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Granule deformation and densification during compression of binary mixtures of granules

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Abstract

The purpose of this study was to investigate whether the deformation and densification during compression of one type of granules are affected by adjacent granules of a different porosity, corresponding to different mechanical strength. Three mixtures were prepared, each consisting of two types of microcrystalline cellulose pellets (intermediate porosity study pellets plus low, intermediate or high porosity surrounding pellets) in the proportion 1:7. The mixtures were compressed and the study pellets were retrieved and analysed in terms of porosity, thickness, surface area and shape. It was shown that the study pellets were compressed by deformation and densification. The degree of densification (decrease in porosity) of the study pellets was independent of the porosity of the surrounding pellets but the deformability (changes in the thickness, surface area and shape) of the study pellets was linked with the porosity of the surrounding pellets. It is concluded that the mode of deformation of the study pellets was regulated by the porosity of the surrounding granules; in a mixture containing granules with a low porosity, compression resulted in irregular study granules with regularly positioned indentations caused by the surrounding granules. The compression properties of the surrounding granules affected the flattening of the study granules to a lesser degree.

Keywords: Microcrystalline cellulose; Extrusion/spheronisation; Intragranular porosity; Deformation; Densification; Mode of deformation

1. Introduction

The most common way to engineer particles used in pharmaceutical manufacturing, e.g. in terms of improving their tabletting properties and their ability to be uniformly coated with a drug release controlling membrane, is to form granules from fine particle mixtures. Consequently, there has been some investigation of the compression behaviour of granules and the possibilities of modifying this behaviour to enable the engineering of granules to be used in immediate and modified release tablets. In this context, it has been shown that granules can be deformed (i.e. can change in shape) (Rubinstein, 1976; Van der

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Zwan and Siskens, 1982; Johansson and Alderborn, 1996) and become more dense (i.e. change in porosity) (Rubinstein, 1976; Van der Zwan and Siskens, 1982; Johansson and Alderborn, 1996; Nicklasson and Alderborn, 1999) during compression. In addition, several reports conclude that granules can fracture or fragment during compression (Selkirk and Ganderton, 1970; Wikberg and Alderborn, 1990; Maganti and Celik, 1993; Adams et al., 1994; Schwartz et al., 1994; Salako et al., 1998). However, experiments performed at our laboratory (e.g. Johansson et al., 1995; Nicklasson et al., 1999) indicate that fragmentation of granules, i.e. the process of splitting them into smaller agglomerates, occurs only to a minor degree during compression and that deformation and densification are the main mechanisms involved in the compression of granules consisting of microcrystalline cellulose. Since granule deformation and densification are probably caused by a flow of primary particles within the granules, i.e. a shearing mechanism, granular factors interfering with the interaction between primary particles within the granule will also affect the compression behaviour of the granules. In this context, the granule porosity seems to be one such granule factor.

In the studies cited above, the investigated powders contained only one type of granule. It is not uncommon, however, for tablets to be formed from a mixture of different types of granules. This is especially applicable to the formation of modified release tablets from granulated drug particles coated with a drug release controlling membrane (commonly referred to as reservoir units). It has, for example, been shown that the compression induced change in drug release from reservoir granules depends on the type of excipient which is combined with the reservoir granules before tabletting (Torrado and Augsburger, 1994; Beckert et al., 1996; Mount and Schwartz, 1996; Pinto et al., 1997; Lundqvist et al., 1998). The characteristics of the excipient particles, often referred to as cushioning particles, thus represent an extragranular material factor that has potential importance for the compression behaviour of granules. For excipient particles which are granules, the compression mechanics can be controlled by varying their porosity (Johansson et al., 1995; Nicklasson and Alderborn, 2000). The purpose of this study was thus to investigate whether the deformation and densification during compression of one type of granules are affected by adjacent granules of a different porosity.

2. Materials and methods

2.1. Materials

Microcrystalline cellulose (Avicel PH101, FMC, Ireland, apparent particle density of 1.58 g/cm^3), deionised water, ethanol (95% Finsprit, Kemetyl, Sweden), red dye (Saturnus AB, Sweden) and magnesium stearate (Ph. Eur., Kebo, Sweden).

2.2. Preparation of pellets

Three batches of pellets of microcrystalline cellulose were prepared by wet granulation followed by extrusion–spheronisation. Different proportions of water and ethanol in the granulation liquid were used to prepare pellets of low, intermediate or high porosity (Table 1). The powder (400 g) was agitated in a planetary mixer (QMM-II, Donsmark Process Technology, Denmark) for 3 min at 500 rpm and the granulation liquid (1.1 times the powder weight) was then sprayed into the mass at a rate of 100 ml/min through a spray nozzle (Schlick model 940, Germany). Wet mixing was continued for 5 min at the same speed. The wet powder mass was then immediately extruded (model E140, NICA System, Sweden) through holes of 1.0 mm diameter and 1.2 mm length and spheronised (model S320-450, NICA System, Sweden) for 3 min on a 32 cm diameter friction plate with a radially designed grid. The pellets were finally dried under ambient conditions for 4 days.

After drying, four sets of pellets were prepared as follows. The size fraction 1000–1250 μm was separated from the batch of pellets with intermediate porosity by dry sieving with a set of standard sieves (Endecotts Ltd., UK). These pellets were then coloured (for recognition during sorting) with red dye dissolved in a mixture of 25%

Table 1
Characteristics of the pellets before compaction

Pellet type	Granulation liquid proportions water: ethanol (% w/w)	Sieve fraction (mm)	Poured density (g/cm^3)	Tapped density (g/cm^3)	Ratio of tapped to poured bulk density (−)	Intergranular voidage (%)	Porosity (%)
Low porosity excipient pellets	100:0	0.71–1.00	0.85 (2.4)	0.86 (1.7)	1.01 (0.78)	42.2 (3.3)	7.50 (3.8)
Intermediate porosity excipient pellets	25:75	0.71–1.00	0.64 (4.1)	0.65 (4.0)	1.02 (0.82)	44.4 (5.2)	27.5 (1.6)
High porosity excipient pellets	15:85	0.71–1.00	0.55 (1.4)	0.56 (1.2)	1.01 (0.54)	44.5 (1.7)	37.6 (0.13)
Study pellets	25:75	1.00–1.25	0.65 (0.96)	0.65 (1.2)	1.01 (0.31)	44.4 (1.2)	26.6 (1.4)

Results are mean values ($n \geq 3$) with relative standard deviation (R.S.D.) (%) given in parentheses.

water and 75% ethanol by dipping the pellets in the dye solution and drying them under ambient conditions. By this procedure, a small amount of dye was deposited mainly on the surface of the pellets. These pellets are hereafter referred to as the study pellets. From all three batches of pellets, the size fraction 710–1000 μm was separated by dry sieving. These pellets are hereafter referred to as the excipient or surrounding pellets.

All four sets of pellets were stored in a desiccator at 40% relative humidity and room temperature for at least 7 days before further investigation. Thus, the moisture content of all pellets used was similar (about 5 wt.%) before further handling.

2.3. Preparation of tablets

Binary granule mixtures were prepared by mixing the study and excipient pellets in a tumbling mixer (Turbula, W.A. Bachofen, Switzerland) at 120 rpm for 5 min in the proportion 1:7 (v/v). The coordination number in a bed of spheres is the maximum number of spheres theoretically able to be in contact with any single sphere. It has been reported that a bed of randomly arranged and loosely packed (by pouring) spheres with a bed voidage of about 45% has a coordination number of approximately seven (Cumberland and Crawford, 1987). Since the bed voidage values obtained for the pellets used in this study (Table 1) were in the same order of magnitude as this, the relative proportions of the two types of pellets was chosen as 1:7, so as to create a packing status before compression in which each study pellet was theoretically surrounded by and in contact with only excipient pellets.

The mixtures of pellets were mixed with 0.5% w/w of magnesium stearate for 100 min in the tumbling mixer. This procedure was used to decrease bonding between the pellets in the formed tablets so as to enable easy mechanical deaggregation of the tablets. We have earlier shown (Johansson and Alderborn, 1996) that a lubricant admixed to microcrystalline cellulose pellets under the conditions chosen in this study will only marginally affect the compression behaviour of the pellets, in terms of the degree of compression as a function of compression pressure, compared with unlubricated pellets.

The lubricated pellet mixtures were compacted in an instrumented single punch press (Korsch EK 0, Germany) equipped with circular flat faced punches (diameter 11.3 mm). For each tablet, the die was manually filled with 500 mg ($\pm$ 5 mg) of pellets and tablets were formed at three different upper punch pressures (40, 80 and 160 MPa). Before each compaction, the punches and die were lubricated with an ethanol suspension of magnesium stearate.

2.4. Deaggregation of tablets

The tablets were gently deaggregated by manually shaking them in a petri dish. The study pellets were then separated from the surrounding pellets in two steps. Firstly, the mixture was sieved through a 1000 μm sieve and, secondly, the two types of pellets were sorted manually from both fractions by colour. The retrieved study pellets were stored in a desiccator at 40% relative humidity and room temperature for at least 7 days before characterisation.

2.5. Characterisation of pellets

The appearance of the pellets was investigated using photomicrographs taken with the aid of a scanning electron microscope (Philips SEM 525, Holland).

The intragranular porosity of the pellets was calculated ($n = 3$ for uncompacted pellets and $n = 2$ for retrieved pellets) as one minus the ratio of the effective and apparent particle densities. The apparent particle density of the microcrystalline cellulose powder was measured using a helium pycnometer (Accupyc 1330, Micromeritics, USA). The effective particle (pellet) density was determined by mercury pycnometry at 100 kPa (approximately corresponding to atmospheric pressure) using a porosimeter (Autopore III 9420, Micromeritics, USA).

The bulk density of the uncompacted pellets was assessed ($n = 3$) using a tap volumeter (J. Engelsmann A.G., Ludwigshafen, Germany, complying with DIN standard 53194). The pellets

were poured into a 50 ml cylinder which was tapped 200 times. The poured and tapped densities were determined from the weight and volume of the pellet bed and the ratio of tapped to poured bulk density was calculated.

The bulk density of the retrieved study pellets was determined ($n = 3$) from the weight and height of beds of pellets held within the container used for permeametry measurements (see below).

The external surface area of the pellets was assessed ($n = 3$) using steady-state air permeametry. The pellets were poured manually into a glass cylinder of 11.5 mm diameter to an approximate bed height of 4 cm and subjected for 10 min to mild vibration. The weight and height of the pellet bed were then measured. The container was connected to a digital differential manometer (P200 S, Digitron Instrumentation Ltd, UK) 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, Brook Instruments B.V., The Netherlands) and the corresponding pressure drop recorded. The permeametry surface area was then calculated according to Eriksson et al. (1993).

The pellet thickness was determined ($n = 2$) by ring gap sizing (F.O.A., Sweden) as described earlier (Nyström and Stanley-Wood, 1976). Suitable vibrating conditions for the sizing table were determined using pretrials. About 1 g of pellets was used for each experiment and the results were analysed in terms of the median of the number distribution.

The shape of the pellets was characterised using image analysis. The pellets were manually dispersed on microscope slides and then photographed in a light microscope (Olympus Vanox, Japan) at two times magnification. The photos were digitalised and the projected area (A), the projected area circle diameter (d) and the perimeter (P) of the pellets were determined ($n = 66$) by image analysis (NIH Image, version 1.61, USA, available on the Internet at http://rsb.info.nih.gov/nih-image/) with a pixel resolution of 5.1–5.3 μm/pixel. The circularity (C) of the pellets (a measure of the closeness of the projected area of the pellet to the area of a circle of the same perimeter) (Cox, 1927) was calculated as:

$$C = \frac{4\pi A}{P^2}$$

and the Heywood shape coefficient, α, (Heywood, 1954) was calculated as:

$$\alpha = S_v d$$

where S_v is the volume specific external surface area of the pellets as determined by permeametry.

3. Results

The preparation procedure used gave pellets with a wide range of intragranular porosity (Table 1), as expected from earlier experience (Johansson et al., 1995). The intragranular porosity was the same for the excipient pellets of intermediate porosity and the study pellets. According to earlier experiences (Johansson et al., 1995; Nicklasson and Alderborn, 2000), the variation obtained in intragranular porosity for the surrounding pellets corresponds to marked differences in their mechanical strength in terms of both the single fracture strength and the compression shear strength of the pellets.

Visual examination of the pellets indicated that they were generally nearly spherical in shape with a smooth surface (Fig. 1a). The values of intergranular voidage and the ratios of tapped to poured bulk density were similar for all four sets of pellets. In addition, these ratios were close to unity, indicating pellets of a high flowability. Thus, the pellets could generally be described as smooth and nearly spherical. The shape measures (circularity and Heywood shape coefficient, Table 2) for the study pellets confirmed that these pellets were nearly spherical in shape before compaction.

After deaggregation of the tablets, the retrieved pellets were similar in size to the original pellets (Fig. 1). Only a few pellet fragments were obtained during deaggregation. Cracks were, however, noticed in some pellets (Fig. 1). The low incidence of fragmentation in these types of pellets during compression is consistent with earlier observations (Johansson et al., 1995) and supports the premise that these types of pellets cannot be described as prone to fragmentation during compression.

Table 2
Characteristics of study pellets before and after compaction[a]

Excipient pellet type	Compaction pressure (MPa)	Surface area [b] (cm^2/cm^3)	Porosity [c] (%)	Bulk density [b,d] (g/cm^3)	Median thickness [c] (μm)	Circularity [e] (−)	Heywood shape coefficient (−)
–	0	63.9 (0.48)	26.6 (1.40)	0.69 (0.09)	926 (0.71)	0.963 (1.73)	7.45
Low porosity	40	67.8 (1.47)	22.2 (1.74)	0.75 (0.74)	849 (0.68)		
	80	80.2 (0.94)	13.9 (1.35)	0.80 (0.35)	794 (0.99)		
	160	86.5 (0.67)	7.71 (2.48)	0.83 (0.22)	747 (1.62)	0.898 (4.65)	10.43
Intermediate porosity	80	69.6 (1.37)	13.9 (5.75)	0.86 (0.31)	757 (0.72)		
	160	73.1 (1.05)	7.20 (1.81)	0.91 (0.16)	701 (0.38)	0.928 (3.53)	8.77
High porosity	40	64.9 (0.75)	21.7 (1.43)	0.77 (0.38)	860 (0.92)		
	80	68.2 (0.72)	13.9 (0.35)	0.86 (0.64)	764 (0.76)		
	160	69.8 (1.65)	7.22 (1.17)	0.93 (0.49)	703 (0.01)	0.954 (2.45)	8.34

[a] Results are mean values with R.S.D. (%) given in parentheses.
[b] $n = 3$.
[c] $n = 2$.
[d] Calculated from vibrated samples.
[e] $n = 66$.

The surface area of the retrieved study pellets increased and their thickness decreased as a result of compaction (Table 2, Figs. 2 and 3). Increased compaction pressure increased the pellet surface area and decreased the pellet thickness. The original porosity of the excipient pellets affected the changes in thickness and surface area of the study pellets in that excipient pellets with the lowest original porosity resulted in less flat study pellets with a higher surface area. Compaction also affected the shape of the individual study pellets (Table 2), resulting in generally more irregular pellets. There was a tendency for the circularity of the study pellets to decrease and the shape coefficient to increase as the porosity of the excipient pellets decreased (Fig. 4).

The photomicrographs (Fig. 1) support the changes in shape of the study pellets with compaction and the influence of the porosity of the surrounding pellets on these changes. Including high porosity excipient pellets in the mixture resulted in elongated but relatively regularly shaped retrieved study pellets. Excipient pellets with lower porosity resulted in study pellets with a more irregular shape: the study pellets had regularly positioned cavities or indentations caused by the surrounding excipient pellets rather than increased flattening (compare Fig. 3). This type of irregularity was most pronounced for study pellets that had been compacted with excipient pellets of the lowest porosity (highest mechanical strength).

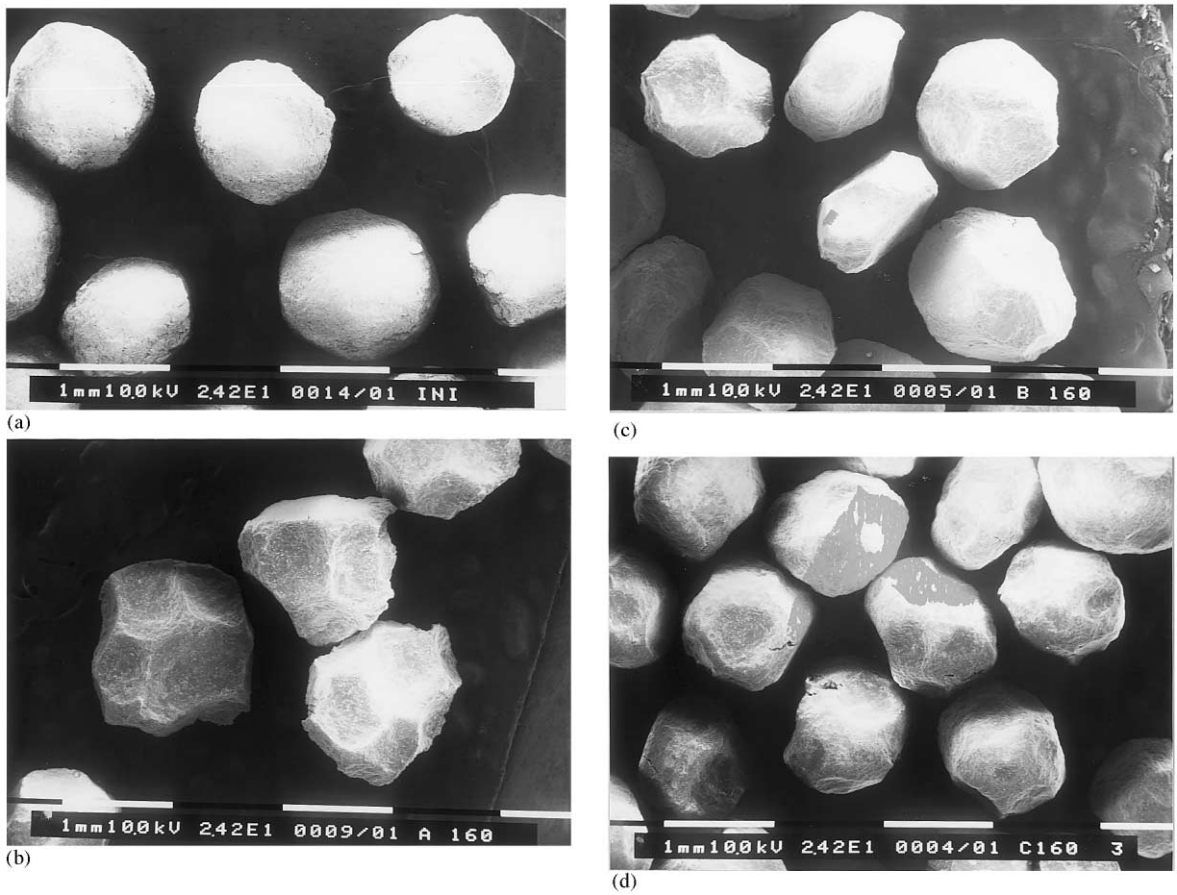

Fig. 1. Scanning electron micrographs of uncompacted study pellets (a) and study pellets compacted at 160 MPa with excipient pellets of (b) low porosity, (c) intermediate porosity and (d) high porosity. The white bar denotes 1 mm.

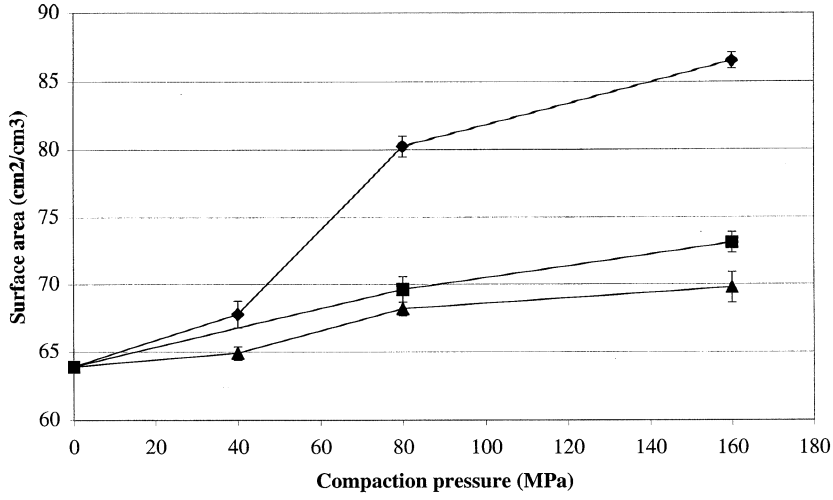

Fig. 2. Volume specific surface area of study pellets as a function of compaction pressure. Study pellets compacted with excipient pellets of low (◆), intermediate (■) or high (▲) porosity. The error bars represent the standard deviation (S.D.).

Compaction also decreased the porosity of the pellets (Table 2). The porosity of the retrieved study pellets was, however, independent of the porosity of the surrounding pellets, i.e. the porosity of the retrieved pellets was dependent only on the compaction pressure.

Changes in the thickness and porosity of microcrystalline cellulose pellets (original porosity 44%) during compaction were determined in an earlier study (Johansson and Alderborn, 1996). Changes in the same characteristics of the pellets used in our study (original porosity 27%) were slightly lower in magnitude, which seems reasonable considering the difference in original porosity.

4. Discussion

Earlier studies (Johansson et al., 1995; Johansson and Alderborn, 1996) have demonstrated that granules formed from microcrystalline cellulose, like those used in this study, will deform and become denser during compaction under pressures of about 5–200 MPa. Those studies also showed that deformation and densification are the dominating mechanisms involved in the compression event, i.e. that, although cracking may occur, actual fragmentation occurs to only a minor degree. The results obtained in this study support those findings. Earlier studies also indicated that the degree of both deformation and densification is affected by the original porosity of the granules, i.e. the original porosity is a granular physical factor which regulates the compression behaviour of those granules that only fragment to a minor degree. The effect of an extragranular material factor (the porosity or mechanical strength of the surrounding granules) on the deformation and densification behaviour of granules has been investigated in this study in order to broaden our understanding of the physical factors regulating the compression behaviour of granules.

The results show that the interaction between the study granules and the surrounding granules was dependent on the compression mechanism studied. The porosity of the surrounding pellets clearly affected the deformation of the study pellets. Although the degree of deformation (the amount of flattening) of the study pellets was affected by the porosity of the surrounding pellets to only a limited degree (Table 2, Fig. 3), changes in the shape of the study pellets (irregularity) with changes in the porosity of the surrounding pellets were more significant (Table 2, Figs. 1 and 4). In contrast, the original porosity of the surrounding pellets had no effect on the densification (decrease

in porosity) of the study pellets during compression (Table 2), despite the differences in deformation.

In earlier discussions of the deformation behaviour of granules, the term mode of deformation (Nicklasson and Alderborn, 1999) has been used to describe the types of changes in shape that granules undergo during compression. Two different modes of deformation (here referred to as mode I and mode II , respectively,) can in a generalised way explain the deformation behaviour of granules. Mode I deformation describes a local change in the geometry of the external surface of a granule in order to conform to the external surfaces of adjacent granules (i.e. no change in bulk dimensions). Mode II deformation describes a change in the main dimensions of the granules, primarily expressed as a flattening of their bulk.

The compression process for microcrystalline cellulose granules has been described from a mechanistic view as occurring in four stages (Johansson and Alderborn, 1996), i.e. granule repositioning (stage 1), granule surface deformation (stage 2), granule bulk deformation and densification (stage 3) and finally, ceased granule deformation (stage 4). It was thus suggested that granules deform at low pressures by a mode I deformation followed at higher pressures by bulk deformation (mode II deformation) parallel with a significant granule densification. Thus, the individual granules will undergo one or both modes of deformation depending on the compaction pressure (the degree of compression). This premise was further developed (Nicklasson and Alderborn, 1999) to suggest that the relative incidence of mode I and mode II was also dependent on the composition of the granules, e.g. the presence of a soft component within the granules. In the discussion below, a possible variation in the deformation and densification behaviour of the pellets dependent on the localisation of the pellets within the powder column held within the die is not considered. Such a variation may occur dependent on a variation in transmitted compression force within the bed of pellets and it is of interest to investigate this problem. It seems though reasonable to assume that the general effects of the importance of the porosity of surrounding pellets for the deformation and densification of the study pellets is independent of the localisation of the pellets within the bed of pellets with the exception for pellets in contact with die wall and punch faces. For these relatively few pellets, their deformation will be controlled by the interaction with the die wall and punch faces rather than by the interaction with surrounding pellets.

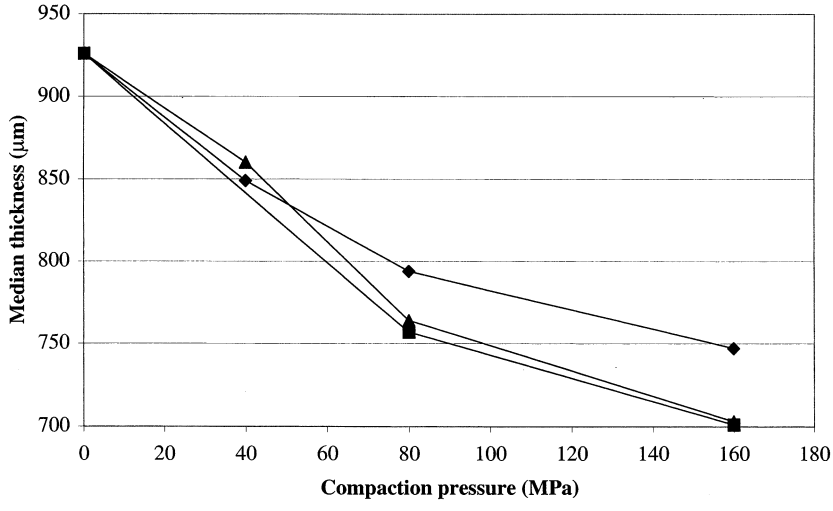

Fig. 3. Median thickness of study pellets as a function of compaction pressure. Study pellets compacted with excipient pellets of low (◆), intermediate (■) or high (▲) porosity.

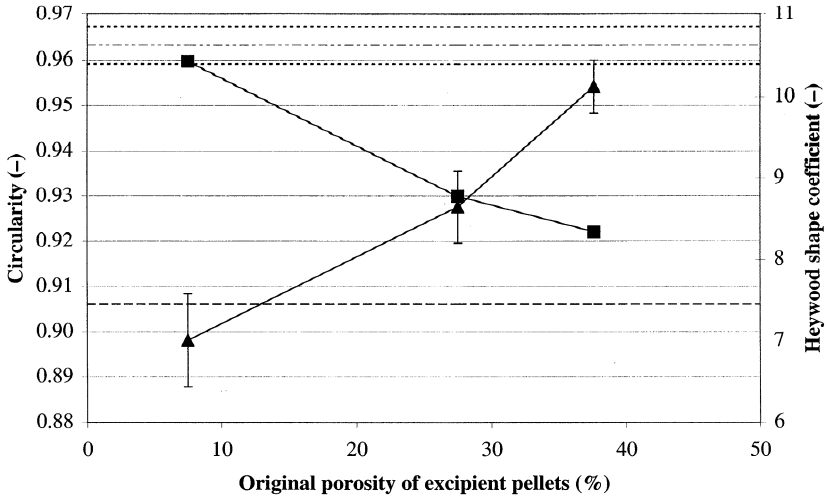

Fig. 4. Values for circularity (- - -) and Heywood shape coefficient (- - -) of study pellets before and after compaction at 160 MPa (circularity ▲, Heywood shape coefficient ■) as a function of original porosity of the excipient pellets. Confidence limits for $P = 0.05$ are shown for circularity values (- - -).

The type of shape change reported in our study can be described as extended mode I deformation, i.e. local deformation leading to conformation with adjacent granule surfaces in such a way that indentations into the study granules were formed (Figs. 1 and 5). Thus, the incidence and character of mode I deformation occurring in a given granule will be dependent on the physical properties of the adjacent granules. The results generated in this study indicate that it is the relative mechanical strength of the adjacent granules that will primarily affect the character of the mode I deformation, i.e. whether indentations will be formed in the study granules or whether the granule surfaces will only be flattened. When the surrounding granules have a higher mechanical strength than the study granules, indentation will occur; however, if the mechanical strength of the surrounding granules is similar or lower than that of the study granules, indentation will not occur but mode I deformation expressed as flattening of the granule surfaces may take place.

Concerning the densification (i.e. the porosity reduction) of the pellets, the results (Table 2) indicate a low porosity reduction at the lowest compaction pressure, followed by a higher densification rate at intermediate pressure which finally will level off. Johansson and Alderborn (1996) suggested that surface deformation was associated only with a limited densification, which became significant during the bulk deformation phase. For the pellets used in our study, one can propose that in the early compression phase, mode I deformation expressed as a local flattening of the pellet surfaces occurs. This type of mode I deformation is associated with limited densification. However, with increased compaction pressure, indentation by the surrounding granules occurs and this type

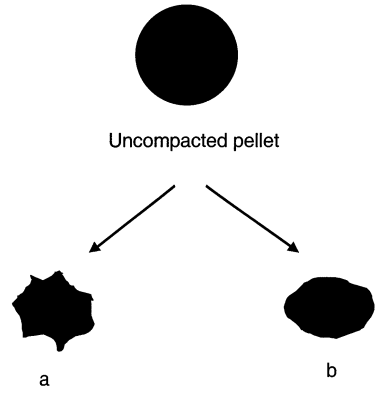

Fig. 5. Schematic representation of the mode of deformation of study pellets compacted with surrounding pellets of (a) lower porosity and (b) higher porosity.

of extended mode I deformation occurs parallel to a significant densification of the pellets.

There was also a tendency for the surrounding granules to affect the thickness of the study granules, i.e. a change towards more irregular study granules was associated with less flattening of these granules (Fig. 3). Thus, the surrounding granules can also affect the mode II deformation of the study granules, but to a less significant degree compared to the effects on mode I deformation.

5. Conclusions

The degree of densification on compression of the study pellets was independent of the porosity of the surrounding pellets. Conversely, the deformation behaviour did depend on the porosity of the surrounding pellets. Less porous surrounding pellets caused indentations into the surface of the study pellets, resulting in irregular pellets with regularly positioned cavities, while more porous surrounding pellets did not indent the study pellets but did flatten their surfaces. Changes in study pellet dimensions were less dependent on the porosity of the surrounding pellets.

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