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The effects of slugging and recompression on pharmaceutical excipients

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Abstract

Slugs of microcrystalline cellulose (MCC), dibasic calcium phosphate (DCP) and Starch 1500 were compressed, either on their own or in various combinations, between 12.7 mm flat faced punches on a single punch tableting machine at 10 different pressures. 10 tablets of each batch were compressed and the crushing strengths for five were determined. The remaining slugs were screened through an oscillating granulator and recompressed at the same pressure used initially. The crushing strengths of the final tablets were again determined. The mean yield pressures were evaluated for the slugs utilizing Heckel analysis. The results indicated that the hardest tablets were produced using 75% MCC:25% DCP. The mean yield pressure values showed that on addition of a further excipient to MCC there is a move away from predominantly plastic deformation. This was very noticeable with blends of MCC and DCP. The latter excipient has a high mean yield pressure value which implies that it is a brittle material which deforms by fragmentation. It would seem that fragmentation of DCP within the 75% MCC:25% DCP blend enhances bonding on compaction and so leads to increased crushing strength. However, for all slugged tablets there was a reduction in the crushing strength of the tablet after the second compression for all the materials investigated. The blends consisting of Starch 1500 showed less of a reduction in the crushing strength than the other excipient blends. These results in general would indicate that the extent of plastic deformation is less when the materials are compressed twice, compared to when they are compacted once. It was concluded that the slugging process is therefore independent of an increase in dwell time.

Keywords: Work hardening; Slugging; Recompression; Mean yield pressure; Microcrystalline cellulose; Dibasic calcium phosphate; Starch 1500

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1. Introduction

Many workers have studied the use of mixtures of direct compression excipients which may have properties superior to those of the individual components. Newton et al. (1977) found that the strength of tablets prepared from dicalcium phosphate and phenacetin was not simply the proportional combination of the strength of tablets of ethe individual components. Various investigations by many workers in recent years have been carried out, with respect to blends of microcrystalline cellulose (MCC) and dicalcium phosphate

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(DCP) for direct compression tableting (e.g., Wells and Langridge, 1981; and more recently Garr and Rubinstein, 1991). This latter study concentrated on the properties of systems containing varying proportions of two direct compression excipients, microcrystalline cellulose (MCC) and dicalcium phosphate (DCP) and found that the mean yield pressure of the compacts decreased with increasing mass fraction of MCC; the mean yield pressure seemed to be directly related to the MCC concentration. They also observed that the particle rearrangement (D_b values) increased to a maximum at 25% w/w addition of MCC to DCP and then decreased with further addition of MCC. They noted that the hardest tablets were produced using a mixture of 75% MCC and 25% DCP.

Kochhar and Rubinstein (1994) have in recent work confirmed those results concerning the mean yield pressure and tablet hardness using blends of microcrystalline cellulose with spray-dried lactose (SDL) and also that of DCP : SDL and MCC : DCP. Collectively these results showed that a blend of 75% MCC : 25% DCP (% w/w) produced the hardest tablets. However on recompression weaker tablets were produced for each of the blends with this reduction in hardness being greatest with the MCC : DCP blends.

This study extends this previous work and examines the slugging characteristics of MCC and DCP in combination with Starch 1500.

2. Materials and methods

2.1. Materials

Dibasic calcium phosphate (DCP) anhydrous powder USP/FCC grade (Rhone Poulenc Basic Chemicals Co., Shelton, U.S.A.), Starch 1500 powder (Colorcon, IN, U.S.A.), Avicel PH 102 (MCC) powder (FMC International, Little Island, Cork) and magnesium stearate was obtained from BDH Chemicals, Poole, U.K.

2.2. Mixing

Each of the excipients were mixed in bulk using a mixer-granulator (T.K. Fielder PMA 25) for 10 min at a speed of 100 rpm with the chopper off. This allowed even mixing of fines and a breakdown of any aggregates. Component blends of the materials were prepared by weighing the appropriate quantities and tumbling in a glass bottle attached to an electric motor at 40 rpm for 10 min. Blends of 50 : 50, 75 : 25 and 25 : 75 (% w/w) ratios were produced in this way for each component system.

2.3. Single punch tableting machine calibration

Before carrying out compressions of the excipients it was necessary to calibrate the force exerted between the upper and lower punch. Strain gauges were mounted on the outer face of the eccentric arm for both the upper and lower punches. These were in turn connected to pen chart recorder. This recorder could be set to 10 or 100 mV/cm depending on the extent of the force between the punches. At low compression forces it was therefore possible to obtain large peaks when using a setting of 10 mV/cm.

Both the upper and lower punches were then removed and a precalibrated load cell, in series with an amplifier, was placed between the eccentric arms. The machine was then operated manually so as to exert a pressure on the load cell. The reading from the amplifier was noted for every five divisions of the chart recorder and as the load cell had already been calibrated with respect to the amplifier it was possible to convert chart recorder divisions into force (kN).

2.4. First compression (slugging)

Compression was carried out using a single punch tableting machine (F-press Manesty Machines Ltd)) fitted with 12.7 mm flat-faced punches. A batch of 10 tablets were produced for each compression at 5.91, 13.78, 23.62, 35.43, 64.96, 94.69, 125.98, 154.45, 181.1 and 222.4 MN m^{-2}. The die wall was cleaned with acetone and prelubricated with 1% w/v magnesium stearate in carbon tetrachloride before each compression.

2.5. Slug characterisation

In order to generate compaction characteristics, measurements of the individual slug weight for each batch of the 10 slugs and their thicknesses were determined using a digital micrometer. The crushing strength for five of the slugs was then measured (a) using a motorised tablet hardness tester (Schleuniger, Model 2E, Switzerland).

2.6. Second compression (tableting)

The remaining slugs were screened through an Erweka oscillating mill granulator, utilising an 18 mesh sieve size, to produce granules. These granules were then recompressed at the same pressures used initially and once again their crushing strengths were determined (b).

2.7. Heckel analysis

The thickness data were sorted using a spreadsheet program to obtain the tablet density. This was then utilised for Heckel analyses (a measure of plasticity) employing the Heckel equation (1961a,b);

$$\ln[1/(1-D)] = KP + A \qquad (1)$$

where D is the relative density of the tablet at pressure P and K denotes a material constant which is the slope of the straight line region. From Eq. 1, the reciprocal of this straight line is the mean yield pressure. A is the intercept of the straight line through the ln axis and is a function of the initial bulk volume.

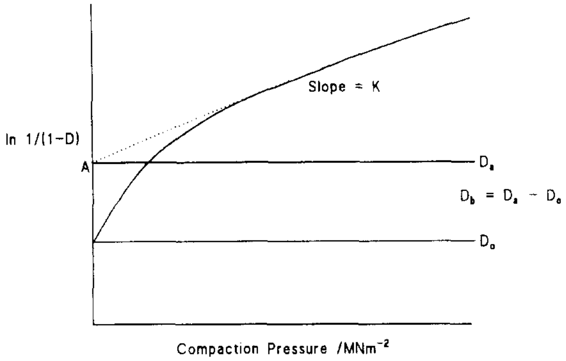


Fig. 1. Schematic representation of the Heckel equation.

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

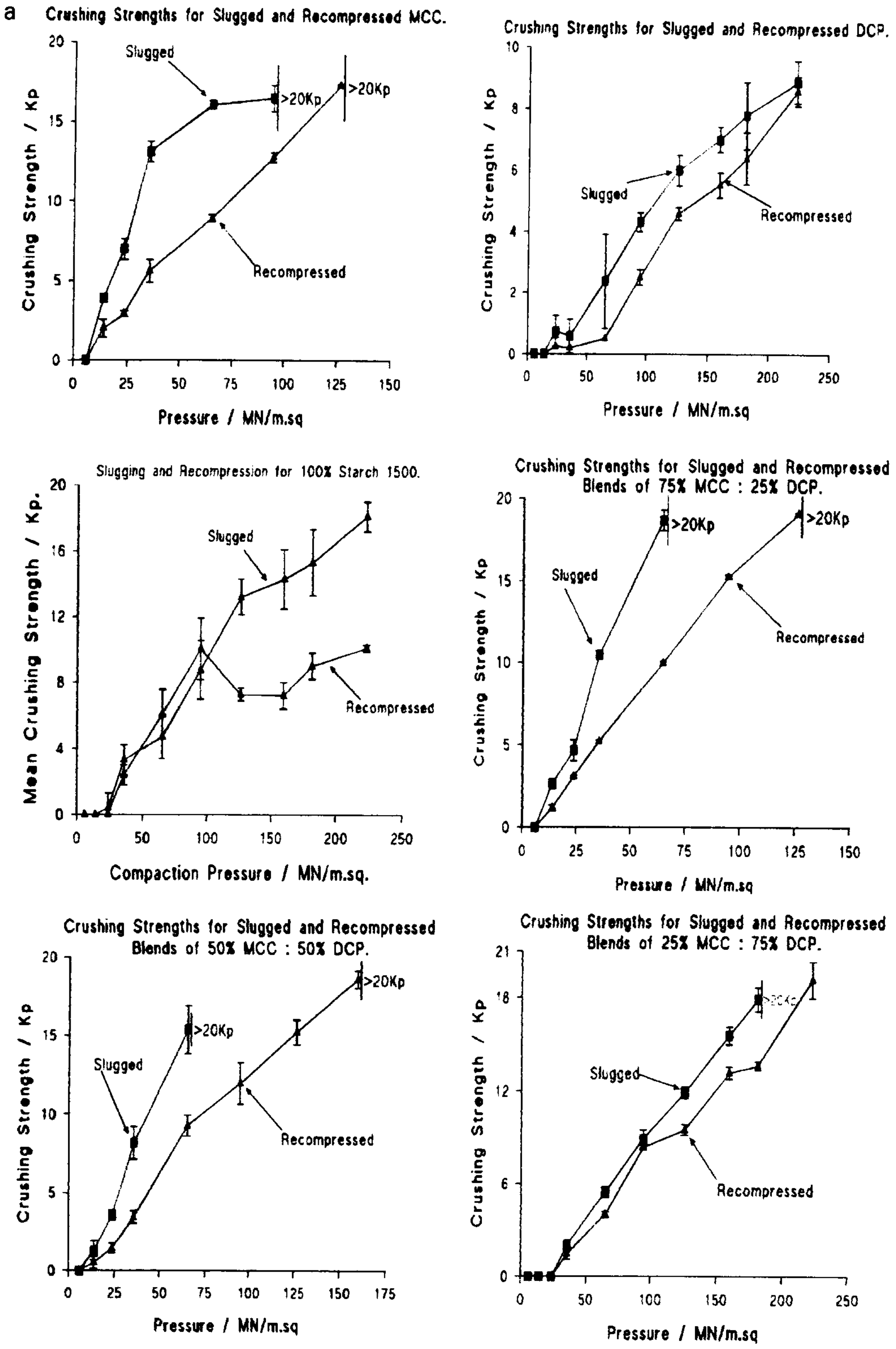
$$D_a = 1 - e^{-A}$$

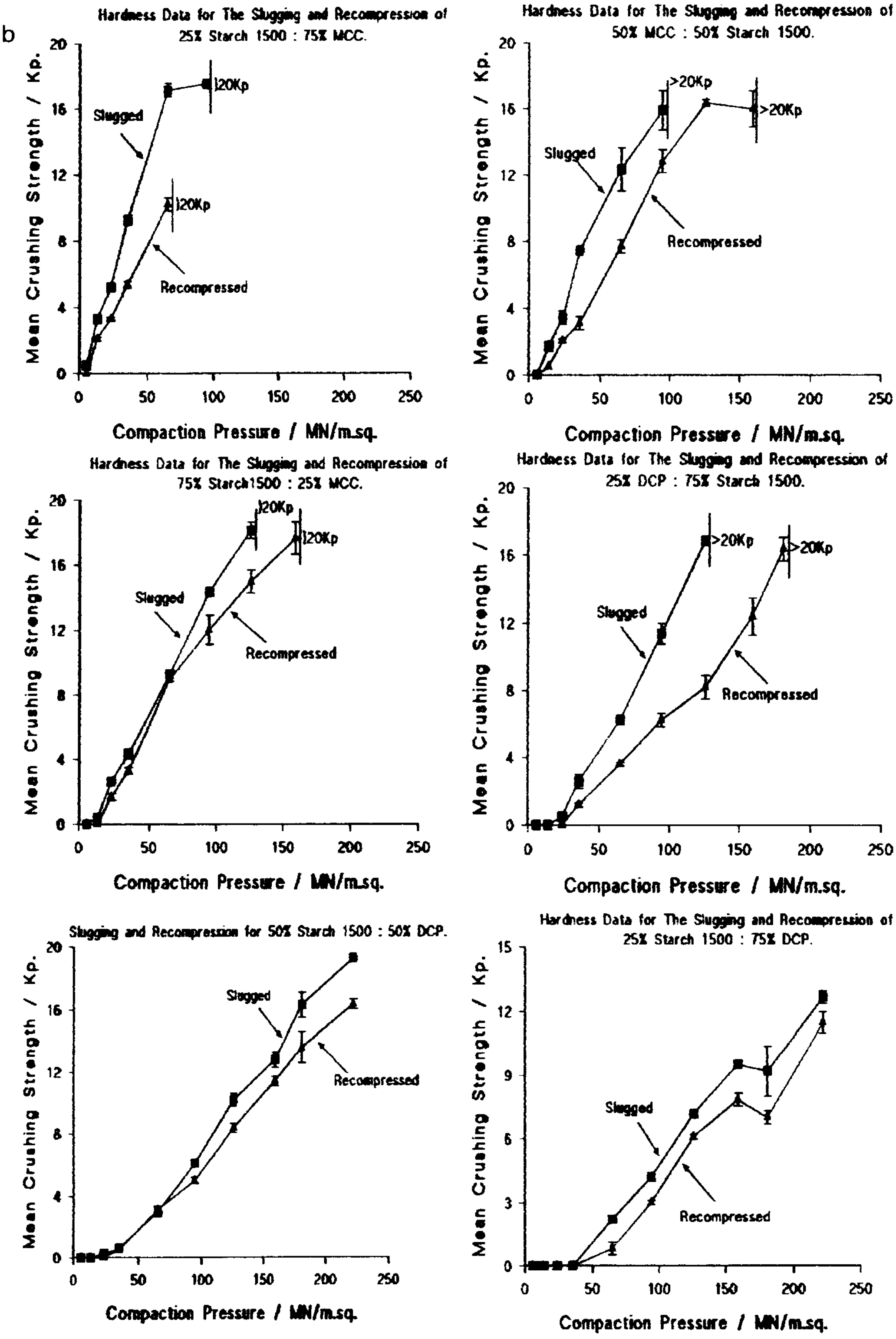
The relative density of the powder at zero pressure (D_0) was also determined by noting where the graph of the Heckel plot intercepted the $\ln[1/(1-D)]$ axis, as shown in Fig. 1. The extent of particle rearrangement (D_b) (Table 1) was determined as the difference between D_a and D_0 (Fig. 1).

Regression analyses were carried out over the pressure range that did not stray from linearity for each Heckel plot and the mean yield pres-

Table 1
Heckel analyses and mean crushing strengths with standard deviations (S.D) at a compaction pressure of 65 MN m^{-2}

Excipient system (% w/w)	Mean crushing strength (Kp)		Heckel analysis		
	Slugged (S.D)	Recompressed (S.D)	Mean yield pressure (MN m^{-2})	D_b values	Correlation coefficient R^2 (%)
100% MCC	16.06 (0.24)	8.94 (0.23)	97.1	0.181	98.75
100% Starch 1500	4.70 (1.35)	6.05 (1.48)	66.0	0.045	95.8
100% DCP	2.38 (0.55)	0.50 (0.00)	648.0	0.255	95.2
75% MCC : 25% DCP	18.60 (0.62)	9.94 (0.11)	156.0	0.234	99.9
50% MCC : 50% DCP	15.38 (0.48)	9.28 (0.67)	465.0	0.299	97.2
25% MCC : 75% DCP	5.46 (0.33)	4.02 (0.19)	381.0	0.287	96.4
75% MCC : 25% Starch 1500	17.14 (0.42)	10.20 (0.35)	112.0	0.240	97.9
50% MCC : 50% Starch 1500	12.34 (1.35)	7.70 (0.40)	213.0	0.306	91.8
25% MCC : 75% Starch 1500	9.28 (0.08)	4.40 (0.20)	132.0	0.223	98.1
75% DCP : 25% Starch 1500	2.22 (0.v19)	0.82 (0.29)	499.0	0.106	96.8
50% DCP : 50% Starch 1500	3.00 (0.29)	3.16 (0.23)	293.0	0.050	97.9
25% DCP : 75% Starch 1500	6.24 (0.05)	3.62 (0.08)	167.7	0.045	99.9


a
Crushing Strengths for Slugged and Recompressed MCC.
Slugged
>20Kp
>20Kp
Recompressed
Crushing Strength / Kp
0
5
10
15
20
0
25
50
75
100
125
150
Pressure / MN/m.sq
Crushing Strengths for Slugged and Recompressed DCP.
Slugged
Recompressed
Crushing Strength / Kp
0
2
4
6
8
10
0
50
100
150
200
250
Pressure / MN/m.sq
Slugging and Recompression for 100% Starch 1500.
Slugged
Recompressed
Mean Crushing Strength / Kp.
0
4
8
12
16
20
0
50
100
150
200
250
Compaction Pressure / MN/m.sq.
Crushing Strengths for Slugged and Recompressed Blends of 75% MCC : 25% DCP.
>20Kp
>20Kp
Slugged
Recompressed
Crushing Strength / Kp
0
5
10
15
20
0
25
50
75
100
125
150
Pressure / MN/m.sq
Crushing Strengths for Slugged and Recompressed Blends of 50% MCC : 50% DCP.
>20Kp
>20Kp
Slugged
Recompressed
Crushing Strength / Kp
0
5
10
15
20
0
25
50
75
100
125
150
175
Pressure / MN/m.sq
Crushing Strengths for Slugged and Recompressed Blends of 25% MCC : 75% DCP.
>20Kp
Slugged
Recompressed
Crushing Strength / Kp
0
6
12
18
21
0
50
100
150
200
250
Pressure / MN/m.sq


b
Hardness Data for The Slugging and Recompression of 25% Starch 1500 : 75% MCC.
Mean Crushing Strength / Kp.
Compaction Pressure / MN/m.sq.
Slugged
Recompressed
]20Kp
]20Kp
Hardness Data for The Slugging and Recompression of 50% MCC : 50% Starch 1500.
Slugged
Recompressed
>20Kp
>20Kp
Hardness Data for The Slugging and Recompression of 75% Starch1500 : 25% MCC.
Slugged
Recompressed
]20Kp
]20Kp
Hardness Data for The Slugging and Recompression of 25% DCP : 75% Starch 1500.
Slugged
Recompressed
>20Kp
>20Kp
Slugging and Recompression for 50% Starch 1500 : 50% DCP.
Slugged
Recompressed
Hardness Data for The Slugging and Recompression of 25% Starch 1500 : 75% DCP.
Slugged
Recompressed
0
4
8
12
16
20
3
6
9
15
50
100
150
200
250

sures were determined for each batch of tablets produced (Table 1).

3. Results and discussion

3.1. MCC:DCP

Table 1 lists the crushing strengths at a compaction pressure of 65 MN m^{-2}. Table 1 indicates how the crushing strengths of each system compared. The slugs produced with the greatest crushing strength were found using an excipient blend of 75% MCC:25% DCP. Indeed, excipient systems containing MCC, generally, gave slugs with the greatest crushing strengths (Table 1 and Fig. 2a and b). A detailed account of MCC:DCP hardness and mean yield pressure values has been given in previous work by Kochhar and Rubinstein (1994) and Garr and Rubinstein (1991).

The extent of particle rearrangement during compaction is indicated by the use of D_b values (Table 1), obtained from the Heckel analysis. D_b is a function of the surface, structure, particle size and shape of the material. The applied pressure must overcome the interparticular attractive forces, mainly friction and cohesion, before slippage and rearrangement of particles can take place.

The D_b values of 100% DCP (0.255) were found to be greater than those for 100% MCC (0.181). This implies that DCP undergoes a more extensive particle rearrangement compared to that of MCC.

On addition of MCC to DCP the D_b value continued to increase, due to the more cohesive nature of MCC, until peaking at 50% MCC. This point probably represents a decrease in the frictional and cohesive forces between the particles. Further additions of MCC progressively reduced the D_b values, due possibly to an increased affinity between the two components at a high mass fraction of MCC. This increased affinity can result in greater interparticulate adhesion which reduces the extent of slippage and rearrangement.

3.2. MCC:Starch 1500

The slugs produced using this combination are generally very hard (Table 1 and Fig. 2b). Only MCC:DCP produced harder slugs (Table 1 and Fig. 2a). The hardest slugs using this combination was found using the 75% MCC:25% Starch 1500 blend. The mean yield pressure of pure Starch 1500 (Table 1 and Fig. 3) indicates that it is an extremely plastic material (66.0 MN m^{-2}).

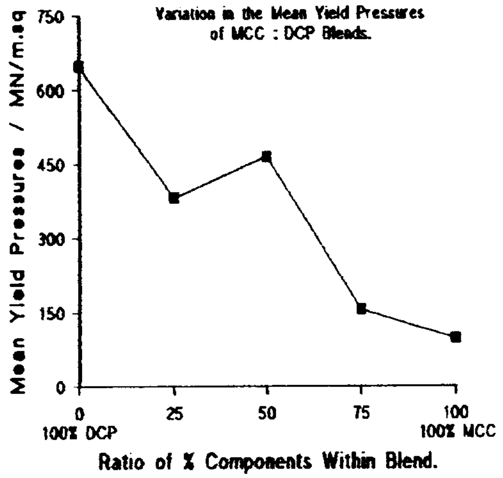
Starch 1500, although a very plastic material, is very different in its physical appearance from that of MCC. Starch 1500 is more granular in shape and on compaction does not simply collapse, as with the hollow fibril structure of MCC, but Starch 1500 has a tendency to recover elastically. The elastic tendency of Starch 1500 may offer an explanation as to why an obviously very plastic blend produces slugs with a reduced hardness to that of MCC:DCP. A further explanation may be due to the lack of fragmentation experienced by the MCC:Starch 1500 combination.

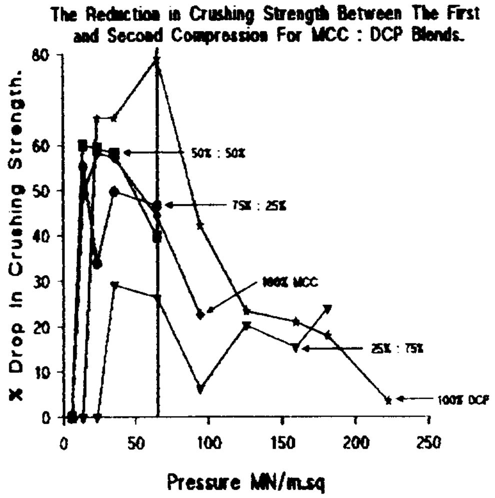
The MCC:Starch 1500 combination produced slugs that were harder than their individual components (Table 1 and Fig. 2a and b). The hardness profile of Starch 1500 indicates slugs of very weak crushing strengths (Fig. 2a). This latter result can be attributed to the elastic tendency of Starch 1500 on compaction. As with the MCC:DCP combination, the hardness of the compact increased as the mass fraction of the more plastic material increased (Table 1).

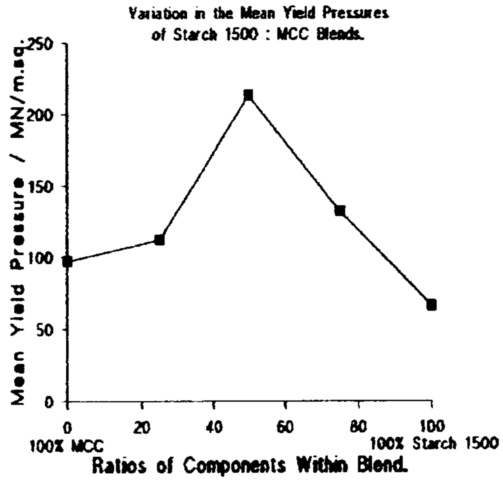
The D_b values reflect a maximum particle rearrangement at 50% MCC:50% Starch 1500 (0.306). What is noticeable is the very low value for pure Starch 1500 (0.045), less than that for MCC and is therefore indicative of a cohesive material. A further point noted is that as with the mean yield value there is an increase in the D_b value when both components are combined (Table 1). This implies that MCC and Starch 1500

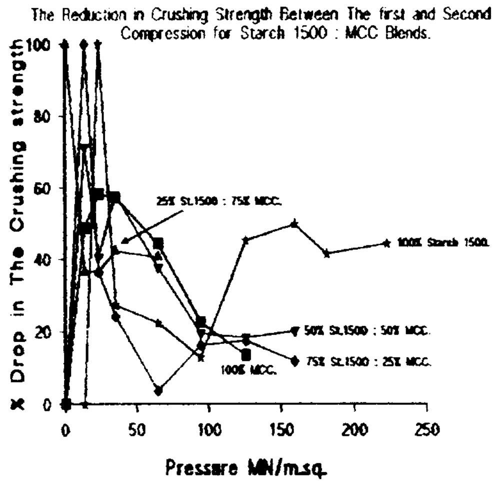
Fig. 2. (a) Crushing strength vs compaction pressure plots. (b) Variation in mean yield pressure.

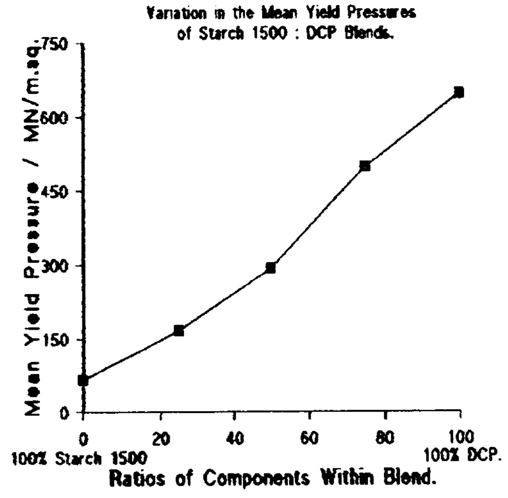
Fig. 3. Reduction in crushing strength between first and second compression.

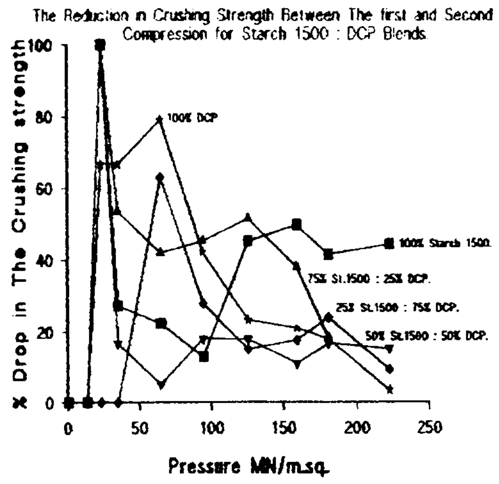

Variation in the Mean Yield Pressures of MCC : DCP Blends.
Mean Yield Pressures / MN/m.sq
750
600
450
300
150
0
0
25
50
75
100
100% DCP
100% MCC
Ratio of % Components Within Blend.


The Reduction in Crushing Strength Between The First and Second Compression For MCC : DCP Blends.
% Drop In Crushing Strength.
80
60
50
40
30
20
10
0
50% : 50%
75% : 25%
100% MCC
25% : 75%
100% DCP
0
50
100
150
200
250
Pressure MN/m.sq


Variation in the Mean Yield Pressures of Starch 1500 : MCC Blends.
Mean Yield Pressure / MN/m.sq.
250
200
150
100
50
0
0
20
40
60
80
100
100% MCC
100% Starch 1500
Ratios of Components Within Blend.


The Reduction in Crushing Strength Between The first and Second Compression for Starch 1500 : MCC Blends.
% Drop in The Crushing strength
100
80
60
40
20
0
25% St.1500 : 75% MCC.
100% Starch 1500.
50% St.1500 : 50% MCC.
75% St.1500 : 25% MCC.
100% MCC.
0
50
100
150
200
250
Pressure MN/m.sq.


Variation in the Mean Yield Pressures of Starch 1500 : DCP Blends.
Mean Yield Pressure / MN/m.sq.
750
600
450
300
150
0
0
20
40
60
80
100
100% Starch 1500
100% DCP.
Ratios of Components Within Blend.


The Reduction in Crushing Strength Between The first and Second Compression for Starch 1500 : DCP Blends.
% Drop in The Crushing strength
100
80
60
40
20
0
100% DCP
100% Starch 1500.
75% St.1500 : 25% DCP.
25% St.1500 : 75% DCP.
50% St.1500 : 50% DCP.
0
50
100
150
200
250
Pressure MN/m.sq.

together result in decreased plasticity and cohesiveness compared to their individual components.

3.3. Starch 1500:DCP

One would expect the results with this combination to be similar to that of the MCC:DCP blend. Indeed, the mean crushing strength profiles are very much alike, peaking at their respective 75%:25% DCP blends (Table 1 and Fig. 2b). However, the crushing strength values for the Starch 1500:DCP are very much less than those for the respective % combinations of the MCC:DCP blend (Fig. 2a and b).

The mean yield pressure values of both pure MCC and Starch 1500 indicate very highly plastic materials, as discussed earlier (Table 1). Also noted earlier is that Starch 1500 is of granular nature and is subject to a degree of elastic recovery once the pressure has been removed. As all tablets were tested for their hardness 24 h after compaction, then it is almost certain that any elastic recovery would already have taken place, hence the production of softer slugs when using Starch 1500 instead of MCC.

The D_b values in Table 1 show that Starch 1500 undergoes very little particle rearrangement. The extent to which Starch 1500 resists this rearrangement is such that even on addition of DCP, which experiences extensive particle rearrangement, there is only a slight increase in particle movement. There is only a notable change in the rearrangement when the blend consists of up to 75% DCP. Unlike the MCC:DCP blend, the particle rearrangement, indicated by the D_b values (Table 1), is much less than that of the Starch 1500/DCP combination and there is no apparent peak, as experienced by 50% MCC:50% DCP. Therefore, it appears, using the D_b values, that Starch 1500 may dampen the extent of particle rearrangement by DCP. As DCP is a fragmentatory material one would expect it to possess a high D_b value. However, with only 25% Starch 1500 the D_b value is greatly reduced. As postulated in earlier work by Kochhar and Rubinstein (1994), the degree of fragmentation is a necessary component in the production of hard tablets, and this may therefore explain why the Starch 1500:DCP combination results in weaker tablets compared to the MCC:DCP combinations (Fig. 2a and b).

3.4. Recompression

All excipients and blends, without exception, showed a reduction in crushing strength when compressed a second time, i.e., recompressed (Fig. 2a, b and 4). Indeed, this reduction was greater than 50% for many of the blends. The reduction in crushing strength was greatest with the MCC:DCP blends, over a substantial part of the pressure range. The hardness and recompression data also suggest that as the recompression pressure increases, there is a levelling off in the reduction of the crushing strengths, for all the blends (Fig. 2a and b). Those blends that exhibited high initial crushing strengths, 75% MCC:25% DCP, had their crushing strengths greatly reduced on recompression. These decreases in crushing strengths on recompression can in a sense be attributed to a reduction in the working potential of an originally easily worked material which produced high crushing strength slugs at low pressures or slugs with initially high crushing strengths.

It is noticeable that the blend comprising 25% MCC:75% DCP shows, in general, the least reduction in crushing strength over the specified pressure range (Fig. 4). This cannot be due solely to a decrease in the amount of the plastic component. If that were the case 100% DCP would indicate the least reduction in crushing strength. When a body is compressed there is a release of energy. This energy that is dissipated may be in the form of plastic, fragmentatory or elastic energy, depending on the type of deformation that a particular material undergoes. The loss in working potential of the 25% MCC:75% DCP blend may be less pronounced due to the release of fragmentatory energy, by DCP, during the first compression being greater than the energy dissipated from the plastic component, MCC, during its deformation. As the potential for plastic deformation is retained then the material is able to be further re-worked during the second compression.

This reduction in the crushing strength on recompression has only previously been noted and investigated with MCC and DCP blends (Langridge and Wells, 1981; Aulton and Marok, 1981). The cited authors attributed this phenomenon to work hardening, which has been described as an increase in resistance to permanent deformation of a material with the amount of deformation that the material is subjected to. Rees and Rue (1978) demonstrated work hardening using sodium chloride.

Work previously carried out by Gunsel and Kanig (1976) described the slugging process as just an elaborate method of increasing the length of time the punch is in contact with the material (dwell time) and was therefore not concerned with work hardening. If this were the case then it would be expected that slugging followed by recompression would indeed increase the hardness of the subsequent tablets. The results show that this is not the case and perhaps more importantly that this result is not isolated and occurs throughout each excipient combination. After slugging, during the sieving process, bonds are broken and new bonds are formed on recompression. It is therefore unlikely that the slugging process can be considered to be a method of increasing the dwell time, as bonds that are formed during slugging are not likely to remain formed during recompression.

4. Conclusions

Although the maximum crushing strength of slugs was achieved using 75% MCC:25% DCP w/w (Table 1 and Fig. 2a), it appears that on recompression there is a loss of potential with respect to the continued re-working of this blend. Indeed, this was the case for each of the blends used in this study. However, those blends which contained Starch 1500 showed the least reduction in crushing strength, after 25% MCC:75% DCP w/w (Fig. 2b) Therefore, as with Kochhar and Rubinstein (1994), it appears that the slugging process is independent of an increase in the dwell time.

It is also apparent that the crushing strength values, in general, can be related to the extent of particle rearrangement at zero pressure (D_b value) prior to the compression of the material (Table 1). Therefore, the extent of slippage and cohesion that a blend experiences may indicate the hardness of tablets that will be produced by direct compression.

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