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Effects of Temperature and Pressure During Compression on Polymorphic Transformation and Crushing Strength of Chlorpropamide Tablets

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Abstract—The effects of temperature on the polymorphic transformation of chlorpropamide during compression and on the physical properties of the tablet have been investigated. A heater and liquid nitrogen pool were mounted on the die of a single punch eccentric tableting machine, and the die temperature was controlled by a thermocontroller. A tableting machine with two load cells (upper and lower punches) and a non-contact displacement transducer were used to measure compression stress, distance and energy. The X-ray diffraction profiles of the deagglomerated compressed sample powder were measured to calculate the polymorphic content. The amount of form C transformed from form A at 45°C was about twice that at 0°C with the same compression energy. The amount of form A transformed from form C by compression at 45°C was almost the same as that at 0°C. This suggests that the mechanochemical effect of form A depended on the compression temperature, but that of form C was independent of temperature. The crushing strength of tablets of form A was about twice that of form C, even at the same porosity. The plots of log (crushing strength of tablet) against porosity of form A tablets compressed at 0 and 45°C were linear with the same slope; the slope for form C tablets compressed at 45°C was less than that at 0°C.

Recently, the polymorphism of pharmaceutical preparations in crystalline bulk powders has attracted interest because the physical state of a preparation may affect its bioavailability and control its dissolution rate. The mechanochemical stability of the polymorphic form of a drug during tableting has practical consequences. Summers et al (1976) reported a reduction in transition temperature of polymorphic forms of sulphathiazole and barbitone on compression. Nogami et al (1969) reported that the metastable form of barbitone was transformed to a stable form by mechanical stress at 30 MPa cm^{-2} during tableting. Ibrahim et al (1977) reported briefly that the metastable form of phenylbutazone was transformed to the stable form by mechanical stress. We reported changes of the physiocochemical properties of cephalexin (Otsuka & Kaneniwa 1984; Kaneniwa et al 1984, 1985), chloramphenicol palmitate (Kaneniwa & Otsuka 1985; Otsuka & Kaneniwa 1986), indomethacin (Otsuka et al 1986) and phenylbutazone (Matsumoto et al 1988) during compression and grinding. However, there are few reports on quantitative studies of the physicochemical property changes of polymorphs due to compression during tableting.

Simmons et al (1973) first reported polymorphic forms of chlorpropamide; form A is the stable form and form C the unstable form at room temperature (20°C), but form C is the stable form at higher temperatures. Various reports have subsequently appeared on the polymorphism of chlorpropamide and their dissolution rates. Ueda et al (1984) reported the dissolution behaviour of polymorphs by the stationary disk method.

We have reported on the polymorphic transformation of chlorpropamide during multi-tableting at room temperature as a model in the study of quantitative mechanochemical treatment (Otsuka et al 1989). Forms A and C were transformed into their counterparts and reached equilibrium at 25% form C, 45% form A with 30% as a non-crystalline solid. The mechanical energy was estimated to be about 10×10^4 J kg^{-1} for transformation of 55% form A into form C and non-crystalline solid. Information on the stability of chlorpropamide polymorphs during single tableting is most important from the practical aspect, because the dissolution rate of form C is faster than that of form A, and it is possible to use form C as a bulk powder in pharmaceutical preparations (Ueda et al 1984).

We have designed the single compression experiments at constant temperature, reported in this paper, as a quantitative model for the study of temperature effects on the polymorphic transformation of drugs during compression.

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Materials and Methods

Preparation of polymorphs of chlorpropamide

Form A chlorpropamide was obtained by recrystallization of commercial bulk powder (Taito Pfizer Co. Ltd) from ethanol. Form C was obtained by heating form A in an oven maintained at 110°C for 3 h, as described by Simmons et al (1973). The sample powders passed No. 42 mesh screen (350 μm) and did not pass No. 60 mesh screen (250 μm).

Density determination

True density was determined by using an air comparison pycnometer (model 930; Beckman-Toshiba Ltd). The values of forms A and C chlorpropamide are summarized in Table 1. The density of the non-crystalline solid was calculated to be 1·501 g cm^{-3} from the density (1·673 g cm^{-3}) of the mixture of 30% non-crystalline 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). The measurement conditions were: target Cu; filter Ni; voltage 30 kV; current 7·5 mA; time constant 1 s; step slit 0·03°; counting time 0·5 s.

Measurement of polymorphic content in mixtures of forms A and C

The polymorphic content of chlorpropamide was measured by X-ray diffraction as reported previously (Otsuka et al 1989). The polymorphic content of chlorpropamide was based on the X-ray diffraction peak area ratio ($2\theta = 11{\cdot}8°$ for form A, and $2\theta = 15{\cdot}0°$ for form C) of the standard mixture with LiF (20%). Each value was the average of 3 measurements.

Tableting apparatus for measurement of compression energy

Two load cells (one each on the upper and lower punch) and a non-contact displacement transducer mounted on a type KS-2 single-punch eccentric tableting machine (Nichiei Seiko Co. Ltd) with a flat-type punch having a diameter of 1·0 cm was 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 controlled by a thermocontroller at $0 \pm 0{\cdot}5$°C and $45 \pm 0{\cdot}5$°C. The compression stress of the upper and the lower punches and distance between punches were measured as described previously (Otsuka et al 1989). Compression speed was 3 rev min^{-1}. The plots of compression stress against distance between punches showed hysteresis. The area under the compression stress-displacement corresponded to the apparent input energy during compression. Järvinen & Juslin (1981) reported on the die friction during tableting and estimated the intrinsic compression energy (E) using equations 1 and 2.

$$W = \int_{h_1}^{h_2} \{F_{up} - (F_u/F_{lp})/\ln(F_{up}/F_{lp})\} dh \quad (1)$$

$$E = L_E - W \quad (2)$$

where F_{up} if the force of upper punch; F_{lp}, force of lower punch; h, distance of powder bed; h_1, distance of initial powder bed; h_2, distance of compaction; W, friction work at die wall; L_E, total compression energy.

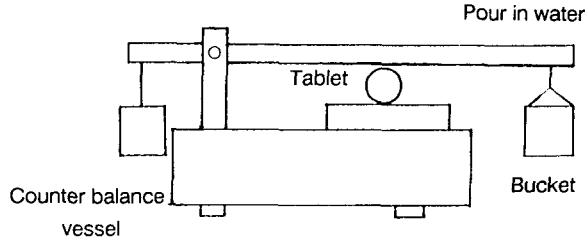

FIG. 2. Schematic diagram of apparatus used to measure the tablet crushing strength.

Preparation of tablets

The punches and die were smeared with 5% stearic acid solution in chloroform, and dried. A 200 mg sample was then put into the die while tapping by hand. The moulded tablet was deagglomerated carefully by hand in an agate mortar with an agate pestle. The changes of polymorphic content produced by this operation were less than about 1% of the crystal content, so the mechanochemical effect during the tablet deagglomeration was neglected in the present study.

Measurement of crushing strength of tablet

The crushing strength of the tablets was measured using the hand operated hardness tester shown in Fig. 2. After balancing, water was poured into the bucket at a constant rate of 600 mL min^{-1}. Each value was the average of 3 measurements. The hardness tester was very sensitive and reproducible for low crushing strength tablets.

Results and Discussion

Effects of temperature on the polymorphic transformation of chlorpropamide during tableting

Fig. 3 shows the effects of temperature on the polymorphic transformation of forms A and C during tableting. At 45°C, 30·9% of form A was transformed into 14% of form C and 16·9% of non-crystalline solid by $11{\cdot}1 \times 10^3$ J kg^{-1} of the

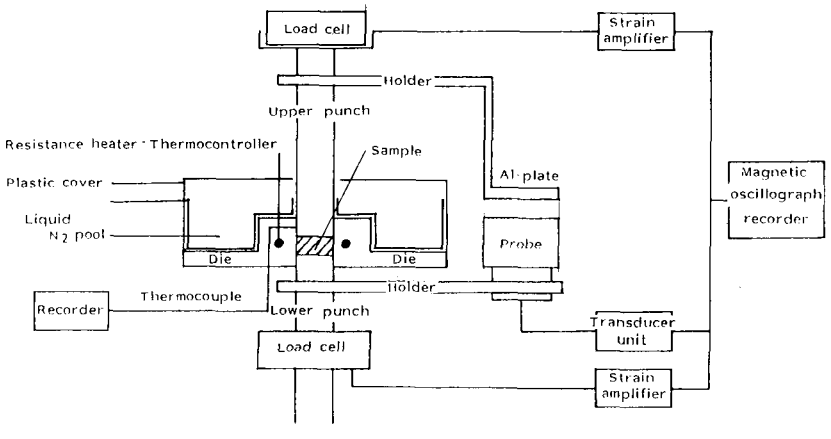

FIG. 1. Block diagram of the tableting compression apparatus.

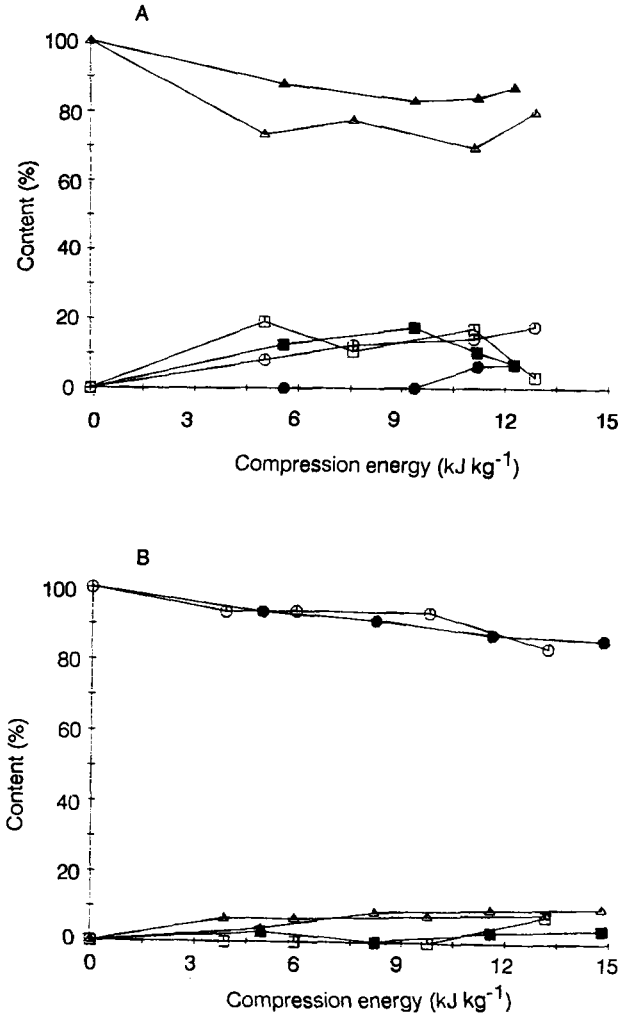

FIG. 3. Effects of temperature on polymorphic transformation of chloropropamide during tableting at different compression energies. (A), form A; (B), form C; △, form A at 45°C; □, form C at 45°C; ○, non-crystalline solid at 45°C; ▲, form A at 0°C; ■, form C at 0°C; ●, non-crystalline solid at 0°C.

compression energy, but at 0°C, only 16·4% of form A was transformed into 6·2% of form C and 10·2% of non-crystalline solid by the same amount of energy (Fig. 3A). In the single compression tests about twice as much form A was lost at 45°C as at 0°C (Fig. 3A). This suggests that the resistance of form A crystal to plastic deformation by mechanical stress was greater at 0°C than at 45°C, and the transformation rate of non-crystalline solid to crystal was faster at 45°C than at 0°C.

At $14{\cdot}8 \times 10^3$ J kg^{-1} compression (Fig. 3B), 14% of form C was transformed into 10·1% of form A and 3·9% of non-crystalline solid. The amount of form A transformed by the compression at 45°C was almost twice that at 0°C. However, the amount of form C transformed to form A by compression at 0°C was almost the same as that at 45°C (Fig. 3B). The decrease in the amount of form C by compression was almost the same at 45°C as at 0°C (Fig. 3B). The deformability of form C crystals by compression was thus not affected by the environmental temperature. From these results, we conclude that the mechanochemical effect on polymorphic transformation of form A crystal depended on temperature, but that of form C crystal was independent.

Table 1. Apparent density (D_a), tapped density (D_t), material density (D_m) and Hausner ratio (HR) of forms A and C of chlorpropamide.

Sample	D_a (g cm^{-3}) (s.d.)	D_t (g cm^{-3}) (s.d.)	D_m (g cm^{-3}) (s.d.)	HR[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

* $P < 0{\cdot}05$ significant difference; [a] $HR = D_t/D_a$.

Effects of temperature on tablet compaction

Apparent density (D_a), tapped density (D_t), material density (D_m) and Hausner ratio (Hausner 1967) of forms A and C powders are summarized in Table 1. The D_a and D_t of form C powder were significantly larger than those of form A powder, but the D_m of form C powder was smaller than that of form A powder. The Hausner ratio (HR) of form C powder was not significantly different from that of form A, and the HR values of both were less than 1·25. This suggests that forms A and C powder have good flow characteristics.

Fig. 4 shows the relation between the porosity of the final

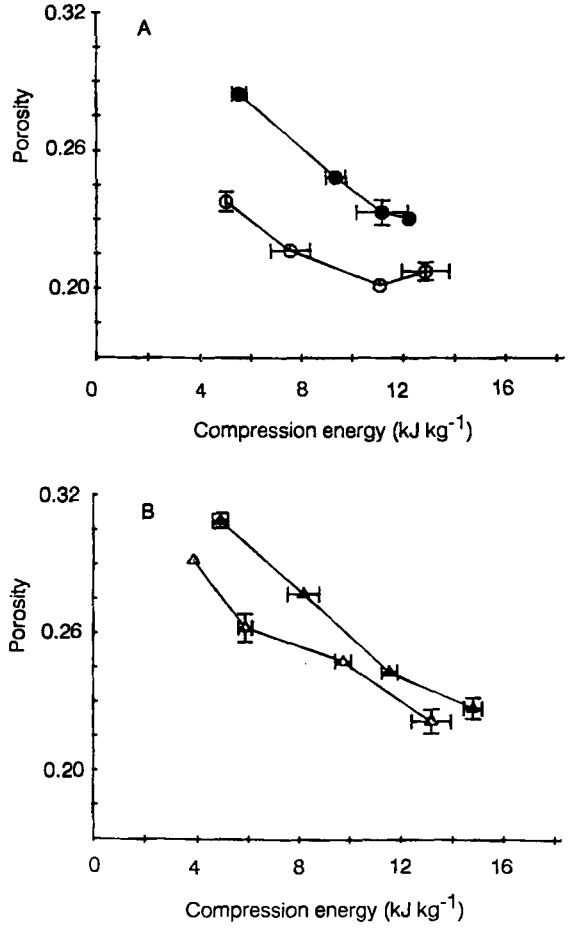

FIG. 4. Relations between tablet porosity of forms A and C and compression energy. (A), form A; (B), form C. Each point: mean ± s.d. (n = 3). ○, form A at 45°C, ●, form A at 0°C, △, form C at 45°C, ▲, form C at 0°C.

tablet and the compression energy. The porosities of both forms A and C tablets, decreased with increase of compression energy. The minimum porosity of form A tablet was about 0·21, and that of form C tablet was about 0·22. The porosities of form A and C tablets compressed at 0°C were greater than those at 45°C.

The compression ratios (CR) of forms A and C are shown in Table 2. The CR of form A at 45°C was larger than that at 0°C, but there was no difference between the CR values of form C at 45°C and 0°C.

Effects of temperature on crushing strength of tablet

Fig. 5 shows the relation between the crushing strength of tablets of the polymorphs of chlorpropamide and compression energy at 0°C and 45°C. The crushing strength of form A and C tablets increased with increase of compression energy. However, the crushing strength of form A tablets was about twice that of form C tablets. Crushing strength of form A and C tablets at 45°C reached plateau at about 3·3 and 1·5 kg, respectively, at more than 10×10^3 J kg^{-1}. However, the crushing strength of forms A and C tablets at 0°C was proportional to the compression energy.

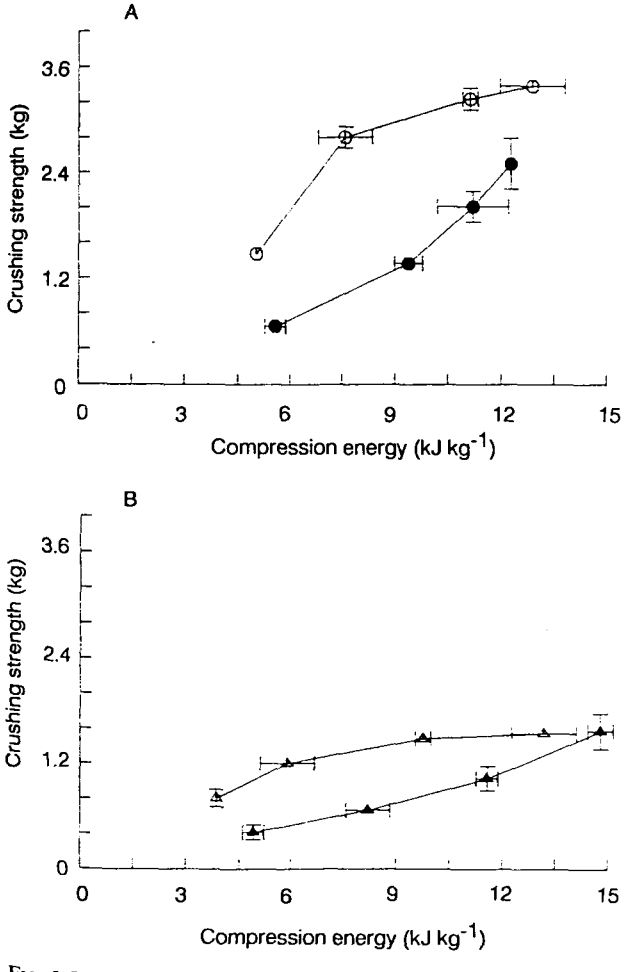

FIG. 5. Relations between the crushing strength of tablet of forms A and C and compression energy. (A), form A; (B), form C. Each point: mean ± s.d. (n = 3). ○, form A at 45°C, ●, form A at 0°C, △, form C at 45°C, ▲, form C at 0°C.

Relations between crushing strength of tablets and porosity

York & Pilpel (1972) reported that the binding of powder by compression was due to local fusion of material caused by the mechanical energy. Shotton & Ganderton (1960a,b) reported that the relation between log (crushing strength) and porosity was linear, suggesting that crushing strength was controlled by the porosity of the tablet. Plots of log (crushing strength) against porosity of form A and C tablets are shown in Fig. 6, and can be fitted to straight lines by the method of least-squares as follows:

Form A 0°C,

$$\log (H) = -9{\cdot}39\ P + 2{\cdot}50 \qquad (r = -0{\cdot}952) \qquad (3)$$

Form A 45°C,

$$\log (H) = -8{\cdot}10\ P + 2{\cdot}15 \qquad (r = -0{\cdot}865) \qquad (4)$$

Form C 0°C,

$$\log (H) = -6{\cdot}62\ P + 1{\cdot}66 \qquad (r = -0{\cdot}981) \qquad (5)$$

Form C 45°C,

$$\log (H) = -3{\cdot}98\ P + 1{\cdot}11 \qquad (r = -0{\cdot}919) \qquad (6)$$

where H = crushing strength in kg and P = porosity.

The crushing strength of form A tablets at porosity 0·23, was about twice that of form C tablets even at the same value of porosity (Fig. 6). The binding characteristics between particles in form A tablets made by compression are not the same as those in form C tablets, because the brittleness, elasticity and plastic deformation of chlorpropamide depend on the polymorphic form.

Form A tablets compressed at 45°C had a larger compression ratio (Table 2) and lower porosity (Fig. 4) than those at 0°C. However, the crushing strength of form A tablets compressed at 45°C was twice that of tablets compressed at 0°C (Fig. 5A), and the amount transformed by compression at 45°C was about twice that transformed at 0°C (Fig. 3A). It appears that the temperature effect on the crushing strength of tablets depended on the amount of polymorph transformed. In the compression of form A powder at 0°C and 45°C, relations between log (H) and porosity had the same

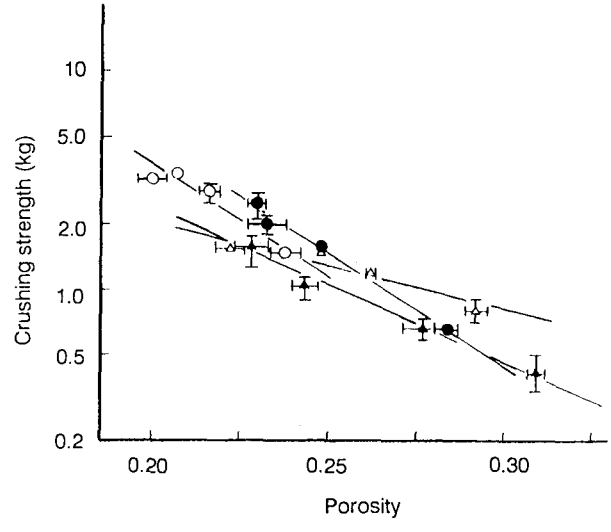

FIG. 6. Relation between log (crushing strength) of form A and C and tablet porosity. Each point: mean ± s.d. (n = 3). ○, form A at 45°C, ●, form A at 0°C, △, form C at 45°C, ▲, form C at 0°C.

Table 2. Tablet compression ratio* (CR) of forms A and C at 0°C and 45°C.

Sample	CR at 80 MPa (Porosity)	CR at 130 MPa (Porosity)	CR 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 = V_a/V_c; V_a, apparent initial volume; V_c, apparent volume at the constant pressure.

slopes (Fig. 6), suggesting 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 relation between log (H) and porosity were linear (Fig. 6). However, the slope of form C tablets compressed at 45°C was less than that at 0°C. The polymorphic content of tablets compressed at 45°C and at 0°C was almost the same (Fig. 3B), suggesting that the crushing strength of form C tablet was not controlled by the amount of crystallographic transformation, and may have been affected more by plastic deformation and/or brittle fracture of form C crystals. The compression properties of form C suggest that the energy of compression of form C powder at 45°C to attain the same tablet porosity, was smaller than that at 0°C.

Conclusion

The polymorphic transformation of chlorpropamide by mechanical treatment was affected by the temperature at compression. The mechanochemical effect for form A crystals on polymorphic transformation depends on the compression temperature, but that for form C crystals was independent of temperature. The crushing strength of chlorpropamide tablets depends on the kinds of polymorphic forms and the compression temperature.

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