Influence of Tabletting Speed on Compactibility and Compressibility of Two Direct Compressible Powders under High Speed Compression

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To examine the influence of tabletting speed on compactibility and compressibility under high speed compression, two direct compressible powders, α-lactose monohydrate and microcrystalline cellulose of different particle size ranges were compressed using an instrumented rotary press with varying tabletting speed and compression force. The maximum applied force and total time during compression (contact time) were determined from a time–force profile, and the relation between these parameters and properties of compacts was examined. For all lactose tablets, the porosity and tensile strength of compacts were less affected by compression rate though they depended on the applied force. However, the properties of microcrystalline cellulose tablets were varied depending on the tabletting speed in addition to the applied force. In an attempt to quantitatively evaluate the effect of compression rate on the compactibility, an empirical equation was derived from the numerical analysis of the experimental data. The compactibility parameters deduced from the equation well elucidated the effect of tabletting speed on the properties of microcrystalline cellulose tablets and lactose tablets made of various particle size powders.

Keywords microcrystalline cellulose; α-lactose monohydrate; compactibility; compressibility; compression rate; high speed compression

Introduction

Tablets are the most common form of pharmaceutical dosage and are widely used in the chemotherapeutical field. Production of tablets, therefore, has been increasing annually with recent great advances in tabletting technology, especially in processing speed and uniformity of the tablets compressed.

A high-speed rotary press is now exclusively used for current large-scale production. However, some unforeseen tabletting troubles, such as loss of hardness, sticking, lamination and capping, have often been experienced when scale-up studies were performed for a candidate formulation, even though no problems were found at low speed trial compression.[1] These troubles have been thought to be caused mainly by differences in compression speed.

Although many papers have reported on compression phenomena from both fundamental and practical viewpoints, there have been only a few focusing on the influence of tabletting velocity. Horikoshi and his colleagues[2] investigated the effect of punch velocity on the viscoplastic behavior of several powders during compression in detail using a single punch press instrumented with force and displacement transducers. Rees and Rue[3] investigated the effect of tabletting speed on the compressibility of some direct compressible excipients using a reciprocating press. Roberts and Rowe[4] also studied the influence of compression rate on the compression behavior of lactose and microcrystalline cellulose with various particle size ranges. Their information seems interesting and useful for preventing the tabletting problems encountered. However, it is questionable whether the same phenomena can also occur in mass production using a high-speed rotary press, because the tabletting mode would differ with the type of tabletting machine used.

From a practical point of view, we recently examined the influence of tabletting speed on the compactibility and compressibility of two different direct compressible powders, α-lactose monohydrate (Lac) and microcrystalline cellulose (Mc), which differ in consolidation mechanism; that is, Lac deforms by a mixed mechanism of particles fracture and plastic deformation at the contact point; and Mc is known to deform plastically.[4a,5] An instrumented rotary press often used for precise detection of the minute force change in a die during compression[6] was used study. After tabletting under various operational conditions, the hardness and porosity of compacts, respective indicators of compactibility and compressibility according to Leuenberger's definition,[7] were determined for both materials with different particle size ranges.

The first objective was to investigate the influence of compression rate on the compressibility and compactibility of two direct compressible powders under high speed compression by the rotary press. Various particle size fractions of Mc and Lac powders were used to show differences in consolidation behavior. The second objective was to attempt quantitative evaluation for the compression-rate-dependency on the consolidation behavior of a powder. An empirical equation was derived from numerical analysis of the experimental data, and the physical meaning of parameters deduced from the equation will be discussed.

Experimental

Materials Mc (Avicel PH-102, Asahikasei Co., Ltd.), Lac (D.M.V., Holland) and magnesium stearate (Nihon-yushi Co., Ltd.) were of JP grade and obtained from commercial sources. Mc and Lac were divided by JP standard sieves into three fractions differing in particle size distribution, 180—250, 150—180, and 100—150 μm. Each powder was well blended with magnesium stearate as lubricant at the 0.5% level before tabletting. All powder samples were placed in an air-conditioned room till tabletting, in which temperature and humidity were controlled at 24±2 °C and 50±10% relative humidity (R.H.), respectively. Moisture content of Mc and Lac determined after drying at 60 °C for 3 h under 5 mmHg was 5.48% and 0.14%, respectively.

Time–Force Curve Measurement System The rotary press (Cleanpress Correct 12HUK; Kikusui Seisakusho Ltd.) was instrumented with a load cell on the shaft of the lower pressure roll. Analog signals generated from the load cell during tabletting were amplified *via* a strain amplifier, digitized and then stored in a microcomputer (IBM PC-AT). Data acquisition was done by a commercially available software package, Asystant+ (Macmillan Software Company). Raw data of 3200 points were collected at the rate of 1000 Hz at every trial.

Tabletting All the tabletting experiments were operated with tooling in four of the stations. The weight of each tablet was controlled at a constant level by adjusting the amount of powder put into a die to 5 mm in depth. The rotary press was run at four different speeds, 30, 40, 50 and 60 rpm, and the compression pressure was varied from 600 to 2400 kg/cm^2 at four different levels. Tablet punches used were of the flat face type and 8 mm in diameter. All the tabletting was conducted in the air-conditioned room under the same conditions as in the storage room, with temperature and humidity controlled at 24±2 °C and 50±10% R.H., respectively.

Determinations of Maximum Applied Force (P_{max}) and Contact Time (CT) P_{max} and CT were automatically determined by computer calculation from a time–force profile output from the instrumented rotary press (Fig. 1). The start point of the time–force curve was recognized as the point where a digitized signal was raised more than 0.005 V from the baseline and was maintained for over 10 ms. The end point of the curve was recognized as the point where the decreasing signal crossed the baseline. P_{max} is the maximum value of the detecting force, which is generally referred to as "tabletting force". CT was the time defference from start point to end point which was defined by Jones[8] as the total time stress was detected during which the die contents remained in contact with the upper and lower punches.

Properties of Compressed Tablets Weight, diameter and thickness of each compressed tablet were measured by an ordinary balance and gages after storage for 2 d at room temperature. Tablet hardness was determined by a motorized instrument (Schleuniger). Tensile strength, T, was calculated by $T=2H/\pi Dl$, according to Newton *et al.*,[9] where H, D and l are crashing force, diameter and thickness of tablet, respectively. Porosity of tablet, ε, was calculated according to the equation, $\varepsilon=1-W/dV$, where W and V are the weight and geometrical volume of the tablet, respectively. d is the true density of materials determined by an air comparison pycnometer (Micromeritic).

Result and Discussion

All the powders of Mc and Lac were compressed with varying compression force and number of machine rotations (RN). The values of P_{max} and CT were determined from the time–force profile, and the hardness and porosity were also measured for all the compacts. To demonstrate the influence of tabletting speed on hardness, the crushing strength of compacts of both materials with different particle size ranges, which were compressed at about 1200 kg/cm^2 and various tabletting speeds, are shown in Table I as typical example of the experimental results.

The hardness of Lac tablets showed practically no change with tabletting speed or particle size of powder. However, Mc tablets of large particle size were found to be obviously affected by the tabletting speed. It also was found that the compression-rate-dependency tended to become smaller as the particle size decreased.

To examine the influence of compression rate and applied pressure on the compressibility, Heckel plots were employed at four different compression rates. Figure 2 shows the Heckel plots for Mc using the 180—250 and 100—150 μm size fraction at two different compression rates. Figure 2a clearly shows that the porosity of compacts was affected

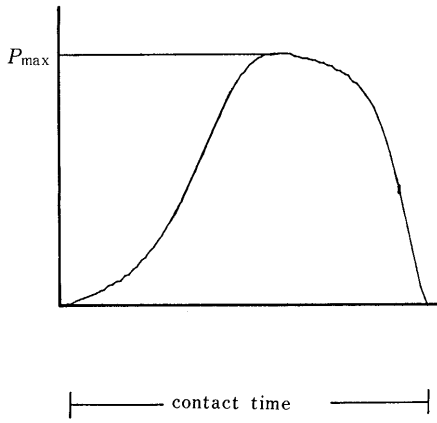

Fig. 1. Time–Force Curve and Definition of P_{max} and CT
Ordinate: compression force (kg/cm^2), abscissa: time (ms).

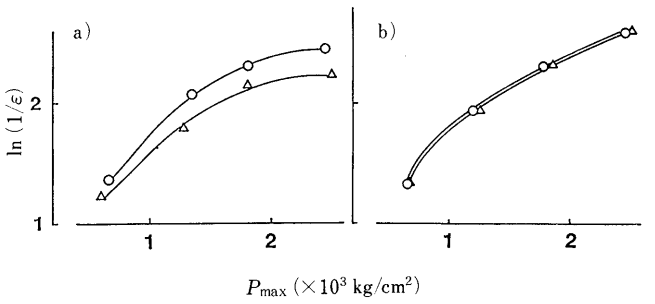

Fig. 2. Effect of Compression Rate on the Consolidation Behavior of Mc, Shown as Heckel Plots of ln(1/ε) against Compression Force (kg/cm^2)
a) 180—250 μm, b) 100—150 μm. ○: 30 rpm, △: 60 rpm.

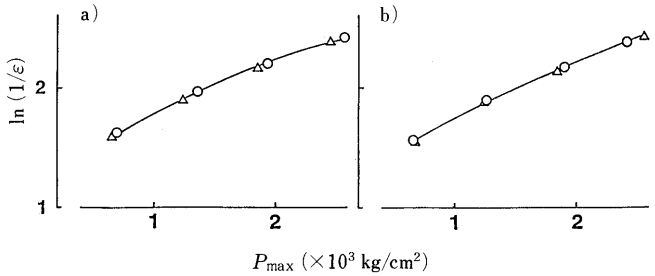

Fig. 3. Effect of Compression Rate on the Consolidation Behavior of Lac, Shown as Heckel Plots of ln(1/ε) against Compression Force (kg/cm^2)
a) 180—250 μm, b) 100—150 μm. ○: 30 rpm, △: 60 rpm.

TABLE I. Crushing Hardness (kg) of Mc and Lac Tablets Compressed at 1200 kg/cm^2 under Various Compression Speeds

Material	Particle size (μm)	*RN* 30 rpm	40 rpm	50 rpm	60 rpm
Mc	180—250	5.50±0.18	4.95±0.14	4.63±0.19	4.57±0.17
	150—180	5.12±0.12	5.00±0.12	4.65±0.12	4.60±0.12
	100—150	6.31±0.15	5.85±0.11	5.86±0.18	6.16±0.21
	Unclassified	8.65±0.17	9.10±0.29	9.10±0.24	8.32±0.27
Lac	180—250	1.30±0.07	1.33±0.10	1.21±0.04	1.15±0.05
	150—180	1.31±0.10	1.28±0.06	1.46±0.13	1.20±0.03
	100—150	1.17±0.21	1.23±0.05	1.30±0.11	1.33±0.13
	Unclassified	1.20±0.06	1.25±0.14	1.15±0.08	1.15±0.07

Each value represents mean±S.D. ($n=10$).

not only by the compression force but by the compression rate, when the larger size fraction was compressed. However, Fig. 2b suggests that, for the tablets of smaller particle size, the porosity changed only slightly with the compression rate at any given applied force. Figure 3 is the Heckel plots for Lac, which indicate that the porosity was practically influenced by neither compression rate nor particle size. Although these results seem to contradict the findings of Roberts and Rowe,[4] it must be noted that they determined the porosity from the punch displacement at pressure, whereas in this study, it was measured two days after the compaction was finished; this was done taking into consideration the fact that the equilibrated porosity after elastic recovery is more important in current tablet production. Such difference in determination procedure would naturally result in a different outcome. Fell and Newton[10] and York[11] mentioned there was a clear difference between the tablet volumes determined from the punch displacement at pressure and those after ejection from a die due to the difference in degree of elastic recovery.[12]

The difference in consolidation behavior between Mc and Lac would be closely related to the difference in compression mechanism: Mc was known to form a tablet mainly by the plastic deformation process whereas Lac is consolidated by fragmentation followed by the formation of new bonds between particles. One possible reason for the compression-rate-dependency found in the consolidation of larger particle size fractions of Mc is: the extent of plastic deformation may depend on the time during which the force is applied to the die contents and longer contact time may therefore form tighter bonds between particles even if the same force is applied. For smaller particle size fractions of Mc, however, it was shown that the compression rate did not have much influence on consolidation behavior. This may be explained by the fact that smaller particles are less subject to plastic deformation than larger particles.[13]

Tensile strength of the tablets of Mc compressed under various rates using larger and smaller particle size ranges are plotted against P_{max} in Fig. 4. It can be seen that all the T values increased with the increase of P_{max}. Also, it was found that T values decreased with increasing compression rate when the P_{max} value was the same; this phenomenon was more clearly observed in larger particle size powder (Fig. 4a).

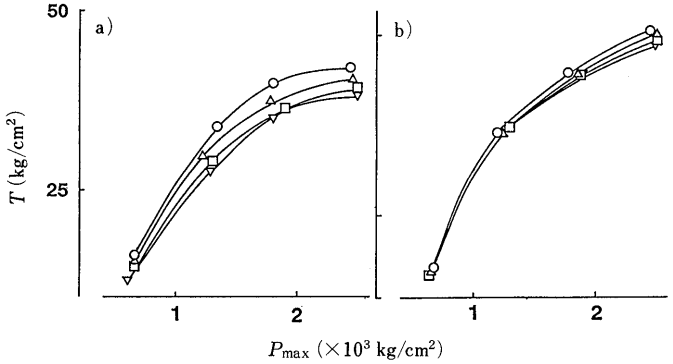

Fig. 4. Relation between P_{max} and T of Tablets of Different Size Fractions of Mc Compressed at Various *RN*s

a) 180—250 μm, b) 100—150 μm. ○: 30 rpm, △: 40 rpm, □: 50 rpm, ▽: 60 rpm.

Figure 5 shows the relation between the porosity and tensile strength of Mc tablets prepared from different particle size fractions at various *RN*s. A good linear relationship between T value and the logarithm of reciprocal porosity, $\ln(1/\varepsilon)$, was found individually in each particle size fraction. This means that tensile strength is directly determined by the porosity of compacts at any compression rate. Therefore, it can be concluded that the difference in tensile strength of a compact is due to the difference in porosity as affected by P_{max} and compression rate. It was also found that smaller particle fractions provided compacts of higher tensile strength than larger particle fractions, even though the porosity was the same. A similar phenomenon was reported by other researchers,[14,15] and they considered the reason to be that smaller particles have more contact points between them, so even if the porosity of the compact is the same, smaller particles can be packed more tightly between larger particles. On the other hand, for Lac tablets, Fig. 6 indicates that T values were practically not affected by compression rate, though they seemed to be slightly affected by particle size. The reason for this was thought to be that the consolidation of Lac particles occurs due to a bond between new surfaces formed by the fragmentation during compression, and the fragmentation does not depend on the compression rate, unlike the plastic deformation.

Quantitative Evaluation of the Effect of *CT* on Compactibility For the quantitative analysis of compression-rate-dependency, it is necessary to know the relation of CT with RN and P_{max}, because CT can be directly influenced by the

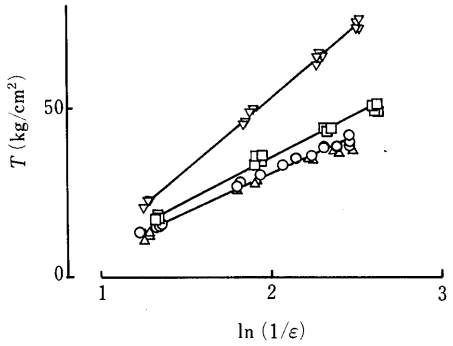

Fig. 5. Relation between $\ln(1/\varepsilon)$ and T of Mc Tablets of Different Particle Size Fractions Compressed at Various *RN*s

○: 180—250 μm, △: 150—180 μm, □: 100—150 μm, ▽: unclassified.

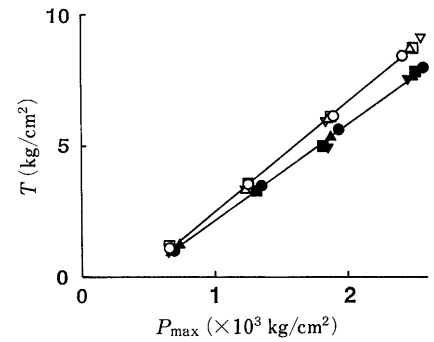

Fig. 6. Relation between P_{max} and T of Lac Tablets Prepared from Different Particle Size Fractions Compressed at Four Different Compression Rates

Close: 180—250 μm, open: 100—150 μm. ○: 30 rpm, △: 40 rpm, □: 50 rpm, ▽: 60 rpm.

mechanical movement of punches.

All the CT values obtained under the four different RN conditions are plotted against P_{max} values in Fig. 7. These values linearly increased with P_{max} in the experimental range from 600 to 2400 kg/cm^2, and the slope of each line was almost the same for the two materials at any given RN. It also was found that the particle size of neither material affected the CT value. These can be simply elucidated from the geometrical movement of the punches during tabletting; that is, when the compression force is increased, punches naturally must move in a more vertical direction, and consequently, the time during which the moving punches are in contact with the content is prolonged. The results suggest that the dependence of CT on P_{max} in the experimental range can be expressed by a simple linear equation.

In order to examine the relation between tabletting speed and CT, the intercepts of each line (CT_0) are plotted against reciprocal RNs in Fig. 8. Good straight lines were also observed, each one almost coinciding with its origin. These relations seem quite reasonable, because reciprocal RN should directly relate to the velocity of moving punches. Therefore, the effects of P_{max} and RN on CT can be expressed overall by the following equation,

$$CT=a_1P_{max}+a_2/RN+a_3 \quad (1)$$

where a_1, a_2 and a_3 are constants. The a_1, a_2 and a_3 values were calculated by the best-fitting method using sixty-four data sets shown in Fig. 7, and Eqs. 2 and 3 were obtained for Mc and Lac, respectively:

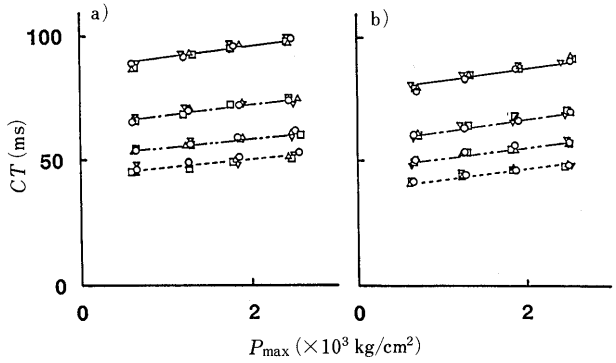

Fig. 7. Relation between P_{max} and CT for Four Particle Size Fractions of Mc and Lac at Four Different Compression Rates

a) Mc, b) Lac. ○: 180—250 μm, △: 150—180 μm, □: 100—150 μm, ▽: unclassified. ——: 30 rpm, -—: 40 rpm, ----: 50 rpm, ------: 60 rpm.

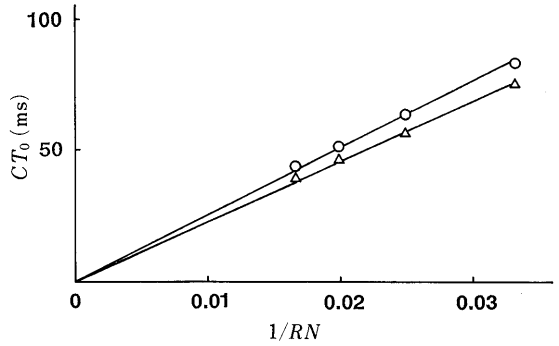

Fig. 8. Relation between Reciprocal RN and CT_0

○: Mc, △: Lac.

$$CT=8.29P_{max}+2695/RN-3.02 \quad (r=0.990) \quad (2)$$

$$CT=9.56P_{max}+2436/RN-3.20 \quad (r=0.993) \quad (3)$$

These equations can be used for the most accurate estimation of CT value at any given P_{max} and RN.

As seen from Fig. 4, unlike Lac, the compactibility of Mc is influenced not only by the compression force but by tabletting speed as well. In such a case, T, an index representing compactibility, can be generally expressed as the function of two parameters, P_{max} and CT, that is,

$$T=f(P_{max}, CT) \quad (4)$$

Then, the total differential of T can be expressed as the following partial differential equation:

$$dT=\left(\frac{\partial T}{\partial P_{max}}\right)_{CT} dP_{max}+\left(\frac{\partial T}{\partial CT}\right)_{P_{max}} dCT \quad (5)$$

Now, under the tabletting condition with a constant P_{max}, the change of T by unit CT is expressed by the function of CT alone:

$$\frac{dT}{dCT}=\left(\frac{\partial T}{\partial CT}\right)_{P_{max}}=g(CT) \quad (6)$$

To estimate the type of function $g(CT)$, T values of Mc tablets (180—250 μm) at various compression forces are plotted against CT values in Fig. 9. Here, to conduct this examination more accurately, the corrected values are used for of all the CT and T; that is, CTs at a given P_{max} were calculated using Eq. 2, and T values at the corresponding P_{max} were obtained with interpolation from the curves in Fig. 4 after smoothing by spline function. Most of the linear relationships were found to hold between CT and T at each P_{max}, though some fluctuation was involved. Thus, $g(CT)$ can be regarded as the constant at each P_{max}. Accordingly, T can be rewritten as:

$$T=K\cdot CT+T_0 \quad (7)$$

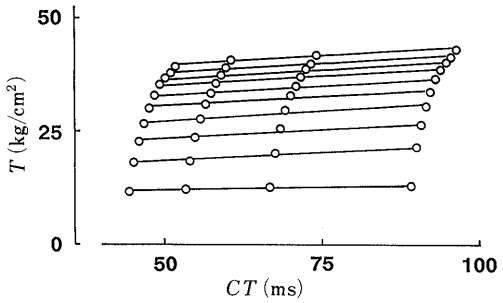

Fig. 9. Relation between CT and T at Various Compression Forces

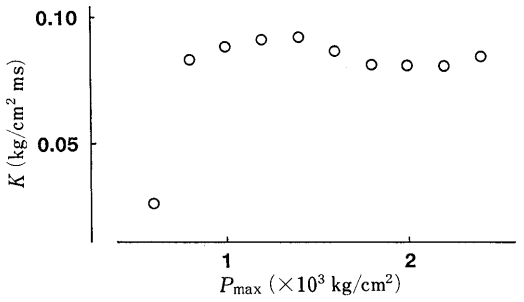

Fig. 10. Relation between P_{max} and K

where K is a constant representing a compression-rate-dependency of the powder whose dimension is given as kg/cm^2·ms. T_0 is the intercept of the linear line (therefore, it depends on P_{max} alone).

Figure 10 shows the P_{max} dependence of K value. K value was at an almost constant level above 800 kg/cm^2 though it became lower below 600 kg/cm^2. This suggests that K is almost independent of P_{max} under an ordinary tabletting condition.

Figure 11 shows the relation between T_0 and P_{max}. T_0 seemed to increase with P_{max} exponentially to a certain value. Thus, for convenience, this relation can be empirically expressed by an exponential function even though it might have less theoretical basis. The equation is given as:

$$T_0 = E \cdot \exp[F/(P_{max} - G)] \quad (8)$$

where E, F and G are constants. E is the T_0 at infinite P_{max}, F is the factor representing the P_{max}-dependency of T_0, and G is the minimum force required to form a compact.

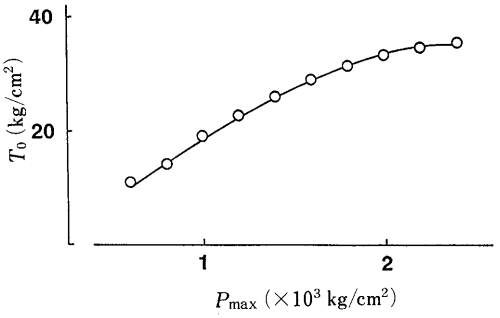

Fig. 11. Relation between P_{max} and T_0

TABLE II. Estimated Values of Compactibility Parameters for Mc and Lac Powders of Various Particle Size Ranges

Material	Particle size (μm)	Compactibility parameters K	E	F	G
Mc	180—250	0.0862	46.22	0.317	0.134
	150—180	0.0427	44.88	0.284	0.139
	100—150	0.0375	58.40	0.262	0.148
	Unclassified	0.0385	88.10	0.288	0.140
Lac	180—250	0.0051	14.76	1.015	0.004
	150—180	0.0016	17.74	1.056	<0.001
	100—150	−0.0008	20.67	1.053	0.054
	Unclassified	0.0031	19.43	1.321	<0.001

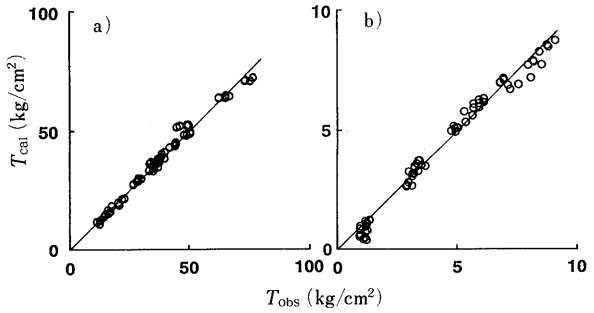

Fig. 12. Comparison of Tensile Strength between Observed and Calculated Values According to Eq. 9

a) Mc, b) Lac. The straight line in the figure coincides with the origin and the slope is one.

Substituting Eq. 8 into Eq. 7, the total expression can be obtained for CT and P_{max} as:

$$T = K \cdot CT + E \cdot \exp[F/(P_{max} - G)] \quad (9)$$

Using the above equation, K, E, F and G values were computed by the best-fit method using the raw data of T, CT, and P_{max} for all the Mc and Lac tablets of various particle size fractions. The calculation results are listed in Table II. To check the accuracy of the values calculated, the observed $T(T_{obs})$ and the calculated $T(T_{cal})$ are compared in Fig. 12. As is clear in the figures, all the calculated T values were well coincident with the observed values. This suggests that Eq. 9 is adequate for analysis of the compactibility of both powders. It seems possible to discuss the characteristics of the consolidation behavior of powders using those parameter values.

As shown in Table II for Mc, K values becomes greater as the particle size increases, suggesting that when the larger particle size fraction is used for tabletting, the hardness of compacts is more easily affected by compression speed. Unclassified powder, the mixture of large and small particles, showed almost the same value as the small powder. This is probably due to the ability of the smaller particle size fraction to occupy the interparticle voids between the larger particles, which dominates in the consolidation of unclassified powder during compression. On the other hand, it was shown that K value for Lac was considerably smaller than that for Mc, suggesting that the compactibility was less affected by CT.

Regarding E value, a distinctive difference was found between particle size fractions for Mc. Unclassified powder had the greatest value, and this became smaller as particle size increased. E can be considered to be a parameter representing the degree of cohesion between powder particles or the number of contact points. Therefore, this tendency is quite reasonable because unclassified powder or smaller particle size has more contact points between particles than larger ones, consequently, the hardness of the compact should be greater. On the other hand, E value of Lac did not much differ between particle sizes; this value was found to be smaller than that of Mc. This supports the well-known fact that the compactibility of Mc is much better than Lac.

Although the values of F and G did not greatly differ between particle sizes of Lac and Mc, there was a clear difference between these two powders. Therefore, both parameters may be useful as indicators characterizing the consolidation behavior of various powders.

In conclusion, Lac which undergoes particle fragmentation during compaction is practically affected by neither particle size distribution nor compression speed on the density and hardness of compacts, whereas Mc, which undergoes plastic deformation during compaction is affected by tabletting speed and particle size. The compression-rate-dependency of both powders can be quantitatively evaluated by applying a series of experimental data of CT, P_{max} and T to Eq. 9. The proposed technique may be a useful approach with which to examine the consolidation behavior of other powders or granules and the influence of compression rate on compactibility and compressibility under high speed compression.

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