New Methods to Evaluate Applicability of Powders and Granules for Tablet Compression

by

Osmo Antikainen

Academic Dissertation

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ABSTRACT

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Knowledge of the compactibility and the flowability of a new pharmaceutical powder composition is essential already in the early formulation stage. This makes a successful transfer of a new powder formulation candidate to the manufacturing level more likely. The aim of this study was to find new methods to evaluate, as early stages of drug development processes as possible, if powder or granules are proper for use in tablet machines.

In this thesis a great number of new parameters were derived from tablet force-time and force-displacement curves. The aim was to provide parameters that could in some cases alone, but more commonly together, lead to a better understanding and predicted behaviour of powders during compression.

Correlations between most of the new parameters and responses (crushing strength and friability of tablets) were statistically significant. The presented new parameters could explain the compression phenomenon from different points of view. The tendency of the material for plastic deformation, fragmentation and elasticity could be also expressed as numerical values, which are comparable between different materials.

A novel way of viewing powder flow test results (self organising map) was introduced and a method of predicting the flow behaviour of pharmaceutical powders using only very small amount of powder (10 ml) was also developed.

The new methods developed to view and predict flowability proved to be working and useful means of evaluating the flow properties of new powder formulations.
TABLE OF CONTENTS

1. INTRODUCTION.................................................................................................................1

2. LITERATURE REVIEW...........................................................................................................3
  2.1 PHARMACEUTICAL POWDERS ..........................................................................................3
  2.2 TESTING OF POWDER FLOW ..........................................................................................3
  2.3 DEFORMATION OF POWDERS ..........................................................................................4
  2.4 STAGES OF TABLET COMPRESSION ...............................................................................6
  2.5 TABLET BONDS..................................................................................................................7
  2.5.1 Distance attraction forces ...........................................................................................8
  2.5.2 Solid bridges ...............................................................................................................8
  2.5.3 Non freely movable binder bridges .............................................................................8
  2.5.4 Bonding due to movable liquids ..................................................................................9
  2.5.5 Mechanical interlocking .............................................................................................9
  2.6 ANALYSIS OF TABLET COMPACTION DATA ...................................................................9
  2.6.1 A relationship between compression force and tablet strength .........................10
  2.6.2 Force-time compression profiles ..............................................................................11
  2.6.3 Force-displacement compression profiles ...............................................................13
  2.7 POROSITY-PRESSURE EQUATIONS ...............................................................................16
  2.7.1 Heckel Plot .................................................................................................................17
  2.7.2 Cooper-Eaton Equation ...............................................................................................21
  2.7.3 Kawakita equation .......................................................................................................22
  2.8 STRESS AND STRAIN TESTS ........................................................................................23
  2.8.1 Stress relaxation test ..................................................................................................23
  2.8.2 Creep test ...................................................................................................................25

3. AIMS OF THE STUDY .........................................................................................................27

4. EXPERIMENTAL ..................................................................................................................28
  4.1 MATERIALS ......................................................................................................................28
  4.1.1 Powders .....................................................................................................................28
  4.1.2 Granules (I) .................................................................................................................29
  4.2 TABLET COMPRESSION AND CHARACTERISATION (I – VII) .....................................29
  4.2.1 Crushing strength of tablets (II-III) ..........................................................................29
  4.2.2 Friability of tablets (II-III) .........................................................................................30
  4.3 POWDER FLOW MEASUREMENTS (IV, V AND VII) .....................................................30
List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDS</td>
<td>Dispersive x-ray spectroscopy</td>
</tr>
<tr>
<td>FLO</td>
<td>A non-commercial flowmeter (Orion Pharma, Finland)</td>
</tr>
<tr>
<td>MCC</td>
<td>Microcrystalline cellulose</td>
</tr>
<tr>
<td>PCA</td>
<td>Principal component analysis</td>
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<tr>
<td>PLS</td>
<td>Partial least squares projection to latent variables</td>
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<tr>
<td>RSD</td>
<td>Relative standard deviation</td>
</tr>
<tr>
<td>SEM</td>
<td>Scanning electron microscopy</td>
</tr>
<tr>
<td>SMCC</td>
<td>Silicified microcrystalline cellulose</td>
</tr>
<tr>
<td>SOM</td>
<td>Self-organising map</td>
</tr>
<tr>
<td>SRS</td>
<td>Strain-rate sensitivity index</td>
</tr>
</tbody>
</table>
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Helsinki, November 2003
List of original publications

This thesis is based on the following original papers, which are referred to in the text by the Roman numerals I-VII.


1. INTRODUCTION

Since the invention of compressed tablet over 150 years ago by Thomas Brockedon, the tablet has become increasingly popular dosage form. Today it is the most common oral dosage form (Rubinstein, 2000), and it has many special benefits compared to other forms. Advantages of tablet are e.g.: accurate dosage, ease of administration, good stability, suitable for large scale production, easy and cheap to package and ship, low cost, special release profiles are possible and good patient acceptance.

The pharmaceutical industry has to produce tablets that have consistent quality from batch to batch. Tablets must be strong enough to withstand exertion caused by packing, storage and handling. They must also disintegrate and release drug reproducible with a desired manner in an alimentary canal.

A knowledge of starting materials and manufacturing processes is essential to fulfil the above requirements. In the development phase of tablet formulation, it is also important as early as possible to ensure that the transfer of the formulation to the manufacturing level is possible (Bjerrum, 2002). Many different characteristics affect whether a new formulation is suitable for fast moving tableting machines. These can be divided into two main characteristics: material and tableting machine characteristics. Fluidity and compressibility are two essential material characteristics. The type of the tablet machine, the shape and the diameter of the punches, compression force and speed are the most common machine characteristics.

A wide number of investigations has been carried out over decades and several theories of tablet bonding mechanism have been founded but there is still no universal theory that could be used to predict the properties of compressed tablets. Rapid uni-axial compression used in tablet machines produces an anisotropic and heterogeneous tablet which density, porosity and strength are spread unhomogeneously throughout the tablet (Nyström et al., 1993). That is why tablet compression is a very difficult phenomenon to model.

Capping, lamination, sticking of powder to punches, flowability problems and too large weight variation of tablets are the most common problems facing tablet manufacturing.
Tablet machines have been instrumented since 1950s (Krycer and Pope, 1982). This has made possible the analysis of the compression phenomena in a novel way. Movement of punches and forces applied to them in different phases of compression are the most commonly measured factors. From the measured data, it is possible to draw different kind of compression profiles. The shape of these profiles are characteristic for different type of materials. Parameterisation of these profiles can give us general material parameters which can help us to understand and control the complicated compression phenomena. These parameters can give information about the good and bad qualities of a material. They can thus help us to find solutions to compression problems and make formulation development quicker and less expensive.

Powder intended for compression into tablets must possess among compactibility good fluidity. An adequate fluidity is needed during powder transport from the hopper of the tablet machine in to the dies. Problems in fluidity cause variations in die filling and consequently tablets that vary in weight and strength. Problems with flowability can cause major economic setbacks for pharmaceutical industry (Prescott and Hossfield, 1994). In order to quantify the flow behaviour of powders, both dynamic and static methods have been developed. Special flow meters represent dynamic methods and different kinds of angles of repose are examples of static methods. Techniques available today for assessing flow are still limited and no single piece of equipment is able to take into account all component factors of the problem (York 1980). New ways to measure and illustrate powder flowability would thus broaden our understanding of this complicated phenomenon and help in the selection of proper formulation excipients.
2. LITERATURE REVIEW

2.1 Pharmaceutical powders

The largest use of powders in pharmacy is to produce tablets and capsules (Staniford 1988). A powder is a heterogeneous system consisting of solid dry particles and air. Air can exist both between and inside particles (Nyström et. al 1993). According to British Standard (BS2955, 1958) the maximum dimension of discrete particles in a material classified as a powder, is less than 1000 μm (York, 1980). Powders are not solids or liquids although they have some properties common to both of them. Powders can flow and have rheological properties typical to liquids. Powders can also deform permanently, fragment to smaller pieces and have elastic behaviour that is typical for solids.

Pharmaceutical powders are usually mixtures that consist of powdered drug plus a variety of excipients, such as diluents, disintegrants, binding agents and lubricants. Most drugs and additives are crystalline materials, or posses a high degree of crystallinity (York, 1983). There are no free electron carriers in crystalline structure of most pharmaceutical materials and thus they are insulators.

During powder handling operations, particles have collisions with each other and with the surfaces of vessel and tools. Normally with each collision, interfacial charge transfers occur. Particles become electrically charged due to this triboelectrostatic charge transfer. The direction of this charge transfer is dependent on the difference of the electron affinity of the two touching materials. Particles with highly polar surfaces have a water sorption layer in normal room conditions, which distributes the transferred charge homogeneously all over the surface. With crystalline particles with a weak polar surface, extremely high values of charge can be induced to the edges of particles. This electrostatic charge produces a tendency for particles to stick to themselves and to other surfaces, which can reduce the flowability of a powder.

2.2 Testing of powder flow

Adequate fluidity is needed that the material can be transported through the hopper of the tablet machine in to the dies. If there is not equal filling of the dies, the tablet machine cannot make tablets of consistent weight and strength. Fine particles (< 100
μm), which have a high surface to mass ratio, are most cohesive. When particle size increases, this tendency becomes less and particles greater than 250 μm are usually relative free flowing. Particle shape has a marked effect on the flow properties of powders, due to differences in inter-particle contact areas. Spheres have optimal flow properties because of small inter-particle contact area. Flakes have a very high surface to volume ratio and consequently possess poor flow properties.

Powder beds are generally composed of particles of different shapes and sizes with interparticulate voids and are in addition, non-homogenous in structure. For this reason, a powder bed contains a multitude of differently interacting surfaces and consequently powder flow takes place in a complex manner (York, 1980). Many different methods for quantifying powder flow have been developed, either direct techniques using dynamic or kinetic methods, or indirect techniques, generally by measurements carried out on static bed (Santomaso et al., 2003; Staniforth, 1988). Most common direct methods of evaluating powder fluidity use the measurement of flow rate through an orifice and various kinds of recording flow meters. Angle of repose, angles of friction (Train, 1958), different kind of packing characteristics (Carr, 1970) and shear cell measurements (Hestand and Wilcox, 1968; 1969; Carr and Walker, 1967; Kocova and Pilpel, 1972) are indirect method commonly used to quantify powder flow. Many studies suggest that results are dependent upon the manner in which the test was formed (Jones and Pilpel, 1966; Schüsele and Bauer-Brandl, 2003). Results can also vary due to differences in the way the samples are handled prior to measurement. Techniques available today for assessing flow are still limited and no single piece of equipment is able to take into account all component factors of the problem (York, 1980).

2.3 Deformation of powders

Pharmaceutical powders vary in their mechanical behaviour during compression. Particles deform elastically, plastically or they can fragment. Elastic deformation is reversible, whereas plastic deformation is irreversible of the whole or part of the particles (Nyström et al., 1993). Fragmentation can be defined as a dividing-up of a particle into a number of smaller, discrete parts (Duberg and Nyström, 1982) (Aldeborn et al., 1985).

Microcrystalline cellulose, starch (Fig. 1), sodium chloride and stearic acid are examples of materials that are considered to deform mainly by plastic flow (Hardman
and Lilley, 1970; David and Ausburger, 1977; Duberg and Nyström, 1982; Roberts and Rowe, 1986). Most drugs and some excipients show a tendency to fracture on compression. Paracetamol, sucrose, and dibasic calcium phosphate dihydrate (Emcompress®) (Fig. 1) are examples of fragmenting materials (McKenna and McCafferty 1982; Roberts and Rowe 1985).

![Figure 1. Two differently deforming materials before (left) and after compression (right). Plastically deforming material Starch 1500 (above) and fragmenting material Emcompress® (below) (Duberg and Nyström 1982).](image)

The deformation mechanism of a specific particle is affected mainly by the molecular and crystal structure of the material (Rasenack and Müller, 2002; Neric, 1987), particle size, defects in the lattices of crystalline material, magnitude of the applied force and compression speed. Hard brittle materials, which have greater shear strength than tensile strength, tend to fragment more easily than soft materials which has lower shear strength than tensile strength (Celik and Driscoll, 1993). Particles also have a critical diameter at which the densification mechanism turns from fragmentation to plastic deformation when particle size decreases (Roberts and Rowe, 1987 and 1996).
Structural changes during compression are opposed by intermolecular forces, which restore the crystal to its original form in elastic deformation. Permanent deformation of material will take place, if these intermolecular forces are exceeded. The plastic deformation of crystals can be attributed to glide (or slip), twinning, and kinking, all in simple shear (Bandyopadhyay and Grant, 2002). Plastic deformation by slip occurs along specific planes in the crystal, called slip planes, and along specific directions. The fracture of crystals in brittle material is associated with crystal lattice defects and imperfections (Hess 1978). Frequency of defects can be related to the method of deformation of crystalline materials during compression (Huettenrauch, 1977).

2.4 Stages of tablet compression

In tablet compression, powder flows first from the hopper of a tablet machine into a dye. Powder is at this stage of the compression still loosely packed. Size, shape and surface properties of the particles in the powder mainly influence density. In addition, speed of the tablet machine, type of the powder feed mechanism and shape of the die have their effects.

When the punch start to penetrate in to the die, the powder is forced to transform to a denser form. At first, smaller particles move to the voids between larger particles. At this stage, compression forces are still very small. Particles that have a regular shape rearrange more easily than particles that have an irregular shape (York, 1978). Irregular, non-isometric, highly textured particles have a greater tendency to produce open arches inside powder bed than more regularly shaped particles (Fig. 2) (Staniforth, 1988). This can increase the risk of entrapping air in the powder bed and promote capping or lamination of tablets with high speed tablet machines.

![images](image1.png)

Figure 2. Two equidimensional powders having the same porosity but different packing geometries (Staniforth, 1988).
When the punch moves further there will not be any more free space for additional relative movement of particles. At this point, stress starts to develop at the particles contact points and material deforms, at first elastically. Once particles have deformed above the specific elastic limit of material, they will not anymore regain their original shape even though the applied force is released. The material starts to deform more or less irreversibly. Depending on the material, particles can start to fragment into smaller units or deform plastically. When the applied force increases, also plastically deforming materials eventually start to fracture. Further increase in compression force deforms and breaks these smaller particles again and particles can go through several deforming stages during compression. When particles deform and fragment, the surface area of the powder and the area capable of forming bonds increase. Particle surfaces must be in close proximity to each other before they are able to form permanent bonds. There are several mechanisms that will contribute to the strength of the bond, although they never act independently (Celik and Driscoll, 1993).

In the decompression phase, the applied pressure is removed. The compact undergoes then a sudden elastic expansion, which is followed by slow viscoelastic recovery.

### 2.5 Tablet bonds

Particles move during compression in closer proximity to each other and the particle surface area that is capable of forming bonds increases. The process by which the consolidated powders are bonded together under pressure is not well understood (de Boer et al., 1978).

The five dominating mechanisms, which are considered to adhere particles together, are (Rumpf, 1958; Turba and Rumpf, 1964):

1. distance attraction forces
2. solid bridges
3. non-freely-movable binder bridges
4. bonding due to movable liquids such as capillary and surface tension forces.
5. mechanical interlocking.
2.5.1 Distance attraction forces

Here are three different types of forces: Van der Waals forces, electrostatic forces and hydrogen bonding. The strength of these forces is affected by the type of material, the distance between the molecules or particles and the surrounding medium (Israelachvili, 1992).

Van der Waals forces are considered to be the most important distance attraction forces holding particles together (Leuenberger et al., 1989). They operate both in vacuum, gas and liquid environments. They can act up to a distance of 100 – 1000 Å.

Hydrogen bonds are also important for some pharmaceutical materials. Hydrogen bonds develop between molecules containing electronegative atoms (e. g., O, N, F, and Cl) and hydrogen atoms (Pauling, 1960). Lactose, sucrose and microcrystalline cellulose add they compact strength considerably by them (Heiner and Teleman, 1997).

Electrostatic forces are not considered to contribute to any large extent to the tensile strength of pharmaceutical compacts (Nyström and Karell, 1996).

2.5.2 Solid bridges

Solid bridges are proposed to form by melting, diffusion of atoms between surfaces or recrystallisation of soluble materials in the compacts. Compression force is spread in to the mass by particle to particle contacts. If particles are irregular and have a very small area at the contact points, the pressure there is very high. This increases atomic thermal motion and diffusion at these contact points. Materials that have low melting point can also as a consequence of plastic flow and friction melt in contact points. Presence of moisture is also reported to be important in the formation of solid bridges (Ahlneck and Aldeborn, 1989; Erikson and Alderborn, 1994).

2.5.3 Non freely movable binder bridges

The powders normally sorb water from moist air. The thickness of the sorbed water layer depends upon the polarity of the powder surface and the humidity of the atmosphere. In a fairly dry atmosphere, the water will be tightly bound, as a non-freely movable layer of water, which is denoted monolayer-adsorbed moisture (York, 1981) or water vapour adsorption (Ahlneck and Aldeborn, 1989). At most, 2-3 layers of vapour are adsorbed (Van Campen et al., 1980; Zografi 1988). The water molecules are linked to
the surface and to each other by hydrogen bonds. If two this kind of particles are brought into close proximity, water sorption layers can interact. The result is strong inter-particular attraction and the particles have a joint water sorption layer.

2.5.4 Bonding due to movable liquids

At high relative humidity, the amount of water in the powder can increase so much that, in addition to the sorption water, there will be separate movable water phase, which is denoted condensed water (York, 1981). Molecules of the solid can dissolve in this water which can lead to deliquescence of the solid. The critical humidity at which this takes place is characteristic of the solid and is the point above which the adsorbed water assumes the character of bulk solution or condensate (Van Campen et al., 1983; Lordi and Shiromani, 1984). Free water liquid bridges can be formed at contact points between particles (Schubert, 1984). Because of the high surface tension of pure water there will be strong attraction between particles.

2.5.5 Mechanical interlocking

Particles, which have a rough texture and irregular shape, can form bonds by mechanical interlocking. Particles are bond together by hooking and twisting.

Long needle form fibres and irregular particles have a higher tendency to hook and twist together during compaction than smooth spherical particles. Microcrystalline cellulose is considered to have the potential to bond by this method (Karehill and Nyström, 1990).

2.6 Analysis of tablet compaction data

It has been possible to study compaction data in tabletting operations since the mid-1950s. Today the instrumentation of tablet machines is widespread and large numbers of different methods and parameters has been derived to evaluate compaction mechanism of pharmaceutical powders. The most popular are methods which quantitate the extent of plastic and elastic deformation, different types of pressure cycle plots (such as force-time, force-displacement and radial versus axial pressure plots), pressure-porosity (volume) relationships and stress relaxation measurements. It is, however, often difficult to compare results from different authors. This is usually due to differences in the
technical setups they have used, although there are also serious conflicts in conclusions of
researchers that have employed similar methods (Krycer et al., 1982).

2.6.1 A relationship between compression force and tablet strength

A simple and very common method of evaluating the compactibility of a certain powder
is to measure the crushing strength of the tablet (the force required to fracture a tablet
across its diameter) as a function of compression force or compression pressure. Often
the upper punch force is taken alone as a measure of compaction (Salpekah and
Ausburger, 1974) (Shukla et al., 1980). For some materials, substantial die wall friction
can be measured. For these kind of materials, it is more satisfactory to average the upper
and lower punch force (or pressure) (Hersey et al., 1967; Shotton and Obiorah, 1973;
Ragnarsson and Sjögren, 1983). If comparison is made between tablets of very different
shapes or sizes, the tensile strength (Eq. 1) is widely used instead of crushing strength
(Fell and Newton 1970) (Ho and Hersey, 1980) (Newton, 1974) (David and Ausburger,
1974).

\[
\sigma_t = \frac{2P}{\pi D I}
\]  

(1)

where \( P \) is load (N/m²) necessary to cause fracture, \( D \) and \( I \) are the diameter and
thickness of the tablet, respectively.

Hiesand and Peot (1974) have, however, pointed out that due to the lack of
uniform density within powder compact, \( \sigma_t \) values, are, at best, an estimate of the correct
values. Rees and Rue (1977 and 1978) have suggested the tensile work of failure (Eq. 2)
to be used instead of the tensile strength

\[
W_f = \frac{2}{\pi D I} \int F dx
\]  

(2)

where \( F \) and \( x \) are the diametrical compaction force and deformation, respectively.

In compression, below a material dependent compression force limit, powder
will not form a coherent tablet (Fig. 3). As the compression force is increased above this
limit, the tablet strength seems first to increase linearly. The slope of this increase is
characteristic to the material used. When the compression force is increased over a
critical limit, the crushing strength will no longer increase, but will start to decrease, and lamination or capping may occur.

![Diagram of tablet strength as a function of compression pressure]

Figure 3. Tablet strength as a function of compression pressure.

2.6.2 Force-time compression profiles

It is suggested that parameterization of the force-time curve would advance our knowledge of the fundamental physico-chemical functions governing the compaction process. Commonly calculated parameters from force-time profiles are:

- maximum compression force, area under the force-time curve, time to the maximum force, time to the inflection point in the compression phase, maximum slope in the compression phase, time of the compression event and width at the half height (Schwartz, 1981; Jones, 1985; Chirlamkurti et al., 1982; Chirlamkurti et al., 1983; Chirlamkurti et al., 1983b; Hoblitzell and Rhodes, 1990). Another way to describe the force-time curve is to parameterise the shape of the entire profile (Dietrich and Mielck, 1984; Juppo et al., 1995). Use of force-time parameters has so far been quite limited.

Different phases of compression, such as consolidation time, contact time (Fig. 4), are easy to understand and define from the force-time profile.
Figure 4. Force-time and force-displacement compression profiles.

If the force-time and displacement-time curves are examined precisely, it is often seen that their maximum values do not occur simultaneously. The compression force reaches its maximum value before upper and lower punches are in closest position (Ho and Jones, 1988) (Von Müller and Caspar, 1984). This effect can naturally also be seen in force-displacement curves (maximum force and maximum displacement are in different positions). The above “peak offset time” (Fig. 4) has been reported even with rotary tablet machine, where peak force was reached before the punches were vertically aligned with the centres of the upper and lower compression roll support pins (Dwivedi et al., 1991). The phenomenon can be explained by stress relaxation of powder. This is a characteristic feature of solids that consolidate by plastic flow. This kind of materials has, over period of time, ability to relieve the stress under conditions of constant strain. Near
the maximum displacement the upper punch moves very slowly and the effect of stress relaxation is possible to detect.

### 2.6.3 Force-displacement compression profiles

Use of force-displacement curves (Fig. 5) has been a common method of evaluating compression properties of pharmaceutical materials especially, during 1970s and 1980s.

![Figure 5. Force-displacement curve](image)

A different amount of work is needed to make coherent tablets from various powders. Evaluation of the work put into the making of tablets should thus increase our knowledge about the packing and deformation mechanics of different powders. Compression work that is calculated from the area that remains under upper punch force-displacement curve is called gross work or upper punch work. Part of this work is done to overcome die wall friction (W\textsubscript{f}) (Fig. 5) and during decompression phase some of the work is recovered (W\textsubscript{exp}) (Fig. 5) because the tablet itself will expand slightly when the pressure on it is relieved. The work that is consumed to a permanent volume reduction of a powder bed, to an interparticulate friction and to a bond formation is called net work (W\textsubscript{net}) (Fig. 5). It is calculated by subtracting W\textsubscript{f} and W\textsubscript{exp} from gross work. Numerous different studies have correlated W\textsubscript{net} or different kind of work ratios to tablet strength (Garr and Rubinstein, 1990; Otuka et al., 1989; Cutt et al., 1989;
Krycer and Pope, 1983). A typical finding from these studies is correlation between a large degree of plasticity and improved tablet strength.

De Blaey and Polderman (1970) suggested that the difference between the upper punch force and the lower punch work may be totally attributed to die wall friction. They suggested that the work of die wall friction \( W_f \) could be calculated according to equation 3.

\[
W_f = \int_{D_s}^{D_m} (F_{up} - F_{lp}) dD
\]  

(3)

Järvinen and Justin (1974) claimed that the method proposed by De Blaey and Polderman overestimates the work of die wall friction. They suggested that the \( W'_f \) should be calculated according to equation 4.

\[
W_f = \int_{D_s}^{D_m} \left\{ \frac{F_{lp} - F_{up} - F_{lp}}{\ln\left(\frac{F_{lp}}{F_{up}}\right)} \right\} dD
\]

(4)

This is because only part of the particles is capable of moving the same distance as the upper punch does. Particles near the lower punch will stay nearly stationary. The work of friction is then about half of that calculated by equation 3. The validity of these two methods has been under debate (Lammens et al., 1980) (Järvinen and Justin, 1981). The De Blaey and Polderman method is more widely used, but results of study made by Ragnarson and Sjögren (1984) support Järvinen and Justin method.

The measured work of expansion \( W_{exp} \) is incomplete. The tablet will continue to expand still long after decompression phase. Ragnarson (1985) has shown that only 65% of the total axial expansion of anhydrous lactose tablets took place in the die. De Blaey and Polderman (1970) have suggested that the real \( W_{exp} \) should be measured by double compression technique. In this method, the same tablet is compressed twice. The upper punch work in the second compression would then reveal the real work of expansion. Krycer et al. (1982) and Armstrong et al. (1982) have criticised this method. They pointed out that the properties of the compact may change on repeated
compressions. For example, the temperature of the tablet can raise 40-50 °C during compression, which is enough to change the physical properties of the material. If the die wall friction is high, neither of the above methods will give complete expansion work. To get as reliable result as possible to the $W_{exp}$ value, the measurements should be done using single-compression technique and pre-lubricated die. The die wall friction could be then reduced as much as possible. The tablets tend also to expand in the radial direction after ejection. This expansion is not recorded in $W_{exp}$.

It has been generally assumed that the part of the net work that is consumed to inter-particulate friction is small compared to the work that is needed to deform particles during compaction. Ragnarsson and Sjögren (1985) studied the effect of lubrication and mixing time on the inter-particulate friction and noticed a significant reduction in $W_{int}$ after magnesium stearate was added to the starch powder. Because the amount of lubricant was small (0.5 %), it is unlikely that the deforming properties of the starch would have changed radically, but the phenomenon is explained by inter-particle friction. For powders where the portion of the inter-particle friction in the $W_{int}$ is large, there is no simple way to correlate $W_{int}$ and the deformation properties of material.

Durr et al. (1972) proposed that by using areas E1, E2 and E3 (Fig. 6) it is possible to classify materials. According to authors’ experience, the shape of the curve should remind as much as possible, a right-angled triangle. The area E1 should be as small as possible and the ratio E2/E3 should be as large as possible.

Stamm and Mathias (1976) calculated plasticity constant ($P1$) according to equation 5.

$$P1 = 100 \times \frac{E2}{E2 + E3}$$  \hspace{1cm} (5)

Materials that have high $P1$ values utilise a large part of the energy input during compression to irreversible deformation. The value of $P1$ is not pressure-independent.
Figure 6. Force-displacement profile including different areas (E1-E3) used in the characterisation of the compression process

There is an essential risk for large errors in force-displacement measurements, because extremely large numbers (force measurement) are multiplied by extremely small ones (displacement measurements). Errors in the compensation of machine deformation and non-linearities in the displacement measurements can thus cause noteworthy errors, especially in equations where different sized work ratios are handled.

2.7 Porosity-Pressure Equations

Mathematical models describing the change of relative density in a powder column as a function of the compression pressure have been investigated first in the field of powder metallurgy. Many of these models have later been adopted in pharmaceutical compression research. Equations proposed by Cooper and Eaton (1962), Heckel (1961,
b) and Kawakita (1956) are most widely applied. These equations were developed to determine the mechanisms of powder compaction and to find material constants for comparison between different powders. None of these equations was derived from considerations of physical models of compaction. They are essentially curve fitting formulae (Sheikh-Salem and Fell, 1981). There are, however, clear indications that the curve fitting equations may give valuable information about effects of batch to batch variations in particle size and degree of agglomeration, or of the changes in the speed of compaction, which is of special interest to the pharmaceutical industry. (Sonnergaard, 2001). The curve-fitting approach, on the other hand, often has problem with the physical interpretation of estimated parameters.

2.7.1 Heckel Plot

The Heckel equation is probably the most widely used porosity-pressure function in the field of pharmacy. Heckel suggest (Heckel, 1961) that the density-pressure relationship during powder compaction is analogous to a first order chemical reaction. The change in density of the powder column as the compression pressure increases, is proportional to the porosity of the powder column according to equation 6

\[
\frac{dD}{dP} = K(1 - D) \tag{6}
\]

where \(D\) is relative density of the tablet (\(D = \text{density of the tablet}/ \text{true density of the tablet powder}\)). \(P\) is pressure, \(1-D\) is porosity and \(K\) is constant. If we integrate equation 6, it yields to equation 7.

\[
\ln \left[ \frac{1}{1-D} \right] = KP + A \tag{7}
\]

In a Heckel plot, \(\ln [1/(1-D)]\) is drawn as a function of \(P\) (Fig. 7). \(A\) is the intercept of the extrapolated linear region of the curve. Its value is related to the density of the powder after die filling and particle rearrangement in the initial phase of compaction before bond formation. \(K\) is the slope of the linear region of the curve. The slope \(K\) gives
information of the plasticity of the compressed powder. The higher the value of the slope \( K \) is, the more plastic is the material. \( K \) is also related to the mean yield pressure (\( P_y \)) of the material (Hersey and Rees, 1971), which is a measure of the material’s resistance for deformation.

![Figure 7. Heckel plot](image)

Mean yield pressure is defined as the reciprocal of \( K \) (Eq. 8).

\[
P_y = \frac{1}{K} \tag{8}
\]

The slope is also related to the yield strength (\( Y \)) of the material according equation 9.

\[
Y = 3 \cdot K \tag{9}
\]

Values of the Heckel plot constants (\( K \) and \( A \)) are based on correct selection of the linear part of the plot. Linear part is determined correctly using first and second derivates of the function (Roberts and Rowe, 1985). In linear part of the plot the first derivate is constant and the second derivate is zero. It is however often difficult to find strictly linear region of the plot. Microfine cellulose (Elema®) for example gave completely nonlinear plot at all applied pressures (Rue and Rees, 1978).
According to Hersey and Rees (1971), it is possible to distinguish two type of powder behaviour by compressing different size fractions of the same material. For plastically deforming powders the Heckel plots, drawn from different size fractions, remain parallel over the entire pressure range, while for brittle materials the plots become coincidental as the compression pressure increases (Fig. 8). In a study on the effect on compression on fatty acids and on lactose mixed with high percentages of fatty acids, York and Pilpel (1973) described third type of volume reduction mechanism of pharmaceutical powders (Fig. 8). Densification occurs here by plastic flow without initial particle rearrangement. After an initial steep linear part, plots become coincidental because material packing fraction approaches unity at quite a low compressive stress level.

![Graph showing Heckel plots](image)

Figure 8. Different types of compression distinguished by Heckel plot

Rue and Rees (1978) pointed out that the main compaction mechanism may be different with different size fractions of the same material. That is why great caution is needed when materials are classified on the basis of changes in the Heckel plots with different particle sizes. They suggested that it would be more useful to quantify the amount of plastic deformation during compaction by measuring the areas under Heckel plots obtained at several contact times. They measured increased volume reduction of microfine cellulose (Elcema®) with increased compression time, whereas little or no increase in consolidation was observed with brittle consolidating material Emcompress®. They proposed that large increase in volume reduction is typical for plastically deforming materials.

Roberts and Rowe (1985) studied the effect of punch velocity on the compaction properties of pharmaceutical powders. They found that the velocity of punch
considerably affected the shape of the Heckel plot and to the constants derived from the plot. They introduced a strain-rate sensitivity index (SRS) according to Eq. 10.

$$SRS = \frac{P_{1.2} - P_{0.033}}{P_{1.2}} \times 100$$  \hspace{2cm} (10)$$

where $P_{1.2}$ and $P_{0.033}$ are the mean yield pressures at the velocities of 300 mm/s and 0.033 mm/s, respectively. According to Roberts and Rowe, plastically deforming materials have higher SRS values than brittle materials and it is possible to rank materials using SRS index.

The porosity of the powder column has also been measured after ejection of the compact from a die. This is called “at zero pressure method” or “ejected tablet method”. Continuous monitoring of the powder column height during the volume reduction process is referred as “tablet in die method” or “at pressure method” method. If “at zero pressure method” is used, several compressions are required at different pressure levels. Heckel plots have in most instances measured using “at pressure method”, even though Heckel himself used “at zero pressure method” in his original publication. Fell and Newton (1971) and York (1979) have shown that the densities measured by “at pressure method” include an elastic component, which results falsely low yield pressure values. Paronen and Juslin (1983) have suggested that a parameter describing the tendency of compact to recover elastically is possible to calculate by subtracting the slope of the Heckel plots obtained from the “ejected tablet method” from the slope obtained from the “tablet in die method”, and taking the reciprocal of that value.

Duberg and Nyström (1986) and Paronen (1987) have also studied the decompression phase of the Heckel plots (Fig. 9). By this method, it is possible to evaluate the elastic behavior of the powder. Paronen has used the reciprocal of the slope, calculated from the downward portion of the plot and called it the yield pressure of fast elastic deformation (Paronen 1987).
Figure 9. Three phases of compression cycle using Heckel function. Low pressure, porosity enhanced by particle fragmentation (Phase I), high pressure, elastic and/or plastic deformation dominate (Phase II), decompression phase (Phase III) (Duberg and Nyström, 1986)

Ragnarsson and Sjögren (1984 and 1985) suggested that the pressure in the Heckel plot should be measured as a mean of upper and lower punch pressures because the upper punch pressure is friction-dependent.

York (1979) has shown that the shape of the Heckel plot is affected at least by the state and type of lubrication, rate of compaction, mode of die filling, contact time, dimensions of tools and techniques used to measure compact dimensions. Because the results of Heckel analysis are so dependent on experimental conditions, it might explain most of the controversial results obtained by various workers. To be able to compare different powders using Heckel plot, compactions should be done in as identical conditions as possible using the “ejected tablet method”.

2.7.2 Cooper-Eaton Equation

Cooper and Eaton (1962) considered the compaction of powders to take place in two stages: firstly, the filling of voids of the same or larger size than the particles by particle movement and rearrangement; secondly, the filling of the smaller voids by plastic
deformation or fragmentation of particles. Based on the probability density of hole filling, they derived the equation 11.

\[
\frac{V_o - V}{V_o - V_m} = a_1 \cdot e^{-\frac{k_1}{P}} + a_2 \cdot e^{-\frac{k_2}{P}}
\]

(11)

\(V_o\) is the initial total volume when no holes are filled (at zero pressure). \(V\) is compact volume and \(V_m\) is compact volume at zero porosity. \(a1\) and \(a2\) are dimensionless constants that indicate the fraction of the theoretical maximum densification which could be achieved by filling voids of the same size \((a1)\) and of a smaller size \((a2)\) than the actual particles. \(k1\) and \(k2\) are coefficients with units of pressure indicating the magnitude of pressure where the particular process has the greatest probability density. \(P\) is pressure.

Cooper and Eaton used their equation for metal and ceramic powders, which are hard and monodisperse materials. With these kinds of powders, equation can distinguish the two separate densification stages. For soft and polydisperse powders (like most pharmaceutical powders), these two densification stages are not always clearly distinguishable, because this kind of powder column densificate by several simultaneous mechanisms. (York and Pípeli, 1973; Kurup and Pípeli, 1978; Armstrong and Morton, 1979; Chowhan and Chow, 1980; Paronen and Juslin, 1983).

2.7.3 Kawakita equation

Kawakita proposed an empirical equation 12 (Kawakita and Tsutsumi, 1966) describing the relation between the pressure and the volume reduction of powder mass.

\[
C = \frac{V_o - V}{V_o} = a \frac{bP}{1+bP}
\]

(12)

where \(C\) is degree of volume reduction, \(V_o\) is initial apparent volume, \(V\) is the volume under the applied pressure \(P\) and \(a\) and \(b\) are constants characteristic for powder being compressed.
When the equation is represented in graphical form, it is rearranged in linear form as (Eq. 13):

\[
\frac{P}{C} = \frac{P}{a} + \frac{1}{a \cdot b}
\]

(13)

The constant \(a\) corresponds to the limiting value of relative reduction of the volume by compression and is considered to describe compressibility of a powder. The constant \(b\) should be equal to the reciprocal of the pressure when the volume value, \(C\), reaches one-half of its limiting value and it is considered to describe an inclination towards volume reduction. The actual physical meaning of the constants \(a\) and \(b\) is still questionable (Kawakita and Lüdde 1970), (Yamashiro et. al. 1983). The constant \(C\) is highly dependent on the initial packing state of the powder (Sheikh-Salem and Fell 1981). The die filling method as well as the shape and the size of the die can thus cause variations in the constants of the Kawakita equation.

### 2.8 Stress and strain tests

In the stress relaxation measurements, powder that is in the compacted state is kept either in constant strain (stress relaxation test) or in constant stress (creep test).

#### 2.8.1 Stress relaxation test

In the stress relaxation tests, the strain is maintained constant while the decay in upper or lower punch force is recorded as a function of time. The recorded force decay is higher with plastically deforming materials than with brittle fracturing materials (Cole et al., 1975) (Rees and Tsaraka, 1993) (Fig. 10).
Figure 10. Stress relaxation results for materials loaded to 2 kN at 10mm/min, showing the decreasing punch force with time (Rees and Tsardaka 1993)

David and Ausburger (1977) have quantified the rate in plastic deformation during relaxation test. By using Maxwell model of viscoelastic behaviour, which involves combining one viscous and one elastic parameter in series, they derived the following relationship (Eq. 14):

\[ \ln \Delta F = \ln \Delta F_0 - k \cdot t \]  \hspace{1cm} (14)

where \( \Delta F \) is the amount of the compressional force left in the viscoelastic region at time \( t \), \( \Delta F_0 \) is the total magnitude of this force at \( t = 0 \) and \( k \) is viscoelastic slope. Materials with high viscoelastic slope, \( k \), deform mainly by plastic flow. They suggest that this viscoelastic slope (\( k \)) could be used to classify materials according to their degree of plastic flow.

Rees and Rue (1978) made relaxation test using much longer continuing measurement times (360 s) than David and Ausburger (10 s). According to their results, powders have an initial rapid rate of relaxation after which materials assume the first order stress relaxation characteristic of a true Maxwell body. The data they measured did not fit to the Maxwell model used by David and Ausburger, and they proposed that the relaxation model should include more than one relaxation time constant.
Hiestand et al. (1977) measured the change of relative pressure (ratio of pressure at time $t$ to maximum pressure applied) as a function of time (in logarithm scale). They followed stress relaxation up to 1000s. They too found that there was a change in rate of stress relaxation after 2-6 s.

Rees and Tsardaka (1993) described the stress relaxation profile by a hyperbolic equation. The measured results showed excellent fit to this hyperbolic relationship. Linear transformation of this hyperbolic stress relaxation profile includes three new viscoelastic parameters. One of the new parameters can quantify the rate of force decay immediately after the known peak load is applied. This has been the most difficult part of the stress relaxation profile to define. Because the pharmaceutical compaction process is of short duration, it is the behaviour of materials during this early stage of stress relaxation that is of special interest (Rue and Rees, 1978).

### 2.8.2 Creep test

In the creep tests, material is held under a constant stress and strain is monitored against time (Staniford et al. 1987; Rossi et al. 1999). Typical creep compliance curves are shown in figure 11. Total creep compliance, $J(\sigma)$, can be calculated according equation 15 (curve $a$ in Fig. 11).

$$J(t) = \frac{\xi}{\sigma}$$

where: $\xi$ is relative strain and $\sigma$ is constant stress.

---

Figure 11. A typical creep compliance response (Tsardaka and Rees, 1988)
Reciprocal of the slope \(k\) in the linear region in the \(J(t)\) plot (curve \(a\) in Fig. 11) is called the apparent viscosity (Tsaraka and Rees, 1988). Materials having low apparent viscosity values are more capable for extensive plastic deformation than the materials with higher values (Malamataris et al., 1992).

The retarded elastic deformation \(J_r(t)\) (curve \(b\) in Fig. 11) can be derived using equation 16

\[
J_v(t) = J(t) - k \cdot t
\]  

(16)

\(J_r(t)\) increases with time \(t\) toward asymptote \(J_i\) (Fig. 11) according equation 17.

\[
J_v(t) = J_i \cdot e^{-\frac{t}{k_2}}
\]  

(17)

\(J_i\) is called the compliance due to retarded elastic deformation at infinite time and \(k_2\) is a direct measure of retardation of the elastic strain. High value of \(k_2\) reflects a low rate of elastic deformation and is typical for plastically deforming material.
3. AIMS OF THE STUDY

In this study, the aim was to find new tools to evaluate the suitability of powders and granules for tablet compression. The specific aims were:

1. to obtain general material parameters which can be used in the evaluation of tableting behaviour of powders or granules,

2. to test how well most important mechanical properties of tablets can be estimated from force-time and force-displacement curves,

3. to parameterise force-time and force-displacement compression profile versatility and to develop a set of numerical parameters which could together describe exactly shapes of the different compression profiles,

4. to develop a method to assess the tendency of material for plastic deformation, fragmentation and elasticity, and to express it as a numerical value, which is comparable between different materials,

5. to combine results of different type of powder flow test data, and present it in an easily understood, visual and linguistic form,

6. to test the ability of self-organising map to predict weight variation in tablets on the basis of flow properties of powders,

7. to test if it is possible to achieve improved compactibility and flow properties of silicified microcrystalline cellulose (Prosolv SMCC90®), by simply mixing Avicel PH-102 and Aerosil in a glass jar,

8. to test if Avicel PH-101/PH-200 mixture is able to produce strong tablets with low weight variation by combining the good compactibility of Avicel PH101 and good flowability of Avicel PH-200,

9. to develop a new method to predict the flow behaviour of pharmaceutical powders using a multichamber microscale fluid bed.
4. EXPERIMENTAL

In this chapter, the materials and methods used in thesis are covered. A more detailed description of materials and methods (e.g. equations for compression parameters) is given in the original publications which are here referred to by their respective Roman numerals I – VII.

4.1 Materials

4.1.1 Powders

Fillers used were 80-mesh α-lactose monohydrate (DMV, Veghel, Netherlands) (I, II, III and VI), silicified MCC, (Prosolv SMCC 90; Penwest Pharmaceuticals, Patterson, United States) (IV, V and VII), non-silicified MCC (Avicel-PH101, PH-102, PH-200, a mixture of Avicel PH-101/PH-200 (75%/25%); FMC International, Cork, Ireland) (IV, V and VIII), maize starch (National Starch & Chemical GmbH, Neustad, Germany) (VI) and dicalcium phosphate dihydrate (Calipharm; Albright & Wilson Ltd., Oldbury, UK) (VI).

The paracetamol powder (Ph. Eur. Grade; Orion Pharma, Finland) was added in proportions ranging from 0 to 30% w/w to Avicel PH-101, PH-102, PH-200, a mixture of Avicel PH-101/PH-200 (75%/25%) and Prosolv SMCC 90 filler materials. The powders were mixed (10 min) in 2-litre glass jars using a laboratory-size turbula mixer (System Schatz, Willy A. Bachhofen, Switzerland) (IV, V and VII).

A mixture of Avicel PH-102 and colloidal silicon dioxide (Aerosil 200, Orion Pharma, Finland) (2 % w/w) was prepared using turbula mixer (System Schatz, Willy A. Bachhofen, Switzerland) and a mixing time of 5 min (V). Scanning electron micrographs were used to assess the deposition of colloidal silicon dioxide in powder samples. For scanning electron microscopy, powder particles were fixed on double-sided carbon tape and coated with platinum (20nm) with sputter coater (Agar sputter coater B7340, Agar Scientific Ltd., United Kingdom). The micrographs were taken with a Zeiss DSM-962 scanning electron microscope (Carl Zeiss, Electron Microscopy Division, Germany). An acceleration voltage of 15 kV and secondary electrons were used for all micrographs. The characteristic x-ray energy spectrum and thus the element composition of the sample could be identified using energy dispersive x-ray spectroscopy (EDS).
4.1.2 Granules (I)

The filler material was 80-mesh α-lactose monohydrate (DMV, Veghel, Netherlands). Two percent of anhydrous theophylline (Ph. Eur.) was added as a marker drug in each batch to be granulated. Batches of 3 kg were granulated using 20% aqueous dispersion of polyvinylpyrrolidone (Kollidon K25, BASF, Germany).

The granules were produced using a pilot-scale automated fluidized-bed granulator (Glatt WSG 5 Glatt GmbH, Binzen, Germany). Granulations were performed according to 3\(^3\) experimental factorial design. Independent variables in the design were amount of granulation liquid and the atomising air pressure. Levels of the atomising air pressure were 1.0, 1.5 and 2.0 bar. Amounts of granulation liquid were 150, 300 and 450 g. Design consisted of 12 granulations, 9 experimental batches and 3 center point replicate batches.

4.2 Tablet compression and characterisation (I – VII)

Tablets were compressed in an instrumented eccentric tablet machine (Korsch EK0; Erweka Apparatebau, Germany) using flat-faced punches with diameter of 9 mm. The target weights of the tablets were 335 mg (I) and 225 mg (IV, V, and VII). The target heights of the tablets were 4.0 mm (II – III) and 3mm (VI). Compression forces were 10 kN (I), 11, 15 and 19 kN (II – III), 4 kN (IV, V and VII), 2–26 kN (VI). Compression speeds were 34 rpm (I, IV, V and VII), 10, 20 and 40 rpm (II-III). Before tabletting, powders were stored three days in a controlled conditions of relative humidity (45 % II-III), (55 % IV, V, VI and VII).

The filler material and magnesium stearate (University Pharmacy, Finland) (0.5% w/w) (I, IV, V, VI and VII) and (1% w/w) (II and III) were mixed (14 rpm) in a Turbula mixer (System Schatz, Willy A. Bachhofer, Switzerland). The filling capacity of the mixer was 400 g (I) and 70 % of the filling capacity (II and III). Mixing time was 2 min (II, III), 5 min (I and V) and 10min (IV, V and VII).

4.2.1 Crushing strength of tablets (II-III)

Crushing strength was measured from 10 tablets (Schleuniger-E, Switzerland)(II and III) and from 20 tablets (Erweka Multicheck, Erweka GmbH, Heusenstamm, Germany)(V).
4.2.2 Friability of tablets (II-III)

Friability was measured from each tablet batch using 20 tablets sample and 100 revolutions in a friabilator (Ernst-Keller & Co. AG, Basel, Switzerland).

4.3 Powder flow measurements (IV, V and VII)

A non-commercial apparatus (FLO Orion Pharma, Finland) was used to study the flow properties of powders. The FLO can measure directly five different parameters. The FLO consist of a stainless steel funnel (Ph. Eur. type) 100 mm in diameter and 120 mm high with a wall angle of 40 degrees and a round orifice of 10 mm, an electric balance and control unit, a video camera, a monitor and a computer (PC). In addition the equipment comprises a stainless steel wire mixer (diameter 1mm; rotating speed 100 rpm) to facilitate flowing.

The FLO measurement procedure consists of two stages. The first stage begins with the opening of the funnel outflow valve. The powder flows onto a round plane with a diameter of 100 mm. The powder falls onto plane until it is full and begins to flow over. The powder weight on the plane is measured 0.1 second intervals during the stage. A powder cone with a regular base diameter is achieved in the end of the first stage. Freely flowing powders forms a low, regular and symmetric cone. Poorly flowing powders form high, irregular and asymmetrical cone There after FLO vibrates the formed cone (cone 1) and a new lower cone is formed (cone 2).

In the second phase of the measurement, a smaller plate (plate B) with a diameter of 24 mm appears from the middle of the cone 2 as the bigger plate is moved downward. A small cone (cone 3) (resembling angle of spatula) is formed from the powder that is left on the plate B. Cone 3 is thereafter also vibrated and the fourth cone is formed (cone 4).

In terms of image analysis the silhouettes of the powder cones were determined by the video camera and entered in the PC. The FLO calculated automatically four different static angles of repose for the powder samples. The flow rate (g/s) was determined from the recorded scales values. In addition to the five directly measured parameters one new parameter “non-uniformity of powder flow” was calculated according to equation 18.
\[ \Delta m_i = m_{i+4} - m_i \]  

(18)

In this equation, weight change occurring with in 0.4 s was determined. The relative standard deviation (RSD) of \( \Delta m \) was the measure of the non-uniformity of powder flow. It was assumed that the powder flow was steady when 10-90 % of the powder had flowed through the funnel. This range was used for the calculations of non-uniformity of powder flow. Measurements were performed in triplicate for all powders.

### 4.4 Microscale fluid bed measurements (VII)

Microscale fluid bed (Ariacon Oy, Helsinki, Finland) consists of four individual fluidization chambers. The conical chambers are made of glass. Diameters of the lower part of the chambers are 20 mm and 100 mm of the upper parts, respectively.

Studied powder (10 ml) was first fluidized 2 minutes at a constant air flow rate, 79 ml/s, so that the fluidization was mainly occurred at the lower part of the chamber. After that the velocity of the fluidization air was slowly decreased to zero. In each of the chambers the pressure difference over the bed was recorded as a function of the velocity of the fluidization air. Also the experimental minimum fluidization velocity \( u_{mf} \) was defined from the decreasing air flow rate. The \( u_{mf} \) represents the point of transition between fixed and fluidized states. At this point, the drag force of upward moving gas counterbalances the weight of the bed of solid particles.

### 4.5 Data analysis

#### 4.5.1 Correlation analysis (II-III)

Pearson correlation coefficients (R) and corresponding probability value (p) between the calculated compression parameters and measured crushing strength and friability of tablets were calculated with Systat v. 5.0 (Systat Inc., USA) PC-program.
4.5.2 Regression model (I-III)

The initial regression model \( Y \) for two independent variables \( (p \) and \( m) \) was as follows equation 19 (I):

\[
Y(p,m) = a_0 + a_1 \cdot p + a_2 \cdot m + a_3 \cdot p \cdot m + a_4 \cdot p^2 + a_5 \cdot m^2 \\
+ a_6 \cdot p^2 \cdot m + a_7 \cdot p \cdot m^2 + a_8 \cdot p^3 \cdot m^2
\]  

(19)

Where \( a_0 \ldots a_8 \) are coefficients of the model. Symbols \( p \) and \( m \) denote the atomizing air pressure and the amount of granulation liquid, respectively.

The second regression model was (Eq. 20) (II-III):

\[
Y(F,t) = a_0 + a_1 \cdot F + a_2 \cdot t + a_3 \cdot F \cdot t + a_4 \cdot F^2 + a_5 \cdot t^2
\]  

(20)

\( a_0 \ldots a_5 \) are coefficients of the model. Symbols \( F \) and \( t \) denote the effective compression force and the compression time, respectively.

Variables were normalised between –1 and +1 before statistical analysis. The models were simplified using stepwise technique. Only statistically significant terms \((p<0.05)\) were included to the final models. Regression models were generated using SYSTAT v. 5.0 (SYSTAT Inc., USA) (I) and MODDE v. 3.0 (Umetric AB, Sweden) (II-III) PC-programs.

4.5.3 Kohonen self-organising map (IV)

A commercial PC program (NEUframe Professional v.3.0, NCS, United Kingdom) was used to generate a two-dimensional map known as the competitive Kohonen layer (Kohonen 1982, 1997). The results of flow measurements (6 parameters) from each measured powder samples were fed as a six dimensional vector \((x_i \text{ in eq. 21})\) to the program.

\[
x_i = (x_{i1}, x_{i2}, ..., x_{i6})
\]  

(21)
The Kohonen layer consisted of 4x5 neurons (grids on Fig.2; IV). To each neuron on the map is included a weight vector (w in eq.22). It is also in this case six dimensional vector. It has random values at the beginning of the learning phase.

\[ w_j = (w_{j1}, w_{j2}, ..., w_{jk}) \]  \hspace{1cm} (22)

In the learning phase one of the input vectors \( x_i \) is selected and the Euclidean distance \( d \) is calculated for each of the weight vectors on the map (twenty in this case).

The neuron with the smallest Euclidean distance \( (d) \) (Eq. 23) is called as the winning neuron (\( N_c \)) for this specific input vector \( (x) \).

\[ d_{i,j} = \sqrt{\sum_{k=1}^{s} (x_k - w_{jk})^2} \]  \hspace{1cm} (23)

The values of the weight vector in \( N_c \) are then changed so that they become even more similar to this specific input neuron. Also the weight vectors in the neighborhood of the \( N_c \) are changed so that they also become more similar with the \( x_c \). The degree to which each neuron is influenced depends on its distance \( (l) \) from \( N_c \). The weights of neurons near \( N_c \) are most strongly changed. This is done in order to group similar flow results near each other on the Kohonen layer. The same procedure is done for all input vectors (measured flow results) several times (learning epochs) until the structure of the map will not any more change. The general presentation of the learning rule for weight vectors is (Eq. 24):

\[ \Delta w_{jk} = \eta(t) \cdot a(l) \cdot (x_{ik} - w_{jk}) \]  \hspace{1cm} (24)

Where \( \eta(t) \) is the function controlling the learning rate and \( a(l) \) is a neighborhood function. The value of \( \eta(t) \) decreases as the training proceeds, \( t \) denote the current learning epoch. The neighborhood function \( a(l) \) decreases with distance \( (l) \) from the winning neuron \( N_c \). The number of learning epochs was 35000.
4.5.4 Principal component analysis (VII)

Shapes of the pressure difference over the bed curves were compared after principal component analysis (PCA) using SIMCA-P (version 8.0, Umetrics, Umeå, Sweden). The first two principal components of the pressure difference curve were drawn as a point on the plane. The values of the first two principal components (scores $t[1]$ and $t[2]$) determined the position of the point on the plane. Pressure difference curves having the same kind of shapes were projected near each other on the plane.

4.5.5 A partial least square regression model (VII)

A partial least square (PLS) regression model was build to model the relationship between the fluidization behavior and the flowability (flow rate and angle of repose measured by the reference method) using SIMCA-P version 8.0, Umetrics, Umeå, Sweden). All microcrystalline cellulose powder mixtures were used as modeling data. The entire graph of the pressure difference over the bed as a function of decreasing velocity of the inlet air (25.0 cm/s) was exploited for modelling. Silicified microcrystalline cellulose powders were used as test data, which were not included in building the regression model.
5. RESULTS AND DISCUSSION

5.1 Force-time curve parameters (I-II)

5.1.1 Relative elasticity of granules (I)

It was assumed that for ideal rubber elastic material force-time curves in an eccentric tablet machine would be symmetrical in respect to the time point when the maximum compression force is achieved. Although the basic assumption is simplification and not exactly right (the time point of the maximum compression force and the time point of the maximum displacement of the upper punch are not precisely the same) the results showed that the developed method to quantify the elastic behaviour of tablets compressed from granules was valid. The two new parameters defined to measure elasticity of granules $R_E, F_p$ and $R_E, F_v$ were dependent on the amount of binder solution. The correlation between new parameters and the binder solution amount was nonlinear. Values of both parameters decreased as the binder solution amount (and obviously the granule size) increased. The change in the elasticity of granules was more clearly seen from the parameter $R_E, F_p$ which was determined from the lower punch force-time curve. The shapes of response surfaces for both parameters had very similar structure and were in general quite stable (Fig. 2 and 3; I). Atomizing air pressure did not have any real effect on relative elasticity. This might be partly due to used granulation system. The levels of atomizing pressures were not accurate constants during granulations but changed in the range -20 % to +20 %. This noise in the values probably made the effect of atomizing air pressure undetectable.

5.1.2 Correlation between force-time compression parameters and mechanical properties of tablets (II)

The same basic assumption of the symmetric force-time curve for ideal rubber elastic material as in the publication I, was used also in the publication II. In this publication the shape of the force-time curve was assumed to be symmetric in respect to the time point when upper punch reaches maximum displacement. A new type of force-time profile called “difference force-time curve” could be derived from that assumption. Instead of calculating different parameters for both the upper and the lower punch measurements a geometrical mean of upper and lower punch force called “effective force” ($F_{eff}$) was
used. Use of this force was assumed to be more precise than the simple mean of the upper and the lower force. This is because in an eccentric tablet machine, the applied force transmission from the upper punch to the lower punch, decays exponentially (Marshall 1986).

The shape of the force-time profile was depicted by parametrizing it very precisely. Nine different parameters, which described different aspects of the force-time curve, were derived. Correlations between all nine parameters and responses (crushing strength and friability of tablets) were statistically depended (p<0.05). The highest correlations (R > 0.92, p<0.0000) between crushing strength and friability were obtained for four parameters G2, G1, EVdiff and NVdiffmax (Table 1). These four parameters were calculated from “difference force-time curves”. Correlations were nonlinear. Also linear seeming correlation between EVdiff and crushing strength would have been nonlinear if the experimental region would have been broader. In all cases the crushing strength and friability of tablets behaved logically: with increasing crushing strength the friability decreased.

**Table 1. Correlation (R) between calculated new parameters and crushing strength and friability of tablets. The seven parameters below dashed line were calculated from “difference force-time curves”**.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Crushing strength</th>
<th>Friability</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVdiff</td>
<td>0.893</td>
<td>-0.895</td>
</tr>
<tr>
<td>RFVdiff</td>
<td>0.838</td>
<td>-0.811</td>
</tr>
<tr>
<td>G2</td>
<td>0.990</td>
<td>-0.977</td>
</tr>
<tr>
<td>G1</td>
<td>0.989</td>
<td>-0.975</td>
</tr>
<tr>
<td>EVdiff</td>
<td>-0.984</td>
<td>0.973</td>
</tr>
<tr>
<td>NVdiffmax</td>
<td>0.927</td>
<td>-0.925</td>
</tr>
<tr>
<td>NFdiff</td>
<td>-0.798</td>
<td>0.780</td>
</tr>
<tr>
<td>FVdiffmax</td>
<td>0.767</td>
<td>-0.808</td>
</tr>
<tr>
<td>ΔVdiff</td>
<td>-0.652</td>
<td>0.619</td>
</tr>
</tbody>
</table>
5.1.3 Use of force-time parameters to describe compression behaviour of powders (II)

$E_{\text{r,eff}}$ and $RE_{\text{r,eff}}$ can be used to quantify the irreversible changes during tablet compression. $E_{\text{r,eff}}$ may also give information on relative amount of plastic deformation and fragmentation of materials if different compression speeds are used. For plastically deforming materials the change in values of $E_{\text{r,eff}}$ would be greater than for brittle materials if compression speed would be altered. This is because plastic flow is time dependent phenomena while fragmentation is only dependent on used pressure.

Values of parameters $G_1$ and $G_2$ correlated best with crushing strength and friability of lactose tablets. Thus they can obviously give information on the time-dependent changes in the powder bed and bond formation during tablet compression. For theoretical rubber-elastic material this parameter can not be defined. These two parameters may also be used in quantitation of relative amount of fragmentation and plastic deformation of materials during tablet compression.

Values of parameters $F_{\text{r,diff}}$ and $N_{\text{r,diff,max}}$ correlate highly with values of $G_1$ and $G_2$. This is because they also describe the symmetry of “difference force-time curve” like parameters $G_1$ and $G_2$. These four parameters had highest correlation to measured responses.

Values of parameters $NF_{\text{r,diff}}$ and $F_{\text{r,diff,non}}$ can in theory vary between 0 and 1. For totally elastic material the value would be 0 and 1 for nonelastic materials. Thus they can give information on the quantification of elastic/nonelastic behaviour of materials.

$\Delta_{\text{r,diff}}$ had lowest correlation to responses. For ideal elastic material this parameter has value 0. The higher values show irreversible deformation during compression.
5.1.4 Dependence of force-time parameters from compression force and compression time (II)

The dependence of parameters from compression force and compression time was examined on one “force-time curve” parameter ($RF_{\text{rel}}$) and from one “difference force-time” parameter ($F_{\text{rel}}$).

The dependence of relative elasticity ($RF_{\text{rel}}$) on compression force ($F_{\text{eff,cons}}$) and compression time is drawn as a surface plot in figure 5 (II). It can be seen that on slow compression speeds the value of relative elasticity is not dependent on compression force ($F_{\text{eff,cons}}$). But as the compression speed increases the importance of the compression force to the value of $RF_{\text{rel}}$ increases and with the highest compression speeds the value of relative elasticity is already highly dependent on compression force. This is understandable, because with high compression forces and short compression times, a smaller relative amount of work done to the system is bound irreversibly in the tablet.

According to figure 7 (II), the elasticity factor $F_{\text{rel}}$ is dependent on the compression time, especially when high compression forces are used. The effect of maximum effective force is clear. The value of the parameter decreases as the compression force increases.

5.2 Force-displacement parameters (III)

5.2.1 Correlation between force-displacement compression parameters and mechanical properties of tablets

The overall shape of the force-displacement curve was attempted to depict by using several parameters. Totally 26 parameters were calculated. A new force-displacement curve called “effective work force curve” was derived from the original force-displacement curve. It was calculated by subtracting the decreasing part of the force-displacement curve from the increasing part. It describes relatively well the force, which is used for the irreversible deformations. On Table 2 statistically significant correlations between calculated new force-displacement parameters and crushing strength and friability of tablets are summarised.
Table 2. Correlation (R) between calculated new parameters and crushing strength and friability of tablets. The eight parameters below dashed line were calculated from “effective work force curves”.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Crushing strength</th>
<th>Friability</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRFI_{q,50}</td>
<td>-0.978</td>
<td>0.985</td>
</tr>
<tr>
<td>NRFI_{q,25}</td>
<td>-0.976</td>
<td>0.963</td>
</tr>
<tr>
<td>NRFI_{q,5}</td>
<td>-0.972</td>
<td>0.966</td>
</tr>
<tr>
<td>NRFD_{q,25}</td>
<td>-0.972</td>
<td>0.961</td>
</tr>
<tr>
<td>NRFD_{q,5}</td>
<td>-0.970</td>
<td>0.959</td>
</tr>
<tr>
<td>NRFD_{q,50}</td>
<td>-0.969</td>
<td>0.958</td>
</tr>
<tr>
<td>R_{T_3}</td>
<td>0.925</td>
<td>-0.930</td>
</tr>
<tr>
<td>RFI_{75/50, eff, max}</td>
<td>0.898</td>
<td>-0.884</td>
</tr>
<tr>
<td>RFI_{50/10, eff, max}</td>
<td>0.869</td>
<td>-0.856</td>
</tr>
<tr>
<td>R_{25}</td>
<td>-0.865</td>
<td>0.852</td>
</tr>
<tr>
<td>RFI_{75/50, eff, min}</td>
<td>0.805</td>
<td>-0.784</td>
</tr>
<tr>
<td>R_{75}</td>
<td>-0.701</td>
<td>0.689</td>
</tr>
<tr>
<td>R_{50}</td>
<td>-0.794</td>
<td>0.782</td>
</tr>
<tr>
<td>RFD_{75/50, eff, min}</td>
<td>-0.659</td>
<td>0.643</td>
</tr>
<tr>
<td>RFD_{75/50, eff, max}</td>
<td>-0.617</td>
<td>0.602</td>
</tr>
<tr>
<td>Ψ_{eff, min}</td>
<td>0.972</td>
<td>-0.946</td>
</tr>
<tr>
<td>Ψ_{eff, eff}</td>
<td>0.964</td>
<td>-0.923</td>
</tr>
<tr>
<td>Ψ_{eff, max}</td>
<td>-0.805</td>
<td>0.783</td>
</tr>
<tr>
<td>Ψ_{2}</td>
<td>0.770</td>
<td>-0.742</td>
</tr>
<tr>
<td>Ψ_{5}</td>
<td>-0.767</td>
<td>0.741</td>
</tr>
<tr>
<td>Ψ_{10}</td>
<td>0.693</td>
<td>-0.669</td>
</tr>
<tr>
<td>R_{Ψ_{eff, min}}</td>
<td>-0.615</td>
<td>0.595</td>
</tr>
<tr>
<td>N_{S_2}</td>
<td>-0.558</td>
<td>0.544</td>
</tr>
</tbody>
</table>

It is evident that all dependencies studied here are more or less exponential. The highest absolute correlation coefficients values have normalised parameters (NRFI_{q,50}, NRFI_{q,25}, NRFI_{q,5}, NRFD_{q,50}, NRFD_{q,25}, NRFD_{q,5}, and NRFI_{q,50}), that describe different quartiles of the
increasing and decreasing parts of the force-displacement curve. Best parameter calculated from the “effective work force curve” is \( F_{\text{eff, max}} \) which describes the maximum height of the “effective work force curve”.

### 5.2.2 Use of force-displacement parameters to describe compression behaviour of powders

\( R_{\text{FI}_{125 \text{ eff}}} \), \( R_{\text{FI}_{60 \text{ eff}}} \), \( R_{\text{FI}_{75 \text{ eff}}} \) and the normalised parameters \( \text{NRFI}_{125} \), \( \text{NRFI}_{60} \), \( \text{NRFI}_{75} \) describe the quartiles of the increasing part of the force-displacement curve. Parameter values for plastically deforming materials should be smaller than with fragmenting materials since the shape of the force-displacement curve should remind more right-angled triangle with plastically deforming materials than with fragmenting materials (Stamm and Mathias, 1976).

\( R_{\text{FD}_{125 \text{ eff}}} \), \( R_{\text{FD}_{60 \text{ eff}}} \), \( R_{\text{FD}_{75 \text{ eff}}} \) and the normalised parameters \( \text{NRFD}_{125} \), \( \text{NRFD}_{60} \), \( \text{NRFD}_{75} \) describe the quartiles of the decreasing part of the force-displacement curve. As the elasticity of the material increases values of these parameters will diminish.

\( R_{25} \), \( R_{50} \), \( R_{75} \) are ratios of the increasing and decreasing parts of the compression curves. They give information on the elastic behaviour of the materials at different stages of the compression. For ideal rubber-elastic material all the ratios would be 1, but in practise the values are always less than 1.

\( R_{\text{max}} \) is ratio between the maximum effective force and maximum punch displacement. Parameter gives information on the compactibility of materials. High values of the parameter indicate materials, that resist strongly deformation during compression.

\( W_{\text{eff}} \) is the area under “effective work force curve” and it describes the net work done to the irreversible changes in the powder bed. The higher the value is, the more work has been done in the formation of tablet. For a rubber-elastic system, where no bondings are formed, the value is naturally 0.

\( \text{NF}_{\text{eff, max}} \) is the ratio of the maximum value of the effective work force and maximum value of the effective force. The value of this parameter is obviously limited to description of the compression behaviour of a single material.
$R_{w_{ef\text{form}}}$ describes the relative position of the maximum value of the “effective work force curve”. For materials that deform totally irreversibly the value of this parameter would be 1. This parameter is not possible to calculate for rubber elastic material.

$N_{5\%}$ and $N_{5\%}$ describes the relative position of 50% quartiles for the increasing ($N_{5\%}$) and decreasing part ($N_{5\%}$) of the effective work force curve. The ability of the parameters to explain crushing strength and friability of tablets was poor. The correlation of $N_{5\%}$ with the responses was not statistically significant.

$S_{m3.}$ describes the relative differences of the 50% quartiles (increasing and decreasing part) of the effective work force curve (Fig. 3; III). The value of the term increases as the elasticity of material increases.

$\varphi_1$ and $\varphi_2$ define two different ratios of areas ($A_i$ and $A_e$) described in figure 3 (III) and equations 25 - 28 (III). $\varphi_1$ approaches a value 1 in compressions when materials are very plastic. For more elastic materials the term will have lower values. $\varphi_2$ approaches 0 for materials which undergoes very irreversible deformation and with higher values of the term the material will act in a more elastic way.

5.2.3 Dependence of force-displacement parameters from compression force and compression time

In the figure 10 (III) are drawn the effects of compression time and maximum effective compression force on two calculated effective work force curve parameters ($F_{w_{ef\text{form}}}$ and $W_{ef}$) and in the figure 11 (III) are presented two force-displacement parameters ($R_{25_{\text{CVD}}}$ and $NR_{50_{\text{CVD}}}$, Fig.11). The two responses in figure 10 are almost independent on compression time with low compression forces. With higher compression forces both responses become more dependent on compression times. The highest values were achieved when a low compression speed and a high compression force were used. The value of $W_{ef}$ increases especially with high compression forces when compression time increases. This indicates that the fraction of irreversible changes increases more with high compression forces when compression speed decreases. This indicates that with low compression forces, all irreversible changes (which are possible with the used material, lactose) occur rapidly. These may include rapid rearrangement and fragmentation of particles, and a certain amount of plastic deformation. With higher
compression forces, melting of material at the contact points as well as plastic flow
assumingly increase. These phenomena will need more time. The two responses shown
in figure 11 (III) behave differently from those in figure 10 (III), being practically
independent of the compression time. This is also important, showing that these
different parameters are able to provide different information on the compression
phenomena.

On the basics of publication II and III it is likely that many compression
parameters-like these presented here, can, in certain cases alone, but more presumably
together, give new possibilities for understanding and also estimating the behaviour of
powders during compression. Later it may be possible to predict the properties of tablets
even in cases where the parameterisation of compression curves is made using an
eccentric tablet machine and the final compression studies with high-speed rotary
machines.

5.3 A method to improve the accuracy of displacement measurement (VI)

In tablet compression studies, the problem is usually white noise in the measured
displacement determinations. A common error caused by this random noise is ± 20 \( \mu \)m. The real path (or displacement) of the upper punch as a function of time can be however
calculated on the basic of the construction of tablet machine. As a consequence of the
mechanics of the eccentric tablet machine, it is known without displacement
measurements, that the real path of the upper punch as a function of time must follow a
parabolic path. Consequently, also the measurements of the upper punch distance values
as a function of time, should without noise, follow this parabolic path. The white noise
from the measured displacement values was filtered out based on this fact. The
measured distance values were used as samples to which the parabolic curve was fitted
(Fig. 1; VI). The filtered displacement values were taken from this parabolic curve. From
the displacement values were thus wiped out practically all error caused by white noise.
This improvement to the accuracy of the displacement measurements made it possible to
see reliably small changes in the shape of the force-displacement profiles near the
compression force maximum.
5.4 A new method to determine the deformation of an eccentric tablet machine dynamically (VI)

The die of the tablet machine was filled manually and all machine settings were kept exactly same in all compressions. The compression force was controlled by changing the amount of powder in the die. When the amount of mass in the die was increased, the compression force increased. It was measured that the upper punch did not ascend as deep when the compression force increased (the amount of powder in the die increased) (Fig. 2; VI). This was because of the deformation of the tablet machine. If there were no elastic deformation in the tablet machine at all, the upper punch would push as deep with different compression forces because of the fixed machine set up. When maximum displacement values were drawn as a function of maximum compression force, it was possible to see that maximum punch displacement values decreased exponentially as the maximum compression force increased (Fig. 3; VI).

The lower punch is not moving during compression phase and the machine set up was kept constant. The deformation of the lower part of the machine was determined by measuring the displacement of the lower punch during maximum compression force. The measured displacement values increased linearly as the compression force increased. The deformation of the lower part of the machine was less than one third of the deformation measured from the upper part of the machine. The total elastic deformation of a running tablet machine is thus sum of the upper and lower part deformation of tablet machine.

5.5 Pressure dependence of plasticity factor PF (VI)

The developed plasticity factor PF (Eq. 5; VI), which describes the extent of plastic flow, had lowest values with dicalcium phosphate dihydrate (Calipharm) and consequently it deformed mainly by fragmentation. With small pressures the rest of the test materials exhibit high PF values, but lactose turned rapidly into a brittle fracturing material as the pressure increased. Avicel PH-101 maintained best its plastic feature also with high pressures (Fig. 6; VI).
5.6 Pressure dependence of elasticity factor EF (VI)
For microcrystalline cellulose and maize starch the values of EF (Eq. 6; VI) first decreased as the compression pressure increased and after a certain compression level start to increase. The minimum elasticity value for Avicel PH-101 was reached at 89.3 MPa and for Avicel PH-200 at 90.8 MPa upper punch compression pressure. For maize starch the minimum was reached 167.6 MPa upper punch pressure. The reason for this kind of minimum is probably air trapped inside tablet. At low compression levels (and low porosity) the amount of trapped air is still high. It creates a kind of “air spring” inside the tablets, which increases the elasticity values. At higher compression pressures and higher tablet densities the influence of trapped air becomes less significant, because it has already been removed from the tablets. The risk of capping is significant for this kind of materials, which has tendency to tarp air inside tablet. For lactose and Calipharm the EF values were lowest with low compression pressures and increased as the compression pressure increased. The elasticity value EF was especially high with maize starch, which was quite expected (Paronen, 1987). Maize starch did not form coherent tablets below 78 MPa compression pressure. EF values were lowest for microcrystalline cellulose tablets and they required the lowest compression pressure levels to form coherent tablets. The elasticity of lactose increased most rapidly as the compression pressure increased (Fig. 7; VI).

5.7 Prediction of flowability of powders using self-organising map (SOM) (IV)
The Kohonen SOM was used to organise powders into different regions on the map according to their flow behaviour in the flow meter (FLO) (Fig. 4; IV). Easily flowing powders are located in the upper left-hand corner of the map. Flowability decreases towards the lower right-hand corner of the map. The filler materials are also organised logically. The top row of the map contains only Avicel PH-200 based powders, and the second row contains Avicel PH-102 based powders (Fig. 4; IV).

The same test powders (in Fig. 4; IV) were compressed to tablets in an eccentric tablet machine. The flow behaviour of the powders in the eccentric tablet machine was divided in four different categories characterised by linguistic quality assessments. The criterion in the categorisation based on the measured relative weight variations (RSD) of

44
compressed tablets. For “good flowing powder” the measured RDS was less than 0.5%, for “fair flowing powder” RDS was between 0.5 -1.75 %, for “poor flowing powders” RSD was over 1.75 % and for “not flowing or very poor flowing powder” tablet was not formed. Each neurone (grid) on the formed Kohonen map was then coloured according to the RSD of the compressed tablets (Fig. 4; IV).

The prediction ability of Kohonen map was tested by feeding six parameter numeric data obtained from the FLO to the same already trained map. This new data was measured from Prosov90 based powders and was not used for the training of the Kohonen map. The predictive power of the map appeared to be very good (Fig 5; IV). All tested powders behaved in the eccentric tablet machine according to the predicted linguistic quality assessments. The Kohonen SOM was found to be able to bring together numerous parameters that describe powder flowability, and present the data in an easily understandable linguistic and visual form.

5.8 Direct compression of tablets from powders containing silicified and non-silicified microcrystalline cellulose (V)

Four different types of commercial microcrystalline cellulose grades and two self-made microcrystalline cellulose mixtures were compared as filler-binders for direct compression. Four commercial microcrystalline cellulose grades were:

- Avicel PH-101
- Avicel PH-102
- Avicel PH-200
- Prosov SMCC90.

Self-made mixtures were:

- simple mixture of PH-101 (75% w/w) and PH200 (25% w/w)
- mixture of Avicel PH-102 and colloidal silicodioxide (Aerosil) (2% w/w).
To distinguish the properties of filler-binders, poor flowing and compacting paracetamol powder was used in tablets.

The idea of making the Avicel PH-101/PH-200 mixture was to produce strong tablets with low weight variation by combining the good compactibility of Avicel PH-101 and good flowability of Avicel PH-200.

The mixture of Avicel PH-102 and Aerosil was made to test, if it was possible to achieve improved compactibility and flow properties of silicified microcrystalline cellulose ProsolvSMCC90, by simply mixing Avicel PH-102 and Aerosil in a glass jar.

### 5.8.1 Flowability of studied microcrystalline grades (V)

Mixing of Aerosil to Avicel PH-102 improved powder flowability remarkably compared to pure Avicel PH-102 binder-filler. With high paracetamol concentrations the flow properties of the Avicel PH-102/Aerosil mixture were even better than with silicified microcrystalline cellulose ProsolvSMCC90. The distribution of colloidal silicon dioxide in Prosolv SMCC90 was found to be uniform. Colloidal silicon dioxide mixed with Avicel PH-102 was not distributed uniformly, which affected the flow and bonding properties. There may have been a certain rearrangement of colloidal silicon dioxide during powder mixing. The Avicel PH-102/Aerosil mixture probably lost more colloidal silicon dioxide than Prosolv SMCC90. When a very cohesive ingredient, paracetamol, was included in the powder mixture, a flow facilitating effect of the “migrated” colloidal silicon dioxide was evident.

The Avicel PH-101/PH-200 mixture did not flow better than Avicel PH-101, apparently because the proportion of the freely flowing, granular Avicel PH-200 was not high enough to improve the extremely poor flow of the PH-101/paracetamol powder.

### 5.8.2 Compactibility of studied microcrystalline cellulose grades (V)

Tablets made of Prosolv SMCC90 were stronger than the tablets made from a simple mixture of Avicel PH-102 and colloidal silicon dioxide. One explanation is that colloidal silicon dioxide was distributed uniformly in Prosolv SMCC90 and had thus better ability to suppress negative effect of the lubricant on the bonding properties than the simple mixture (Bolhuis and Hölzer, 1996). Small-sized and rod-shaped Avicel PH-101 binder-
filler resulted in strongest tablets in the study (Fig. 7. IV). The mixture of Avicel PH-101/PH-200 and ProsolvSMCC90 yielded tablets of practically equal strength and were the next strongest. The compactibility of Avicel PH-102/Aerosil mixture was equal to pure Avicel PH-102. Avicel PH-200 produced weakest tablets, which was quite expected because it has the largest mean particle size.

5.9 Shape of the pressure curves and the value of minimum fluidization velocities (u_{mf}) as a mean to predict flowability of powders (VII)

The flowability of the pharmaceutical powders was predicted using a multichamber microscale fluid bed. Only 10 mL of powder (equal to 2 to 4 g) was needed to one test.

When the amount of poorly flowing substance paracetamol was increased in the tested powders, the flowability got worse. The shape of the pressure curves changed correspondingly logically as the amount of paracetamol was increased (VII, Fig. 3). Also the values of u_{mf} moved to the higher values(VII, Fig. 4). Worsen fluidization behaviour and the higher experimental u_{mf} were a consequence of the increasing interactions and the interparticle forces of fine paracetamol particles. Especially, the electrostatic forces were emphasised due to the low moisture content of the process air (< 0.5 g/m³).

Between the amount of paracetamol and experimental u_{mf} was found a clear correlation (Fig. 4) (VII). The results suggested that the changes in the experimental u_{mf} and fluidization behaviour could be used to predict powder process behaviour.

5.10 Prediction of flowability using principal components analysis (PCA) (VII)

The determination of the experimental u_{mf} is sometimes subjective and quite difficult. If powder have wide particle size and shape distribution and between particles are strong interparticle forces, different modes of fluidization are occurred and overlapped. The utilisation of the whole graph of the pressure difference over the bed could be more informative and objective than the simple determination of the experimental u_{mf}. The whole pressure difference curve over the bed can be reduced as a point (score plot) on
the plane after the PCA. The points on the score plot projected along specific path as the shapes of the corresponding pressure difference curves changed due to increased paracetamol content (Fig. 5; VII). The points on the upper right corner of the plane corresponded pressure difference curves of free flowing powders. As the flowability of the powders got worse (amount of paracetamol in the powder increased) the points on the plane removed toward upper left part of the plane. Also the weight variation of compressed tablets increased as the points moved toward upper left part of the plane. To the figure 5 (VII) is drawn line on the score plot which distinct weight variation under and over 1 %. On the right side of the line the weight variation of compressed tablets were less than 1% and on the left side of the line over 1%.

At low level of paracetamol powders was ordered logically on the score plot according to their fluidization and flow behaviour (VII, Fig. 5). The order of paths from left to right is MCC101 (finest), MCC101/MCC200 (75%/ 25%), MCC102, MCC200 and SMCC. MCC200 and SMCC were near each other indicating similar and good fluidization and flow behaviour. When the amount of paracetamol in the powder mixtures was increased, the fluidization behaviour became quite identical and the paths approached each other on the upper left corner of the plane. According to results, pressure difference over the bed graphs could be used to characterize and to predict powder process behaviour.

5.11 Prediction the flow rate and the angle of repose by the pressure difference over the bed curves using PLS model (VII)

A partial least squares (PLS) regression model was used to predict the flow rate and the angle of repose of silicified microcrystalline cellulose. The measured curves of the pressure difference over the bed (from Avicel based powders) were used as factors (predictors) in the model. The created PLS model over estimate lightly the flow rate results (Fig. 6; VII). One reason for the differences in the results might be that, due to differences in bulk densities of powders, mass flow results might give distorted results in the flow tester (Schüssele and Bauer-Brandl, 2003). Another source of error is the restricted size of the modelling data. The results of the angle of repose were quite precisely predicted by the PLS model (Fig. 7; VII).
6. SUMMARY AND CONCLUSION

Force-time and force-displacement profiles were parameterised in a new way. These parameters give novel information of the compression behaviour of powders and granules. They also, together with advanced data analysis, give possibilities of finding ways to predict the rotary tablet behaviour of powders and granules on the basis of eccentric tablet machine test compressions.

The tendency of the material for plastic deformation, fragmentation and elasticity could be expressed as numerical values, which are comparable between different materials. The dependence of these numerical values on the compression pressure could be quantified.

The accuracy of the displacement measurement in the eccentric tablet machine was improved by filtering out noise from the measurement data by a novel method.

A new method was introduced to define an elastic deformation of a running eccentric tablet machine very precisely.

The Kohonen self organizing map (SOM) was able to bring together numerous parameters that describe powder flowability, and present the data in an easily understandable, linguistic and visual form. The trained map was also able to predict reliably weight variation of tablets on the basic of flow meter results.

The mixture of Avicel PH-102 and Aerosil flowed better than Prosolv SMCC90 despite their similar particle size, size distribution and particle shape. Simply mixed, unevenly distributed colloidal silicon dioxide decreased attractions between the powder particles more than co-processed, uniformly distributed colloidal silicon dioxide.

Mixing 25 % (w/w) of free-flowing Avicel PH-200 grade with poorly flowing Avicel PH-101 grade did not improve the flowability of the mixture.

A novel method of predicting the flow behaviour of pharmaceutical powders using a micro-scale fluid bed (only 10 ml of powder is needed) was developed.
REFERENCES


50


