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European Journal of Pharmaceutics and Biopharmaceutics 47 (1999) 225–230

European Journal of Pharmaceutics and Biopharmaceutics

Research paper

# Effect of crystallinity of microcrystalline cellulose on the compactability and dissolution of tablets

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Received 4 March 1998; accepted in revised form 30 November 1998

**Abstract**

Microcrystalline cellulose (MCC) was pulverized with a vibrational rod mill. The degree of crystallinity of MCC decreased from 65.5 to 12.1% with pulverization time due to mechanochemical effect. Pulverized MCCs were compressed at 155.6 MPa using a compression test apparatus, and the two parameters relating to compactability, the *B* value and yield pressure, were calculated using a Heckel plot. These values were lowered as the degree of crystallinity of MCC became smaller. These results suggest that the crystal region and the amorphous region in MCC particles may be mainly fractured and deformed plastically during compression, respectively. Then the dissolution test was performed for the acetaminophen-MCC (10:90) tablets. Dissolution profiles showed an interesting phenomenon, namely, the dissolution rate of acetaminophen from MCC tablet decreased when the degree of crystallinity of MCC was in the range from 65.5 to 37.6%, however, it increased markedly when the degree of crystallinity of MCC was in the range from 25.8 to 12.1%. The amount of water absorbed into tablets changed in accord with the dissolution rates of acetaminophen from tablets. The dissolution data indicate that drug release can be modified by changing the degree of crystallinity of MCC. 

*Keywords:* Microcrystalline cellulose; Crystallinity; Compactability; Heckel plot; Dissolution rate

## 1. Introduction

Microcrystalline cellulose (MCC) was commercialized as Avicel® by FMC corporation in 1962, and it was registered in the supplement to the National Formulary, twelfth edition, in 1966. Although Avicel was only the brand-name production of MCC until about 1980, since then, considerable numbers of MCC productions have been launched in various countries. MCC has been widely used as an additive for direct compression because of its good flowability and compactability.

MCC is manufactured by the following process: at first, woodpulp made from needle-leaf trees or returnpulp made from cotton-seed fiber is hydrolyzed with mineral acid. The intermediates are then neutralized and washed after removing the amorphous region and impurities to purify the MCC [1]. Therefore, it has often been indicated that differences in the characteristics of MCC among manufacturers are due to the kinds of pulp used as raw materials and their manufacturing conditions, which affect the compactability [2,3]. Thomas et al. [4] reported that the Compactability Index differed among five brand-name MCCs. Rowe et al. [5] pointed out that the particle size of MCC affected tablet characteristics much more than the crystallinity of MCC because crystallinities among 11 brand-name MCCs measured by powder X-ray diffraction patterns and infra-red absorption spectra were almost the same, and their degree of crystallinity were in the range of 61.8–65.0% in powder XRD method, 57.7–69.4% in IR method. Pesonen et al. [6] reported that the compactability of Avicel and Emcocel® (Finnish Sugar) were almost equal as the results of evalua-

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0939-6411/99/$ - see front matter 
PII: S0939-6411(98)00102-7

tion using Kawakita's equation. They concluded that the most important materials property affecting the breaking strength of tablets was the specific surface area of the starting material, and no correlation between crystallinity, particle size or particle shape of starting material and the strength of tablets was observed. However, as the degree of crystallinity of MCC used in their study were almost the same, 63 and 68% for Avicel and Emcocel, respectively, the effect of crystallinity of MCC did not seem to be clear. Landin et al. reported that yield pressure, which is one of the parameters in a Heckel plot [7,8] related to the compactability of powder, exhibited no significant difference among four brand-name MCCs manufactured in Finland, India, Ireland and Japan, though their chemical composition, crystal structure and particle size were different [9]. Ikeda et al. evaluated the compactability of powder cellulose, which has a higher degree of polymerization than MCC, using Kawakita's equation and a Heckel plot [10]. Although some of these studies described the effect of the difference in crystallinity among various brand-named MCCs on the compactability, we could hardly find any articles examining the effect of change in crystallinity in the same brand-named MCC on the compactability and dissolution characteristics of tablets.

MCC as well as the other additives is often pulverized in pharmaceutical processes, therefore it is important for assurance of the quality of drug products to clarify the effect of changes in physicochemical properties of MCC caused by pulverization on physical characteristics, such as granulation and compression and chemical characteristics, such as content uniformity and dissolution.

We reported that the degree of crystallinity of MCC affects the characteristics of granules manufactured using a high-shear mixer in a previous paper [11]. In this study, we took notice of crystallinity in various physicochemical properties of MCC, and examined the effect of the degree of crystallinity of MCC on the compactability and dissolution characteristics of tablets.

## 2. Materials and methods

### 2.1. Materials

MCC (Avicel PH101, Asahi Chemical Industry) and acetaminophen (Yamamoto Chemical Industry), 75-150 m, were used. They were of JPXIII grade.

### 2.2. Pulverization of materials

Ten grams of MCC were pulverized using a vibrational rod mill (Sample Mill, Heiko, Japan) for 2–30 min and then passed through a 150 m sieve. In addition, MCC pulverized with a jet mill (PJM-NP, Nihon Pneumatic, Japan) under the following conditions was prepared in order to evaluate the effect of particle diameter on the dissolution rate: compressed air consumption, 2.0 kg/nm$^3$ per min; air pressure, 6.5 kg/cm$^2$; sample feed, 0.5 kg/h, and then passed through a 150 m sieve.

### 2.3. Measurement

Powder X-ray diffraction patterns were measured using a Mac Science X-ray diffractometer with Ni-filtered Cu-K $\alpha$ radiation. Voltage 35 kV, current 20 mA, receiving slit 0.15 mm, scanning speed 2° per min. The crystallinity of each material was calculated by Harman's method.

The particle size of each material was measured in ethanol by a particle size analyzer using laser diffraction (Microtrac II, Leeds & Northrup, USA).

Electron micrographs were taken with a Hitachi S-2360 scanning electron microscope. The samples were coated with gold, using a direct current sputter technique.

The equilibrium moisture curves were measured with a Integrated Microbalance System MB 300G (VTI Corporation, USA).

Each material was compressed with a compression test apparatus (Autograph AG5000B, Shimadzu, Japan) using flat-face punches of 8 mm diameter ($n$ = 3). The compression speed and the reverse speed of an upper punch was set at 10 mm/min and 100 mm/min, respectively. The compression force was removed at the time when the pressure of an upper punch reached at the set pressure. The time course was always identical in compression study. Tablet weight for each sample was 200 mg. No lubricant was used in this compression study. The stress transmission was calculated by dividing the lower punch pressure by the upper punch pressure at 155.6 MPa. The compression energy was calculated from a displacement-force curve for the upper punch.

Heckelplot analysis was applied to estimate how MCC deforms in the compression process. Heckel found that the reduction in voidage obeys a first-order kinetics type of reaction with applied pressure. Heckel's equation is as follows [12]:

$$\ln[1/(1-\rho_r)] = KP_a + A$$

where $\rho_r$ is the relative density of the compact, K and A are constants determined from the slope and intercept of the extrapolated linear region of the plot, respectively. K is expressed as the reciprocal of yield pressure ($P_y$) which reflects the plasticity of the sample. The difference between the relative density at the point where measurable force was applied, and the relative density calculated from the intercept of Heckel plot linear portion is expressed as the $B$ value which reflects the extent of densification by movement and reorientation of the particles, and the magnitude of fracture of the sample particles.

Tablet hardness was measured with a tablet-hardness tester (Tablet Tester 6D, Schleuniger, $n$ = 3), and the crushing strength, that is to say, tensile strength, was calculated.

Tablets containing 20 mg of acetaminophen and 180 mg of MCC with different degree of crystallinity were prepared

Table 1

Mean particle diameters of I-MCC and R-MCC

| Pulverization time (min) | Degree of crystallinity (%) | Mean particle diameter ($\mu$m) |
|---|---|---|
| I-MCC | | |
| 0 | 65.5 | 44 |
| R-MCC | | |
| 2 | 54.6 | 20 |
| 5 | 48.2 | 30 |
| 10 | 37.6 | 19 |
| 20 | 25.8 | 20 |
| 30 | 12.1 | 15 |
| J-MCC | | |
| | 63.3 | 16 |

with the compression test apparatus described above. A dissolution tests for tablets were performed by the JPXIII paddle method at 50 rpm in 900 ml of water at 37 ($n$ = 3). Acetaminophen was assayed spectrophotometrically (243 nm).

The amount of water absorbed into a tablet and the swelling ratio of the tablets were measured at room temperature using the apparatus reported by Nogami et al. [13] ($n$ = 3). The amount of water absorbed into a tablet was determined by measuring the weight change before and after the test, and the swelling ratio was estimated by measuring the change in the tablet thickness caused by water absorption. These measurements were carried out after establishing apparent equilibrium.

## 3. Results and discussion

### *3.1. Characterization of pulverized materials*

Intact MCC, MCC pulverized with a vibrational rod mill, and MCC pulverized with a Jet mill are abbreviated as I-MCC, R-MCC, and J-MCC, respectively, in the following sentences. Table 1 shows the mean particle diameters and the degree of crystallinity of I-MCC, R-MCC and J-MCC.

The mean particle diameter and the degree of crystallinity of I-MCC were 44 m and 65.5%, respectively. Those of R-MCC were reduced to 30-15 m and 54.6–12.1% with grinding time. Decrease in crystallinity is due to a mechanochemical effect as previously reported by Nakai et al. [14]. However, the particle diameter of J-MCC was as small as that of R-MCC ground for 30 min, but the degree of crystallinity scarcely changed by grinding. The reason for the difference of the degree of crystallinity between R-MCC milled by a vibrational rod mill for 30min and J-MCC milled by a jet mill was presumed that the grinding mechanism between a vibrational rod mill and a Jet mill is different. The main mechanism of a vibrational rod mill is the friction while that of a Jet mill is the collision. Therefore, the reduction in crystallinity has to be higher for a vibrational rod mill.

Fig. 1 shows SEM photographs of I-MCC and R-MCC. The shape of the MCC was also changed by pulverization, that is, R-MCC particles were almost round in shape, while I-MCC particles were fibrous.

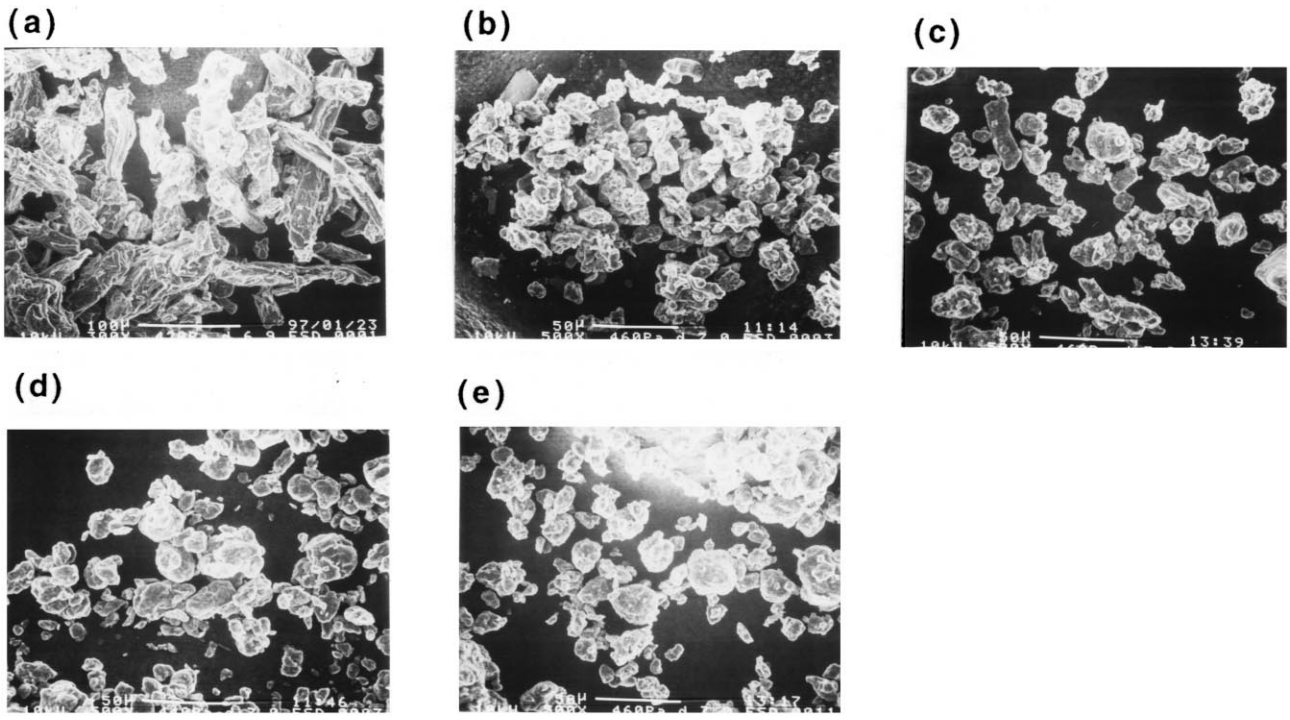


Fig. 1. Scanning electron micrographs of I-MCC and R-MCC (a) I-MCC (b) R-MCC pulverized for 5 min (c) R-MCC pulverized for 10 min (d) R-MCC pulverized for 20 min (e) R-MCC pulverized for 30 min.

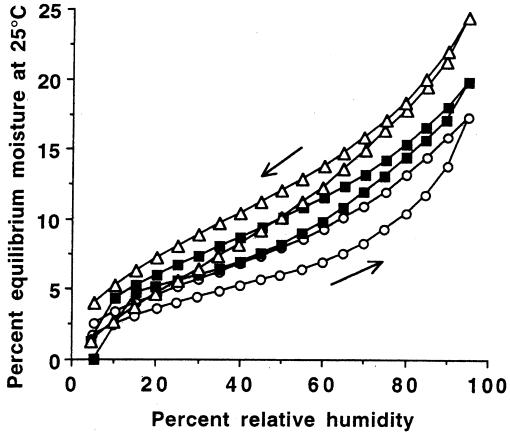


Fig. 2. Water vapor adsorption curves of MCC with various degrees of crystallinity at 25°C. Degree of crystallinity: I-MCC: (○) 65.5%; R-MCC: (■), 37.6%; (△) 25.8%.

The equilibrium moisture curves of MCC with various degree of crystallinity are shown in Fig. 2. The amount of water adsorbed by MCC at a constant relative humidity increased with a decrease in the degree of crystallinity. This phenomenon was caused due to the fact that the amorphous region is more hydrophilic than the crystalline region.

### 3.2. Compactability of MCC

The parameter of compactability was changed among the samples. Fig. 3 shows the relationship between the parameters of compactability and the degree of crystallinity of MCC.

The stress transmission from the upper punch to the lower punch was almost at the same level among the MCC samples. However, the compression energy was lowered with a decrease in the degree of crystallinity of the MCC samples. A Heckel plot analysis was performed in order to obtain information regarding the rolls of the crystalline region and the amorphous region in MCC to the crushing strength of tablets. A Heckel plot analysis is often applied to evaluate the compactability of MCC with different bland-names. However, to the authors' knowledge, no report has been published to estimate the compactability of ground MCC using a Heckel plot.

Table 2 shows the results of calculation of the parameters. The *B* value mainly expresses the magnitude of fracture of the particles caused after densification by movement and reorientation of particles, and yield pressure (1/K in the Heckel equation) is mainly related to the plastic deformation of particles during compression. It was found that these values were lowered as the degree of crystallinity of MCC became smaller. The results suggested that the crystalline region and the amorphous region in the MCC particles may be fractured and deformed plastically during compression, respectively. The reason why compression energy was proportional to the degree of crystallinity as shown in Fig. 3 was considered as follows: the crystalline region with a hard

Table 2

Results of Heckel plot analysis of MCC with various degrees of crystallinity

| Degree of crystallinity (%) | $B$[a] | Yield pressure (MPa)[b] |
|---|---|---|
| I-MCC | | |
| 65.5 | 0.1415 | 232.0 |
| R-MCC | | |
| 54.6 | 0.0899 | 194.1 |
| 48.2 | 0.0811 | 191.8 |
| 37.6 | 0.0751 | 178.4 |
| 25.8 | 0.0697 | 174.0 |
| 12.1 | 0.0663 | 148.5 |

[a]Difference between the relative density at the point where measurable force was applied and the relative density calculated from the intercept of the Heckel plot linear portion.
[b]The reciprocal of the slope in Heckel plot linear portion which would reflect plasticity of the sample.

structure required considerable energy to be fractured; however, the amorphous region with a soft structure required relatively small energy compared to crystalline region, because it only deformed plastically. Table 3 shows the crushing strength of tablets compressed at 155.6 MPa, it was recognized that the crushing strength reduced as the decreasing the degree of crystallinity of MCC. Fig. 4 shows the relationship between compression energy and the crushing strength of tablets. The crushing strength of tablets was almost proportional to the compression energy. These results suggest that compression energy may mainly consume to fracture the crystal region in MCC, and that fractured crystal region may contribute to increase the crushing strength of tablets. In addition, MCC might be collapsed by strong impact of a rod during pulverization. Therefore, the number of contact points among R-MCC particles each other in a tablet may decrease with pulverization time. As the results of this, the decrease in crushing strength of R-MCC tablets may be observed.

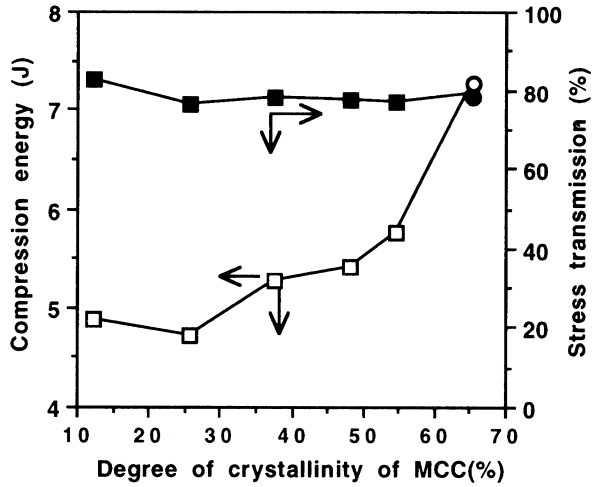


Fig. 3. Effect of crystallinity on compression energy and stress transmission of MCC, (○), (●): I-MCC; (□), (■): R-MCC.

Table 3

Crushing strength of tablets compressed at 155.6 MPa

| Degree of crystallinity of MCC (%) | Crushing strength ($kg/mm^2$) |
|---|---|
| I-MCC | |
| 65.5 | 0.44 |
| R-MCC | |
| 54.6 | 0.34 |
| 48.2 | 0.32 |
| 37.6 | 0.28 |
| 25.8 | 0.23 |
| 12.1 | 0.22 |

In previous studies [5,9], the characteristics of MCC were compared among different brand-named MCCs. However, the effect of the degree of crystallinity of MCC on the compactability could not be detected clearly, because the differences of the degree of crystallinity among various brand-named MCCs were very small. In our study, the relationship between the degree of crystallinity of MCC and the compactability could be clarified by changing the degree of crystallinity in wide range for the same brand-named MCC. Duberg and Nyström investigated the effect of the particle size of on the characterization of a Heckel plot using several numbers of excipients sieved to a small and a large fraction [14]. They reported that the difference in parameters of a Heckel plot between a small fraction and a large fraction of excipients was scarcely observed. These results in their study supported that the difference in parameters of Heckel plot among MCC samples may be mainly caused by the difference of degree of crystallinity rather than that of the particle size.

### *3.3. Effect of crystallinity on dissolution of tablets*

Fig. 5 shows the dissolution profiles of MCC tablets containing acetaminophen.

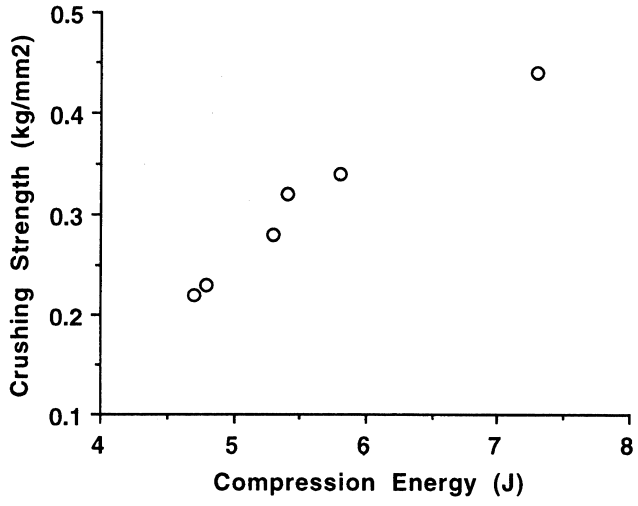


Fig. 4. The relationship between compression energy and the crushing strength of tablets.

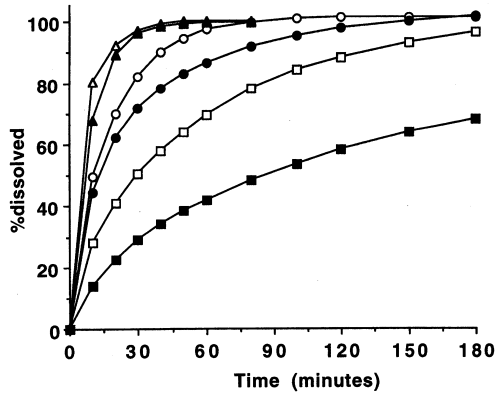


Fig. 5. Dissolution profiles of acetaminophen from tablets containing MCC with various degrees of crystallinity. Crystallinity of MCC in tablets: I-MCC: (○), 65.5%; R-MCC: (●), 54.6%; (□), 48.2%; (■), 37.6%; (△), 25.8%; (▲), 12.1%.

Disintegration was not observed in each tablet except for the I-MCC tablet during the dissolution test, though the tablets containing R-MCC exhibited swelling.

The dissolution rate was decreased as the degree of crystallinity decreased from 65.5 to 37.6%. However, the dissolution rates for tablets with a low degree of crystallinity from 25.8 to 12.1% markedly increased. Similarly, the amount of water absorbed into the tablets and the swelling ratio of the tablets changed with the degree of crystallinity of MCC as shown in Fig. 6.

The crushing strength of a tablet decreased with the reduction of the degree of crystallinity of MCC as shown in Table 3. In general, the crushing strength of a tablet is closely in correlated with the dissolution rate. The dissolution tests, therefore, were performed for tablets whose crushing strength was adjusted within the range from 0.27 $kg/mm^2$ to 0.32 $kg/mm^2$ as shown in Table 4. The compression force was set at 77.8 MPa for I-MCC, 155.6 MPa for R-MCC ground for 5 min and 233.4 MPa for R-MCC ground for 20 min, respectively. Fig. 7 shows the dissolution pro-

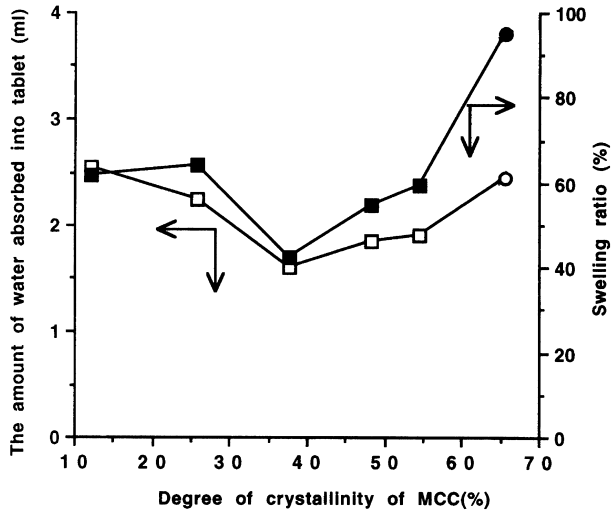


Fig. 6. Effect of crystallinity of MCC on the amount of water uptake and swelling ratio of MCC tablets. (○), (•): I-MCC; (□), (■): R-MCC.

Table 4

Crushing strength of tablets compressed at various compression force

| Degree of crystallinity of MCC (%) | Compression force (MPa) | Crushing strength ($kg/mm^2$) |
|---|---|---|
| I-MCC | | |
| 65.5 | 77.8 | 0.30 |
| R-MCC | | |
| 48.2 | 155.6 | 0.32 |
| 25.8 | 233.4 | 0.27 |

files for tablets with equivalent crushing strength. The order of the dissolution rates among these tablets was the same as Fig. 5, i.e. R-MCC ground for 20 min > I-MCC > R-MCC ground for 5 min.

The dissolution testing for tablets made of J-MCC was carried out to evaluate the effect of the particle size of MCC on the dissolution rate. Although the degree of crystallinity of J-MCC and I-MCC were almost equal each other, the particle size of J-MCC was apparently smaller than that of I-MCC. Compression force at 50.6 MPa was applied to prepare J-MCC tablets in order to adjust its crushing strength to I-MCC tablets compressed at 155.6 MPa, because the tablet hardness will often affect the dissolution rate. Fig. 8 shows the result of dissolution test. The dissolution profiles of these tablets were almost the same.

These results suggest that the dissolution rate of acetaminophen from MCC tablets depend upon the crystallinity of MCC, and that it is not affected by the particle size of MCC.

As is evident from the results, the degree of crystallinity of MCC may become a dominant factor in controlling the dissolution rate of directly compressed tablets including MCC. We should, therefore, pay attention to the degree of crystallinity of MCC during pulverization process, because it may affect the dissolution properties of tablets. However, drug dissolution rate from the MCC tablet did not linearly changed with the degree of crystallinity of MCC. Further studies will be required to clarify this phenomenon.

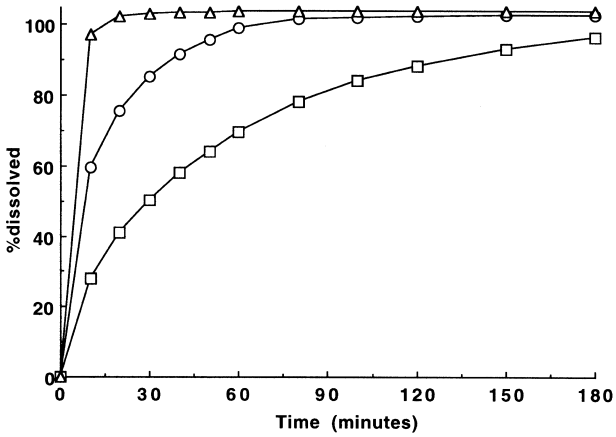


Fig. 7. Dissolution profiles for acetaminophen tablets with a equivalent crushing strength. Crystallinity of MCC in tablets: I-MCC: (○), 65.5%; R-MCC: (□), 48.2%; (△), 25.8%.

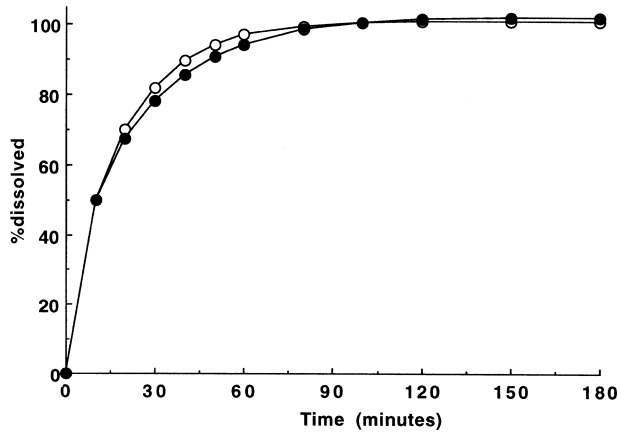


Fig. 8. Dissolution profiles for acetaminophen tablets consist of MCC pulverized with a vibrational rod mill or a Jet mill. (○), R-MCC; (●), J-MCC.

## Acknowledgements

We would like to thank Dr. Takahiro Matsumoto for supplying the computer software to calculate the parameters in the Heckel plot analysis.

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