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Effects of the Mechanical Energy of Multi-tableting Compression on the Polymorphic Transformations of Chlorpropamide

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Abstract—The effects of the mechanical energy of tableting compression on the polymorphic transformation of chlorpropamide have been examined. A single-punch eccentric tableting machine with a load cell and a non-contact displacement transducer were used to measure compression stress, distance and energy. An amount of 100 mg of the stable form A or the meta-stable form C of the drug was loaded into the press and the sample compressed with a compression stress of 196 MPa at room temperature (20°C). The compression cycle was repeated from 1 to 30 times. The powder X-ray diffraction profiles of the deagglomerated compressed sample powder were measured to calculate the polymorphic content. The results on forms A and C suggested that both forms were transformed into each other in the solid state by mechanical energy during tableting. The contents of forms A and C reached equilibrium at a constant value above 100 J g^{-1} of compression energy after more than 10 cycles. After 30 tableting cycles of forms A and C, the contents of A, C and the non-crystalline solid were almost constant at about 45, 25 and 30%, respectively. The compression energies were estimated to be about 500–600 J g^{-1}. From the results it seems that the transformation mechanism of forms A and C during tableting were as follows. The crystal form of A or C was converted to a non-crystalline solid by the mechanical energy, and the solid was then transformed into form A or C.

There are few reports of the changes produced by the mechanochemical effects of tableting on the physicochemical properties of bulk powders used for pharmaceutical preparations. Summers et al (1976) reported reduction in the transition temperature of polymorphic forms of sulphathiazole and barbitone, and concluded that the polymorphic transition of sulphathiazole form II was due to the production of dislocations in the crystal, and the distortion of the crystals at crystal boundaries formed in the compressed materials. Nogami et al (1969) reported that the metastable form of barbital was transformed to a stable form during tableting by mechanical stress at 294 MPa. Ibrahim et al (1977) reported briefly that the metastable form of phenylbutazone was transformed into the stable form by mechanical stress. We have reported (1982, 1985) changes in the physicochemical properties of cephalexin during compression and grinding, and concluded that the effect was caused by non-crystallization of cephalexin crystals during the mechanical treatment.

Since Simmons et al (1973) first reported three polymorphic forms of chlorpropamide, various reports have appeared on the polymorphism of the drug and their dissolution rates. The meta-stable forms have faster dissolution rates than the stable form, when determined by the rotating basket method of the USP XIX. Ueda et al (1984) reported the dissolution behaviour of polymorphs of chlorpropamide by the stationary disk method, and suggested that the dissolution rate of the metastable form C decreased after compression at 196 MPa because it was transformed into the stable form A.

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In the present work, we have used chlorpropamide as the model drug and investigated the mechanochemical stability of the bulk powder used for pharmaceutical preparations during tableting compression, and relations between the mechanochemical effect on the physicochemical properties of the bulk powder and compression energy.

Materials and Methods

Preparation of polymorphs of chlorpropamide

Form A was obtained by suspending commercial bulk drug powder (Pfizer Taito Co. Ltd) in an aqueous ethanol solution. Form C was obtained by heating form A in an oven at 110°C for 3 h as described by Simmons et al (1973).

Powder X-ray diffraction analysis

Powder X-ray diffraction was measured at room temperature (20°C) with a type 11 PA diffractometer (Nihon Denshi Co., Ltd). The measurement conditions were as follows: 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 the polymorphic content in the mixtures of forms A and C

Physically standard mixtures were obtained by mixing forms A and C. 20% of lithium fluoride was mixed in the standard sample as an internal standard material. The calibration curve for measuring the polymorphic content of chlorpropamide was based on the diffraction peak area ratio of the standard mixture and LiF. In this study, a tablet was assumed to be a homogeneous system and the polymorphic contents of a tablet were calculated from the calibration curves.

Tableting apparatus for measurement of compression energy
A load cell 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 at 3 rev min^{-1}, and the compression stress and distance between punches were measured as described by Kaneniwa et al (1984). The plots of compression stress against distance between punches showed hysteresis; the area of the compression stress-displacement distance loop corresponded to the input energy (E) during the tableting compression process.

Preparation of tablets
The punches and die were smeared with 5% stearic acid solution in chloroform, and dried. A 100 mg sample was then put into the die with tapping by hand. 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 and deagglomerated 1 to 30 times. The changes produced by this operation were less than 1% in peak intensity on X-ray diffraction profiles as shown in Table 1, so the effect was neglected in the present study. A 100 mg sample of powder was compressed initially producing a weight loss in forms A and C samples at 30 compressions of 18·5% and 11·1%, respectively (Table 2).

Table 1. Effect of the particle size (D) of powder on the diffraction peaks of forms A and C of chlorpropamide.

	Peak height (mean ± s.d. cps; n = 5)		
D (μm)	form A $2\theta = 6{\cdot}7°$	form A $2\theta = 11{\cdot}8°$	form C $2\theta = 15{\cdot}0°$
37–63	655 ± 21	624 ± 23	262 ± 14
	NS	NS	NS
148–250	651 ± 64	612 ± 17	242 ± 20
	*	NS	NS
Ground sample of 148–250	507 ± 57	611 ± 31	238 ± 26

NS; not significantly different by Student's *t*-test
* Significant difference: $P < 0{\cdot}05$

Table 2. Weight loss of sample powder of forms A and C during multi-tableting compression.

Sample tableting cycles	E (J g^{-1})	Weight loss (%)
Form A		
1	13·8	0·2
5	101·0	2·5
10	192·2	3·9
20	348·1	12·7
30	518·8	11·1
Form C		
1	14·5	0·2
5	102·7	6·7
10	207·7	9·3
20	432·8	14·0
30	620·3	18·5

Results

Identification of polymorphs of chlorpropamide
The X-ray diffraction profiles of forms A and C are shown in Fig. 1. The X-ray diffraction pattern and the main diffraction angles of forms A and C agreed with the data of Simmons et al (1973).

Determination of the content of polymorphs of chlorpropamide
Since the diffraction peaks at $2\theta = 6{\cdot}7°$ and $11{\cdot}8°$ due to form A and the peak at $2\theta = 15{\cdot}0°$ due to form C did not overlap each other, it was possible to use them to determine the content of forms A and C. Table 1 shows the effects of sample particle size on the diffraction peaks of forms A and C. This result suggests that the diffraction peaks at $2\theta = 11{\cdot}8°$ and at $2\theta = 15{\cdot}0°$ are useful to determine the content of forms A and C, respectively, because those peak intensities were independent of sample particle size. The diffraction intensity of the peak at $2\theta = 6{\cdot}7°$ varied with sample particle size because the X-ray diffraction peak intensities were affected by the orientation of the sample powder particles. The results of ground samples of 148-250 μm suggested that the mechanochemical effect when the compressed tablet was deagglomerated to a powder sample was neglible in this experiment.

The calibration curves for determining the content of forms A and C were both straight lines, and were estimated by the least-squares method as follows:

$$Y_a = 0{\cdot}0219\ X_a + 0{\cdot}0257\ (r = 0{\cdot}998)$$
$$Y_c = 0{\cdot}00901\ X_c + 0{\cdot}0110\ (r = 0{\cdot}996)$$

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.

Effects of tableting compression on polymorphic transformation of chlorpropamide
Figs 2 and 3 show the changes in the X-ray diffraction profiles of forms A and C after tableting by multi-compression. As form A was repeatedly compressed, the diffraction peaks due to it decreased with increase in 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 the peaks due to form A appeared.

Effect of compression energy on polymorphic transformation of chlorpropamide forms A and C
Figs 4 and 5 show the relation between the polymorphic content of the drug and the compression energy. Compression of form A decreased the content of form A, and increased the content of form C with increasing numbers of compressions. The contents of forms A and C, and the noncrystalline solid were almost constant at 45%, 25% and 30%, respectively, after the tableting compression of over 300 J g^{-1} of compression energy.

In the case of form C, the content of form C decreased with increase in the numbers of compressions, and that of form A increased. After compression with energy of more than 300 J

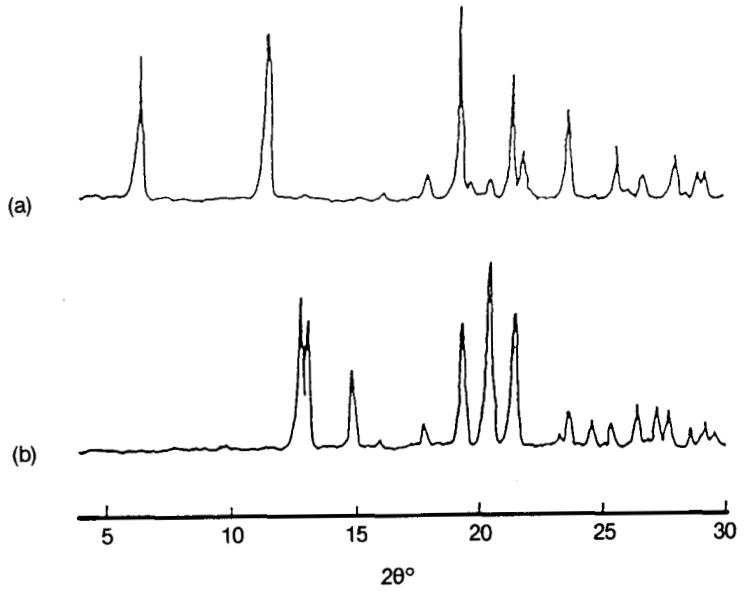

FIG. 1. Powder X-ray diffraction profiles of polymorphs of chlorpropamide: (a) form A, (b) form C.

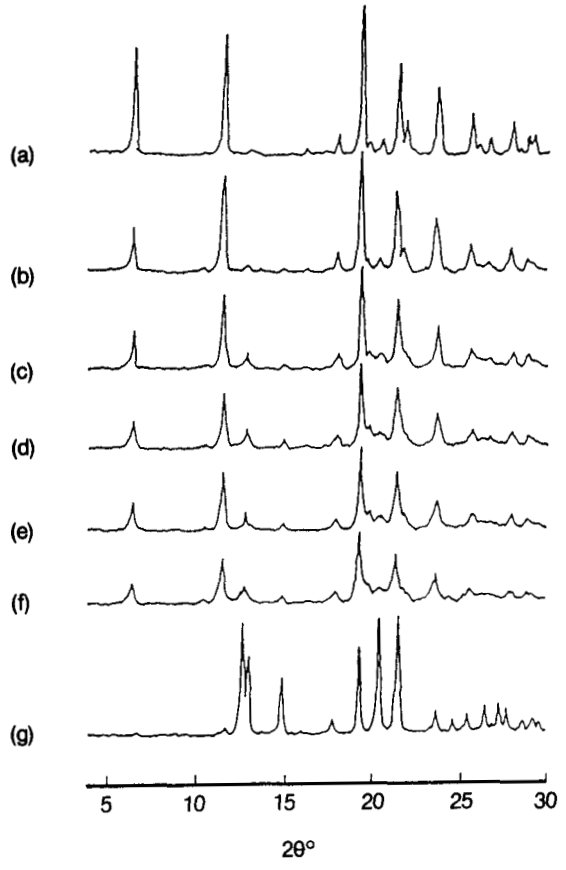

FIG. 2. Change in X-ray diffraction profiles of form A due to compression: (a) intact form A, (b) after 1 compression, (c) 3 cycles, (d) 5 cycles, (e) 10 cycles, (f) 30 cycles, (g) intact form C.

g^{-1}, the contents of forms A and C, and the non-crystalline solid reached equilibrium at the constant values of 45, 25 and 30%, respectively.

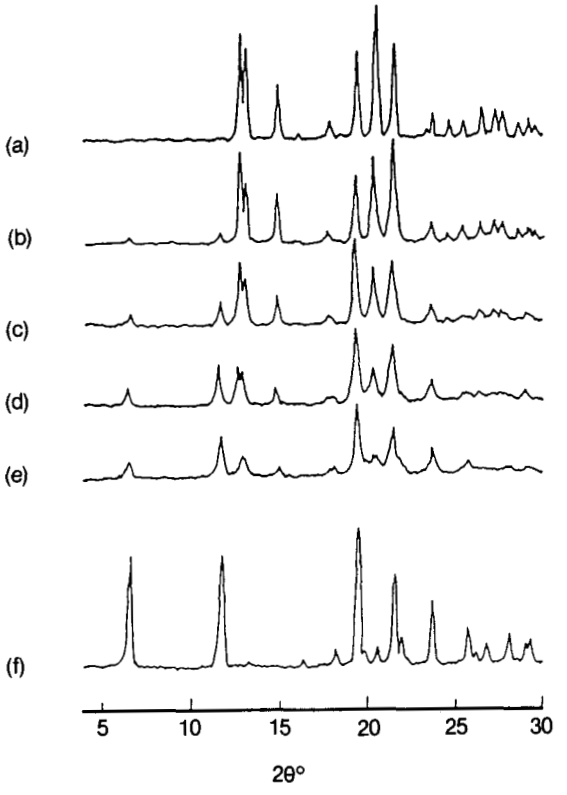

FIG. 3. Change in X-ray diffraction profiles of form C due to compression: (a) intact form C, (b) after 1 compression, (c) 3 cycles, (d) 5 cycles, (e) 10 cycles, (f) 30 cycles, (g) not shown intact form A as in Fig. 1a.

Discussion

Ueda et al (1984) concluded that the polymorphs of chlorpropamide were transformed by compression energy during tableting and the dissolution rate of the more soluble form C decreased.

The energy of tableting compression is dispersed in many

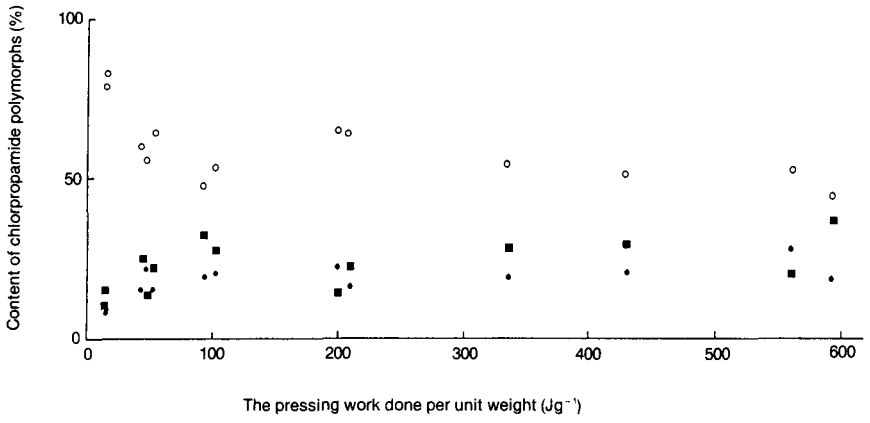

FIG. 4. Relation between the content of forms A and C and compression energy for form A of chlorpropamide: ○, content of form A; ●, content of form C; ■, content of non-crystalline solid.

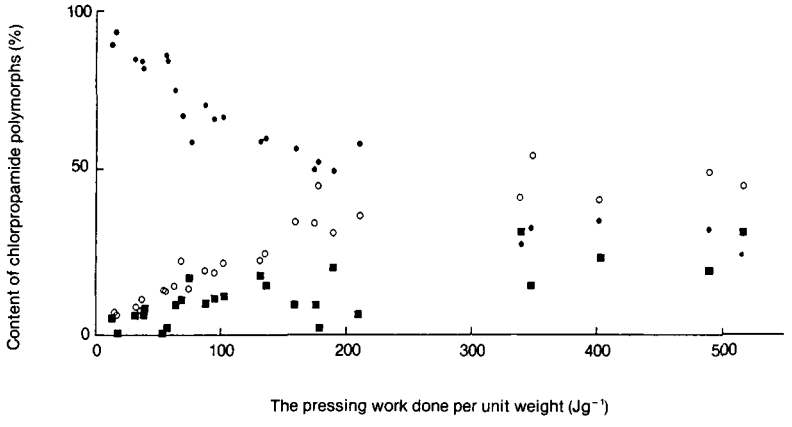

FIG. 5. Relation between content of forms A and C and compression energy for form C of chlorpropamide: ○, content of form A; ●, content of form C; ■, content of non-crystalline solid.

directions, i.e. rearrangement, fragmentation, bond formation, deformation of particles or crystals, friction at the die wall, etc. We measured the total mechanical input energy used in these changes from the tableting hysteresis loop. However, the compression energy is presumed to be a useful quantitative parameter for estimating mechanochemical effect, because one portion of this energy was utilized for crystallographic changes.

It seems that most of the compression energy was used for crystallographic changes, and the packing of the tablet in the experimental conditions described, because the powder bed was well packed by the tapping and the tableting speed was slow, so the rheological character of the powder bed was negligible.

The result of polymorphs of chlorpropamide suggested that the compression of the metastable form C was about 10% transformed to the stable form A during one compression at 196 MPa with compression energy of 14·5 J g^{-1} and the stable form A was about 8% transformed into the metastable form C during one compression at 196 MPa with compression energy of 13·8 J g^{-1}. The results of the compression of either form A or C suggested that each was transformed into the other by mechanical energy. The contents of forms A and C reached equilibrium at a nearly constant value when the mechanical energy of compression exceeded 200 J g^{-1}. After 30 compressions, the compression energies of the forms A and C were estimated to have reached 620 and 519 J g^{-1}, and the polymorphic contents of forms A and C, and non-crystalline solid were 45, 25 and 30%, respectively.

In general, the crystals that have lattice defects and/or lattice distortions, are brittle, fracture, and have elastic deformation after mechanical treatment. We reported mechanochemical effects on the physicochemical properties of cephalexin (Otsuka & Kaneniwa 1983; Kaneniwa et al 1984), chloramphenicol palmitate (Kaneniwa & Otsuka 1985; Otsuka et al 1986) and indomethacin (Otsuka et al 1986) during grinding. These drugs were converted into the non-crystalline solid during grinding. If the noncrystalline solid so produced was stable in the experimental conditions (e.g. indomethacin ground at 4°C by Otsuka et al 1986), then all of the crystals were converted into non-crystalline solid; but if the non-crystalline solid was unstable (e.g. indomethacin ground at 30°C by Otsuka et al 1986), then the crystallinity of the drug reached equilibrium at some constant level because crystals regrew in the non-crystalline solid during grinding.

The findings in the present study were that the mechanochemical effects of the polymorphic transformation of chlorpropramide, and probably the transformation mechanism of forms A and C during tableting compression were as follows: Some of the crystals of forms A and C were

converted into non-crystalline solid by mechanical energy, and the solid then transformed into form A or C in the experimental conditions, since the non-crystalline solid was unstable.

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References

Ibrahim, G., Pisano, F., Bruno, A. (1977) Polymorphism of phenylbutazone: properties and compressional behavior of crystals. J. Pharm. Sci. 66: 669–673

Kaneniwa, N., Imagawa, K., Otsuka, M. (1984) Compression properties of cephalexin powder and physical properties of the tablet. Chem. Pharm. Bull. 32: 4986–4993

Kaneniwa, N., Imagawa, K., Otsuka, M. (1985) Effect of tableting on the degree of crystallinity and on the dehydration and decomposition points of cephalexin crystalline powder, Ibid. 33: 802–809

Kaneniwa, N., Otsuka, M. (1985) Effect of grinding on the transformation of polymorphs of chloramphenicol palmitate. Ibid. 33: 1660–1668

Nogami, H., Nagai, T., Fukuoka, E., Yotsuyanagi, T. (1969) Dissolution kinetics of Barbital polymorphs. Ibid. 17: 23–31

Otsuka, M., Kaneniwa, N. (1982) Effect of grinding on the degree of crystallinity of cephalexin powder. Ibid. 31: 4489–4495

Otsuka, M., Kaneniwa, N. (1983) Effect of grinding on the physicochemical properties of cephalexin powder. Ibid. 32: 1071–1079

Otsuka, M., Kaneniwa, N. (1986) Effect of seed crystals on solid-state transformation of polymorphs of chloramphenicol palmitate during grinding J. Pharm. Sci. 75: 506–511

Otsuka, M., Matsumoto, T., Kaneniwa, N. (1986) Effect of environmental temperature on polymorphic solid-state transformation of indomethacin during grinding. Chem. Pharm. Bull. 34: 1784–1790

Simmons, D. L., Ranz, R. J., Gyanchandani, N. D. (1973) Polymorphism in pharmaceuticals III: Chlorpropamide. Can. J. Pharm. Sci. 8: 125–127

Summers, M. P., Enever, R. P., Carless, J. E. (1976) The influence of crystal form on the radial stress transmission characteristics of pharmaceutical materials. J. Pharm. Pharmacol. 28: 89–99

Ueda, H., Nambu, N., Nagai, T. (1984) Dissolution behavior of chlorpropamide polymorphs. Chem. Pharm. Bull. 32: 244–250