ELSEVIER

International Journal of Pharmaceutics 157 (1997) 127–136

international journal of pharmaceutics

Research papers

Effect of compression speeds on the compaction properties of a 1:1 paracetamol–microcrystalline cellulose mixture prepared by single compression and by combinations of pre-compression and main-compression

O.F. Akande, M.H. Rubinstein *, P.H. Rowe, J.L. Ford

Pharmaceutical Technology and Drug Delivery Group, School of Pharmacy and Chemistry, Liverpool John Moores University, Byrom Street, Liverpool L3 3AF, England, UK

Received 29 November 1996; received in revised form 2 June 1997; accepted 15 June 1997

Abstract

A 1:1 blend of paracetamol and microcrystalline cellulose was compacted at different compression speeds by single compression or combinations of pre- and main-compression. The tensile strengths of the tablets decreased from 0.74 ± 0.01 to 0.44 ± 0.05 MPa as the compression speed was increased from 78 to 390 mm/s when a single compression pressure of 80 MPa was used to compress the tablets. When combinations of pre- and main-compression of 320 and 240 MPa were used to compress the tablets, tensile strengths decreased from 3.12 ± 0.67 MPa at a compression speed of 78 mm/s to 1.24 ± 0.36 MPa when the compression speed was 390 mm/s. The energies of compression and the ratio of elastic to plastic energies increased with increase in compression speed. This was because the material was becoming more elastic and more energy was required for the elastic expansion leading to a reduction in the energy available for plastic deformation and bond formation which resulted in a decrease in tensile strengths. Pre-compression played a major role at high compression speeds. The tensile strengths of tablets (1.2 ± 0.08 MPa) compressed with a pre-compression of 160 MPa followed by a main-compression of 80 MPa (compression speed of 390 mm/s) were similar to the tensile strengths of tablets (1.1 ± 0.10 MPa) compressed using a single compression of 320 MPa at the same compression speed of 390 mm/s. Thus, combinations of lower pressures can be employed to compress the material to the same tensile strength as a high single compression. © 1997 Elsevier Science B.V.

Keywords: Compression speed; Pre-compression; Main-compression; Microcrystalline cellulose; Paracetamol; Tensile strength; Stress relaxation; Elastic recovery

* Corresponding author. Tel.: +44 151 2312065; fax: +44 151 2072620.

PII S0378-5173(97)00185-3

1. Introduction

The compression speed during tableting should be optimised since some formulations are highly sensitive to the transition from development to production or change from one press to another or even to alteration in compression speed (Pitt et al., 1987).

The effect of compression speed or punch velocity on compacts has been reported in the literature. David and Augsburger (1977) studied the effect of the duration of the overall compression cycle on the tablet strengths of the direct compression excipients lactose, direct compressible sugar, microcrystalline cellulose and compressible starch. They observed that an increase in the duration of the overall compression cycle from 0.09 to 10 s resulted in significant increases in the tensile strengths of tablets prepared from microcrystalline cellulose and compressible starch fillers, but not with lactose or compressible sugar. This was attributed to differences between the extent of plastic flow of the microcrystalline cellulose or compressible starch and the other materials used. Rees (1980) confirmed that the strengths of perfectly elastic-brittle particles showed no compression rate dependence whereas visco-elastic particles, capable of plastic deformation, manifested changes in strengths with compression speeds.

In a study on the effect of pre-compression using a rotary press on tablet strengths, Vezin et al. (1983) found that at higher machine speeds (1200–1500 tablets/min), tablets prepared with pre-compression and main-compression greater than 200 M/Nm^2 showed signs of lamination, but tensile strengths appeared to be unaffected. Such behaviour was more typical of tablet failure involving the formation of strong integral laminae of individual tensile strengths approximating to that of the intact tablet, which is sometimes characteristic of a compressed mass failure (Hiestand et al., 1977) rather than of bonding failure of the mass which may occur with entrapped air. Vezin et al. (1983) concluded that the advantages of pre-compression are dependent upon individual formulation components and their behaviour under stress, tablet shape and machine speed.

Garr and Rubinstein (1991a) observed that the capping pressures of tablets containing paracetamol decreased with an increase in speed of compression with the corresponding hardness becoming less than 1.5 kP, showing that paracetamol is inherently poorly compressible. Garr and Rubinstein (1991b) similarly found that the tensile strengths of compacts containing a mixture of microcrystalline cellulose and dibasic calcium phosphate dihydrate decreased with an increase in rate of compression.

Paracetamol is poorly compressible and deforms elastically (Obiorah, 1978). Microcrystalline cellulose forms extremely strong tablets and deforms plastically (David and Augsburger, 1977). The radial tensile strength of microcrystalline cellulose tablets decreased with compression speed which was attributed to the formation of less particle to particle bonds when the compression speed was increased (Garr, 1992). Holman and Leuenberger (1989) also showed that the stress relieving properties of microcrystalline cellulose diminish with an increase in compression speed. The optimal mixture of the two powders with respect to tensile strength, friability and absence of capping was a 50:50 microcrystalline cellulose paracetamol mixture (Yu et al., 1988). These blends may exhibit plasto-elastic behaviour (Bangudu and Pilpel, 1985).

There have been no reports in the literature on the effect of compression speed on the compact properties when pre-compression and main-compression are applied. The aim of this work was to investigate the effect of compression speed on single compression and on the application of pre-compression and main-compression pressures to a 1:1 paracetamol and microcrystalline cellulose powder mixture.

2. Materials and methods

2.1. Materials

Paracetamol B.P. (Sterling Organics, England) and microcrystalline cellulose (Avicel® PH 101; FMC, PA) were used. They were separately sieved on a nest of test sieves (Endecott, London, Eng-

land) placed on a sieve shaker (Pascall, Sussex, England) to obtain their 45–125 μm size fractions. These were dried in an oven to constant weight at 110°C. A 1:1 blend of the powders was mixed using a tumbling mixer (Erweka Apparatebau GmbH, Germany). The mixture, which had a moisture content of 0.91%, was stored over silica gel in a desiccator until use.

2.2. Methods

2.2.1. Compression

The powder mixture was compressed using a Compaction Simulator (ESH, West Midlands, England) as modified by the Liverpool School of Pharmacy and Chemistry, fitted with a 12.5 mm, circular flat-faced, punch and die set. The die and punch faces were cleaned with acetone before each compression, and lubricated with a suspension of 4% w/v of magnesium stearate in acetone. Compression was monitored using a micro-link data rack which contained the compression profile that controlled the movement of the upper and lower actuator rams as well as recording the compaction data which were the upper and lower punch forces and displacements. A sawtooth profile on both the upper and lower punches was used for the single compressions to provide extreme compression condition with no dwell time during tableting (Akande et al., 1997). Double sawtooth profiles, which provided the required maximum pre-compression and main-compression pressures were used for the double compressions.

Punch displacements were adjusted so that the tablets were compressed at pressures of 80, 160, 240 or 320 MPa for single compression and combinations of 80/160, 160/80, 240/320 or 320/240 MPa, were used for pre-compression and main-compression. A lag time of 0.53 s was maintained between the pre-compression and main-compression pressures. The combinations of pre-compression and main-compression pressure were chosen to simulate the most commonly used pressures in tableting research. Tablets were made at compression speeds of 78, 120, 210 or 390 mm/s to simulate the range of punch speeds found in single punch eccentric and rotary tableting machines. Four tablets (500 ± 1 mg) were produced at each pressure setting and compression speed.

2.2.2. Tablet analyses

The radial and axial thicknesses of the tablets were determined with a digital micrometer (Mitutoyo Mfg, Tokyo, Japan) to an accuracy of ± 1 μm, immediately after compression. The crushing strengths were determined using a Schleuniger Model 2E hardness tester (Dr. K. Schleuniger and Co., Zurich, Switzerland) which with the tablet dimensions were used to determine the tensile strengths of tablets (Fell and Newton, 1970).

2.2.3. Compression data analyses

The plastic and elastic energies of compression were determined from the plots of the compression force-displacement data captured during compression and the ratios of the elastic energy to plastic energy were determined at each compression speed (Ragnarsson and Sjogren, 1983, 1985). The gross energies were determined as the areas under the compression portion of the upper punch force-punch separation plots, while the elastic energies were the areas under the decompression portion. The plastic energies were then determined as the differences between the areas under the compression and decompression portions. The elastic recoveries of the tablets were determined (Armstrong and Haines-Nutt, 1972) as the differences in thicknesses of the compacts after ejection and the thicknesses of the compacts in-die expressed as percentage of the compact thicknesses in-die. Stress relaxations were determined from the thicknesses when the compacts had lost contact with the upper punch and the thicknesses at maximum compression pressure in-die, expressed as percentage of the compact thicknesses at maximum pressure in-die (Malamataris et al., 1984). All the data were subjected to statistical analyses using the two way analysis of variance and Tukey's test for the multiple comparison of means.

3. Results

3.1. Single compression

Fig. 1. shows the effect of compression speed on the tensile strengths of tablets made by single

compression. The tensile strengths of tablets decreased from 0.74 ± 0.01 to 0.44 ± 0.05 MPa or from 2.33 ± 0.15 to 1.1 ± 0.10 MPa with increase in compression speed from 78 to 390 mm/s (Fig. 1), when single compression pressures of 80 or 320 MPa respectively were used to compress the tablets. The decrease in tensile strengths of the tablets were generally significant ($p < 0.05$ by two way analyses of variance) for all the compression speeds and pressures. However, compression speed seemed to have less effect on the tensile strengths when a pressure of 80 MPa was used as single compression. The decrease in tensile strengths between compression speeds of 78 and 210 mm/s were not statistically significant ($p > 0.05$; Tukey's test) at this pressure. The tensile strengths increased with increase in compression pressure at equivalent compression speed (Fig. 1). Two way analysis of variance showed that compression pressure had a significant effect ($p < 0.05$) on the tensile strengths of the tablets.

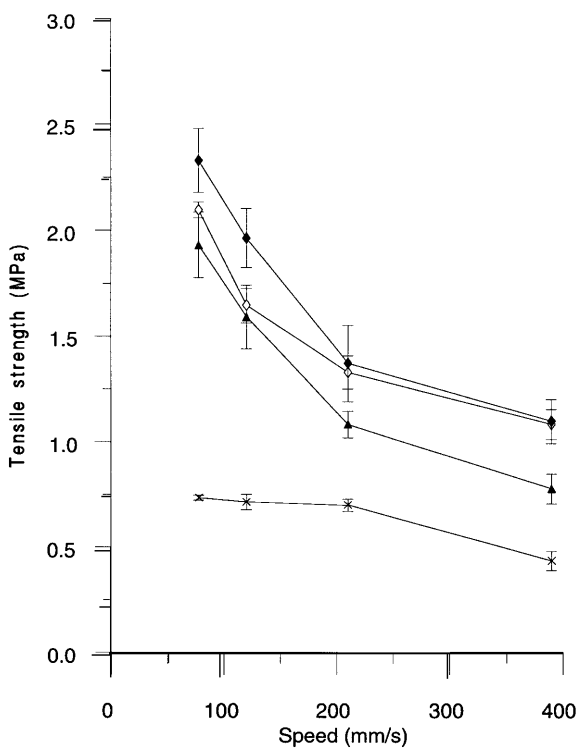

Fig. 1. Effect of compression speed on the tensile strengths of tablets made by single compression pressure – × – 80, – ▲ – 160, – ◇ – 240 and – ◆ – 320 MPa.

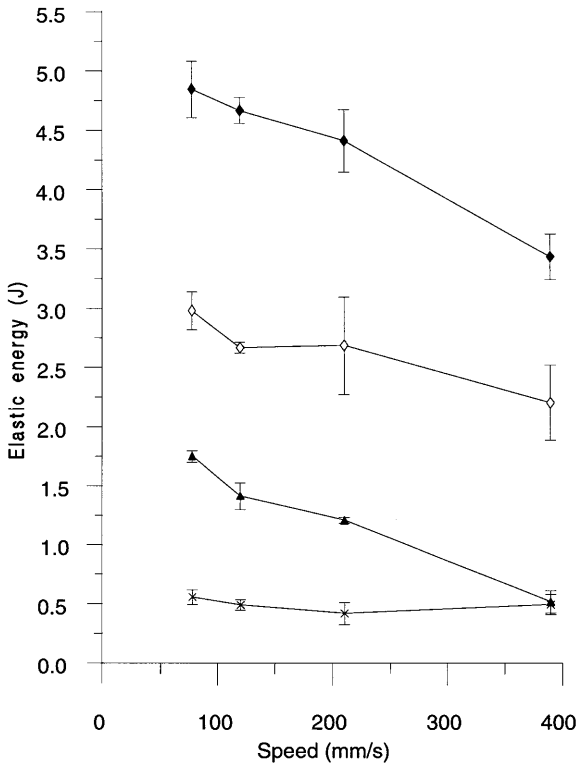

Fig. 2. Effect of compression speed on the elastic energies of compression for tablets made by single compression pressure – × – 80, – ▲ – 160, – ◇ – 240 and – ◆ – 320 MPa.

The elastic energies decreased (Fig. 2) while the plastic energies of tablets made by single compression increased (Fig. 3) as the compression speed increased from 78 to 390 mm/s. The ratios of plastic energy to plastic energy decreased with increase in compression speed (Fig. 4).

The stress relaxation during compression (Fig. 5) generally decreased while the elastic recoveries of the tablets on ejection (Fig. 6) increased with increase in compression speed.

3.2. Combinations of pre-compression and main-compression

The effect of compression speed on the tensile strengths of tablets compressed with various combinations of pre-compression and main-compres-

sion are shown in Fig. 7. The tensile strengths generally decreased with increase in compression speeds. The percentage reductions in tensile strengths of tablets as the compression speeds were increased from 78 to 390 mm/s are given in Table 1.

The percentage reductions in tensile strengths of tablets as the compression speeds were increased from 78 to 390 mm/s were greater when the tablets were compressed with pre-compression and main- compression pressure combinations of 240/320 MPa than when the combinations of pre-compression and main-compression pressures were 80/160, 160/80, 160/240 or 240/160 MPa (Table 1). With the exception of the pre-compression of 160 MPa followed by a main-compression of 240 MPa, there was a general increase in tensile strength decrease with increase in compression pressures. When the main-compression was lower compared to pre-compression, the percentage decreases of tensile strength were higher. The tensile strength was higher when a high pre-compression was followed by a low main-compression compared to when the condition is reversed (Akande et al., 1997).

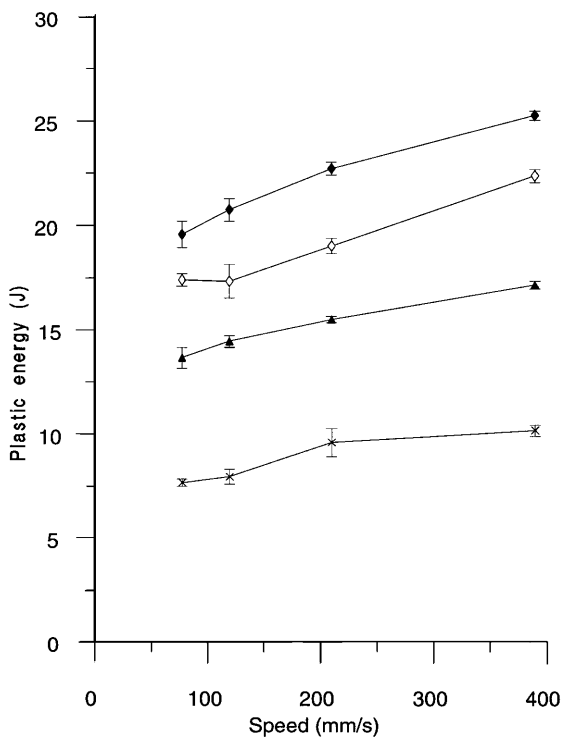

Fig. 3. Effect of compression speed on the plastic energies of compression for tablets made by single compression pressure – × – 80, — ▲ — 160, — ◇ — 240 and – ◆ – 320 MPa.

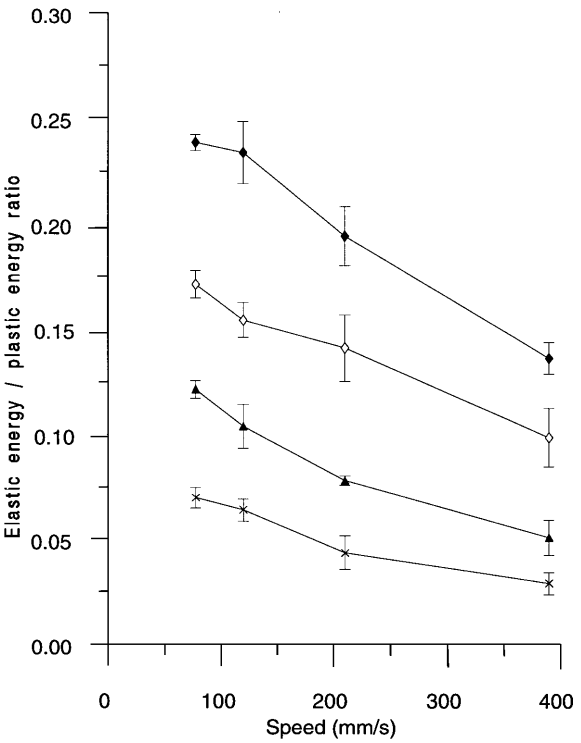

Fig. 4. Effect of compression speed on the ratio of elastic energy to plastic energy of compression for tablets made by single compression pressure – × – 80, — ▲ — 160, — ◇ — 240 and – ◆ – 320 MPa.

The tensile strengths of tablets generally increased as the magnitude of the main-compression pressures increased at the same compression speeds (Fig. 7). The exceptions were when combinations of pre-compression and main-compression pressures of 320/240 or 240/320 MPa at the compression speed of 390 mm/s were used (Fig. 7).

The total elastic energies for pre-compression and main-compression combined probably did not change as the compression speed increased, (Fig. 8). Although two-way analysis of variance showed that both compression speed and compression pressures affected the total elastic ener-

gies, Tukey's test could not differentiate ($p > 0.05$) the total elastic energies as the compression speed increased from 78 to 210 mm/s for most of the combinations of pressures.

The total plastic energies for the pre-compression and main-compression pressures combined increased with increase in compression speed (Fig. 9). Two-way analysis of variance showed that both compression speed and compression pressures significantly ($p < 0.05$) affected the total combined plastic energies. The increase in the total plastic energies could not be differentiated ($p > 0.05$; Tukey's test) at some of the combinations of pressures and compression speeds. For example, no significant differences took place when a pre-compression of 240 MPa was followed by a main-compression of 320 MPa as the compression speed increased from 78 to 210 mm/s or when a pre-compression of 320 MPa was followed by a main-compression of 240 MPa at the compression speeds of 210 and 390 mm/s (Fig. 9).

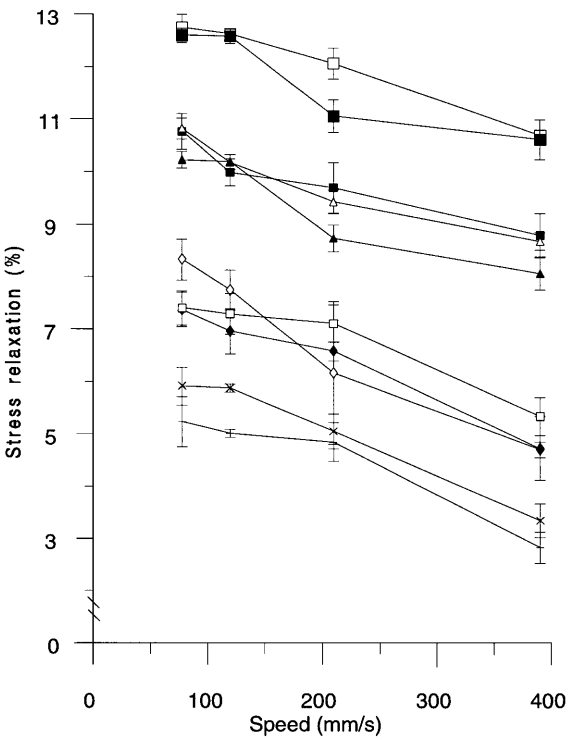

Fig. 5. Effect of compression speed on the stress relaxation during compression by single compression and during pre-compression for compacts made with combinations of pre-compression and main-compression pressures – × – 80, – ▲ – 160, – ◇ – 240 and – ◆ – 320 MPa.: – □ – 80/160, – ■ – 160/80, – △ – 160/240, – | – 240/160, – □ – 240/320 and – ■ – 320/240 MPa.

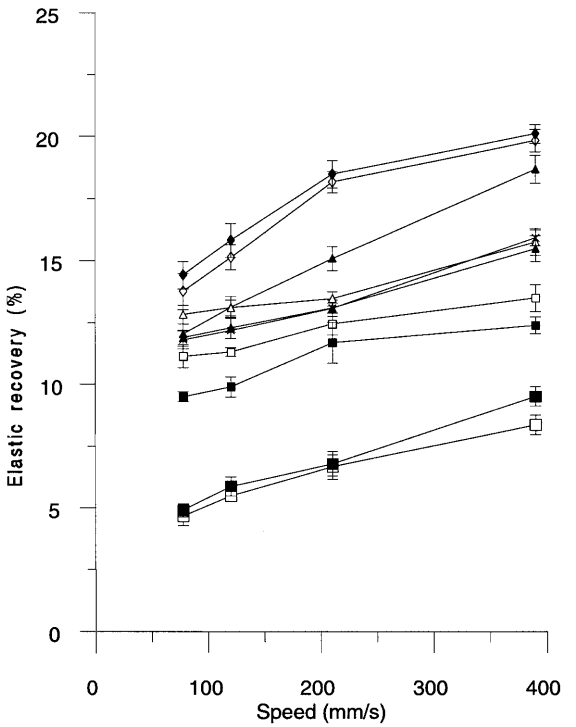

Fig. 6. Effect of compression speed on the elastic recoveries of tablets made by single compression and by combinations of pre-compression and main-compression pressures – × – 80, – ▲ – 160, – ◇ – 240 and – ◆ – 320 MPa.: – □ – 80/160, – ■ – 160/80, – △ – 160/240, – | – 240/160, – □ – 240/320 and – ■ – 320/240 MPa.

The ratios of total elastic energy to total plastic energy of the pre-compression and main-compression pressures combined decreased as the compression speeds increased from 78 to 210 mm/s (Fig. 10). The ratios tended to increase when combinations of high pressures of 240/160, 240/320 or 320/240 MPa were used as the compression speed increased from 210 to 390 mm/s.

The stress relaxation during pre-compression (Fig. 5) generally showed a decrease as the compression speed increased indicating that less bonding was taking place during pre-compression at higher speeds. The elastic recoveries of tablets on ejection after pre-compression and main-compres-

sion (Fig. 6) increased as the compression speeds increased from 78 to 390 mm/s.

4. Discussion

The decrease in tensile strengths with an increase in compression speed was likely due to there being less time available for the material to consolidate by plastic deformation as the extent of stress relaxation decreased at higher compression speeds. It has been reported that viscoelastic materials (e.g. microcrystalline cellulose) are sensitive to compression speed; an increase in compression speed leading to reduction in tablet strengths (Armstrong and Palfrey, 1989). These differences have been explained in terms of time of exposure to compression.

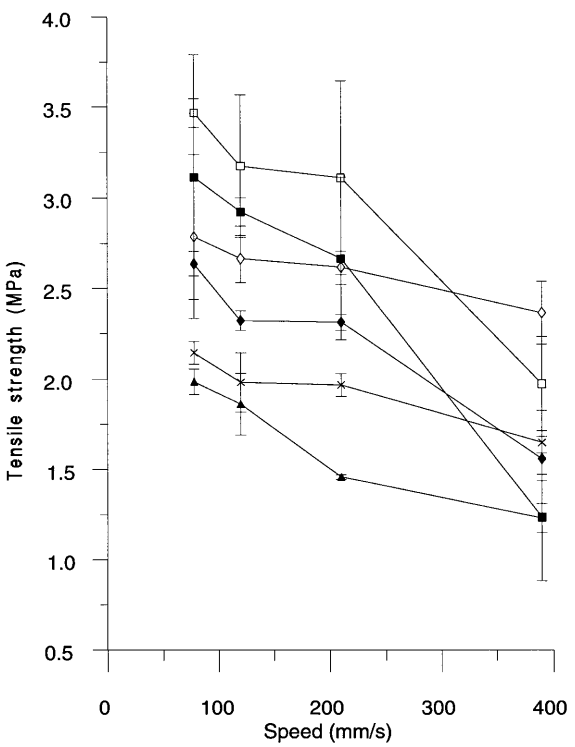

Fig. 7. Effect of compression speed on tensile strengths of tablets made by combinations of pre-compression and main compression pressures – × – 80/160 — ▲ — 160/180, — ◇ — 160/240 and – ◆ – 240/160, — □ — 240/320 and — ■ — 320/240 MPa.

Table 1
Decrease in tensile strengths of tablets caused by an increase in compression speed from 78 to 390 mm/s

Combinations of pre-compression and main compression pressures (MPa)	Decrease in tensile strengths of tablets (%)
80/160	23
160/80	36
160/240	15
240/160	40
240/320	43
320/240	60

The increase in energies of compression at higher compression speeds was because more energy was required for elastic deformation, fragmentation and formation of bonds (Garr and Rubinstein, 1990, 1991b). There is a possibility that part of the net energies might be utilised in particle rearrangement, die-wall friction and increase in interparticulate friction that may occur at high compression speed. Increasing the compression speed resulted in a decrease in elastic energies during compression. The contribution of elastic energies to the gross energies during compression of ibuprofen was reported to increase with increase in compression speed (Nokhodchi et al., 1995). However this was not the case in this work. The decrease in elastic energies with increase in compression speed may be due to a reduction of time available for the material to relieve the elastic energies. Generally, the plastic energies increased as the compression speed increased. That is, more energy was required to form the tablets at higher compression speed. This may be due to the utilisation of more energy to overcome the increased cohesiveness of particles that occurred at higher compression speed (Nokhodchi et al., 1995).

Elastic energy is not used for bonding but is stored as deformation energy under stress. The release of this stored energy at the end of a compression cycle allows the particles to return to their original shape and so rupture weak particle-particle bonds (Yu et al., 1988). The plastic energies tend to increase while the elastic energies

decrease with increase in compression speed and therefore, a more important parameter to measure is the ratios of elastic energy to plastic energy (Garr, 1992). The decrease in the ratios of elastic energy to plastic energy during compression may be because most of the energies were either used for bond formation or to overcome increased cohesiveness of the tablets as the speed increased. Another possibility could be that with increase in compression speed most of the energy stored in the tablets could not be relieved by the end of the compression cycle.

A decrease in ratios of elastic energy to plastic energy as the compression speed increased was an indication that more energy was used for the consolidation of the material. However, the studies on the plasticity of the material during compression (stress relaxation), post compression (elastic recovery) and tensile strengths indicated otherwise. There appeared to be an inverse relationship between the plastic flow as determined by the stress relaxation and the plastic energies involved in the plastic deformation as the compression speed increased.

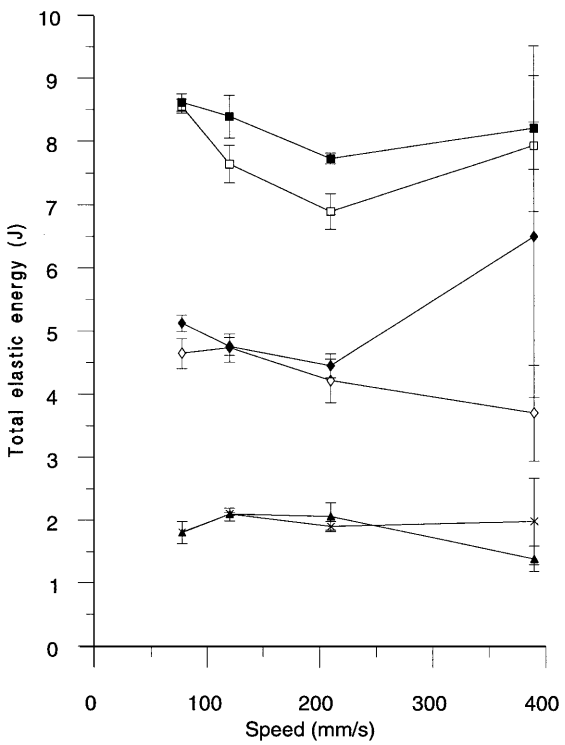

Fig. 8. Effect of compression speed on the elastic energies of compression for tablets made with combinations of pre-compression and main compression – × – 80/160, — ▲ — 160/80, — ◇ — 160/240, – ◆ – 240/160, – □ – 240/320 and — ■ — 320/240 MPa.

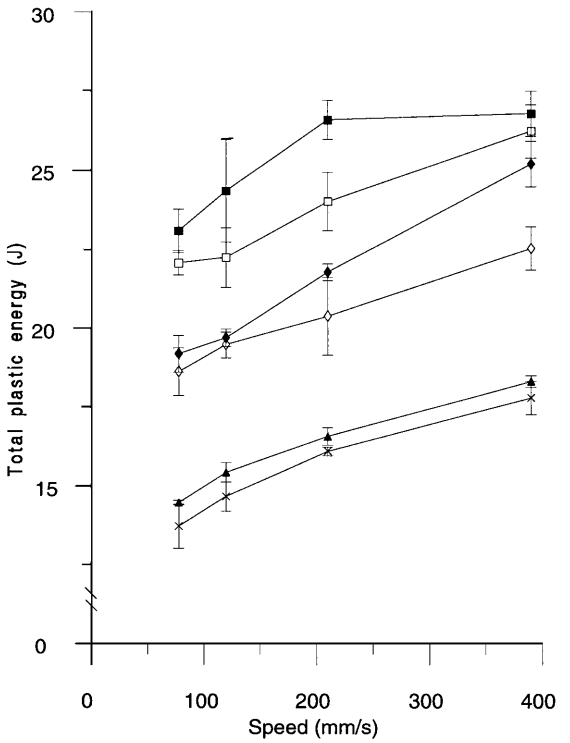

Fig. 9. Effect of compression speed on the plastic energies of compression for tablets made with combinations of pre-compression and main compression – × – 80/160, — ▲ — 160/80, — ◇ — 160/240, – ◆ – 240/160, – □ – 240/320 and — ■ — 320/240 MPa.

Plastic flow and bond formation usually takes place during stress relaxation while disruption of bonds occurs during elastic recovery. The decrease in stress relaxation with increase in compression speed occurred because there was less time for plastic deformation and bond formation. The decreased stress relaxation resulted in the observed increase in elastic recoveries of the tablets on ejection (Fig. 6) as there was less bond formation at high compression speed leading to formation of tablets with decreased tensile strengths.

The use of combinations of pre-compression and main-compression did not prevent the tensile strengths of tablets from decreasing as the compression speed increased. However, the application of pre-compression and main-compression irrespective of the orientation of the pressures produced compacts with higher tensile strengths than when single compression was used to compress the tablets. For example, at a compression speed of 390 mm/s, the tensile strengths of tablets produced with a combination of pre-compression and main-compression pressure of 160/80 was 1.2 ± 0.08 MPa which was similar to the tensile strengths of 1.1 ± 0.10 for tablets made with a single compression pressure of 320 MPa. This may be because the prior application of pre-compression increased the consolidation of the material as the periods of contact with the pressure were doubled with the application of pre-compression and main-compression pressures, providing additional time for stress relaxation of the material to further consolidate and produce an increase in strength. This is a major advantage of the use of pre-compression and main-compression over single compression because it means that less compression pressure can be employed to achieve compaction to similar tablet strengths at production rates.

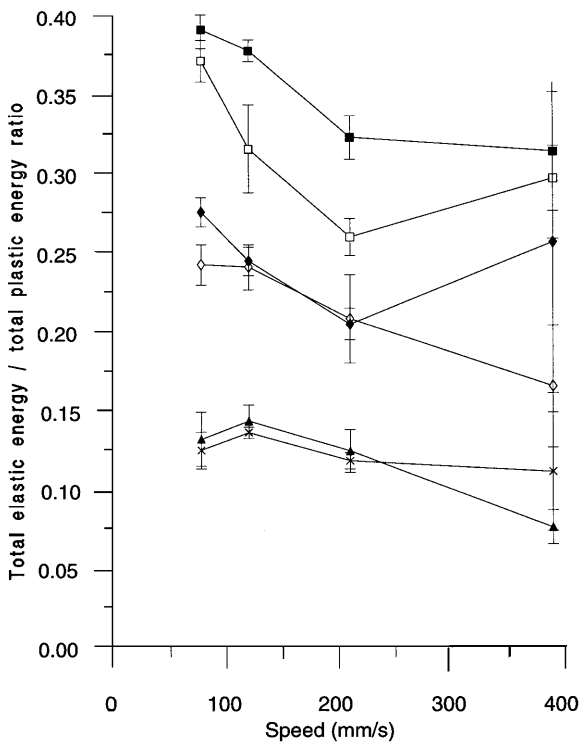

Fig. 10. Effect of compression speed on the ratios of combined elastic energies to combined plastic energies of compression for tablets made with combinations of pre-compression and main compression pressures – × – 80/160, – ▲ – 160/80, – ◇ – 160/240, – ◆ – 240/160, – □ – 240/320 and – ■ – 320/240 MPa.

5. Conclusion

The tensile strengths of the tablets decreased with increase in compression speed when single compression and combinations of pre-compression and main-compression were used to compress the material. This has been ascribed to the time-dependent consolidation of the paracetamol and microcrystalline cellulose powder mixture, as sufficient time required for stress relaxation and plastic deformation to take place was not available at higher compression speeds. Although the plastic energies of compressions generally increased, the ratios of the elastic energy to plastic energy also increased as the material become more elastic leading to decreased tensile strengths with an increase in compression speed. The elastic recoveries also increased with increase in compression speed due to the decrease in stress relaxation and bond formation, as less energy has been used for actual consolidation of the material. Combinations of lower compression pressures are preferred to a high single compression at high compression speed. This could reduce wear and tear on the tablet press. Double compression led to higher tensile strengths of the tablets single compression.

References

Akande, O.F., Rubinstein, M.H., Ford, J.L., 1997. The compaction properties of a 1:1 acetaminophen: microcrystalline cellulose mixture using pre-compression and main compression. J Pharm Sci. 86, 900–907.

Armstrong, N.A., Haines-Nutt, R.F., 1972. Elastic recovery and surface area changes in compacted powder systems. J. Pharm. Pharmacol. 24 (Suppl.), 135P–136P.

Armstrong, N.A., Palfrey, L., 1989. The effect of machine speed on the consolidation of four directly compressible tablet diluents. J. Pharm. Pharmacol. 41, 149–151.

Bangudu, A.B.N, Pilpel, N., 1985. Effect of composition, moisture and stearic acid on the plasto-elasticity and tableting of paracetamol-microcrystalline mixtures. J. Pharm. Pharmacol. 37, 289–293.

David, S.T., Augsburger, L.L., 1977. Plastic flow during compression of directly compressible fillers and its effect on tablet strength. J. Pharm. Sci. 66, 155–159.

Fell, J.T., Newton, J.M., 1970. Determination of tablet strength by diametral compression test. J. Pharm. Sci. 59, 688–691.

Garr, J.S.M., (1992). Compaction characteristics of direct compression tableting excipients. PhD. Thesis, Liverpool Polytechnic, Liverpool, UK.

Garr, J.S.M., Rubinstein, M.H., 1990. Direct compression characteristics of xylitol. Int. J. Pharm. 64, 223–226.

Garr, J.S.M., Rubinstein, M.H., 1991a. An investigation into the capping of paracetamol at increasing speeds of compression. Int. J. Pharm. 72, 117–122.

Garr, J.S.M., Rubinstein, M.H., 1991b. The effect of rate of force application on the properties of microcrystalline cellulose and dibasic calcium phosphate mixtures. Int. J. Pharm. 73, 75–80.

Hiestand, E.N., Wells, J.E., Peot, C.B., Ochs, J.E., 1977. Physical processes of tableting. J. Pharm. Sci. 66, 510–519.

Holman, L.E., Leuenberger, H., 1989. Effect of compression speed on the relation ship between normalised solid fraction and mechanical properties of compacts. Int. J. Pharm. 57, R1–R5.

Malamataris, S., Bin-Baie, S., Pilpel, N., 1984. Plasto-elasticity and tableting of paracetamol, avicel and other powders. J. Pharm. Pharmacol. 36, 616–617.

Nokhodchi, A., Rubinstein, M.H., Larhrib, H., Guyot, J.C., 1995. The effect of moisture content on the energies involved in the compaction of ibuprofen. Int. J. Pharm. 120, 13–20.

Obiorah, B.A., 1978. Possible prediction of compression characteristics from pressure cycle plots. Int. J. Pharm. 1, 249–255.

Pitt, K.G., Newton, J.M., Richardson, R., Stanley, P., 1987. The effect of punch velocity on the tensile strength of aspirin tablets. J. Pharm. Pharmacol. 39 (Suppl) 65P.

Ragnarsson, G., Sjogren, J., 1983. Work of friction and net work during compaction. J. Pharm. Pharmacol. 33, 201–204.

Ragnarsson, G., Sjogren, J., 1985. Force-displacement measurements in tableting. J. Pharm. Pharmacol. 33, 145–150.

Rees, J.E., 1980. Formulation and compaction behaviour of direct-compression materials. In: Proceedings of the Postgraduate School on Theory and Practice of solid dosage form and manufacture. Pharmaceutical Society of Great Britain, London, pp. 196–213.

Vezin, W.R., Pang, H.M., Khan, K.A., Malkowska, S., 1983. The effect of pre-compression in a rotary machine on tablet strength. Drug Dev. Ind. Pharm. 9, 1465–1475.

Yu, H.C.M., Rubinstein, M.H., Jackson, I.M., Elsabbagh, H.M., 1988. Multiple compression and plasto-elastic behaviour of paracetamol and microcrystalline cellulose mixtures. J. Pharm. Pharmacol. 40, 669–673.