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Slugging and recompression characterisation of some blends of pharmaceutical excipients

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Abstract

Slugs of microcrystalline cellulose (MCC), dibasic calcium phosphate (DCP) and spray-dried lactose (SDL) were compressed, either on their own or in various combinations, between 12.7 mm flat faced punches on a single punch tabletting 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. This would indicate that the extent of plastic deformation is less when the materials are compressed twice, compared to when the materials 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; Spray-dried lactose

1. Introduction

Work hardening is an increase in resistance to permanent deformation of a material with the amount of deformation that the material is subjected to. Studies of this phenomenon have principally focused on single excipient systems. However, normally pharmaceutical tablets are produced using blends of powders. Rees and Rue (1978) demonstrated work hardening using sodium chloride and suggested that an increase in the number of dislocations are produced at weak

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points. This increase in dislocation density and thereby an increase in the potential energy of the dislocation lattice, makes it more difficult to introduce further dislocations into the crystal structure. It was suggested that this was due to the raised energy levels of the dislocations already present, rendering the material more resistant to further deformation. Langridge and Wells (1980) found a reduction in the compressibility of blends containing microcrystalline cellulose (MCC) and dibasic calcium phosphate (DCP) and attributed this to work hardening. Aulton and Marok (1981) showed that the indentation hardness of some tablet excipients, including Starch 1500, DCP, anhydrous lactose and MCC increased with increasing compaction pressure. This latter study showed that these excipients were capable of being work hardened. Malkowska and Khan (1983) examined the effects of re-compression on Starch 1500, DCP and MCC and found a reduction in the tablet strength, which they attributed to work hardening. However, work 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.

This study investigates if slugging can be considered to be just a method of increasing the dwell time or whether the process of work hardening is also involved. The literature indicates that little work has been carried out to investigate the phenomenon of work hardening with a range of excipients and blends. This study also examines the compaction characteristics of many popular pharmaceutical excipients.

2. Materials and Method

2.1. Materials

Fast-flo (spray-dried) lactose hydrous powder (Foremost Whey Products), dibasic calcium phosphate (DCP) anhydrous powder USP/FCC grade (FMC International, Little Island, Cork), Avicel PH 102 (MCC) powder (FMC International) 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 (Fielder) 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 rotating at 40 rpm for 10 min. Blends of 50:50, 75:25 and 25:75 ratios were produced in this way for each component system.

2.3. First compression (slugging)

Compression was carried out using a single punch tabletting machine (Manesty F-press) 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.

2.4. Slug characterisation

In order to generate compaction characteristics, measurements of the individual slug weight for each batch of the 10 slugs and their thickness was 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).

2.5. Second compression (tabletting)

The remaining slugs were screened through a Erweka oscillating mill granulator, utilising a no. 18 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).

2.6. Heckel analysis

The thickness data were sorted using a spreadsheet program and then subsequently utilised for

Heckel analysis (a measure of plasticity) employing the Heckel (1961a,b) equation:

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

where D is the relative density of the tablet at pressure P, K denotes a material constant which is the slope of the straightline region of the plot, the reciprocal of which is the mean yield pressure, and where A is the intercept of the straight line through the logarithmic axis (this being an indicator of particle arrangement at zero pressure if so required). Regression analyses were carried out over the whole pressure range for each Heckel plot and the mean yield pressure was determined for each batch of tablets produced. The relative density D was obtained utilising an air pycnometer (Beckman^{USA}), to give the true density D_o, and using the data already obtained the density of the compact D_a, was evaluated using Eq. 2:

$$D = D_a/D_o \quad (2)$$

3. Results and discussion

3.1. Slugging

Table 1 lists the crushing strengths at a compaction pressure of 65 MN m^{-2}. This shows trends that were generated over the whole pressure-crushing strengths range as noted with Fig. 1 (a, b). The data in Table 1 indicate that excipient systems containing MCC generally produced slugs with the greatest crushing strengths, over the complete pressure range utilised. This is probably due to MCC being a very plastic material as denoted by the low mean yield pressure value of 97 MN m^{-2}. Indeed, Fig. 2 indicates that the incorporation of MCC significantly reduces the mean yield pressure values and therefore brings about an increase in the plasticity of the blend. It therefore should follow that 100% MCC should produce slugs with the greatest crushing strength. This, however, as can be seen from Table 1 is not the case. An excipient blend of 75% MCC:25% DCP produces the highest crushing strength slugs. The graphs in Fig. 1 indicate that at higher pressures this result is even more pronounced. The excipient blend of 50% MCC:50% DCP also emphasizes the apparent strength of blends between these two excipients (Table 1). MCC is a material which is made up of hollow fibrils which collapse on compaction. MCC is thus a very plastic material with negligible elasticity. This explains to some extent why MCC blends have in general high crushing strengths. DCP, on the other hand, is a crystalline material which fragments on compaction, as shown by the high mean yield pressure value of 648 MN m^{-2}. It is therefore apparent that blends of a predominantly plastic material, such as MCC with a predominantly brittle

Table 1
Mean crushing strengths, standard deviations (S.D), and mean yield pressure values 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})	Correlation coefficient (R^2) (%)
100% MCC	16.06 (0.24)	8.94 (0.23)	97	98.75
100% DCP	2.38 (0.55)	0.50 (0.00)	648	95.2
100% SDL	3.14 (0.53)	2.28 (0.78)	210	95.4
75% MCC:25% DCP	18.60 (0.62)	9.94 (0.11)	156	99.9
50% MCC:50% DCP	15.38 (0.48)	9.28 (0.67)	465	97.2
25% MCC:75% DCP	5.46 (0.33)	4.02 (0.19)	381	96.4
75% MCC:25% SDL	12.60 (1.14)	6.00 (0.00)	110	96.5
50% MCC:50% SDL	9.40 (0.29)	3.50 (0.00)	111	93.2
25% MCC:75% SDL	4.56 (0.57)	3.08 (0.31)	98	98.4
75% DCP:25% SDL	3.70 (0.35)	2.40 (0.43)	213	95.75
50% DCP:50% SDL	4.16 (0.38)	3.12 (0.24)	398	96.3
25% DCP:75% SDL	5.78 (0.34)	3.16 (0.42)	271	97.3

material, such as DCP, yield very hard slugs. This could be due to an increase in surface area of DCP on fragmentation, which then allows an increased number of physical bonding sites for the other excipient to bind onto. The results indicate that maximum bonding efficiency occurs using the 75% MCC:25% DCP blend, as found by Garr and Rubinstein (1991).

SDL is a material which incorporates both plastic and fragmentatory forms of deformation (Roberts and Rowe, 1985). Inherently, it is brittle and fragments under compression. It is known to

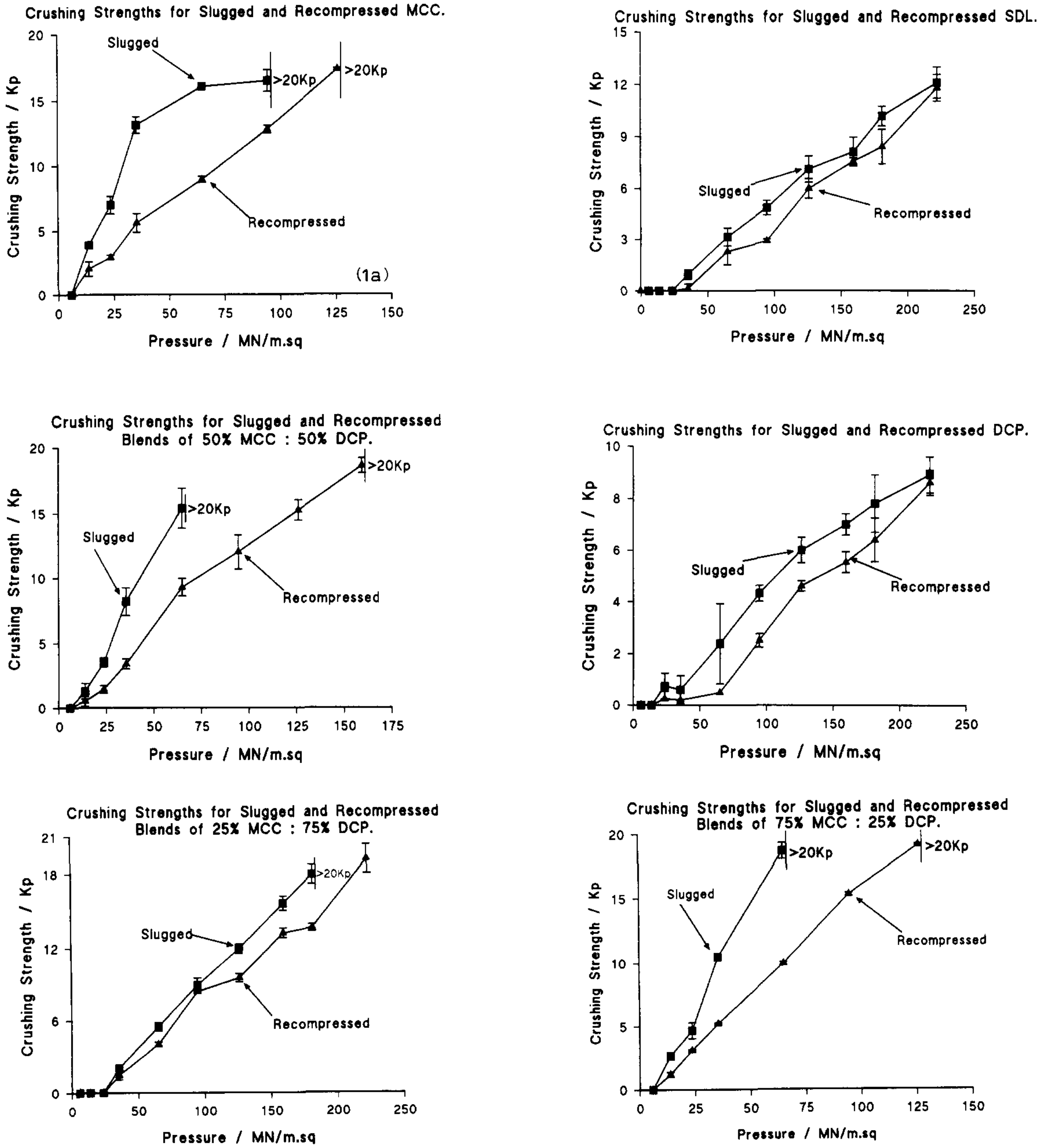

Fig. 1. Crushing strength vs compaction pressure plots.

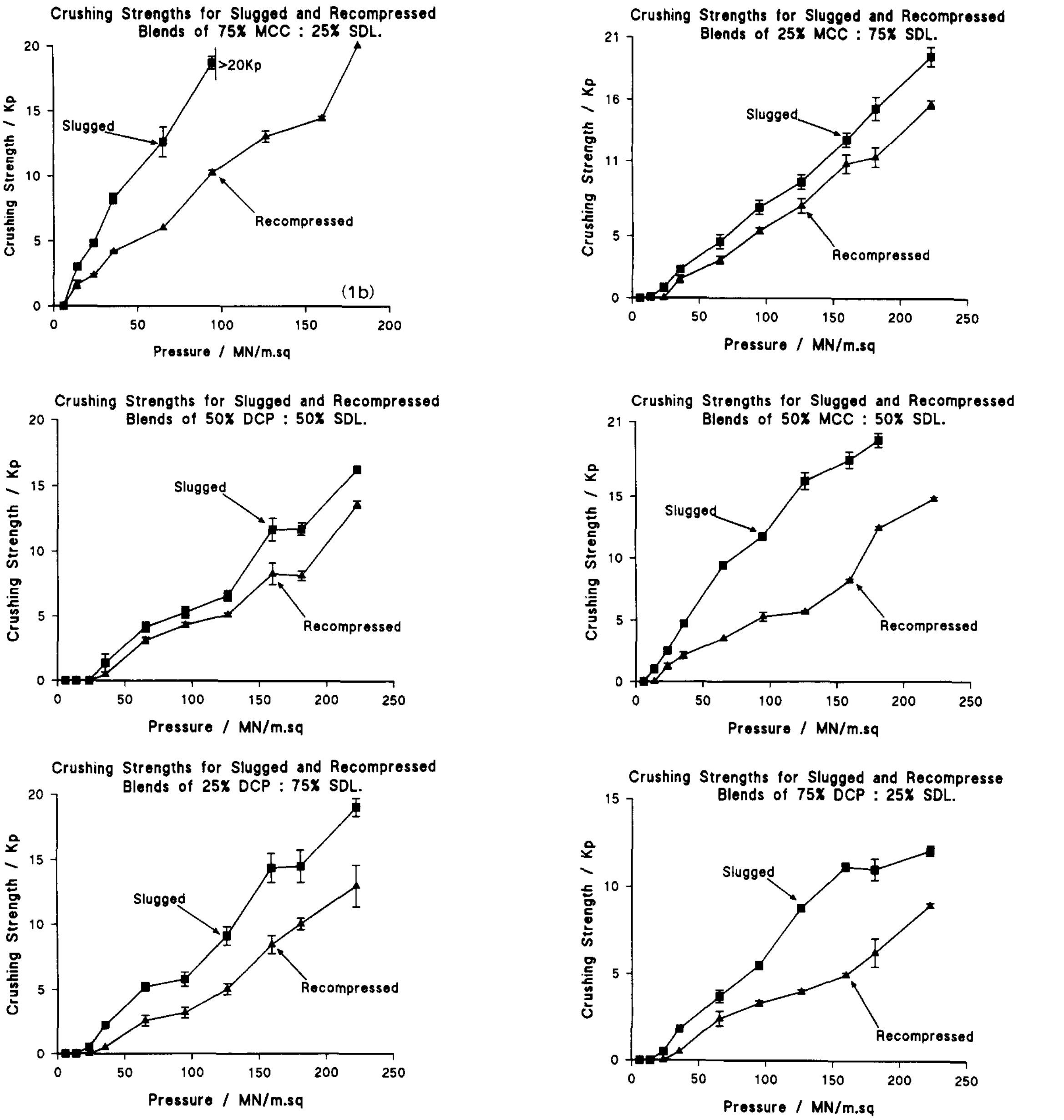

Fig. 1 (continued).

also be composed of amorphous material. Its brittle deformation behaviour probably accounts for its low crushing strength. As with DCP, 25% SDL in 75% MCC produces high crushing strength slugs. From Table 1, the mean yield pressure value for SDL (210 MN m^{-2}) indicates that it is less plastic than MCC (97 MN m^{-2}) and less fragmentatory than DCP (648 MN m^{-2}). Slugs containing SDL and MCC generally therefore exhibit lower crushing strengths (Table 1) than similar tablets containing DCP and MCC. However, corresponding mean yield pressure values indicate that SDL/MCC tablets exhibit greater plasticity than DCP/MCC tablets. It would therefore appear that fragmentation also plays a very important role in the formation of hard slugs.

Combinations of DCP and SDL generally have intermediate mean yield pressure values similar to that of 100% SDL with a value of 210 MN m^{-2}. However, the crushing strengths of the tablets of the DCP:SDL combinations exhibit the lowest values of all the tablet combinations. Since these tablets consolidate predominantly by fragmentation with little plasticity, this demonstrates that for strong particle to particle bonding and the production of hard tablets a high degree of plastic deformation under compression must occur.

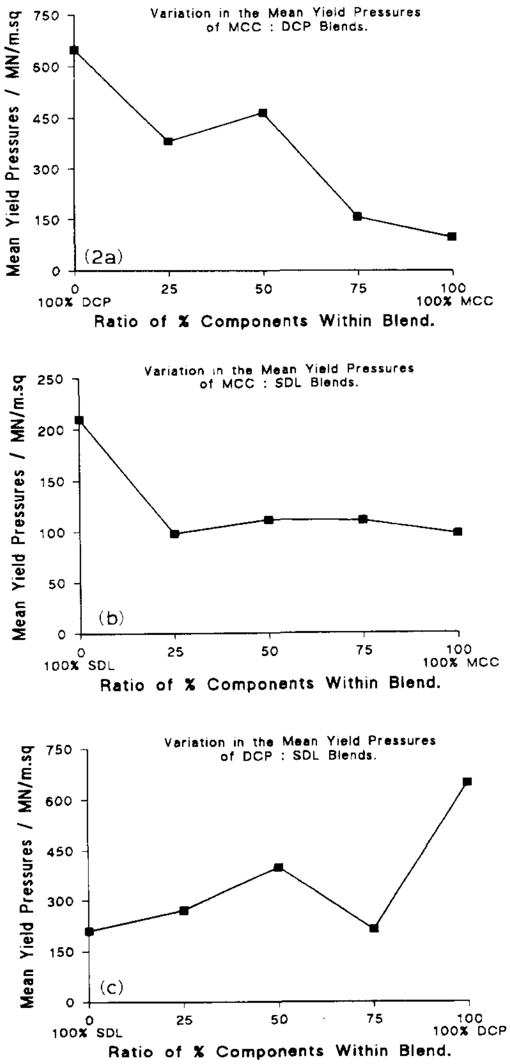

Fig. 2. Variation in the mean yield pressures.

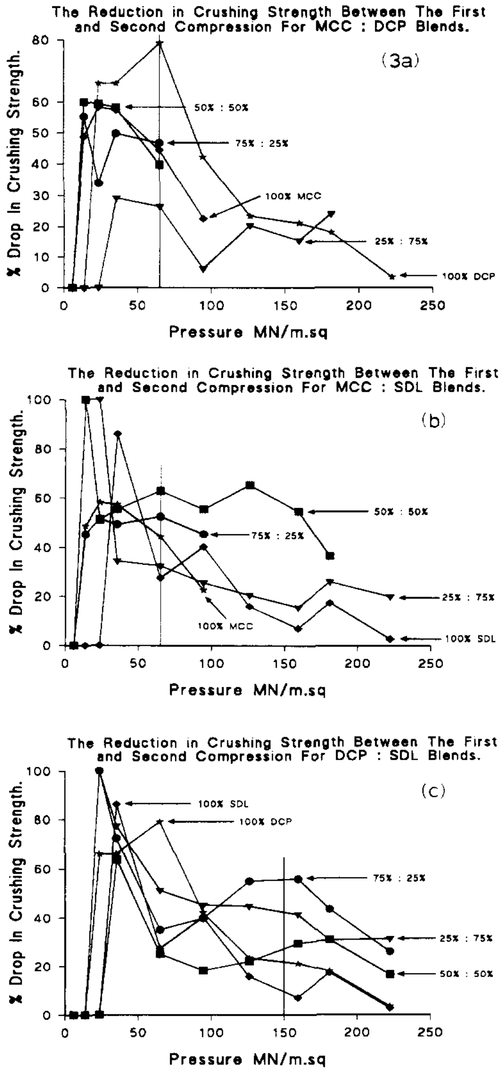

Fig. 3. Reduction in crushing strength between first and second compression.

3.2. Recompression

All excipients and blends, without exception, showed a reduction in crushing strength when compressed a second time, i.e., recompressed. Indeed, this reduction was greater than 50% for many of the blends, generally at pressures around 5O MN m^{-2} as shown in Fig. 3. Fig. 3 shows that the percentage reduction in crushing strength was greatest with the MCC:DCP blends, over a substantial part of the pressure range. These data also suggest that as the recompression pressure increases, there is a levelling off in the % drop in crushing strength, for all the blends. Those blends that exhibited high initial crushing strengths 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 and likewise 25% MCC:75% SDL show, in general, the least reduction in crushing strength over the specified pressure range. 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. The loss in working potential of the blend may be less pronounced with 25% MCC due to the release of fragmentatory energy of the other component being greater than the energy dissipated from plastic deformation, thus allowing the re-working potential to be retained.

4. Conclusions

It was found that maximum crushing strength of slugs was achieved using a combination of 75% MCC and 25% DCP. This combination produced the optimum degree of fragmention coupled with a high level of plastic deformation. However, there is a reduction in the crushing strength of the tablets after the second compression for all the materials investigated. This indicates that compressibility was not as profound when these materials were compacted twice. It is therefore suggested that the slugging process is independent of an increase in dwell time.

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