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Compression behaviour and compactability of microcrystalline cellulose pellets in relationship to their pore structure and mechanical properties

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Abstract

Two series of microcrystalline cellulose pellets were produced by extrusion-spheronization and the size fraction 710–1000 μm was prepared by sieving. The preparation procedure gave nearly spherical pellets with similar shape and surface characteristics but markedly different porosity and mechanical properties. The pellets compressed by permanent deformation rather than by fragmentation. The degree of pellet deformation increased with an increased original pellet porosity while the mechanical strength of the pellets was not a primary factor in the compression behaviour of the pellets. The compactability of the pellets related directly to the original pellet porosity. The results indicate thus that the pellet porosity determined the degree of their deformation during compression which in turn controlled the pore structure and the tensile strength of the compact formed. A high degree of pellet deformation gave a low intergranular separation distance in the compact and promoted the formation of intergranular bonds of a high bonding force.

Keywords: Microcrystalline cellulose; Extrusion-spheronization; Pellet porosity; Pellet pore size; Pellet fracture force; Pellet deformation; Tablet pore structure; Tablet strength

1. Introduction

An understanding of the relationship between physical granule or pellet properties before compaction on the one hand and the compression behaviour and the ability of such particles to form compacts on the other is important in the design and control of granulation and pelletization processes, i.e., particle engineering from the perspective of optimal compaction behaviour. Studies on typical pharmaceutical granules as a model system, consisting of a filler and a binder and being relatively irregular in shape, have indicated (Wikberg and Alderborn, 1991, 1992a, 1993) that the original granule porosity is of importance for their volume reduction behaviour which seemed to control their compactability. The term compactability is the ability of the bed of particles to cohere into or form a compact of a defined

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mechanical strength. A reasonable interpretation of the results is that the porosity of the granules controlled the incidence of granule deformation and fragmentation of the granules during the compression. The terms granule deformation and fragmentation is here referred to structural changes of the granules as such and not to the primary particles of which the granules are formed (Nyström and Alderborn, 1993), i.e., the shape of the granules change by deformation or the granules break down to smaller aggregates by fragmentation.

Due to the irregular structure of the filler-binder granules, it was not possible to establish the dominating compression mechanism for the granules. Furthermore, the question of the effect of granule porosity and granule strength for the compactability of granules needs to be better understood, since apparently conflicting results have been reported (Wikberg and Alderborn, 1991, 1992a; Riepma et al., 1993). Thus, there is a need to focus further on the volume reduction behaviour of pharmaceutical granules and the relationship between volume reduction behaviour and compactability, as well as to understand the role of granule porosity and granule strength in the compaction performance of granules. In this article, these issues are addressed for pellets of microcrystalline cellulose. This model system was chosen for two reasons:

(i) The well-defined shape characteristics of these pellets enables a more detailed description of the volume reduction behaviour of the pellets, i.e., the mechanistic understanding of the compaction process for porous particles can be improved.

(ii) It represents an interesting type of pellets due to their potential use in the production of multiple-unit-dose tablets. A detailed understanding of the volume reduction behaviour of such pellets is of interest both for the construction of the drug pellets and for the choice of a suitable filler. There is still a limited number of studies (Millili and Schwartz, 1990; Béchard and Leroux, 1992; López-Rodriguez et al., 1993; Maganti and Celik, 1993, 1994; Torrado and Augsburger, 1994) focused on the compaction properties of pellets.

2. Materials and methods

2.1. Materials

2.1.1. Microcrystalline cellulose

The microcrystalline cellulose employed was Avicel PH 101 (FMC, USA).

2.1.2. Salicylic acid

Salicylic acid (puriss) was obtained from Merck, Germany (nominal particle size 40–60 μm prepared by milling in a mortar followed by air classification (Alpine A100 MZR, Germany)).

2.1.3. Magnesium stearate

Magnesium stearate (Ph.Eur.) was purchased from Apoteksbolaget AB (Sweden); permeametry surface area 1.66 m^2/g.

2.1.4. Ethanol

Ethanol was supplied as Finsprit 95% w/w by (Kemetyl, Sweden).

2.2. Preparation of pellets

Two series of pellet masses were prepared. In the first series (1–5), pellets of microcrystalline cellulose were produced and in the second series (I–IV), pellets of microcrystalline cellulose and salicylic acid in different proportions were produced. The amounts of salicylic acid used in the second series were 0, 15, 30 and 45% of the total weight of the dry mass.

The powder (200 g) was placed in a planetary mixer (Braun Multipractice Plus electronic UK20, Germany), equipped with a specially designed mixer blade, and dry mixed for 10 min at 700 rpm. The agglomeration liquid, in a proportion of 1.1 times the weight of the dry mass, was poured into the mixing bowl at an approximate rate of 100 ml/min. For pellet mass 1–5, mixtures of ethanol and water was used and for pellet mass I–IV, water was used as agglomeration liquid (Table 1). After the addition of liquid, the wet mass was agitated further at 700 rpm for 5 min and thereafter extruded in a radial screen extruder (model E140, Nica System, Sweden), fitted with a 1.2 mm thick screen with holes of 1.0 mm

in diameter. The extrudate was then spheronized for 3 min at 1022 rpm on a radial plate spheronizer (model S450, Nica System, Sweden) with a plate diameter of 45.0 cm and the pellets obtained were dried overnight at 35° C. Finally, the size fraction 710–1000 μm was prepared by dry sieving.

Pellets from pellet masses I–IV were placed in ethanol and the salicylic acid was removed from the pellets by repeated extraction. The amount of dissolved salicylic acid in the ethanol was analysed spectrophotometrically (Zeiss Spektralphotometer PM6, Carl Zeiss, Germany) at 303 nm and for all masses, at least 95% of the salicylic acid in the pellets was removed. The pellets were dried at room temperature overnight and the size fraction 710–1000 μm was prepared by dry sieving.

The pellets were stored in a desiccator at 40% relative humidity and room temperature for at least 7 days before any characterization or tabletting.

Table 1
Composition of the agglomeration liquid

Denomination of pellets	Ethanol/water (% w/w)
1	0:100
2	30:70
3	60:40
4	80:20
5	90:10
I	0:100
II	0:100
III	0:100
IV	0:100

2.3. Characterization of pellets

2.3.1. Appearance

Photomicrographs of the pellets were taken with the aid of a scanning electron microscope (Philips SEM 525, The Netherlands). The pellets were also inspected with an optical light microscope (Vanox Universal Research Microscope, Japan).

2.3.2. Bulk densities

A 50 ml cylinder (inner diameter of 25 mm) was filled with pellets to a volume of 50 ml and the poured and tapped (after 200 taps) densities were determined by a tap volumeter (Eberhard Baur D7300, Germany) ($n = 3$).

2.3.3. Porosity (intragranular porosity) and voidage (intergranular porosity)

The porosity of the pellets ($n = 3$) was calculated from the apparent particle density, i.e., the mass of a particle divided by the volume of the particle excluding open pores but including closed pores, and the effective particle density, i.e., the mass of a particle divided by the volume of the particle including open and closed pores (definitions according to British Standard 2955:1958, section 5). The apparent particle density was measured by an air comparison pycnometer (Beckman, model 930, USA) and the effective particle density by mercury pycnometry according to Wikberg and Alderborn (1990a). The voidage of the pellet masses was calculated from the tapped bulk density and the effective particle density.

2.3.4. Pore size

The intragranular pore structure was assessed by mercury intrusion measurement (Micromeritics Pore Sizer 9320, USA) and the relationship between the intruded volume of mercury and the intrusion pressure was analysed. Intrusion pressures between 0.010 and 207 MPa were used. The pore sizes corresponding to the intrusion pressures were calculated by assuming circular pore openings, a surface tension for mercury of 480 mN/m and a contact angle between mercury and the material of 130° (Orr, 1969/1970).

The size of the intragranular pores was also assessed by a spin echo NMR technique (Ek et al., 1994). Before these measurements, the pores of the pellets were filled with cyclohexane by adding an excess amount of cyclohexane to the dry pellets and leave this slurry in an evacuated desiccator for 24 h. Thereafter, the excess liquid was removed by firstly, decantation and secondly, evaporation under reduced pressure. The evaporation process was stopped when the pellets became free flowing, i.e., the external surface of the pellets was nearly dry. A nearly dry surface of the cyclohexane pellets was important in order to

avoid the inclusion of intergranular voids in the pore size distributions obtained by the technique.

By the spin echo NMR technique, the mobility of liquid molecules, expressed as an apparent diffusion coefficient ($D(t)$), can be estimated during different diffusion times, from 10 ms up to about a few seconds. When the liquid is localized in a net work of pores, the pore walls will act as a restriction against diffusion of the liquid molecules. During short diffusion times, only a few molecules have had the time to collide against pore walls and the apparent diffusion coefficient will be close to the diffusion coefficient as a bulk liquid. If the diffusion time is long, more molecules have had the time to collide against the pore walls and the apparent diffusion coefficient will be reduced. The apparent diffusion coefficient can be transformed into a diffusion distance, x, as: $x = \sqrt{[2D(t)t]}$. A plot of the ratio between the apparent diffusion coefficient and the diffusion coefficient as a bulk liquid as a function of the diffusion distance will represent a pore size distribution. From this distribution, a median pore diameter can be determined. For the pellets used in this study, the lower pore size limit measurable with the spin echo NMR technique was 1–2 μm.

2.3.5. Mechanical properties

Pellets for mechanical testing were size fractionated also by a ring gap sizer (F.O.A., Sweden) as described by Nyström and Stanley-Wood (1976) and the fraction 761–840 μm was selected. The force needed to fracture the pellets and the slope of the force-displacement profiles (which were approximately linear from 1 N up to the fracture force) were determined for 30 pellets as described by Wikberg and Alderborn (1992a).

2.3.6. External surface area

The air permeability of the beds of pellets ($n = 3$) was determined by a transient permeameter specially designed for permeability analysis of coarse particulate powders (Eriksson et al., 1990) and the permeability coefficient and the surface area of the pellets were calculated (Wikberg and Alderborn, 1990a; Eriksson et al., 1993).

2.3.7. Thickness

The median thickness of the pellets was determined ($n = 1$) by ring gap sizing (F.O.A., Sweden) as described by Nyström and Stanley-Wood (1976).

2.4. Preparation of tablets

Pellets were compacted in an instrumented single punch press (Korsch EK 0, Germany) at maximum upper punch pressures of 50, 100 and 200 MPa. The press was equipped with flat-faced punches with a diameter of 1.13 cm. For each tablet, 500 mg of pellets was weighed on an analytical balance and then manually filled into the die. The position of the lower punch was adjusted to obtain the required pressure. Before each compaction, the die was lubricated with a suspension of 1% by weight of magnesium stearate in ethanol.

Lubricated pellets were also compacted at an upper punch pressure of 100 MPa. 7 g of the pellets was mixed for 100 min with 0.5% by weight magnesium stearate in a Turbula mixer (W.A. Bachofen, Switzerland) at 90 rpm. A long mixing time was chosen to ensure that a film of magnesium stearate which was similar in structure for the different type of pellets was formed around the pellets. The intention was to lower the bonding properties between the pellets during compaction as much as possible, i.e., the mixing conditions is an experimental tool rather than a reflection of suitable applied mixing conditions.

In addition to the registration of the upper punch force, the upper punch displacements were registered, as described earlier (Alderborn et al., 1987), during the compaction at 200 MPa ($n = 1$). After correction for upper punch deformation, the height of the compact in-die at an applied pressure P (H_P) was estimated at each applied pressure. The degree of compression (C) of the pellets in-die was thereafter calculated as: $C_{\%} = ((H_0 - H_P)/H_0) \times 100$, where H_0 is the estimated height of the pellet bed in-die before compression (i.e., calculated from the poured bulk density, the powder weight and the die diameter).

2.5. Characterization of tablets

2.5.1. Appearance

Photomicrographs of the upper and fracture (after diametral compression) surfaces of tablets, compacted from unlubricated pellets at 100 MPa, were taken on a scanning electron microscope (Philips SEM 525, The Netherlands).

2.5.2. Tensile strength

The tablets were stored for at least 7 days in a desiccator at 40% relative humidity and room temperature and thereafter compressed diametrically ($n = 3–10$) by a materials testing machine (model M30K, J.J. Lloyd Instruments Ltd, UK) at a compression rate of 5 mm/min. From the force needed to fracture the tablet, a tablet tensile strength was derived as given by Fell and Newton (1970).

2.5.3. Porosity

The total porosity of the tablets was calculated from the height and weight data of the tablets and the apparent particle density of the pellets ($n = 3–10$).

2.5.4. Air permeability

The air permeability of tablets, prepared from unlubricated pellets at compaction pressures between 20 and 100 MPa, was measured by constant volume permeameters as described earlier (Alderborn et al., 1985; Eriksson et al., 1990). For each tablet, the permeability coefficient was calculated (Wikberg and Alderborn, 1990a). The

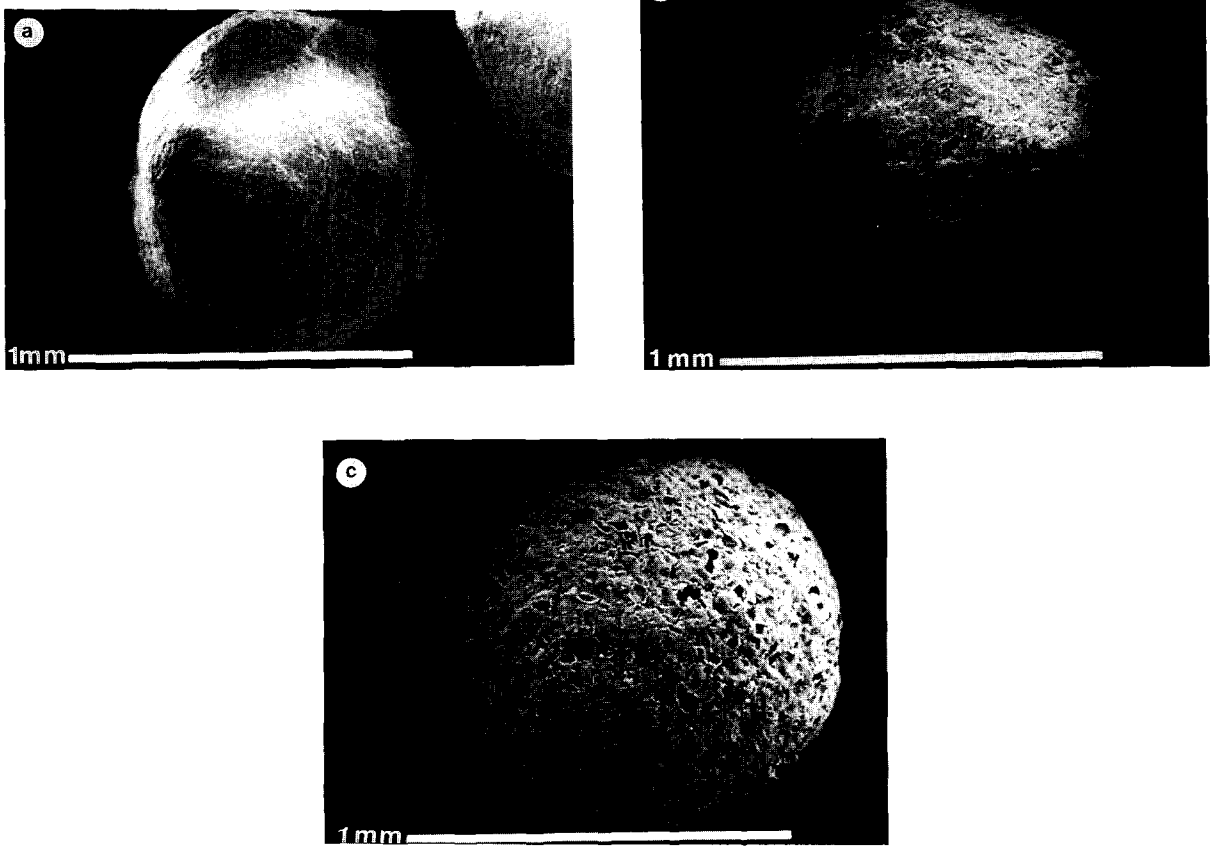

Fig. 1. SEM photomicrographs of some pellets. (a) Pellet 1, (b) pellet 5 and (c) pellet IV. The white bar denotes 1 mm.

presented values are single measurements, or for 100 MPa tablets, mean values of five measurements.

3. Results and discussion

3.1. Dimensions, pore structure and mechanical properties of pellets

Examinations of the pellets by SEM (Fig. 1a–c) showed that the pellets generally were nearly spherical in shape and possessed a smooth surface. The pellets were of similar size although a small spread in the measures of surface area and thickness (Table 2) were obtained. For both series of pellets, a similar range of porosity was obtained with a 4-fold increase in porosity within each series (Table 2). An increased proportion of ethanol in the agglomeration liquid resulted in more porous pellets in the first series (1–5) and a larger amount of salicylic acid in the powder mixture during pelletization gave, as expected, a higher pellet porosity in the second series (I–IV). The bulk densities varied markedly due to a variation in pellet porosity. Thus, the calculated intergranular voidages were generally similar supporting the view that the pellets generally possessed similar size and shape characteristics.

The mercury intrusion measurements generally gave bimodal pore size distributions within the range of intrusion pressures used. For series 1–5, two distinctly separated peaks were obtained and the first peak was considered to correspond entirely to intergranular voids. The photomicrographs of the surface of these pellets indicated that the intragranular pores were small (Fig. 1a,b) and probably considerably smaller than the intergranular voids. The pressure threshold at which mercury began to penetrate the intragranular pores was thus defined as the start of the second peak. For series I–IV, the peaks of the intra and intergranular pores overlapped each other and the start of the second peak was more difficult to determine. In the preparation of these pellets, salicylic acid particles of nominal size 40–60 μm were used. Thus, it can be expected that the largest intragranular pores would have a diameter of approx. 50 μm. This was supported by examination of photomicrographs of the surface of pellets I–IV (Fig. 1c). Thus, for these pellets, the pressure threshold at which mercury began to penetrate the intragranular pores was defined as the pressure corresponding to a pore diameter of 50 μm.

Based on these definitions of the largest intragranular pores, the total amount of mercury which could be intruded into the intragranular pores was determined. By combining these volumes with the total volume of solid used during the analysis, a second estimate of the porosity of the pellets was calculated. A good correlation between porosity values obtained by pycnometry and by intrusion was obtained (Table 2). However, the

Table 2
Particulate and packing characteristics of pellets

Denomination of pellets	Bulk density of pellets (g/cm^3)		Tapped voidage of pellet masses (%)	Porosity of pellets (%)		Thickness of pellets (μm)	External surface area of pellets (cm^2/g)
	Poured	Tapped		Pycnometry	Intrusion		
1	0.81 (2.5)	0.83 (1.4)	40	11.0(1.06)	6.4	760	45.0 (1.14)
2	0.75 (1.4)	0.78 (0.37)	41	14.4(1.16)	13.2	720	49.4 (0.117)
3	0.61 (1.6)	0.63 (1.8)	44	27.2(2.41)	26.3	730	53.2 (0.715)
4	0.50 (0.58)	0.52 (0.53)	44	40.1(0.38)	39.2	725	48.1 (7.57)
5	0.44 (1.3)	0.46 (0.63)	45	46.4(0.76)	44.1	760	50.2 (0.498)
I	0.83 (0.54)	0.86 (0.22)	37	11.7(0.61)	7.8	740	42.0 (0.963)
II	0.68 (0.73)	0.70 (0.73)	42	21.7(0.53)	18.3	770	46.0 (0.253)
III	0.56 (0.66)	0.58 (0.24)	44	33.0(0.80)	30.4	810	48.0 (0.984)
IV	0.45 (0.95)	0.47 (0.94)	44	45.9(0.13)	44.8	805	59.7 (2.28)

Mean, relative standard deviation given in parentheses, $n = 3$.

intrusion based values were generally slightly lower and there seems to be a constant discrepancy between the values obtained by the respective methods. This discrepancy is probably related to the measuring principle of assessing the porosity of the pellets. Nevertheless, the two techniques provide values of pellet porosity which compare favourably with each other, which indicates that the definitions of intragranular pores used in the determination of intragranular pore size distribution were reasonably valid.

From each cumulative pore size distribution (Fig. 2a,b), a median pore size was estimated for all pellets and the median pore size was generally very low, i.e., below 1 μm. This is consistent with earlier reports (Rahman et al., 1991) where mercury intrusion measurements have been used to assess the size of intragranular pores in pellets of a mixture of microcrystalline cellulose and lactose. If the pores at the surface of the pellets are small and atypical compared to the pores within the pellets (e.g., due to a marked densification of the pellet surfaces during spheronization), pore size distributions which are non-representative for the interior of the pellets will be obtained by an intrusion based method. It seems reasonable that the mechanical properties of pellets will be controlled by the packing characteristics of the particles across the whole cross-sectional area of the pellet, rather than by the packing characteristics of the particles at the pellet surface. In order to validate the pore size data obtained by mercury intrusion, an attempt to assess the size of the pores in the interior of the pellets by spin echo NMR measurements was made. Pore size results obtained with this technique had earlier been shown (Ek et al., 1994) to compare favourably with size results by mercury intrusion for porous cellulose beads. For all pellets except pellet IV, a considerable portion of the pores, i.e., above 50%, was assessed to be below 1–2 μm and no median values could thus be determined. For pellet IV, the value was approximately 4 μm which is considerably larger than the median values from mercury intrusion data. The NMR measurements thus support the view that the pores of these pellets generally were very small, also in the interior of the pellets. It is thus suggested that

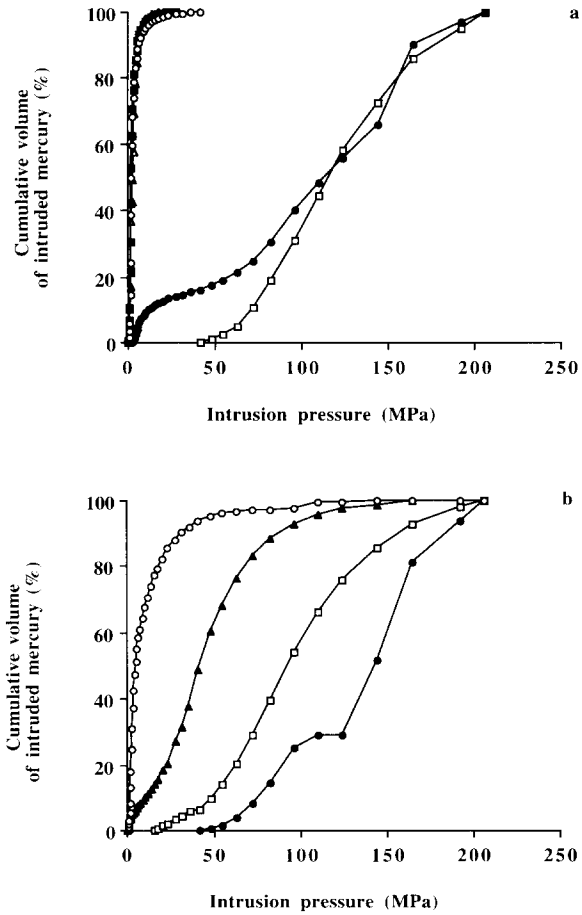

Fig. 2. Cumulative volume of intruded mercury as a function of the intrusion pressure during mercury intrusion measurements of the pellets. (a) Pellets 1–5; (□) 1, (●) 2, (△) 3, (■) 4, (○) 5 (b) pellets I–IV; (●) I, (□) II, (▲) III, (○) IV.

the mercury intrusion results, despite errors connected with the estimation of a pore diameter from an intrusion pressure, reasonably well reflect the size of the pores in the whole pore structure of the pellets.

For both series of pellets, the fracture force of the pellets increased with a decreased pellet porosity (Fig. 3a). However, pellets of series I–IV generally possessed a higher fracture force compared to pellets of series 1–5, although the former pellets possessed a wider size distribution including a fraction of comparatively large intragranular pores. It seems thus that for these pellets, a few large pores present in the pellets

cannot act as defects which initiates a fracture of the pellet. On the contrary, it seems that the median pore size of the pellets was related to the force needed to fracture the pellets (Fig. 3c).

During diametral compression of the individual pellets, it was visually observed that the pellets deformed slightly, probably a permanent deformation, before a crack was obtained in the pellets. As a measure of the deformability of the pellets, the slope of the force-displacement profile was calculated (Wikberg and Alderborn, 1992a). Also the deformability increased with an increased pellet porosity (Fig. 3b). There was a general tendency that series 1–5 possessed higher deformability. However, the relative influence of the porosity or the pore size of the pellets on their deformability (Fig. 3b,d) is difficult to state. However, it is possible that for these pellets, formed of a plastic rather than a brittle material, the mean separation distances between the particles which constitute the pellet will control the resistance of the pellet to fracture, while the packing fraction of the particles in the pellet has a greater importance on their deformability.

To summarise, the initial physical characterization of the pellets indicates that the preparation procedures used in this study gave a series of pellets which can all be described as nearly spher-

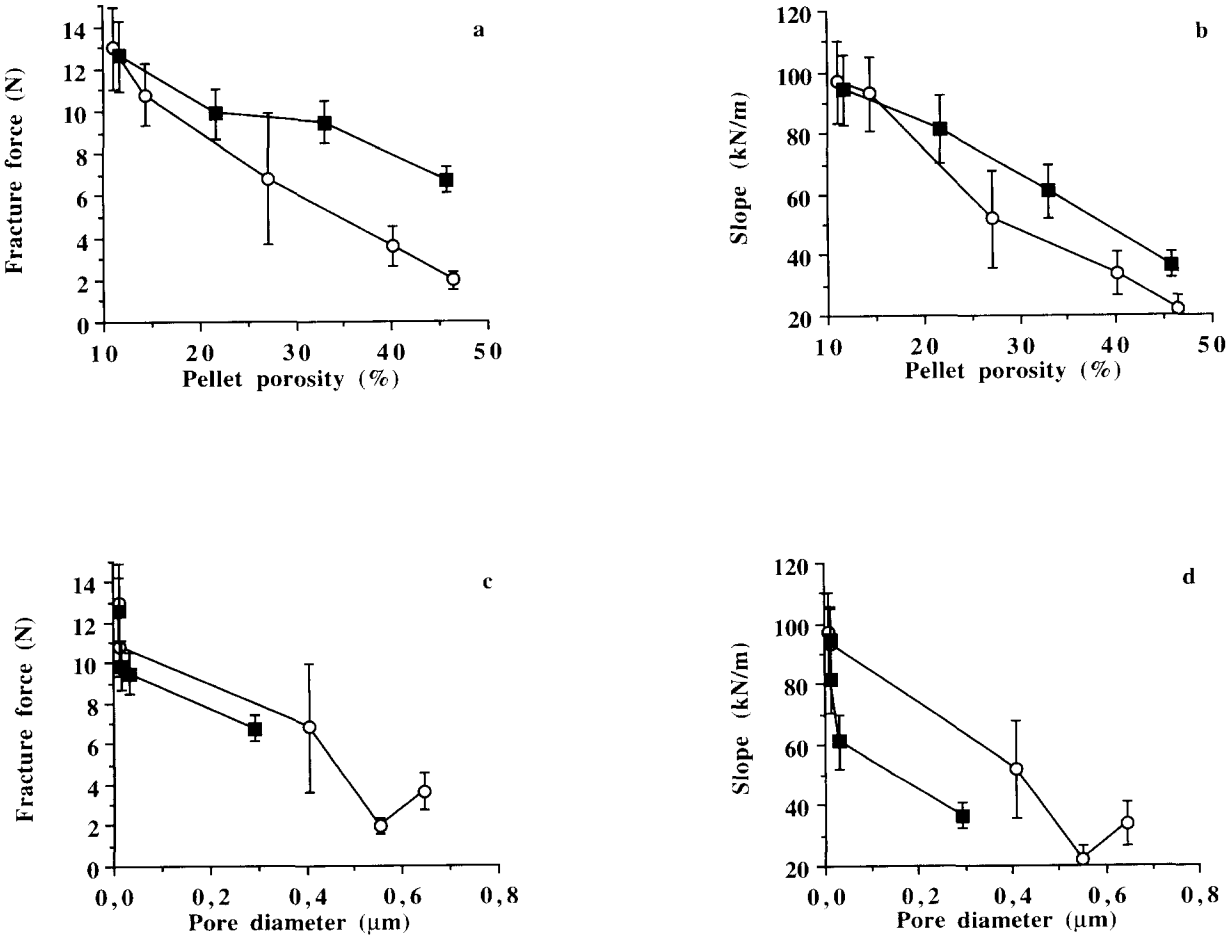

Fig. 3. Fracture force and the slope from the force-displacement profile as a function of the pellet porosity (a,b) and as a function of the median pore diameter of the pellets, determined from mercury intrusion data (c,d). Bars denote 95% confidence interval of the mean. (○) Pellets 1–5 and (■) pellets I–IV.

ical with a relatively smooth surface and of similar size. The pellets thus possess suitable dimensional properties before compression for an evaluation of the dominating mechanism of compression. The preparation procedures also gave two series of pellets with a wide and similar range of pellet porosities. However, with respect to the pellet porosity, the fracture resistance of the pellets differed between the series due to differences in their median pore size. Thus, the two series of pellets are suitable model systems for an evaluation of the respective influence of porosity and fracture resistance on the compression behaviour of pellets.

3.2. Compression behaviour of pellets

3.2.1. Photomicrographs

In Fig. 4a–h, photomicrographs of the upper and the fracture surfaces of tablets compacted at 100 MPa of pellets I–IV are presented (which are also representative for the other series of compacts). Although the pellet porosity before compaction varied considerably, the porosities of the compacts prepared at 100 MPa were similar (Table 3).

Generally, discrete pellets can clearly be distinguished within the compact although the separation distances between the pellets are very low. Moreover, the size and appearance of the pellets in the compact are similar to these characteristics of the original pellets. Thus, it seems that the pellets tend to keep their integrity when compacted and do not fragment into smaller units. Hence, the dominating mechanism of compression of these pellets seems to be deformation, perhaps in combination with a densification of the pellets. One can also notice that the shape of the pellets exposed to the upper tablet surface is more regular than the shape of the pellets exposed at the tablet fracture surface. In addition, an increased original porosity gave flatter, more deformed pellets within the compact. Thus, an increased pellet porosity seems to increase the degree of deformation of the pellets which occurred during the compression. This deformation seems to occur mainly in the same direction as the stress is applied during compression.

At the fracture surface of the compact, one can notice some fractured pellet surfaces, especially for compacts prepared from pellets of higher porosity. Those fractured surfaces could be the result of limited fragmentation of pellets during the compression. However, it could also be caused by the propagation of the fracture during the tablet strength analysis across, and not only around, the pellets. If this latter conclusion is valid, it seems that the intergranular coherency approached the coherency between the primary particles within the pellets for compacts prepared from pellets of higher porosity.

Table 3
Tensile strength, total porosity and permeability ratios of tablets compacted at 100 MPa

Denomination of pellets	Tablet tensile strength (MN/m^2)		Total porosity of tablets (%)	Permeability ratio [b] ($\times 10^6$) (–)
	Unlubricated	Lubricated		
1	0.05 (20.0)	[a]	17.7 (0.63)	12200
2	0.12 (16.7)	[a]	20.9 (0.35)	5240
3	1.57 (17.8)	[a]	20.7 (0.16)	817
4	3.71 (4.58)	[a]	20.1 (0.28)	4.72
5	5.02 (5.38)	0.27 (1.17)	19.8 (0.30)	0.652
I	0.034 (46.2)	[a]	18.7 (0.47)	9640
II	0.93 (6.30)	[a]	19.7 (0.27)	867
II	3.01 (2.96)	0.064 (20.8)	19.3 (0.24)	50.8
IV	5.25 (3.20)	0.60 (6.60)	19.6 (0.27)	2.72

Mean, relative standard deviation given in parentheses, $n = 8–10$.
[a] Tablets were coherent after compression but failed to record a fracture force.
[b] Ratio between the permeability of a compact prepared at 100 MPa and that of the bed of pellets before compaction.

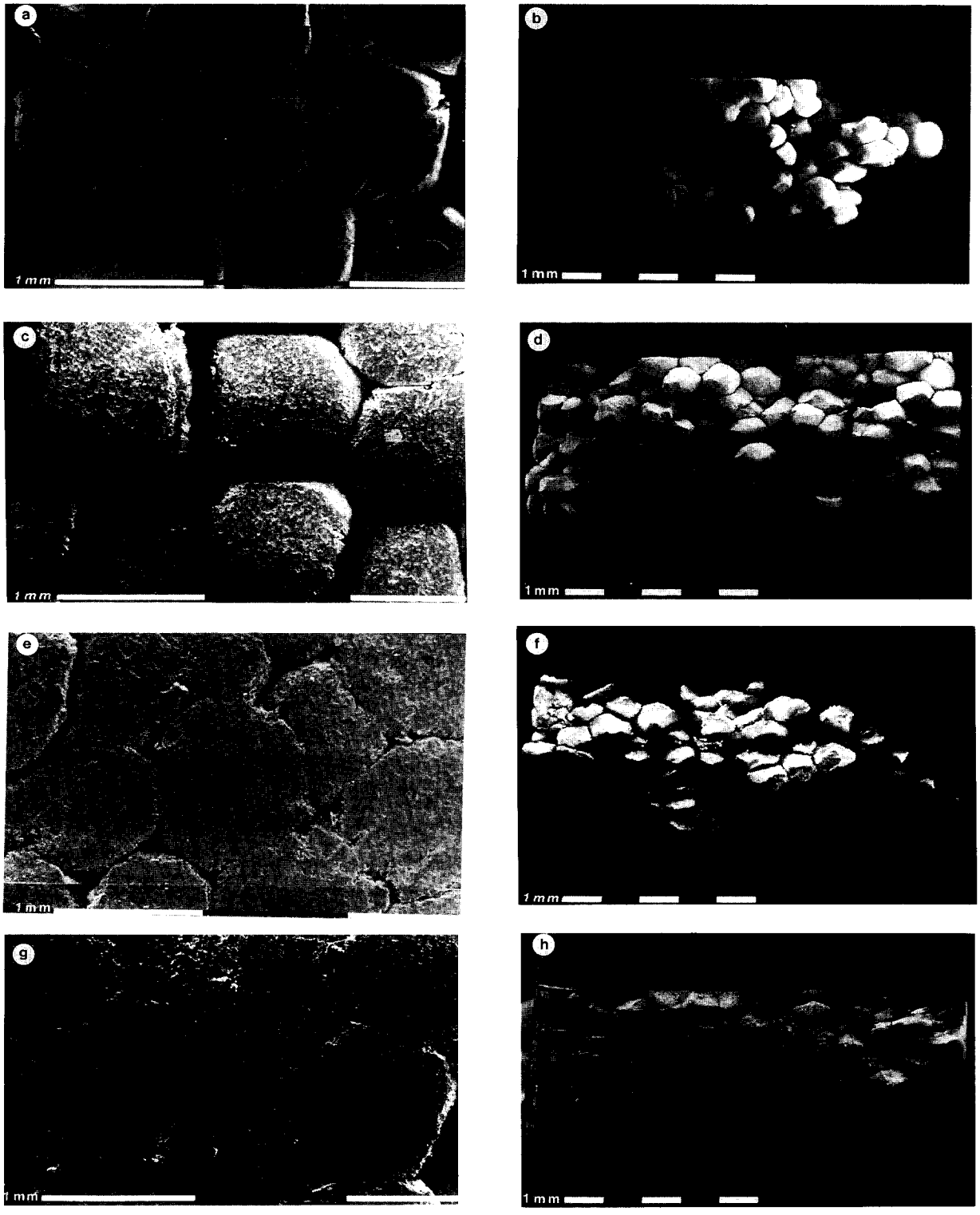

Fig. 4. SEM photomicrographs of the upper surface and the fracture surface of tablets compacted from unlubricated pellets at 100 MPa. (a,b) Pellet I, (c,d) pellet II, (e,f) pellet III and (g,h) pellet IV. The white bar denotes 1 mm.

3.2.2. Effect of magnesium stearate addition on pellet compactability

The incorporation of magnesium stearate in a tablet mass is normally expected to decrease the tablet strength. This is usually explained in terms of a reduction of the bonding force between particles, due to the presence of a film of magnesium stearate on the particle surface (De Boer et al., 1978). The degree of particle surface coverage of magnesium stearate before compression and the formation of new surfaces during compaction, e.g., due to particle fragmentation, can consequently affect the distribution of interparticulate bonds in the compact. Thus, the relative decrease in tensile strength of a compact due to the addition of magnesium stearate has been suggested as a measure of the degree of fragmentation of the particles during compaction (De Boer et al., 1978; Duberg and Nyström, 1982), provided a similar degree of surface coverage could be obtained before compaction. The pellets used in this study had similar shape and surface properties and the conditions used during the mixing process and the amount of magnesium stearate added were held constant for all pellets. Thus, the surface coverage of magnesium stearate on the pellets is therefore assumed to be similar for all pellets used. Moreover, the mixing conditions, i.e., an excess amount of lubricant admixed for a long period of time, was chosen to obtain a near complete film of lubricant on the surface of the pellets.

The lubricated pellets were generally able to form compacts but the tensile strength of the compacts was in many cases lower than the detection limit of the apparatus used during the strength analysis. Also for the pellets which cohered into compacts of measurable tensile strength, the tensile strength were low compared to the strength of tablets of unlubricated pellets (Table 3). The effect of magnesium stearate on the compactability of the pellets thus supports the view that pellet deformation is the dominating mechanism of volume reduction for these pellets and that the incidence of pellet fragmentation generally is limited or non-existent. However, there is a tendency that an increased pellet porosity reduced the strength reduction effect of the lubricant. Thus, especially for pellets of the highest porosity, some fragmentation might have occurred during compression. It cannot be excluded however, that a marked deformation of the pellets during compression can rupture the magnesium stearate film and expose clean pellet surfaces. The results can thus also be interpreted as an effect of pellet porosity on the degree of deformation which the pellets undergo during compression.

3.2.3. Degree of compression-applied pressure relationships

The degree of compression of the pellets increased dramatically at low applied pressures fol-

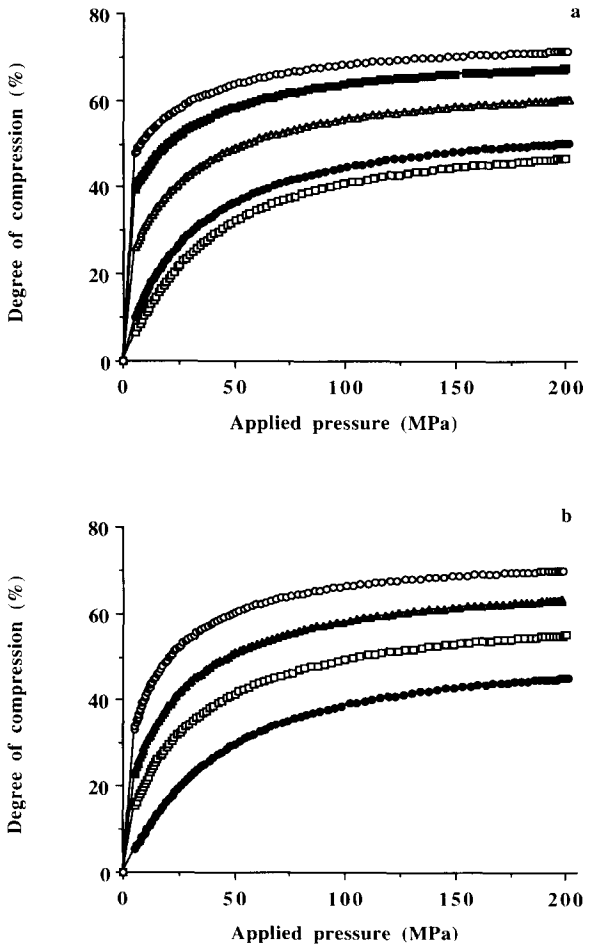

Fig. 5. Degree of compression of the pellets in-die as a function of the applied pressure. (a) Pellets 1–5 and (b) pellets I–IV. Symbols as in Fig. 2.

lowed by a levelling off at the upper end of the range of applied pressures used (Fig. 5a,b). The reduction in powder bed volume is a reflection of pellet repositioning and of the changes in physical properties which the pellets undergo during compression. As discussed above, the pellets used in this study compressed by deformation and the incidence of fragmentation is probably low. It is thus reasonable to assume that the degree of compression of the pellet mass in the die is a reflection of the degree of deformation of the individual pellets which took place during compression.

Generally, an increased porosity and a decreased fracture force of the pellets corresponded to an increased degree of compression (Fig. 6a,b). The two series of pellets gave two separate relationships between the degree of compression and pellet fracture force, but gave a unique, almost linear relationship between degree of compression and pellet porosity. Thus, an increased pellet porosity increased the degree of deformation of the pellets during compression. The degree of deformation of the pellets seemed to be controlled by their porosity before compression, rather than their ability to withstand an applied force as individual pellets.

A deformation of a pellet during compression is probably caused by a repositioning of the primary particles which constitute the pellet. The results obtained in this study indicates that the possibility of repositioning of the primary particles within the pellet is controlled by the total volume of air which surrounds the primary particles rather than how this air phase is distributed, as reflected by the pore size distribution. At high porosities, the primary particles can find new positions within the pellets relatively easily and a marked pellet deformation will be the consequence of the applied compression stress. With a reduced porosity, the possibility for the primary particles to find a sufficient space to move into when the pellets are stressed will be limited and the degree of deformation which the pellets undergo during compression will be low. Furthermore, at low porosities, the primary particles might be rigidly positioned relative to each other which can also affect the possibility of the particles to reposition. The results indicate also that for these pellets, their resistance against fracturing will not be a primary factor in the compression behaviour of the pellets, but might correlate with the compression behaviour due to a parallel relationship with the pellet porosity. However, this conclusion might not be applicable to pellets or granules which possess a marked fragmentation during compression. Here, the resistance to fracturing might be the primary pellet characteristic which controls the compression behaviour of the pellets.

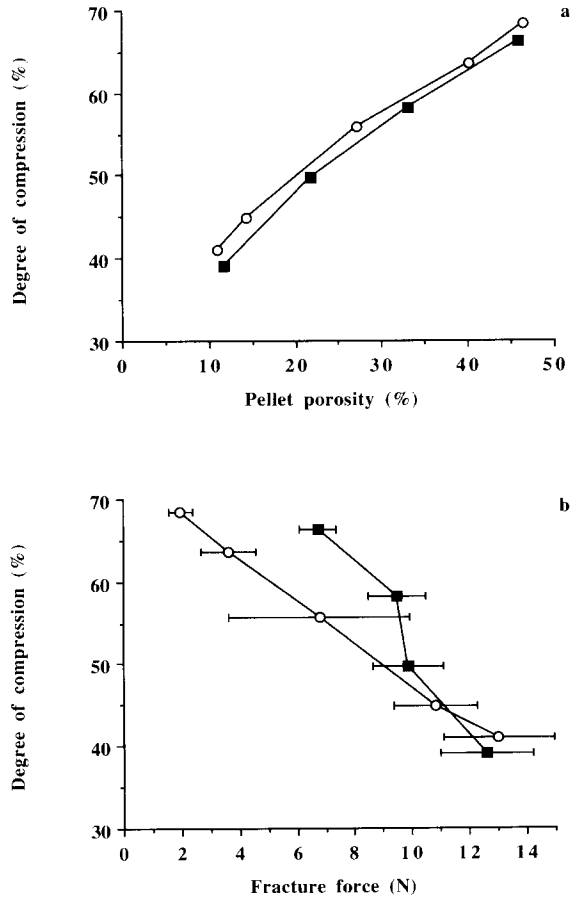

Fig. 6. Degree of compression of the pellets in-die at 100 MPa as a function of (a) the pellet porosity and of (b) the fracture force of the pellets. Bars denote 95% confidence interval of the mean. Symbols as in Fig. 3.

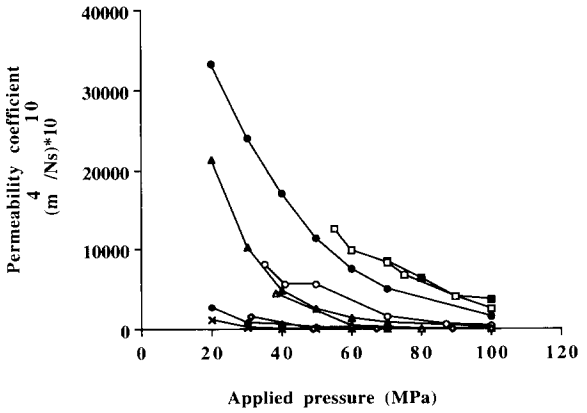

Fig. 7. Permeability coefficient of tablets as a function of the applied pressure for tablets prepared from pellets. (■) 1, (●) 2, (▲) 3, (◆) 4, (×) 5, (□) I, (○) II, (△) III, (◇) IV.

3.2.4. Tablet permeability-applied pressure relationships

The permeability coefficient of the compacts decreased generally in a non-linear way with increased compaction pressure (Fig. 7) and seemed to asymptotically reach an impermeable compact. An increased porosity of the original pellets gave a greater reduction in tablet permeability at low compaction pressures. This relationship between tablet permeability and applied pressure, as well as the effect of pellet porosity on the air permeability, are consistent with earlier observations on lactose-binder granules (Wikberg and Alderborn, 1993). As a measure of the change in permeability with compaction pressure, the ratio between the permeability of a compact prepared at 100 MPa and the permeability of the bed of pellets before compaction (Table 3) was calculated. The values of the ratio decreased almost linearly with an increased pellet porosity while no unique relationship was obtained between the ratio and the fracture force of the pellets (Fig. 8a,b). Furthermore, the air permeability of compacts formed at 100 MPa and the degree of compression of the pellets in-die at the corresponding pressure (Fig. 9), seem to be related to each other. Thus, it seems that the permeability of a compact formed at a certain pressure is controlled by the porosity of the pellets, i.e., a higher porosity gave a more closed intergranular pore structure. Moreover, it is suggested that this difference in the character of the intergranular pore system is caused by differences in the degree of deformation of the pellets which takes place during the compression process.

3.3. Compactability of pellets

The tensile strength of tablets compacted from unlubricated pellets increased almost linearly with applied pressure (Fig. 10). A dramatic difference in compactability between the different pellets was obtained due to differences in their original

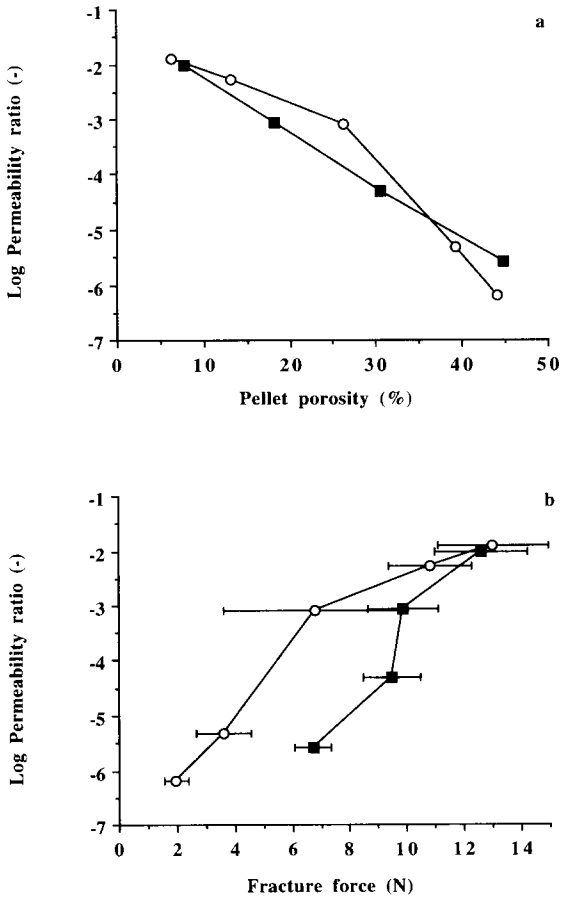

Fig. 8. Logarithm of the permeability ratio (the permeability coefficient of the tablet formed at 100 MPa divided by that of the bed of pellets before compaction) as a function of (a) the pellet porosity and of (b) the fracture force of the pellets before compaction. Bars denote 95% confidence interval of the mean. Symbols as in Fig. 3.

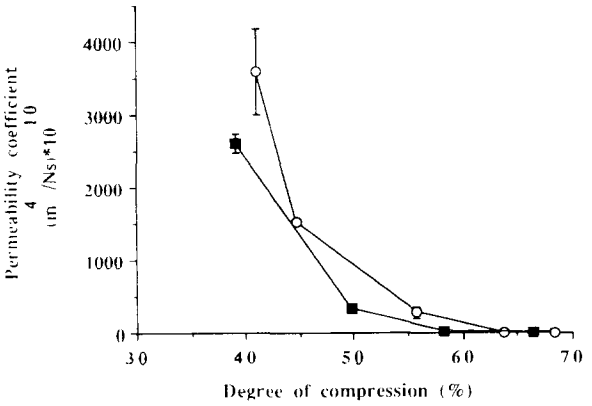

Fig. 9. Permeability coefficient of tablets compacted at 100 MPa as a function of the degree of compression of the pellets in-die at 100 MPa. Bars denote 95% confidence interval of the mean. Symbols as in Fig. 3.

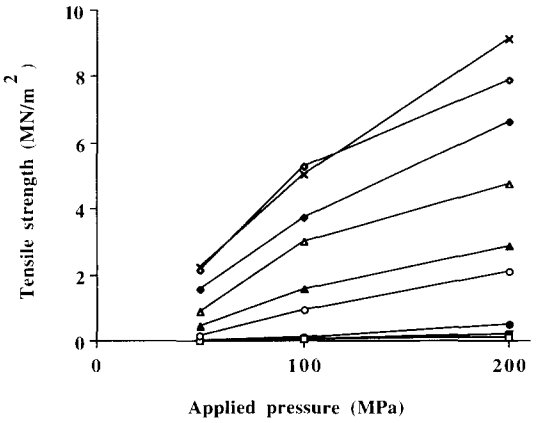

Fig. 10. Tensile strength of tablets compacted from unlubricated pellets as a function of the applied pressure. Symbols as in Fig. 7.

porosity (Fig. 11). At each compaction pressure, the total tablet porosity was similar for all compacts independent of the original pellet porosity (Table 3), i.e., the difference in tablet strength at a given pressure did not correspond to a difference in total tablet porosity. However, a clear relationship between the tablet air permeability and the tablet strength was obtained, i.e., a lower permeability, corresponding to a more closed intergranular pore structure, gave tablets of a higher tensile strength (Fig. 12a). This is consistent with earlier relationships obtained between the tensile strength and the pore structure, as measured by air permeametry, of tablets formed of lactose-binder granules (Alderborn et al., 1987; Wikberg and Alderborn, 1990b, 1991). An alternative way of presenting this relationship between tablet strength and tablet pore structure is to plot the changes in tablet tensile strength with applied pressure (i.e., the compactability) as a function of the changes in tablet air permeability with applied pressure (i.e., the compression behaviour) (Fig. 12b). These two characteristics of the pellets were directly related to each other. The results can be interpreted as that the structure of the intergranular pore system will be of significant importance for the tensile strength of the compact. A reasonable explanation is that the bonding forces between the pellets in the compact generally are lower than the bonding forces between the primary particles constituting the pellet. Thus, when the compact is stressed, a fracture plane will be created between and around the pellets and the tablet strength will be controlled by the number and the bonding force of the ruptured intergranular bonds. This conclusion is supported by the results of the effect of magnesium stearate addition on the strength of the compacts. However, the number of intergranular bonds in a cross-section of the compact will probably be similar for compacts of all the pellets used in this study, due to the similar dimensions

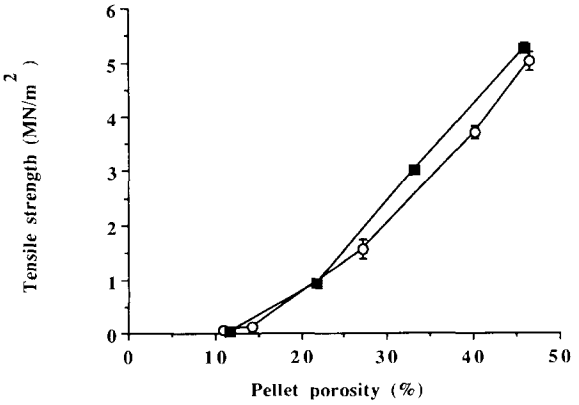

Fig. 11. Tensile strength of tablets compacted from unlubricated pellets at 100 MPa as a function of the pellet porosity. Bars denote 95% confidence interval of the mean. Symbols as in Fig. 3.

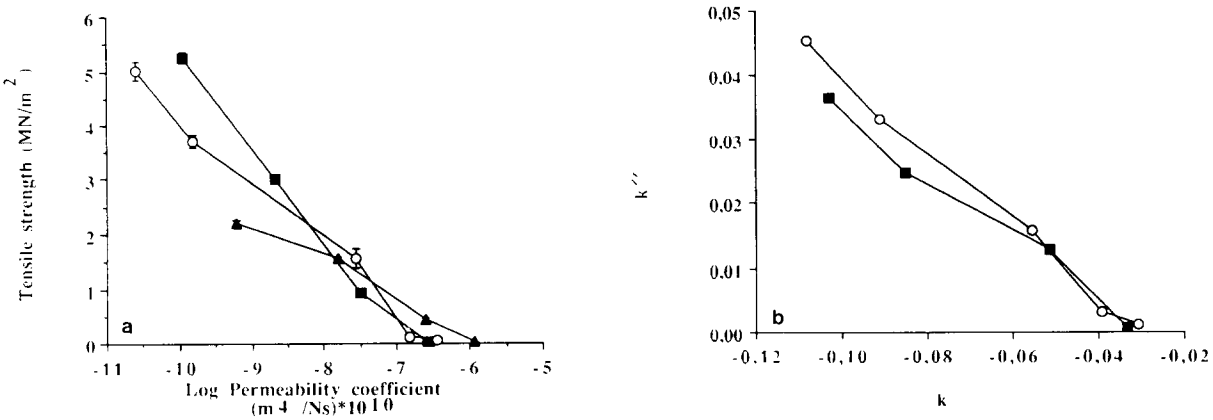

Fig. 12. (a)Tensile strength of tablets compacted from unlubricated pellets as a function of the logarithm of the tablet permeability coefficient. Bars denote 95% confidence interval of the mean. (○) Pellets 1–5, 100 MPa; (■) pellets I–IV, 100 MPa; and (▲) pellets 1–5, 50 MPa. (b) Slope k'' (calculated from the plot of the tensile strength vs the applied pressure) as a function of the slope k' (calculated from the plot of the logarithm of the permeability coefficient vs the applied pressure). Symbols as in Fig. 3.

of the 'compact pellets'. Thus, a reduced intergranular separation distance will probably correspond to an increased intergranular contact area, due to the increased degree of pellet deformation, which will increase the bonding force of the intergranular bonds. This discussion indicates also that the dominating mechanism of bonding in the compacts can be described as intermolecular attraction forces acting over some separation distance between extragranular surfaces.

4. Conclusions

The compression behaviour and the compactability of a series of nearly spherical pellets of microcrystalline cellulose has been evaluated. With respect to the compaction of unlubricated pellets, their behaviour corresponds in two respects to that of lactose granules studied previously (Wikberg and Alderborn, 1990a,b, 1991, 1992a,b, 1993):

(i) An increased initial pellet porosity promotes the formation of a closed intergranular tablet pore structure during compression.

(ii) The intergranular tablet pore structure is directly related to the tensile strength of the compact.

In addition, it has been shown that:

(i) the pellets compressed by deformation and the incidence of pellet fragmentation was low or non-existent. Hence, when an assembly of the pellets was held in a confined space and subjected to a compression force, the individual pellets responded preferentially to the applied force by deformation rather than by fragmentation. Repositioning of primary particles within the pellets by shearing seems thus to be a process requiring less energy than the separation of primary particles by the formation of a fracture plane. This difference in energy consumption between shearing and fracturing might be caused by the unique stress conditions on the individual pellets during uniaxial compression in a die, i.e., the pellets are stressed from several directions simultaneously, making a fracturing of the pellets relatively difficult. The limited incidence of fragmentation during compression might also be enhanced by the character of the pellets used in this study, i.e., spherical, smooth pellets of a high fracture force consisting of substrate particles with ductile properties which can make a crack propagation process difficult. The generality of the observation on the dominating compression mechanism for the pellets can thus be questioned and can be affected by the physical and mechanical properties of the pellets. Depending on such properties, pellets or granules might consequently

respond to the dynamic loading by deformation or by fragmentation.

(ii) the pellet porosity, rather than the size distribution of the pores in the pellets or the fracture force of the pellets, controlled the degree of deformation which the pellets underwent during the compression. Thus, the degree of deformation of the pellets, caused by a reposition of primary particles within the pellet, seemed to be controlled by the total volume of air which surrounds the primary particles in the pellets.

(iii) the degree of pellet deformation during compression controlled both the degree of compression of the pellet mass during compaction as well as the pore structure of the compact. Thus, the degree of compression of the pellet mass seems to be a measure of the degree of deformation of the individual pellets during compression when the incidence of pellet fragmentation is low.

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