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Crystallinity and Physical Characteristics of Microcrystalline Cellulose

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Microcrystalline cellulose (M.C.C.) having various ratios of crystal region to amorphous one obtained by grinding. Crystallinity was determined for M.C.C. and ground M.C.C. by X ray diffraction method (powder method) using Hermans'theory. Crystallinity was also determined by infrared measurement in converting hydroxyl groups into deuteroxyl groups in amorphous region of M.C.C. Crystallinities by both methods showed linear relationship for the samples.

Specific surface area was measured by adsorption methods of nitrogen gas and water vapor for M.C.C. and ground samples. The same value of 1 m^2/g was given by nitrogen gas adsorption for M.C.C. and ground samples. In water vapor adsorption ground samples increased in surface area with grinding time from 150 m^2/g of intact M.C.C. to 360 m^2/g of 32 hr ground M.C.C. This is due to the conversion of crystal into amorphous state by mechanical force. The linear relationships between specific surface area by water vapor adsorption and heat of wetting in water was obtained for ground samples.

Porosity in compression and hardness of tablet was measured for ground samples. It was found that intact M.C.C. showed larger porosity in compression and higher tablet hardness than ground M.C.C.

Keywords——microcrystalline cellulose; crystallinity determination; X-ray analysis; deuteration of microcrystalline cellulose; nitrogen gas adsorption; water vapor adsorption; grinding; tablet compression; heat of wetting

Microcrystalline cellulose (M.C.C.) has been used as a vehicle for tableting and encapsulation especially for powder tableting because of its high binding property in compression. M.C.C. is a spray dried powder of wood cellulose hydrolyzed in hydrochloric solution and washed by water. It is well known that wood cellulose consists of crystalline and amorphous regions. As hydrolysis occurs in the amorphous region of wood cellulose, the ratio of crystalline region to amorphous one is an important characteristic of M.C.C. Measurement of crystallinity of M.C.C. has not been reported although some reports were found as concerns some physical characteristics such as specific surface area by nitrogen gas adsorption.[2]

In the present work, M.C.C. samples which had various ratios of crystalline region to amorphous one were made by grinding of M.C.C. Crystallinity was determined for the samples by X ray diffraction method (powder method) and infrared method. Specific surface areas of ground samples were measured by adsorption method of nitrogen gas and that of water vapor. The relationships between crystallinity and specific surface area were examined. Heat of wetting of the ground samples was also measured and compared to the specific surface area by water adsorption method. Porosity in compression and hardness of tablet were measured for the ground samples, and the effect of the crystalline region of M.C.C. on compression and hardness was examined.

Experimental

(1) Material——Microcrystalline cellulose[3] was kept in a desiccator containing $CaCl_2$ at room temperature for a week. Water content of the dried sample was 4%.

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2) K. Marshall and D. Sixsmith, *Drug Development Communications*, **1**, 51 (1974—1975).
3) Avicel PH-101 (Asahikasei).

(2) **Grinding of M.C.C.**——Vibrational mill[4] was used. Volume of pot was 2000 ml, diameter of balls 17.7 mm, number of balls 370, amplitude of vibration 5 mm and frequency 1750 cpm. Pot and balls were made of alumina.

(3) **X Ray Diffraction (Powder Method)**——Rigakudenki D-3F was used. Target Cu, Filter Ni, Voltage 30 kv, Current 15 mA, Receiving slit 0.15 mm, Detector G.M. Counter, Count range 250 cps, Time constant 2 sec, Scanning speed 0.5°/min, Chart speed 10 mm/min. Background correction for radiation scattering by air was so small as to be neglected, and the radiation due to thermal agitation of atoms and Compton radiation was corrected by subtracting the background intensity of well ordered sucrose crystals.

(4) **Hydrogen-deuterium Exchange in Hydroxy Groups of Cellulose**——Hydroxyl groups in amorphous region of cellulose were converted to deuteroxyl groups for crystallinity determination by infrared measurement. Apparatus shown in Fig. 1 was used. Procedures of the deuteration was as follows. Deuterium oxide was introduced into tube B and cock H was closed. Cocks I and J were closed after evacuating through F. Sample cell A containing about 50 mg of M.C.C. or ground M.C.C. was evacuated through E for 5 hr to remove the adsorbed water from the sample, then cock G was closed. Opening I and H, deuterium oxide vapor was introduced into cell A. The cell A was immersed in a thermoregulated water bath and kept at a temperature 5—10° higher than room temperature so as to keep the relative humidity in cell A lower than 75%. Under this humidity, the ground M.C.C. did not crystallize in form II of cellulose. Deuteration went on for two days. After the deuteration, tube B containing deuterium oxide was immersed in liquid nitrogen to remove deuterium oxide adsorbed on the sample. After cock H was closed, tube B containing deuterium oxide was removed and tube C containing hexachlorobutadiene (H.C.B.) used as the solvent for infrared measurement was fixed. Cock H was opened and sample cell A was immersed in liquid nitrogen after evacuating through F. H.C.B. vapor transferred from C to sample cell A by vapor pressure difference between A and C. H.C.B. vapor adsorbed on the surface of the sample and it became a suspension of cellulose in H.C.B.. Infrared spectra were recorded by Hitachi EPI-G3 using NaCl cell for the sample in suspension. In these procedures, M.C.C. samples did not contact water vapor in air.

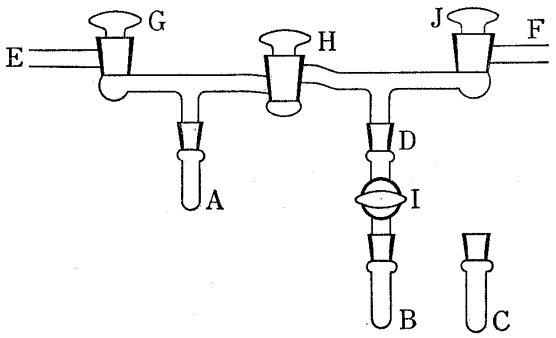

Fig. 1. Schematic Drawing of Microcrystalline Cellulose Deuterating Apparatus

A: sample cell
B: deuterium oxide container
C: hexachlorobutadiene container

(5) **Measurement of Nitrogen Gas Adsorption**——Adsorption apparatus was made in this laboratory following the specifications of the Technical Bulletin of Mellon Institute of Industrial Research.[5] Dead space was measured using He gas.

(6) **Measurement of Water Vapor Adsorption**——Sample of about 1 g was dried to constant weight in evacuated desiccator containing P_2O_5. After 48 hr, N_2 gas was introduced into the desiccator. The dried sample was taken out of the desiccator and sealed immediately. These dried samples were put it a well closed container which contained a saturated solution of a salt to keep a constant relative humidity at 35± 0.1°. The samples were weighed after 3 days. It was recognized for the adsorption to be at equilibrium in the period. Adsorbed water content was calculated from the difference of the weights before and after adsorption.

(7) **Measurement of Heat of Wetting**——Dewar's vessels calorimeter of twin type[6] was used. Pyrex glass ampules containing about 0.3 g sample were evacuated for 1 hr at room temperature and then for 3 hr at 95°. The ampules were sealed by fusing the inlet tube of the ampule under evacuation after drying. Weight of the dried sample was measured by difference between weight of the ampule containing dried samp leand that of the ampule. These ampules were set in Dewar's vessels containing 120 g water. One of the vessels was used as control. The ampule was kept under water level in the Dewar's vessel, and was broken after thermal equilibrium had been recognized. Temperature difference was measured by thermister between Dewar's vessel in which ampule was broken and that of the control. Heat of wetting was calculated from heat capacity of the calorimeter and the temperature difference.

(8) **Compression of M.C.C.**——M.C.C. was compressed in stainless steel die of 8 mm ϕ in one minute and the pressure was kept constant for 3 minutes before pressure was released. Compression force was measured by load cell. Values of the force were 322, 483, 805, 1200 and 1611 kg/cm^2.

4) Chuokakoki B-1.
5) P.A. Faeth and C.B. Williham, "Technical Bulletin on the Assembly, Calibration, and Operation of a Gas Adsorption Apparatus," 1955.
6) H. Fukuzawa, Y. Nakai, K. Shiizu, and S. Nakajima, *Yakuzaigaku*, **30**, 21 (1970).

(9) **Hardness Test of Tablets**——Hardness tester was made in this laboratory. Tablet was kept vertically between metal disk and steel plate. Vertical pressure was applied to a tablet by the elastic force of the steel plate up to destruction, and the pressure was measured by strain meter. This tester can measure up to 5 kg/cm^2.

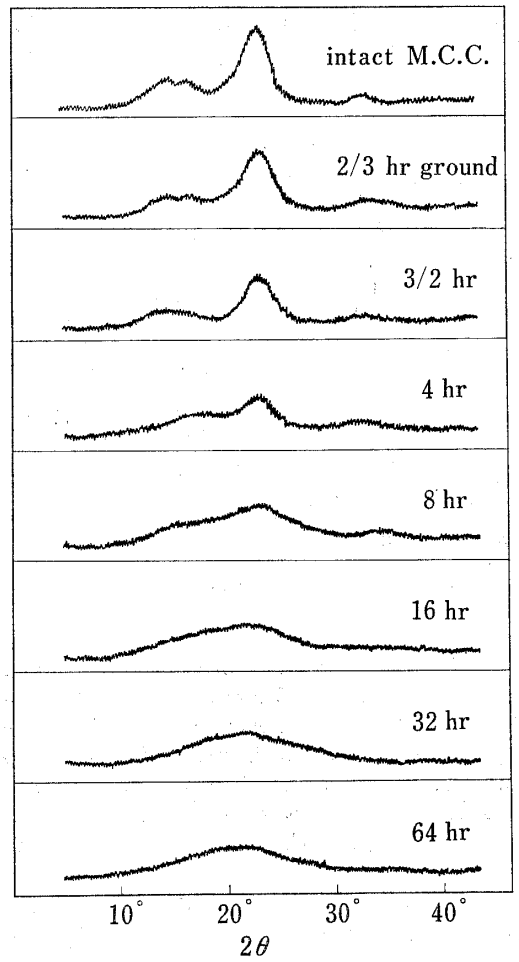

Fig. 2. X Ray Diffraction Patterns of Intact and Ground Microcrystalline Cellulose (M.C.C.)

Results and Discussion

(1) Measurement of Crystallinity of M.C.C.

Fig. 2 shows X ray diffraction patterns of M.C.C. and ground M.C.C. of various grinding times. Crystalline peaks of M.C.C. decreased with grinding time, and after 32 hr, only halo pattern was observed. This result shows that the microcrystals of M.C.C. were destroyed by the grinding force and converted into disordered or "amorphous" state. Crystallinity of M.C.C. was determined by Hermans' method[7] using these diffraction patterns as follows. Denoting the mass of crystalline and amorphous regions as M_c and M_a respectively, the relationships between the mass and the integrated intensity of reflection were given for crystalline and amorphous regions respectively,

$$M_c = k_c \int I_c(\theta) d\theta$$
$$M_a = k_a \int I_a(\theta) d\theta \qquad (1)$$

where k_c and k_a are constants. Sum of M_c and M_a is equal to total mass M,

$$M_c + M_a = M. \qquad (2)$$

From the above, crystallinity X_{cr} is given by

$$X_{cr} = M_c/M = \int I_c(\theta) d\theta \Big/ \left[\int I_c(\theta) d\theta + k_a/k_c \int I_a(\theta) d\theta\right] \qquad (3)$$

Therefore X_{cr} can be determined, if k_c/k_a is known and the integrated intensity of crystalline peaks and of amorphous region can be determined from the diffraction pattern. In this experiment, diffraction angles were confined to the region between 7° and 42° since whole crystalline peaks fell in this range, and only diffuse background was observed at 7° and 42°. Background correction scattered by air was neglected since it was very little. Background radiation is still to be corrected for the radiation due to the thermal agitation of the atoms and Compton radiation. In order to correct for the radiation, background intensity of well ordered crystals of sucrose was measured and substracted from that of the cellulose over the range. Crystalline peaks were separated from diffuse background by extrapolating smoothly the background curve near a crystalline peak and connecting the two end points of the peak.

Determination of k_c/k_a. From equations (1) and (2), the following relationship can be given,

$$\int I_a(\theta) d\theta = -(k_c/k_a) \int I_c(\theta) d\theta + M/k_a \qquad (4)$$

This equation shows the linear relationship between $\int I_a(\theta) d\theta$ and $\int I_c(\theta) d\theta$, and the value of

7) P.H. Hermans and A. Weidinger, *J. Applied Physics*, **19**, 491 (1948).

k_c/k_a is given by the gradient. Fig. 3 shows the result with M.C.C. The value of k_c/k_a was 0.721. Values of crystallinity of M.C.C. ground in every grinding time are shown in the 2nd column of Table I. Intact M.C.C. had 63% of crystallinity and crystallinity decreased with grinding time.

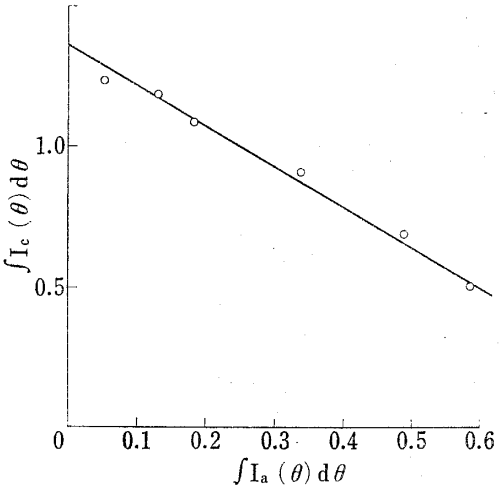

Fig. 3. Relationship between $\int I_a(\theta)\,d\theta$ and $\int I_c(\theta)\,d\theta$

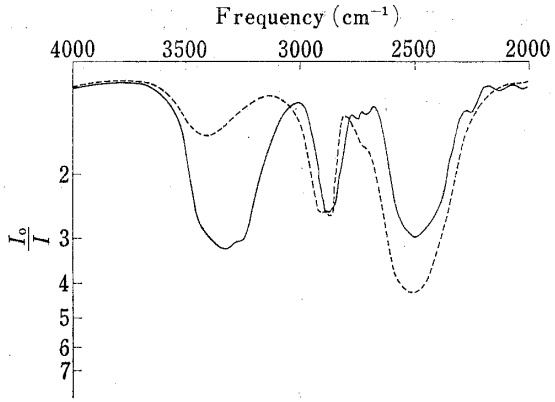

Fig. 4. Infrared Spectra of Intact (——) and 32 hr Ground (-----) Microcrystalline Cellulose after Deuteration

Table I. Crystallinity of Ground Microcrystalline Cellulose measured by X Ray Diffraction Method and Infrared Method as a Function of Grinding Time

Grinding time hr	Crystallinity %	
	X Ray diffraction method	Infrared method
0	63	59
2/3	49	57
3/2	34	—
4	20	—
8	14	38
16	6	—
32	0	10

Crystallinity of M.C.C. was also determined by infrared analysis. Hydroxyl groups of cellulose molecules in amorphous region are rapidly converted to deuteroxyl groups in treatment with deuterium oxide vapor, whereas the deuteration is very slow in crystalline region.[8] The comparison of areas of absorption band due to hydroxyl and deuteroxyl groups leads to determination of the ratio of crystalline region to amorphous one for ground M.C.C. Fig. 4 shows infrared spectra of intact and 32 hr ground M.C.C. after deuteration. Ground M.C.C. increased in the area of the band at 2500 cm^{-1} due to OD stretching vibration and decreased in the area of the band at 3500 cm^{-1} due to OH stretching vibration whereas the area at 2800 cm^{-1} due to CH vibration remained unchanged. Three methods are available for determination of crystallinity by infrared measurement,[9] that is, the first is the comparison of absorption areas between CH and OH band, the 2nd is that between CH and OD band, and the 3rd is that between OH and OD band. In this experiment, the 3rd method was used

8) H.J. Marrinan and J. Mann, *J. Applied Chem.*, **4**, 204 (1954).
9) K. Sofue and S. Fukuhara, *Kogyokagaku-zasshi*, **63**, 520 (1960).

since the absorption area of CH band was relatively small and the absorption peaks of OH and OD overlapped. The results are shown in the 3rd column of Table I. Ground M.C.C. decreased in crystallinity with grinding time. Good linearity was obtained between values of crystallinity measured by X ray diffraction and infrared method. Some difference, however, was observed in the values by two methods for a sample. It has been generally said that the values of crystallinity were considered as relative value rather than absolute one for a method.[10] The difference might be caused by the crystal definitions depending upon the methods.

(2) Specific Surface Areas of M.C.C. and Ground M.C.C.

The area was measured by BET method of nitrogen gas and water vapor adsorption. Table II shows the results. All samples had small surface area of 1 m^2/g for nitrogen gas adsorption. The values of area were not affected by grinding although the value of crystallinity varied. This result means that the dense structure was constructed in the amorphous region. In contrast with nitrogen gas adsorption, specific surface area of water vapor adsorption increased with grinding time. Correlation between the crystallinities by infrared method and the specific surface areas by water vapor adsorption method is shown in Fig. 5. The figure showed a linear relationship between them. This result shows that both methods are essentially identical and the increment of amorphous region by grinding provides the adsorption sites for water vapor adsorption and deuterium substitution.

Table II. Specific Surface Area of Ground Microcrystalline Cellulose by N_2 and H_2O Adsorption Method as a Function of Time

Grinding time hr	Specific surface area m^2/g	
	N_2 adsorption	H_2O adsorption
0	1.0	149
2/3	1.2	161
8	—	278
16	—	306
32	1.0	350
64	1.0	361

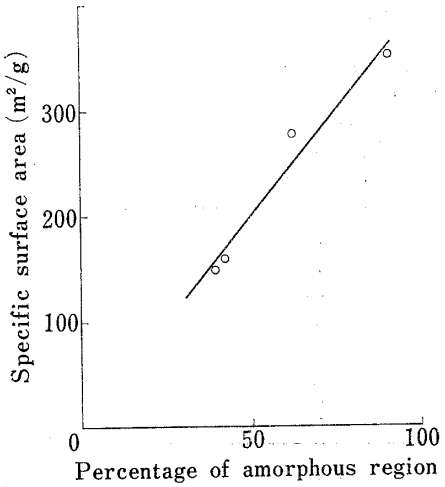

Fig. 5. Specific Surface Areas Measured by Water Vapor Adsorption as a Function of Amorphous Percentage Determined by Infrared Method

Heat of wetting was measured to examine the effect of the amorphous region on wetting as shown in Table 3. Ground M.C.C. increased in heat of wetting with grinding time. Calories per unit surface area measured by water vapor adsorption are nearly equal. However it is necessary for the comparison to correct the value for heat of transformation from amorphous state to crystal form II of cellulose.[11]

(3) Porosity in Compression and Tablet Hardness of Ground M.C.C.

Fig. 6 shows values of porosity under pressure for M.C.C. and ground M.C.C. It can be seen from the result that ground M.C.C. had small porosity and compressed densely. Fig. 7

10) L.E. Alexander, "X-ray diffraction methods in Polymer Science," John Wiley & Sons, Inc., New York, 1969.
11) P.H. Hermans and A. Weidinger, *J. Am. Chem. Soc.*, **68**, 2547 (1946).

Table III. Heat of Wetting of Microcrystalline Cellulose and Ground Microcrystalline Cellulose

Grinding time hr	Heat of wetting cal/g	Heat of wetting per unit surface area[a] cal/m^2×10^{-2}
0	12.4	8.32
2/3	15.1	9.37
32	29.7	8.48

a) Specific surface areas measured by water vapor adsorption method were used for these calculation.

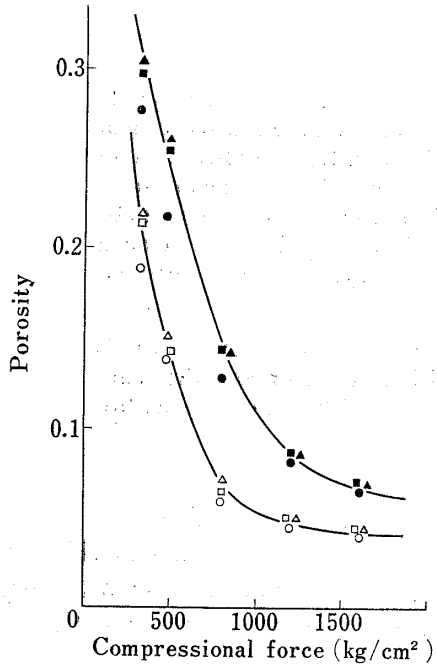

Fig. 6. Relationship between Porosity and Compressional Force for Intact (Filled Symbols) and 32 hr Ground (Open Symbols) Microcrystalline Cellulose

key; weight of tablet, △▲: 450 mg, □■: 350 mg, ○●: 250 mg

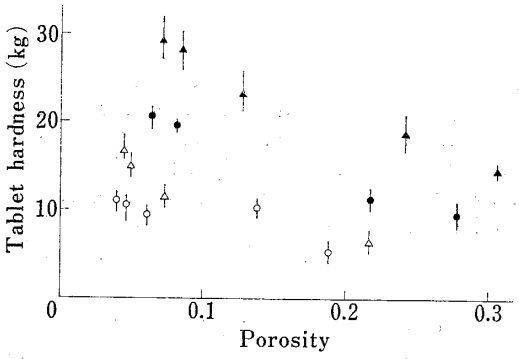

Fig. 7. Relationship between Porosity and Tablet Hardness for Intact (Filled Symbols) and 32 hr Ground (Open Symbols) Microcrystalline Cellulose

key; weight of tablet, △▲; 450 mg, ○●: 250 mg
Each bar represents experimental variation.

shows correlation between porosity and hardness of tablets. Amorphous M.C.C. decreased in tablet hardness for the sample weight of 250 mg and 450 mg in the entire range of porosity values. This result shows that microcrystals in M.C.C. gave a tablet high binding property. Numbers of cracks were observed on the surface of tablet which was made of ground M.C.C. under high compression force. In the case of M.C.C. tablet, the cracks were not observed. It can be said that microcrystals make the tablet structure homogeneous and cohesive with cellulose molecules of amorphous region in micro-environment immediately surrounding the crystals.