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Research paper

Microcrystalline cellulose and its microstructure in pharmaceutical processing

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Abstract

Mercury porosimetry and nitrogen adsorption methods were used in pore structure and pore surface area characterisation of microcrystalline cellulose powder, granules and tablets. The effect of compression on pore structure and surface area of tablets compressed with three different compression pressures of powder and granules was determined. Densification of MCC in wet granulation led to decreased compactibility in tableting. Effects of granulation on the microstructure of microcrystalline cellulose and plastic deformation of powder during compression were detected with nitrogen adsorption, at the diameter range 3–200 nm. Structure of granules was destroyed during tableting when compression pressures of 196 MPa were used. Fragmentation and deformation of granules were observed from the results determined using both methods. Due to different measurement ranges, different theoretical basis of the methods and behaviour of the samples during analysis, results obtained with mercury porosimetry and nitrogen adsorption methods are not strictly comparable. Results obtained with mercury porosimetry give information on the behaviour of powder and granule particles in granulation or compression, whereas nitrogen adsorption brings out the changes in intraparticular structure of particles. The results obtained using these methods together can be used in the characterisation of behaviour of materials in granulation and tableting.

Keywords: Microcrystalline cellulose; Mercury porosimetry; Nitrogen adsorption; Pore structure; Surface area

1. Introduction

Due to the excellent compression properties of microcrystalline cellulose (MCC), it is commonly used in direct compression, but also in wet granulation and pelletisation. MCC works as a binder in wet granulation [1], but the good compactibility of MCC has been found to disappear due to loss of plasticity in wet granulation [2]. Decrease of compactibility of MCC during the extrusion/spheronisation process has also been reported [3]. Fragmentation and plastic deformation of the pellets were detected only with very high compression forces. Similarly, Maganti and Celik [4] have observed low tensile strength of tablets compacted from MCC pellets, and elastic deformation and brittle fragmentation of pellets during compaction. Increase in the amount of water in water/ethanol mixture used in pelletisation has decreased compactibility of MCC pellets [5]. The mechanism of densification of MCC in wet granulation or pelletisation has been named autohesion [6]. Staniforth and Chatrath [7] have named reduced compactibility of MCC after wet granulation 'quasi-hornification'. Recently, Kleinebudde [8] has explained the behaviour of MCC in wet granulation, extrusion and spheronisation by a crystallite gel model. The discussion of the behaviour of MCC during processing with water has just recently started [9]. The effect of wet granulation on the microstructure of MCC has not been thoroughly studied with the surface area or pore structure analysis. The effect of compression on specific surface area and porosity of MCC tablets compressed from powder has been studied [10]. However, deformation of MCC granules in compression with mercury porosimetry or nitrogen gas adsorption methods has not been thoroughly studied.

In pharmacy, some articles concerning comparison of mercury porosimetry and nitrogen adsorption methods have been reported. The surface area values of lactose tablets when measured with mercury porosimetry have been higher than those determined with nitrogen adsorption method [11]. According to Dees and Polderman, the correlation between the two techniques is acceptable if the theoretical assumptions and the inaccuracy of the methods are

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taken into account. Volume pore size distributions of dicalcium phosphate dihydrate tablets have been equal at the overlapping pore size range when measured with these methods [12]. For magnesium trisilicate and Degussa aerosols, equal volume pore size distributions have been obtained [13]. On the other hand, for silicas, adsorbents and catalysts, non-similar distributions have been determined [14,15]. In our previous study with mannitol powder, granules and tablets, surface area determined with nitrogen adsorption method was markedly smaller than that measured with mercury porosimetry [16]. Volume pore size distribution of the tablets had a similar structure at the overlapping pore size range, but the intensity of the curves was different. Together these techniques described well the behaviour of powder and granules in compression. However, further comparison of the results of pharmaceutical samples obtained with these methods is needed.

The aim of the present work was to study the effect of wet granulation on the pore structure and surface area of microcrystalline cellulose with nitrogen adsorption and mercury porosimetry methods. Furthermore, the effect of compression on the pore structure and surface area of microcrystalline cellulose powder and granules were studied. The pore structure and surface area were measured with these two techniques in order to compare the methods.

2. Materials and methods

2.1. Granulation

Granules were produced from microcrystalline cellulose (MCC), Emcocel (Edward Mendell, USA) using a high-shear mixer (Fielder PMA 25/2G, T.K. Fielder Ltd, UK). The granulation liquid used for microcrystalline cellulose was 4% polyvinylpyrrolidone solution in distilled water. The binder solution was added at a speed of 200 ml/min to the final amount of 400 ml/kg. The granule batch size was 2 kg. After granulation the granules were forced through a 2 mm sieve and dried on trays at 21°C and 43% relative humidity for 2 days. Granulation has also been described in a previous paper [17].

2.2. Characterisation of MCC powder and granules

Percentage porosities of powder and granules were calculated from true and bulk density values, as described in our previous paper [16]. The bulk density was determined with a graduated glass cylinder and true density with a helium pycnometer (Multipycnometer MVP-1, Quantachrome Corp., Boynton Beach, FL, USA). Total pore volume, total pore surface area, median and mean pore sizes were measured with a high-pressure mercury porosimeter (Autoscan 33 Porosimeter, Quantachrome). Total pore volume, volume pore size distribution and specific surface area of the powders and granules were measured by the nitrogen adsorption method (Coulter SA 3100, Coulter Corp., Miami, FL, USA). The total pore volume and volume size distribution of MCC granules was not obtained, because the equipment was not able to determine and calculate the pore volume values. The volume of the pores was so small that it was outside of the detection range of the equipment. Mercury porosimetry and nitrogen adsorption methods have been described in detail in our previous paper [15].

2.3. Compression

Tablets were compressed with a rotary press (Kilian, RU-24 III, Kilian & Co. GmbH, Köln, Germany) from MCC powder and granules. Polyvinylpyrrolidone (1.6%, PVP, Kollidon K25, BASF, Ludwigshafen, Germany) was added to the powder mass as binder. Magnesium stearate (1%, Mallinckrodt, Deventer, Netherlands) was mixed into the tablet masses in a Turbula-mixer (T 10 B, Willy A. Bachofen AG Maschinenfabrik, Basle, Switzerland) for 12 min 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 granule tablets was 230 mg and that of the powder tablets was 190 mg. The bulk density of powder mass was so small that 190 mg was the maximum possible weight of the tablets to be compressed with the tablet press. The rotation speed of the tablet press was kept constant. The compression time was approximately 70–90 ms depending on the material used The target compression pressures used were 72 MPa, 122 MPa and 196 MPa. The temperature during tableting was 20–21°C and relative humidity 13–15%.

2.4. Characterisation of the tablets

Breaking force was measured (Erweka TBH 28, Erweka Apparatebau, Hensenstamm, Germany) from twenty tablets. Porosity of tablets based on tablet dimensions was calculated as presented in our previous paper [16]. Porosity parameters of the tablets were determined with a high-pressure porosimeter in the same way as for powders and granules. Sample size for the analysis was three tablets. Total pore volume, volume pore size distribution and specific surface area of the tablets (sample size 15 tablets) were measured by the nitrogen adsorption method as described above 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

When measured with mercury porosimetry, the pore volume of powder is larger than that of the granules (Table 1). This is due to the voids between powder particles that are measured with this method, as with mannitol

Table 1
Porosity parameters of MCC powder, granules and the tablets compressed with three different compression pressures as measured with 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 MCC powder and the tablets compressed from MCC powder								
Powder	0.45	0.01	7.7	0.7	230	30	3000	200
Powder tablet								
72 MPa	0.15	0.02	4.0	0.8	160	40	1300	100
122 MPa	0.11	0.01	4.5	0.7	100	10	800	0
196 MPa	0.08	0.01	3.9	1.2	80	20	600	0
Porosity parameters of MCC granules and the tablets compressed from MCC granules								
Granules	0.30	0.02	6.6	0.2	170	10	4300	130
Granule tablet								
72 MPa	0.15	0.01	4.0	0.9	150	40	2000	200
122 MPa	0.10	0.00	4.7	0.2	90	0	1200	100
196 MPa	0.06	0.01	2.1	0.4	120	10	1000	100

powder and granules [16]. The mean pore size of powder is larger than that of granules, whereas the median pore size of granules is larger than that of powder. The different calculation of these parameters, which we presented in our previous paper, explains why the mean and median pore size results are different [16]. Densification of MCC powder during wet granulation is observed from the volume pore size distribution curves measured with mercury porosimetry (Fig. 1). The pores with diameter larger than 1 μm of Emcocel are voids between particles (Fig. 1). Decrease in the volume of these pores takes place in granulation, as expected, because particle size increases.

Determination of total pore volume of granules was not possible (Table 2). This indicates the denser structure of granules when compared to powder. Densification of

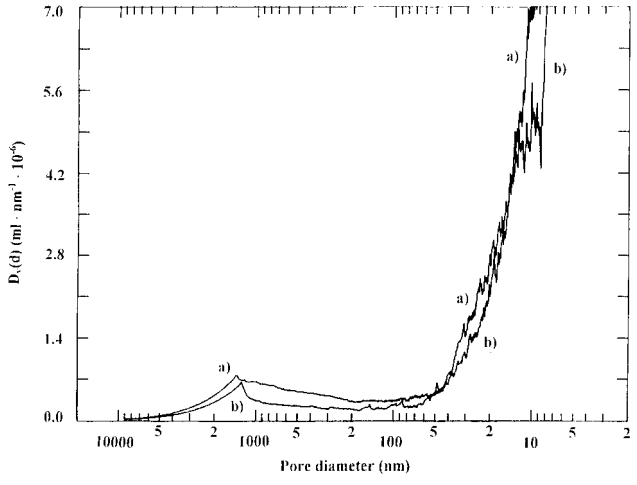

Fig. 1. Pore volume size distributions of (a) MCC powder and (b) MCC granules determined by mercury porosimetry.

MCC in wet granulation [2] has been reported. Millili and Schwartz [5] have observed denser structure of MCC pellets produced with water when compared to those produced with ethanol. In the paper industry, loss of bonding capacity of cellulose after wetting and drying is called hornification [18]. No clear explanation for the hornification has been found. Staniforth and Chatrath [7] have proposed the term 'quasi-hornification' to describe increased hydrogen bonding of MCC in wet granulation. Millili [6] has reported that the degree of hydrogen bonding of MCC is not responsible for harder pellets produced with water. He has explained densification of MCC by autohesion, solid–solid diffusion. When MCC is in contact with water, it swells and becomes plasticised, and polymer chain ends become more mobile. Due to plasticity and processing, particle–particle deformation occurs. Interfacial contact area between particles increases and the polymer chain ends diffuse across the particle–particle interface into the swollen microcavities within MCC. Finally, during drying, due to capillary pressure caused by evaporating granulation fluid, microcavities collapse onto the diffused polymer chain ends, resulting in a strong, stable link across the interface [6]. Recently, a crystallite gel model has been developed to explain behaviour of MCC during wet-granulation, extrusion and pelletisation [8]. In that model, the crystallites or their agglomerates of MCC form a framework by cross-linking with hydrogen bonds at the amorphous ends. However, Ek and Newton [9] have explained the deformation of MCC with water by a sponge model. According to the result of this study, the densification caused by wet granulation takes place at the determination range of the nitrogen gas adsorption method (pore diameter 3–200 nm).

For powder, nitrogen adsorption gave markedly smaller total pore volume values when compared to those measured

Table 2
Percentage porosities, breaking forces ($n = 20$) and parameters of MCC powder, granules and tablets compressed with different compression pressures as measured with the nitrogen adsorption method ($n = 3$)

Sample	Porosity (%)	Breaking force (N)		Total pore volume (ml/g)		Specific surface area (m^2/g)	
0		Mean	SD	Mean	SD	Mean	SD
Powder	82	–	–	0.004	0.000	1.35	0.01
Powder tablets							
72 MPa	33	62	9	0.005	0.000	1.33	0.03
122 MPa	24	102	16	0.017	0.002	1.16	0.01
196 MPa	18	119	9	0.015	0.001	0.95	0.05
Granules	62	–	–	[a]		0.64	0.00
Granule tablets							
72 MPa	27	10	2	[a]		0.80	0.01
122 MPa	20	19	4	[a]		0.69	0.01
196 MPa	15	51	6	[a]		0.62	0.00

[a] Not measurable.

with mercury porosimetry (Tables 1 and 2). This is due to the different measurement ranges of the equipment. Mercury porosimetry also determines the voids between the particles, which in this case affect more the volumes measured than the voids of the internal pores of particles. Volume pore size distributions of powder have similar shape at the overlapping pore size range (Fig. 2), although the intensity of the curves is different.

3.1.2. Surface area of powder and granules

According to mercury porosimetry, the total pore surface area of granules is only slightly smaller than that of powder (Table 1). The specific surface area measured by the nitrogen adsorption method of granules is markedly smaller than that of the powder (Table 2). This indicates the dense structure of the granules. This result also indicates, that densification of MCC occurs at the pore diameter range 3–200 nm. Surface area values observed with mercury porosimetry are higher than those obtained with the nitrogen adsorption method. In our previous study with mannitol [16], lactose tablets [11] and silica samples [19], surface area values obtained with mercury porosimetry have likewise been larger than nitrogen gas adsorption results.

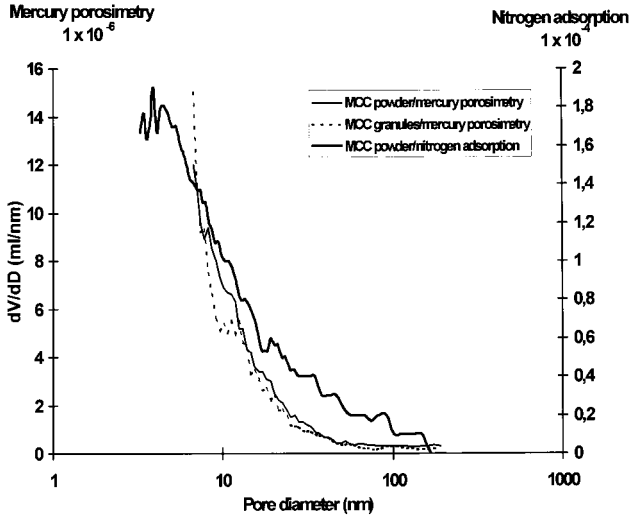

Fig. 2. Pore volume size distributions of MCC powder and MCC granules determined by nitrogen gas adsorption and mercury porosimetry methods.

3.2. Tablets

3.2.1. Compression

The breaking forces of tablets compressed from granules are markedly lower than those of the tablets compressed from powder (Table 2). When compressed, porosity percent of powder decreases more than that of the granules, indicating greater densification of MCC powder in compression (Table 2). Thus, the compactibility of MCC is decreased in wet granulation. Hydrogen bonding, large particle surface area, filamentous structure of the cellulose microcrystals and mechanical interlocking of irregular long elongated particles are responsible for the excellent binding properties of microcrystalline cellulose [20]. MCC powder deforms plastically [2,21–23]. Strength of interparticle bonding has been greater for the powder samples of MCC when compared to those of the granules [2]. Staniforth et al. have also shown that in the granules most of the compression force was utilised in breaking up the primary granule structure and hence did not establish areas of intimate contact to provide strong bonds between the cellulose particles. According to our breaking force result (Table 2), the structure of granules is destroyed when a compression pressure of 196 MPa is reached. Due to this, mean pore size of granule tablets is increased between compression pressures 122 and 196 MPa (Table 1). Schwartz et al. [3] have reported the pellets produced from microcrystalline cellulose by extrusion/spheronisation to be hard and not easily deformable or broken. During compression of pellets at high compressional pressure, some fracture and plastic deformation took place. Maganti and Celik [4] have reported elastic deformation and brittle fragmentation of MCC pellets

resulting in low tensile strength of tablets. They claimed that the bonding of MCC was decreased on the basis of its changes in shape, size and possibly by the reduction in the number of bonding sites after pelletisation. In this study, decreased compactibility of MCC after wet granulation is related to smaller specific surface area values of granules when compared to those of powder (Table 2). In our previous study [16], the specific surface area of mannitol increased during wet granulation, which lead to increased compactibility in tableting. In this case, specific surface area measured using the nitrogen adsorption method appears to be a simple method to predict the compactibility of granules after processing.

3.2.2. Pore structure of tablets

Mercury porosimetry. Deformation of powder and decrease in the size of the voids between powder particles during compression is observed from the volume pore size distribution at 200–2000 nm pore diameter range as a shift of the maximum towards smaller pores and at the <40 nm diameter range as a decrease in the volume of the pores (Fig. 3a). With increasing compression pressure, the densification of powder mass is also seen as decreased total pore volume, and decreased mean and median pore size values (Table 1). Total pore volume values obtained with mercury porosimetry are in consistent with porosity percent values (Table 2).

Deformation of granules is also observed from the volume pore size distribution curves at the 500–2000 nm pore diameter range as a shift of maximum towards smaller pores (Fig. 3b). The decrease is clearly observed when granule tablets compressed with 72 and 122 MPa are compared with those compressed with 196 MPa (Fig. 3b). Due to this, mean pore size increases between compression pressures 122 and 196 MPa (Table 1). This change is in agreement with increased breaking force values of granule tablets when compression pressure exceeds 122 MPa (Table 2). Apparently, the structure of granules is destroyed when a compression pressure of 196 MPa is reached.

Nitrogen adsorption. Unexpectedly, total pore volume of powder at 3–200 nm pore diameter range is greater when compressed with 122 MPa and 196 MPa when compared to values of powder and powder tablets compressed with 72 MPa (Table 2). Sixmith [10] has reported the increased surface area of Avicel tablets when compression pressure exceeds 125 MPa. According to volume pore size distributions of tablets (Fig. 4), MCC powder densifies plastically, as expected. From the distribution curve, decrease in the volume of the pores with increasing compression pressure is observed. The pore volume is determined in the adsorption phase, whereas the volume pore size distribution is measured from the desorption phase. According to Conner et al. [13], volume pore size distributions obtained with mercury intrusion and nitrogen desorption are comparable, because both methods determine the larger radii of pore network first. Plastic deformation appears to be the deformation mechanism according to the mercury porosimetry (Table 1), and also judging by the specific surface area values determined with nitrogen adsorption (Table 2).

3.2.3. Comparison of the methods

Total pore volume values obtained with mercury porosimetry are markedly larger than those measured with nitrogen adsorption (Tables 1 and 2). In accord with the results of this study, total pore volume values of mannitol tablets were markedly larger when measured with mercury porosimetry [16]. Equal total pore volume values of silica samples when measured with these methods have been reported [19]. In silica samples, the pores are very small and they are mainly measured with the gas adsorption method. If there are pores outside the measurement range of mercury porosimetry or nitrogen adsorption methods, total pore volume values are not comparable, as expected. In pharmaceutical samples, such as powders, granules and tablets, total pore volume determined with mercury porosimetry is larger due to the voids between particles and larger intragranular pores that are outside the determination range of nitrogen adsorption.

Volume pore size distributions of tablets obtained with these methods are not equal at the overlapping pore range (Fig. 5). Faroongsarng and Peck [12] have found the volume size distributions of dicalcium phosphate dihydrate tablets determined by nitrogen gas adsorption and mercury porosimetry to be fairly consistent in the range of overlapping pore sizes. In their study, however, pores of powder tablets were so large that they were mainly measured with mercury porosimetry. Stanley-Wood and Johansson [24] and Conner et al. [13] have obtained similar pore size distributions for uncompacted magnesium trisilicate and Degussa aerosols with these two techniques. In our previous study for mannitol tablets [16], distributions obtained with these methods had the same shape but different intensity on overlapping pore size range. Pores of mannitol powder tablets were so large that they were observed only with mercury porosimetry. Brown and Lard [14] and De Wit and Scholten [15] have obtained non-similar pore size distributions for silicas, adsorbents and catalysts when determined with these methods. They explained the difference in terms of the compression of highly porous silica, non-capillary pore structure of samples and limitations of the Washburn equation in characterising the smallest detectable pores during mercury porosimetry analysis. In this study, tablets remained intact after the measurement. However, the microstructure of a MCC tablet can be compressed in analysis, because the maximum of the curves obtained with mercury porosimetry is at a larger pore size than that obtained with nitrogen adsorption. The shift of the maximum can be caused because the results in this study are presented as they are, and no corrections were made for example for contact angle of mercury or the moving point in mercury porosimetry analysis.

3.2.4. Surface area of tablets

The total pore surface area of powder and granules deter-

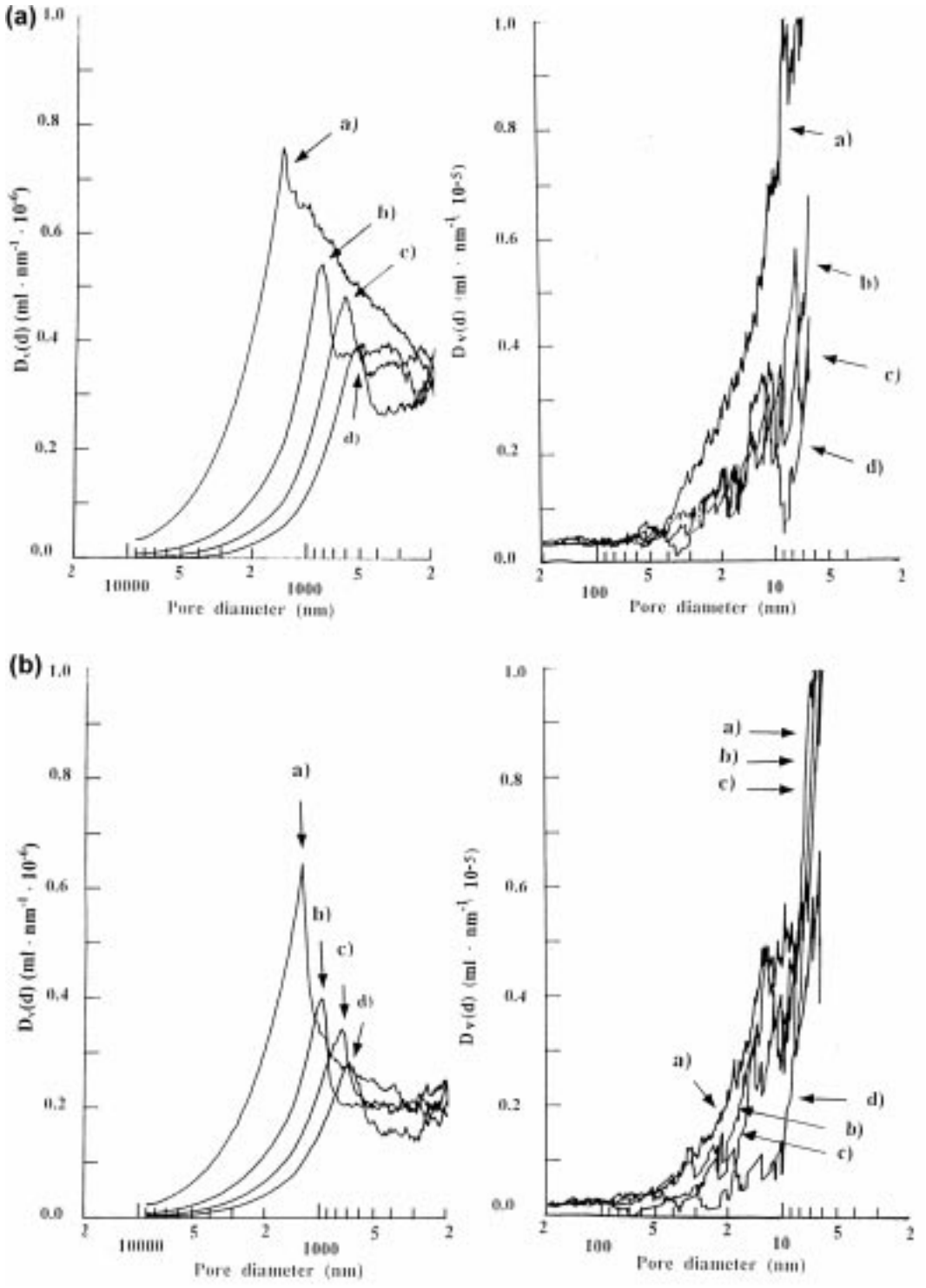

Fig. 3. (a) Pore volume size distributions of (a) MCC powder and MCC powder tablets compressed with (b) 72 MPa, (c) 122 MPa and (d) 196 MPa measured with mercury porosimetry. (b) Pore volume size distributions of (a) MCC granules and MCC granule tablets compressed with (b) 72 MPa, (c) 122 MPa and (d) 196 MPa measured with mercury porosimetry.

mined with mercury porosimetry decreases due to densification in compression, as expected (Table 1). Total pore surface area of powder measured with mercury porosimetry is unaffected by the compression pressure. Decrease in total pore surface area of granules is observed when tablets compressed with 72 MPa and 122 MPa are compared with those compressed with 196 MPa. The breaking force, and thereby the mean pore size results increase when compression pressure of 196 MPa is used (Tables 1 and 2). This result indicates, that the structure of the particles is

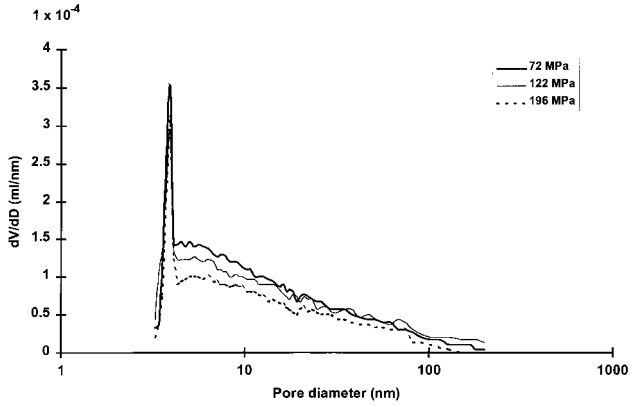

Fig. 4. Pore volume size distributions of MCC powder tablets compressed with different compression pressures measured with nitrogen adsorption.

destroyed when this compression pressure (196 MPa) is used.

Specific surface area of MCC powder tablets measured with the nitrogen adsorption method decreases with increasing compression pressure due to the plastic deformation of Emcocel in compression (Table 2). Sixmith [10] has reported increase in specific surface area of Avicel tablets when compression pressure exceeds 125 MPa. However, this was not observed in specific surface area values of our study. Specific surface area of granule tablets also decreases with increasing compression pressure (Table 2). However, increase in specific surface area of granules when compressed with 72 MPa occurs because of fragmentation of granules. Similarly, fragmentation of magnesium oxide has been reported as increased specific surface area during compression [25]. It is suggested [26] that in compression, primary granule structure is destroyed and then followed by deformation of individual MCC particles. A decrease in plastic deformation in wet granulation has been reported

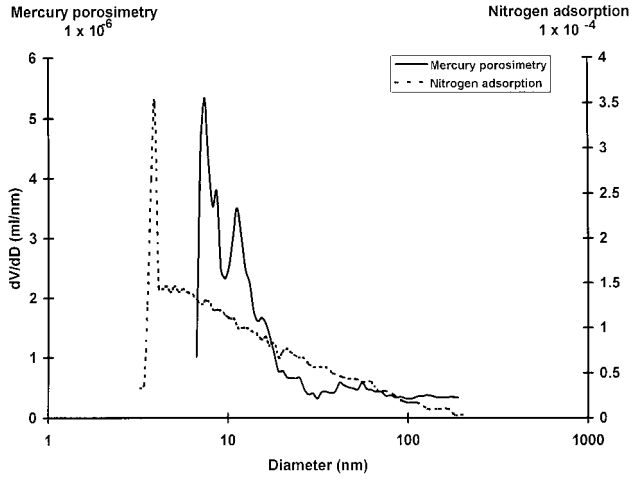

Fig. 5. Pore volume size distributions of MCC powder tablets (compression pressure 72 MPa) measured with nitrogen gas adsorption and mercury porosimetry methods.

[2]. However, fragmentation is not the only deformation mechanism of MCC granule mass in this study, because the specific surface area of granule mass decreases with increased compression pressure.

Surface area values of tablets measured with mercury porosimetry are markedly higher than those measured with nitrogen adsorption method (Tables 1 and 2). With pharmaceutical tablets, surface area values obtained with mercury porosimetry have been larger than those obtained with the gas adsorption method [11,16]. A similar result has also been obtained with silica samples [19]. Existence of ink-bottle pores in the samples are one reason for the result. The narrow pore opening allows pores to be filled at higher pressure in mercury porosimetry. However, Mikijelj and Varela [27] have reported surface area values of magnesium oxide and diatomite compacts obtained with these methods to be similar. In their study, the highest pressure in mercury porosimetry was 103 MPa, so that only the largest pores were measured (diameter larger than 14 μm). Adkins and Davis [28] made the surface area values of alumina and zirconia to be comparable by correcting the contact angle used in mercury porosimetry measurement. In their study, however, surface areas of the samples were as high as 46–130 m^2/g. With higher surface area samples, no correlation existed. According to Milburn and Davis [29], the correlation between surface areas obtained with these methods in the samples owing very low BET surface areas is poor. In our study, no corrections were made to the parameters. Although the specific surface area values measured with the methods used are not equal, they describe the change in the pore microstructure of the material during compression.

4. Conclusions

Decreased compactibility of microcrystalline cellulose was observed during wet granulation. Densification of microcrystalline cellulose caused by wet granulation was detected at the detection range of nitrogen gas adsorption (pore diameter range 3–200 nm) in the form of decreased specific surface area values. Plastic deformation of powder was shown in the results determined with nitrogen adsorption, whereas fragmentation and plastic deformation of granules during compression were observed with both methods used. Structure of granules was destroyed when a compression pressure of 196 MPa was reached. Although nitrogen gas adsorption is not capable of characterising pore structure of dense granules, it proved to be a good method in the characterisation of intragranular porosity. Mercury porosimetry better emphasises changes in intergranular pore structure during compression. Due to different measurement ranges, results obtained with mercury porosimetry and nitrogen adsorption were not strictly comparable. However, the results obtained with mercury porosimetry and nitrogen adsorption together can be used in the charac-

terisation of behaviour of pharmaceutical materials during processing.

Acknowledgements

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