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An investigation into the capping of paracetamol at increasing speeds of compression

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Summary

A study of the capping tendency of paracetamol using a wide range of compression speeds (24–850 mm/s) has been performed. Capping pressure, plastic energy (PE) and elastic energy (EE), EE/PE ratio, work of compaction and mean yield pressure derived from Heckel analysis were used as the basis of the investigation. The capping intensity of paracetamol was observed to increase with an increase in the speed of compression, due to the significant increase of 65.24% in the elastic energy compared to a 32.87% increase in plastic energy over the same speed range. The relatively high increase in elastic energy appears to be a more important factor than air entrapment in the capping tendency of paracetamol compacts. The work of compaction was found to increase with compression speed, ascribed to a high energy input required for elastic deformation, fragmentation of particles and formation of bonds. A good correlation was observed between the natural logarithm of compression speed and capping pressure and an equation has been proposed to describe the relationship. The critical excipient content was found to be 25% and 50% w/w of microcrystalline cellulose (MCC) at a speed of 24–300 mm/s and 500 mm/s, respectively, however incorporation of 25% dibasic calcium phosphate dihydrate (DCP)/75% w/w microcrystalline cellulose (MCC) in paracetamol formulations was found to have greater resistance to capping and produced tablets with double the tensile strength of compacts containing 25% w/w of MCC alone.

Introduction

Capping and lamination is a problem which frequently occurs during tablet formulation. Burlinson (1968) first attributed capping to the presence of air entrapped in the interstices of the tablet during compression, which expanded on decompression, causing failure.

In an investigation of the influence of punch and die tolerance on the capping behaviour of three formulations at several compression speeds, Mann et al. (1981) concluded that the presence of entrapped air and the rate of air release from the granule bed during compression significantly influenced the incidence of capping. It was also observed that capping pressure is related to the amount of air present in the granule bed prior to compression and that removal of the majority of this air by reducing the surrounding air pressure causes a reduction in the incidence of capping. In

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these cases capping was noted to be replaced by lamination which still occurred and apparently was unaffected by changes in air pressure (Mann et al., 1983).

Malamataris et al. (1984) noted that the incidence of capping and lamination during production of pharmaceutical tablets, followed by ejection from the die, depends on the plastic and elastic behaviour of the material used and they proposed that the ratio of elastic recovery to the plastic compression (ER/PC) was a useful parameter to measure capping tendency. The suitability of utilising the ER/PC ratio and energy analysis as a means of measuring capping tendency was examined by Yu et al. (1988). It was concluded that in order to produce acceptable avicel/paracetamol tablets, the percentage energy ratio should be higher than 10%.

The aim of the present study was to examine the effect of compression speed in the range 24–850 mm/s on the capping pressure, plastic energy (PE), elastic energy (EE), EE/PE ratio, work of compaction and mean yield pressure of pure paracetamol compacts, derived from Heckel analyses. In addition, the critical excipient content at various speeds of compression were evaluated and the 25% dibasic calcium phosphate dihydrate (DCP) and 75% microcrystalline cellulose (MCC) mixture in paracetamol formulation examined (Garr and Rubinstein, 1990).

Materials and Methods

Materials

Microcrystalline cellulose (MCC) and dibasic calcium phosphate dihydrate (DCP) were obtained from Forum Chemicals Ltd, Surrey, U.K. Paracetamol BP powder grade was obtained from Sterling Organics, Northumberland, U.K., whilst magnesium stearate was from BDH Chemicals, Poole, U.K.

Particle size fractions

45–125 μm sieve fractions of unsieved paracetamol powder, MCC and DCP were obtained by sieving the materials through test sieves on a mechanical vibrator (Endecott Ltd).

Mixing

Blends of the materials were prepared by weighing the appropriate quantities and tumbling in a glass bottle attached to an electric motor rotating at 40 rpm for 15 min to produce homogeneous mixes of 0, 25, 50, 75 and 100% of paracetamol/MCC and 25% DCP/75% MCC. All the materials were dried in an oven to constant weight at 110°C and stored for 5 days in an oven at 20°C and 45% relative humidity before compression.

Compression

Compression was carried out using The Liverpool School of Pharmacy High Speed Compaction Simulator (Bateman, 1988a,b), fitted with 12.5 mm flat-faced punches. A sawtooth time-displacement profile was used to control both upper and lower punches. Four tablets were produced at compression speeds from 24 to 850 mm/s. 500 mg constant weight was maintained for all the materials and mixtures, and each tablet was compressed to a maximum compaction force of 20 kN. The die wall was cleansed with acetone and prelubricated with 4% w/v magnesium stearate in carbon tetrachloride before each compression.

During compression, upper punch load and punch separation were monitored to an accuracy of ± 0.05 kN and ± 12 μm, respectively. The compression data were manipulated in an identical manner to that earlier described by Bateman (1988a,b).

Determination of capping pressures

Paracetamol tablets were made at various speeds ranging from 24 to 620 mm/s at varying compression pressures. The capping pressure at each speed of compression was determined by close visual examination of compacts on ejection for horizontal striations.

Measurement of plastic energy, elastic energy and work of compaction

The plastic and elastic energies along with the work of compaction of paracetamol tablets at varying speeds were measured using energy analysis on a force-punch separation plot. A computer

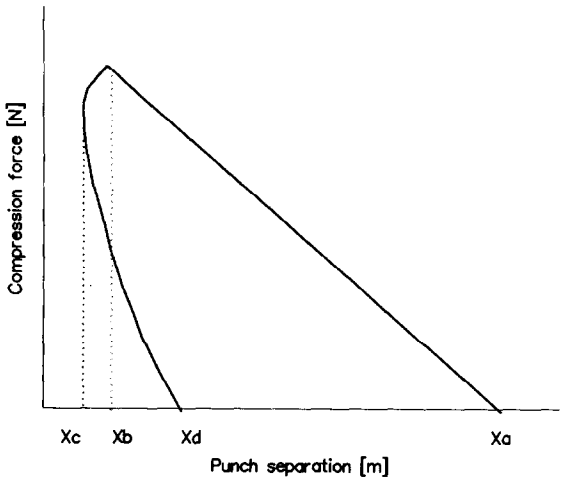

Fig. 1. Schematic diagram of force-punch separation plot used in the energy analysis.

program was employed to calculate plastic and elastic energies from the transient recorder data.

Fig. 1 illustrates schematically the force-punch separation plot, where Xa is the punch separation at the first measurable force, Xb is the first occurrence of peak force, Xc is the minimum punch separation and Xd is the decompression force. The area under the curve XaXb (AUC XaXb) is the plastic energy (or net energy input), the area under the curve XaXc (AUC XaXc) is the gross energy input. The work of compaction (Wc) was determined as

$$Wc = \frac{\text{AUC XaXb}}{\text{AUC XaXc}} \times 100$$

Determination of critical excipient content

The critical excipient content is the maximum amount of microcrystalline cellulose incorporated into paracetamol tablet formulations necessary to prevent capping or lamination at a given speed of compression. The critical excipient content was determined by compressing each of the paracetamol-MCC mixtures at various compression speeds ranging from 24 to 620 mm/s at a fixed compaction force of 20.00 kN. Capping or lamination of compacts at each speed was evaluated by a close visual examination for horizontal striations.

Application of 25% DCP/75% MCC mix in the paracetamol formulation

In previous work (Garr and Rubinstein, 1990), 25% dibasic calcium phosphate (DCP) and 75% microcrystalline cellulose (MCC) mixture was found to have significant advantages as an excipient over a wide range of compression speeds. The mixture was incorporated into a 75% w/w paracetamol tablet formulation. The combination of DCP and MCC in a suitable proportion in paracetamol formulations would be expected to increase the bonding capacity and reduce capping tendency.

Results and Discussion

Paracetamol powder was dried at 110°C to a constant weight in an attempt to eliminate the effects of moisture on capping. This process is important because excessive moisture might cause the powder to exceed its limiting density, thereby leading to an elastic rebound. At high compaction pressures, there is also a possibility of condensed moisture being squeezed out on to the particle surface, so reducing inter-particle bonding and increasing elastic recovery.

The intensity of capping of paracetamol compacts appears to increase with an increase in compression speed. This observation is related to changes in plastic and elastic energies with compression speeds, since both plastic and elastic energies increase with an increase in compression speed (Table 1). Plastic energy increases from 5.80 to 8.64 J which is a percentage increase of 32.87%, whilst elastic energy increases from 0.57 to 1.64 J, a percentage increase of 65.24% over the same speed range of 24 to 850 mm/s. The significant increase in elastic energy, double that of plastic energy, is an indication of an overall increase in the elastic nature of the material which causes recovery and hence capping.

The relative increase in elastic energy over plastic energy (Table 1) appears to be a more important factor than air entrapment in the capping tendency of paracetamol tablets. Elastic energy is not used for bonding, but is stored as deformation energy under stress. The release of this stored

TABLE 1
Effect of compression speed on the energy analysis of paracetamol tablets at a compaction force of 20 kN

Compression speed (mm/s)	Plastic energy (J)	Elastic energy (J)	EE/PE ratio (%)	Work of compaction (%)
24.00	5.80	0.57	9.83	75.77
43.00	5.97	0.71	11.89	84.95
60.00	6.15	0.88	14.31	89.05
150.00	6.33	0.99	15.64	93.20
300.00	6.41	1.09	17.00	92.75
500.00	7.85	1.20	15.30	98.06
620.00	7.28	1.37	18.82	80.32
850.00	8.64	1.64	18.98	98.64

energy at the end of the compression cycle allows the distorted particles to return to their original shape and so rupture weak particle-particle bonds (Yu et al., 1988). For most materials, both plastic and elastic energies tend to increase with compression speed and therefore a more important parameter to measure will be the ratio of elastic energy (EE) to plastic energy (PE), This EE/PE ratio increases with compression speed, which again suggests that the compacts became relatively more elastic as compression speed increases (Table 1).

The work of compaction is the total energy input required for making a compact. Increasing compression speed of paracetamol compacts seems to require an increase in work of compaction which is necessary for elastic deformation, fragmentation of particles and formation of bonds (Table 1).

It is well known that materials that cap can often be made into tablets below some critical pressure, but higher pressures might initiate capping. From Fig. 2, it appears that there is a good correlation between the natural logarithm of compression speed and capping pressure for the paracetamol tablets. It can be described by the equation:

$$Cp = K - A \ln S$$

where Cp denotes the capping pressure (MPa), S is the compression speed (mm/s), K represents the intercept and A is the slope of the line, with a correlation coefficient of 0.972. The capping pressures decrease with increasing speed of compression and the corresponding hardness was less than 1.50 Kp, attributed to the rather low inherent compressibility of paracetamol.

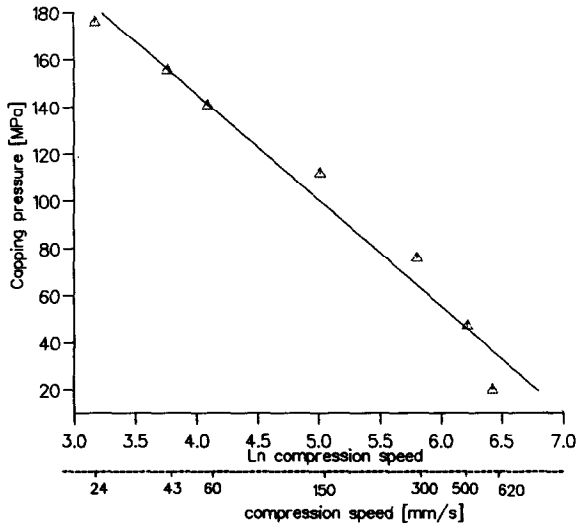

Fig. 2. The relationship between compression speed and capping pressure of paracetamol tablets.

The mean yield pressure obtained as a reciprocal of the slope of the straight line portion of the Heckel plots, over a best-fit pressure range of 40–140 MPa, appears to increase slightly up to a compression speed of 300 mm/s. This is due possibly to a reduction in plastic flow, which was followed by a decrease in yield pressure at a speed of 500 mm/s (Table 2). This latter reduction in yield pressure may be attributed to a possible

TABLE 2
Effect of compression speed on the mean yield pressure of paracetamol tablets at a compaction force of 20 kN

Compression speed (mm/s)	Mean yield pressure (MPa)
24.00	67.14
43.00	66.29
60.00	71.62
150.00	71.91
300.00	84.55
500.00	80.61
620.00	87.61
850.00	89.50

increase in brittle behaviour, hence suggesting a likely presence of a mixed mechanism of consolidation, (Doelker and Shotton, 1977; Humbert-Droz et al., 1983; Roberts and Rowe, 1985).

One of the few disadvantages of direct compression in comparison with wet granulation is a limitation in producing tablets containing a high percentage of active drug substances. A study of drug-excipient systems at varying speeds of compression would be useful in improving excipient design. The critical excipient content, which is the maximum amount of microcrystalline cellulose incorporated into the tablet formulation necessary to prevent capping and lamination, is illustrated in Fig. 3. 25% w/w was adequate to prevent capping up to 300 mm/s (with a corresponding mean tablet tensile strength below 0.342×10^{-3} MPa), but at a higher speed of 500 mm/s, 50% w/w of MCC was required. 75% w/w MCC was inadequate to prevent capping at 850 mm/s. At higher speeds of compression, the compression event is extremely short, and elastic recovery during the decompression phase is therefore rapid.

Plastic deformation of MCC, which is known to be time dependent, appears to be unable to produce adequate inter-particle bonding during compression at high speeds. After compression, decompression produces high elastic recovery of the compact and since little time was available during the compression phase for plastic flow to occur and for bonding to take place, the net result is that the tablet recovers elastically, which causes capping. A combination of low overall plasticity due to high compression speeds and relatively high elasticity after the compression force has been removed, results in a greater tendency to cap. This explains why 75% w/w MCC was unable to prevent capping at high speeds.

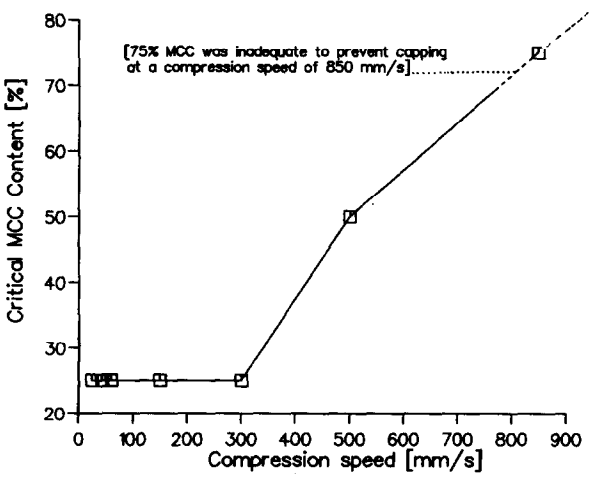

Fig. 3. Excipient content at varying speed of compression.

TABLE 3

Compaction properties of paracetamol-25% DCP/75% MCC systems at a compaction force of 20 kN

Compression speed (mm/s)	Mean yield pressure (MPa)	Tensile strength (MPa) ($\times 10^{-3}$)	Elastic recovery (%)
24.00	89.83	1.41	5.43
43.00	98.51	1.34	5.93
60.00	93.89	1.26	5.76
150.00	80.36	0.68	8.34
300.00	80.01	0.60	9.07
500.00	60.55	Ct	Ct
620.00	58.99	c	c

Ct, a trace of capping; c, a capping.

The combination of DCP, which consolidates principally by fragmentation and is capable of forming strong compacts without any tendency to cap and MCC (which undergoes extensive plastic deformation) in a suitable proportion in paracetamol formulations would be expected to increase bonding capacity and reduce capping tendency. Table 3 summarises the compaction properties of paracetamol-DCP-MCC systems.

The mean yield pressure of the systems showed a progressive decrease with increasing speeds of compression due to a decrease in brittle behaviour of the DCP. The tensile strengths of tablets decreased and elastic recovery increased with speed of compression, which is attributable to the significant influence of MCC (which manifest time dependent plastic flow) on the overall properties of the other components.

25% DCP/75% MCC mixture (present as 6.25% w/w DCP and 18.75% w/w MCC) was found to be very good in preventing capping of compacts containing 75% w/w of paracetamol at compression speed up to 300 mm/s with a corresponding tablet radial tensile strength of 0.60×10^{-3} MPa (Table 3); almost double the tensile strength

(0.342×10^{-3} MPa) of compacts containing 25% w/w MCC alone. The improved tablet strength with the incorporation of 25% DCP/75% MCC is probably due to the extensive fragmentation of DCP leading to efficient filling of void spaces, optimum force ultilization and better particle-particle bonding. In addition whilst extensive capping was observed with the 25% MCC 75% paracetamol compacts at 500 mm/s, only a trace of capping was observed with the incorporation of 25% DCP/75% MCC (Table 3).

Conclusion

In a study of the capping tendency of paracetamol, capping was found to increase with an increase in the speed of compression over the range 24–850 mm/s, due to the significant increase of 65.24% in elastic energy compared to a corresponding increase of 32.87% in plastic energy. The relative increase in elastic energy appears to be a more important factor than air entrapment in the capping tendency of paracetamol compacts. The overall EE/PE ratio also increased with speed, also suggesting that the compacts became relatively more elastic as compression speed increases.

The work of compaction was found to increase with speed of compression, due to a significant increase in energy input required for elastic deformation, fragmentation and formation of bonds. There appears to be a good correlation between the natural logarithm of compression speed and capping pressure and an equation has been proposed to describe the relationship.

The critical excipient content in the paracetamol formulation was found to be 25 and 50% w/w MCC at compression speed of 24–300 and 500 mm/s, respectively. However the incorporation of 25% DCP/ 75% MCC was found to produce tablets with much better resistance to capping over a much wider range of compression speeds and produced tablets with almost double the tensile strengths compared to formulations containing 25% w/w of MCC alone.

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