Identification and Variation of some Functionality Related Characteristics of Pharmaceutically Relevant Solid Materials and their Effect on Product Performance

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Abstract

The aim of this thesis was to identify some functionality related characteristics of pharmaceutically relevant solid materials and to study the effect of their variation on processing behaviour and product performance. For this purpose, particles with different characteristics were prepared under a variety of conditions by crystal agglomeration, wet granulation and spray drying. The effect of particle size distribution on the evolution of the tablet microstructure during and after compression was investigated. The compression behaviour of particles with different nominal strength and degrees of agglomeration was studied and the influence of the surfactant concentration of amorphous particles on the compression behaviour was examined. The response of the powders to compression was described with the help of various techniques characterising the microstructure and tensile strength of the tablets produced.

Furthermore, a method suitable for observing drug release from single matrix granules was developed and used to study the effect of granule porosity and compaction pressure on the drug release process.

The particle size distribution did not influence the evolution of the tablet porosity or the tensile strength during compression, but it could have an effect on the evolution of the tablet microstructure during short-term storage, depending on the instability mechanism. The compression behaviour of particles prepared by crystal agglomeration and wet granulation was dependent on their degree of agglomeration and their failure strength. For particles with similar solid state properties and compression behaviour, the surface energy appears to have an effect on the bonding strength of adsorption bonds acting at particulate junctions. Using the method developed to observe the drug release from single matrix granules, reproducible data was obtained enabling the drug release process to be characterised. Depending on the type of matrix and the compaction pressure, the drug release rate could be enhanced or retarded.

Keywords: Particle size distribution, Degree of agglomeration, Amorphous lactose, Matrix agglomerates, Drug release, Compactability, Tablet tensile strength, Particle fracture strength, Surfactant, Compression

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This thesis is based on the following papers, which are referred to in the text by the Roman numerals assigned below:


III Fichtner, F., Welch, K., and Alderborn, G., Effect of surfactant concentration on the compactability of amorphous lactose particles. In manuscript.


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My contribution to the above papers was as follows:
I  Involved in all parts
II Not involved in the determination of the degree of agglomeration
III Involved in all parts
IV Not involved in the theoretical data analysis
V  Involved in all parts
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Abbreviations

\( A \) cross-sectional area of the compact
\( A \) agglomerate
ANOVA analysis of variance
\( A_p \) particle projected area
\( a \) compression parameter
\( a_m \) cross-sectional area of the manometer arm
\( AR \) particle aspect ratio
\( \frac{1}{b} \) compression parameter
\( °C \) degrees Celsius
\( C \) degree of compression
\( C/A \) crystals per agglomerate
\( C_{at\, pressure} \) degree of compression at 300 MPa
\( cm \) centimetre
\( C_p \) particle circularity
\( C_{remaining} \) degree of compression as the upper punch detaches from the powder bed
\( C_s \) drug solubility in the dissolution medium
\( \epsilon_s \) drug solubility in pellet
\( D \) tablet diameter
\( D_{eff} \) effective diffusion coefficient
DSC differential scanning calorimetry
\( d_F \) Feret diameter
\( d_p \) diameter of a circle of equivalent area
\( ER \) elastic recovery
\( F \) force needed to cause particle breakage
FDA food and drug administration
\( FF \) particle form factor
\( F_t \) compression force needed to fracture a tablet
\( G \) granule
\( g \) standard acceleration of gravity
\( g \) gramme
Hz Hertz
\( h_1 \)  
stop point an the manometer arm

\( h_2 \)
start point on the manometer arm

\( h_{2N} \)
tablet height at 2N after compaction

\( h_{\text{at, pressure}} \)
tablet height at maximum pressure

\( h_t \) 
tablet height

\( k \) 
kilo

\( L \) 
height of the compact

MPa mega Pascal

MCC microcrystalline cellulose

MDT mean dissolution time

m metre

mg milligramme

min minute

ml millilitre

mm millimetre

N Newton

NaCl sodium chloride

kN kilo Newton

P pressure

PAT process analytical technology

\( P_c \) 
permeability coefficient

\( P_p \) 
particle perimeter length

\( P_y \) 
yield pressure

r particle radius

RD relative dispersion coefficient

rpm revolutions per minute

RH relative humidity

s second

\( S_0 \) 
initial concentration of solid drug in the pellet

SA salicylic acid

SEM scanning electron microscopy

T random variable

t time interval over which airflow is maintained

V volume at applied pressure \( P \)

V Volt

\( V_0 \) 
initial volume

VDT variation of dissolution time

\( \Omega \) 
Ohm

w tablet weight

\( \delta \) 
density of the manometer liquid

\( \varepsilon \) 
porosity

\( \varepsilon_p \) 
pellet porosity
<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>$\varepsilon_t$</td>
<td>tablet porosity</td>
</tr>
<tr>
<td>$\mu g$</td>
<td>microgramme</td>
</tr>
<tr>
<td>$\mu m$</td>
<td>micrometer</td>
</tr>
<tr>
<td>$\kappa$</td>
<td>dissolution rate constant</td>
</tr>
<tr>
<td>$\rho_{300 \text{ MPa}}$</td>
<td>density of the powder bed at 300 MPa</td>
</tr>
<tr>
<td>$\rho_{app}$</td>
<td>apparent particle density</td>
</tr>
<tr>
<td>$\rho_{bulk}$</td>
<td>bulk density</td>
</tr>
<tr>
<td>$\sigma_N$</td>
<td>nominal particle fracture strength</td>
</tr>
<tr>
<td>$\sigma_t$</td>
<td>tablet tensile strength</td>
</tr>
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Introduction

Recent and ongoing trends in the pharmaceutical research have been focused on gaining knowledge on the effect that the properties of raw materials have on the behaviour of the materials during the production process and how they eventually influence the product. In the pharmaceutical industry attempts are made to guarantee the quality of the product by controlling the production process. Process Analytical Technology (PAT) is a term often mentioned in this context. The Food and Drug Administration (FDA) has defined PAT as a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality. However, if PAT is to be applied to a production process, it is necessary that the process is well understood. Any possible variation that could be critical in the production process needs to be identified and their respective influence on the product needs to be explained.

Pharmaceutical excipients need to meet the pharmacopoeial specifications, which define the physical and chemical limits. Conformance to pharmacopoeial specifications proves identity and purity, but it does not provide any sufficient information about the functionality related characteristics of the excipient that affect the behaviour of the material during processing and the performance of the product. The term functionality related characteristic is defined as a controllable physical or chemical characteristic of an excipient that is shown to impact on its functionality, but in itself is without any associated health risk (Pharmeuropa, 2006). Ongoing attempts to extend the pharmacopoeial specifications to functionality related characteristics leads to the following questions being raised: Which are the functionality related characteristics of a material? How does their variation affect the product performance? Many pharmaceutical excipients are used for a number of different purposes, and can thus be described as multifunctional. The functionality of a polymer, for example, depends on whether it is used for film coating, as a binder or as a matrix tablet.
In the production of solid dosage forms, in particular, batch to batch variation may strongly influence the particle behaviour during processing and the performance of the product. Some literature exists concerning different particle preparation methods and how variations in processing conditions will affect the particles produced. For some materials, data showing the correlation between selected particle properties and product performance have been published, however, the successful application of a PAT or another ‘quality by design’ environment on the production of solid dosage forms, needs the key functionality related characteristics to have been identified and the impact of their variation to have been understood. It is obvious that there is a need to increase the existing knowledge about which characteristics of a material are functionality related and how their variation affects the production process and the final product.
Preparation of particles by crystallisation

Crystallisation is surely amongst the oldest operations in chemical engineering science. It is a cheap method by which to purify solid material, and the great number of variable process parameters provides the scientist with powerful tools with which to control the physical and mechanical properties of the particles produced. For the preparation of pharmaceutical and fine chemical powders, several different methods are used. Precipitation is a popular laboratory technique and often referred to as fast crystallisation. It requires a high initial supersaturation, that results in fast nucleation and the formation of a large number of small crystals. In melt crystallisation, substance separation and purification occurs owing to the different melting points of the materials. In its industrial application, crystallisation by sublimation involves the vaporisation and condensation of a solid (Mullin, 2001). The method used in this thesis is crystallisation from a solution, which is applicable to those substances whose solubility is reduced significantly with decreasing solvent temperature.

Preparation of particles by controlled cooling of a solution

For crystallisation from a solution to be possible, supersaturation is an essential requirement. A supersaturated solution is obtained by slowly cooling a saturated one. The crystallisation process can be divided into several steps: nucleation, crystal growth, agglomeration, breakage, and ageing. Nucleation can occur spontaneously or may be initiated by vibration or agitation. It involves the formation of minute solid bodies that act as centres for crystallisation. The nuclei grow to form visible crystals and the growth rate of the different crystallographic faces determines the crystal morphology. In addition to the crystallisation conditions, the crystal structure and the defects contained control the growth rate of the faces. Agglomeration can occur when small crystals collide and form bonds that resist breakage when subject to
collision with, for example, the equipment, or with other particles. During ageing, the number of crystals is reduced because small crystals dissolve in support of larger ones, a process referred to as Ostwald ripening.

Through intentional variation of the process conditions it is possible to control the crystallisation product. Agitation, for example, influences the final particle size distribution and results in smaller, more uniform crystals of higher purity because less mother liquor is retained. The cooling rate controls the rate of nucleation, such that rapid cooling results in a larger number of nuclei being produced and, thus, a larger number of smaller crystals being produced. The addition of impurities and the solvent used can both act as habit modifiers and influence the degree of agglomeration. These possibilities to induce variation or combinations of them are commonly used in industrial crystallisation processes to influence the material produced (Mullin, 2001).
Particle size enlargement by granulation

Wet granulation

Wet granulation is a size enlargement operation often also referred to as agglomeration or pelletisation. During the wet granulation process, a granulation liquid is sprayed onto agitated particles to transfer the smaller primary particles into larger secondary ones, which are referred to as granules or agglomerates. In a wide range of industrial sectors, e.g. the processing of agricultural products, foodstuffs, feeding stuff, pharmaceuticals, and fine chemicals, particle aggregation is the key step to achieving a powder with desired properties. Some of the properties that are desirable for powders from a pharmaceutical perspective are improved flow and handling, reduced dustiness, improved compactability, the prevention of powder segregation during handling, improved dispersion and dissolution properties, and an improved powder appearance (Iveson, et al., 2001).

The granulation process is commonly divided into three steps: wetting and nucleation, consolidation and growth, and breakage and attrition (Ennis and Litster, 1997, Tardos, et al., 1997). During the wetting and nucleation step, the granulation liquid is distributed through the dry powder and nuclei granules are formed. Collision between granules and between granules and equipment leads to granule consolidation and growth. If a critical granule size is attained, attrition and breakage occurs due to impact (Iveson, et al., 2001).

The formation of bonds of a sufficient strength between the primary particles is essential for successful granulation. It has been suggested that there are five bonding mechanisms involved in granulation as follows (Rumpf, 1958): (1) The formation of solid bridges owing to crystallisation after the evaporation of solvent, (2) mobile liquid bridges attributable to capillary forces and surface tension, (3) adhesion and cohesion forces between immobile liquid films on the surface of the particles caused by a high viscosity granulation liquid or hydrogen bonds between adsorbed water layers, (4) attraction forces be-
tween particles owing to intermolecular forces known as van der Waals forces, and (5) mechanical interlocking arising from irregular particle shape and surface roughness.

It is possible to influence the properties of the granules by choosing a reasonable combination of the raw material quality, which involves the particle size and size distribution of the feed powder as well as the type and viscosity of the granulation liquid, and the process design which includes the type of granulator and operation parameters. It has been shown that the type (Johansson, et al., 1995, Millili and Schwartz, 1990, Wikberg and Alderborn, 1991) and amount (Ganderton and Hunter, 1971, Jaegerskou, et al., 1984, Mehta, et al., 2000) of granulation liquid used during the wet granulation process may affect the porosity and the pore structure of the granules. In the pharmaceutical industry, water and alcohols, or their blends are the most common granulation liquids, to which a polymeric binder is often added.

The most common granulators used in the pharmaceutical industry are low and high shear mixers, and fluidized bed granulators. In general granules processed using a fluidized bed granulator are of higher porosity, lower bulk density and better compressibility than granules from a high shear mixer (Gao, et al., 2002, Ragnarsson and Sjögren, 1982).

Pelletisation by extrusion and spheronisation

Spheronisation and extrusion can be used after wet granulation to obtain spherical granules, which often are referred to as pellets. There are four stages involved in pellet preparation: (1) Granulation, (2) extrusion, which shapes the wet mass into cylinders, (3) spheronisation, which refers to the rounding of the cylindrical particles into spheres and (4) drying of the pellets. According to Vervaet et. al (Vervaet, et al., 1995), this process was reported first by Reynolds (Reynolds, 1970) and Conine and Hadley (Conine and Hadley, 1970). The properties of the pellets obtained can be related to the formulation composition (Sousa, et al., 2002), the processing conditions (Alvarez, et al., 2002, Chopra, et al., 2001, Sousa, et al., 1996) and the equipment used (Berggren, et al., 2004, Pinto, et al., 2001). Because of their spherical shape, pellets have excellent flow properties and low friability. Their particle size distribution is narrow and coating is easy (Reynolds, 1970). In the pharmaceutical industry pellets are commonly used to
prepare multiple unit dosage forms by filling them into hard gelatine capsules or compacting them into tablets (Conine and Hadley, 1970, Millili and Schwartz, 1990). Coated pellets have applications in controlled drug release formulations, controlling the drug release by variation in thickness and composition of the coating (Akhgari, et al., 2006, Lundqvist, et al., 1998, Schultz and Kleinebudde, 1997, Schultz, et al., 1997). Pelletisation needs materials that meet the requirements of the pelletisation procedure. For the extrusion process, this is the ability to form a cohesive homogenous mass, and for the spheronisation process, this is a balance between plasticity and brittleness of the wet mass. Microcrystalline cellulose is widely used as a pelletisation aid because of its ideal rheological behaviour as a wet mass. The high internal porosity and the large surface area provide microcrystalline cellulose with good moisture retaining properties, making it suitable for pelletisation (Chatlapalli and Rohera, 1998). It has been shown that the porosity of pellets prepared with water or a mixture of water and ethanol increases as the proportion of ethanol rises (Chopra, et al., 2002, Johansson, et al., 1995).

As pellets of microcrystalline cellulose do not disintegrate, drug release is prolonged, so the formulation is inappropriate when fast drug release is required. Because of this, alternative materials are of great interest, but only a few studies can be found in the literature investigating the use of other materials as pelletisation aids. Chatlapalli reported that pellets with acceptable properties could be obtained using cellulose ethers (Chatlapalli and Rohera, 1998), whereas (Almeida Prieto, et al., 2005) used starch as the principal excipient. Tho et al., introduced pectinic acid as a pelletisation aid (Tho, et al., 2002b) and optimised the process conditions (Tho, et al., 2002a, Tho, et al., 2003). And finally, κ-carrageenan was found to be a possible substitute for microcrystalline cellulose (Bornhöft, et al., 2005).

Preparation of particles by spray drying

Spray drying is a commonly used particle preparation technique with a wide range of areas in which it can be applied, such as the processing of foods (e.g., milk and eggs), ceramics, fertilisers, pharmaceuticals and chemicals. In a one step process, a solution or suspension is atomised into droplets and transferred into a fine powder by rapid evaporation of the solvate. The spray drying process can be divided into four stages (Broadhead, et al., 1992): (1) Atomisation of the feed into a
spray, (2) spray-air contact, (3) drying of the spray and (4) separation of the dried product from the drying gas. Generally spray driers consist of a feed delivery system, an atomiser, a heated air supply, a drying chamber, a solid-gas separator and a product collection system (Corrigan, 1995). Spray driers can be of a co-current design, which implies that the spray and the gas pass through the drying chamber in the same direction, or of a counter-current design, which means that the spray and the drying gas enter the drying chamber at opposite ends. The co-current design is preferred for the drying of heat sensitive materials as the dry product is only in contact with the coolest air. The atomisation process enables a large surface area to be in intimate contact with the drying gas, thereby allowing the droplets to dry in between less than 100 milliseconds to a few seconds through fast mass and heat transfer (Johnson, 1997). Evaporation cooling keeps the temperature of the solid low and, thus, makes the technique suitable for heat-sensitive materials. The short drying time hampers the formation of ordered crystal lattices and promotes the production of amorphous materials (Corrigan, 1995). Particles obtained by spray drying are often hollow spheres, but may also have convoluted surfaces, asperities, holes or voids (Johnson, 1997). Factors determining the shape of spray dried particles include the drying rate, and the liquid’s surface tension and viscosity (Alexander and King, 1985). Furthermore, variation in spray drying conditions makes it possible to control the particle size distribution, the bulk and particle density, the flowability and the moisture content of the product (Broadhead, et al., 1992, Corrigan, 1995). The large surface area and the high porosity enhance the solubility and dissolution rate of the spray dried particles and the spherical shape improves the powder flowability, which improves the processability of powders.

The spray drying process has found applications in a number of pharmaceutical areas and can be used for microencapsulation of antibiotics intended for parenteral (Bittner, et al., 1999), respiratory (O'Hara and Hickey, 2000) and ocular (Gavini, et al., 2004) drug delivery, and the production of sustained release formulations of vitamins (Esposito, et al., 2002, Shi and Tan, 2002) and analgesics (Rattes and Oliveira, 2007). Furthermore, protein formulations for inhalation (Niven, et al., 1994) can be produced successfully by spray drying. When producing tablets, spray dried excipients often have the advantage of good flowability and better compactability than non-spray dried ones (Broadhead, et al., 1992). Spray dried lactose, which is suitable for direct compaction because of its high propensity to deformation, is
probably the most well-established spray dried material in the pharmaceutical area (Gunsel and Lachman, 1963).
The influence of particle and powder properties on the mechanical properties of tablets

Crystal morphology

Many substances used in the pharmaceutical industry are known for their ability to crystallise into several polymorphic forms or to form amorphous solids. Polymorphs are crystalline solids that are equal in their chemical composition, but different in their crystal lattices. Their physical and mechanical properties, such as their melting point, solubility, density, hygroscopicity, brittleness, and plasticity vary from one material to the next. These variations can affect the processability as well as the physical stability and the bioavailability of the substance. Owing to differences in their physical properties, thermo analysis and X-ray diffraction can be used to distinguish between them. Paracetamol, for example, exists in at least three polymorphic forms, of which two are stable ones and one is unstable (Martino, et al., 1997). Because of the difficult and laborious preparation of orthorhombic paracetamol (Martino, et al., 1997), the monoclinic form is used for tablet manufacturing, although it is reported that the orthorhombic form shows better compactability and a reduced propensity to capping (Di Martino, et al., 1996, Etienne, et al., 1998).

Amorphous materials do not possess long-range order in the form of a crystal lattice, but they do exhibit short-range order over a few molecular dimensions (Hancock and Zografi, 1997). In the literature, these materials are also described as “disordered”, “non-crystalline”, or “glassy”. The physical and mechanical properties of amorphous materials differ from the properties of the respective crystalline forms (Hancock, et al., 2002). They are of lower density and often softer and less brittle. Their internal energy is higher than in the crystalline form and their greater molecular mobility makes them unstable and enables
crystallisation to occur. Amorphous or partly amorphous materials can, for example, be obtained by rapid precipitation from a solution, as occurs when spray drying (Corrigan, et al., 1984, Yonemochi, et al., 1999), by mechanical treatment such as milling (Elamin, et al., 1994a, Eriksson and Alderborn, 1995b, Yonemochi, et al., 1999) or compaction (Elamin, et al., 1994b, Eriksson and Alderborn, 1995b), or by the supercooling of a melt (Yoshioka, et al., 1994). Amorphous lactose is probably the most used amorphous material in the pharmaceutical area. Compared to crystalline lactose, amorphous lactose has improved compaction properties. Furthermore, the high deformability may increase the number of intermolecular bonding sites over the effective contact area (Sebhatu and Alderborn, 1999). It was observed that, in contrast to crystalline lactose, amorphous lactose showed an increased propensity to form solid bridges by particle fusion during compression (Sebhatu, et al., 1997). For lactose samples, varying in surface crystallinity, differences in surface energy were found (Ticehurst, et al., 1996). Variation in the surface energy may also explain the differences in the compactability of crystalline and amorphous lactose (Sebhatu and Alderborn, 1999). Furthermore, increasing the tablet tensile strength by increasing the proportion of amorphous lactose in the formulation was observed (Vromans, et al., 1987).

Particle size and shape

Particle size and shape can be influenced and controlled during processing through the choice of a suitable particle preparation method and variation in the processing conditions. In addition to which, mechanical treatment can be applied to modify the particle size and shape. Hence, it is not abstruse that there is a wide literature on the effect of particle size and shape on the mechanical properties of tablets.

It has been claimed that the initial particle size is an important factor for the compactability of a powder and thus for the mechanical strength of the tablet produced (Alderborn, et al., 1985, De Boer, et al., 1986, Elamin, et al., 1994b, Vromans, et al., 1987). For most materials, compaction of small particles results in stronger tablets than compaction of larger particles owing to the larger surface area available for bonding (Shotton and Ganderton, 1961, Sun and Grant, 2001). However, the initial particle size was found to have a very limited effect on tablet tensile strength in materials prone to fragmentation.
Increased tablet tensile strength with increased initial particle size was reported for sodium chloride and explained by the formation of strong bonds in the form of solid bridges (Elamin, et al., 1994b). When studying the effect of particle shape on tablet tensile strength, it was found that more irregular particles resulted in tablets of higher tensile strength. Moreover, the tablet tensile strength of plastically deforming materials was vitally affected by variation in the particle shape, while the strength of tablets made of materials prone to fragmentation was independent of the original particle shape. For plastically deforming materials, the increase in tablet tensile strength with increased particle irregularity was explained by the formation of a larger number of solid bridges as a result of the increased bonding surface area and the enhanced opportunity for interparticulate friction and plastic flow at the contact points (Elamin, et al., 1994b, Wong and Pilpel, 1990).

Nominal particle strength
Composite particles of powders intended for tablet processing need to be of sufficient compressibility at the same time as they need to be strong enough to prevent unwanted breaking during handling. The most common way to determine the fracture strength of a particle is to apply a load diametrically and measure the force needed to cause fracture (Ålander, et al., 2003). Correlations were found between the fracture strength measured on single particles and the compression behaviour of particles surrounded by neighbouring particles and die walls. For weak granules it was observed that the tablet tensile strength increased with increasing granule strength (Horisawa, et al., 1995). Furthermore, it was stated that harder granules were more difficult to deform. Similar correlations between granule strength and both compressibility and tablet strength had been found earlier (Danjo, et al., 1994).

Comparable results were obtained for pellets. The deformability of pellets made of microcrystalline cellulose could be related to their tensile and shear strength and was found to be reduced for stronger pellets (Bashaiwoldu, et al., 2004). Tablets produced from the weaker pellets were of higher tensile strength.
Surface texture and energy

As particles interact at surfaces, the nature of the particle surface is vital for controlling the particle interaction with other materials. Thus, knowledge about the particle surface is important if one is to understand particle behaviour during processing and the performance of the resulting product. Much research has been done to link particles’ surface properties, such as the surface energy and surface roughness, to the behaviour of the particles during processing and thus to optimise the processing conditions and predict the properties of the resulting product. Surface energy affects the tendency for cohesion and adhesion and therefore controls particle aggregation and deaggregation, as well as determining the extent of adherence to carrier particles (Chawla, et al., 1993) or delivery devices (Parsons, et al., 1982). If particles of roughly similar elasticity and plasticity are compacted, it is the adhesiveness of the particles that dominates the tablet strength (Katikaneni, et al., 1995). Additionally, it was found that an increase in particle roughness resulted in stronger tablets owing to the formation of a larger surface area for bonding and more particle interlocking (Karehill, et al., 1990b).

Degree of agglomeration

It was observed that the agglomeration propensity during crystallisation may be controlled through the selection of solvent composition (Granberg, et al., 1999). When characterising agglomerates, the degree of agglomeration reflecting the number of crystals per agglomerate can be used (Ålander, et al., 2003, Ålander, et al., 2004). Furthermore, work has been published addressing the properties of unagglomerated crystals and crystals agglomerated during crystallisation (Di Martino, et al., 2000, Rasenack and Müller, 2002). But there is a deficiency of literature investigating the correlation between the degree of agglomeration and the compressibility and compactability of particles.

Particle size distribution

The particle size distribution of a powder depends on the particle preparation method and on further particle processing. Through randomly controlled and slowly proceeding particle growth, processes such as crystal growth or the biological growth of starch usually result
in a particle size that is normally distributed. Asymmetric particle size
distributions with larger numbers of small particles are obtained by
fast, not undisturbed and directed particle preparation methods as
spray drying and precipitation.

The effect of the particle size distribution on the compression and
compaction behaviour and on the characteristics of the resulting tab-
lets is hardly addressed at all as a direct issue in the pharmaceutical
literature, but some studies do include this aspect in a supplementary
way. Different packing properties were observed for powders when
the particle size distribution was altered (Muñozruiz, et al., 1994). The
particle size distribution was found to may have an effect on the comp-
actability of granulated microcrystalline cellulose (Badawy, et al.,
2006) and on spray dried particles (Hansen, et al., 2004). In compari-
son to typical monosized calcium carbonate, when calcium carbonate
was ground, improved packing was observed during compaction, with
a close to log-normal particle size distribution being observed. Never-
theless, the systematic investigation of the correlation between the
particle size distribution and the processability of a powder has been
neglected so far.

**Particle porosity**

The porosity of granules made of lactose could be correlated to the
degree of fragmentation during compression, and increased tablet ten-
sile strength was observed for granules undergoing extensive fragment-
tation (Wikberg and Alderborn, 1991). Conforming with these find-
ings, studies on microcrystalline cellulose showed that pellets of
higher porosity deformed more than those of lower porosity
(Bashaiwoldu, et al., 2004, Johansson and Alderborn, 1996, Johansson
and Alderborn, 2001, Johansson, et al., 1995) and formed tablets of
greater strength. Furthermore, it was observed that granules of higher
porosity were more prone to friction and the increase in tablet tensile
strength was explained by plastic deformation that arose as a result of
friction, local melting caused by so called friction induced “hot spots”,
by small particles acting as binding argents, and by increased surface
energies due to partial amorphisation of the surfaces (Krycer, et al.,
1982).
Powder compression mechanism

The term compression describes the volume reduction of a powder bed caused by the application of stress and the compressibility describes the ability of a powder to reduce in volume. Compression can result in compaction, which is the transformation of a powder into a coherent specimen of defined shape. Hence, the term compactability is used to describe the ability of a powder to compact (Leuenberger, 1982).

A volume reduction in response to an applied pressure can correspond to particles undergoing elastic deformation, plastic deformation or fragmentation, or any combination of these three. Elastic deformation corresponds to particles deforming temporarily and reversibly, while plastic deformation corresponds to an irreversible change in shape. Particle fragmentation involves the break-up of the original particles into smaller fragments.

The process of volume reduction for a powder has been object of a number of studies, and several different suggestions describing the compression mechanism can be found in the literature. Alderborn and co-workers, for example, suggested a mechanism involving the rearrangement of particles into a more closely packed structure, plastic and elastic particle deformation and parallel particle fragmentation followed by rearrangement and deformation of small particle fragments (Alderborn, et al., 1985).

For elastic materials it was suggested that three stages are involved, particle rearrangement, plastic deformation and elastic deformation (Sun and Grant, 2001).

As interparticular and intraparticular pores are present in the powder bed of powders consisting of secondary particles such as granules or agglomerates their compression behaviour is more complex than the behaviour of powders consisting of primary particles such as crystals. In characterising the compression behaviour of these types of powders the properties of the primary and secondary particles have to be taken into consideration. In the literature, four stages for the compression of granulated inorganic materials have been suggested (van der Zwan and Siskens, 1982): (1) Filling of the holes between the granules, (2) fragmentation and plastic deformation of the granules, (3) filling of the holes between the primary particles, and (4) fragmentation and plastic deformation of the primary particles.
The dominating compression mechanism depends on the mechanical properties of the material, but it also depends on the velocity of compression as the degree of plastic deformation was shown to be time dependent (Sun and Grant, 2001).

Numerous attempts have been made to develop a compression equation fitting the whole compression process to characterise and describe the compression behaviour of a powder mathematically. Nevertheless, no generally valid equation has been found so far and different areas of interest tend to use different equations. For pharmaceutical materials, the most commonly used equations are those developed by Heckel and Kawakita, which were also used to evaluate the data in this thesis.

The Heckel equation
The relationship between compression pressure and powder bed porosity was described as follows by Heckel (Heckel, 1961a, Heckel, 1961b):

\[
\ln \left( \frac{1}{\varepsilon} \right) = \frac{P}{P_y} + \text{intercept}
\]

where \( \varepsilon \) is the porosity of the compressed powder bed at an applied pressure \( P \) and \( P_y \) is the yield pressure. The compression of a powder is assumed to follow a first order reaction where the pores act as the reactant and the densification as the product. Usually the Heckel plot has a linear part, but it is curved at the low and high pressure ends. The yield pressure is defined as the stress at which plastic deformation of the particles is initiated (Alderborn, 2002) and can be derived from the linear part of the Heckel plot. As far as the non-linear parts of the curve are concerned, it has been suggested that the initial curvature at low pressure reflects particle fragmentation and rearrangement, while the deviation from a straight line at higher pressure may be caused by capping and lamination of the powder. The Heckel plot and thus the derived parameters are very sensitive to variations in the experimental conditions, such as the maximum compression pressure applied (Sonnergaard, 1999).

The Kawakita equation
The relationship between the compression pressure and the relative volume reduction was described using the following equation introduced by Kawakita and Lüdde (Lüdde and Kawakita, 1966):

\[
\ln \left( \frac{1}{\varepsilon} \right) = \frac{P}{P_y} + \text{intercept}
\]
where \( C \) is the degree of volume reduction (i.e., the ratio between the volume change, which is the difference in the initial volume \((V_0)\) and the volume at applied pressure \((V)\), and the initial volume)
\[
C = \frac{V_0 - V}{V_0},
\]
\( P \) is the applied compression pressure, and \( a \) and \( b \) are constants characterising the compression behaviour of the powder. The linear relationship between \( \frac{P}{C} \) and \( P \) makes it possible to derive values for the constants \( a \) and \( b \) by linear regression. The compression parameter \( a \) reflects the total degree of compression at infinite pressure and the reciprocal of the compression parameter \( b \), \( \frac{1}{b} \), is considered to provide an indication of the deformation or failure stress of the particles (Adams and McKeown, 1996, Kawakita, et al., 1977, Nicklasson and Alderborn, 2000). Mathematically, \( \frac{1}{b} \) is the pressure needed to compress the powder to one half of the total volume reduction, predicted as \( a \). The Kawakita equation is best used for soft and fluffy powders compressed into high porosity powder beds under a low compression pressure (Denny, 2002, Kawakita and Lüdde, 1971), and thus it is frequently used for investigations of pharmaceutical powders. Particular attention has to be paid to the determination of the initial volume of the powder to prevent deviation from the equation.

During compression, the particles are brought into close proximity, but formation of a cohesive compact requires that interparticulate bonds are developed. For dry powder compression, the five bonding mechanisms introduced by Rumpf (1958) can be reduced to three types (Führer, 1977): Solid bridges, attraction forces, and mechanical interlocking. Van der Waals forces were found to contribute significantly to the tensile strength of tablets (Luangtana-Anan and Fell, 1990). Particle deformation and fragmentation during compression increase the surface area and, thereby, the total area of contact between the particles. It can be assumed that a large area of contact between the particles results in tablets of increased strength (Alderborn and Nyström, 1982). The tensile strength of tablets has been explained
by proposing a bond summation concept which assumes that the interparticulate bond structure of a tablet can be described as the product of the number of bonds and the mean bonding forces (Eriksson and Alderborn, 1995b). The number of bonds is mainly affected by particle fragmentation, while particle deformation contributes to the bonding force. In granulated and agglomerated materials, fragmentation leads to an increased surface area and a decreased separation distance between the particles and thus an increased granule fragmentation propensity increases the tensile strength of the formed tablets (Alderborn, et al., 1987, Wikberg and Alderborn, 1990, Wikberg and Alderborn, 1991).

The development of permanent interparticulate bonding is vital for tablet formation. Elastic recovery occurs after unloading and results in the rupture of bonds formed during compression. Thus, a high degree of elastic particle deformation has a negative impact on the tablet strength.

**Powder surface area**

The total surface area of a powder consists of the sum of the total surface area of all the individual particles. The total surface area of an individual particle includes the external, “visible” surface area and the internal “invisible” one. The internal surface area involves fine fissures, and open and closed pores. Three different methods are used to determine the surface area of powders, gas adsorption, mercury porosimetry, and gas permeametry. The values obtained differ from method to method depending on the pores accessible by the penetration medium.

As mentioned above, Alderborn and Nyström, (1982b) assumed that the strength of tablets is higher the larger the contact area between particles. A large bonding surface area is provided if the total surface area of the particles in the tablet is large, which is achieved for powders of fine particle size, materials prone to extensive fragmentation or by powders of qualities where there is pronounced surface roughness.
The effect of short-term storage conditions on mechanical tablet properties

Mechanical instability of tablets during storage has been observed, described and quantified in terms of changes in mechanical strength by several authors (Ahlneck and Alderborn, 1989, Bhatia and Lordi, 1979, Down and McMullen, 1985, Elamin, et al., 1994b, Eriksson and Alderborn, 1994, Eriksson and Alderborn, 1995a, Karehill, et al., 1990a, Malamataris, et al., 1996, Rue and Barkworth, 1980, Sheikh-Salem and Fell, 1981). The most investigated materials in this context are probably sodium chloride and sucrose. In a number of studies the effect of relative humidity during storage on the changes in mechanical stability of tablets was investigated. The adsorption of water to the surfaces of tablets stored at elevated relative humidity is followed by condensation of water in the pores of the tablet. It was observed that such condensation resulted in decreased tablet strength. This reduction in strength was explained by a reduction in the bonding forces between the particles caused by intermolecular attraction between water and the particles (Ahlneck and Alderborn, 1989, Elamin, et al., 1994b, Karehill, et al., 1990a, Luangtana-Anan and Fell, 1990). Shifting a tablet from a humid environment to one with a decreased relative humidity can cause crystallisation of the dissolved material as a result of desorption of water and might, therefore, lead to an increase in the tablet strength as solid bridges are formed (Ahlneck and Alderborn, 1989).

Two mechanisms referred to as $\alpha$ and $\beta$ were proposed to explain the observed mechanical instability of tablets during storage (Eriksson and Alderborn, 1994, Eriksson and Alderborn, 1995a). For the $\alpha$-mechanism a diffusion-like transport of molecules or ions was suggested. For this process to arise, it is necessary that the molecules and ions at the particle surface are mobile. Adequate mobility would be obtained in water sorbed to the surfaces of disordered material or when amorphous material is stored close to its glass transition temperature (Elamin, et al., 1994b). The increase in the tablet tensile
strength was explained by the formation of new bonds in the form of solid bridges and by intermolecular attraction forces at locations where particle surfaces are close to each other. The other mechanism, the $\beta$-mechanism was characterised by a decelerating increase in strength caused by moisture on the particle surface. However, the total increase in the strength of the tablet during storage can be moisture independent. This time-dependent increase in tablet strength was explained by changes in the interparticulate bond structure owing to viscous or visco-elastic particle deformation after ejection from the die. The increase in the strength of the tablets during storage was not accompanied by a measurable change in tablet pore structure.
Drug release from matrix granules

Drug release from matrix granules is complex and no universal drug release mechanism is valid for all kinds of matrixes. Instead, various factors, such as polymer swelling, drug dissolution and diffusion, and structural properties like the geometry and porosity of the matrix control the drug release, although combinations of these factors are likely to be important. When a drug loaded porous matrix comes into contact with an appropriate dissolution medium, drug release from the matrix surface starts immediately. However, for the drug molecules located in the core to be released, the dissolution medium needs to fill the pores of the matrix and dissolve the drug. As the pores fill with dissolution medium, diffusion transports the drug to the surface where it is released. It was found that the amount of drug released from matrix formulations follows the square root of the time of the exposure to the dissolution medium. Equations valid for non porous (Higuchi, 1961) and porous formulations (Higuchi, 1963, Lapidus and Lordi, 1966, Lapidus and Lordi, 1968) have been published. These equations assume that matrix swelling and dissolution is negligibly small, that the drug loading is larger than the drug solubility in the matrix, and that drug dissolution is rapid in comparison to the subsequent drug release by diffusion. Recently a complementary model has been developed that is valid for slowly dissolving drugs, irrespective of the drug loading (Frenning, 2004). Most studies on drug release from matrix granules are carried out on tablets and performed according to the European or US pharmacopoeia. However, little that has been published about the investigation of drug release from single granules (Borgquist, et al., 2002, Hoffman, et al., 1986). Measuring such drug release enables a more detailed investigation to be made of the effect of granule properties and process variables on the drug release mechanism. In this thesis the investigation of granules’ properties and of process variables are confined to the porosity of granules and the impact of compression pressure.
The effect of granule porosity

As mentioned above, granule porosity can be controlled by the choice of granulation liquid and the amount of liquid used. Metha et al., (2000) used different amounts of water as the granulation liquid and varied the spheronisation time and the drug loading of the granules to obtain pellets with different porosities. Porosity parameters, such as the pore size distribution, total pore surface area, mean pore diameter, and the shape and morphology of the pores were found to correlate well with the drug release rate. Millili and Schwartz (1990) prepared pellets of varying porosities using different proportions of water and ethanol. They measured increased drug release rates for tablets made of pellets of higher porosity. This was confirmed by Chopra et al. (2002) and Tunón et al. (2003), who found that the drug release was inversely correlated to the pellet porosity. Nevertheless, the drug release rate does not only depend on the total granule porosity alone, but also on the total pore surface area and the mean pore diameter (Costa, et al., 2004).

The effect of compression pressure

It has been shown that the mechanical properties of granules are related to their porosity (Millili and Schwartz, 1990, Sousa, et al., 2002, Tunón, et al., 2003) and that the porosity has an effect on the drug release, as mentioned immediately above. Millili and Schwartz (1990) found that pellets granulated with water or ethanol varied in terms of their compactability and strength. Tablets made of pellets granulated with water disintegrated during dissolution testing and their drug release profile was almost identical to the drug release profile of uncompacted pellets. In contrast, tablets consisting of pellets granulated with ethanol persisted, and showed decreased drug release rates with increasing compaction pressure.

In addition, some studies on the effect of compression on granule microstructure have been published. For example, it was found that granules made of microcrystalline cellulose deform and become more dense during compression and that the degree of deformation and densification increased with increasing granule porosity (Johansson and Alderborn, 1996, Johansson, et al., 1995, Tunón and Alderborn, 2001). As compression affects the microstructure of the matrix granule, it can be assumed that compression also has an effect on the drug release and that, depending on the degree of deformation, densifica-
tion and fragmentation, the drug release rate could be enhanced or decreased.
Aims of the thesis

The overall aim of the thesis was to identify some functionality related characteristics of solid, pharmaceutically relevant materials and to investigate the effect of their variation on the performance of the products. By applying commonly used particle preparation methods and varying the processing conditions, particles with different properties were prepared. The aims of the individual projects included in this thesis were:

- To investigate the effect of the particle size distribution of free-flowing powders on the evolution of tablet structure and strength during compression and during the short-term post-compaction storage of tablets (Paper I).

- To study the effect of the fracture strength of paracetamol agglomerates, prepared by precipitation from different solvents, on the compression behaviour and their tablet forming ability (Paper II).

- To study the effect of surfactant concentration on the compactability of spray dried lactose particles (Paper III).

- To develop a method suitable for investigating the drug release from single matrix granules under controlled conditions (Paper IV).

- To study the effect of compression on the release of a model drug from single matrix pellets (Paper V).
Materials and methods

Materials
Micronised paracetamol (Rhone-Poulenc chimie, France) was used for the crystallisation and granulation experiments in Papers I and II. Microcrystalline cellulose (MCC) (Avicel PH101, FMC, Ireland, with an apparent density of 1.571 g/cm³) was used as the pellet-forming excipient in the studies for Paper IV. As the lubricant for tableting in the Papers I-III and V magnesium stearate powder (Ph. Eur. Kebo, Sweden), was used.

Desiccator chemicals
0% RH P₂O₅ (I, III)
40% RH NaI (I), K₂CO₃ (IV)
57% RH NaBr (I)

Paper I
Sodium chloride (crystalline puriss, Kebo, Sweden) and sucrose (crystalline, Ph. Eur., Prolabo, France) were used as received. Deionised water was the crystallisation solvent.

Paper II
For granulation, ethanol 99.5% (LS/Ph. Eur. Solveco Chemicals AB, Täby, Sweden), methanol 99.8% (LiChrosolv, Merck, Germany), acetone 99.8% (LiChrosolv, Merck, Germany) and deionised water were used.
For crystal agglomeration ethanol 99.7% (Solveco chemicals AB, Sweden), methanol 99.8% (Anala R BDH Laboratory Supplies Poole, England), acetone 99.5% (Anala R BDH Laboratory Suppliers Poole, England) and deionised water were used.
**Paper III**
The lactose was: α-lactose monohydrate (Pharmatose 200M, DMV, the Netherlands), also required was polysorbate 80: Polyoxyethylene-sorbitan Monooleate, supplied by Sigma-Aldrich Chemie GmbH, Germany.

**Paper IV**
Salicylic acid (SA) (extra pure, Merck, Germany, with an apparent density of 1.426 g/cm$^3$), and sodium chloride (NaCl) (extra pure, Merck, Germany, apparent density of 2.165 g/cm$^3$) were used as the model drugs.
The granulation liquids were ethanol (Etax A, 95.5 vol%, Primalco, Finland) and deionised water.

**Methods**

**Preparation of powders**

**Preparation of particle size distributions (Paper I)**
The raw materials, sodium chloride and sucrose, were subdivided into a number of size fractions by dry sieving (ASTM test sieves, Retsch, Germany). Different size distributions were prepared by mixing predetermined quantities of the various size fractions in a shear mixer (Turbula, W.A. Bachofen AG, Maschinenfabrik, Basel, Switzerland) for 10 min at 46 rpm. For both materials, three size distributions were designed, with a narrow unimodal distribution, a wide unimodal distribution, and a wide bimodal distribution.
The narrow and the wide unimodal particle size distributions were mixed separately with magnesium stearate powder in a Turbula mixer. An amount of magnesium stearate corresponding to a specific amount of 5 and 50 $\mu$g/cm$^2$ was mixed with 10 g of each powder for 100 min (the proportions of magnesium stearate in the mixture were about 0.05 and 0.5% by weight, respectively). The external surface area of the sodium chloride and sucrose powders was estimated as the ratio between the Heywood shape coefficient of the particles (literature values used from (Alderborn and Nyström, 1982)) and the median value of the particle size distribution.
Preparation of agglomerates (Papers I and II)

Paracetamol powders were prepared by precipitation from a saturated solution of water at 60° C (Paper I) and ethanol, methanol, acetone and a mixture of acetone and water at 50° C (Paper II). The relevant amount of paracetamol needed to obtain a saturated solution at these temperatures was dissolved in each liquid. A 2-l double-walled glass beaker with water circulating between the walls was used to cool down the saturated solutions to 10° C using cooling rates of 0.20° C/min, 0.40° C/min, 0.50° C/min and 0.66° C/min for water, 0.50° C/min for methanol, 0.56° C/min for ethanol and acetone (Julabo FP45, Germany) and 1.11° C/min for acetone/water (Julabo FP50, Germany). The beaker was equipped with baffles and a propeller shaped impeller was used for stirring. During the precipitation from water, the agitation rate was 680 rpm at cooling rates of 0.2° C/min, 0.5° C/min, and 0.66° C/min and 1000 rpm at a cooling rate of 0.4° C/min. 2 g seeds (125-200 \( \mu \)m) were added at 52° C to the 0.2° C/min experiment. In all other cases, the agitation rate was 400 rpm (RW 20 DZW Janke & Kunkel, Germany). At 10° C the agglomerates were separated from the solution by filtration and dried at room temperature. The particles that precipitated from the water were dried in a ventilated heating cabinet at 60° C. The particle size distribution of the powders was determined by dry sieving. The batches prepared at cooling rates of 0.5° C/min and 0.66° C/min from water exhibited similar particle size distributions and were combined to form one batch for further use. The other powders prepared from water were used as harvested. For Paper II, the particle size fraction 500-710 \( \mu \)m was obtained by dry sieving and used for the experiments. All powders were stored at 40% RH for at least 7 days before further experiments took place.

Preparation of granules (Paper II)

For the wet granulation, a planetary mixer (Kenwood Major, UK) was used. Paracetamol was poured into the mixer and the relative mixing speed was set to two. The granulation liquids ethanol, methanol, acetone, and the acetone/water-mixture were pumped to the powder at a flow rate of 100 ml/min. The mixer was stopped after two minutes of mixing and the granules were distributed on a plate for drying. After at least two days of drying, the particle size fraction 500-710 \( \mu \)m was separated out using stainless steel laboratory sieves and a mechanical sieve shaker. The powders were stored at 40% RH for at least 7 days before further experimentation.
Preparation of powders by spray drying (Paper III)

Three different powders consisting of only lactose or of lactose and a small proportion of polysorbate 80 were prepared by spray drying. A solution containing 1% (w/w) polysorbate 80 was prepared using deionised water as the solvent. The polysorbate 80 solution was dropped into the lactose to obtain two batches of lactose containing a weight proportion of 0.001% and 0.01% (w/w) polysorbate 80. Lactose without additive and lactose containing 0.001% and 0.01% (w/w) polysorbate 80 were then dissolved in deionised water. The final mass ratio of solid material/water was 1:28. The lactose solutions were kept under agitation for 24 hours and than spray-dried in a counter-current spray dryer (Niro Atomizer A/S, Denmark), equipped with a rotary atomizer. A peristaltic pump (Watson Marlow 505S, England) at a relative feed rate of 6-7 was used to supply the atomizer with the solution. The inlet and outlet temperatures were 190±5°C and 96±5°C, respectively. The powders obtained were stored in an evacuated desiccator at 0% RH until the moisture content was constant below 3% after at least 10 days. The moisture content of the powders was derived from the weight loss of powder samples, of approximately 300 mg, when exposed to 150°C for 10 minutes using a Halogen Moisture Analyzer (HR73, Mettler Toledo, Switzerland).

Preparation of pellets (Papers IV and V)

Pellets consisting of MCC only, MCC and NaCl, and MCC and SA were prepared by wet granulation followed by extrusion-spheronization. The weight fraction of the model drugs NaCl and SA in the dry mixture was 10%. For each composition, different proportions of water and ethanol comprised the granulation liquid for preparation of pellets of low and high porosity (Tunón, et al., 2003). The powder (360 or 400 g) was agitated in a planetary mixer (QMM-II, Donsmark Process Technology, Denmark) at 500 rpm for 5 min and the granulation liquid (1–1.1 times the MCC weight) was then sprayed (Schlick, Model 940, Germany) into the mass at a rate of ~100 ml/min. Wet mixing continued over a period of 5 min at 500 rpm. The wet powder was then immediately extruded (model E140, NICASystem, Sweden; with holes of 1.0 mm diameter and 1.2 mm length) and spheronized (model S 320-450, NICASystem) for 3 min on a 32 cm diameter friction plate with a radially designed grid at a rotation speed of 800 rpm. The pellets were spread out on plates in a thin layer and dried under ambient conditions for 4 days. The size fraction 800-900 μm was separated by dry sieving using a set of stan-
standard sieves with square openings (Endecotts, UK) and a mechanical shaker (Retsch, Type RV, Germany) for 10 min at a relative agitation intensity of 30. The size fraction obtained was used exclusively for the remainder of the experiments. The pellets were stored in a desiccator at 40% relative humidity and room temperature for at least 7 days before further investigation. The pellets used in Paper V were lubricated with an amount of magnesium stearate corresponding to 0.009% w/w in a Turbula mixer (Bachofen AG, Switzerland) for 100 min at 67 rpm and stored under ambient laboratory conditions.

Characterisation of particles

Particle dimensions (Papers II, IV and V)

Pictures of at least 20 particles of each sample investigated were taken using a CCD camera (Olympus DP 50 CCD, Japan) connected to a light microscope (Olympus Vanox, Japan). Digital images with a pixel resolution of 1.8 μm/pixel were acquired at 5x magnification. A steel sphere (SKF, Sweden) with a diameter of 1 mm and an assumed circularity of 1.00 was used as the reference (Eriksson, et al., 1993). For each particle, the projected area ($A_p$), the perimeter length ($P_p$), the circularity ($C_p$) (called the form factor, abbreviated to $FF$, in Paper II) were determined using the non-commercial software ImageJ and its plug-in “Enclose” (Papers IV and V) or “Shape Descriptors” (Paper II) (available at http://rsb.info.nih.gov/ij/, National Institutes of Health, USA). Additionally, in Paper II, the aspect ratio ($AR$) was determined and the radius ($r$) of a circle of corresponding area was calculated. In Paper IV, the diameter of a circle of corresponding area ($d_p$), and in Paper V the maximum Feret diameter ($d_F$) were determined in addition. The maximum Feret diameter is defined as the largest distance possible between any two points along the perimeter of the projected area of a particle (Russ, 2002) (hereafter referred to as the Feret diameter). The radius ($r$) of a circle of corresponding area was calculated in the following way:

$$r = \sqrt{\frac{A_p}{\pi}}.$$

According to the software specification, the circularity and the aspect ratio were calculated using the following equations:

$$C_p = \frac{4\pi A_p}{P_p^2}$$ (Cox, 1927)
The apparent particle density and bulk density
The apparent particle densities ($\rho_{\text{app}}$) of the used raw materials and of the powders prepared were determined by helium pycnometry (AccuPyc 1130, Micromeritics, USA).

The bulk density ($\rho_{\text{bulk}}$) of the powders was calculated from the weight and the volume of a variable amount of powder poured into a graduated 10 ml cylinder (20° C, graduation: 0.1 ml).

The surface area of powders (Papers II and III)
The volume and weight specific surface area of the powders were determined by air permeametry. Samples of each powder were poured into a sample holder and compressed manually to a porosity of approximately 50%. The sample holder was connected to a Blaine apparatus and the time required for a known volume of air to pass through the powder bed was measured (Blaine, 1943). The volume specific surface area was calculated using the slip flow corrected Kozeny-Carman equation (Alderborn, et al., 1985).

Solid state structure (Paper III)
The powders in Paper III were analysed by X-ray diffraction using a Diffraktometer D5000 (Siemens, Germany) equipped with a scintillation detector, using Cu-Kα radiation, 45 kV and 40 mA. One sample of each powder was scanned in steps of 0.2° from 6° to 30° (2θ).

Differential scanning calorimetry (Paper III)
For the thermal analysis carried out in Paper III, a Seiko DSC 220 differential scanning calorimeter (SSC/5200h, Seiko, Japan) was used. Three samples of each powder were weighed into aluminium pans and covered with a lid, which had been perforated with a pin. An empty pan was used as the reference. Measurements were made in a dry nitrogen atmosphere scanning the temperature range from 20° C - 300° C using a heating rate of 5° C/min. The instrument was calibrated using indium, tin and gallium.

Nominal particle fracture strength (Paper II)
Single particles were fractured in a materials testing machine (Texture Analyser TA-HDi, Stable Micro Systems Ltd, UK), using a 5 kg load.
cell and a flat faced cylindrical 6 mm steel punch. Measurements were made one by one on about 50 particles from each batch at a loading rate of 3 mm/min (0.05 mm/s). The values recorded for the force increased until the first major breakdown of the agglomerate occurred. At that point, the force dropped, creating a peak, the value of which was taken as the agglomerate strength. Particle breakage was considered to have occurred when the force dropped below the threshold value, which was set to 0.0098 N. The program “Texturexpert Exceed 2.16” was used to analyse the data collected.

From the mean projected area and the mean force ($F$) needed to cause breakage, the nominal particle fracture strength ($\sigma_N$) was calculated as follows:

$$\sigma_N = \frac{F}{A_p}.$$

The degree of agglomeration (Paper III)

For the agglomerates, the number of crystals per agglomerate designated the C/A number was estimated as reported earlier by Ålander and co-workers (Ålander, et al., 2003, Ålander, et al., 2004). For single crystals, the C/A number is equal to 1. Agglomerates consisting of two or more crystals are characterized by C/A numbers higher than 1. The number fraction of particles consisting of less than 2 crystals per particle, i.e., the number fraction of unagglomerated crystals was used to determine the degree of agglomeration. The degree of agglomeration is high for agglomerates with a low number fraction of unagglomerated crystals and low for agglomerates with a high number fraction of unagglomerated particles. For the granules, the number of crystals per particle was estimated roughly from the relation between the dimensions of the raw material and the size of the granules.

Pellet porosity (Papers IV and V)

The intragranular pellet porosity was calculated as the difference between 1 and the ratio between the effective and apparent pellet densities. Values for the pellet components found in the literature were used to calculate the apparent density of the pellets as explained by Jerwanska and co-workers (Jerwanska, et al., 1995). The effective pellet density was determined by mercury pycnometry at 207 kPa using a porosimeter (Autopore III 9420, Micromeretics, USA). In a graph showing the cumulative volume of mercury intruded into the pores of the pellets as a function of pressure, a plateau was observed around this
pressure which indicated that the intergranular voids had been filled. The pellets used for these experiments had been stored in a desiccator at 0% RH for at least two days.

Compression behaviour

A materials testing machine (Zwick/Roell Z100, Germany) equipped with flat-faced circular punches (diameter of 11.3 mm) was used to apply a maximum pressure of 300 MPa to 300 mg powder beds. The movable upper punch was connected to a 100 kN load cell and an external extensometer was used to record the upper punch position. The lower punch and the die were stationary and mounted to the lower grip. At a pre-load of 2 N, the compression speed was set to 25 mm/min. Data collection started at a force of 100 N. The upper punch position and pressure data were monitored and collected by the software “testXpert V11.0” and saved in intervals of 10 N. With the intention of determining the elastic deformation of the punches and the punch holder, punch deformation curves were recorded by pressing the punches against each other at the compression speed used in the experiments. System deformation data (n=3) was recorded and force-displacement curves were plotted. With the exception of the initial part, at low pressures, the force-displacement curves showed linearity. The equation \[ y = k_a x + l_a + l_b e^{-k_b x} \], 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 the powder compression was corrected for the system deformation error, calculated with the above equation, to assess the correct compact height. The system deformation was approximately 0.5 \( \mu m/MPa \).

Compression parameters

Heckel parameters

The Heckel equation was used to derive in-die and out-of-die compression parameters for Papers II and III, and I and III, respectively. The Heckel plots, obtained using the compression data recorded by operating the materials testing machine as described above, were linear for pressures between 50 MPa and 150 MPa. Thus, this pressure interval was used to derive the compression parameters by linear regression.
The out-of-die compression parameters were obtained by evaluation of tablet porosity data from tablets prepared with the Korsch press, see below.

*Kawakita parameters*

In Paper III the compression data were plotted according to Kawakita and, from the linear profiles obtained for pressures between 1 and 300 MPa, the compression parameters, \( \frac{1}{b} \) and \( a \), were derived by linear regression.

**Elastic recovery (Papers II and III)**

The elastic in-die recovery (ER), which describes the percentage of axial expansion of a compact, was calculated from the tablet height at 2 N (\( h_{2N} \)), the pressure at which the punch is considered to lose contact with the surface of the powder bed and the height at maximum pressure (\( h_{\text{at pressure}} \)) according to following equation:

\[
ER(\%) = \frac{h_{2N} - h_{\text{at pressure}}}{h_{\text{at pressure}}} \cdot 100.
\]

The degree of compression at the time the upper punch detached from the compact will be referred to as \( C_{\text{remaining}} \) and used as an indicator for the permanent deformation of the particles.

**Permeability coefficient (Papers II and III)**

The materials testing machine was used to apply pressure to a powder bed poured into a die that could be connected to a Blaine apparatus as described earlier (Elamin, et al., 1994b). The permeability coefficient (\( P_c \)) was calculated using the following equation:

\[
P_c = \frac{\ln \left( \frac{h_2}{h_1} \right) \cdot L \cdot a_m}{A \cdot t \cdot 2 \cdot \delta \cdot g}
\]

where \( h_2 \) and \( h_1 \) are the start and stop points on the manometer arm, \( L \) is the height of the compact, \( a_m \) the cross-sectional area of the manometer, \( A \) the cross-sectional area of the compact, \( t \) the time during which an air flow was maintained, \( \delta \) the density of the manometer liquid, and \( g \) the acceleration due to gravity. The distance between the punches at 2 N during the upward movement of the upper punch was chosen as the compact height \( L \).
The degree of compression (Paper II)

The degree of compression of the powder beds at a load of 300 MPa ($C_{\text{at pressure}}$) was calculated with the help of the following equation:

$$C_{\text{at pressure}} = \frac{\rho_{300\text{MPa}} - \rho_{\text{bulk}}}{\rho_{300\text{MPa}}}$$

where $\rho_{300\text{MPa}}$ is the density of the powder bed at 300 MPa, calculated from the dimensions of the powder bed at that pressure and the apparent density of the material.

Preparation of tablets (Papers I - III)

Tablets were prepared with an instrumented single punch tablet press (Korsch EK 0, Germany) at a series of different compaction pressures. The tablet press was equipped with circular flat-faced punches. In Papers I and II, the punch diameter was 11.3 mm. Additionally, in Paper I, punches with a diameter of 5.74 mm were used to prepare tablets at a compaction pressure higher than 300 MPa. In Paper III, the punch diameter was reduced to 5.65 mm to obtain higher compaction pressures.

A small paintbrush was used to pre-lubricate the punch and die surfaces by spreading magnesium stearate powder on them. For each tablet, a defined amount of powder was weighed separately and poured manually into the die. During compression, the lower punch was stationary and the upper punch machine driven, i.e., the machine was started when the upper punch was in its uppermost position relative to the die. The maximum compaction pressure was recorded for each tablet and a variation in compaction pressure of +/- 5% of the nominal value was accepted.

Preparation of dividable tablets (Paper V)

Dividable tablets were only prepared from high and low porosity pellets containing sodium chloride. The materials testing machine, equipped with flat-faced circular 11.3 mm punches, was used to compact the pellets into tablets that could be divided into three layers. Each of the layers, which were separated by tin foil, consisted of 300 mg pellets. The pellets that composed the bottom layer were poured into the die and covered with a piece of tin foil fitting exactly the die. A pressure of 2 N was applied to level out the pellet layer. Pellets building the central layer were added and covered with a piece of tin foil. A pressure of 2 N was applied before adding the pellets for
the top layer. Finally, a maximum pressure of 100, 170, 240 or 300 MPa was applied to compact the pellets into tablets. The tablet layers were separated carefully and disintegrated to regain the compacted pellets. Only those pellets from the top and bottom layers were collected and used for further experiments.

Characterisation of tablets

Porosity and tensile strength of tablets (Paper I-III)
The porosity of the tablets ($\varepsilon_i$) was calculated from the apparent particle density ($\rho_{\text{app}}$) and the diameter ($D$), height ($h_i$) and weight ($w$) of each tablet immediately after ejection in the following way:

$$\varepsilon_i = 1 - \frac{4w}{\pi h_i D^2 \rho_{\text{app}}}.$$

The compression force ($F_i$) needed to fracture the tablets along their diameters was determined in a materials testing instrument (Holland C50, UK) at a loading rate of 1 mm/min. Thereafter, the tensile strength of the tablets ($\sigma_i$) was derived according to (Fell and Newton, 1970), i.e.:

$$\sigma_i = \frac{2F_i}{\pi h_i D}.$$

Additionally, the tablets investigated in Paper I were stored in desiccators at 0% and 57% RH for 10000 min. The tablet porosity and tensile strength were calculated from the tablet dimensions and fracture force after storage.

Characterisation of tablet surface (Paper III)
In Paper III, the upper tablet surface was analysed more closely. The materials testing machine was used to form two 300 mg tablets of each powder at a pressure of 140 MPa. One tablet of each material was fractured using a materials testing instrument (Holland C50, UK) operated at a loading rate of 1 mm/min. The tablets and tablet fragments obtained were stored at 0% RH for five days before SEM pictures were taken of the upper tablet surfaces and the fracture surfaces with an environmental SEM (XL 30 ESEM-FEG, FEI/ Philips, the Netherlands).
Drug release from pellets (Papers VI and V)

**The instrument**

The experimental set-up utilized a recirculation flow-through system for the dissolution medium (Figure 1). The dissolution medium was pumped from the liquid container through the pellet holder, containing a single pellet, and back into the liquid container. A peristaltic pump (Masterflux L/S, Cole-Parmer, USA) and PharMed Tubings (with an inner diameter of 0.8 mm) were used for this purpose. The liquid container was equipped with a magnetic stirrer and had two gold electrodes mounted on opposite sides of it. To prevent evaporation of the dissolution medium, the liquid container was covered with a lid. The alternating ionic current technique was used to monitor the drug concentration of the dissolution medium (Frenning, et al., 2002). A Synthesizer Function Generator (HP3325A, Hewlett-Packard, Palo Alto, USA) provided a sinusoidal voltage with amplitude of 1.0 V and frequency of 10.0 kHz. The voltage across the measuring cell was measured with a digital multimeter (HP34401A, Hewlett-Packard). The current conducted through the measuring cell was measured using a voltage divider, utilizing a 10 kΩ resistor and a multimeter of the same type as described in detail by Frenning and Strømme (Frenning and Strømme, 2003).

![Figure 1. Schematic illustration of the instrument used to measure the drug release from single matrix pellets, consisting of a combined liquid container/conductivity cell equipped with gold electrodes, a magnetic stirrer, a peristaltic pump, and a pellet holder. The electrical circuit is included.](image-url)
The experiment

All measurements of the drug release from single pellets were conducted at room temperature. In Paper IV, the drug release was measured using both low and high dissolution-medium flow rates of 1 and 5 ml/min, respectively. Within the pellet holder, these flow rates corresponded to linear velocities of 0.84 and 4.2 mm/s, respectively. In Paper V, drug release measurements were only performed at the higher flow rate of the dissolution medium. For the high dissolution-medium flow rate, the Reynolds number for the flow through the pellet holder may be calculated and was found to be 21, which is two orders of magnitude smaller than the critical value, and hence well within the laminar regime (Nakayama and Boucher, 1998). The time-scale was corrected for the time taken for the dissolution medium to reach the measuring cell. Time zero was defined as the time at which a sustained increase in the current was first observed.

Statistical analysis

The mean dissolution time (MDT), the variation in the dissolution time (VDT), and the relative dispersion coefficient (RD) were used as model independent measures. A random variable $T$ was defined as the release time of a randomly selected drug molecule in the pellet. The MDT and VDT are the expectation value and variance of the random variable $T$, respectively. The relative dispersion coefficient (RD) was calculated as $RD = \frac{VDT}{MDT^2}$ (Lánský and Weiss, 2003, Tanigawara, et al., 1982, Tunón, et al., 2003). The fraction of the drug released was determined using the cumulative distribution function for $T$, i.e., the MDT and VDT values were calculated from the experimental release data (Lánský and Weiss, 2003, Tunón, et al., 2003). Specifically, the calculation was performed according to the procedure described by Lánský and Weiss (2003), using the KaleidaGraph data analysis software (version 3.6, Synergy Software, USA) in Paper IV and the free software environment for statistical computing “R” (http://www.r-project.org/) in Paper V.

In Paper IV, the effect of each of the three factors drug solubility, porosity and flow rate on the MDT was evaluated performing analyses of variance (ANOVA) on two levels.

In Paper V individual two-way ANOVAs for pellets of high and low porosity were carried out to test for the significance of the effect of the compaction pressure (4 levels) and the original pellet location in the tablet (2 levels) on the MDT. Additionally, a one-way ANOVA was per-
formed with the compaction pressure as the only factor (5 levels) and uncompressed pellets as the control.
Results and Discussion

Particle processing and the impact on the properties of particles

The size distribution of particles and its influence on the evolution of tablet structure and tensile strength

**Particle size distributions**

By mixing weighed particle fractions that had been pre-sorted by size, three powders of each of the materials sodium chloride and sucrose were obtained. For each material, the median particle size of the powders was consistent but the spread in particle size varied. The median particle size of the sodium chloride powders was slightly lower than that of the sucrose powders. For both materials, the spread in the particle size of two of the powders can be described as unimodal, whilst the other one was bimodal.

The crystallisation conditions were varied for three batches of paracetamol to obtain samples with different median particle sizes and different particle size distributions. The particle size distribution of two of the batches was unimodal. The batch with the lower median particle size showed a more skewed distribution, with a right hand sided tail. The particle size distribution of the third batch tended towards a bimodal distribution and exhibited a markedly higher median particle size. Frequency distributions of the particle size of the different powders are shown in Figure 2. Paracetamol can be crystallised into at least two forms, monoclinic and orthorhombic (Di Martino, et al., 1996, Joiris, et al., 1998), with different melting points. For the three batches of paracetamol, a melting point of about 171° C was observed, which corresponds well with the melting point of 169° C reported by Di Martino and co-workers (1996) for the monoclinic form. Thus, it can be concluded that the paracetamol was monoclinic.
Figure 2. Frequency distributions showing the particle size distributions of the different batches of sodium chloride (left column), sucrose (middle column), and paracetamol (right column). Note that the third distribution for each material is bimodal, whereas the others are unimodal.

The particles of the sodium chloride and sucrose powders were primary particles. The sodium chloride particles were nearly cubic in shape, while the sucrose particles were more elongated and angular. Crystallisation of paracetamol resulted in both primary and secondary particles and irregular particles caused by agglomeration were observed (Figure 3).

Evolution in tablet structure during compression
Macroscopic tablet properties such as porosity and tensile strength were used to examine the changes in microstructure of the tablets during compression. The evolution of these properties was followed by plotting the measured values as a function of the compression pressure.

For sodium chloride and sucrose, the relationships between tablet porosity and compaction pressure, and between tablet tensile strength and compaction pressure showed considerable consistency within each material (Figure 4). Generally, sucrose powders produced tablets of higher porosity and tablet tensile strength than tablets made of sodium chloride powders, a result that is consistent with the expected
propensity of the particles to deform during confined powder compression (Rowe and Roberts, 1996). The differences between the materials could be supported by calculating the Heckel compression parameter and the Alderborn compression parameter (Alderborn, 2003). For sucrose, the values of 276 and 621 MPa, and for the sodium chloride the values 178 and 474 MPa, respectively, for these compression parameters, confirmed that sodium chloride is softer than sucrose. However, the values derived for sodium chloride were higher than those usually reported (Rowe and Roberts, 1996; Alderborn, 2003) and indicative of a relatively hard quality of sodium chloride. The spread in particle size did not affect the powder compactability as assessed directly after tablet formation.

Figure 3. SEM images of particles of the different paracetamol powders.
Figure 4. The tensile strength (upper panel) and porosity (lower panel), measured 1 min after powder compaction, of sodium chloride (left) and sucrose (right) tablets as a function of compaction pressure (• wide, ■ narrow, ▲ bimodal).

For paracetamol, the range of compaction pressures used was lower than for the other substances. This was because lamination and capping of the tablets prevented the formation of tablets at compaction pressures above 120 MPa. Furthermore, for this substance, the relationships between the tablet tensile strength and tablet porosity and the compaction pressure did not show any variation dependent on the spread in particle size. Despite the differences in the spread of particle size, median particle size and particle structure (i.e., the incidence of agglomerates), similar trends were revealed in the compression and compaction behaviour of the three powders investigated (Figure 5). It was not possible to calculate a reliable Heckel compression parameter because of the limited pressure range used during compression and the fact that the tablets were similar in volume at pressures above 100 MPa. The compressibility and the compactability of the test substances were not significantly dependent on the spread in particle size. Thus, it can be concluded that the evolution in tablet microstructure during the compression process is independent of the variations in the particle size distribution.
Post-compaction changes in the tensile strength of tablets formed from lubricant free powders

Possible changes that can occur to the mechanical strength of tablets after the compaction process were studied over a time period using the wide and narrow unimodal particle size distributions of sodium chloride and sucrose powders only. During short-term storage, the substances differed in their behaviour (Figure 6). Independent of the relative humidity of the environment used for storage, the sodium chloride tablets were unstable for up to 10 min. Thereafter, a stable tablet tensile strength was attained. This behaviour was expected of sodium chloride and is consistent with the instability of the $\beta$-type mechanism (Eriksson and Alderborn, 1994). However, the effect of storage humidity did not correspond to the idea that an increased relative humidity slows down the rate of increase in the tensile strength of tablets (Eriksson and Alderborn, 1994). No humidity related differences could be observed over the time period investigated, but tablets made from the powder with a narrow particle size distribution were more prone to an increase in tablet tensile strength than tablets made from particles with a wide distribution of sizes. Thus, the spread in particle size was a significant factor for the post-compaction increase in tensile strength for sodium chloride tablets.

For sucrose, the short-term storage behaviour was independent of the particle size distribution, but dependent on the relative humidity of the environment in which the tablets were stored. At the lower relative humidity, no variation in tablet tensile strength was observed, while at the higher relative humidity the tablet tensile strength increased. This
behaviour was expected for sucrose (Alderborn and Ahlneck, 1991) and was consistent with the instability behaviour of the $\alpha$-type. The particle size distribution of lubricant free powders affected the short-term instability of tablets made of sodium chloride, but did not affect the short-term instability of tablets made of sucrose. The effect of the original particle size distribution may depend on the type of restructuring process taking place in the tablet. An effect of particle size on the increase in the short-term tensile strength of tablets made of sodium chloride was observed earlier (Eriksson and Alderborn, 1995a). It has been proposed that either viscous deformation of particles or a temperature-related stabilisation of the adhesive interactions formed at the interparticulate joints is the underlying process responsible for the short-term storage instability that occurs according to the $\beta$-mechanism (Eriksson and Alderborn, 1994). Both mechanisms may be affected by stress at the interparticulate junctions that evolved during the compression and interparticulate junctions may be more heterogeneously distributed within a tablet formed from powder with a wider distribution of particle sizes.

![Figure 6](image.png)

*Figure 6.* The tensile strength of sodium chloride (left) and sucrose (right) tablets prepared from the wide ($) and narrow ($\bar{\gamma}$) particle size distributions without lubricant and stored at 0% (upper graphs) and 57% (lower graphs) relative humidity for different post-compaction storage times.
Post-compaction changes in the tensile strength of tablets formed from lubricated powders

The effect of lubricant on the short-term storage behaviour of tablets was studied for tablets stored at 57% relative humidity only. Generally, the addition of lubricant reduced the tensile strength of the tablets obtained, with the sucrose powders showing a lower lubricant sensitivity than the sodium chloride powders (Figure 7). This was expected as it is well known that the addition of lubricant generally reduces compactability and that the lubricant sensitivity is partly related to the fragmentation propensity of the particles. Tablets of sodium chloride containing the higher concentration of lubricant were prepared under a higher compaction pressure.

Within the tablets made of the sodium chloride powders, an effect related to the spread in particle size was observed only on the short-term storage behaviour for the narrow particle size distribution containing the lower lubricant concentration.

For sucrose tablets made of the wide particle size distribution, the increase in tablet tensile strength observed during short-term storage for unlubricated tablets stored at 57% relative humidity was inhibited by the presence of lubricant. For tablets with the narrow particle size distribution, a storage-related tensile strength increase was observed, however this was not as apparent as for the lubricant free tablets.

Lubricant addition restrains the increase in the post compaction tensile strength for both materials, possibly because the lubricant inhibits the tablet restructuring or interferes with the formation of interparticulate bonds. For a material behaving according to the $\beta$-mechanism (corresponding to viscous deformation), bond formation during the restructuring process may be prevented by the presence of lubricant covering

Figure 7. The tensile strength of sodium chloride (left) and sucrose (right) tablets prepared from powders with lubricant of two concentrations (5 and 50 $\mu$g/cm²) and stored at 57% relative humidity for different post-compaction storage times.
the particle surfaces. For the $\alpha$-mechanism, it has been suggested that diffusion-like transport of molecules in the vicinity of the interparticulate junctions may occur, possibly as a result of moisture adsorption. The restructuring may be hindered at particle surfaces covered with lubricant and thus only takes place at lubricant free surfaces. For both lubricated materials, the particle size distribution had an effect on the short-term storage behaviour and it is likely that both instability mechanisms are present. Since it has been proposed that changes of the tensile strength of tablets which occur according to both the $\alpha$- and the $\beta$-mechanism involve lubricant free surfaces, it is possible that the distribution in particle size may affect the fraction of lubricant free surfaces in the tablet formed during or after compression.

The effect of the fracture strength of paracetamol agglomerates on their compression behaviour and tablet forming ability

As shown above, the distribution in agglomerate size of paracetamol agglomerates formed by crystallisation in water, did not have any effect on the compactability of the agglomerates. Hitherto there is no literature dealing with the question of whether agglomerates of different nominal fracture strength behave differently when subjected to confined compression. Four batches of paracetamol agglomerates prepared by crystal agglomeration using different solvents were compared with four batches of paracetamol agglomerates prepared by wet granulation using the same solvents. In accordance with the preparation procedure, the first type of secondary particles is referred to as agglomerates (A) and the latter one as granules (G).

The particle and powder characteristics are summarised in Table 1. The projected area of the particles indicates that the particles obtained were of equal size. The higher bulk density of the agglomerates can be an indication of a higher intra-granular porosity of the granules. The degree of agglomeration was determined for the agglomerates and estimated for the granules and found to be between 2.0 and 6.9 for the agglomerates and about 100 times larger for the granules. A higher nominal particle fracture strength was observed for the agglomerates, than for the granules. The nominal particle fracture strength was almost linearly related to the bulk density of the powders (Figure 8a), thus, the differences obtained in nominal particle fracture strength
could, at least partly, be explained by a variation in the intra-granular porosity of the particles.

**Table 1. Characteristics of individual particles and powders**

<table>
<thead>
<tr>
<th>Material</th>
<th>Projected area ($A_p$)</th>
<th>Nominal fracture strength ($\sigma_N$)</th>
<th>Apparent particle density ($\rho_{app}$)</th>
<th>Bulk density ($\rho_{bulk}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEthanol</td>
<td>0.461 (0.091)</td>
<td>0.045</td>
<td>1.291 (0.002)</td>
<td>0.400 (0.018)</td>
</tr>
<tr>
<td>GMeOH</td>
<td>0.445 (0.090)</td>
<td>0.046</td>
<td>1.292 (0.000)</td>
<td>0.382 (0.006)</td>
</tr>
<tr>
<td>GAacetone</td>
<td>0.395 (0.106)</td>
<td>0.036</td>
<td>1.292 (0.001)</td>
<td>0.387 (0.009)</td>
</tr>
<tr>
<td>GAacetone/water</td>
<td>0.413 (0.112)</td>
<td>0.022</td>
<td>1.292 (0.000)</td>
<td>0.344 (0.007)</td>
</tr>
<tr>
<td>AEthanol</td>
<td>0.428 (0.126)</td>
<td>0.062</td>
<td>1.289 (0.001)</td>
<td>0.420 (0.007)</td>
</tr>
<tr>
<td>AMethanol</td>
<td>0.463 (0.102)</td>
<td>0.076</td>
<td>1.293 (0.000)</td>
<td>0.477 (0.009)</td>
</tr>
<tr>
<td>AAacetone</td>
<td>0.385 (0.091)</td>
<td>0.118</td>
<td>1.291 (0.000)</td>
<td>0.512 (0.014)</td>
</tr>
<tr>
<td>AAacetone/water</td>
<td>0.397 (0.099)</td>
<td>0.095</td>
<td>1.292 (0.000)</td>
<td>0.502 (0.011)</td>
</tr>
</tbody>
</table>

Mean values, standard deviation in parenthesis

The compression parameters, $P_y$ according to Heckel and $\frac{1}{b}$ according to Kawakita, were calculated to characterize the compressibility of the powders, and used to describe the evolution of the tablet porosity and volume as the compression pressure was increased. The Heckel parameter (Table 2) grouped the particles according to their preparation method. For the Kawakita parameter, a positive correlation was obtained with the nominal particle fracture strength (Figure 8b) for each type of particle and, thus, it seems that the Kawakita parameter discriminates between the particles depending on their nominal fracture strength. The degree of deformation or fragmentation during compression of the powders was further investigated using the degree of deformation during loading (referred to as $C_{at\ pressure}$ in Table 2) and the degree of permanent deformation after unloading (referred to as $C_{remaining}$ in Figure 8c) as indicators.

As paracetamol is a material well known for exhibiting elastic expansion during unloading (Malamataris, et al., 1996), the elastic recovery ($ER$) (Table 2) was used as an indicator for the degree of elastic particle deformation.
Table 2. Characteristics of powder compression properties

<table>
<thead>
<tr>
<th>Material</th>
<th>$P^a$ (MPa)</th>
<th>$E.R^b$</th>
<th>$C_{at pressure}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEthanol</td>
<td>100.9 (1.413)</td>
<td>6.599 (0.667)</td>
<td>0.691 (4.118*10^-4)</td>
</tr>
<tr>
<td>GMethanol</td>
<td>101.0 (0.715)</td>
<td>6.220 (0.149)</td>
<td>0.705 (2.450*10^-4)</td>
</tr>
<tr>
<td>GAcetone</td>
<td>104.8 (1.387)</td>
<td>6.350 (0.300)</td>
<td>0.701 (4.054*10^-4)</td>
</tr>
<tr>
<td>GAcetone/water</td>
<td>102.6 (0.940)</td>
<td>7.429 (0.356)</td>
<td>0.734 (2.698*10^-4)</td>
</tr>
<tr>
<td>AEthanol</td>
<td>85.6 (7.499)</td>
<td>6.543 (0.759)</td>
<td>0.678 (1.662*10^-3)</td>
</tr>
<tr>
<td>AMethanol</td>
<td>85.6 (1.097)</td>
<td>7.047 (0.285)</td>
<td>0.636 (3.464*10^-3)</td>
</tr>
<tr>
<td>AAcetone</td>
<td>83.5 (3.260)</td>
<td>7.442 (2.590)</td>
<td>0.609 (8.476*10^-4)</td>
</tr>
<tr>
<td>AAcetone/water</td>
<td>82.2 (3.107)</td>
<td>8.035 (1.506)</td>
<td>0.617 (7.608*10^-4)</td>
</tr>
</tbody>
</table>

$^a$ Yield pressure determined in the pressure interval 50-150 MPa
$^b$ Elastic recovery

Since the total and the permanent degree of compression, and the permeability of the tablets varied with the bulk density and nominal fracture strength of the single particles (Figure 8c and d), it is concluded that a variation in the fracture strength of the particles gave a variation in the degree of deformation or fragmentation expressed during and persistent after compression.

![Figure 8](image_url)

**Figure 8.** (a) Nominal particle fracture strength plotted as a function of the bulk density, (b) Kawakita $b^{-1}$ plotted as a function of the nominal particle fracture strength, (c) Kawakita $C$ at 2 N after compaction ($C_{remaining}$) plotted as a function of the nominal particle fracture strength, and (d) the permeability coefficient for compacts prepared at 20 MPa plotted as a function of the nominal particle fracture strength for granules (▲) and agglomerates (■).

The compactability of the powders was assessed by the relationship between the tablet tensile strength and the applied compaction pres-
As described earlier, paracetamol shows poor compactability and is prone to lamination or capping (Malamataris, et al., 1996). At relatively low applied compaction pressures, the tablet tensile strength levelled off owing to capping of the tablets. Generally, the tablets were of low tensile strength. In the pressure range in which apparently flawless tablets were obtained, the evolution of tensile strength of the tablets made of granules depended on their failure strength, while the tablets made of agglomerates had similar compactability profiles.

For the granules, the variation in compactability tended to vary with the particle strength, i.e., the compactability increased as bulk density decreased, which is consistent with earlier findings (Zuurman, et al., 1994). It can be assumed that the variation in evolution of the compactability observed for the granules is related to the variation in the degree of deformation that is expressed during compression and which arises because of the variation in their failure strength. Thus, it is proposed that permanent deformation is the dominant compression mechanism for the granules.

A possible explanation for the limited variation in the compactability exhibited by the agglomerates is that the dominant compression mechanism is fragmentation.
The effect of surface energy on the compression behaviour and tablet forming ability of amorphous lactose

To investigate the relationship between the surface energy and the compactability of powders the tensile strength of tablets similar in microstructure but made of particles which vary in surface energy should be studied. Lactose is considered to be a suitable test material because spray dried lactose is known for its spherical shape and its irreversible deformation during compression, and because it bonds predominantly by particle-particle adsorption (Sebhatu, et al., 1997, Sebhatu and Alderborn, 1999). Furthermore, it was shown that the bonding ability of spray dried lactose can be modified by adding surfactant to the feeding solution (Berggren, et al., 2004).

Solid state, powder and compression properties

The three batches of lactose prepared by spray drying and containing no or a low proportion of polysorbate 80 (respectively, 0%, 0.001% and 0.01% w/w) differed negligibly in their apparent particle density and showed similar X-ray patterns, that indicated that the particles were predominately amorphous. In the thermogrammes recorded by differential scanning calorimetry, a step change at approximately 115°C could be observed for all batches. This value agrees with the values reported in the literature for the glass transition of amorphous lactose (Berggren, et al., 2004). For all powders, the particle size was estimated to be 5-20 μm for particles suspended in peanut oil and inspected using a light microscope at a 100-fold magnification. No statistically significant differences in the bulk density and in the volume specific surface area were observed between the powders.

The propensity of the particles to fragment was studied by comparing the specific powder surface area with the specific surface area of tablets compacted at 80 MPa. The specific surface area of the lactose powder was similar to the specific surface area of the lactose tablet. For the powders containing polysorbate 80, the specific surface area of the tablets was smaller than of the powders. These results indicated that particle deformation dominated the compression process and that particle fragmentation was limited (Table 3). The SEM images (Figure 10) of the tablet surfaces show deformed and partially cracked particles which are similar in size to the original ones. The cracks can be seen to propagate from the edges to the centre. Furthermore, the images of the fracture surfaces indicate that particle fusion had occurred.
locally and that solid bridges were formed during compression. The images confirm that the particles have a limited propensity to fragment.

<table>
<thead>
<tr>
<th>Tablet surface</th>
<th>Fractured surface</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose</td>
<td></td>
</tr>
<tr>
<td>Lactose / polysorbate 80 0.001% (w/w)</td>
<td></td>
</tr>
<tr>
<td>Lactose / polysorbate 80 0.01% (w/w)</td>
<td></td>
</tr>
</tbody>
</table>

*Figure 10.* SEM pictures of the upper (left column) and the fractured (right column) surfaces of tablets compacted at 140 MPa.

It is possible that the formation of solid bridges could explain the reduced surface area obtained for tablets made of particles containing polysorbate 80 compared to the surface area of the respective powders without it. However, it can be assumed that the addition of small proportions of polysorbate 80 had a limited effect on the evolution of the tablet microstructure, expressed in terms of the increased propensity of the polysorbate 80-containing particles to fuse, which resulted in
the formation of solid bridges. It is possible that this effect can be explained by a depressed glass transition temperature and by increased molecule mobility caused by the presence of polysorbate 80, which was preferentially located at the particle surfaces. Further indications of the similarity in compression behaviour of the powders were the fact that there were only subtle variations in the permeability coefficient, elastic recovery, Heckel parameters (Table 3) and the coinciding porosity-compaction pressure profiles (Figure 11).

![Figure 11. Tablet porosity-compaction pressure profiles of the different lactose powders.](image)

**Table 3. Characteristics of the powders and their compression properties**

<table>
<thead>
<tr>
<th>Material</th>
<th>Powder surface area (cm²)</th>
<th>$P_r$ in die (MPa)</th>
<th>$P_r$ out of die (MPa)</th>
<th>Tablet permeability coefficient $^{a}$ (Ns²/m) * 10⁵</th>
<th>Tablet surface area (cm²)</th>
<th>Elastic recovery (in die) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose</td>
<td>7409.1 (227.3)</td>
<td>117.9</td>
<td>209.1</td>
<td>1.1271 (0.0190)</td>
<td>7419 (142)</td>
<td>1.617</td>
</tr>
<tr>
<td>Lactose / polysorbate 80 0.001% (w/w)</td>
<td>7430.9 (428.4)</td>
<td>108.5</td>
<td>219.6</td>
<td>1.1675 (0.1181)</td>
<td>6828 (127)</td>
<td>2.100</td>
</tr>
<tr>
<td>Lactose / polysorbate 80 0.01% (w/w)</td>
<td>7441.2 (487.7)</td>
<td>127.7</td>
<td>219.7</td>
<td>1.1535 (0.0681)</td>
<td>7034 (33)</td>
<td>1.561</td>
</tr>
</tbody>
</table>

$^{a}$ for tablets compacted at 80 MPA; 5% confidence intervals in parenthesis.

From the results presented, it can be concluded, that the particles were of similar solid state and that the tablets they formed were of similar microstructure. The particle composition did not affect the compres-
sion of the powders, and deformation was the dominant compression mechanism whereas the propensity to fragmentation was low. Thus, it can be assumed that the original particle surfaces were involved in particle-particle bonding. Finally, it was expected that the surface energy of the particles would be changed owing to the presence of polysorbate 80.

![Graph](attachment:image.png)

**Figure 12.** Compactability profiles of (a) the initial part and (b) the whole pressure range for tablets made of (●) lactose, (■) lactose / polysorbate 80 0.001% (w/w) and (▲) lactose / polysorbate 80 0.01% (w/w).

**Powder compactability**

The compactability of the powders was described by the evolution in tablet tensile strength with increasing compaction pressure (Figure 12). To form a tablet strong enough to be handled requires the application of pressure above a critical formation pressure. Above this pressure, the tensile strength of the tablet increased almost linearly with increasing compaction pressure until a pressure interval was reached where the tablet tensile strength levelled out or decreased as the compaction pressure was further increased. Approximate values for the critical formation pressures and the slopes of the initial part of the compactability profiles were obtained by linear regression and extrapolation to zero tablet strength. The evolution in the tablet tensile strength was dependent on the composition of the particles, as indicated by the reduction of the critical formation pressure and the slope of the pressure dependent region of the compactability profiles with increasing proportions of polysorbate 80 (Table 4). These observations correlate well with the effects of small proportions of polysorbate 80 on amorphous lactose particles reported earlier (Berggren, et al., 2004). The pressure dependent interval was followed by a pressure independent interval that was characterised by merging compactability profiles with large spreads in the tensile strength and even decreasing
tensile strength. A common explanation for the reduced tensile strength of tablets, despite an increase in the compaction pressure is capping (Shotton and Ganderton, 1961).

Table 4. Characteristics of powder compaction properties

<table>
<thead>
<tr>
<th>Material</th>
<th>Critical formation pressure (MPa)</th>
<th>Slope of the compaction profile(^a) (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactose</td>
<td>78.51</td>
<td>0.0290 (0.9671)</td>
</tr>
<tr>
<td>Lactose / polysorbate 0.001% (w/w)</td>
<td>90.74</td>
<td>0.0173 (0.9617)</td>
</tr>
<tr>
<td>Lactose / polysorbate 0.01% (w/w)</td>
<td>101.76</td>
<td>0.0101 (1.0000)</td>
</tr>
</tbody>
</table>

\(^a\) R\(^2\) values of the corresponding linear relationships, in parenthesis

From the results presented, it can be concluded that the surface energy affects the bonding strength of adsorption bonds. Furthermore, it was shown that particles that have similar solid state properties, but different compression behaviours can be prepared by the addition of small amounts of polysorbate 80 to the feed solution used for spray drying.

Drug release from single microcrystalline cellulose pellets

The effect of pellet porosity, dissolution medium flow rate and drug solubility

**Unlubricated uncompacted pellets**

In this part of the study, unlubricated pellets of high and low porosity, containing NaCl and salicylic acid (SA) were used. The difference in the porosity between the high and low porosity batches was significant. The particle size varied to a limited degree, but the particle size distribution within each batch was narrow. The pellets were spherical as the values for the circularity of close to one indicate.

**Drug release**

In Figure 13 the release profiles determined for pellets containing NaCl (I) and SA (II) are presented. The displays (a)–(d) show five measurements for each combination of pellet porosity and dissolution medium flow rate. Note the different time-scale used for NaCl and
SA. Slight inter-pellet variations between measurements determined under identical conditions were observed for both model drugs and all combinations of pellet porosity and dissolution medium flow rate.

Figure 13. Release profiles for NaCl (I) and SA (II). Each display (a)-(d) shows the results for a certain combination of pellet porosity and dissolution-medium flow rate, as indicated in the figure. Five measurements were made for each combination, and each curve corresponds to the release from a single pellet.

It was observed that the drug release from low porosity pellets was slower than from high porosity ones and that the drug release of a poorly soluble drug was slower than the drug release of a highly soluble one. The effect of dissolution medium flow rate was limited.

The MDT, VDT, and RD were calculated and used to characterise the drug release process. In Table 5, the values obtained for the MDT and RD are summarised. ANOVA, using MDT with the pellet porosity, drug solubility and dissolution medium flow rate as factors confirmed highly significant effects of the drug solubility and the pellet porosity on the MDT (p<0.001), but no significant effect of the dissolution medium flow rate on the MDT was observed. A strong interaction (p<0.001) between pellet porosity and drug solubility was observed. An increase in the porosity reduces the MDT much more for the less soluble drug (SA) than for the more soluble one (NaCl).
Table 5. Non-parametric characteristics of the release process: MDT and RD

<table>
<thead>
<tr>
<th>Drug</th>
<th>Porosity</th>
<th>Flow rate</th>
<th>MDT (s)</th>
<th>RD (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaCl</td>
<td>High</td>
<td>Low</td>
<td>78.7 ± 10.1</td>
<td>1.93 ± 0.35</td>
</tr>
<tr>
<td>NaCl</td>
<td>High</td>
<td>High</td>
<td>60.6 ± 2.8</td>
<td>2.02 ± 0.17</td>
</tr>
<tr>
<td>NaCl</td>
<td>Low</td>
<td>Low</td>
<td>74.8 ± 5.3</td>
<td>2.01 ± 0.43</td>
</tr>
<tr>
<td>NaCl</td>
<td>Low</td>
<td>High</td>
<td>76.1 ± 6.7</td>
<td>2.39 ± 0.43</td>
</tr>
<tr>
<td>SA</td>
<td>High</td>
<td>Low</td>
<td>3850 ± 380</td>
<td>0.744 ± 0.049</td>
</tr>
<tr>
<td>SA</td>
<td>High</td>
<td>High</td>
<td>4450 ± 210</td>
<td>0.534 ± 0.048</td>
</tr>
<tr>
<td>SA</td>
<td>Low</td>
<td>Low</td>
<td>8100 ± 420</td>
<td>0.761 ± 0.025</td>
</tr>
<tr>
<td>SA</td>
<td>Low</td>
<td>High</td>
<td>6500 ± 380</td>
<td>0.652 ± 0.0035</td>
</tr>
</tbody>
</table>

The values given are mean values ± standard errors of the mean.

The RD is significantly larger for NaCl than for SA. Changes in the release mechanisms (Lánský and Weiss, 2003) or in the physicochemical properties of the drug substances could explain this.

By using the model proposed by (Frenning, 2004), it was possible to determine values for the effective diffusion coefficient ($D_{eff}$), the drug solubility ($C_s$) and the dissolution rate constant ($\kappa$). For a porous matrix the parameter, $\xi_s$ may be calculated as:

$$\xi_s = \frac{e_p C_s}{S_0}$$

and interpreted as a measure of the drug solubility in the matrix in relation to the initial drug loading, where $e_p$ is the pellet porosity, $C_s$ the drug solubility in the dissolution medium and $S_0$ is the initial concentration of solid drug in the pellet. The parameter $\kappa$ is a dimensionless dissolution rate constant as defined by (Frenning, 2004). The effective diffusion coefficient, the drug solubility and the dissolution rate constant were determined from the drug release process at the lower flow rate only and summarised in Table 6. These parameters can be used to characterise the release process.

Table 6. Physicochemical parameters of the release process for experiments using low dissolution-medium flow rates: effective diffusion coefficient ($D_{eff}$), solubility/dose ratio ($\xi_s$), and non-dimensional dissolution rate constant

<table>
<thead>
<tr>
<th>Drug</th>
<th>Porosity</th>
<th>$D_{eff}$ ($10^{-5}$ cm/s)</th>
<th>$\xi_s$ (%)</th>
<th>$\kappa$ (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaCl</td>
<td>High</td>
<td>1.51 ± 0.32</td>
<td>72 ± 18</td>
<td>25 ± 20</td>
</tr>
<tr>
<td>NaCl</td>
<td>Low</td>
<td>0.91 ± 0.24</td>
<td>59 ± 14</td>
<td>56 ± 36</td>
</tr>
<tr>
<td>SA</td>
<td>High</td>
<td>2.39 ± 0.90</td>
<td>0.13 ± 0.02</td>
<td>240 ± 110</td>
</tr>
<tr>
<td>SA</td>
<td>Low</td>
<td>0.37 ± 0.06</td>
<td>0.42 ± 0.06</td>
<td>76 ± 7</td>
</tr>
</tbody>
</table>

The values given are mean values ± standard errors of the mean.
The effective diffusion coefficient describes the drug transport in the pore system. The value obtained for high porosity NaCl pellets is close to the value presented in the literature for unhindered NaCl diffusion, while the value obtained for high porosity SA pellets is larger than the respective literature value. The dissolution rate is described by $\kappa$. The $\kappa$-value for high porosity SA pellets is strikingly high. As far as the drug solubility in the matrix is concerned, the values for NaCl pellets and low porosity SA pellets were as expected, while the value obtained for high porosity SA pellets was unexpectedly low. Solvent migration during drying may have resulted in non-uniform distribution of the drug, particularly within the high porosity SA pellet, as SA is much more soluble in ethanol than in water. A higher concentration of SA at the exposed pellet surface may thus explain the unrealistically high values obtained.

The effect of compaction pressure and pellet location within a tablet

**Lubricated uncompacted pellets**

In this part of the drug release study, only pellets of high and low porosity containing NaCl were used. The pellets were lubricated with magnesium stearate using a Turbula mixer to make deaggregation after compaction possible. All data presented in the following section were derived from experiments on lubricated pellets. It was expected that the long mixing time could affect the pellet size and geometry due to surface erosion. When the lubricated and unlubricated pellets are compared, it can been seen that the mixing process has a limited effect on the low porosity pellets, while the lubricated high porosity ones were of higher bulk density, higher circularity, and smaller projected area than the respective unlubricated pellets. A potential explanation of this is that the high porosity pellets might have become smaller and more even as a result of surface erosion during the mixing process. The high porosity pellets were smaller in size than the low porosity ones, but both types of pellets were spherical in shape, as indicated by the high circularity (Figure 14) and the SEM-pictures (Figure 15). The drug release profiles of both pellet types showed inter-pellet variation (Figure 16), but were generally equal.
Figure 14. Projected area, Feret diameter and circularity at different compaction pressures for pellets of high and low porosity collected from the top layer of the tablets. Error bars indicate the 5% confidence interval.
High porosity pellets

Low porosity pellets

Original

100 MPa

170 MPa

240 MPa

300 MPa

Figure 15. Pellets of high and low porosity uncompacted and compacted at 100 MPa, 170 MPa, 240 MPa, and 300 MPa, collected from the top layer of the tablets; magnification: 50x.
Figure 16. Drug release from single uncompacted and lubricated pellets, (a) high porosity pellets, and (b) low porosity pellets.

As in the previous study, the statistical measures MDT, VDT, and RD were calculated and used to characterise and compare the dissolution profiles. As far as the porosity differences and the results obtained when measuring drug release from unlubricated pellets were concerned, it may be unexpected that the MDT was similar for both types of pellets. Inspection of the release profiles of the lubricated pellets reveals that the low porosity pellets tended towards a biphasic drug release profile. A faster initial drug release rate was followed by a slower one in the upper part of the profile. The higher VDT of the low porosity pellets may be explained by this tendency to a more biphasic profile. It is possible that an increase in the concentration of the drug close to the external surface explains the biphasic release profile. Drug molecules deposited in the outer part of the matrix pore system would be released, predominantly by dissolution directly into the dissolution liquid, while the release of molecules located in the interior of the matrix is controlled by transport of the solute in the pore system. As discussed above, the high porosity pellets were more prone to abrasion than the low porosity ones. During the mechanical treatment in the Turbula mixer, the high porosity pellets lost more of the outer part of their matrix containing the high drug concentration. Thus, the slower initial drug release of high porosity pellets can be explained by the loss of matrix containing a high concentration of drug in the outer parts of the pellet. It is thus suggested that, for the high porosity pellets, transport of dissolved drug in the matrix pore system is the dominant release mechanism, while direct dissolution followed by pore transport dominates the release from the low porosity pellets.
It has been suggested previously that the relative dispersion coefficient (RD) may reflect the dominant mechanism for transporting a drug during the release process (Pinto, et al., 1997). Although the RD values obtained lay beyond the range covered and characterised by Pinto et al. (1997), it is possible that the variation of RD is indicative of such changes in the drug release behaviour of the pellets. The differences in RD between the pellets may support the discussion above and the assumption that different mechanisms are involved in the drug release process.

**Retrieved pellets**

*Compression behaviour*
The pellets were compacted into tablets and carefully deaggregated. The compression-induced changes in physical appearance and drug release were studied using the single pellets retrieved.

Generally, the pellets deformed owing to compression and cracks at the pellet surfaces could be observed (Figure 15). It may be assumed that the high porosity pellets also densified during compression (Johansson, et al., 1998). The differences between the high and low porosity pellets’ response to the compression pressure were studied using the descriptors: projected area, Feret diameter and the circularity derived from 2-dimensional images. For low porosity pellets, these three descriptors were affected by compaction pressure only to a limited degree in contrast to high porosity pellets, for which the projected area and the Feret diameter increased and the circularity decreased with increasing compaction pressure. These assumptions were supported independently for high and low porosity pellets by ANOVAs using the three descriptors with the compression pressure on four levels as the factor and uncompressed pellets as the control. Consistent with earlier observations on pellets made of microcrystalline cellulose (Johansson, et al., 1995, Tunón, et al., 2003), it was found that the degree of deformation during compression for low porosity pellets was lower than for high porosity ones.

*Drug release*
The measures derived from the release profiles of pellets collected from the top and bottom layer of the tablets are given as a function of compaction pressure in Figure 17. Two-way- ANOVAs were performed
individually for pellets of high and low porosity using the MDT values with the compaction pressure (4 levels) and the location within the tablet (2 levels) as the factors. As no significant effect of pellet location within the tablet was observed, one-way ANOVAs with the pressure as the only factor (5 levels) were carried out and comparisons with uncompressed pellets, as the control, were made. The aspect of pellet location within the tablets is not covered further in the following discussion.

![Figure 17](image)

**Figure 17.** MDT, VDT, and RD at different compaction pressures for pellets of high and low porosity collected from the top (■) and bottom (□) tablet layer. Error bars indicate the 5% confident interval.

For high porosity pellets compacted at 100 MPa, both MDT and VDT decreased and, thereafter, both measures increased with increasing...
compaction pressure. With increasing compaction pressure the RD tended to increase and approached a value similar to the RD values obtained for the low porosity pellets. The relationship between the drug release rate, as assessed by the MDT, and the compaction pressure can be explained by assuming that the release rate can be both retarded and enhanced by changes in the physical structure of the inert matrix during compression. During compression, pellet densification occurs and reduces the matrix porosity as well as the pore size, retarding the drug release. The retarding process is dominant in the lower compaction pressure region (below 100 MPa) used in this study. In the upper compaction pressure region (above 100 MPa) the drug release process is accelerated owing to crack formation. Thus, the dissolution of drug particles located at the exposed pellet surfaces dominates the process. In parallel with the increase in MDT, the VDT and RD increased, indicating a change in the overall release profile and, therefore, the mechanism responsible for the release. The fact that the RDs of the compacted high porosity pellets approach the values of the original low porosity pellets may support the discussion above in which it is suggested that a change in the release pattern is indicative of a significant degree of direct dissolution of the drug from external surfaces. In Figure 18a, the release profiles are presented for high porosity pellets compacted at 100 and 300 MPa. The increase in compaction pressure seemed to result in a biphasic profile.

![Conductance vs Time for High Porosity Pellets Compacted at 100 MPa and 300 MPa](image1)

![Conductance vs Time for Low Porosity Pellets Compacted at 100 MPa and 300 MPa](image2)

**Figure 18.** Drug release profiles for (a) high and (b) low porosity pellets compacted at 100 MPa (—) and 300 MPa (—.—).

As for the low porosity pellets, MDT, VDT and RD did not change with compaction pressure, so it can be concluded that the drug release process was unaffected by, and independent of the compaction pressure used. If direct dissolution is assumed to be an important mecha-
nism for drug release for these pellets, the absence of a compaction pressure induced effect may be explained. As the propensity of these pellets to densify during compaction as a result of their low original porosity is low, drug release is not retarded by compression. Figure 18b presents the drug release profiles for low porosity pellets compacted at 100 and 300 MPa.
Summary and conclusions

The overall aim of this thesis was to identify some functionality related characteristics of solid pharmaceutically relevant materials and to investigate the effect of their variation on the product performance. The impact that the particle size distribution, the degree of agglomeration, the particle failure strength, and the surface energy have on the compressibility and compactability of a powder was investigated. Furthermore, a new method applicable for the investigation of the drug release profile from single pellets was introduced and used to examine how the porosity and compaction pressure can influence the mechanism by which drugs are released from single matrix pellets made of microcrystalline cellulose. The specific conclusions were:

- For the materials tested, the spread in particle size had no influence on the evolution of the tablet porosity and tensile strength during compression. However, the spread in particle size was observed to have a significant, and complex, influence on the short-term post-compaction increase in tablet tensile strength. This effect was related to the instability mechanism and also to the presence of lubricant. For unlubricated powders, only mechanism $\beta$ showed a dependence on the original distribution in particle size. However, the presence of lubricant introduced a dependence on the original distribution in particle size that could not be observed in tablets of the same unlubricated powder. It was concluded that the spread in the size of particles within the coarse particulate domain is not critical for the tablet porosity, but may give rise to significant and complex effects on tablet strength owing to a post-compaction reaction.

- Using two different particle preparation methods, crystal agglomeration and wet granulation, it was possible to obtain particles varying in their degree of agglomeration and with different failure strengths. It was observed that only the compac-
tability of the granules varied with particle failure strength. Thus, it is proposed that the dominant mechanism of compression for the granules was permanent deformation while for the agglomerates it was fragmentation.

- It was possible to prepare particles which were likely to vary in surface energy but formed tablets of similar microstructure by spray drying solutions containing small but different proportions of surfactant. It was believed that the surface energy affects the bonding strength of adsorption bonds (i.e., intermolecular bonding forces) acting at the inter-particulate junctions.

- Using the new method presented for characterizing the drug release from single matrix granules, it was possible to obtain reproducible data for drug release that was of sufficient quality for meaningful parameters describing the drug release process to be determined. Furthermore, it was shown that drug solubility and agglomerate porosity had a highly significant effect on drug release, while the flow-rate of the dissolution medium had no significant effect.

- The drug release rate of single matrix pellets was dependent on the physical changes brought about to the matrix during compression. Depending on the type of matrix and the compaction pressure, the drug release rate could be enhanced or retarded. Retardation is believed to be attributable to a densification of the matrix, and acceleration thought to arise from crack formation in the external surface of the matrix.
Zusammenfassung


Der Einfluss der Partikelgrößenverteilung eines Pulvers auf die Bruchfestigkeit von Tabletten und auf deren Strukturumwandlung während der Lagerung wurde anhand von Pulvern untersucht, die sich in ihrer Partikelgrößenverteilung und der zugesetzten Menge des Schmiermittels Magnesiumstearat unterschieden. Wie die mechanischen Eigenschaften einzelner Partikel das Komprimier- und Kompaktierverhalten ihrer Pulver beeinflussen, wurde mit Hilfe von Paracetamolpartikeln untersucht, die durch Kristallisieren aus und Granulieren mit unterschiedlichen Lösungsmitteln hergestellt wurden und sich so in ihrer Bruchfestigkeit und ihrem Agglomerationsgrad unterschieden. Amorphe Laktosepulver, die unterschiedliche aber sehr niedrige Konzentrationen der oberflächenaktiven Substanz Polysorbat 80 enthielten, wurden durch Sprühtrocknung gewonnen. Die Auswirkungen dieser niedrigen aber unterschiedlichen Konzentrationen an Polysorbat 80 auf das Komprimier- und Kompaktierverhalten der Pulver wurden untersucht.

Im Rahmen dieser Arbeit wurde auch eine neue konduktrometrische Methode entwickelt, die es ermöglicht die Wirkstofffreisetzung aus einzelnen Matrixpartikeln zu beobachten. Diese Methode wurde angewandt um zu analysieren, welche Auswirkungen die Porosität der Matrix, die Löslichkeit des Modellwirkstoffs und der Pressdruck beim Tablettieren auf die Wirkstofffreisetzung haben können.

Es konnte gezeigt werden, dass die Partikelgrößenverteilung nur eine untergeordnete Rolle für die Kompaktierbarkeit der Pulver und die Eigenschaften der Tabletten direkt nach dem Tablettieren spielt. Während der Lagerung allerdings scheint die Partikelgrößenverteilung und

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