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Effect of pellet size on degree of deformation and densification during compression and on compactability of microcrystalline cellulose pellets

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Abstract

Microcrystalline cellulose pellets (size fractions 425–500 and 1250–1400 μm, porosity 38%) were prepared and compacted. The porosity and tensile strength of tablets of unlubricated pellets were determined. Tablets of lubricated pellets were deaggregated and the porosity and the main dimensions of the retrieved pellets were measured. The dominating mechanisms of compression for the pellets were deformation and densification. The original size of the pellets did not affect the volume or porosity changes of the tablet with tablet formation pressure. Consequently, the degree of densification of individual pellets, which occured during compression, was independent of the original pellet size. However, the degree of deformation of individual pellets during compression was higher for larger pellets. There was thus a different dependence of pellet size for the dominating mechanisms of compression for this type of aggregates. An explanation for this is that deformation is a phenomenon related to the force distribution in the pellet bed during compression, while densification is related to the total stress applied to the pellet bed during compression. The results obtained in this study have also shown that the compactability of pellets at moderate applied pressures was independent of the original pellet size, but at 160 MPa, the larger pellets formed tablets of a slightly higher tensile strength.

Keywords: Microcrystalline cellulose; Compaction; Pellet size; Pellet deformation; Pellet densification; Tablet porosity; Tablet tensile strength

1. Introduction

Particles prepared by aggregation of smaller particles—drugs and excipients—represent the most common type of particles handled in phar-

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maceutical tablet production. A series of compression mechanisms has been suggested to be involved in the compression process for such aggregates (Alderborn and Wikberg, 1996), i.e. repositioning, deformation, densification, fragmentation and attrition of aggregates. In most of these studies, aggregates of irregular shape have been used and it has thus been difficult to obtain conclusive results on relevant compression mechanisms. Also, the possibility to quantitate the compression behaviour in terms of the degree of occurrence of the compression mechanisms has been limited. In two recent studies (Johansson et al., 1995; Johansson and Alderborn, 1996), the compression behaviour of pelletised aggregates of microcrystalline cellulose has been investigated. It was concluded that for these pellets, the relevant compression mechanisms was permanent deformation, (i.e. a change in the shape of the individual pellets) and densification, (i.e. contraction or porosity reduction of the individual pellets) and that fragmentation of pellets was minute. Deformation and densification were parallel phenomena and were controlled by the porosity of the pellets before compression. However, these data were obtained for pellets of similar original size.

There are few studies in the literature which have specifically reported a relationship between original pellet size and the compression behaviour of the pellets. Adams and McKeown (1996) derived an agglomerate strength from compression data and suggested that this strength was independent of pellet size. For slow release coated pellets, it has been concluded (Béchard and Leroux, 1992; Ragnarsson et al., 1992) that the coating on small pellets was less affected by the compression process than the coating on larger pellets, in terms of the release of the drug from the pellets. A possible explanation is that small pellets tend to deform or densify to a lesser degree during tabletting than coarser pellets.

In the studies on the compression behaviour of the microcrystalline cellulose pellets (Johansson et al., 1995; Johansson and Alderborn, 1996), it was shown that the compactability of the pellets (as measured by the tensile strength of the tablets) was also controlled by the pellet porosity. Other studies on the compactability of granules have indicated that also, the size of the aggregates can affect their compactability. The most frequently reported effect of granule size seems to be that reduction in size corresponds with an increase in tablet strength (Li and Peck, 1990; Wikberg and Alderborn, 1990a; Riepma et al., 1993). However, Bangudu et al. (1991) reported that the tablet strength was independent of granule size and the same finding was reported by Rehula (1985) for granules of the size 0.26–1.5 mm. In the latter study, the strength of the tablets did increase when granules >1.5 mm were compacted.

The original size of granules and pellets seems to be an important property which can affect the compression and compaction properties of aggregates and affect the structure and thus, the pharmaceutical quality of the prepared tablets, such as the release of the drug from the preparation. There are however, no studies in the literature which have in detail, studied the effects of aggregate size on the compression behaviour of the aggregates. The aim of this study is to investigate the effect of original pellet size on the degree of pellet deformation and densification which occur during compression and on the compactability of pellets of microcrystalline cellulose.

2. Materials and methods

2.1. Materials

Microcrystalline cellulose (Avicel PH101, FMC, USA; apparent particle density 1.56 g/cm^3). Magnesium stearate (purchased from Apoteksbolaget AB, Sweden; apparent particle density 1.02 g/cm^3 and permeametry surface area 0.798 m^2/g). Ethanol 99.5% w/w (Finsprit Kemetyl, Sweden).

2.2. Preparation of pellets

Two size fractions of pellets were prepared. The pellet fraction 425–500 μm was prepared by wet agglomeration followed by spheronisation. The pellet fraction 1250–1400 μm was prepared by wet agglomeration and extrusion-spheronisation. The preparation procedure was designed to obtain the pellets of both sizes of similar porosity and acceptable sphericity.

The process variables during wet agglomeration are given in Table 1.

2.2.1. Wet agglomeration

The powder (200 g) was placed in a planetary mixer (Braun Multipractice Plus electronic UK20, Germany), equipped with a specially designed mixer blade and was dry mixed for 1 min at 750 rpm. The agglomeration liquid was poured into the mixing bowl and the wet mass was agitated at 750 rpm for a further 3 min.

2.2.2. Extrusion

The wet powder mass was immediately extruded at 70 rpm through a radial screen extruder (model E140, Nica system, Sweden), supplied with a 1.5 mm thick screen with a screen opening diameter of 1.5 mm.

2.2.3. Spheronisation

A radial plate spheroniser with a plate diameter of 45.0 cm was used (model S450, Nica system, Sweden). The wet powder mass or the extrudate was spheronised for 1 min as the speed was increased from 0 to 1220 rpm and then for 2 min at the full speed, 1220 rpm. The wet pellets were dried in a tray drier overnight and the two size fractions were separated by sieving. The pellets were stored in a desiccator at 40% relative humidity and room temperature for 3 days before any further treatment.

Table 1
Wet agglomeration conditions

Size	425–500 μm	1250–1400 μm
Agglomeration liquid	Ethanol/water 70/30	Ethanol/water 70/30
Amount of agglomeration liquid (g)	180	240
Addition rate (g/min)	90	120
Wet massing time (min)	3	3
Pelletization procedure	Spheronization	Extrusion-spheronization

2.3. Characterisation of pellets

2.3.1. Bulk densities

The pellets were poured into a 50 ml cylinder (inner diameter 25 mm) to a vol. of 50 ml and the poured as well as the tapped (after 160 taps) density was determined using a tap volumeter (Eberhard Bauer D7300, Germany) ($n = 3$).

2.3.2. Pellet porosity

The porosity of the pellets was calculated from both the apparent and the effective particle densities ($n = 2$–3). The apparent particle density was measured using a helium pycnometer (Micromeritics Accypuc 1330, USA). The effective particle density was determined using mercury pycnometry as described by Wikberg and Alderborn (1990b).

2.3.3. External surface area

The surface areas of the pellets were determined using a steady state permeameter. The pellets were poured manually into the container to a height of ≈ 55 cm. The container was tapped ten times and the height and weight were recorded. The container was connected to a Blaine apparatus which was used as a water manometer to detect the pressure drop over the bed of pellets. Air was pumped through the bed at a series of controlled flow rates (Brook flow meter, model 5850E, Brook Instruments B.V., The Netherlands) and the corresponding pressure drop was recorded. The permeametry surface area ($n = 3$) was calculated according to Eriksson et al. (1993).

2.3.4. Determination of pellet dimensions

Median values based on a number distribution of the breadth, length and thickness of the pellets were determined and calculated as described earlier (Johansson and Alderborn, 1996). The shape of the pellets was evaluated by calculating the elongation ratio and the flakiness ratio from the pellet dimensions as described by Johansson and Alderborn (1996).

2.4. Preparation and deaggregation of tablets from lubricated pellets

The pellets were mixed for 100 min with an amount of magnesium stearate corresponding to 5 μg per cm^2 external pellet surface area in a Turbula mixer (Willis A. Bachofen, Switzerland) at 90 rpm. The lubricated pellets were stored in a desiccator at 40% relative humidity for at least 5 days before any characterisation or tabletting.

Tablets of lubricated pellets were compacted in an instrumented single punch press (Korsch EK 0, Germany) at applied pressures of 10, 20, 40 and 80 MPa. The press was equipped with flat-faced punches with a diameter of 1.5 cm. The position of the lower punch was adjusted to obtain the required pressure. An amount of pellets corresponding to a compact height of at least ten pellet layers (1.10 g) was chosen. The amount was weighed on an analytical balance and then manually poured into the die. The die wall was lubricated with a suspension of 1% w/w magnesium stearate in ethanol before each compaction. The force of the upper punch was recorded and its displacement was registered as described earlier (Alderborn et al., 1987) during the compression at 80 MPa. The degree of compression of the pellet mass during compression was calculated according to Johansson et al. (1995).

After compaction, the tablets were placed in a petri dish and the petri dish was then shaken carefully by hand until the tablets fell apart completely. The pellets thus obtained are hereafter referred to as retrieved pellets (Johansson and Alderborn, 1996).

2.5. Characterisation of pellets from deaggregated tablets

The dimensions and the porosity of the retrieved pellets were determined as described above.

2.6. Preparation and characterisation of tablets from unlubricated pellets

Tablets were prepared from unlubricated pellets of both size fractions at applied pressures of 10, 20, 40, 80 and 160 MPa. Five tablets were compacted at pressures of 10–80 MPa and seven tablets at 160 MPa as described above and the degree of compression was calculated from the punch displacement signal at 80 MPa, as described earlier (Johansson et al., 1995). After compaction, the tablets were stored in a desiccator at 40% relative humidity and room temperature for not less than 3 days before any characterisation.

The tablets prepared at 10, 20, 40 and 80 MPa were loaded diametrically using a tablet hardness tester (Holland C50, U.K.) at a loading rate of 4 mm/min until they fractured in tension. Tablets prepared at 160 MPa were loaded diametrically in a materials testing machine (model M39K, J. J. Lloyd Instruments, U.K.) at a loading rate of 5 mm/min. The tensile strength was derived from the force needed to fracture the tablets, as described by Fell and Newton (1970).

The total porosity of each compact was calculated from the weight and height of the compact and the apparent particle density of the pellets ($n = 5$). The intergranular porosity of the compact was also calculated, as described earlier (Johansson and Alderborn, 1996).

3. Results

3.1. Dimensions, shape and porosity of pellets before compression

Inspection of the pellets in a scanning electron microscope (Philips SEM 525, The Netherlands) showed that they were generally almost spherical in shape (Fig. 1a,b). This was confirmed by the measures of dimensions and shape of pellets (Tables 2 and 3). The inspection also showed that the surface of the pellets was relatively smooth. The external surface area of the large pellets was almost 3-fold less than that of the smaller ones (60 vs. 141 cm^2/g). However, the porosity of the pellets before compression was almost equal (Tables 2 and 3). Thus, it could be concluded that the two size fractions represented a suitable combination of materials for the study of the effects of pellet size on both volume reduction behaviour during compression and compactability.

(a)

(b)

Fig. 1. SEM photomicrographs of pellets before compression: (a) Small pellets 425–500 μm; and (b) large pellets 1250–1400 μm. The white bars denote 1 mm.

3.2. Degree of compression–applied pressure relationships

The relationship between the degree of compression and the applied pressure was assessed for both lubricated and unlubricated pellets in the pressure range 2–80 MPa. The degree of compression at 80 MPa was $\approx$55% for both size fractions of pellets, independently of the presence of lubricant. Thus, the tablet volume–applied pressure relationships in-die were not affected by size or the addition of the lubricant. This latter

Table 2
Dimensions, shape measures and intragranular porosity of pellets[d]

Applied pressure (MPa)	Breadth[a]	Length[a] (μm)	Thickness[b] (μm)	Elongation	Flakiness	Pellet porosity[c] (%)
0	468	521	435	1.11	1.06	37.9 (0.81)
10	467	529	418	1.13	1.09	36.7 (2.06)
20	470	538	402	1.14	1.12	34.5 (1.50)
40	476	551	376	1.16	1.22	28.4 (7.60)
80	494	571	344	1.16	1.36	20.8 (1.72)

[a] Median values from size distributions by number.
[b] Median values from size distributions by number, i.e. calculated from size distributions by weight.
[c] Arithmetic mean values with relative SD in brackets.
[d] From fraction 425–500 μm, before and after compression at pressures from 10–80 MPa.

finding is consistent with earlier results (Johansson and Alderborn, 1996). It is thus reasonable to assume that the compression behaviour of lubricated pellets, as assessed by changes in shape and porosity as discussed below, is representative of that in unlubricated pellets.

3.3. Dimensions, shape and porosity of compressed and retrieved pellets

The retrieval of individual pellets by deaggregation after compression resulted in pellets similar in size to the original pellets (this was valid for both size fractions), although at high applied pressures, some fragments of pellets were observed. The lack of fragmentation was supported by inspection of the pellets in a SEM (Fig. 2 a–d). The photomicrographs showed also that compression changed the shape of the pellets towards more irregular particles.

Increasing the pressure during compression changed the main dimensions of the retrieved pellets of both size fractions in such a way that the length and breadth increased and the thickness decreased (Tables 2 and 3). The overall effect was towards more elongated and flatter pellets as the applied pressure increased and the most pronounced effect of increased pressure was an increased particle flakiness. An examination of the fracture and the upper surfaces of the tablets (Fig. 3 a–d) showed that flattening of the pellets occurred mainly in the direction of the applied pressure. Flattening during compression was more marked for the larger pellets, while elongation occurred to a similar extent for pellets of both sizes (Tables 2 and 3). The porosity of the pellets decreased with increased pressure (Tables 2 and 3), independently of the original pellet size.

3.4. Porosity and tensile strength of compacts from unlubricated pellets

The total porosity of the compacts made from both size fractions of unlubricated pellets decreased due to a reduction in both intergranular and intragranular porosity during compression (Table 4). In particular, the intergranular porosity decreased dramatically, so that most of the air within the compact was located within the pellets at the higher applied pressures.

The tensile strength increased nearly rectilinearly with applied pressure for both size fractions of pellets (Fig. 4). The tensile strength was independent of the original pellet size at applied pressures up to 80 MPa. At 160 MPa, however, the tablets made from the larger pellets were significantly stronger ($p = 0.05$).

4. Discussion

4.1. Effect of pellet size on compression behaviour and mechanisms

The analysis of the retrieved pellets confirmed (Johansson and Alderborn, 1996) that pellets formed from microcrystalline cellulose showed minute fragmentation during compaction and that

Table 3
Dimension, shape measures and intragranular porosity of pellets

Applied pressure (MPa)	Breadth[a] (μm)	Length[a] (μm)	Thickness[b] (μm)	Elongation	Flakiness	Pellet porosity[c] (%)
0	1269	1387	1145	1.09	1.10	38.2 (0.42)
10	1264	1402	1097	1.11	1.13	36.8 (0.19)
20	1274	1427	1028	1.12	1.21	33.9 (0.44)
40	1293	1455	952.2	1.12	1.32	28.4 (3.50)
80	1347	1524	857.6	1.13	1.51	20.7 (0.37)

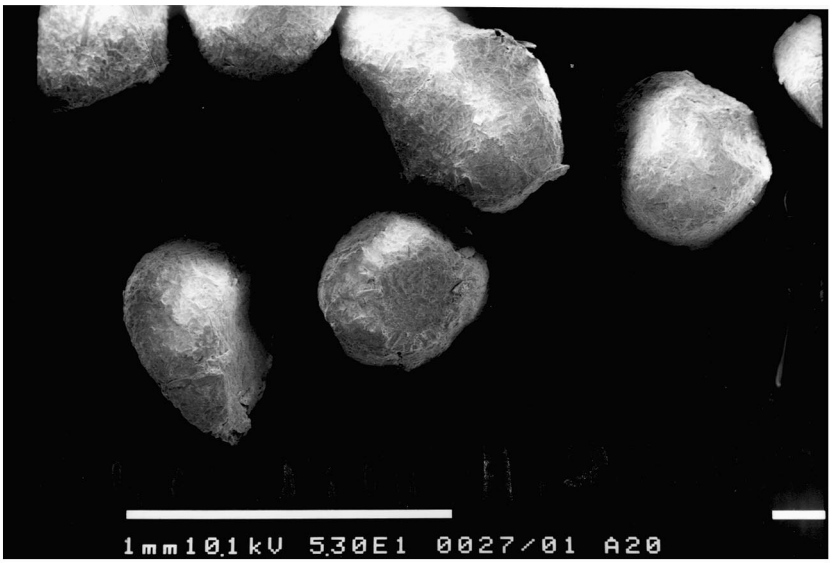
[a] Median values from size distributions by number.
[b] Median values from size distributions by number, i.e. calculated from size distributions by weight.
[c] Arithmetic mean values with relative SD in brackets.
[d] From fraction 1250–1400 μm, before and after compression at pressures from 10–80 MPa.

the significant mechanisms involved in the compression process were deformation and densification (contraction). However, our results indicate that the dependence of original pellet size for the degree of deformation and densification differ between these two mechanisms.

In terms of changes in tablet volume in-die and tablet porosity out-of-die (Table 4 and Fig. 5), the original pellet size did not affect the compression behaviour of the pellets. Earlier studies (Johansson et al., 1995; Johansson and Alderborn, 1996) have shown that a tablet formed of microcrystalline cellulose pellets can be described as a large aggregate of cohered pellets and the volume of air located within the tablet can consequently be subdivided into intra- and intergranular pores. Before compression, the inter- and intragranular porosities were similar for both types of pellets. During compression, the intergranular porosity was reduced markedly with applied pressure, indicating that the pellets can be described in general terms as markedly deformable particles. Also the intragranular porosity was reduced with applied pressure, i.e. the pellets densify or contract significantly, but not to the same degree as for the intergranular porosity. The process of removing air from the spaces between pellets was thus easier than the process of removing air from the interior of the pellets and, consequently, over a broad range of compaction pressures, most of the air within the tablets was located within the pellets. The relatively high total porosity of the tablets prepared from the pellets was thus a result of the fact that a considerable volume of air was located within the pellets also after compaction, while a marked pellet deformation gave an intergranular pore structure of low porosity. In terms of porosity changes, the pellet densification process and the process of removing air from the spaces between pellets was independent of the original pellet size.

Although the reduction in pellet porosity was independent of the pellet size, the larger pellets were deformed to a higher degree than the smaller ones during compression at pressures >10 MPa (Fig. 6). It seems reasonable that both densification and deformation of the pellets are the result of repositioning of the primary particles within the pellet, i.e. during compression, primary particles will flow or reposition within the pellets resulting in the pellets changing shape, but also with the consequence that some of the air located within the pellets is squeezed out of the pellets. However, the observations in this study indicate that densification and deformation of pellets with similar original porosities are controlled in different ways: The degree of pellet densification during compression was controlled only by the pressure or stress applied while the degree of deformation was controlled by both the applied pressure and the size of the pellets.

There might be different explanations for the effect of pellet size on the degree of deformation of the pellets during compression. Firstly, during uniaxial compression of an assembly of particles, it is normally assumed that the force applied to

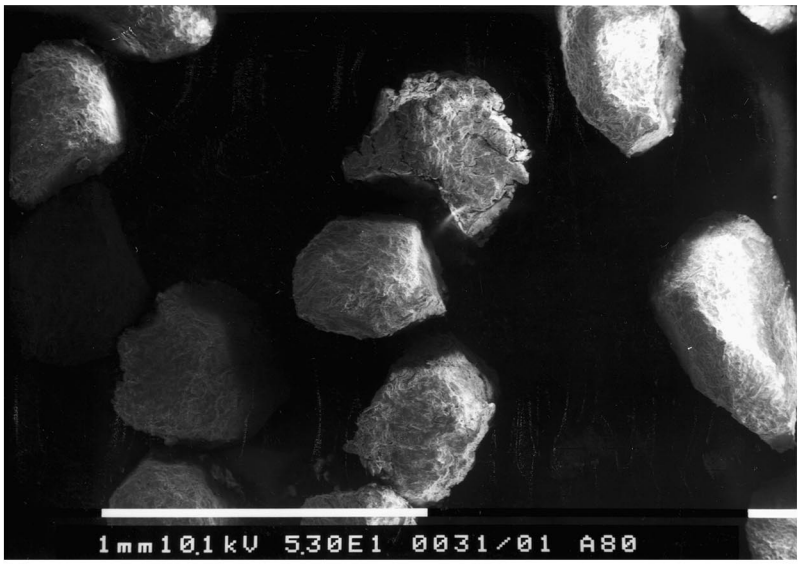


(a)

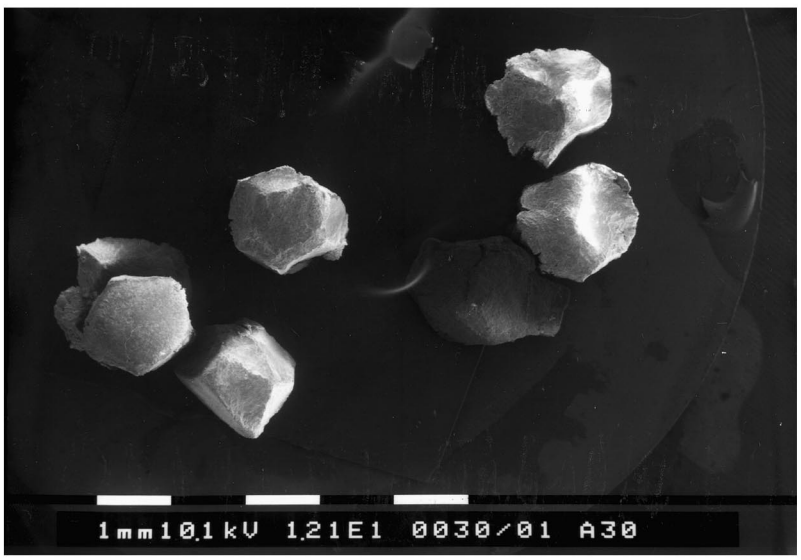
(b)

Fig. 2. SEM photomicrographs of retrieved pellets after compression at 20 and 80 MPa: (a) Small pellets 425–500 μm at 20 Mpa; (b) large pellets 1250–1400 μm at 20 MPa; (c) small pellets 425–500 μm at 80 MPa; (d) large pellets 1250–1400 μm at 80 MPa. The white bars denote 1 mm.

the powder is transmitted through the powder bed at points of interparticulate contact. Increasing the size of the particles will reduce the number of force transmission points. Thus, the contact force at each interparticulate contact point will increase, which might lead to increased pellet deformation. The consequence of this explanation is that deformation is a phenomenon related to the force distribution in the pellet bed during compression. Secondly, the pores between the pellets are probably larger for the larger pellets and larger spaces might allow a higher degree of de-



(c)

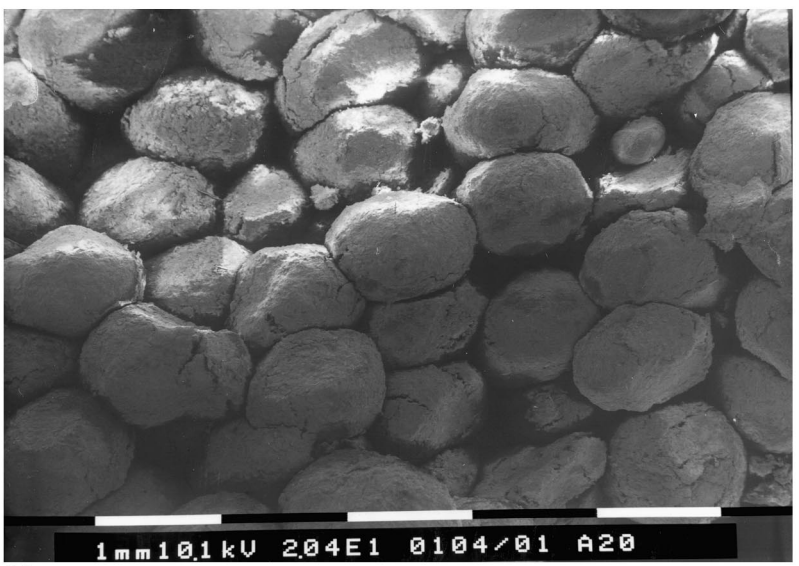


(d)

Fig. 2. (*Continued*)

formation, i.e. the size of the pores constitutes a restriction for continuing deformation. This might explain a reduced degree of deformation at very low intergranular tablet porosities but also, the more limited degree of deformation for smaller pellets. Finally, it seems reasonable that larger pellets have a larger probability for a wider distribution in porosity and pore size within the pellets. This variation can give rise to a higher deformability of the pellet if deformation occurs by a flow of primary particles within the pellets.

(a)

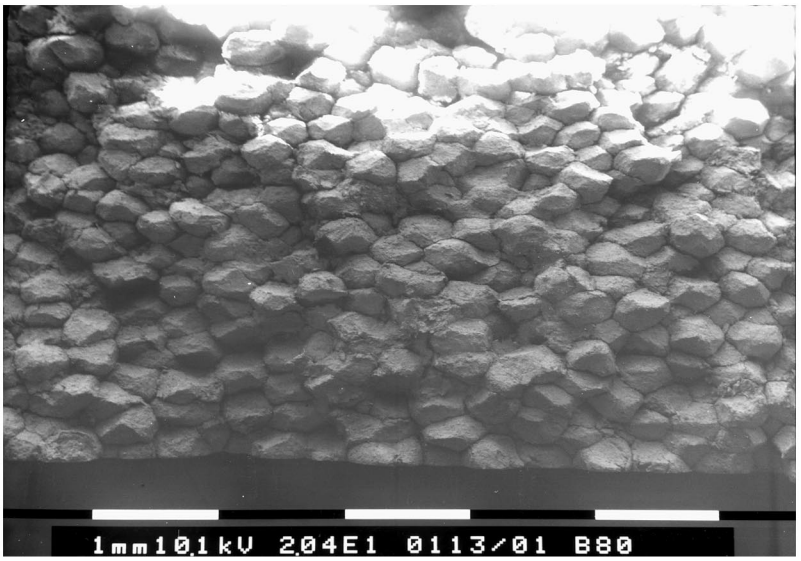


(b)

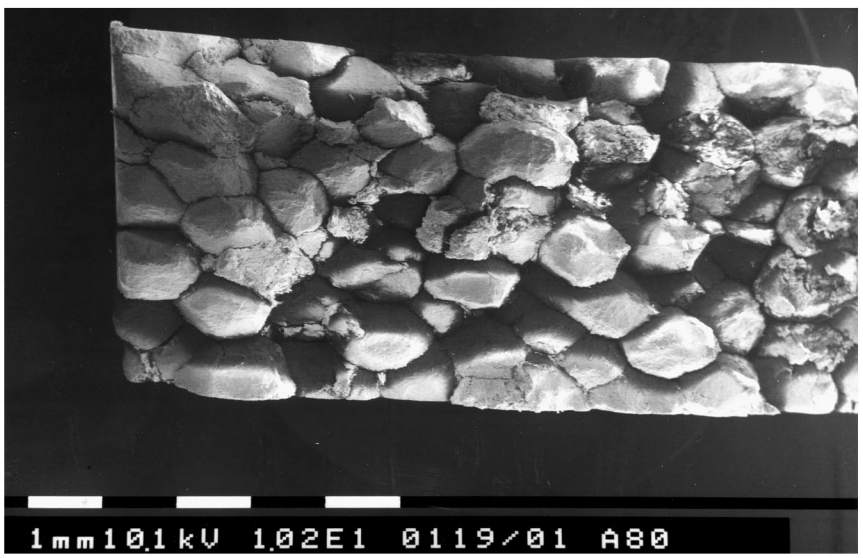
Fig. 3. SEM photomicrographs of fracture surfaces of tablets prepared from unlubricated pellets at 20 and 80 MPa: (a) Tablets prepared from small pellets 425–500 μm at 20 MPa; (b) tablets prepared from large pellets 1250–1400 μm at 20 MPa;(c) tablets prepared from small pellets 425–500 μm at 80 MPa; (d) tablets prepared from large pellets 1250–1400 μm at 80 MPa. The white bars denote 1 mm.

4.2. Effect of pellet size on tablet tensile strength

The general trend in the tablet strength data (Fig. 4) is that the tensile strength is independent of the original pellet size, although a tendency can be seen that the tensile strength increased somewhat steeper with applied pressure for compacts formed from the larger pellets. Johansson et al. (1995) showed that a tablet formed of pellets of microcrystalline cellulose can be described in



(c)



(d)

Fig. 3. (*Continued*)

physical terms as an aggregate of deformed pellets. During fracturing of these tablets, the fracture occurred mainly around rather than through the pellets, i.e. the structure of the intergranular pore system will control the fracture event. This fracturing behaviour was valid also for the tablets prepared for this study (Fig. 3). Although the tablets consisted of pellets of different size and thus show a different physical structure in general terms, the porosity of the intergranular pore system was similar for tablets prepared from both type of tablets. This might indicate that the structure of the intergranular pore system was similar between tablets prepared of the differently sized pellets. If the stress needed to initiate and propagate a crack is controlled by the structure of the

Table 4
Characteristics of tablets compacted of unlubricated pellets

Pellet size	Applied pressure (MPa)	Tablet tensile strength (MN/m^2)	Total porosity (%)	Intergranular porosity %)
425–500 μm	0		62.9	44.9
	10	0.08 (—)	55.3 (2.2)	29.4
	20	0.26 (3.8)	45.7 (1.05)	17.1
	40	0.75 (4.0)	35.7 (0.14)	10.2
	80	1.89 (2.6)	24.6 (0.73)	4.80
	160	4.28 (7.7)	14.2 (3.7)	—
1250–1400 μm	0		64.0	45.0
	10	0.04 (—)	54.7 (0.38)	28.3
	20	0.17 (5.9)	46.8 (0.26)	19.5
	40	0.65 (9.2)	36.0 (0.25)	10.6
	80	1.98 (5.1)	23.6 (1.4)	3.66
	160	4.86 (4.7)	12.7 (1.6)	—

[a] Arithmetic mean values with relative SD in brackets.

intergranular pore system, the assessed strength will be similar for tablets from both pellet sizes.

Another mechanistic view to explain the tensile strength of tablets (Eriksson and Alderborn, 1995) is to use a bond summation concept, i.e. the tensile strength of the tablet equates the number of interparticulate bonding zones in a cross section of the tablet times the mean bonding force of the bonding zones. The shape analysis of the retrieved pellets supported the assumption that larger pellets deformed more markedly during compression (Tables 2 and 3). The area of bonding zones between pellets will probably be in-

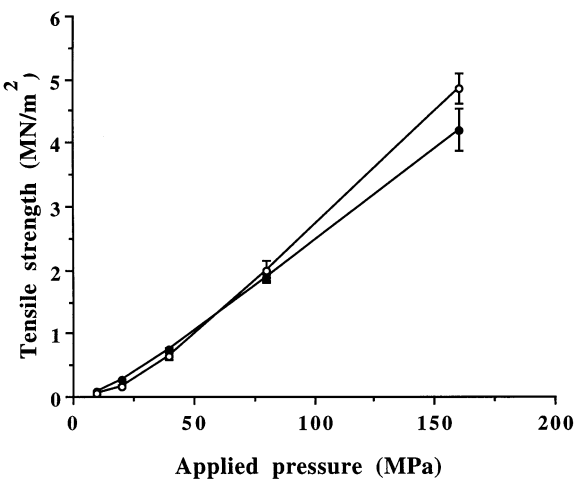


Fig. 4. The tensile strength of tablets prepared from unlubricated pellets as a function of the pressure applied during compression: ●, Small pellets 425–500 μm; ○, large pellets 1250–1400 μm.

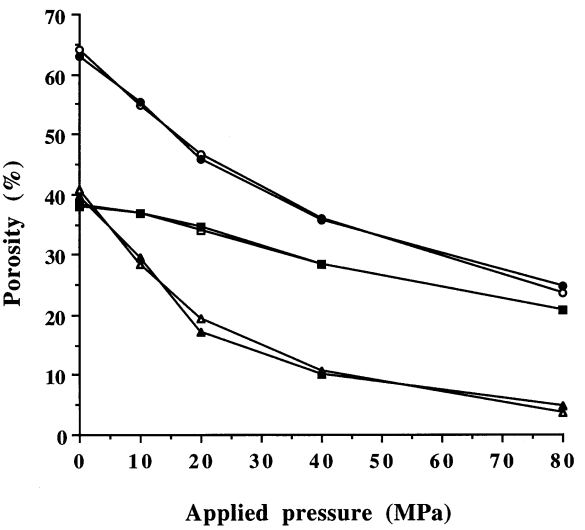


Fig. 5. The tablet porosity (relative amount of air in a tablet), pellet porosity (relative amount of air in a pellet) and the intergranular porosity (relative amount of intergranular air in tablet) as a function of the pressure applied during compression. ●, Tablet porosity, small pellets 425–500 μm; ○, tablet porosity, large pellets 1250–1400 μm; ■, pellet porosity, small pellets 425–500 μm; □, pellet porosity, large pellets 1250–1400 μm; ▲, intergranular porosity, small pellets 425–500 μm; △, intergranular porosity, large pellets 1250–1400 μm.

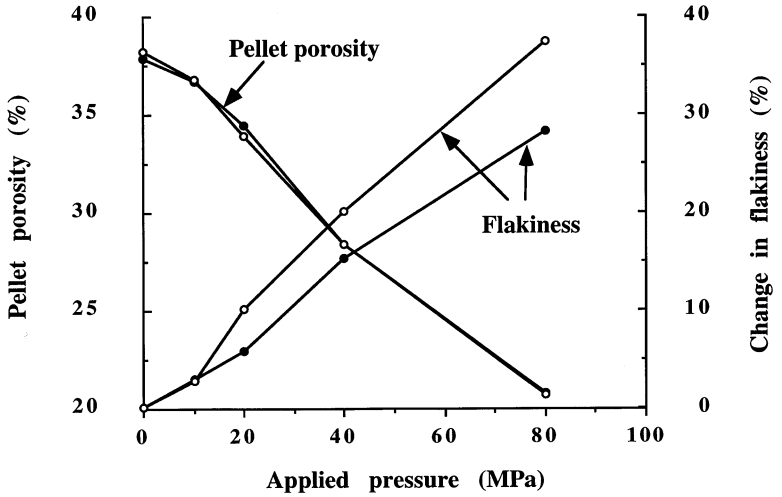


Fig. 6. The pellet porosity (degree of densification) and the relative change in flakiness (degree of deformation) as a function of the pressure applied during compression. Symbols as in Fig. 4.

creased as the degree of deformation of the pellet increases. The bonding force of these bonding zones will thus increase. It can therefore be argued, that in tablets compressed from larger pellets, there are fewer bonding zones over a unit cross section but the bonding forces of the bonding zones are higher. However, since the tensile strength of tablets was independent of pellet size, it is suggested that the sum of the bonding forces over a unit cross section is equal for tablets made of either large or small pellets. Thus, in terms of total bond strength in a tablet cross section, a reduced number of bonding zones will be balanced by increased bonding force in the bonding zones.

At the highest pressure applied, the larger pellets gave tablets of a higher tablet strength. At this pressure, the intergranular porosity of the tablets was very low. Earlier results (Johansson and Alderborn, 1996) indicated that, at low tablet porosities, even a very limited increase in pellet deformation resulted in a marked increase in tablet strength. At such low porosities, the intergranular pore system might have been more closed for tablets prepared from the larger pellets, corresponding to large areas of contact between pellets. This can explain a higher compactability of tablets made from the larger pellets.

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