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Compression Mechanics of Powders and Granular Materials Probed by Force Distributions and a Micromechanically Based Compaction Equation

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Abstract

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The internal dynamics of powder systems under compression are as of yet not fully understood, and thus there is a necessity for approaches that can help in further clarifying and enhancing the level of understanding on this subject. To this end, the internal dynamics of powder systems under compression were probed by means of force distributions and a novel compaction equation.

The determination of force distributions hinged on the use of carbon paper as a force sensor, where the imprints transferred from it onto white paper were converted through calibration into forces. Through analysis of these imprints, it was found that the absence of friction and bonding capacity between the particles composing the powder bed had no effect on how the applied load was transferred through the system. Additionally, it was found that pellet strength had a role to play in the homogeneity of force distributions, where, upon the occurrence of fracture, force distributions became less homogenous.

A novel compaction equation was derived and tested on a series of systems composed of pellets with differing mechanical properties. The main value of the equation lay in its ability to predict compression behavior from single particle properties, and the agreement was especially good when a compact of zero porosity was formed.

The utility of the equation was tested in two further studies, using a series of pharmaceutically relevant powder materials. It was established that the A parameter of the equation was a measure of the deformability of the powder material, much like the Heckel $1/K$ parameter, and can be used as a means to rank powders according to deformability, i.e. to establish plasticity scale. The equation also provided insights into the dominating compression mechanisms through an invariance that could be exploited to determine the point, at which the powder system became constrained, i.e. the end of rearrangement. Additionally, the robustness of the equation was demonstrated through fruitful analysis of a set of diverse materials.

In summary, this thesis has provided insights and tools that can be translated into more efficient development and manufacturing of medicines in the form of tablets.

Keywords: compression, powder, mechanical properties, pellet, tablet, compaction equation, force distribution

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List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

- I Frenning, G., Mahmoodi, F., Nordström J., Alderborn, G., An effective-medium analysis of confined compression of granular materials. *Powder Technology*, 194(2009):228–232
- II Mahmoodi, F., Alderborn, G., Frenning G., Effect of lubrication on the distribution of force between spherical agglomerates during compression. *Powder Technology*, 198(2010):69–74
- III Mahmoodi, F., Alderborn, G., Frenning G., Effect of spherical-agglomerate strength on the distribution of force during uniaxial compression. *Powder Technology*, 206(2011):286–290
- IV Mahmoodi, F., Alderborn, G., Frenning, G., An experimental evaluation of an effective medium based compaction equation. *European Journal of Pharmaceutical Sciences*, 46(1-2)(2012):49-55
- V Mahmoodi, F., Klevan, I., Nordström, J., Alderborn, G., Frenning, G., On the practical utility of an effective medium based compaction equation: application to a diverse set of pharmaceutically relevant materials. Manuscript.

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Comments on my contributions to the appended papers:

Paper I: I was only involved in problem formulation through some initial experimental work. I was not involved in the theoretical development of the model.

Papers II-V. I was involved in all parts of the work i.e. experimental work (except Paper V), writing, data analysis and interpretation of results.

“...Arts, crafts and sciences uplift the world of being,
and are conducive to its exaltation.”

Bahá'u'lláh 1817-1892

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Abbreviations

ρ_{poured}	Poured bulk density of powder bed
ρ_{tapped}	Tapped bulk density of powder bed
ρ_{rel}	Relative density of powder bed
$\rho_{rel,0}$	Initial relative density of the powder bed
ρ_{solid}	Apparent density of powder particle
ρ_{mix}	Apparent binary mixture density
ε	Porosity of powder bed
K	Heckel parameter
P	Pressure
P_1	Starting pressure
<i>EM equation</i>	Effective medium equation
A	EM equation parameter
α	EM equation parameter
H_{min}	EM equation parameter
H	Powder bed height
H_1	Starting powder bed height at some starting pressure
C	Degree of powder bed compression
C_{max}	Maximal degree of powder bed compression
a	Kawakita parameter
b	Kawakita parameter
V_o	Initial powder bed volume
V	Powder bed volume at some pressure
ω_1	Weight fraction of component 1
ω_2	Weight fraction of component 2
ρ_1	Apparent density of component 1
ρ_2	Apparent density of component 2
φ_c	Packing fraction for random loose packing
D_p	Projected area diameter
A_p	Projected area
σ_y	Yield stress
D	Mean pellet diameter
dF/dx	Slope of force displacement plot
<i>DEM</i>	Discrete element method
<i>FEM</i>	Finite element method
<i>NaCl</i>	Sodium chloride
<i>MCC</i>	Microcrystalline cellulose

<i>PEG</i>	Polyethylene glycol 6000
<i>MLP</i>	Low porosity MCC pellets
<i>MHP</i>	High porosity MCC pellets
<i>MPLP</i>	Low porosity pellets of MCC and PEG
<i>MPHP</i>	High porosity pellets of MCC and PEG
<i>MCC LP</i>	Low porosity MCC pellets
<i>MCC HP</i>	High porosity MCC pellets
<i>MCC PEG</i>	Low porosity pellets of MCC and PEG
<i>MCC LAC</i>	Low porosity pellets of MCC and lactose

1 Introduction

1.1 Pharmaceutics

The field of pharmacy encompassing this thesis is known as pharmaceutics, which is also referred to as galenic pharmacy. Galenic refers to *Galen* (approximately 130-200 AD) an ancient Greek physician of renown, whose talents spanned; anatomy, physiology, pathology, neurology, philosophy and logic [1-3]. His association with pharmaceutics is due to his compounding of medicines [4], he was probably the first formulation scientist.

Pharmaceutics is the study of how to optimise the administration of a medication, through rational scientific design. It is a multidisciplinary science and draws knowledge from any field of science that would assist in the development of a formulation for a certain route of drug delivery. Pharmaceutics encompasses all routes of drug administration, such as the topical, parenteral, nasal, ocular, aural, pulmonary, rectal, vaginal and oral routes. Each route can be composed of multiple different formulations and dosage forms for administration.

1.2 The oral route

Out of the several routes enveloped by pharmaceutics, the oral is the most common [5]. The fundamental reason for this is that the mouth is the most natural route by which to introduce substances systemically into the body (just consider the necessity of ingesting food), and is thus more accepted and comparably risk free relative to other routes. The oral route comprises different dosage forms such as solutions, suspensions, capsules and tablets. Of these, tablets are the most common, as they are [5]:

- Chemically and physically stable.
- Provide an accurate and reproducible dose.
- In most cases, easy and cheap to manufacture.
- Easy to handle by the patient.
- Can be formulated to optimise drug effect.

The combined reasons given above ensure the dominance of tablets as the default route of drug administration for most medicinal candidates. It is due to this dominance that the pharmaceuticals group at the department of pharmacy in Uppsala University has directed much of their research efforts toward better understanding the processes involved in tablet manufacture. This thesis is a part of that effort.

1.3 A very brief history of tableting

The sixth edition of the European Pharmacopeia describes tablets as being [6];

“solid preparations each containing a single dose of one or more active substances. They are obtained by compressing uniform volumes of particles or by another suitable manufacturing technique, such as extrusion, moulding or freeze-drying (lyophilisation).”

For the purposes of this thesis however, tablets are made by compressing a powder in an enclosed cavity. The first powder press was patented in 1843, and was hand operated [7, 8]. It was initially designed for producing superior graphite for pencils, but its pharmaceutical potential led to it being patented for “shaping pills, lozenges and black lead by pressure in dies” [7, 8]. An obvious problem with the hand operated tablet press is that the applied pressure depends on the operator. This is not conducive to therapeutically effective tablet production, as the availability of the medicine for absorption by the patient would rely on the physical strength and judgement of the operator. To remedy this, simple pressure gauges began to be fitted to tablet presses in the 1930s in an attempt to standardise and better control the tableting process [8]. Further advancements in tableting were made in the 1950s with the introduction of industrial electronics [8]. Today’s tableting machines are computerised and can produce vast quantities of tablets per hour, for example, the GEA Performa™ P can produce at least 157,000 tablets per hour and the GEA Performa™ S can produce up to 405,000 tablets per hour [9]. Apart from industrial scale tableting machines, technological advancements have resulted in the introduction of material testers, which although not specifically designed to compress powders, can be adapted to do so. The Zwick Roell Z100 is an example of one such machine, and was used in the experiments presented in this thesis.

2 Solid oral dosage forms: powders, tablets and tablet manufacturing

2.1 Powders

In the pharmaceutical context, powder systems are generally thought of as being assemblages of discrete particles ranging in size from $1\mu\text{m}$ to $1000\mu\text{m}$ [10, 11]. The volume occupied by a powder system is normally greater than the combined volume of the discrete particles. The remaining volume is, as a consequence of the random packing of the discrete particles, composed of voids. In normal pharmaceutical use these voids are occupied by air. As such, a powder system can be described as a dispersion of a solid in air [12]. Furthermore, the presence of the voids (pores) allows for the particles to move relative to each other. It is this motion that underlies powder flow [10]. The ability to flow, although shared by liquids, is unique in powders, as unlike a liquid, when a powder flows down a slope, there is no simultaneous motion throughout its bulk, but rather just on its surface [13].

The composing particles of a powder system can be in the form of either primary or secondary particles. Primary particles as their name suggests are singular entities, whereas secondary particles are composed of two or more primary particles joined together to form an agglomerate or granule. This can be accomplished through granulation [14], or by cohesive/adhesive forces between primary particles in the powder bed [10]. Where granulation is involved, the secondary particles can take the form of irregular coarse agglomerates or spherical agglomerates (pellets) [15]. These secondary particles are porous, which adds a layer of complexity when studying powder compression, as their internal porosity becomes a variable in the total response of the powder to compression pressure [16-20].

2.1.1 Pertinent powder properties

What follows is a general description of powder properties which are pertinent to compression. Upon being poured into a container, a powder will occupy a certain volume, which as mentioned above will be composed of the

solid particles and pores. The ratio of the powder mass and volume at this point is known as the poured bulk density. The contact areas between neighbouring particles at this point are small relative to the compressed state, and as such the resulting structure as a whole is fragile compared to the compressed state. The structure at this stage is much like a “house of cards”. Analogous to pushing over a “house of cards”, disturbing the container, such as tapping it, vibrating it or pressing on the powder bed results in the particles collapsing and displacing the pores, a process known as rearrangement. Rearrangement is the powder bed flow that occurs during powder compression. It must be noted that the degree of rearrangement is directly related to the fragility of the structure formed upon pouring, which is dependent on particle size, shape and surface texture [21]. Larger particles such as pellets undergo little if any volume reduction due to rearrangement [21, 22], whereas smaller particles undergo a greater degree of rearrangement [21, 23-25]. Continued disturbance of the powder bed eventually results in a situation where much like knocking over every card, further densification is not possible. If the disturbance is due only to tapping, the density of the powder bed is known as the tapped bulk density. It should be apparent now that the tapped bulk density is higher than the poured bulk density, as such, the ratio of the two, known as the Hausner ratio [26, 27], gives an indication of the flowability of the powder. Another commonly used measure of flowability based on poured and tapped bulk densities is the Carr’s index [28], which calculates the percentage compressibility of the powder bed. The equations for the Hausner ratio and Carr’s index are shown below [10]:

$$\text{Hausner ratio} = \frac{\rho_{\text{tapped}}}{\rho_{\text{poured}}} \quad \text{Equation 1}$$

$$\text{Carr's index} = \frac{\rho_{\text{tapped}} - \rho_{\text{poured}}}{\rho_{\text{tapped}}} \times 100 \quad \text{Equation 2}$$

Where ρ_{poured} is the poured bulk density and ρ_{tapped} is the tapped bulk density. From the above discussion it should be apparent that a decrease in porosity is the same as an increase in density i.e. both describe the closeness of neighbouring particles. A direct measure of this closeness is the relative density of the powder bed:

$$\rho_{\text{rel}} = \frac{\rho_{\text{bulk}}}{\rho_{\text{solid}}} \quad \text{Equation 3}$$

Where ρ_{rel} is the relative density, ρ_{solid} is the apparent density of the non-porous material the particles are composed of, and ρ_{bulk} is the bulk density

(poured or tapped depending on the situation). Following on from this, the porosity (ε) of the powder bed can be calculated as:

$$\varepsilon = 1 - \rho_{rel} \quad \text{Equation 4}$$

If we assume that the powder is composed of spherical particles of uniform size, as would be the case with pellets, then the porosity of the bed upon pouring would lie between 0.37 and 0.40 [29]. If however these spheres were arranged in a cubic packing arrangement and a rhombohedral arrangement the porosities would be 0.48 and 0.26 respectively [10]. It seems that the random packing geometry of spheres is somewhere between cubic and rhombohedral. It must be noted however, that in the case of pellets, the intra-granular porosity would result in a higher porosity value, even at the most dense packing arrangement. Furthermore it is interesting to note that the porosity of pharmaceutical tablets generally lies between 0.05-0.35 [12], which at the upper limit is close to the random packing arrangement of poured spheres, and greater than a rhombohedral packing arrangement.

The mechanical properties of the individual particles be they primary or secondary play a key role in the compression and tablet forming ability of powders. Three main mechanical properties are commonly described, these are; fragmentation, plastic deformation and elastic deformation [30, 31]. Fragmentation as the name suggests involves the breaking up of the particle into two or more separate pieces, dicalcium phosphate is an example of a fragmenting material [32]. Plastic deformation is a permanent change in the particle, sodium chloride is an example of a plastically deforming materials [33, 34]. Elastic deformation is where the particle only remains deformed so long as a force is applied to it, once the force is removed the particle returns back to its original form, paracetamol is an example of an elastic material [35]. Powders, depending on their mechanical properties, can exhibit time dependent behavior when compressed [36-38]. Strain rate sensitivity (SRS) is a measure of the sensitivity of a material to the rate at which it is strained i.e. compressed, and can be used to compare different materials [31, 36]. SRS can be seen as the percentage difference between the yield stress of a material measured at a high compression rate and that measured at a lower compression rate [31]. Fragmenting materials are generally not strain rate sensitive, whereas those that undergo deformation are [36-38]. Fragmenting materials can however transition into becoming deformable, this occurs at a critical particle size, which is known as the brittle ductile transition [39-42].

2.2 Tablets

A tablet is an amount of powder that has been compressed in an enclosed cavity to such an extent that it forms a solid unit whose strength can be measured. Powders take the shape of the container in which they are placed, and this is evidenced by the many shapes that tablets come in. A few are shown below. They can also come in different colours, either through coating the finished tablet or by blending the powder with a colorant prior to compaction. Shape and colour are convenient ways in which a company can distinguish their tablet from the rest of the market. Additionally, patients can often identify their tablets by these characteristics. A tablet can take virtually any cylindrical shape; so long as a mold can be made in that shape, see Figure 1.



Figure 1. Photographs of different tablet shapes and colours (All images are from Fass.se).

2.3 Brief description of tableting machines

Pharmaceutical tablet production involves compression of free flowing powder in an enclosed cylindrical cavity of defined geometry (die cavity), situated within a die, which is itself situated in a die table [22], see Figure 2. Compression is applied in a uniaxial direction by punches, which are analogous to pistons. There are two punches; an upper punch which enters the die to apply the compression force, and the lower punch that seals the base of the cylindrical die cavity. These components are made of stainless steel and collectively known as tablet tooling. The tablet tooling can be manufactured such that the die cavity has a certain shape, and the punch surfaces can be engraved or embossed to decorate the tablet faces.

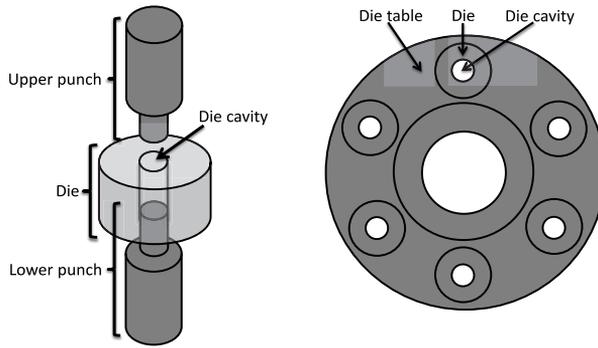


Figure 2. Diagrams of tablet tooling.

Two basic types of tableting machine are used today in tablet production; the single punch (eccentric) tablet press, and the rotary tablet press [22]. The eccentric press has only one die and one pair of punches. Powder is fed through a hopper to a hopper shoe and enters the die cavity gravitationally. The hopper shoe then slides off the die cavity orifice, carrying the source powder with it. The upper punch then descends into the cavity and compresses the powder. Once the designated compression pressure is reached, the upper punch ascends out of the die cavity, shortly followed by the lower punch, whereby the tablet is ejected, see Figure 3.

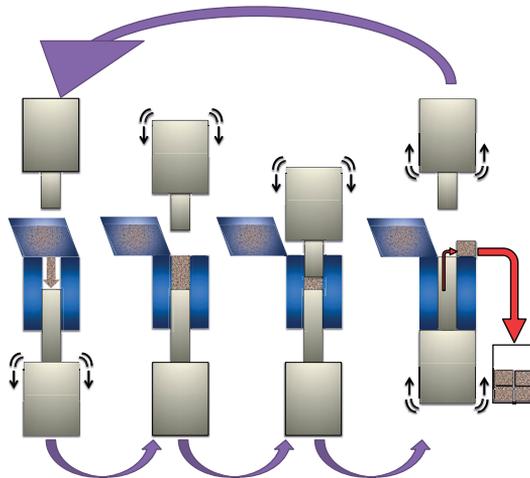


Figure 3. Schematic diagram of stages of tablet production using an eccentric tablet press.

The rotary tablet press as its name suggests is based around a rotating die table, which allows for the incorporation of multiple dies and their concomi-

tant punches. The die and its punches are paired throughout the rotation cycle. This type of setup allows for mass production of tablets. The compression force is generated by a cam system, which directs the upper punch into the die cavity. A simple diagram of a rotary tablet press is presented in Figure 4.

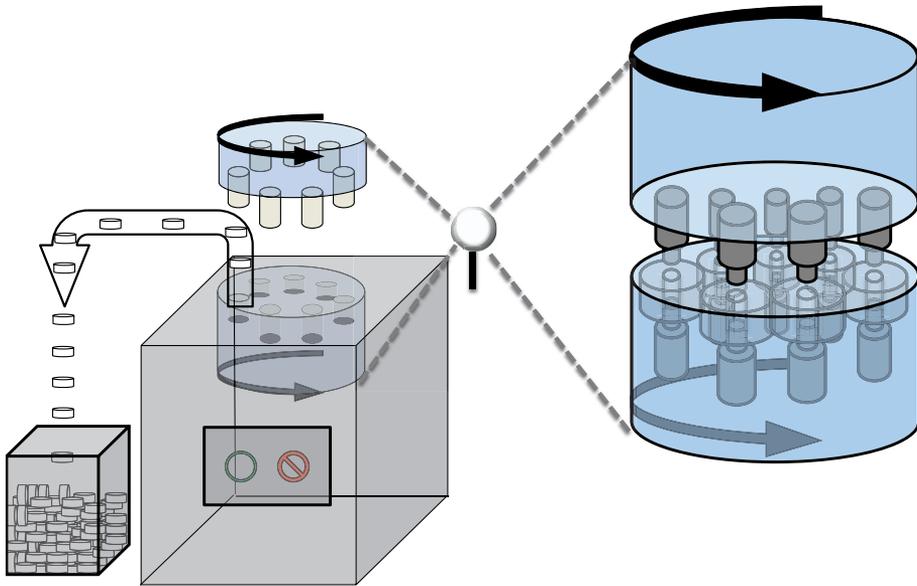


Figure 4. Simple diagram of a rotary tablet press.

3 Phenomenological descriptions of powder compression

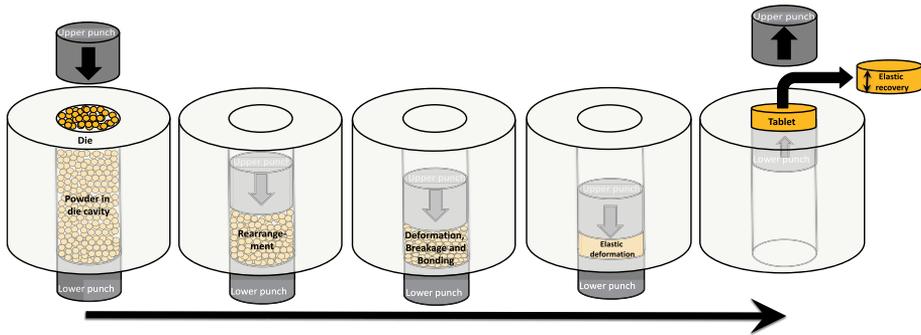


Figure 5. Schematic diagram of stages in powder compression.

3.1 Stages in the compression process

The process of powder compression into a tablet (compaction) can be generally divided into four predominant stages, which although sequential can in reality occur simultaneously [43-46]. These are; rearrangement, plastic particle deformation and/or fragmentation, elastic compact deformation and elastic recovery following unloading and tablet ejection, see Figure 5.

3.1.1 Rearrangement/fragmentation

Immediately after pouring the powder into the die cavity, the “house of cards” situation arises. In this case any ensuing rearrangement is as a result of the upper punch contacting and pressing down on the powder bed. Soon thereafter, the system reaches a state where its capacity to rearrange is exhausted as the particles are constrained or locked into position by more structurally stable contact with their neighbours. This junction can be referred to as a constrained state. Although the house of cards analogy describes the collapse of a fragile solid skeleton, there is also a degree of fragmentation that can occur during this initial stage of powder compression [24, 44].

3.1.2 Plastic deformation and/or fragmentation

Upon reaching the constrained state, any further reduction in the porosity of the powder bed can only occur as a result of a mechanical change in the structure of each of its composing particles. This/ese change/s must take place in order to accommodate the increased force that is applied to the powder system. To simplify things, we can imagine two major routes of accommodation; deformation and fragmentation/breakage [17, 25, 30, 31, 42, 43, 45, 47-49]. If the particles are plastic or elastic in nature they will deform to accommodate the increasing applied force. If a particle is brittle in nature, it will break into smaller pieces which then displace the pores. Assuming the applied force is large enough, the particles can undergo one or all of these structural changes. It is during this transitional phase that bonding occurs between the contacting surfaces of the powder particles, either as in the case of deformation, by an increased area of contact between particles, or by an increase in the number of bonding sites as in the case of breakage [46, 50-52].

3.1.3 Elastic deformation and recovery

Finally, at the maximum compression pressure, where the porosity is reduced to 5-10% [53] i.e. when nearly all pores are eliminated, the powder will no longer be a system of distinct particles, but rather a single solid unit. Further compression past this point will invariably be controlled by the elastic deformation of this solid unit [54], as there is no other avenue for permanent structural change. Consequently, when the pressure is removed (unloading), the solid (tablet) begins to relax into its final dimensions, a process referred to as; elastic recovery [25].

3.1.4 Further remarks on the stages

It must be noted that as mentioned above, the stages of compression are not always distinct. Breakage, plastic and elastic deformation can occur simultaneously to different degrees. This intermeshing of phases underpins the complexity of the compression process. In any case, if the definition of a tablet is to be satisfied, the degree of bond formation between powder particles must be high enough, to yield the strength necessary, to maintain the structure of the newly formed compact upon ejection and subsequent handling.

From the above discussion, it should be clear that the combined response of the individual particles to the applied force, translates into the bulk property of the powder bed i.e. the whole is a reflection of its parts. A material that is very stiff (resistant to deformation) and does not fragment will have great difficulty forming a compact. An elastic material e.g. paracetamol [35], although deformable, regains its shape after the applied force is removed. Any bonds must therefore be strong enough to resist the forces generated by elastic recovery [55, 56].

The terms compressibility and compactibility are often used to describe a powder [57], see Figure 6. A very compressible powder is one that upon compression significantly densifies. Powders with very small particle size are normally very compressible. However, this does not mean that they are able to form tablets. The compactibility of a powder determines whether or not it can form a tablet. To clarify the point, rubber can be used as an example. If a batch of rubber powder with very small particle size were to be compressed, it would densify a great deal, but no matter how much pressure is applied, once that pressure is removed, the rubber would fail to form a coherent compact with a measurable strength i.e. it would have a very low or zero compactibility.

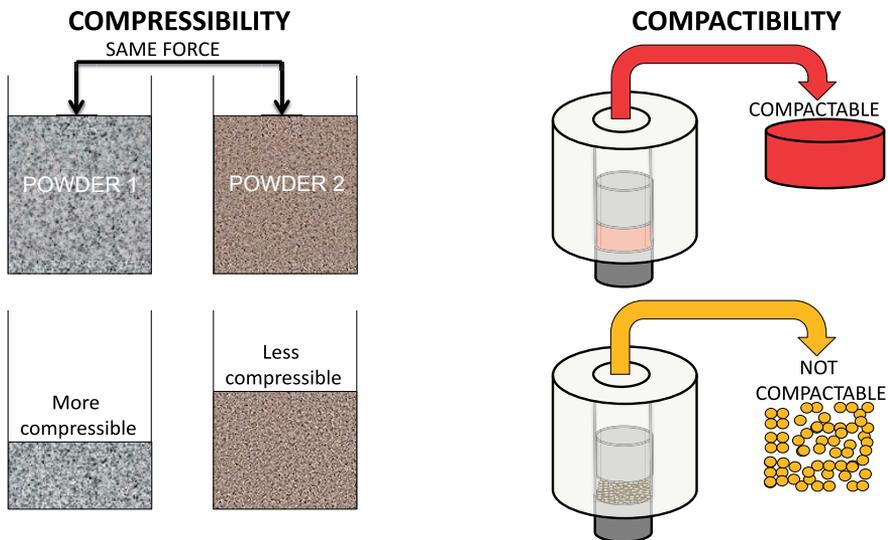


Figure 6. Examples of compressibility and compactibility.

3.2 Force transmission

3.2.1 Percolation

A powder bed or tablet can be viewed as a binary/dual phase disperse system, composed of solid particles and pores [12, 46, 58]. The degree to which the vicinity of neighboring particles is reduced determines whether the pores or particles form the continuous phase. If the particles form the continuous phase, then the system can be viewed as being analogous to Swiss cheese [46], alternatively in the opposite case the system has been likened to a “particulate dispersion in air” [46]. In a powder bed or tablet, any contiguous pore channels or contiguous particle contacts span certain distances in three dimensions, and can manifest as multiple isolated clusters. The analogies of Swiss cheese and fluidized particles represent two opposing ends of a spectrum within which the powder system can exist.

Percolation theory is a means by which to describe the contiguousness of a phase within a multiphase system. Since as mentioned above, a powder bed is a dual phase system, the concept of percolation can be put to use in its visualization and description. A percolating system can be understood as one that is composed of contiguous networks in an infinitely large three dimensional lattice [59-61]. In terms of a powder bed, these contiguous networks can be pores or solid particles. Percolating clusters can be either finite or infinite [59]. A finite percolating cluster is one where the range of the contiguous network is limited to a small region within the whole volume of the system. An infinite cluster occurs at the percolation threshold [59, 61] and is a contiguous network that spans the entire system. Figure 7 is a diagrammatic representation of finite and infinite clusters. In the case of a powder in a die, an infinite cluster occurs when either the pores or solid particle contacts form a contiguous network spanning the walls and punch surfaces.

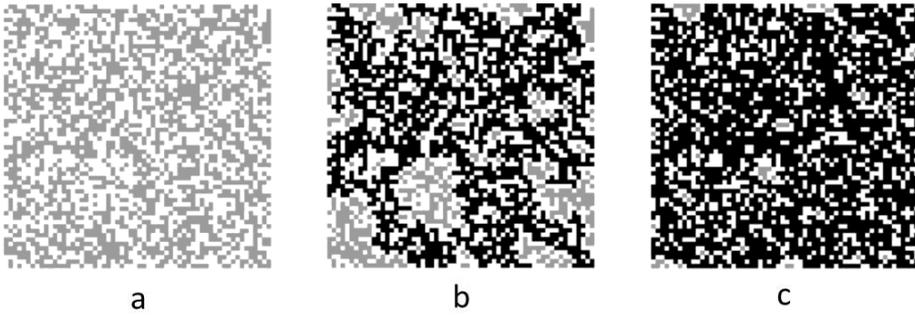


Figure 7. Diagrammatic representation of a) finite solid clusters (grey regions), b) the percolation threshold with an infinite cluster (black regions) spanning the entire system, within which are interspersed finite clusters (grey regions), c) An infinite cluster with greater density and homogeneity than at the percolation threshold.

Percolating clusters can be described both in terms of *contiguously occupied sites*, known as *site* percolation, and *contiguous connections* within a particular phase, known as *bond* percolation [59-61]. Bond percolation can be described in terms of open and closed bonds [61]. An open bond signifies a contiguously occupied cluster of sites i.e. it necessitates contact, and a closed bond signifies non-contiguous occupied sites i.e. it necessitates the absence of contact. It should be apparent that contiguously occupied sites and open bonds can be used interchangeably in qualitative description. The difference between the two can be seen when quantitatively describing a system. If we imagine a 2D grid composed of four segments, three of which are contiguously occupied, then the probability of site occupation is $\frac{3}{4}$ whereas the probability of contact is $\frac{1}{2}$, see Figure 8.

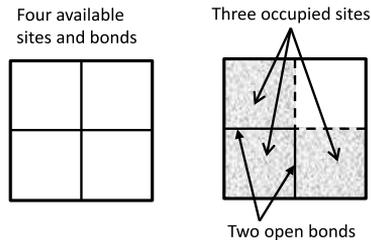


Figure 8. Examples of quantitative difference between site and bond percolation.

In the case of a powder bed in a die cavity, the 3D lattice is contained within the bounds of the volume occupied by the powder. The beginning of the compression cycle marks an increase in the extent of solid particle contacts,

while simultaneously reducing the degree of contiguousness of the pore channels. This dual process alters the balance between the two phases. As the degree of compression is increased the solid particle contacts begin to dominate, and the Swiss cheese scenario is accomplished. Percolation in terms of powder compression is mathematically described via the probability of bond formation [58-61]. A bond formation probability of 1 indicates that all possible bonds are formed, and that the compact is at its maximum possible strength with a porosity of zero [59].

3.2.2 Lateral/Radial force transmission

If the weight of a powder is immediately measured from the lower punch after being poured into the die cavity, it would be found that it is less than that which was measured prior to pouring [62, 63]. This is due to a supporting force provided by the side wall of the die cavity due to static friction [13]. The powder bed essentially supports part of its own weight by laterally pushing against the side wall, see Figure 9. If the side wall were to be lubricated sufficiently, such that the friction between the powder particles and itself is zero, then the full weight of the powder bed would be experienced by the lower punch.

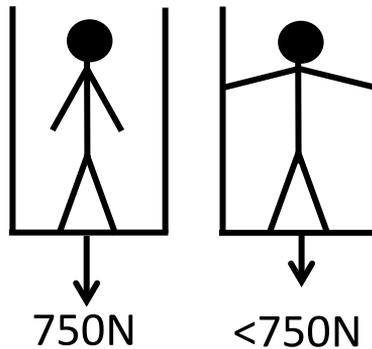


Figure 9. Analogy for radial force transmission.

3.2.3 Axial force transmission

The discussion about percolation sets the stage for an understanding of how forces are transmitted through a powder bed. It should be intuitively apparent that in order for a contact force to be transmitted, it requires a medium to do so. The medium in the case of a powder bed in a die cavity are the contacting powder particles. The transmission of force is predominantly in the

vertical/axial direction, since this is the direction that the punch descends into the die cavity. Although lateral force transmission does occur, this is limited, so long as the die walls are adequately lubricated. During the initial rearrangement phase of compression, there is no infinite cluster of solid particles. The constrained state is where the infinite cluster of solid particles is formed i.e. the percolation threshold, and has been extensively discussed in the physics literature, where it is referred to as the jamming transition (see [64, 65] and references therein). On a relativistic scale the powder at this stage can be considered as “the first dense tablet” [59]. However, once established, the load bearing chains of solid particles that form the infinite cluster are not homogeneously distributed throughout the powder bed. As the applied force is increased, the density and homogeneity of the infinite cluster increases and with sufficient pressure eventually results in a system of homogeneously load bearing chains. It must be borne in mind that, as well as load bearing chains, there are many non-load bearing chains/dead zones in the powder bed. From the discussion in section 3.2.1 regarding open and closed bonds, we can now extend the idea to apply to this system in its current configuration. As it is, the load bearing chains can be viewed as contiguous occupied sites of solid particles with open bonds, whereas the non-load bearing chains can be viewed as contiguously occupied sites of solid particles with closed bonds. The open and closed description of bonds in this context refers to contacts that contribute (open bonds) or not (closed bonds) to the tablet strength. The non-load bearing chains, as is apparent from the name, do not contribute to the strength of the tablet. A consequence of the above discussion is that the strength of the tablet is not homogeneously distributed throughout its structure, which contributes to the mechanical strength anisotropy of the tablet [66-70]. If it was somehow possible to isolate the infinite cluster in a tablet, it would be found that the structure is basically a skeleton of load bearing chains of strongly bonded solid particles enveloping the inactive dead zones (Figure 10). Illustrative images of active force chains have been presented by Drescher [71], Lui et. al. [72] and Travers et. al [73]. The measurement of the homogeneity of the force chains necessitates some kind of force sensor/detector and quantitative description. A suitable and simple force sensor which has been used is carbon paper with force distributions as the means of quantification [72, 74-78].

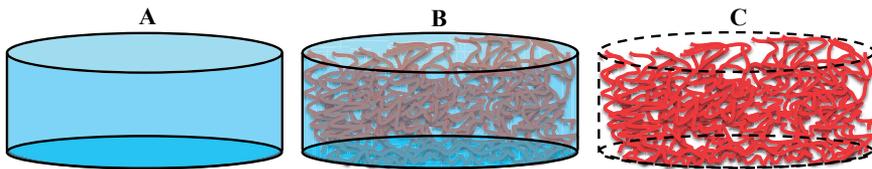


Figure 10. Diagrammatic representation of force network.

4 Mathematical descriptions of powder compression

Powder systems can be modeled using computers to apply sophisticated numerical techniques such as the finite and discrete element methods [79-85]. The finite element method (FEM) [79] essentially involves a macroscopic view of the system being modeled. The discrete element method (DEM) is a higher resolution technique that considers the system being modeled on a microscopic level, where the physics of individual powder particles can be controlled [80, 81, 83]. The use of one method does not preclude the other, as both can be used in conjunction with each other [84, 85]. For the purposes of this summary however, we will not focus on these techniques but rather, will turn our attention to compression equations.

It is the authors understanding that the aim of any mathematical equation attempting to describe powder compression, is the quantitative extraction of a powder/particle characteristic in the form of an equation parameter to help shed more light on and describe the compression process. In order for the equation to have practical applicability, it necessitates variables whose values are known. These are normally pressure, and some quantitative measure of the distance between individual particles i.e. porosity, density, volume, powder bed height etc. Furthermore, a compression equation can be developed from two opposing perspectives, firstly; single powder properties being extracted from bulk powder behavior as has been done by Heckel [86, 87] and Kawakita [88], whose equations bare their names, and secondly, bulk powder behavior being derived from single particle properties, as has been done by Adams [89, 90].

4.1 The Heckel and Kawakita equations

The Heckel equation [86, 87] shown below, was empirically derived from compression data of metal powders.

$$\ln\left(\frac{1}{1-\rho_{rel}}\right) = KP + \textit{Intercept} \quad \text{Equation 5}$$

Here ρ_{rel} is the relative density of the powder, thus equating $1 - \rho_{rel}$ to porosity, P is pressure, K is a constant and slope of the linear region of the plot. Heckel assumed that the rate of powder compression followed first order kinetics i.e. that the greater the porosity of the powder system, the greater the degree of its densification. A schematic Heckel plot is shown in Figure 11.

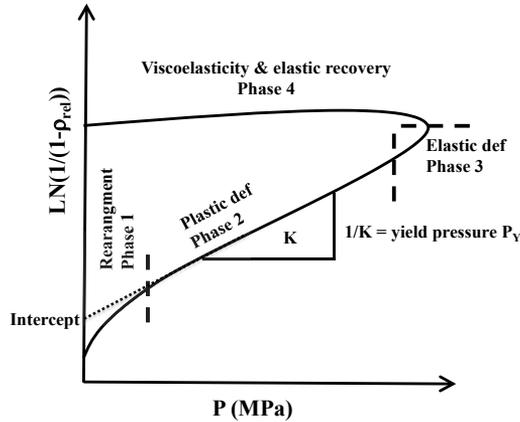


Figure 11. Schematic Heckel plot.

The Heckel plot can be divided into four general regions highlighting processes occurring in the die as the powder is compressed. As mentioned in section 3.1 these processes can occur simultaneously or sequentially. Phase 1 is generally regarded as densification by the powder particles flowing past each other (rearrangement) or due to some initial fragmentation [24, 44]. The second phase occurs after the constrained state is reached, where the mechanical properties of the powder particles determine volume reduction. The third phase is the elastic deformation of the compact [54], and the fourth and final phase is the elastic relaxation phase, where elastic recovery (if any) of the compact takes place. The linear region of the Heckel plot has roused much debate as to what it actually represents. Paronen [91] asserts that it is a measure of the elasticity of the powder bed, whereas Heckel himself thought of it as an indication of hardness and plastic deformation [86, 87]. Roberts and Rowe have argued that if the powder is below its brittle ductile transition, the linear region is a measure of the yield stress of the particles [30, 42], and Hassanpour and Ghadiri [80] have through DEM found that the Heckel parameter only represents yield stress when the ratio of Young's modulus [92, 93] to yield stress exceeds a certain limiting value. They also found that if this ratio is below approximately 30, the linear region of the Heckel plots represents the Young's modulus of the material, and advise caution in the use of the Heckel equation. Whatever the interpretation of this

linear region, the fact remains that, it represents a stage in powder compression where the powder system behaves as a single unit regardless of the compression mechanism.

Another famous compression equation is the Kawakita equation [88] for pharmaceutical (fluffy) powders:

$$C = \frac{abP}{1+bP} \quad \text{Equation 6}$$

where C is the degree of compression and a and b are constants. The degree of compression is in turn calculated as

$$C = \frac{V_0 - V}{V_0} \quad \text{Equation 7}$$

where V_0 is the initial powder bed volume and V is the powder volume upon compression. The Kawakita constant a describes the maximum degree of compression, and $1/b$ is the pressure applied to get $\frac{1}{2}$ the maximum degree of compression or $a/2$.

The non-linear Kawakita equation (Equation 6) may be rewritten in the linear form:

$$\frac{P}{C} = \frac{P}{a} + \frac{1}{ab} \quad \text{Equation 8}$$

The Kawakita equation can be plotted both linearly and non-linearly, as schematically shown in Figure 12.

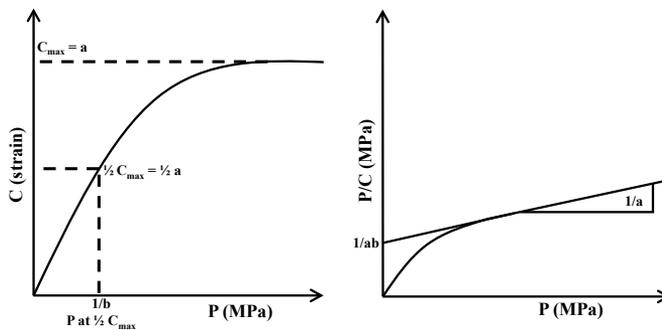


Figure 12. Schematic non-linear and linear Kawakita plots.

Much like the Heckel equation, the Kawakita equation has spurred debate as to the physical meaning of its parameters. Nordström et al. [23, 94] have

performed compaction studies on various materials in order to identify the role of the Kawakita parameters in the compression process. They have found that the product of the a and b parameters gives an indication of the degree of rearrangement of powder particles, and have proposed that this can be used to form a scale to help characterize powders. Adams [89, 90] while deriving a theoretical equation that relates the bulk compression of powder to single particle failure stress, makes the assertion that the Kawakita b parameter is proportional to the reciprocal of the single particle failure stress i.e. the Kawakita b parameter is a measure of the fracturing of powder particles.

Both the Heckel and Kawakita equations are essentially describing the same process using variables with different units. They both describe how the distance between powder particles is reduced with the application of force. Kawakita describes the closeness of particles in terms of degree of compression (engineering strain) as a function of applied pressure. Heckel describes the closeness of particles in terms of porosity as a function of applied pressure.

There are two features that the Heckel and Kawakita plots have in common. The first is an initial curvature in both plots. This curvature is a result of powder flow. In this context flow is the free movement of powder particles relative to one another with the end result of increasing the powder bed density i.e. rearrangement. The second are the conspicuous linear regions in both plots. These linear regions indicate that the powder system is acting as a single unit. Any linearity indicates that the compaction equation has the ability to capture an aspect of the unified group behavior of the powder particles. Since the mechanical properties of the powder bed are a reflection of its component's properties, any parameters that can be drawn from the linear regions can be interpreted as some particle property. The Kawakita profile produces linear plots also when the pressure term is replaced by number of taps. Although the taps densify the system by a rearrangement process, the number of rearrangements is such that on average the behavior becomes predictable and therefore linear. Although not impossible in principle, it seems that the randomness of particle rearrangement precludes the formulation of an accurately descriptive model.

5 Aims

Papers II and III

The aim of these papers was to probe the transmission of force through a bed of powder. Since force transmission is the impetus for the densification of a powder bed, then knowing the factors that affect it will deepen our understanding of the processes that take place inside the powder bed, and can be used as the basis for assumptions or variables in mathematical models of the powder compression process. In Paper II the effects of inter-particle friction and particle bonding were eliminated to see if they had any effect on force transmission. In Paper III we tested the effect of particle strength on force transmission.

Papers I, IV and V

The aim of Paper I was to derive a compression equation based on assumptions that if pertinent would deepen our understanding of the compression process and enable a more accurate prediction of the compression behavior of powder systems. In Papers IV and V we aimed to use experimental data to determine the equation parameters and see if any useful descriptive parameters could be drawn from the equation. By being able to extract a descriptive parameter from the equation, we would be able to have some sort of quantifiable and reliable means by which to better understand, rank, describe and use different powders (excipients) for making tablets.

6 Materials

The materials used in this thesis are listed below, see appended papers for more details.

PAPER I

- Microcrystalline cellulose (Avicel PH101 , FMC, Ireland)
- α -lactose monohydrate (Pharmatose 200M, DMV, Netherlands)
- Polyethylene glycol 6000 (Sigma Aldrich, Germany)
- Ethanol (95% w/w, Solveco Chemicals AB, Sweden)
- Deionised water
- Magnesium stearate (Ph. Eur., Kebo, Sweden)

PAPERS II and III

- Magnesium stearate (Ph. Eur., Kebo, Sweden)
- De-ionised water
- Microcrystalline cellulose (Avicel PH101, FMC, Ireland)
- Ethanol (Solveco Etanol A96%, Solveco AB, Sweden)
- Polyethylene glycol 6000 (Fluka Chemie GmbH, Germany)
- Black carbon paper (Radex 1200, Kores, Austria)
- White photo quality paper (Epson photo quality inkjet paper, S041068, Seiko Epson Corp., Japan)

PAPER IV

- Sodium chloride (Fluka Analytical, Switzerland)
- Lactose monohydrate (Pharmatose 50M, DMV, Netherlands)

PAPER V

- Aspirin (Sigma–Aldrich, Stockholm, Sweden)
- Dicalcium phosphate (Sigma–Aldrich, Stockholm, Sweden)
- Maize starch (Sigma–Aldrich, Stockholm, Sweden)
- Mannitol (Sigma–Aldrich, Stockholm, Sweden)
- Paracetamol (Sigma–Aldrich, Stockholm, Sweden)

- Sodium bicarbonate (Sigma–Aldrich, Stock-holm, Sweden)
- Sodium chloride (Sigma–Aldrich, Stockholm, Sweden)
- Talc (Sigma–Aldrich, Stockholm, Sweden)
- α -monohydrate lactose (Pharmatose 90 M, donated by DMV Fonterra Excipients, Goch, Germany)
- Polyethylene glycol 6000 (Sigma Aldrich, Steinheim, Germany)
- Polyvinylpyrrolindone (PVP 17PF, BASF, Limburgerhof, Germany)
- FlowLac 100 (Spray-dried α -monohydrate lactose, donated by Meggle, Wasserburg, Germany)
- MicroceLac (Spray-dried mixture of 75% Lactose monohydrate and 25% Microcrystalline cellulose, donated by Meggle, Wasserburg, Germany)
- StarLac (Spray-dried mixture of 85% Lactose monohydrate and 15% Maize starch, donated by Meggle, Wasserburg, Germany)
- Avicel HFE-102 (Microcrystalline cellulose and Mannitol, donated by FMC BioPolymer, Leeds, England)
- Avicel PH-102 (Microcrystalline cellulose, MCC, donated by FMC BioPolymer, Leeds, England)
- Starch 1500 (Partially pregelatinized Maize starch, Colorcon, Dartford, England)

7 Experimental methods

The specifics of experimental methods will not be repeated in this section, but rather a general description will be given. The reader is referred to the attached papers for specifics.

7.1 Preparation of powders and granular materials

7.1.1 Pellet Production

The production of all pellets was performed via extrusion and spheronisation. Essentially, powder was aerated in a high shear mixer (QMM-II, Donsmark Process Technology, Denmark) and agglomeration liquid was manually poured onto the dry mass at a controlled rate. The resulting wet mass was mixed for a further period of time and then extruded (NICA System AB, model E140, Sweden; holes 1.0 mm in diameter and 1.2 mm long). The extrudate was spheronised (NICA System AB, model S 320-450, Sweden) on a 32 cm diameter friction plate with a radially designed grid. Where necessary the porosity and deformability of the pellets were modulated by incorporation of ethanol and PEG [15, 17, 47, 95].

7.1.2 Powder milling

Where powder milling was necessary, a pin disc mill was employed (Alpine 63C Contraplex Labormuhle, Alpine AG, Augsburg, Germany).

7.1.3 Particle size separation

Desired particle size fractions were obtained via vibrational sieving (Retsch, Type RV, West Germany, and Endecotts Ltd, London, England).

7.1.4 Pellet lubrication

Lubrication involved mixing of pellets with magnesium stearate in a tumbling mixer (Turbula Mixer, Willy A. Bachofen AG Maschinenfabrik, Basel, Switzerland) for a period time and at a desired mixing frequency.

7.2 Basic characterisation of powders and granular materials

7.2.1 Density and porosity

Apparent particle densities were determined using a helium pycnometer (AccuPyc1330, Micromeritics, USA). The apparent density of mixtures was calculated via [96]:

$$\rho_{mix} = \frac{\omega_1 + \omega_2}{\omega_1/\rho_1 + \omega_2/\rho_2} \quad \text{Equation 9}$$

where ρ_{mix} is the apparent binary mixture density and ω_1 , ω_2 , ρ_1 and ρ_2 are respectively the weight fraction and apparent densities of the two components of the mixture.

To determine poured bulk and tapped densities, material was weighed in volumetric cylinders. Bulk density was simply the ratio between the poured mass and the volume it occupied. To determine tapped density, the volume of material was determined after applying a desired number of taps on a tap density tester (Pharma Test PT-TD, Hainburg, Germany). The resulting ratio of mass and volume yielded tapped densities.

Pellet porosity ε was where necessary, estimated through calculation:

$$\varepsilon = 1 - \frac{\rho_{tapped}}{(\varphi_c \rho_{solid})} \quad \text{Equation 10}$$

where ρ_{tapped} is tapped density, ρ_{solid} is apparent particle density and φ_c is the packing fraction for random loose packing [75], where the interaction is composed of both normal forces and transverse frictional forces, with a value of 0.6284, which is within the range generally obtained for spherical particles [29].

7.2.2 Size and shape

Pellets were spread out on a flatbed scanner (Epson Perfection 1640SU Scanner, Seiko Epson Corp., Japan) and covered by a black background. 1600 dpi images of the pellets were captured. The images were analyzed via ImageJ [97], a public domain image analysis program. The projected-area diameter (D_p) was calculated through the equation:

$$D_p = \sqrt{4A_p/\pi} \quad \text{Equation 11}$$

where A_p is the projected area of the pellet. The ImageJ parameter “fit ellipse” was used to determine circularity.

7.3 Mechanical characterization of powders and granular materials

7.3.1 Single pellet compression

Individual pellets were compressed using a texture analyzer (TA HDi texture analyzer, Stable Micro Systems, UK). The slopes of the initial linear region of the force displacement plots were used in the calculation of yield stress through the equation [81, 98, 99]:

$$\sigma_y = \frac{4}{\pi D} \frac{dF}{dx} \quad \text{Equation 12}$$

where D denotes the mean pellet diameter and dF/dx is the slope. Additionally, the first peak preceding a drop on the force displacement plots was chosen as the pellet fracture point.

7.3.2 Bulk compression

Bulk compressions were carried out in the Zwick Z100 materials tester, equipped with a mobile upper punch and a stationary lower punch and die. The die cavity wall was lubricated with a magnesium stearate suspension. Material was poured into the die and subsequently compressed to a desired pressure.

7.3.3 Carbon paper method

Calibration was performed to relate carbon imprint area and force. Circular pieces of carbon and white photo quality paper were cut out ($\text{Ø}11.3 \text{ mm}$) using a stencil tool designed for the purpose. These were placed in a double layer, with the carbon paper on top of the white paper. This arrangement was used for both the calibration and bulk compression procedures. Calibration was carried out on single pellets placed in a rig specifically designed to mimic a physically constrained environment, see Figure 13, with compression being applied via the Stable Microsystems TA HDi texture analyzer. Calibrations at 100 N were performed using the Zwick Z100 materials tester (Zwick/Roell, Zwick GmbH & Co. KG, Germany).

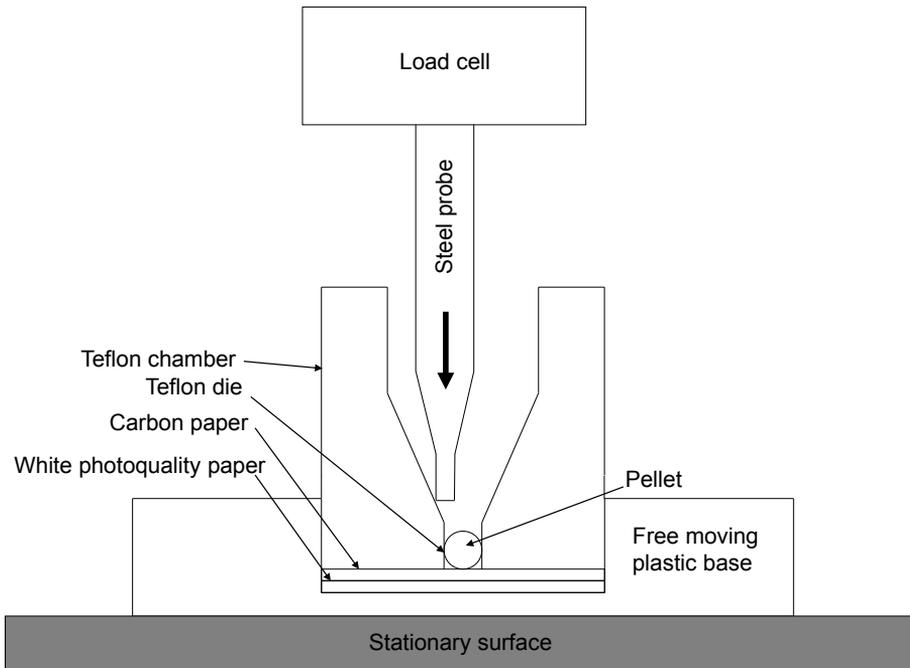


Figure 13. Schematic diagram of confined calibration rig.

7.4 Data analysis

7.4.1 Image analysis

For Papers II and III, image capture, preparation and analysis were required. Images were captured via the Epson flatbed scanner mentioned above. Adobe Photoshop Elements 5 (Adobe Corporation) was used to prepare the images for analysis by the removal of unnecessary artifacts and defects. Image analysis was performed using the ImageJ program [97], which yielded the parameters necessary for calibration and subsequent transformation into force.

7.4.2 Statistical analysis

For Papers II and III the R statistical software program [100] was used to determine the force distributions and the 2D pair and mark correlation functions.

7.4.3 Equation fitting

Equation fitting was performed by the solver algorithm in excel (Microsoft corporation) which yielded values of the effective medium (EM) equation parameters.

7.4.4 Heckel and Kawakita analysis

The Heckel and Kawakita parameters were determined from the plots generated in the Kaleidagraph program (Synergy Software). The linear regions were determined by visual inspection of the plots.

8 Summary and main findings of appended papers

8.1 Force distributions: Papers II and III

In these papers we were interested in studying the distribution of force through beds of spherical agglomerates (pellets). Unlike a solid body, when a constrained powder is compressed, not all the regions in the system experience that stress. Upon reaching the percolation threshold [59], there are distinct columns transmitting the applied force. Carbon paper was employed as a force sensor, and a means from which force distributions could be obtained. The basic premise behind the use of carbon paper was that the area of a transferred imprint would in some way be related to the force that caused it. See Figure 14.

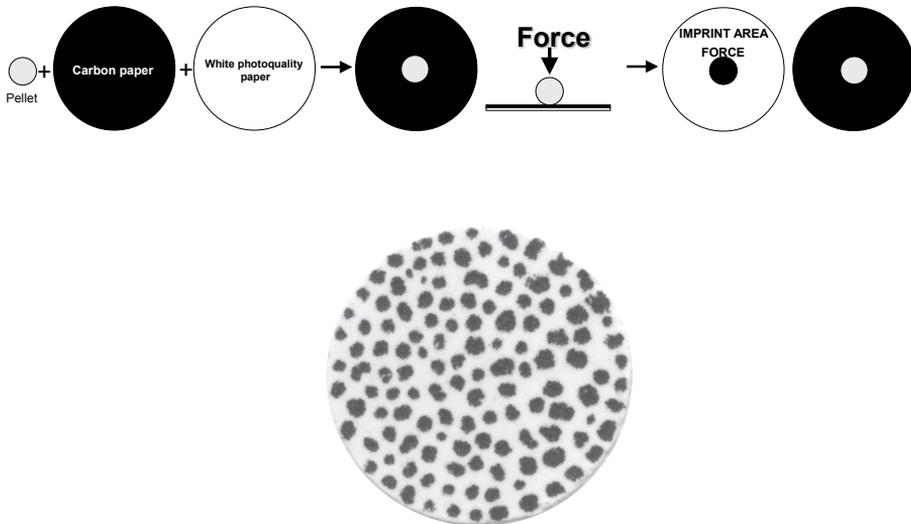


Figure 14. Carbon paper technique.

In Paper II, we employed the carbon paper technique as a means to obtain force and spatial distribution data, upon compression of approximately 1 mm sized pellets of microcrystalline cellulose (MCC). The aim was to study if

the absence of friction and inter-particulate bonding had any effect on force and spatial distributions in the pellet bed. To this end, pellets of MCC were produced via wet granulation followed by extrusion and spheronisation. A batch of these pellets was lubricated with magnesium stearate, so as to eliminate any inter-particulate friction and bonding capacity [17, 32]. Pellet beds were compressed at three pressure steps; 10, 20 and 30 MPa. The areas of the imprints were, through calibration, related to the force experienced by the pellets that made them. The digitized images of these imprints were analyzed with image analysis software to yield the imprint data required to calculate the force and spatial distributions. We found that the absence of friction and inter-particulate bonding did not have a significant effect on the distribution of forces between the pellets (Figure 15), and that the lubricated pellets exhibited a higher packing order than the unlubricated ones at 10 and 20 MPa, a difference that could not be observed at 30 MPa.

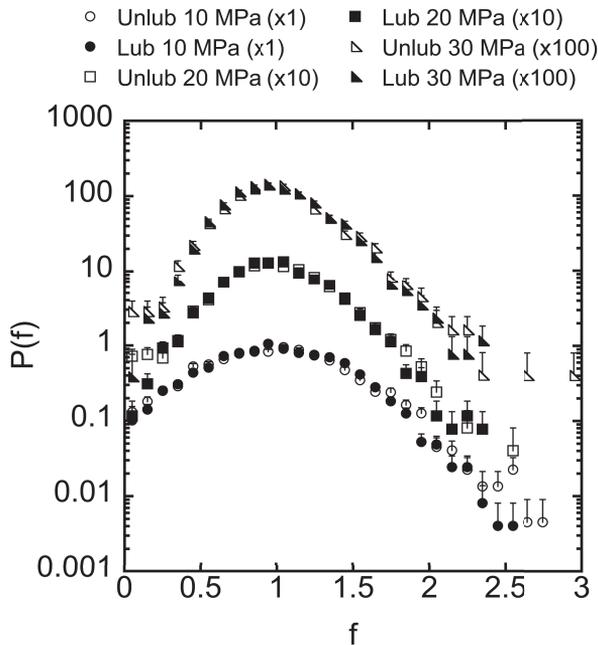


Figure 15. Force distribution for lubricated and unlubricated MCC pellets.

In Paper III, we employed the same carbon paper technique as in Paper II. In this case the aim was to investigate the effect of spherical-agglomerate (pellet) strength on force distributions. To this end, pellets with differing strengths were produced through wet granulation, and subsequent extrusion followed by spheronisation. The strengths of the pellets were modulated by

incorporating polyethyleneglycol into them [47, 95], and by the addition of ethanol to the agglomeration liquid thus yielding higher porosities [15, 17]. The pellets were both plastically deformable and brittle to the extent that they could develop localized cracks, while remaining largely intact. We termed this behavior as fracturing. The force at which the pellets cracked was determined from single pellet compressions, and was termed the fracture force. Previous work on non-fracturing systems had found that the distribution of normalized forces narrowed with increasing particle deformation [74, 75, 78]. In this paper however, some narrowing was observed, but, after the point of fracture, the width of the distributions was found to increase, see Figure 16. This was elegantly demonstrated by a linear slope when the distribution width was plotted against the difference between the mean force and the pellet fracture force, see Figure 17. Further corroborative evidence came in the form of spatial force–force correlations (Figure 18), where a marked change occurred once the fracture force of the pellets was exceeded. It would seem that when deformation occurs, the transmitted force paths are homogeneously distributed, however, since fracture or fragmentation create new random paths for forces to transmit through, a less homogenous force distribution ensues.

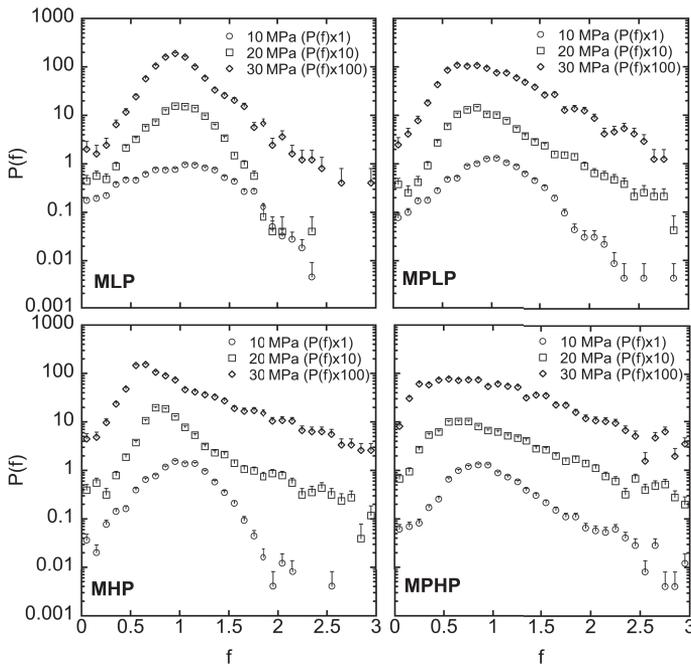


Figure 16. Force distributions of four pellet types.

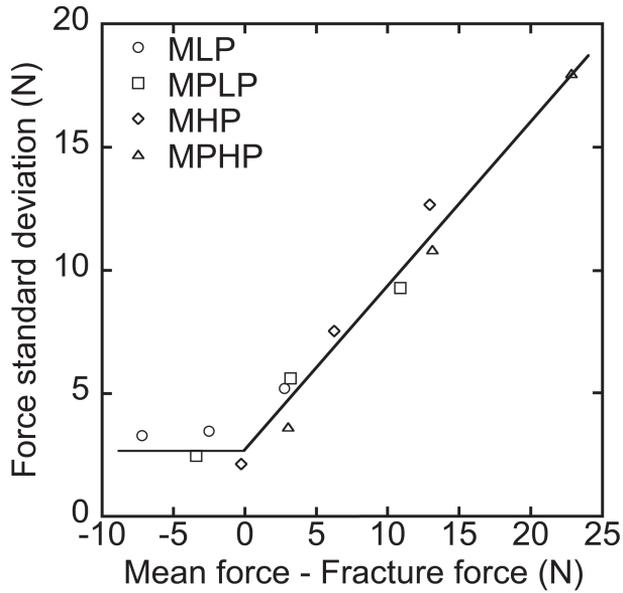


Figure 17. Correlation between force distribution as denoted by force standard deviation and pellet fracture force.

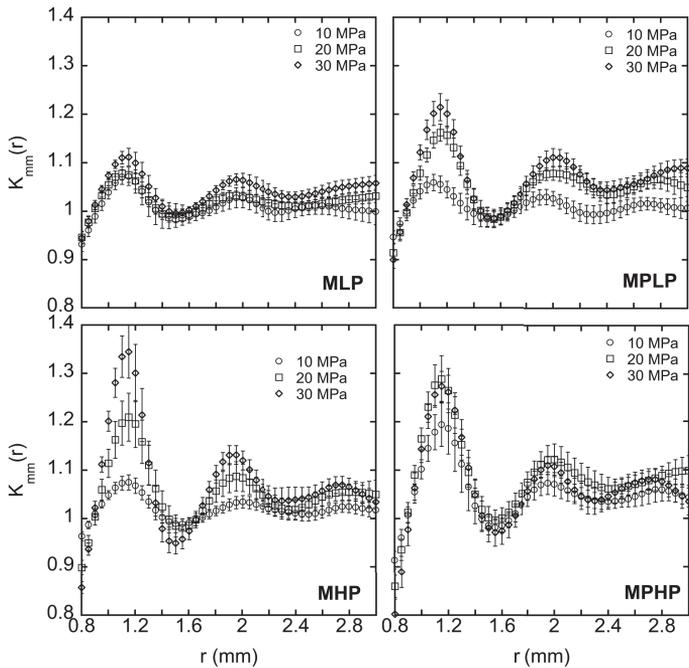


Figure 18. Force-force correlations showing deviations where the fracture force of each pellet type was exceeded.

8.2 The Effective Medium equation:

8.2.1 Paper I

The effective medium (EM) equation was derived in Paper I. The derivation hinged on the assumption that two mechanical processes took place during the compression of powders, see Figure 19. These were plastic deformation (K_A) and elastic deformation (K_B). Plastic deformation was thought of as occurring over a range of particle center to center distances (L_A to L_B). L_B was assumed to coincide with a compact of zero porosity. Distances below L_B would require much higher forces and could only be achieved by elastic deformation.

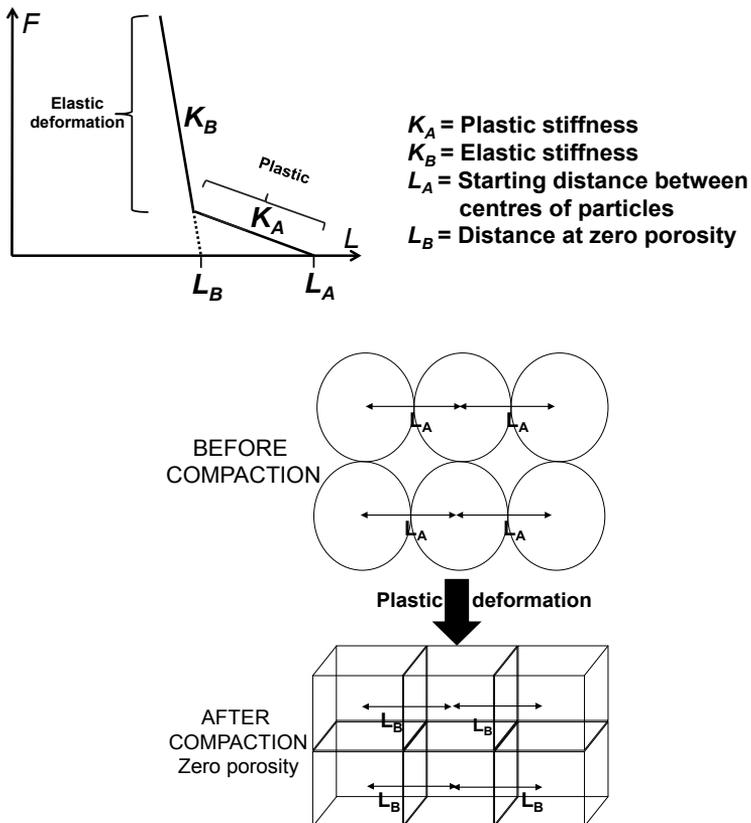


Figure 19. Conceptual basis behind EM equation.

A simple powder system was modeled using a central force network [101, 102] i.e. a network of spheres representing powder particles, and springs representing their interactions with one another. Three possible interactions were assumed to take place; plastic (K_A), elastic (K_B) and no interaction (0). The force network was further simplified, by averaging all interactions (K) to yield a homogenous system (Figure 20), in which the effects of a fourth interaction (an impurity spring) could be easily studied.

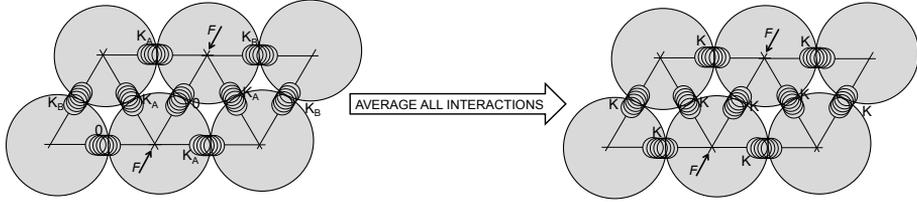


Figure 20. Schematic diagram demonstrating three different interactions and their averaging to yield a homogenous system.

The Watson integral [101] was introduced to enable study of different geometries e.g. face centered and the body centered cubic lattices. The Watson integral was twice the ratio between the spatial dimension and the number of nearest neighbors. It was assumed that the coordination number and hence the probability of an interaction varied linearly with relative density, and that the averaged interaction K was the gradient of the force displacement plot. This meant that it was possible to derive an engineering strain plot from the yield stress and diameter of a powder particle i.e. bulk powder behavior from single particle properties. The final form of the equation is shown below:

$$P = A \left[\alpha \ln(1 - C) - \ln \left(1 - \frac{C}{1 - \rho_{rel,0}} \right) \right] \quad \text{Equation 13}$$

Where P is pressure, C is degree of compression, $\rho_{rel,0}$ is the initial relative density and A and α are parameters.

In addition to its derivation, the EM equation was used to predict experimental compression profiles of data previously obtained from the compression of pellets [94]. This was done by insertion of independently derived parameters, and variation of the Watson integral. The four pellet systems with which the predictive ability of the EM equation was tested varied in porosity and composition. The EM equation was able to competently describe the compression behavior of the pellet system composed of MCC and PEG, where, the pellets were soft enough to deform such as to yield a compact of zero porosity (see Figure 21), which was an integral assumption in the derivation of the EM equation.

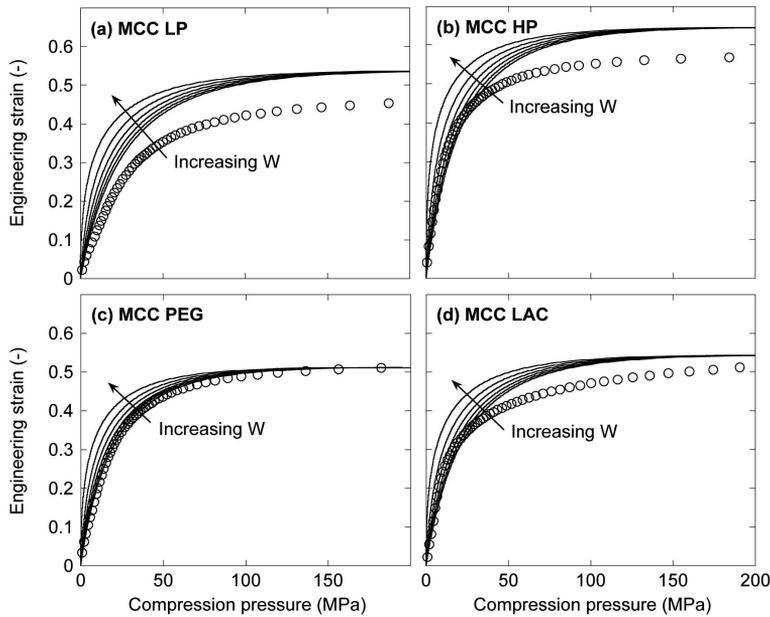


Figure 21. Comparisons between EM equation predictions and compaction data of four pellet types. The open symbols are the experimental data, and the solid lines are different predictions provided by Equation 13 ($W = \text{Watson integral}$).

8.2.2 Paper IV

The aim of this paper was to experimentally validate the EM equation with well defined and characterized powder systems. Since particle size and mechanical properties are two very important governing factors of powder compression, it was thought that selecting powders with differing mechanical properties and sizes would give an important initial indication of the breadth of the EM equation's applicability. To this end, two powder types with widely contrasting mechanical properties were chosen as test subjects, and each one was separated into three size fractions. The powders were; NaCl, which primarily compacts via plastic deformation [33, 34] and lactose, which is known to undergo brittle fracture and fragment during compaction [34]. The three size fractions were; $<30\mu\text{m}$, $125\text{-}212\ \mu\text{m}$ and $212\text{-}300\ \mu\text{m}$. Thus, a total of six powder systems were examined.

The data from five compression runs was used for analysis of each powder system. Since this was the first experimental evaluation of the EM equation

on powder systems, points of comparison were necessary. These came in the form of Heckel and Kawakita plots, and their corresponding parameters. The Heckel yield stress ($1/K$), as well as the Kawakita a , $1/b$ and C_{max} parameters were determined. All data analysis procedures are detailed in the corresponding appended article.

A critical juncture in the development of Paper IV occurred during reflection on the EM equation and its general form. When written in terms of powder bed heights, an inherent invariance present in the equation was revealed. The modified EM equation is,

$$P - P_1 = A \left[\alpha \ln \left(\frac{H}{H_1} \right) - \ln \left(\frac{H - H_{min}}{H_1 - H_{min}} \right) \right] \quad \text{Equation 14}$$

where P_1 is some starting pressure, H_1 is the powder bed height at P_1 , P is some pressure after P_1 , and H is the powder bed height at P , and A , α and H_{min} are parameters.

Since P_1 , H_1 , P and H are readily available from compression experiments, then rearranging Equation 14 to Equation 15

$$e^{-(P-P_1)/A} = \frac{(H-H_{min})}{(H_1-H_{min})(H/H_1)^\alpha} \quad \text{Equation 15}$$

allows for the determination of A , α and H_{min} by optimization.

The result is that, so long as the powder has passed its rearrangement phase, the values of A , α and H_{min} should according to Equation 14 remain constant (see Figure 22). This invariance provides parameters that can be used to describe the powder bed. Additionally, the height at which the powder bed reaches its constrained state can be determined from experimental compression data. This would eliminate the need for any guess work by quantitatively determining the degree of rearrangement in a powder system, if any.

It was found by comparison with the Heckel parameter, that the EM equation's A parameter was a measure of the yield stress of the powder system. It was not the absolute value, but rather gave an indication sufficient to form a relative scale for comparison. The α parameter, which is an indirect measure of coordination number, was hypothesized to be an indicator of the degree of rearrangement at the onset of compression.

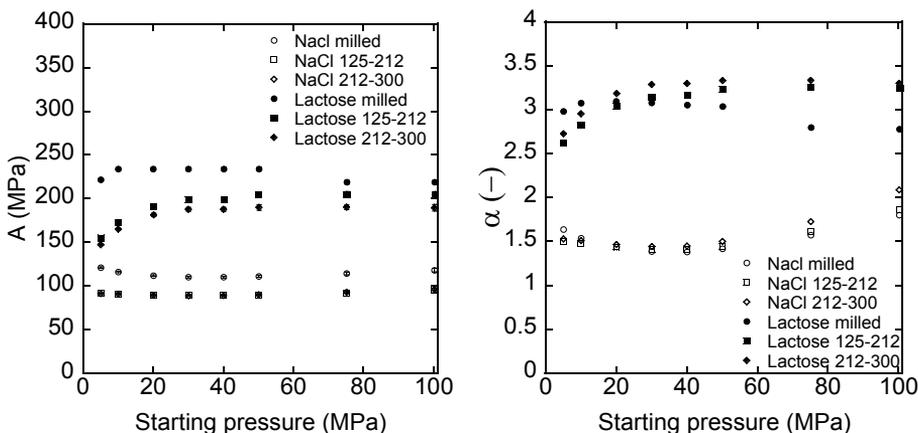


Figure 22. Average EM A and α parameters against varying starting pressures.

8.2.3 Paper V

The data for this paper was obtained from a study previously published in our group [103]. This paper was a natural continuation from Paper IV, where we extracted EM equation parameters from the compression data of 17 widely differing pharmaceutically relevant materials (see section 6). In light of the fact that the data was from a diverse set of materials differing in mechanical properties and dimensions, we demonstrated the robustness of the EM equation through two observations. Firstly, the consistent extraction of the parameters mentioned in section 8.2.2, and secondly, the fact that the parameters generally remained constant over wide pressure ranges (50-75 MPa), see Figures 23 and 24. Furthermore, we argued that the A parameter of the EM equation can be viewed as a measure of the plasticity of the powder system much like the Heckel 1/K parameter. The basis for this argument lay partly in the correlation observed between the A parameter and the Heckel 1/K parameter obtained from the same materials (taken at 50 MPa), see Figure 25. Additionally, we suggested that the A parameter can be used to develop a scale of plasticity since it showed unambiguous invariance in the diverse set of materials comprising the data set.

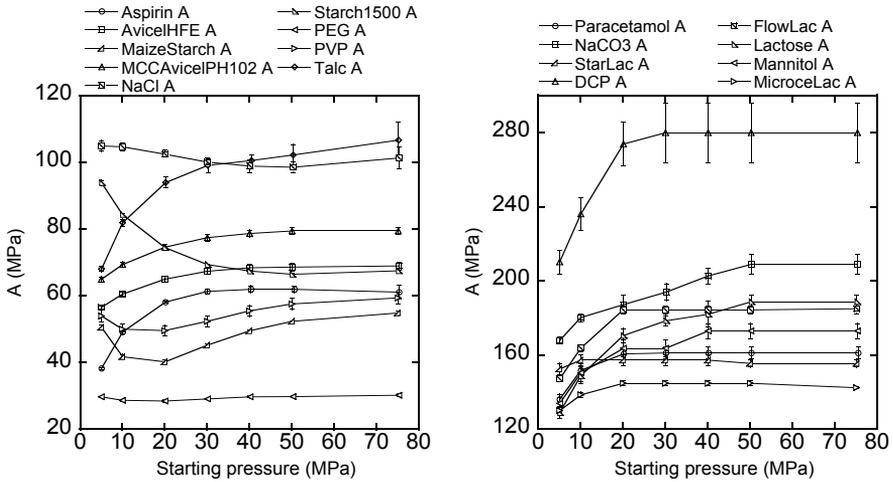


Figure 23. Average EM A parameters against varying starting pressures (the lines are drawn as a visual guide).

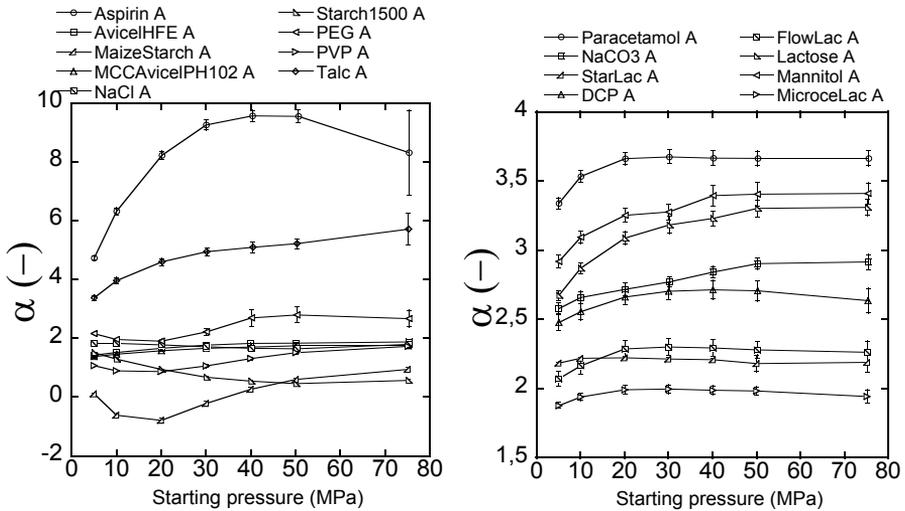


Figure 24. Average EM α parameters against varying starting pressures (the lines are drawn as a visual guide).

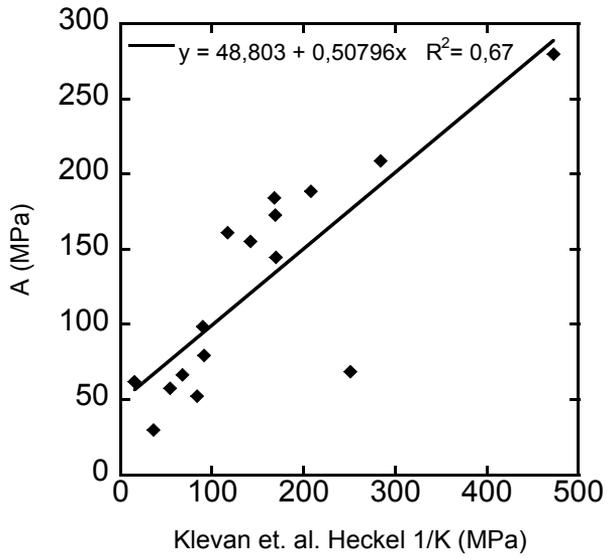


Figure 25. EM equation A parameter values plotted against Klevan et al. Heckel $1/K$ values for the same materials.

9 Discussion and future outlook

Fundamentally a powder bed is a medium within a medium. It can either be viewed as air dispersed in solid or solid dispersed in air. In the initial poured state, assuming that the particles form a “house of cards” type structure, the system can be viewed as a solid in air dispersion [46]. At higher pressures, when the porosity is decrease sufficiently, the system transforms into an air in solid dispersion “Swiss cheese” [46]. During compression, a duality occurs where there is a process of simultaneous structural collapse and structural consolidation. The consolidation comes in the form of increased congruity between powder particles, and the collapse comes in the form of reduced congruity of the pore structure. In the initial phase of compression, when the house of cards collapses, the congruous open bond percolation of pores is destroyed, and it can be said that this phase is marked by filling of pores/expulsion of air. The constrained state can be viewed as a transition point. Past this critical point, any further impetus for volume reduction comes from the mechanical response of the powder particles. The foundation of this thesis lay in trying to understand the internal dynamics/processes of powders as they are compressed.

In contrast to the empirical equations of Heckel and Kawakita [86-88], in Paper I we derived a novel compression equation, which could be used to predict bulk powder compression behavior from single particle properties i.e. yield stress and particle size, as well as relative density. The assumptions underlying the derivation of the EM equation were adequate in describing the compression behavior of mm sized agglomerates, especially those that were most deformable i.e. MCC PEG [47, 95]. What this highlights is the fact that although imperfect, the EM equation is at the very least firmly pointing in the right direction. The consequence of this is that further refinement of the equation by means of added assumptions, variables and constants will lead to better resolution in terms of modeling accuracy. The EM equation has shown its potential as a tool in the modeling of powder compression behavior, which is of value in tablet production, as it can potentially be used in industry as a means by which to gain insights into the likely compression behavior of a material. This can potentially save a great deal of time in formulation development, as many excipients can be quickly vetted to find the one that is best suited for the need.

In Papers IV and V the EM equation was fitted to the data to determine its parameters. We found that experimentally determining the variables of the EM equation led to two useful parameters. The first of these was the invariance of the A parameter, which once achieved was shown to be a measure of the deformability of the powder bed. The A parameter can be used to rank materials according to deformability. The second was as a consequence of the invariance of A, α and H_{\min} , whereby the occurrence of the constrained state could be determined. This can be used as a means by which to measure the rearrangement capacity of powders of differing size and shape. Shape factors such as the Heywood shape factor [104] can be incorporated into the EM equation to enhance its precision in predicting rearrangement capacity based on particle shape.

In Paper II we found that the creation of bonds between particles was inconsequential to the distribution of force through the system. Paper III showed us that the opposite was true when bonds were broken, as happens when particles fracture. The breaking of bonds causes the force distributions throughout the system to widen. This finding can be used as an added assumption or variable in the refinement of the effective medium equation. Since a number of excipients are known to fragment, a variable that can quantify fragmentation tendency can be incorporated into the EM equation when dealing with such materials, thereby improving its resolution. Additionally, it may be possible to incorporate bond breakage into the central force network, thus allowing for a greater general accuracy in the modelling ability of the EM equation, as most materials even if very deformable will experience some bond breakage e.g. NaCl [105].

10 Conclusions

The main conclusions of this work are as follows:

Paper II

- Bonding and friction between particles does not have a significant impact on the force distributions in beds of mm sized pellets.

Paper III

- The occurrence of fracture during compression of mm sized particles causes a widening of the force distributions in beds of mm sized pellets.

Paper I

- The EM equation is able to adequately model the compression behavior of powder systems.
- The resolution of the model is enhanced if the material being compressed reaches an end porosity of zero.

Papers IV and V

- The A parameter of the EM equation is a measure of the plasticity of a powder system and can be used to rank materials accordingly.
- The EM equation can be used to determine the point at which rearrangement ceases.
- The absence of an invariant region in the compression analysis is indicative of brittle fracture and rearrangement.
- The robustness of the equation has been demonstrated through the fruitful analysis of widely differing powder systems in terms of material mechanical properties, particle size and shape.

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Foad

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