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Adjustment of precompression force to reduce mixing-time dependence of tablet tensile strength

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The dependence of tablet tensile strength on lubricant mixing time, pre- and main compression pressure was measured with microcrystalline cellulose, dicalcium phosphate dihydrate and starch 1500 on a rotary tablet machine. Loss of tablet tensile strength arising from lubricant overmixing can be substantially reduced in the case of microcrystalline cellulose by adjustment of pre- and main compression. This facility may be used in addition to or instead of reducing mixing time, or displacing lubricant by adding extra formulation components.

The dependence of tablet tensile strength upon lubricant mixing time has received recent attention (Bolhuis et al 1975, 1980). The most pronounced time-dependent reductions in tablet strength are unfortunately shown by the most common and most effective tablet lubricants such as di- and trivalent metal soaps, particularly magnesium stearate. The phenomenon appears to arise from ordered mixing by adsorption of lubricant multi-layers to formulation or excipient particles (Hersey 1975; Bolhuis & Lerk 1981). This may lead to variation in batch-to-batch tablet hardness, a problem occasionally encountered in production with some formulations and arising from the difficulty in exactly reproducing mixing procedure.

Recent documented attempts to reduce the effect of mixing time on tablet strength include adding small quantities of competitive adsorbants of high specific surface, such as colloidal silica to reverse the effect (Ragnarsson et al 1979) or simply reducing mixing time (Bolhuis & Lerk 1981), the latter having the effect of omitting or adding less lubricant.

This study was carried out to examine the extent to which the use of compression properties of common excipients, and adjustment of machine speed, precompression and main compression forces, reverse, or ameliorate, mixing time-dependent reduction of tablet tensile strength arising from ordered mixing of magnesium stearate.

MATERIALS AND METHODS

Magnesium stearate (Durham Raw Materials Ltd, Durham, U.K.) was added in single lots of 0·5% by weight to 2 kg batches of dicalcium phosphate dihydrate, Emcompress (K. & K. Greeff Ltd, Surrey, U.K.), microcrystalline cellulose, Avicel PH102 (Honeywill & Stein Ltd, Surrey, U.K.) and starch 1500, Sta-Rx (Colorcon, Orpington, U.K.) and mixed at slowest speed (speed 1) in a Hobart model A120 planetary mixer, using a 'beater' blade. 20 g samples were removed for tableting after mixing for 0·5, 1, 2, 4, 8, 16 and 32 min.

The same excipients without lubricant were used as test samples, representing zero mixing time. Unlubricated dicalcium phosphate dihydrate was compressed with dies and punches pre-lubricated for individual tablets with a solution of stearic acid in chloroform.

Tablets were prepared with a rotary machine (Betapress Manesty Machines Ltd, U.K.) instrumented as described by Ridgway Watt & Rue (1979). Cylindrical dies and flat-faced punches of nominal diameter 10 mm were used to produce tablets of weight 300 mg ± 5 mg. Dwell and contact times were measured from recordings taken with a u.v. oscillograph (Type 6008, S.E. Labs, E.M.I. Limited, U.K.). Unless otherwise stated, machine speed was kept constant at 65 rev min^{-1} (=1050 tablet min^{-1}) although this was occasionally changed to examine the effect of variation of dwell and contact times. Tablet tensile strengths were determined from diametral crushing strengths (Fell & Newton 1970) obtained on a motorized hardness tester (G. B. Caleva Ltd, Ascot, U.K.).

RESULTS AND DISCUSSION

Figs 1, 2 and 3 show tensile strength – main compression pressure profiles of microcrystalline cellulose containing 0·5% w/w magnesium stearate, and their dependence upon precompression and mixing time. A decrease in tablet strength with increase in mixing

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time is shown, in general agreement with other work cited. In addition, increases in tablet strength with precompression, and an increased dependence of tablet strength on precompression with increased mixing time are apparent. At longer mixing times (Figs 2, 3) lamination and capping are also substantially reduced by precompression. At mixing times of 8 min and above, an increase in tablet strength by a factor of 3 is attainable by adjustment of pre- and main compression alone.

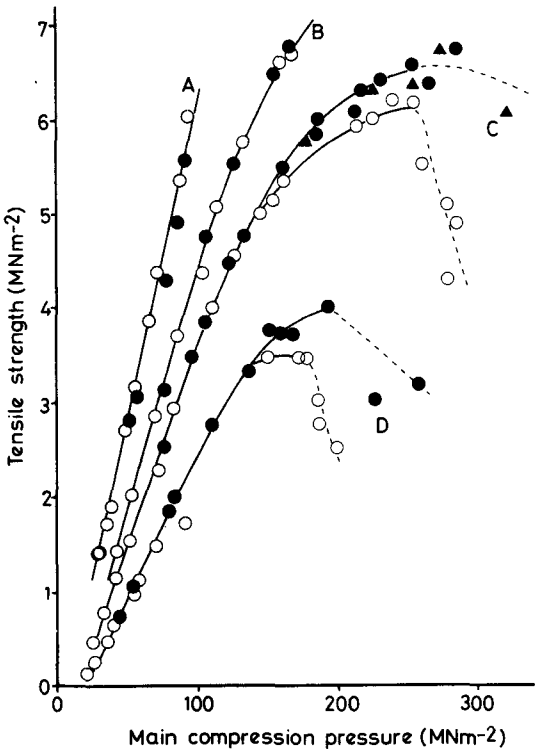
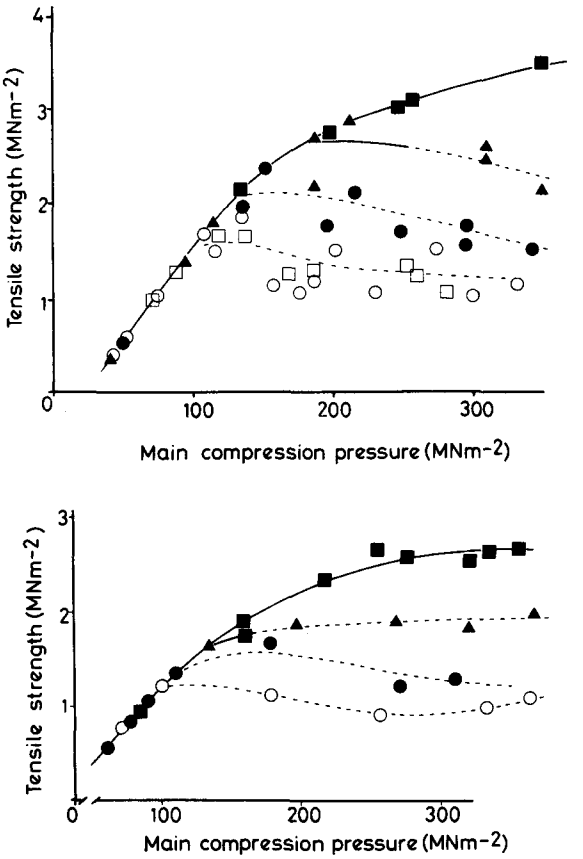


FIG. 1. Dependence of tensile strengths of 300 mg flat-faced tablets of microcrystalline cellulose containing 0·5% w/w magnesium stearate, upon precompression and main compression. Mixing times are (A) Zero, (B) 1 min, (C) 2 min, (D) 4 min. Tablet strength is invariant with precompression ≥ 25 MNm^{-2} at mixing times <4 min. For symbols, see Figs 2, 3.

No further significant reduction in tablet strength was observed after 16 min mixing, suggesting that the final state of ordered mixing had been attained by that time. The upper limit of advantageous precompression also appears to increase with mixing time from 13 MNm^{-2} at 2 min mixing (Fig. 1) increasing to 76 MNm^{-2} at 16 min (Fig. 3) and 102 MNm^{-2} at 32 min. These effects may be characteristic of plastic deforming materials, where compaction will cause gross changes in particle shape, producing new surface or dislocation areas essentially free or depleted of lubricant. Any increase in specific surface may be regarded as a function of a number of compression variables: dwell and contact times, machine speed, pre- and main compression pressures and pressure profile shapes, and time separation of



FIGS 2 and 3. Dependence of tensile strengths of 300 mg flat-faced tablets of microcrystalline cellulose containing 0·5% w/w magnesium stearate, upon precompression and main compression. Mixing times 8 and 16 min. Precompression values are ○ Zero; ● 13 MNm^{-2}; ▲ 25 MNm^{-2} and ■ 51 MNm^{-2}, all at 1050 tablets min^{-1}. □ Zero precompression at 760 tablets min^{-1}. Broken lines indicate visible incidence of lamination.

pre- and main compression events: these would be nearly constant for a given machine setting. The improvement in tablet strength brought about by the use of precompression may be due either to increased contact time as defined by Jones (1981), or

to time-dependent elastic relaxation occurring within the interval, separating the two compression events. Hiestand et al (1977) proposed, in the context of single compression, that freedom from lamination on ejection may depend upon the existence of time-dependent effects. It has also been suggested that expulsion of sufficient air may be a prerequisite with some formulations (Mann et al 1981).

In order to examine the role of increased contact and dwell times, another range of tablets was prepared without precompression, from the 8 min mix, at slower machine speeds (760 min^{-1}), increasing total contact times to those previously measured on preparing a full range of tablets with 51 MNm^{-2} precompression at a fixed speed of 1050 min^{-1} (70 ms). The quality (lamination) and tensile strengths of the tablets prepared at reduced speed without precompression were indistinguishable from those obtained without precompression at 1050 tablets min^{-1}. Thus, it appears that the improvement brought about by precompression (top and bottom curves Figs 2, 3) is not due to increases in dwell and contact time (20 ms) but to a significantly greater separation in time of two distinct compaction events (273 ms), possibly providing a longer interval in which time-dependent effects (stress relaxation and escape of air) may occur.

Starch 1500, in contrast, shows both a continuous decrease in tensile strength and a decrease in the effects of precompression, with increasing mixing time (Fig. 4). Tablets cannot be formed at mixing times of 8 min and above. Such physical incompatibility may be characteristic of more elastic or less malleable excipients or due to a lack of time-dependent relaxation, where little or no new surface is produced on compaction.

In addition, tablets prepared from a brittle-fracturing material, such as dicalcium phosphate dihydrate in the absence of other excipients, show virtually no mixing-time-dependent reduction in tensile strength and no precompression-dependent phenomena (Fig. 5). It would appear that with a brittle material a much increased cohesive surface area free of magnesium stearate contamination is formed during compaction by particle or aggregate comminution (cf. De Boer et al 1978).

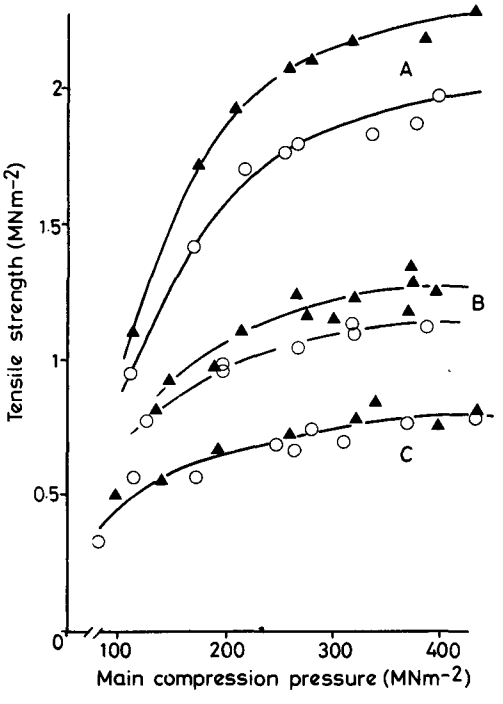


FIG. 4. Variation of tensile strength – main compression pressure profiles of 300 mg flat-faced starch 1500 tablets containing 0·5% w/w magnesium stearate, with precompression and mixing time of (A) Zero, (B) 1 min and (C) 2 min. Precompression values are ○ Zero; ▲ 76 MNm^{-2}.

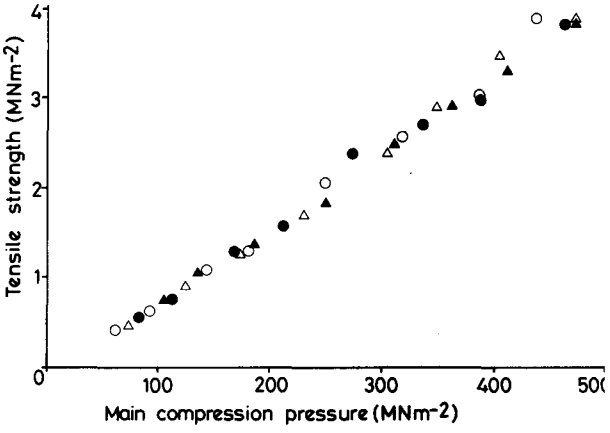


FIG. 5. Tensile strength – main compression pressure profiles of flat-faced 300 mg tablets of dicalcium phosphate dihydrate containing 0·5% w/w magnesium stearate. ○ and ●, zero and 78 MNm^{-2} precompression, 1 min mix. △ and ▲, zero and 78 MNm^{-2} precompression, 32 min mix.

Conclusion

Deterioration in tablet tensile strength due to lubricant over-mixing may be much reduced in some formulations by careful independent adjustment of main and precompression forces on a rotary tablet machine. This may lead to a much increased latitude (×4–8) of mixing time. Such effects, where present, appear to involve relatively long-term events (e.g.

stress relaxation and escape of air) within the compact occurring largely between the two separate compaction events. It is suggested that the improvement brought about by the use of pre-compression on a fast speed rotary machine is probably not due to increase in dwell and contact time.

REFERENCES

Bolhuis, G. K., Lerk, C. F. (1981) J. Pharm. Pharmacol. 33: 790

Bolhuis, G. K., Lerk, C. F., Broesma, P. (1980) Drug Develop. Ind. Pharm. 6: 15–33

Bolhuis, G. K., Lerk, C. F., Zulstra, H. T., De Boer, A. H. (1975) Pharmaceut. Weekbl. 110: 317–325

De Boer, A. H., Bolhuis, G. K., Lerk, C. F. (1978) Powder Technol. 20: 75–82

Fell, J. T., Newton, J. M. (1970) J. Pharm. Sci. 59: 688–691

Hiestand, E. N., Wells, J. E., Peot, C. B., Ochs, J. F. (1977) J. Pharm. Sci. 66: 510–519

Hersey, J. A. (1975) Powder Technol. 11: 41–44

Jones, T. M. (1981) Int. J. Pharm. Technol. Prod. Manuf. 2: 17–24

Mann S. C., Bowen, D. B., Hunter B. M., Roberts, R. J., Rowe, R. C., Tracy, R. H. T. (1981) J. Pharm. Pharmacol. 33: 25P

Ragnarsson, G., Hölzer, A. W., Sjögren, J. (1979) Int. J. Pharm. 3: 127–131

Ridgway Watt, P., Rue, P. J. (1979) Proc. Int. Conf. Pharm. Technol. Prod. Manuf. Copenhagen, December 1979