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Minitabletting: improving the compactability of paracetamol powder mixtures

P. Lennartz, J.B. Mielck *

Department of Pharmaceutical Technology, University of Hamburg, Bundesstr. 45, 20146 Hamburg, Germany

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Abstract

Powder mixtures of paracetamol and a spray-dried lactose, Pharmatose® DCL 11, after adding glidant and lubricant, were continuously tabletted on an eccentric tabletting machine into convex-faced tablets with diameters ranging from 1.5 to 5 mm, to graded maximum relative densities and a ratio of overall thickness at minimum distance of the punch faces to, diameter of one, resulting in tablets with identical geometrical proportions. Force at upper and lower punches and the distance between the upper and lower punch holders were measured during tabletting, and the resulting tablets were tested for mechanical strength and tendency to cap. The results indicate that the mechanical stability of minitablets containing paracetamol is equal to, and at high pressures higher than that of normal-sized tablets. The capping tendency of minitablets is reduced. This leads to the conclusion that higher contents of paracetamol could be tabletted, if minitablets were produced.

Keywords: Minitablets; Compactability; Paracetamol; Capping; Capacity

1. Introduction

Minitablets are tablets with a diameter equal to or smaller than 2–3 mm. They are made by ordinary reciprocating or rotary tabletting machines, using a multiple tooling. Because of the manufacturing process, defined sizes and strengths can be easily produced, and the variability within a batch is small (Pich and Moest, 1989; Munday, 1994). Minitablets are mostly used for the production of multiple-unit dosage forms. They can be filled into capsules, directly or after coating. Ophthalmica-inserts are also described (Satteone et al., 1990, 1995). Minitablets are competing with pellets. Because of their uniform size, smooth surface, low porosity and high attainable strength, minitablets should be coated more reproducibly than usual pellets or granules. They are more robust and they need less coating material (Mun-

* Corresponding author. Tel.: +49 40 41233479; fax.: +49 40 41236573; e-mail: mielck@chemie.uni-hamburg.de

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day and Fassihi, 1989; Pich and Moest, 1989; Munday, 1994). The tooling used must meet special requirements regarding precision and mechanical stability, because of the higher die-wall friction compared with normal tooling. If the fitting is not exact, a high amount of abrasion could occur (Pich and Moest, 1989). The problems connected with the durability of small-sized punches has been described first in a patent by Hershberg (1965). The particle size of the tabletting mixtures must have a definite upper limit (Arreco et al., 1976; Flemming and Mielck, 1995). Therefore, direct compression is the most appropriate method for minitabletting, if a mixture with sufficient flow properties can be obtained. The requirements regarding flow properties have been investigated by Flemming and Mielck (1995). The tabletting behaviour of tabletting mixtures using small diameters seems to provide advantages. A patent of the Nordmark company (Pich and Moest, 1989) points out that they were able to produce minitablets, but not 10-mm tablets, with a content of 99.5% pancreatin. The aim of this study is to find out whether mixtures not able to form normal-sized tablets could be tabletted to minitablets of sufficient physical quality. Paracetamol is used as model drug, the poor tabletting properties of which have been described frequently. Paracetamol has been used as standard reference for the determination of the capacity of direct compression excipients for drugs with poor tabletting characteristics (Wells and Langridge, 1981; Minchom and Armstrong, 1987; Mollan and Celik, 1994). It is very difficult to produce tablets with sufficient mechanical properties with a high content of crystalline paracetamol, because of its high capping tendency. This capping tendency of paracetamol has also been described in the literature frequently (Leigh et al., 1967; Alderborn and Nyström, 1984; Malamataris et al., 1984; Bangadu and Pilpel, 1985). It was related to an elastic component of the mainly brittle material (Carless and Leigh, 1974; Nyström and Glazer, 1985; Lin and Duncan-Hewitt, 1994; Malamataris et al., 1996). This leads to stress inside the tablet, which is not released by plastic deformation, but by elastic recovery, which in turn destroys the bonds formed during the compaction process (Carless and Leigh, 1974; Hiestand et al., 1977; Jetzer and Leuenberger, 1984; Malamataris et al., 1996). Remaining stress, which is not released, also weakens the tablet (Parmentier, 1980). Furthermore, crystalline paracetamol shows anisotropic properties (Lin and Duncan-Hewitt, 1994), which also causes stress which weakens the tablet (Parmentier, 1980; Jetzer and Leuenberger, 1984). There are different ways of improving the tabletting properties of paracetamol. One could use a different polymorphic form (Di Martino et al., 1996), or special crystal habits (Fachaux et al., 1993; Femi-Oyewo and Spring, 1994; Ettabia et al., 1997), but application of the granulation process is the most widely used method (Leigh et al., 1967; Carless and Leigh, 1974; Krycer et al., 1982; Fachaux et al., 1993). We intentionally chose fine-grade paracetamol with irregularly shaped crystals, because needle-shaped crystals have especially poor tabletting characteristics (Hong-guang and Ruhua, 1995). Because of the poor flow properties of the paracetamol used, we chose a spray-dried lactose as excipient, which has very good flow properties but a capacity of only about 20% for drugs with poor tabletting properties (Peck et al., 1989; Shangraw, 1989). So when mixtures with even a low content of paracetamol are tabletted, which have sufficient flow properties, capping tendencies should be provoked and sensitively determined.

The size dependence of tensile strength has also been described early in literature. Stanley and Newton (1977) found a clear indication that the strength of the material of tablets of different size varies significantly. Several reasons were suggested for this observation, such as structural differences caused by friction effects and different stress distribution due to different tablet-forming conditions or tablet dimensions. Varying flaw distributions were also discussed. Kennerley et al. (1977) prepared cylindrical tablets of two different volumes, but with identical ratio of diameter to thickness and found a decrease in mean fracture stress with decrease in size. The tablets produced in their work were much larger than the tablets which had to be investigated in this work, so differences could be expected.

Jacob and Hüttenrauch (1982) explained that the mechanical activation decreases with increasing tablet diameter, leading to a lower strength following the activation theory of tablet formation. The tablets prepared by Jacob and Hüttenrauch were also larger and were altered either in diameter or in height, so the results cannot be compared with the results of this work directly.

Another possible reason for an increased strength of smaller tablets is a better force transmission due to less material between the punches with decreasing tablet height, resulting in a greater overall pressure. However, the work of Flemming (1998) shows that the force transmission becomes smaller when the diameter of the tablets is decreased to values under 3 mm, due to a higher amount of friction. Therefore force transmission should not be the reason for a higher mechanical strength of minitablets.

2. Material and methods

2.1. Material

Paracetamol (Rhone Poulenc, Lot No.: 92-282-10-2); magnesium stearate (Riedel-de Haen, Lot No.: 91320); Aerosil® 200 (Degussa AG, Lot No.: 1238); Pharmatose DCL 11® (DMV, Lot No.: 10074499).

2.2. Mixtures

Four mixtures were produced containing 0, 10, 30 and 50% (w/w) paracetamol, adding 0.5% magnesium stearate and 0.5% Aerosil® 200. After sieving the paracetamol and the DCL 11® (400 μm) in order to destroy agglomerates, and after adding the Aerosil® 200, the materials were mixed for 15 min in a steel drum (2.4 l volume, filled to 50–60%) using a Turbula T2A (W. Bachofen, Basel, Switzerland) at 54 rpm. Then the magnesium stearate was added, followed by further mixing for 5 min. This procedure was chosen in order to lessen the deleterious effect of magnesium stearate on the binding properties (Lerk et al., 1977).

The true densities of the powder mixtures were determined by Helium pycnometry (Stereopycometer SPY 2, Quantachrome, New York). Three samples of each mixture were analysed, each sample was read five times, the overall means were used.

The mixtures were stored for at least 30 days at the climatic conditions for tabletting.

2.3. Tabletting

2.3.1. Tooling

A reciprocating tabletting machine (Hanseaten Exacta XI, W. Fette GmbH, Schwarzenbeck, Germany) equipped with a standard filling shoe was used. The tooling has been described in detail by Flemming and Mielck (1996). Punch holders are equipped with several punches of 1.5, 2, 3 and 5 mm diameter, respectively, and a die holder is equipped with the matching dies. Because of the poor flow properties of the mixtures, three punches were arranged in a row (two punches in the case of 5 mm), in order to reduce weight differences by filling all dies at the same time (Fig. 1) by the standard filling shoe.

The punches are curved (deep concave), all with the same relative radius of curvature, r, of $0.7 \times d$, the diameter of the punch.

2.3.2. Force measurement

The punchholders are equipped with strain gauges, which have been calibrated quasi statically using a calibrated load cell (GTM-K-6, Gassmann Theiss Meßtechnik, Seeheim-Jungenheim, Germany).

The signals were amplified and recorded in the same way as described in Section 2.3.4. The results of calibration are equivalent to those of Flemming and Mielck (1996).

Fig. 1. Arrangement of punches in parallel to the leading edge of the filling, to continuously produce tablets on an eccentric tabletting machine.

2.3.3. Displacement measurement

The distance between the edge of the cap holding the upper punches and the base of the lower punch holder was measured using a remote inductive transducer (NCDT 300, Micro Epsilon Meßtechnik, Ortenburg, Germany).

The sensor is mounted at the cap of the upper punch holder, in the same way as described by Flemming (1998). However, the target was mounted to the lower piston via a connector. The force-related deformation of the punches was calculated by means of the elastic moduli. Therefore, the measured length of the punches was reduced by the height of a cylinder which has the diameter of the corresponding punch and the volume of the segment of the sphere formed by the punch curvature. The deformation of the lower punch holder was determined by measurement of the punch holder's reduction in length caused by known applied axial forces, which were induced via a massive upper punch. The equipment described for the displacement measurement was used, but with the sensor attached to the massive upper punch, assuming that the deformation of this upper punch could be neglected. By correcting the displacement data sampled during tabletting for deformation of the punches and the lower punch holder, the distance between the punch faces was calculated.

2.3.4. Sampling of data

The strain gauges were connected to a digital amplifier system (MGC/MC55 S6, Hottinger Baldwin Meßtechnik, Darmstadt, Germany). These signals, and the signals of the remote inductive transducer were digitized and registered by a 16-bit A/D converter (DT 2827, Data Translation Inc., Malboro, MA) and stored on a PC (32-20, Siemens AG, München, Germany) using the software system ASYST 4.0 (Keithley Instruments, Inc., Taunton, MA). Further handling of the data was done using ASYST and EXCEL (Microsoft Corporation).

2.3.5. Tabletting conditions

A low tabletting speed was chosen (24 ± 1 strokes/min) in order to prevent capping due to entrapped air (Mann et al., 1983).

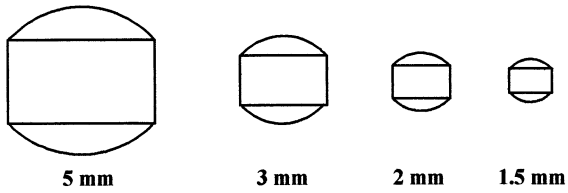

Fig. 2. Tablet sizes and geometrical proportions of tablets (ratio of overall thickness to diameter at maximum densification is equal to one for all sizes).

The tabletting room was conditioned at 22.5 ± 1°C and 39 ± 1% r.h.

2.3.6. Tabletting procedure

The mixtures were compressed into tablets of 1.5, 2, 3 and 5 mm diameter to graded relative densities ($\rho_{\text{apparent}} \cdot \rho_{\text{true}}^{-1}$) at minimum distance between punch faces. Very high maximum relative densities (between 0.90 and 0.99) were chosen in order to provoke capping. Furthermore, the eccentric was adjusted carefully in order to obtain a ratio between overall thickness and diameter of the tablets at the minimum distance between punch faces of one for all tablet diameters. By using curved punches with equal relative radius of curvature (Section 2.3.1), tablets with very similar geometrical proportions, only differing in scale or in content of paracetamol were to be compared (Fig. 2).

This geometrical similarity was the reason for the compressing to graded maximum relative densities instead of graded maximum pressures as the endpoint of the compression phase. The maximum degree of densification can be set precisely by setting the travel of the upper punch and regarding elastic deformation of the punches. In contrast, precisely graded maximum pressures while simultaneously maintaining geometrical similarity can only be achieved by trial and error.

2.4. Physical analysis of the tablets

2.4.1. Apparent tensile strength (ts_{app})

A diametral compression test was performed after 24 h with an Erweka TBH 28 (Erweka Apparatebau, Heusenstamm, Germany) with an accuracy of 1 N. All tablets from five successive

compression cycles were tested, i.e. 15 of the 1.5-, 2- and 3-mm tablets, and ten of the 5-mm tablets, respectively.

The apparent tensile strength was calculated as described by Fell and Newton (1970), using the overall thickness of the tablet.

2.4.2. Capping during diametral compression test (C_D)

The fragments, which had been generated by the diametral compression test, were examined visually and classified using a point system, as shown in Fig. 3. It must be noted that capping occurred only on the upper side of the tablet, because of the higher pressure achieved during the one-sided compression. Nearly 100% of the fragments fitted with one of the fragmentation types shown. The sum of a group of 15 and ten tablets, respectively, was divided by the highest possible number of points and than multiplied by 100. The resulting value C_D should give an impression of the proneness to capping of the tablets.

2.4.3. Capacity for active drug

In order to evaluate the capacity of DCL 11 for paracetamol in relation to tablet size, a method similar to that suggested by Minchom and Armstrong (1987) was used. The apparent tensile strength was plotted against the upper punch pressure and a quadratic regression of the former on the latter was performed, followed by integration of the regression curve between fixed points. The resulting areas under the curves were normalized with respect to the area for 0% paracetamol content. The resulting values, A_{rel}, were plotted against the amount of paracetamol to get a visual impression of the change of capacity of DCL 11 for paracetamol with decreasing tablet size. Extrapolation of a linear regression, resulting in an intercept indicating a definite paracetamol content as it is suggested by Minchom and Armstrong (1987), was not thought justified because of the small number of mixtures tested.

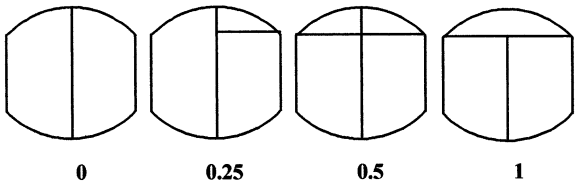

Fig. 3. Fragmentation types of tablets at the diametral compression test, and numbers assigned for calculation of C_D.

2.4.4. Capping tendency (C_F)

The determination of capping tendency was performed as suggested by Nyström et al. (1978) using a Roche friabilator (Erweka). Ten tablets were placed into the friabilator and rotated 500 times at 40 rpm. After ten revolutions, the amount of tablets capped was determined, replacing the capped tablets by stabile tablets with the same size.

The numbers of capped tablets were plotted against the number of revolutions, and a linear regression was performed. The slope of the regression line, C_F, is used as an indication for the capping tendency.

3. Results and discussion

Eq. (1) is used frequently for the calculation of the tensile strength, σ_0, of flat-faced, but not of convex-faced, tablets at the diametral compression test (Fell and Newton, 1970).

$$\sigma_0 = \frac{2P}{\pi \cdot D \cdot t} \quad (1)$$

where P is fracture load, t is tablet thickness and D is diameter.

We used this equation even though convex-faced tablets were produced, because the tensile strength of these tablets should be closely related to the overall tablet thickness due to the high ratio between central cylinder thickness and diameter (Pitt et al., 1988). Therefore Eq. (1) results in an apparent tensile strength of the tablets produced in this study. This apparent tensile strength, ts_{app}, may be used for the comparison of the tablets with differing size, because the error made can be taken as constant due to the geometrical specifications.

The equation for determination of the tensile strength, σ_f, of convex-faced tablets (Eq. (2)) developed by Pitt et al. (1988), which is based on a

stress analysis with dimensional considerations, could not be used because of the different ratios between central cylinder thickness and diameter, which were between 0.06 and 0.3 for the tablets investigated by Pitt et al. (1988) and 0.6 for the tablets produced in this investigation.

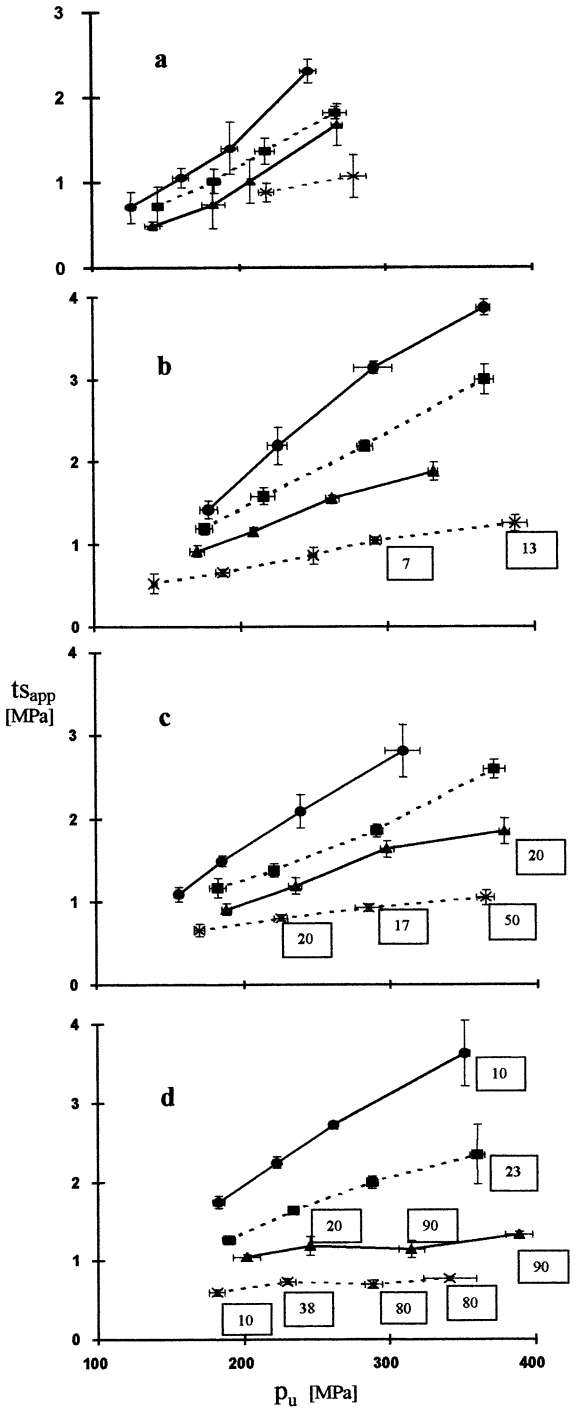

Fig. 4.

$$\sigma_f = \frac{10P}{\pi D^2}\left(2.84\,\frac{t}{D} - 0.126\,\frac{t}{W} + 3.15\,\frac{W}{D} + 0.01\right)^{-1} \quad (2)$$

where P is fracture load, t is overall tablet thickness, D is diameter and W is central cylinder thickness.

If we apply Eq. (2), nevertheless, certain simplifications can be adopted because of the geometric specifications of the tablets. Because of the tabletting procedure and because of the constant relative curvature of the punches, one may assume that the ratio between central cylinder thickness and diameter and the ratio between overall thickness and diameter are constant. Therefore the ratios t/D, t/W and W/D, and therefore the term inside of the parentheses, may be taken as constant.

Eq. (2) then transforms into Eq. (3)

$$\sigma_f = \frac{2P}{\pi \cdot D \cdot t}(K)^{-1} \quad (3)$$

where K is a constant, which represents the error made by applying Eq. (1) for the tablets produced in this investigation but, because of the considerations mentioned above, K cannot be determined precisely without stress analysis.

Although the true values of the tensile strength have not been determined, tablets with the same geometrical proportions may be compared, under the assumption that the error is constant. The variable ts_{app} would then correspond to $\sigma_f \cdot K$ in Eq. (3).

Fig. 4. Apparent tensile strength, ts_{app}, of tablets from mixtures of Pharmatose® DCL 11, 0.5% magnesium stearate, 0.5% Aerosil® 200 and increasing content of paracetamol as a function of maximum pressure at the upper punch, pu, (mean values ± S.D., $n = 5$): (●) 0%; (■) 10%; (▲) 30%; (×) 50% paracetamol (w/w); (a) 1.5 mm, (b) 2 mm, (c) 3 mm and (d) 5 mm tablet diameter; rectangles indicate values for capping tendency during diametral compression, C_D.

The mechanical stability of tablets of different paracetamol content is shown in Fig. 4 by means of compaction profiles, i.e. apparent tensile strength as a function of maximum pressure at the upper punch, separately for each tablet diameter. The pressure increases with increasing maximum relative density. The values within the rectangles represent the corresponding C_D values, which are also listed in Table 1. Values for $C_D = 0$ are not printed. All figures show that, with increasing content of paracetamol, the tensile strength and the slope of the curves decrease. No capping was noticed with the 1.5-mm tablets (Fig. 4a). No further conclusion can be drawn, because of the high standard deviations caused by the low fracture loads measured. Tablets containing 50% paracetamol, which had been compressed to low relative densities, could not be tested with the TBH 28 because of the limited sensitivity and the low fracture loads. The 2-mm tablets containing 50% paracetamol compressed to high relative densities show low C_D values which correlates with a slight flattening of the curve at higher pressures (Fig. 4b). This is also evident for the mixture with 30% paracetamol, where no capping was detected. The correlation between slope and C_D values becomes more obvious with the 3-mm tablets (Fig. 4c). The slope of the curve for 50% paracetamol is lower than the slopes of the other curves and is accompanied by high C_D values up to 50. The curve for 30% paracetamol also flattens out at the highest pressure accompanied by a C_D value of 20. Tablets of 5 mm diameter (Fig. 4d) containing 30 and 50% paracetamol demonstrate no significant increase in apparent tensile strength with increasing pressure. This is connected with high C_D values up to 90. The 5-mm tablets produced at high pressure containing 0 and 10% paracetamol show C_D values of 10 and 23, which is connected with high standard deviations of the apparent tensile strength, compared to the values at lower pressures, also indicating capping tendencies (Alderborn and Nyström, 1984). Looking at Table 1, one could notice an increase of C_D with increasing maximum relative density, which is equivalent to increasing upper punch pressure, and increasing content of paracetamol. This was expected. But one could also see an increase of C_D with increasing diameter of the tablets.

Table 1
Capping tendency, C_D, for different tablet diameters, d, and content of paracetamol, P

d (mm)	P (%)	D					
		0.906	0.925	0.945	0.963	0.985	0.995
1.5	0	—	0	0	0	0	—
	10	—	0	0	0	0	—
	30	—	0	0	0	0	—
	50	—	—	—	0	0	—
2	0	0	0	—	0	0	—
	10	0	0	—	0	0	—
	30	0	0	—	0	0	—
	50	0	0	—	0	7	13
3	0	0	0	0	0	—	—
	10	0	0	0	0	—	—
	30	0	0	0	20	—	—
	50	0	20	17	50	—	—
5	0	0	0	0	10	—	—
	10	0	0	0	23	—	—
	30	0	20	90	90	—	—
	50	10	38	80	80	—	—

D, maximum relative density.

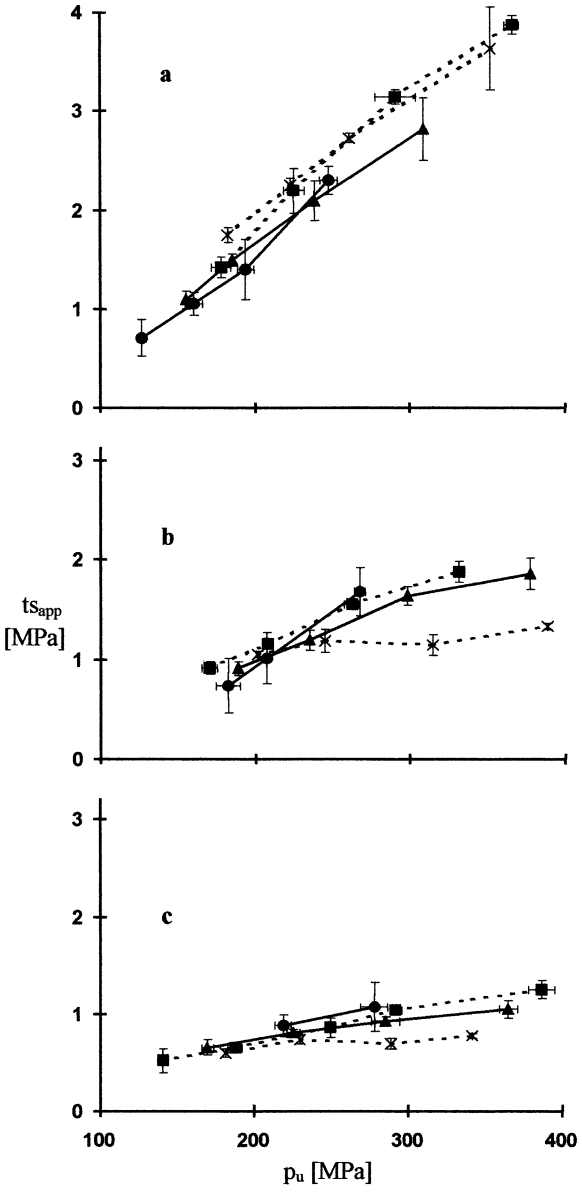

Fig. 5. Tensile strength, ts_{app}, of tablets from mixtures of paracetamol, Pharmatose® DCL 11, 0.5% magnesium stearate and 0.5% Aerosil® 200 for increasing tablet diameter as function of maximum pressure at the upper punch, pu, (mean values ± S.D., $n = 5$): (●) 1.5 mm; (■) 2 mm; (▲) 3 mm; (×) 5 mm diameter; (a) 0% paracetamol, (b) 30% paracetamol and (c) 50% paracetamol (w/w).

Fig. 5 demonstrates the effect of tablet diameter on the mechanical stability of tablets by means of compaction profiles for three different paracetamol contents (0, 30, 50%). The mixture containing 0% paracetamol demonstrates the usual increase of apparent tensile strength with increasing pressure (Fig. 5a), but no clear difference between the tablet diameters can be noticed. At a content of 30% paracetamol (Fig. 5b) for tablets with a greater diameter the increase of the apparent tensile strength diminishes at higher pressure. This leads to a increasing tensile strength with decreasing diameter at high pressures. The same phenomenon can be seen in Fig. 5c, where the data for the mixtures with 50% paracetamol are shown.

Fig. 6 illustrates the change in capacity of DCL 11 for paracetamol with tablet diameter by normalised values for the area under the respective compression profiles, A_{rel} (Section 2.4.1). Because small A_{rel} values indicate a deleterious effect on the tablet strength, it can be seen that the weakening influence of the increasing paracetamol content decreases with decreasing diameter of the tablets. This means that the capacity of DCL 11 for paracetamol increases with decreasing tablet diameter.

The capping tendency C_F, as determined according to Nyström et al. (1978) in Table 2, increases with increasing maximum relative density, which is equivalent to increasing upper punch pressure with increasing content of parac-

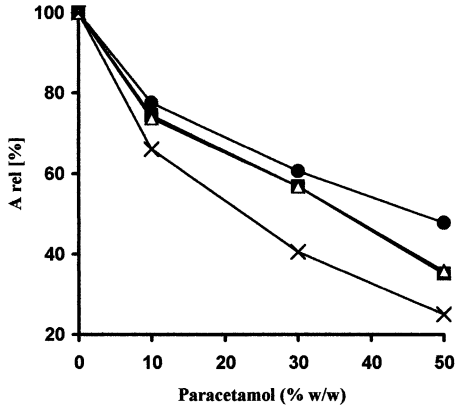

Fig. 6. Capacity of Pharmatose® DCL 11 for paracetamol, expressed as relative areas under the compaction profile, A_{rel}, for mixtures of DCL 11 with increasing content of paracetamol (w/w) relative to the area for pure DCL 11, at different tablet diameters: (●) 1.5 mm, (■) 2 mm, (▲) 3 mm and (×) 5 mm diameter.

Table 2
Capping tendency, C_F, according to Nyström et al. (1978) for different tablet diameters, d, and content of paracetamol, P

d (mm)	P (%)	D					
		0.906	0.925	0.945	0.963	0.985	0.99
1.5	0	—	0	0	0	0	—
	10	—	0	0	0	0	—
	30	—	0	0	0	0	—
	50	0	0	0	0	0	—
2	0	0	0	—	0	0	—
	10	0	0	—	0	0	—
	30	2.3	0	—	0	0	—
	50	3.0	0	—	0	0	0
3	0	0	0	0	0	—	—
	10	0	0	0	0	—	—
	30	0	0	0	0	—	—
	50	0	0	2.6	12.1	—	—
5	0	0	0	0	1.2	—	—
	10	0	0	0	1.3	—	—
	30	0	0	5.2	22.7	—	—
	50	1.2	3.2	9.6	13.9	—	—

D, maximum relative density.

etamol, and with increasing diameter. It must be noted, however, that the stress inside the friabilator also increases with increasing diameter.

Looking at the results of this study it is obvious that the mechanical stability of minitablets containing paracetamol is equal to, and at high pressures higher than, that of normal-sized tablets, and that the weakening influence of paracetamol is lower.

The often proposed reason for a higher strength of smaller tablets is the flaw distribution inside the tablet. Because of the reduced size of the tablet, the possibility for a flaw of a given severity leading to tablet failure should also be reduced (Davies and Newton, 1996). However, the results of this work indicate a higher strength of smaller tablets only at high pressures and high paracetamol content, due to reduced capping of the minitablets. Therefore the flaw distribution cannot completely explain these results.

The reason for the higher mechanical stability of minitablets, as demonstrated by the compression profiles and increase in capacity of a d.c. excipient derived therefrom, as well as reduced capping tendency, quantifiable both by C_D and C_F values, may lie in the main difference between minitablets and normal-sized tablets, namely the ratio between the outer surface and volume of the tablet. This ratio increases with decreasing tablet size, leading to a higher relative amount of material exposed to the surfaces of punches and die. Consequently the region of volume exposed to shear stress, which is connected with die wall friction, is larger in relation to the total volume of the mass in the die forming the tablet. This will result in a higher relative amount of shear stress which leads to a wider distribution of relative density over the volume of the tablet and thus locally to more binding sites without necessarily increasing the elastic deformation of the particles. This possibly forms a protecting shell around the tablet, which enhances strength and prevents capping. Such a shell could be expected for all tablet sizes, but with decreasing tablet size it may become more predominant, especially in ranges smaller than 3 mm diameter of the tablet.

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References

Alderborn, G., Nyström, C., 1984. Radial and axial tensile strength and strength variability of paracetamol tablets. Acta Pharm. Suec. 21, 1–8.

Arreco, D., Bassi, M., Gabrielli, B., Merlini, A., 1976. Tecnologia delle polveri farmaceutiche: compresse a tecnologia speziale. Boll. Chim. Farm. 115, 680–701.

Bangadu, A.B., Pilpel, N., 1985. Effects of composition, moisture and steric acid on the plasto–elasticity and tableting of paracetamol–microcrystalline cellulose mixtures. J. Pharm. Pharmacol. 37, 289–293.

Carless, J.E., Leigh, S., 1974. Compression characteristics of powders: radial die wall pressure transmission and density changes. J. Pharm. Pharmacol. 26, 289–297.

Davies, P.N., Newton, J.M., 1996. Mechanical strength. In: Alderborn, G., Nyström, C. (Eds.), Pharmaceutical Powder Compaction Technology (Drugs and the Pharmaceutical Sciences Series/71). Marcel Decker, New York, p. 181.

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.

Ettabia, A., Joiris, E., Guyot-Hermann, A.-M., Guyot, J.-C., 1997. Preparation of a pure paracetamol for direct compression by spherical agglomeration. Pharm. Ind. 59, 625–631.

Fachaux, J.M., Guyot-Hermann, A.-M., Guyot, J.-C., Conflant, P., Drache, M., Huvenne, J.P., Bouche, R., 1993. Compression ability improvement by solvation/desolvation process: application to paracetamol for direct compression. Int. J. Pharm. 99, 99–107.

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

Femi-Oyewo, M.N., Spring, M.S., 1994. Studies on paracetamol crystals produced by growth in aqueous solutions. Int. J. Pharm. 112, 17–28.

Flemming, J., 1998. Experimentelle Mikrotablettierung: Fließeigenschaften von Hilfsstoffen und Tablettierverhalten von Cellactose® bei Herstellung von Tabletten mit einem Durchmesser von 5 bis 1.5 mm. Ph.D. Thesis, University of Hamburg.

Flemming, J., Mielck, J.B., 1995. Requirements for the production of micro tablets: Suitability of direct-compression excipients estimated from powder characteristics and flow rates. Drug Dev. Ind. Pharm. 21, 2239–2251.

Flemming, J., Mielck, J.B., 1996. Experimental micro tableting: construction of an instrumented punch holder for an eccentric tabletting machine. Eur. J. Pharm. Biopharm. 42, 212–214.

Hershberg, E.B., 1965. Apparatus for punching miniature tablets. US Patent 3 175 521, 30 March.

Hiestand, E.N., Wells, J.E., Poet, C.B., Ochs, J.F., 1977. The physical process of tabletting. J. Pharm. Sci. 66, 510–519.

Hong-guang, W., Ru-hua, Z., 1995. Compaction behavior of paracetamol powders of different crystal shapes. Drug. Dev. Ind. Pharm. 21, 863–868.

Jacob, J., Hüttenrauch, R., 1982. Abhängigkeit der Preßdruckverteilung von der Tablettengeometrie. Acta Pharm. Technol. 28 (1), 44–52.

Jetzer, W., Leuenberger, H., 1984. Zur Bestimmung der Deckeltendenz von pharmazeutischen Wirk- und Hilfsstoffen. Pharm. Acta Helv. 59, 2–7.

Kennerley, J.W., Newton, J.M., Stanley, P., 1977. The influence of dimensions on the strength and strength variability of tablets. J. Pharm. Pharmacol. 29, 39p.

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

Leigh, S., Carless, J.E., Burt, B.W., 1967. Compression characteristics of some pharmaceutical materials. J. Pharm. Sci. 56, 888–892.

Lerk, C.F., Bolhuis, G.K., Smedema, S.S., 1977. Interaction of lubricants and colloidal silica during mixing with exipients. Pharm. Acta Helv. 52, 33–39.

Lin, M.-C., Duncan-Hewitt, W.C., 1994. Deformation kinetics of acetaminophen crystals. Int. J. Pharm. 106, 187–200.

Malamataris, S., bin Baie, S., Pilpel, N., 1984. Plasto-elasticity and tableting of paracetamol, avicel and other powders. J. Pharm. Pharmacol. 36, 616–617.

Malamataris, S., Hatjichristos, Th., Rees, J.E., 1996. Apparent compressive elastic modulus and strength isotropy compacts formed from binary powder mixes. Int. J. Pharm. 141, 101–108.

Mann, S.C., Roberts, R.J., Rowe, R.C., Hunter, B.M., Rees, J.E., 1983. The effect of high speed compression at sub-atmospheric pressures on capping tendency of pharmaceutical tablets. J. Pharm. Pharmacol. 35, 44p.

Minchom, C.M., Armstrong, N.A., 1987. A proposed technique for expressing the capacity of directly compressible tablet diluents. J. Pharm. Pharmacol. 39, 69p.

Mollan, M.J. Jr., Celik, M., 1994. Tabletability of maltodextrins and acetaminophen mixtures. Drug Dev. Ind. Pharm. 20, 3131–3149.

Munday, D.L., 1994. A comparison of the dissolution characteristics of theophylline from film coated granules and mini-tablets. Drug Dev. Ind. Pharm. 20, 2369–2379.

Munday, D.L., Fassihi, A.R., 1989. Controlled release delivery: effect of coating composition on release characteristics of mini-tablets. Int. J. Pharm. 52, 109–114.

Nyström, C., Glazer, M., 1985. Studies on direct compression of tablets. XIII. The effect of some dry binders on the tablet strength of compounds with different fragmentation propensity. Int. J. Pharm. 23, 255–263.

Nyström, C., Malmqvist, K., Mazur, J., Alex, W., Hölzer, A.W., 1978. Measurement of axial and radial tensile strength of tablets and their relation to capping. Acta Pharm. Suec. 15, 226–232.

Parmentier, W., 1980. Warum deckeln Tabletten? Pharm. Ind. 42, 752–756.

Peck, G.E., Balay, G.J., McCurdy, V.E., Banker, G.S., 1989. Tablet formulation and design. In: Lieberman, H.A., Lachman, L., Schwartz, J.B. (Eds.), Pharmaceutical Dosage Forms: Tablets, vol. 1, 2nd ed. Marcel Decker, New York, p. 98.

Pich, C.H., Moest, T., 1989. Magensaftresistent überzogene zylindrische Pankreatin-Mikrotabletten. EU Patent EP 0 166 315 B1, 8 August.

Pitt, K.G., Newton, J.M., Stanley, P., 1988. Tensile fracture of doubly-convex cylindrical discs under diametral loading. J. Mater. Sci. 23, 2732–2738.

Satteone, M.F., Chetoni, P., Torraca, M.T., Giannaccini, B., Naber, L., Conte, U., Sangalli, M.E., Gazzaniga, A., 1990. Application of the compression technique to the manufacture of pilocarpine opthalmic inserts. Acta Pharm. Technol. 36, 15–19.

Satteone, M.F., Chetoni, P., Mariotti Bianchi, L., Giannaccini, B., Conte, U., Sangalli, M.E., 1995. Controlled release of timolol maleate from coated ophthalmic minitablets prepared by compression. Int. J. Pharm. 126, 79–82.

Shangraw, R.F., 1989. Compressed tablets by direct compression. In: Lieberman, H.A., Lachman, L., Schwartz, J.B. (Eds.) Pharmaceutical Dosage Forms: Tablets, vol. 1, 2nd ed. Marcel Decker, New York, p. 205.

Stanley, P., Newton, J.M., 1977. Variability in the strength of powder compacts. J. Powder Bulk Solids Technol. 1, 13–19.

Wells, J.I., Langridge, J.R., 1981. Dicalcium pholphate dihydrate—microcrystalline cellulose systems in direct compression tabletting. Int. J. Pharm. Technol. Prod. Mfr. 2, 1–8.