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Effects of Environmental Temperature and Compression Energy on Polymorphic Transformation During Tabletting

MAKOTO OTSUKA* AND YOSHIHISA MATSUDA

KOBE WOMEN'S COLLEGE OF PHARMACY,

Motoyama-Kitamachi, Higasi-Nada, Kobe 658, Japan.

ABSTRACT

The effects of temperature on the polymorphic transformation and the compression of chlorpropamide forms A and C during tabletting were investigated by X-ray diffractometry. The X-ray diffraction profiles of the sample powders deagglomerated after compression were recorded to calculate the degree of polymorphic transformation. A single punch eccentric tabletting machine equipped with two load cells (upper and lower punches) and with a noncontact displacement transducer was used to measure the compression stress, energy and distance between punches. A heater and a liquid nitrogen pool were mounted on the die of the tabletting machine, and the die temperature was controlled with a thermocontroller. Two types of compression methods, multi-tabletting at room temperature and single tabletting at 0-45°C, were used in the present study. In the first method, the stable form A or metastable form C was loaded in to the die and the sample was compressed with a compression

* to whom correspondence should be addressed.

stress of 196 MPa. Compression was repeated from 1 to 30 times. The results for forms A and C suggested that both forms were mutually transformed, and that the content of forms A and C reached equilibrium above 100 J/g of compression energy after more than 10-times compression. After 30-times compression, the content of A, C, and the noncrystalline solid form were almost constant at about 45%, 25% and 30%, respectively. The compression energy was estimated to be 500-600 J/g. In the second method, single tabletting at 0° and $45^{\circ}C$, the amount of form C transformed from form A at $45^{\circ}C$ was about two times larger than that at $0^{\circ}C$ at the same compression energy. The amount of form A transformed from form C at $45^{\circ}C$ was almost the same as that transformed at $0^{\circ}C$. This suggests that the mechanochemical stability of form A was affected by compression temperature, while that of form C was independent of temperature. The crushing strength (CS) of from A tablet was about two times higher than that of form C even at the same porosity. The relationships between log (CS) of form A tablets compressed at 0 or $45^{\circ}C$ and porosity showed straight lines with the same slope, but the slope for form C tablets compressed at $45^{\circ}C$ was smaller than that for those compression at $0^{\circ}C$. From these results it appears that the transformation mechanism of forms A and C during compression was as follows: Form A or C was converted to a noncrystalline solid by mechanical energy, and then the solid was transformed into form A or C. The transformation of every form was affected by the environmental temperature.

INTRODUCTION

Tabletting is an important process that is necessary for making the most common dose form of pharmaceutical preparations. Although there have been many studies of the tabletting process, in which attempts have been made to clarify its underlying

physical mechanisms (1, 2) and its intrinsic interparticle bonding mechanisms, but its mechanism of this process is still not clear.

Since the physicochemical state of a drug controls its dissolution rate and affects its bioavailability (3), the polymorphism of pharmaceutical drugs in the crystalline form has recently attracted the interest of many investigators. Since many drugs are manufactured in tablet form, the mechanochemical stability and compaction behavior of the polymorphic form of a drug during tabletting is very important in practice. Some qualitative studies have been made of mechanical effects on the polymorphism of drugs: Summers et al. (4) reported lowering in the transition temperature of polymorphic forms of sulphathiazole and barbitone due to tabletting compression. Nogami et al. (5) reported that a metastable form of barbital was transformed to a stable form during tabletting. Ibrahim et al. (6) reported briefly that the meta-stable form of phenylbutazone was transformed to the stable form by mechanical stress. We also reported changes in the physicochemical properties of cephalexin (7), chloramphenicol palmitate (8,9), indomethacin (10) and phenylbutazone (11) during compression and grinding. However, there have been few produced in quantitative studies of the physicochemical changes though polymorphs by mechanochemical effects during tabletting, even these changes may seriously affect the bioavailability of the preparation.

Chlorpropamide (CPM) is used clinically as an oral anti-diabetic drug; it is very slightly soluble. Since Simmons et al. (12) first reported the existence of three polymorphic forms of CPM, of which form A is the stable form and form C is unstable form at room temperature, but stable at high temperature, several reports have appeared on CPM polymorphs and their dissolution behavior. Ueda et al. (13) reported the dissolution behavior of

polymorphs of the drug by the stationary disk method. The dissolution rate of the metastable form C is greater than that of the stable form A. Since the polymorphs of the drug were shown to be transformed by compression, the dissolution rate of CPM may be affected by tabletting compression. Therefore, the relationship between polymorphic transformation and compression properties is important.

In general, the compression energy is consumed in many processes, i.e. rearrangement, fragmentation, bond formation, deformation of particles or crystals, friction between particles and the die wall, etc. In the present study, we measured the total mechanical input energy consumed in these processes from the hysteresis loop of compression curves. Compression energy is presumed to be a useful quantitative parameter for estimating mechanochemical effect, since some of this energy would be available for crystallographic change. Under our experimental condition it seems that most of the compression energy was consumed for the crystallographic changes of CPM, and for the packing of the powder, since the powder bed was packed very well by tapping and the tabletting speed was very slow. Therefore the rheological characteristics of the powder bed were negligible. In the first section of the experiment (14), we investigated the mechano-chemical stability of CPM as a model drug during tabletting at room temperature, and the relationship between mechano-chemical effects on the physicochemical properties of the bulk powder and compression energy.

In the second section (15), to clarify the mechanism of the interparticle bond, we designed single compression experiments at 0 and 45°C as a quantitative model for investigating the environmental temperature dependency of polymorphic transformation during tabletting, and for investigating the

Table 1. Apparent density (Da), tapped density (Dt), material density (Dm), and Hausner ratio (H.R.) of CPM form A and C

Sample	Da (g/cm^3) (S.D.)	Dt (g/cm^3) (S.D.)	Dm (g/cm^3) (S.D.)	H.R.[a]
Form A	0.417 (0.008)*	0.487 (0.005)*	1.747	1.17
Form C	0.469 (0.010)	0.538 (0.008)	1.687	1.15

*, $p<0.05$ significant difference; a, H.R. = Dt/Da.

relationship between the crushing strength of the tablet and compression energy.

Materials and Methods

Preparation of CPM polymorphs

Form A CPM was obtained by recrystallization of commercial bulk powder (Taito Pfizer Co. Ltd., Tokyo, Japan) from ethanol solution. Form C was obtained by heating form A in an oven maintained at 110°C for 3 hours, as described by Simmons et al. (12). The sample powders passed through a No. 42 mesh screen (350 μm) and did not pass through a No. 60 mesh screen (250 μm).

Density determination

True density was determined by using an air comparison pycnometer (model 930; Beckman-Toshiba Ltd., Tokyo, Japan). The values for CPM forms A and C are summarized in Table 1. The density of the CPM noncrystalline solid was calculated to be 1.501 g/cm^3, from the density (1.673 g/cm^3) of a mixture of 30% noncrystalline solid and 70% form A, obtained by grinding.

Powder X-ray diffraction analysis

Powder X-ray diffraction was measured at room temperature with a type 11 PA diffractometer (Nihon Denshi Co. Ltd., Tokyo, Japan). The measurement conditions were: target, Cu; filter, Ni; voltage, 30 kV; current, 7.5 mA; time constant, 1 sec; step slit, 0.03°, and counting time, 0.5 sec.

Measurement of polymorphic content in mixtures of forms A and C

The polymorphic content of CPM was measured by X-ray diffraction as reported previously (14). This content was based on the X-ray diffraction peak area ratio ($2\theta=11.8^{\circ}$ for form A, and $2\theta=15.0^{\circ}$ for form C) of the standard mixture and LiF (20%). In this study, a tablet was assumed to be a homogeneous system and the polymorphic content of a tablet was calculated from the calibration curves. Each value was the average of 3 measurements.

Tabletting apparatus for measurement of compression energy

Two load cells (one each on the upper and lower punch) and a noncontact displacement transducer mounted on a type KS-2 single-punch eccentric tabletting machine (Nichiei Seiko Co., Tokyo, Japan) with a flat-type punch (diameter of 1.0 cm) were used, as shown in Fig. 1. A resistance heater and liquid nitrogen pool were mounted on the die for temperature control. The average die temperature was measured by a thermocouple and was controlled by a thermocontroller at $0 \pm 0.5^{\circ}C$ and $45 \pm 0.5^{\circ}C$. The compression stress of the upper and the lower punches and distance between punches were measured as described previously (14, 15). Tabletting compression speed was set at 3 rpm. Figure 2 shows the plots of compression stress against distance between punches. The compression curves showed a hysteresis loop. The area under the compression stress-displacement corresponded to the apparent input energy during tabletting compression. Jarvinen et al. (16) reported on die friction during tabletting and estimated compression energy (E) by using the following equations, 1 and 2:

$$W = \int_{h1}^{h2} \{F_{up} - (F_{up} - F_{lp}) / \ln (F_{up} / F_{lp})\}\, dh \quad \text{eq 1.}$$

$$E = LE - W \quad \text{eq. 2}$$

F_{up}, force of upper punch; F_{lp}, force of lower punch;

h, distance of powder bed; h_1, distance of initial powder bed;

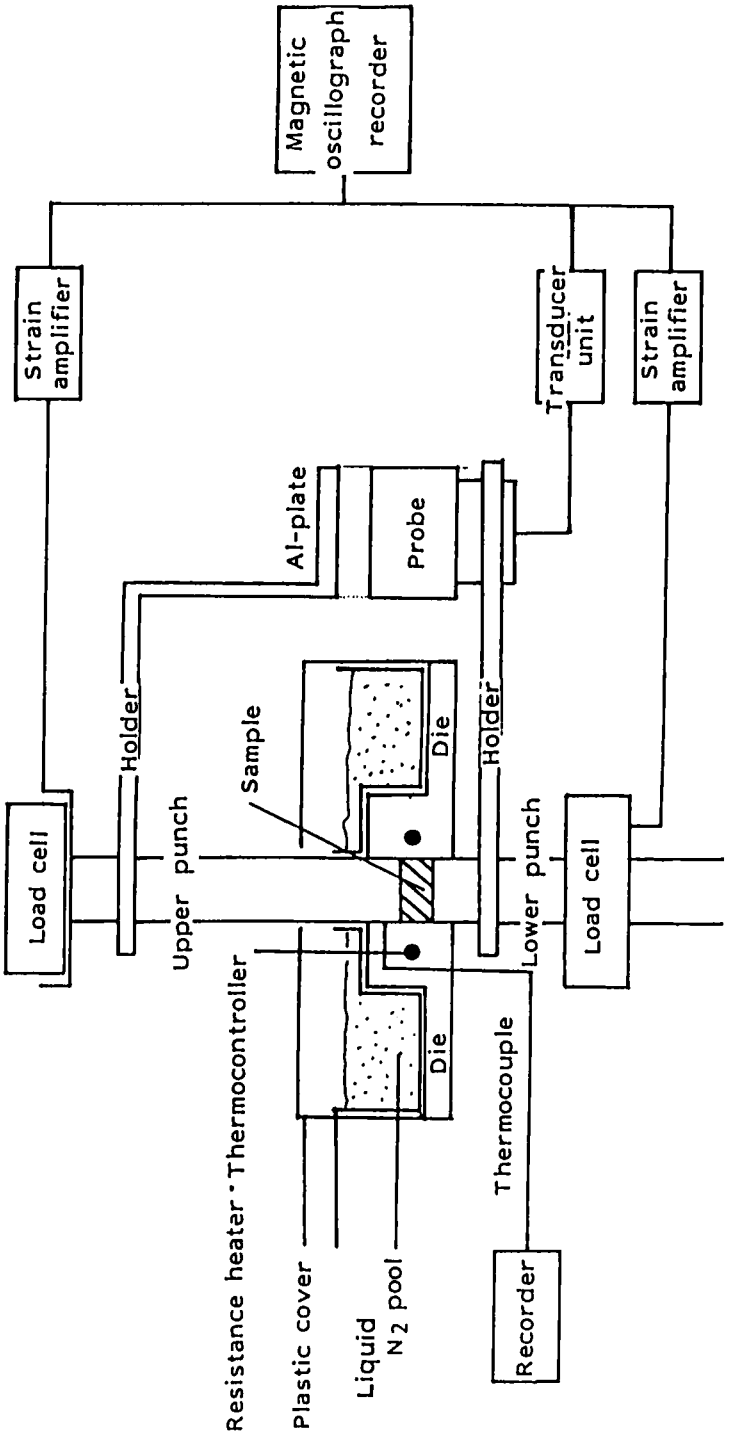

Fig. 1 Block diagram of tabletting compression apparatus

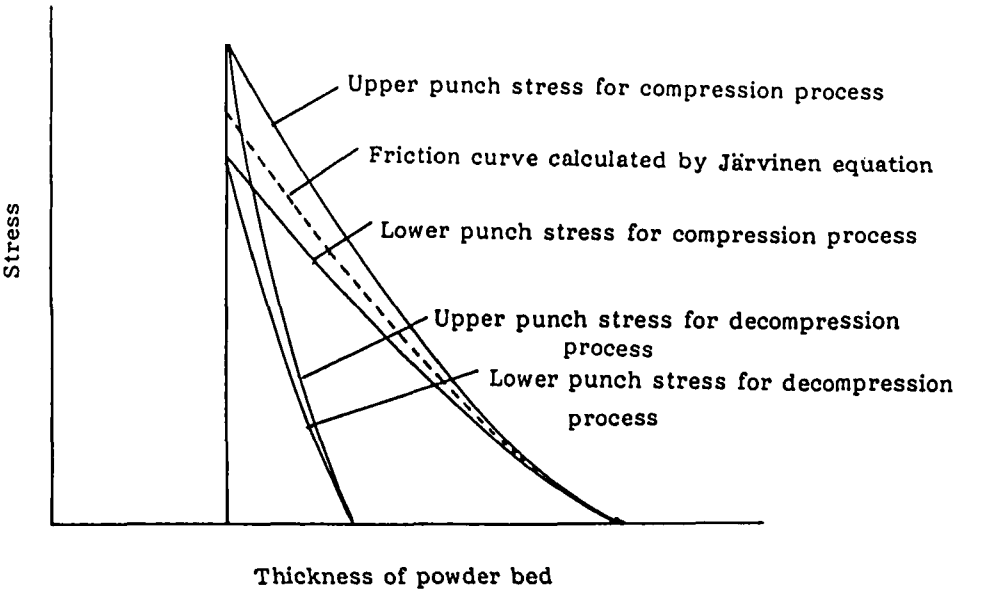

Fig. 2 Relationship between compression pressure and thickness of powder bed

h_2, distance of compaction; W, friction work at die wall; LE, total compression energy.

Preparation of tablets

The punches and die were smeared with 5% stearic acid in chloroform solution and dried. A 100- or 200-mg sample was used for multi- and single compression experiments, and this was then tapped into the die by hand. In the case of the multi-compression experiment, the sample powder was compressed at 196 MPa at room temperature. The molded tablet was carefully deagglomerated by hand in an agate mortar with an agate pestle. The individual powder samples (13 samples of form A and 24 samples of form C) were compressed 1 to 30 times and deagglomerated. The changes produced by this operation were less than 1% in peak intensity on the X-ray diffraction profiles, as

Table 2 Effect of the particle size (D) of powder on the diffraction peaks of CPM forms A and C

D (μm)	Peak height (mean ± S.D. cps; n=5) form A 2θ=6.7°	form A 2θ=11.8°	form C 2θ=15.0°
37 - 63	655 ± 21	624 ± 23	262 ± 14
	N.S.	N.S.	N.S.
148 - 250	651 ± 64	612 ± 17	242 ± 20
	p*<0.05	N.S.	N.S.
Ground sample of 148 - 250	507 ± 57	611 ± 31	238 ± 26

N.S.; differences not significant by Student's t-test
*; significant difference: p<0.05

Table 3. Weight loss of form A and C sample powder during multitabletting compression

Sample tabletting no. of compression	E (J/g)	Weight loss (%)
Form A		
1 time	13.8	0.2
5 times	101.0	2.5
10 times	192.2	3.9
20 times	348.1	12.7
30 times	518.8	11.1
Form C		
1 time	14.5	0.2
5 times	102.7	6.7
10 times	207.7	9.3
20 times	432.8	14.0
30 times	620.3	18.5

shown in Table 2, so this effect was neglected in the present study. A 100-mg sample of powder was compressed initially, at 30 compressions producing a weight loss of 18.5% and 11.1%, respectively, in the samples of forms A and C (Table 3). In the case of single compression, the molded tablet was deagglomerated carefully by hand in an agate mortar with an agate pestle after compression at 0 or 45°C. The changes of polymorphic content produced by this operation were less than about 1% of the crystal content, so the mechanochemical effect during tablet deagglomeration was neglected in the present study.

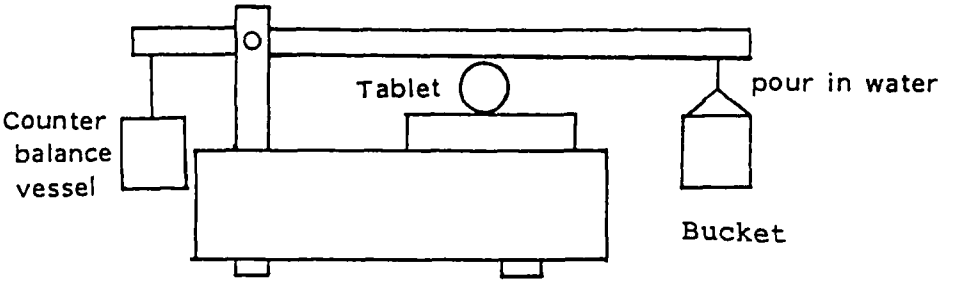

Fig. 3 Schematic diagram of apparatus used to measure tablet crushing strength

Measurement of crushing strength of tablet

The crushing strength of the tablets was measured by using the hand operated hardness tester shown in Fig. 3. After balancing, water was poured into the bucket at a constant rate of 600 ml/min. Each value was the average of 3 measurements. This hardness tester was very sensitive and had reproducible results for a tablet of low crushing strength.

RESULTS AND DISCUSSION

Identification of CPM polymorphs

The X-ray diffraction profiles of forms A and C are shown in Fig. 4. The X-ray diffraction pattern and the main diffraction angles of forms A and C agreed with the data of Simmons et al. (12). Figure 5 shows the infrared (IR) spectra of forms A and C. These spectra were identical to previously reported data (12). Figure 6 shows the differential scanning calorimetry (DSC) curves of forms A and C. The DSC curve of form A showed an endothermic peak at 120°C due to melting, a subsequent exothermic peak due to crystallization to form C at 125°C, and an endothermic peak due to form C at 130°C. The DSC curve of form C shows only an endothermic peak due to melting at 130°C. These

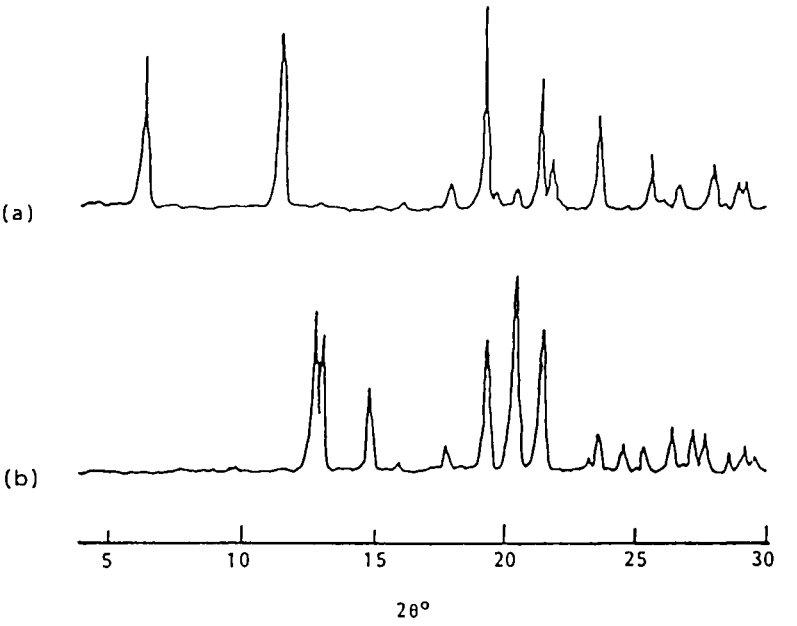

Fig. 4 Powder X-ray diffraction profiles of chlorpropamide polymorphs (a), form A; (b), form B

characterization results suggested that these samples were pure polymorphic forms.

Determination of the content of CPM polymorphs

Since the diffraction peaks at $2\theta=6.7^{o}$ and 11.8^{o} due to form A and the peak at $2\theta=15.0^{o}$ due to form C did not overlap, it was possible to use them to determine the content of forms A and C. Table 2 shows the effects of sample particle size on the diffraction peaks of forms A and C. This result suggested that the diffraction peaks at $2\theta=11.8^{o}$ and at $2\theta= 15.0^{o}$ are suitable for determining the content of forms A and C, respectively, because these peak intensities were independent of sample particle size. The diffraction intensity of the peak at $2\theta=6.7^{o}$ varied with sample particle size, since the X-ray diffraction peak intensities were affected by the orientation of the sample

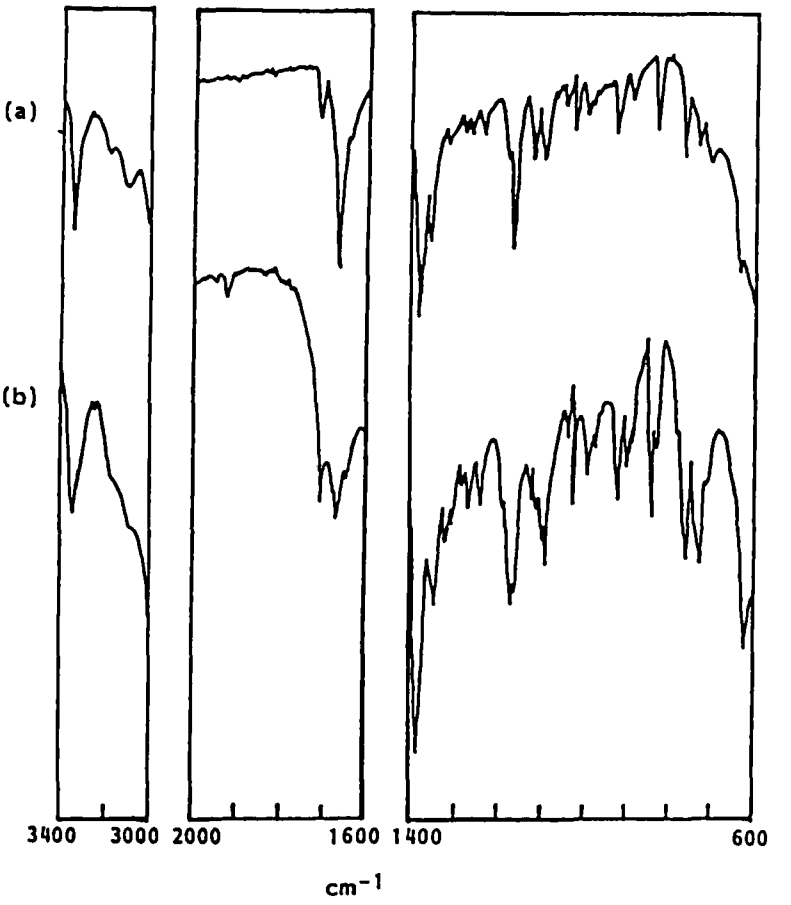

Fig. 5 IR spectra of chlorpropamide polymorphs

(a), form A; (b), form B.

powder particles. The results for ground samples 148 - 250 μm in size suggested that the mechano-chemical effect when the compressed tablet was deagglomerated to a powder sample was negligible in this experiment.

Figure 7 shows the calibration curves for determining the content of forms A and C; these were both straight lines, and

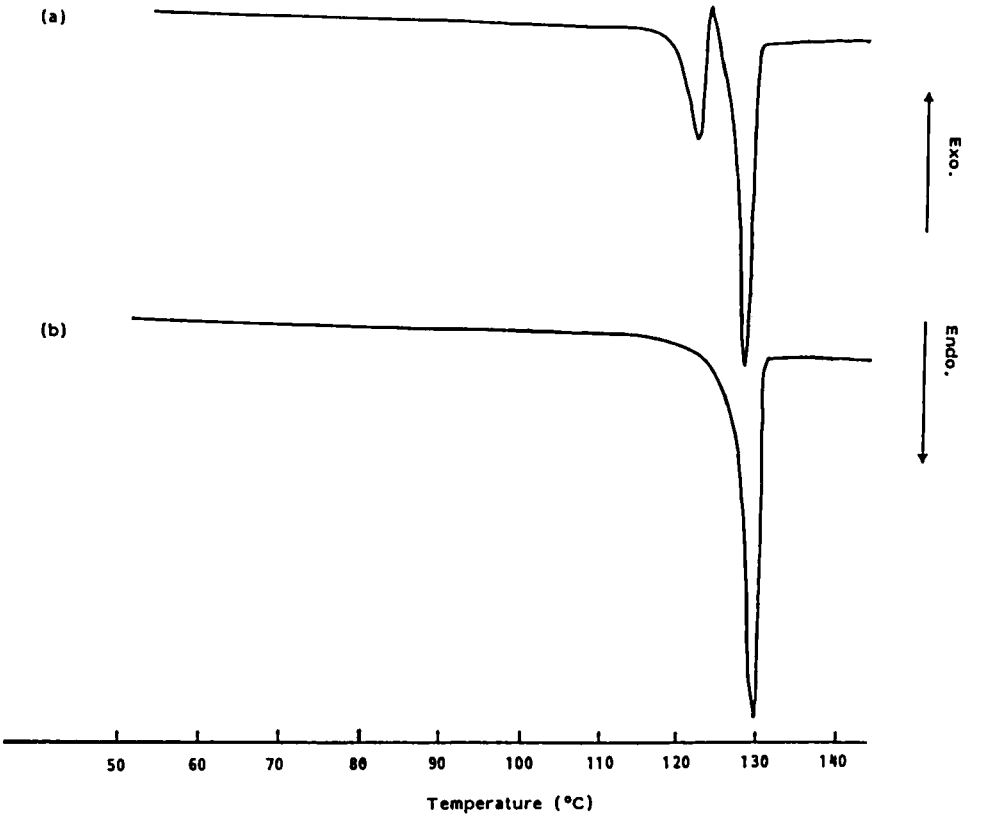

Fig. 6 DSC curves of chlorpropamide polymorphs (a), form A; (b), form B.

were estimated by the least-squares method, as follows:

$$Y_a = 0.0219\ X_a + 0.0257 \quad (r = 0.998) \quad \text{eq. 3}$$

$$Y_c = 0.00901\ X_c + 0.0110 \quad (r = 0.996) \quad \text{eq. 4}$$

Where Y_a = intensity of form A; Y_c = intensity of form C; X_a = content of form A; X_c = content of form C; and r = correlation coefficient.

The content of forms A and C was calculated from both straight calibration curves.

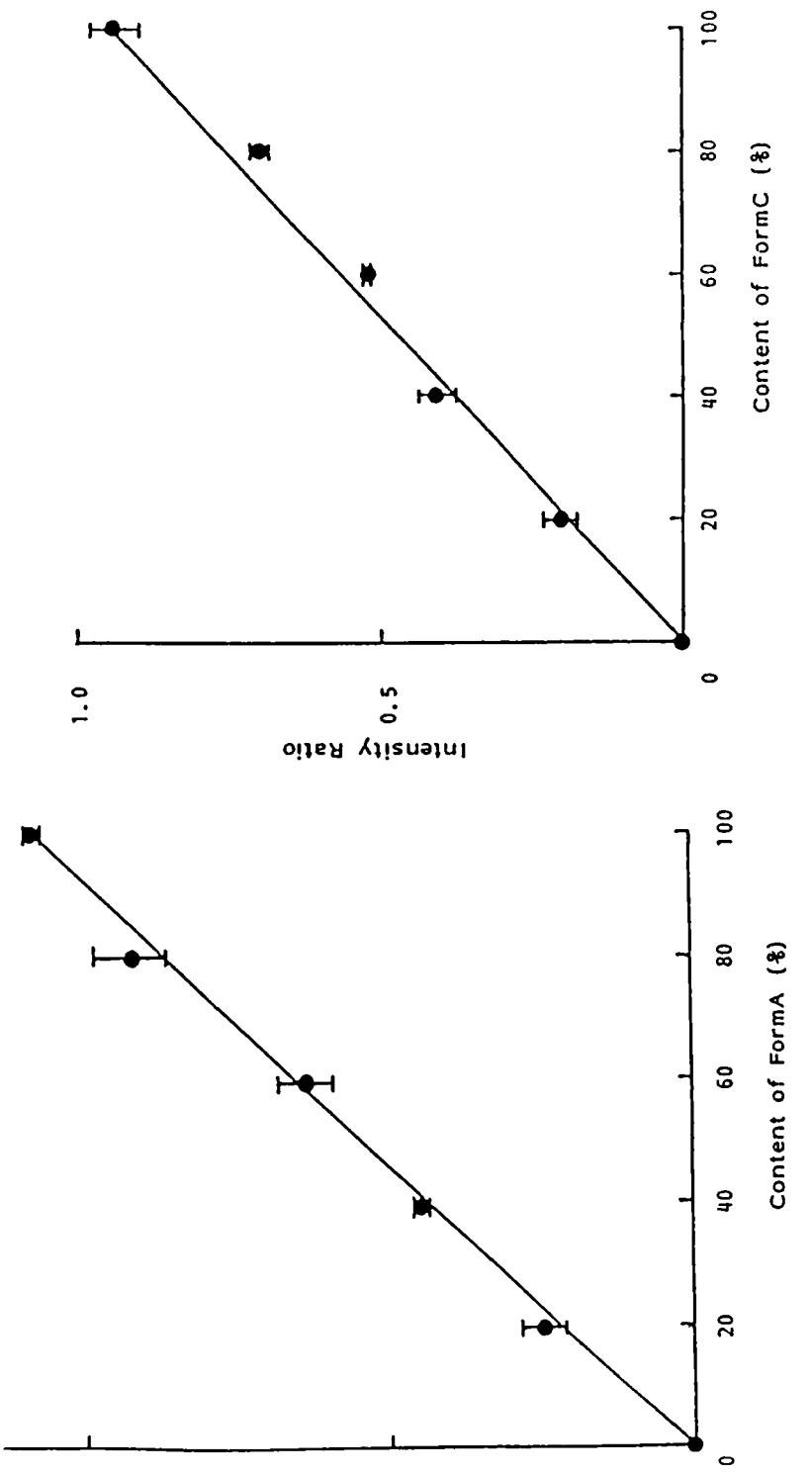

Fig. 7 Relation between polymorphs content and X-ray diffraction intensity ratio
(a), form A; (b), form C; internal standard is LiF; each point represent the mean of 3 measurements.

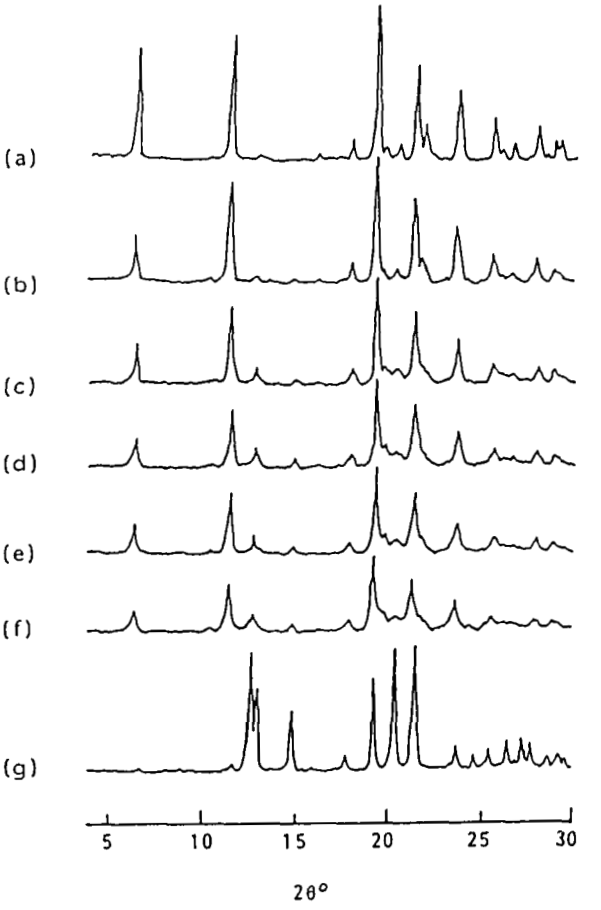

Fig. 8 Changes in X-ray diffraction profiles of form A produced by tabletting compression

(a) intact form A,
(b) after 1 compression,
(c) after 3 times,
(d) after 5 times,
(e) after10 times,
(f) after 30 times,
(g) intact form C.

Effects of multi tabletting compression on polymorphic transformation of CPM

Figures 8 and 9 show the changes in the X-ray diffraction profiles of forms A and C after tabletting by multi compression at room temperature. As form A was repeatedly compressed, the

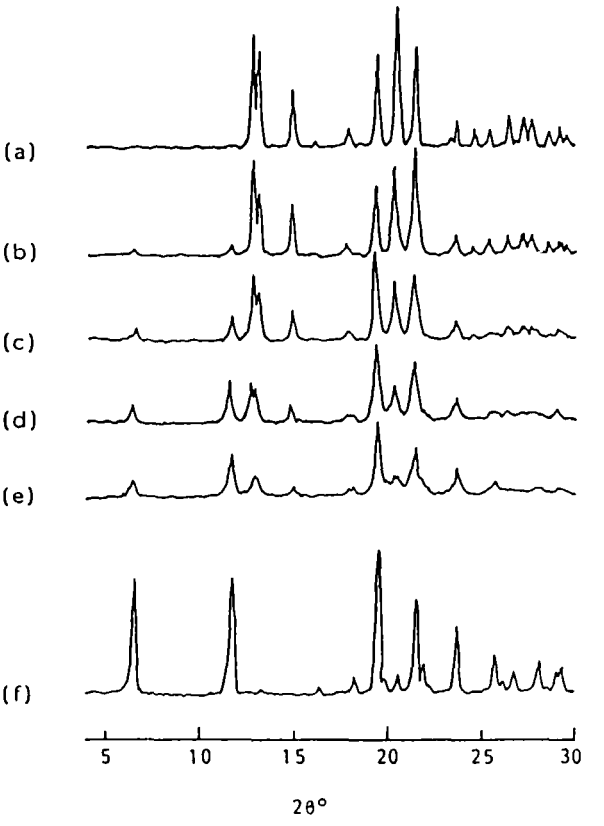

Fig. 9 Change in X-ray diffraction profiles of form C by tabletting compression
(a) intact form A, (b) after 1 compression, (c) after 3 times, (d) after 5 times, (e) after10 times, (f) after 30 times, (g) intact form A.

diffraction peaks due to form A decreased with increasing numbers of compressions, and the peaks due to form C increased. The diffraction peaks due to form C decreased with increasing numbers of compressions of form C, and peaks due to form A appeared.

Effects of compression energy on polymorphic transformation of CPM forms A and C during multi tabletting compression

Figures 10 and 11 show the relationship between the polymorphic content of CPM and compression energy. Compression

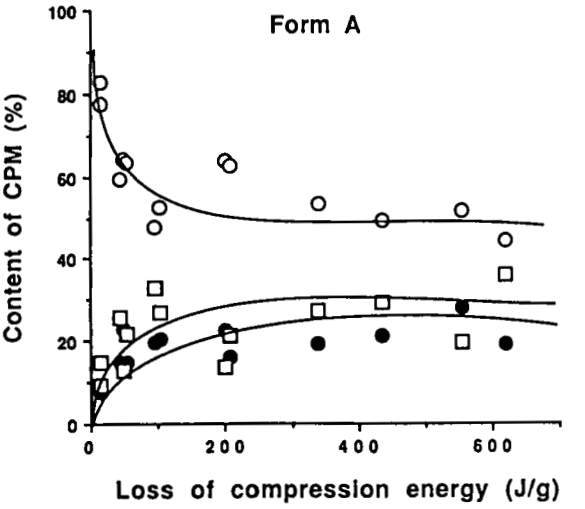

Fig. 10 Relationship between content of forms A and C and compression energy for CPM form A ○, content of form A; ●, content of form C; □, content of noncrystalline solid.

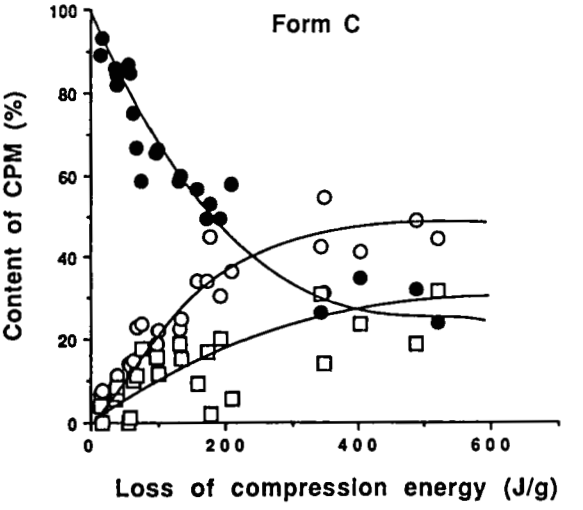

Fig. 11 Relationship between content of forms A and C and compression energy for CPM form C ○, content of form A; ●, content of form C; □, content of noncrystalline solid.

of form A decreased the content of form A, and increased the content of form C with increasing numbers of compressions (Fig. 10). The content of forms A and C and the noncrystalline solid were almost constant at 45%, 25% and 30%, respectively, after tabletting compression of over 300 J/g of compression energy.

The content of form C (Fig. 11) decreased with increasing numbers of compressions, and that of form A increased. After compression with energy of more than 300 J/g, the content of forms A and C and the noncrystalline solid reached equilibrium at constant values of 45%, 25%, and 30%, respectively. The result CPM polymorphs suggested that the meta-stable form C was about 10% transformed to the stable form A during one tabletting compression at 196 MPa with compression energy of 14.5 J/g and the stable form A was about 8% transformed into the meta-stable form C during one compression at 196 MPa with compression energy of 13.8 J/g. The results for the compression of both forms A and C suggested that they were mutually transformed by mechanical energy. The content of forms A and C reached equilibrium at a nearly constant value when the mechanical energy of compression exceeded 200 J/g. After 30 tabletting compressions, the compression energies of forms A and C were estimated to have reached 620 and 519 J/g, and the polymorphic content of forms A and C and the noncrystalline solid were 45%, 25%, and 30%, respectively.

Effects of temperature on the polymorphic transformation of CPM during tabletting

Figure 12 shows the effects of temperature on the polymorphic transformation of forms A and C during tabletting. At 45°C, 30.9% of form A was transformed into 14% of form C and 16.9% of noncrystalline solid by 11.1 x 10^3 J/kg of compression energy, but at 0°C, only 16.4% of form A was transformed into

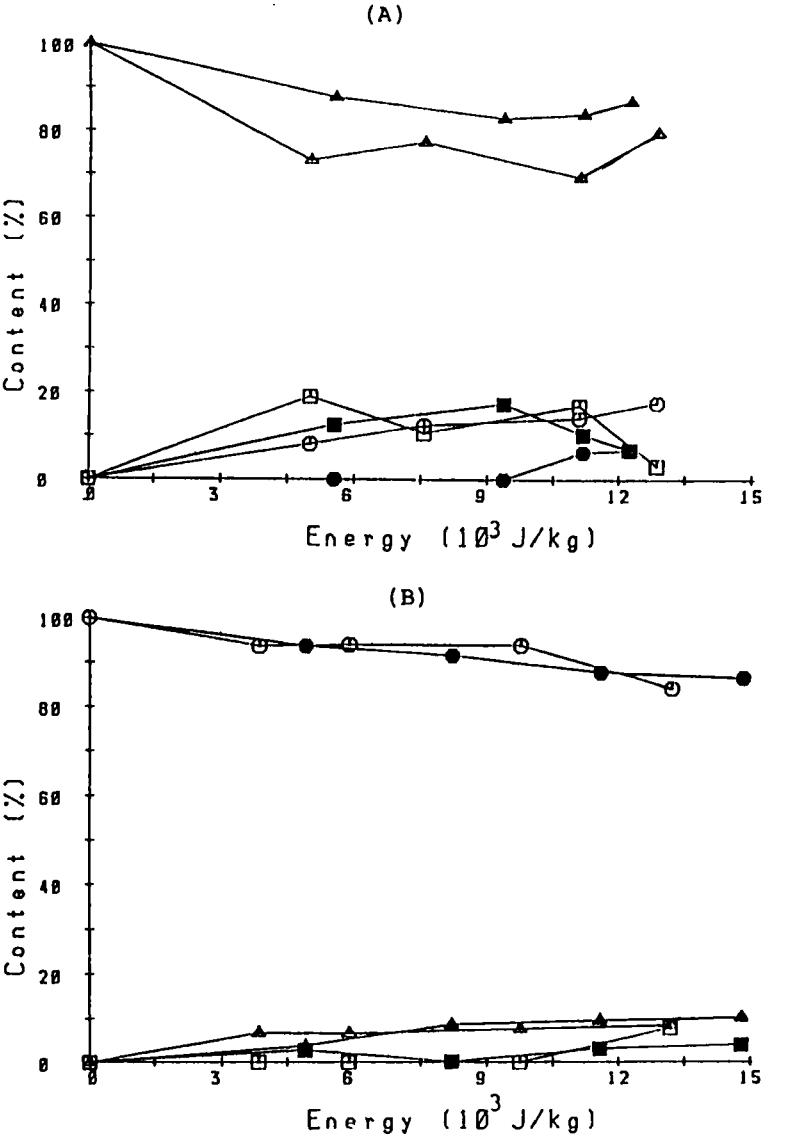

Fig. 12 Effects of temperature on polymorphic transformation of CPM during tabletting (A), form A; (B), form C; △, form A at 45°C; ○, form C at 45°C; □, noncrystalline solid at 45°C; ▲, form A at 0°C; ●, form C at 0°C; ■, noncrystalline solid at 0°C.

6.2% of form C and 10.2% of noncrystalline solid by the same amount of energy at (Fig. 12-(A)). In the single compression tests, the decrease in the amount of form A at 45°C was about twice as much as that at 0°C (Fig. 12 -(A)). This suggests that the resistance of form A crystal to plastic deformation by mechanical stress was greater at 0° than at 45°C, and that the transformation rate of noncrystalline solid to crystal was greater at 45°C than at 0°C.

At 14.8 x10^3 J/kg compression (Fig. 12 - (B)), 14% of form C was transformed into 10.1% of form A and 3.9% of noncrystalline solid. The amount of form A transformed by the compression at 45°C was almost two times that transformed at 0°C. However, the amount of form C transformed to form A by compression at 0° C was almost the same as that transformed at 4°C (Fig. 12 - (B)). The decrease in the amount of form C produced by compression was almost the same at 45°C as at 0°C (Fig. 12 -(B)). The deformability of form C crystals by compression was not affected by the environmental temperature. From these results, it can be concluded that the mechanochemical effect on the polymorphic transformation of form A crystal depended on temperature, but that on form C crystal was independent of temperature.

Effects of temperature on tablet compaction

The apparent density (Da), tapped density (Dt), material density (Dm), and Hausner ratio (17) of form A and C powders are summarized in Table 1. The Da and Dt of form C powder were significantly larger than those of form A powder, but the Dm of form C powder was smaller than that of form A powder. The Hausner ratio (H.R.) of form C powder was not significantly different from that of form A, and the H.R. of both were less than 1.25. This suggests that form A and C powders have good flowability.

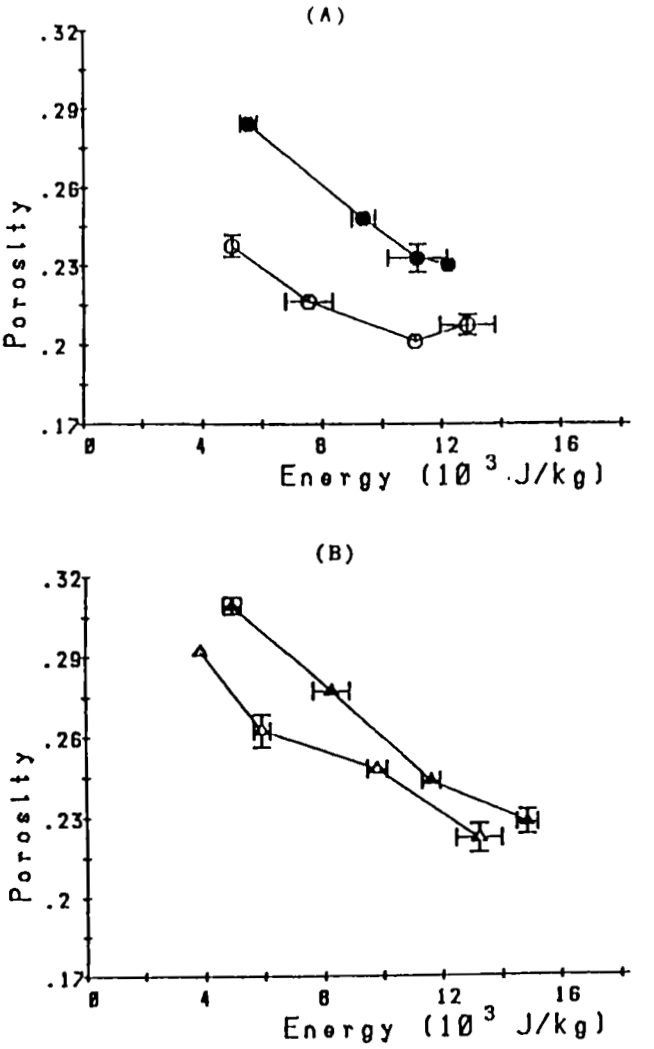

Fig. 13 Relationship between tablet porosity of forms A and C and compression energy
(A), form A; (B), form C;
each point: mean ± S.D. (n = 3);
○, form A at 45°C; ●, form A at 0°C;
△, form C at 45°C; ▲, form C at 0°C.

Figure 13 shows the relationship between porosity of the tablet after ejection and compression energy. The porosity of both form A and C tablets decreased with increasing compression energy. The minimum porosity of the form A tablet was about 0.21, and that of the form C tablet was about 0.22. The porosity

Table 4. Tablet compression ratio* (C.R.) of forms A and C at 0°C and 45°C

Sample	C.R. at 80 MPa (Porosity)	C.R. at 130 MPa (Porosity)	C.R. at 200 MPa (Porosity)
Form A at 0°C	2.89 (0.284)	3.04 (0.255)	3.16 (0.235)
Form A at 45°C	3.08 (0.238)	3.18 (0.221)	3.27 (0.210)
Form C at 0°C	2.55 (0.290)	2.66 (0.261)	2.75 (0.233)
Form C at 45°C	2.62 (0.270)	2.70 (0.251)	2.76 (0.223)

*, Tablet compression ratio = Va/Vc;
Va, apparent initial volume;
Vc, apparent volume at constant pressure.

of form A and C tablets compressed at 0°C was greater than that of those compressed at 45°C.

The compression ratios (C.R.) of forms A and C are shown in Table 4. The C.R. of form A at 45°C was greater than that at 0°C, but there was no difference between the C.R. of form C at 45°C and that at 0°C.

Effects of temperature on crushing strength of tablet

Figure 14 shows the relationship between the crushing strength of CPM polymorphs tablets and compression energy at 0°C and 45°C. The crushing strength of form A and C tablets increased with increasing of compression energy. However, the crushing strength of form A tablets was about 2 times that of form C tablets. The crushing strength of form A and C tablets at 45°C reached plateaux at about 3.3 kg and 1.5 kg, respectively, at more than 10 x 10^3 J/kg. However, the crushing strength of form A and C tablets at 0°C was proportional to the compression energy.

Relations between crushing strength of CPM tablet (H) and porosity (P)

York et al. (18) reported that the binding of powder by compression was due to the local fusion of material produced by

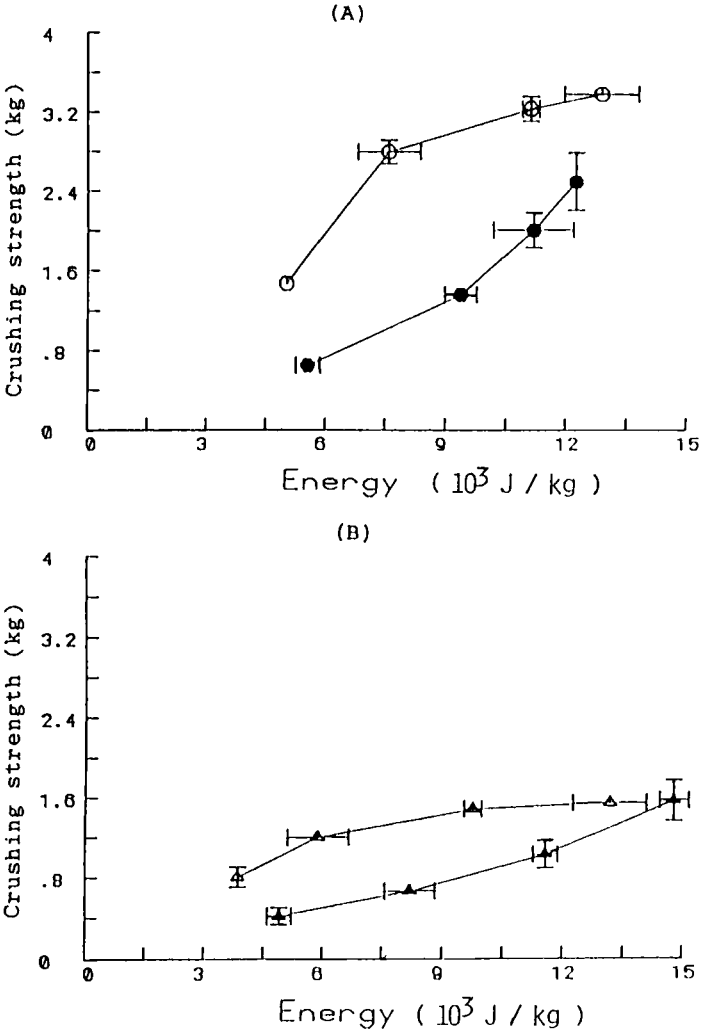

Fig. 14 Relationship between crushing strength of tablet of forms A and C and compression energy (A), form A; (B), form C.
Each point: mean ± S.D. (n = 3)
○, form A at 45°C; ●, form A at 0°C;
△, form C at 45°C; ▲, form C at 0°C.

mechanical energy. Shotton et al. (19) reported that the relationship between log H (crushing strength) and porosity (P) was linear, since crushing strength was controlled by the porosity of the tablet. Plots of log H against porosity for form A and C tablets are shown in Figure 15. The plots for form

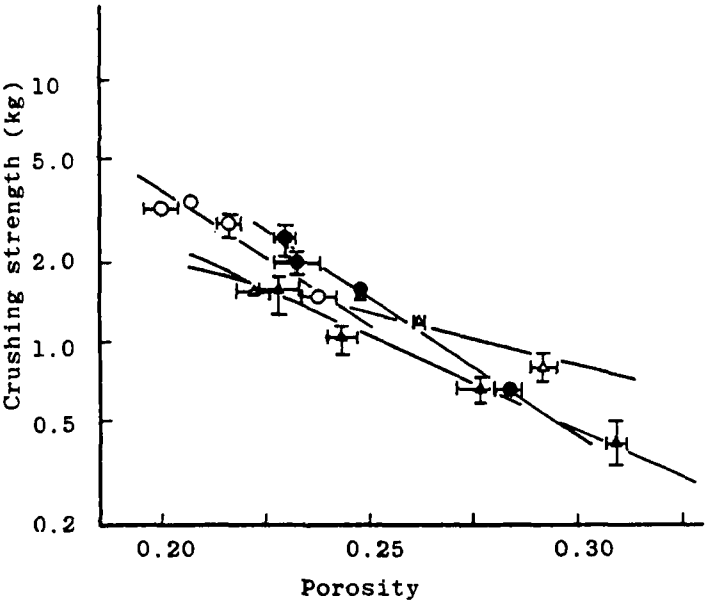

Fig. 15 Relationship between log (crushing strength) of form A and C and tablet porosity
Each point: mean ± S.D. (n = 3)
○, form A at 45°C; ●, form A at 0°C;
△, form C at 45°C; ▲, form C at 0°C.

A tablets compressed at 0°C and 45°C were straight lines, estimated by the least-squares method as follows:

$$\log (H) = -9.39 P + 2.50 \quad (r = -0.952) \quad \text{eq. 5}$$

$$\log (H) = -8.10 P + 2.15 \quad (r = -0.865) \quad \text{eq. 6}$$

Equations 5 and 6 are for form A tablets compressed at 0° C and 45° C, respectively, and r is the correlation coefficient.

Plots for form C tablets compressed at 0°C and 45°C were also straight lines. These plots were estimated as follows:

$$\log (H) = -6.62 P + 1.66 \quad (r = -0.981) \quad \text{eq. 7}$$

$$\log (H) = -3.98 P + 1.11 \quad (r = -0.919) \quad \text{eq. 8}$$

Equations 7 and 8 are for form C tablets compressed at 0°C and 45°C, respectively.

The crushing strength of form A tablets at a porosity of 0.23 was about two times that of form C tablets even at the same

porosity value (Fig. 15). The binding characteristics between particles in form A tablets made by compression were not the same as those in form C tablets, since the brittleness, elasticity, and plastic deformation of CPM depends on the polymorphic form.

Form A tablets compressed at 45°C had a larger compression ratio (Table 4) and lower porosity (Fig. 13) than those compression at 0°C. However, the crushing strength of form A tablets compressed at 45°C was two times that of tablets compressed at 0°C (Fig. 14-A), and the amount transformed by compression at 45°C was about two times that transformed at 0°C (Fig. 12-A). It seems that the effect of temperature the crushing strength of tablets depended on the amount of transformed polymorph. In the compression of form A powder at 0°C and 45°C the relationship between log (H) and porosity had the same slopes (Fig. 15), this suggests that the crushing strength of form A tablets was controlled by porosity.

In the compression of form C at 0°C and 45°C the relationship between log (H) and porosity was linear (Fig. 15). However, the slope for form C tablets compressed at 45°C was smaller than that for tablets compressed at 0°C. The polymorphic content of tablets compressed at 45° and at 0°C was almost the same (Fig.12-B). This result suggests that the crushing strength of form C tablets was not controlled by the amount of crystallographic transformation; it may have been affected more by plastic deformation and/or brittle fracture of the form C crystals. The compression properties of form C suggested that the amount of compression energy of this powder required to obtain the same tablet porosity was less at 45°C than that at 0°C.

Effects of temperature on the transformation pathway of polymorphs during mechanical treatment

As shown in the results for CPM as a model drug, in general, crystals have lattice defects and/or lattice distortions, are

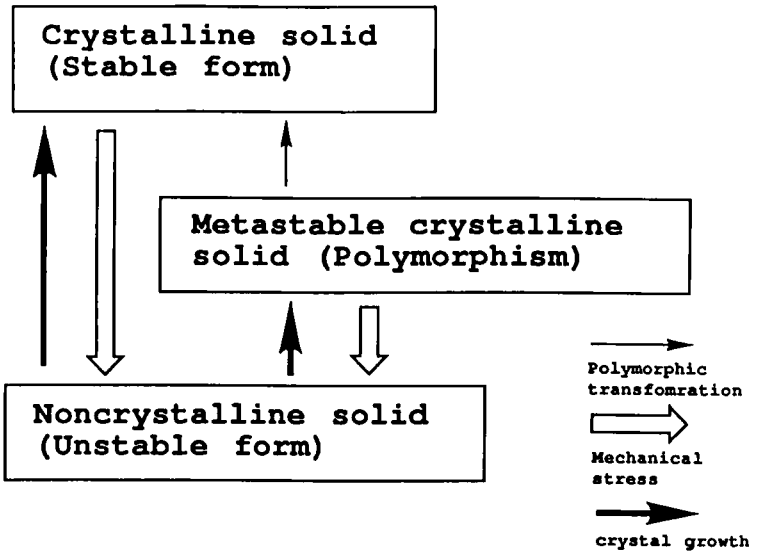

Fig. 16 Polymorphic Transformation Pathway by Mechanical Treatment

brittle, fracture, and have elastic deformation after mechanical treatment. We have reported mechano-chemical effects on the physico-chemical properties of cephalexin (7), chloramphenicol palmitate (8, 9), and indomethacin (10) during grinding. These drugs were converted into noncrystalline solids during this process. If the converted noncrystalline solid was stable under experimental condition s(e.g., indomethacin ground at 4°C (10)), then all of the crystals were converted into noncrystalline solid, but if the converted noncrystalline solid was unstable (e.g., indomethacin ground at 30°C (10)), then the crystallinity of the drug reached equilibrium at some constant level, since crystals regrew in the noncrystalline solid during grinding.

On the other hand, from the pharmaceutical aspect, both the U. S. Pharmacopeia and the British Pharmacopoeia require that preparations of chloramphenicol palmitate must contain no more than 10% of the stable form A, since the dissolution rate of this

form is very slow and preparations of form A have low bioavailability in humans. Contamination in which metastable form crystals are changed to the stable form by mechanical treatment affects the dissolution behavior of bulk powder for pharmaceutical preparations, and the stable crystals act as seed crystals which accelerate transformation of the metastable form into the stable form during storage.

CONCLUSION

The findings during multi tabletting compression were that the mechano-chemical effects of the polymorphic transformation of CPM occurred at room temperature, and that the transformation of forms A and C probably occurred during tabletting compression, (Fig. 16). Some of the crystals of forms A (stable form) and C (metastable form) were converted into noncrystalline solid by mechanical energy, and the solid then transformed into form A or C under these experimental conditions, since the noncrystalline solid was very unstable at room temperature. The polymorphic transformation of CPM produced by mechanical treatment was affected by the temperature at compression. The mechanochemical effects on polymorphic transformation of form A crystal depended on the compression temperature, but this effect on the transformation of form C crystal was independent of temperature. The crushing strength of CPM tablets depended on the kinds of polymorphic forms and on the compression temperature, since the brittleness, elasiticty, and plastic deformability of the polymorphs depended on the temperature. These results suggested that conditions during mechanical treatment affect the physicochemical properties of bulk powders and, thus, the bioavailability of preparations. We might therefore conclude that the effect of environmental temperature on the stability of the crystalline form under tabletting compression is a very

important factor in the production of high quality pharmaceutical preparations.

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