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Crystallinity and Physical Characteristics of Microcrystalline Cellulose. II.[1] Fine Structure of Ground Microcrystalline Cellulose

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Nitrogen gas adsorption isotherms are obtained on intact, 8 and 32 hours ground microcrystalline cellulose. Before the determination of adsorption isotherms, each specimen is dispersed into water, then the water is changed to ethanol, ethanol to *n*-pentane, and the *n*-pentane is evaporated *in vacuo*. Specific surface area is determined from the nitrogen gas adsorption method as 79, 153 and 250 m^2/g for each sample, using B.E.T. equation. This result shows that the effective surface available to water molecules is equivalent to that available to nitrogen molecules.

Pore size distribution was determined from both nitrogen gas desorption isotherms and X-ray small angle scattering. Significant change in pore size distribution by grinding is not observed. The effective surface area of microcrystalline cellulose is composed of pores which range in diameter is up to 300 Å, and relatively small pores, up to 100 Å, play an important role.

Recrystallization of amorphous cellulose is observed to be caused by the solvent displacement, to the same crystal form as cellulose II. The possible relation of these observations to the fine structure of ground microcrystalline cellulose is discussed.

Keywords——microcrystalline cellulose; crystallinity; fine structure; surface area; pore size distribution; recrystallization of cellulose; adsorption; X-ray small angle scattering

In recent years, microcrystalline cellulose has been used in various fields. In the pharmaceutical field, especially, it is known to be an excellent excipient for tablets formed by direct compression. There has been much discussion about the tablet strength and disintegrant properties obtained with microcrystalline cellulose in comparison with other excipients, such as lactose and potato starch.[3] However, there are only a few reports about cellulose structure which is responsible for the excellent compressibility and disintegrant properties of microcrystalline cellulose.[4]

In the previous paper,[1] the crystallinity of microcrystalline cellulose was determined as 63% by X-ray diffraction method and it was shown that the crystallinity decreased with increasing time of grinding. Also, specific surface area was measured by nitrogen gas and water vapor adsorption methods, and a significant difference was observed between the two values.

In the present investigation, in order to elucidate the reason for this difference in specific surface area obtained by the two methods, the microcrystalline cellulose samples were sequentially immersed in different polarity solvents (solvent displacement), and dried under reduced pressure. Then the specific surface area was measured by the nitrogen gas adsorption method. The fine structure of microcrystalline cellulose was also examined from the nitrogen gas de-

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[1] Part I: Y. Nakai, E. Fukuoka, S. Nakajima, and J. Hasegawa, *Chem. Pharm. Bull.* (Tokyo), **25**, 96 (1977).

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[4] K. Marshall and D. Sixsmith, *Drug Development Communications*, **1**, 51 (1974—1975).

sorption isotherm and X-ray small angle scattering. Moreover, from the X-ray diffraction pattern, it was observed that amorphous cellulose was recrystallized by the solvent displacement, so the degree of recrystallization was determined.

Experimental

1) **Materials**——Microcrystalline cellulose was Avicel PH-101 manufactured by Asahi Chemical Industrial Co., Ltd. Cellulose II was obtained by mercerization of microcrystalline cellulose. Thus, microcrystalline cellulose was immersed in 17.5% NaOH aqueous solution, thoroughly washed with distilled water, then dried in a desiccator containing P_2O_5.

2) **Grinding of Cellulose Samples**——The procedure previously described was used for grinding microcrystalline cellulose.[1] For grinding cellulose II, a stainless steel shaker mill was used. The volume of the mill was 38 ml, diameter of balls 11 mm, number of balls 17 and weight of sample 2 g.

3) **Procedure for the Solvent Displacement of Microcrystalline Cellulose**——In order to make the surface of microcrystalline cellulose available for nitrogen gas adsorption, solvent displacement was carried out as follows.[5] Cellulose samples were swollen and macerated in water; the mixture was shaken and centrifuged. After the supernatant was removed, an equal volume of absolute ethanol was added to the tube which was again shaken and centrifuged. The operation was repeated ten times. Changing the solvent from ethanol to *n*-pentane, the same operation was repeated a further ten times. The cellulose samples dispersed in *n*-pentane were finally dried *in vacuo* using a cold trap.

4) **Measurement of the Nitrogen Gas Adsorption Isotherm**——Nitrogen gas adsorption isotherms were determined using the low-temperature nitrogen adsorption apparatus previously described.[1]

5) **X-Ray Diffraction (Powder Method)**——A Rigakudenki D-3F instrument was used. Measuring conditions and methods of correction were as previously described.[1]

6) **X-Ray Small Angle Scattering**——Scatterings were recorded using a Rigakudenki X-ray small angle diffractometer 2202. The source of radiation used was a Rigakudenki D-3F. The copper radiation was Ni-filtered and detected by a Geiger-Muller counter. Scattering due to the apparatus and air was corrected by a measurement using only the sample holder. Measuring conditions were the same as those of the powder method previously reported,[1] except scanning speed was 1/15°/min. Width of first slit was 0.5 mm, second slit 0.3 mm and counter slit 0.1 mm respectively.

Results and Discussion

In the previous paper,[1] using B.E.T. equation,[6] specific surface area was determined by the nitrogen gas and water vapor adsorption methods for original microcrystalline cellulose and the ground samples. A 150 to 350 fold difference was observed between the values obtained from the two methods. Table I represents the specific surface areas of cellulose samples determined by various methods. About 1 m^2/g was obtained from the nitrogen gas adsorption method for all samples, and values of 149 and 350 m^2/g from the water vapor adsorption method for original and 32 hours ground samples respectively. Specific surface area and

TABLE I. Specific Surface Area of Various Microcrystalline Cellulose

Grinding time (hr)	Specific surface area, (m^2/g)		
	N_2 adsorption		H_2O adsorption
	Non-solvent displaced	Solvent displaced	Non-solvent displaced
0	1.0	79.4(70)[a]	149
2/3	1.2	—	161
8	—	153 (63)	278
32	1.0	250 (44)	350

a) The number in parentheses represents the *c*-value calculated.

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5) E.F. Thode, J.W. Swanson, and J.J. Bechen, *J. Phys. Chem.*, **62**, 1036 (1958).

6) S. Brunauer, H. Emett, and E. Teller, *J. Am. Chem. Soc.*, **60**, 309 (1938).

c-value calculated from the nitrogen gas adsorption isotherm for solvent displaced cellulose samples are shown in column 3 of Table I.

For the original microcrystalline cellulose, about an 80 fold increase in specific surface area is observed, in comparison with the non-solvent displaced figure of about 1 m^2/g previously obtained. This area is 53% of that determined by the water vapor adsorption isotherm. For ground samples, as a result of the solvent displacement, specific surface area calculated from the nitrogen gas adsorption isotherms approximated to the values which were obtained from the water vapor adsorption isotherms. These results show that the adsorption sites available for water vapor are also exposed to nitrogen gas by the solvent displacement.

The hydroxyl groups in cellulose chains form intra- and inter-molecular hydrogen bonds and are presumably also hydrogen bonded with water molecules.[7] It is assumed that a great number of hydrogen bonds would be disrupted by the solvent displacement. However, since not all of the hydrogen bonds would be disrupted, due to residual water in the solvent displaced samples and the surface tension of *n*-pentane, complete agreement is not obtained between the values of specific surface area calculated from water vapor adsorption isotherms and nitrogen gas adsorption isotherms after solvent displacement.

When the adsorbate brings about structural deformation of the adsorbent, the equation of adsorption of Rowen and Simha, based on Flory-Huggins' theory of solution,[8] must be considered instead of B.E.T. equation. But, in this case, as the effective surface area of microcrystalline cellulose is directly obtained by the nitrogen gas adsorption method, the surface area calculated from the water vapor adsorption isotherm is the intrinsic surface area, and it is not necessary to apply the Flory-Huggins dissolution mechanism to water vapor adsorption of microcrystalline cellulose.

Adsorption sites available to nitrogen molecules are usually concealed and lose the ability for adsorption, since the hydroxyl groups in cellulose chains form intermolecular hydrogen bonds. But the energy of the hydrogen bonding is so weak that the hydrogen bonds are easily disrupted by immersion in water, and then the adsorption sites are exposed by the solvent displacement, and a cellulose open structure is obtained. Thus, structural deformation of microcrystalline cellulose does not occur during the water vapor adsorption process, and the effective surface available to water molecules is equivalent to that available to nitrogen molecules. It seems reasonable to apply B.E.T. equation to water vapor adsorption isotherms and calculate specific surface area of cellulose samples.

Pore Size Distribution of Microcrystalline Cellulose

The Kelvin equation has frequently been applied directly to adsorption isotherms and the results obtained give a qualitative expression of pore structure. Cranston and Inkley assumed that, at any relative pressure, P/P_0, between 0 and 1, all pores with radii larger than some value r contained an adsorbed layer of thickness t on their walls, while all pores smaller than r were filled, owing to the joint effects of multilayer adsorption and capillary condensation.[9] This led to equation (1) for calculating the pore size distribution from the adsorption isotherm.

$$V_{12} = R_{12}[v_{12} - k_{12} \sum_{d_2+1/2\Delta d}^{d_{\max}} (d-2t_{12}) V_d \Delta d/d^2] \qquad (1)$$

where V_{12} is the volume of pores having radii between r_1 and r_2, Δd is an increment of pore diameter, $V_d \Delta d$ represents the volume of pores having diameter between $(d-\Delta d/2)$ and $(d+\Delta d/2)$, $d_{\max}$ is the diameter of the largest pore, v_{12} is the total volume of nitrogen adsorbed and R_{12}, k_{12} are constants determined individually.

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[7] *a*) A.G. Assaf, R.H. Haas, and C.B. Purves, *J. Am. Chem. Soc.*, **66**, 66 (1944); *b*) H.J. Marrinan and J. Mann, *J. Appl. Chem.*, **4**, 204 (1954).

[8] J.W. Rowen and R. Simha, *J. Phys. Colloid Chem.*, **53**, 921 (1949).

[9] R. Cranston and F. Inkley, *Adv. in Catalysis*, **9**, 143 (1957).

Using this equation, pore size distribution was determined on both unground and ground solvent displaced microcrystalline cellulose. Figure 1 shows adsorption and desorption isotherms of nitrogen gas on each cellulose sample. Figures 2 and 3 represent pore size distribution patterns which are calculated from the desorption branch of isotherms that is known to be in a thermodynamic equilibrium state.[10] The distribution patterns of both samples

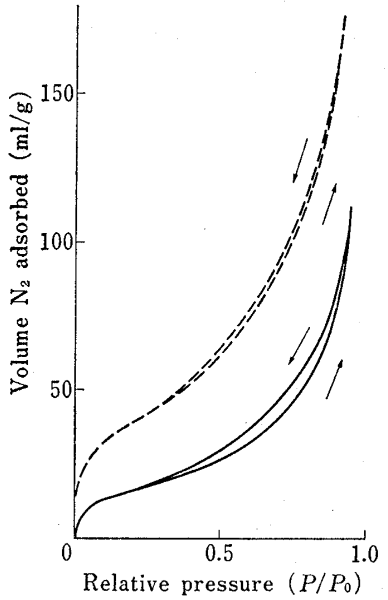

Fig. 1. Adsorption and Desorption Isotherms of Nitrogen Gas on Solvent Displaced Microcrystalline Cellulose

——, original microcrystalline cellulose.
-----, 32 hours ground microcrystalline cellulose.

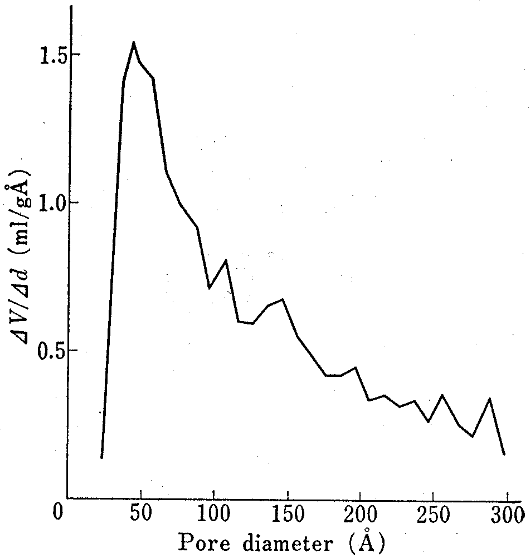

Fig. 2. Pore Size Distribution of Original Solvent Displaced Microcrystalline Cellulose Calculated from Cranston and Inkley Method[9]

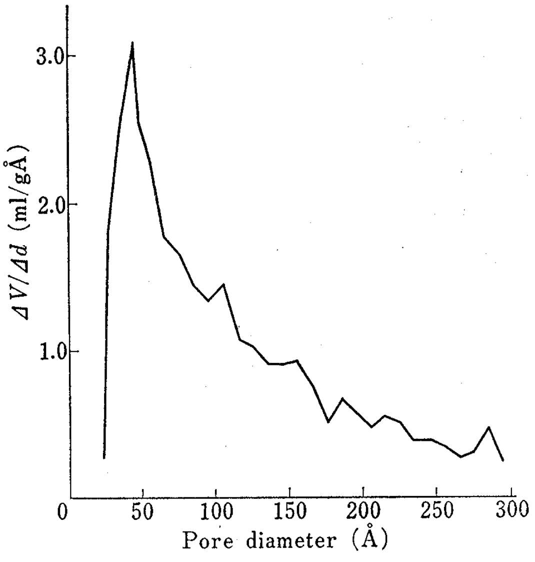

Fig. 3. Pore Size Distribution of Ground Solvent Displaced Microcrystalline Cellulose Calculated from Cranston and Inkley Method[9]

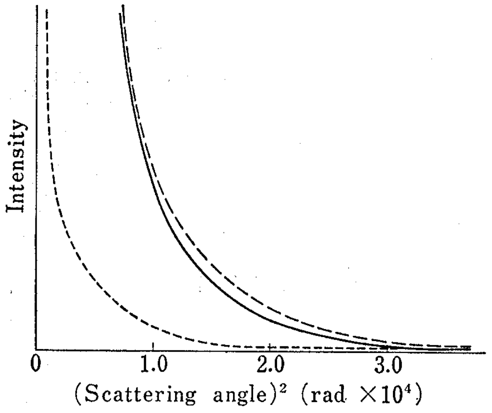

Fig. 4. X-Ray Small Angle Scattering of Various Microcrystalline Cellulose

------, original microcrystalline cellulose.
——, original solvent displaced microcrystalline cellulose.
-----, ground solvent displaced microcrystalline cellulose.

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[10] C. Orr and J.M. Dallavalle, "Fine Particle Measurement," The Macmillan Co., New York, 1959, p. 267.

show almost the same tendency and the pore volume of pores having a pore diameter of about 40 Å being especially large. Pore volumes are increased by grinding over the whole range of pore sizes calculated, especially the increase in the volume, about 40 Å diameter, is observed. Thus, the effective surface area of cellulose depends on pores whose diameter is less than 300 Å, and relatively small pores, up to 100 Å, play an especially important role. As the ratio of the specific surface area calculated from the B.E.T. equation and the cumulative surface area calculated by the Cranston and Inkley method is 1.1 for original microcrystalline cellulose, and 1.3 for ground one, pores are thought to have slightly ink-bottle like forms.

On the other hand, many analytical methods have been suggested for measurement of pore size distribution by X-ray small angle scattering, which is caused by difference of electron densities within the specimen.[11] Guinier reported that X-ray small angle scattering by spherical particles is given by the equation (2).[12]

$$I = c \exp\left[-\frac{r^2}{5}\left(\frac{2\pi R}{s\lambda}\right)^2\right] \tag{2}$$

where I is scattering intensity, s specimen-to-slit distance, r particle radius and R is radius of Debye ring. Thus a plot of log I and R^2 yields a curve, the slope of which establishes particle radius. However, when a polydispersed system is used, the curve is not straight but convex. So a tangent to the experimental curve is drawn at the greatest angle. The values corresponding to this tangent are subtracted from the original curve, and a new corrected curve is obtained. In a similar manner, the next tangent of minimum slope is drawn to the new curve, and this procedure is repeated. The volume fractions of particles of each of the radii are calculated using the slopes and intersepts of these lines.

Guinier plot of cellulose samples are presented in Fig. 4. These curves indicate the presence of a nonuniformity of electron densities having about 20—200 Å radii. Comparing X-ray small angle scattering of original microcrystalline cellulose with pore size distribution calculated from the nitrogen gas desorption isotherm and the dimensions of the cellulose molecule, this nonuniformity is estimated as vacant pores. Table II shows pore radii and volume fractions obtained from the Guinier plot. These pore size patterns show good agreement with those calculated from the desorption isotherm method.

TABLE II. Pore Size Distribution of Solvent Displaced Microcrystalline Cellulose by X-Ray Small Angle Scattering

	Pore radius r (Å)	$k/r^3 \times 10^4$	Volume fraction[a]
Original	23.6	68	0.49
	48.8	38	0.27
	69.5	18	0.13
	113	10	0.072
	186	5.1	0.036
Ground	22.1	74	0.48
	40.0	32	0.21
	65.3	42	0.27
	76.3	3.0	0.019
	132	4.1	0.026

a) Ratio of the pore volume to the total pore volume.

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11) M.H. Jellinek, E. Solomon, and I. Fankuchen, *Ind. Eng. Chem.*, *Anal. ed.*, **18**, 174 (1946).
12) A. Guinier, *Ann. Phys.*, **12**, 161 (1939).

It is similarly confirmed from X-ray small angle scattering, that the effective surface of microcrystalline cellulose is composed of pores whose range of diameters is up to 300 Å, and pores less than 100 Å in diameter constitute a large part of total pore volume.

Recrystallization of Amorphous Cellulose

X-Ray diffraction pattern is shown in Fig. 5 for solvent displaced amorphous cellulose. From this X-ray pattern, it can be observed that recrystallization of amorphous cellulose has occurred. Its crystal form is apparently different from that of microcrystalline cellulose. Cellulose is capable of existing in many polymorphic forms, among them, the most stable form being cellulose II.[13] Hayashi *et al.* reported that, in cellulose II, intramolecular hydrogen bonding is formed between O_3 and O_5', showing "bent and twist" type conformation.[14] The X-ray diffractogram shown in Fig. 5 is identical with that of cellulose II.[15] The above result shows that amorphous cellulose recrystallizes into cellulose II during the solvent displacement. Dispersion of amorphous cellulose into water and continuous dehydration seem to induce rearrangement of the cellulose molecular chain and contribute to recrystallization.[16]

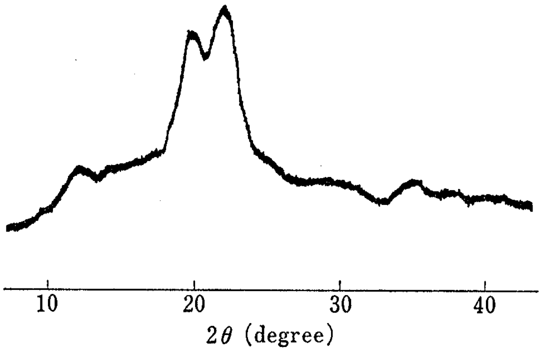

Fig. 5. X-Ray Diffraction Pattern of Ground Solvent Displaced Microcrystalline Cellulose

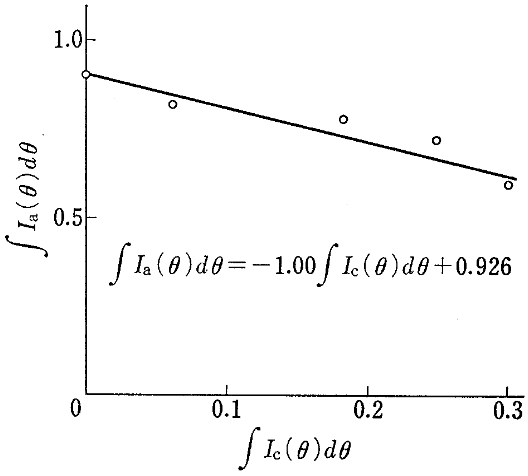

Fig. 6. $\int I_c(\theta)d\theta - \int I_a(\theta)d\theta$ Plot of Cellulose II

The degree of recrystallization of amorphous cellulose is evaluated by Hermans' method as previously described,[17] using mercerized cellulose (cellulose II). By changing the grinding time of cellulose II, several specimens are obtained with different crystallinity. Since the cellulose specimen which is ground for 330 min represents only a halo pattern, the crystallinity of this cellulose is defined 0%. Integrated intensities of scattering due to crystalline and amorphous regions are separated into two parts, $\int I_c(\theta)d\theta$ and $\int I_a(\theta)d\theta$ respectively, by assuming the position of halo is fixed. Figure 6 shows the $\int I_c(\theta)d\theta$ and $\int I_a(\theta)d\theta$ plot obtained. The slope is calculated to be -1.00 by the least square method. Using this value, the crystallinity of the recrystallized cellulose shown in Fig. 5 is determined as 26%.

It was found that amorphous cellulose showed no structural change such as melting or recrystallization before thermal decomposition.[18] However, the formation of stable crystals is enhanced by the solvent displacement procedure, involving dispersion of amorphous cellulose into water and disrupting the hydrogen bonding between cellulose molecules.

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13) B.R. Manjunath and N. Peacock, *J. Appl. Polymer Sci.*, **16**, 1305 (1972).
14) J. Hayashi, T. Yamada, and T. Watanabe, *Sen-i Gakkaishi*, **30**, T190 (1974).
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16) P.H. Hermans and A. Weidinger, *J. Am. Chem. Soc.*, **68**, 2547 (1946).
17) P.H. Hermans and A. Weidinger, *J. Appl. Phys.*, **19**, 491 (1948).
18) T. Yurugi, H. Iwata, and M. Okuma, *Nippon Kagakukaishi*, **8**, 733 (1975).

In the previous paper,[1] a linear relationship between crystallinity and the specific surface area of microcrystalline cellulose determined by the water vapor adsorption method was observed. This result shows that the formation of crystalline regions due to recrystallization causes a decrease in the effective surface area of cellulose. As may be seen from Table I, surface area determined from the nitrogen gas adsorption isotherm after the solvent displacement did not agree with that determined from water vapor adsorption isotherm. This difference seems to result from the recrystallization of cellulose specimens, in addition to residual water and surface tension of *n*-pentane during the solvent displacement previously mentioned.