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Particle size distribution and evolution in tablet structure during and after compaction

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Abstract

The objective of this study was to investigate the effect of the distribution in size of free-flowing particles for the evolution in tablet structure and tablet strength. For sucrose and sodium chloride, three powders of different size distributions were prepared by mixing predetermined quantities of particle size fractions. For paracetamol, three batches with varying particle size distributions were prepared by crystallisation. The powders were formed into tablets. Tablet porosity and tensile strength were determined directly after compaction and after short-term storage at two different relative humidities. Tablets were also formed after admixture of a lubricant (magnesium stearate) and the tablet tensile strength was determined. For the test materials used in this study, the spread in particle size had no influence on the evolution in tablet porosity and tensile strength during compression. However, the spread in particle size had a significant and complex influence on the short-term post-compaction increase in tablet tensile strength. The effect of the spread was related to the instability mechanism and the presence of lubricant. It is concluded that the distribution in size of free-flowing particles is not critical for the tablet porosity but may give significant effects on tablet tensile strength due to a post-compaction reaction.

Keywords: Particle size distribution; Tablet tensile strength; Tablet porosity; Storage; Relative humidity; Lubricant

1. Introduction

The need to understand in more depth functional properties of materials used in pharmaceutical preparations, including their manufacturability, and to develop methods of analysis of such properties is growing (Hardy and Cook, 2003). Since the tablet is the dominating dosage form, the tabletting behaviour, such as the ability of particulate solids to be formed into tablets, is an important manufacturing property of drugs in particulate form. To the formulation scientist, there is thus a need to be able to control critical properties of materials for their readiness or ability to form a tablet.

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From a particle engineering perspective, tablet structure and strength is often discussed in terms of a relationship between the properties of the particulate material and the properties of the formed tablet. The properties of a powder controlling the evolution in tablet structure during powder compression, which will also relate to the fracture toughness and the tensile strength of the tablets, are the compression mechanics of the particles and their dimensions. In addition, the structure and strength of a tablet may change after its formation, both from a short-term and a long-term perspective.

Since the size of particles can be varied or controlled during particle formation by crystallisation or by spray drying and by further mechanical treatment (size reduction and size enlargement), there is a wide literature on the effect of particle size on the mechanical strength of tablets. The traditional conception (Alderborn, 1996) is that the tablet strength will show some inverse proportionality with the original mean particle diameter. A reduced particle size within a compact will also increase the fracture toughness of the solid (Kendall, 1988). The relationship between original particle size and tablet strength has however empirically been shown to be complex, i.e. the original size can relate to the tablet strength in different ways (Alderborn, 1996). A contributing factor to the complex behaviour can be that a change in tablet structure, and thus in mechanical strength, can occur during storage. Different mechanisms may be responsible for such a change in tablet strength and a critical factor controlling or affecting instability in tablet strength is the relative humidity of the environment during storage. Eriksson and Alderborn (1994, 1995a) proposed two mechanisms, referred to as α and β, responsible for the observed instability in tablet strength. A common denominator in studies on the importance of particle size for the evolution in tablet structure and strength is that the size distribution is not systematically varied but kept narrow (e.g. Sun and Grant, 2001).

In the crystallization of organic fine chemicals and pharmaceutical compounds, there is however an increasing demand for control of the product particle size distribution. The product particle size distribution has a strong influence on the downstream filtration and washing, and hence on product purity, and may also be a key parameter in shipping and handling of the powder. It has for example been stated (Shekunov and York, 2000) that the distribution in particle size is a factor for the processing behaviour of a powder during pharmaceutical manufacturing. There is, however, still a need for reports providing evidence for a correlation between the particle size distribution and the manufacturability of powders. To our knowledge, no data has hitherto been reported on the importance of the width or type of particle size distribution for the tablet forming ability of a powder. The objective of this study was thus to investigate the effect of the distribution in size of free-flowing particles on the evolution of tablet structure and strength during compression and during short-term post-compaction storage of tablets.

2. Materials and methods

2.1. Materials

Three test materials that differ regarding their compression mechanics and their behaviour during short-term storage after compaction were chosen for the experiments.

Sodium chloride (crystalline puriss, Kebo, Sweden) can be described as a soft material (Rowe and Roberts, 1996) that shows limited fragmentation during compression (Alderborn et al., 1985). Tablets formed from unmilled sodium chloride increase in tensile strength after compression with a mechanism described as a particle viscous deformation or a temperature-related bond stabilisation and denoted mechanism β (Eriksson and Alderborn, 1994, 1995a).

Sucrose (crystalline, Ph. Eur., Prolabo, France) can be described as a moderately hard material (Eriksson and Alderborn, 1995b; Rowe and Roberts, 1996) that shows marked fragmentation during compression (Alderborn et al., 1985). Tablets formed from sucrose increase in tensile strength after compression with a mechanism described as a moisture-dependent molecular rearrangement at the interparticulate junctions and denoted mechanism α (Eriksson and Alderborn, 1994).

Paracetamol (Rhone-Poulenc chimie, France) forms weak tablets during compaction with a high tendency to cap or laminate (Krycer et al., 1982). The material can be described as moderately hard (Rowe and Roberts, 1996) and fragments strongly during compression (Alderborn et al., 1985).

Table 1
Apparent particle density, calculated specific surface area, median and spread in particle size for sodium chloride and sucrose powders

	Distribution	Density (g/cm^3)	Median (μm)	Range (μm)	Surface area (cm^2/cm^3)
NaCl	Wide	2.153	378	180–500	184
	Narrow		362	300–425	199
	Bimodal		417	125–500	176
Sucrose	Wide	1.586	449	250–850	208
	Narrow		427	355–425	220
	Bimodal		479	250–850	220

2.2. Preparation of particle size distributions

Two of the raw materials (sodium chloride and sucrose) were subdivided into a number of size fractions by dry sieving (ASTM test sieves, Retsch, Germany). Different size distributions were then prepared by mixing predetermined quantities of the size fractions in a shear mixer (Turbula, W.A. Bachofen AG Maschinenfabrik, Basel, Switzerland) for 10 min at 46 rpm. For both materials, three size distributions were designed, i.e. a narrow unimodal distribution, a wide unimodal distribution, and a wide bimodal distribution. The range of particle size used is given in Table 1 and in Fig. 1, graphical representations of the distributions are presented.

Four batches of paracetamol were prepared by precipitation from a solution of deionised water during cooling. Eighty grams paracetamol were dissolved in 2 kg water of 60 °C and the solution was cooled down to 10 °C. Four different linear cooling rates were used, i.e. 0.2, 0.4, 0.5 and 0.66 °C/min. The agitation rate was 680 rpm at cooling rates of 0.2, 0.5 and 0.66 °C/min and 1000 rpm at a cooling rate of 0.4 °C/min. Two grams seeds (125–200 μm) were added at 52 °C to the 0.2 °C/min experiment. After filtration through paper filters, the crystals were dried in a ventilated heating cabinet at 60 °C. Batches 3 and 4 (i.e. the batches prepared at cooling rates of 0.5 and 0.66 °C/min) showed similar particle size distribution and were combined to one batch for further use.

All prepared powders were stored at room temperature in chambers of 40% relative humidity (dessicators with saturated NaI–water solutions) for at least 7 days before further experiments.

The particle size distributions of the paracetamol batches were determined by dry sieving using a series of stainless steel laboratory sieves (ASTM test sieves, Retsch, Germany) of nominal opening sizes between 180 and 800 μm (Fig. 1). For each batch, 10–15 g of powder was sampled with a spoon and then sieved for 30 min with a mechanical sieve shaker (Retsch, type RV, Germany) at a relative vibration intensity of 60. The sieving procedure was difficult to perform due to build up of charges on the surfaces of the paracetamol particles.

2.3. Mixing with lubricant

For sodium chloride and sucrose, the narrow and the wide unimodal particle size distributions were mixed with magnesium stearate (magnesium stearate powder, Kebo, Sweden) in the Turbula mixer. An amount of magnesium stearate corresponding to a specific amount of 5 and 50 μg/cm^2 was mixed with 10 g of powder for 100 min (the proportions of magnesium stearate in the mixture were about 0.05 and 0.5% by weight, respectively). The external surface area of the sodium chloride and sucrose powders was estimated as the ratio between the Heywood shape coefficient of the particles (literature values used from Alderborn and Nyström, 1982) and the median value of the particle size distributions.

2.4. Preparation of tablets

Tablets of 500 mg were prepared with an instrumented single punch press (Korsch EK 0, Germany) at applied pressures of 50, 75, 100, 200 and 275 MPa by using circular (diameter of 11.3 mm) flat-faced punches and at 400, 500, 600 and 700 MPa by using circular (diameter of 5.74 mm) flat-faced punches.

For each tablet, the powder was poured manually into the die which was pre-lubricated by spreading magnesium stearate powder (Kebo, Sweden) on the punch and die surfaces with the aid of a small paint

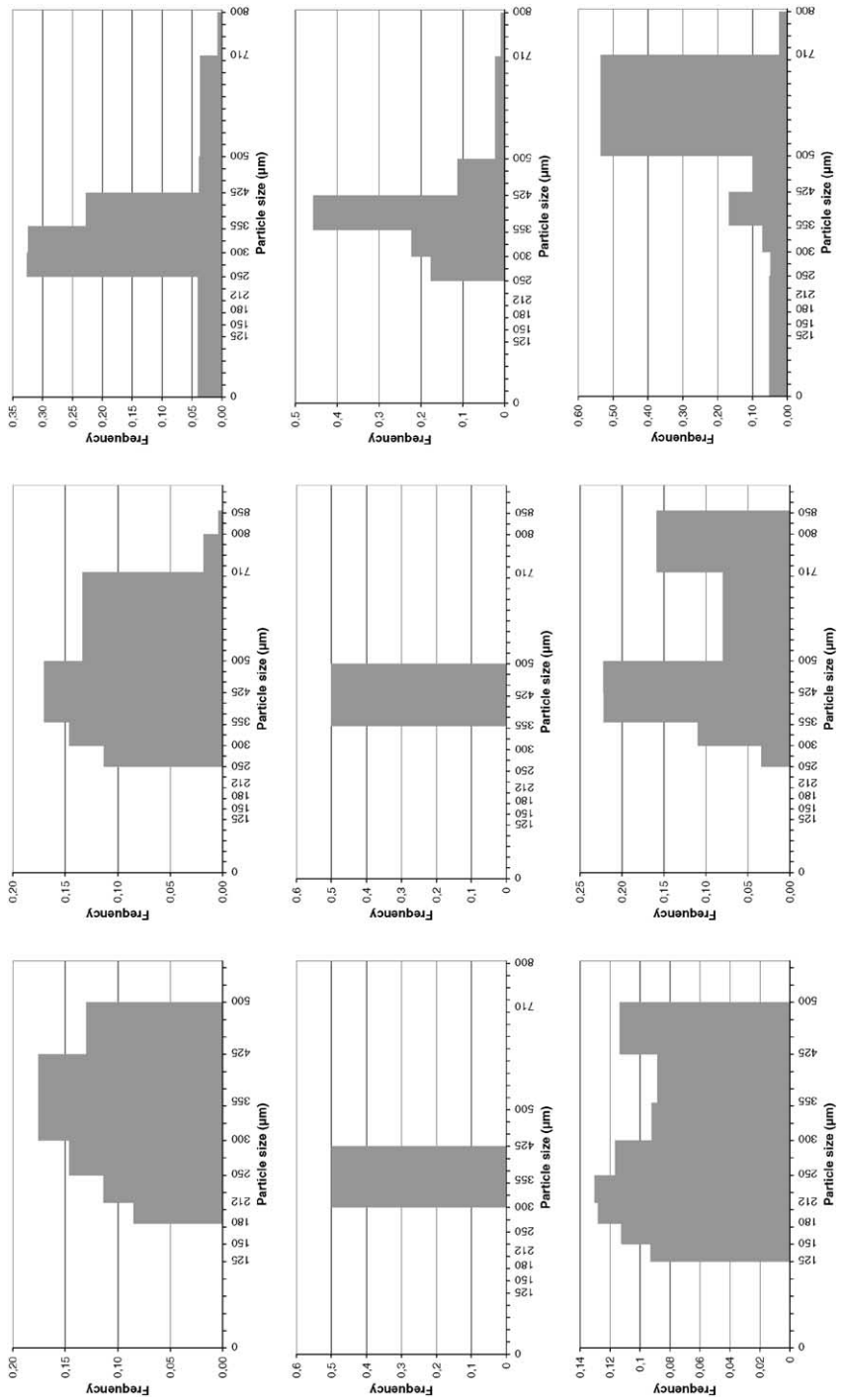

Fig. 1. Frequency distribution for the different types of particle size distributions of sodium chloride (left column), sucrose (middle column) and paracetamol (right column).

brush in-between every powder compression. The lower punch was stationary during compression and the upper punch machine driven, i.e. the machine was started when the upper punch was in its upper most position relative to the die. The compaction pressure was recorded for each tablet and a variation in compaction pressure of ±3% of the nominal value was accepted.

2.5. Determination of porosity and tensile strength of tablets

The porosity of the tablets (ε_t) was calculated from the apparent particle density (ρ_p) and the diameter (D), height (t) and weight (w) of each tablet in the following way:

$$\varepsilon_t = 1 - \frac{4w}{\pi t D^2 \rho_p}$$

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

$$\sigma_t = \frac{2F_t}{\pi t D}$$

2.6. Experimental design and statistical analysis

To assess the evolution in tablet structure during the compression phase, the characteristics (tensile strength and porosity) of the tablets were determined about 1 min after powder compaction. The data are presented as compression and compaction profiles with 95% confidence limits for the arithmetic mean of at least five measurements for the determined characteristics. Powders for all three substances were used for these experiments.

To assess the evolution in tablet structure during short-term post-compaction storage of the tablets, tensile strength of tablets formed from the narrow and wide unimodal distributions of sodium chloride and sucrose was determined at a series of time intervals after the compaction, i.e. 1, 10, 100 and 10,000 min. All reported values are the mean (arithmetic) of at least five measurements. During the time period between tablet formation and tablet strength testing, tablets were kept in desiccators at a low (about 0%) and a high (about 57%) relative humidity (rh). The rh in the desiccators was controlled by P_2O_5 (low rh) and by a saturated NaBr–water solution (high rh). Lubricated tablets were only stored at higher rh. For these experiments, tablets were formed at 100 MPa from the pure test materials, at 200 from the mixtures with magnesium stearate (low concentration of magnesium stearate for both substances and high concentration of magnesium stearate for sucrose) and at 300 MPa (high concentration of magnesium stearate for sodium chloride). Tablet strength data obtained after short and long storage times (1 and 10,000 min) were subjected to a two-way analysis of variances test.

3. Results and discussion

3.1. Particle size distributions

The problem of the importance of the size of particles and their distribution for the pharmaceutical engineering properties of a powder must be put into the perspective of the process application. In this study, the engineering property examined is the compression and compaction behaviour of the powders. From an applied perspective, the powders used must show good flowability in order to be processable in a tablet machine. Thus, for all three substances, powders with particle sizes corresponding to free-flowing powders were prepared, i.e. a coarse particle domain.

For sodium chloride and sucrose, the particle size distributions were obtained by mixing weighed quantities of particles that were pre-sorted by size. The objective was to obtain a nearly consistent median particle size but a variation in spread of particle size in terms of width and shape of the distribution. Limiting factors in the preparation of the distributions were the sieves at hand in the laboratory and the size distributions of the raw materials. Thus, sodium chloride powders were prepared with generally slightly lower median particle size compared to sucrose powders (Fig. 1 and Table 1). Two of the distributions can be described as unimodal, i.e. the particles were uniformly distributed around the median value, and one distribution was bimodal.

For sodium chloride and sucrose, the specific powder surface area was also calculated from the particle size distributions as the ratio between the Heywood

Table 2
Apparent particle density, melting point, median and spread in particle size for paracetamol powders

	Distribution	Density (g/cm^3)	Melting point (°C)	Median (μm)	Range (μm)
Paracetamol	P1	1.291	171	323	0–800
	P2	1.291	171	372	0–800
	P3	1.293	171	514	0–800

shape coefficient (values from Alderborn and Nyström, 1982) and the median particle size. For the respective substance, the surface area (Table 1) was similar between the powders with a lower surface area for the sodium chloride powders compared to the sucrose powders.

For paracetamol, a more applied approach to prepare powders of different particle size distributions was used by crystallising particles from water solutions under different conditions. Paracetamol can be crystallized into at least two forms, the monoclinic and the orthorhombic form (Di Martino et al., 1996; Joiris et al., 1998). The monoclinic form is the type of paracetamol normally used in tablet manufacturing although it is reported (Di Martino et al., 1996; Joiris et al., 1998) that the orthorombic form shows better compactability with less capping tendency. The same melting points were obtained for all three batches (Table 2). A melting point of about 171 °C compares favourably with a melting point of 169 °C reported by Di Martino et al. (1996) for the monoclinic form and it is thus concluded that all three batches constituted of crystals of the monoclinic form.

The used variations in crystallisation condition affected the size distribution (Fig. 1) in such a way that a similar width in distribution was generally obtained but the median size and the shape of the distributions differed between the three batches. Two batches showed unimodal particle size distributions but different median values. The batch with the lower median particle size showed a more skewed distribution with a right hand sided tail. The third batch showed a tendency towards a bimodal distribution with a markedly higher median particle size.

For sodium chloride and sucrose, particles of all sieve fractions were primary particles with consistent shape, i.e. nearly cubic for sodium chloride and more elongated, angular particles for sucrose (Alderborn and Nyström, 1982). Paracetamol crystallised into both primary and secondary particles (Fig. 2) and the incidence of agglomeration was marked, giving irregular particles.

3.2. Evolution in tablet structure during compression

As indicators of the evolution in tablet structure during compression, the change in tablet porosity and tablet strength as a function of compression pressure was used. The characteristics used, i.e. porosity and tensile strength of the tablets, are macroscopic properties that however reflect the structure of the tablet on meso- and microscopic levels.

For sodium chloride, the relationships between tablet porosity and compaction pressure coincided between the powders and thus, the spread in particle size did not affect the powder compressibility in a systematic way. The same pattern was obtained also for the sucrose powders. The sucrose powders gave tablets of higher porosity than sodium chloride. This rank order between the substances in compressibility is consistent with the expected propensity of the particles to deform during confined powder compression (Rowe and Roberts, 1996). To support this difference between the materials, the Heckel compression parameter and the Alderborn compression parameter were calculated as described elsewhere (Alderborn, 2003) from all the tablet porosity and tablet strength data derived. For sucrose, values of 276 and 621 MPa, respectively were obtained which compares favourably with an earlier experience (Alderborn, 2003). For sodium chloride, values of 178 and 474 MPa, respectively were obtained. These values support that sodium chloride is softer than sucrose but the derived values are higher than usually reported (Rowe and Roberts, 1996; Alderborn, 2003) indicating a relatively hard sodium chloride quality.

For sodium chloride and sucrose, the evolution in tablet strength with compaction pressure followed the same principle pattern as for the changes in tablet porosity with compaction pressure, i.e. for the respec-

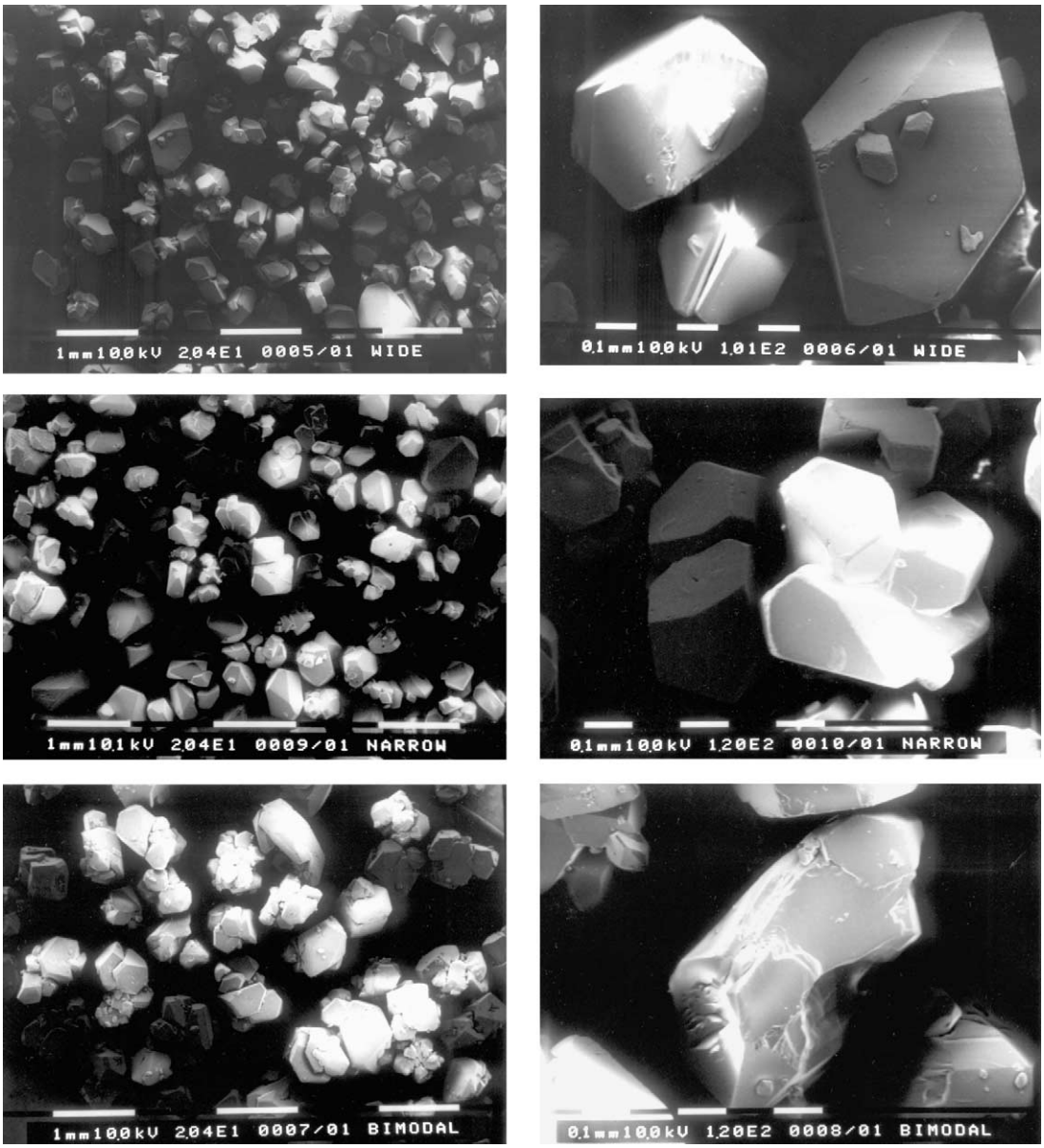

Fig. 2. Images prepared by S.E.M. of paracetamol particles of all three batches: P1 (top row), P2 (middle row) and P3 (bottom row).

tive substance the relationships more or less coincided. Sodium chloride gave generally tablets of lower tensile strength than sucrose (Figs. 3 and 4). Thus, the spread in particle size did not affect the powder compactability, as assessed directly after tablet formation.

For paracetamol, the range in compaction pressure used was lower than for the other substances due to lamination and capping of the tablets which prevented formation of tablets at compaction pressures above 120 MPa. Also for this substance, the relationships between tablet tensile strength or tablet porosity and compaction pressure did not differ dependent on the spread in particle size. Thus, although there were differences in spread in particle size, median particle size

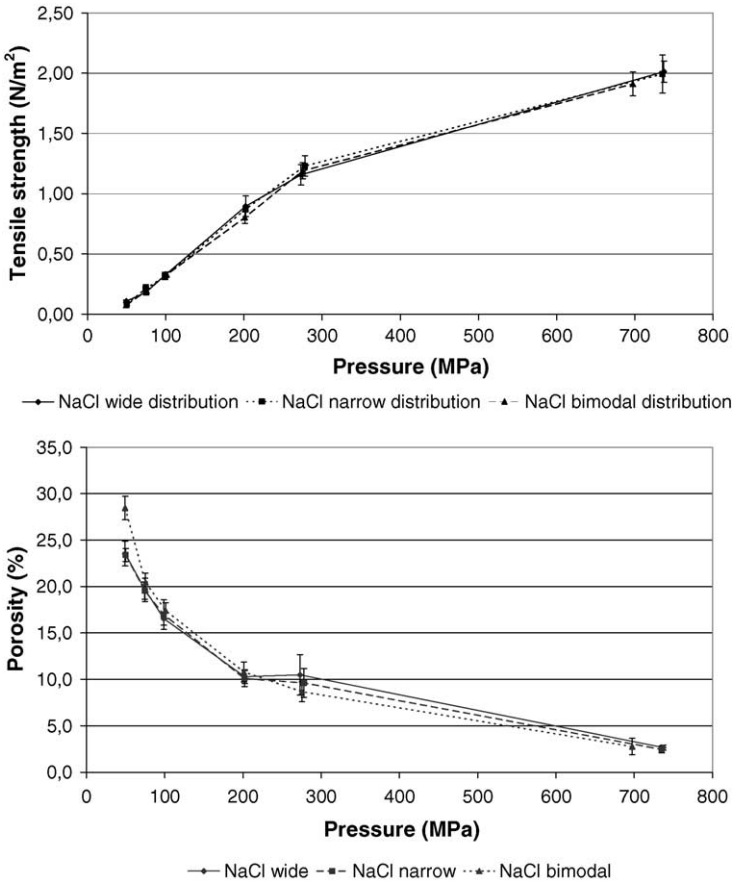

Fig. 3. Tensile strength (upper panel) and porosity (lower panel), measured 1 min after powder compaction, of sodium chloride tablets as a function of compaction pressure.

and particle structure (incidence of agglomerates) between the batches, the three batches used showed similar compression and compaction behaviour (Fig. 5).

Due to the limited range of pressure used in the preparation of paracetamol tablets in combination with the fact that the ejected tablets showed similar volume after pressures above about 100 MPa, it was not possible to calculate a reliable Heckel compression parameter.

In conclusion, within the coarse particle domain, the compressibility and the compactibility of the test substances were not significantly dependent on the spread in size of the particles. We thus conclude that the evolution in tablet meso- and microstructure during the compression process is independent of the used variations in particle size distribution.

3.3. Post-compaction changes in tensile strength of tablets formed from lubricant free powders

It is recognised in the literature that the mechanical strength of a tablet may change during a period of time after the compaction process. The equilibrium level in tablet strength reached may however depend on the relative humidity of the environment during the isothermal equilibration phase. In order to assess the possible effect of the spread in particle size for the short-term (here defined as up to 7 days) mechanical instability, further experiments on two particle size distributions (narrow and wide unimodal distributions) for sodium chloride and sucrose were undertaken.

The tensile strength of both sodium chloride and sucrose tablets measured directly (1 min) after com-

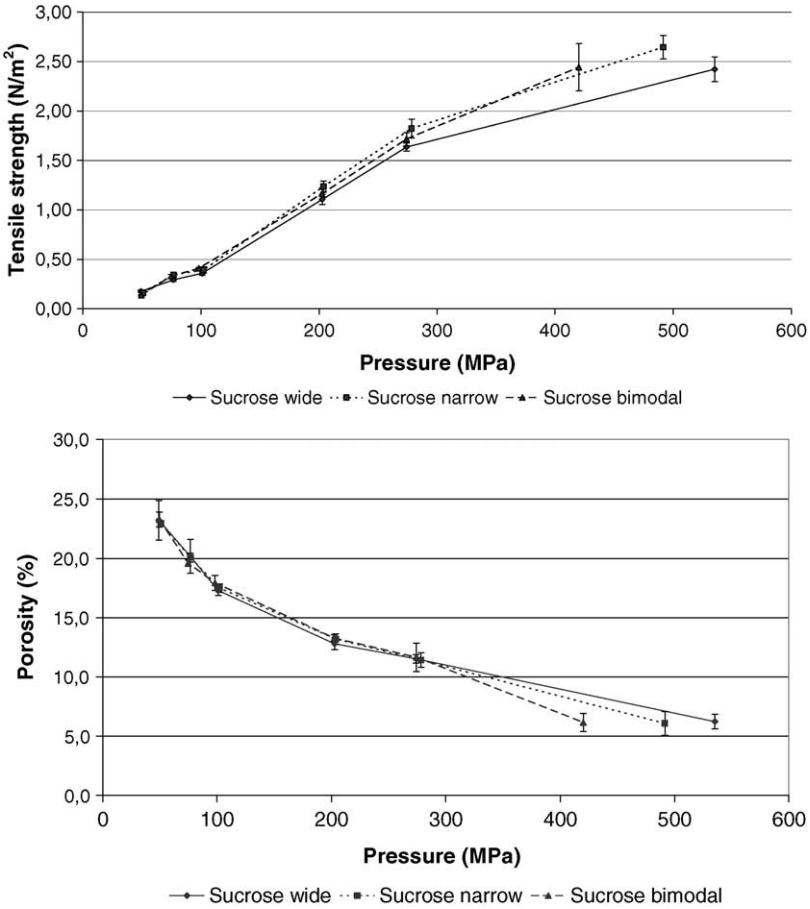

Fig. 4. Tensile strength (upper panel) and porosity (lower panel), measured 1 min after powder compaction, of sucrose tablets as a function of compaction pressure.

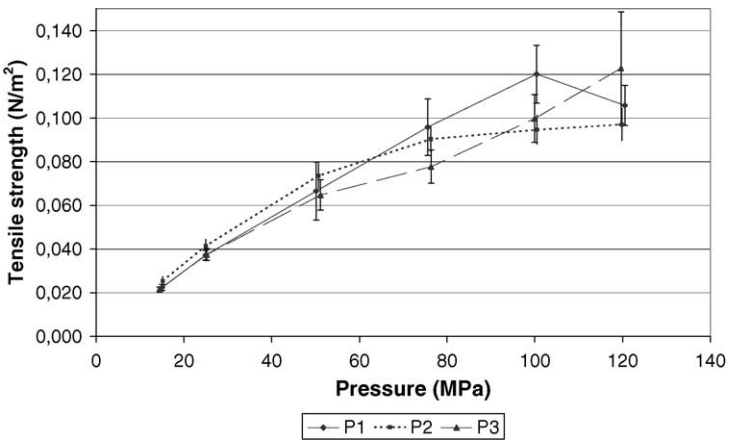

Fig. 5. Tensile strength, measured 1 min after powder compaction, of paracetamol tablets as a function of compaction pressure.

Table 3
ANOVA table for the tensile strength of sodium chloride tablets prepared from narrow and wide unimodal particle size distributions and stored at 57% relative humidity for 1 and 10,000 min

Source	d.f.	Sum Sq	Mean Sq	*F* value	Pr (>*F*)
Material: sodium chloride, Mg-stearate: 0 μg/cm^2, relative humidity: 57%					
Distribution	1	0.028901	0.02891	11.3858	0.003864**
Storage time	1	0.172207	0.172207	67.8414	3.792×10^{-7}***
Distribution: storage time	1	0.019102	0.019102	7.5253	0.014434*
Residuals	16	0.040614	0.002538		
Material: sodium chloride, Mg-stearate: 5 μg/cm^2, relative humidity: 57%					
Distribution	1	0.0039845	0.0039845	9.6151	0.006868**
Storage time	1	0.0039920	0.0039920	9.6330	0.006827**
Distribution: storage time	1	0.0044314	0.0044314	10.6934	0.004813**
Residuals	16	0.0066305	0.0004144		
Material: sodium chloride, Mg-stearate: 50 μg/cm^2, relative humidity: 57%					
Distribution	1	0.0070465	0.0070465	9.4332	0.007305**
Storage time	1	0.005446	0.0005446	0.7291	0.405791
Distribution: storage time	1	0.008425	0.0008425	1.1279	0.303991
Residuals	16	0.0119518	0.0007470		

* Significant code: 0.001.
** Significant code: 0.01.
*** Significant code: 0.05.

Table 4
ANOVA table for the tensile strength of sucrose tablets prepared from narrow and wide unimodal particle size distributions and stored at 57% relative humidity for 1 and 10,000 min

Source	d.f.	Sum Sq	Mean Sq	*F* value	Pr (>*F*)
Material: sucrose, Mg-stearate: 0 μg/cm^2, relative humidity: 57%					
Distribution	1	1.648×10^{-6}	1.648×10^{-6}	0.0009	0.9762
Storage time	1	1.12763	1.12763	627.2326	2.911×10^{-14}***
Distribution: storage time	1	0.00259	0.00259	1.4398	0.2476
Residuals	16	0.02876	0.00180		
Material: sucrose, Mg-stearate: 5 μg/cm^2, relative humidity: 57%					
Distribution	1	0.0052073	0.0052073	6.9887	0.0176978*
Storage time	1	0.0137738	0.0137738	18.4859	0.0005512***
Distribution: storage time	1	0.0088307	0.0088307	11.8517	0.0033452**
Residuals	16	0.0119216	0.0007451		
Material: sucrose, Mg-stearate: 50 μg/cm^2, relative humidity: 57%					
Distribution	1	0.10826	0.0010826	3.8926	0.066032†
Storage time	1	0.0090180	0.0090180	32.4258	3.321×10^{-5}***
Distribution: storage time	1	0.0031995	0.0031995	11.5043	0.003724**
Residuals	16	0.0044498	0.0002781		

* Significant code: 0.001.
** Significant code: 0.01.
*** Significant code: 0.05.
† Significant code: 0.1.

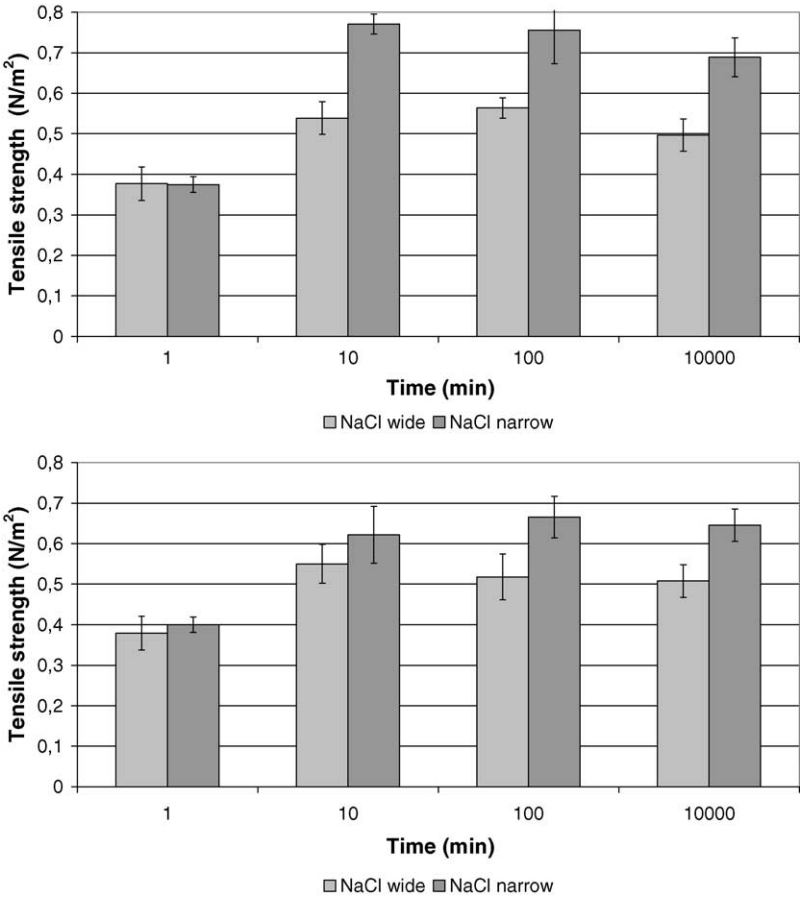

Fig. 6. Tensile strength of sodium chloride tablets formed without lubricant and stored at 0% (upper graph) and 57% (lower graph) relative humidity for different post-compaction storage times.

paction (Figs. 6 and 7) was independent of the particle size distribution which is a reproduction of the earlier data reported in Figs. 3 and 4. During short-term storage, different storage behaviour was obtained dependent on the substance (Figs. 6 and 7 and Tables 3 and 4).

For sodium chloride, all tablets were unstable independent of the storage relative humidity for a short period of time (up to 10 min) and thereafter, stable tablet strength values were reached. This short-term storage behaviour is expected for sodium chloride and is consistent with instability behaviour of the β type (Eriksson and Alderborn, 1994). One should notice though that the effect of storage humidity is not consistent with an earlier suggestion (Eriksson and Alderborn, 1994) where an increased relative humidity was suggested to slightly slow down the rate of tablet strength increase. For the time periods used here a humidity related rate difference could not be observed. The narrow size distribution gave tablets more prone to increase in tablet tensile strength during short-term storage regardless of the relative humidity. Thus, the spread in particle size was a significant factor for the post-compaction increase in tensile strength for sodium chloride tablets.

For sucrose, all tablets were stable at the lower humidity while an increase in tablet strength was obtained for tablets stored at higher humidity. The increase in tablet strength occurred until the last time point for measurement has elapsed. This short-term storage behaviour being dependent on the relative humidity of the environment is expected for sucrose (Ahlneck and Alderborn, 1991) and consistent with an instability

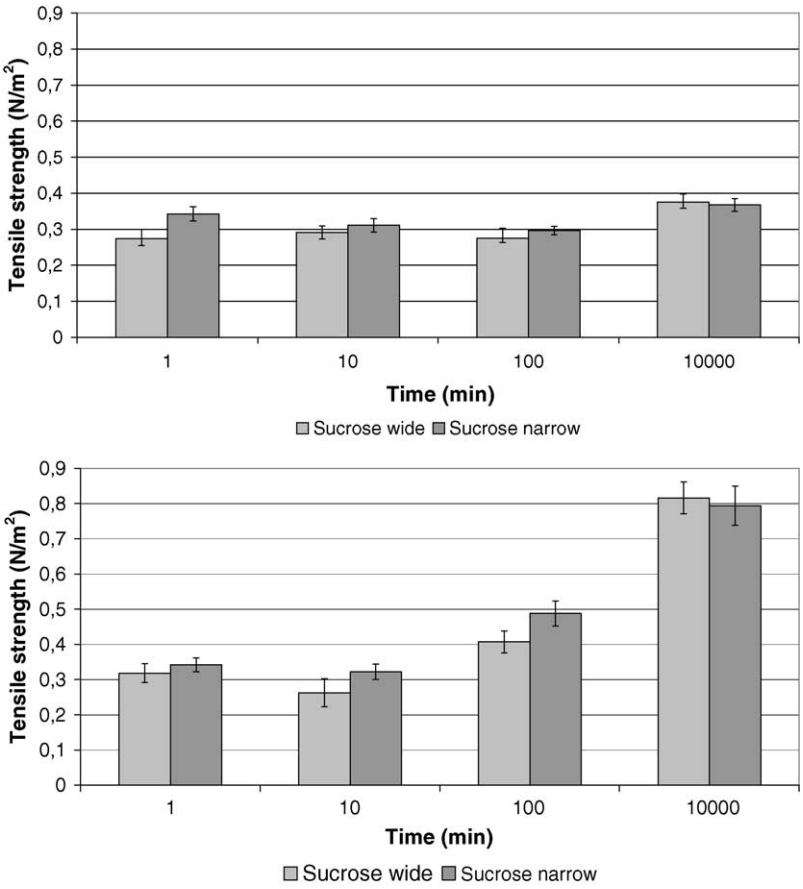

Fig. 7. Tensile strength of sucrose tablets formed without lubricant and stored at 0% (upper graph) and 57% (lower graph) relative humidity for different post-compaction storage times.

behaviour of the α type. Contrary to the sodium chloride results, the spread in particle size did not affect the storage behaviour, i.e. the post-compaction restructuring of the tablet occurring in the moist atmosphere was not related to the original distribution in particle size.

Thus, for the lubricant free powders, the particle size distribution was a factor of importance for the short-term instability for sodium chloride but not for sucrose, i.e. the effect of the original particle size distribution may depend on the type of restructuring process active in the tablet. It has earlier been shown (Eriksson and Alderborn, 1995a) that the short-term increase in tensile strength for tablets formed from free-flowing sodium chloride powders is lower for smaller particles than for coarser. The underlying processes responsible for the short-term storage instability of the β type have been proposed (Eriksson and Alderborn, 1994) as either particle viscous deformation that occurs during some period of time after compaction or as a temperature-related stabilisation of the adhesive interactions formed at the interparticulate joints. Both mechanisms may be affected by the stress conditions at the interparticulate junctions evolved during the compression that may be more heterogeneously distributed within a tablet formed from a wider size distribution.

3.4. Post-compaction changes in tensile strength of tablets formed from lubricated powders

It is well known that a lubricant can affect the tablet forming ability of a powder in such a way that the

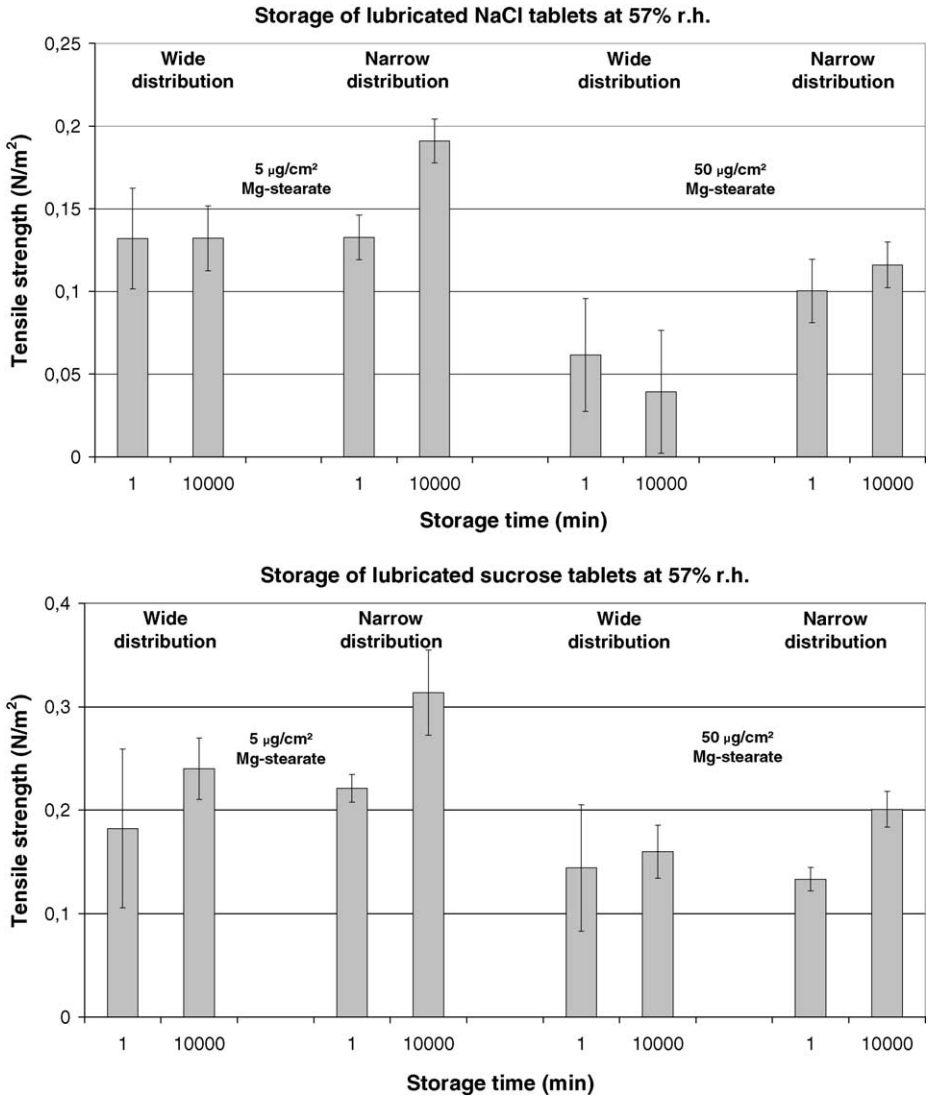

Fig. 8. Tensile strength of sodium chloride (upper graphs) and sucrose (lower graphs) tablets formed with lubricant of two concentrations (5 and 50 $\mu g/cm^2$) and stored at 57% relative humidity for different post-compaction storage times.

compactibility is reduced. It is also generally recognised that the lubricant sensitivity is partly related to the fragmentation propensity of the particles to be compacted. Also in this study, the sucrose powders showed generally a lower lubricant sensitivity than the sodium chloride powders and a higher compaction pressure was used in the formation of tablets from sodium chloride powder mixed with the higher concentration of magnesium stearate. For both substances, an increased proportion of lubricant tended to reduce the compactibility of the powders (Fig. 8 and Tables 3 and 4).

For sodium chloride, the lubricant restrained the storage-related increase in tensile strength with one exception, i.e. the narrow distribution lubricated with the lower proportion of magnesium stearate for which an effect of the spread in particle size was obtained.

For sucrose, the incorporation of lubricant inhibited the storage-related increase in tensile strength for

tablets prepared from the wide particle size distribution. For the narrow particle size distribution, a storage-related increase (although a lower absolute change than for the unlubricated powders) in tablet strength was however obtained at both lubricant concentrations. Thus, the particle size distribution, which was of no importance in the unlubricated sucrose powders, was a factor for the short-term instability in the lubricated powders.

For both sucrose and sodium chloride tablets, the addition of lubricant had in general terms a restraining effect on the post-compaction tensile strength increase. This may be interpreted in two ways: The lubricant may inhibit a restructuring of tablet or the lubricant may interfere with the formation of interparticulate bonds as a consequence of a restructuring.

For the type β process described as a viscous deformation, a restructuring may occur but is not expressed in terms of bond formation between lubricant covered particle surfaces. Thus, the lubricant does not restrain a restructuring process but represents a barrier towards bond formation.

For the type α mechanism, it is suggested that absorbed moisture can modulate the mobility of the molecules and thus initiate a diffusion like transport of molecules in the vicinity of the interparticulate junctions. Such a process may be hindered by a lubricant, covering the particle surfaces, and the restructuring takes place at lubricant free surfaces only.

It seems also that for the lubricated powders, the particle size distribution was a factor of importance for the short-term instability for both sodium chloride and sucrose, i.e. the effect of the spread in particle size was applicable to both types of instability mechanisms active in the tablets. Since it is proposed that the short-term strength instability of a tablet of both α and β type involves lubricant free surfaces, it is possible that the distribution in particle size may affect the fraction of lubricant free surfaces in the tablet formed during or after compression.

4. Conclusions

In this study, the importance of the spread in size of particles for their tabletting behaviour within a domain of particle size corresponding to a free-flowing powder has been investigated. For the test materials used in this study, the spread in particle size had no influence on the evolution in tablet porosity and tensile strength during compression. However, the spread in particle size had a significant and complex influence on the short-term post-compaction increase in tablet tensile strength. This effect of spread in particle size was related to the instability mechanism and the presence of lubricant. For the unlubricated powders, only mechanism β showed a dependence on original distribution in particle size. The addition of lubricant had in general terms a restraining effect on the post-compaction increase in tablet tensile strength. However, the presence of lubricant triggered an effect on original distribution in particle size that could not be observed in tablets of unlubricated powder. It is concluded that spread in size of particles within the coarse particulate domain is not critical for the tablet porosity but may give significant and complex effects on tablet strength due to a post-compaction reaction or process.

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References

Ahlneck, C., Alderborn, G., 1991. Moisture adsorption and tabletting. III. Effect on tablet strength—post compaction storage time profiles. Int. J. Pharm. 73, 249–258.

Alderborn, G., 1996. Material properties of importance for powder volume reduction and compact strength: particle dimensions. In: Alderborn, G., Nyström, C. (Eds.), Pharmaceutical Powder Compaction Technology. Marcel Dekker Inc., New York, pp. 245–282.

Alderborn, G., 2003. A novel approach to derive a compression parameter indicating effective particle deformability. Pharm. Dev. Technol. 8, 367–377.

Alderborn, G., Nyström, C., 1982. Studies on direct compression of tablets. III. The effect on tablet strength of changes in particle shape and texture obtained by milling. Acta Pharm. Suec. 19, 147–156.

Alderborn, G., Pasanen, K., Nyström, C., 1985. Studies on direct compression of tablets. XI. Characterisation of particle fragmentation during compaction by permeametry measurements of tablets. Int. J. Pharm. 23, 79–86.

Di Martino, P., Guyot-Hermann, A.-M., Conflant, P., Drache, M., Guyot, J.-C., 1996. A new pure paracetamol for direct compression: the orthorhombic form. Int. J. Pharm. 128, 1–8.

Eriksson, M., Alderborn, G., 1994. Mechanisms for post-compaction changes in tensile strength of sodium chloride compacts prepared from particles of different dimensions. Int. J. Pharm. 109, 59–72.

Eriksson, M., Alderborn, G., 1995a. The effect of original particle size and tablet porosity on the increase in tensile strength during storage of sodium chloride tablets in a dry atmosphere. Int. J. Pharm. 113, 199–207.

Eriksson, M., Alderborn, G., 1995b. The effect of particle fragmentation and deformation on the interparticulate bond formation process during powder compaction. Pharm. Res. 12, 1031–1039.

Fell, J.T., Newton, J.M., 1970. Determination of tablet strength by the diametral compression test. J. Pharm. Sci. 59, 688–691.

Hardy, I.J., Cook, W.G., 2003. Predictive and correlative techniques for the design, optimisation and manufacture of solid dosage forms. J. Pharm. Pharmacol. 55, 3–18.

Joiris, E., Di Martino, P., Berneron, C., Guyot-Hermann, A.-M., Guyot, J.-C., 1998. Compression behaviour of orthorombic paracetamol. Pharm. Res. 15, 1122–1130.

Kendall, K., 1988. Agglomeration strength. Powder Metallurgy 31, 28–31.

Krycer, I., Pope, D.G., Hersey, I.A., 1982. The prediction of paracetamol capping tendencies. J. Pharm. Pharmacol. 34, 802–804.

Rowe, R.C., Roberts, R.J., 1996. Material properties of importance for powder volume reduction and compact strength: mechanical properties. In: Alderborn, G., Nyström, C. (Eds.), Pharmaceutical Powder Compaction Technology. Marcel Dekker Inc., New York, pp. 283–322.

Shekunov, B.Y., York, P., 2000. Crystallization processes in pharmaceutical technology and drug delivery design. J. Crystal Growth 211, 122–136.

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