

Preparation and Evaluation of a Compressed Tablet Rapidly Disintegrating in the Oral Cavity

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In order to make a compressed tablet which can rapidly disintegrate in the oral cavity, microcrystalline cellulose and low-substituted hydroxypropylcellulose were used as disintegrants, and ethenzamide and ascorbic acid were chosen as poorly and easily water soluble model drugs, respectively.

The mixture of microcrystalline cellulose and low-substituted hydroxypropylcellulose was compressed at 100–500 kgf in the absence of an active ingredient. The properties of these tablets, such as hardness, porosity, the time required for complete wetting of a tested tablet (wetting time), water uptake and disintegration time determined by a new disintegration apparatus, were investigated to elucidate the wetting and disintegration characteristics of these tablets. When the MCC/L-HPC ratio was in the range of 8:2 to 9:1, the shortest disintegration time was observed. The disintegration of tablets containing ethenzamide or ascorbic acid was examined next. Tablet disintegration time in the oral cavity was also tested, and good correlation between the disintegration behaviors *in vitro* and in the oral cavity was recognized.

Key words rapidly disintegrating tablet; disintegration; wetting; microcrystalline cellulose; low-substituted hydroxypropylcellulose; disintegration apparatus

The physiology and psychology of the elderly are different from those of young people. Due to their decline in swallowing ability, oral drug administration to the elderly is a significant problem and has recently become the object of public attention. Some useful methods have been developed and their clinical applications were attempted.^{1–6} However, since there exist a great number of drugs having different characteristics, more studies are still expected. The purpose of our study was to develop a rapidly disintegrating tablet with a simple and low-cost manufacturing process. To achieve this object, it is necessary to find a suitable disintegrant having excellent compactibility and disintegrating properties as well as a pleasant taste. Another important subject is to establish an *in vitro* test for rapidly disintegrating tablets which can simulate disintegration behavior in the oral cavity.

Experimental

Materials Ethenzamide (ETZ) (Yoshitomi Pharmaceutical Industries, Ltd., Japan) and ascorbic acid (Vc) (Takeda Chemical Industries, Ltd., Japan) were chosen as model drugs. Microcrystalline cellulose (MCC) (Avicel PH 102, Asahi Kasei, Co., Ltd., Japan) and low-substituted hydroxypropylcellulose (L-HPC) (LH-11, Shin-Etsu Chemical Co., Ltd., Japan) were used as disintegrants. Tablettose (Meggler, Germany), Celluphere (CP-203, Asahi Kasei, Co., Ltd., Japan) and Cellulac (Meggler, Germany) served as glidants for direct compression, and magnesium stearate (St-Mg) (Yoneyama Pharmaceutical Industries, Ltd., Japan) was used as a lubricant.

Physical Properties of Tablet Excipients The powder characteristics of tablet excipients such as the angle of repose, and loose and dense bulk density, were measured using a powder tester (PT-D Hosokawa Micron, Co., Japan). Dense bulk density was the density at tapping number 180 (60 taps/min, 3 min), and compressibility, *C*, was calculated as follows:

$$C(\%) = 100(D - L)/D \quad (1)$$

where *D* and *L* denote dense and loose bulk density respectively. The true density was measured with a helium-air pycnometer (Model 1302, Micromeritics Instrument Co., U.S.A.). Heywood diameter and shape factor, *SF*, were determined by an image analyzer (Luzex 500, Nireco Co., Japan). The measurement of water absorption was carried out using the method described by Kawashima *et al.*⁷⁾ Data obtained are

listed in Table 1.

Preparation of Tablet Flat faced direct compression tablets, 202 mg in weight and 8 mm in diameter, were prepared using a rotary tableting machine (12 HUK-AW, Kikusui Seisakusho, Ltd., Japan) at compression forces of 100, 200, 300, 400 and 500 kgf (pre-compression forces, 1/3 that in each case). Tablet compositions are shown in Table 2.

To clarify the disintegration mechanism and to determine the optimal MCC/L-HPC ratio, lot A tablets were made of MCC and/or L-HPC without active ingredients. Lots B and C consisted of tablets containing 25 w/w% ETZ or Vc as the model drug, respectively. For all formulations, powders (or granules) were blended in a V-type mixer for 10 min and then St-Mg was added, followed by 5 min mixing. The granules of the B1 formulation were produced as follows: the powder mixture, except the lubricant, was kneaded with distilled water, and granules were prepared by the extrusion method. The granules were dried at room temperature for 12 h and then at 80°C for 4 h, followed by mixing with a lubricant (St-Mg) for 5 min. ETZ granules in formulation B2 were prepared with an agitating fluidized bed granulator (MP-01, Powrex Co., Ltd., Japan) using 7 w/v% hydroxypropylcellulose (L EP, Shin-Etsu Chemical Co., Ltd., Japan) aqueous solution as a binder. ETZ granules were then mixed with other powdered materials.

Measurement of Tablet Tensile Strength The tablet crushing load, which is the force required to break a tablet by compression in the radial direction, was measured using a tablet hardness tester (TS-50N, Okada Seiko Co., Ltd., Japan). The plunger was driven down at a speed of 20 mm/min. Tensile strength for crushing (*T*) was calculated using the

Table 1. Physical Properties of Excipients

	MCC (Avicel PH 102)	L-HPC (LH-11)
Particle size (μm) ^{a)}	56.4	84.1
$SF = (A/ML^2)4\pi^{1/3}$	0.336	0.231
True density (g/cm^3)	1.56	1.45
Loose bulk density (g/cm^3), <i>L</i>	0.31	0.33
Dense bulk density (g/cm^3), <i>D</i>	0.47	0.52
Angle of repose ($^\circ$)	45	51
Compressibility (%), <i>C</i>	34.0	36.5
Contact angle ($^\circ$)	21	50
Water absorbing ability (ml/g)	1.12	5.08

a) Heywood diameter ($n=600$). b) Shape factor *SF* represents sphericity of particle (when particle is spherical, $SF=1$). *ML*: maximum length of particle, *A*: projection area of particle ($n=600$).

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Table 2. Tablet Formulations

Material (mg/tablet)	Lot A							Lot B					Lot C
	A1	A2	A3	A4	A5	A6	A7	B1 ^{a)}	B2 ^{b)}	B3	B4	B5	C1
MCC	80	100	120	140	160	180	200	120	120	60	60	60	120
L-HPC	120	100	80	60	40	20	—	30	30	15	15	15	30
Tabletose	—	—	—	—	—	—	—	—	—	75	—	—	—
Celluphere	—	—	—	—	—	—	—	—	—	—	75	—	—
Cellulac	—	—	—	—	—	—	—	—	—	—	—	75	—
ETZ	—	—	—	—	—	—	—	45	50	50	50	50	—
HPC	—	—	—	—	—	—	—	5	—	—	—	—	—
Vc	—	—	—	—	—	—	—	—	—	—	—	—	50
St-Mg	2	2	2	2	2	2	2	2	2	2	2	2	2
Total weight	202	202	202	202	202	202	202	202	202	202	202	202	202

a) Powders were granulated by the extrusion method. b) ETZ granules prepared by the agitating fluidized bed method were mixed with other powdered materials.

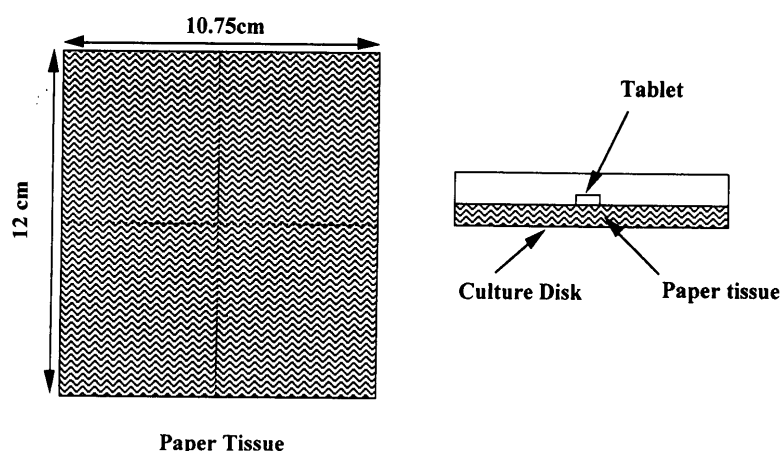


Fig. 1. A Simple Method for the Measurement of Wetting Time and Water Absorption Ratio of a Tablet

following equation:

$$T = 2F/(\pi dt) \quad (2)$$

where F is the crushing load, and d and t denote the diameter and thickness of the tablet, respectively.

Measurement of Tablet Friability Four grams of tablets were placed in a Roche friabilator which was rotated for 4 min at 30 rpm. The tablets were weighed and the loss in weight (%) was calculated.

Measurement of Tablet Porosity A mercury penetration porosimeter (Poresizer 9305, Micromeritics Instrument Co., U.S.A.) was used. The contact angle between mercury and the tablet was 140° , and the surface tension was 0.486 N/m . The measurement range of pore size was from 360 to $0.06 \mu\text{m}$.

Wetting Time and Water Absorption Ratio The method shown in Fig. 1 was used to measure tablet wetting time and water absorption ratio. A piece of paper tissue folded twice was placed in a small culture dish (i.d. = 6.5 cm) containing 6 ml of water, a tablet was put on the paper, and the time for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio, R , was determined according to the following equation:

$$R = 100(W_a - W_b)/W_b \quad (3)$$

where W_b and W_a are the weight before and after water absorption, respectively.

Measurement of Disintegration Time Instead of the disintegration apparatus described in JP XII, a modified dissolution apparatus (JP XII paddle method) was proposed. Figure 2 is a schematic view of the testing apparatus. Nine hundred milliliters of water maintained at 37°C and stirred with a paddle at 100 rpm was used as the disintegration fluid. Disintegration time was determined at the point at which the tablet disintegrated completely and passed through the screen of the sinker.

Disintegration in Oral Cavity The time required for complete

disintegration in the oral cavity was collected from six healthy volunteers, who were randomly administered 4 kinds of tablets at 24-h intervals.

Results and Discussion

Mechanism of Disintegration of MCC/L-HPC Tablets and Determination of Optimal MCC/L-HPC Ratio Tablet Tensile Strength: The tensile strength of MCC/L-HPC tablets is shown in Fig. 3. Tensile strength increased with the content of MCC, and tablets containing 40% of MCC showed especially low values compared with other compositions. It was generally recognized that tablet tensile strength was influenced by the number of contact points between the powder particles and the interparticle bonding force, such as the surface molecular interaction and mechanical interlocking. The number of contact points was altered by the porosity of the tablet and by the shape and diameter of constituent particles. MCC was easily compressed, and the porosity of a tablet was smaller than that of L-HPC (see next paragraph). Moreover, MCC showed a smaller particle diameter and larger value in degree of circularity (SF) compared to L-HPC, which is almost completely fibrous, so that the number of contact points in a unit cross-sectional area of the fracture plane of an MCC tablet was considered to be larger than that of L-HPC. On the other hand, MCC has more free hydroxyl groups than L-HPC (some of which are substituted by hydroxypropyl groups), and the interaction force in a contact point may thus be stronger because the

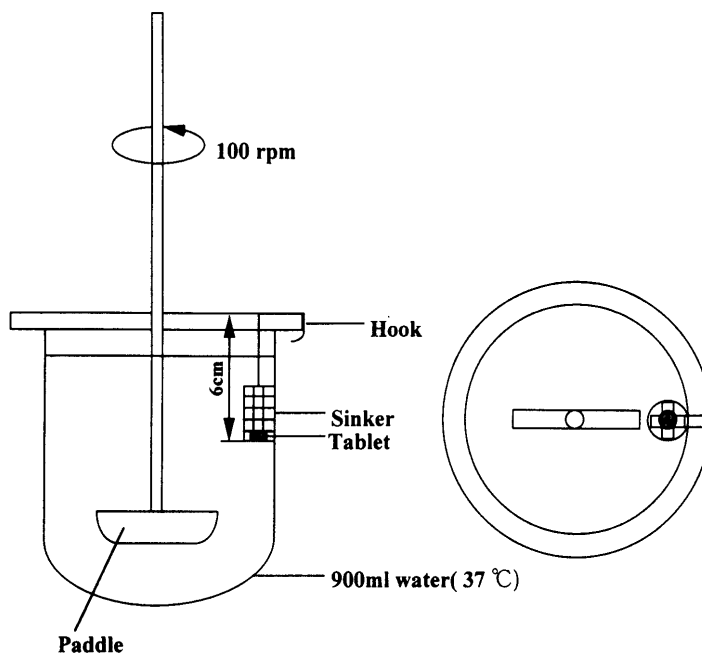
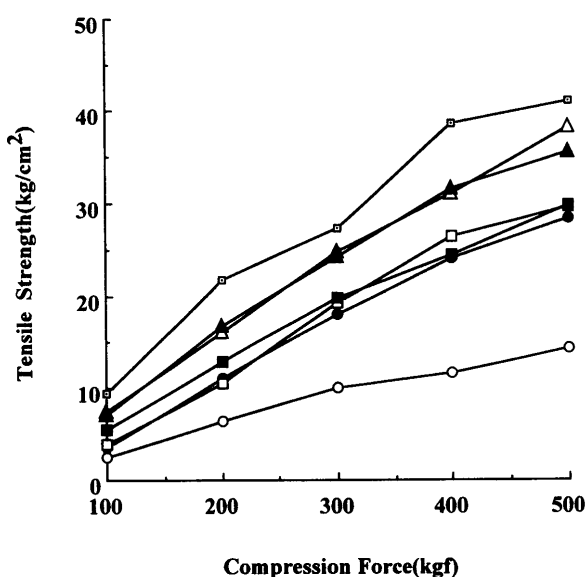


Fig. 2. Schematic View of Disintegration Apparatus

Fig. 3. Tensile Strength of MCC/L-HPC Tablets as a Function of Compression Force ($n=3$)

MCC:L-HPC ratios: —○—, 4:6; —●—, 5:5; —□—, 6:4; —■—, 7:3; —△—, 8:2; —▲—, 9:1; —□—, 10:0.

hydrogen bond of hydroxyl groups is considered to be stronger than that of hydroxypropyl groups.

Tablet Porosity: As shown in Fig. 4a, b, both the porosity and average pore size decreased with increasing compression force. With an increase in MCC content, the decrement in porosity became marked, indicating that MCC was more compressible than L-HPC.

Water Absorption and Wetting Time: Figure 5 shows the relationship between the water absorption ratio and MCC content in a tablet. Water uptake increased with an increased content of L-HPC and caused a great deal of swelling.

During the manufacture of MCC, accessible amorphous regions of cellulose molecules are hydrolyzed away, so that MCC shows relatively high crystallinity. It

can absorb only small amounts of water, and reaches equilibrium rapidly. On the other hand, for L-HPC, only a small proportion of the three hydroxyl groups per glucose subunit are converted to hydroxypropyl ether, and thus its crystallinity is far lower than that of MCC.⁸⁾ Water uptake to the amorphous region of L-HPC was superior to that of MCC. Therefore, in an MCC/L-HPC system, the properties of tablets changed with the composition of the material.

Figure 6 shows the time required for complete wetting of a testing tablet (wetting time) as a function of MCC content (%) in an MCC/L-HPC mixture. This figure can be obtained by the interpolation method using the data of variation of wetting time with porosity at each compression force.

Wetting is closely related to the inner structure of tablets and to the hydrophilicity of excipients. According to Eq. 4 proposed by Washburn,⁹⁾ the water penetration rate into the powder bed is proportional to the pore radius and is affected by the hydrophilicity of powders (which is expressed by contact angle θ and surface tension γ).

$$dl/dt = r\gamma \cos \theta / (4\eta l) \quad (4)$$

where l is the length of penetration, r is the capillary radius, γ is the surface tension, η is the liquid viscosity, t is the time and θ is the contact angle.

It is obvious that pore size becomes smaller and wetting time increases with an increase in compression force or a decrease in porosity. Since the hydrophilicity of L-HPC is lower than MCC, wetting time generally decreases with an increased MCC content.

When the MCC content exceeded 90%, however, the wetting time showed a reverse tendency. This suggested that the inner structure of these tablets underwent some change at a high MCC concentration. Since MCC particles are of a concave-convex shape and their pores are fairly collapsed by compression, the tortuosity of a pore

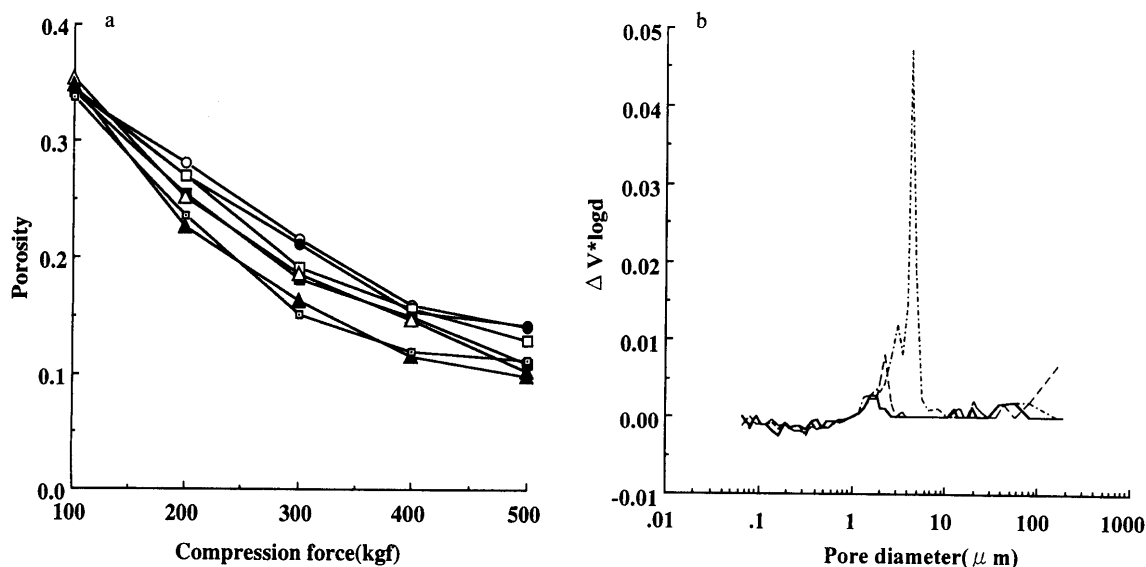


Fig. 4a. Porosity of MCC/L-HPC Tablets as a Function of Compression Force ($n=3$)

MCC:L-HPC ratios: —○—, 4:6; —●—, 5:5; —□—, 6:4; —■—, 7:3; —△—, 8:2; —▲—, 9:1; —◻—, 10:0.

Fig. 4b. Pore Size Distribution of MCC/L-HPC (6:4) Tablets

V, pore volume; d, pore diameter. Compression force: ----, 100 kgf; ·····, 300 kgf; —, 500 kgf.

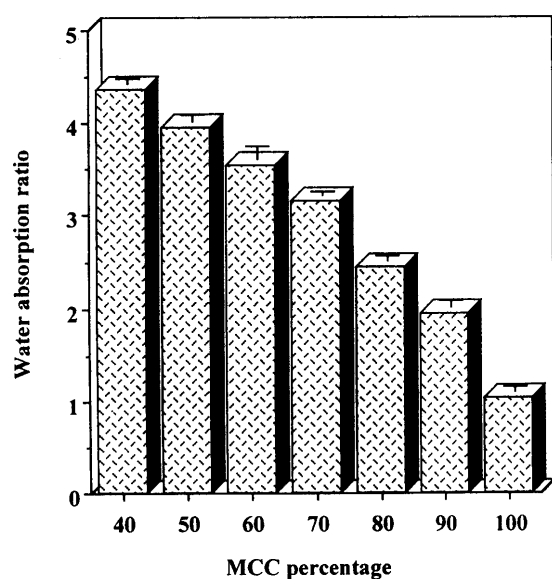


Fig. 5. Water Absorption Ratio of MCC/L-HPC Tablets

Compression force: 100 kgf, values are the means \pm S.D., $n=3$.

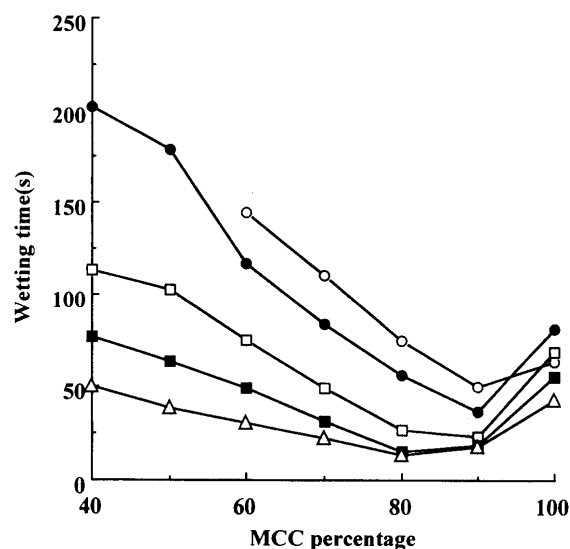


Fig. 6. Effect of Tablet Porosity on the Relationship between Wetting Time and Composition of MCC/L-HPC Tablets

Tablet porosity: —○—, 0.125; —●—, 0.15; —□—, 0.20; —■—, 0.25; —△—, 0.30.

in MCC tablets was greater than that of tablets containing L-HPC, so that wetting time was prolonged to some extent.

Disintegration Mechanism: When the disintegration method described in JP XII was applied, the disintegration of tablets prepared in this study was too fast to distinguish the difference in disintegration behavior of each tablet, and the data were not in accordance with those obtained from the in oral cavity test described above. A new method was then introduced.

Disintegration time profiles of MCC/L-HPC tablets are shown in Fig. 7, which were similar to those of wetting time. The relationship between the wetting time and disintegration time of MCC/L-HPC tablets is shown in Fig. 8. A linear correlation was observed, suggesting that wetting is an important step for the disintegration

process. Tablets with 100% MCC did not disintegrate, even after 12 h, and retained their original shape.

Micrography was used for investigating the swelling characteristics of MCC and L-HPC particles microscopically. It was observed that L-HPC swelled significantly, that is, all the particles, even small ones, swelled, while the expansion of MCC particles was less, and their original dry texture form was partially retained (Fig. 9). Gissinger and Stamm showed that the maximum swelling of L-HPC was about 10 times of that of MCC.¹⁰⁾ The swelling process is always accompanied by expanding force: the more the particle swell, the bigger the force will be. The weak swelling of MCC particles resulted in only a small expanding force, which would be one of the reasons the MCC tablet did not disintegrate. The mechanical interlocking force between MCC particles would also con-

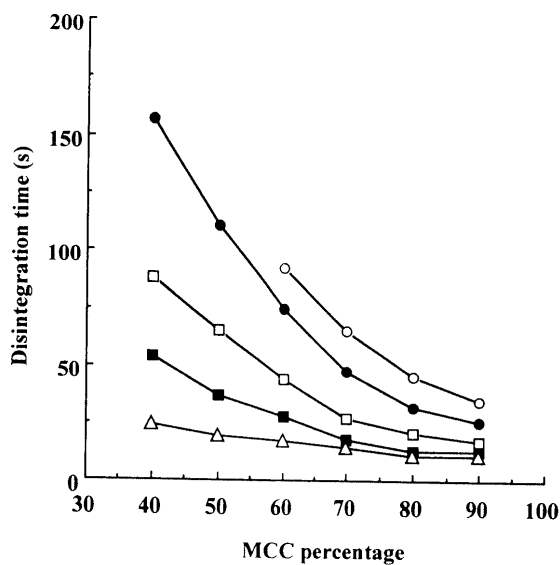


Fig. 7. Effect of Tablet Porosity on the Relationship between Disintegration Time and the Composition of MCC/L-HPC Tablets

Tablet porosity: —○—, 0.125; —●—, 0.15; —□—, 0.20; —■—, 0.25; —△—, 0.30.

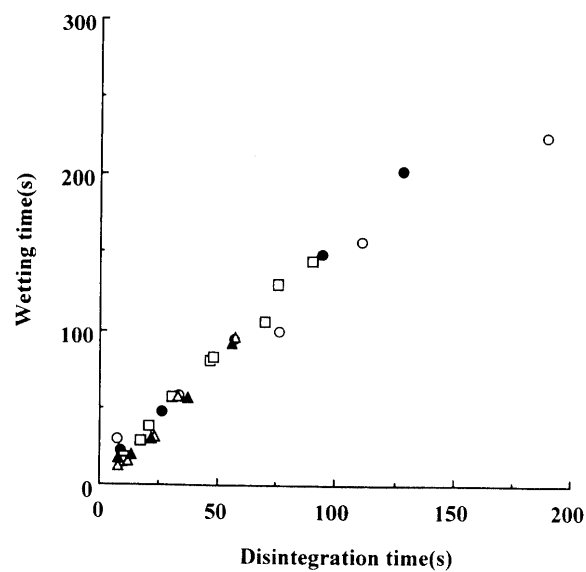
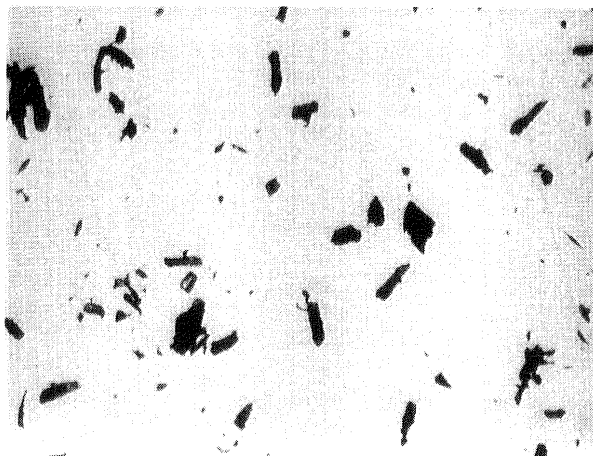


Fig. 8. Relationship between Wetting Time and Disintegration Time for MCC/L-HPC Tablets

$y = 8.019 + 1.383x$, $R^2 = 0.959$. x , disintegration time (s); y , wetting time (s).
MCC:L-HPC ratios: ○, 4:6; ●, 5:5; □, 6:4; ■, 7:3; △, 8:2; ▲, 9:1.



L-HPC(LH-11)



MCC(Avicel PH 102)

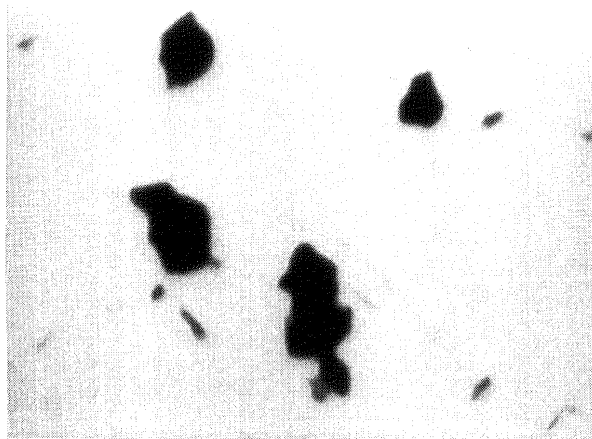


Fig. 9. Micrographs of MCC and L-HPC before and after Water Absorption

Left, before water absorption; right, after water absorption.

tribute to this phenomenon. Consequently, the sum of the expanding force in a particle and the agitation force due to water current was not enough to break down the MCC network.

It follows from the above findings that the disintegration of MCC/L-HPC tablets is affected mainly by tablet porosity, hydrophilicity, swelling ability and interparticle force. Using the regression method, the disintegration time, z (s), was expressed by the following equation:

$$z = -1.41x - 1.54y + 0.0042x^2 + 0.0049y^2 + 0.0090xy + 129.7 \quad (5)$$

$$N=27 \quad R^2=0.977 \quad T(21)<0.05 \quad F(5,21)=193.3 \quad S.D.=3.13$$

where x stands for microcrystalline cellulose concentration, y refers to tablet porosity, N is the number of samples, R is the multiple correlation coefficient, T denotes the P value determined by Student's t -test, and F , that obtained by the F -test. Here, x and y were normalized in such a way that the minimum and maximum were regarded as zero and one hundred, respectively. The minimum and the maximum are 40, 100 for x , and 0.125, 0.3 for y .

Disintegration time significantly decreased with the increase of both MCC content and tablet porosity. At low tablet porosities, disintegration time decreased rapidly with the increase of MCC content, and the effect of porosity on disintegration time was more significant when MCC content was low.

From above results, tablets containing MCC in the range of 80–90% were of sufficient hardness, and the disintegration time as well as wetting time were also desirable. In the disintegration studies of tablets containing an active ingredient, the powder mixture of MCC and L-HPC (mixing ratio 4:1) was used as a disintegrant.

Ethenzamide Tablet Formulations The mixture of ETZ (25%) and MCC/L-HPC (75%) could not form tablets satisfactorily with a rotary tableting machine, due to small bulk density and poor flowability. Therefore, granules of a powder mixture prepared by the extrusion method (Lot. B1 in Table 2), a mixture of granules of ETZ made by the agitating fluidized bed method and MCC/L-HPC powder (B2), and a mixture of ETZ, MCC/L-HPC (disintegrant) and various excipients for direct compression (B3,4,5) were examined. Here, Tablettose and Celluphere in B3 and B4 were granules made of lactose and MCC, respectively, and Cellulac in B5 is granules made of a lactose and MCC (3:1) mixture. All of these three excipients showed high flowability and were useful in facilitating the tableting process. In Table 3, characteristics relating to flowability are shown for every formulation.

However, not every formulation was satisfactory, as indicated in Fig. 10. For B5 formulation, disintegration time was extremely long. For B4 formulation, disintegration and wetting time were satisfactory but the crushing load was too low. Though tablets of the B1 formula-

Table 3. Characteristics of Lot B Powders or Granules

Formulation	ETZ 25% MCC:L-HPC 8:2 powder 75%	B1 (granule)	B2 (EZM granules mixed with powders)	B3	B4	B5
Angle of repose	53	44	43	50	50	48
L (g/cm ³)	0.31	0.37	0.35	0.46	0.52	0.41
D (g/cm ³)	0.59	0.43	0.51	0.74	0.83	0.68
C (%)	47.3	14.7	32.7	38.3	37.8	40.1

L , D , C are the same as those of Table 1. All of the data are average values of three runs.

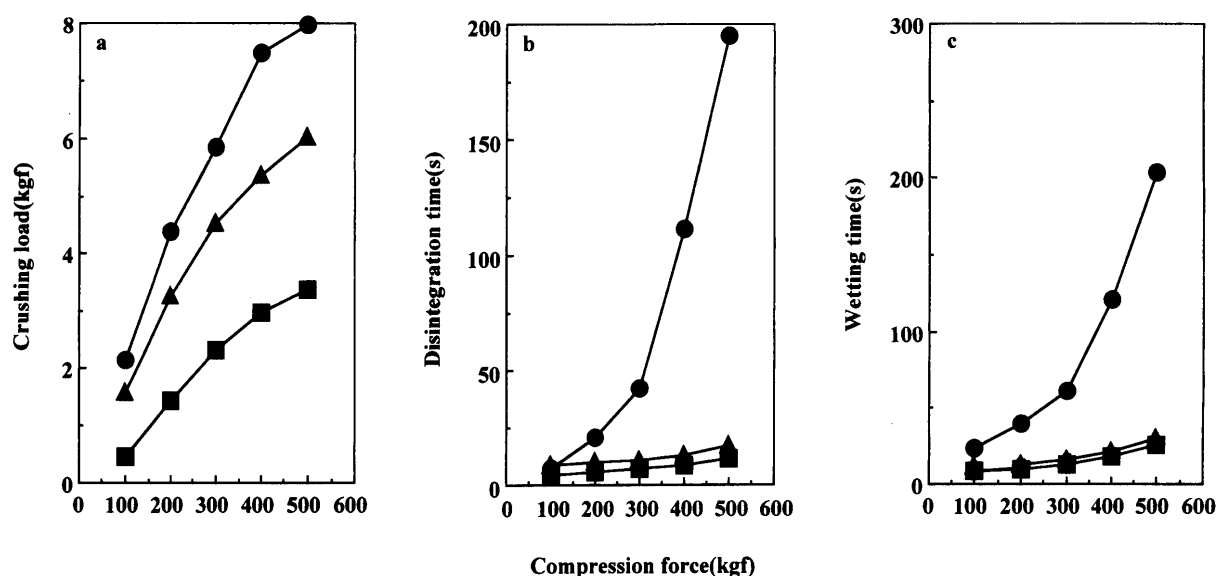


Fig. 10. Crushing Load, Disintegration Time and Wetting Time of Lot B Tablets ($n=10$)

▲, B3; ■, B4; ●, B5.

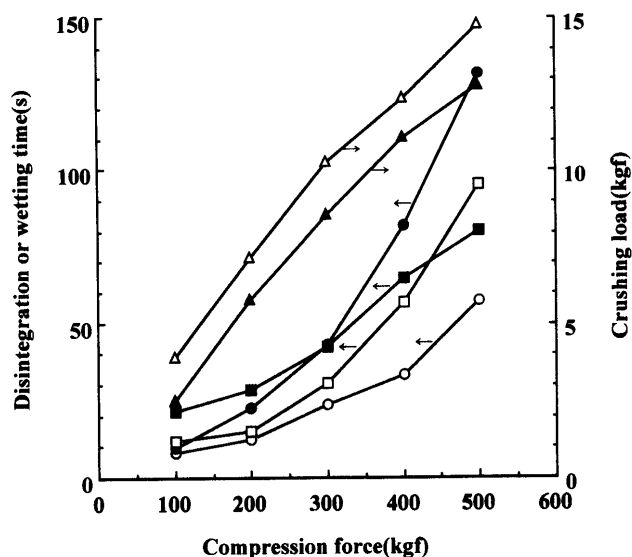


Fig. 11. Comparison of Tablets without and with Vc

Open symbols: MCC/L-HPC (ratio 4:1) tablets without Vc, closed symbols: MCC/L-HPC (ratio 4:1, 75%) tablets containing 25% of Vc ($n=10$). —○—, disintegration time; —□—, wetting time; —△—, crushing load.

tion disintegrated into granules within a short time, the granules could not break into small particles at all. This is unacceptable for oral administration, because of its unpleasant sensation on the tongue. B2 tablets made from ETZ granules showed very high compressibility, but did not show ideal disintegration ability. Tablets of the B3 formulation could be wetted and disintegrated within a short time, and its tablet crushing load was desirable. The friability of the tablet was less than 1%, indicating that the tablet was durable, permitting transportation without obvious damage.

Ascorbic Acid Tablets Ascorbic acid was used as an easily water soluble model drug, the content of which in tablets was 25 w/w%. In Fig. 11, the crushing load, wetting time and disintegration time were compared with a system without Vc. In crushing load and wetting time, no remarkable differences were observed between the two. For disintegration time, however, tablets containing Vc prepared under a high compression force were non-swelling, and disintegration time was much longer than in those without Vc. For tablets compressed at a low pressure, the disintegration time was not so long, suggesting that they possessed relatively high porosity and good wetting ability.

Disintegration Test in the Oral Cavity and the Evaluation of an *in Vitro* Disintegration Test Method To investigate the correlation between *in vitro* and in oral cavity disintegration tests, four kinds of tablets were examined. As shown in Fig. 12, the rank order of disintegration time in the oral cavity was similar to the *in vitro* test, and most of the six volunteers indicated that tablets of this type were of a suitable dosage form for rapid disintegration in the oral cavity.

As *in vitro* disintegration data under mild testing conditions were reproducible, they should be used for predicting of the disintegration time in the oral cavity.

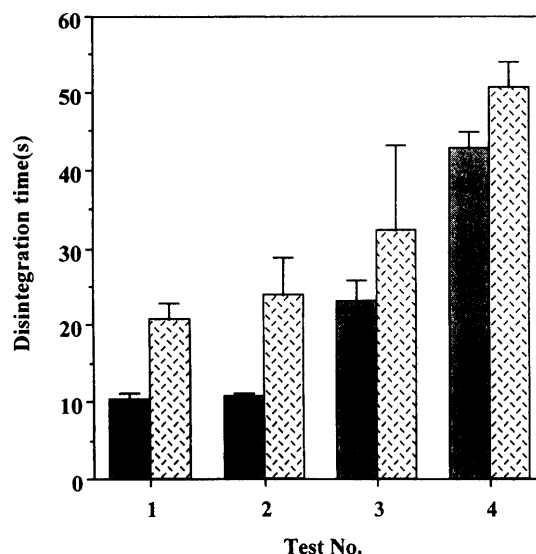


Fig. 12. The Comparison of Disintegration Data *in Vitro* and in Oral Cavity

1. Tablettose: L-HPC 8:2 tablet, 2. lot B3, 3. lot A5, 4. lot C. Compression force of above tablets was 300 kgf ($n=6$), ■, *in vitro*; ▨, in oral cavity.

Conclusions

In order to develop a rapidly disintegrating tablet, the disintegrating property of a mixture of microcrystalline cellulose and low-substitute hydroxypropylcellulose was examined. It was suggested that important factors for the disintegration process of tablets are tablet porosity, hydrophilicity, swelling ability of the particle, and inter-particle force. A new disintegration apparatus in which a gentle water current was produced was introduced for assessing rapidly disintegrating tablets. When the MCC/L-HPC ratio was in the range of 8:2 to 9:1, the disintegration time was shortest. Thus, the powder in which MCC and L-HPC were mixed in a ratio of 8:2 was chosen as a disintegrant for the ETZ or Vc tablet. Disintegration data for oral cavity tests were closely related to those for *in vitro* tests. It was supposed that some of the tablet formulations in the present study were useful and practical for a rapidly disintegrating dosage form for the elderly.

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