Chapter 1

Introduction

1.1 General introduction

The tablet is still the most frequently administered dosage form for medical applications (1). A tablet has numerous advantages over other dosage forms, among which the convenient way of administration to patients and the stability of a drug substance in a dry dosage form (1). Furthermore, tablets are easy to handle, to store, to distribute and to manufacture in large quantities. A tablet is not only a carrier of the active component, the drug substance, but must also comply with a whole scale of demands. One of these demands is that the strength of a tablet should be sufficiently high to withstand the different handlings in the logistic chain from producer to patient.

Basically, tablets are produced by the compaction of powders. The compaction of powders preceded only by mixing of the individual materials is called “direct compaction”. To make tablet production by direct compaction possible, it is necessary that the powders to be compacted fulfil a number of criteria (1). Therefore, various excipients specifically designed for direct compaction have been introduced during the last forty years (2). For an excipient to be useful as a “filler-binder”, it should meet the requirements as given in Table 1.1.

Table 1.1. Properties of an ideal filler-binder (direct compression excipient).

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<table>
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<tbody>
<tr>
<td>1.</td>
<td>The material should enhance the tablet strength.</td>
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<td>2.</td>
<td>It should have a good compaction pressure-tablet strength profile.</td>
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<td>3.</td>
<td>It should have a low lubricant sensitivity.</td>
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<td>4.</td>
<td>It should have a good flowability.</td>
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<td>5.</td>
<td>It should be compatible with all types of drug substances.</td>
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<td>6.</td>
<td>It should not interfere with the bioavailability of drug substances.</td>
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<td>7.</td>
<td>Mixtures with various drug substances should have a low tendency for segregation.</td>
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<td>8.</td>
<td>It should not show any physical or chemical change on ageing and should be stable to air, moisture and heat.</td>
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<td>9.</td>
<td>It should have a high dilution capacity, which is defined as the amount of active ingredients that the filler-binder can successfully carry in the direct compaction technique. The dilution capacity is generally expressed in terms of percentage of non-compressible material or as optimum drug to filler-binder ratio.</td>
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<tr>
<td>10.</td>
<td>It should be relatively cost effective.</td>
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However, not a single excipient fulfils all these requirements. It is general practise to use a combination of two (sometimes more) filler-binders in a tablet formulation in order to obtain a compact with acceptable properties. Among the various requirements, one of the most important functions of a filler-binder is the enhancement of the tablet strength. For this reason, most of the research on direct compaction focuses on the compaction behaviour and binding properties of existing and new filler-binders. Unfortunately, studies often investigate and report only the compaction behaviour of a filler-binder as a single component and hardly in combination with other filler-binders or other main components in the tablet formulation.

Tablets produced by the pharmaceutical industry contain several ingredients. In addition to one or multiple filler-binders and drug substances, generally a disintegrant, a lubricant and other substances such as glidants are present in the tablet formulation. It should be realised that every component in a formulation may affect the compaction properties of the powder blend and may influence the tablet strength or other mechanical properties. Even low-concentrated additives in a tablet formulation can have enormous effects on the tablet strength. For example, the interactions between lubricants and filler-binders in relation to tablet strength are well described (e.g. 3, 4).

Although a tablet commonly contains combinations of filler-binders and drug substances, only a limited number of studies have investigated the interactions between two main components during the compaction of a binary powder blend (5). So far, the complexity of all different binary mixtures made it impossible to establish a consistent theory to describe the compaction behaviour of a mixture of two materials and the resulting tablet strength.

As physically blended binary mixtures are mixed powders containing single particles of two materials, this introduction will start by discussing the densification mechanism (section 1.2) and relaxation behaviour (section 1.3) of powders consisting of a single material. At the end of these sections, the few studies that have been published on binary mixtures are summarised. Section 1.4 describes the internal structure of a tablet, which is a result of the phenomena mentioned in sections 1.2 and 1.3. This final tablet structure is important for the different tablet properties. Section 1.5 reports the relations between the tablet structure and the mechanical properties of porous compacts and describes the theories developed on tablet strength. The structural changes in tablets compressed from a single material and from binary mixtures are described by the percolation theory in section 1.6. This section also gives a summary of reported tablet strength changes of tablets compressed from binary mixtures. Finally, the aim of this thesis is given in section 1.7.
1.2  Densification of a powder bed

1.2.1  Densification mechanisms

The compaction of a tablet starts with applying pressure to a powder bed. The bulk volume of the powder bed decreases as an effect of a series of processes that happen sequentially or in parallel (6). The first stage of the consolidation process is characterised by particle rearrangement at low pressures. At a certain relative density, the particles are more or less in a fixed arrangement. Due to the resistance of a material against deformation (strain), the stress inside the particles increases. If the applied stress is released before the deformation reaches a specific critical value, the deformation is reversible, and the particles inside the powder bed regain their original shapes. Until this critical value, the stress is linearly proportional to the deformation and is characterised by the elastic or Young’s modulus (\(E\), Fig. 1.1a). The following stage can be divided into two main deformation mechanisms:

- Particles fragment into smaller units at a certain stress value (\(\sigma_f\), Fig. 1.1b). This stress is the fracture strength. These materials are referred to as brittle materials.
- After a critical stress (\(\sigma_y\), Fig. 1.1c), the particles yield and start to deform plastically. This critical stress is the yield strength of a material. Whereas elastic deformation is a reversible process, plastic deformation results in a permanent change of the particle shape. These materials are referred to as ductile or plastic materials. Material fracture will eventually occur at higher deformations.

![Stress-strain graph](image)

Figure 1.1. Macroscopic stress-strain relations: a. reversible elastic deformation; b. brittle behaviour; c. ductile behaviour (c1. normal plastic flow; c2. strain-hardening).
Whether particles behave ductile or brittle under compression depends on the material and its physical condition. Roberts and Rowe demonstrated (7,8) that materials possess a critical particle diameter at which the densification mechanism turns from brittle to ductile when the particle size decreases (Fig. 1.2). The stress necessary to cause particle fracture increases when the particle size decreases, whereas the stress causing plastic deformation of a material is independent of the particle size. When the fracture stress reaches the level of the yield strength, particles with diameters lower than the critical diameter will yield instead of fracturing. Many materials used as a filler-binder in the pharmaceutical industry can be classified into groups of materials that only have a brittle or ductile deformation behaviour due to their extremely low (e.g. inorganic compounds) or high (e.g. cellulosics and starches) critical particle diameters (9). The critical particle diameters of other materials are close to the particle sizes of powders used in practice, such as α-lactose monohydrate.

Fig. 1.2. Schematic representation depicting the effect of particle size on yield strength or fracture strength.

1.2.2 Characterisation of powder densification

The determination of the densification behaviour of a powder is usually based on the measurement of the relative density of the powder bed as a function of the pressure necessary to obtain that relative density. Table 1.2 shows an overview of relations used to describe the effect of the pressure on the degree of densification.
Table 1.2. Powder densification-compaction pressure ($P$) relations used to characterise the densification mechanism of a powder bed

<table>
<thead>
<tr>
<th>Name</th>
<th>Equation</th>
<th>Parameters</th>
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<tr>
<td>Heckel equation</td>
<td>$\ln\frac{1}{1-\rho_r} = KP + A$</td>
<td>$\rho_r$ is the relative density of the powder bed.</td>
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<tr>
<td></td>
<td></td>
<td>$K$ and $A$ are constants.</td>
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<tr>
<td>Kawakita equation</td>
<td>$\frac{V_i - V_p}{V_p} = \frac{abP}{1 + bP}$</td>
<td>$V_i$ and $V_p$ are the initial volume and volume under pressure of the powder, respectively.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$a$ and $b$ are constants.</td>
</tr>
<tr>
<td>Cooper and Eaton</td>
<td>$\frac{V_i - V_p}{V_i - V_t} = C_1 \exp\left(-\frac{K_1}{P}\right) + C_2 \exp\left(-\frac{K_2}{P}\right)$</td>
<td>$V_i$ is the true powder volume. $C_1$, $C_2$, $K_1$ and $K_2$ are constants.</td>
</tr>
<tr>
<td>Walker and Bal’shin</td>
<td>$V_r = C_3 - K_3 \log P$</td>
<td>$V_r$ is the relative density of the powder. $C_3$ and $K_3$ are constants.</td>
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</table>

The equation most commonly employed in pharmaceutical compaction research is the Heckel-equation (10, 11). This equation assumes a linear section of the relationship between the logarithm of the relative density under pressure and the applied pressures (Table 1.2). Slope $K$ is related to the yield strength ($\sigma_y$, Fig 1.1c) of a material by:

$$\sigma_y = \frac{1}{3K}$$

(1)

The reciprocal of the slope $K$ has been found to reflect the yield pressure $P_y$ of a material (12). This means that the yield pressure $P_y$ of a material is equal to $3 \cdot \sigma_y$. The value $A$ of the intercept with the y-axis has been related to the relative density of the fixed packing after particle rearrangement (10,11). As Heckel attributed the linear section to plastic deformation, equation 1 is in principle only appropriate to examine the densification behaviour of plastic materials. Nevertheless, Roberts et al. (13) modified the yield pressure $P_y$ to the deformation stress $\sigma_d$, which is a plastic deformation stress, a fracture deformation stress or a combination of both, in order to calculate the fracture stress of particles with diameters larger than the critical diameter. Furthermore, particle size (e.g. 14, 15), compaction speed (e.g. 15, 16) and moisture content (e.g. 17, 18) influence the slope of the linear section of equation 1 and consequently the value of the yield pressure.
1.2.3 Densification behaviour of binary mixtures

The densification behaviour of a binary mixture is usually examined by the change in yield pressure as a function of the mixture composition. Binary mixtures can be divided into three categories with respect to the main densification behaviours of the single materials: ductile-ductile, brittle-brittle and ductile-brittle. The different changes in yield pressure caused by alterations in the mixture composition will be evaluated as schematically depicted in Fig. 1.3. The relationships between the yield pressure and the mixture composition were divided into groups based on three different changes: a linear interpolation of the individual yield pressures and positive or negative deviations of this linear relationship.

![Fig. 1.3. Schematically depicted positive (+) and negative (-) trends in yield pressure of binary mixtures compared to linear interpolation (0).](image)

For mixtures consisting of two plastically deforming materials, the most frequently reported relationship between the yield pressure and the mixture composition is a linear one (19, 20). The explanation given in the literature for this observation is that the particles of the materials will not obstruct or enhance the yielding of the mixture. The yield pressure of a powder mixture is the sum of the relative contributions of both yield pressures.

The yield pressures of binary mixtures containing two brittle components show no direct dependency on the mixture composition (19). A positive deviation from linear interpolation can be explained by the fact that a network of the more rigid particles in the powder mixture tends to support the applied load on the powder bed (19, 21). The opinion given by Ilkka and Paronen (19) is that the more fragile particles will be protected from fracture by this more rigid network. These explanations are
thought to be questionable. The fragile particles will weaken the network of the more rigid particles. Most of the fragile particles will already fracture at low stress values at the initial phase of the compression process.

The most frequently investigated binary mixtures are the blends of ductile particles and particles that behave brittle under compression. For these blends, two main results for the change in yield pressure have been reported: a linear relationship (20, 22), and slight negative deviations from this linear relationship (19, 23, 24). To explain the lower yield pressures than expected from linear interpolation, Ilkka and Paronen (19) suggested that the plastically flowing material at higher concentrations occupies the pore spaces around the brittle particles preventing the stress to reach the fracture stress. Additionally, Sheikh-Salem and Fell (23) stated that the early fragmentation of high amounts of the brittle component might slow down the yielding of the plastically deforming material.

1.3 Tablet relaxation

1.3.1 Characterisation of tablet relaxation

During and after the removal of the applied load, a compressed powder bed generally shows an elastic recovery of its volume as an effect of stress relaxation. In case of a permanent deformation, the volume expansion will be small, whereas large tablet relaxations are caused by an important elastic component (6). The driving force for tablet relaxation has been suggested to be the elastic energy stored in the particles during densification (25, 26). On the other hand, the bonding between particles is regarded as the counteracting force against tablet relaxation.

Tablet relaxation is commonly expressed by a change in tablet height, volume or porosity (25, 27). During densification, some compacts may even show an increase in density above their own material density at high compaction pressures. The total tablet relaxation can be a combination of a fully reversible decrease of the true density to the material density and an increase in tablet porosity. The tablet expansion expressed as porosity expansion was found to be independent of the applied load (25). Similarly as has been described for the densification of a powder bed (section 1.2.1), the relaxation propensity of a tablet is influenced by the compaction speed (15, 28), moisture content (29, 18) and particle size (14, 15).

Malamataris et al. (30) defined the plasto-elasticity of materials as the ratio between the stress relaxation (change in tablet height under maximum load for a
certain period of time; \( SR \) and the elastic recovery (change in tablet height after ejection from the die; \( ER \)). This \( SR/ER \) ratio describes the ability of a material to deform plastically under load and recover elastically after the application of the load.

### 1.3.2 Relaxation behaviour of binary mixtures

Mixtures containing a brittle and a ductile material are interesting tools to examine the effect of relaxation behaviours of the individual components on the total tablet relaxation. Most authors (31, 32, 33) reported no direct relationship between elastic recovery of tablets consisting of blends and their compositions. Tablets compressed from mixtures show capping or lamination when the tablets contain less than about 15-25\% of the ductile material and/or when the ratio between the stress relaxation and elastic recovery (\( SR/ER \)) is higher than 9 (30, 34). In contrast, Sheikh-Salem et al. (31) have found a lower critical value of 1.5 for the \( SR/ER \) ratio of tablets that showed a significant capping behaviour. A possible explanation of the discrepancy between these two values (1.5 and 9) given by the authors (31) is the correction of the punch deformations, which gives a better estimation of the powder bed height under pressure. However, in all three studies (30, 31, 34) the tensile strength of tablets compressed from paracetamol-microcrystalline cellulose blends could be related to the \( SR/ER \)-ratio.

### 1.4 Tablet structure

The final tablet structure is the combined result of the consolidation of the powder bed and relaxation of the tablet. As both processes are influenced by the different factors mentioned in section 1.2.1 and 1.3.1, the final tablet structure also depends on these factors. In all situations, the internal tablet structure can be seen as a combination of particles and voids. But, the axial compaction of powders leads to anisotropy and heterogeneous tablet structures (35).

The predominant bonding mechanisms between particles in compacts compressed from pharmaceutical materials are intermolecular forces, i.e. Van der Waals forces, electrostatic forces and hydrogen bonding (36), and solid bridge formation in case of salts such as sodium chloride, potassium chloride and sodium bicarbonate (37). Different approaches and techniques have been developed to describe and measure quantitatively the surface energy and bonding capacity of materials, e.g. the solubility parameter, which equals the root of the cohesive energy density (38), atomic force
measurements (39), inverse gas chromatography (40) or tablet strength measurements in liquids with different dielectric constants (41, 42). With the help of the solubility parameter, theoretical estimations of an adhesive interaction parameter can be made between different materials in powder blends (43, 44).

The particles inside the tablet structure directly influence the size of voids. Mercury intrusion porosimetry, a commonly used technique to measure the pore size distribution, is based on the pressures necessary to enforce mercury into pore openings. According to Bockstiegel’s observation for compacts of iron particles (45, 46), tablets compacted from ductile materials show a decrease of the larger pores at increasing compaction pressures, while the smaller pores do not change in size and number (47, 48, 49). The fragmentation of particles of a brittle material results in an increase of smaller particles and consequently a different change in the pore size distribution as an effect of compression. The disappearance of larger pores is accompanied by an increase in the amount of small pores (48, 49, 50). In tablets compressed from ductile materials, the pore size will be dependent on the initial particle size. Brittle fracture will to a large extent eliminate the effects of the initial particle size.

1.5 Mechanical properties of compacts

1.5.1 Porosity-mechanical properties relationships

Mechanical properties of compacts such as tensile strength, elastic modulus and indentation hardness are known to be largely dependent on the compact structure. Mechanical properties commonly decrease with an increase of the tablet’s porosity. The change in mechanical property as a function of the porosity is normally fitted by an exponential relationship (51, 52). The extrapolated value at zero porosity of this function is normally regarded as an indication of the material property. However, this interpretation has been questioned in several studies; different authors showed that a smaller initial particle size leads to an increase of the mechanical property (53, 54). However, it is interesting to note that direct relationships have been demonstrated between the calculated cohesive energy densities of several materials and their elastic moduli (55), tensile strengths (56) and the critical stress intensity factors (56) (see sec. 1.5.3).

The tablet relaxation after compaction results in an increase of the tablet porosity and consequently into a decrease of the tensile strength. Remarkably, some crystalline
materials, such as sodium chloride and potassium chloride, have been found to give an increase in tablet strength after compaction (57, 58). The authors postulated that the stress relaxation caused by recrystallisation creates extra bonding forces between particles.

1.5.2 Bond summation mechanism

Two main theories have been developed to describe the important factors controlling the strength of a porous compact. One of these theories is the bond summation mechanism. The tablet strength is the sum of interparticle bonding forces between surfaces with spherical curvatures in the diametrical failure plane of the compact (59, 60). The surface area taking part in the interparticle attraction is small and difficult to measure. Therefore, secondary definitions of bonding surface areas of powders and tablets are used to explain changes in tablet strength (37, 61). The specific surface area of tablets compressed from crystalline lactoses has been found to be directly related to the tablet strength (49). A similar relationship has been reported for tablets compressed from binary mixtures of different types of crystalline lactose (62). However, this relationship could not be established for other materials (37, 61). Recently, views are more focused on fracture mechanism theory.

1.5.3 Fracture mechanism

The fracture mechanism theory is based on the assumption that pores in the tablet structure act as stress concentrators. Fracture of a porous material occurs when the stress of the pores at the bonding sites of the particles is higher than the cohesive energy of the material and high enough to initiate fracture. To continue tablet fracture, the elastic energy released must be higher than the energy necessary to form new pore openings. Inglis (63) was the first author to postulate that pores or cracks perpendicular to the applied load concentrate stress at their tips and consequently decrease the fracture strength of a material (Fig. 1.4). The ratio between the material strength with or without a crack for elastic-brittle fracture is given by:

$$\frac{\sigma_{\text{material}}}{\sigma_{\text{measured}}} = 1 + 2\left(\frac{l}{\rho}\right)$$

(2)

where $\sigma_{\text{material}}$ is the cohesive strength of the material, $\sigma_{\text{measured}}$ the measured compact strength, $l$ the length of the pore and $\rho$ the diameter of the curvature of the pore tip.
Griffith (64) further developed equation 2 into a universal theory based on thermodynamical considerations. He argued that two energies have to be taken into account when a crack propagates: a release of elastic energy that is stored in the material and an increase of surface energy. The combination of these two energies resulted into:

$$\sigma_{\text{measured}} = \sqrt{\frac{2E\gamma_s}{\pi a}}$$

with $E$ is the elastic modulus of the body, $\gamma_s$ the surface energy and $a$ is the half of pore length $l$. The stress around a crack in a material is reflected by the critical stress intensity factor $K_{ic} = (2E\gamma_s)^{1/2}$ and is a measure of the stress necessary to start and develop a failure surface (65).

The theory of elastic-brittle fracture can also be applied to tablet fracture. Stanley (66) states that the fracture of porous compacts behaves in a brittle fashion, i.e. no plastic deformation occurs before fracture starts. As defined by Griffith’s equation, larger cracks or pores give a higher decrease of the tablet strength. In literature, there are indications that the tablet strength is related to the median pore diameter, which is primarily affected by the larger pores (50, 67, 68).
1.6 Compacts consisting of binary mixtures

1.6.1 Percolation theory

During the last two decades, percolation theory has been used to explain macroscopic changes in compact structures. Percolation theory, developed since the 1970’s and introduced by Stauffer (69) and Leuenberger (70, 71) in pharmaceutical research, regards a compact structure as a complex of sites. The sites can be occupied randomly by particles or pores (site-percolation). A group of sites consisting of particles is considered to belong to the same cluster when bonds are formed between the neighbouring particles (bond-percolation). The percolation theory describes phenomena whereby tablet properties divert, vanish or start to appear at a certain tablet composition. Particles of a material transform from fractional clusters to a continuous network (matrix), or vice versa, at this critical tablet composition, which is defined as the percolation threshold. Percolation theory can be used to describe structure changes in compacts compressed from single materials and from blends.

Even a compact consisting of a single material has different percolation thresholds. The compact not only contains particles, but also pores between these particles and can therefore be regarded as a composite structure. At very low relative densities, particles of a material only form a loose powder. A compact with finite mechanical properties is first established when the relative density of the powder compact becomes larger than the relative tapped density ($\rho_1$). This relative tapped density is regarded as the percolation threshold of the solid matrix formed by particles. Above a certain relative density, the pores between the particles will no longer form a continuous network ($\rho_2$) which is the percolation threshold of air (72).

According to the percolation theory, a property $Y$ of a tablet changes in the vicinity of the percolation threshold of the material following a power law:

$$Y = Y_{\text{max}} (\rho_r - \rho_c)^T$$

(4)

where $Y_{\text{max}}$ is the maximum value, $\rho_r$ the relative density of the compact, $\rho_c$ the critical relative density (the percolation threshold) and $T$ the critical exponent. Practical cases already have shown that equation 4 is also valid for a broader range of relative densities higher than the percolation threshold (73). The critical exponent $T$ reflects the rate of change in property $Y$ towards the percolation threshold. The value of the critical exponent $T$ depends on the different types of particle packaging (70, 71). In these studies, the relative tap density functions as the percolation threshold $\rho_c$ of the solid particles in tablets consisting of a single material. The relative density, which
equals the volume fraction, was used as an indirect measure to explore the relations between the relative amount of interparticle bonds and the mechanical properties. In further research, the normalised solid fraction $N$ was defined as a ratio between the number of bonds formed and the maximum number of bonds possible (72, 74), resulting in:

$$N = \frac{\rho_r - \rho_c}{1 - \rho_c} \quad (5)$$

The normalised solid fraction $N$ is a functional parameter describing the three-dimensional bonding between particles in porous compacts. Assuming $T$ to have a value of 1, the combination of equations 4 and 5 gives a general relationship for the change in property $Y$:

$$Y = \frac{Y_{\max}}{1 - \rho_c} (\rho_r - \rho_c) \quad (6)$$

This equation is usually not obeyed: the normalised solid fraction reflects the dependence of property $Y$ on three-dimensional bonding, and the change of property $Y$ should be described by:

$$Y = Y_{\max} \left( \frac{\rho_r - \rho_c}{1 - \rho_c} \right)^T \quad (7)$$

For describing the particle structure in compacts compressed from binary mixtures, site percolation is an important concept. At different concentrations of materials A and B, different percolation thresholds can be expected:

- At concentrations of A lower than the percolation threshold of material A, clusters of particles A are dispersed in a matrix of B.
- At concentrations of A between the percolation thresholds of both materials, both materials form an individual matrix.
- At concentrations of material A higher than the percolation threshold of material B, particles of material A only form an infinite matrix combined with clusters of particles B.
Actually, tablets compressed from binary mixtures contain a third component: air. The percolation threshold of air in tablets compressed from single materials and binary mixtures is usually found at a volume fraction of about 0.10 (72, 75).

The percolation thresholds of materials in tablets compressed from binary mixtures depend on the differences in particle packaging, particle size, particle size distribution, shape of the particles and yield pressure between both materials (70, 76, 77).

1.6.2 Tablet strength of binary mixtures

Studies that investigated the tablet strength of compacts compressed from mixtures of two materials have reported a series of contradictory results. As in section 1.2.3, the mixtures were distinguished by the combination of the individual densification behaviour of the materials in the blends. The results of these studies were examined correspondingly as the change in yield pressure of powder blends (Fig. 3).

For mixtures of which all particles deform plastically under densification, very different changes of the tablet strengths versus the mixture composition are observed. Some show a linear relationships (78, 79, 80) and others positive (81, 82) or negative (83, 84) deviations from this relation. Mattson and Nyström (82, 85) researched the positive effect of a “soft binder” on the tablet strength of a ductile material. They found that the ability of a soft binder to fill voids between the compound particles plays a decisive role in the increase of the tablet strength.

Most binary mixtures containing materials that have brittle densification behaviours show a similar relationship between the tablet strength and the relative proportions of the two components. The tablet strengths of these mixtures are mostly found to be linearly related to their compositions (62, 78, 86). The strength of a tablet consisting of a blend can be calculated from the tablet strengths of the pure materials.

In contrast to tablets compressed from brittle-brittle mixtures, compacts consisting of a brittle and a ductile material rarely show a linear trend of the tablet strength as a result of composition changes. The strength of compacts produced from these mixtures is found to be higher (24, 77, 84, 87) or lower (23, 86, 83, 79) than the linear extrapolation of the individual material strengths. However, a reason for these, sometimes large, deviations in observed tablet strengths has not been presented. Different authors have postulated that a higher tablet strength can be caused by a higher bonding strength between both materials (42, 79), an increase of the number of interparticle bonding sites in the compact (82, 85), a higher densification of the mixture (82, 83, 85) or a combination of these phenomena.
1.7 Aim of this thesis

As described in section 1.6, many studies have been conducted to elucidate the change in tablet strength of compacts consisting of mixtures. However, it is impossible to draw straightforward conclusions because of the different experimental set-ups and results. Compaction pressure, particle size, compaction speed, moisture content and other factors that can influence the compact strength differ between these studies. As explained in sections 1.5 and 1.6, the final tablet strength, more than these factors, is directly related to the tablet structure. The change in tablet strength of mixtures should be based on the volume fractions of both materials, rather than the experimentally more convenient mass fractions. Proceeding on this line of thought, an important step to describe the change in strength of tablets compressed from blends as an effect of alterations in mixture composition is to choose a constant porosity instead of a constant compaction pressure. This is a different approach than usually found in other studies that have focused on this subject.

To investigate the mechanisms that influence the densification behaviour, relaxation behaviour and final tablet strength of mixtures, the chapters in this thesis are based on studies in which only two model materials, sodium chloride and pregelatinised starch, will be used. The materials are selected on the following criteria: both materials are known to behave ductile during compaction, both materials differ in densification and relaxation behaviour, the chemical-physical properties of the single materials are well described and the materials are available as pure materials.

This thesis investigates the changes in tablet structure of blends composed of the two model components. It aims to establish relations between the compaction behaviour of blends and the tablet strength. At the end, a model is presented to describe a relative particle interaction between both materials and to predict properties of tablets compressed from mixtures from the individual material properties.
1.8 References


53 Sun, C., Grant, D.J.W., Effects of initial particle size on the tableting properties of L-lysine monohydrochloride dihydrate powder. *Int. J. Pharm.*, 215 (2001) 221-228.


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