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Research paper

Mercury porosimetry of microcrystalline cellulose tablets: effect of scanning speed and moisture

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Abstract

The effect of pretreatment and scanning speed of mercury porosimetry on the porosity result of microcrystalline cellulose tablets was studied. The porosity parameters followed were total pore volume, mean and median pore size, and volume pore size distribution. Scanning speed did not affect the total pore volume of tablets compressed from microcrystalline cellulose. With increasing speed, the smallest pores of powder tablets were not properly determined, which increased the mean pore size. The median pore size of tablets compressed from powder and granules decreased and the maximum at the pore size range 500–1000 nm changed towards smaller pores with increasing scanning speed. Scanning speed appears to affect in different ways the samples with different physical structures. In tablet samples, scanning speed affects the volume of the pores at the whole pore size range determined. Thus, it is important to use about the same, reasonably low scanning speed in the measurements when comparing the samples. Swelling of microcrystalline cellulose in tablet samples is observed by mercury porosimetry measurement; a change in the pore structure is detected after storage at 88% relative humidity as increased total pore volumes and median pore sizes. Due to swelling, the maximum at the pore size range 500–2000 nm changed towards larger pores with increasing moisture. Swelling is observed similarly in tablets manufactured from powder and granules. When storing in humid conditions, water fills the smallest pores of microcrystalline cellulose powder tablets, hinders the intrusion of mercury and, thus, the mean pore size increases. Contrary to this, the volume of the smallest pores of granule tablets compressed with the highest compression pressure increased with increasing moisture. Careful pretreatment before the measurements is important.

Keywords: Microcrystalline cellulose; Mercury porosimetry; Moisture; Pore structure; Scanning speed; Tablet

1. Introduction

In mercury porosimetry, the effect of scanning speed on the porosity results has been studied in cement and aluminum samples [1,2]. With fast scanning, the time used for the analysis is the shortest, which means cost savings in the laboratories. On the other hand, the mercury may not have enough time to intrude into the pores [2]. Because mercury porosimetry is used also in the analysis of pharmaceutical samples, knowledge of the effect of the scanning speed on the results of these samples is needed. In our previous studies concerning powders, granules and mannitol tablets [3,4] the total pore volumes of the samples were equal with different scanning speeds. If only this parameter is to be determined, fast scanning would be the choice. However, the smallest pores of the samples were not determined accurately enough when fast scanning was used [3,4]. With mannitol tablets [4], however, the scanning speed affected even pores at a larger pore size range. According to this, scanning speed affects in different ways the porosity result of pharmaceutical samples with different structures. Thus, the effect of scanning on the porosity of tablets compressed from other starting materials warrants further study.

Water content of the sample is another parameter that affects the mercury porosimetry result. According to our previous study [3], water in mannitol and microcrystalline cellulose (MCC) granules increased the volume of the smallest detectable pores. It was supposed to be related to the structure of the granules, because no increase was observed in the result of MCC powder [3] or mannitol tablets [4]. Water in mannitol tablets decreased unexpectedly the pore volume at the pore size range 50–1000 nm, although the moisture content of the tablets was only 1.2% at the highest. This was supposed to be due to the formation of water puddles in the corners and cavities of tablet pores [5] and also by the diffusion of water on the surface of the pores of

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the tablets [6]. Contrary to mannitol, MCC is a hygroscopic ingredient, which contains 9% of water when stored in 88% humidity for 3 days [3]. The effect of storage on the mercury porosimetry result of MCC tablets is supposed to be greater. Seasonal variation in moisture contents of microcrystalline cellulose samples can be remarkable without conditioning. Therefore, temperature and relative humidity should be taken into consideration in formulation design and production [7]. Similarly, relative humidity and water content of the sample must be controlled also during analysis. When moisturized, microcrystalline cellulose swells. A high swelling force of MCC tablets has been observed when in contact with water [8]. It is therefore probably extremely important that the moisture content in the samples is similar before mercury porosimetry analysis. The importance of preparation technique of mortar samples before mercury porosimetry analysis has been reported previously [9]. Landín et al. [10] observed increased total porosity values of MCC powder tablets after storage in 90% relative humidity when determined by high-pressure mercury porosimetry. However, the effect of water on the pore structure of tablets manufactured from MCC powder or granules has not been reported previously.

The aim of this study is to determine the effect of scanning speed and moisture content of the sample on the mercury porosimetry result of microcrystalline cellulose tablets compressed from powder and granules.

2. Materials and methods

2.1. Tableting

Tablets were compressed from microcrystalline cellulose (MCC) (Emcocel, Edward Mendell, USA) powder and granules with a rotary press (Kilian, RU-24 III, Kilian & Co. GmbH, Cologne, Germany) as described in a previous paper [11]. Granules were produced in a high-shear mixer (Fielder PMA 25/2G, T.K. Fielder Ltd., Eastleigh, UK). The granulation liquid used 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 is presented in our previous paper [3]. The tablet machine was equipped with a pair of instrumented flat punches with a diameter of 9 mm (Portable Press Analyzer, Puuman Oy, Kuopio, Finland). The weight of the granule tablets was 230 mg and that of the powder tablets 190 mg. Tablet weights are presented in Table 1. 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 60–70 ms. Target compression pressures used were 72, 122 and 196 MPa. The temperature during the tableting was 20–21°C and relative humidity 13–15%.

Table 1
Weights of the tablets manufactured from microcrystalline cellulose ($n = 100$)

Sample (MPa)	Mean tablet weight (g)	SD
Powder tablet		
72	189	3
122	191	3
196	193	3
Granule tablet		
72	225	5
122	228	3
196	229	4

2.2. Moisture and porosity measurements

Tablets were stored in three different humidity conditions (vacuum and 43% and 88% humidities) as described in Table 2. The storage conditions are the same as presented in our previous paper [3]. The moisture content of the tablets was measured by Karl Fischer titration (Mettler DL 18, Greifensee, Switzerland). Measurements were done in triplicate ($n = 3$).

After storage, total pore volume, mean and median pore sizes of tablets were determined with a high-pressure mercury porosimeter (Autoscan 33 Porosimeter, Quantachrome Corp., Boynton Beach, FL) as described in Westermarck et al. [12]. Total intruded volume of mercury (V_{tot}), mean pore diameter (d_{mean}), median pore diameter (d_{median}) and volume pore size distribution ($D_V(d)$) were calculated from the intrusion data with Quantachrome Autoscan PORO2PC Software, Version 2.17. Calculation of these parameters is presented in more detail in paper Westermarck et al. [12]. Tablets were placed into the sample cell which was evacuated for about 3 min (below 7 Pa) and filled with mercury (filling apparatus for Autoscan porosimeter, Quantachrome). The scanning speeds used in the high-pressure porosimeter were 220, 500 and 1010 kPa/s, respectively. Porosity measurements were done in triplicate ($n = 3$).

Statistical analyses were performed by multiple linear regression analysis (Modde version 4.0, Umetrics AB, Umeå, Sweden).

Table 2
Storage conditions of microcrystalline cellulose tablets before moisture content and porosity measurements

Relative humidity (%)	Temperature (°C)	Time (h)
Vacuum oven	20	24
43	25	72
88	25	72

Table 3
Porosity parameters of the tablets compressed from microcrystalline cellulose powder measured by mercury porosimetry ($n = 3$)

Pretreatment rel. humidity (%)	Scanning speed (kPa/s)	Total intruded volume (ml/g)	SD	Mean pore size (μm)	SD	Median pore size (μm)	SD
Compression pressure 72 MPa							
Vacuum	220	0.15	0.02	0.16	0.04	1.28	0.14
Vacuum	500	0.15	0.00	0.16	0.04	1.16	0.07
Vacuum	1010	0.17	0.01	0.22	0.02	1.18	0.04
43	220	0.17	0.01	0.16	0.01	1.38	0.21
43	500	0.16	0.00	0.15	0.02	1.30	0.05
43	1010	0.16	0.01	0.18	0.05	1.25	0.12
88	220	0.19	0.01	0.17	0.01	2.15	0.12
88	500	0.19	0.01	0.18	0.01	2.06	0.11
88	1010	0.19	0.00	0.18	0.01	1.92	0.06
Compression pressure 122 MPa							
Vacuum	220	0.11	0.01	0.10	0.01	0.78	0.02
Vacuum	500	0.12	0.01	0.12	0.02	0.86	0.09
Vacuum	1010	0.11	0.00	0.11	0.01	0.78	0.02
43	220	0.11	0.01	0.08	0.02	0.80	0.14
43	500	0.11	0.01	0.10	0.01	0.82	0.03
43	1010	0.11	0.00	0.09	0.01	0.78	0.05
88	220	0.14	0.00	0.12	0.02	1.65	0.17
88	500	0.14	0.01	0.12	0.01	1.58	0.01
88	1010	0.14	0.00	0.14	0.02	1.63	0.06
Compression pressure 196 MPa							
Vacuum	220	0.08	0.01	0.08	0.02	0.59	0.05
Vacuum	500	0.08	0.01	0.06	0.01	0.50	0.10
Vacuum	1010	0.07	0.00	0.07	0.01	0.53	0.06
43	220	0.07	0.01	0.06	0.01	0.51	0.04
43	500	0.07	0.00	0.06	0.00	0.51	0.04
43	1010	0.07	0.01	0.08	0.02	0.54	0.06
88	220	0.11	0.00	0.09	0.01	1.39	0.04
88	500	0.10	0.00	0.10	0.01	1.32	0.07
88	1010	0.11	0.01	0.10	0.02	1.23	0.07

3. Results and discussion

3.1. Effect of scanning speed on pore structure

The total pore volume of MCC tablets compressed from powder or granules is unaffected by scanning speed (Tables 3–5), nor does it affect the total pore volume of MCC powder, mannitol and MCC granules [3] or mannitol tablets [4]. In addition to these pharmaceutical samples, Hearn and Hooton [1] reported that scanning speed does not affect the total pore volume of cement samples. Thus, if the only porosity parameter of interest is total pore volume, fast scanning can be the choice.

However, the mean pore size of powder tablets increases with increasing scanning speed (Tables 3 and 5). This indicates a decreased volume of the smallest pores of tablets determined with increasing scanning speed. This is observed also in the volume pore size distributions of MCC tablets compressed from granules with the smallest compression pressure as a decrease in volume in the pore size range <20 nm (Fig. 1). Volume pore size distributions are presented as mean of three parallel measurements. In our previous studies with MCC powder, mannitol and MCC granules [3] and mannitol tablets [4], similarly, the volume of the smallest pores at the detection range were smallest with the fastest scanning. The structure of microcrystalline cellulose densifies in granulation and tableting [11]; thus the scanning speed does not affect the smallest pores of tablets compressed from granules with higher compression pressures. Hearn and Hooton [1] also observed the effect of scanning speed from the volume pore size distributions of cement samples, although the total pore volume values were unaffected. Like us, Moscou and Lub [2] also showed that too fast scanning would not determine the pores accurately. However, no effect of scanning speed was observed in the pore size distributions of aluminum samples between slow and fast scanning. In that study [2], the pore size distribution was determined by the method where the pressure pump stops automatically when intrusion occurs and waits for equilibrium. The intrusion phase is thus determined by a step-by-step method instead of continuous intrusion, which was applied in our study. According to Allen [13], the continuous or scanning mode is suitable for low-porosity samples and quality control purposes.

Table 4
Porosity parameters of the tablets compressed from microcrystalline cellulose granules measured by mercury porosimetry ($n = 3$)

Pretreatment rel. humidity (%)	Scanning speed (kPa/s)	Total intruded volume (ml/g)	SD	Mean pore size (μm)	SD	Median pore size (μm)	SD
Compression pressure 72 MPa							
Vacuum	220	0.15	0.01	0.15	0.04	2.02	0.19
Vacuum	500	0.15	0.01	0.18	0.05	2.08	0.11
Vacuum	1010	0.15	0.01	0.23	0.05	1.95	0.09
43	220	0.15	0.01	0.17	0.05	2.29	0.19
43	500	0.14	0.01	0.15	0.02	1.98	0.08
43	1010	0.15	0.01	0.15	0.01	2.05	0.16
88	220	0.17	0.01	0.16	0.04	2.80	0.18
88	500	0.16	0.00	0.20	0.02	2.83	0.04
88	1010	0.16	0.01	0.19	0.03	2.61	0.09
Compression pressure 122 MPa							
Vacuum	220	0.10	0.00	0.09	0.00	1.19	0.11
Vacuum	500	0.09	0.01	0.14	0.04	1.27	0.03
Vacuum	1010	0.10	0.01	0.13	0.03	1.26	0.06
43	220	0.10	0.01	0.09	0.01	1.28	0.04
43	500	0.09	0.01	0.10	0.01	1.24	0.12
43	1010	0.09	0.00	0.09	0.01	1.12	0.10
88	220	0.12	0.01	0.11	0.01	1.93	0.05
88	500	0.12	0.00	0.13	0.03	1.89	0.03
88	1010	0.12	0.00	0.13	0.01	1.76	0.04
Compression pressure 196 MPa							
Vacuum	220	0.06	0.01	0.12	0.01	0.96	0.07
Vacuum	500	0.07	0.00	0.11	0.01	0.86	0.01
Vacuum	1010	0.07	0.00	0.08	0.01	0.77	0.07
43	220	0.06	0.01	0.07	0.00	0.89	0.04
43	500	0.06	0.01	0.07	0.00	0.87	0.14
43	1010	0.06	0.00	0.07	0.01	0.76	0.04
88	220	0.08	0.00	0.09	0.02	1.29	0.10
88	500	0.08	0.00	0.08	0.01	1.22	0.02
88	1010	0.08	0.00	0.12	0.04	1.18	0.04

The median pore size of MCC tablets decreases with increasing scanning speed (Tables 3–5). This is observed from the volume pore size distributions of tablets as a shift of maximum at the pore size range 100–1000 nm towards smaller pores (Figs. 1 and 2). Surprisingly, the maximum of the volume pore size distribution at this pore size range is highest with the fastest scanning. A similar shift of maximum towards smaller pores at the same pore size range was observed also in mannitol powder tablets [4]. Because the distributions of powders or granules do not reveal this [3], it is evidently related to the structure of tablets. The pore structure of tablets is more rigid when compared to that of powder and granules. No packing or rearrangement of individual particles, which is possible in mercury porosimetry measurement of powder and granules, takes place during intrusion of mercury into the tablets. The voids between particles also decrease in tableting, especially the size of the pores at the surface of tablets that determine the intrusion of mercury. Mercury may not have time to intrude into the pores with fast scanning, whereas the mercury intrudes later, and the volume is detected at the smaller pore size range. These may be the reasons why the effect of scanning is observed also at the pore size range 100–1000 nm.

3.2. Effect of moisture on pore structure

The moisture content of tablets increases with increasing humidity of storage chamber, as expected (Table 6). According to a previous study [14], at relative humidities greater than 80%, water sorption of MCC increases significantly, which is in agreement with the results of this study.

A change in the pore structure of tablets compressed from microcrystalline cellulose powder and granules is observed after storage in 88% relative humidity (Tables 3 and 4). The total pore volume and median pore size of tablets increase, whereas these parameters are similar in tablets stored in vacuum or in 43% relative humidity (Tables 3 and 4). This is due to the swelling of MCC caused by water sorption which takes place although MCC is granulated and tableted. Similarly, Landín et al. [10] observed increased total porosity values of MCC tablets after storage at 90% relative humidity. In our previous study with MCC powder and granules, on the other hand, the total pore volume of the

Table 5
Multiple linear regression analysis for MCC tablets[a]

		Q^2	R^2
Powder tablets ($n = 81$)			
Total pore volume	−0.04p + 0.02mo + 0.01p*p + 0.02mo*mo + 0.10	0.96	0.96
Mean pore size	46.77p + 6.15mo + 9.20sc + 25.77p*p + 21.05mo*mo + 86.35	0.76	0.80
Median pore size	−364.93p + 404.16mo − 36.23sc + 156.48p*p + 367.63mo*mo + 752.77	0.96	0.97
Granule tablets ($n = 81$)			
Total pore volume	0.04p + 0.01mo + 0.02p*p + 0.01mo*mo + 0.09	0.96	0.97
Mean pore size	−43.20p − 2.00mo + 29.40p*p + 28.9mo*mo + 83.8	0.61	0.66
Median pore size	−638.55p + 265.27mo − 63.79sc + 315.72p*p + 251.13mo*mo − 66.34p*mo + 1128.55	0.94	0.95

[a] p, compression pressure; sc, scanning speed; mo, moisture.

samples decreased with increasing moisture in high-pressure porosimetry analysis [3]. In agreement with the result of present study, the maximum of volume pore size distribution of powder and granules changed towards larger pores, which was determined at the detection range of the low-pressure porosimeter [3].

Landín et al. [10] reported increased friability and reduced tensile strength of Emcocel powder tablets after storage in 90% relative humidity for 2 and 4 months. The tablets in our study, however, were intact after the high-pressure porosimetry measurement. Thus, the swelling observed did not break the structure of tablets. According to Ek et al. [15], mercury porosimetry is not capable of characterizing wet swollen cellulose. In our study, however, the water content of the sample was 9% at the highest, and the pore structure of tablets was still measurable by a porosimetry procedure.

Khan and Pilpel [16] explained the interaction of water with MCC in three stages, and changes in structure of MCC at 3% w/w and 6% w/w of water. According to Khan et al. [17], no swelling of microcrystalline cellulose takes place if the amount of water in the sample is below 3% w/w. During the first stage, water is bound to the amorphous part of microcrystalline cellulose, to the anhydroglucose units in a proportion of 1:1 [18]. At higher relative humidities, up to 60%, those bonds will break and water starts to bind to water molecules already bound to anhydroglucose units. At even higher relative humidities, water starts to bind to water molecules not bound to anhydroglucose units [18]. This explains our result that the pore structure of MCC tablets changes when stored in 88% relative humidity (Tables 3 and 4). The specific surface area has been reported to decrease and the structure of MCC to densify in wet granulation [11,19]. Thus, the interaction and bonding between sorbed water and MCC might be different in granulated mass from that described above. However, a similar increase in pore volume of tablets compressed from MCC powder and granules was observed.

The maximum of the pore size distribution of tablets compressed from powder and granules at the pore size range 500–2000 nm changes towards larger pores with increasing moisture (Figs. 3 and 4). In humid conditions, the smallest pores of the samples fill first with water due to the capillary condensation according to the Kelvin equation [20]

$$\ln\frac{P}{P_0} = \frac{2\gamma V}{rRT}\cos\theta \quad (1)$$

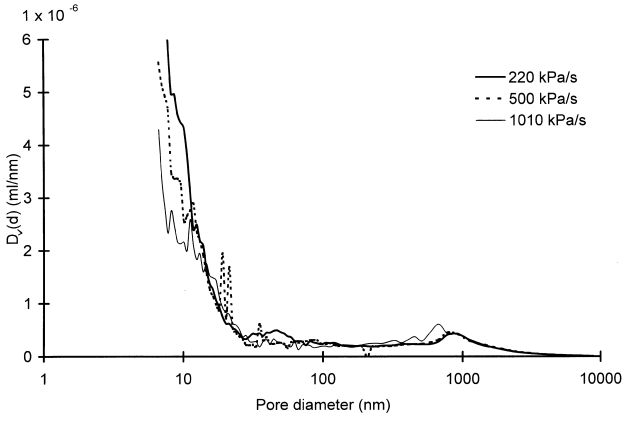

Fig. 1. Pore volume size distributions of MCC granule tablets compressed with 72 MPa, stored in vacuum and determined with three different scanning speeds.

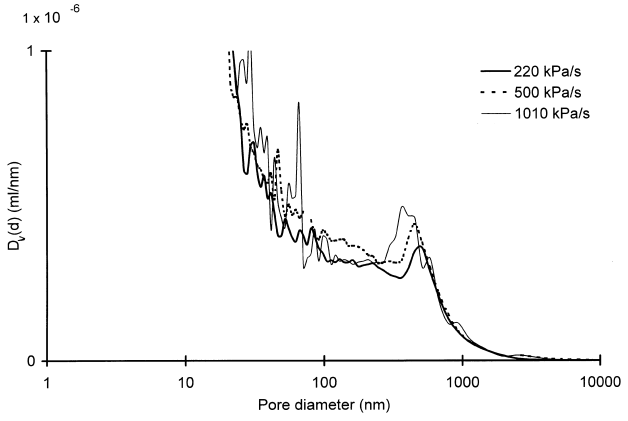

Fig. 2. Pore volume size distributions of MCC powder tablets compressed with 196 MPa, stored in vacuum and determined with three different scanning speeds.

Table 6
Moisture contents of microcrystalline cellulose tablets determined with Karl Fischer -titration ($n = 3$)

Sample (MPa)	Moisture content (%)	
	Mean	SD
Powder tablet		
Vacuum oven		
72	1.5	0.5
122	0.7	0.2
196	0.4	0.1
43% Humidity		
72	5.2	0.2
122	5.0	0.2
196	4.8	0.5
88% Humidity		
72	7.7	0.6
122	8.5	0.7
196	9.5	0.4
Granule tablet		
Vacuum oven		
72	0.3	0.1
122	0.2	0.0
196	0.7	0.4
43% Humidity		
72	5.2	0.4
122	5.2	0.1
196	5.4	0.2
88% Humidity		
72	8.2	0.4
122	8.8	1.1
196	9.2	0.3

where P is the equilibrium vapor pressure of the liquid in a pore of radius r, P_0 the equilibrium pressure of the same liquid on a plane surface, γ the surface tension, V the molar volume of a liquid, θ the contact angle with which the liquid meets the pore wall, R the gas constant and T the temperature.

This capillary condensation is greater in tablets than in powder or granules because of the denser structure of tablets as compared to the starting materials [21]. Water molecules settle to the surface of the sample first as a monolayer and with increasing moisture as multilayers. Although the smallest pores fill first, with increasing moisture some pores of cement tiles have been reported to fill completely while others remain empty when determined by the NMR method [22]. Allen et al. [5] reported that bulk water can form puddles into the cavities and corners of the pores at the same time with physisorption. They studied the porosity of porous silicas with the NMR technique of cryoporometry. According to Zografi [6], additional layers of water on the surface of sample can diffuse along the surface. On the other hand, samples are vacuumed during filling of sample cells with mercury. During this process, water can be removed partly or totally or change place in the porous structure of the samples. These are the probable explanations why the maximum of volume pore size distribution of MCC tablets after storage in moist conditions changes towards larger

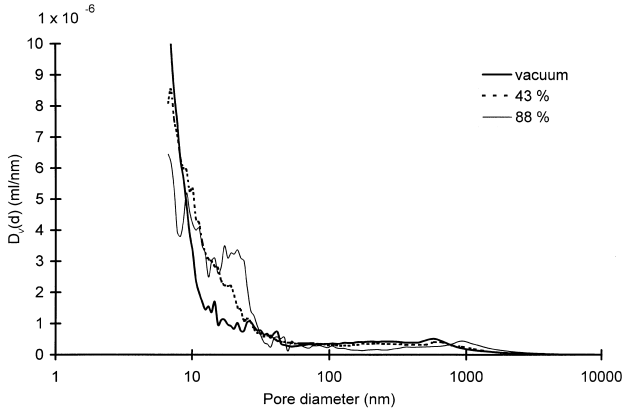

Fig. 3. Pore volume size distributions of MCC powder tablets compressed with 122 MPa, measured with the lowest scanning speed (220 kPa/s) and stored in three different moisture conditions before measurement.

pores at the pore size range 500–2000 nm. Similarly, the maximum of the volume pore size distribution of mannitol tablets changed towards larger pores at this pore size range with increasing moisture [4]. This effect is thus not only related to microcrystalline cellulose as a material, but also to the structure of the tablets. A change in contact angle of mercury on the surface of the sample caused by water can also partly affect the movement of the maximum. Cyclohexane on the surface of aluminum changes the contact angle of mercury in mercury porosimetry analysis and the pore size distribution of aluminum powder towards larger pores [2].

The mean pore size increases with increasing moisture in tablets compressed from powder (Tables 3 and 5). This is observed also from the volume pore size distributions of MCC powder tablets (Fig. 3) where the volume of the smallest pores (diameter < 9 nm) is greatest when stored in a vacuum oven. This is in agreement with the capillary condensation theory; water fills the smallest pores first. According to Hearn and Hooton [1], water on the structure of the porous sample can behave as a solid and hinder the intrusion of mercury. In granule tablets compressed with 196 MPa, on

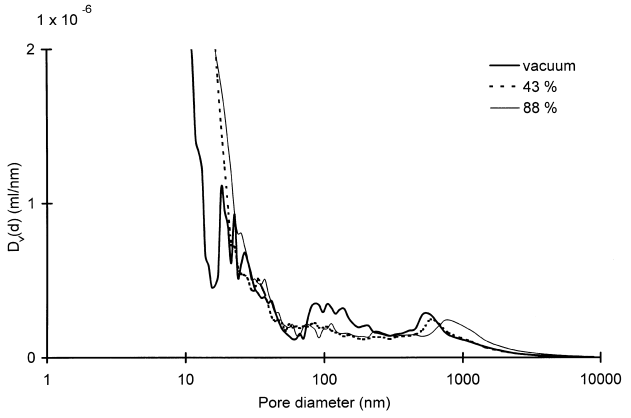

Fig. 4. Pore volume size distributions of MCC granule tablets compressed with 196 MPa, measured with the lowest scanning speed (220 kPa/s) and stored in three different moisture conditions before measurement.

the other hand, the volume of the smallest pores (<40 nm) increases with increasing moisture (Fig. 4), whereas moisture does not affect the volume of the smallest pores of granule tablets compressed with lower compression pressures. The structure of granules is destroyed in tableting with this highest compression pressure [11]. Similarly with the result of this study, in our previous work [3] the volume of the smallest pores of mannitol and Emcocel granules increased with increasing moisture. Water in these samples thus increases the volume of the smallest pores during mercury porosimetry measurement. Water may be pushed deeper into the structure of the sample in front of the intruding mercury and form new pores.

4. Conclusions

Scanning speed had no effect on total pore volume values of microcrystalline cellulose tablets. Because the total pore volumes of powders, granules and tablets are unaffected by scanning speed, this parameter can be determined by fast scanning. However, the effect of scanning speed is observed in the other porosity parameters. The mean pore size of microcrystalline cellulose powder tablets increased and median pore size of tablets compressed from powder or granules changed towards smaller pores with increasing scanning. In tablet samples, the effect of scanning speed is observed at a wide pore size range. Because the scanning speed appears to affect in different ways samples with different physical structures, use of slow scanning is recommended. Swelling of microcrystalline cellulose affects all the porosity parameters of the tablets determined. The total pore volume increases and the maximum of the volume pore size distribution at pore size range 500–2000 nm changes towards larger pores. Microcrystalline cellulose in powder and granule tablets swells similarly. When stored in humid conditions, water fills the smallest pores of powder tablets, hinders the intrusion of mercury and, thus the mean pore size of powder tablets increases. In granule tablets compressed with 196 MPa, however, the volume of the smallest pores increases with increasing water content. According to this study, the effect of moisture in mercury porosimetry analysis is related to the physical structure of the sample. Pretreatment of the samples before mercury porosimetry measurement is recommended.

Acknowledgements

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