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Porosity parameters of lactose, glucose and mannitol tablets obtained by mercury porosimetry

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Abstract

The effect of compression force, compression speed and the amount of granulation liquid on the porosity parameters determined from lactose, glucose and mannitol tablets by high-pressure mercury porosimetry was investigated. Compression force affected all parameters measured, except the total pore surface area of lactose tablets. The changes in tablet microstructure with increasing compression force were particularly well detected from the pore volume size distributions of tablets. Compression speed affected the total pore volume of lactose tablets, both mean and median pore diameters of lactose tablets and mannitol tablets compressed from granules produced with a low amount of liquid, and the median pore diameter of glucose tablets. The compression speed dependence of these parameters was a sign of the time-dependent deformation of materials during compression. The amount of granulation liquid affected the total pore surface area of lactose and mannitol tablets. With a high amount of liquid, the surface area of pores was greater. The mean pore size of all tablets and the median pore diameter of mannitol tablets were smaller when a high amount of granulation liquid was used. Even when compressed with a high force, the pore volume size distributions of mannitol tablets with a low amount of granulation liquid were broader and the maxima were at larger pore diameters. It was concluded that each porosity parameter measured characterised the pore structure of compressed tablets from a different aspect. Thus, the use of all porosity parameters proved to be useful.

Keywords: Lactose; Glucose; Mannitol; Tablet; Porosity; Mercury porosimetry

1. Introduction

The densification of materials in compression has been studied by several methods. The earliest study was made by Train, 1956, where coloured powder layers were compressed and the density distribution of compacts was determined from the depths of cross-sectional layers. Recently, ^{1}H-NMR microscopy has been used for characterisation of density distribution in tablets (Nebgen et al., 1992). The instrumentation of the tablet presses and the force and displacement sensors made possible the measurement of the force-displacement curve. This curve has been measured

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by several methods, most generally by Heckel, 1961. Using this method, the porosity–force function in the die is determined. The Heckel plot can also be determined outside the die where the displacement measurement is replaced with the measurement of the tablet dimensions (Paronen and Juslin, 1983). The calculation of tablet porosity is possible when the outer volume of the tablet, the tablet weight, and the so-called true density of tablet, either measured from the tablet, granules or the materials used for manufacturing the tablet, are known (Selkirk and Ganderton, 1970b, Healey et al., 1973, de Boer et al., 1986, Wikberg and Alderborn, 1991). The true density of tablet can be measured with a helium pycnometer or with an air pycnometer. Mercury pycnometry can be used to determine the effective density for porosity calculations. The specific surface area of tablet is also a measure of densification. Tablet surface area is measured by air permeametry (Wikberg and Alderborn, 1990, 1991, Ganderton and Selkirk, 1970) or by the gas adsorption method (Stanley-Wood and Johansson, 1978) based on the BET theory.

The disadvantage of the methods mentioned above is that they do not give information about the pore size distribution. Microscopic analyses with image analysis can produce an estimation of pore structure from a two-dimensional point of view (Bockstiegel, 1966, Wang and Zaidi, 1991). Scanning electron microscopy has also been used as a descriptive method for determining the densification of powders in compression (de Boer et al., 1978; Paronen and Juslin, 1983). The multipoint gas adsorption method measures the pore size distribution at a pore range of 0.4–200 nm, when nitrogen is used as adsorptive gas. The tablet pore structure can also be investigated using liquid penetration tests based on the capillary forces within tablet pores (Ganderton and Selkirk, 1970). Mercury porosimetry is based on the penetration of mercury into the sample. The advantage of mercury porosimetry is the wide pore range which it measures, 2.2 nm to 220 μm, depending on the pressure used. The pore range detectable by mercury porosimetry covers large intergranular pores and small intragranular and interparticle pores. Mercury porosimetry has been successfully used for determination of pore size distribution of tablets compressed from powders (Reich and Gstirner, 1968, Stanley-Wood, 1978, Vromans et al., 1985, de Boer et al., 1986, Mbali-Pemba and Chulia, 1995) and even from granules (Ganderton and Selkirk, 1970, Wikberg and Alderborn, 1992). However, the effect of compression speed on the pore structure of tablets has not been investigated previously. Furthermore, the effect of compression variables observed in the different porosity parameters obtained by mercury porosimetry, has not been previously studied.

The aim of this study was to investigate the effects of compression force, compression speed, and the amount of liquid used in the preparation of lactose, glucose and mannitol granules on total pore volume, total pore surface area, mean and median pore sizes, and pore volume size distribution of tablets compressed from granules.

2. Materials and methods

2.1. Granulation and compression

The tablets were compressed from lactose, glucose and mannitol granules prepared in a high shear granulator using two amounts of 20% polyvinylpyrrolidone (PVP) solution: 90 and 120 ml/kg. The speeds of compression were 30, 47 and 64 rpm, and the target values of maximum force of upper punch were 4, 8, 12 and 16 kN for lactose and glucose granules, and 4, 8 and 12 kN for mannitol granules. The particle size distributions of raw materials, granulation, size distributions and porosity parameters of prepared granules and compression have been described previously in more detail (Juppo et al., 1992, Juppo and Yliruusi, 1994, Juppo, 1996).

2.2. Porosity parameters of tablets

Porosity parameters were determined by a high-pressure porosimeter (Autoscan 33, Quantachrome Corp., USA) according to a method described previously (Juppo, 1996). Before the porosimeter run, the moisture content of tablets was checked with an infra-red dryer (IR-Sartorius

Thermocontrol YTC 01L, Sartorius GmbH, Germany). The moisture contents of lactose, glucose and mannitol tablets varied by 0.7–1.1, 4.8–6.0 and 0.8–1.0%, respectively. The relatively high moisture content of glucose tablets may reduce the pore volume measured. Total intruded volume of mercury and volume pore size distribution $D_v(d)$ were calculated as described in a previous study (Juppo, 1996). Total pore surface area (S) was calculated by Eq. 1:

$$S = \frac{1}{\gamma|\cos\theta|}\int_0^{V_{tot}} PdV \quad (1)$$

where P is the pressure, V the intruded volume of mercury, γ the surface tension and θ the contact angle of mercury and V_{tot} the total intruded volume of mercury. The mean pore diameter was calculated by Eq. 2:

$$d_{mean} = 4 \cdot \frac{V_{tot}}{S} \quad (2)$$

based on the assumption of cylindrical shape of pores open at ends. Median pore diameter (d_{median}) is the pore diameter at which 50% of the total intruded volume of mercury is intruded.

The morphology of the fracture surface of tablets was studied by scanning electron microscopy (Jeol JSM-840A, Japan). Analysis of variance (ANOVA), and Fisher's protected least significant difference (PLSD) test as a post-hoc test, were run with the StatView statistical program for Macintosh (Abacus Concepts, Inc., USA).

3. Results and discussion

3.1. Total pore volume

The maximum compression force used strongly affects the intruded volume of mercury (Fig. 1, Table 1). The primary particles of fragmented lactose granules remain intact when compressed with a force of 4 kN (Fig. 2a). The fracture surface of a lactose tablet compressed with a force of 12 kN (Fig. 2b) shows that primary particles are partly fused so that boundaries are undetectable. Glucose granules which are the most resistant to compression show only a small decrease in total pore volume (Fig. 1b). Glucose tablets already have a very small total pore volume when compressed with the lowest compression force; further densification is thus more difficult. As seen from the fracture surface of a glucose tablet compressed with the lowest force (Fig. 3a), the entire granule tends to keep its integrity. The fracture of the glucose tablet occurs along the granule surface. Further increase in compression force causes further coalition of glucose granules and formation of bonds so strong that the tablet fractures also across the granules

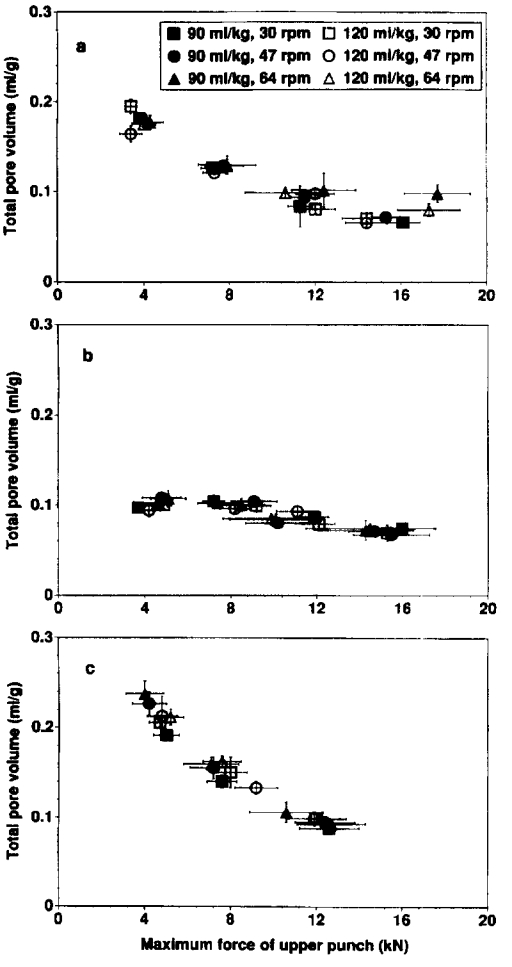

Fig. 1. Mean total pore volume ($n = 3$) vs. mean maximum compression force ($n = 40$) of (a) lactose, (b) glucose and (c) mannitol tablets. Error bars represent ± standard deviation.

Table 1
p-Values obtained by analysis of variance (ANOVA) with Fisher's PLSD test for total pore volume of lactose, glucose and mannitol tablets

Diluent	Liquid amount	Compression speed	Compression force	Liquid amount and compression speed	Liquid amount and compression force	Compression speed and compression force	Liquid amount and compression speed and compression force	Fishers PLSD test for compression speed		
								30–47 rpm	30–64 rpm	47–64 rmp
Lactose ($n = 72$)	0.123	0.002	<0.001	0.068	0.737	<0.001	0.085	0.770	0.003	0.001
Glucose ($n = 72$)	0.170	0.320	<0.001	0.330	0.352	0.524	0.002	0.859	0.167	0.227
Mannitol ($n = 54$)	0.216	<0.001	<0.001	0.002	0.412	0.039	0.069	0.028	<0.001	0.022

(Fig. 3b). The densification appears to occur by plastic deformation at the contact points of granule surfaces and to some degree by fragmentation of granules. With increasing force, the reduction in the pore volume of mannitol tablets is the most drastic (Fig. 1c). The highly porous microstructure of the mannitol tablet is further densified with increased compression force (Fig. 4a and Fig. 4b). No granule boundaries can be observed on the fracture surfaces of any mannitol tablets.

The total pore volumes of lactose tablets compressed with the two highest forces and at the highest speed are larger than those of others (Fig. 1a, Table 1). Apparently, the high compression speed causes greater total pore volume because of less time-dependent deformation at the contact points of the lactose particles. The total pore volume of glucose and mannitol tablets is not affected by compression speed. The amount of granulation liquid has no effect on the total pore volume of any type of tablet (Fig. 1, Table 1).

3.2. Total pore surface area

With increasing compression force, the increase in pore surface area of lactose tablets is the least profound of any of the tablets studied (Fig. 5a). A directly proportional and linear relationship between compaction pressure and total pore surface area of lactose powder tablets has been reported (Vromans et al., 1985, de Boer et al., 1986). Obviously, the lactose granules behave differently from lactose powder in compression. According to Wikberg and Alderborn (1991), the surface area of a lactose granule tablet measured by permeametry was also linearly dependent on the compression force. In their study, fragmentation of lactose granules with increasing force caused further increase in tablet pore surface area. On the basis of the SEM graphs (Fig. 2a and Fig. 2b), the lactose particles fragment with increasing force. However, the increase in the total pore surface area of lactose tablets is negligible (Fig. 5a). The total pore surface area determined by mercury porosimetry is highly influenced by the amount of pores with a very small diameter. When fragmentation of lactose granules and primary particles produces mainly relatively large pores, as in the case of lactose tablets (Fig. 2a and Fig. 2b), the

total pore surface area is not affected as much as if small pores had been created during fragmentation. The total pore surface area of glucose and mannitol tablets, however, increases linearly with increasing compression force (Fig. 5b and Fig. 5c). Thus, it can be presumed that glucose and mannitol granules produce small pores by deformation. Compression speed does not affect the surface area of pores of any tablets (Table 2).

The amount of granulation liquid affects the total pore surface areas of lactose and mannitol tablets (Fig. 5, Table 2). Mannitol tablets produced from the granules prepared with high amounts of liquid have a greater pore surface area due to the larger amount of porous granules compressed (Juppo and Yliruusi, 1994).

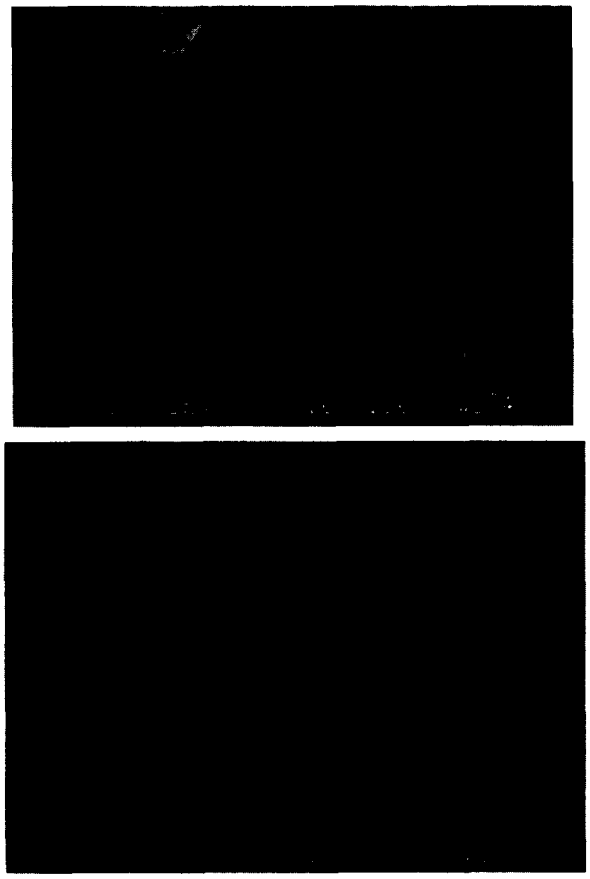

Fig. 2. Scanning electron micrographs of the fracture surface of lactose tablet compressed with the maximum force level of (a) 4 and (b) 12 kN (amount of granulation liquid, 120 ml/kg; compression speed, 30 rpm). Bars represent 100 μm.

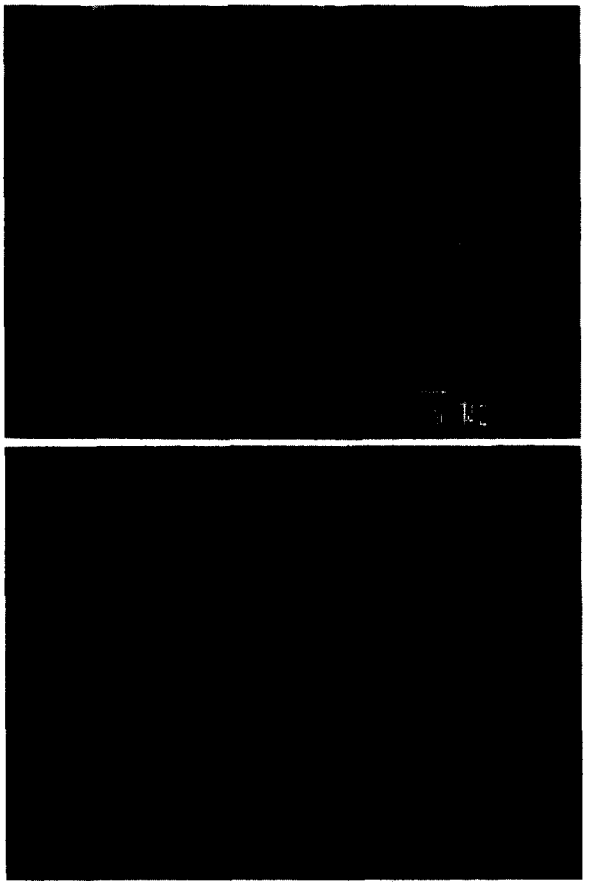

Fig. 3. Scanning electron micrographs of the fracture surface of glucose tablet compressed with the maximum force level of (a) 4 and (b) 12 kN (amount of granulation liquid, 120 ml/kg; compression speed, 30 rpm). Bars represent 100 μm.

3.3. Mean and median pore diameter

Mean pore size is highly dependent on the smaller pores, because the surface area which is used in calculation is highly affected by small pores. This is the reason why the mean pore size is remarkably smaller than the median pore size (Fig. 6). The three types of tablets are in a different ranking order according to their median pore diameters, and according to their mean pore sizes (Fig. 7). This is due to the fact that the median size is taken from the cumulative pore volume versus pore diameter curve, where 50% of the total volume of intruded mercury has been intruded. Thus, the larger pores with greater volumes are under more intense scrutiny.

Due to the fragmentation of lactose granules and particles, the mean and the median pore diameters of lactose tablets are affected most profoundly by the maximum compression force of tablets studied (Fig. 6a, Fig. 7a). The mean and the median pore diameters of lactose tablets compressed at the highest compression speed, especially with a high amount of binder solution, are clearly larger than those of tablets compressed at other speeds (Fig. 6a and Fig. 7a, Table 3 and Table 4). This is consistent with the behaviour of total pore volume values (Fig. 1a). For glucose tablets, the same phenomenon is observed for the median pore diameters of the tablets compressed with the two highest levels of compression force

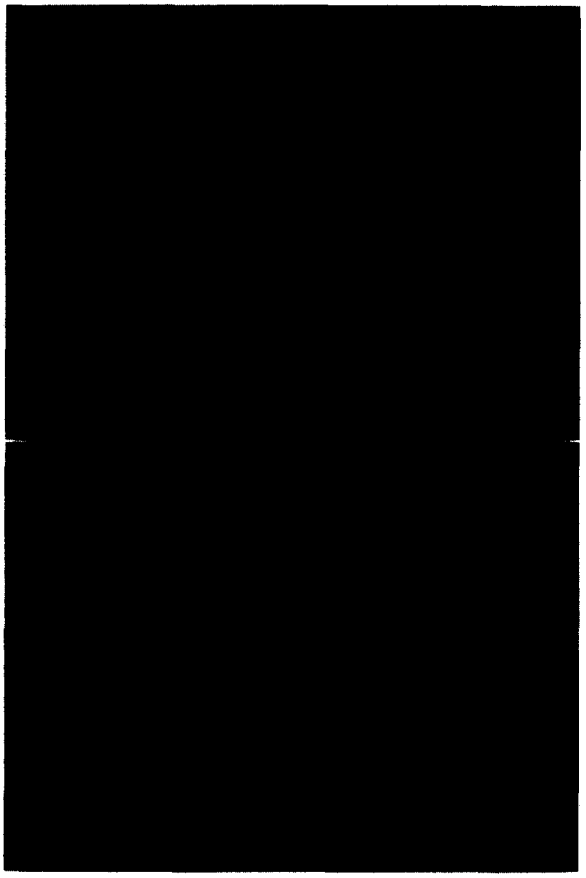

Fig. 4. Scanning electron micrographs of the fracture surface of mannitol tablet compressed with the maximum force level of (a) 4 and (b) 12 kN (amount of granulation liquid, 120 ml/kg; compression speed, 30 rpm). Bars represent 100 μm.

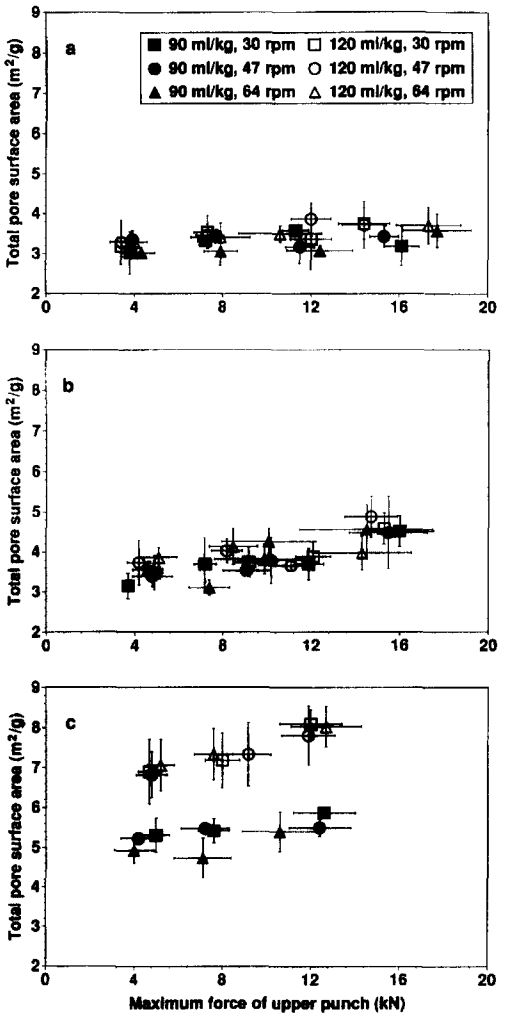

Fig. 5. Mean total pore surface area ($n = 3$) vs. mean maximum compression force ($n = 40$) of (a) lactose, (b) glucose and (c) mannitol tablets. Error bars represent ± standard deviation.

(Fig. 7b, Table 4). At the highest speed, there is less time for deformation of material. The mean and median pore diameters can be considered to be measures of spaces within the solid material in the tablet. The smaller the pore diameter, the closer to each other the granules and primary particles are. The more fragmented the material, the smaller the pore diameter.

For mannitol tablets prepared from granules with low amounts of liquid, the effect of compres-

Table 2
p-Values obtained by analysis of variance (ANOVA) with Fisher's PLSD test for total pore surface area of lactose, glucose and mannitol tablets

Diluent	Liquid amount	Compression speed	Compression force	Liquid amount and compression speed	Liquid amount and compression force	Compression speed and compression force	Liquid amount and compression speed and compression force	Fisher's PLSD test for compression speed		
								30 rpm 47 rpm	30 rpm 64 rpm	47 rpm 64 rpm
Lactose (n = 72)	0.011	0.439	0.042	0.868	0.820	0.846	0.366	0.364	0.741	0.217
Glucose (n = 72)	0.102	0.742	<0.001	0.728	0.089	0.338	0.207	0.455	0.599	0.823
Mannitol (n = 54)	<0.001	0.469	<0.001	0.176	0.219	0.806	0.984	0.559	0.222	0.519

sion speed is clearly observed (Fig. 6c and Fig. 7c, Tables 3 and 4). With increasing compression speed, both the mean and the median pore diameter increase systematically. In the case of mannitol tablets, further densification of the tablet with increasing compression force occurs, obviously by plastic deformation of mannitol, thus the mean pore size of the mannitol tablet is dependent on the compression speed. The plasticity of mannitol powder has been reported previously (Roberts and Rowe, 1987).

Mannitol granules produced with a high amount of granulation liquid, 120 ml/kg, contain higher numbers of large and highly porous granules than those produced with low amounts of liquid (Juppo et al., 1992). The degree of plastic deformation of these highly porous mannitol granules is less than that of mannitol particles and smaller granules. Instead of plastic deformation, the highly porous granules tend to fragment. The mean and the median pore sizes of tablets compressed from granules prepared with highamounts of granulation liquid is considered to be independent of compression speed (Fig. 6c and Fig. 7c).

3.4. Pore volume size distribution

When the maximum compression force increases, the difference in pore volume size distributions found previously (Juppo, 1996) for lactose tablets compressed from granules with two different amounts of liquid, at the lowest force, and at the lowest speed, is no longer detectable for tablets compressed at medium speed (Fig. 8a and Fig. 8b). This is due to further fragmentation of primary particles which neutralizes the effect of structure of the former granules (Selkirk and Ganderton, 1970a, Healey et al., 1973).

The increase in maximum compression force in lactose tablets causes a shift in pore volume size distribution to smaller pore diameters. According to Bockstiegel (1966), the pores of iron powder compacts disappear strictly in order of size with increasing compression force. Vromans et al. (1985) have stated that this kind of be-

haviour is related to plastic deformation of the material, whereas fragmentation of material also creates a new population of pores. They have compared the change in pore volume size distributions of dicalcium phosphate and microcrystalline cellulose tablets with increasing compression pressure. With increasing pressure, dicalcium phosphate powder fragmented, large pores disappeared, and the proportion of smaller pores increased, as in this study. This phenomenon, although consider-ably weaker, was also observed with the results obtained from the compression of microcrystalline cellulose, which is considered to be a plastically deformable material. Plastic deformation causes some increase in the proportion of small pores because the former large pores between

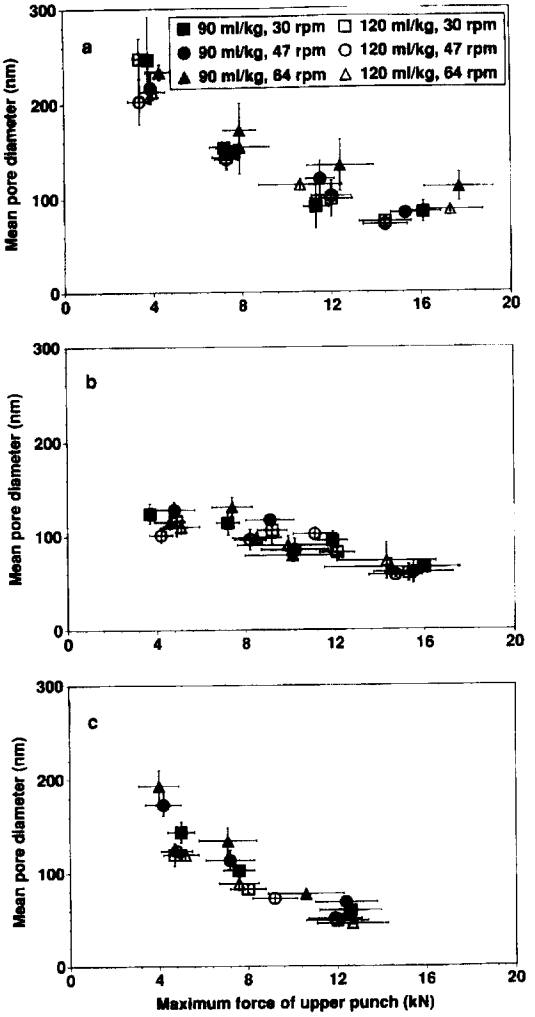

Fig. 6. Mean values of mean pore diameter ($n = 3$) vs. mean maximum compression force ($n = 40$) of (a) lactose, (b) glucose and (c) mannitol tablets. Error bars represent ± standard deviation.

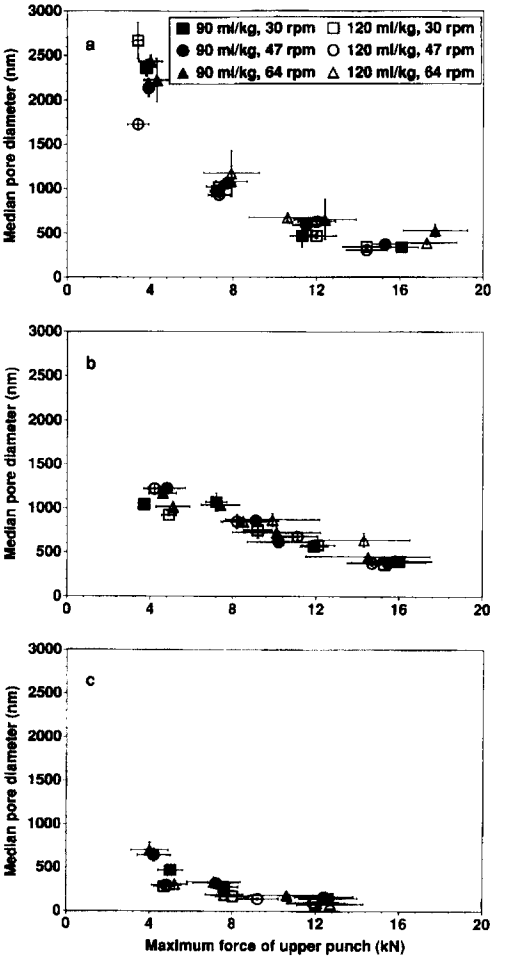

Fig. 7. Median values of mean pore diameter ($n = 3$) vs. mean maximum compression force ($n = 40$) of (a) lactose, (b) glucose and (c) mannitol tablets. Error bars represent ± standard deviation.

Table 3
p-Values obtained by analysis of variance (ANOVA) with Fisher's PLSD test for mean pore diameter of lactose, glucose and mannitol tablet

Diluent	Liquid amount	Compression speed	Compression force	Liquid amount and compression speed	Liquid amount and compression force	Compression speed and compression force	Liquid amount and compression speed and compression force	Fisher's PLSD test for compression speed		
								30–47 rpm	30–64 rpm	47–64 rpm
Lactose ($n = 72$)	0.006	0.013	<0.001	0.228	0.978	0.010	0.980	0.228	0.069	0.003
Glucose ($n = 72$)	0.003	0.743	<0.001	0.772	0.001	0.207	0.015	0.489	0.953	0.526
Mannitol ($n = 54$)	<0.001	<0.001	<0.001	<0.001	<0.001	0.023	0.251	0.011	<0.001	0.001

Table 4
p-Values obtained by analysis of variance (ANOVA) with Fisher's PLSD test for median pore diameter of lactose, glucose and mannitol tablets

Diluent	Liquid amount	Compression speed	Compression force	Liquid amount and compression speed	Liquid amount and compression force	Compression speed and compression force	Liquid amount and compression speed and compression force	Fisher's PLSD test for compression speed		
								30–47 rpm	30–64 rpm	47–64 rpm
Lactose ($n = 72$)	0.902	<0.001	<0.001	0.002	0.547	<0.001	0.002	0.001	0.051	<0.001
Glucose ($n = 72$)	0.005	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Mannitol ($n = 54$)	<0.001	<0.001	<0.001	<0.001	<0.001	0.002	0.016	0.002	<0.001	0.063

particles or granules not only disappear, but they may also be reduced in size, being detectable at a smaller pore range. This kind of change in the pore volume size distribution has also been found for polymer matrix tablets (Carli et al., 1981).

With increasing compression force, the voids between the glucose granules decrease with increasing compression force. This may manifest as reduction of greater pores (>1 μm) and as a creation of smaller pores by the fragmentation of

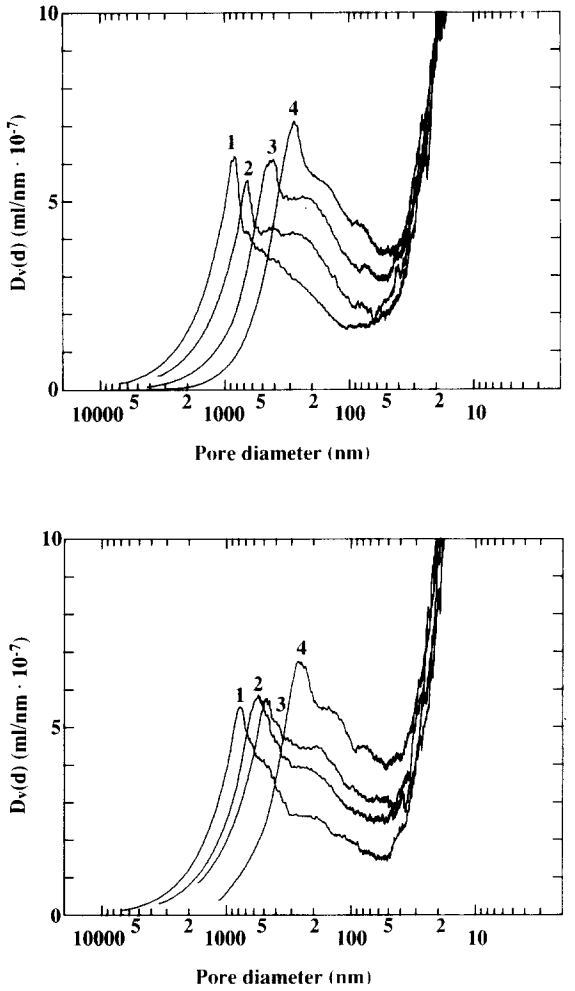

Fig 8. Pore volume size distributions (D_v(d)) of lacrose tablets. Amount of granulation liquid: 90 (a) and 120 ml/kg (b). Compression speed is 47 rpm and maximum compression force levels: 4 (1), 8 (2), 12 (3) and 16 kN (4).

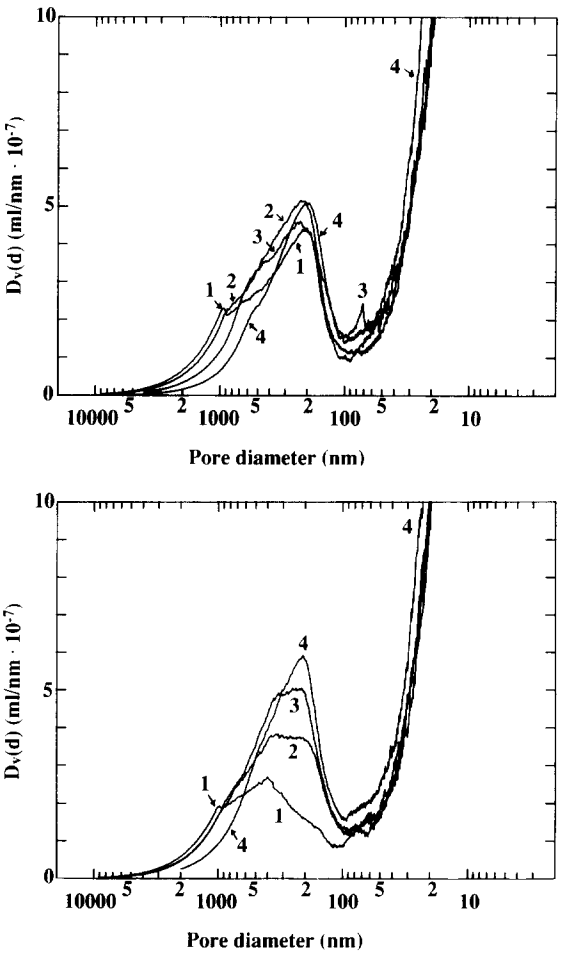

Fig 9. Pore volume size distributions (D_v(d)) of glucose tablets. Amount of granulation liquid: 90 (a) and 120 ml/kg (b). Compression speed is 47 rpm and maximum compression force levels: 4 (1), 8 (2), 12 (3) and 16 kN (4).

cluster-like glucose granules (Figs. 3 and 9). The D_v(d) values of pores smaller than 60 nm increase clearly with increasing compression from 12 to 16 kN (Fig. 9a and Fig. 9b). This is consistent with the behaviour of total pore surface area and mean pore diameter. The pore structure of glucose tablets is obviously ruptured and small pores are created.

The densification of mannitol granules with increasing compression force also causes a shift in

pore volume size distribution to smaller pore diameters (Fig. 10). The tailing in the maximum of volume size distribution inherited from the bimodality of pore volume size distribution of granules (Juppo, 1996) vanishes with increasing compression force. This disappearance of large pores is a sign of fragmentation. The tablets compressed from granules with low amounts of liquid have a broader distribution, with maxima at larger pore diameters than tablets compressed with the higher amounts of binder solution. The difference in the magnitude of the $D_v(d)$ values between granules prepared with two different amounts of liquid and compressed tablets also remains, regardless of the increased compression force level. Thus, the effect of pore structure of mannitol granules on the pore structure of the tablet is not eliminated with increasing compression force.

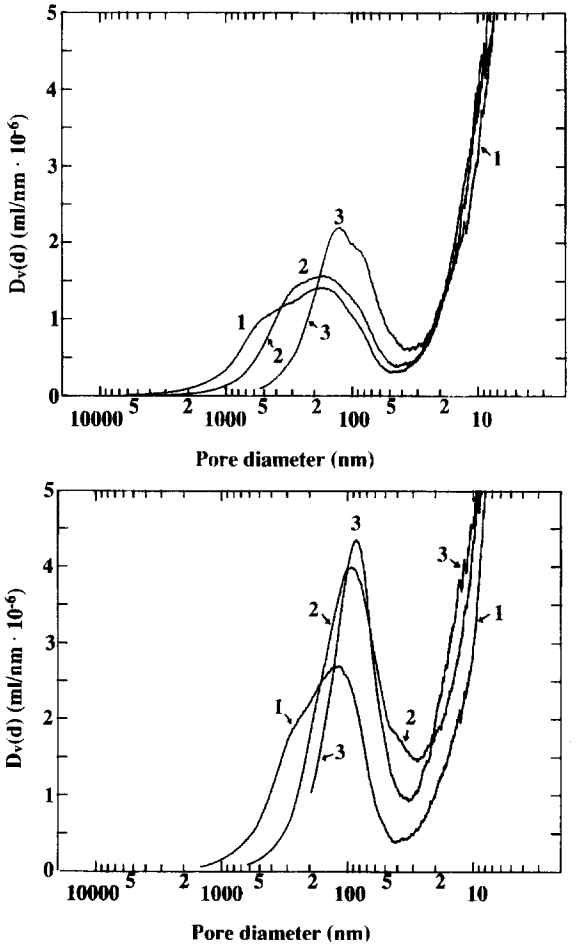

Fig. 10. Pore volume size distributions ($D_v(d)$) of mannitol tablets. Amount of granulation liquid: 90 (a) and 120 ml/kg (b). Compression speed is 47 rpm and maximum compression force levels: 4 (1), 8 (2) and 12 kN (3).

4. Conclusions

The effect of compression force, compression speed, and the amount of liquid used in the granulation were found to strongly affect the pore structure of tablets studied. The three types of tablets were also distinguishable on the basis of porosimetry results. The compression speed dependence of porosity parameters is a sign of time-dependent deformation of material during compression. Compression at increasing speed allows less deformation which results in larger pores. The effect of the variables on the pore structure was detected within each porosity parameter determined from different points of view. Thus, the use of all porosity parameters is reasonable and justified in compression studies. The advantages of pore volume size distribution are that it provides information about the proportion of pores with different diameters and shows the pore structure visually. On the other hand, single numerical parameters obtained from a porosimeter analysis give more accurate comparisons and make statistical analysis possible.

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