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Change in porosity parameters of lactose, glucose and mannitol granules caused by low compression force

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Abstract

The change in porosity parameters, i.e., total pore volume, porosity percentage and pore volume size distribution of lactose, glucose and mannitol granules caused by compression with a low force was investigated. In compression, fragmentation of lactose and glucose granules increased total pore volume and porosity percentage, whereas the total pore volume and porosity percentage of mannitol granules was clearly decreased. This was due to the highly porous structure of mannitol granules, which densified easily in compression. Lactose and glucose granules were shown to resist deformation more. The pore volume size distributions of lactose and glucose tablets showed that large pores ($>$ 14 μm) decreased in size. For mannitol tablets, the large pores vanished and simultaneously the small granule pores ($<$ 14 μm) reduced in size. The features of the pore structure of granules were detected in the pore volume size distributions of compressed tablets. Mercury porosimetry, assisted by scanning electron microscopy, was shown to be an adequate method to evaluate the deformation of granules in compression.

Keywords: Compression; Granules; Lactose; Glucose; Mannitol; Porosity

1. Introduction

The volume reduction mechanisms of granules affect the pore structure of compressed tablets. Rearrangement and fragmentation of granules, plastic or elastic deformation and fragmentation of resulting particles modify the pore network of the produced tablet. Depending on the shape and the size of granules, the ability of granules to slide by each other varies in compression. The tendency of granules to fragment is highly dependent on the strength of the granule. According to Wikberg and Alderborn, 1992, the degree of granule fragmentation affected especially the size of the intergranular pores of lactose tablets. The densification of lactose granules by fragmentation occurring even at a low pressure ($<$ 20 MPa) could be detected as an increase in the tablet surface area as determined by permeametry (Wikberg and Alderborn, 1990).

There are contradictory opinions as to whether the granule properties affect the porosity parameters of compressed tablets. Selkirk and Ganderton, 1970a found that the amount of granulation liquid affected the intergranular porosity of lac-

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Table 1
Total pore volumes of lactose, glucose and mannitol granules and tablets compressed from the granules (standard deviations in brackets ($n = 3$))

	Liquid amount (ml/kg)	Total pore volume of granules (ml/g)		Total pore volume of tablets (ml/g)
		Pore size range 14-220 μm	Pore size range 6.5 nm to 14 μm	Pore size range 6.5 nm to 14 μm
Lactose	90	0.630 (0.067)	0.077 (0.020)	0.182 (0.003)
	120	0.399 (0.030)	0.076 (0.007)	0.19 (0.008)
Glucose	90	0.131 (0.020)	0.050 (0.013)	0.097 (0.002)
	120	0.069 (0.011)	0.057 (0.017)	0.100 (0.005)
Mannitol	90	0.375 (0.067)	0.341 (0.012)	0.191 (0.004)
	120	0.260 (0.002)	0.405 (0.016)	0.205 (0.006)

tose tablets compressed with a low compression force. With increased compression force, causing more fragmentation of granule, this effect disappeared. According to Healey et al., 1973, the effect of intra-granular porosity on the porosity of the tablet is eliminated by compression, except on tablets compressed to very low pressures (< 80 MPa). On the other hand, the two methods of granulation, dry and wet, caused different tablet porosities and pore size distributions (Selkirk and Ganderton, 1970b). Also the size of compressed lactose granules influenced the intergranular porosity. Selkirk, 1973 compared two wet granulation methods and noticed that the method had no effect on the porosity of compressed tablets. For the dry granulated product, with a greater slugging force used in granulation, a broader pore size distribution was obtained (Riepma et al., 1993). Zuurman et al., 1994, found that the lactose granules with a low bulk density contributed to tablets with a small average pore diameter. According to Wikberg and Alderborn, 1991, also the type of binder solvent affected the porosity of tablets compressed. Use of water as a solvent contributed to a lower tablet porosity than the use of ethanol.

The differences in fragmentation tendency and densification mechanism of granules can be detected more easily when relatively low compression forces are used. This has been utilised in several studies (Selkirk and Ganderton, 1970a, Healey et al., 1973, Wikberg and Alderborn, 1990). However, the change in the granule pore size distribution caused by compression has not been previously studied. The aim of this study was to investigate the change in the total pore volume, porosity percentage and pore volume size distribution of lactose, glucose and mannitol granules caused by low compression force.

2. Materials and methods

2.1. Granules

The granules were prepared from α-lactose monohydrate (EP D 80, Meggle Milchindustrie GmbH, Germany), anhydrous α-glucose (Suomen Xyrofin Ltd, Finland) and D-mannitol (Merck, Germany) using two amounts of 20% polyvinylpyrrolidone (PVP) solution: 90 and 120 ml/kg. Granulation was made in a high-shear granulator (Fielder PMA 25/2G, T.K. Fielder

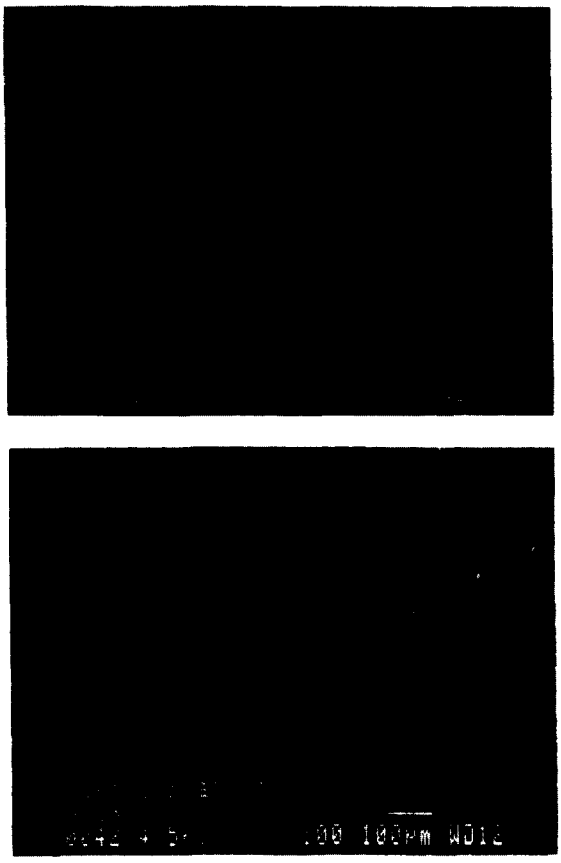

Fig. 1. Scanning electron micrographs of (a) lactose granules prepared with liquid (90 ml/kg) and (b) surface of compressed lactose tablet. Bars represent 100 μm.

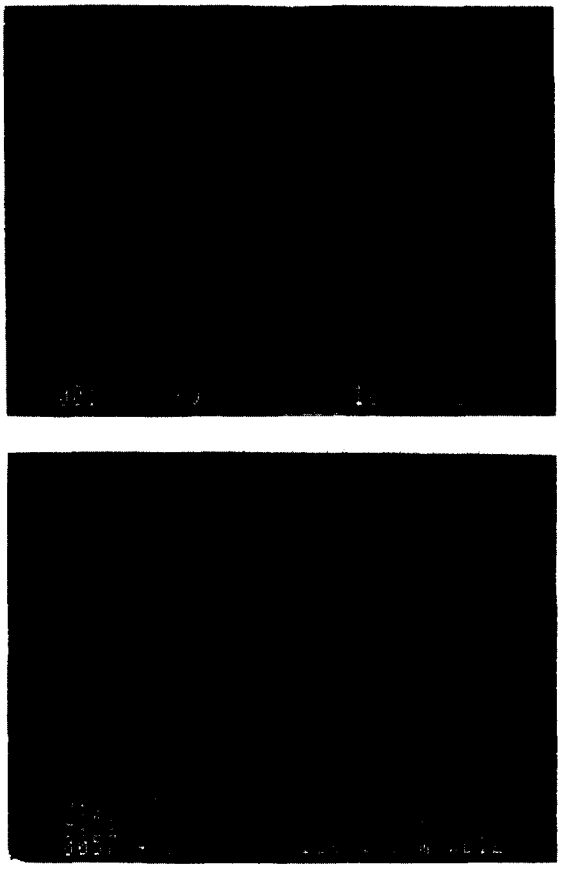

Fig. 2. Scanning electron micrographs of (a) glucose granules prepared with liquid (90 ml/kg) and (b) surface of compressed glucose tablet. Bars represent 100 μm.

Ltd., UK). Granulation and resulting granule size distributions have been described previously (Juppo et al., 1992). The particle size distributions of raw materials and methods for determining the porosity parameters of granules have also been presented in an earlier study (Juppo and Yliruusi, 1994). Total pore volumes, total pore surface areas and pore volume size distributions of granules were determined both with a low-pressure porosimeter (pore diameter range 14–220 μm) and with a high-pressure porosimeter (pore diameter range 6.5 nm to 14 μm, Autoscan 33, Quantachrome Corp., USA).

2.2. Compression

Tablets were compressed from granules mixed with 1% magnesium stearate. Tableting was made in an instrumented production-scale rotary press (Kilian RU-24II, Kilian and Co. GmbH, Germany) without a feeder using bevel-edged flat punches 9 mm in diameter. The compression speed was 30 rpm and the target maximum force of upper punch was set 4 kN. Compression has been described in detail in a previous study (Juppo et al., 1995).

2.3. Porosity parameters of tablets

Porosity parameters, total pore volume, total pore surface area and pore volume size distributions, were determined by a high-pressure porosimeter (Autoscan 33, Quantachrome Corp., USA). The contact angle of mercury (Outo-

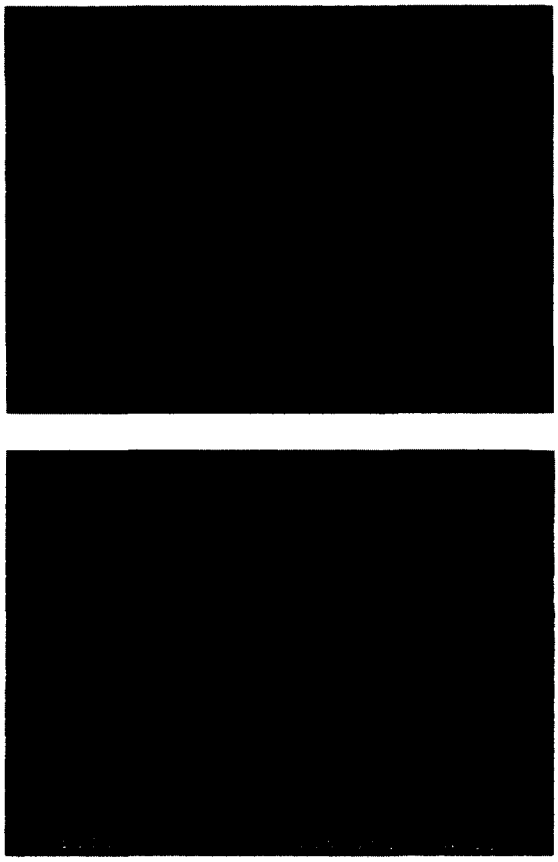

Fig. 3. Scanning electron micrographs of (a) mannitol granules prepared with liquid (90 ml/kg) and (b) surface of compressed mannitol tablet. Bars represent 100 μm.

kumpu, Finland) was approximated to 140° and the surface tension to 480 mN/m. Before the porosimeter run, a sample of six tablets (1.3–1.4 g) was packed into a sample cell 6.5 cm^3 in volume and evacuated and filled with mercury (Filling Apparatus, Quantachrome Corp., USA). The volume of capillary stem was 0.5 cm^3. The pressure range of the high-pressure porosimeter was 0.1–227 MPa, corresponding to pores 6.5 nm to 14 μm in diameter. The scanning speed used was 47 MPa/min. Porosimeter tests were made in triplicate.

The pressure and intruded volume readings were filed in the memory of a computer. Total intruded volume of mercury and volume pore size distribution $D_v(d)$ and total pore surface area were calculated from the intrusion data with Quantachrome Autoscan PORO2PC Software, Version 2.17. $D_v(d)$ (i.e. dV/dd) was calculated by Eq. 1:

$$D_v(d) = \frac{P}{d} \cdot \frac{dV}{dP} \quad (1)$$

where P is the pressure, d the pore diameter and V the intruded volume of mercury. The porosity percentage (epsilon) of granules and tablets based on the porosimeter analysis was calculated by Eq. 2:

$$\varepsilon = \left(\frac{V_{tot}}{V_{tot} + \frac{1}{\rho_h}} \right) \cdot 100\% \quad (2)$$

where ρ_h is the true density of granules determined by helium pycnometer. The method for measuring true density and the calculation of porosity percentage of tablets based on the geometrical shape of tablet have been presented in a previous paper (Juppo et al., 1995). The surface morphology of granules and tablets was studied by taking scanning electron micrographs with a scanning electron microscope (Jeol JSM-840A, Japan).

3. Results and discussion

3.1. Total pore volume

Total pore volume measured in the high-pressure range (6.5 nm to 14 μm) increases when lactose and glucose granules are compressed into a tablet (Table 1). This is obviously due to the change from large pores (14–220 μm) into smaller ones. Both lactose and glucose granules have a cluster-like structure (Juppo and Yliruusi, 1994, Fig. 1a and Fig. 2a). Pores larger than 14 μm in diameter are assumed to be intergranular pores which diminish in size during compression, enabling detection by high-pressure porosimetry. The reduction of intergranular pores of lactose granules is caused by the fragmentation of granules into primary particles, as can be detected also in the SEM micrograph of the surface of

Table 2
Porosity percentages of lactose, glucose and mannitol granules and tablets compressed from the granules <TB2>

	Liquid amount (ml/kg)	Maximum compression force ($n = 0$) (kN) Mean ± S.D.	Porosity of granules calculated on the basis of total intruded volume of mercury (%)	Porosity of granules determined by mercury pycnometry (%)	Porosity of tablets calculated on the basis of tablet dimensions (%)	Porosity of tablets calculated on the basis of total intruded volume of mercury (%)
Lactose	90	3.8 ± 0.2	10.7	8.6	22.9	22.0
	120	3.4 ± 0.3	10.4	8.0	22.0	23.0
Glucose	90	3.7 ± 0.3	7.1	4.1	21.7	12.9
	120	4.9 ± 0.4	8.1	7.0	19.7	13.3
Mannitol	90	5.0 ± 0.6	33.9	33.0	23.5	22.3
	120	4.7 ± 0.5	37.9	37.6	24.1	23.6

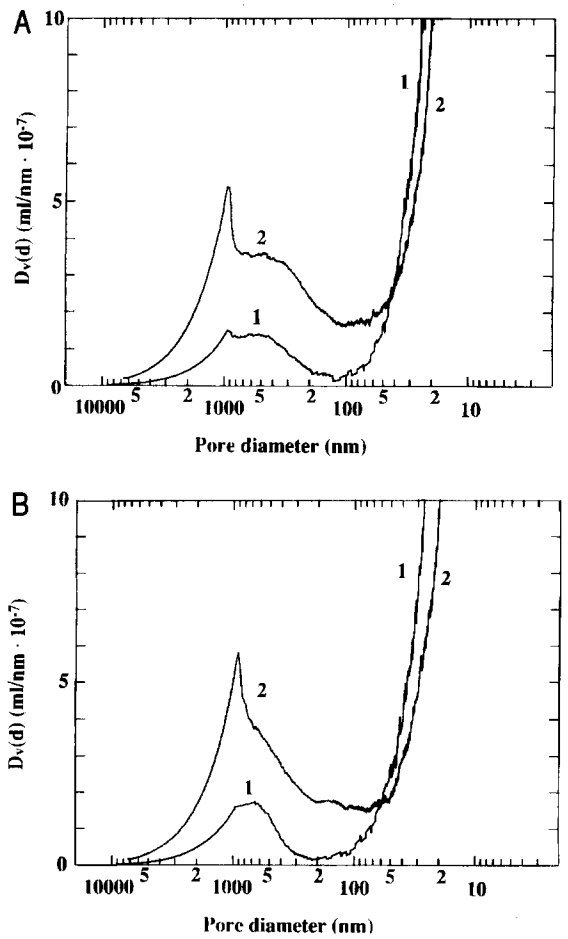

Fig. 4. Pore volume size distributions (D_v(d)) of lactose granules (1) prepared with liquid amounts of 90 (a) and 120 (b) ml/kg, and tablets (2) compressed from the granules.

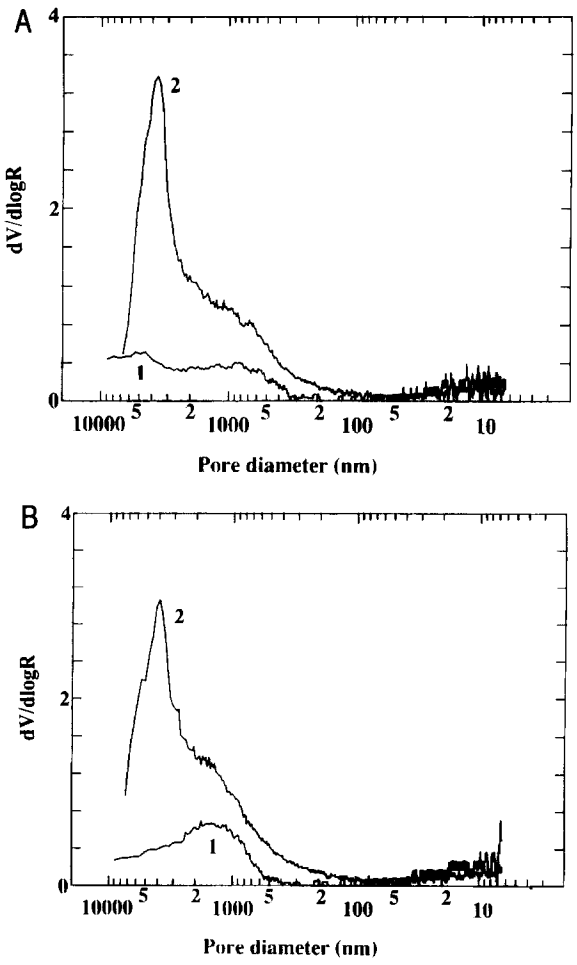

Fig. 5. Logarithmic volume size distributions (dV/d logR) of pores of lactose granules (1) prepared with liquid amounts of 90 (a) and (b) 120 (b) ml/kg, and tablets (2) compressed from the granules.

lactose tablet (Fig. 1b). Fragmentation of granules has made the boundaries between granules difficult to separate. The granules prepared with the low amount of granulation liquid have larger total pore volume of large pores (Table 1, Juppo and Yliruusi, 1994). This effect, however, is not detected on the total pore volume of compressed lactose tablets in the pore diameter range of 6.5 nm to 14 μm. Glucose granules resist more compression: they keep their integrity (Fig. 2b). The differences in the total pore volumes of glucose granules prepared with two liquid amounts in the pore diameter range 14–220 μm are no longer observed in the total pore volumes of tablets (Table 1). Thus, compression even with a low force (corresponding approx. 60 MPa) eliminates the differences in the total pore volume of lactose and glucose granules. Healey et al., 1973 found that the effect of intragranular porosity on the porosity of tablet is negligible, expect on tablets compressed with very low pressures ($<$ 80 MPa).

Mannitol granules are porous and irregularly elongated (Fig. 3a). High porosity of mannitol granules makes them easy to densify so that no granule boundaries can be detected in the micrograph of the tablet surface (Fig. 3b). Total

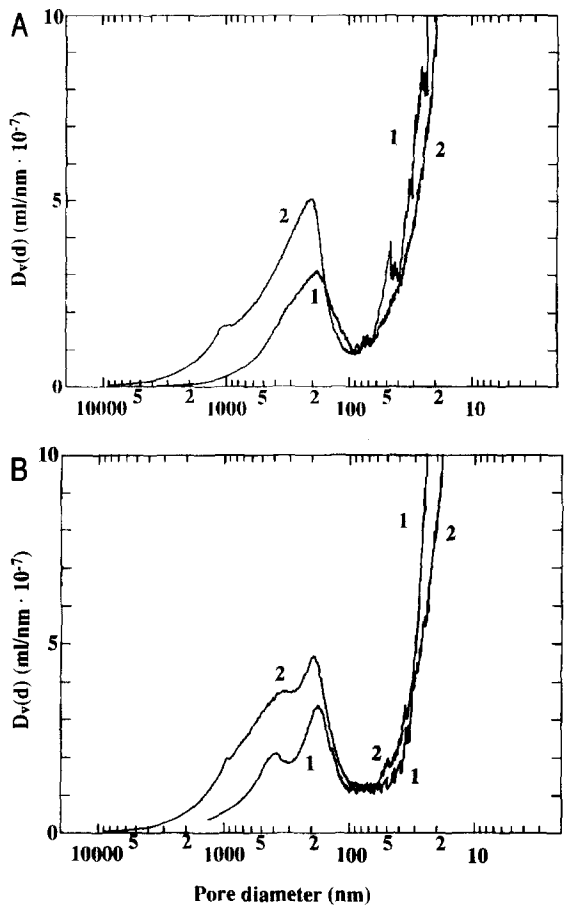

Fig. 6. Pore volume size distributions (D_v(d)) of glucose granules (1) prepared with liquid amounts of 90 (a) and 120 (b) ml/kg, and tablets (2) compressed from the granules.

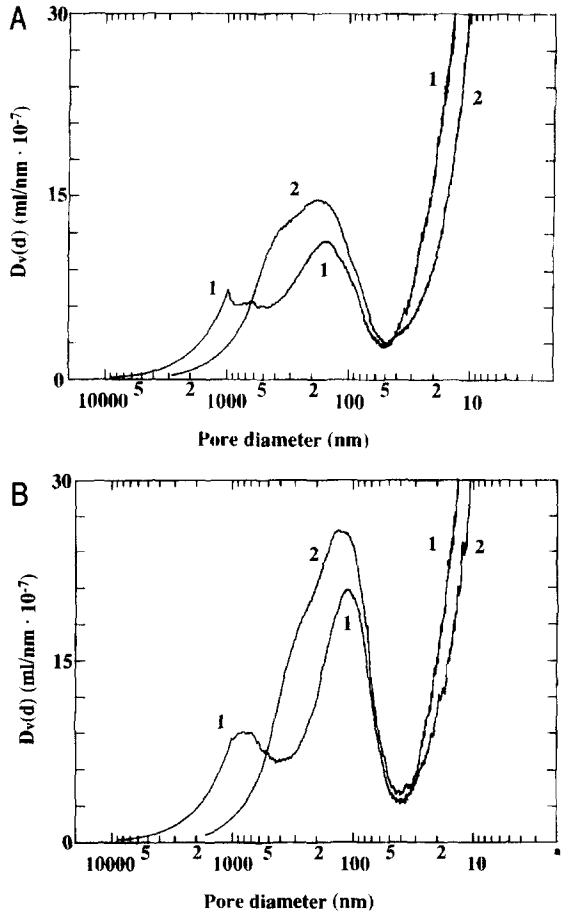

Fig. 7. Pore volume size distributions (D_v(d)) of mannitol granules (1) prepared with liquid amounts of 90 (a) and 120 (b) ml/kg, and tablets (2) compressed from the granules.

pore volume of mannitol tablets is clearly smaller than that of mannitol granules (Table 1). Large pores vanish and the volume of smaller pores is reduced. This means that the intragranular porosity of mannitol granules is also affected even when a low compression force is used. The differences in the total pore volume of mannitol tablets caused by the amount of liquid are insignificant.

3.2. Porosity percentage

As in the case of total pore volume in the pore diameter range 6.5 nm to 14 μm, the porosity of lactose and glucose tablets is higher than that of lactose and glucose granules. The porosity of mannitol granules decreases when compressed due to densification of the highly porous structure of granules. Evidently, the fragmentation of lactose and glucose granules causes an increase in porosity. The amount of granulation liquid has no remarkable effect on the tablet porosity as is the case with total pore volume (Table 2). According to the results of Wikberg and Alderborn, 1991, too, the porosity of lactose granules had no effect on the tablet porosity calculated from the tablet dimensions and apparent particle density.

The porosities of lactose and mannitol tablets determined by two different methods are relatively

consistent with each other (Table 2). The porosity of glucose tablets calculated on the basis of intruded volume of mercury, however, is smaller. The porosity of granules determined with a mercury pycnometer and the porosity of granules and tablets based on the total intruded volume of mercury includes all open pores smaller than 14 μm in diameter. Intergranular pores which are larger than 14 μm in diameter can be detected on the surface of the glucose tablet (Fig. 2b). These cavities are neglected when the tablet dimensions are measured with a micrometer. Thus, tablet volume calculated on the basis of dimensions includes those large pores on the surface of tablets. Furthermore, the porosity calculated on the basis of tablet dimensions includes, in addition to small pores, also pores larger than 14 μm in diameter. For glucose tablets, this was ensured by checking the total pore volume in the pore diameter range 14–220 μm with a low-pressure porosimeter using the method described previously (Juppo and Yliruusi, 1994).

3.3. Pore volume size distributions

The shape of pore volume size distribution of lactose granules remains about the same even when compressed (Fig. 4a and Fig. 4b). The disappearance of pores larger than 14 μm by fragmentation of granules and rearrangement of resulting particles produces pores which are measurable in the high-pressure range. According to Wikberg and Alderborn, 1992, lactose granules with a low porosity were shown to produce tablets with a wider pore size distribution. In this study, granules prepared with 120 ml/kg have a lower porosity, in the pore range 14–220 μm, but the porosities of granules are identical in the pore range 6.5 nm to 14 μm. However, the dV/dD distribution of tablets compressed from the granules with 90 ml/kg appears to be broader.

As an example, also, the dV/d log R functions, where R is the pore radius, are presented for lactose granules and tablets (Fig. 5a and Fig. 5b). With a logarithmic transformation, the portion of larger pores becomes pronounced and the fine structure of distribution at large pore diameters can be examined. The generation of pores larger than 2 μm in diameter is more clearly detected in these graphs than in the dV/dd distributions. The maxima are located at larger pore diameters than in dV/dd distributions due to the emphasis of large pores. The dV/d log R distribution is useful when the differences of interest in the pore volume size distributions are in the pore diameter range 1–14 μm. In this study, however, the most drastic differences were observed in pores smaller than 1 μm. For this reason, D_v(d) distributions are chosen to characterize pore size distributions.

A similar change in the pore volume size distribution of glucose and lactose granules was observed due to compression (Fig. 6a and Fig. 6b). The intergranular space, i.e., pores greater than 14 μm in diameter, of glucose granules densifies into smaller pores. With a granulation liquid amount of 90 ml/kg, the volume size distribution of tablet pores appears to be bimodal. The same results with glucose granules prepared with 120 ml/kg. These two maxima of pore volume size distribution of glucose granules remain in the distribution of compressed tablets. In addition to two maxima, a third maximum at 1 μm, generated from the granule pores larger than 14 μm in diameter, exists in the pore volume distributions of tablets.

The elimination of large pores in compression is seen in the D_v(d) distributions of mannitol (Fig. 7a and Fig. 7b). Large pores vanish, or they are reduced in size. The volume size distribution of tablet pores is tailing to the left. The tailing is obviously a relic from the second maximum of pore volume size distribution of granules at 1 μm, or from the maximum at 15 μm measured previously with low-pressure porosimetry (Juppo and Yliruusi, 1994). As compared with lactose and glucose granules and tablets, the values of maxima of D_v(d) for mannitol granules and tablets are approximately three times higher, which means that mannitol granules and tablets have a greater total volume in that pore range. The amount of granulation liquid affects also the maxima; the greater liquid amount the higher the maxima.

4. Conclusions

The pore volume size distributions show that

the differences in the compression behaviour of granules can be determined by porosimetry. A trace of the history of the tablet, i.e., the pore stucture of the granules, can be observed in the pore structure of the tablets. Lactose and glucose granules resist compression more than mannitol granules, which can be detected from the change in pore volume size distribution of tablets compressed with a low maximum force. Even for mannitol tablets, some characteristics of pore structure of granules are still detectable in the pore volume size distributions of tablets. Porosity percentage or total pore volume are not sensitive enough to bring out these differences in densification behaviour. Mercury porosimetry together with scanning electron micrographs proved to be an acceptable method to explain the deformation of granules in compression.

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