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RESEARCH PAPER

Influence of Granulating Method on Physical and Mechanical Properties, Compression Behavior, and Compactibility of Lactose and Microcrystalline Cellulose Granules

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ABSTRACT

The physical and mechanical properties of lactose (LC) and microcrystalline cellulose (MCC) granules prepared by various granulating methods were determined, and their effects on the compression and strength of the tablets were examined. From the force-displacement curve obtained in a crushing test on a single granule, all LC granules appeared brittle, and MCC granules were somewhat plastically deformable. Intergranular porosity ε_{inter} *clearly decreased with greater spherical granule shape for both materials. Decrease in intragranular porosity* ε_{intra} *enhanced the crushing force of a single granule* F_g*. Agitating granulation brought about the most compactness and hardness of granules. In granule compression tests, the initial slope of Heckel plots* K_1 *appeared closely related to ease of filling voids in a granule bed by the slippage or rolling of granules. The reciprocal of the slope in the succeeding step* $1/K_2$ *in compression of MCC granules indicated positive correlation to* F_g*, while in LC granules, no such obvious relation was evident.* $1/K_2$ *differed only slightly among granulating methods. Tensile strength of tablets* T_t *obtained by compression of various LC granules was low as a whole and was little influenced*

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by granulating method. For MCC granules, which are plastically deformable, tablet strength greatly depended on granulation. Granules prepared by extruding or dry granulation gave strong tablets. Tablets prepared from granules made by the agitating method showed particularly low T_t. *From stereomicroscopic observation, the contact area between granule particles in a tablet appeared smaller; this would explain the decrease in intergranular bond formation.*
Key Words: *Compactibility; Compressibility; Granulating method; Granule strength; Radical tensile strength.*

INTRODUCTION

The tablet is the most frequently employed dosage form, and many preparation techniques have been adopted. Among them, the granulation method is still utilized since granules are free flowing and easily compressed to form compacts with optimum mechanical strength. Moreover, granulation makes it possible to avoid segregation of fine particles of ingredients, causing production of tablets with an excellent content uniformity.

In our previous studies, physical and mechanical properties of wet masses of powder, as well as granules, prepared by the extruding granulation technique were studied (1). It was elucidated that the adhesive and cohesive properties of powder particles were influenced by the type and amount of binder solutions (2,3). The relationship between strength of granules and strength of tablets produced from the granules was also examined (4). In connection with direct compression in tableting, a number of studies on static compression of powders in a die have been carried out. However, relatively few studies on granule compression have been performed.

Zwan and Siskens (5) suggested that there would be four stages during bulk volume reduction in granule compression: (*a*) filling the holes between granules, (*b*) fragmentation and plastic deformation, (*c*) filling the holes between the primary particles, and (*d*) fragmentation and plastic deformation of the primary particles. Kawashima and coworkers (6,7) described that compaction of granules exhibited the following four steps in accordance with the hypothesis of Train (8): (*a*) transitional repacking, (*b*) formation of temporary struts, (*c*) fracturing, and (*d*) densifying.

Effects of the granulation method on the physical and mechanical properties of final products (tablets) have been studied, using various powdered materials (9–15). Many investigators have reported that facets of the granule structure such as porosity, pore diameter, surface area, and bulk density affected the tablet strength (11–14,16–27). However, it was supposed that the results seemed to depend on both the material and the method used.

The relation between mechanical properties of granules and tablet strengths has also been discussed frequently. Krycer and Pope (11), Wikberg and Alderborn (17–20), and Kawashima et al. (6) suggested that the tablet strength increased with the degree of granule fragmentation during compaction. On the contrary, Doelker and Shotton (28) found that soft granules led to weak compacts when the base material exhibited little plastic flow. Jarosz and Parrott (29) described that the tensile strength of tablets was influenced by the crushing strength of granules; however, the compression force and concentration of the binder appeared to be related more basically to the tablet strength.

The objective of the present article was to evaluate the physical and mechanical properties of both lactose (LC) and microcrystalline cellulose (MCC) granules prepared by various granulation methods and to examine the effects of these properties on the tensile strength of tablets prepared by static compression of granules.

EXPERIMENTAL

Materials

The powdered materials used were LC (Pharmatose 200M, DMV, Veghel, The Netherlands), MCC (PH-101, Asahi Chem. Ind., Tokyo, Japan). The Heywood diameter, determined by an image analyzer (Luzex 500, Nireco, Tokyo, Japan), and true density, measured by a helium-air pycnometer (model 1302, Micromeritics Instrument, GA), for both materials are shown in Table 1. Sugar

Table 1

Sample Powders Used

Material	Mean Particle Diameter D_p (μm)	True Density ρ_t (kg · dm^{-3})
Lactose	94.8	1.53
Microcrystalline cellulose	27.3	1.56

spheres (Nonpareil [NP], Freunt, Tokyo, Japan) were used as received. Polyvinylpyrrolidone (PVP; Kollidon 90, BASF, Ludwigshafen, Germany) was used as a binder.

Methods

Granulation

Lactose

For fluidized bed granulation, LC (800 g) was granulated with 160 g of 5% (w/w) PVP aqueous solution in a fluidized bed granulator (Uni-glatt, Glatt, Binzen/Lorrach, Germany). The binder solutions were applied intermittently at a rate of 10 g/min. The net rate of application was approximately 5 g/min because breaks for shaking of filters were necessary. The temperature of the inlet air was 60°C. The moist granules obtained were ultimately dried to a constant weight at an outlet temperature of 50°C and then sieved to obtain the particle size fraction of 0.85–1.18 mm (LC-1).

For extruding granulation, LC (800 g) was mixed with 160 g of 5% (w/w) PVP aqueous solution using a kneader (AR400, Erweka, Heusenstamm, Germany). The wet mass was forced through a 1-mm screen by hand. The extruded granules were dried at 60°C for 3 hr and sieved to obtain the same particle size fraction as LC-1 (LC-2).

For agitating granulation, LC-3 was prepared with the same binder solution using a high-shear mixer granulator (Vertical Granulator FM-VG-10P, Powrex, Osaka, Japan) at a cross-screw speed of 3000 rpm and a blade speed of 300 rpm for 10 min. After granulation, moist granules were sphered with a spheronizer (Marumerizer Q-230, Osaka, Fuji Poudal, Japan) and then dried and sieved as described above.

Microcrystalline Cellulose

For extruding granulation, MCC powder was agglomerated with water in the same manner as LC-2 (MCC-1).

For dry granulation by roller compaction, MCC powder compacts were prepared with a roller compactor (Roller Compactor TF-Mini, Freund, Tokyo, Japan) equipped with two rollers revolving toward each other. The compacts were crushed with a roll granulator (Crack-U-Lator, Nihon Granulator, Shizuoka, Japan) to obtain granules. MCC-2 and MCC-3 were made from compacts compressed under pressures of 5 MPa and 10 MPa, respectively.

Table 2

Physical and Mechanical Properties of Granules Used

Physical and Mechanical Property	LC Granules			
	LC-1	LC-2	LC-3	NP Granules
Mean granule diameter[a] D_g (μm)	1038 (94)	1016 (36)	896 (58)	934 (29)
Shape index[a] ψ_g	0.558 (0.051)	0.553 (0.042)	0.829 (0.038)	0.927 (0.014)
Crushing force of a granule[a] F_g (N)	0.99 (0.46)	0.83 (0.31)	4.80 (1.37)	2.51 (0.62)
Granule density ρ_g (kg · dm^{-3})	1.027	1.075	1.220	1.297
Bulk density ρ_b (kg · dm^{-3})	0.411	0.424	0.631	0.748
Intragranular porosity ε_{intra}	0.329	0.297	0.203	0.184
Intergranular porosity ε_{inter}	0.600	0.606	0.483	0.423
Loose-packing porosity ε_0	0.731	0.723	0.588	0.530

Physical and Mechanical Property	MCC Granules				
	MCC-1	MCC-2	MCC-3	MCC-4	MCC-5
Mean granule diameter[a] D_g (μm)	1096 (105)	1050 (95)	1117 (90)	1023 (66)	943 (83)
Shape index[a] ψ_g	0.538 (0.036)	0.584 (0.046)	0.602 (0.041)	0.774 (0.072)	0.882 (0.027)
Crushing force of a granule[a] F_g (N)	7.50 (5.02)	6.77 (3.94)	8.31 (4.99)	14.34 (3.47)	13.74 (2.00)
Granule density ρ_g (kg · dm^{-3})	1.070	1.179	1.252	1.352	1.379
Bulk density ρ_b (kg · dm^{-3})	0.425	0.425	0.497	0.647	0.805
Intragranular porosity ε_{intra}	0.296	0.224	0.176	0.111	0.093
Intergranular porosity ε_{inter}	0.603	0.640	0.603	0.521	0.416
Loose-packing porosity ε_0	0.720	0.720	0.673	0.574	0.470

[a]Results represent the mean ± SD (in parentheses).

For agitating granulation, MCC powder was granulated with water using the same equipment and same operating conditions as for the production of LC-3. MCC-4 and MCC-5 were samples made without and with the spheration process before drying and sieving, respectively.

Measurement of Mean Granule Size and Shape

The particle size (Heywood diameter) and shape index ψ_g were determined with an image analyzer (Luzex FS, Nireco, Osaka, Japan). The value of ψ_g was obtained by dividing the actual projected area of a particles S by the area of a circle having a circumference equivalent to the perimeter length of the projected image $\overline{PM}$ as follows:

$$\psi_g = 4\pi S/\overline{PM}^2 \quad (1)$$

Therefore, the values of ψ_g ranged from 0 to 1, and its value decreased as the irregularity or roughness of the particle surface increased.

Measurement of Bulk Density

A cylinder with an inner diameter of 16 mm was filled with 1 g of granules, and the height of the bed was measured.

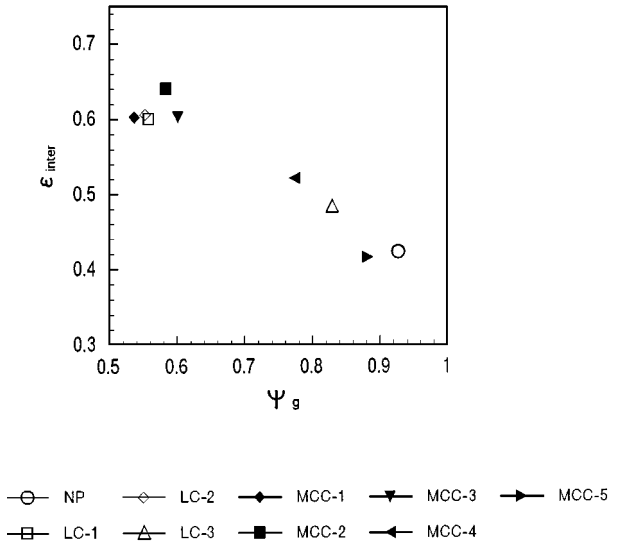


Figure 1. Relationship between shape index of granule ψ_g and intergranular porosity, ε_{inter}: ○, NP; □, LC-1; ◇, LC-2; △, LC-3; ◆, MCC-1; ■, MCC-2; ▼, MCC-3; ◀, MCC-4; ▶, MCC-5.

Measurement of Granule Density

Granule density was determined by the mercury displacement method using a mercury porosimeter (Pore S9305, Micromeritics Instrument, GA).

Crushing Test of Single Granule Particle

The single granule hardness (crushing force) F_g was measured with a particle hardness tester (Glano, Okada Seiko, Tokyo, Japan) for more than 30 particles. When plural peaks or notches were observed on a force-displacement curve, the last one was chosen as the representative value.

Compression Test of Granule Bed

Almost the same number of granules (about 1 g) was utilized in each sample. Granules were compressed with a universal testing machine (Autograph AG-5000E, Shimadzu, Kyoto, Japan) equipped with a flat-faced punch of 16 mm in diameter at a rate of 1.0 mm/min to obtain force-displacement profiles (F-D curves). Krycer and others (13) suggested that upper punch work W_u and work of elastic deformation W_{ED} could be calculated from F-D curves.

Measurement of Degree of Compression

The degree of compression C of the granules in-die was calculated by the following equation:

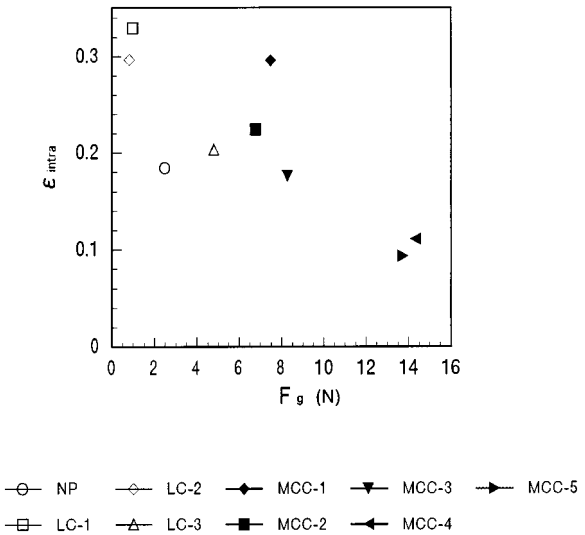


Figure 2. Relationship between crushing force of a single granule F_g and intragranular porosity ε_{intra}. Symbols as in Fig. 1.

$$C = (H_0 - H_P)/H_0 \times 100 \quad (2)$$

where H_0 and H_P are the heights of the granule bed in-die before compression and at a pressure P, respectively.

Measurement of Elastic Recovery of Compact

The elastic recovery *ER*, which is defined as the percentage of axial expansion of a compact (tablet), is measured from Eq. 3:

$$ER = (H_e - H_P)/H_P \times 100 \quad (3)$$

where H_e is the height of the compact after standing for 24 hr after ejection from the die.

Measurement of Radial Tensile Strength of Tablet

The tensile strength of tablets T_t ejected from the die and allowed to stand 24 hr was determined by the diametral compression test using a universal testing machine (Autograph AG-5000E, Shimadzu). T_t was calculated from the following equation (30):

$$T_t = 2F_t/(\pi D_t L) \quad (4)$$

where F_t is the compression force required to split a tablet. D_t and L are the diameter and thickness of the tablet, respectively.

Microscopic Observation

Surfaces of the original and split tablets were examined with a stereomicroscope (SMZ-T, Nikon, Tokyo).

RESULTS AND DISCUSSION

Physical and Mechanical Properties of Granules

The physical and mechanical properties of granules are shown in Table 2. Figure 1 represents the relationship between the shape index of granules ψ_g and the intergranular porosity ε_{inter} calculated from the true density ρ_t and bulk density ρ_b. In the present situation, the adhesive force between granules was negligible to the weight of a granule particle. Therefore, the possibility of filling the holes in a granule bed due to rolling or slippage (i.e., transitional repacking) was supposed to depend on the granule shape. This is because a bed of granule particles with higher surface roughness exhibits higher interparticle porosity.

In the F-D curve obtained by the crushing test of a single granule of LC and NP granules, the force was reduced distinctly to near zero at a certain strain, and resulting small fragments could be observed clearly, which suggested that brittle fracture of the granule occurred. For granules of MCC, although the reduction of force was detected on each F-D curve, it was incomplete (not reduced to near zero), or an immediate increase of force was shown after reduction. On the granule aftertest, only local cracks and/or partial fractures were observed. Therefore, it appeared that MCC granules have a less brittle property, and they are somewhat plastically deformable materials. In the preparation of LC granules, LC and the binding agent in a granulating liquid were deposited between adjacent LC particles, forming a solid bridge. In that of MCC granules, molecular chains of hydrous cellulose linked with each other to form hydrogen bonds. This difference in the mechanism of granule formation may affect the physical and mechanical properties of granules.

It was supposed that the crushing load of a single granule F_g increased as the degree of void in the sample decreased. Figure 2 shows the intragranular porosity ε_{intra}, which was calculated from ρ_t and ρ_g, as a function of F_g. For both LC and MCC granules, a decrease in ε_{intra} led to an increase in F_g, as expected. Among various granulating methods, it was found that the agitating method brought about the most compactness and hardness of

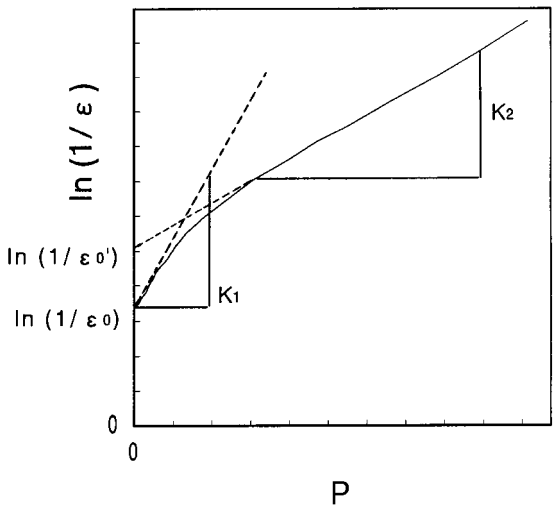


Figure 3. Typical Heckel plots.

granules for both series, which caused the reduction of the fragmentation propensity or deformability.

Compression of Granule Beds

As stated above, in the compaction of granule beds, at least two stages should be added to the powder compaction processes: filling the void in the beds and fracture and/or plastic deformation of the testing granules. These stages are considered to be related closely to the properties of an individual granule particle (6,7,25,31,32). Through the compression measurement, the mean particle size and the sample weight (number of granules) were almost the same to simplify the points at issue.

The compression processes were analyzed by the Heckel equation (33).

$$\ln(1/\varepsilon) = K_i P + \ln(1/\varepsilon_0) \quad (5)$$

where ε and ε_0 are the porosity at pressure P and 0, respectively, and K_i is a constant. A typical pressure versus logarithm of the reciprocal of porosity profiles is illustrated in Fig. 3, in which K_1 is the initial slope of the curve and is supposed to be related to the filling of the void by slipping or rolling of granules (31). K_2 is the slope of the succeeding process, and ε_0' is the porosity at $P = 0$ obtained by extrapolating the linear portion to the axis of ordinates. The parameters obtained are listed in Table 3.

Figure 4 shows the relationship between K_1 and $(\varepsilon_0 - \varepsilon_0')$. As was observed in Table 2 and Fig. 1, ε_0 and ε_{inter} increased with a decrease in shape index or an increase in surface roughness of the granule particle. Thus, K_1 was approximately proportional to $(\varepsilon_0 - \varepsilon_0')$, meaning that the incipient stage of compaction largely depended on the shape of the granule particle.

Every granule presented excellent linearity within the

Table 3

Parameters of Heckel Plots for Granules Tested

Parameter	LC Granules			Powder	NP Granules
	LC-1	LC-2	LC-3		
Initial stage					
K_1 (MPa^{-1})	0.251	0.326	0.122	1.646	0.125
$-\ln \varepsilon_0$	0.310	0.317	0.510	0.561	0.646
r^2	0.993	0.992	0.962	0.966	0.961
Second stage (2–10 MPa)					
K_2 (MPa^{-1})	0.063	0.062	0.051	0.048	0.058
$-\ln \varepsilon_0$	0.562	0.609	0.569	0.945	0.747
r^2	0.990	0.988	0.992	0.988	0.985
$1/K_2$ (MPa)	15.92	16.14	19.65	20.95	17.35
ε_0'	0.570	0.544	0.575	0.389	0.474
$[\varepsilon_0 - \varepsilon_0']$	0.163	0.184	0.026	0.182	0.050

Parameter	MCC Granules					MCC Powder
	MCC-1	MCC-2	MCC-3	MCC-4	MCC-5	
Initial stage						
k_1 (MPa^{-1})	0.145	0.303	0.238	0.076	0.063	0.178
$-\ln \varepsilon_o$	0.356	0.385	0.424	0.653	0.765	0.302
r^2	0.968	0.965	0.960	0.975	0.981	0.960
Second stage (2–10 MPa)						
K_2 (MPa^{-1})	0.041	0.046	0.036	0.018	0.015	0.041
$-\ln \varepsilon_0$	0.490	0.574	0.580	0.713	0.813	0.409
r^2	0.993	0.995	0.991	0.997	0.998	0.998
$1/K_2$ (MPa)	24.64	21.66	27.46	56.36	65.74	24.12
ε_0'	0.613	0.564	0.560	0.490	0.443	0.664
$[\varepsilon_0 - \varepsilon_0']$	0.088	0.117	0.095	0.030	0.022	0.744

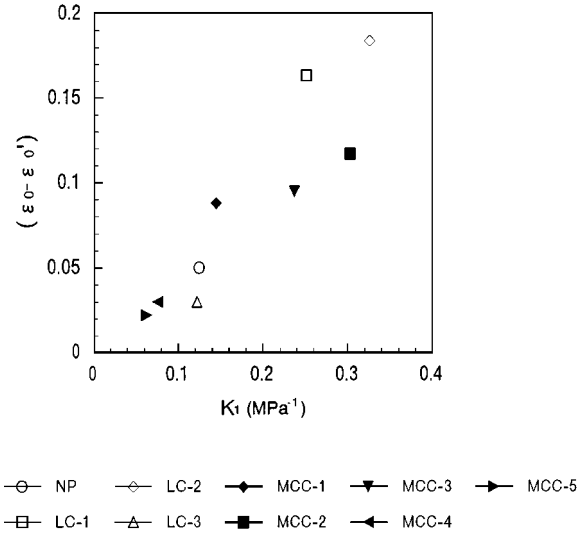


Figure 4. Relationship between constant K_1 and $(\varepsilon_0 - \varepsilon_0')$. Symbols as in Fig. 1.

compression pressure range 2–10 MPa. The reciprocal of K_2 in the Heckel equation has been regarded as the yield pressure of sample materials (i.e., the ability of material to deform plastically). Figure 5 shows the relationship between $1/K_2$ and the crushing force of a single granule F_g for each material. Since MCC granules were considered to perform plastic deformation, positive correlation was observed between these two parameters,

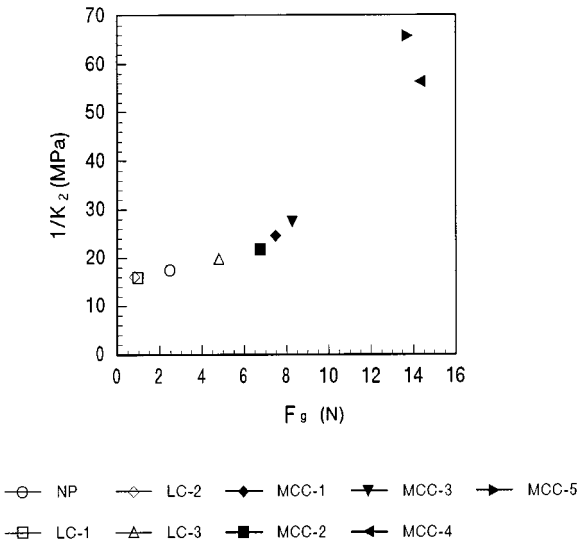


Figure 5. Relationship between crushing force of a single granule F_g and reciprocal of constant K_2. Symbols as in Fig. 1.

while in LC and NP granules with brittle fracture property, there was no such obvious relation between them. The value of $1/K_2$ differed only slightly among granulating methods, and those values were almost equivalent to that of lactose powder, suggesting that the LC granules used here fractured into nearly primary particles under pressures up to 2 MPa.

Tablet Strength

It has been recognized that the tablet strength depends on applied compression stress, total or net work done in compaction, elastic recovery of the tablet, and so on. In the compaction of granule beds, the kind of granule property that directly affects the tensile strength of tablet T_t is of great interest.

Granules were compressed at applied pressures of 50, 100, 150, 200, and 250 MPa to form tablets. Figures 6a and 6b show the change in tablet porosity after ejection from a die ε_t (which was calculated from ρ_t and tablet weight) with the applied pressure P. In Fig. 6a, the data of NP were added for a reference. Figures 7a, 7b, 8a, and 8b indicate T_t as a function of P and ε_t, respectively. From these figures, it is found that, for brittle LC granules, the tablet strength is low and is influenced little by the granulating method, indicating that the relationship between T_t and properties of a single granule particle such as F_g and ε_{intra} was not so clear. This result was in accord with the studies of Healey et al. (22) and Jarosz and Parrot (29). As stated above, LC granules are fractured into near-powdered materials in the incipient stage of compaction; therefore, the tablet strengths are not so different from those prepared by direct compression of LC powder (Table 4). The tensile strengths of all the MCC tablets prepared from various granules provided smaller values than those of the tablets obtained by direct compression of MCC powder. Tablets produced from granules prepared by the agitating method (MCC-4 and MCC-5), which exhibited large F_g and small ε_{intra} values, showed particularly low T_t. Maganti and Çelic (34) examined the strength of tablets produced from MCC powders and granules (pellets) and described that the compaction of powders produced strong tablets, whereas the tablets obtained from pellets exhibited lower tensile strength.

From stereomicroscopic studies, it was evident that the surface of tablets prepared from MCC powder seemed to be smooth, while that of those from granules was rough, especially in MCC-4 or MCC-5, and granules kept their integrity (Photos 1 and 2). Photograph 2b shows the fracture state after the tensile test, which re-

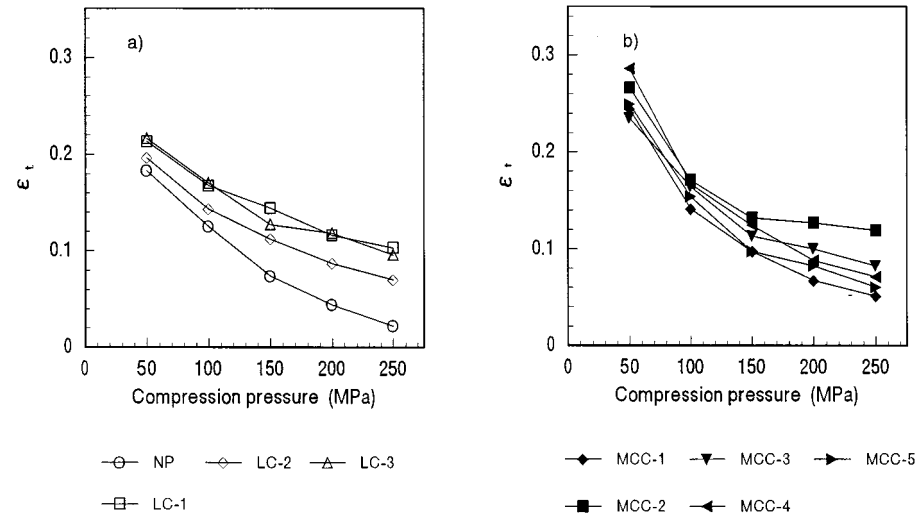


Figure 6. Tablet porosity ε_t versus applied compression pressure: (a) LC granules and NP; (b) MCC granules. Symbols as in Fig. 1.

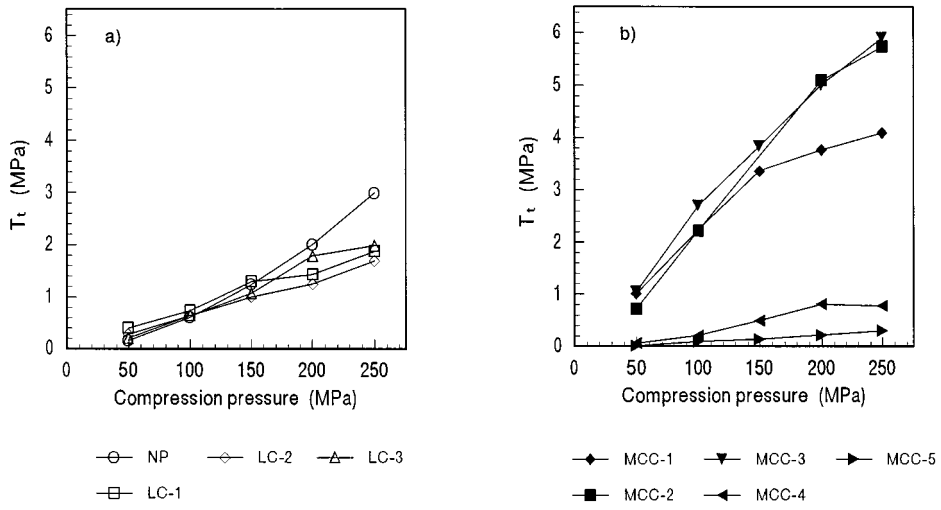


Figure 7. Tablet strength T_t versus applied compression pressure: (a) LC granules and NP; (b) MCC granules. Symbols as in Fig. 1.

vealed that tablet fragmentation occurred at the granule boundaries. It was thus suggested that plastic deformation of granules during compaction was inferior to that of the powdered material. In those granules having large F_g or $1/K_2$ values, the contact area between granule particles in a tablet appeared smaller, and this would explain the decrease in intergranular bond formation.

Table 4 lists the compaction behavior and characteristics of each tablet compressed at 250 MPa, where W_u is the upper punch work supplied during compaction, and W_{ED} is the work of elastic deformation (expansion) during decompression. Both values are obtained from compression force versus displacement of upper punch profiles. $(W_u - W_{ED})$ is considered to be a measure of the net work utilized in compaction of a granule bed, although the work of die-wall friction is included in it. Ragnarsson and Sjogren (35) pointed out that T_t of tocinide hydrochloride showed an obviously much better correlation to the net work input than to the compaction pressure. In the present granule compaction study, the relationship between

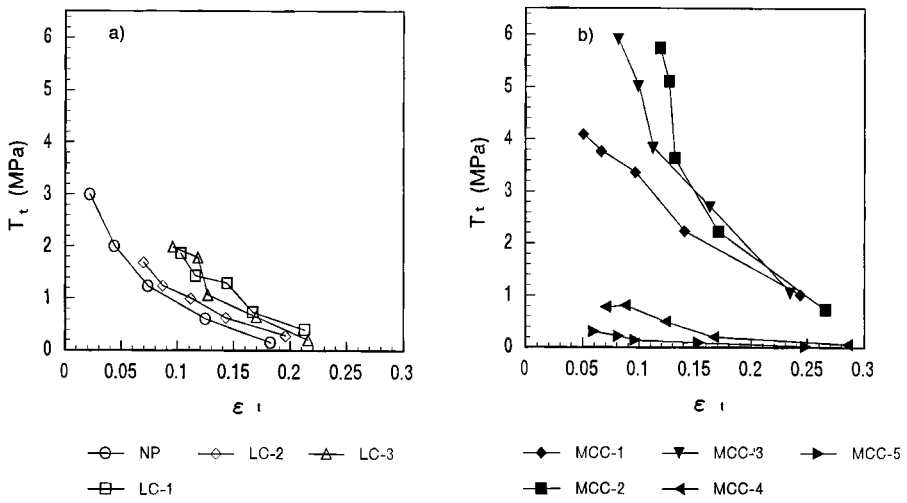


Figure 8. Relationship between tablet porosity ε_t and tablet strength T_t. Symbols as in Fig. 1.

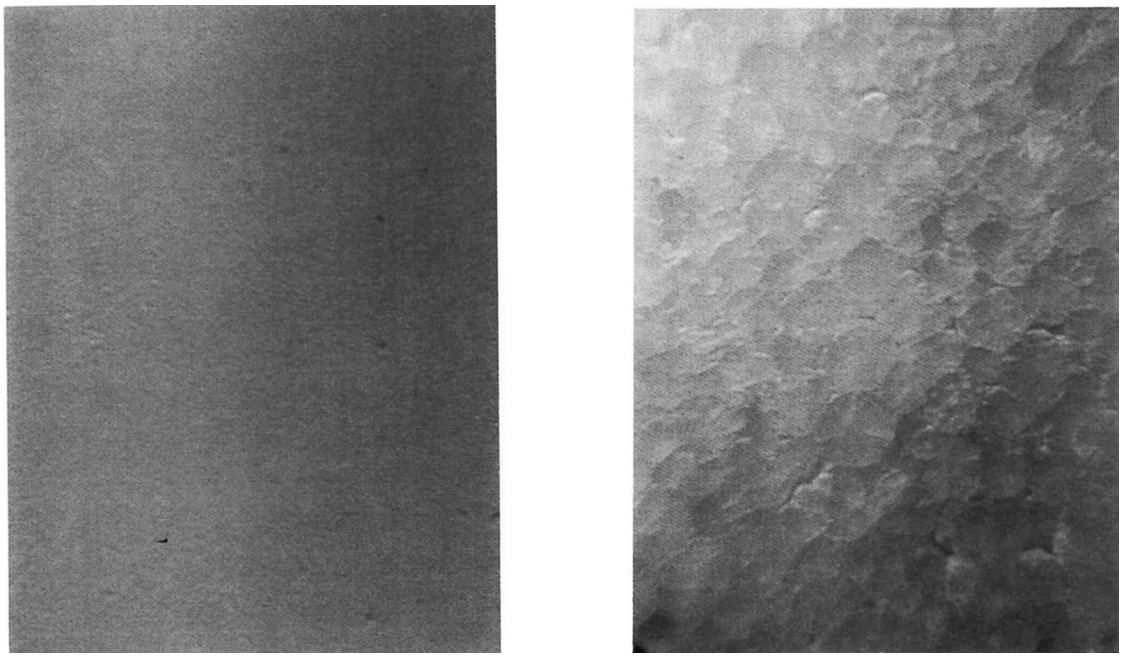
W_u or $(W_u - W_{ED})$ and T_t seemed to be the reverse of the general concept in powder compaction (35–38), suggesting that the large portion of work input was devoted to the reduction of inter- and intragranular porosity rather than the formation of intergranular bonds. A similar reversion was observed in *ER*. Examinations of MCC pellets with different porosities and mechanical properties were carried out by Johansson et al. (23). They described that the degree of compression of the granule bed in-die *C* is a reflection of the degree of deformation of the individual pellets during compression. They concluded that the degree of pellet deformation increased with an increase in original pellet porosity, and a high degree of pellet deformation promoted the formation of intergranu-

Table 4

Compaction Behavior and Characteristics of Tablets Compressed at 250 MPa

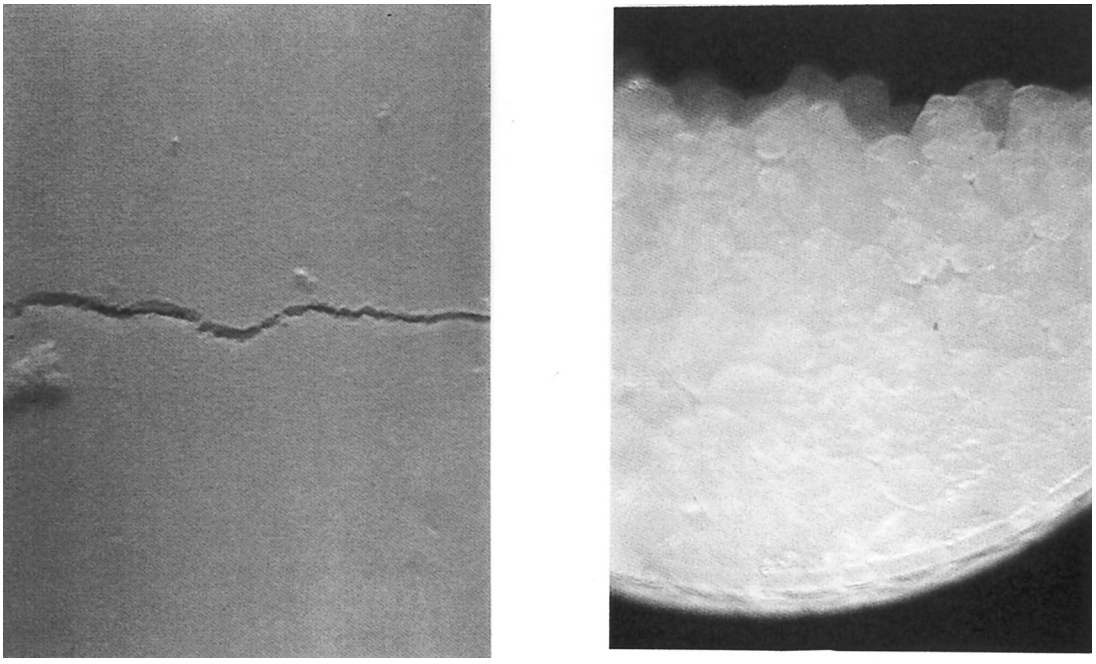
	LC Granules			Lactose Powder	NP Granules
	LC-1	LC-2	LC-3		
Upper punch work W_u (J)	28.9	27.8	31.3	33.5	36.5
Work of elastic deformation W_{ED} (J)	15.0	15.6	13.8	14.7	13.6
$(W_u - W_{ED})$ (J)	13.9	12.2	17.5	18.8	22.9
Elastic recovery *ER* (%)	90.8	84.2	48.4	42.8	42.4
Degree of compression *C* (%)	84.5	83.8	69.8	66.8	64.4
Porosity of tablet ε_t	0.103	0.070	0.096	0.063	0.022
Tablet tensile strength T_t (MPa)	1.87	1.68	1.98	2.19	2.99

	MCC Granules					MCC Powder
	MCC-1	MCC-2	MCC-3	MCC-4	MCC-5	
Upper punch work W_u (J)	42.0	31.1	35.6	45.9	44.2	49.3
Work of elastic deformation W_{ED} (J)	16.4	15.3	15.4	16.1	14.7	15.8
$(W_u - W_{ED})$ (J)	25.6	15.8	20.2	29.8	29.5	33.5
Elastic recovery *ER* (%)	58.5	125.3	75.3	50.9	43.6	48.3
Degree of compression *C* (%)	81.6	83.8	78.9	66.5	60.0	82.3
Porosity of tablet ε_t	0.051	0.119	0.082	0.071	0.060	0.046
Tablet tensile strength T_t (MPa)	4.10	5.75	5.91	0.77	0.30	11.34



(a) (b)

Photo 1. Stereomicroscopic photographs of the flat face of MCC tablet: (a) MCC powder; (b) MCC-5.



(a) (b)

Photo 2. Stereomicroscopic photographs of MCC tablet after tensile test: (a) MCC powder; (b) MCC-5.

lar bonds, which gave a high tablet strength. The results obtained in this study indicated that the degree of compression of granules C was related substantially to the tensile strength of the tablet T_t.

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