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Research paper

The effect of shape and porosity on the compression behaviour and tablet forming ability of granular materials formed from microcrystalline cellulose

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Abstract

The compression behaviour of two types of granules prepared from microcrystalline cellulose was evaluated. Three sets (low, intermediate and high intragranular porosity) of irregular granules and three sets of nearly spherical granules (called pellets) were prepared from microcrystalline cellulose by wet agglomeration or wet agglomeration followed by extrusion/spheronisation. The granules and pellets were similar in size. The range of intragranular porosity, although wide, was also similar for both types. The compression behaviour was evaluated in terms of the degree of compression, the appearance of the tablets and the size distribution of retrieved aggregates (after deaggregation). The compactability of the granules and pellets was also studied. Both types of granules kept their integrity during compression. The dominant mechanism during compression appeared to be permanent deformation. However, during compression of high porosity granules, fragmentation or attrition seemed to occur alongside deformation. Tablets formed from granules had a closer pore structure than those formed from pellets of equal intragranular porosity and the granules seemed to deform to a higher degree during compression. The total tablet porosity was almost independent of the intragranular porosity and the shape of the granules before compression. It is suggested that the degree of granule deformation was controlled by the intragranular porosity and voidage of each bed of granules before compression. The tensile strength of the tablets was also dependent on the porosity and the shape of the granules; tablets formed from irregular granules were stronger than those formed from pellets of an equal intragranular porosity.

Keywords: Microcrystalline cellulose; Wet granulation; Granule shape; Intragranular porosity; Intergranular voidage; Compression behaviour; Tablet tensile strength

1. Introduction

A common approach to engineer particles in pharmaceutical manufacturing in terms of their flowability and tablet forming ability is to form granules from powder mixtures. Over recent years, the compression behaviour and tablet forming ability of different types of pharmaceutical granules – of different size and shape and with or without a solution binder – have been under investigation in our laboratory. In the first series of experiments [1] irregular granules were investigated and it was suggested that four compression mechanisms are involved in the compression process: fragmentation (fracturing of granules into smaller agglomerates), deformation (a change in shape of individual granules), densification (a reduction in granule porosity) and attrition (primary particles are sheared off from the granules during compression). A similar series of compression mechanisms for granules was already earlier suggested by Van der Zwan and Siskens[2]. It was further suggested by Wikberg [1] that changes in the intragranular porosity would change the propensity of the granules to respond to compression by fragmentation and deformation.

The irregular shape of the granules used in the studies by Wikberg [1] made it difficult to determine the relative degree of occurrence of the different compression mechanisms suggested. Accordingly, in a second series of experiments [3–6], nearly spherical granules (hereafter referred to as pellets) were studied. It was concluded that the relevant compression mechanisms involved in the compression of those pellets were permanent deformation and densification. Fragmentation and attrition occurred only to a minute degree. The degree of pellet deformation and densification was dependent on the intragranular porosity of the pellets before compression and was not directly related to the resistance of the pellets to fracture or to their intragranular pore

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size distribution. The results also showed that the pore structure and the tensile strength of tablets formed from pellets were dependent on the intragranular porosity before compression, an observation that was consistent with the findings reported by Wikberg[1].

A consistent characteristic of the non-fragmenting microcrystalline cellulose pellets used in the studies cited above is thus that the original porosity of the pellets is critical for the evolution of tablet structure and strength during compression. For granules formed from other materials, the granule fracture strength has been the subject of concern in discussing their compression behaviour[7–10]. A model by which a measure of the failure stress of the individual agglomerates during in-die compression can be assessed, has also been derived[7,8]. This approach has also been applied to pellets formed from microcrystalline cellulose [11] as a means to derive a measure of their compression shear strength.

The literature thus indicate that there might be a difference in the number of mechanisms involved in the compression process for granules and pellets. It can thus be hypothesised that increasing the irregularity and roughness of granules will change the compression behaviour towards a more complex process including fragmentation and attrition of the granules. Support for such a hypothesis may be found in the literature. Wikberg and Alderborn [12] reported that the friability of granules is related to their shape rather than to their fracture resistance or porosity. Moreover, a relationship between the surface roughness and the degree of attrition has also been reported for $CaCO_3$ agglomerates [13] and the authors concluded that the attrition of the agglomerates was related to the surface roughness rather than to the mechanical properties of the agglomerates.

The purpose of this study was to investigate the effect of original shape and porosity of granules for their compression behaviour and tablet forming ability. The granules were prepared from microcrystalline cellulose particles. The compression behaviour of both types of granular material was evaluated in terms of the degree of compression during tabletting, the appearance of the tablets and the size distribution of retrieved aggregates (after deaggregation of the tablets). The compactability of the granular materials, without and with the addition of a lubricant, was also studied. The study represents an attempt to broaden our understanding of the mechanisms involved in the compression of granules and to investigate how the relative occurrence of these mechanisms varies with original shape and porosity and how these physical properties affect the evolution of tablet structure and strength.

2. Materials and methods

2.1. Materials

Microcrystalline cellulose (Avicel PH101, lot number 6017, FMC Co, Philadelphia, PA, USA, apparent particle density of 1.56 g/cm^3). Magnesium stearate (Ph. Eur. Apoteksbolaget AB, Stockholm, Sweden, apparent particle density of 1.02 g/cm^3 and a permeametry surface area of 0.798 m^2/g). Ethanol (Finsprit 95% w/w, Kemetyl, Haninge, Sweden).

2.2. Preparation of pellets and granules

Six sets of granules were prepared from microcrystalline cellulose by wet agglomeration (hereafter referred to as the granules) or by wet agglomeration followed by extrusion/spheronisation (hereafter referred to as the pellets). The preparation process was varied to obtain granules and pellets of different original porosities (low, intermediate and high intragranular porosity) but within the same size range (0.71–1.0 mm) (Table 1) for both granules and pellets.

2.2.1. Granules

The powder (200 g) was placed in a planetary mixer (Braun Multipractice Plus electronic UK20, Frankfurt am Main, Germany) equipped with a specially designed mixer blade. The powder was dry mixed for 1 min at 800 rpm. The agglomeration liquid (ethanol/water) was poured into the mixing bowl at an approximate rate of 100 ml/min. The wet mass was agitated at 800 rpm for 7–9 min. The amounts of agglomeration liquid and the wet massing times are specified in Table 1. The wet mass was forced through a 2.0 mm screen in an oscillating granulator (Manesty Rotogran Mark III, Manesty Machines Ltd, Liverpool, U.K.).

2.2.2. Pellets

The powder (200 g) was agglomerated as for granules (described above) and the wet mass was agitated further at 800 rpm for 5–8 min. Process variables are presented in Table 1. The wet powder mass was then immediately extruded (model E140, Nica System AB, Mölndal, Sweden) through a radial screen extruder at 70 rpm through holes of 1.0 mm diameter and 1.2 mm length thereafter and spheronised (model S320-S450, Nica System AB, Mölndal, Sweden) for 3 min at 1150 rpm on a 32 cm diameter friction plate with a radially designed grid.

2.2.3. Drying and storage of pellets and granules

The granules and pellets were dried in a fluid-bed dryer

Table 1
Process variables during pellet and granule preparation

Aggregate sets	Agglomeration liquid ethanol/water (% w/w)	Amount of agglomeration liquid (g)	Wet massing time (min)
G1	0/100	200	7
G2	50/50	270	7.5
G3	80/20	240	9.2
P1	0/100	220	5
P2	50/50	240	5
P3	80/20	245	8

(Aeromatic AG, Muttenz, Switzerland) at 35°C until the temperature of the outlet air was 35°C. The size fraction 0.71–1.0 mm was prepared by sieving and the granules and pellets were stored at 40% relative humidity and room temperature for seven days before any further characterisation or tabletting.

2.3. Characterisation of pellets and granules

2.3.1. Appearance

The granules and pellets were inspected in a scanning electron microscope (Philips SEM 525, Eindhoven, The Netherlands) and under a light microscope (Wild laboratory stereo microscope, Heerbrugg, Switzerland).

2.3.2. Bulk densities

The tapped and poured bulk densities ($n = 3$) of the granules and pellets were determined using a tap volumeter (J. Engelsmann A.G., Ludwigshafen, Germany, complying with DIN standard 53194) equipped with a 50 ml cylinder with an inner diameter of 22 mm. The column of granules and pellets was tapped until a constant bed height was reached (about 1000 taps for the granules and 400 taps for the pellets). The ratio between the tapped and poured bulk densities (often referred to as the Hausner ratio) was thereafter calculated.

The poured bulk density was also determined in a 10 ml glass cylinder with an inner diameter of 10 mm, and these values were used in the calculations of the degree of compression (see below).

2.3.3. Porosity and voidage

The intragranular porosity of the granules and pellets was calculated from their apparent particle density and the effective particle density ($n = 3$) as described earlier[3]. The apparent particle density was measured using a helium pycnometer (AccuPyc 1330, Micromeritics, Norcross, GA, USA) and the effective particle density was determined using mercury pycnometry as described by Wikberg and Alderborn[14]. The voidage of each bed of granules and pellets was calculated from the tapped bulk density and the effective particle density.

2.3.4. External surface area

The surface area of the granules and pellets was determined using a steady state permeameter ($n = 3$). The permeametry surface area and the permeability coefficient of a bed of granular material were calculated according to Eriksson et al.[15].

2.3.5. Shape

The Heywood shape coefficient, α [16]was calculated for each set of pellets and granules as measures of the shape of the particles as

$$\alpha = S_v * d$$

The external surface area (S_v)was derived from permeametry data as described above and the projected area circle diameter (d) was measured by image analysis in the following way: Pellets and granules were manually dispersed on microscope slides and then photographed in a light microscope (Olympus Vanox, Olympus, Tokyo, Japan) at two times magnification. The photos were digitised and the projected area of the pellets and granules ($n = 66$) were determined by image analysis (NIH Image, U.S.A., available on the Internet at http://rsb.info.nih.gov/nih-image/) with a pixel resolution of 5.1–5.3 μm/pixel. The corresponding circle diameters of the projected areas of the granules and pellets were finally calculated.

2.3.6. Degree of compression

Unlubricated granules and pellets were compressed in an instrumented single punch press (Korsch EK 0, Berlin, Germany) at an applied pressure of 200 MPa. The press was equipped with flat-faced punches with a diameter of 1.13 cm. The die was prelubricated before every second compaction by compression of magnesium stearate powder. 500 mg samples of granules and pellets ($n = 3$) were weighed on an analytical balance and then manually filled into the die. The displacement and force of the upper punch were registered as described earlier [17] and the degree of compression of the granules and pellets during compression was calculated according to Johansson et al.[3].

2.4. Preparation of tablets from unlubricated granular materials

Tablets of unlubricated granules and pellets were compacted in an instrumented single punch press (Korsch EK 0, Berlin, Germany) at applied pressures of 50, 100, 150 and 200 MPa as described above. The prepared tablets were stored at 40% relative humidity and room temperature for at least four days before subjected to characterisation.

Tablets of both pellets and granules were also compacted at an applied pressure of 15 MPa as described above ($n = 6$). These tablets were used in the deaggregation studies.

2.5. Characterisation of tablets

Tablets ($n = 5$) were compressed diametrically in a materials testing machine (model M30K, J.J. Lloyd Instruments Ltd, Fareham, UK) at a compression rate of 5 mm/min. The tensile strength was derived from the force needed to fracture the tablets as described by Fell and Newton[18].

The total tablet porosity ($n = 5$) was calculated from the height and weight of the tablets and the apparent particle density of the granular material.

2.6. Deaggregation of tablets and characterisation of retrieved granular material

The tablets prepared at an applied pressure of 15 MPa

were deaggregated after compaction. The tablets were placed in a petri dish and shaken carefully by hand until they broke into discrete units. The retrieved aggregates were sorted for size by dry sieving ($n = 2$). The aggregates were also examined under a light microscope at four times magnification.

2.7. Preparation of tablets from lubricated materials

An 8 g amount of the pellets or granules was mixed with magnesium stearate in quantities corresponding to 0.2, 2, 5, 20 and 100 μg per cm^2 external surface area of granular material in a Turbula mixer (W. A. Bachofen, Basel, Switzerland) at 90 rpm for 320 min in a 20 ml bottle. The lubricated pellets and granules were stored at 40% relative humidity for at least 4 days before tabletting.

Tablets of these lubricated granules and pellets were compacted at an applied pressure of 100 MPa in the instrumented single punch press as described above. After compaction, the tablets were stored at 40% relative humidity for at least 4 days before their tensile strength and porosity were determined as described above ($n = 5$).

3. Results and discussion

3.1. Primary characteristics of pellets and granules

The preparation procedures used gave pellets and granules with a wide porosity range (Table 2), wider for the granules. The inspection of the pellets and granules by microscopy (Figs. 1 and 3) showed that the pellets were nearly spherical in shape with a smooth surface although pellets of the highest original porosity were less spherical and smooth. The granules of high and intermediate porosity were more irregular in shape with a rougher surface texture compared to the pellets while the granules with the lowest original intragranular porosity were also nearly spherical and smooth. The shape coefficients [16] support these conclusions regarding shape of the pellets and granules, i.e. coefficients around 6 (Table 2) for all the pellets and the granules with the lowest original intragranular porosity, indicating that these particles are spheres, and coefficients around 10 (Table 2) for granules with the intermediate and high original intragranular porosity, indicating that the shape of these particles deviated significantly from spherical shape. One should note that for pellet P1 and P2, a calculated value slightly below 6 was obtained, i.e. a coefficient below the lowest possible shape coefficient. An approximation of 6 is thus used in the presentation of data.

Except for those of the lowest porosity, the granules had a higher surface area, a higher bed voidage and a higher Hausner ratio than the pellets (Table 2). These data can be explained by the more irregular shape of the granules with the high and intermediate original intragranular porosity compared to the other particles.

In conclusion, the primary characterisation of the granular materials showed that the pellets and granules prepared for the study were of similar sizes and possessed a wide range of intragranular porosities. Four of the six sets of granular material had nearly spherical particles while the shapes of two sets of granules (intermediate and high porosity) were markedly different from the others in terms of a more irregular shape and less smooth surface.

3.2. Compression mechanisms of pellets and granules

The fracture and upper surfaces of tablets prepared from high porosity pellets compared favourably with earlier experience [3] and the pellets seemed to remain as coherent units after compression, although some cracks were noticed. The upper surfaces of tablets prepared from high porosity granules indicated that the granules remained as coherent units after compression while the fracture surfaces of the corresponding tablets had a more complicated structure, in accordance with earlier experience[1], and were thus more difficult to analyse in terms of the integrity of the granules during compression. This could have been the combined effect of the irregular shape before compression, marked

Table 2
Primary characteristics of pellets and granules[a]

Aggregate sets	Effective particle density	Intragranular porosity	External surface area	Permeability coefficient $\times 10^5$	Heywood shape coefficient	Voidage of aggregate bed	Hausner ratio
	g/cm^3	%	cm^{-1}	$m^4/Ns)^b$	–	% [c]	– [d]
G1	1.44 (0.64)	7.76 (7.3)	70.1 (0.18)	2.37 (2.01)	6.6	37.9	1.057 (0.80)
G2	1.06 (0.60)	32.1 (1.3)	99.9 (0.18)	2.98 (0.96)	10	45.3	1.107 (0.41)
G3	0.80 (0.56)	48.4 (0.6)	97.5 (1.60)	3.15 (6.44)	9.6	45.5	1.126 (0.89)
P1	1.36 (0.41)	13.0 (2.8)	64.6 (0.16)	2.45 (2.09)	6[e]	36.7	1.057 (0.61)
P2	1.19 (3.01)	23.5 (9.8)	70.5 (0.34)	2.73 (0.71)	6[e]	39.6	1.042 (0.53)
P3	0.96 (0.97)	38.6 (1.5)	75.2 (0.18)	2.54 (1.28)	6.4	40.1	1.038 (0.65)

[a] Mean values, relative standard deviation given in parenthesis ($n = 3$).
[b] Measured by a steady state permeameter and calculated according to Eriksson et al.[15].
[c] Calculated from the effective particle density and the tapped bulk density.
[d] The ratio between the tapped and poured bulk densities.
[e] An approximation of the calculated value to 6.

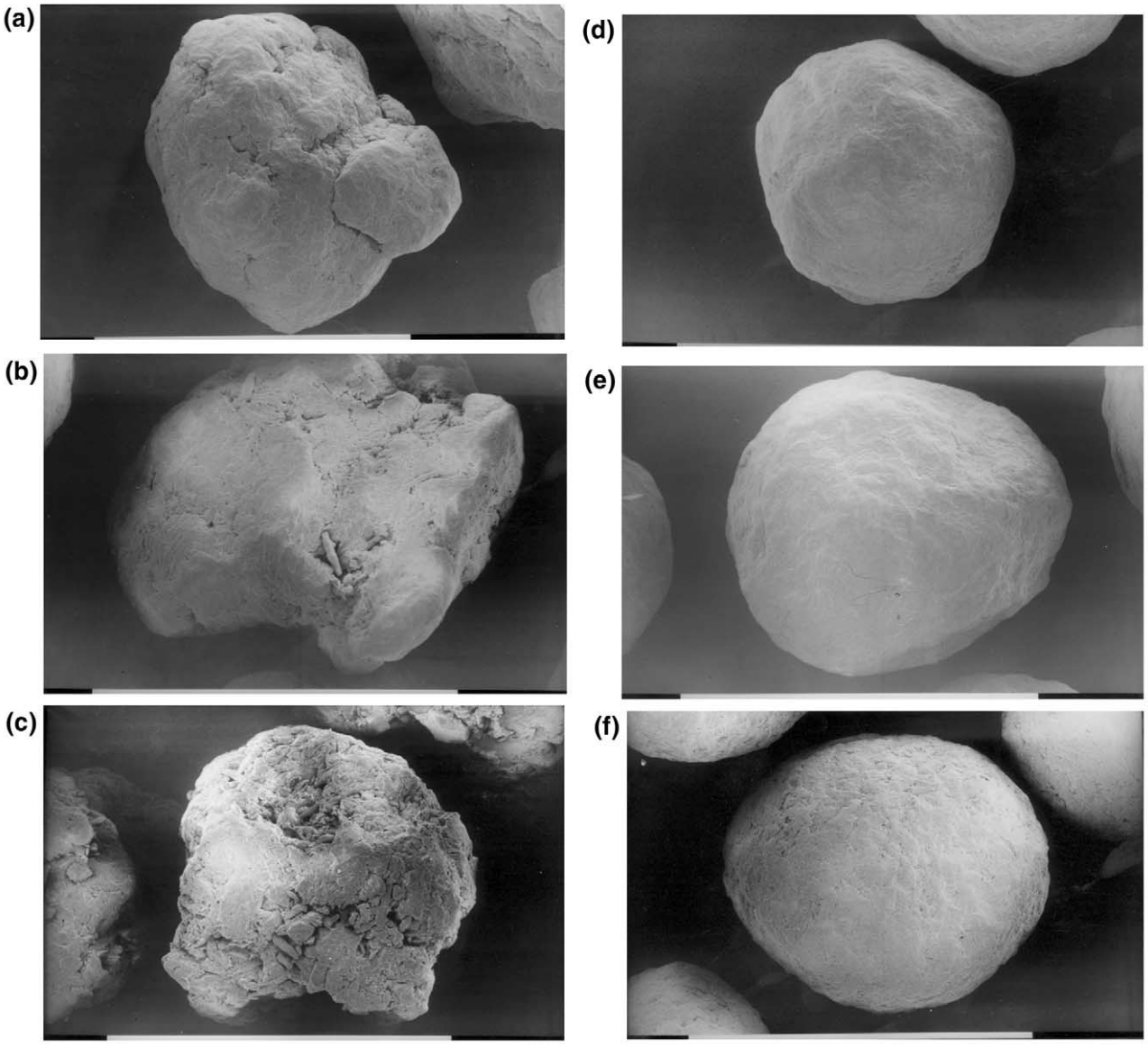

Fig. 1. SEM photomicrographs of granules (G) and pellets (P) before compression: (a) G1, (b) G2, (c) G3, (d) P1, (e) P2, (f) P3 The white bars denote 1 mm.

deformation and some fragmentation/ attrition during compression, and the fracturing of granules during tablet failure in the diametral compression test[6].

In order to estimate whether the pellets and granules fragmented or eroded during compression, tablets prepared at a low pressure (15 MPa), were deaggregated after compaction and the size of the retrieved pellets and granules was determined. For the retrieved pellets of all porosities and for the low and intermediate porosity granules, the retrieved pellets and granules were similar in size to the uncompacted pellets and granules (Fig. 2a). The high porosity retrieved pellets tended to be smaller than the original pellets. Visual examination of these retrieved pellets indicated that the reduction in size had been caused by deformation rather than fragmentation, i.e. the pellets were slightly flatter after compression (Fig. 3). For high porosity retrieved granules, a broader size distribution than the original granules was obtained (Fig. 2b). Since a fraction of quite small particles (less than 0.18 mm in diameter) were obtained, it is reasonable that individual particles or clusters of a few particles were sheared off from the surface of the granules during compression, i.e. granule attrition. These findings are illustrated by microscopy pictures of the retrieved pellets and granules (Fig. 3).

In conclusion, microscopy examination of the tablets indicated that the dominating mechanism of compression for both pellets and granules was permanent deformation, i.e. fragmentation of the granules occurred to a limited degree. This is consistent with earlier findings for pellets[3,4,6]. The tablet deaggregation experiments, although performed on tablets formed at a low compaction pressure, generally supported this conclusion. Thus, chan-

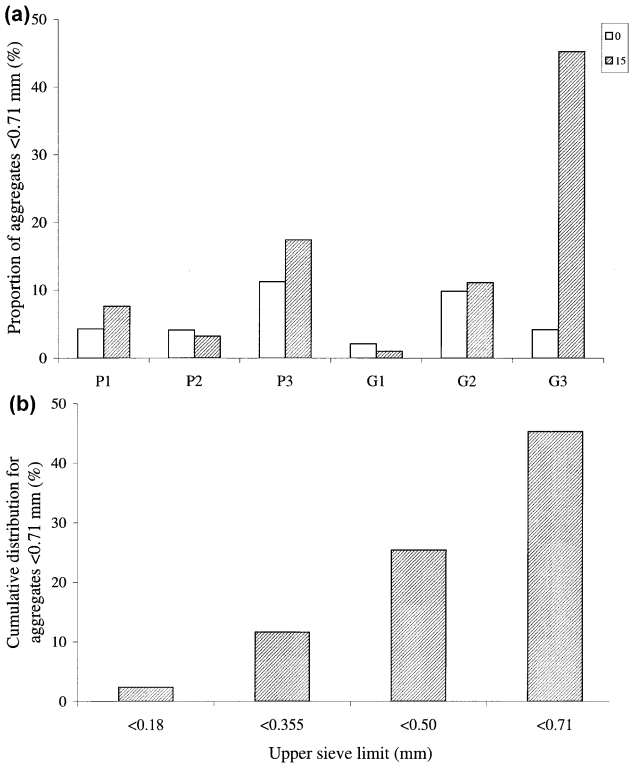

Fig. 2. The size (% by weight) of granules and pellets before compression and of retrieved granules and pellets after compression at 15 MPa. (a) The proportion of granular material less than 0.71 mm for granules and pellets before and after compression. (b) The cumulative distribution below 0.71 mm of high porosity granules after compression at 15 MPa.

ging the shape of the granules did not affect what could be described as the dominating compression mechanism for granular material formed from microcrystalline cellulose. However, it was also concluded from these experiments that some attrition of high porosity irregular granules occurred during compression. Thus, irregularly shaped granules may show a more complex compression behaviour, in terms of the number of involved compression mechanisms, than nearly spherical granules.

3.3. Compression behaviour of pellets and granules

The total tablet porosity decreased as the applied pressure increased for both pellets and granules (Table 3). As shown previously, total tablet porosity appears to be generally independent of the intragranular porosity before compression[3,19]. The shape of the pellets or granules with similar original intragranular porosities had only a minor effect on tablet porosity i.e. tablet porosity was mainly dependent on the pressure applied during compression, while the physical properties of the granules were of minor importance.

It has been suggested [3] that the degree of compression of a bed of non-fragmenting granules during tabletting reflects the degree of deformation and densification which the individual granules undergo during the compression process. Thus, the relationship between degree of compression and applied pressure can be used as an indirect measure of the deformation and densification properties of the granules and pellets used in this study.

The degree of compression of the pellets and granules increased in a non-linear way with applied pressure (Fig. 4). The degree of compression seemed to reach nearly limiting values within the pressure range used but at different levels (40–75%) for the different pellets and granules. The differences in compressibility between the pellets and granules were significant already at pressures below 50 MPa. For each type of particle, increasing the original intragranular porosity (Fig. 5a) increased the degree of compression at a given applied pressure[3,19]. However, the relationship between the degree of compression and the porosity of the particles before compression differed between granules and pellets. A change towards a more irregular shape (Fig. 5b) tended to increase the degree of compression of the granular material, i.e. more irregular granules were more compressible. One can finally notice, that when the degree of compression was plotted as a function of the poured bulk densities of the particles (Fig. 5c), the relationships for pellets and granules at a given compaction pressure coincided. It seems thus that the bulk density of the granular material before compression controlled the degree of compression.

The bulk density is a function of the effective density and the packing density of the porous particles. The latter is affected by a series of particle properties such as size, shape and surface roughness. Since the granules were more irregular in shape than the pellets but of similar size, the shape difference is the probable explanation for their looser packing structure, and therefore a lower bulk density. Thus, in addition to the original porosity, the shape also seemed to be a significant factor for the degree of compression, and thus for the deformation and densification properties, of the pellets and granules during compression. When the size and shape of the granules, and thus the spaces surrounding the granules, are similar, the intragranular porosity regulates the potential for deformation. For two types of granular material with different shapes and thus different voidage, the combined effect of the intragranular porosity and the granule shape will regulate the potential for granule deformation. A more irregular shape will increase the voidage but increased irregularity of shape can also increase the possibility that the granules will locally deform more easily. In addition, it cannot be excluded that attrition of granules, which can be initiated by a change towards a more irregular shape as suggested above, might also affect the degree of compression in such a way that the granules can slide more easily past each other and thus facilitate compression.

In comparison, it has been suggested that making non-porous particles more irregular will increase their compressibility if the particles reduce in volume mainly by deformation [20] but will have no effect if the particles reduce in volume mainly by fragmentation[20,21].

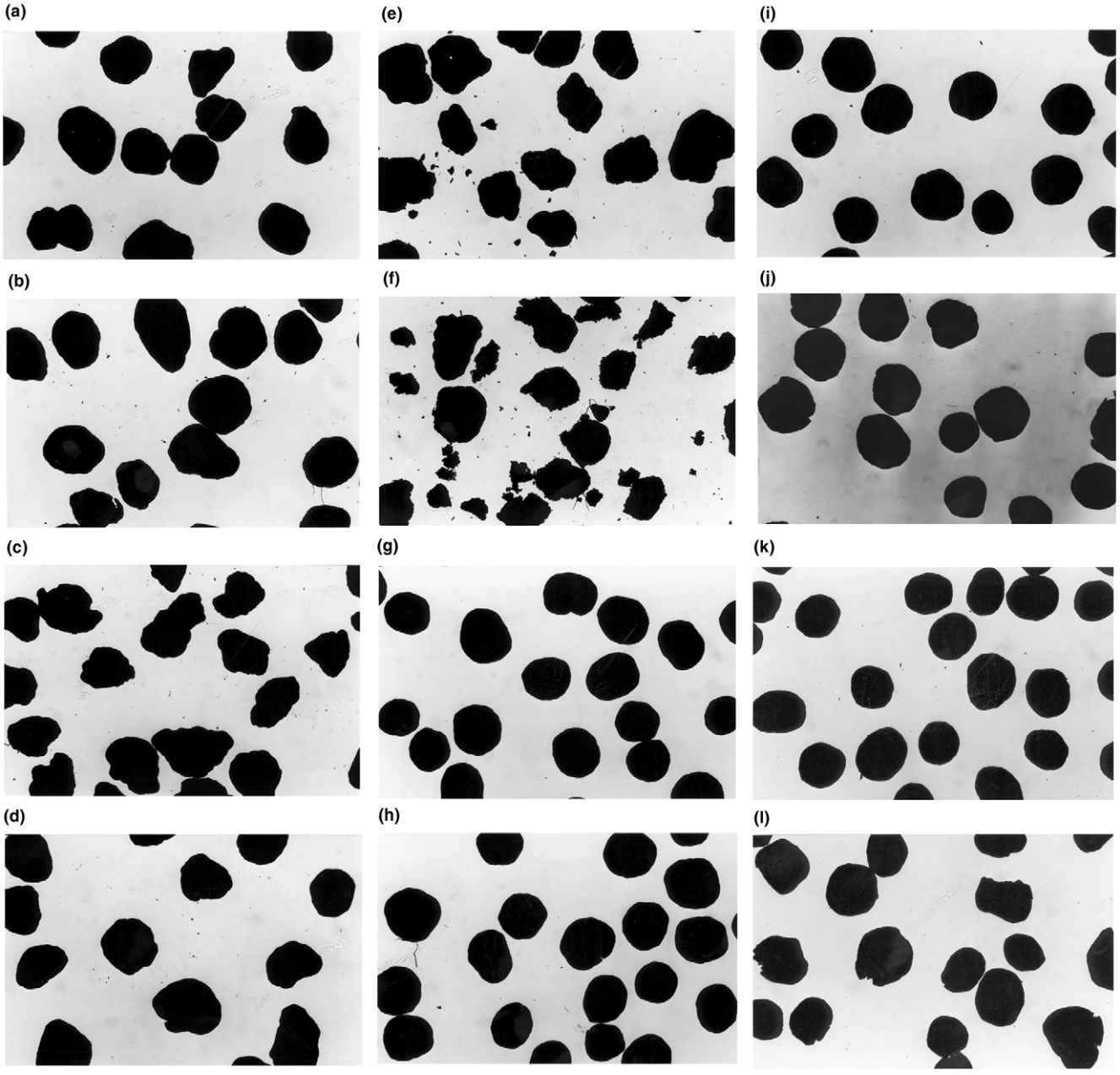

Fig. 3. Light microscopy photomicrographs (at four times magnification) of the granules and pellets before and after compression at 15 MPa: (a) G1 before, (b) G1 after, (c) G2 before, (d) G2 after, (e) G3 before, (f) G3 after (g) P1 before, (h) P1 after, (i) P2 before, (j) P2 after, (k) P3 before, (l) P3 after.

3.4. Compactability of pellets and granules

3.4.1. Unlubricated powders

The tablet tensile strength increased almost linearly with the upper punch pressure for both pellets and granules (Table 3) in the pressure range used. Higher intragranular porosity [3] and granule irregularity before compression gave tablets with a higher tensile strength (Figs. 6a,b). At any given intragranular porosity, a higher tensile strength was obtained for tablets prepared from granules compared to those prepared from pellets, throughout the whole pressure range used. Thus, both the porosity and the shape of the pellets and granules were of significant importance for the tensile strength of the tablets.

Since the total tablet porosity was almost independent of both the original porosity and the shape of the particles, there was no relationship between total tablet porosity and tablet tensile strength. However, in general terms, a decreased poured bulk density corresponded to an increased tablet tensile strength (Fig. 6c). It has also been shown previously that for granules formed from lactose powders[22], a decreased bulk density of the granulation correlated with an increased tablet strength. Thus, the results obtained in this study are, in this respect, consistent with the earlier

Table 3
Height, porosity and tensile strength of tablet compacted at 50, 100, 150 and 200 MPa[a]

Aggregate sets	Applied pressure (MPa)	Tablet height (mm)	Tablet porosity (%)	Tablet tensile strength (MN/m^2)
G1	50	*	*	*
	100	3.89 (0.11)	18.4 (4.7)	0.054 (48)
	150	3.67 (0.14)	14.3 (5.0)	0.09 (44)
	200	3.57 (0.17)	10.5 (1.4)	0.11 (23)
G2	50	4.70 (0.26)	33.0 (0.54)	0.83 (11)
	100	4.02 (0.34)	20.8 (1.4)	2.24 (5.5)
	150	3.67 (0.31)	12.6 (2.3)	3.52 (7.1)
	200	3.58 (0.23)	10.6 (1.5)	4.30 (3.3)
G3	50	4.57 (0.42)	30.8 (0.32)	1.88 (4.3)
	100	3.94 (0.32)	19.4 (4.0)	3.97 (22)
	150	3.65 (0.31)	12.1 (2.1)	6.66 (5.0)
	200	3.55 (0.12)	9.82 (1.8)	8.08 (4.7)
P1	50	*	*	*
	100	*	*	*
	150	*	*	*
	200	*	*	*
P2	50	4.36 (0.91)	27.3 (2.2)	0.15 (11)
	100	3.80 (0.40)	15.8 (2.1)	0.84 (15)
	150	3.56 (0.10)	10.8 (0.74)	1.20 (12)
	200	3.53 (0.41)	8.92 (4.2)	1.34 (14)
P3	50	4.57 (0.26)	30.7 (0.39)	0.81 (9.9)
	100	3.95 (0.28)	19.3 (4.0)	2.22 (8.7)
	150	3.63 (0.13)	11.5 (1.79)	4.17 (6.0)
	200	3.55 (0.24)	9.75 (2.0)	4.57 (4.8)

[a] Mean, relative standard deviations are given in parentheses ($n = 5$). *A coherent unit was formed during compression but fell apart during handling.

report. However, Zuurman et al. [22]concluded that the effect of bulk density was due to an effect of a variation of the intragranular porosity on the tablet forming ability of the granules, an effect of intragranular porosity which earlier was reported for other lactose granules[1], while the intergranular porosity had no marked effect on tablet strength. The results of this study indicate however that both the intra- and intergranular porosities may have a significant effect on the tablet forming ability of granular material.

It seems thus that the bulk density of the pellets and granules affected both the compressibility and the compactability of the granules. Hence, the total degree of compression (Fig. 6d) appears to be of importance for the tablet strength. A non-linear relationship was obtained, indicating that with a reduction in intergranular tablet porosity, further volume reduction of the tablet will markedly affect the tablet strength.

The finding that the strength of the tablets is related to the degree of compression of granules indicates that, irrespective of the shape of the granule, the degree of granule deformation will control the evolution of tablet structure in terms of the intergranular pore size and the areas of intergranular contact. The deformation process during compression will probably begin at surface asperities, involving a local flattening of the external granule surface. At a later stage, deformation will probably involve a change in shape for the whole granule[3,19]. Both local deformation and bulk deformation will probably reduce the intergranular distance between the granules and larger areas of the intergranular contact zones, at which intergranular bonds are established, will be developed. It is also possible that the higher tensile strength of tablets formed from granules could be affected by the occurrence of attrition of the granule surfaces during compression.

3.4.2. Lubricated powders

The addition of a lubricant to the pellets and granules before compression reduced the compactability of both pellets and granules (Fig. 7). The sensitivity to an added

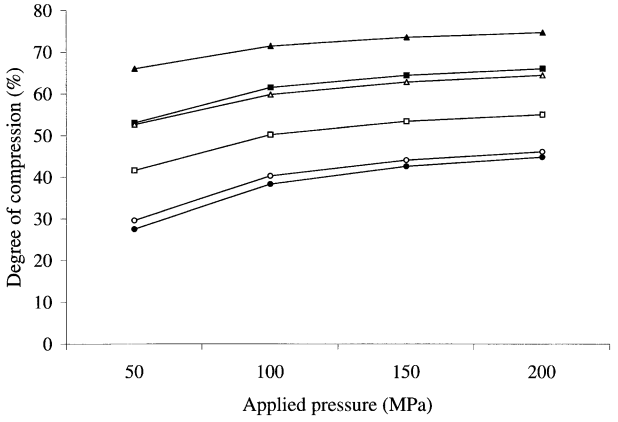

Fig. 4. Degree of compression as a function of the applied pressure during compression for all granules (G) and pellets (P). Error bars corresponding to 95% confidence intervals for the mean ($n = 3$) are hidden behind the symbols. ● G1; ■ G2; ▲ G3; ○ P1; □ P2; △ P3.

lubricant decreased with increased original porosity of the pellets and granules, as is consistent with earlier observations for microcrystalline cellulose pellets[3]. Only the high porosity pellets formed coherent tablets of a measurable tensile strength after lubricant addition and then only with the lowest amount added. For the high porosity pellets, there was a minor increase in the tensile strength at the smallest amount of lubricant added, which may have been caused by the facilitated repositioning of the pellets in the die.

The granules were less sensitive to the addition of a lubri-

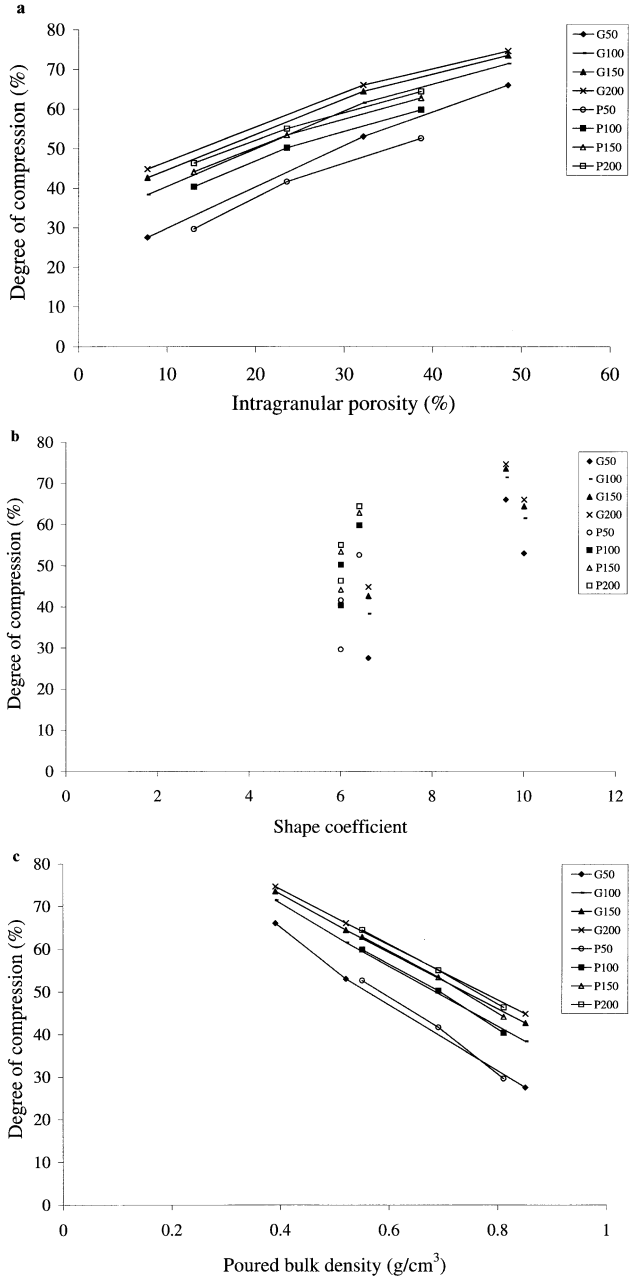

Fig. 5. Degree of compression for all granules (G) and pellets (P) during compression at 50, 100, 150 and 200 MPa as a function of (a) the intragranular porosity, (b) the shape coefficient and (c) the bulk density (poured) of the granules.

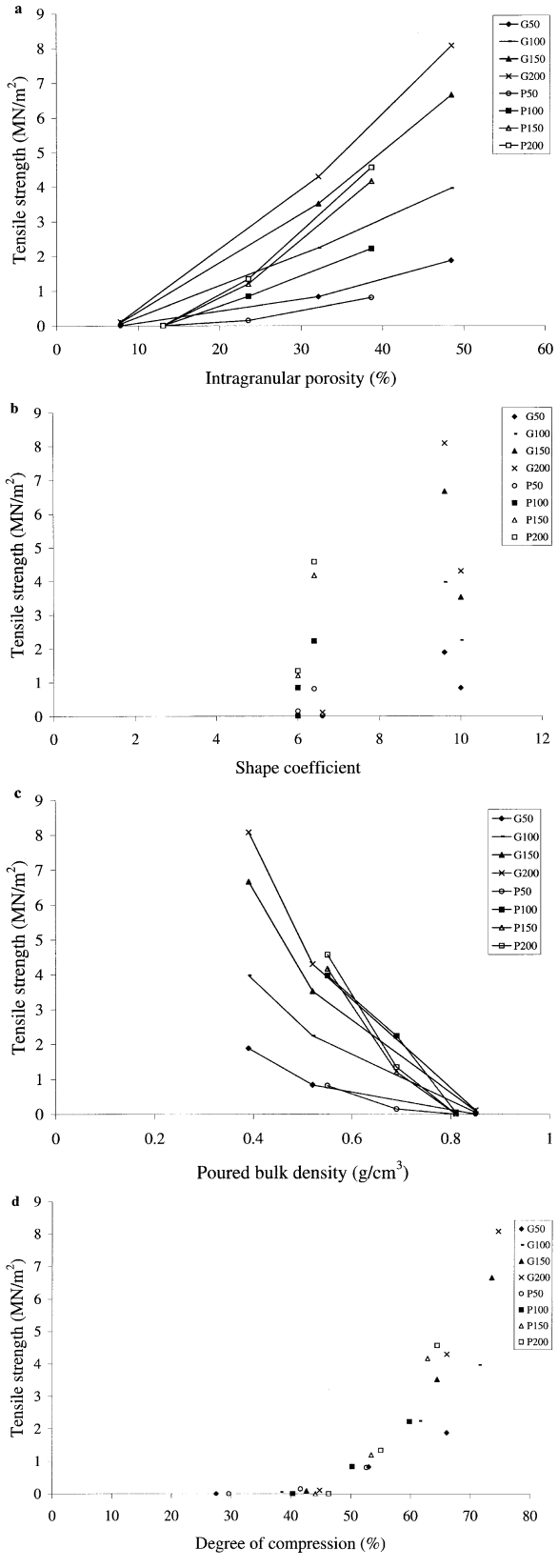

Fig. 6. Tensile strength of tablets compacted at 50, 100, 150 and 200 MPa from all granules (G) and pellets (P) as a function of (a) the intragranular porosity (b) the shape coefficient, (c) the bulk density (poured) and (d) the degree of compression of the granules.

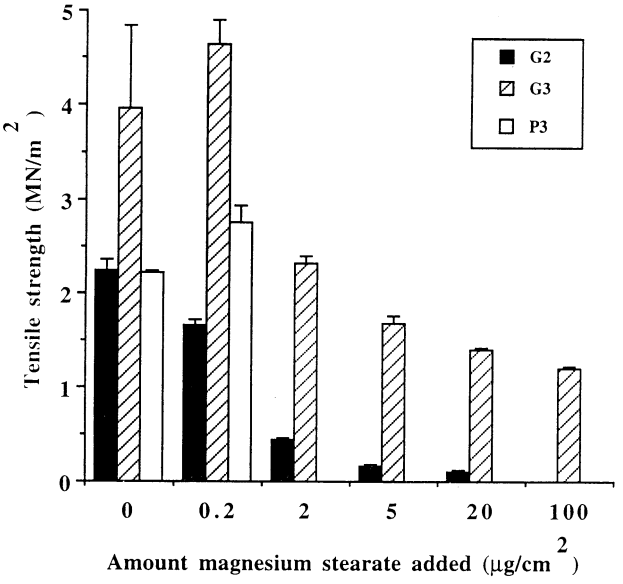

Fig. 7. Tensile strength of tablets compacted at 100 MPa as a function of the amount of magnesium stearate added to the granules and pellets before compression for the intermediate and high porosity granules (G2 and G3) and the high porosity pellets (P3). Error bars represent the 95% confidence limits.

cant. Tablets formed of high porosity granules possessed a high tensile strength even at the largest amounts of lubricant added. The lower lubricant sensitivity of the granules could be explained by a rupture of the lubricant film during compression because of more extensive deformation[6], especially local deformation of granule surfaces, but also by the occurrence of granule attrition which will create new, lubricant-free surfaces available for intergranular bonding. In addition, the lubricant may have covered a smaller proportion of the surface of the granules before compression, compared to the pellets, because of the rougher surfaces. Firstly, magnesium stearate may have been located in the surface cavities, preventing complete surface coverage [23–25] or secondly, the lower bulk density and thus lower flowability of the granules [26] might have slowed down and thus decreased the magnesium stearate film formation process on the granule surfaces before compression. A relationship between the flowability, expressed as the bulk density, and the lubricant sensitivity, has been obtained for starch and cellulose granulations and it was suggested that a low bulk density is the most important factor for the sensitivity of a granulation to magnesium stearate film formation[26].

4. Conclusions

In this study, the tabletting behaviour of granules of different shape was investigated. For all granules irrespective of their shape, the following applied:

1. The granules kept their integrity during compression irrespective of the original shape, and the dominating volume reduction mechanism seemed to be permanent deformation.
2. The total tablet porosity was almost independent of the original intragranular porosity and the granule shape before compression.
3. Increased intragranular porosity increased the degree of compression and gave tablets of a closer pore structure and a higher tensile strength.

The effects of intragranular porosity on the tabletting behaviour of granules was consistent with the effects obtained earlier for pellets of microcrystalline cellulose[3].

A change in the structure of the granules used towards a more irregular shape and a rougher surface affected the tabletting properties in the following way:

1. A change in granule shape towards a more irregular shape, induced a more complex compression behaviour of the granules, i.e. primarily attrition of the granules were induced.
2. The degree of granule deformation which occurred during compression seemed to depend on the combined effects of the intragranular porosity and the granule shape. A more irregular shape increased the bed voidage which allowed an increased degree of deformation which the granules underwent during compression.
3. A shape-induced increased degree of granule deformation during compression gave tablets of a more closed pore structure and a higher tensile strength.
4. An irregular shape and a rougher surface texture made the granules less sensitive to lubrication in terms of their compactability. This was possibly the result of a rupture of the lubricant film due to deformation or attrition during compression, or of an incomplete surface coverage of the granules by the lubricant before compression.

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