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Morphological effect of microcrystalline cellulose particles on tablet tensile strength

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Abstract

An attempt was made (1) to fractionate microcrystalline cellulose (MCC) particles of Avicel® PH-101 (PH grade) and Ceolus® KG-801 (KG grade) into four sieve fractions by using an air-jet sieve and (2) to disclose effects of morphology of the particle on tablet tensile strength, T. The morphology of MCC particles is one of the most important factors affecting T. T increased with an increase in the ratio of L/D for particles (L, length; D, width). KG grade consists of a larger number of rod-shaped particles than PH grade, giving significantly higher compressibility than PH grade. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Elongation ratio; Microcrystalline cellulose; Morphology; Particle; Tablet; Tensile strength

1. Introduction

Microcrystalline cellulose (MCC) is a deformable material (David and Augsburger, 1977) and has excellent compressibility. For this reason, it has been employed as a tableting excipient in pharmaceutical manufacturing for more than 30 years. Furthermore, as cellulose has three hydroxyl groups in each glucopyranose unit, it can be easily swelled by water and such tablets will disintegrate rapidly in water.

Asahi Chemical Industry Co., Ltd. (Tokyo, Japan) has developed a new type of MCC, Ceolus® KG-801 (hereafter referred to as KG grade), in order to improve compressibility of a standard type, Avicel® PH-101 (hereafter referred to as PH grade) (Asahi Chemical Industry Co., Ltd.). The hardness of tablets made of the KG grade is about 1.5 times higher than that of the standard PH grade, but both tablets can be disintegrated easily within the same short period once they are

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thrown into water. The high compressibility of KG grade will enable us to improve the tensile strength of tablets of OTC (over-the-counter) drugs in which the volume of MCC used was limited. It will also enable us to make tablets of sensitive drugs, as, for example, an enzyme which easily loses its activity due to rapid temperature increase during compression at high pressure (Miyamoto, 1996).

Many researchers have investigated the effects of chemical, physical and mechanical properties of MCC on compressibility (see, for example, Malamataris et al., 1984; Roberts and Rowe, 1986; van der Watt, 1987; Khan et al., 1988; Bassam et al., 1990; Garr and Rubinstein, 1992; Doelker, 1993; Stubberud et al., 1996; Ono et al., 1997; Williams et al., 1997), but few quantitative works has been done on the specific effects of MCC particle morphology.

Concerning the effect of particle morphology on compressibility, Wong and Pilpel (1990) have reported that tensile strength of coarse powders such as Starch 1500 and sodium chloride increased with an increase in irregularity of particles. They concluded that the observed increase in tensile strength was due to the increased area of contact between particles as they deformed. McKenna and McCafferty (1982) have investigated the effects of particle size variation on the tensile strength of tablets formed from spray-dried lactose and Avicel® PH-101. They concluded that particle size variation has a marked effect on the tensile strength of spray-dried lactose, while in the case of Avicel® PH-101 it could be seen that particle size variation had little effect on the tensile strengths of tablets. Examining their results on Avicel® PH-101, we thought that there is a small, but not a negligible difference on tablet tensile strength between MCC fractions with different particle size. Whiteman and Yarwood (1988) reported that MCC samples, including Avicel® PH-101, with similar median particle size and size distribution gave tablets having quite different strength, and they explained that their observed results to McKenna and McCafferty's result, because they combined MCC with magnesium stearate and crospovidone.

We supposed that those differences on tablet tensile strength in the reports mentioned above resulted from differences in physical properties of the MCC particles.

Table 1 summarizes the physical properties of MCC, structural factors and the size, which we consider of fundamental importance. Tablet tensile strength T is one of the physical properties and is thought to be affected by the structural factors listed in columns 3–5 in Table 1. In other words, compressibility of MCC particles is dominated by their supermolecular structures in microcrystals, aggregated particles and tablets.

In this study, two kinds of MCC—i.e. PH grade and KG grade—were employed to compare the effects of several structural factors on tablet tensile strength T. By evaluating five structural factors of column 4 such as (1) particle size, (2) particle true density, (3) bulk density, (4) specific surface area and (5) particle morphology, we examined the relationship between these factors and tablet tensile strength T to disclose the dominant factor controlling T.

2. Materials and methods

2.1. Materials

A 50-g portion of Avicel® PH-101 (Asahi Chemical Industry Co. Ltd., Tokyo, Japan) was sieved using an air-jet sieve (type 200LS; Alpine, Germany) into four fractions. Sieve size ranges were 0–38, 38–45, 45–75 and 75–150 μm. The weight of MCC particles in each fraction was measured to calculate the weight fraction f_w of the fraction. The same procedure was conducted with Ceolus® KG-801 (Asahi Chemical Industry Co. Ltd., Tokyo, Japan).

2.2. Methods

2.2.1. Image analyses of particles

Heywood diameter d (μm), length of particle L (μm) and width of particle D (μm) were evaluated from optical micrographs of particles in each fraction of the PH and KG grades. More than 400 particles were selected randomly to measure their

Table 1
Structural factors dominating tablet properties and size

Properties	Size				
	(1) Primary structure, 0.1–1 nm, molecular structure (cellulose)	(2) Secondary structure, 1–10 nm, conformation (type I crystal)	(3) Third structure, 10–100 nm, supermolecular structure (microcrystalline)	(4) Fourth structure 100 nm to 1 mm, aggregated structure (aggregated particles)	(5) Fifth structure, 1–50 mm, formed structure (granules, tablets)
Relative properties					
Physical properties		Hardness (also T)	Hardness (also T)	Hardness (also T)	Hardness (also T)
		Disintegration	Disintegration	Disintegration	Disintegration
Chemical properties	Reactivity	Reactivity			
	Heat stability	Heat stability			
Structural factors					
	Chemical structure	Conformation of molecular chain	Orientation	Morphology of particles	Shape form
	–Monomer	Structure of crystalline/amorphous regions	–Molecular chain	Particle size	–Tablets
	–Branch-linkage	Thermal movement	–Crystal plane	Bulk density	–Granules
	–Side-chain	Helical structure	–Crystal size	Particle true density	Packing fraction
	Molecular weight distribution	Random coil	–Crystallinity	Particle orientation	Specific surface area
	Copolymer	Crystal type	Dispersion of crystal/amorphous regions	Surface	
	–Component	Formation of hydrogen bond	Mobility of water molecules	–Roughness	
	–Block			–Electric charge	
	–Graft			–Specific surface are	
	Blend content			Internal surface area	
	Tacticity				

morphology in each fraction. Heywood diameter was determined using an image processor (Hyper 700 II; InterQuest Co., Ltd., Osaka, Japan), by calculating the diameter of circle whose area was equivalent to the actual projected area A of a particle, as shown by Eq. (1):

$$d = \left(\frac{4A}{\pi}\right)^{1/2} \tag{1}$$

Length of particle L (μm) and width of particle D (μm) corresponded to the major and minor axes of a circumscribed rectangle to the particle, respectively, under the condition that the area of the rectangle was minimized.

The geometric standard deviation σ_g was obtained by plotting the logarithm of particle size against the cumulative frequency on a probability scale (Williams et al., 1997). A distribution in which σ_g is equal to unity is monodisperse, and as σ_g deviates from unity the distribution becomes more polydisperse.

The shape coefficient α is usually employed to evaluate particle shape and is given by Eq. (2):

$$\alpha = \frac{\alpha_s}{\alpha_v} \tag{2}$$

where α_s is surface shape coefficient and α_v is volume coefficient (see, for example, Orr and Dalla Valle, 1959).

Here, we evaluated α using Eq. (3):

$$\alpha = S_w \rho_s d_s \tag{3}$$

where S_w is surface area per unit weight, ρ_s is particle true density (see, for example, Orr and Dalla Valle, 1959) and d_s is particle diameter. d_s is defined by Eq. (4):

$$d_s = \frac{\sum fd}{n} \tag{4}$$

where f is an existing probability of particles with Heywood diameter d, and n is number of particles examined. f was given by Hatch and Choate (1929) as Eq. (5):

$$f = \frac{\sum n}{(2\pi)^{1/2} \ln \sigma_g} \exp\left[- \frac{(\ln d - \ln M)^2}{2 \ln^2 \sigma_g} \right] \tag{5}$$

where M is the geometric mean diameter of particles and σ_g the geometric standard deviation (see, for example, Orr and Dalla Valle, 1959). In the calculation of α by Eq. (3), we used d instead of d_s because the values are almost equal. Furthermore, assuming that the particles are a quadrate regular prism with length L and width D in the side face (D is also the length of a side in its quadrate base), apparent specific surface area S_a [$S_a = N(2D^2 + 4LD)$] was employed instead of S_w. Here, the number of particles per unit weight, N, was calculated using particle true density of MCC particles ρ_s on the assumption that all the particles are spherical: $N = 6/(\pi \rho_s d^3)$.

Table 2 shows the weight fraction f_w, d, σ_g and N for fractions prepared from the PH and KG grades.

Table 2
Weight fraction f_w, Heywood diameter d, geometric standard deviation σ_g, shape coefficient α and number of particles per unit weight N for fractions prepared from the PH and KG grades

Microcrystalline cellulose	Sieve size range (μm)	f_w	d (μm)	σ_g	α	N (pieces/g)
Avicel® PH-101	150–75	0.23	110.0	1.20	12.3	257 144
	75–45	0.23	76.0	1.31	10.5	678 563
	45–38	0.13	61.8	1.40	10.5	1 301 948
	38–0	0.41	25.8	1.50	10.1	19 427 611
Ceolus® KG-801	150–75	0.2	125.1	1.30	11.9	177 208
	75–45	0.2	71.8	1.32	10.7	915 835
	45–38	0.13	55.9	1.22	9.9	1 912 888
	38–0	0.47	31.8	1.57	10.5	10 250 748

2.2.2. Powder properties

After drying particles at 105°C for 120 min, the particle true density ρ_s (g/cm^3) was determined with a Beckman air comparison pycnometer (model 930; Beckman Instruments, USA). Their specific surface area S_{BET} (m^2/g) was measured by the nitrogen adsorption method (Flowsorb II 2300; Micromeritics, Norcross, GA, USA). MCC particles (20 g) of each fraction were poured into a 100-ml graduated cylinder without adding any vibration to the cylinder and the volume of piled particles V_b (cm^3) was estimated. Bulk density ρ_b (g/cm^3) was calculated using Eq. (6):

$$\rho_b = \frac{W_p}{V_b} \tag{6}$$

where W_p (g) is weight of particles poured into the cylinder. Angle of repose A_r (degrees) was measured by Sugihara's method (Nogami et al., 1965). Water content w_c (%) of particles was measured by using an electric moisture balance (FD-220; Kett Kagaku Kenkyujo, Tokyo, Japan); 1 g of MCC particles was heated at 105°C and weight loss on drying was measured.

2.2.3. Compression and tablet analyses

Each 0.3 g of MCC particles of the eight fractions was compressed by using 1.13-cm diameter flat-faced lubricated punch and die set installed in a tableting machine (Tableting Tester SK-02; Sankyo Piotech, Osaka, Japan). Tablets were prepared under conditions where maximum compression pressure P_{max} ranged from 10 to 50 MPa and the rate of compression was constant at 0.03 cm/s. The compression pressure was released immediately after the pressure reached P_{max}, that is an upper punch was not kept holding at P_{max}. Tablets were stored in airtight vials for 24 h and then their final thickness T_t and tablet tensile strength T were measured.

T was evaluated by the method of Fell and Newton (1970) through Eq. (7):

$$T = \frac{2H}{\pi D_t T_t} \tag{7}$$

where H is hardness of the tablets (kgf), D_t is tablet diameter and T_t tablet thickness (cm). H was measured by a motorized tablet hardness tester (Tableting Tester 6D; Dr. K. Schleuniger & Co., Switzerland). Packing fraction of the tablets P_f was obtained by Eq. (8):

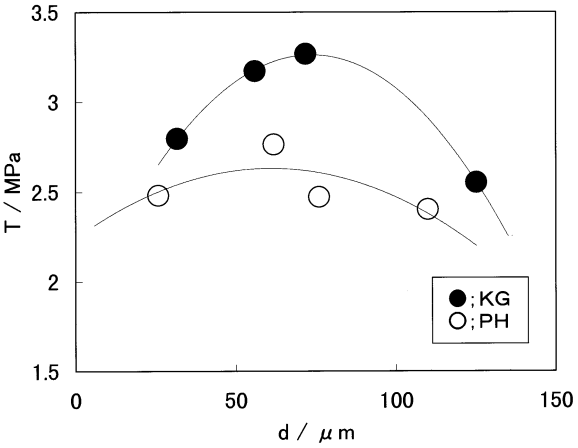

Fig. 1. Effect of Heywood diameter d of MCC particles on tablet tensile strength T. $P_{max} = 30$ MPa; packing fraction $P_f = 0.61–0.65$. Open circle, PH grade; closed circle, KG grade.

$$P_f = \frac{\rho_t}{\rho_s} \tag{8}$$

where ρ_t is apparent density of tablet and ρ_s is particle true density. ρ_t was calculated by using Eq. (9):

$$\rho_t = \frac{W_t}{(D_t/2)^2 \pi T_t} \tag{9}$$

where W_t is weight of a tablet.

3. Result and discussion

3.1. Relationship between Heywood diameter d and tensile strength T of MCC particles

Using unfractionated MCC particles of KG grade and PH grade, tablets were made under condition of $P_{max} = 30$ MPa. T of the unfractionated KG tablet was larger than that of the unfractionated PH tablet. Fig. 1 shows the relationship between d and T of the eight fractions listed in Table 2. In this figure, plots on the same curve correspond to the sieve size ranges of 0–38 μm

($d = 31.8$ μm for KG, $d = 25.8$ μm for PH), 38–45 μm (55.9, 61.8 μm), 45–75 μm (71.8, 76.0 μm) and 75–150 μm (125.1, 110.0 μm), respectively. When T was compared between KG and PH at the same d, tablets made of KG grade indicate greater T than those of PH grade in the whole particle size range. In the both grades, T increased with an increase in d, showing a maximum, then decreased. Tablets made of the second and third KG fractions, where d was 55.9 and 71.8 μm, respectively, were harder than those from two other KG fractions. Tablets made of the PH fraction with d of 61.8 μm were the hardest among the four PH fractions.

In general, it seems that when d becomes smaller, the total area of contact interface between particles constituting a tablet increases and T becomes larger. Unfortunately, we could not explain the difference in T between the fractionated MCC particles with this simple model.

3.2. Relationship between several physical properties and tablet tensile strength T of MCC particles

In Table 2, the magnitude of f_w and σ_g of fractions of PH grade were almost the same as those of the corresponding fractions of KG grade. Therefore, there is little correlation between f_w and T, and between σ_g and T.

Fig. 2 shows the relationship between w_c, ρ_s, ρ_b, A_r, S_{BET}, α and T of the fractions shown in Table 2. Correlation coefficient r is indicated in the figures. There is no correlation between these properties and T.

Regarding other chemical and physical properties, the KG and PH grades have almost the same average degree of polymerization (PH, 241; KG, 242; determined by the solution viscosity method of Japanese Pharmacopoeia XIII) and also the same degree of crystallinity (PH, 68.9%; KG, 69.8%; measured by X-ray diffractometer, type RAD-rB + RU-200; Rigaku Co., Tokyo, Japan). Accordingly, there seems to be little difference in properties from the primary structure to the third structure (defined in Table 1) among the two grades.

Fig. 3 shows the relationship between d and apparent specific surface area S_a, S_{BET} and internal surface area S_i for the fractions of the PH and KG grades. Number of particles per unit weight N is summarized in Table 2. S_i was defined as the surface area existing inside aggregated MCC particles. Nitrogen molecules can access the internal surface and adsorb there, so that S_i was roughly obtained by subtracting S_a from the specific surface area S_{BET} of uncompressed MCC particles, i.e. $S_i = S_{BET} - S_a$. In Fig. 3, S_a decreased monotonously with an increase in d for both grades, S_{BET} was almost constant in a whole range of d for both the PH and KG grades and S_{BET} of KG was larger than that of PH. Accordingly, S_i of KG was evaluated to be larger than that of PH, indicating that the apparent density of particles of KG was smaller than that of PH.

As mentioned before, T of KG is larger than that of PH; however, S_i increased monotonously with an increase in d. In other words, the relation between d and S_i in Fig. 3 shows no peaks, unlike the relation between d and T in Fig. 1. Therefore, we concluded that with respect to an effect of S_i on T, there is little correlation between S_i and T.

3.3. Optical microscopic observation of MCC particles and relationship between elongation ratio L/D and tablet tensile strength T of MCC particles

Fig. 4 shows optical microscopic photographs of particles in the fractions from the PH and KG grades. We distinguished two types of morphology of particles and separated the eight fractions into two groups: one mainly consists of rod-shaped particles and the other of round particles. In Fig. 4(b,c,f,g) ($d = 55.9$, 71.8, 61.8 and 76.0 μm, respectively), the rod-shaped particles predominate. In Fig. 4(a,d,e,h) ($d = 31.7$, 125.1, 25.8 and 110.0 μm, respectively), we found much rounder particles than rod-shaped particles.

Fig. 5 shows the relationship between d and elongation ratio L/D of the fractions both for the PH and KG grades. This figure corresponds fairly well to Fig. 1.

Fig. 6 shows the relationship between elongation ratio L/D and T. In the figure, data of tablets

having approximately the same P_f were plotted using the same mark regardless of the MCC grade. Log T was proportional to L/D, and T increased with an increase in L/D. The slope of the line decreases with an increase in P_{max}. From these facts, degree of orientation of MCC particles in a tablet along the direction at right angles with compression force seems to increase with an increase in L/D, becoming almost the same in larger P_{max} regions regardless of L/D. A total area of contact interface between MCC particles would be increased with an increase in the degree of orientation. Accordingly, L/D is one of the most dominant factors controlling T. We will discuss the orientation of MCC particles in a tablet quantitatively elsewhere.

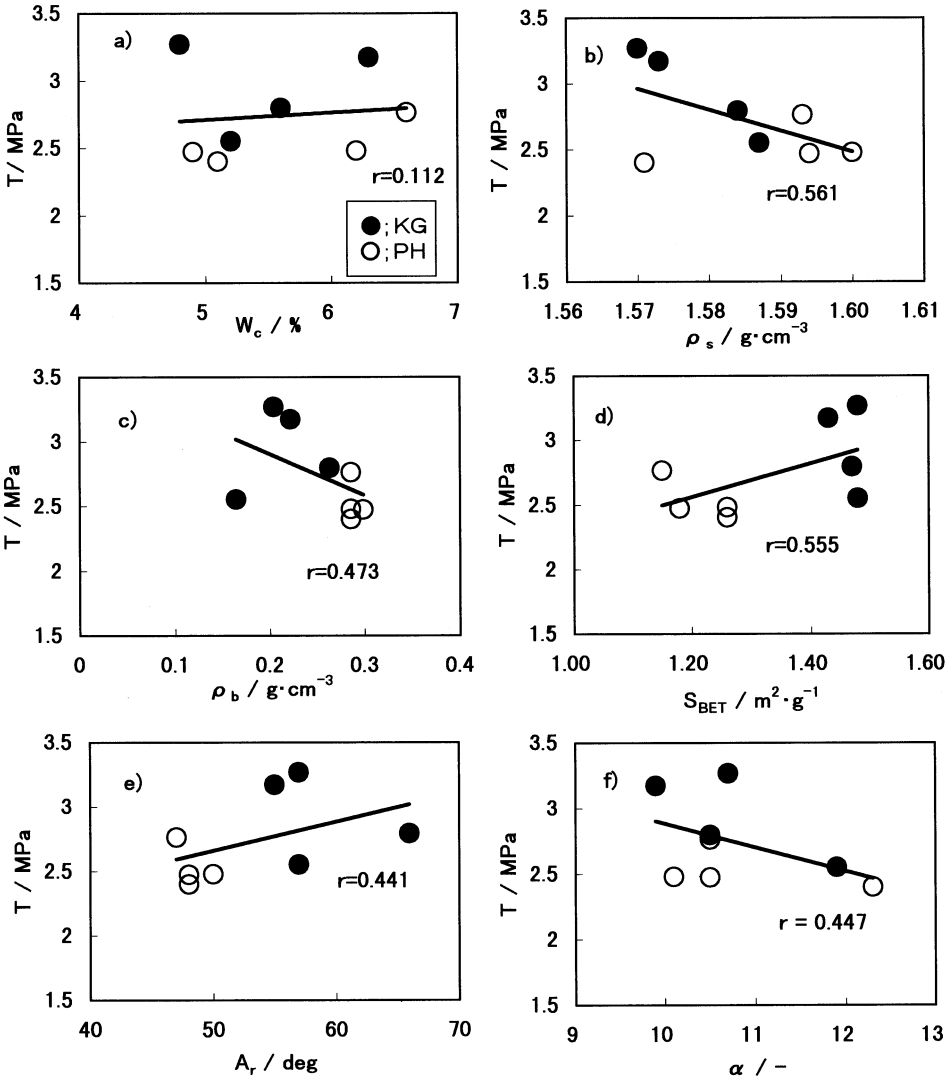

Fig. 2. Relationships between tablet tensile strength T and physical properties of MCC particles: (a) water content w_c; (b) particle true density ρ_s; (c) bulk density ρ_b; (d) specific surface area S_{BET}; (e) angle of repose A_r; (f) shape coefficient α. Open circle, PH grade; closed circle, KG grade. r, stands for correlation coefficient.

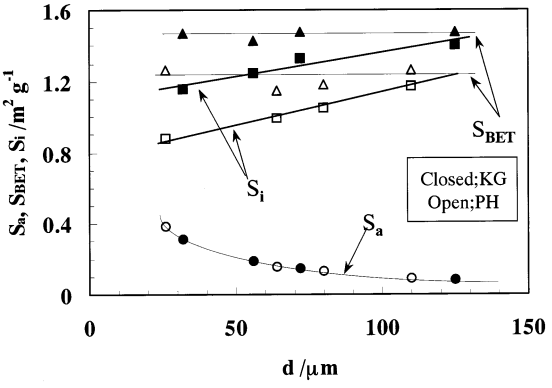

Fig. 3. Relationship between Heywood diameter d and calculated apparent surface area S_a, specific surface area measured by BET method S_{BET}, and calculated internal surface area S_i. Open circle, S_a of PH grade; closed circle, S_a of KG grade; open triangle, S_{BET} of PH; closed triangle, S_{BET} of KG. Open square, S_i of PH; closed square, S_i of KG.

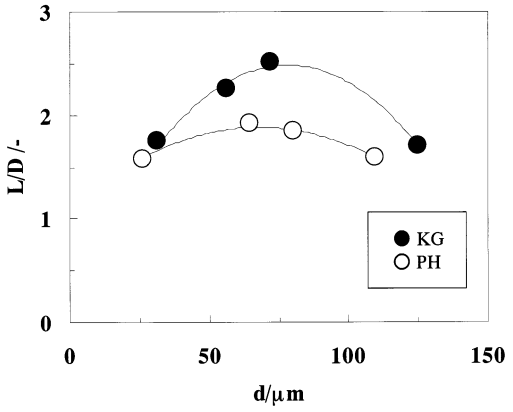

Fig. 5. Relationship between Heywood diameter d and L/D (L, length of particle; D, width of particle) of the fractions both for the PH and KG grades. Open circle, PH grade; closed circle, KG grade.

3.4. Relationship among length L, width D, tensile strength T and number distribution of MCC particles

Fig. 7 is a contour map of T in a D–L plane for the eight fractions of the KG and PH grades. P_f of all tablets was constant at 0.4. In the case where L increases with constant D (in the direction of arrow I), T increases gradually. In the case where D decreases with constant L (in the direction of arrow II), T also increases gradually. Accordingly, the highest peak was located near the point of $D = 45$ μm and $L = 130$ μm. From the fact that rod-shaped particles with higher L/D ratio exhibit larger T, it was concluded that the

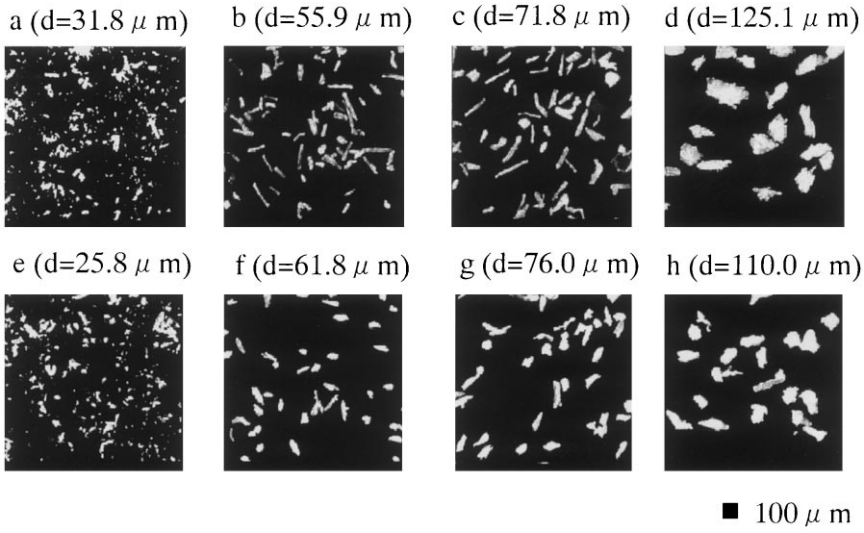

Fig. 4. Morphology of particles in each fraction of the PH and KG grades: (a) KG grade, $d = 31.8$ μm; (b) KG grade, $d = 55.9$ μm; (c) KG grade, $d = 71.8$ μm; (d) KG grade, $d = 125.1$ μm; (e) PH grade, $d = 25.8$ μm; (f) PH grade, $d = 61.8$ μm; (g) PH grade, $d = 76.0$ μm; (h) PH grade, $d = 110.0$ μm. A side of a dosed square stands for 100 μm.

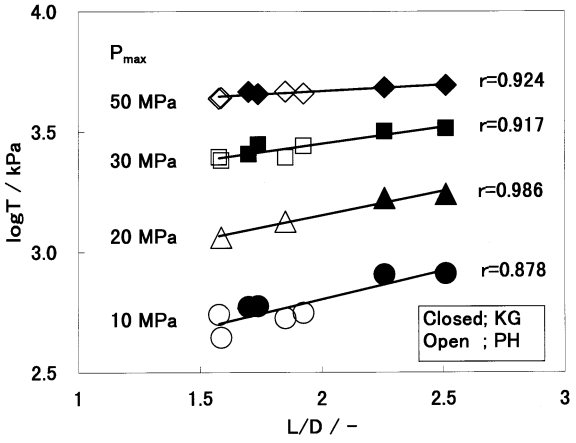

Fig. 6. Relationship between log T and L/D. Open circle, PH grade, $P_f = 0.41–0.43$; open triangle, PH grade, $P_f = 0.52–0.54$; open square, PH grade, $P_f = 0.61–0.65$; open diamond, PH grade, $P_f = 0.68–0.74$, closed circle, KG grade, $P_f = 0.41–0.43$; closed triangle, KG grade, $P_f = 0.52–0.54$; closed square, KG grade, $P_f = 0.61–0.65$; closed diamond, KG grade, $P_f = 0.68–0.74$. r, stands for correlation coefficient.

long and narrow rod-shaped particles exhibit larger T than the round-shaped particles when they are compressed.

Fig. 8(a,b) shows the number distribution of MCC particles on a $D–L/D$ plane. Darker region

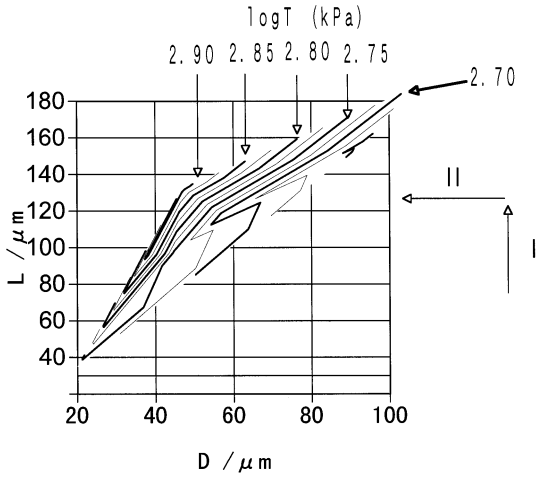

Fig. 7. Effects of L and D of MCC particles on tablet tensile strength T. $P_f = 0.4$.

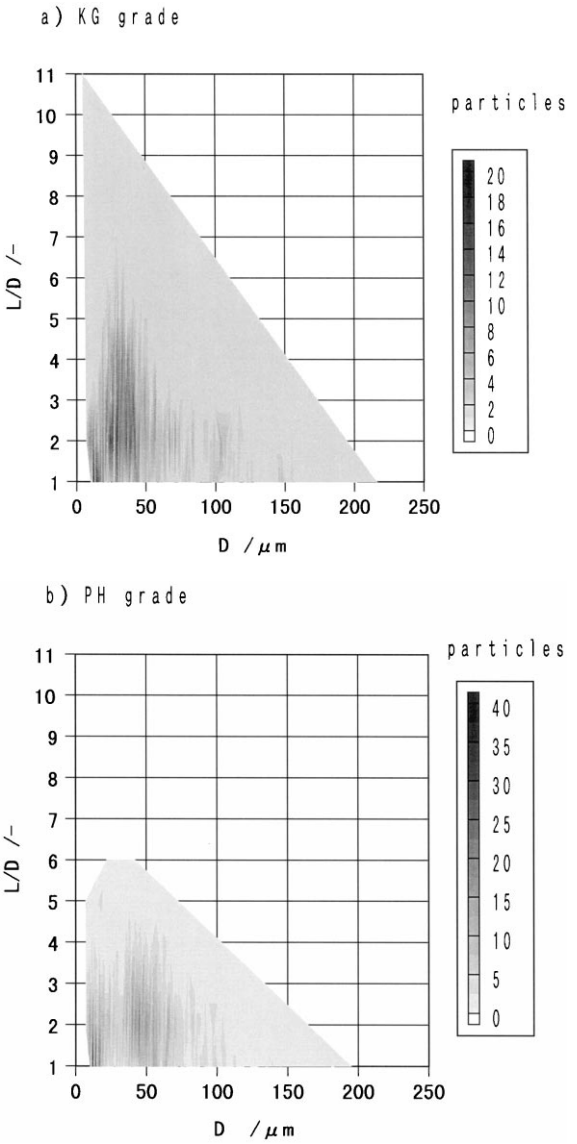

Fig. 8. Number distribution of MCC particles on a $D–L/D$ plane: (a) KG grade, (b) PH grade

indicates larger number of particles. Both grades have almost the same range of D ($10 \sim 200$ μm), but the range of distribution of L/D was clearly wider in the KG grade. Furthermore, KG grade has the highest population in the area of higher L/D ratio than PH grade. This is the reason why KG grade can exhibit higher compressibility than PH grade.

4. Conclusions

1. The logarithm of tablet tensile strength T of MCC particles is proportional to L/D.
2. The morphological factor, i.e. L/D ratio, was one of the most important factors determining T of MCC particles. Rod-shaped particles with higher L/D ratio tend to exhibit larger T than round-shaped particles when they are compressed.
3. Comparing number distribution of particles in a D–L/D plane between the two grades, we found that the KG grade had the highest population in the area of higher L/D ratio than the PH grade. This is the reason why KG grade can exhibit higher compressibility than PH grade.

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