the derived Kawakita parameters, was investigated by using three different weights of powder, giving three initial aspect ratios (1.4, 0.7 and 0.4 in Paper I).

The Adams parameter τ_0 was determined by linear regression in the estimate linear interval (0.2 < natural strain < 0.5, $R^2 > 0.997$ for all materials, Paper I).

In Paper IV the slope (k) of the *SKH*-profiles was calculated by linear regression in the pressure range from 50 MPa up to 150 MPa, R^2-values > 0.994 for all materials. Curve-fitting of the theoretical and the experimental values of the *SKH*-profiles was done by a least square method (*i.e.* minimizing the sum of squared deviations $\Sigma(\text{Exp.value} - \text{Theor. value})^2$), and the compression parameter f in the Shapiro GCE [90] was calculated in three different pressure ranges; $\ln E_{0\text{BD}}$ to 50 MPa ($R^2 > 0.996$ for the coarser powders and $R^2 > 0.928$ for the finest powder), 0.3 to 50 MPa ($R^2 > 0.995$ for the coarser powders and $R^2 > 0.974$ for the finest powder), and finally, 1 to 50 MPa ($R^2 > 0.999$ for all powders), where E_{0BD} is the initial powder bed porosity transformed from the bulk density of the powder.

Binary mixtures of powders

The Kawakita parameters for the binary mixtures of ductile granules (Paper II) were generally calculated from the experimental compression data in the pressure range of 10 – 250 MPa. However, for some mixture compositions the lower pressure limits was somewhat higher in order to get the same fit in the linear regression for all materials, $R^2 > 0.999$.

In addition the effective Kawakita parameters for the mixtures were calculated from the Kawakita parameters derived for the single components. The details of the model used is described in Paper II, but is briefly explained below.

For sufficiently high compression pressures, the degree of compression is a linear function of $1/P$, as may be seen by Taylor expanding *Equation 4* around $1/P = 0$, giving:

$$C = \frac{V^{(0)} - V}{V^{(0)}} \approx a\left(1 - \frac{1}{bP}\right) \qquad \textit{Equation 6}$$

From the assumption of independent behaviours of the components, it follows that each component obeys equations analogous to *Equations 4* and *6*. Provided that $b_iP >> 1$, the change in volume of component i can be expressed as:

$$\Delta V_i \approx a_i\left(1 - \frac{1}{b_iP}\right)V_i^{(0)} = a_i\left(1 - \frac{1}{b_iP}\right)v_iV_{mix}^{(0)} \qquad \textit{Equation 7}$$

where V_{mix} is the volume of the mixture calculated as the sum of the volume of all components and $v_i = V^{(0)}{}_i / V^{(0)}{}_{mix}$ is the initial volume fraction of component i. Adding all volume changes ΔV and dividing by the initial volume of the mixture, the following expression is obtained:

$$C_{mix} = \frac{\Delta V_{mix}}{V_{mix}^0} = \frac{\Sigma_i \Delta V_i}{V_{mix}^0} \approx \Sigma_i v_i a_i - \Sigma_i \frac{v_i a_i}{b_i}\frac{1}{P} \qquad \textit{Equation 8}$$

Finally, by comparing *Equations 8* and *6* the effective Kawakita parameters for the mixtures can be calculated as:

$$a_{mix} = \Sigma_i v_i a_i \text{ and } \frac{1}{b_{mix}} = \frac{1}{a_{mix}}\Sigma_i \frac{v_i a_i}{b_i} \qquad \textit{Equations 9 \& 10}$$

Characterization of tableting behaviour

Tablet surface area

In Paper IV an instrumented single-punch press (Korsch EK0, Berlin, Germany), equipped with 11.3 mm diameter flat-faced punches, was oper-

ated manually by hand to produce five tablets from each material and size fraction of the solid particles (with the exception of the coarsest sucrose powder) at an applied pressure of 50 MPa according to a compaction and measurement procedure described elsewhere [81]. An amount of ~500 mg powder was weighed on an analytical balance and poured by hand into a special die, built to fit a Blaine air permeameter. The weight (analytical balance) and the height of the tablets (Mitutoyo Digimatic, ID-C, Tokyo, Japan) were measured and the die was thereafter immediately connected to the permeameter and the time for a predetermined volume of air to pass through the tablet was determined. The volume specific surface area of the tablet (S_T) was finally calculated with a slip flow corrected Kozeny-Carman equation [81].

To assess the degree of fragmentation of particles expressed during compression the relationship between the permeametry surface area of tablets and the compaction pressure was studied [81, 91] and as an estimate of the change in particle diameter (Δd) that occurred during compression up to an applied pressure of 50 MPa, the difference in the reciprocals of the volume specific surface area of the original powder (S_0) and of the tablet (S_T) was calculated as $\Delta d = 10*(1/S_0 - 1/S_T)$.

In Paper V spherical granules of a quantity corresponding to an aspect ratio of 0.7 (450-600 mg, depending on granule type) were compacted in the same manner as described above [81, 92], at applied pressures of 25, 50, 100 and 150 MPa (n = 3 for each pressure) and the permeability to air of the prepared tablets was determined with a steady-state permeameter (n = 3 for each tablet). The die was connected to a pump and air was pumped through the tablet at a series of controlled flow rates (Brook flow meter, Brook Instruments B.V., The Netherlands) and the corresponding pressure drop was recorded by a digital differential manometer (P200 S, Digitron Instrumentation Ltd, UK). The permeability coefficient P_c was calculated from the linear relationship between flow rate and pressure drop as described in a previous work [80].

Tablet tensile strength

In Paper V and VI the porous particles were compacted at twelve different applied pressures between 25 and 300 MPa (n = 3 for each compaction pressure) in a materials testing machine (Zwick Z100, Zwick/Roell Zwick GmbH & Co. KG, Germany) according to the procedure described above. The prepared tablets were immediately ejected from the die with the aid of a device specially designed to fit the materials testing machine and, after the height (t) and the diameter (d) of the tablet been measured, compressed diametrically in a tablet-testing machine (Holland C50, UK) at a loading rate of 1 mm/min. The tablet tensile strength σ_t was thereafter derived from the force (F_t) needed to fracture the tablets according to Fell and Newton [54], $\sigma_t = 2F_t/\pi t d_t$.

Compactibilty

To describe the tablet forming ability of a material the relationship between the attained tablet tensile strength (σ_t) and the applied compaction pressure (P_{app}) was investigated to derive some descriptors of the compactibility in Paper V and VI according to a model previously described [40]. The slope of the profile was calculated in a pressure range up to 150 MPa, the critical formation pressure P_0 was calculated as the magnitude of the ratio between the intercept and the slope and as a measure of the maximum attained tensile strength, the tensile strength of tablets formed at an applied pressure of 300 MPa was used.

Appearance

Scanning Electron Microscopy (SEM) images of tablet surfaces were prepared using a high resolution SEM (LEO 1550 FEG) or an ordinary SEM (LEO 440). The tablets were produced at three different compaction pressures (50, 150 and 500 MPa) and for the lower two the tablets were immediately split after compaction to create a cross-section of the tablet surfaces (Paper V).

Results & Discussion

In the following sections, the main results of the publications that this thesis is based upon will discussed.

Some important characteristics of the model materials

Characteristics of the solid particles (Paper III and IV)

The four different model materials were chosen based on the respective compression mechanics, according to earlier experiences [56, 65, 93]. Sucrose and lactose are classified as moderately hard materials that show marked fragmentation and limited deformation during compression [93, 94], whereas sodium chloride can be described as a moderately soft plastic material [94] that shows limited fragmentation but high degree of deformation during compression. Finally, sodium bicarbonate is also considered to be a moderately hard material that shows limited deformation during compression but also limited particle fragmentation during compression [56]. The preparation of different particle size fractions of each material was done to further affect the compression behaviour of the powders.

The volume specific surface area (S_0) values supported that for each model material, four powders of different fineness (here denoted as 1, 2, 3 and 4) were successfully obtained with a similar range in powder fineness.

Since the apparent particle density varied between the materials, the coordination number, *i.e.* the number of particles in contact with any given particle, calculated from the porosity of the powder bed can be a better representation of the packing of the particles than the bulk density (ρ_{bulk}) . For irregular particles with a spread in particle size, a simplified means to derive an indication of the coordination number is to use expressions derived for mono-sized spheres [95-97]. The coordination numbers obtained varied between 7 and 10 and tended to increase with increased particle size (Table 1).

The Hausner ratio (*HR*) increased as the original particle size decreased, *i.e.* smaller particles were more prone to compress during tapping. Using a common system for classification of powder flowability [98, 99], the flow properties of the model powders ranged from "good" ($1.12 < HR < 1.18$) to "very, very poor" ($HR > 1.60$). The coordination numbers calculated for the powders after tapping showed generally a smaller spread compared to the

untapped powders, *i.e.* the tapping tended to compress the powder until a packing density was reached that was independent of particle size.

Sodium chloride showed in relative terms a small change in surface area and particle size (Δd) with applied pressure, supporting that particles of sodium chloride showed limited fragmentation during compression in region I of the *SKH*-profile. The data indicate further that lactose was most prone to fragment during compression while sucrose and sodium bicarbonate showed an intermediate behaviour with a tendency for sucrose to be more prone to fragment. The surface areas of the powder (S_0) and of the tablets (S_T) indicate that the materials could be rank-ordered with respect to their fragmentation tendency in the following way: Sodium chloride < sodium bicarbonate < sucrose < lactose. Regarding the effect of original volume specific surface area of the powders, the general trend was that an increased original powder surface area corresponded to a larger increase in surface area during compression which is consistent with earlier observations [56]. An exception was however sodium bicarbonate for which the coarsest fraction showed a relatively large increase in surface area during compression. Regarding the change in estimated particle size that occurred during compression, there was a trend that a decreased original particle size corresponded to a smaller change in particle size during compression, ranging from an estimated change in particle size from ~ 250 μm to ~ 6 μm.

Table 1. Some characteristics of the solid particles

Material		S_0 [a] (cm^{-1})	ρ_{bulk} [b] (g/cm^3)	HR [c] (-)	$c.n._{poured}$ [d] (-)	S_T [e] (cm^{-1})	Δd [f] (μm)
Sodium chloride	1	313 (0.01)	1.02 (0.03)	1.26 (0.04)	9.1	349 (0.20)	33
	2	623 (0.06)	0.80 (0.04)	1.43 (0.03)	8.3	826 (0.04)	49
	3	2559 (0.03)	0.70 (0.05)	1.62 (0.04)	7.9	2986 (0.07)	6
	4	3115 (0.04)	0.48 (0.01)	1.89 (0.01)	7.1	4066 (0.05)	8
Sucrose	1	406 (0.06)	0.95 (0.02)	-	10.1	2940 (-)*	213*
	2	676 (0.03)	0.64 (0.01)	1.22 (0.01)	8.5	2550 (0.05)	109
	3	1393 (0.05)	0.63 (0.06)	1.32 (0.04)	8.5	2667 (0.02)	34
	4	2945 (0.03)	0.43 (0.01)	1.65 (0.03)	7.4	6417 (0.05)	18
Sodium bicarbonate	1	454 (0.03)	0.93 (0.01)	1.12 (0.01)	8.6	4567 (0.05)	198
	2	756 (0.01)	0.88 (0.01)	1.29 (0.02)	8.5	2165 (0.05)	86
	3	1968 (0.01)	0.71 (0.01)	1.45 (0.01)	7.8	3316 (0.24)	21
	4	3619 (0.06)	0.61(0.06)	1.69 (0.06)	7.5	5666 (0.08)	10
Lactose	1	330 (0.21)	0.70 (0.01)	1.13 (0.01)	8.9	2037 (0.01)	254
	2	655 (0.04)	0.72 (0.01)	1.17 (0.01)	9.0	2875 (0.02)	118
	3	1033 (0.05)	0.66 (0.02)	1.27 (0.02)	8.7	3306 (0.03)	67
	4	3040 (0.01)	0.38 (0.05)	1.93 (0.05)	7.3	14046 (0.07)	26

a) Volume specific surface area of the powders, b) Bulk density, c) Hausner ratio calculated at N =1000, d) Coordination number, calculated from the poured bulk density, e) Volume specific tablet surface area at 50 MPa, f) Estimated change in particle size, *) single value

In conclusion, the powders showed a significant variation in powder surface area and thus particle size and initial packing density which is consistent with the aim of the preparation procedure of the model powders. Further on, the powders showed various compression behaviour in terms of the degree of particle rearrangement, particle deformation and particle fragmentation propensity.

Characteristics of the porous particles (Paper I, II, V and VI)

The intention of the preparation procedure used in Paper I, II and V was to form fairly coarse, nearly spherical and relatively smooth porous particles of a small spread in size (also referred to as pellets), in order to avoid significant initial compression due to granule rearrangement. All granules were nearly spherical (circularity ~ 0.96) and relatively smooth but the circularity was significantly lower for the MCC LAC granules (~ 0.91), indicating a slightly more irregular shape and rougher surface structure. No significant differences between the granules in terms of apparent particle density, the granule diameter, and the external surface area were found (Table 2 and *Figure 1* in Paper I).

Three spherical granules (pellets) of low and similar porosity (about 11-14 %) and one of a higher porosity (about 32-39%) were prepared. Since the granulated particles all had nearly the same apparent particles densities, the differences in bulk density are due to differences in porosity, shape or size. Granulated particles of low porosity are expected to have a higher bulk density than a more porous particle of similar size and composition. As expected from the granule porosity, the bulk density of the granules was similar for the MCC LP and MCC PEG granules, and higher than the value obtained for the MCC HP granules. An intermediate bulk density value was obtained for the MCC LAC granules, indicating that this system packs less densely. A packing fraction (calculated as ρ_{bulk}/ρ_{eff}) of 0.56 was obtained for the MCC LAC granules compared to about 0.60 for the other granules. The unexpected low bulk density for MCC LAC granules is thus explained by a less dense packing due to a lower circularity and a rougher surface of these granules compared to the other types. Since all pellets were of similar size and shape, the bulk density values provided a good indication of the pellet porosity (Paper II).The more irregular shaped granules had a lower bulk density than the spherical pellets of similar size and composition and finally, the bulk density decreased with decreasing granule size (Table 1 in Paper VI).

The composition and porosity of the porous particles was hence controlled in such a way that in terms of the mechanics of the single granules, in terms of their stiffness, plasticity, brittleness and fracture strength, a range of properties was expected [11, 24]. All the profiles over the relationship between the applied nominal pressure and the engineering strain of single granules exhibit the same qualitative features, indicating elasto-plastic deformation

behaviour of the granules, *i.e.* an initial elastic region, during which the applied pressure increases non-linearly with strain, followed by a plastic region with a nearly linearly relationship between these two variables (Fig. 2 in Paper I). Finally, a certain pressure was reached where the pressure dropped significantly and a first peak of the profile was obtained. This peak did not in general correspond to a catastrophic fracture of the granules into two or more fragments but rather to the formation of a crack in the granules.

The highest yield pressure (σ_y) (corresponding to granules with low deformation propensity. *i.e.* pellets that resist larger stresses before yielding) was obtained for MCC LP followed by MCC LAC, MCC PEG and finally MCC HP. Thus, the yield pressure values derived from single granule testing supports the assumed deformability of the granules and their categorization from hard to soft (Table 2). The MCC LAC and MCC LP granules showed similar Young's modulus (E_{mod}) and the MCC PEG and MCC HP granules also showed similar but considerably lower Young's modulus than the other two types. Regarding the stiffness of the granules, they could be categorized in two groups of, in relative terms, low and high stiffness.

For MCC LP, MCC PEG and MCC HP granules, the fracture strength (σ_{0S}) rank ordered the granules in the same way as the yield pressure. The ANOVA test supports that there are significant differences between the various granule types regarding both the fracture strength and yield pressure (data not shown). The lowest fracture strength was obtained for MCC LAC granules although the yield pressure and the Young's modulus were high for this type of granule, probably due to a more brittle character due to presence of lactose in the composition. The ratio between the stiffness and the fracture strength of the granules were considerably higher for the MCC LAC granules than for the other three granules. This may further indicate that the MCC LAC granules showed a deviating and more brittle mechanical behaviour than the other granules which, in relative terms, showed similar mechanical, less brittle mechanical behaviour.

Table 2. Some characteristics of some of the porous particles.

Material	S_0 [a] (cm^{-1})	ρ_{bulk} [b] (g/cm^3)	*Porosity* [c] (%)	d [d] (μm)	σ_0 [e] (MPa)	σ_y [f] (MPa)	E_{mod} [g] (GPa)
MCC	68.60	0.849	11.2	905	24.74	135	1.82
LP	(0.02)	(0.02)	(0.30)	(0.03)	(0.11)	(0.084)	(0.18)
MCC	68.76	0.823	10.9	912	14.47	101	1.22
PEG	(0.03)	(0.01)	(0.09)	(0.03)	(0.23)	(0.24)	(0.19)
MCC	66.07	0.648	32.1	890	12.07	87	1.14
HP	(0.03)	(0.01)	(0.16)	(0.03)	(0.21)	(0.15)	(0.24)
MCC	69.10	0.759	11.6	865	9.97	117	1.93
LAC	(0.12)	(0.02)	(0.42)	(0.03)	(0.26)	(0.18)	(0.21)

a) Volume specific surface area of the powders, b) Bulk density, c) Porosity d) Size, e) Nominal granule tensile strength, f) Yield pressure, g) Modulus of elasticity

General description of the compression behaviour

Stress-strain relationships and Kawakita parameters for the solid particles

Since a high initial compression at low compression pressures was generally obtained for the all powders in Paper III and IV (*Figure 4*), the *C*-values of the powder bed were calculated not only from the recorded volume in the die at a certain applied force but also by using an initial volume transformed from the bulk density of the powder bed. As a result, two sets of Kawakita parameters were derived by using two different indications of the initial volume of the powder bed, *i.e.* V_0 recorded at an applied force of ~ 34 N and V_0 transformed from bulk density (Table 2 in Paper III).

For powder fractions 1 to 3, the indication of the initial volume had a limited effect on the C_{max} obtained and thus on the derived Kawakita parameter *a*. However, for the finest powders the indication of the initial volume had a marked effect on both the C_{max} and on the Kawakita parameter *a*. When V_0 transformed from ρ_{bulk} was used a considerably higher infinite engineering strain was obtained than when recorded V_0 was used. This indicates that for the finest powders (fraction 4), significant compression was obtained already at very low compression forces. The use of V_0 transformed from bulk density is therefore considered to be the preferred procedure for solid particles in order to get a good representation of the compression profiles and the total degree of compression that could be achieved.

The most obvious effect of original particle size on the compression profiles was that the finest powders (fraction 4) generally showed the highest final engineering strain (highest C_{BDmax}-values) and the highest initial compression. Thus, the highest values of Kawakita parameter *a* and the lowest values of Kawakita parameter b^{-1} were obtained for the finest powders. For the other powders (fraction 1 to 3) the effect of initial particle size on the overall compression profiles was smaller and not generally consistent. Regarding the Kawakita parameter *a*, for fractions 1 to 3 the trend was that a decreased original particle size decreased the value of the parameter, *i.e.* reduced the infinite ability of the powder to compress. A somewhat larger spread in values was obtained for fraction 1 to 3 for the Kawakita parameter b^{-1} compared to the parameter *a* and the trend was that a decreased original particle size increased the parameter, *i.e.* the powders became more resistant to compression in the lower pressure range. A deviation from this general pattern was however the sodium chloride powders that showed a more complex dependency of original particle size.

That a reduced particle size tended to reduce the ability of the powders to compress may reflect that the particles became less deformable with a decrease in particle size and, thus that particle deformation is a mechanism of importance for the Kawakita parameters. The trend regarding the effect of

original particle size was broken for the finest powders (fraction 4) for which generally compression was facilitated and the final degree of compression increased. Hence, it seems that at a critical particle size, the compression behaviour of the powders changed markedly.

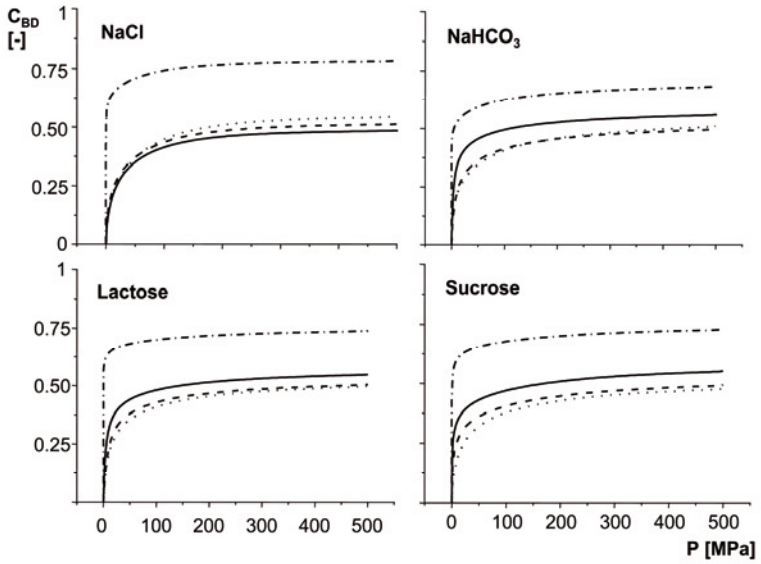

Figure 4. Engineering strain as a function of compression pressure (0-500 MPa) during continuous compression for all solid particles. The four powder finesses are distinguished as follows; fraction 1, 250-300 µm = (——), fraction 2 = 125-180 µm (— —), fraction 3, ~75 µm = (·····) and fraction 4, <50 µm = (— · —).

SKH-profiles and Shapiro parameters for the solid particles

The overall shape of the *SKH*-compression profiles for the solid particles depended both on the material and on the original particle size (*Figure 5*). At low pressures, all powders showed bended profiles and with increasing compression pressure, all powders showed a nearly linear compression profile. Thus, all powders expressed a compression behaviour associated with region I and II (see Theoretical aspects). For fraction 1-3 of three of the materials (sodium chloride, lactose and sucrose), a clear bending also of the upper part of the *SKH*-profiles was obtained, which is a behaviour associated with region III. All the finest powders (fraction 4) and all sodium bicarbonate powders showed limited bending at high pressures, *i.e.* only some of the powders expressed all three compression regions in the pressure range used in this study. For some of the lactose and sodium chloride powders, negative tablet porosities were obtained at high compression pressures, which might be

explained by changes of the particle density at high pressures associated with particle elastic deformation [9, 28].

The compression pressures at which the transitions between the different regions of the compression profile occurred varied between the powders. Nevertheless, in order to compare the compression properties of the powders in a systematic but simple way in region I and II, fixed pressure ranges were used to define these regions. The transition pressure between region I and II was set to 50 MPa and the pressure range for region II was set to 50-150 MPa in accordance with the literature [8, 9] and are indicated in *Figure 5* by dotted vertical lines.

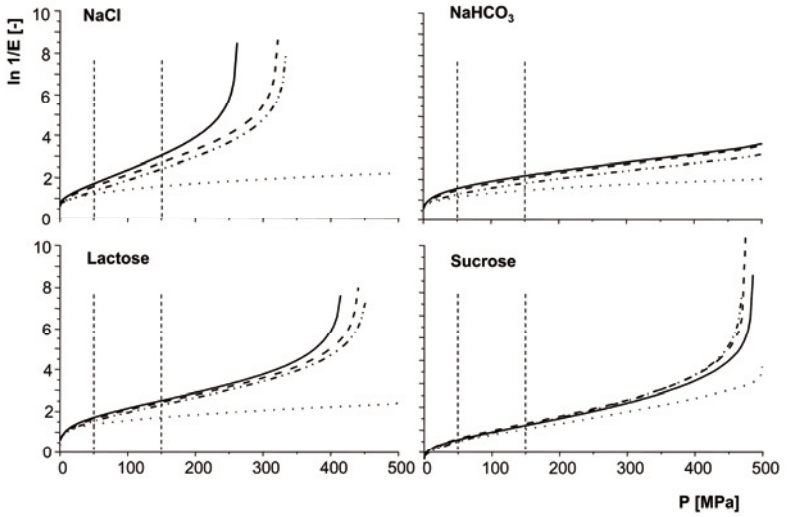

Figure 5. Shapiro-Konopicky-Heckel compression profiles for all solid particles in the pressure range 0-500 MPa. The dotted vertical lines indicate the boundaries between the three different regions of the compression profiles. The four powder finesses are distinguished as follows; fraction 1, 250-300 µm = (——), fraction 2, 125-180µm = (— —), fraction 3, ~75 µm = (— ·· —) and fraction 4, <50 µm = (·····). Please note the difference in legends between Figure 4 and Figure 5.

In general terms, the derived values of the yield pressure (P_y) indicate that the materials could be rank-ordered in terms of their plasticity in the following way: Sodium chloride > lactose > sucrose > sodium bicarbonate (Table 1 in Paper IV). For the respective material, the original powder surface area had a limited effect on the P_y values for fraction 1-3 powders without any consistent trend. However, for the respective material the highest P_y values were obtained for fraction 4 powders. Thus, the original particle size had a relatively limited effect on particle plasticity until a low particle size was reached for which the plasticity was markedly reduced.

Visual examination of the *SKH*-compression profiles in region I indicates that the finest powders (fraction 4) generally showed the highest rate of initial compression and the values of the *f* parameter were for the finest powders consequently strongly dependent on the value of the initial powder bed porosity (E_0) (Table 2 in Paper IV). For the coarser powders, a much smaller influence of the initial porosity was obtained. Further on, the finest powders (fraction 4) showed the sharpest bending of the profile in region I. Consequently, for the set of values of the *f* parameter based on bulk porosity measurements (*i.e.* the f_1 parameter), the finest powders showed generally the highest f_1 values.

Concerning the effect of original powder surface area, the f_1 parameter tended to reduce with an increase in original powder surface area for fractions 1-3 (Table 2 in Paper IV). This trend was broken with markedly increased values of the f_1 parameter for fraction 4.

Stress-strain relationships for the porous particles

The variation in starting force had generally a limited effect on the calculated Kawakita parameters and the ranking of the granules based on the respective Kawakita parameter was not affected. This can be explained by the assumption that the initial rearrangement of granules is limited and that the compression process is dominated by other mechanisms. In the further discussion, the reported data are derived from the determination of the initial volume as the transition point in the force-displacement profile during compression.

For the spherical granules (pellets), the MCC HP and the MCC LP represented the highest and the lowest maximal engineering strain (C_{max} -values, *Figure 6 a*). The difference in compressibility is thus consistent with previous works that demonstrated the importance of granule porosity for the degree of deformation and densification of granules expressed during compression [62]. Both the MCC PEG and MCC LAC pellets showed higher maximal engineering strain than the MCC LP even though they are of similar porosity. For the MCC PEG granules, this may be due to the effect of the PEG on the ability of the particles of which the granules are formed to rearrange which thus may facilitate deformation and densification [11]. More on, it has been suggested that the PEG is a material that may undergo some densification [100] at high applied pressures resulting in an apparent high compressibility of the granules during an *in situ* experiment.

The compression profiles for the two different sizes of low porosity MCC pellets were almost identical, indicating that the pellets size do not determine the deformation behaviour. The transition towards a more irregular shape increased the degree of compression (Paper VI).

For the initial compressibility (*e*-values, Table 4 in Paper I), the MCC HP showed the highest and the MCC LP the lowest initial compressibility. The MCC LAC granules showed an initial compressibility close to the MCC HP granules and the MCC PEG granules showed an initial compressibility in-between the MCC LP and MCC HP granules. There was thus a general tendency that an increased maximal engineering strain corresponded to an increased initial compressibility.

Typical compression profiles for the 50 : 50 (w/w) mixtures of the ductile pellet types are shown in *Figure 6 b*. It may be seen that the results obtained for the MCC PEG/MCC HP and MCC LP/MCC HP mixtures were virtually identical but significantly different than the one for the MCC LP/MCC PEG mixture.

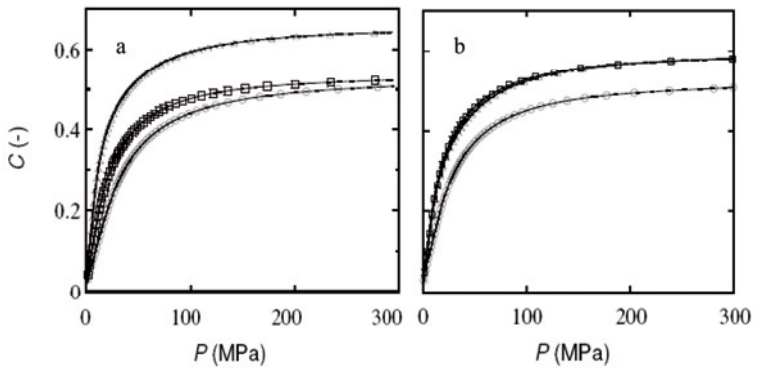

Figure 6. Typical compression profiles from the three types of ductile pellets a) single component (circles = MCC LP, squares = MCC/PEG and triangles = MCC HP), b) 50:50 mixtures (circles = MCC LP : MCC PEG, squares = MCC/PEG : MCC HP and triangles = MCC LP : MCC HP).

Physical interpretation of some compression parameters

The Kawakita parameters as estimates of particle rearrangement

As previously discussed, a fine powder will be characterized by firstly, a high rate of initial compression at low compression pressures and, secondly, a high maximal engineering strain. The expression of particle rearrangement affected simultaneously both the Kawakita parameters, *i.e.* the finest powders (fraction 4) generally showed the lowest values of parameter b^{-1} and the highest values of parameter *a*. The combination of these into a single value, *i.e.* the product of the Kawakita parameters *a* and *b*, may hence be used as an indicator of the expression of particle rearrangement during compression. The product *ab* was therefore derived for all powders (Table 2 in Paper III).

For fractions 1 to 3, a range of index values between 0.022 and 0.059 was obtained with a trend that the index decreased with a reduced original particle size was observed. For fraction 4, considerably higher index values were generally obtained (0.124 – 0.221) with the two highest values for the powders with the largest volume specific surface area (S_0), *i.e.* a clear difference between fraction 4 powders relative to the all other powders was obtained (about a five fold difference).

In *Figure 7*, the relationship between the ab_{BD} values and estimates of the original particle size (d_{S0}) is shown for all powders. The sudden increase in ab_{BD} values associated with the expression of particle rearrangement during compression seemed to coincide with a d_{S0} of about 40 µm. It is thus suggested that a particle size of about 40 µm represented a threshold or a critical particle size at which the particle rearrangement was expressed to a significant degree for the powders studied in this thesis.

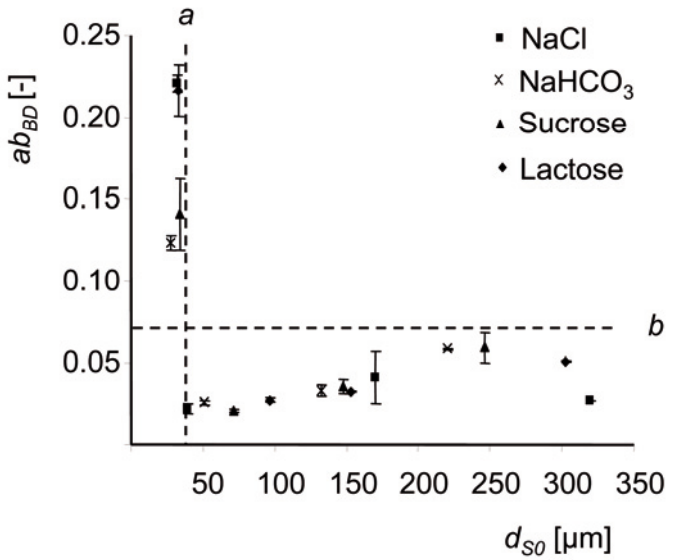

Figure 7. The product of the Kawakita parameters ab_{BD} during continuous compression, V_0 transformed from bulk density, as a function of particle size d_{S0} estimated from the powder surface area S_0. The error bars indicate the standard deviations. The dotted lines indicate a) a suggested particle size threshold value (< 40µm) below which the particle rearrangement becomes significant and b) a suggested threshold value (> 0.075) of the index ab_{BD} above which significant particle rearrangement occurs. The error bars indicate the standard deviations.

Regarding the coordination number, a similar relationship was also obtained with a marked increase in ab_{BD} values around a coordination number of 7.5. These powders showed a low packing density characterized by relatively few contacts with surrounding particles. For such powders, the compression can be understood in terms of an increase in the coordination num-

ber due to particle rearrangement until a critical packing density is reached after which particle rearrangement will cease and other mechanisms of compression will dominate the compression process. For powders with a coordination number below ~ 7.5, particle rearrangement will be expressed. For powders which initially pack with a packing density above this critical level, particle rearrangement will be negligible for the overall compression process. The coordination numbers for powders after tapping was generally above 8.7, *i.e.* all powders had the potential to increase the packing density above the suggested critical level by particle rearrangement.

Using the *SKH*-model to determine the fragmentation propensity of solid particles

When comparing the different materials, the powders of sodium chloride generally showed the least pronounced curvature of region I (*Figure 5*). For these powders, the bending occurred primarily at low pressures (P < 5 MPa) and the profile tended to become linear already within the chosen pressure range of region I. The other materials showed a curvature extended over a larger range of pressures. Accordingly, the sodium chloride powders showed generally the lowest values of the f_1 parameter while lactose, the most fragmenting material, showed the highest values (Table 2 in Paper IV).

Since no general relationship between the index *ab* and the f_1 parameter was obtained it was assumed that particle rearrangement is not the only process controlling the shape of region I of a *SKH* compression profile (and hence the f_1 parameter). As described above, the bending of the compression profile in region I is generally consistent with the ranking of the fragmentation tendency of the materials, *i.e.* particle fragmentation also is a process of importance for the initial bending of the *SKH* profile.

For the powders expressing limited particle rearrangement during compression, *i.e.* fractions 1-3 of all materials, the relationship between the f_1 parameter and the change in particle size during compaction (Δd) is presented in *Figure 8*. It seems that all fractions followed a single, non-linear relationship. It is 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 an *SKH* profile. A powder showing both limited rearrangement and fragmentation will display a linear type of profile in region I.

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 a rearrangement may facilitate compression at low applied pressures. Secondly, the reduction in particle diameter due to particle fragmentation will progressively increase the hard-

ness (reduce the plasticity) of the particles, corresponding to an increased yield pressure. The resistance towards compression will consequently be controlled by a drifting yield pressure until particle fragmentation ceases to occur [101]. From this point on, the hardness will be approximately constant and the rate of compression will obey the *SKH* model, *i.e.* the *SKH* profile will become linear.

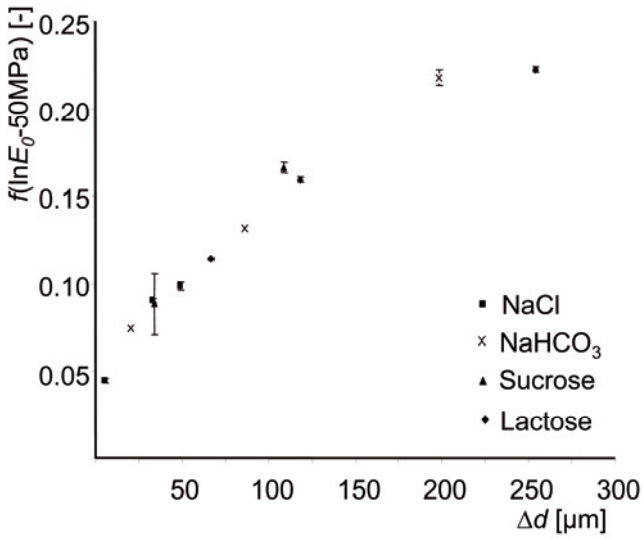

Figure 8. The relationship between the estimated change in particle size and the compression parameter *f* for the three coarsest fractions of the solid particles. The error bars indicate the standard deviations.

The conception that fragmentation and deformation are the two processes controlling the compression in region I and II of a compression profile is interesting since it offers the opportunity to derive indicators of both the fragmentation propensity and the deformation propensity of particles in a single compression test.

The Kawakita and the Adams parameters as descriptors of the compressibility for porous particles

Since the incidence of granular rearrangement and granule fragmentation is expected to be low for the ductile type of pellets (MCC LP, MCC HP and MCC PEG), the terms initial compressibility and maximal engineering strain can be interpreted in terms of different deformation propensity and deformation capacity of the pellets. As expected from the porosity of the pellets, the values of the Kawakita *a* parameter obtained for the MCC LP and MCC PEG pellets are similar, and significantly lower than for the MCC HP pel-

lets. The C_{max} -values were generally close to the to the Kawakita *a*-values which is in accordance with the interpretation of the *a* parameter [4] an it is thus conclude that the Kawakita *a* parameter gave a good approximation of the total degree of compression of the granular solids independent of their single granule mechanics (*Figure 9* based on values from Table 4 in Paper I and Table 2 in Paper VI).

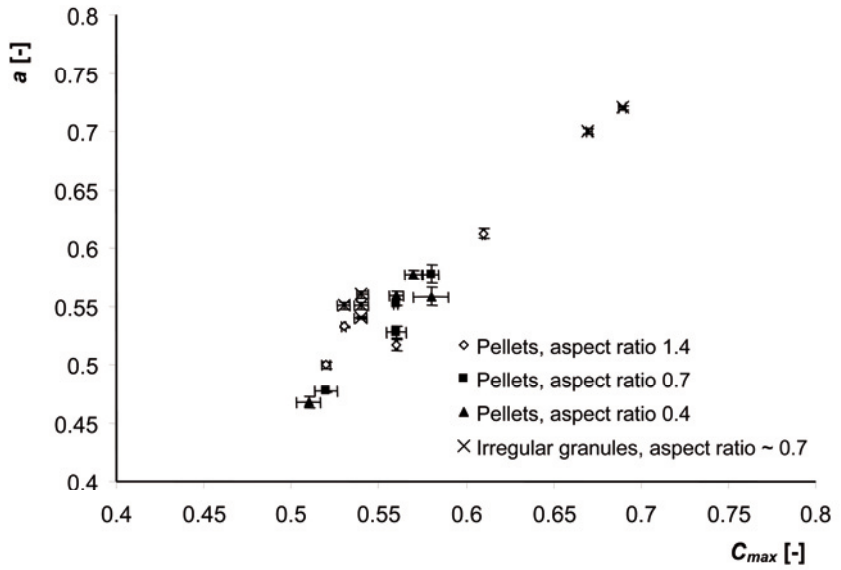

Figure 9. Relationship between the Kawakita parameter *a* and the maximal degree of compression C_{max} for the agglomerated porous particles. The error bars indicate the standard deviations.

In *Figure 10 a*, the relationship between the *e*-values and the Kawakita parameter b^{-1} for the pellets studied in Paper I is presented. For the three granules that can be described as ductile, the Kawakita b^{-1} parameter gave a good approximation of the initial compressibility of the granular solids independent of their deformation properties. For the brittle granule (MCC LAC), a high initial compressibility (*i.e.* a low *e*-value) comparable to the MCC HP granules was obtained was obtained while the Kawakita b^{-1} parameter was higher. The overall shape of the compressibility profile of the MCC LAC granules differ from the other three by having a faster initial compression followed by a more extended approach to the plateau of the compression profile. Thus, the Kawakita b^{-1} parameter cannot be used as a physically defined descriptor of this initial compression phase.

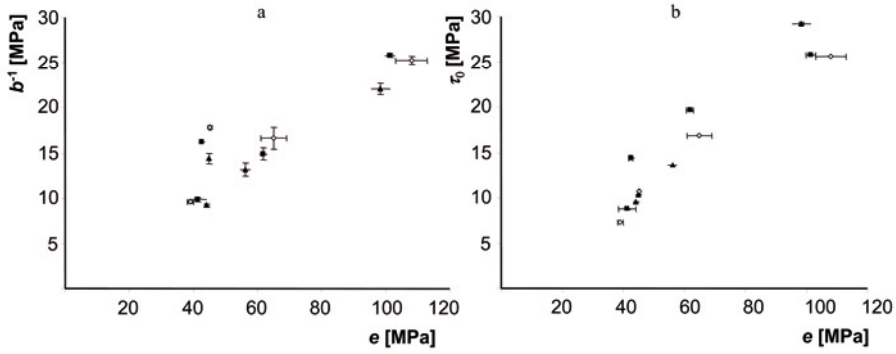

Figure 10. a) The relationship between the Kawakita parameter b^{-1} and the initial compressibility *e*, b) the relationship between the Adams parameter τ_0 and the initial compressibility *e*. The error bars indicate the standard deviations.

Earlier experiences on the compression behaviour of granules made from MCC and a MCC PEG mixture indicate that they do not fragment during compression [11, 24]. Also for a granule consisting of MCC and a hard material (calcium phosphate) it has been shown [69] that fracturing of the granules is limited and thus, also for the MCC LAC granules it is assumed that the dominant compression mechanism is deformation. This assumption is supported by images of the fracture surface of tablets (*Figure 16*). As also indicated by the images of the tablet fracture surface, some cracking of the granules occurred at the granule surface and, most pronounced for the MCC LAC tablets, small fragments of granules were located in the inter-granular voids. These fragments were thus probably formed by local fragmentation at the inter-granular junctions as a result of surface cracking. Thus, the most brittle type of granule (MCC LAC) deviated slightly in compression behaviour relative the other types in terms of a higher degree of local granule cracking and fragmentation. Such a cracking process may thus facilitate initial compression.

The Adams parameter τ_0 is a parameter that indicate the stress needed to fail granules with a crack opening mechanism and has earlier been suggested to correlate with the Kawakita b^{-1} parameter [20]. Also here, a reasonable correlation between these two parameters was obtained. However, the Adams parameter showed a better relationship to the initial compressibility (the *e*-values) (*Figure 10 b*). The relationships thus support the conception suggested above that the rate controlling mechanism for the initial compression is the cracking of the granules. The Adams parameter may be used as a descriptor of the initial compressibility, expressed in terms of a failure stress of the granules.

When studying the binary mixtures the MCC LP, MCC HP and the MCC PEG pellets were chosen as model materials due to their relatively well-defined and non-complex compression behaviour and should be ideal model

granular solids for an initial evaluation of the prediction of *Equations 9* and *10* described in Experimental section. The obtained Kawakita parameters are shown in *Figure 11* as functions of the composition of the mixtures, expressed in terms of the initial volume fractions. The solid lines in *Figure 11* represent predictions based on the equations with the mean parameter values for the single component systems as input (Table 3 in Paper II).

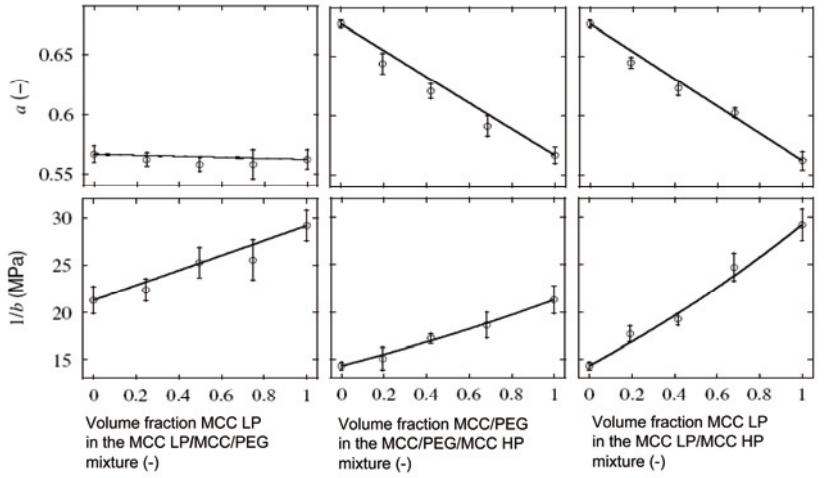

Figure 11. A comparison between the measured (symbols) and predicted (solid lines) Kawakita parameters for binary mixtures of ductile pellets, the error bars indicate 95 % confidence intervals.

The results for the MCC LP/MCC PEG mixture show the behaviour of the Kawakita parameters when only the deformation propensity varies (and the deformation capacity thus is constant). As expected, the a parameter is then independent of composition, whereas the b^{-1} parameter increases linearly with volume fraction MCC LP pellets in the mixture. A linear variation of the b^{-1} parameter is predicted by *Equation 10* when all a_i are the same.

The results for the MCC PEG/MCC HP mixture show the behaviour of the Kawakita parameters when only the deformation capacity varies (and the deformation propensity thus remains constant). It can be observed that both the a and b^{-1} parameters are affected in this case, and in relative terms they both appear to vary equally much. Since the a values of the components differ, *Equation 10* predicts a nonlinear dependence of b^{-1} on composition, but as seen in the figure, the nonlinearity is not very pronounced.

Finally, for the MCC LP/MCC HP mixture both the deformation propensity and capacity vary at the same time. In this case the a parameter depends linearly on composition in the same way as for the MCC PEG/MCC HP mixture, whereas a slightly nonlinear dependence of b^{-1} is predicted. In relative terms the b^{-1} parameter exhibits a much stronger dependence on composition than the a parameter. This may, however, be an effect of a larger rela-

tive variation of the deformation propensity than of the deformation capacity.

In general the agreement between measured and predicted Kawakita parameters is good. Thus the assumption of ideal mixing behaviour was valid for this type of systems and therefore the linearity between C and $1/P$ (at sufficiently high compression pressures P) implies that effective Kawakita parameters for the mixture may be expressed in terms of the parameters of its components. Whereas *Equation 9* predicts a linear dependence of a on composition, the dependence of b^{-1} predicted by *Equation 10* is nonlinear in general.

Using the Kawakita and the Adams parameters to estimate single granule mechanics

The Kawakita a parameter was evaluated in relationship to the Young's modulus, the yield pressure and the fracture strength of the granule. A nearly linear relationship was obtained between the Kawakita a parameter and the yield pressure (*Figure 12*) while a similar single relationship was not obtained to the other properties. Thus, the propensity of the granules to deform permanently seemed to control their maximal engineering strain which can be approximated with the Kawakita a parameter.

Also the Kawakita b^{-1} parameter was evaluated in relationship to the Young's modulus, the yield pressure and the fracture strength of the granule. Also here, only for the yield pressure (*Figure 12*) a relationship that could be described as a single relationship was obtained. Thus, also the Kawakita b^{-1} parameter is a descriptor of the compression process that is related to the plasticity of single granules.

Since it was concluded that the Adams parameter τ_0 was a better descriptor of the initial rate of compression of the granules than the Kawakita b^{-1} parameter, the initial compressibility, as described by the e-value, was related also to the single granule fracture strength σ_0. A reasonably correlation between the e-value and the single granule fracture strength (*Figure 11* in Paper I) was obtained. This relationship thus supports further the conclusion that the initial compressibility is controlled by the cracking of the granules, *i.e.* the failure of the granules due to cracking was more significant for the initial compression process than the granule deformation, which however probably occurred in parallel.

The combined use of the Kawakita parameters a and b^{-1} and the Adams parameter τ_0 may therefore give a comprehensive representation of the compression behaviour of granules.

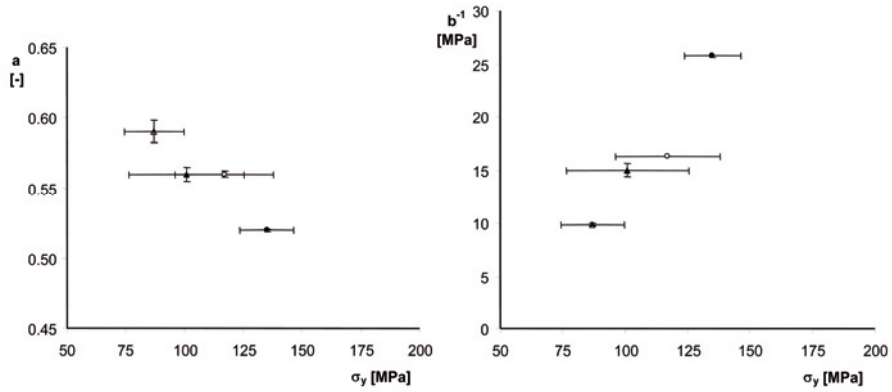

Figure 12. Relationship between the Kawakita parameters and single granule plasticity. The error bars indicate the standard deviations.

Classification of powders with compression analysis

Classification of powders based on particle rearrangement

As previously mentioned, the compression process of a powder is often described in terms of a model outlining the different stages, defined in terms of dominating or rate controlling compression mechanism, involved in the process. In Table 3, the proposed stages involved in compression of powders are presented. The last portion of a compression profile, *i.e.* the formation of a compact of nearly zero porosity, is considered to reflect the elastic deformation of a stiff solid body located in the die. This model has attained wide acceptance in the field of compression technology.

As a consequence of the discussion of the expression of particle rearrangement dependent on original particle size or packing density, a system to categorize powders into groups may be proposed. A simple classification into four classes is here used and in Table 3, the stages characterizing each class of powder are proposed. The last stage of the compression profile, the tablet elastic deformation, is probably common for all powders and is therefore excluded in the classification. Class IA and IB powders show significant compression due to primary particle rearrangement (*i.e.* rearrangement of the original particles) followed by fragmentation and deformation dependent on their fragmentation propensity. Class IIA and IIB powders show limited compression due to primary particle rearrangement. However, if fragmentation is significant due to a high fragmentation propensity, secondary particle rearrangement may occur, *i.e.* rearrangement of the fragments formed during particle breakage.

It is suggested that above a critical original particle size of a powder, particle rearrangement is limited and independent of particle size. Below the critical particle size, particle rearrangement is significant. A particle size of ~ 40 μm may represent a critical threshold that determines if a powder belongs to class I or class II.

The application of the type of classification system proposed here is that the interpretation of the physical significance of compression parameters, such as the Kawakita parameters, will possibly depend on the importance of particle rearrangement for the overall compression profiles. For example, in the thesis it is suggested that during the compression of granules for which the initial granule rearrangement phase was negligible, the Kawakita a and b^{-1} parameter described the plasticity of the granules (*Figure 12*). Thus, a classification of powders into different groups based on an index describing the extent of particle rearrangement during compression can be used as a means to facilitate the physical interpretation of global compression parameters.

Table 3. Possible stages involved in the compression of powders and the stages involved in the compression of class I and II powders dependent on the degree of particle fragmentation.

Stage	Stages	Class	Stages
1	Primary particle rearrangement	IA	1 + 4
2	Particle fragmentation	IB	1 + 2 + 3 + 4
3	Secondary particle rearrangement	IIA	4
4	Particle deformation	IIB	2 + 3 + 4
5	Tablet elastic deformation		

A new classification of powders based on *SKH*-profiles

Depending on the effect of original particle size on the shape of a *SKH* profile, a classification of such profiles has been proposed in the literature [21]. Based on the results presented in this thesis, a new categorization of *SKH* profiles into three types, dependent on the bending of the profile in region I with associated mechanistic explanation, is proposed (*Figure 13*). The first category, denoted Type 1, is characterized by a sharp bending of region I due to significant particle rearrangement in combination with particle fragmentation. The second category, denoted Type 2, is characterized by a smoother and more extended bending of region I due to significant particle fragmentation without primary particle rearrangement. The third category, denoted Type 3, is characterized 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 and a region III, associated with elastic deformation of the stiff tablet formed in the die, may appear dependent on the range of compression pressures used. None of the profile types is associated with a

merger of profiles at high compression pressures during the compression of particles of the same material but of different particle size.

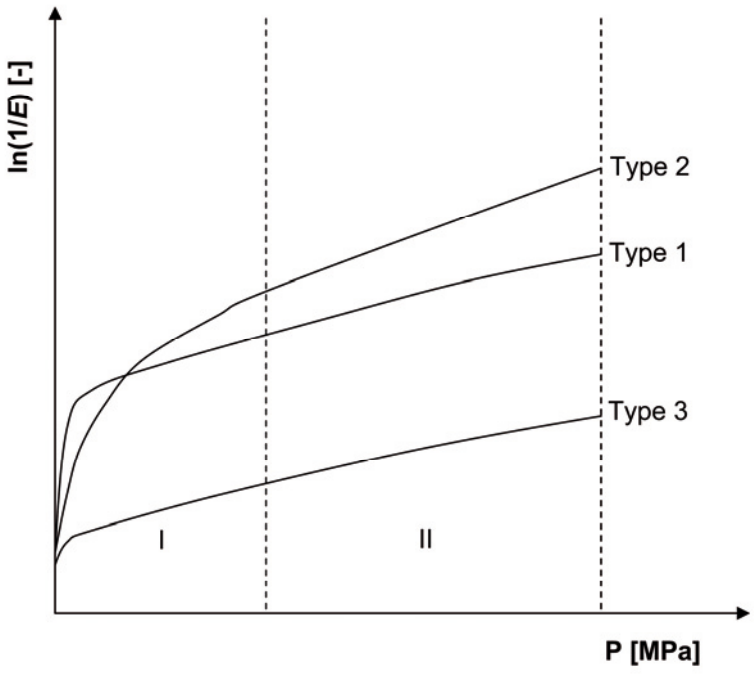

Figure 13. A schematic illustration of the three different types of *SKH*-profiles. Type I powders undergoes significant initial particle rearrangement, Type 2 powders fragments during compression and Type 3 powders deform plastically without significant initial particle rearrangement.

Application of compression analysis for some granular solids

In order to investigate the relevance of using traditional global compression equations as descriptors of powder functionality, other comparative approaches are necessary. The relationship between mechanical properties of single granules and the evolution in tensile strength and tablet microstructure was therefore explored (Paper V).

General description of the compactibility of the porous particles

To describe the tablet forming ability of the model materials, the relationship between the attained tablet tensile strength (σ_t) and the applied compac-

tion pressure (P_{app}) was investigated to derive some established descriptors of the compactibility [40] (see *Figure 14* and Table 2 in Paper V and Table 2 in Paper VI).

For the two types of MCC spherical granules (also referred to as pellets), the evolution in tablet tensile strength with compaction pressure is faster for the high porosity MCC pellets (MCC HP) than for the pellets of low porosity (MCC LP) in accordance with reported findings [24]. The addition of a small amount of PEG in the granulation liquid when producing the low porosity MCC granules gave an increased rate of tablet strength evolution. Finally, the spherical MCC LAC granules gave a rate of tablet strength evolution in between the MCC HP and the PEG pellets. Thus, in terms of the rate of tablet strength evolution, the spherical granules showed markedly different behaviour and they could be rank ordered.

When the size and shape of the porous granulated particles varied (instead of the composition), it could be seen that the two different size fractions of low porosity MCC pellets showed approximately the same and the lowest evolution of tablet tensile strength and had the lowest attained maximal tablet tensile strength. The three different size fractions of irregular low porosity MCC granules all showed the same tableting behaviour and had a slightly higher evolution of tablet tensile strength than the low porosity MCC pellets and a higher maximal attained tablet tensile strength. The irregular shaped high porosity MCC W/E granules showed the greatest evolution of tablet tensile strength and the highest maximal attained tablet tensile strength, and the corresponding pellets of high porosity (MCC W/E pellets) showed slightly lower values. These findings corresponds to previous reported results, where a higher intragranular porosity or a more irregular shape gave more deformable pellets and granules which produced tablets of a more closed pore structure and of higher tensile strength [24, 62], whereas the granule size has been shown to have moderate influence of compression behaviour and tablet tensile strength [61].

As previously discussed, these types of pellets and granules reduce in volume under compression mainly due to plastic deformation and keep the integrity during compression even though some crack opening occurs. Changing the shape might generate a more complex compression mechanism, including granule attrition. The cylindrical shape of the MCC W extrudate clearly affected the compactibility behaviour, showing a high evolution of tablet tensile strength and a high maximal attained tablet tensile strength in the same magnitude as the high porosity granules. It is reasonable to believe that the large cylindrical granules break into smaller fractions during compression, which also was visually observed during the tableting experiments.

In conclusion, the various granulated powders used in this study showed a wide range of tablet forming abilities. It can also be noted that the tablet tensile strength showed a large variation between the different granulated particles at a specified applied compression pressure.

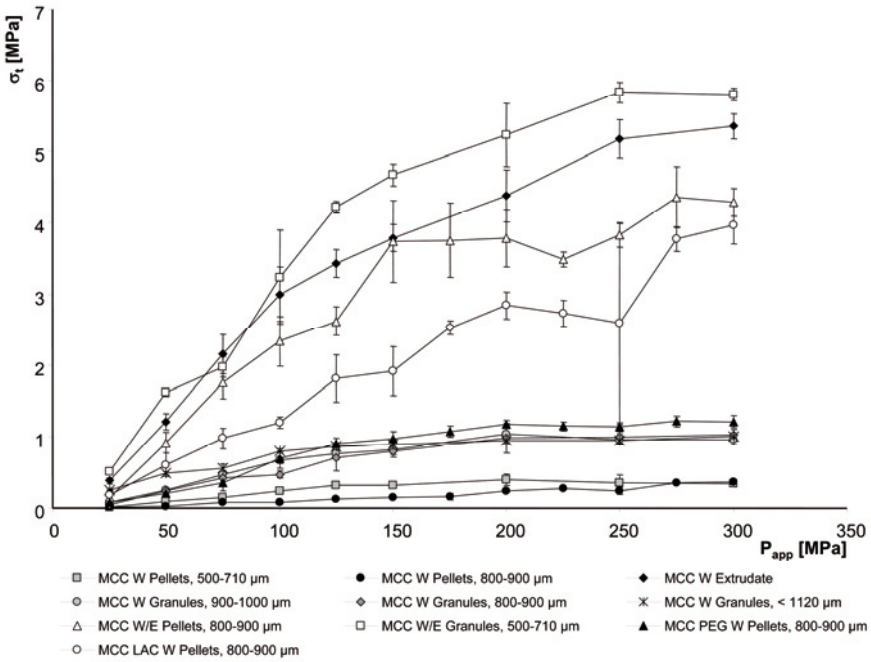

Figure 14. Tablet tensile strength as a function of applied pressure. The error bars indicate the standard deviations. Please note that MCC LP = MCC W Pellets. MCC HP = MCC W/E Pellets, MCC PEG = MCC PEG W Pellets and MCC LAC = MCC LAC W Pellets.

The role of plasticity for the compactibility

Since the plasticity of granules is a significant factor for the degree of compression of a powder bed it is logical that the plasticity of granules is important also for the evolution in tensile strength of tablets, which is in agreement with earlier reports stating that an increased degree of deformation of granules expressed during the compression gave an increased tablet tensile strength [35, 102]. Other factors than the plasticity of granules, such as granule shape [58, 62] and size may influence the degree of deformation of granules that is expressed during compression and thus the micro-structure and tensile strength of tablets [68, 103]. The four spherical model granules (pellets MCC LP, MCC HP, MCC PEG and MCC LAC) used here showed a variation in plasticity but not in size or shape, and thus seem useful in order to enhance the understanding of the importance of the plasticity of granules for their tablet forming ability.

By studying the relationship between the relative tablet tensile strength (σ_{rel}) and the effective compaction pressure (P_{eff}), the inverted relative compactibility C_A, *i.e.* the inverted slope from the linear part of the relationship

between σ_{rel} and P_{eff} can be obtained (*Figure 3* in Paper V). It has been suggested [40] that C_A is an indication of the effective deformability of particles during confined compression. The softer granules (MCC HP and MCC PEG) had similar values of C_A than the two less deformable granules (MCC LP and MCC LAC) that showed similar but considerably higher values (Table 2 in Paper V). In *Figure 15*, C_A is given as a function of the yield pressure (σ_y) of single granules. A reasonable correlation between these properties was obtained. Assuming a single relationship, a slope of about 2 was obtained which corresponds reasonably with earlier experiences [40]. This slope could be seen as a constraint factor between hardness and yield pressure of the granules and the values of the constraint factor were 2.3 for the MCC LP and 2.4 for the MCC LAC granules, and 1.8 for the MCC HP and 1.5 for the MCC PEG granules.

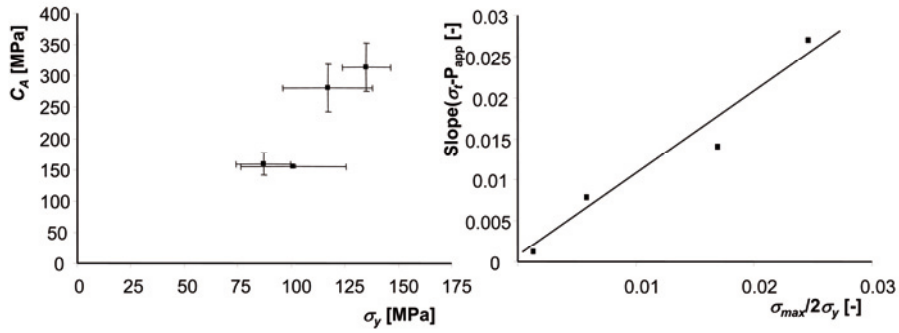

Figure 15. To the left, the inverted relative compactibility C_A as a function of the yield pressure of single granules is shown. The slope from the tablet tensile strength – applied pressure relationship (see *Figure 14*) as a function of the ratio between maximal tablet tensile strength and yield pressure is shown to the right. The error bars indicate the standard deviations.

The significance of the C_A parameter is, firstly, that it corresponds to a faster evolution in relative tablet strength with compaction pressure and, secondly, that it represents the range of pressures in which the tablet strength changes with pressure [40], *i.e.* the range between the lower and upper pressure thresholds in a compactibility profile (the range between the critical formation pressure and the pressure at which the maximum attained tablet strength is reached). The role of the plasticity of granules for their tablet forming ability is thus to affect the rate of compactibility and the pressure range needed to reach the maximal attained tablet strength.

The physical significance of this role of granule plasticity is possibly that it affects the contact process between granules in terms of the area of the inter-granular joints. For the three granules categorized as ductile, the change in inter-granular void structure with pressure relates to the plasticity of the granules, *i.e.* an increased plasticity will give a more closed inter-granular pore structure which correlates with the development of the dimen-

sion of the inter-granular joints (assessed by the permeability to air). The MCC LAC granule gave the most closed inter-granular voids, although these granules showed the lowest plasticity (Table 2). The size of the inter-granular voids is a function of several events, besides deformation also cracking and fragmentation of granules. For the more brittle granule, the incidence of cracking and fragmentation has been suggested to be higher and will contribute to a more closed inter-granular void structure [41]. The photo-micrographs of cross sections and upper tablet surfaces (*Figure 16*) generally support this discussion on the inter-granular void structure of the tablets.

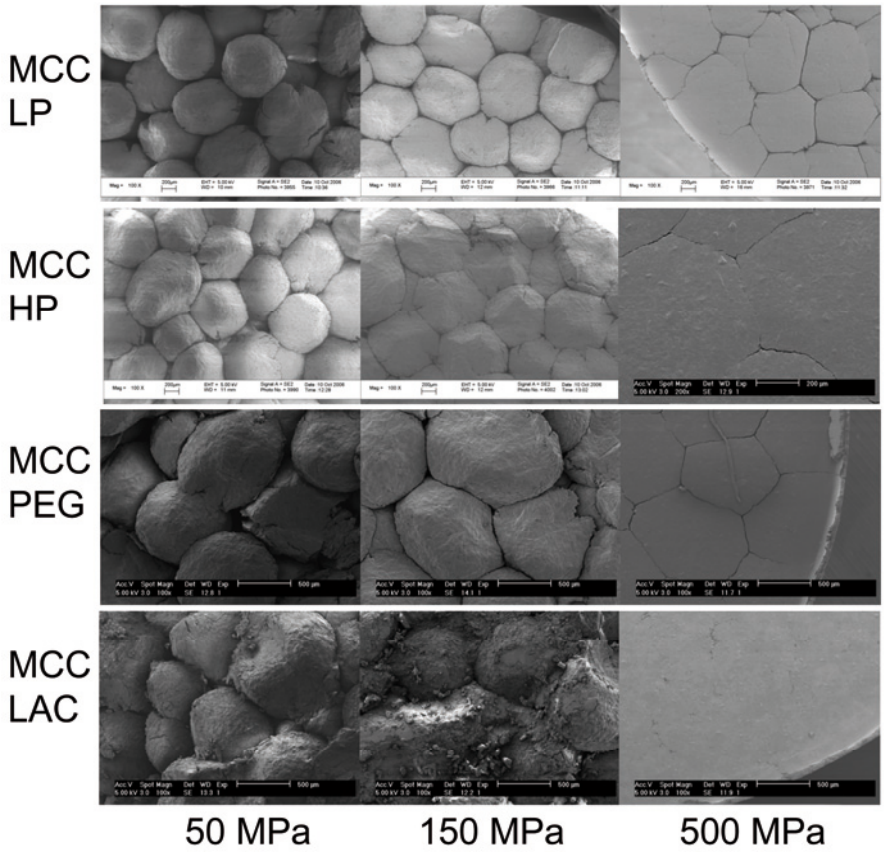

Figure 16. SEM pictures of tablets surfaces produced from spherical granules at three different compression pressures (50, 150 and 500 MPa).

The maximal attained tensile strength σ_{max} varied between the granules (*Figure 14* and Table 2 in Paper V) and is a complex property that depends on several factors, including the physical structure of the tablet and the adhesion and fracture mechanics properties of the granules. An increased plasticity seems to correspond also to an increased propensity for local adjustment of granule surfaces to each other. This ability for local adjustment has earlier been denoted a different mode of deformation [69]. The role of the plasticity of

granules seems thus also to affect the mode of deformation which is reflected in the maximal attained tensile strength.

By considering the compaction of a tablet as a percolation process [104] with an exponent of unity, the slope taken from the relationship between the tablet tensile strength and applied pressure in the region between the lower and upper percolation thresholds (here the lower and upper applied pressure thresholds) can be described as dependent on two factors; the maximal attained tablet strength (the scaling factor) and the yield pressure of the granules, *i.e.* Slope = σ_{max} / (xσ_y), where x is a constraint factor. This relationship is presented in *Figure 15* with a constraint factor of 2. A reasonable positive correlation was obtained supporting the role of the yield pressure of granules for their tablet forming ability.

Degree of compression as an indicator of tablet tensile strength

A series of porous particles were prepared from MCC and the porosity, shape and the size of the particles were varied. The possible use of the degree of compression as a process indicator was then investigated and compared with other indicator of the tablet tensile strength.

The relationship between the logarithm of the attained tablet tensile strength as a function of the total porosity of the ejected tablet, known as the Ryskewitch profile [105, 106], is one common way to describe the tablet forming ability of a material (*Figure 17*). The tablet porosity transformed from in die measurement of the tablet height could hence be a potential process indicator of the tablet tensile strength. For each granulated material studied in Paper V and Paper VI, the tablet tensile strength increased when the tablet porosity decreased until a maximal attainable tensile strength was obtained. Thereafter, the tablet porosity could be decreased further without any significant change in tablet strength (corresponding to the plateau in the compactability profile). At a constant tablet porosity, the tensile strength of the tablets for the respective type of granules varied markedly, *i.e.* the total tablet porosity is not a generally related to tablet strength. A contributing factor to this is the fact that the porosity of a tablet formed from granulated porous particles is the sum of the intra- and the inter-granular porosities and the structure of the inter-granular pores and contacts is not generally proportional to the total tablet porosity [35]. The granulated powders analyzed in this thesis seemed to organize them selves in to two groups; one of less deformable granulated particles and one of more deformable ones which show a larger change in tablet porosity with applied pressure (*Figure 17*).

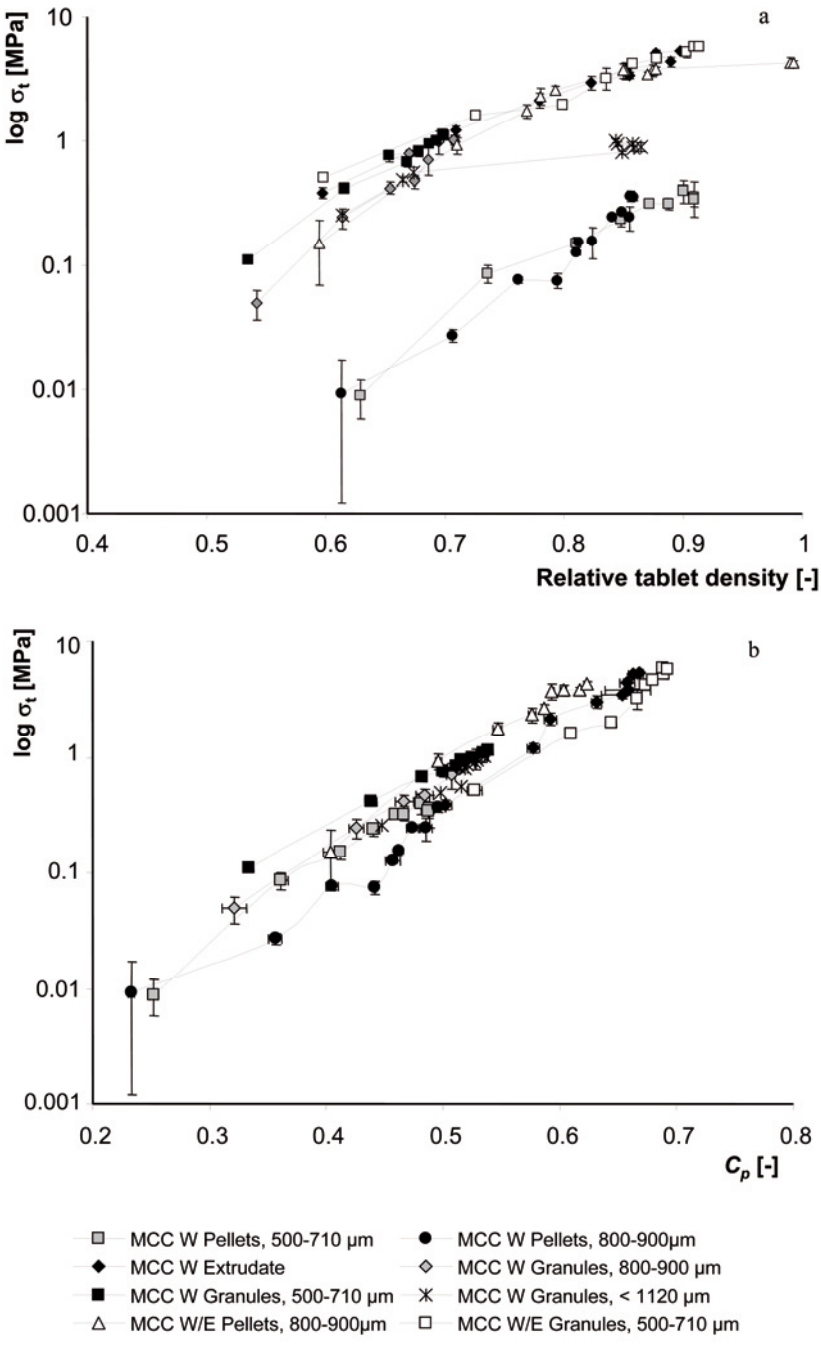

Figure 17. The relationship between the logarithm of the tablet tensile strength and a) the relative tablet density and b) the degree of granule bed compression. The error bars indicate the standard deviations. Please note that MCC LP = MCC W Pellets. MCC HP = MCC W/E Pellets, MCC PEG = MCC PEG W Pellets and MCC LAC = MCC LAC W Pellets.

From the relationship between the degree of compression C_p and the attained tablet strength σ_t at the different applied compaction pressure it can be observed that a higher degree of compression of the granulated particles during tableting gave tablets of a higher tensile strength. When the logarithm of the attained tablet tensile strength was plotted as a function of the degree of compression at the applied pressure P (C_p) (*Figure 17*) all the systems collected them self around a straight line, giving one single relationship. At a fixed value of tablet tensile strength, a smaller spread in degree of compression was obtained in comparison with the compression pressure and the relative tablet density.

In conclusion, the degree of bed compression at an applied compaction pressure hence appears to be a better descriptor of the tablet tensile strength than the applied compaction pressure or the tablet porosity for granulated particles. The maximal attained tablet tensile strength seems mainly to be determined by the capacity of the granules to deform permanently. The C_{max}-values ranked the materials in the same order as the σ_{max}-values, *i.e.* the MCC W spherical pellets and the MCC W/E irregular granules had the lowest and the highest maximal engineering strain respectively (*Figure 6* and Table 2 in Paper VI), further supporting that the degree of compression is an interesting technical property of granulated powders. The degree of compression could thus be measure under production as an estimate of the tensile strength of the tablets. This type of knowledge may contribute to the transition from a batch-to-batch production of tablets towards a continuous manufacture.

Summary and conclusions

The aim of this thesis was to contribute to an enhanced tablet formulation technology by suggesting characterization schemes for the determination of manufacturability of dense and porous powder particles.

Analysis of force-displacement data collected during confined compression was chosen as a method mainly for two reasons; a small amount of sample is required and the technical properties of poorly compactable materials can also be determined. Model materials of different compression mechanics were prepared and analyzed and the relevance of some global compression equations that describe the compression behaviour of the whole powder bed was investigated. The understanding of the physical significance of the derived compression parameters was improved and their potential use as descriptors of powder functionality discussed. The mechanics of single granules (in terms of tensile strength, plasticity, elasticity and fragmentation propensity) was used as a comparative method in this evaluation.

The results indicated that for granules for which the initial granule rearrangement phase is negligible, the compression process can in mechanistic terms be divided into two regions. The first compression region was almost linear and associated with cracking and deformation of granules. It is suggested that the rate controlling process for the initial compression is the cracking of granules which is reflected by the Adams parameter τ_0. The second region corresponds to a successively reduced rate of compression which is associated with deformation and densification of granules. Plastic deformation of granules is suggested to be the rate controlling process in this region. The Kawakita a parameter approximated the total degree of compression of the granular solids and both the Kawakita a and b^{-1} parameter reflected reasonably the plasticity of single granules.

The Kawakita equation was also shown to be useful to improve the understanding of the compression behaviour of binary mixtures of ductile granules.

It was thus concluded that the both the compressibility of a bed of granules and the plasticity of single granules can be approximated with compression analysis and combined use of the Kawakita parameters a and b^{-1} and the Adams parameter τ_0 may give a comprehensive representation of the compression behaviour of porous particles.

When investigation on the different stages in the compression process for solid particles was done it was concluded that the fragmentation propensity

of powder particles could also be estimated from compression analysis by using the Shapiro General Compaction Equation, which opens up for the possibility of deriving indicators of both the fragmentation propensity and the deformation propensity (in terms of yield pressure) of solid particles in one single compression test by constructing traditional Heckel profiles.

A prerequisite for the interpretations mentioned above is however that the incident of particle rearrangement during initial compression at low pressures does not significantly influence the whole compression profile. It was concluded that a powder showing a high rate of compression at low compression pressures, (a low b^{-1}-value), in combination with a high degree of total compression, (a high a-value), undergoes significant particle rearrangement. Consequently, the product of the Kawakita parameters a and b may be used as an indication of particle rearrangement during compression and a classification system of powders into groups dependent on the incidence of particle rearrangement could be used as tools to enable rational interpretations of global compression parameters.

The relationship between mechanical properties of single granules and the evolution in tensile strength and tablet micro-structure was also explored as a part of the thesis. It is suggested that the plasticity of a granule influences the tablet tensile strength in two different ways; firstly, the rate of compactibility and consequently the pressure range needed to obtain the maximal attained tablet strength is affected, and secondly, the mode of deformation of the granules is altered and as a result the maximal attained tablet strength. A decrease in yield pressure (*i.e.* an increased plasticity) of single granules increased the tablet tensile strength at a given compaction pressure. The yield pressure can be controlled by the granule composition and porosity.

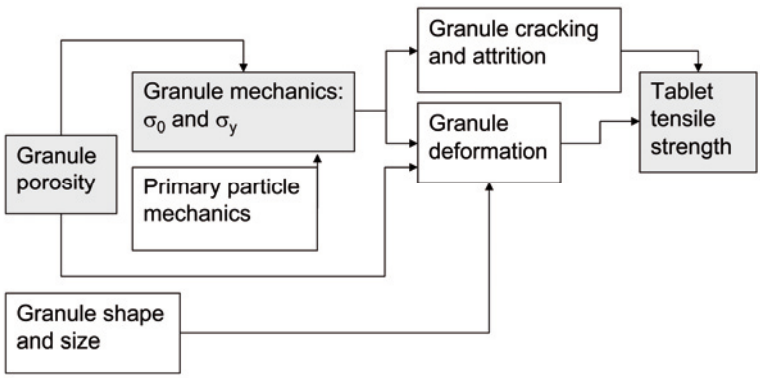

Figure 18. Schematic description over some granule properties that can be modified in order to control tablet tensile strength.

The degree of deformation of granules that is expressed during compression and thus the micro-structure and the tensile strength of the produced tablets can be influenced by a number of factors, such as the plasticity, shape

and size of single granules (*Figure 18*). Further demonstrating the application of compression analysis, it was suggested that the degree of powder bed compression is a better indicator of the tablet tensile strength than the two descriptors traditionally used (applied compaction pressure and total tablet porosity) for granular materials.

In conclusion, compression analysis can be used to derive global compression parameters that function as descriptors of the technical properties of dense and porous particles that are critical for their compressibility and the mechanical properties of the tablet (Table 4).

Table 4. Summary and ranking of the investigate compression parameters. + indicates high robustness of the model, *i.e.* all the following criteria were fulfilled; 1. a good fit to the experimental data in a wide pressure range, 2. a high reproducibility and 3. an insensitivity to changes in the experimental and data analysis conditions. * indicates for which type of particles the compression parameters are applicable.

Parameter	Robustness	Physical significance	Solid particles	Porous particles
Kawakita b^{-1}	+	Formability		*, σ_y
Kawakita a	+	Formability		*, σ_y
Adams τ_0		Fracture strength		*, σ_0
Shapiro f		Fragmentation propensity	*, Δd	
Heckel k		Formability	*, P_y	
Kawakita ab		Particle rearrangement	*	*

Svensk populärvetenskaplig sammanfattning

Jämfört med andra orala läkemedelsformer har tabletter en rad fördelar. Tabletter ger en säker dosering, har god fysikaliska och kemisk stabilitet och lämpar sig bra för masstillverkning. Många patienter upplever dessutom tabletter som ett bekvämt och lätthanterligt sätt att ta en medicin. Tabletter utgör därför merparten av alla läkemedelsprodukter på marknaden och är fortfarande förstahandsvalet då nya läkemedel utformas. Tabletter tillverkas oftast genom att applicera ett tryck på ett pulvermaterial (fasta partiklar plus luft) i en sluten volym (matris). Komprimering av pulver är därför en viktig process att förstå i farmaceutiskt utvecklingsarbete och under tillverkning av läkemedel.

Farmaceutiska pulver har ofta ett komplicerat komprimeringsbeteende som involverar flera olika händelser; initialt då pulvret hälls i matrisen sker en förflyttning av pulverpartiklarna. Då trycket ökar kommer partiklarnas dimensioner förändras genom permanent eller tillfällig deformation. Parallellt börjar spröda material att fragmentera. Dessa mindre fragment kan i sin tur förflytta sig och deformeras. Komprimeringsbeteendet avgör viktiga funktionella egenskaper hos den färdiga tabletten, som t ex porositet och mekanisk hållfasthet. Porositeten hos en tablett, dvs strukturen hos det nätverk av luft mellan eller inuti pulverpartiklarna, har inverkan på tablettens upplösning i vätska vilket är viktigt för läkemedelsupptaget i kroppen. En tablett måste också ha tillräcklig hållfasthet för att inte gå sönder under produktion, paketering och transport, men ändå vara enkel för patienten att bryta sönder.

Under tillverkningen av tabletter krävs förståelse för olika mekaniska egenskaper hos råmaterialen för att kunna tillsätta farmaceutiska hjälpämnen med rätt egenskaper som matchar de hos den aktiva substansen, för att ge tabletten önskade funktionella egenskaper. Att förstå vilka egenskaper som är avgörande för komprimeringsbeteendet stimuleras också av det pågående Process Analytical Technology (PAT) initiativet från regulatoriska myndigheter som syftar till att öka förståelsen och kontrollen av olika tillverkningsprocesser för att få en effektivare och säkrare tillverkning med högre produkt tillförlitlighet.

Ett sätt att öka förståelsen för olika processer är att genom modeller försöka beskriva förloppet på ett så enkelt men ändå så korrekt sätt som möjligt. Inom farmaceutiska vetenskaper används modeller som beskriver komprime-

ring av pulver i form av relationen mellan pulvermassans volym och det pålaga trycket för att skapa en matematisk representation av processen. Det finns ett stort antal modeller som kan användas för att behandla experimentella data och få fram komprimeringsparametrar som deskriptorer på olika funktionella egenskaperna hos pulvret. Eftersom komprimering av farmaceutiska pulver är en så komplex process är ofta tolkningen av dessa parametrar oklar. Det finns därför ett behov av att utvärdera och utveckla befintliga metoder för att bestämma tillverkningsegenskaperna hos ett pulver.

Avhandlingen speglar därför ambitionen att utveckla materialsnåla metoder för karakterisering av tekniska egenskaper hos fasta material som är kritiska för det färdiga preparatets egenskaper. Komprimeringsdata för olika pulverformiga modellsystem (både täta och porösa partiklar) analyserades med hjälp av olika globala komprimeringsmodeller and betydelsen av olika parametrar utvärderades.

Resultaten visar att det genom komprimeringsanalys går att bestämma formbarheten hos partiklar, vilken har visats sig vara kritiskt för utvecklandet av tabletthållfastheten. Vidare visas att täta partiklars fragmentering i form av dimensionsförändring också kan bedömas utifrån en komprimeringsanalys. Detta gör det möjligt att med ett enda test bestämma både partiklarnas fragmenteringsbenägenhet och deformation.

En förutsättning i bägge fallen var dock att betydelsen av partikelförflyttning under komprimeringsförloppet var liten och ett index för att bedöma denna aspekt har därför utvecklats. Utifrån detta föreslås också ett klassificeringssystem för pulvers komprimeringsegenskaper som kan underlätta tolkningen av globala komprimeringsparametrar.

Tillämpbarheten av komprimeringsanalys visas ytterligare dels genom att påvisa en direkt proportionalitet mellan porösa partiklars formbarhet och deras tablettbildande förmåga (kompakterbarhet) och dels genom att visa att töjningen hos en pulvermassa under komprimering korrelerar med hållfastheten hos tabletterna. Töjning är en processparameter med potentiell användning i adaptiva tablettprocesser.

Sammanfattningsvis så kan komprimeringsanalys användas för att ta fram parametrar som beskriver olika tekniska egenskaper hos pulverpartiklar, kritiska för deras kompakterbarhet och för tabletters mekaniska egenskaper.

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Josefina

References

1. http://en.wikipedia.org/wiki/Galen. 2008.
2. http://home.swipnet.se/PharmHist/Forelasn/index.html.
3. N. Alfrey, Oxford Dictionary of National Biography, 2004. http://dx.doi.org/10.1093/ref:odnb/3471.
4. P.J. Denny, Compaction equations: a comparison of the Heckel and Kawakita equations. Powder Technology, 2002. 127(2): p. 162-172.
5. http://www.fda.gov/Cder/guidance/5815dft.htm, 2007.
6. http://www.fda.gov/cder/OPS/PAT.htm.
7. H. Leuenberger, The compressibility and compactibility of powder systems. International Journal of Pharmaceutics, 1982. 12(1): p. 41-55.
8. M. Duberg and C. Nyström, Studies on direct compression of tablets XVII. Porosity--pressure curves for the characterization of volume reduction mechanisms in powder compression. Powder Technology, 1986. 46(1): p. 67-75.
9. C. Sun and D.J.W. Grant, Influence of elastic deformation of particles on Heckel analysis. Pharmaceutical Development and Technology, 2001. 6: p. 193-200.
10. J. van der Zwan and C.A.M. Siskens, The compaction and mechanical properties of agglomerated materials. Powder Technology, 1982. 33(1): p. 43-54.
11. F. Nicklasson and G. Alderborn, Modulation of the tabletting behaviour of microcrystalline cellulose pellets by the incorporation of polyethylene glycol. European Journal of Pharmaceutical Sciences, 1999. 9(1): p. 57-65.
12. E.E. Walker, The Properties of Powders. Part VI. The Compressibility of Powders. Trans. Faraday Soc., 1923. 19: p. 73-82.
13. A. Hassanpour and M. Ghadiri, Distinct element analysis and experimental evaluation of the Heckel analysis of bulk powder compression. Powder Technology, 2004. 141(3): p. 251.
14. R.W. Heckel, Density-pressure relationships in powder compaction. Trans.-Metall. Soc. AIME, 1961. 221: p. 671-675.
15. M.S. Kadiri, et al., Pharmaceutical powders compaction: Experimental and numerical analysis of the density distribution. Powder Technology, 2005. 157(1-3): p. 176.
16. R. Ramberger and A. Burger, On the application of the Heckel and Kawakita equations to powder compaction. Powder Technology, 1985. 43(1): p. 1-9.

17. J.M. Sonnergaard, Investigation of a new mathematical model for compression of pharmaceutical powders. European Journal of Pharmaceutical Sciences, 2001. 14(2): p. 149-157.
18. C.Y. Wu, et al., Modelling the mechanical behaviour of pharmaceutical powders during compaction. Powder Technology, 2005. 152(1-3): p. 107.
19. K. Kawakita and K.-H. Lüdde, Some considerations on powder compression. Powder Technology, 1970. 4: p. 61-68.
20. M.J. Adams and R. McKeown, Micromechanical analyses of the pressure-volume relationship for powders under confined uniaxial compression. Powder Technology, 1996. 88(2): p. 155-163.
21. P. Paronon and J. Ilkka, Porosity-Pressure Functions. in Pharmaceutical Powder Compaction Technology, Eds. Alderborn G. and Nyström C., Marcel Dekker, New York, 1996: p. 55-77.
22. I. Shapiro, PhD Thesis, University of Minnesota, 1944.
23. K. Konopicky, Radex Rundsch, 1948: p. 141.
24. B. Johansson, et al., Compression behaviour and compactability of microcrystalline cellulose pellets in relationship to their pore structure and mechanical properties. International Journal of Pharmaceutics, 1995. 117(1): p. 57-73.
25. M. Wikberg and G. Alderborn, Compression characteristics of granulated materials II. Evaluation of granule fragmentation during compression by tablet permeability and porosity measurements. International Journal of Pharmaceutics, 1990. 62(2-3): p. 229-241.
26. M. Duberg and C. Nyström, Studies on direct compression of tablets VI. Evaluation of methods for the estimation of particle fragmentation during compaction. Acta Pharm. Suec., 1982. 19(6): p. 421-436.
27. W.C. Duncan-Hewitt and G.C. Weatherly, Modeling the uniaxial compaction of pharmaceutical powders using the mechanical properties of single crystals. II: Brittle materials. Journal of Pharmaceutical Sciences, 1990. 79(3): p. 273-278.
28. J.M. Sonnergaard, A critical evaluation of the Heckel equation. International Journal of Pharmaceutics, 1999. 193(1): p. 63-71.
29. P. York, Consideration of Experimental-Variables in the Analysis of Powder Compaction Behavior. Journal of Pharmacy and Pharmacology, 1979. 31(4): p. 244-246.
30. F. Kiekens, et al., Influence of the punch diameter and curvature on the yield pressure of MCC-compacts during Heckel analysis. European Journal of Pharmaceutical Sciences, 2004. 22(2-3): p. 117-126.
31. K.M. Picker, A new theoretical model to characterize the densification behavior of tableting materials. European Journal of Pharmaceutics and Biopharmaceutics, 2000. 49(3): p. 267-273.
32. K.M. Picker, The 3D Model: Explaining Densification and Deformation Mechanisms by Using 3D Parameter Plots. Drug Development and Industrial Pharmacy, 2004. 30(4): p. 413 - 425.

33. K.M. Picker-Freyer, The 3-D model: Experimental testing of the parameters d, e, and omega and validation of the analysis. Journal of Pharmaceutical Sciences, 2007. 96(5): p. 1408-1417.
34. J.M. Sonnergaard, Impact of particle density and initial volume on mathematical compression models. European Journal of Pharmaceutical Sciences, 2000. 11(4): p. 307-315.
35. B. Johansson and G. Alderborn, Degree of pellet deformation during compaction and its relationship to the tensile strength of tablets formed of microcrystalline cellulose pellets. International Journal of Pharmaceutics, 1996. 132(1-2): p. 207-220.
36. R.J. Oates and A.G. Mitchell, Calculation of punch displacement and work of powder compaction on a rotary tablet press. J.Pharm.Pharmacol., 1989. 41: p. 517-523.
37. K. Kawakita and K.-H. Ludde, Some considerations on powder compression equations. Powder Technology, 1971. 4(2): p. 61-68.
38. M. Yamashiro, et al., An experimental study on the relationships between compressibility, fluidity and cohesion of powder solids at small tapping numbers. Powder Technology, 1983. 34(2): p. 225-231.
39. A.B. Yu and J.S. Hall, Packing of fine powders subjected to tapping. Powder Technology, 1994. 78(3): p. 247-256.
40. G. Alderborn, A novel approach to derive a compression parameter indicating effective particle deformability. Pharma. Dev. Technol. , 2003. 8: p. 367-377.
41. M. Wikberg and G. Alderborn, Compression characteristics of granulated materials. III. The relationship between air permeability and mechanical strength of tablets of some lactose granulations. International Journal of Pharmaceutics, 1990. 63(1): p. 23-27.
42. J.T. Carstensen and X.-P. Hou, The Athy--Heckel equation applied to granular agglomerates of basic tricalcium phosphate [3Ca3PO4)2Ca(OH)2]. Powder Technology, 1985. 42(2): p. 153-157.
43. F. Nicklasson and G. Alderborn, Analysis of the compression mechanics of pharmaceutical agglomerates of different porosity and composition using the Adams and Kawakita equations. Pharmaceutical Research, 2000. 17(8): p. 949-954.
44. S.F. Yap, et al., Single and bulk compression of pharmaceutical excipients: Evaluation of mechanical properties. Powder Technology, 2008. 185(1): p. 1-10.
45. M.J. Adams, et al., Agglomerate strength measurement using a uniaxial confined compression test. Powder Technology, 1994. 78(1): p. 5-13.
46. J.T. Fell, Compaction properties of binary mixtures. In Alderborn, G. and Nyström, C. (Eds.), Pharmaceutical powder compaction technology. Marcel Dekker Inc, New York, 1996. Ch. 15.

47. A. Tunon and G. Alderborn, Granule deformation and densification during compression of binary mixtures of granules. International Journal of Pharmaceutics, 2001. 222(1): p. 65-76.
48. A. Tunon, et al., Drug release from reservoir pellets compacted with some excipients of different physical properties. European Journal of Pharmaceutical Sciences, 2003. 20(4-5): p. 469-479.
49. C.M. Ramaswamy, et al., Compaction of mixtures of materials. The Chemical Engineering Journal, 1970. 1(2): p. 168-171.
50. P.M. Belda and J.B. Mielck, The difficulty in the assessment of the compression behaviour of powder mixtures: Double layer tablets versus arithmetic additivity rule. European Journal of Pharmaceutics and Biopharmaceutics, 2005. 60(1): p. 133.
51. H. Vromans and C.F. Lerk, Densification properties and compactibility of mixtures of pharmaceutical excipients with and without magnesium stearate. International Journal of Pharmaceutics, 1988. 46(3): p. 183-192.
52. J. Ilkka and P. Paronen, Prediction of the compression behaviour of powder mixtures by the Heckel equation. International Journal of Pharmaceutics, 1993. 94(1-3): p. 181-187.
53. J.M. Newton, et al., A method of evaluating the mechanical characteristics of powders from the determination of the strength of compacts. Powder Technology, 1992. 72(1): p. 97-99.
54. J.T. Fell and J.M. Newton, Determination of tablet strength by diametral compression test. J. Pharm. Sci., 1970. 59: p. 688-691.
55. C. Nystrom, et al., Bonding Surface-Area and Bonding Mechanism - 2 Important Factors for the Understanding of Powder Compactibility. Drug Development and Industrial Pharmacy, 1993. 19(17-18): p. 2143-2196.
56. G. Alderborn and C. Nyström, Studies on direct compression of tablets XIV. The effect of powder fineness on the relation between tablet permeametry surface area and compaction pressure. Powder Technology, 1985. 44(1): p. 37-42.
57. C. Sun and D.J.W. Grant, Effects of initial particle size on the tableting properties of -lysine monohydrochloride dihydrate powder. International Journal of Pharmaceutics, 2001. 215(1-2): p. 221-228.
58. L.W. Wong and N. Pilpel, The effect of particle shape on the mechanical properties of powders. International Journal of Pharmaceutics, 1990. 59(2): p. 145-154.
59. G. Alderborn, et al., Compression characteristics of granulated materials. I. Fragmentation propensity and compactibility of some granulations of a high dosage drug. International Journal of Pharmaceutics, 1987. 37(1-2): p. 155-161.
60. M. Wikberg and G. Alderborn, Compression characteristics of granulated materials. IV. The effect of granule porosity on the fragmentation propensity and the compatibility of some granulations. International Journal of Pharmaceutics, 1991. 69(3): p. 239-253.

61. B. Johansson, et al., Effect of pellet size on degree of deformation and densification during compression and on compactability of microcrystalline cellulose pellets. International Journal of Pharmaceutics, 1998. 163(1-2): p. 35-48.
62. B. Johansson and G. Alderborn, The effect of shape and porosity on the compression behaviour and tablet forming ability of granular materials formed from microcrystalline cellulose. European Journal of Pharmaceutics and Biopharmaceutics, 2001. 52(3): p. 347-357.
63. I.J. Hardy and W.G. Cook, Predictive and correlative techniques for design, optimisation and manufacture of solid dosage forms. J. Pharm.Pharmacol. , 2003. 55: p. 3-18.
64. S. Jain, Mechanical properties of powders for compaction and tableting: an overview. Pharmaceutical Science & Technology Today, 1999. 2(1): p. 20-31.
65. R.J. Roberts and R.C. Rowe, The compaction of pharmaceutical and other model materials - a pragmatic approach. Chemical Engineering Science, 1987. 42(4): p. 903-911.
66. R.J. Roberts, et al., The relationship between the fracture properties, tensile strength and critical stress intensity factor of organic solids and their molecular structure. International Journal of Pharmaceutics, 1995. 125(1): p. 157-162.
67. G. Alderborn and C. Nyström, Studies on direct compression of tablet IV: The effect of particle size on the mechanical strength of tablets. Acta Pharm. Suec. , 1982. 19(5): p. 381-390.
68. K. Zuurman, et al., The relationship between bulk density and compactibility of lactose granulations. International Journal of Pharmaceutics, 1994. 102(1-3): p. 1-9.
69. F. Nicklasson, et al., Tabletting behaviour of pellets of a series of porosities--a comparison between pellets of two different compositions. European Journal of Pharmaceutical Sciences, 1999. 8(1): p. 11-17.
70. R.C. Rowe and R.J. Roberts, Mechanical Properties. Pharmaceutical Powder Compaction Technology, Eds. Alderborn G. and Nyström C., Maqrcel Dekker, New York, 1996: p. 283-323.
71. D.M. Kremer and B.C. Hancock, Process simulation in the pharmaceutical industry: A review of some basic physical models. Journal of Pharmaceutical Sciences, 2006. 95(3): p. 517-529.
72. R.W. Lewis, et al., A combined finite-discrete element method for simulating pharmaceutical powder tableting. International Journal for Numerical Methods in Engineering, 2005. 62(7): p. 853-869.
73. G. Frenning, Analysis of pharmaceutical powder compaction using multiplicative hyperelasto-plastic theory. Powder Technology, 2007. 172(2): p. 103-112.
74. O. Skrinjar and P.-L. Larsson, On discrete element modelling of compaction of powders with size ratio. Computational Materials Science, 2004. 31(1-2): p. 131-146.

75. D.L. Vanderhart and R.H. Atalla, Studies of Microstructure in Native Celluloses Using Solid-State C-13 Nmr. Macromolecules, 1984. 17(8): p. 1465-1472.
76. European Pharmacopoeia 6th Edition 2008 (6.0).
77. G.K. Bolhuis and Z.T. Chowhan, Materials for direct compression. In Alderborn, G. and Nyström, C. (Eds.), Pharmaceutical powder compaction technology. Marcel Dekker Inc, New York, 1996.
78. R.C. Rowe, et al., 2006. Handbook of Pharmaceutical Excipients 5th ed.Pharmaceutical Press.
79. J. Berggren and G. Alderborn, Drying behaviour of two sets of microcrystalline cellulose pellets. International Journal of Pharmaceutics, 2001. 219(1-2): p. 113-126.
80. M. Eriksson, et al., The use of air permeametry for the assessment of external surface area and sphericity of pelletized granules. International Journal of Pharmaceutics, 1993. 99(2-3): p. 197-207.
81. G. Alderborn, et al., Studies on direct compression of tablets X. Measurement of tablet surface area by permeametry. Powder Technology, 1985. 41(1): p. 49-56.
82. G. Alderborn and C. Nyström, Studies on Direct Compression of Tablets III. The effect in tablet strength of changes in particle-shape and texture obtained by milling. Acta Pharm. Suec., 1982. 19(2): p. 147-156.
83. Cox, A method of assessing numerical and percentage values to the degree of roundness of sand grains. J. Paleontol, 1927. 1: p. 179-183.
84. E. Jerwanska, et al., Effect of water content on tensile fracture force and deformability of ram extruded cylinders. International Journal of Pharmaceutics, 1997. 149(1): p. 131-136.
85. H.H. Hausner, Friction conditions in a mass of metal powder. Int. J. Powder Metall., 1967. 3(4): p. 7-13.
86. C. Thornton and Z. Ning, A theoretical model for the stick/bounce behaviour of adhesive, elastic-plastic spheres. Powder Technology, 1998. 99(2): p. 154-162.
87. A. Samimi, et al., Single and bulk compressions of soft granules: Experimental study and DEM evaluation. Chemical Engineering Science, 2005. 60: p. 3993-4004.
88. W.A. Strickland, et al., The Physics of Tablet Compression .9. Fundamental Aspects of Tablet Lubrication. Journal of the American Pharmaceutical Association, 1956. 45(1): p. 51-55.
89. K.D. Ertel and J.T. Carstensen, An examination of the physical properties of pure magnesium stearate. International Journal of Pharmaceutics, 1988. 42(1-3): p. 171-180.
90. I. Shapiro, Compaction of powders 11. Application of the general equation to both metal powders and ceramic powders. Advances in powder metallury and particulate materials., 1994. 3: p. 41-55.
91. G. Alderborn, et al., Studies on direct compression of tablets. XL Characterization of particle fragmentation during compaction by

permeametry measurements of tablets. International Journal of Pharmaceutics, 1985. 23(1): p. 79-86.
92. M. Eriksson, et al., Evaluation of a permeametry technique for surface area measurements of coarse particulate materials. International Journal of Pharmaceutics, 1990. 63(3): p. 189-199.
93. M. Eriksson and G. Alderborn, The effect of original particle size and tablet porosity on the increase in tensile strength during storage of sodium chloride tablets in a dry atmosphere. International Journal of Pharmaceutics, 1995. 113(2): p. 199-207.
94. R.J. Roberts and R.C. Rowe, Brittle/ductile behaviour in pharmaceutical materials used in tabletting. International Journal of Pharmaceutics, 1987. 36(2-3): p. 205-209.
95. C.S. Chang, et al., Micromechanical Modeling of Cemented Sands under Low Amplitude Oscillations. Geotechnique, 1990. 40(2): p. 251-263.
96. F. Trentadue, A micromechanical model for a non-linear elastic granular material based on local equilibrium conditions. International Journal of Solids and Structures, 2001. 38(40-41): p. 7319-7342.
97. S. Debbas and H. Rumpf, On the randomness of beds packed with spheres or irregular shaped particles. Chemical Engineering Science, 1966. 21(6-7): p. 583-608.
98. R.L. Carr, Evaluating flow properties of solids. Chem. Eng. , 1965. 72: p. 163-168.
99. European Pharmacopoeia Supplement 5.08 2006. 2.9.36: p. 3363-3366.
100. S. Mattsson, et al., Evaluation of Critical Binder Properties Affecting the Compactibility of Binary Mixtures. Drug Development and Industrial Pharmacy, 2001. 27(3): p. 181 - 194.
101. R.J. Roberts, et al., Brittle--ductile trasitions in die compaction of sodium chloride. Chemical Engineering Science, 1989. 44(8): p. 1647-1651.
102. L. Maganti and M. Celik, Compaction studies on pellets I. Uncoated pellets. International Journal of Pharmaceutics, 1993. 95(1-3): p. 29-42.
103. H. Santos, et al., Compaction, compression and drug release properties of diclofenac sodium and ibuprofen pellets comprising xanthan gum as a sustained release agent. International Journal of Pharmaceutics, 2005. 295(1-2): p. 15-27.
104. H. Leuenberger and L. Ineichen, Percolation theory and physics of compression. European Journal of Pharmaceutics and Biopharmaceutics, 1997. 44(3): p. 269-272.
105. E. Ryskewitch, Compression strength of porous sintered alumina and zirconia. J.Am.Ceram.Soc. , 1953. 36: p. 65-68.
106. W.H. Duckworth, Discussion of Ryshkewitch paper by Winston Duckworth. J. Am. Ceram. Soc., 1953. 36: p. 68.

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