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EFFECT OF RE-COMPRESSION ON THE PROPERTIES OF TABLETS PREPARED BY DRY GRANULATION

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ABSTRACT

The effect of re-compression on the tableting properties of some direct compression excipients (directly compressible starch, dicalcium phosphate dihydrate and microcrystalline cellulose) and their formulations was examined. Re-compression generally reduced the tablet strength and this reduction was more significant when the initial compaction was carried out at a higher pressure. The reason for the reduction of tensile strength upon re-working is attributed to work hardening and the production of robust granules, which have increased resistance to deformation compared to unworked granules.

INTRODUCTION

Slugging is widely used for formulating moisture sensitive drugs in medium and high dose ranges and as a re-working process. However, information on the suitability of excipients as slugging

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aids and their re-working potential is lacking. The mechanism by which slugging facilitates bonding in tablet manufacture is also not fully understood. Gunsel and Kanig[1] hypothesized that slugging was "just a rather elaborate method of subjecting a material to increased compression time". This, however, has never been substantiated. This study was designed to examine the relationship between re-compression and dwell time and to obtain some semi-quantitative data on the re-working potential of some direct compression excipients and formulations.

MATERIALS

Directly compressible starch, Starch 1500 (Colorcon, Orpington, U.K.). Microcrystalline cellulose, Avicel PH102 (Honeywill & Stein Ltd., Surrey, U.K.). Dicalcium phosphate dihydrate, Emcompress (K & K Greeff Ltd., Surrey, U.K.). Magnesium stearate (Durham Raw Materials Ltd., Durham, U.K.).

METHOD

The following formulations were used:

A. In order to study similar particle size ranges for both initial compaction and re-compression, directly compressible starch (D.C. Starch), microcrystalline cellulose (MCC) and dicalcium phosphate dihydrate (DCP) were separated into sieve fractions (D.C. Starch, 100-160μm; MCC and DCP, 32-160μm). No lubricant was added to MCC and D.C. Starch, but 0.5%w/w magnesium stearate, prescreened through a 250μm sieve, was incorporated into the DCP fraction by mixing in a planetary mixer at slow speed for 5 minutes.

B. To confirm that the compressional properties of the sieve fractions of direct compression excipients were similar to the unsieved material, tablets of MCC and DCP raw materials were also prepared. Since direct compression and slugging formulations often contain

blends of two or more excipients, the following mixtures of MCC and DCP were selected: (i) MCC 66% - DCP 33%, (ii) MCC 50% - DCP 50%, (iii) MCC 33% - DCP 66%. 0.5%w/w magnesium stearate was incorporated as a lubricant as described above.

Granule Properties

The tapped densities of the excipients were determined before and after milling the initial compacts using the procedure described by Neumann[2]. One hundred taps were used to obtain the final tapped volume. Scanning electron photomicrographs of excipient sieve fractions before and after initial compression were also taken.

Tableting

The direct compression excipients and their sieve fractions as well as the blends of MCC and DCP were compressed at slow speed (dwell time 0.1 s) on an instrumented single punch tablet machine (F, Manesty, Speke, Liverpool, U.K.) using 9.5mm flat faced punches at a range of pressures ($9-116 MNm^{-2}$). The target weights of the MCC, D.C. Starch and DCP tablets were 200mg, 300mg and 400mg respectively. The tablets prepared from MCC and DCP blends weighed 350mg.

Tablets compressed at two pressures (e.g., 23 and $116 MNm^{-2}$) for D.C. Starch) were then reduced using an Apex comminuting mill (Apex Construction Ltd., Northfleet, Kent, U.K.) fitted with a 0.04 inch aperture screen operating at slow speed with hammers forward. The tablets prepared from sieve fractions (described under A) were milled and separated into the same sieve fractions used for initial compression. An additional 0.5% magnesium stearate was incorporated extra-granularly for formulations containing DCP.

The sieve fractions and granules obtained from formulations described under B, were re-compressed under the same conditions

(e.g., pressures, tablet weight) used for initial compaction. To examine the effect of dwell time on tablet strength, only the sieve fractions described under A were used. A dwell time of 15 seconds was achieved by rotating the flywheel of the tablet machine manually and held for 15 seconds at the maximum compressive force. To test Gunsel and Kanig's[1] hypothesis, the effect of increased dwell time was compared with that achieved by re-compression.

Tablet Properties

The uniformity of tablet weight was measured by weighing 5 tablets and calculating the coefficient of variation. The dimensions of five tablets were determined using a screw micrometer. Tablet porosity was calculated from the true densities of the excipients, obtained from the literature[3,4] and tablet

$$\text{Reworking potential} = \frac{\text{Area under recompression curve (A)}}{\text{Area under 1st compression curve (A+B)}} \times 100$$

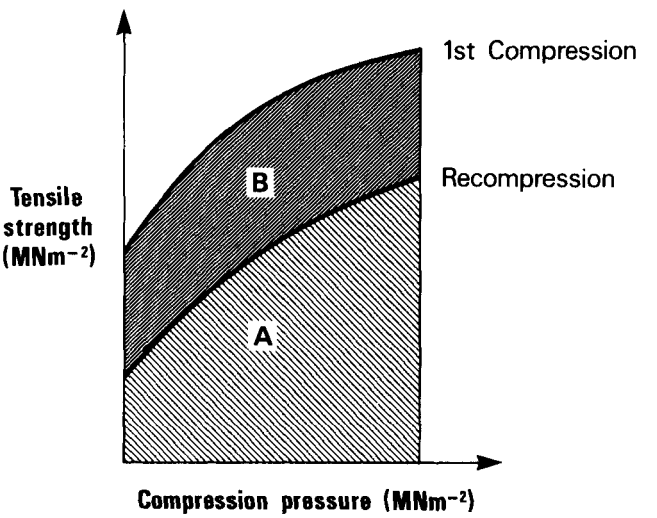

FIGURE 1

The determination of re-working potential

weight and volume measurements. Tablet tensile strength was determined from the force required to fracture tablets by diametral compression on a motorised hardness tester (G.B. Caleva Ltd., Ascot, U.K.) using the method described by Fell and Newton[5]. The tablet friability was determined using a Beecham Friabilator[6].

The re-working potential of the direct compression excipients and blends was calculated by determining the area under the tensile strength/re-compression pressure profile expressed as a percentage of the area under the initial tensile strength/pressure profile (Fig. 1).

RESULTS AND DISCUSSION

The coefficient of weight variation of tablets obtained before and after re-compression was below 2%, indicating good weight uniformity. Table 1 shows the effect of initial compression pressure on the tapped density of the granules obtained from excipients, their sieve fractions and blends.

Table 1 shows that the granules obtained from milled compacts, have higher tapped densities compared to the uncompressed raw material, and the tapped density increases with increasing compaction pressure. These results are similar to those previously reported by Khan and Musikabhumma[6]. They suggested that slugging produced denser and less porous granules and that as the initial compaction pressure increased, the granules obtained from the slugs become more robust.

Re-compression appears to have little or no effect on tablet porosity (Table 2). Therefore, although re-compression significantly affects tablet strength (Figs. 2-4), this is not reflected in their porosity values.

Fig. 2 shows the effect of re-compression on the tensile strength/compression pressure profiles of tablets prepared from

TABLE 1

The effect of compression on the tapped density of granules

MATERIAL	APPLIED COMPRESSION PRESSURE (MNm^{-2})	TAPPED DENSITY (gcm^{-3})
D.C. Starch (100-160μm)	-	0.82
	23	0.86
	70	0.88
MCC (32-160μm)	-	0.34
	9	0.36
	28	0.42
DCP (32-160μm)	-	0.81
	9	0.94
	28	0.97
MCC raw material	-	0.37
	18	0.44
	46	0.55
DCP raw material	-	0.81
	18	1.29
	46	1.34
MCC 66% - DCP 33%	-	0.47
	18	0.65
	46	0.72
MCC 50% - DCP 50%	-	0.54
	18	0.72
	46	0.79
MCC 33% - DCP 66%	-	0.61
	18	0.83
	46	0.92

D.C. Starch. This excipient is known to compact by time dependent plastic deformation[7] and, therefore, it is not surprising that increasing the dwell time from 0.1 to 15 seconds during the initial compaction causes a 50% increase in the tablet tensile strength. However, re-compression of granules, obtained from tablets initially compressed at 23 and $70MNm^{-2}$, significantly

TABLE 2

The effect of compression on tablet porosity

MATERIAL	APPLIED COMPRESSION PRESSURE (MNm^{-2})	TABLET POROSITY		
		INITIAL	RECOMPRESSED (LOW INITIAL PRESSURE*)	RECOMPRESSED (HIGH INITIAL PRESSURE*)
D.C.Starch (100-160μm)	23	28.6	31.4	32.3
	47	12.8	22.6	23.0
	70	20.8	19.6	20.5
	93	19.9	18.8	19.7
	116	20.5	18.7	19.2
MCC (32-160μm)	9	51.8	51.6	49.1
	18	39.2	39.5	39.2
	28	32.6	32.7	32.6
	37	27.4	26.2	27.7
	46	22.6	22.6	23.2
DCP (32-160μm)	9	42.1	41.8	38.0
	18	37.8	35.1	33.1
	28	33.5	31.7	31.1
	37	31.4	29.3	28.4
	46	29.6	27.9	26.9

*The low and high initial pressures for D.C. starch are 23 and $70MNm^{-2}$ and for MCC and DCP are 9 and $28MNm^{-2}$.

reduces the tablet strength. Therefore, subjecting D.C. Starch to an increased dwell time has the opposite effect to that achieved by slugging and this finding conflicts with the hypothesis of Gunsel and Kanig[1]. It is also evident that granules obtained from compacts initially compressed at $70MNm^{-2}$ produce softer tablets compared with those obtained from compacts initially compressed at $23MNm^{-2}$. Khan and Musikabhumma[6] also showed a progressive decrease in the tensile strength of potassium phenethicillin tablets with an increase in the slugging pressure. Although an increase in dwell time from 0.1 to 15 seconds has been shown to improve the tablet strength during initial compaction, the effect of dwell time during re-compression is only marginal (Fig. 2). This can be explained by the change in

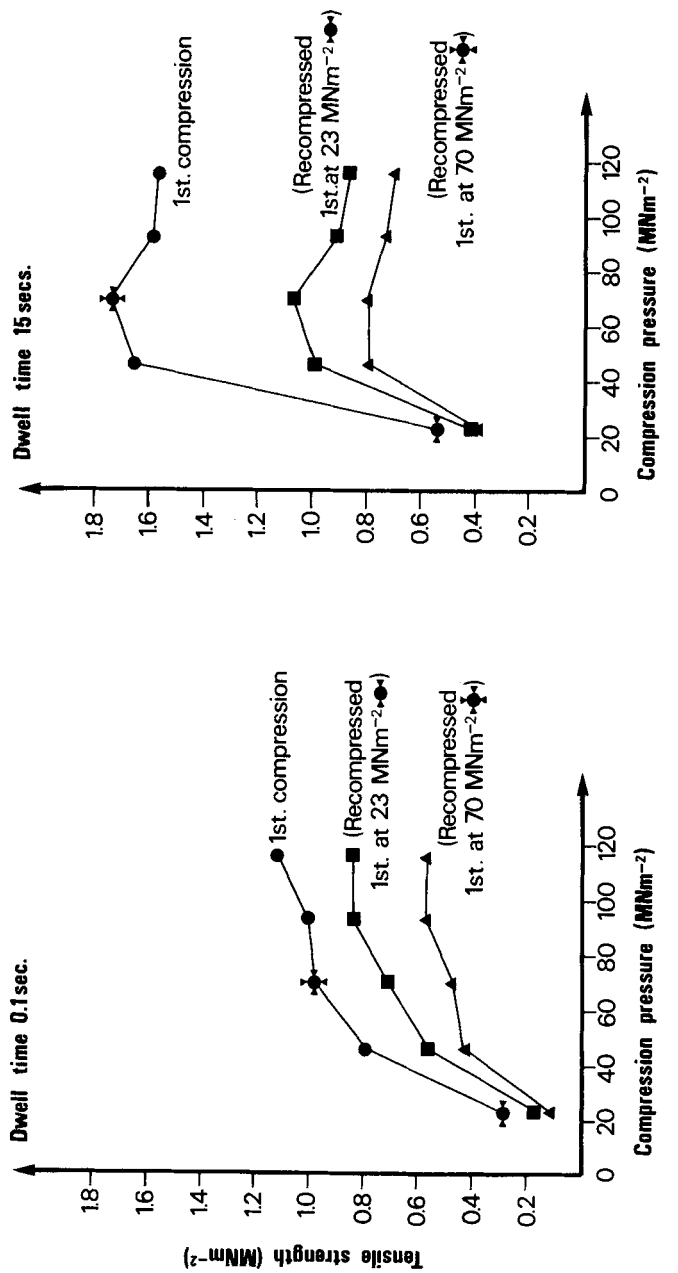

FIGURE 2

The effect of re-compression on the tensile strength/compression pressure profiles of D.C. Starch at two dwell times

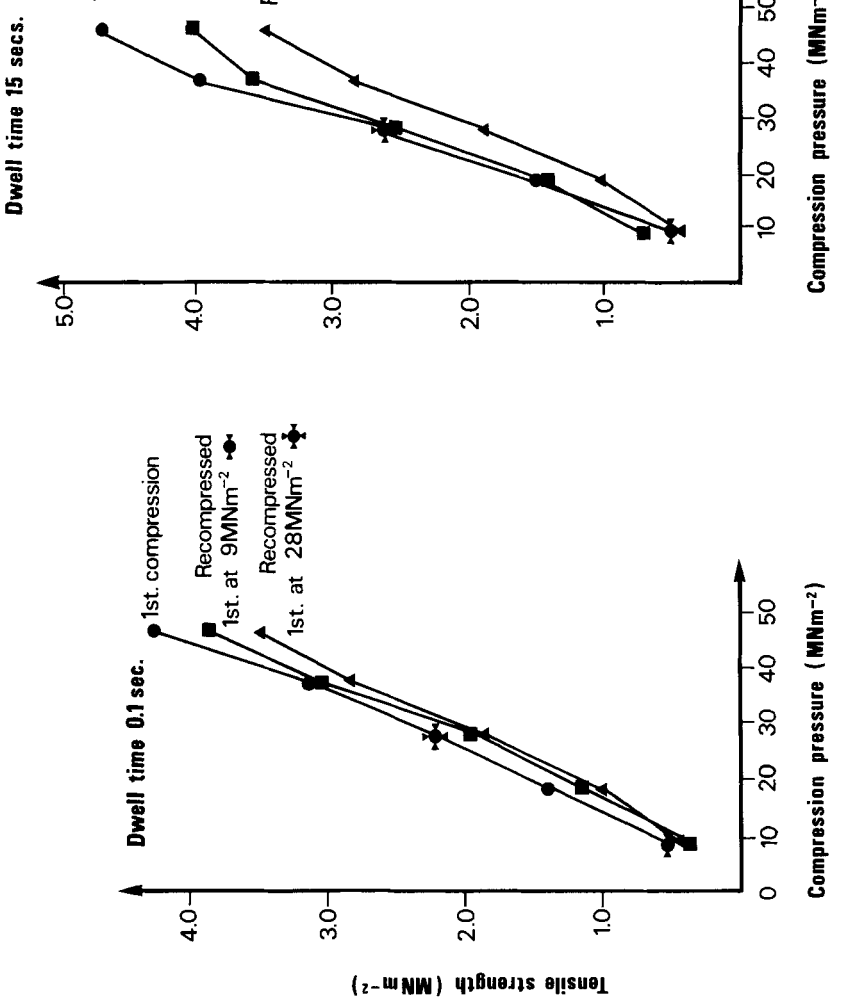

FIGURE 3

The effect of re-compression on the tensile strength/compression pressure profiles of microcrystalline cellulose at two dwell times

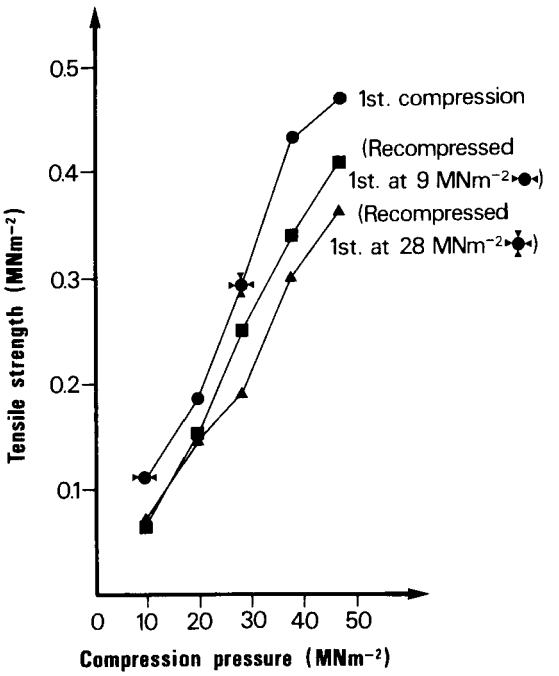

FIGURE 4

The effect of re-compression on the tensile strength/compression pressure profile of dicalcium phosphate dihydrate (dwell time 0.1s)

compaction mechanism of D.C. Starch from a plastically deforming to a more brittle material, which is less affected by an increase in dwell time.

Fig. 3 shows the effect of re-compression on the tensile strength/compression pressure profiles of tablets made from -32 + 160μm fractions of MCC at two dwell times. An increase in dwell time from 0.1 to 15 seconds enhances tablet strength although this increase is considerably smaller than D.C. Starch (Fig. 2). Re-compression,on the other hand, marginally reduces the tensile strength and although the magnitude of effect is different, both D.C. Starch and MCC demonstrate that an increased dwell time has the opposite effect to that of re-compression. The reason for the excellent re-workability of MCC has been

attributed to its fibrous structure, which undergoes significant plastic deformation on compaction[7].

The authors recognise that slugging is known to improve the compressibility of some formulations. However, the results presented in Figs. 2 and 3 cast doubts on the validity of the extended dwell time hypothesis[1]. It can also be argued that during slugging and subsequent milling, many bonds are broken and on re-compression new bonds are formed. Thus most of the initial bonds could not have been subjected to an increased compression time.

Fig. 4 shows the effect of re-compression on the tensile strength/compression pressure profile of tablets prepared from a sieve fraction of DCP. The compressibility of this excipient is not affected by changes in dwell time[8], but as for D.C. Starch and MCC, re-compression reduces the tensile strength of DCP tablets (Fig. 4). Similarly, tablets made from granules obtained from compacts initially compressed at $9MNm^{-2}$ are stronger than those prepared from granules obtained from compacts made at $28MNm^{-2}$. This further supports earlier claims that lower slugging pressures are likely to yield tablets of higher strength[6].

Fig. 5 summarises the re-working potential (see Fig. 1) of sieve fractions of D.C. Starch, MCC and DCP. A decrease in the re-working potential of these excipients is probably caused by work hardening, which is defined as "the resistance to permanent deformation of a material increasing with the amount of deformation". Aulton & Marok[9] have recently shown that the indentation hardness of some tablet excipients, including D.C. Starch and DCP, increases with increasing compression pressure. An indentation hardness index was determined, which had previously been used to estimate the work hardening of metals[10]. A graph of this index plotted against compaction pressure showed that both D.C. Starch and DCP were capable of being work

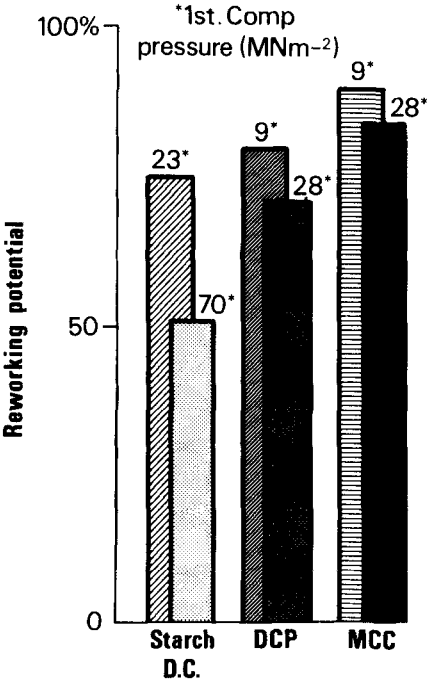

FIGURE 5

Re-working potential of direct compression excipients (sieve fractions)

hardened. It has been suggested that during plastic deformation, dislocations are generated at weak points in the crystalline structure of the materials[9]. These dislocations tend to increase upon cold working, which in turn increases the dislocation density and the potential energy of the dislocation lattice[9]. It, therefore, becomes more difficult to introduce new dislocations into the crystal structure, due to the raised energy levels of the dislocations already present, thus rendering the materials more resistant to further deformation. It is interesting that both plastically deforming (MCC and D.C. Starch) and brittle (DCP) excipients are capable of being work hardened.

Scanning electron photomicrographs of the direct compression excipients were taken and in most cases, no distinguishable

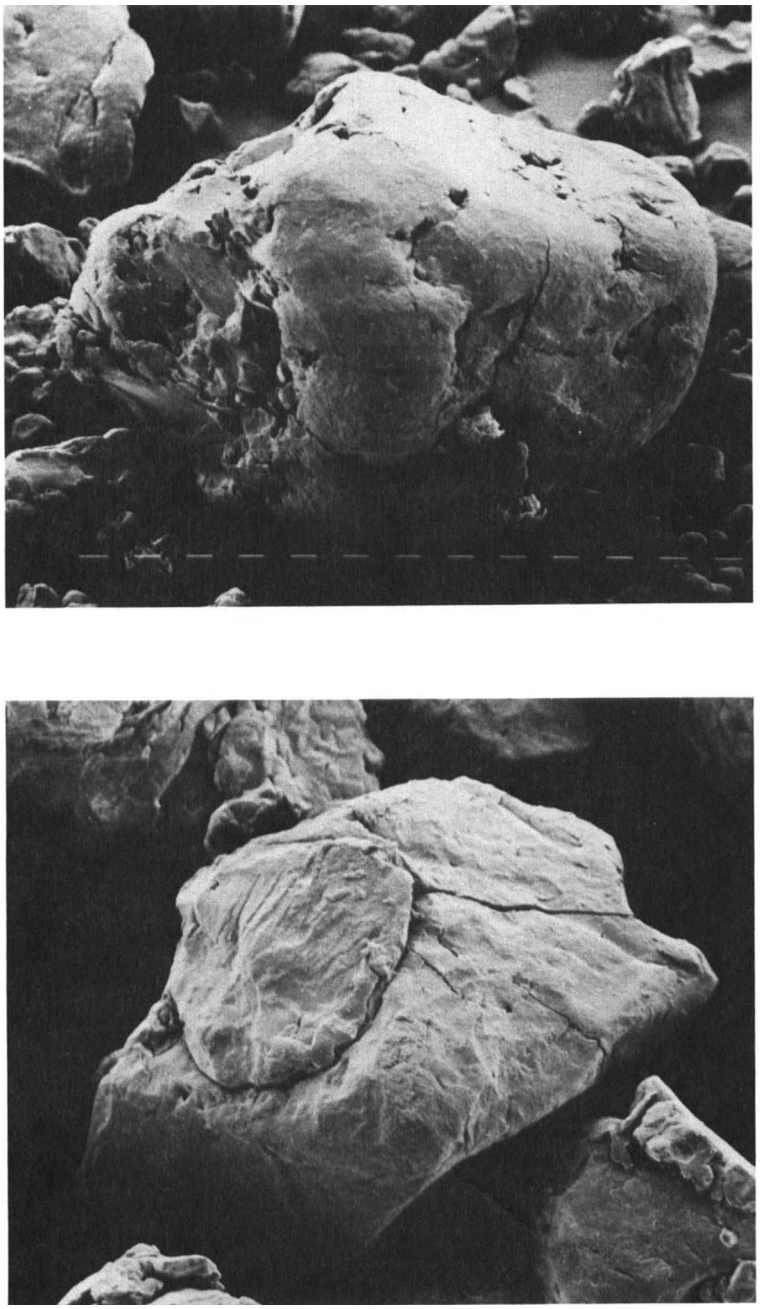

FIGURE 6

Scanning electron photomicrographs of D.C. Starch before (TOP) and after compaction at 70MNm^{-2} and milling (BOTTOM)

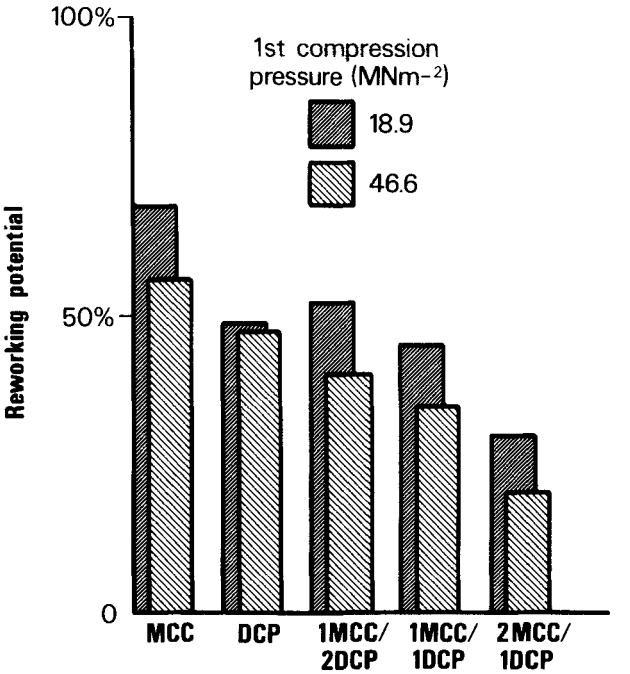

FIGURE 7

Re-working potential of microcrystalline cellulose and dicalcium phosphate dihydrate raw materials and their blends

differences in the granule structure before and after compression were revealed. However, some granules of D.C. Starch, obtained after milling the initial compacts, showed more cracks in their structure (Fig. 6) probably caused by elastic recovery and work hardening.

Fig. 7 shows the re-working potentials of MCC and DCP raw materials and their blends. The re-working potential of a blend of 2 parts MCC and 1 part DCP is considerably lower than that of a blend containing 1 part MCC and 2 parts DCP, although MCC itself has an excellent re-working potential (Figs. 5 & 7). This difference can be explained by the mechanism of compaction of these excipients. When a blend of 2 parts MCC and 1 part DCP is directly compressed, the strength of the compacts may largely be determined by the plastic deformation of MCC. However, on

re-compression the presence of DCP crystals on the dislocation areas of MCC fibres would be expected to reduce the extent of plastic deformation. At the same time, fragmentation of DCP may also be reduced by the cushioning effect of MCC and the net result of these factors will be a weaker, more friable compact. However, when the ratios are reversed i.e., (1 part MCC and 2 parts DCP) the re-working potential is virtually identical to that of DCP alone (Fig. 7). MCC in these granules is largely contaminated by DCP and thus, although work hardened DCP crystals still undergo some fragmentation, the contribution of MCC fibres to the overall strength of these tablets is now minimal. As may be expected, the re-working potential of the formulation containing equal parts of MCC and DCP is intermediate between the 2:1 and 1:2 blends.

Table 3 shows some typical results of the effect of re-compression on tablet friability. The friability of MCC tablets is unaffected, but there is a significant increase in the friability of systems containing DCP. The range of compression pressure ($9-116 MNm^{-2}$) used in this study produced rather friable DCP tablets, although these figures are indicative of flat faced tablets and the stringent test conditions[6]. Using the same test and flat faced tablets, Wells & Langridge[11] also found that the friability of DCP tablets compressed at $120 MNm^{-2}$ was 8.4% and decreased to 4.5%

TABLE 3

Effect of re-compression on the friability of tablets initially compressed at $47 MNm^{-2}$

RE-COMPRESSION PRESSURE (MNm^{-2})	FRIABILITY (%)			
	DCP	MCC	1 MCC/2 DCP	2 MCC/1 DCP
-	15	0.9	6.4	2.2
19	35	0.5	-	-
47	36.9	0.7	47.9	39.4
105	Sticking	1.4	-	-

for compacts made at 240MNm^{-2}. The friability values of tablets prepared from MCC/DCP 1:2 and 2:1 blends are 6.4% and 2.2% respectively (Table 3), but they increase to over 40% on re-working. Similar results are obtained when both the initial compaction and re-compression are carried out at significantly higher pressures. For example (not included in Table 3) tablets containing 2 parts MCC and 1 part DCP initially compressed at 108MNm^{-2} have a friability value of 3% which increase to 7% on re-compression at the same pressure. This is further evidence of work hardening of inter-particulate bonds yielding brittle tablets.

CONCLUSIONS

This study shows that re-working potential is influenced by the compaction behaviour of excipients. However re-compression properties of multi-component formulations may be difficult to predict. The compressibility upon re-working decreases with an increase in the initial compaction pressure, which implies that slugging at a high compaction pressure should be avoided. Since re-working of tablets may reduce their compressibility by work hardening, re-compression studies should be included in the process optimisation and validation programme.

ACKNOWLEDGMENTS

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