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Compression Properties of Cephalexin Powder and Physical Properties of the Tablet[1]

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The compression process of cephalexin (CEX) powder was studied by using a tabletting machine with punches of 0.7, 1.0 and 2.0 cm diameter, and the maximum compression stress (*MP*), the compression loss energy (*LE*), the elastic energy (*EE*), the compression energy (*CE*), the hardness of the tablet (*H*) and the elastic recovery (*R*) were measured. The compression process followed Bal'shin's equation, and was independent of sample weight in the range of 110 to 300 mg. In the compression process with the 0.7 cm punch the plot of the compression stress *versus* the thickness of the powder bed was shifted to the slightly higher pressure side as compared with the plots for the 1.0 and 2.0 cm punches, presumably because the die wall friction of the 0.7 cm punch was larger than that of the 1.0 and 2.0 cm punches. Elastic behavior appeared on high-pressure compression of CEX powder. The Young's modulus obtained from the relation between *MP* and *R* was calculated to be 4.75×10^9 dyn/cm^2. The tensile strength (*TS*) and *R* value increased with increasing value of *MP*.

Keywords——cephalexin; compression property; compression energy; tensile strength; tablet elastic behavior

Introduction

There are many reports on equations describing the compression of powder materials,[2,3] the rheological properties during the compression process[4] and the hardness of molded tablets.[5] In order to obtain basic data for studies of the mechanochemistry of organic medicinal powders, we have investigated the compression of cephalexin (CEX) powder. The stress and thickness of the powder bed during the compression of CEX powder were measured, and the compression properties and compression energy were determined. The relationship between compression characteristics and molded tablet properties (hardness and elasticity) was studied.

Experimental

Materials——CEX bulk powder (Larixin; Toyama Chemical Co., Ltd., lot HJ-595E) was used. The average particle size, the crystal form and the tapped apparent specific volume of the bulk powder were 45 μm by using the sedimentation method (SKN type; Seishin Kigyo Co., Ltd.), plate crystal and 1.5 cm^3/g, respectively. The bulk powder was identified as phase IV CEX by X-ray diffractometry; phase IV is a stable monohydrate under the usual conditions of temperature and relative humidity in the laboratory, as described in a previous paper.[6]

Apparatus and Procedures——Tabletting Machine: A single-punch eccentric tabletting machine (type KS-2; Nichiei Seiko Co., Ltd.) with flat-type punches having diameters of 0.7, 1.0 and 2.0 cm was used at 60 rpm.

Measurement of the Compression Stress: A load cell (LC/2C; Shinkoh Co., Ltd.) was positioned on the side of the upper punch, and the compression stress was measured in terms of the voltage change.

Measurement of the Punch Distance: In order to measure the punch distance, a noncontact displacement transducer (Shin Nippon Sokki Co., Ltd.) and an aluminium plate were fixed to the lower and upper punch, respectively (see Fig. 1). The punch distance, like the compression stress, was converted to voltage change, and both were recorded with a magnetic oscillograph (5L30; San-Ei Instrument Co., Ltd.).

Procedures: The punches and die were smeared with 5% stearic acid solution in chloroform, and dried, then a sample was put into the die with tapping by hand.

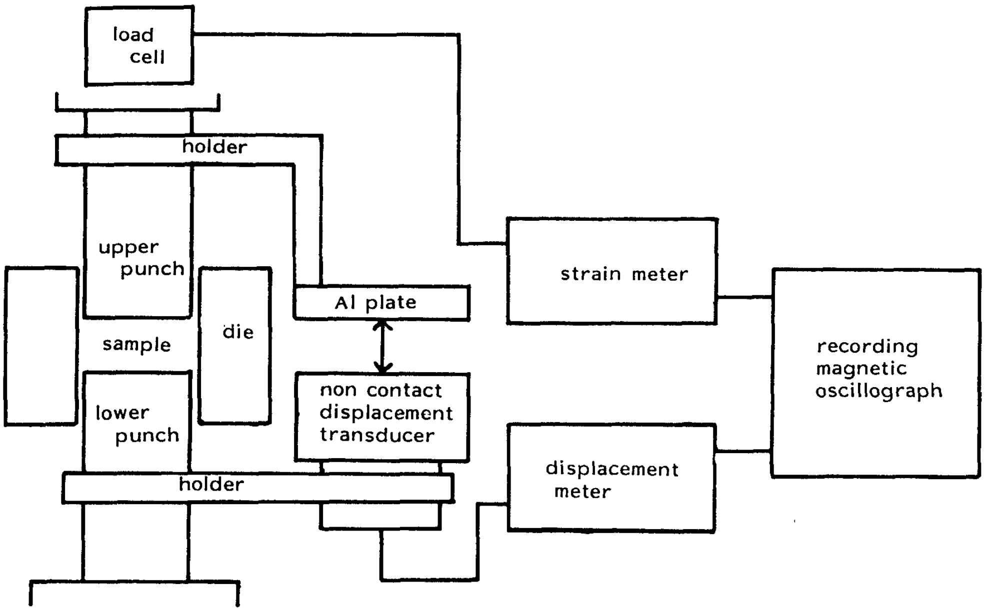

Fig. 1. Block Diagram of the Apparatus

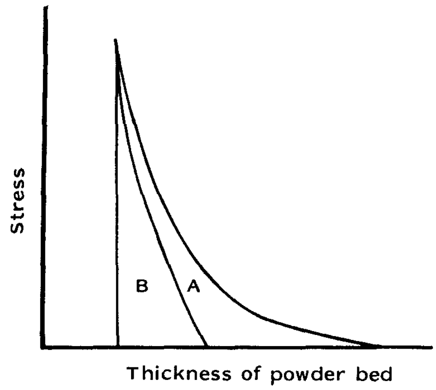

Fig. 2. Relation between Compression Stress and Thickness of the Powder Bed

Measurement of Mechanical Energy——The plots of the compression stress against the thickness of the powder bed showed a hysteresis loop (Fig. 2). The area of the hysteresis loop (A) corresponds to the compression loss energy (LE), the area of the decompression process (B) corresponds to the compression elastic energy (EE), and the total area of the compression ($A+B$) corresponds to the compression energy (CE); all these areas were determined with a planimeter.

Tablet Hardness and Thickness——The tablet hardness was measured with a Kiya hardness tester. The thickness of the molded tablets was measured with a micrometer.

Results and Discussion

Compression Properties of CEX Powder

Effect of Sample Weight on Compression Properties——Plots of log (stress) *vs.* the thickness of the powder bed during the compression of CEX powder with the 1.0 cm punch are shown in Fig. 3. A linear relation was obtained at each sample weight (110, 190 and 300 mg) and is expressed by Eq. 1. This result suggests that the compression process follows Bal'shin's equation (Eq. 2).

$$\ln P = kt + C \quad (1)$$

$$\ln P = -C_1(V/V_\infty) + C_2 \quad (2)$$

where P is the compression stress, t is the thickness of the powder bed at P, V is the volume at

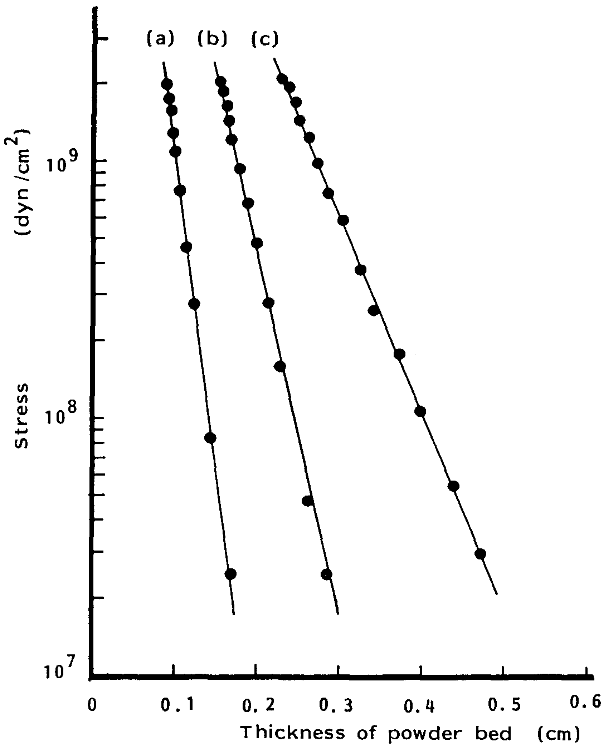

Fig. 3. Effect of Sample Weight on the Compression Process by the 1.0 cm Punch
(a) 110 mg, (b) 190 mg, (c) 300 mg sample weight.

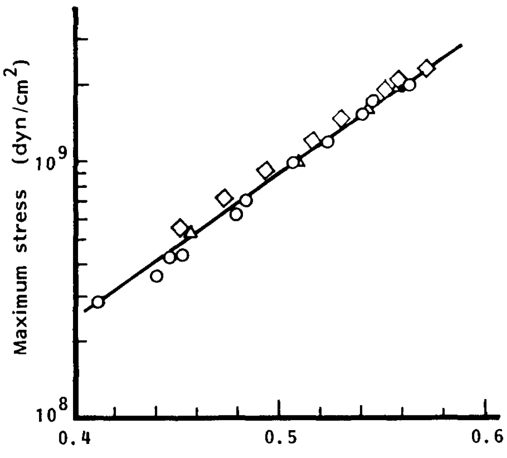

Fig. 4. Relation between Maximum Stress and Maximum Strain by the 1.0 cm Punch
△, 110 mg; ○, 190 mg; ◇, 300 mg sample weight.

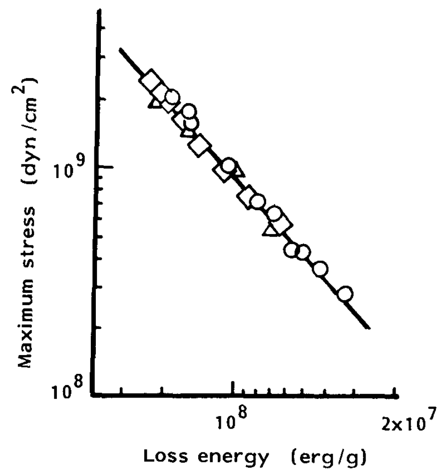

Fig. 5. Relation between Maximum Stress and Loss Energy by the 1.0 cm Punch
△, 110 mg; ○, 190 mg; ◇, 300 mg sample weight.

P, V_∞ is volume at infinite stress, and k, C, C_1 and C_2 are constants.

The ratio of the thickness of the powder bed before compression to that at the maximum stress (MP) is defined as the maximum strain (MS) (Eq. 3). Figure 4 shows the relation between log (MP) and MS with various sample weights. Bessho *et al.*[2] reported that the compression equation was independent of sample weight when the thickness of the powder bed was replaced by the dimensionless parameter, N_b (Eq. 4):

$$MS = t/t_0 \tag{3}$$

$$N_b = D^2 \rho\, t/m = 4t/\pi t_0 \tag{4}$$

where t_0 is the thickness of the powder bed before compression (tapped volume of phase IV),[7]

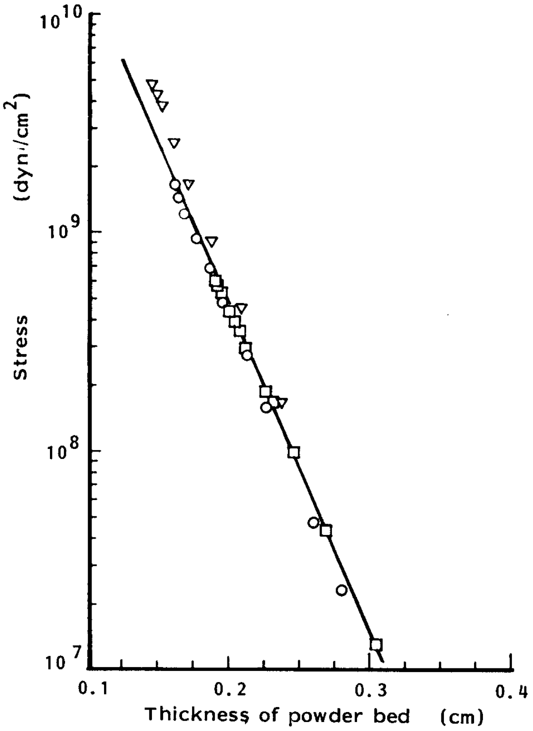

Fig. 6. Effect of Punch Diameter on the Compression Process

▽, 0.7 cm diameter (93 mg); ○, 1.0 cm diameter (190 mg); □, 2.0 cm diameter of punch (760 mg).

t_0 is the thickness corresponding to the true specific volume, ρ is the density, m is the sample weight, and D is the punch diameter. As shown by Eqs. 3 and 4, MS and N_b are both functions of the thickness of the powder bed.

Figure 5 shows that a linear relation exists between MP and LE for the compression of CEX powder at all sample weights tested. These results suggest that the compression process of CEX powder is independent of sample weight in the range of 110 to 300 mg.

Effect of Punch Diameter on Compression Properties——Figure 6 shows the effect of punch diameter on the compression process. In order to get the same thickness of powder bed, samples of 93, 190 and 760 mg were put into the dies (these sample weights were proportional to the punch area) for punch diameters of 0.7, 1.0 and 2.0 cm, respectively. The plots of log P against t are linear, suggesting that the compression process follows Bal'shin's equation, though the plot for the 0.7 cm punch is shifted slightly to the higher pressure side (This phenomenon of the tabletting process is presumably due to increased frictional resistance at the die wall).

Compression Stress and Compression Loss Energy

The compression energy (CE) is obtained as a function of P by integration as shown in Eq. 5.

$$CE=\int_{V_1}^{V_2} PdV \tag{5}$$

The compression process of CEX powder follows Bal'shin's equation, and substituting Eq. 2 into Eq. 5 yields Eq. 6:

$$\begin{aligned} CE&=\int_{V_1}^{V_2} k_1 \exp(V/V_\infty)dV=k_1/V_\infty\int_{V_1}^{V_2} \exp(V)dV \\ &=k_1/V_\infty[\exp(V_2)-\exp(V_1)]_1^2=k_2 \exp(V)+CE_0 \end{aligned} \tag{6}$$

Now $CE_0=0$ before compression, $V_2=V$, and from Eq. 2, we have

$$CE=(k_2/k_3)\ P=k_4P \tag{7}$$

where V_1 is the volume before compression, V_2 is the volume after compression, and k_1, k_2, k_3 and k_4 are constants. The compression of the powder is elastic as shown in Fig. 2, and therefore,

$$CE=LE+EE \tag{8}$$

When EE may be neglected, we have

$$CE=LE \tag{9}$$

When MP was plotted against CE (Fig. 7), a good linear relation was obtained for

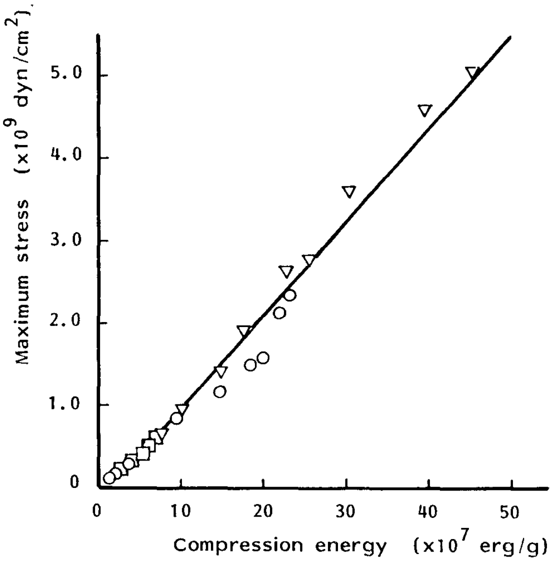

Fig. 7. Relation between Maximum Stress and Compression Energy

▽, 0.7 cm diameter (93 mg); ○, 1.0 cm diameter (190 mg); □, 2.0 cm diameter of punch (760 mg).

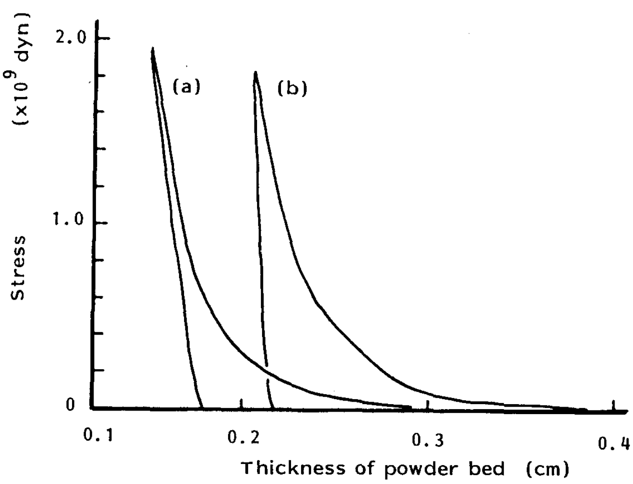

Fig. 8. Hysteresis Loop in the Process of Compression

(a) 0.7 cm diameter (93 mg), (b) 2.0 cm diameter of punch (760 mg).

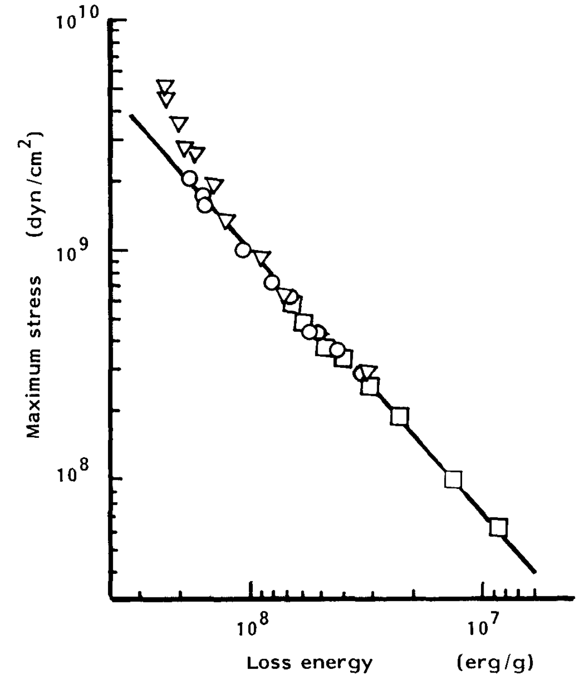

Fig. 9. Relation between Maximum Stress and Loss Energy

▽, 0.7 cm diameter (93 mg); ○, 1.0 cm diameter (190 mg); □, 2.0 cm diameter of punch (760 mg).

compression with the various punches, as expected from Eq. 7, and the results confirm that the compression process of CEX powder follows Bal'shin's equation.

When the stress of the tabletting machine is plotted against the thickness of the powder bed, the relation shows hysteresis. For example, the results of compression with the 0.7 and 2.0 cm punches are shown in Fig. 8. Since the *CE* is better utilized for compression of powder by the 2.0 cm punch, the area corresponding to the *EE* is small, whereas that for compression by the 0.7 cm punch is larger, reflecting a greater degree of elastic behavior of the tablet.

The relation between *MP* and *LE* is shown in Fig. 9. A linear relationship was obtained for the 1.0 and 2.0 cm punches, since *EE* is much smaller than *LE* as expected from Eqs. 7, 8 and 9. However, the results for the 0.7 cm punch deviated from the linear relationship, even though the compression process follows Bal'shin's equation, because of the increased frictional loss at the die wall, and the elastic property of the powder bed is greater in compression with the 0.7 cm punch.

Elastic Properties of Tablets

The compression of powder during tabletting was studied rheologically by Sagawa *et al.*,[4] who analyzed the compression mechanism on the basis of viscoelastic models, and calculated the rheological and elastic constants. The elastic behavior was most marked on higher pressure compression of CEX powder. The *MP* obtained by compression with various diameter punches was plotted against the thickness of the powder bed or ejected tablet, as shown in Fig. 10. The thickness of the ejected tablet is almost constant on compression at *MP* larger than 1×10^9 dyn/cm^2, but a good proportionality was maintained at *MP* less than 1×10^9 dyn/cm^2. The plot of the thickness of the powder bed of compressing tablet *vs.* log

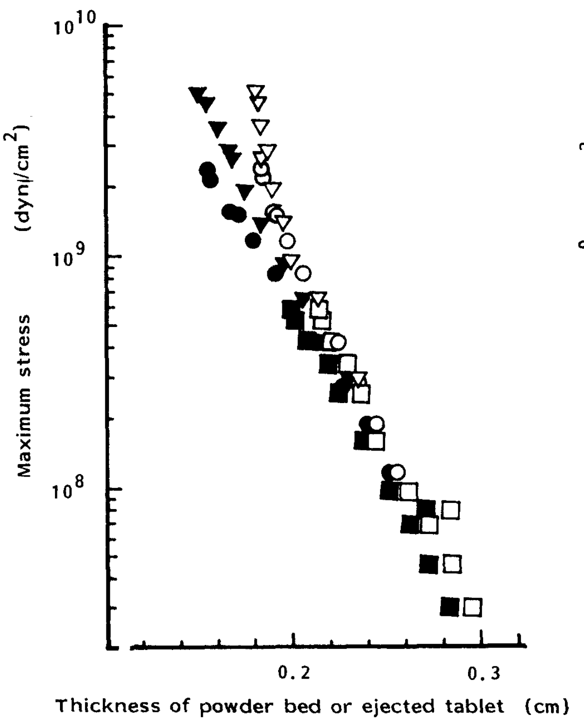

Fig. 10. Relation between Maximum Stress and Minimum Thickness of Powder Bed or Ejected Tablet

Ejected tablet: ▽, 0.7 cm diameter; ○, 1.0 cm diameter; □, 2.0 cm diameter. Compressing tablet: ▼, 0.7 cm diameter; ●, 1.0 cm diameter; ■, 2.0 cm diameter of punch.

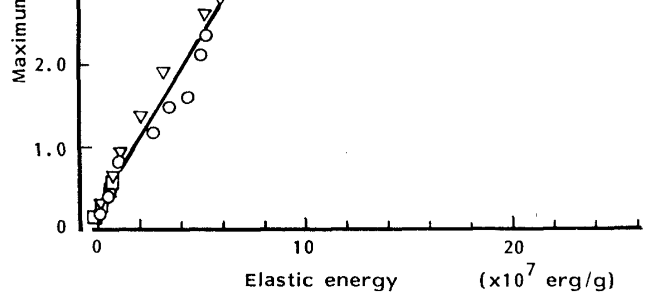

Fig. 11. Relation between Maximum Stress and Elastic Energy

▽, 0.7 cm diameter (93 mg); ○, 1.0 cm diameter (190 mg); □, 2.0 cm diameter of punch (760 mg).

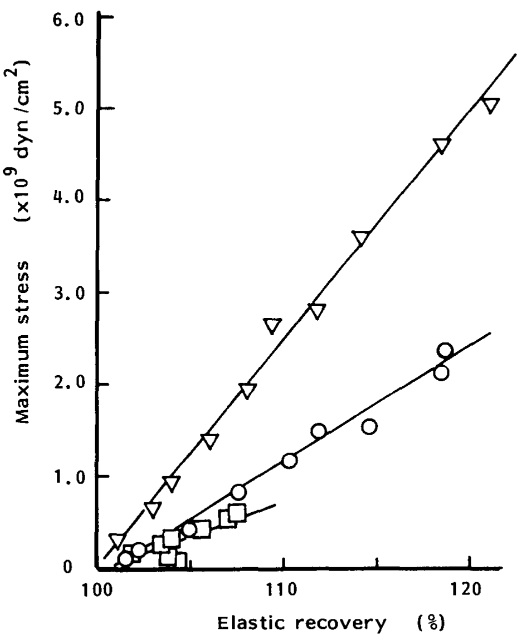

Fig. 12. Relation between Maximum Stress and Elastic Recovery

▽, 0.7 cm diameter (93 mg); ○, 1.0 cm diameter (190 mg); □, 2.0 cm diameter of punch (760 mg).

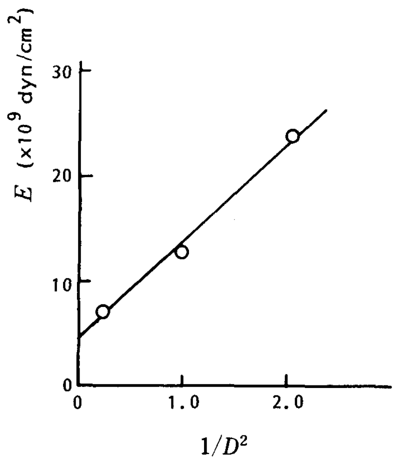

Fig. 13. Relation between Apparent Young's Modulus and $1/D^2$

(MP) showed a linear relation. This result suggests that the expansion of the tablet after compression is greater with increasing MP.

The relation between MP for compression with the various punches and EE is shown in Fig. 11; EE is proportional to the MP at MP less than 3×10^9 dyn/cm^2. This plot suggests that the EE increases markedly in higher pressure compression.

The elastic recovery (R) is defined as the ratio of the thickness of the powder bed at MP (t_c) to the thickness of the ejected tablet (t_a), as shown in Eq. 10, and is a parameter of the elastic behavior of the tablet.

$$R = t_a/t_c \qquad (10)$$

The relation between R and MP for compression with the various punches was linear, as shown in Fig. 12, except for the 2.0 cm punch at lower pressure, when the hardness of the molded tablets could not be measured. In general the relation between stress and strain follows Hooke's law, and the Young's modulus (E) is the characteristic constant of the material. However, the E of CEX powder changes with the diameter of the compression punches. The apparent E calculated from Fig. 12 is linearly related to $1/D^2$, as shown in Fig. 13. This suggests that a small-diameter punch is likely to require a larger compression stress than a large diameter punch. The E value at $1/D^2 = 0$ (a punch of infinite diameter) is a characteristic of CEX powder compression free from the effect of friction at the die wall and in the present study on CEX it was calculated to be 4.75×10^9 dyn/cm^2.

Relation between Compression Stress and Tablet Hardness

The relation between MP and the hardness of the molded tablet (H) is shown in Fig. 14. The plots are linear except in the case of compression with the 0.7 cm punch at higher pressure; the larger the diameter of the punch, the less the slope of the plot. Newton *et al.*[8] studied the hardness of tablets of various diameters, and suggested the tensile strength (TS), given by Eq. 11, as a hardness parameter.

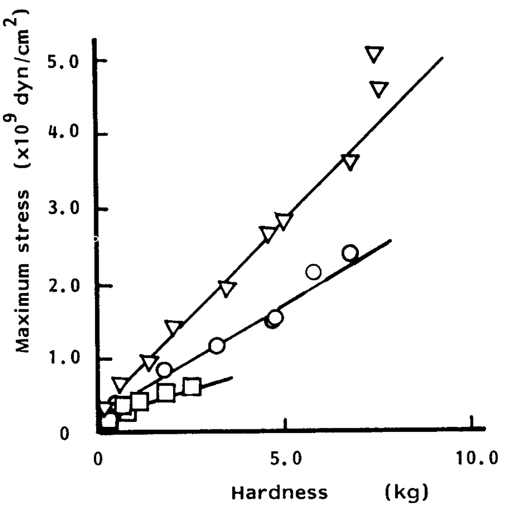

Fig. 14. Relation between Maximum Stress and Hardness of Tablet

▽, 0.7 cm diameter (93 mg); ○, 1.0 cm diameter (190 mg); □, 2.0 cm diameter of punch (760 mg).

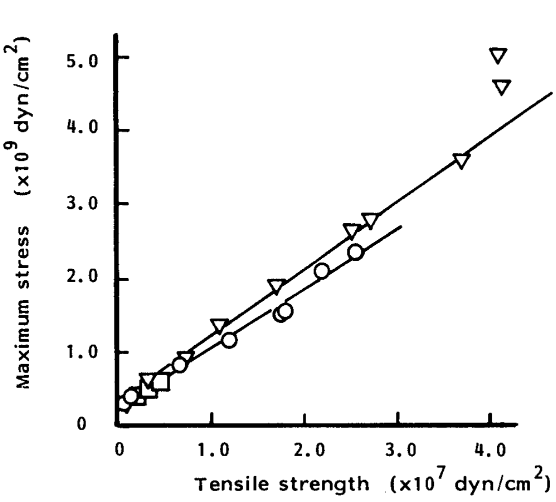

Fig. 15. Relation between Maximum Stress and Tensile Strength

▽, 0.7 cm diameter (93 mg); ○, 1.0 cm diameter (190 mg); □, 2.0 cm diameter of punch (760 mg).

$$TS = 2H/\pi D t_1\ (1-\varepsilon) \qquad (11)$$

where H is the hardness, ε is the porosity, and t_1 is the thickness of the tablet. The tensile strength is independent of the compression punch diameter. The relation between the *MP* in compression with various punches and the *TS* is shown in Fig. 15. The plots are linear except for the case of the 0.7 cm punch at higher pressure, where the friction at the die wall and the *EE* increase and the energy available for molding the tablet decreases relatively. Sagawa *et al.*[4] reported that the longer the decompression time, the more the elastic recovery decreased and the hardness of the tablet increased, when tablets of lactose, starch and aspirin were molded at constant pressure. Asahina[9] reported that tablets of granular lactose and starch showed larger elastic recovery when compressed at higher pressure. In the pressure region used in our study, the hardness increased with increasing compression stress, as did elastic recovery. Thus, the hardness may be an effective parameter of the mechanical energy accepted by the powder bed during the compression. However, the result of compression using the 0.7 cm punch at higher pressure deviates from linearity (Fig. 15) because of the increasing effects of friction and the elastic behavior. Therefore compression using a 0.7 cm punch is not suitable to determine the mechanical energy of the compression process.

References and Notes

1) Presented at the 99th Annual Meeting of the Pharmaceutical Society of Japan, Sapporo, August 1979.
2) S. Bessho, S. Tomioka and S. Ito, *Yakugaku Zasshi*, **88**, 1495 (1968); *idem, ibid.*, **89**, 291 (1969).
3) M. Y. Bal'shin, *Vestnik Metalloprom.*, **18**, 124 (1938).
4) Y. Sagawa, T. Sakamoto and H. Maekawa, *Yakuzaigaku*, **36**, 135 (1976); *idem, ibid.*, **37**, 80 (1977); M. Morii, N. Takeguchi and I. Horikoshi, *Chem. Pharm. Bull.*, **21**, 589 (1973).
5) N. Kaneniwa and K. Imagawa, *Micromeritics*, **23**, 94 (1979).
6) M. Otsuka and N. Kaneniwa, *Yakugaku Zasshi*, **102**, 359 (1982).
7) M. Otsuka and N. Kaneniwa, *Chem. Pharm. Bull.*, **31**, 230 (1983).
8) J. M. Newton, G. Rowley, J. T. Fell, P. G. Peacock and K. Ridgway, *J. Pharm. Pharmcol.*, **23**, Suppl. 195s (1971).
9) K. Asahina, *Yakugaku Zasshi*, **76**, 41 (1956).