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Research paper

Pore structure and surface area of mannitol powder, granules and tablets determined with mercury porosimetry and nitrogen adsorption

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Abstract

Two methods used in pore structure characterisation, mercury porosimetry and nitrogen adsorption, were compared. Pore structure and surface area of mannitol powder, granules produced in wet granulation and tablets compressed with three compression pressures were studied. Greater surface area, more porous structure and greater number of small pores in granules, when compared with powder, increased the compactibility of mannitol granules in tableting. Plastic deformation and fragmentation of powder and granules in compression were observed in volume pore size distributions and surface areas measured with these methods. Pore volume and volume pore size distribution obtained with mercury porosimetry describe densification of mass better than those obtained with nitrogen adsorption. In spite of differences between the methods, the volume pore size distribution curves of samples in the overlapping pore size range had the same shape. The specific surface area of tablets, measured by the nitrogen gas adsorption method described well the deformation under compression. Fragmentation increased the surface area of powder, and plastic deformation decreased the surface area of granules in the pore size range determined. Surface area values measured with mercury porosimetry were larger than those determined with nitrogen adsorption.

Keywords: Mannitol; Mercury porosimetry; Nitrogen adsorption; Pore structure; Surface area

1. Introduction

Due to its low moisture content and non-hygroscopic character, mannitol is suitable for use with active ingredients that are sensitive to moisture. It is compatible with various inorganic and organic excipients. Use of mannitol has increased lately, when it has partly replaced lactose as an additive, due to lactose intolerance. Owing to the poor flowability of mannitol powder, it is often granulated. Some articles on the tableting behaviour of mannitol powder and granules have been published. Bassam et al. [1] have studied the mechanical characteristics of mannitol powder with the four-point beam bending technique and Debord et al. [2] have studied the compression of powders and granules. Krycer et al. [3] have studied the compaction of mannitol powder and granules produced by dry granulation in a rotary ball mill and by preliminary compression granulation methods, and Juppo et al. [4] have studied compression of granules produced by wet granulation.

Commonly, the tableting behaviour of materials is evaluated by studying the parameters measured during the compression cycle. However, studying the pore structure of tablets compressed with different compression pressures also gives information on the behaviour of the material in tableting. Mercury porosimetry has proved to be a useful method in the characterisation of the pore structure of mannitol granules and tablets [5]. The pore structure of mannitol tablets compressed from powder has not been studied previously. With high-pressure mercury porosimetry, pores in

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the diameter range 7 nm to 14 μm can be measured. With nitrogen adsorption, smaller pores, diameter range 3–200 nm can be determined. Total pore volume, volume pore size distribution and surface area are parameters that can be measured by both methods. With the nitrogen adsorption technique, total pore volume and volume pore size distribution are determined by filling the pores with nitrogen. In mercury porosimetry, mercury is forced into the pores with pressure. Total pore volume values of silica samples have been equal, when measured by these techniques [6]. The pore size distributions determined by the two techniques have been equal for dicalcium phosphate dihydrate tablets at the overlapping pore size range [7]. The pores of the tablets compressed from powder were so large that the pore size range was mainly outside the operation range of the nitrogen adsorption method. Almost equal pore volume size distributions have been determined also for magnesium trisilicate [8] and Degussa aerosols [9].

Specific surface area is measured by adsorbing nitrogen molecules on the surface of a sample. Total pore surface area determined by mercury porosimetry is the surface area of the walls of the pores filled with mercury during analysis. With lactose tablets, the surface area values measured by mercury porosimetry have been higher than those determined by nitrogen adsorption [10]. Similar results have been reported also with silica samples [6]. However, Mikijelj et al. [11] have reported that the specific surface areas of diatomite and magnesium oxide compacts measured with these methods were quite similar. The two methods have not been compared thoroughly with pharmaceutical samples.

The aim of this work was to study the effect of compression on the pore structure and surface area of mannitol powder tablets and mannitol granule tablets. The pore structures and surface areas determined with nitrogen adsorption and mercury porosimetry were compared.

2. Materials and methods

2.1. Granulation

Granules were produced from D-(−)-mannitol (Merck, Darmstadt, Germany) using a high-shear mixer (Fielder PMA 25/2G, T.K. Fielder, Eastleigh, UK). The binder solution, 20% polyvinylpyrrolidone (PVP, Kollidon® K 25, BASF, Ludwigshafen, Germany) solution in distilled water, was added at a speed of 150 ml/min to the final amount of 75 ml/kg. The mannitol granule batch size was 5 kg.

2.2. Characterisation of mannitol powder and granules

Scanning electron micrographs were taken, using a scanning electron microscope (JSM-840A, Jeol, Tokyo, Japan). The porosity of powder and granule masses was determined according to Eq. (1)

$$\epsilon = \left(1 - \frac{\rho_b}{\rho_h}\right) \cdot 100\% \quad (1)$$

where ρ_b is bulk density and ρ_h is true density. Bulk density was determined with a graduated glass cylinder, and true density with a helium pycnometer (Multipycnometer MVP-1, Quantachrome, Boynton Beach, FL).

Porosity parameters were determined with a high-pressure porosimeter (Autoscan 33 Porosimeter, Quantachrome). The pressure and mercury intruded volume readings were filed in the memory of a computer. Total intruded volume of mercury (V_{tot}), total pore surface area (S), mean pore diameter (d_{mean}), median pore diameter (d_{median}) and $D_V(d)$, volume pore size distribution, were calculated from the intrusion data with Quantachrome Autoscan PORO2PC software, version 2.17.

Total pore surface area was calculated by Eq. (2)

$$S = \frac{1}{\gamma|\cos\theta|} \int_0^{V_{tot}} p\,dV \quad (2)$$

where p is the pressure, V is the intruded volume of mercury, γ is the surface tension, θ is the contact angle of mercury and V_{tot} is the total intruded volume of mercury. The mean pore diameter was calculated by Eq. (3)

$$d_{mean} = 4 \cdot \frac{V_{tot}}{S} \quad (3)$$

based on the assumption of cylindrical shape of pores open at the ends. Median pore diameter (d_{median}) is the pore diameter at which 50% of the total intruded volume of mercury is intruded. $D_v(d)$ is defined as the pore volume per unit interval of pore radius [12] by Eq. (4)

$$D_v(d) = \frac{p}{d} \cdot \frac{dV}{dp} \quad (4)$$

Profiles were plotted with moving average point 81 and minimum delta volume 0% full-scale. Samples were dried in a vacuum for 24 h at 40°C and kept below 10 Pa before the measurement. Scanning speed was 216 kPa/s. Porosity measurements were done in triplicate. Total pore volume, volume pore size distribution, and specific surface area of the powders and granules were measured in triplicate using nitrogen adsorption (Coulter SA 3100, Coulter, Miami, FL). Specific surface area was calculated according to the BET-equation [13]

$$\frac{p}{v(p_0 - p)} = \frac{1}{v_m c} + \frac{c - 1}{v_m c}\frac{p}{p_0} \quad (5)$$

where v is the volume adsorbed, v_m is the volume of the monolayer, p is the sample pressure, p_0 saturation pressure and c a constant related to the enthalpy of adsorption.

The BET surface area (S_{BET}) is then calculated from the following

$$S_{BET} = \frac{v_m \cdot n_a \cdot a_m}{m_v} \quad (6)$$

where n_a is Avogadro's number, a_m is the cross-sectional area occupied by each adsorbate molecule (0.162 nm^2) and m_V is the gram-molecule volume (22.414 ml).

The pore size distribution is determined according to the BJH model [14]. The Kelvin equation is used to calculate the relative pressure of nitrogen in equilibrium with the porous solid, to the size of the pores where capillary condensation takes place. Pore volume is the volume of the pores smaller than 100 nm in diameter, and is determined from the adsorption phase. Pore size distribution is determined from desorption data. The samples were dried in a vacuum (vacuum oven Heraeus VTR 5022, Heraeus, Köln, Germany, with vacuum pump Trivac S4A, Leybold–Heraeus, Köln, Germany) below 10 Pa 40°C for 24 h. The specific surface area was measured from 12 points at the relative nitrogen pressure range 0.05–0.20 and the pore size distribution from 88 points at the relative nitrogen pressure range 0.98–0.37. The temperature during measurement was −196°C. Particle size distributions of the powder and granules were measured by laser diffractometry [15].

2.3. Compression

Tablets were compressed from powder and granules with a rotary press (Kilian, RU-24 III, Kilian, GmbH, Köln, Germany). Polyvinylpyrrolidone (1.6%) was mixed with the powder mass to achieve similar contents to that of the granule mass. Magnesium stearate (1%) (Mallingrot, Netherlands) was mixed into the tablet masses for 12 min in a Turbula mixer (T 10 B, Willy A. Bachofen, AG Maschinenfabrik, Basle, Switzerland) and sieved through a 2-mm sieve before tableting. The tablet machine was equipped with a pair of instrumented flat punches with a diameter of 9 mm (Portable Press Analyser, Puuman Oy, Kuopio, Finland). The weight of the tablets (230 mg) and the rotation speed of the tablet press were kept constant. The compression time was approximately 60–70 ms, depending on the material used. A force-feeder was not used. The target compression pressures used were 72 MPa, 122 MPa and 196 MPa. The temperature during tableting was 21–23°C and the relative humidity was 15–17%.

2.4. Characterisation of the tablets

Breaking force was measured (Erweka TBH 28, Erweka Apparatebau GmbH, Hensenstamm, Germany) from 20 tablets. The porosity of tablets, based on tablet dimensions was calculated according to the Eq. (7)

$$\epsilon = \left(1 - \frac{\frac{m}{V}}{\rho_h}\right) \cdot 100\% \quad (7)$$

where m is the mass of the tablets and V the volume of the tablets. The porosity parameters of the tablets were determined with a high-pressure porosimeter, as described for powder and granules. The sample size in these analyses was three tablets. The total pore volume and the specific surface area of the tablets (sample size 15 tablets) were measured by nitrogen adsorption as described for powder and granules. Measurements were made in triplicate.

3. Results and discussion

3.1. Granules

3.1.1. Pore structure of powder and granules

The total intruded volume of powder determined with mercury porosimetry is greater than that of granules (Table 1). Mercury porosimetry measures both interparticu-

Table 1

Porosity parameters of mannitol powder, mannitol granules and tablets compressed with different compression pressures as measured with high-pressure mercury porosimetry ($n = 3$)

Sample	Total intruded volume (ml/g)		Total pore surface area (m^2/g)		Mean pore size (nm)		Median pore size (nm)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Porosity parameters of mannitol powder and tablets compressed from mannitol powder								
Powder	0.43	0.02	3.7	0.6	470	80	5400	80
Powder tablet (MPa)								
72	0.15	0.01	4.7	0.6	130	24	1200	120
122	0.12	0.01	5.1	0.7	97	15	810	70
196	0.11	0.00	5.4	0.5	78	5	600	50
Porosity parameters of mannitol granules and tablets compressed from mannitol granules								
Granules	0.12	0.01	4.7	0.4	99	10	600	320
Granule tablet (MPa)								
72	0.16	0.00	6.2	1.0	106	17	740	150
122	0.10	0.04	7.9	0.9	52	16	160	90
196	0.08	0.00	7.6	1.7	42	8	87	6

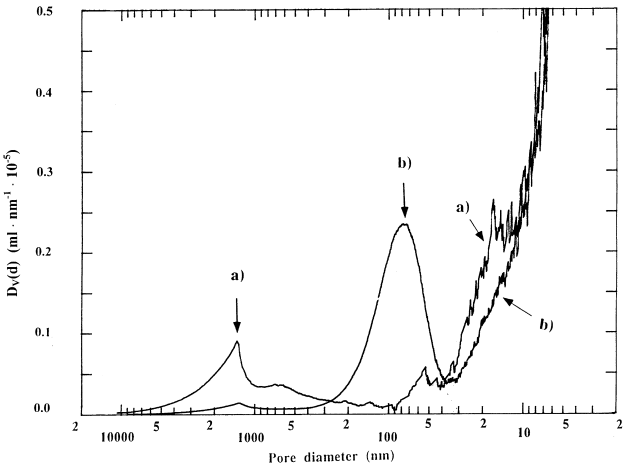

Fig. 1. Pore volume size distributions of (a) mannitol powder and (b) mannitol granules determined by mercury porosimetry.

lar and intraparticular pores. The voids between particles of mannitol powder are measured with high-pressure porosimetry, whereas the voids between granules are so large that they are not observed. Therefore, the median and mean pore size values of the powder are larger than those of the granules (Table 1).

Volume pore size distribution emphasizes differences of the pore volume at a small pore size intervals. Pores of the powder sample are in the diameter range 1–5 μm, which are voids between particles (Fig. 1). The volume of these pores decreases markedly during wet granulation, and new pores are formed on the granules in the diameter range 40–300 nm. These intraparticular pores are formed when powder particles are bound together by binder or when mannitol is recrystallised. Difference in particle size distribution of mannitol powder and granules is observed (Table 2). Also, Juppo et al. [16] have reported bimodal volume pore size distribution of mannitol granules.

In contradiction, when measured by nitrogen adsorption, the pore volume of powder is smaller than that of granules (Table 3). This method determines smaller pores than does mercury porosimetry, so that the pores observed are pores of the particles. The larger pores determined by mercury porosimetry affect the pore volume result more than do the smaller pores determined by nitrogen adsorption. The difference in volume pore size distributions between powder and granules that was measured with mercury porosimetry was observed also with nitrogen adsorption (Fig. 2).

Table 2

Particle size results of mannitol powder and mannitol granules measured by laser diffraction method (n = 3)

Sample	10% fractile (μm)		Median (μm)		90% fractile (μm)	
	Mean	SD	Mean	SD	Mean	SD
Powder	20	1	100	4	400	10
Granules	40	1	200	3	1400	30

Table 3

Porosity percents, breaking forces (n = 20) and parameters of mannitol powder, mannitol granules and tablets compressed with different compression pressures as measured with nitrogen adsorption method (n = 3)

Sample	Porosity percent	Breaking force (N)		Pore volume (ml/g)		Specific surface area (m^2/g)	
		Mean	SD	Mean	SD	Mean	SD
Powder	64	–	–	0.001	0.000	0.34	0.00
Powder tablet (MPa)							
72	21	15	3	0.002	0.000	0.58	0.00
122	14	19	3	0.003	0.000	0.59	0.03
196	14	26	4	0.003	0.000	0.61	0.02
Granules	59	–	–	0.004	0.000	1.60	0.02
Granule tablet (MPa)							
72	26	58	8	0.005	0.001	1.55	0.04
122	20	90	11	0.004	0.000	1.47	0.02
196	17	141	15	0.005	0.001	1.26	0.02

According to the results, granules are more porous than powder. In spite of basic differences in the methods, pores in powder and granules are detected in the same pore size range with both methods in the overlapping pore size area (Fig. 2).

3.1.2. Surface area of powder and granules

Total pore surface area values of powder and granules are similar when measured with mercury porosimetry (Table 1), whereas with nitrogen adsorption the specific surface area of granules is markedly higher than that of powder (Table 3). This is partly due to the dissolution and recrystallisation of mannitol. Surface area values obtained with mercury porosimetry are markedly higher than those measured with nitrogen adsorption. Similar results have been obtained with lactose tablets [10] and with silica samples [6]. The result has been explained by the assumption of cylindrical

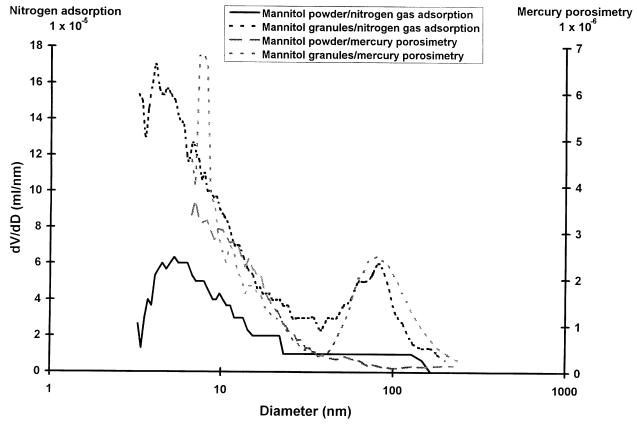

Fig. 2. Pore volume size distributions of mannitol powder and mannitol granules determined by nitrogen gas adsorption and mercury porosimetry methods.

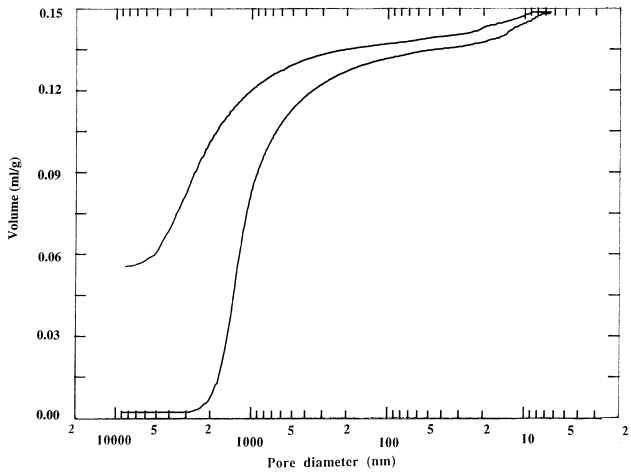

Fig. 3. Intrusion–extrusion curve of tablet compressed from mannitol powder with 72 Mpa.

pores in mercury porosimetry. So-called ink-bottle pores with a narrow neck and a large volume, observed from the intrusion–extrusion curve in Fig. 3, also increase the calculated total pore surface area in mercury porosimetry.

3.2. Tablets

3.2.1. Compression

In compression of mannitol granules, mechanical interlocking, fragmentation and plastic deformation of porous granules with fibrous structure takes place. Mannitol powder is moderately hard and ductile [17]. The breaking forces of the granule tablets are markedly higher than those of powder tablets (Table 3), indicating that wet granulation improves the compactibility of mannitol. The porosity percentage of granule tablets decreases more in compression than that of the powder tablets, when the results of tablets compressed with 72 and 196 MPa are compared (Table 3). The result is consistent with the total pore volume values of tablets obtained with mercury porosimetry (Table 1). In compression, air from the granules has to escape and the large granules of porous structure are more deformed than those of the needle-shaped mannitol powder particles (Fig. 4).The higher strength of the tablets compressed from granules can be explained by the large area available for bond formation, which is due to the fragmentation of large porous granules and also by the greater specific surface area of the granules compared with that of powder (Table 3). The crushing strength of tablets compressed from mannitol powder or granules increases with increasing porosity of the raw material [3].

3.3. Pore structure of tablets

3.3.1. Mercury porosimetry

Densification of the powder mass with increasing compression pressure is detected from pore volume and pore size values obtained by mercury porosimetry, shown in Table 1. From the volume pore size distribution curves, measured with mercury porosimetry, of powder and tablets compressed from powder, densification is observed in the pore diameter range 200–2000 nm (Fig. 5A). The pores measured are the voids between powder particles. The largest pores of the plastically deforming material disappear first, pore size decreases, and the maximum of the distribution moves towards the smaller pores. However, a new pore population in the pore size range 20–50 nm is created in powder tablets compressed with the highest compression pressure, indicating fragmentation of powder particles (Fig. 5A). Fragmentation increases the number of small particles contributing a new group of pores [18]. This new pore population is related to increased breaking force of the tablets, which is almost the same for tablets compressed at the two lowest compression pressures, 72 and 122 MPa (Table 3). When the number of pores larger than 500 nm decreases and the number of pores smaller than 200 nm increases, the breaking force of the tablets increases [19].

During compression, greater densification of the granules takes place in this pore size, compared with that of the powder mass. When the tablets compressed with 72 MPa and 196 MPa are compared, a greater decrease in the total pore volume of granule tablets is observed, compared with that of the powder tablets (Table 1). A similar result is observed also from the porosity percents of tablets (Table 3). Deformation is observed in the volume pore size distributions of granule tablets (Fig. 5B). The largest pores of granule tablets disappear with increasing compression pressure. With the highest compression pressure, the largest detectable pores are 500 nm in diameter. Similarly, Juppo [19] has reported fragmentation of granules with increasing compression pressure, when measured with mercury porosimetry. The pores of the granules in the diameter range 40–200 nm are unaffected by the lowest compression pressure. When higher compression pressures were used, deformation shifted the maximum from the pore size range 40–200 nm to smaller values. Due to the fragmentation, more small pores (diameter $<$20 nm) are created in the granule tablets

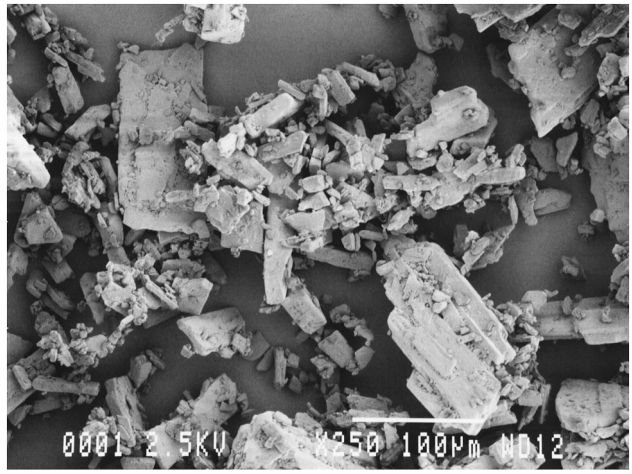

Fig. 4. SEM graph of mannitol powder.

compressed with the two highest compression forces, 122 and 196 MPa. The broad size distribution of mannitol granules was still detectable in mannitol granule tablets with a wide pore size distribution (Fig. 5B).

3.3.2. Nitrogen adsorption

With nitrogen adsorption, the pore volume of powder increases when compressed, indicating the formation of new pores in the pore size range measured (Table 3). When the volume of the pores of tablets compressed at three different compression pressures is compared, no change in the volume of the pores is observed. The pore size distribution of powder tablets obtained by nitrogen adsorption has only one maximum for tablets compressed at the two lowest pressures (72 and 122 MPa) in the smallest detectable pore size range (diameter <7 nm) (Fig. 6a). Bimodal distribution is seen after compression at the highest pressure, 196 MPa. This indicates that the volume of these pores increases with increasing compression pressure, probably because of fragmentation of the particles.

The pore volume of granule tablets is unaffected by the compression pressure in the pore size range measured

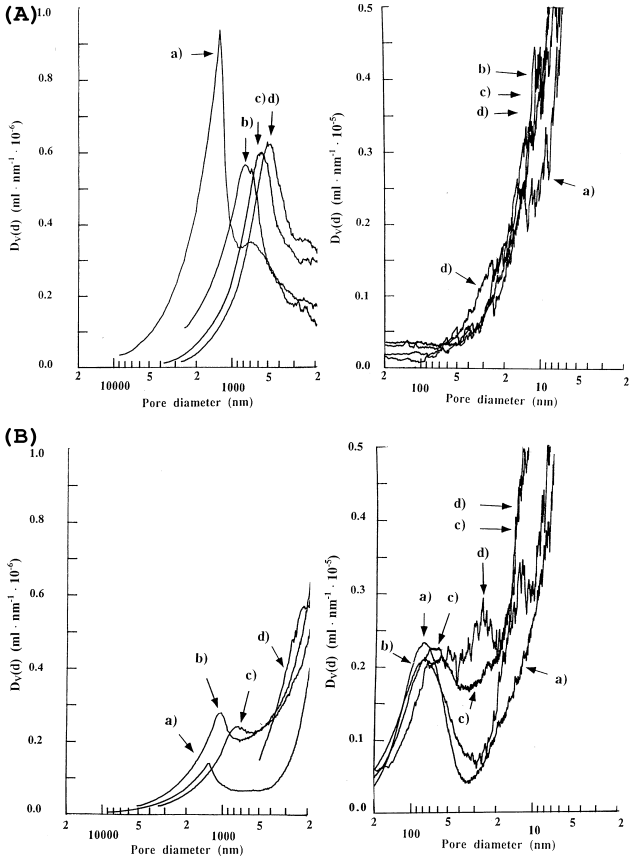

Fig. 5. (A) Pore volume size distributions of (a) mannitol powder and mannitol powder tablets compressed with (b) 72 MPa (c) 122 MPa and (d) 196 MPa measured with mercury porosimetry. (B) Pore volume size distributions of (a) mannitol granules and mannitol granule tablets compressed with (b) 72 MPa, (c) 122 MPa and (d) 196 MPa measured with mercury porosimetry.

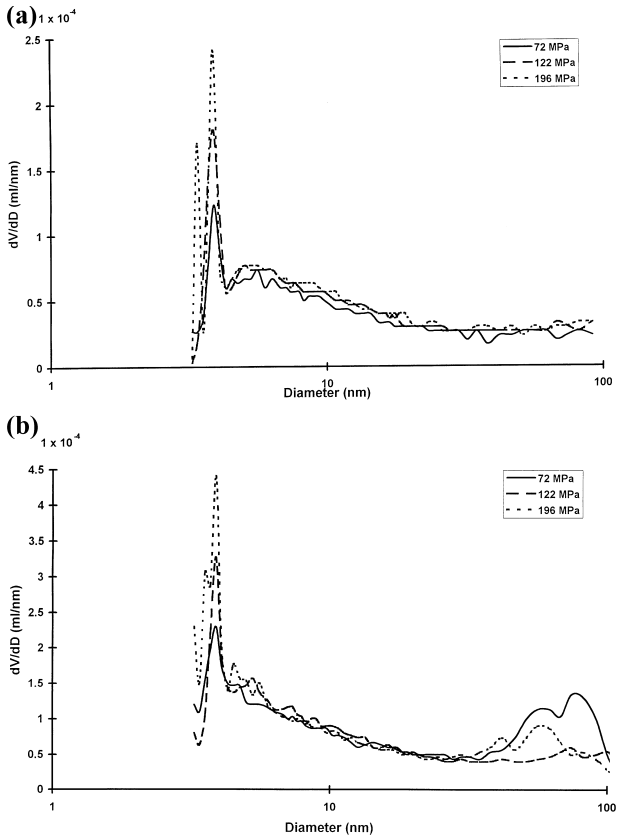

Fig. 6. (a) Pore volume size distributions of mannitol powder tablets compressed with different compression pressures measured with nitrogen adsorption. (b) Pore volume size distributions of mannitol granule tablets compressed with different compression pressures measured with nitrogen adsorption.

(Table 3). The pore volume size distribution of granule tablets measured with the nitrogen gas adsorption method is bimodal (Fig. 6b), one maximum showing pores of the granules in the pore size range 50–100 nm. The volume of these pores is highest in the tablets compressed at the smallest compression pressure (72 MPa), indicating densification of the mass with increasing compression pressure. Similarly to powder tablets, the volume of the smallest detectable pores (diameter <7 nm) increases with increasing compression pressure, probably due to fragmentation.

3.3.3. Comparison of the methods

Total pore volumes of tablets measured by mercury porosimetry are markedly higher than those measured by nitrogen adsorption. Mercury porosimetry determines larger pores, which have more effect on the total volume. These large pores are not within the detection range of nitrogen adsorption. The total pore volumes of silica samples obtained with these methods have been similar [6]. This is because pores of silica are very small, so that pores are determined mainly by nitrogen adsorption. The volume pore size distributions of tablets measured with nitrogen adsorption and mercury porosimetry have the same shape

in the overlapping pore size region (Fig. 7), although the scales of the curves differ from each other. Damage or compression of highly porous particles like silica and alumina samples has been reported [20,21]. Thus, the result of this study emphasises that no compression or damage of the samples takes place during mercury porosimetry analysis. Faroongsarng et al. [7] have reported that the pore size distributions of dicalcium phosphate dihydrate tablets obtained by the nitrogen adsorption method and mercury porosimetry are consistent in the range of overlapping pore size values. In their study, however, the pores of the tablets compressed from powder were so large that the pore size range was mainly outside the operation range of nitrogen adsorption. Stanley-Wood [8] has also reported almost the same pore size distribution for uncompacted magnesium trisilicate and Conner et al. [9] for Degussa aerosols, when determined with these techniques.

3.3.4. Surface area of tablets

Total pore surface areas of the tablets measured with mercury porosimetry are unaffected by compression pressure (Table 1). The pore surface area of tablets compressed from granules is larger than that of tablets compressed from powder, due to the more porous structure and greater surface area of granules.

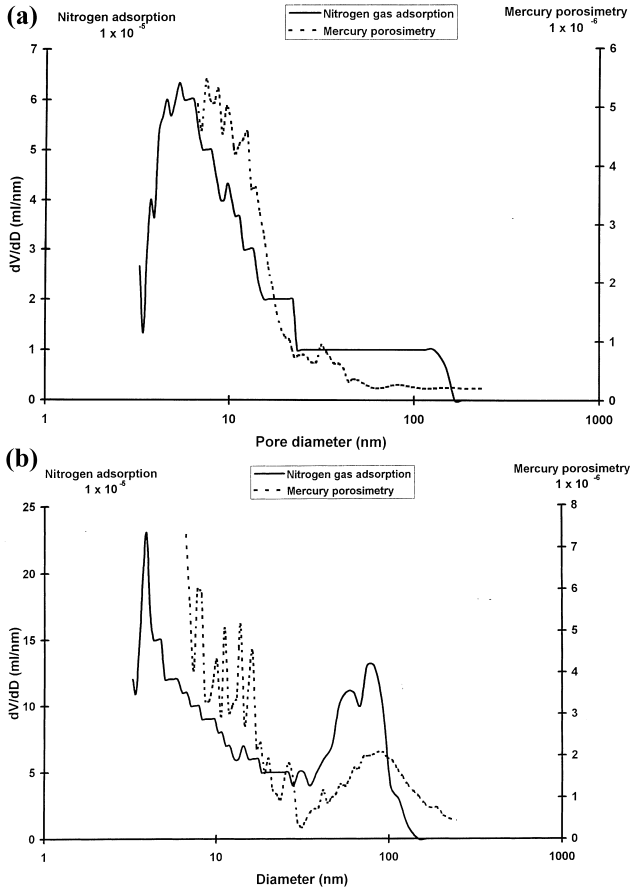

Fig. 7. (a) Pore volume size distributions of mannitol powder tablets (compression pressure 72 MPa) measured with nitrogen gas adsorption and mercury porosimetry methods. (b) Pore volume size distributions of mannitol granule tablets (compression pressure 72 MPa) measured with nitrogen gas adsorption and mercury porosimetry methods.

The specific surface area values obtained by nitrogen adsorption for tablets compressed from powder are smaller than those for tablets compressed from granules (Table 3). The specific surface area values of tablets compressed from powder tend to increase with increasing compression pressure, indicating fragmentation of particles and formation of new surfaces that are detectable with this method. In contrast, the surface area of granule tablets decreased, due to more plastic deformation of the mass compared with that of the powder mass.

The surface area values of mannitol tablets obtained by mercury porosimetry are many times higher than those obtained by nitrogen adsorption. This is due to the complex pore structure and ink-bottle-shaped pores of the tablets. The surface area in mercury porosimetry is calculated from the volume intruded in pore diameter intervals assuming cylindrical pores with round pore openings. The so-called ink-bottle pores tend to increase surface area values calculated from mercury porosimetry data, because the volume of the pores with small necks can be remarkable. Dees et al. [10] reported higher surface area values with mercury porosimetry than with nitrogen adsorption, for lactose tablets. They concluded that nitrogen adsorption results were more accurate. A similar result has been obtained also with silica samples [6]. In contrast, Mikijelj at al. [11] have found the pore surface areas of porous magnesium oxide and diatomite compacts measured by mercury porosimetry and nitrogen adsorption methods to be equivalent. In their study, the highest pressure in mercury porosimetry was 103 MPa, and the diameter of the smallest detectable pores 14 nm. The surface area values of the samples were 2–50 m^2/g, indicating that the pores were very small. Thus the pores were probably mainly in the detection range of nitrogen adsorption, and mercury porosimetry was not capable of measuring them, or the entire surface area. In our study, nitrogen adsorption was more capable of detecting changes in the tablet surface area caused by compression.

4. Conclusions

Porous structure, greater number of small pores (diameter $<$200 nm) and higher surface area of mannitol granules compared with mannitol powder result in increased bonding and higher strength of granule tablets. Plastic deformation and fragmentation of powder and granules in compression were observed in volume pore size distribution curves and surface area values obtained with both mercury porosimetry and nitrogen adsorption methods.

Due to different measurement ranges, pore volume values obtained with nitrogen adsorption and mercury porosimetry methods were not equal. The deformation of granules and powder with increasing compression pressure is more

clearly observed in the pore volume of tablets measured with mercury porosimetry. Volume pore size distributions determined with these two methods were almost the same in the overlapping pore size range. Volume pore size distribution proved to be a good parameter in the characterisation of deformation under compression. With mercury porosimetry, reduction of the size or disappearance of interparticular pores of powder and fragmentation of granules were also observed. The volume pore size distribution obtained with nitrogen adsorption emphasises changes in intraparticular pores of the particles. The surface area values obtained with these methods were not equal, due to complex pore structure, non-cylindrical pore shapes and differences between the methods. The specific surface area measured with nitrogen adsorption proved to be better than the total pore surface area measured with mercury porosimetry in characterising the deformation during tableting. Fragmentation of powder and plastic deformation of granules were observed. Mercury porosimetry, together with nitrogen adsorption, characterises well the pore structure of mannitol powder, granules and tablets and even the deformation of materials under compression.

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