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USE OF MERCURY POROSIMETRY AND NITROGEN ADSORPTION IN CHARACTERISATION OF THE PORE STRUCTURE OF MANNITOL AND MICROCRYSTALLINE CELLULOSE POWDERS, GRANULES AND TABLETS

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ABSTRACT

USE OF MERCURY POROSIMETRY AND NITROGEN ADSORPTION IN CHARACTERISATION OF THE PORE STRUCTURE OF MANNITOL AND MICROCRYSTALLINE CELLULOSE POWDERS, GRANULES AND TABLETS

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The effects of pretreatment and scanning speed of mercury porosimetry on the mercury porosimetry results of non-hygroscopic mannitol and hygroscopic microcrystalline cellulose powder, granule and tablet samples were studied. Behaviour of water in the structure of these samples during mercury porosimetry was evaluated. The effect of granulation and tableting on the pore structure of mannitol and microcrystalline cellulose was investigated. Furthermore, mercury porosimetry and nitrogen adsorption methods were compared.

Granules were manufactured by wet granulation with a high-shear mixer. Tablets were prepared both by direct compression and from granules with an instrumented rotary press using three compression pressures. Porosity parameters were determined with mercury porosimetry and nitrogen adsorption.

Pretreatment has an effect on mercury porosimetry results of non-hygroscopic mannitol and hygroscopic microcrystalline cellulose samples. Water affects with different mechanisms the results of samples of different physical structures, i.e. powder, granule and tablet samples. Water surprisingly increases the volume of the smallest pores of both mannitol and microcrystalline cellulose granules in high-pressure mercury porosimetry. Similarly, water increases the volume of the smallest pores of microcrystalline cellulose tablets compressed from granules with the highest compression pressure used in the study. Water condenses into the smallest pores of microcrystalline cellulose tablets manufactured by direct compression, hinders the intrusion of mercury and decreases the volume of the smallest determined pores. Water settles into the structure of mannitol and microcrystalline cellulose tablets in the pore diameter range of 50 – 2000 nm and 500 – 2000 nm, respectively. Maximum of the volume pore size distribution at this pore size range shifts towards larger pores with increasing moisture. Proper pretreatment and determination of water content of the samples before mercury porosimetry measurement is important.

Due to low scanning speeds used in the measurements, scanning speed does not have an effect on the result of low-pressure porosimetry analysis. Total pore volume determined with high-pressure porosimetry is unaffected by scanning speed, too. However, other porosity parameters determined with high-pressure porosimetry were influenced when different scanning speeds were used in determinations. The smallest pores of the samples were not accurately determined with fast scanning. In tablet samples, scanning speed affected the pore structure determinations even in the larger pore size range. Therefore, slow scanning speed in the measurements is preferable.

Wet granulation increased the compactibility of mannitol, but decreased that of microcrystalline cellulose. Mannitol granules had a porous structure, whereas microcrystalline cellulose granules were hard, dense and non-porous. Mannitol powder and granules deformed by fragmentation and plastic deformation under compression. Microcrystalline cellulose powder deformed plastically, and the structure of hard granules was destroyed when compressed with the highest compression pressure.

The pore structure obtained with mercury porosimetry describes the behaviour of powder and granules and the voids between them in granulation and compression. Nitrogen adsorption emphasizes the changes in the intraparticular structure of the particles during compression. Due to the low porosity of pharmaceutical samples and the different measurement ranges of these methods, total pore volume, specific surface area and intensities of volume pore size distributions obtained with these two methods are not equivalent. Pores of mannitol samples are detected at the same pore size range with both methods. However, microcrystalline cellulose samples may be deformed during mercury porosimetry measurement, because the pores are not determined at the same pore size range as with nitrogen adsorption. Volume pore size distribution is a useful parameter showing where the changes in the structures of the samples occur during processing. Specific surface area obtained with nitrogen adsorption describes well the behaviour of pharmaceutical materials during compression. Together mercury porosimetry and nitrogen adsorption describe well the behaviour of materials in pharmaceutical processes.

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original papers, which are referred to in the text by the Roman numerals I – V.

I Westermarck, S., Juppo, A.M., Koiranen, K. and Yliruusi, J., 1998. Mercury porosimetry of pharmaceutical powders and granules. J. Porous Mater. 5, 77-86.

II Westermarck, S., Juppo, A.M., Kervinen, L. and Yliruusi, J., 1998. Pore structure and surface area of mannitol powder, granules and tablets determined with mercury porosimetry and nitrogen adsorption. Eur. J. Pharm. Biopharm. 46, 61-68.

III Westermarck, S., Juppo, A.M., Kervinen, L. and Yliruusi, J., 1999. Microcrystalline cellulose and its microstructure in pharmaceutical processing. Eur. J. Pharm. Biopharm. 48, 199 – 206.

IV Westermarck, S., Juppo, A.M. and Yliruusi, J., 2000. Mercury porosimetry of mannitol tablets: effect of scanning speed and moisture. Pharm. Dev. Technol. 5 (2), 181 – 188.

V Westermarck, S., 2000. Mercury porosimetry of microcrystalline cellulose tablets: effect of scanning speed and moisture. Eur. J. Pharm. Biopharm. 50, 319 – 325.

ABBREVIATIONS

A	area
a_m	cross-sectional area of molecule
c	BET constant
d	diameter
d_{mean}	mean pore diameter
d_{median}	median pore diameter
$D_v(d)$	volume pore size distribution
G	Gibbs free energy
L	length
m	weight
n	number of moles
n_a	Avogadro constant
p	pressure
p_{GAS}	gas pressure above ambient
p_0	saturated vapor pressure
r	radius
R	gas constant
S	total pore surface area
S_{BET}	specific surface area
T	absolute temperature
V	volume
V_c	condensed volume
V_L	molar volume
V_m	volume of monolayer
V_{TOT}	total pore volume
W	work
ε	porosity
γ	surface tension
γ_{LV}	liquid-vapor interaction
γ_{SL}	solid-liquid interaction
γ_{SV}	solid-vapor interaction
ρ_b	bulk density
ρ_h	true density
θ	contact angle

1 Introduction

Mannitol and microcrystalline cellulose are commonly used diluents in the pharmaceutical industry. Mannitol is non-hygroscopic and microcrystalline cellulose is hygroscopic, swelling with water. In pharmaceutical processing, these materials are usually granulated and tableted. Thus, knowledge of the behaviour of these materials in these processes is important. The effect of wet granulation on the pore structure of these materials has not been thoroughly investigated, nor has pore structure measurement been used to compare direct compression of powder and tableting of granules.

Mercury porosimetry is widely used to characterize the pore structure of cement samples, catalysts and adsorbents. Its use in the pharmaceutical industry has increased recently. In pharmacy, the method is used to characterize samples with different physical structures, such as powders, granules and tablets. However, the need for pretreatment of samples before mercury porosimetry analysis has not been studied previously. Theoretically, the pore structure of dried samples differs from that of samples stored under humid conditions. Pharmaceutical excipients and products usually have porous structure, and moisture from the air is adsorbed to the surface and pores of samples. Knowledge of the adsorption behaviour of water in the pores of samples is important, because this water can cause problems in pharmaceutical production. The effect of water on the structure of pharmaceutical samples during mercury porosimetry analysis has not been reported.

Behaviour of pharmaceutical samples during mercury porosimetry analysis or the effect of mercury porosimetry scanning speed on measurement results has not been studied previously. Pore structure of samples determined using fast and slow scanning speed may differ from each other. Further, if scanning speed does not seem to have an effect on the pore structure of samples, time could be saved in determinations by choosing faster scanning. Nitrogen adsorption method determines smaller pores than does mercury porosimetry. Although these methods differ in principle, both are used in characterisation of the microstructure of pharmaceutical samples. The pore size ranges of the two methods overlap, and the same porosity parameter values may be obtained. Correspondence of the results of these methods is dependent on the structure of the sample. These methods or their use in characterisation of pharmaceutical samples have not been compared to any large extent, although the proper use of expensive analytical methods would save resources in the pharmaceutical industry.

2 Theory

2.1 Porosity

Porosity refers to the pore space in a material (Sing et al. 1985). Internal surface of the material comprises the pores and cracks that are deeper than they are wide. An open pore (Fig. 1.) is a cavity or channel that communicates with the surface of the particle. Closed pores (Fig. 1.) are inside the material. These open and closed pores are called intraparticular porosity of the material. A void is a space between particles, i.e. interparticular porosity. Powder porosity consists of the pores in and voids between the particles.

Pores are classified according to size into three categories; micropores (pore diameter smaller than 2 nm), mesopores (pore diameter 2 – 50 nm) and macropores (pore diameter larger than 50 nm) (Sing et al. 1985). With nitrogen gas adsorption, depending on the equipment used, pore diameter range of 0.3 – 300 nm, i.e. mesopores and macropores, are determined. Low-pressure mercury porosimetry determines macropores (pore diameter 14 – 200 μm), and high-pressure porosimetry mesopores and macropores (pore diameter 3 nm – 14 μm), depending on the equipment.

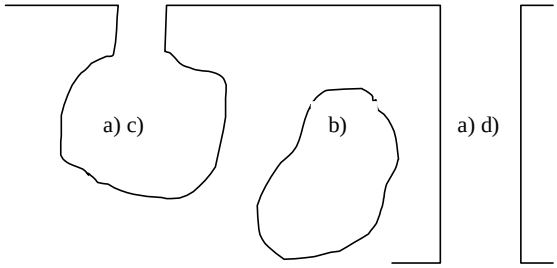


Figure 1. Pore types a) open pore b) closed pore c) ink-bottle pore d) cylindrical, open- ended pore.

2.2 Mercury porosimetry

2.2.1 Mercury porosimetry procedure

In mercury porosimetry, gas is evacuated from the sample cell, and mercury is then transferred into the sample cell under vacuum and pressure is applied to force mercury into the sample. During measurement, applied pressure p and intruded volume of mercury, V, are registered. As a result of analysis, an intrusion-extrusion curve is obtained (Fig. 2.). Parameters describing the pore structure of the sample can be calculated from the data obtained.

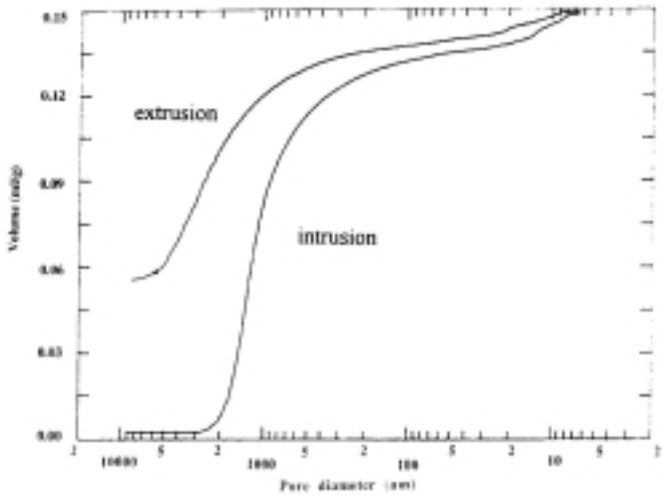


Figure 2. Intrusion-extrusion curve.

2.2.2 Washburn equation

Mercury porosimetry is based on the Washburn equation (Washburn 1921)

$$p \cdot r = -2 \cdot \gamma \cdot \cos\theta, \quad (1)$$

where r is the radius of the pore where mercury intrudes, γ surface tension of mercury and θ contact angle of the mercury on the surface of a solid sample. Generally used values for surface tension and contact angle of mercury are 480 mNm^{-1} and 140°, respectively.

The Washburn equation (1) can be derived from the equation of Yang and Dupre

$$\gamma_{SV} = \gamma_{SL} + \gamma_{LV} \cdot \cos\theta, \quad (2)$$

where γ_{SV} is interfacial tension between solid and vapor, γ_{SL} interfacial tension between solid and liquid, γ_{LV} interfacial tension between liquid and vapor and θ the contact angle of the liquid on the pore wall (Lowell & Shields 1991).

The work, W, required when liquid moves up the capillary during capillary rise when the solid-vapor interface disappears and solid-liquid interface appears is

$$W = (\gamma_{SL} - \gamma_{SV})\, \Delta A, \quad (3)$$

where ΔA is the area of the capillary wall covered by liquid when its level rises. According to equations (2) and (3),

$$W = -(\gamma_{LV} \cdot \cos\theta)\, \Delta A. \quad (4)$$

The work required to raise a column of liquid a height h in a capillary with the radius r is identical to work that must be used to force liquid out of the capillary. When a volume V of liquid is forced out of the capillary with a gas at a constant pressure above ambient, Δp_{GAS}, the work is presented as

$$W = V\Delta p_{GAS} \quad . \quad (5)$$

When equations (4) and (5) are combined

$$\Delta p_{GAS}\, V = -(\gamma \cdot \cos\theta)\, \Delta A. \quad (6)$$

When the capillary is circular in cross-section, parameters V and ΔA are given by $\pi r^2 L$ and $2\pi rL$, when L is length of the capillary. When these terms are substituted to the equation (6), it yields the Washburn equation (1)

$$p \cdot r = -2 \cdot \gamma \cdot \cos\theta.$$

2.2.3 Total pore volume and total pore surface area

Total pore volume (V_{tot}) is the total intruded volume of mercury at the highest pressure determined.

Total pore surface area (S) is calculated by Equation 7

$$S = \frac{1}{\gamma|\cos\theta|} \int_0^{V_{tot}} p dV \, . \quad (7)$$

Total pore surface area is the area above the intrusion curve (Fig. 2.), and it is thus modelless and independent of the geometrical pore shape (Rootare & Prenzlow 1967).

2.2.4 Mean and median pore diameter

The mean pore diameter (d_{mean}) is calculated by Equation 8

$$d_{mean} = 4 \cdot \frac{V_{tot}}{S} \quad , \quad (8)$$

based on an assumption of cylindrical shape of pores open at ends (Emmett & Dewitt 1943). Median pore diameter (d_{median}) is the pore diameter at which 50% of the total intruded volume of mercury is intruded into the sample (Dees & Polderman 1981). In

general, mean pore diameter emphasizes the smaller pores rather more than median pore diameter.

2.2.5 Volume pore size distribution

Volume pore size distribution, $D_v(d)$, is defined as the pore volume per unit interval of pore diameter (d) by Equation 9

$$D_V(d) = \frac{p}{d} \cdot \frac{dV}{dp} \tag{9}$$

(Ritter & Drake 1945). Volume pore size distribution is based on a model of cylindrical pores (Fig. 1.).

2.2.6 Use of mercury porosimetry in pharmaceutical powder technology

Mercury porosimetry has been used in the studies presented in the following table.

Table 1. Examples of the use of mercury porosimetry in pharmaceutical powder technology.

Subject	Author
Powders	Marshall & Sixmith 1975, Stanley-Wood 1978, Krycer et al. 1982, Carli & Motta 1984, Zouai et al. 1996, Tobyn et al. 1998
Granules	Strickland et al. 1956, Fujiwara et al. 1966, Nicholsson & Enever 1974, Opankule & Spring 1976, Stanley-Wood & Shubair 1979, Krycer et al. 1982, Veillard et al. 1982, Zoglio & Carstensen 1983, Juppo et al. 1994, Knight et al. 1998
Tablets	Reich & Gstirner 1968, Selkirk & Ganderton 1970, Selkirk 1974, Sixmith 1977, Stanley-Wood 1978, Dees & Polderman 1981, Vromans et al. 1985, Riippi et al. 1992, Wikberg & Alderborn 1992, Landin et al. 1993a, Pourkavoos & Peck 1993, Faroongsarng & Peck 1994, Juppo 1996a, Juppo 1996b, Juppo 1996c, Zouai et al. 1996, Riippi et al. 1998
Cellulose beads	Ek. et al. 1994, Ek. et al. 1995
Pellets	Millili & Schwartz 1990, Niskanen 1992a, Niskanen 1992b, O´Connor & Schwartz 1993, Bataille et al. 1993, Vertommen et al. 1998

Although mercury porosimetry has been widely used in determination of pharmaceutical samples, pretreatment of the samples before measurement or the effect of scanning speed on the results of pharmaceutical sample determinations has not been studied.

2.2.7 Advantages and limitations of mercury porosimetry

Mercury porosimetry is a relatively rapid method, with which a wide pore diameter range (3 nm - 200 μm) and variety of porosity parameters can be determined. However, the method is rarely used in quality control measurements, because the time used for a single analysis is 30 – 45 minutes (Webb & Orr 1997). The measurement itself is automatic, which allows personnel to engage other work at the same time. Dimensions of the sample cell limit the size of the sample. However, the diameter of the sample cell is commonly 1 cm, which normally allows the determination of pharmaceutical samples. With the method, only pores that reach the surface of the sample can be determined. The sample must be dry, because mercury cannot intrude into the sample when voids are filled with another liquid (Ek et al. 1995). Samples with a fine pore structure are difficult to degas, and adsorbed layers reduce effective pore diameter and pore radius values (Allen 1997).

During measurement, high pressures to force mercury into small pores may compress the sample (Palmer & Rowe 1974, Dees & Polderman 1981, Johnston et al. 1990, Ek. et al. 1994, Allen 1997, Webb & Orr 1997). This effect can be shown especially in samples containing closed pores (Webb & Orr 1997), and is observed as a too large volume of small or medium sized pores. Damage or compression of highly porous silica has been reported (Brown & Lard 1974, Johnston et al. 1990). However, no damage or sample compression of lactose, mannitol or glucose tablets or carbon black particles has been observed (Moscou & Lub 1981, Dees & Polderman 1981, Juppo 1995). In addition to compression of sample, also mercury, the sample cell or residual air may be compressed with increasing pressure (Allen 1997). These compressional effects and the effect of a rise in temperature (van Brakel et al. 1981) can be eliminated with the use of hydraulic oil as a medium for transferring pressure (Lowell 1980).

Usually, constant surface tension and contact angle values are used for mercury (Allen 1997). However, contact angle may differ due to differences in the surfaces of the samples. Contact angle can be determined for each material studied, and the corrected value can be used in determinations.

Mercury porosimetry overestimates the volume of the smallest pores (Auvinet & Bouvard 1989). This is due to ink-bottle shaped pores (Dees & Polderman 1981, Allen 1997) and interconnected pores (Allen 1997) that shift the volume pore size distribution towards smaller pores. The diameter of the pore opening into the surface of the sample determines when mercury is intruded into the sample. Large pores with a small opening are thus filled at high pressures, and detected as smaller pores than they actually are. Pore size distributions obtained with incremental and continuous mode differ (Allen 1997), and the results obtained with these two methods are thus not comparable. In incremental mode, the pressure is increased in steps. In continuous mode, the pressure is increased continuously at a predetermined rate.

Non-capillary pore structure and limitations of the Washburn equation in determination of the smallest pores are the reasons for the differences between pore size distributions determined with mercury porosimetry and nitrogen adsorption (De Wit & Scholten 1975).

However, total pore volume and pore surface area results are not dependent on pore shape (Rootare & Prenzlow 1967), and the shape of pore size distribution is not remarkably different from the true distribution in spite of the assumption of a circular cross section of the pores (Ritter & Drake 1945). The pore size distribution obtained with mercury porosimetry has been a useful parameter in characterisation of tablets (Juppo 1995).

2.3 Nitrogen gas adsorption method

2.3.1 Total pore volume and volume pore size distribution

Total pore volume, i.e. volume of the pores in a pre-determined pore size range can be determined from either the adsorption or the desorption phase.

The volume pore size distribution is determined according to the BJH model (Barrett et al. 1951). The corrected Kelvin equation

$$\ln\frac{p}{p_0} = -\frac{2\gamma V_L}{rRT}\cos\theta \qquad (10)$$

is used to calculate the relative pressure of nitrogen in equilibrium with a porous solid, and applied to the size of the pores where capillary condensation takes place. The equation was presented in its original form by Thomson (1871).

In the Kelvin equation, p is the equilibrium vapor pressure of a liquid in a pore of radius r, p_0 the equilibrium pressure of the same liquid on a plane surface, γ surface tension of the liquid, V_L molar volume of the liquid, θ the contact angle with which the liquid meets the pore wall, R the gas constant and T absolute temperature. When the meniscus of condensate is concave, capillary condensation will proceed in pores of radius r as long as the adsorptive pressure is greater than pressure p.

The equation is derived as follows. Liquid within the pore is in equilibrium with its vapour. A molar quantity of liquid (dn) outside of the pore, where its equilibrium pressure is p_0, is changed inside of the pore, where its equilibrium pressure is p. During the process, the total increase in free energy dG is the sum of three energies; $d\mathrm{G}_1$ = evaporation of dn moles of liquid at pressure p_0, $d\mathrm{G}_2$= changing dn moles of vapor from pressure p_0 to pressure p and $d\mathrm{G}_3$= condensation of dn moles of vapor to liquid at pressure p.

Condensation and evaporation are equilibrium processes, $d\mathrm{G}_1 = d\mathrm{G}_3 = 0$. Thus, the change in free energy during the process is presented as

$$dG_2 = RT\ln\left(\frac{p}{p_0}\right)dn, \qquad (11)$$

when the vapor behaves as a perfect gas.

During condensation of vapor in the pores, the solid-liquid interface increases and solid-vapor interface (dA) decreases. The change in free energy during this process is

$$dG_4 = dA\,(\gamma_{SV} - \gamma_{SL}). \tag{12}$$

When $\gamma_{SV} - \gamma_{SL} = -\gamma_{LV}\cos(\theta)$, wetting angle θ is 0, and $dG_4 = dG_2$, the equation can be presented as

$$RT\ln\left(\frac{p}{p_0}\right)dn = -\gamma_{LV}\cos(\theta)dA. \tag{13}$$

The volume condensed in the pores is $dV_c = V_L dn$, where V_L is molar volume. Thus, the equation can be presented as

$$\frac{dV_c}{V_L}RT\ln\left(\frac{p}{p_0}\right) = -\gamma_{LV}\cos(\theta)dA. \tag{14}$$

The equation can be further organized to be

$$\frac{dV_c}{dA} = \frac{-V_L\cdot\gamma_{VL}\cos\theta}{RT\ln\left(\frac{p}{p_0}\right)}. \tag{15}$$

For cylindrical pores with radius r and length L, $V_c = \pi r^2 L$ and $A = 2\pi rL$, and

$$\frac{V_c}{A} = \frac{r}{2}, \tag{16}$$

which leads to the Kelvin equation (10)

$$\ln\frac{p}{p_0} = -\frac{2\gamma V_L}{rRT}\cos\theta.$$

Pore size distribution can be determined from the adsorption or desorption data of the isotherm. A cylindrical pore model is assumed, with the further assumption of open-ended pores and absence of pore networks. The pore size distribution determined from nitrogen desorption data and the distribution obtained from the intrusion phase of mercury porosimetry describe pore structure similarly (Conner et al. 1986).

2.3.2 Specific surface area

Specific surface area is calculated according to the BET equation (Brunauer et al. 1938)

$$\frac{p}{V(p_0 - p)} = \frac{1}{V_m c} + \frac{c-1}{V_m c}\frac{p}{p_0}, \quad (17)$$

where V is volume adsorbed, V_m volume of monolayer, p sample pressure, p_0 saturation pressure and c constant related to the enthalpy of adsorption (BET constant). The specific surface area (S_{BET}) is then calculated from V_m by the following equation

$$S_{BET} = \frac{V_m \cdot n_a \cdot a_m}{m \cdot V_L}, \quad (18)$$

where n_a is Avogadro constant, a_m the cross sectional area occupied by each nitrogen molecule (0.162 nm^2), m weight of the sample and V_L the molar volume of nitrogen gas (22414 cm^3). The theory is based on the assumption that the first adsorbed layer involves adsorbate/adsorbent energies, and the following layers the energies of the adsorbate/adsorbate interaction.

2.3.3 Use of nitrogen adsorption in pharmaceutical powder technology

Nitrogen adsorption has been used in studies listed in the following table.

Table 2. Examples of the use of nitrogen adsorption in pharmaceutical powder technology.

Subject	Author
Powders	Marshall & Sixmith 1975, Stanley-Wood & Johansson 1978, Stanley-Wood & Shuibar 1979, Zografi et al. 1984, Niskanen et al. 1990, Landin et al. 1993a, Landin et al. 1993b, Stubberud et al. 1996
Granules	Stanley-Wood & Shuibar 1979, Stubberud et al. 1996
Tablets	Sixmith 1977, Stanley-Wood & Johansson 1978, Vromans et al. 1988, Faroongsarng & Peck 1994, Riippi et al. 1998
Pellets	Niskanen et al. 1990, Niskanen 1992a, Niskanen 1992b

2.3.4 Advantages and limitations of nitrogen gas adsorption

Many parameters that describe the pore structure of a sample, for example pore volume, specific surface area and pore size distribution, can be determined with this method. One drawback is that the time used for a single analysis can be hours. However, measurements can be done automatically for example during the night. The pore diameter range that can be determined is from 0.3 to 300 nm, a range not completely covered by mercury porosimetry.

With nitrogen adsorption, only open pores are determined, and the cylindrical pore model is assumed in pore size distribution measurements (Allen 1997). The desorption isotherm in the characterisation of pore size distribution is affected by the pore network; when pressure is reduced, liquid will evaporate from large open pores, but pores of the same size that are connected to the surface with narrower channels remain filled (Allen 1997). This changes the shape of the pore size distribution. The samples come into contact with the temperature of liquid nitrogen (-196°C) during analysis, which may destroy the sample.

2.3.5 Comparison of nitrogen adsorption and mercury porosimetry methods

Pore structure analysis by mercury porosimetry is faster than by nitrogen adsorption. In mercury porosimetry and nitrogen adsorption determinations, two different physical interactions take place. Both methods are based on surface tension, capillary forces and pressure. With mercury porosimetry, large pores at the intrusion phase are determined first, while with nitrogen adsorption, the smallest pores are measured first at the adsorption phase (Webb & Orr 1997). The determination range of high-pressure mercury porosimetry is wider (pore diameter 3 nm – 14 μm) than that of nitrogen adsorption (0.3 – 300 nm), and mercury porosimetry determines larger pores that are out of the detection range of nitrogen adsorption (Fig. 3.). With nitrogen adsorption, the smallest pores that are out of range of mercury porosimetry, can be determined. However, results of the two methods can be compared. The comparable parameters are total pore volume, volume pore size distribution and specific surface area/total pore surface area. Although the pore size range that can be determined with adsorption is narrower than that obtained with mercury porosimetry, it is more widely used (Allen 1997).

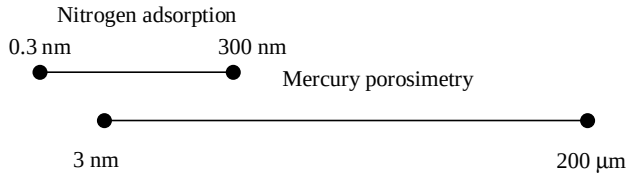


Figure 3. Pore diameter ranges determined with mercury porosimetry and nitrogen adsorption.

Milburn et al. (1991) have obtained similar pore volume values for silica samples with these methods. If the sample contains pores larger than 300 nm, the pore volume obtained with mercury porosimetry is larger than that determined with nitrogen adsorption (Webb & Orr 1997). Pore size distributions determined from mercury porosimetry intrusion data and nitrogen desorption data describe the pore structure similarly (Conner et al. 1986). Stanley-Wood (1978) and Conner et al. (1986) have formed almost the same pore size distributions with the two methods for uncompacted magnesium trisilicate and for Degussa aerosols, and Faroongsarn and Peck (1994) consistent pore size distributions for dicalcium phosphate dihydrate tablets. On the other hand, different pore size distributions have been obtained with these methods for silicas, iron oxide-chromium oxide catalyst, aerosil powder and chrysotile powder (Brown & Lard 1974, De Wit & Scholten 1975).

Even if the pore volume values obtained do not agree, surface area values may be similar (Webb & Orr 1997). This is because small pores have a larger effect on the surface area. According to Webb and Orr (1997), these two techniques are equal when pore size ranges from 3 to 300 nm are compared. Larger surface area values have been obtained with mercury porosimetry than with nitrogen adsorption for lactose tablets (Dees & Polderman 1981) and for silica samples (Milburn et al. 1991). Mikijelj & Varela (1991) obtained equivalent surface area results for magnesium oxide and diatomite compacts. Adkins and Davis (1988) have used a corrected contact angle in mercury porosimetry to make the surface area values similar. According to Milburn and Davis (1993), the correlation between surface areas obtained with these methods is poor if the samples have low surface area.

2.4 Water vapour adsorption

2.4.1 Adsorption of water on the surface of a solid sample

Water settles on the surface of a solid first as a monolayer and with increasing moisture as multilayers (Zografi 1988). The first layer is hydrogen bonded to the surface of the solid (Ahlneck & Zografi 1990) and is immobile (Ozeki et al. 1991). Additional layers can behave as a liquid (Ozeki et al. 1991), move along the surface of the sample (Zografi 1988, Ahlneck & Zografi 1990) and even cause dissolution of the solid (Ahlneck & Zografi 1990). According to Ozeki et al. (1991), at least the first layer of adsorbed water on the surface of chrysotile crystal has behaved like a solid, and water in fourth and higher layers behaved like liquid.

2.4.2 Behaviour of water in the pores

The diameter of a water molecule is 0.28 – 0.3 nm (Ozeki 1989). Micropore filling is a primary physisorption process, whereas physisorption in mesopores occurs in two stages; monolayer-multilayer adsorption and capillary condensation (Sing et al. 1985). At first, water is adsorbed into the surface of the pore wall (Fig. 4.), and then water is condensed and fills the core of the pore (Aharoni 1997). The reason why condensation occurs is that the surface of the condensed water in the pore is concave, and its vapor pressure is smaller than saturation pressure (Aharoni 1997). Relation between the diameter of the water-filled pores and the condensation pressure can be calculated with Equation (10), which is valid only in the pore radius range from 1.8 to 30 nm, part of which is measurable by high-pressure mercury porosimetry.

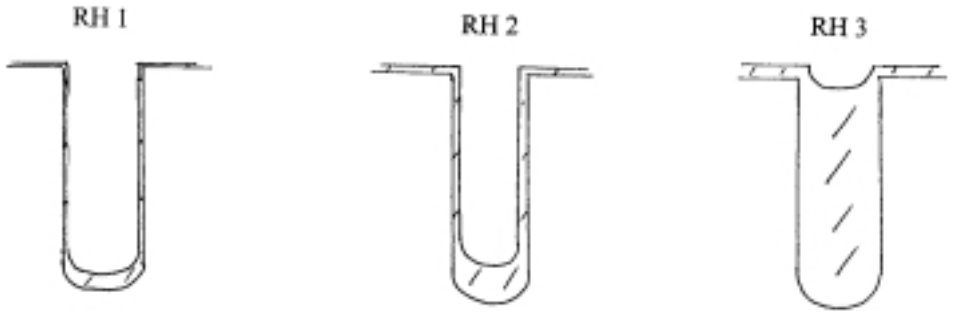


Figure 4. Adsorption and capillary condensation of water into a pore with radius r with increasing relative humidity RH1 < RH2 < RH3. At low relative humidity (RH1) water adsorbs as layers to the walls of the pore. With increasing relative humidity (RH2), thickness of adsorbed layers increases. Finally, at even higher relative humidity (RH3), water fills the pore.

At low relative humidities, water fills the smallest pores and adsorbs in layers to the surface of the sample. The capillary condensation model cannot be used for micropores. Also, the Kelvin equation handles the liquid-vapor interface within the pore as curvature and contact angle, which cannot be used with micropores (Aharoni 1997). When humidity of the surrounding air increases, water fills the larger pores. The first adsorbed layer is immobile, but in some cases water behaves like a liquid on flat surfaces and in wide pores (Ozeki et al. 1991). Ozeki et al. (1991) have studied the behaviour of water molecules on chrysotile crystal samples with cylindrical mesopores of 7 nm in diameter. Water molecules were adsorbed by capillary condensation to the mesopores, and formed a liquid-like phase. However, some pores of cement tiles have been reported at intermediate humidity to fill completely while others have remained empty (Bohris et al. 1998). Allen et al. (1998) observed with NMR technique that bulk water in the pores of silica forms puddles into the corners and cavities of irregular pores. This occurs even at low filling fractions of water together with physisorbed layers.

2.5 Mannitol

2.5.1 Characteristics of mannitol and its behaviour in wet granulation and tableting

Mannitol is a sugar alcohol and isomeric with sorbitol (Fig. 5.). Mannitol is used as a filler in conventional tablets. It is non-hygroscopic, and resists moisture sorption even at high relative humidities. Therefore, it has special value in tableting of moisture-sensitive drugs. Solubility of mannitol is 17 g/ 100 g of water at + 25°C.

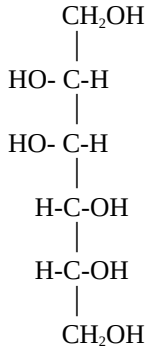


Figure 5. Structural formula of mannitol.

Due to its needle-like shape and thus poor flowability, mannitol powder is often granulated. Mannitol has poor wettability in wet granulation, which is due to the electric charge and cohesivity of dry mannitol powder (Juppo et al. 1992). This has led to bimodal size distribution and angular shape of mannitol granules after wet granulation. Mannitol particles dissolve and recrystallise on the larger particles during wet granulation (Juppo 1995). The small particles also attach to each other by solid bridges formed by recrystallised mannitol or by binder. The granules produced have a high porosity percentage (Juppo & Yliruusi 1994). The needle-like particles form a fibrous network with a large number of small pores.

Compression of mannitol powder has been presented in few papers. Mannitol is characterised as ductile, that deforms plastically under loading (Roberts & Rowe 1987, Bassam et al. 1990). Evidently, hydrogen bonding due to the hydroxyl groups (Fig. 5.) is one bonding mechanism for mannitol powder (Juppo 1995). In addition, van der Waals attractions, electrostatic forces and mechanical interlocking takes place under compression. Mannitol tablets compressed from crystals have had lower strength than those compressed from granulated powder (Krycer et al. 1982).

Porous mannitol granules have deformed plastically and also fragmented under compression (Juppo et al. 1995). Under compression, porous mannitol granules with a fibrous structure interlock mechanically and undergo fragmentation and plastic deformation. When mannitol is compressed with low compression pressure, large pores vanish, the volume of smaller pores is reduced, indicating that the intragranular porosity of mannitol granules also decreases (Juppo 1996a).

2.6 Microcrystalline cellulose

2.6.1 Characteristics of microcrystalline cellulose and its mechanism of swelling

Microcrystalline cellulose powder is composed of porous particles. Microcrystalline cellulose is used as binder/diluent in wet granulation and direct compression. It is hygroscopic in nature, and insoluble in water, but swells when in contact with water. The

structural formula of microcrystalline cellulose is presented in Figure 6. Glucose molecules are linked via beta-glucoside bonds. Intermolecular hydrogen bonds are formed between these cellulose polymers, glucan chains aggregate and form fibres. Thus, the structure has microcrystalline nature.

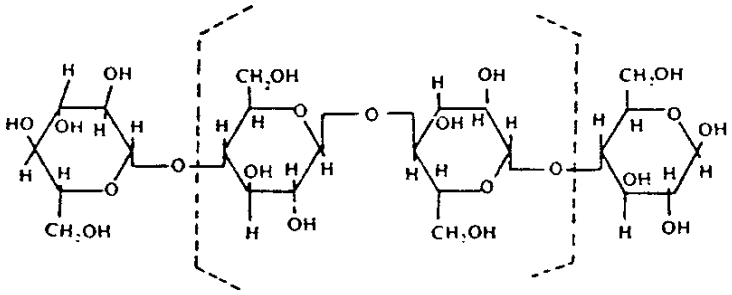


Figure 6. Structural formula of microcrystalline cellulose.

When microcrystalline cellulose is stored under humid conditions, water penetrates the amorphous structure (Zografi et al. 1984). Khan et al. (1988) have reported that water molecules are accommodated into the internal structure of microcrystalline cellulose in the spaces between the cellulose chains when the amount of water in the sample is below 3 wt%, and that no swelling occurs. According to Khan and Pilpel (1987), water disrupts the cellulose-cellulose bonds and forms new hydrogen bonds between them, which causes swelling of the sample and increases the volume of the particles. Figure 7 shows the mechanism of hydrogen bonding between water molecules and cellulose. At first, one sorbed water molecule is linked to two 6-OH groups in neighbouring cellulose chains (Fig. 7 a). When 3 wt% of moisture is present (Fig. 7 b), each water molecule is attached to the cellulose chain by only one hydrogen bond. When more moisture is absorbed, 6-OH groups in cellulose chain are hydrogen bonded with water, and weakly hydrogen-bonded water probably forms a bulk water phase (Fig. 7 c). This phase takes place when 6 wt% of water or more is absorbed to the structure of microcrystalline cellulose.

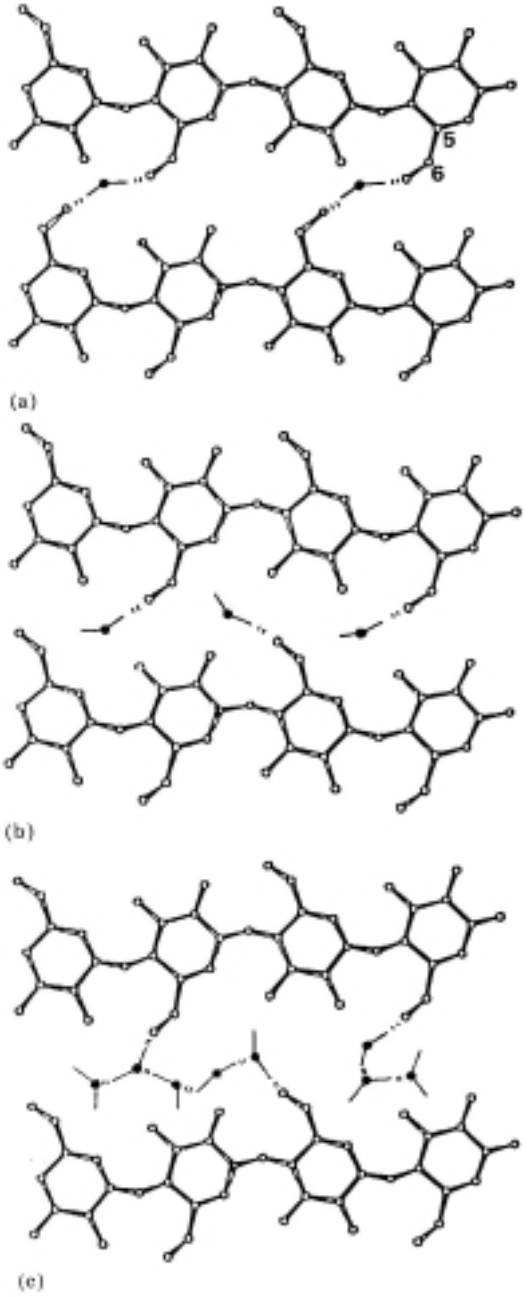


Figure 7. Absorption of water into the structure of microcrystalline cellulose (Khan & Pilpel 1987)[1].

[1] Reprinted from Powder Technology, 50, Khan & Pilpel, An investigation of moisture sorption in microcrystalline cellulose using sorption isotherms and dielectric response, p. 239, copyright (1987), Elsevier Science.

Similarly, Zografi and Kontny (1986) have explained water vapour sorption of microcrystalline cellulose with a three-step model. At low relative humidities, water is bound to available anhydroglucose units in the amorphous regions of cellulose with a stoichiometry of one water molecule per anhydroglucose unit. At relative humidities up to about 60 %, polymer-polymer hydrogen bonds are broken, which makes more primary binding sites available and allows water to begin to bind to other water molecules already bound to anhydroglucose units. Finally, at even higher relative humidities, water can also bind to other water molecules, including those not bound to primary sites.

2.6.2 Behaviour of microcrystalline cellulose in wet granulation and tableting

Microcrystalline cellulose works as a binder in wet granulation (Doelker 1993), but its good compactibility has been found to disappear due to loss of plasticity in wet granulation (Staniforth et al. 1988). Millili (1990) has reported that the degree of hydrogen bonding of microcrystalline cellulose is not responsible for harder pellets produced with water. He has explained densification of microcrystalline cellulose by autohesion, solid solid diffusion. Chatrath (1992) has called the reduced compactibility of microcrystalline cellulose after wet granulation 'quasi-hornification' to describe the increased intraparticle hydrogen bonding. Kleinebudde (1997) has explained the behaviour of microcrystalline cellulose in wet granulation, extrusion and spheronization by a crystallite gel model. In that model, the crystallites or their agglomerates of microcrystalline cellulose form a framework by crosslinking with hydrogen bonds at the amorphous ends. During drying, more hydrogen bonds are formed. No changes were observed at the level of individual crystallites. Increased internal hydrogen bonding in microcrystalline cellulose after wet granulation was observed with near IR –technique by Buckton et al. (1999). Ek and Newton (1998) have explained the deformation of microcrystalline cellulose during extrusion/spheronization with water by a sponge model. Various explanations for the behaviour of microcrystalline cellulose during processing with water have been put forward recently. However, increased internal hydrogen bonding appears to be the reason for the densified structure of microcrystalline cellulose granules after wet granulation.

Hydrogen bonding, large particle surface area, filamentous structure of the cellulose microcrystals and mechanical interlocking of irregular elongated particles are responsible for the excellent binding properties of microcrystalline cellulose in tableting (Bolhuis & Lerk 1973). Microcrystalline cellulose powder deforms plastically (Lamberson & Raynor 1976, David & Augsburger 1977, Shangraw et al. 1981, Staniforth et al. 1988). The modal pore radius of microcrystalline cellulose tablets compressed from powder has decreased with increasing compression pressure (Sixmith 1977). Strength of interparticle bonding was greater for the powder samples of microcrystalline cellulose than for granules (Staniforth et al. 1988). Staniforth et al. (1988) suggested that in the granules most of the compression force was used for breaking up the primary granule structure and hence did not establish areas of intimate contact to provide strong bonds between the cellulose particles. In compression of pellets, the dominating mechanism of compression has been permanent deformation in combination with densification of the pellets (Johansson et al. 1995, Johansson & Alderborn 1996, Johansson et al. 1998). Only limited fragmentation of pellets during compression has occurred. The effect of compression on specific surface

area and porosity of microcrystalline cellulose tablets compressed from powder (Sixmith 1977, Zouai et al. 1996), from pellets (Johansson et al. 1995, Johansson & Alderborn 1996, Johansson et al. 1998) and also from granules (Chatrath 1992) has been studied. However, studies concerning the deformation of microcrystalline cellulose granules under compression based on pore structure with mercury porosimetry and nitrogen adsorption have not been thoroughly reported.

3 Aims of the study

1. Study the effect of pretreatment of non-hygroscopic mannitol and hygroscopic microcrystalline cellulose powder, granule and tablet samples by vacuum drying or storage in moisture conditions on the result of mercury porosimetry analysis, and the role of moisture in the structure of the samples during mercury porosimetry

2. Study the effect of scanning speed on the result of mercury porosimetry analysis of powder, granules and tablets

3. Study wet granulation of mannitol and microcrystalline cellulose and compare direct compression and tableting of granulated mass by using the pore structure determination

4. Compare mercury porosimetry and nitrogen adsorption methods in determination of the pore structure of powder, granules and tablets

4 Experimental

4.1 Materials (I-V)

Two starting materials, D(-)- mannitol (Merck, Darmstadt, Germany) and microcrystalline cellulose (Emcocel® 50M, Edward Mendell, New York, USA), were used in the study. Mannitol was chosen due to its non-hygroscopic character, and microcrystalline cellulose because of its hygroscopic nature.

For mannitol granulation, 20% polyvinylpyrrolidone (PVP, Kollidon® K 25, BASF, Ludwigshafen, Germany) solution in distilled water was used as a binder. Granulation liquid used for microcrystalline cellulose was 4% polyvinylpyrrolidone solution in distilled water. Polyvinylpyrrolidone powder (1.6 %) was added also to the mannitol and microcrystalline cellulose powder masses before direct compression to achieve similar contents to those of the granule masses. Polyvinylpyrrolidone is a hygroscopic ingredient. Thus its concentration is constant in every mass of this work.

Magnesium stearate (1%) (Mallingrot, Deventer, Netherlands) was added to the tablet masses as lubricant. This commonly used concentration was added into every mass, although the particle size and thus effective surface area where magnesium stearate adheres is different in every mass.

4.2 Characterisation of powders

4.2.1 Particle size, appearance, water adsorption isotherms and moisture content (I)

Particle size distribution of the powders was measured by laser diffraction (Malvern Instruments, Worcestershire, UK). Focal lengths of the lenses used for mannitol and microcrystalline cellulose powders were 600 and 300 mm, respectively. Measurements were done in triplicate (n=3). Appearance of mannitol and microcrystalline cellulose powders was studied by a scanning electron microscope (Jeol JSM-840A, Jeol, Tokyo, Japan).

Water adsorption isotherms of mannitol and microcrystalline cellulose powders were measured by gravimetric humidity method described by Juslin et al. (1994). The moisture contents of the powders were measured by Karl Fischer titration (Mettler DL 18, Greifensee, Switzerland) after conditioning before mercury porosimetry and nitrogen adsorption measurements. Measurements were done in triplicate (n=3).

4.2.2 Pore structure obtained by mercury porosimetry (I-III)

Mannitol and microcrystalline cellulose powders were stored under three different humidity conditions before mercury porosimetry measurement. The powders were stored in a vacuum oven (Heraeus VTR 5022, Heraeus, Cologne, Germany, with vacuum pump

Trivac S4A, Leybold-Heraeus, Cologne, Germany) below 10 Pa at + 20°C and in different desiccators containing saturated salt solutions at room temperature (+ 25°C). The saturated salt solutions were Na_2CO_3 and K_2CrO_4, which gave relative humidities of 43% and 88%, respectively. Powders were stored in these two humidities for 72 hours and in vacuum for 24 hours. Total pore volume, total pore surface area, mean and median pore diameters, and pore size distributions of the powders were determined using both a low-pressure (Filling apparatus for Autoscan porosimeter, Quantachrome Corporation, Boynton Beach, FL, USA) and a high-pressure mercury porosimeter (Autoscan 33 Porosimeter, Quantachrome Corporation, Boynton Beach, FL, USA). Determination range of low-pressure porosimetry is 14 μm – 200 μm and that of high-pressure porosimetry 7 nm - 14 μm. Due to electrostatic effects, it was not possible to determine the effect of scanning speed or moisture on the pore structure of mannitol powder. Powders (0.5 - 0.8 g) were placed into the sample cell, which was evacuated for about 3 minutes (below 7 Pa) and filled with mercury in the filling apparatus. Scanning speeds in low-pressure porosimetry were 50, 280 and 610 Pa/s and in high-pressure porosimetry 220, 500 and 1010 kPa/s. Pore structure measurements were done in triplicate (n=3).

4.2.3 Pore structure and specific surface area obtained by nitrogen adsorption (I–III)

Total pore volume, volume pore size distribution and specific surface area of the powders were measured in triplicate by using nitrogen adsorption (Coulter SA 3100, Coulter, Miami, FL, USA). The samples were dried in vacuum (vacuum oven Heraeus VTR 5022, Heraeus, Cologne, Germany, with vacuum pump Trivac S4A, Leybold-Heraeus, Cologne, Germany) below 10 Pa at + 40°C for 24 hours. Total pore volume determined from the adsorption phase, is the volume of the pores smaller than 100 nm. The specific surface area based on BET theory was measured from 12 points at the relative nitrogen pressure range 0.05 - 0.20 from the adsorption phase and the pore size distribution according to BJH theory from 88 points at the relative nitrogen pressure range 0.98 - 0.37 from the desorption phase. Temperature during measurement was -196°C.

4.3 Granulation (I-V)

Granules were produced using a high shear mixer (Fielder PMA 25/2G, T.K. Fielder Ltd, Eastleigh, UK). For mannitol, the binder solution was added at a speed of 150 ml/min to the final amount of 75 ml/kg. For microcrystalline cellulose, the binder solution was added at a speed of 200 ml/min to the final amount of 400 ml/kg. The mannitol granule batch size was 5 kg and that of microcrystalline cellulose granules 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 two days.

4.4 Characterisation of granules

4.4.1 Particle size, appearance, water adsorption isotherms and moisture content (I)

Particle size distribution of the granules was measured by laser diffraction (Malvern Instruments, Worchestershire, UK). Focal lengths of the lenses used were 1000 mm for mannitol granules and 100 and 1000 mm for microcrystalline cellulose granules. Measurements were done in triplicate (n=3). Appearance of the mannitol and microcrystalline cellulose granules was studied by a scanning electron microscope (Jeol JSM-840A, Jeol, Tokyo, Japan).

Water adsorption isotherms of mannitol and microcrystalline cellulose granules were measured by gravimetric humidity method described by Juslin et al. (1994). The moisture contents of the granules were measured by Karl Fischer titration (Mettler DL 18, Greifensee, Switzerland) after conditioning before mercury porosimetry and nitrogen adsorption measurements. Measurements were done in triplicate (n=3).

4.4.2 Pore structure obtained by mercury porosimetry (I-III)

Total pore volume, total pore surface area, mean and median pore diameters, and volume pore size distributions of the granules were determined as for powders.

4.4.3 Pore structure and specific surface area obtained by nitrogen adsorption (I-III)

Total pore volume, volume pore size distribution and specific surface area of the granules were measured as for powders.

4.5 Characterisation of powder and granule masses before tableting

Porosity (ε) of powder and granule masses was determined according to Equation 19

$$\varepsilon = \left(1 - \frac{\rho_b}{\rho_h}\right) \cdot 100\%, \tag{19}$$

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

4.6 Tableting (II-V)

Tablets were compressed from powder and granules with a rotary press (Kilian, RU-24 III, Kilian & Co. GmbH, Cologne, Germany). Polyvinylpyrrolidone was dry-mixed with the powder masses to achieve similar contents to those of the granule masses. Magnesium stearate (Mallingrot, Deventer, Netherlands) was mixed into the tablet masses for 12

minutes in a Turbula mixer (T 10 B, Willy A. Bachofen AG Maschinenfabrik, Basel, Switzerland) and the masses were then 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 mannitol powder and granule tablets and microcrystalline cellulose granule tablets was 230 mg. The weight of the microcrystalline cellulose powder tablets was 190 mg, because the bulk density of powder mass was so low 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, i.e. the compression time was approximately 60-90 ms depending on the material used. Force feeder was not used. Target maximum compression pressures used were 72 MPa, 122 MPa and 196 MPa. For mannitol tablets the temperature during tableting was 21 - 23°C and relative humidity 15 - 17%, and those for microcrystalline cellulose tablets 20 - 21°C and 13 - 15%.

4.7 Characterisation of tablets

4.7.1 Breaking force and moisture content (II-V)

Breaking force was measured (Erweka TBH 28, Erweka Apparatebau, Hensenstamm, Germany) from twenty tablets. Moisture content was determined with Karl Fischer titrator after conditioning before mercury porosimetry and nitrogen adsorption measurements as for powders and granules.

4.7.2 Porosity based on tablet dimensions (II-III)

Porosity (ε) of tablets based on tablet dimensions was calculated according to Equation 20

$$\varepsilon = \left(1 - \frac{\frac{m}{V}}{\rho_h} \right) \cdot 100\%, \tag{20}$$

where m is the weight of the tablets and V volume of the tablets. Measurements were made from twenty tablets.

4.7.3 Pore structure obtained by mercury porosimetry (II-V)

Porosity parameters of the tablets were determined with a high-pressure porosimeter in the same way as for powders and granules. Sample size was three tablets.

4.7.4 Pore structure and specific surface area obtained by nitrogen adsorption (II-III)

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.

4.8 Statistical analysis (I, IV-V)

The results were analysed statistically by analysis of variance (ANOVA) with Statview statistical software (Abacus Concepts, Inc., Berkeley, USA) and by multiple linear regression analysis (Modde version 4.0, Umetrics AB, Umeå, Sweden).

5 Results and discussion

5.1 Effect of pretreatment by vacuum drying or by storage in moisture conditions on the result of mercury porosimetry analysis, and the role of moisture in the structure of the samples during mercury porosimetry

5.1.1 Non-hygroscopic mannitol and hygroscopic microcrystalline cellulose powder (I)

Due to electrostatic effects of mannitol powder in the sample cell, unfortunately, it was not possible to determine the effect of pretreatment on the pore structure of mannitol powder with mercury porosimetry. Mannitol powder adhered to the walls of the sample cell and came out of the sample cell during vacuum in the filling process. Due to swelling, after storage in moisture conditions and thus with increasing water content, the total pore volume of microcrystalline cellulose powder increased in low-pressure mercury porosimetry. According to the pore size results and the volume pore size distributions determined with low-pressure mercury porosimetry (i.e. pore diameter 14 – 200 μm), the volume of the smallest pores in microcrystalline cellulose powder was greatest when the samples were pretreated in vacuum conditions before measurement.

In the range of high-pressure porosimetry used in this work (pore diameter 7 nm – 14 μm), the total pore volume of microcrystalline cellulose powder decreased due to the moisture in the sample. Moisture did not affect other porosity parameters of the powder. Swelling increased the particle size of microcrystalline cellulose powder, and the voids between particles were determined in the range of low-pressure porosimetry. According to the theory on adsorption and condensation of water into pores, the smallest pores are filled first with water, which decreases the volume of the pores determined. However, no water-induced change in the volume of the smallest pores of microcrystalline cellulose was observed in high-pressure mercury porosimetry. According to the low- and high-pressure mercury porosimetry results of microcrystalline cellulose powder, proper pretreatment of the samples before mercury porosimetry analysis is important.

5.1.2 Non-hygroscopic mannitol and hygroscopic microcrystalline cellulose granules (I)

Pretreatment had no effect on the porosity parameters of mannitol granules in low-pressure porosimetry analysis. However, the total pore volume of microcrystalline cellulose granules increased due to swelling after storage in moisture conditions at the pore size range of low-pressure porosimetry. The median pore diameter of microcrystalline cellulose granules was smallest after storage in vacuum oven, which was evident also in the volume pore size distributions. The total pore surface area and volume of the smallest pores of microcrystalline cellulose granules increased with increasing moisture in low-pressure porosimetry analysis.

Moisture had no effect on the total pore volume of mannitol granules in high-pressure porosimetry analysis. However, the total pore volume of microcrystalline cellulose granules decreased due to the swelling with increasing moisture. With increasing moisture content, the total pore surface area of mannitol granules increased and the mean pore size decreased. The increase in the volume of the smallest pores of mannitol granules is also shown from the volume pore size distributions. The decrease in mean pore size was detected also in the microcrystalline cellulose granules.

During the adsorption, water fills the smallest pores determined with high-pressure mercury porosimetry first and the volume of these pores is supposed to decrease. Hearn and Hooton (1992) have presented that water would fill the pores of the samples and thus hinder the intrusion of mercury. Similarly, Ek et al. (1995) have suggested that mercury cannot intrude into the pores filled with another liquid. However, the volume of the smallest pores of the granules manufactured from mannitol and microcrystalline cellulose increased in this study. Because the water affects the volume of the smallest pores, it can be assumed that water settles into the smallest pores of granules. The structures of these granulated masses differ; mannitol granule mass consists of porous mannitol granules and partly of non-porous mannitol powder, whereas microcrystalline cellulose granules have a dense, non-porous structure. Water contents of the samples also differ remarkably. However, the increase in the volume of the smallest pores is most likely related to the complicated structure of granulated masses, because it was not observed with microcrystalline cellulose powder. One explanation could be that water is pushed through the pore structure of granules into new small pores in the face of an advancing mercury interface. On the other hand, Webb and Orr (1997) have suggested that the volume of the smallest pores and surface area values can be falsely large due to the compression of the samples during analysis. Thus, water may induce some compression of granulated samples during mercury porosimetry analysis. The median pore size was not affected, because this parameter reflects differences in the larger pore diameter range.

Pretreatment affects more the mercury porosimetry analysis of granules manufactured from hygroscopic material than of non-hygroscopic material, as expected. Pretreatment affected even the porosity parameters of non-hygroscopic mannitol granules, although the water contents of the samples were 1.2 % at the highest. Similar pretreatment of parallel samples before mercury porosimetry measurements is recommended.

5.1.3 Tablet samples (IV, V)

5.1.3.1 Tablets manufactured by direct compression from mannitol and microcrystalline cellulose

Total pore volume of microcrystalline cellulose tablets compressed from powder increased due to the swelling of microcrystalline cellulose with increasing moisture, while the pore volume of mannitol powder tablets was unaffected. The change in microcrystalline cellulose tablets was observed after storage in 88% humidity. Moisture did not affect the volume of the smallest pores of mannitol tablets (pore diameter < 30 nm). However, for microcrystalline cellulose, mean pore size of tablets increased with increasing moisture.

The maximum of the volume pore size distribution of mannitol tablets (pore size range 50 – 2000 nm, Fig. 8) and microcrystalline cellulose tablets (pore size range 500 – 2000 nm) changed towards larger pores with increasing humidity. This was observed also as increased median pore size values.

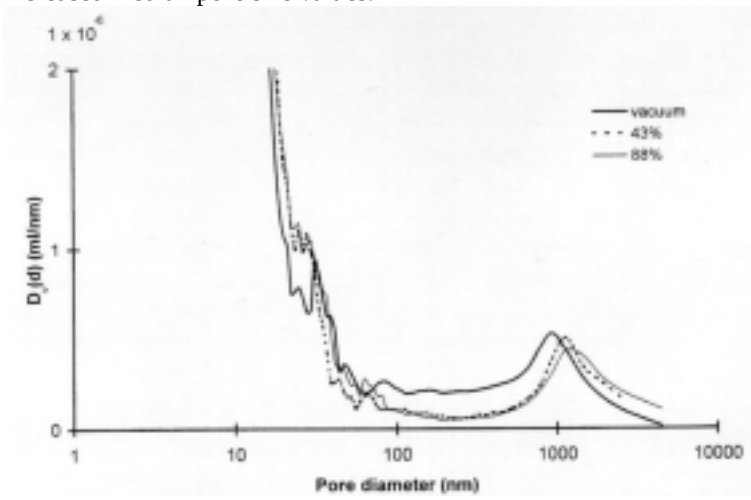


Figure 8. Volume pore size distributions of mannitol powder tablets compressed with 72 MPa and stored in different moisture conditions[2].

In tableting, the powder is bound together and the structure of the mass is densified. Therefore, water does not affect the structure of the tablets in the same way as it affects the starting materials. The possibility of capillary condensation increases due to the densified structure of the samples after tableting (El-Sabaawi & Pei 1977). In the present work, volume of the smallest determined pores of microcrystalline cellulose powder tablets decreased due to the water, whereas that of mannitol powder tablets remained unchanged. The water content in microcrystalline cellulose tablets is remarkably greater than that in mannitol tablets. The result of this work is consistent with the presentation of Hearn and Hooton (1992), that water in the sample behaves as a solid and thus hinders the intrusion of mercury. Similarly, according to Ek et al. (1995), mercury cannot intrude into pores already filled with another liquid.

Surprisingly, water settles in the pore size range of 50 - 2000 nm to the mannitol tablets and in the pore size range 500 – 2000 nm to the microcrystalline cellulose tablets. Some possible explanations are presented in the following. At the beginning of mercury porosimetry analysis, the sample is dried in order to fill the sample cell with mercury. Part of the water, especially from the smallest detected pores, is removed during this drying, and can be moved to the larger pores. During mercury porosimetry, the water on the surface of the sample can cause changes in the structure of the material studied under high pressure in the sample cell. The sample may for example be compressed during measurement. The water on the surface of the sample can be mobile under different

[2] Reprinted from Pharmaceutical Development and Technology, 5(2), Westermarck et al., Mercury porosimetry of mannitol tablets: effect of scanning speed and moisture, p. 186, copyright (2000), Marcel Dekker.

conditions, and even promote chemical degradation or other types of physical changes (Ahlneck & Zografi 1990). On the other hand, puddles can be formed in the irregular pores of this size, which would decrease the volume of the pores (Allen et al. 1998). In addition to this, cyclohexane has been reported to cause a change in the contact angle of mercury on the surface of aluminium, and increase the determined pore size (Moscou & Lub 1981). Similarly, water on the surface of the tablet can change the contact angle of mercury and change the maximum of the pore size distribution towards larger pores.

According to the present results, the effect of pretreatment of samples appears to be very important when comparing tablets manufactured with direct compression. The pore structures of microcrystalline cellulose powder, granule and tablet samples are affected differently when stored in moisture conditions. The effect of pretreatment and water is observed even at the pore size range of larger pores (50 – 2000 nm) of tablets. Thus, if the effect of manufacturing on the pore structure of the sample is of interest, pretreatment of the samples should be similar before measurement.

5.1.3.2 Tablets compressed from mannitol and microcrystalline cellulose granules

The effect of water in the structure of tablets compressed from granules is even more complicated than its effects in the tablets manufactured by direct compression. Total pore volume of microcrystalline cellulose granule tablets increased due to the swelling with increasing moisture content, while the total pore volume of mannitol tablets was unaffected. The specific surface area of microcrystalline cellulose decreases and the structure is densified remarkably during wet granulation. The interaction and bonding between water and microcrystalline cellulose in humid conditions, which leads to swelling of microcrystalline cellulose, would appear to be different in the case of tablets compressed from granules when compared to tablets compressed from powder. However, according to moisture contents and total pore volume results of tablets, granulated mass adsorbs water and swells to the same extent after storage in humid conditions as does the powder in tablets. The water is thus evidently not adsorbed only to the outer surface of the granulated mass. Chatrath (1992) has also observed that microcrystalline cellulose granules adsorb water similarly to powder. According to her, hydrogen bonds formed into the granules during wet granulation break during adsorption of water into the granules. This theory appears to be correct according to this work.

Water did not decrease the volume of the smallest pores of mannitol tablets. However, volume of the smallest pores of microcrystalline cellulose granule tablets compressed with the highest compression pressure (196 MPa) increased with increasing moisture, as did that of the granules. Volume of the smallest pores of granule tablets compressed with lower compression pressures remained unchanged. Structure of hard microcrystalline cellulose granules is deformed when compressed with the highest compression pressure (196 MPa), which explains the result. Water molecules probably move in the structure of these granule tablets in front of the mercury that is intruding into the sample. Water can also cause some compression of these samples during a mercury porosimetry run. The median pore size of the tablets compressed from granules increased and the maximum of pore size distribution changed towards larger pores with increasing moisture (pore diameter range 50 – 2000 nm for mannitol tablets and 500 – 2000 nm for microcrystalline cellulose tablets), similarly to

the tablets manufactured by direct compression. Although microcrystalline cellulose swells with increasing moisture, this trend is not related to the swelling, but to the settlement of the water molecules into the structure of tablets, to the maximum of the pore size range.

5.2 Effect of scanning speed on the result of mercury porosimetry analysis

5.2.1 Powder samples (I)

The effect of scanning speed on the pore structure of mannitol powder could not be determined. Mannitol adhered to the walls of the sample cell, and came out of the sample cell during filling with mercury. Scanning speed had no effect on the result of microcrystalline cellulose powder in low-pressure porosimetry analysis. Scanning speeds used in low-pressure analysis are low, and the differences between possible scanning speeds are small, which explains why no differences in low-pressure analysis were found.

Scanning speed had no effect on the total pore volume of microcrystalline cellulose powder in high-pressure mercury porosimetry. However, according to volume pore size distributions, the volume of the smallest pores of microcrystalline cellulose powder decreased with increasing scanning speed. This was shown also as decreased total pore surface area and increased mean pore size values with increasing scanning speed. According to the result, small pores of the powder were not accurately detected with fast scanning. Apparently, mercury does not have enough time to intrude into the smallest pores with fast scanning. Moscou and Lub (1981) have suggested a similar explanation. In the study of Hearn and Hooton (1992) on cement samples, likewise, scanning speed had no effect on total pore volume, but did have an effect on volume pore size distributions. The effect of mercury porosimetry scanning speed on the result of pharmaceutical samples has not been reported previously.

5.2.2 Granule samples (I)

Scanning speed did not affect porosity values of mannitol or microcrystalline cellulose granules in low-pressure porosimetry analysis. In high-pressure porosimetry, scanning speed did not affect the total pore volume of mannitol or microcrystalline cellulose granules. Total pore surface area values were greatest and the mean pore size values smallest with the lowest scanning speed. Thus, the smallest pores of the granules were determined more accurately with the slowest scanning speed, which was evident also in the volume pore size distributions. No clear effect on the median pore size was observed, because this parameter emphasizes differences in the larger pore diameter range. The suggestion by Moscou and Lub (1981) that mercury may not have enough time to intrude into the pores is in accordance with the result of this study. Also, the result of Hearn and Hooton (1992), that scanning speed does not affect total pore volume values but volume pore size distributions, is consistent with the result of granules.

5.2.3 Tablets (IV, V)

5.2.3.1 Tablets manufactured by direct compression

Scanning speed did not affect the total pore volume values of mannitol or microcrystalline cellulose tablets manufactured by direct compression. However, the smallest mean pore size was observed with the slowest scanning speed, which was evident also in the volume pore size distribution curves as the greatest volume of the smallest pores. Thus, with the fastest scanning the volume of the smallest pores is lowest because of the lack of time for the mercury to intrude into the pores properly.

The maximum of the volume pore size distribution of mannitol powder tablets (pore diameter 1000 nm) and microcrystalline cellulose powder tablets shifted towards smaller pore sizes (pore size range 100 – 1000 nm) with increasing scanning speed. The median pore size, which emphasizes changes at this large pore size range, was unaffected for mannitol tablets, whereas the median pore size of microcrystalline cellulose tablets decreased with increasing scanning speed. This result is consistent with the shift of maximum of pore size distribution towards smaller pore sizes. The result is related to the structure of tablets, because it was not observed in the measurements of powders or granules. This is probably because with higher scanning speeds mercury does not have time to intrude into the pores of this size range at the right time. Intrusion takes place later and the intruded mercury is detected at the smaller pore size range. The pore structure of direct compressed tablets is more rigid than 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.

5.2.3.2 Tablets compressed from granules

The total pore volumes of mannitol and microcrystalline cellulose tablets compressed from granules were unaffected by scanning speed. The mean pore size of tablets compressed from mannitol and microcrystalline cellulose granules with the smallest compression pressure was smallest with the slowest scanning speed. Thus, the smallest pores of granule tablets are also determined more accurately with slow scanning. This result can be observed also from the volume pore size distributions. However, the mean pore size of microcrystalline cellulose tablets compressed from granules with the two highest compression pressures (122 and 196 MPa) was unaffected by the scanning speed.

Surprisingly, in contrast with the result of mannitol tablets manufactured by direct compression, the median pore size of mannitol granule tablets increased with increasing scanning speed. The median pore size values of granule tablets are lower than those of powder tablets. This denser structure together with the more complex pore structure of granule tablets are the reasons why the effect of scanning speed is different in granule tablets. However, the shift of determined pore size was so small that it was not observed in the volume pore size distributions. In contrast to the result of mannitol granule tablets, the median pore size of microcrystalline cellulose granule tablets decreased with increasing

scanning speed. Similarly to tablets manufactured with direct compression, the maximum in the pore size range 100 – 1000 nm changed towards smaller pores with increasing scanning speed. The pore structure of granule tablets is more complicated than that of powder tablets, and thus the effect of scanning speed is not similar. Based on these results, no clear conclusions can be drawn on the effect of scanning speed on the pore structure of tablets compressed from granules.

5.3 Effect of wet granulation and tableting on the pore structure of mannitol and microcrystalline cellulose

5.3.1 Mannitol (II)

5.3.1.1 Wet granulation

Pores in mannitol powder i.e. voids between particles, were determined with high-pressure porosimetry in the diameter range 1 – 5 μm. The volume of these pores decreased markedly during wet granulation, and new intragranular pores were formed in the diameter range 40 – 300 nm. This was observed with both high-pressure porosimetry and nitrogen adsorption. These intragranular pores were formed when powder particles were dissolved during granulation and recrystallised on the larger particles (Juppo 1995). According to Juppo (1995), small particles also attach to each other by solid bridges formed by recrystallised mannitol or by binder. According to mercury porosimetry and nitrogen adsorption, granules were more porous than powder.

5.3.1.2 Pore structure of tablets after direct compression

Densification of the powder mass with increasing compression pressure was detected in the pore diameter range from 7 nm to 14 μm from the total pore volume and pore size values obtained by mercury porosimetry. From the volume pore size distribution curves of powder and tablets compressed from powder measured with mercury porosimetry, densification was observed in the pore diameter range from 200 to 2000 nm (Fig. 9(A)). These pores are the voids between powder particles. The largest pores disappeared first, pore size decreased, and the maximum of the distribution moved towards the smaller pores indicating plastic deformation. However, a new pore population in the pore size range from 20 to 50 nm was created in tablets compressed with the highest compression pressure (196 MPa) due to the fragmentation of powder (Fig. 9(A)). Fragmentation increased the number of small particles, contributing to the appearance of a new group of pores (Vromans et al. 1985). This new pore population was related to increased breaking force of the tablets, which was almost similar for tablets compressed at the two lowest compression pressures, 72 and 122 MPa. When the number of pores larger than 500 nm decreases and the number of pores smaller than 200 nm increases, breaking force of tablets increases (Juppo 1996c).

With nitrogen adsorption, the pore volume of mannitol powder in the pore diameter range from 3 to 200 nm increased when compressed, indicating formation of new pores in the pore size range measured. Size of the voids between powder particles decreased, and these voids were determined at the detection range of nitrogen adsorption. No difference in pore volume of tablets compressed from powder with different compression pressures was observed. The pore size distribution obtained by nitrogen adsorption had only one maximum for tablets compressed at the two lowest pressures (72 and 122 MPa). Bimodal distribution was created after compression at the highest pressure, 196 MPa, indicating fragmentation of powder particles. The specific surface area of tablets determined with

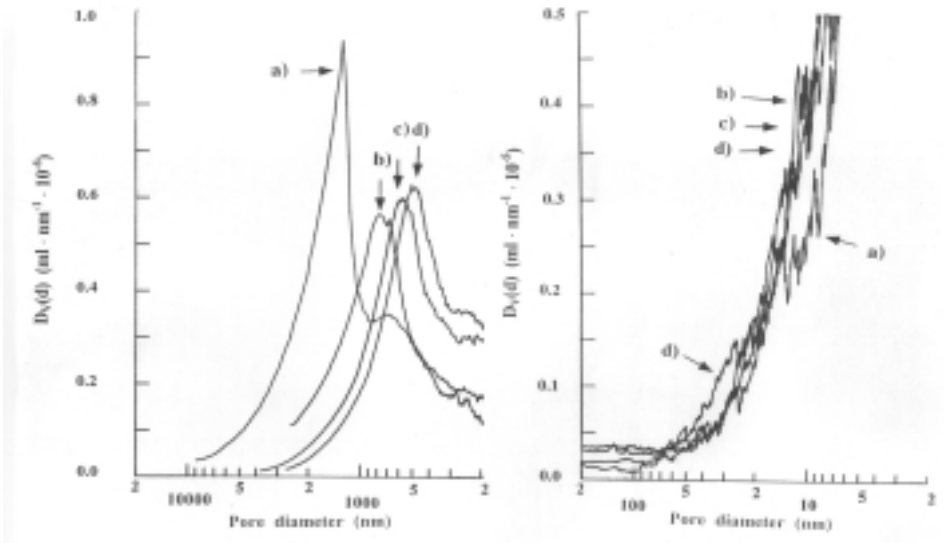
nitrogen adsorption increased with increasing compression pressure, also indicating slight fragmentation of mannitol at this pore size range (3 – 200 nm).

5.3.1.3 Pore structure of tablets after compression from granulated mass

Deformation of granules is observed from the total pore volume, mean and median pore size and the volume pore size distributions of granule tablets determined with mercury porosimetry; the largest pores of tablets disappeared with increasing compression pressure due to fragmentation of granules (Fig. 9(B)). Juppo (1996b) has reported fragmentation of granules with increasing compression pressure when measured with mercury porosimetry. In the present work, pores of mannitol granules were unaffected by the lowest compression pressure. When higher compression pressures were used, deformation shifted the maximum of pore size distribution to smaller values. Due to the fragmentation of granules, more small pores (diameter less than 20 nm) were created in the tablets compressed with the two highest compression forces, 122 and 196 MPa (Fig. 9(B)). The broad size distribution of mannitol granules is still detectable in tablets. Selkirk and Ganderton (1970) have shown that granules have caused a wider pore size distribution for tablets than powder, which is consistent with the result of mannitol tablets in this study.

The volume pore size distribution of granule tablets measured with nitrogen adsorption is bimodal, one maximum showing pores of the granules in the pore size range from 50 to100 nm. The volume of these intragranular pores is highest in the tablets compressed at the smallest compression pressure (72 MPa). Due to densification, the volume of these pores decreases with increasing compression pressure. The volume of the smallest detectable pores (diameter < 7 nm) increases with increasing compression pressure, probably due to fragmentation. Specific surface area of granule tablets decreased with increasing compression pressure due to plastic deformation of the mass at this pore size range (3 – 200 nm). Thus, plastic deformation and fragmentation of mannitol granules were observed with nitrogen adsorption.

(A)



(B)

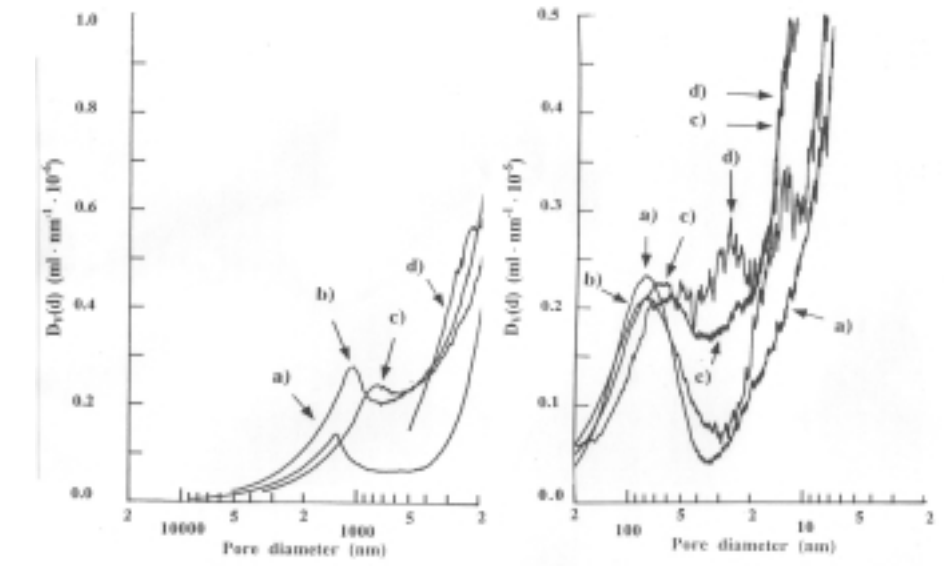


Fig. 9. Volume pore size distributions determined with mercury porosimetry (A) a) mannitol powder and mannitol powder tablets compressed with b) 72 MPa c) 122 MPa and d) 196 MPa. (B) a) mannitol granules and mannitol granule tablets compressed with b) 72 MPa, c) 122 MPa and d) 196 MPa[3].

[3] Reprinted from European Journal of Pharmaceutics and Biopharmaceutics, 46, Westermarck et al., Pore structure and surface area of mannitol powder, granules and tablets determined with mercury porosimetry and nitrogen adsorption, p. 66, copyright (1998), Elsevier Science.

5.3.1.4 Comparison of direct compression and compression of granules

The breaking forces of the granule tablets were markedly higher than those of powder tablets, indicating that wet granulation improves the compactibility of mannitol. During compression, greater densification of the granules was observed at the detection range of high-pressure porosimetry (i.e. pore diameter 7 nm – 14 μm) when compared to the densification of the powder mass. Good compressibility and strong tablets compressed from mannitol granules has been reported by Juppo et al. (1995). Larger specific surface area values of granules and of tablets compressed from granules, obtained with mercury porosimetry and nitrogen adsorption, than of powder and of tablets manufactured by direct compression also indicate a more porous structure and deformation of granules during compression. Under compression, large porous granules are deformed more than is needle-shaped mannitol powder. Mannitol powder deforms more plastically (Roberts & Rowe 1985), and mannitol granules by fragmentation and plastic deformation (Juppo et al. 1995). Plastic deformation of mannitol powder was observed from the porosity parameters obtained with mercury porosimetry. However, some fragmentation of also mannitol powder takes place, as observed from the volume pore size distributions obtained with mercury porosimetry and nitrogen adsorption, and from the specific surface area results determined with nitrogen adsorption. Fragmentation of granules was observed from the volume pore size distributions obtained with both methods.

The specific surface areas obtained with nitrogen adsorption and the porosity parameters determined with mercury porosimetry show plastic deformation of mannitol granules. According to Krycer et al. (1982), the crushing strength of tablets compressed from mannitol powder or granules increases with increasing porosity of raw material. The porosity percentages and total pore volumes of granule tablets decrease more under compression due to greater deformation than those of powder tablets, when tablets compressed with 72 MPa and 196 MPa are compared. In general, tablets compressed from granules have higher strength when compared to those compressed from powder. Consistent with the result of mannitol in this study, strength is related to the large area available for bond formation and to the material undergoing fragmentation (Nyström et al. 1993).

5.3.2 Microcrystalline cellulose (III)

5.3.2.1 Wet granulation

The structure of microcrystalline cellulose was densified in wet granulation. Slight densification of the powder mass after wet granulation was observed from the volume pore size distribution obtained with mercury porosimetry. New pores were not formed, which generally takes place during granulation. Millili (1990) has explained densification during pelletisation by autohesion, which is not related to hydrogen bonding. According to Kleinebudde (1997), hydrogen bonds are formed between crystallites or their agglomerates during pelletisation and drying (crystallite gel model). However, wet granulation and pelletisation are not directly comparable processes, and microcrystalline cellulose behaves differently during these two processes. Chatrath (1992) has explained her theory of

increased hydrogen bonding in wet granulation by a similar ability of microcrystalline cellulose powder and granules to adsorb water vapor. In her study, intraparticular bonds in granules were more disrupted during water vapor adsorption than those in microcrystalline cellulose powder, which explains the hydrogen bonding theory. Similarly in our study, water vapor adsorption in powder and granules was equal, and thus densification in wet granulation is related to hydrogen bonding. Buckton et al. (1999) have observed the increased intraparticular hydrogen bonding of microcrystalline cellulose after wet granulation with near IR technique. Densification of microcrystalline cellulose in wet granulation according to this work takes place at the determination range of nitrogen adsorption, in the pore diameter range from 3 to 200 nm.

The structure of the granules was so dense and the volume of the pores so small that the pore volume or the volume pore size distribution could not be determined with the Coulter SA 3100 nitrogen adsorption method. However, the specific surface area of microcrystalline cellulose obtained with nitrogen adsorption decreased markedly after wet granulation, indicating densification of the mass. A similar result has been obtained by Chatrath (1992).

5.3.2.2 Pore structure of tablets after direct compression

Deformation of powder and decrease in the size of the voids between powder particles after compression was observed from the volume pore size distribution obtained with mercury porosimetry (Fig. 10(A)). The maximum in the pore diameter range from 200 to 2000 nm shifted towards smaller pores, and the volume of pores smaller than 40 nm decreased. Consistent with this study, Vromans et al. (1985) have reported that the volume pore size distribution of tablets compressed from microcrystalline cellulose powder shifted to smaller pore diameters with increasing compression force. In this study, with increasing compression pressure, the total pore volume and mean and median pore size values decreased, indicating densification of the mass. In a study by Sixmith (1977), the modal pore radius of microcrystalline cellulose tablets compressed from powder decreased with increasing compression pressure. According to the volume pore size distribution obtained with mercury porosimetry in this study, microcrystalline cellulose deforms plastically, and no evidence of fragmentation was found. Microcrystalline cellulose is known as a material that deforms plastically (Lamberson & Raynor 1976, David & Augsburger 1977, Schangraw et al. 1981, Staniforth et al. 1988). Hydrogen bonding and mechanical interlocking of irregular particles together with a large particle surface area and filamentous structure of microcrystalline cellulose lead to good compressibility of powder (Bolhuis & Lerk 1973). In this study, the total pore surface area of powder determined with mercury porosimetry decreased when compressed. However, the total pore surface area of tablets does not change with increasing compression pressure.

Unexpectedly, the total pore volume of powder determined with nitrogen adsorption in the pore diameter range from 3 to 200 nm was greater when compressed with 122 MPa and 196 MPa when compared to values of powder and powder tablets compressed with 72 MPa. Sixmith (1977) has reported an increased surface area of Avicel® tablets when compression pressure exceeded 125 MPa. According to volume pore size distributions of

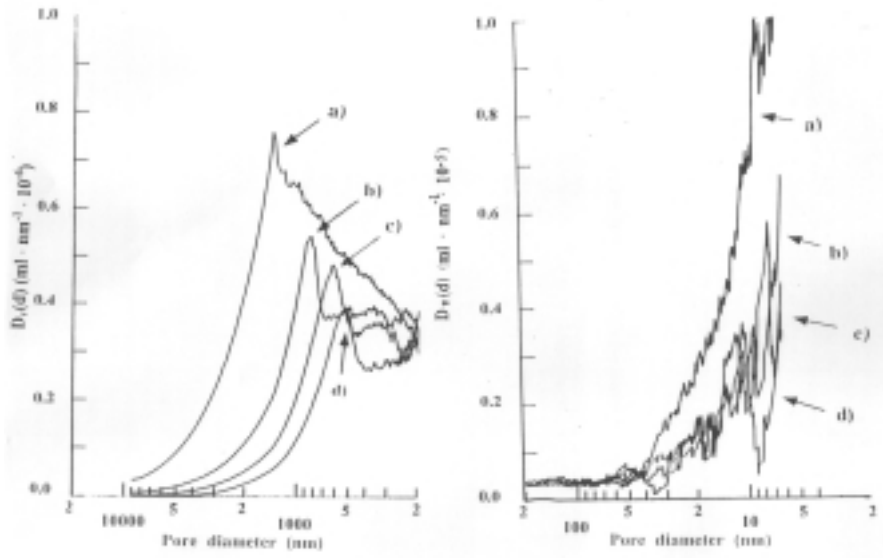
tablets obtained with nitrogen adsorption, the volume of the pores decreased with increasing compression pressure, indicating plastic deformation of microcrystalline cellulose in this pore size range. The pore volume is determined in the adsorption phase, while the volume pore size distribution is measured from the desorption phase. The reason for the pore volume result may be the opening up of closed pores of microcrystalline cellulose in compression (Sixmith 1977). The specific surface area of powder tablets measured with nitrogen adsorption decreased with increasing compression pressure due to the plastic deformation of microcrystalline cellulose in compression.

5.3.2.3 Pore structure of tablets after compression from granulated mass

Deformation of granules was observed from the volume pore size distribution curves in the pore diameter range from 500 to 2000 nm as a shift of maximum towards smaller pores (Fig. 10(B)). The decrease in the volume of pores < 50 nm in diameter is clearly observed when pore volumes of granule tablets compressed with 72 and 122 MPa are compared with those of tablets compressed with 196 MPa. Therefore, the mean pore size increased and total pore surface area decreased between compression pressures 122 and 196 MPa. This change is in agreement with the increased breaking force values of granule tablets when compression pressure exceeds 122 MPa. Johansson et al. (1998), similarly, reported an increase in tensile strength of microcrystalline cellulose tablets compressed from pellets when compression pressure reached as high as 160 MPa. According to Staniforth et al. (1988), most of the compression force was used to break up the primary granule structure of microcrystalline cellulose. Schwartz et al. (1994) have observed some fracture and plastic deformation of microcrystalline cellulose pellets during compression. According to Maganti and Celik (1993), the bonding of microcrystalline cellulose decreased in pelletisation due to changes in shape and size and the reduction of bonding sites after pelletisation. They reported elastic deformation and brittle fragmentation of microcrystalline cellulose pellets in compression. Deformation, densification and only limited fragmentation of microcrystalline cellulose pellets has occurred in compression (Johansson et al. 1995, Johansson & Alderborn 1996, Johansson et al. 1998).

The specific surface area of granule tablets decreased with increasing compression pressure when determined with nitrogen adsorption (pore diameter range 3 – 200 nm). However, an increase was observed in specific surface area when granules were compressed with 72 MPa due to fragmentation. Unfortunately, the structure of the granules was so dense and thus the volume of the pores so small that other porosity parameters could not be determined with the Coulter SA 3100 nitrogen adsorption method.

(A)



(B)

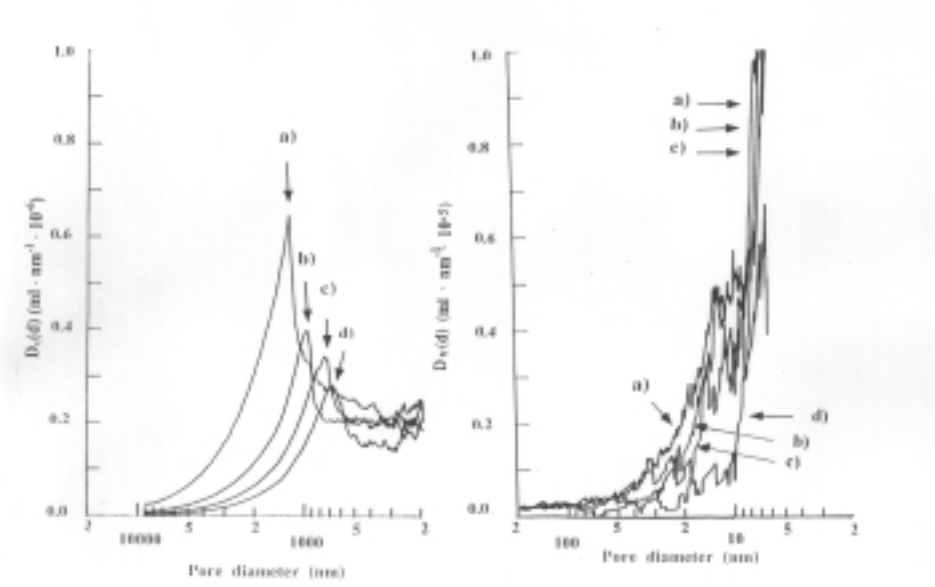


Fig. 10. Volume pore size distributions determined with mercury porosimetry (A) a) microcrystalline cellulose powder and microcrystalline cellulose powder tablets compressed with b) 72 MPa c) 122 MPa and d) 196 MPa. (B) a) microcrystalline cellulose granules and microcrystalline cellulose granule tablets compressed with b) 72 MPa, c) 122 MPa and d) 196 MPa[4].

[4] Reprinted from European Journal of Pharmaceutics and Biopharmaceutics, 48, Westermarck et al. Microcrystalline cellulose and its microstructure in pharmaceutical processing, p. 204, copyright (1999), Elsevier Science.

5.3.2.4 Comparison of direct compression and compression of granules

The breaking forces of microcrystalline cellulose tablets compressed from granules were markedly lower than those of the tablets compressed from powder. Similarly, Staniforth et al. (1988) observed greater strength of interparticle bonding for powder samples of microcrystalline cellulose than for granulated mass. In this study, the porosity percent of powder decreased more when compressed than that of granules. This indicates greater densification of microcrystalline cellulose powder in compression. Thus, the compressibility of microcrystalline cellulose decreased in wet granulation. This result is consistent with the result of the study of Staniforth et al. (1988). Microcrystalline cellulose powder deforms plastically (Lamberson & Raynor 1976, David & Augsburger 1977, Shangraw et al. 1981, Staniforth et al. 1988), whereas deformation in combination with densification and only limited fragmentation of pellets manufactured from microcrystalline cellulose has been observed (Johansson et al. 1995, Johansson & Alderborn 1996, Johansson et al. 1998). Plastic deformation of microcrystalline cellulose powder is clear from the results obtained in this study with mercury porosimetry and nitrogen adsorption. For powder, no evidence of fragmentation was observed. The structure of granules was deformed when compression pressure reached 196 MPa, because the breaking force of tablets increased remarkably between the compression pressures of 122 and 196 MPa. Due to deformation, the volume of the pores < 50 nm in diameter decreases between the compression pressures of 122 and 196 MPa. Similarly to the result of this work, Johansson et al. (1998) have reported increased tensile strength of tablets compressed from microcrystalline cellulose pellets when compression pressure reached 160 MPa. However, in the present work, densification of granules was observed in the detection range of nitrogen adsorption (pore diameter range 3 – 200 nm) as decreasing specific surface area values with increasing compression pressure. In this study, decreased compactibility of microcrystalline cellulose after wet granulation was related to the smaller specific surface area values of granules when compared to those of powder.

5.4 Comparison of mercury porosimetry and nitrogen adsorption methods in determination of pore structure

Webb and Orr (1997) have suggested that pore structures obtained with mercury porosimetry and nitrogen adsorption are comparable only if the pore size range from 3 to 300 nm is compared. In this work, volume pore size distributions are compared in the overlapping pore size range (i.e. diameter range from 7 nm to 200 nm). However, the total pore volume, surface area and volume pore size distributions obtained with these methods are compared as they are obtained with these methods without applying corrections. One aim of this work was to study how to use mercury porosimetry and nitrogen adsorption in an effective and correct way in the analyses of pharmaceutical samples. In the pharmaceutical industry, the use of these methods is easier if the results can be evaluated as they are determined. That is why corrections were not applied to the results. Volume pore size distributions were determined with mercury porosimetry from the intrusion phase and with gas adsorption from the desorption phase, because the obtained distributions describe the pore structure similarly (Conner et al. 1986).

5.4.1 Powders (II, III)

Due to different measurement ranges, nitrogen adsorption gave markedly smaller total pore volume values for mannitol and microcrystalline cellulose powders than did mercury porosimetry. According to Webb and Orr (1997), the pore volume measured with mercury porosimetry is larger than the one determined with nitrogen adsorption if the sample contains pores larger than 300 nm. Pharmaceutical powders tend to have low porosity in the detection range of nitrogen adsorption. Mercury porosimetry determines also the voids between the particles, which affect the determined volume more than does the internal porosity of the particles. Milburn et al. (1991) have obtained similar pore volume values for silica samples with these methods. Pores of the silica samples, however, were markedly smaller and the structure of silica more porous than those of mannitol and microcrystalline cellulose powders. Thus, the pores were determined mainly in the detection range of nitrogen adsorption. Stanley-Wood (1978) and Conner et al. (1986) have obtained almost the same pore size distributions for magnesium trisilicate and for Degussa aerosols with these techniques. However, non-similar pore size distributions have been obtained for silicas, iron oxide-chromium oxide catalyst, aerosil powder and chrysotile powder (Brown & Lard 1974, DeWit & Scholten 1975). Moscou and Lub (1981) and Johnston et al. (1990) have reported damage or compression of highly porous silica and aluminium samples during mercury porosimetry. In this study, pores in the mannitol and microcrystalline cellulose powders were detected in the same pore size range with both methods in the overlapping pore size area, which indicates that no compression of the samples takes place during mercury porosimetry. Although the pore size distributions had a similar shape, the intensities of the curves were different.

5.4.2 Granules (II)

Total pore volume of mannitol granules determined with mercury porosimetry was markedly larger than that obtained with nitrogen adsorption, as it was for mannitol and

microcrystalline cellulose powder. The structure of microcrystalline cellulose granules was so dense, unfortunately, that the pore structure could not be determined with Coulter SA 3100 nitrogen adsorption method. The volume of the pores was so small that it was out of the detection range of the method. However, pores in the mannitol granules were detected in the same pore size range with both methods. The intensities of the curves were different for the two methods, as they were for powders. The structure of the mannitol granules was not destroyed or compressed during mercury porosimetry.

5.4.3 Tablets (II, III)

The total pore volumes of mannitol and microcrystalline cellulose tablets determined with mercury porosimetry were markedly higher than those measured with nitrogen adsorption, as they were for mannitol powder and granules and microcrystalline cellulose powder. Mercury porosimetry determines larger pores that are not within the detection range of nitrogen adsorption and which have more effect on the total volume.

The volume pore size distributions of mannitol tablets measured with nitrogen adsorption and mercury porosimetry had the same shape in the overlapping pore size region, although the scales of the curves differed from each other. Damage or compression of highly porous particles such as silica and alumina samples has been reported (Moscou & Lub 1981, Johnston et al. 1990). Judged by the consistent pore size distributions obtained with both nitrogen adsorption and mercury porosimetry, no compression or damage of the mannitol tablets took place during mercury porosimetry analysis. However, the volume pore size distributions of microcrystalline cellulose tablets compressed from powder were not equal in the overlapping pore size range when determined with these methods. The microstructure of a microcrystalline cellulose tablet may be deformed in analysis. According to Webb & Orr (1997), compression of the samples in mercury porosimetry can be observed as a large volume of medium-sized or small pores. In this work, maximum of the pore size distribution determined with mercury porosimetry was in the smallest detectable pore size range (i.e. diameter < 10 nm). At this pore size range, no maximum was detected in distribution obtained with nitrogen adsorption. Faroongsarng and Peck (1994) have reported consistent pore size distributions of dicalcium phosphate dihydrate tablets obtained by nitrogen adsorption and mercury porosimetry in the overlapping pore size range. Also, Stanley-Wood (1978) has reported almost similar pore size distributions for magnesium trisilicate and Conner et al. (1986) for Degussa aerosols when determined with these techniques. However, similarly to the present result with microcrystalline cellulose tablets, Brown and Lard (1974) and De Wit and Scholten (1975) obtained non-similar pore size distributions for silicas, iron oxide-chromium oxide catalyst, aerosil powder and chrysotile powder. Differences were explained with 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. In our study, however, microcrystalline cellulose tablets remained whole after porosimetry measurement.

5.4.4 Surface area results (II, III)

The surface area values of mannitol and microcrystalline cellulose powder, granules and tablets obtained with mercury porosimetry are markedly higher than those measured with nitrogen adsorption. This is because mercury porosimetry determines larger pores than nitrogen adsorption, and further because of the complex pore structure of the samples, ink-bottle shaped pores and low porosity of pharmaceutical samples. Surface area in mercury porosimetry is calculated from the volume intruded in pore diameter intervals, assuming cylindrical pores with a round pore opening. Ink-bottle pores tend to increase surface area values calculated from mercury porosimetry data, because the volume of pores with a small neck can be remarkable. Dees and Polderman (1981) have reported higher surface area values with mercury porosimetry than with nitrogen adsorption for lactose tablets. They concluded that nitrogen adsorption results were more accurate. A similar result has been obtained also with silica samples (Milburn et al. 1991). In contrast, Mikijelj and Varela (1991) have found the pore surface areas of magnesium oxide and diatomite compacts measured with these methods to be equivalent. In their study, the highest pressure in mercury porosimetry was 103 MPa, and the diameter of the smallest detectable pores 14 nm. Surface area values of the samples were 2 - 50 m^2/g, indicating that the pores were very small. Thus, the pores were probably mainly in the detection range of nitrogen adsorption. Adkins and Davis (1988) have made the surface area values of alumina and zirkonia comparable by correcting the contact angle used in mercury porosimetry. In their study, surface areas of the samples were from 46 to 130 m^2/g. With higher surface areas, results were no longer comparable. According to Milburn and Davis (1993), the correlation between surface areas obtained with these methods in samples of very low surface areas is poor. In the present study on pharmaceutical samples, no corrections were made to these parameters, and nitrogen adsorption was more capable of detecting changes in the tablet surface area caused by tableting.

6 Conclusions

The conclusions drawn from this study are:

1. Water-induced swelling affected the mercury porosimetry analysis of microcrystalline cellulose powder and granules. Water in the sample increased the volume of the smallest pores of both mannitol and microcrystalline cellulose granules in high-pressure porosimetry. This increase is related to the complicated structure of the granulated mass.

Swelling increased the total pore volume values of microcrystalline cellulose tablets. Due to swelling and adsorbed water, the volume of the smallest pores of microcrystalline cellulose powder tablets decreased when stored in humid conditions. In contrast, the volume of the smallest pores of microcrystalline cellulose granule tablets compressed with the highest compression pressure, where the structure of granules is deformed in compression, increased with increasing moisture. Water molecules settle to the pore diameter range from 50 to 2000 nm in mannitol tablets and to the pore diameter range from 500 to 2000 nm in microcrystalline cellulose tablets. The maximum of the volume pore size distribution of mannitol and microcrystalline cellulose tablets in this pore size range changed towards larger pores with increasing moisture.

Pretreatment affects even the mercury porosimetry results of non-hygroscopic mannitol. However, pretreatment has a more significant effect on hygroscopic microcrystalline cellulose. Pretreatment has different effects on the result of samples with different physical structures i.e. powders, granules and tablets. Measurement of water content together with proper drying of the samples before the mercury porosimetry measurement is recommended.

2. Scanning speed did not affect the result of low-pressure mercury porosimetry analysis. Thus, low-pressure porosimetry measurements can be done with fast scanning.

Scanning speed did not affect the total pore volume results of the samples in high-pressure mercury porosimetry. If only the total pore volume is of interest, fast scanning can be used. Clear differences in porosity values due to different scanning speeds were observed in the total pore surface area, mean and median pore diameter and volume pore size distribution results. Therefore, all porosity parameters obtained should be interpreted when analysing the results. In high-pressure porosimetry analysis, the smallest pores (diameter < 20 nm) of the samples could not be detected accurately with fast scanning. Mercury does not have enough time to intrude into the smallest pores with fast scanning. In tablet samples, the scanning speed affects the pore structure results in a wide pore size range.

Because of the different kinds of effects that scanning speed has on determinations of samples with different physical structures, scanning should be done slowly in high-pressure mercury porosimetry measurements.

3. New intragranular pores were formed into mannitol in wet granulation. Greater surface area, more porous structure and greater number of small pores in granules, when compared to powder, increased the compactibility of mannitol after wet granulation. Plastic deformation and fragmentation of mannitol powder in the detection range of high-pressure mercury porosimetry (pore diameter range 7 nm – 14 μm) and fragmentation of mannitol powder particles in the detection range of nitrogen adsorption (pore diameter range 3 – 200 nm) were observed. Plastic deformation and fragmentation of mannitol granules was detected with both methods.

Densification of microcrystalline cellulose took place in wet granulation in the detection range of nitrogen adsorption. This densification lead to decreased compactibility of microcrystalline cellulose granules when compared to powder. According to mercury porosimetry and nitrogen adsorption, microcrystalline cellulose powder deforms plastically under compression. The structure of hard microcrystalline cellulose granules was deformed when compression pressure reached as high as 196 MPa. Volume pore size distribution is a very useful parameter, because it brings out the pore size range where the changes due to processing take place.

4. The pore structure results obtained with mercury porosimetry best describe the behaviour of powder and granule particles and voids between them in granulation or under compression, whereas nitrogen adsorption brings out the changes in intraparticular structure of particles and granules. Due to the low porosity of pharmaceutical samples, wider pore size range and larger pores determined with mercury porosimetry, the total pore volume and surface area values obtained with mercury porosimetry are larger than those determined with nitrogen adsorption. In spite of the differences between the methods, with mannitol samples the volume pore size distribution curves of the samples in the overlapping pore size range have the same shape. However, probably due to compression of the samples during mercury porosimetry analysis, volume pore size distributions of microcrystalline cellulose tablets determined with these methods are not strictly comparable. The specific surface area of tablets determined with nitrogen adsorption described well the deformation of materials under compression. The low porosity of the samples does not limit the use of mercury porosimetry. The results obtained with these methods together can be used in the characterisation of the behaviour of materials in granulation and tableting.

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