Compression Behavior of Orthorhombic Paracetamol

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Received December 7, 1997; accepted March 14, 1998

Purpose. Orthorhombic crystals of paracetamol exhibit good technological properties during compression. The purpose of this study was to investigate the compression behavior of this substance and to compare it to that of monoclinic paracetamol. From the crystal structure, it could be hypothesized that sliding planes are present in the orthorhombic form, and could be responsible for an increase in crystal plasticity.
Methods. Compression of pure orthorhombic or monoclinic paracetamol tablets was carried out on a fully instrumented single punch machine. Data was used to establish Heckel's profiles. Images of compressed crystals were obtained by scanning electron microscopy.
Results. Tabletability of the orthorhombic crystals was far better than that of the monoclinic ones, and capping was not observed even at high compression pressure. Compared to the monoclinic form, orthorhombic paracetamol exhibited greater fragmentation at low pressure, increased plastic deformation at higher pressure, and lower elastic recovery during decompression. Plastic behavior was confirmed by SEM - micrographs showing that crystals folded under pressure. A compactibility study showed that the nature of interparticle bonds was similar for both polymorphs, the number of bonds being greater for orthorhombic paracetamol.
Conclusions. Unlike the monoclinic form, orthorhombic paracetamol is suitable for the direct compression process. The crystalline structure accounts for its better compression behavior, because of the presence of sliding planes.

KEY WORDS: paracetamol; polymorphism; compression behavior; plasticity; elasticity; fragmentation.

INTRODUCTION

The paracetamol commonly used in the manufacturing of therapeutic tablets, i.e. the monoclinic form, cannot be compressed directly, due to poor densification properties (1). Paracetamol tablets have usually to be produced through a wet granulation process.

The densification process of powders can be divided into several stages (2). Slippage and rearrangement of particles occur during die filling and the initial stage of compression. Elastic deformation is a reversible phenomenon hindering tablet formation, whereas brittle fracture and plastic deformation of particles are irreversible and promote tablet formation. Paracetamol mainly exhibits particle fragmentation, and a relatively high elastic deformation leading to tablet capping (1,3).

Hüttenrauch (4) suggested that rational design of powder particles can modify their compression behavior. More recently, York reviewed some possibilities offered by crystal engineering and particle design to improve the powder compaction process (5). A few studies have been reported, relating to the obtaining of paracetamol crystal aggregates by recrystallization or agglomeration methods, with subsequent improvement of compression behavior (6,7).

In a previous paper, we developed a completely different approach: a polymorphic form of paracetamol, the orthorhombic form, was studied. Its very good compression properties were described (8): and apparently no capping of tablets was observed, even at high compression pressures.

The aim of the present work is to assess the compression mechanism of orthorhombic paracetamol, compared to that of the monoclinic form. The physical structures of the two different polymorphic modifications of paracetamol have been described by Haïsa *et al.*(9,10). In the crystal of orthorhombic paracetamol (Figure 1A) the p-hydroxyl group donates one hydrogen bond to the carbonyl of the molecule related through the "b" glide plane and accepts another hydrogen bond from the amide of the molecule related by the "a" glide plane (9). The two kinds of hydrogen bond form two-dimensional sheets parallel to the "ab" plane and the sheets are stacked along the "c" axis with Van der Waals contacts. On the contrary, the crystalline monoclinic structure (Figure 1B) is stiffer (10): between the parallel planes formed by the aromatic polar rings, acetyl groups of molecules belonging to two different planes are interpenetrated.

Therefore, in the crystalline orthorhombic structure, no molecule or any chemical groups are interposed between the parallel planes. These planes are characterized by high molecular density and by weak interplane bonds. It can be hypothesized that, under compression, these planes could behave like sliding planes. This behavior could be the basis of plastic deformation. Similar behavior has been suggested by Hess for acetylsalicylic acid (11). In contrast, with monoclinic paracetamol, the isotropic transmission of compression forces is not possible, probably owing to the stiffer structure.

To confirm this hypothesis, a complete study of the compression behavior of the two polymorphic paracetamols was carried out. In the first step, the respective tabletability of two modifications was compared. The relation between tensile strength, porosity, elastic recovery and compression pressure was established for several paracetamol samples. Heckel's equation was used to study densification behavior and to assess which deformation mechanisms modify the crystals.

MATERIALS AND METHODS

Paracetamol Powders

Pure commercialized monoclinic paracetamol (form I): "Granular" paracetamol (Mallinckrodt, Metz, France), was used as "reference" paracetamol in this work. The 200–400 μm sieved fraction was recovered.

Fused monoclinic paracetamol (form I) was obtained by the melting method, according to Di Martino *et al.* (12). The

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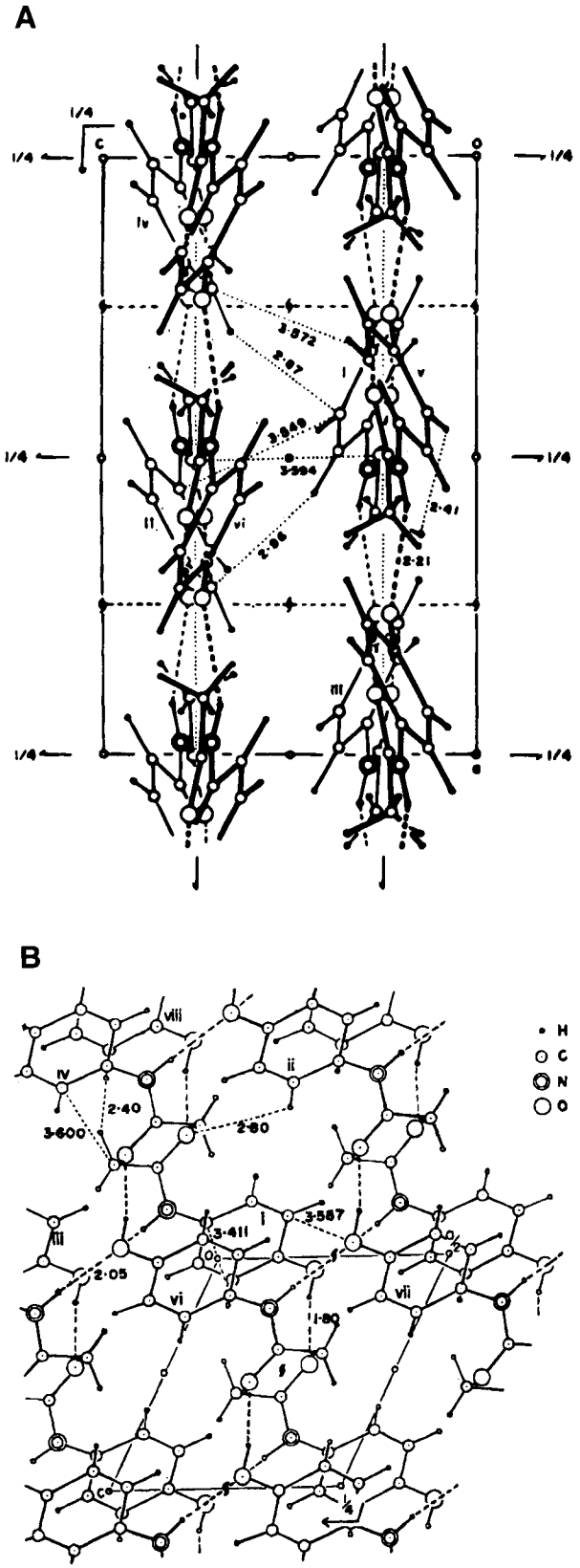

Fig. 1. Projection, viewed along the *b* axis, of the crystal structure of orthorhombic (A) and monoclinic (B) paracetamol. Broken lines show hydrogen bonds, and dotted lines intermolecular contacts. Reproduced from Haïsa *et al.* (9,10).

commercialized monoclinic paracetamol was melted. A very rapid cooling down to room temperature of the melted mass favors its immediate recrystallization in a monoclinic form. This solidified substance was then gently ground with mortar and pestle. The 200–400 μm fraction was recovered by sieving.

Orthorhombic paracetamol (form II) was obtained according to Di Martino *et al.* (12), by melting the monoclinic form. After melting and slow cooling to room temperature, the solidified substance was gently ground, and two sieved fractions were recovered: the 200–400 μm sieved fraction and the <200 μm sieved fraction.

Particle Size and Density

Median particle size was determined by the counting of Feret's diameter of 400 particles of each powder, with a Wild Leitz M20 optical microscope (Heerbrugg, Switzerland).

Particle density was measured without any further grinding of the sieved fractions with a Beckman A930 air pycnometer (Beckman, Gagny, France). Results are the mean of five determinations.

Compression

Compression was carried out in controlled ambient conditions (20% relative humidity; 20°C temperature). Powders were compressed with an instrumented Frogerais OA single punch tablet machine (Frogerais, Vitry, France) equipped with 11.3 mm flat-faced punches, by introducing samples manually into the prelubricated die, according to Lefebvre *et al.* (13). Powder mass was varied to obtain 3 mm thick compacts at each compression pressure. For each mass five cycles were performed. All results are the mean of these five measurements. For a single compression cycle, both the compression pressures on the upper and lower punches and the displacement of the upper punch were measured and recorded at a frequency of 4000 Hz. Correction of the displacement transducer data for machine looseness and punch deformation was carried out according to Juslin and Paronen (14).

Tablet Characterization

During compression, all values relative to the forming compacts were listed; during a single compression cycle, each compression pressure could be related to the thickness, porosity, apparent density of compact before its ejection from the die.

The thickness and diameter of intact ejected tablets were measured with an electronic micrometer (Mitutoyo, Japan) immediately after ejection, whereas dimensions of capped tablets were not measured. Tablet porosity was calculated from tablet dimensions and powder density.

Crushing force was measured immediately after compression with a Schleuniger 6D Tablet Tester (IMA, Rueil Malmaison, France). Tensile strength Q (15) was calculated according to equation 1:

$$Q = 2\,H/\pi \cdot d \cdot t \qquad (1)$$

where H is the crushing force, d the diameter, and t the thickness of the tablet.

Elastic Recovery

Several methods could be used to characterize elastic recovery. In this study, only immediate elastic recovery has been considered. It was calculated according to Armstrong and Haines-Nutt (16):

$$\% \text{ Immediate Elastic Recovery} = [(t_1 - t_2)/ t_1] \cdot 100 \quad (2)$$

where t_1 is the minimal thickness of the powder bed in the die and t_2 is the thickness when pressure is completely removed, before tablet ejection.

Densification Study

The densification behavior of powders was studied using Heckel's equation (17)

$$\ln 1/1\text{-}D = KP + A \quad (3)$$

where D is the relative density of the compressed powder bed at applied pressure P. K is a material-dependent constant, i.e. the slope of the straight linear portion of the Heckel plot and the reciprocal of K is the mean yield pressure (P_Y). The constant A is the sum of two densification terms:

$$A = \ln (1/1 - D_0) + B \quad (4)$$

where $\ln (1/1 - D_0)$ is related to the initial die filling, and B is the densification due to the slippage and rearrangement of both primary and fragmented particles. Constants A and B can be expressed as relative densities using:

$$D_A = 1 - e^{-A} \quad (5)$$

$$D_B = D_A - D_0 \quad (6)$$

To make a clearer distinction between densification due to the movements of the original particles and that due to brittle fracture, Doelker proposed modifying the definition of D_0 (and subsequently that of D_B) by using a relative precompression density D_0' term (18), which also includes the initial rearrangement of particles. D_0' corresponds to the relative density of the powder at the moment when the last recorded applied pressure is still nil.

Two procedures can be used to study densification behavior using Heckel's analysis (17):

—in the first method the relative densities "at zero pressure" are measured on the compacts recovered from the die. It is necessary to prepare compacts at several different pressures;

—in the second method, relative densities are calculated from dimensions of the compacts while under applied pressure and they are known as calculation "at pressure densities". The profile can be established from a single compression cycle (continuous method). This method also makes it possible to obtain results from compacts affected by capping after pressure is removed. However, with this method, the value of K is affected by the elastic deformation process, and its reciprocal P_Y will then be known as "apparent mean yield pressure".

In this work, the relative densities were calculated using this second method and Heckel's profiles were established from single compression cycles. Heckel plots were generated from tablets compressed approximatively at 150 MPa. Parameters P_Y, D_A, D_0', D_B' were calculated using a precompression pressure value of 1.5 MPa, and data ranging from 50 to 100 MPa for linear regression analysis. Each value is a mean of five measurements.

Scanning Electron Microscopy

Scanning Electron Microscopy (SEM) was carried out with a Jeol CX 100 ASID-4D device (Jeol, Croissy, France) on powders and tablets obtained at a pressure of approximatively 150 MPa. The tablets were broken into two parts along the vertical cross-section by the Schleuniger 6D Tablet Tester (IMA, Rueil Malmaison, France). The specimens were mounted on a metal stub with a double sided adhesive tape and coated under vacuum with gold in an argon atmosphere prior to observation. The analysis was carried out on the vertical cross-section. Several magnifications were made.

RESULTS AND DISCUSSION

Characterization of Paracetamol Powders

The four paracetamol samples exhibited some differences in size and shape, that were visible on SEM micrographs (Figure 2). The reference sample was composed of regular polyhedral crystals, with a median particle size of 355 μm. Some small particles stick on the smooth surface of crystals. The aspect of the three other samples was typical of ground substances, with the presence of relatively isodimensional big crystals with no particular shape. Several smaller particles were produced by the grinding process and were not separated by sieving, probably because of their agglomeration. Consequently, the median size of these fractions was smaller: 210 and 235 μm for 200–400 μm orthorhombic and monoclinic melted samples, and only 70 μm for the <200 μm orthorhombic fraction. As previously described for the reference sample, the surface of ground substances appeared smooth, with numerous adhering small broken particles.

Particle densities were measured by pycnometry. Values of 1.29 ± 0.01 g/cm^3 were found for both monoclinic samples, and 1.35 ± 0.01 g/cm^3 for the two sieved fractions of orthorhombic paracetamol. It should be noted that these values are closely related to those calculated by Haïsa *et al.* (9,10) from crystal structure (1.296 g/cm^3 and 1.342 g/cm^3 for monoclinic and orthorhombic crystals respectively). Hence, it could be reasonably supposed that closed pores were not present in our samples, and that these particle densities correspond to true density values.

Tabletability

Tabletability is the capacity of a powdered material to be transformed into a tablet of specified strength under the effect of compression pressure. From a technological viewpoint, this is an important parameter. In Figure 3, the tabletability of the four paracetamol samples is reported.

Both monoclinic paracetamols, i.e. the reference one and the paracetamol obtained by fast cooling after melting, could only be studied at pressures between 50 and 120 MPa. At higher compression pressures, it was not possible to obtain tablets due to capping. At similar compression pressures, the orthorhombic paracetamol showed far better tabletability and, at higher pressures, tablet capping never occurred.

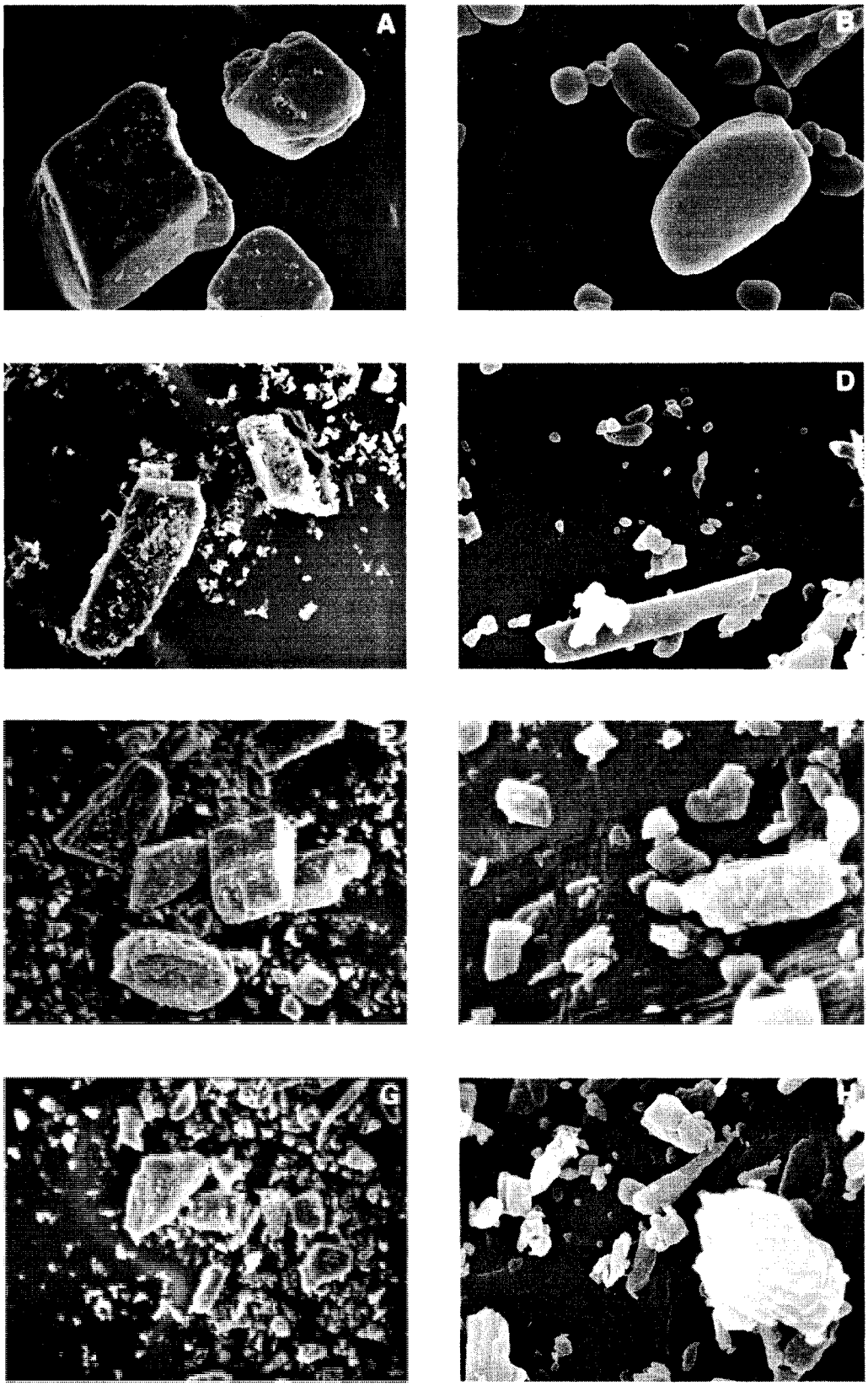

Fig. 2. Scanning Electron Microscopy of paracetamol samples. A, B = Monoclinic paracetamol from Mallinckrodt (200–400 μm); C, D = Monoclinic paracetamol obtained by melting (200–400 μm); E, F = Orthorhombic paracetamol (200–400 μm); G, H = Orthorhombic paracetamol (< 200 μm). Left panel: general view (magnification 100). Right panel: detailed view of crystal surface (magnification 3000).

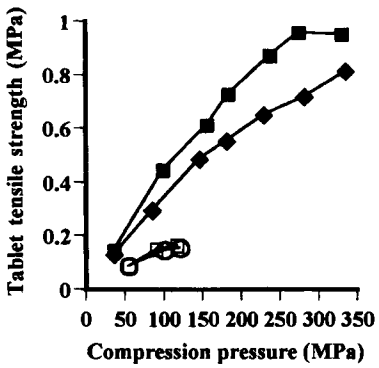

Fig. 3. Tabletability of paracetamol samples. Tablet tensile strength is quoted as a function of maximal upper punch pressure. Each point is the mean of five measurements. □ = Monoclinic paracetamol powder from Mallinckrodt (200–400 μm). ○ = Monoclinic paracetamol powder obtained by melting (200–400 μm). ◆ = Orthorhombic paracetamol powder (200–400 μm). ■ = Orthorhombic paracetamol powder (< 200 μm).

A comparison of the two orthorhombic granulometric fractions (200–400 μm and <200 μm) shows the better tabletability of the <200 μm fraction: for the same compression pressure, the tablet tensile strength is higher than that of the 200–400 μm fraction. This observation concords with Erikson *et al.*, who showed the effect of particle size on tablet tensile strength for compounds like sodium chloride (19).

Compressibility

The compressibility of a material is its ability to be reduced in volume as a result of an applied pressure. The simplest method to compare the compressibility of a set of substances consists in representing the gradual change in tablet porosity as a function of any increase in compression pressure. The results obtained for all paracetamol samples are presented in Figure 4a.

It can be observed that the compressibility of the two monoclinic samples was comparable: tablet porosity after compression at 100 MPa was about 12.5%. So, the melting—cooling procedure did not seem to affect the compressibility of monoclinic paracetamol.

In contrast, the compressibility of orthorhombic paracetamol is far better. Porosity reached after 100 MPa compression was about 8.5% for the 200–400 μm fraction; it could be diminished to 5.2% at higher pressures. Particle size had a small negative effect on the behavior of orthorhombic paracetamol: the <200 μm fraction exhibited a porosity of 9.5% after compression at 100 MPa.

This increase in the compressibility of orthorhombic paracetamol could be derived from an increase in densification during compression or from a decrease in elastic recovery during decompression. In order to check the implied mechanism(s), both minimal porosity and immediate elastic recovery are quoted as functions of compression pressure (Figures 4b and 4c). These parameters are measured before tablet ejection; hence, values could also be obtained for monoclinic paracetamol at high compression pressures.

For the same compression pressure, the minimal porosity of orthorhombic paracetamol was found to be below that of

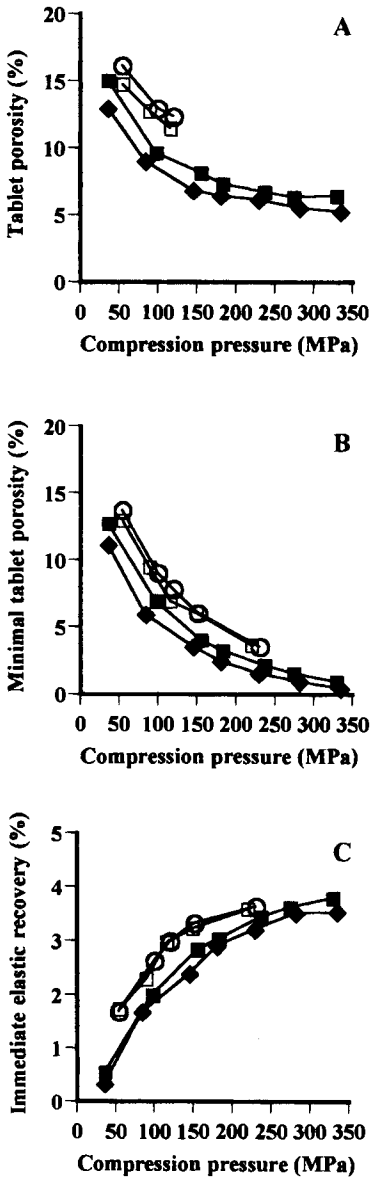

Fig. 4. Compressibility of paracetamol samples. Tablet porosity (A), minimal porosity during compression (B) and elastic recovery (C) are quoted as a function of maximal upper punch pressure. Legend as in Figure 3.

monoclinic samples, reaching a value as low as 0.5% for the 200–400 μm fraction at high pressure (335 MPa), and 0.9% for the <200 μm fraction (330 MPa).

An evaluation of elastic recovery is fundamental to appreciating the ability of a powder bed to be deformed by permanent consolidation. Immediate elastic recovery (IER) of paracetamol samples increased with maximal compression pressure. In the median pressure range (150 MPa), IER reached about 2% for orthorhombic samples and 3% for the monoclinic ones. In this case, the particle size of orthorhombic paracetamol did not seem to have any impact.

It appeared from these results that the better compressibility of orthorhombic paracetamol was due, on one hand, to better powder bed deformation during compression and, on the other hand, to lower compact expansion during decompression.

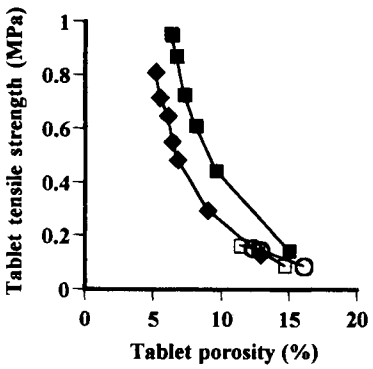

Fig. 5. Compactibility of paracetamol samples. Tablet tensile strength is quoted as a function of tablet porosity. Legend as in Figure 3.

Compactibility

Compactibility is the ability of a material to produce tablets with sufficient strength under the effect of densification. Figure 5 presents the relationship between tablet porosity and tensile strength for the different paracetamol samples.

Owing to the poor compressibility of monoclinic paracetamol and to its capping tendency at high pressures, different porosity ranges were obtained for monoclinic and orthorhombic paracetamol. However, for a porosity value of about 13%, the curves were superimposed for all three compounds of the same particle size (200–400 μm).

This result strongly suggested that the interparticle bond structure of both paracetamol polymorphs was similar. Consequently, it could be supposed that the good tabletability of orthorhombic paracetamol resulted from its high compressibility and not from a change in the nature of interparticle bonds.

It can also be observed on Figure 5 that, for a similar porosity, the tensile strength of tablets of <200 μm orthorhombic paracetamol was higher than that of the 200–400 mm fraction. In actual fact, the nature of interparticle bonds was strictly the same for both fractions. Considering the tensile strength of a tablet as a pure function of its fracture mechanics, this result indicates that by compressing the fine particle fraction, less flaws with appropriate size and orientation, which can propagate under the influence of an applied strain, are formed.

Densification Behavior

It was previously shown that, during compression, orthorhombic paracetamol particles came into closer contact than those of monoclinic samples. In order to elucidate the basic mechanism responsible for this improved compressibility, compression data of all samples was re-analyzed according to Heckel's equation. Corresponding results are summarized in Table I and Figure 6.

Comparison of Reference and Melted Monoclinic Paracetamol (200–400 μm Fractions)

The D'_0 value of the melted substance was higher than that of the reference substance. This indicates that slippage and rearrangement of melted particles were greater during the early stages of compression. Looking at all 4 values of D'_0 in Table I, it appears as though the melting process and/or the subsequent grinding is responsible for the change in this property. It can be hypothesized that the small particles produced by grinding could fill the void spaces between the bigger particles, hence leading to more compact structure of powder beds.

However, D_A and P_Y parameters were similar for the two monoclinic paracetamols. Consequently, once a medium pressure was obtained, both substances became indistinguishable. It could be concluded that the melting procedure did not affect paracetamol behavior as far as any monoclinic modification was concerned.

Comparison of Orthorhombic and Monoclinic Forms Obtained by Melting (200–400 μm Fractions)

D'_0, which corresponds to the first point on Heckel's compression cycle curve, was slightly but significantly higher for orthorhombic paracetamol. However, it has been shown (Figure 2) that particle shape, size, and roughness seemed comparable for the two fused substances. Hence, this increase in D'_0 remains difficult to explain.

The initial curve of the first part (0–50 MPa) of Heckel's plots is generally considered as the expression of the solid brittle fracture tendency. According to Doelker (18), fragmentation propensity can be estimated by calculating D'_B (Equation 6). This parameter showed a higher value for orthorhombic paracetamol, indicating a higher fracture tendency for this modification.

Plastic flow of the particles occurs mainly after the rearrangement and fragmentation steps. Plastic deformation propensity is generally estimated from data in the medium pressure range. In this area, Heckel's plots for both paracetamols exhibited linear profiles, making it possible to calculate P_Y. These values were very different, notably lower for the orthorhombic form.

A comparison of the densification mode for the two paracetamols obtained by the melting process showed differences depending on the crystalline structure. Several factors contribute to improving the densification of orthorhombic paracetamol:

—the initial particle arrangement, before the applying of pressure;

—a distinct tendency to solid brittle fracture, at low compression pressures;

Table I. Heckel Parameters and 95% Confidence Intervals for the Four Paracetamol Samples

	Monoclinic (commercial) 200–400 μm	Monoclinic (melted) 200–400 μm	Orthorhombic (melted) 200–400 μm	Orthorhombic (melted) < 200 μm
D'_0	0.592 ± 0.005	0.634 ± 0.001	0.659 ± 0.001	0.647 ± 0.002
D_A	0.790 ± 0.002	0.785 ± 0.002	0.840 ± 0.003	0.814 ± 0.001
D'_B	0.198 ± 0.004	0.151 ± 0.002	0.181 ± 0.002	0.167 ± 0.002
P_Y	112.3 ± 3.1	113.6 ± 3.3	92.6 ± 1.0	96.3 ± 2.1

—a distinct tendency to plastic deformation, at high compression pressures.

Comparison of Orthorhombic Paracetamols of Different Sizes

The 200–400 μm fraction and the <200 μm fraction of orthorhombic paracetamol were compared. D'_0, D_A and D'_B values were slightly lower for the small fraction, and P_Y value was higher than that of the orthorhombic 200–400 mm fraction. Consequently, all densification processes were slightly reduced in the case of small particles, leading to lower densification. This observation is compatible with a mechanism of plastic deformation. Indeed, it is generally accepted that, for a brittle material, fragmentation tends to level out the initial influence of particle size, whereas, for a plastic material, a larger size favors deformations (20).

Analysis by Scanning Electron Microscopy

It was possible to observe on the micrographs of monoclinic paracetamol the tendency of crystals to solid brittle fracture under compression and the rounded aspect of the smaller particles (Figure 7a). Intact or fragmented crystals remained relatively individualized, indicating the weakness of interparticle bonding.

For orthorhombic paracetamol, it was possible to point out a very characteristic behavior (Figure 7b and c): the crystals folded under compression pressure. This could correspond to a displacement of molecules along sliding planes inside the crystal lattice, resulting as development of steplike structures. These deformations were not visible on all particles of orthorhombic paracetamol. Indeed, it is highly probable that they only occurred if crystal lattice was properly faced, parallel to the direction of applied pressure. The main consequence of this plastic deformation was that crystals, while retaining their original internal structure, could change their external shape and come in closer contact with neighboring particles, making the establishment of numerous interparticle bonds possible.

On the other hand, plastic flow was not the sole deformation occurring on orthorhombic crystals: the tendency toward solid brittle fracture could also be observed (Figure 7d). These fractures seemed to arise and propagate perpendicularly to the sliding planes. Steplike structure provoked by plastic flow was clearly visible at the top of the fracture.

CONCLUSIONS

Orthorhombic paracetamol exhibits better tabletability than the monoclinic form. Its ability to reduce in volume as a result of applied pressure is accompanied by low elastic recov-

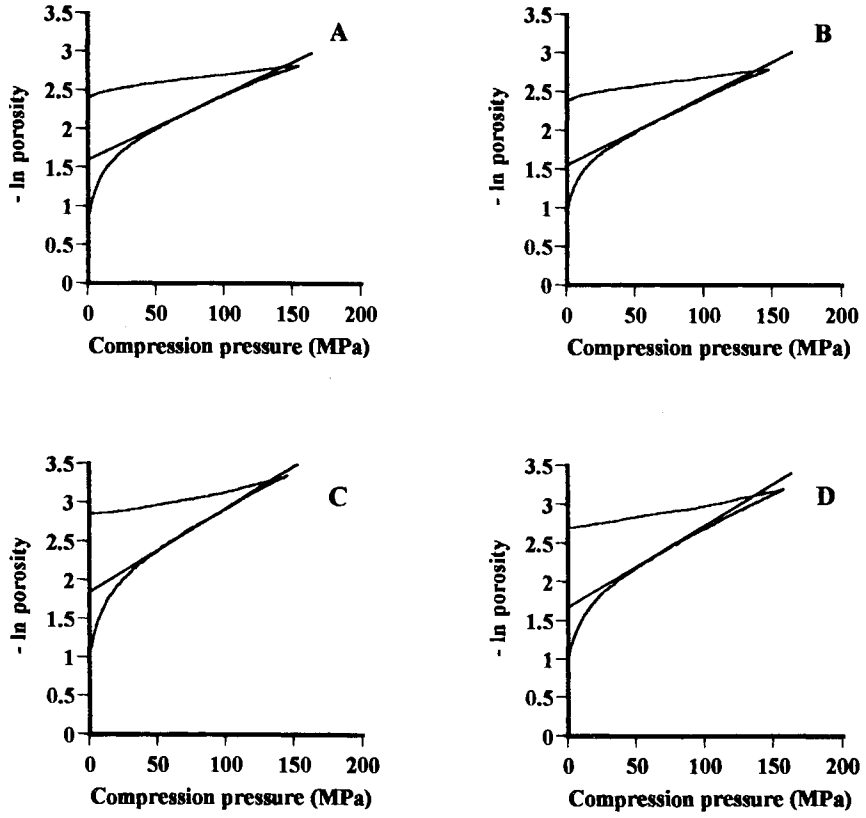

Fig. 6. Typical Heckel's plots for the four paracetamol samples, obtained from a single compression cycle. Straight lines correspond to linear regression analysis of data ranging from 50 to 100 MPa. A = Monoclinic paracetamol powder from Mallinckrodt (200–400 μm). B = Monoclinic paracetamol powder obtained by melting (200–400 μm). C = Orthorhombic paracetamol powder (200–400 μm). D = Orthorhombic paracetamol powder (< 200 μm).

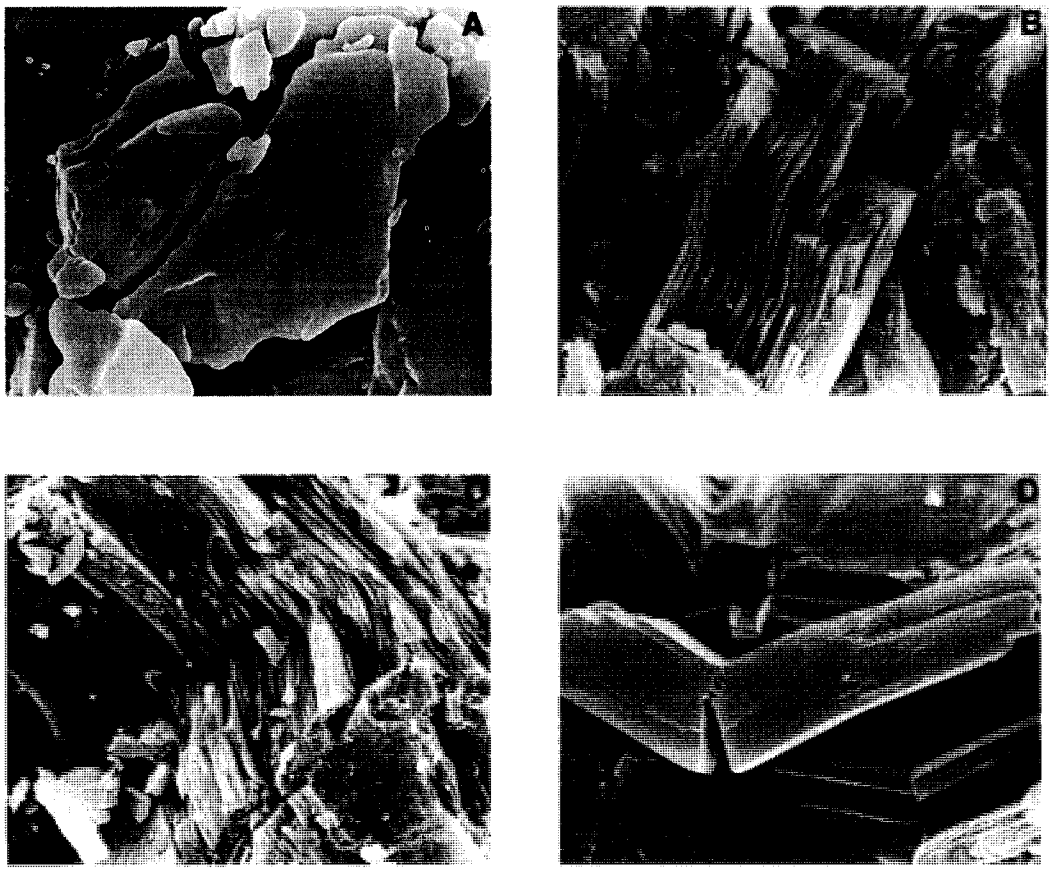

Fig. 7. Scanning Electron Microscopy of paracetamol samples, after compression at about 150 MPa. A: tablet of monoclinic paracetamol obtained by melting (magnification 2000). B, C, D: tablet of orthorhombic paracetamol (magnifications 500, 800 and 500 respectively).

ery. Volume reduction is particularly significant at the beginning of the compression cycle, which is the consequence of an interparticle rearrangement phenomenon. The great tendency to solid brittle fracture at low compression pressures and the plastic behavior at higher compression pressures constitute the real densification mechanism. Consequently, it is possible to imagine that particles come into closer contact with neighboring crystals and that supplementary interparticle bonds are formed, responsible for an increase in compact cohesion. The orthorhombic crystalline structure is responsible for this better compression behavior, because of the presence of parallel sliding planes.

ACKNOWLEDGMENTS

The authors would like to thank for their kind help: Mrs. Tavernier for the translation into English and Loïc Brunet, C.C.M.E., Lille I University, for the scanning electron microscopy studies.

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