International Journal of Pharmaceutics, 73 (1991) 75–80
Elsevier Science Publishers B.V.
ADONIS 037851739100245 2

IJP 02440

The effect of rate of force application on the properties of microcrystalline cellulose and dibasic calcium phosphate mixtures

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(Received 30 June 1990)
(Modified version received 10 September 1990)
(Accepted 25 September 1990)

Key words: Force application rate; Mean yield pressure; Tensile strength; Elastic recovery; Microcrystalline cellulose; Dibasic-calcium phosphate

Summary

The effect of rate of force application over the range 24–1100 mm/s on the compaction characteristics of various combinations of a microcrystalline cellulose (MCC) and dibasic-calcium phosphate dihydrate (DCP) have been studied using mean yield pressure, extent of particle rearrangement (D_b) obtained from Heckel analysis, tablet radial tensile strength and elastic recovery as the basis of the investigation. A simple relationship was observed with increasing mass fraction of MCC on mean yield pressure and elastic recovery of the compacts. At all rates of force application, mean yield pressure decreased while elastic recovery increased with increasing mass fraction of MCC, ascribed to the dominating effect of plastic deformation of the microcrystalline cellulose. No simple relationship was observed with properties such as extent of particle rearrangement (D_b) and tensile strength. In some cases the properties of some mixtures were greater than or less than either of the two pure components. At all rates of force application, 25% w/w of MCC and 75% w/w DCP resulted in peak values for D_b, which can be ascribed to a decrease in frictional and cohesive forces between particles. Higher concentrations of MCC resulted in a decrease in D_b due to adhesion of the particles, which reduces the extent of particle slippage and rearrangement towards a minimum between 75 and 100% w/w MCC. The tensile strength of the mixtures decreased with increasing rate of force application. Increasing levels of MCC increased tensile strength and a plateau was obtained at 50–75% w/w MCC at all rates. 75% w/w MCC produced tablets with higher tensile strength than the individual materials respectively, due to extensive fragmentation of DCP which enhanced the filling of void spaces during compression leading to optimum force utilization, improved consolidation and better bonding of MCC. It appears from this study that a mixture of 25% w/w DCP and 75% w/w MCC may have advantages over the individual materials.

Introduction

Direct compression excipients should be free flowing; high compressible so as to produce tablets with a good hardness-pressure profile; physiologically inert and not impair the drug bioavailability; chemically compatible with the drug; colourless; tasteless and have a good mouth feel; relatively inexpensive; capable of reworking with no loss of flow or compressibility and able to produce tablets containing a high proportion of non-compressible material. These properties are not embodied in a single material and in practice it is desirable to blend two or more compression aids together

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(Wells and Langridge, 1981). Many workers have studied the use of mixtures of direct compression excipients which may have properties significantly better than the individual components.

Fell and Newton (1970) observed that the tensile strength of tablets prepared from mixtures of different forms of lactose at a slow compaction rate could be predicted from a knowledge of the tensile strength of tablets of the pure materials. Newton et al. (1977), however, found that the strength of tablets prepared from mixtures of dicalcium phosphate and phenacetin was not a simple function of the strength of the tablets of the individual components.

Wells and Langridge (1981) examined the flexibility of microcrystalline cellulose and dicalcium phosphate hydrate blends in direct compression tableting and studied the properties of the mixtures after slugging. They found that the best tablets were produced when they were composed of 66–99% microcrystalline cellulose and 10–33% dicalcium phosphate dihydrate. Suitable tablets were also produced when these binary mixtures contained up to 20% of acetaminophen.

In an earlier study, Lerk et al. (1974) studied the characteristics for direct compression of blends of Emcompress Special, Celutab, dextrose monohydrate, lactose with Avicel PH101, PH102, Sta-Rx 1500 or amylose V, respectively. The blends of excipients from the group with disintegrant properties may result in synergistic or antagonistic combinations of the properties exhibited by each group. A combination of Emcompress Special or of lactose with Avicel resulted in blends with excellent overall performance for direct compression.

From the survey of the literature, it appears that no significant work has been reported on the effect of rate of force application on mixtures of tablet excipients. The principal aim of the present study was to examine the effect of rate of force application over the range 24–1100 mm/s using a high-speed compaction simulator on the properties of mixtures of MCC and DCP, employing mean yield pressure, extent of particle rearrangement (D_b), tablet radial tensile strength and elastic recovery for evaluation.

The two materials consolidate principally by different mechanisms: MCC by plastic deformation and DCP by fragmentation. MCC has a high degree of compressibility, produces tablets of low friability, has a high capacity and is synergistic with other disintegrants, but it has poor flow properties (Khan and Rhodes, 1975). DCP, on the other hand, assists deaggregation, has a capacity of up to 40%, is non-hygroscopic and is very free flowing. Optimum tableting characteristics may be expected from blends of the two materials.

Materials and Methods

Materials Microcrystalline cellulose (Emcocel 90 M) and dibasic calcium phosphate dihydrate (Emcompress) were obtained from Forum Chemicals Ltd, Surrey, U.K., whilst magnesium stearate was obtained from BDH Chemicals, Poole, U.K.

Particle size fractions 45–125 μm sieve fractions of unmilled MCC and DCP were obtained by sieving the materials on a Pascall sieve shaker (Pascall Engineering Co. Ltd, Sussex, U.K.).

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% w/w of DCP/MCC. The mixtures were stored for 5 days in an oven at 20 °C and 45% relative humidity before compression.

Compression Compressions were carried out using The Liverpool School of Pharmacy Modified High Speed Compaction Simulator (ESH Testing Ltd, Brierley Hill, West Midlands, U.K.), fitted with 12.5 mm flat-faced punches. The simulator consists of a load frame, hydraulic power pack and electronic control unit. A sawtooth time-displacement profile was used to control both upper and lower punches. The data points of the profile are output at a pre-determined rate via a digital/analogue converter to the servo-controller in the main control unit and on to the control valves situated on the load frame. The signal supplied to the valves determines the flow of hydraulic fluid from the power pack through the valves to the actuators. It is this flow of fluid which causes movement of the actuators according to the

intended profile. The output rate of the profile may be set to produce compaction rates up to 3000 mm/s and to a maximum compaction force of 50 kN.

Four tablets were produced at four rates of force application from 24 to 1100 mm/s. 500 mg constant weight was maintained for all the materials and mixtures, and each tablet was compressed to a maximum force of 15 kN. The die wall was cleaned 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 (Bateman, 1988a,b).

Manipulation of compression data The force and displacement data from the upper and lower load cells and the linear variable differential transducers (LVDTs) were captured using a transient recorder and plotted in the form of separate load/time and displacement/time curves using a Servogor 461 plotter. The data were subsequently transferred to an Apple IIe microcomputer for examination as well as storage on to floppy disc, and again transferred to a mainframe computer, using a Fortran program to sort the data, and the area under the compression curve (mean punch force vs punch separation) obtained.

An output file of the sorted data was produced and used for analysis, employing the Heckel equation (1961);

$$\ln \frac{1}{1-D} = KP + A$$

where D is the relative density of the tablet at pressure P, and K is a material constant which is the slope of the straight line region of the plot, the reciprocal of which is the mean yield pressure. A is the value of the intercept of the straight line and is a function of the initial bulk volume. Regression analyses were carried out on the Heckel plots and the mean yield pressure and intercept A from four compressions per rate of force application were determined.

The relative density (D_a) was obtained from the equation:

$$D_a = 1 - e^{-A}$$

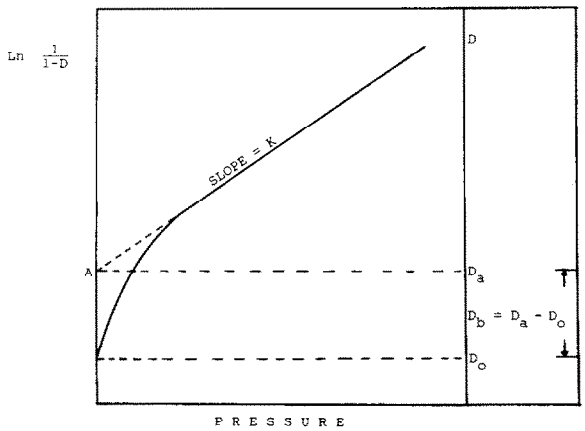

Fig. 1. Schematic representation of Heckel equation used in the compression analysis.

The relative density of the powder at the point when a measurable force is applied (D_o) was determined, the extent of particle rearrangement (D_b) was determined as the difference between D_a and D_o (Fig. 1), whilst rates of force application were calculated from the load/time trace using the point at which the first measurable force was recorded (Bateman, 1988b).

Radial tensile strength Tensile strength was determined from the force required to fracture tablets by diametral compression on a motorised tablet hardness tester (Schleuniger, Model 2E, Switzerland) and the corresponding tensile strength calculated according to the equation of Fell and Newton (1970).

Elastic recovery The ability of formulated powders to form satisfactory tablets depends on their plastic deformation during compression and on their elastic recovery during decompression. The determination of elastic recovery is important because most pharmaceutical materials possess elastic, plastic and brittle properties and may manifest a certain degree of bond disruption and/or rebonding during decompression.

The elastic recovery of the compacts was calculated using the equation described by Armstrong and Haines-Nutt (1972), and Malamataris et al. (1984). The tablets' properties were evaluated after storage for 24 h under ambient conditions.

Results and Discussion

Panaggio et al. (1984), in a study of the properties of systems containing varying proportions of two direct compression tablet matrices, dicalcium phosphate dihydrate and pregelatinized starch, attributed some of the observations to the use of unidentical particle size distribution. In this present study, the same particle size fractions of MCC/DCP were used in an effort to enhance proper mixing and minimise the possible effect of particle size on consolidation.

The mean yield pressure of the compacts decreases with increasing mass fraction of MCC at all rates of force application. In the early stages of compaction, after particle rearrangement has ceased, MCC will compact by plastic deformation, while DCP will undergo extensive fragmentation, which is more efficient at these early stages. With increasing pressure, the compaction of MCC is expected to be more prominent. As fragmentation takes place, the compaction load is borne by greater contact points. The different mechanisms of the two materials will influence the effect one will have on the other during compaction (Sheikh-Salem and Fell, 1981).

The early fragmentation of DCP may slow down the compaction of MCC as it fills the pores more efficiently. MCC, on the other hand, may prevent fragmentation of DCP by preventing the critical force for fracture being achieved on the DCP particles. The relative effects of the above processes would be expected to depend on the mass fraction of each material and the rate of force application. The mean yield pressure of the mixtures appears to be directly related to the MCC concentration and this seems to hold at all the rates of force application employed (Fig. 2).

The extent of particle rearrangement (D_b) values obtained from the Heckel analysis gives an indication of the extent of particle rearrangement during compaction. D_b is a function of the surface structure, particle size and shape. The applied pressure must overcome the interparticular attractive forces, mainly friction and cohesion, before slippage and rearrangement of particles can take place. At all rates, the D_b values of pure DCP were greater than those of pure MCC, which implies that DCP undergoes greater particle rearrangement. This observation can be ascribed to the cohesive nature of MCC which would be expected to offer resistance to the rearrangement process (Fig. 3).

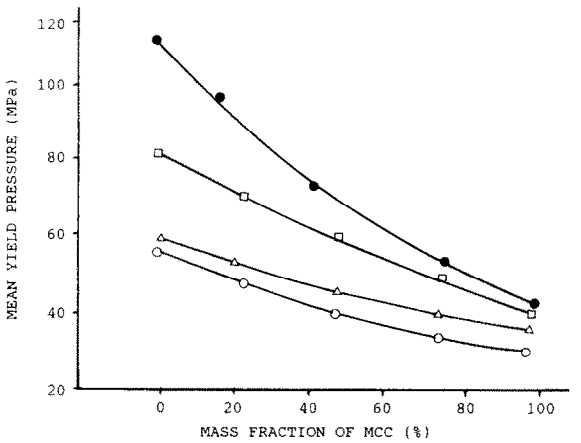

Fig. 2. The effect of rate of force application on the mean yield pressure of MCC/DCP mixtures. (○) 24 mm/s, (△) 300 mm/s, (□) 500 mm/s, (●) 1100 mm/s.

At all rates of force application, 25% addition of MCC resulted in peak values for D_b, due possibly to a decrease in the frictional and cohesive forces between the particles. Further addition of MCC progressively reduces the D_b values, the affinity between the two components of the mixtures at high mass fractions of MCC resulting in

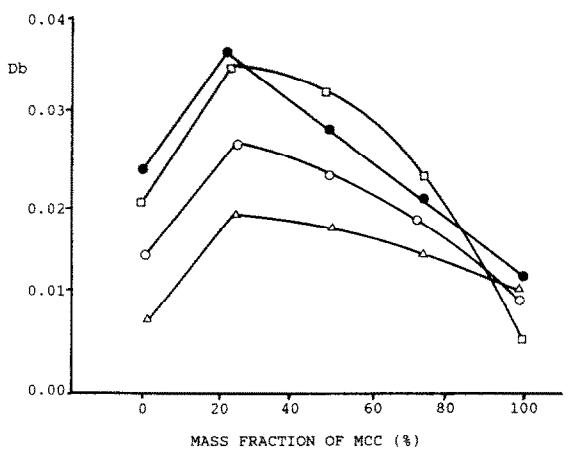

Fig. 3. Extent of particle rearrangement (D_b) for MCC/DCP mixtures at varying rates of force application. (○) 24 mm/s, (△) 300 mm/s, (□) 500 mm/s, (●) 1100 mm/s.

adhesion of the particles which reduces the extent of slippage and rearrangement towards a minimum between 75 and 100% of MCC (Fig. 3).

The tensile strength of the mixtures decreased with increasing rate of force application (Fig. 4). Increasing amounts of MCC increased the tensile strength and a plateau was obtained at 50–75% w/w of MCC. It is interesting to note that a 25% DCP and 75% MCC mixture produced tablets with higher tensile strengths than the individual materials. 100% MCC might be expected to produce tablets with the highest tensile strength, but the present observation at all rates of force application can be ascribed to the presence of 25% w/w DCP having a synergistic effect (Fig. 4).

The tensile strength of tablets will be a function of the fundamental strength of the material, the bonding created by the compaction pressure and the pore structure of the tablets. The mechanism by which MCC-DCP mixtures form good tablets is that MCC predominantly undergoes plastic deformation and its mechanical strength is largely controlled by hydrogen bonding which is related to the proximity of adjacent particles. The number and area of the contact points will increase with compaction pressure leading to an increase in the tensile strength. DCP, on the other hand, increases the tensile strength of the tablets by improving flow and the initial filling of the die. It fills the void spaces during compression as a result of extensive fragmentation, leading to optimum force utilisation, improved consolidation and better bonding of MCC.

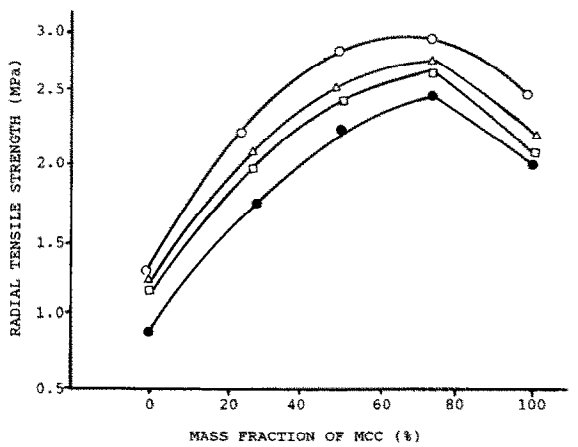

Fig. 4. The effect of rate of force application on tablet radial tensile strength for MCC/DCP mixtures. (○) 24 mm/s, (△) 300 mm/s, (□) 500 mm/s, (●) 1100 mm/s.

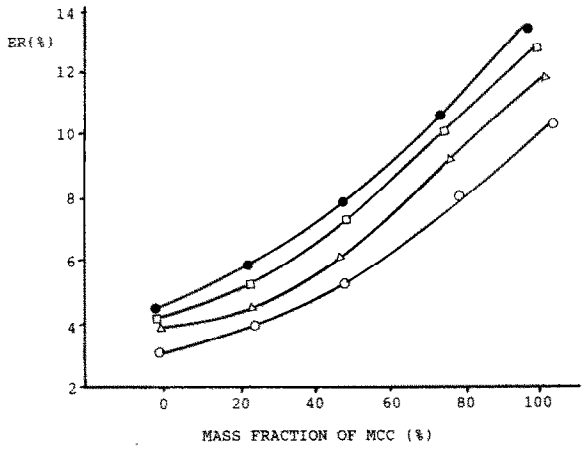

Fig. 5. The elastic recovery (ER) of compacts prepared from MCC/DCP mixtures at varying rates of force application. (○) 24 mm/s, (△) 300 mm/s, (□) 500 mm/s, (●) 1100 mm/s.

The elastic recovery of MCC-DCP mixtures was found to increase with rate of force application. This can be related to the tensile strength values. Compacts formed at high rates are less able to resist the recovery of the elastic component of the material. There is a possibility of a shift in energy utilisation from plastic to elastic with increasing rate of force application (Fig. 5). At all rates, increasing the percentage mass fraction of MCC increased the elastic recovery, due to the time-dependent nature of the plastic deformation of MCC.

Conclusion

The compaction characteristics of mixtures of MCC and DCP which exhibit predominantly different compression behaviour have been evaluated at varying rates of force application using mean yield pressure, extent of particle rearrangement (D_b) obtained from Heckel analysis, tablet radial tensile strength and elastic recovery as the basis of investigation.

The effect of increasing mass fraction of MCC on mean yield pressure of the compacts, at all rates of force application, decreases with increas-

ing levels of MCC due to the dominating effect of microcrystalline cellulose. In a similar manner, increasing mass fraction of MCC, increased the elastic recovery of the compacts, attributed to the time-dependent nature of plastic deformation of MCC compared to the fragmentation of DCP.

Properties such as extent of particle rearrangement (D_b) and tensile strength did not obey such a simple relationship, in some cases, the properties of some mixtures were greater than or less than either of the two pure components. At all rates of force application, 25% w/w MCC and 75% w/w DCP resulted in peak values for D_b which can be ascribed to a decrease in the frictional and cohesive forces between the particles. Further additions resulted in adhesion of the particles which reduced the extent of particle slippage and rearrangement towards a minimum between 75 and 100% w/w MCC.

The tensile strength of the mixtures decreased with increasing rate of force application. Increasing level of MCC increased the tensile strength and a plateau was obtained at 50–75% w/w. It is of interest to note that a 25% w/w DCP and 75% w/w MCC mixture produced tablets with far higher tensile strengths than the individual components. This observation can be attributed to the extensive fragmentation of DCP which enhanced filling of void spaces during compression, leading to optimum force utilisation, improved consolidation and better bonding of MCC.

The study indicates that mixtures of dibasic-calcium phosphate dihydrate and microcrystalline cellulose especially at the 25/75% ratio may have significant advantages over the individual materials over a wide range of rates of force application.

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