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PREDICTIVE STRESS TESTS IN THE SCALE-UP OF CAPSULE FORMULATIONS

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SUMMARY

In early development, supplies of bulk active are limited and capsule formulations are developed on a small scale. However they should be suitable for scale-up. In this report, the Turbula T2C is shown to mimic the prolonged stirring and stressing of powder blends in the large hopper of a dosator type machine, e.g. Zanasi LZ64. The degree of mixing affects the lubricity and wettability of capsule blends containing magnesium stearate and stressing powder blends in a Turbula T2C highlights changes in blend properties which occur on scale-up. Measuring tapped bulk density, wettability and disintegration of stressed blends identifies robust formulations which are unaffected by long "lubrication" times and scale. Changes in blend properties are influenced more by shearing energy than the extent of mixing.

INTRODUCTION

Scale-up of a formulation from development to production remains an inexact discipline. Proportionality does not apply; there are imposed equipment changes and the risk of failure and financial penalty increases with scale.

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We have therefore attempted to develop small scale tests (Davison & Wells, 1986), which pre-empt formulation weaknesses that only emerge on scale-up and long machine runs.

This paper deals with the scale-up of capsule formulations using simple stress tests without the need to encapsulate or run the filling machine for several hours.

MATERIALS AND METHODS

The materials used to produce the capsule blends were Lactose Fast Flo, mean particle size 120 μm (Foremost *ex* K & K Greef Ltd.), Lactose regular, mean particle size 85 μm (Lactochem) Starch 1500 (Colorcon), maize starch (Ceristar UK Ltd.), microcrystalline cellulose (Avicel PH101, FMC Corp.) mannitol (Roquette (UK) Ltd.), dibasic calcium phosphate (Rhone Poulenc (UK) Ltd.), magnesium stearate (Durham Raw Materials Ltd.) and colloidal silicon dioxide (Aerosil 200, Degussa). The formulations of the capsule blends are shown in Table 1. All blends were lubricated with 1% w/w magnesium stearate for 5 minutes in a Turbula T2C at 42 rpm prior to further mixing. Further mixing operations were performed in a Turbula T2C mixer (W.A. Bachhofen, Basle, Switzerland) at speeds up to 90 rpm. The effect of mixing time was determined by mixing 500 g blend aliquots at 42 rpm for up to 6 hours. At 0, 1, 2, 4 and 6 hours, samples of blend were removed and tapped bulk density, fluid penetration and disintegration times measured.

The effect of mixing speed was determined for selected blends by mixing 500 g blend aliquots for one hour at 20, 30, 42, 62 and 90 rpm.

TABLE 1

Capsule Blends % w/w

INGREDIENTS	BLENDS					
	A	B	C	D	E	F
Lactose Fast Flo	66	-	-	-	-	-
Lactose Regular	-	66	-	33	-	-
Starch 1500	33	-	-	-	-	-
Maize Starch	-	33	20	-	25	20
Avicel PH101	-	-	80	66	-	75
Mannitol	-	-	-	-	75	-
Dibasic Calcium Phosphate	-	-	-	-	-	5

Tapped Bulk Density

Tapped bulk density was determined using a scaled down version of BS 1460: 1967. An aliquot of blend was accurately transferred to a pre-weighed 10 ml measuring cylinder. The volume of powder was measured after 0, 5, 10, 15, 20, 25, 35 and 50 taps.

Fluid Penetration

Powder wettability was determined by the method of Wells and Walker (1983). The end of a glass syringe was loosely plugged with a small amount of cotton wool prior to packing the syringe with powder blend to a constant bulk

density corresponding to a 200 mg capsule fill weight (size 1), i.e. 0.4167 g/ml. The filled syringe was placed upright in a reservoir of water and the time taken for the water to penetrate to the top of the powder bed was recorded.

Powder blend was hand filled into size 1 opaque hard gelatin capsules to a fill weight of 200 mg. Disintegration time was determined by the method of the BP.

RESULTS AND DISCUSSION

The powder blends are common vehicles for capsule formulations. They can be divided into those blends which are cohesive and can be retained in the dosators without the need to tamp, but still have sufficient flow, e.g. B and E, and those which are extremely free flowing and compressible, so that limited tamping on a dosator type machine is adequate to produce an intact plug, e.g. A, C, D and F. Dibasic calcium phosphate in Blend F acts as a carrier in low dose capsule formulations, where an ordered mix is required to achieve dose uniformity. The good compressibility and flow of Blend A means that it is also suitable for the preparation of tablets by direct compression.

(i) Effect of Mixing Time

(a) Tapped Bulk Density

The effect of mixing time on the tapped bulk density of Blends A-F is shown in Figure 1.

Blends D and F show significant increases in tapped bulk density (TBD)

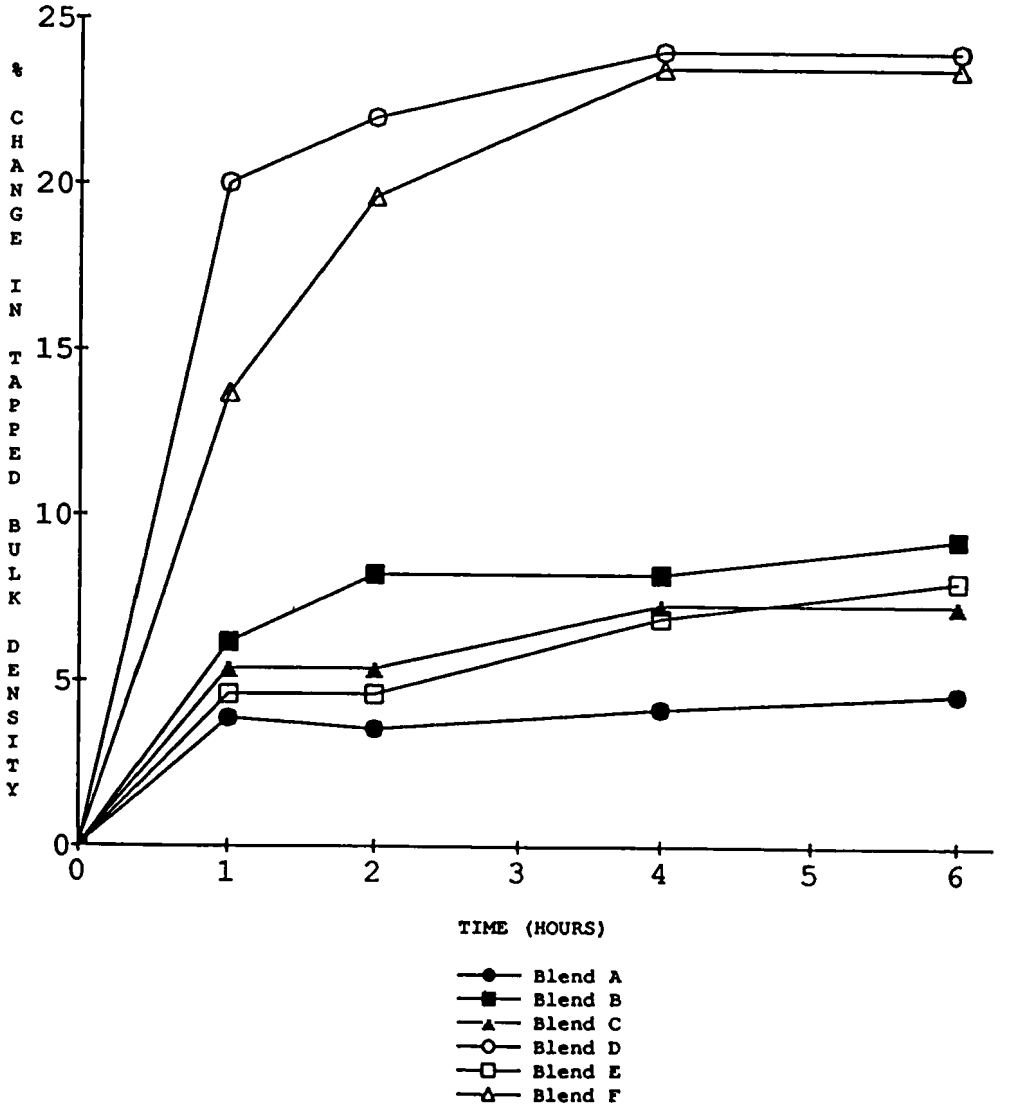

FIGURE 1

Effect of mixing time in a 2 litre Turbula on the tapped bulk density, tbd, (50 taps) of capsule blends

occurs after one hour of mixing, thereafter it plateaus. Despite these large changes in tested TBD, the consolidation properties, D_{50} (Hill & Wicks 1987) do not change significantly. The D_{50} value is the number of taps required to achieve a TBD equal to 50% of the maximum TBD. This can be related to the ease with which a powder bed can be consolidated. Hill & Wicks (1987) found that blends with D_{50} values less than 15 taps would run well and give acceptable capsule weight variation. All of the blends tested have D_{50} of less than 15 taps. Increased lubrication resulting from prolonged mixing will increase the rate of consolidation of a powder bed. However, this may be detrimental for certain blends as it reduces their cohesive properties compromising plug formation.

Blends C and E show a gradual sustained increase in TBD with mixing time, but that of Blend A does not vary significantly. The tendency for the TBD of powder Blends A, E and F to plateau may reflect shear induced deagglomeration of the magnesium stearate to yield particles which adhere or smear onto the excipient surface. Once formed, the surface cover on the excipient is unlikely to increase with further mixing.

(b) Fluid Penetration

Figure 2 illustrates the effect of mixing time on the rate of water penetration into powder beds of the capsule blends. The extent of lubrication of the blend increases with duration of mixing and is limited only by complete surface coverage of the excipients by magnesium stearate. Thus the hydrophobicity of the powder bed will increase with a subsequent decrease in wettability. All blends show a decrease in water penetration, the greatest change occurs with Blend C. During prolonged mixing, magnesium stearate may adhere to the hydrophilic surfaces of microcrystalline cellulose and starch and it

is this extent of distribution that is likely to have the greatest effect on wicking and wettability of the powder bed. With Blend A, maximum surface coverage of excipient appears to occur after two hours mixing, and the rate of fluid penetration reaches a plateau. Blend F differs from Blend C by the inclusion of dibasic calcium phosphate (DCP) yet this has a significant effect on the wettability of these formulations. The abrasive nature of DCP may cause deagglomeration of other excipient particles during mixing exposing new surfaces for lubricant coverage.

(c) Disintegration

Figure 3 shows the effect of mixing time on disintegration of Blends A to F. Comparison of these results with that of Figure 2 shows that a decrease in wettability is associated with an increase in disintegration for powder beds packed to the same bulk density. The process of disintegration of solid dosage forms requires two consecutive steps. Fluid penetration followed by particle separation. We have therefore used the capillary penetration of a packed bed, applying a modified form of the Washburn equation (1921), to simulate the first step in disintegration as shown in Figure 2. There is a qualitative relationship between increases in disintegration time with mixing and a corresponding decrease in fluid penetration. Only one formulation shows a close correlation (Blend C) since measuring fluid penetration does not monitor particle separation rates, which will dictate the actual time taken to disintegrate. However overall, the results obtained demonstrate a mixing time dependent change in TBD, fluid penetration and disintegration performance which is influenced by the formulation.

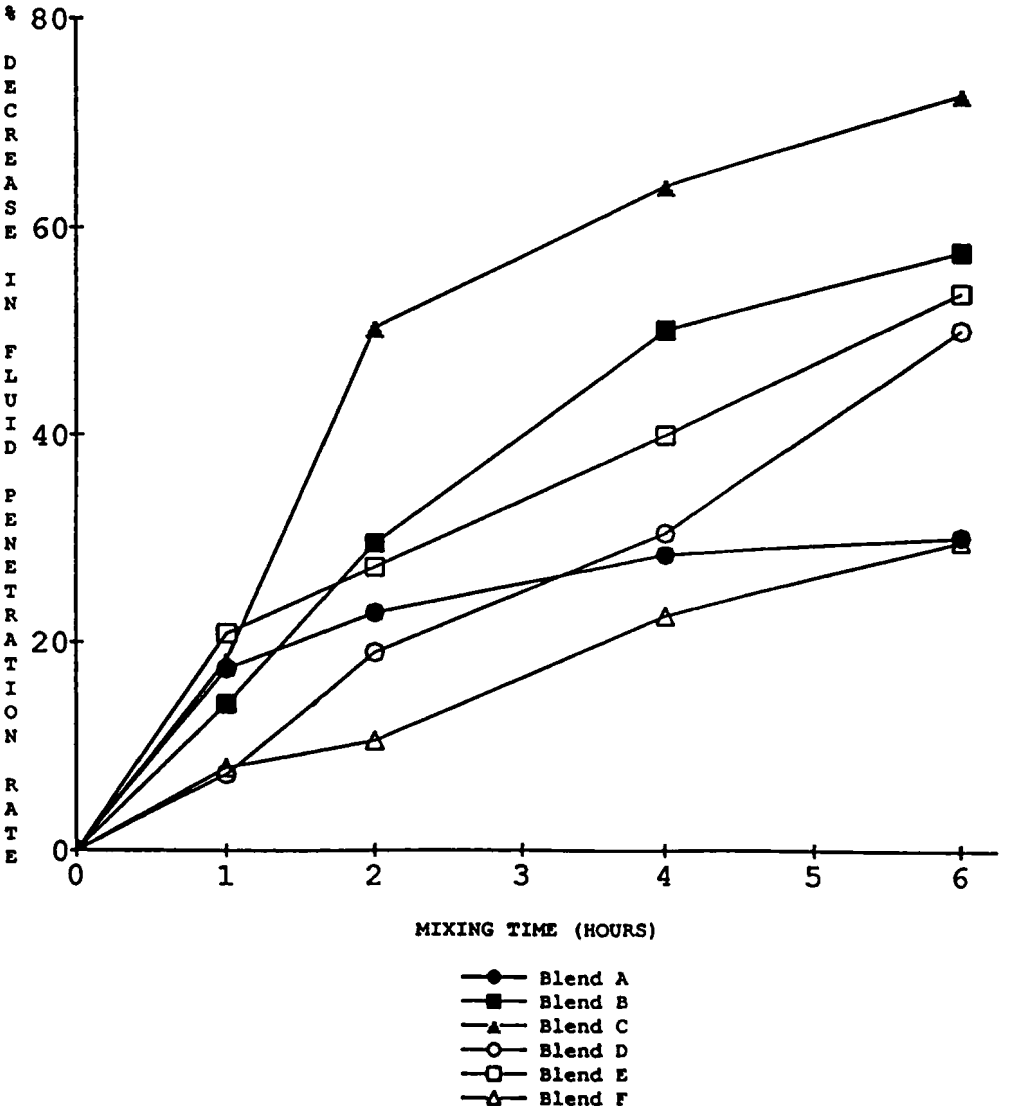

FIGURE 2

Effect of mixing time on the percentage decrease (from initial) in rate of fluid penetration into powder beds of different capsule blends

(ii) Effect of shearing energy

The degree of mixing, both in duration and shearing energy will affect the lubricity of the powder blends and liquid penetration rate. The first part of this work concentrated on the effect of duration of mixing. This has been extended to relating changes in blend properties to the input of energy (rotation speed) of the Turbula, to optimise the mixing time necessary to highlight changes occurring on scale-up since it is the kinetic energy rather than extent of mixing which is critical. 500 g aliquots of Blends A, E and F were mixed in a Turbula at 20, 30, 42, 62 and 90 rpm for one hour and TBD, fluid penetration and disintegration time were monitored as described previously. The flow properties and wettability of Blend A, a compressible vehicle, does not vary significantly with duration of mixing at 42 rpm. Blend E is a cohesive vehicle. Blend F, a ternary mixture, shows significant changes in TBD with prolonged mixing.

(a) Tapped Bulk Density

Davison and Wells (1986) showed that the efficiency of the Turbula T2C simulates the energy of mixing in large scale blenders.

The effect of mixing speed on the lubricity of the three blends is shown in Figure 4. The significance of the kinetics of mixing is evidenced by comparison of Figures 1 and 4. Changes in the kinetic energy of the system (speed of rotation) highlight differences between the blends. The TBD of Blend A is unaffected by extent and energy of mixing. Changes in TBD of Blend F plateau after mixing for one hour at 62 rpm compared with 4 hours at 42 rpm. Increased speed of rotation produces a gradual increase in lubricity of Blend E.

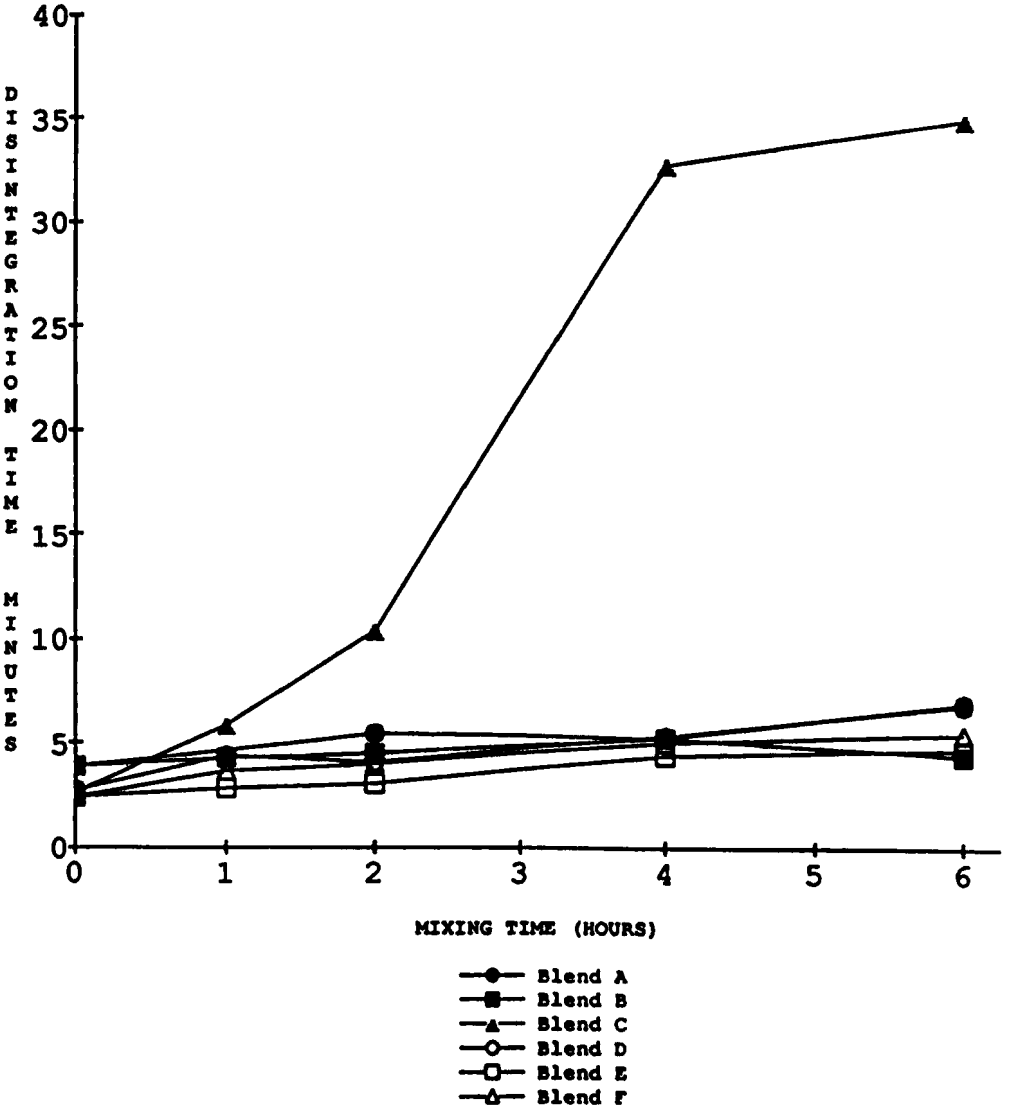

FIGURE 3

Effect of mixing time in a 2 litre Turbula on the disintegration of powder blends hand filled into capsules

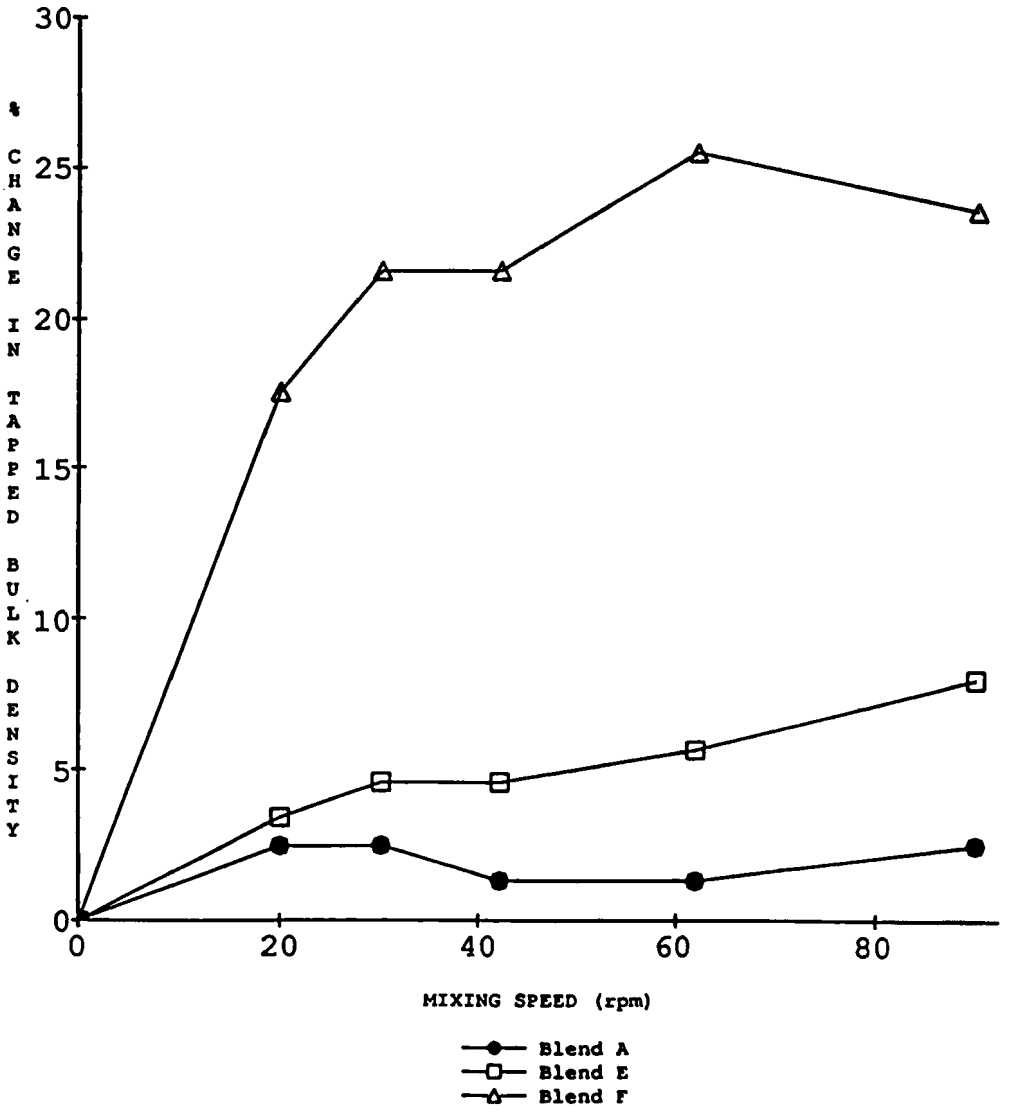

FIGURE 4

Effect of speed of mixing in a 2 litre Turbula on the tapped bulk density, tbd, (50 taps) of capsule blends

(b) Fluid Penetration/Disintegration

Figure 5 illustrates the effect of mixing speed on powder wettability. The hydrophobicity of Blends E and F increases with shearing energy, as reflected by a large decrease in wettability. For blends A and F there is a close correlation between hydrophobicity and disintegration. Indeed increased energy of mixing has a more profound effect on disintegration of Blend F than duration of mixing (Figure 6).

(iii) Effect of Degree of Mixing on Similar Capsule Blends

These results demonstrate the ability of small scale stress tests to discriminate between diverse capsule blends and identify robust formulations, exemplified by Blend A. We have expanded this work to see if these tests are sensitive to small yet influential changes in formulation. Thus three similar capsule blends (Table 2) were evaluated.

500 g aliquots of Blends F, G & H were stressed by mixing in a Turbula T2C at 42 rpm for up to 6 hours. The effect of duration of mixing on TBD, fluid penetration and disintegration is shown in Figures 7-9.

As reported previously Blend F shows dramatic changes in lubricity with mixing time. The TBD of Blend H did not vary significantly with duration of mixing, however wettability and disintegration showed mixing time dependence. The flow properties and wettability of Blend G are not influenced by duration of mixing. Reduced levels of magnesium stearate plus Aerosil 200 (a glidant) improve the resistance of the formulations to mixing (*cf.* Blends G and F). However, the amount of brittle material(DCP) present in the

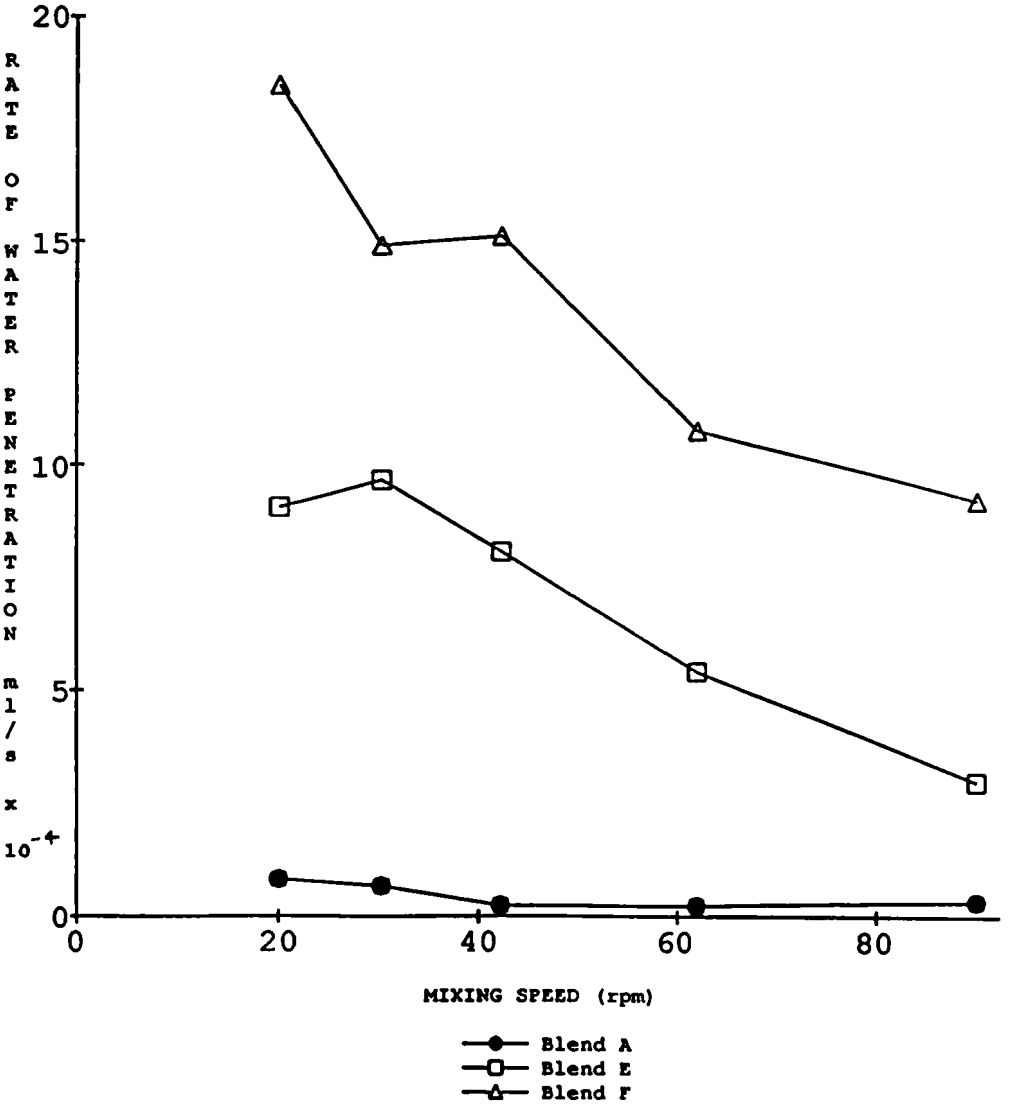

FIGURE 5

Effect of speed of mixing in a 2 litre Turbula on the rate of penetration of water into powder beds of different capsule blends

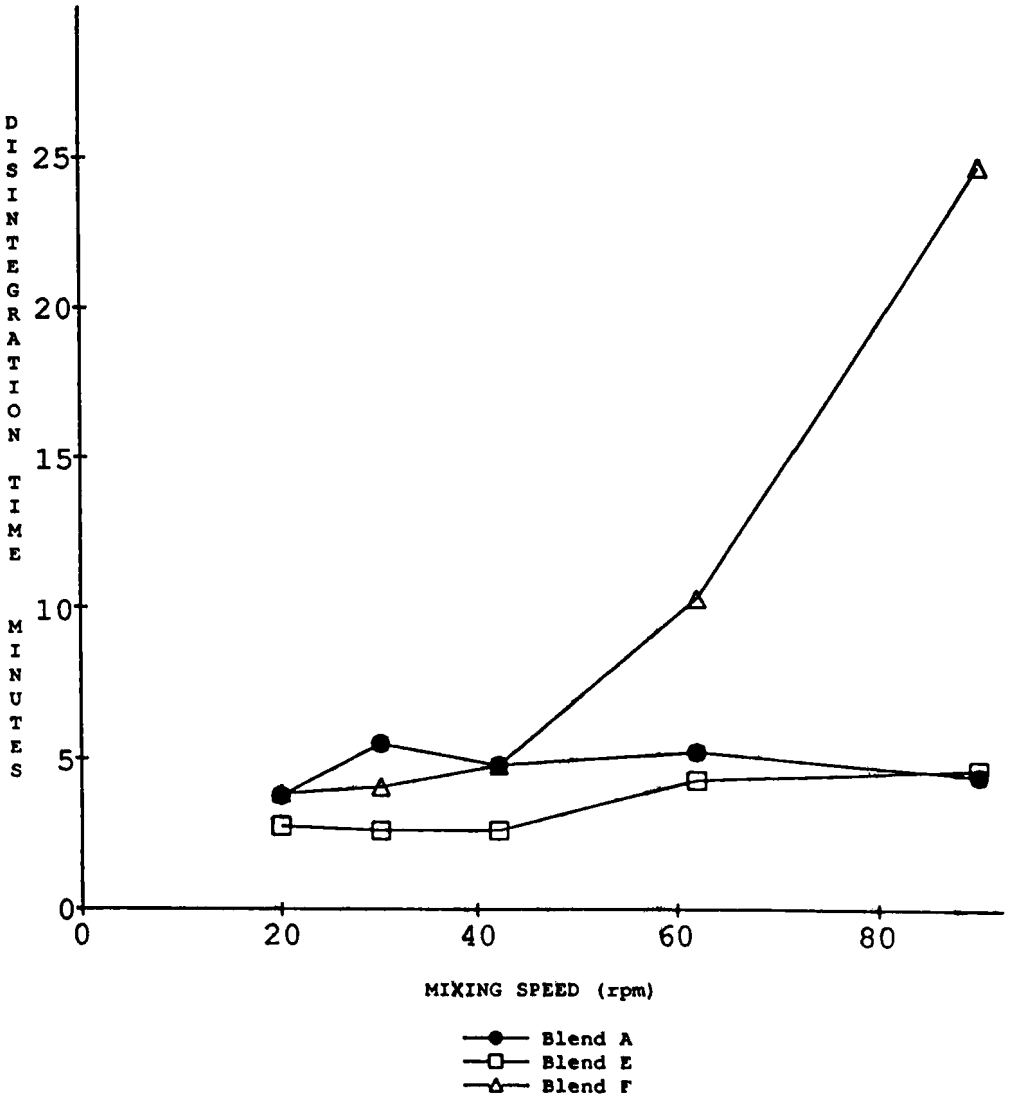

FIGURE 6

Effect of speed of mixing in a 2 litre Turbula on the disintegration of powder blends hand filled into capsules

TABLE 2

Formulae of Capsule Blends % w/w

INGREDIENTS	BLENDS		
	F	G	H
Dibasic calcium phosphate (DCP)	5	5	2.5
Maize starch	20	20	20
Avicel PH101	75	74.8	77.3
Aerosil 200	-	0.2	0.2
Magnesium stearate	1.0	0.5	0.5

formulation is of equal importance. Although changes in lubricity (TBD) are not evident for Blend H, wettability is reduced with extent of mixing. Lubricants such as magnesium stearate are known to have a greater negative effect on plastic excipients. To gain an understanding of the effect of changes in the parameters described on flow and filling properties of the blends, capsule fill weight variations were monitored. 500 g aliquots of Blends F, G and H were mixed in the Turbula T2C for 0, 1, 2, 4 and 6 hours. The timed samples were transferred to the small hopper of a Zanasi LZ64. The dosators were set to a known fill weight and were not re-adjusted throughout the filling process. The capsules were weighed at regular intervals during each run to determine weight variation and flow properties. The results are shown in Figure 10. The robustness of Blend G is evidenced in Figures 7-10. Although the TBD of

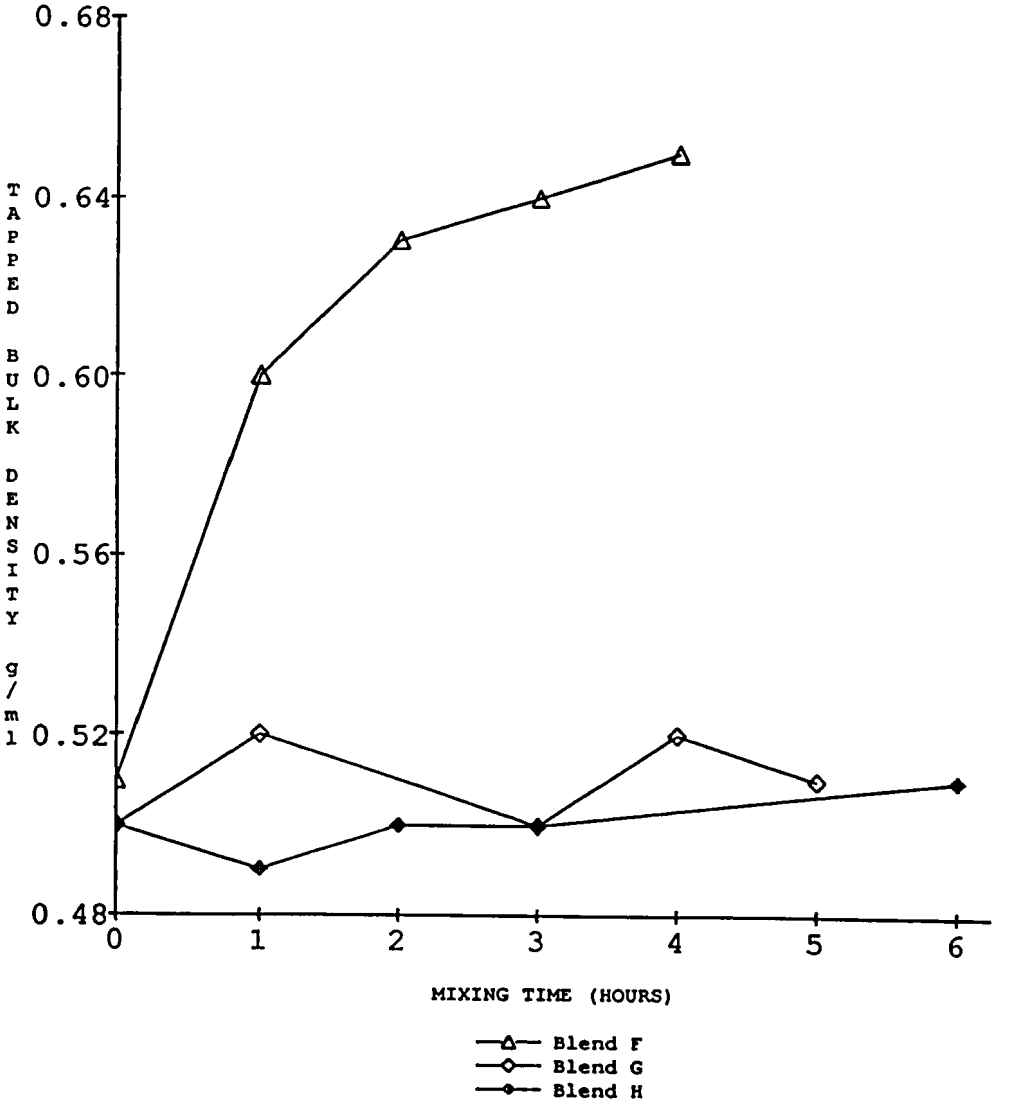

FIGURE 7

Effect of mixing time in a 2 litre Turbula on the tapped bulk density (50 taps) of capsule blends

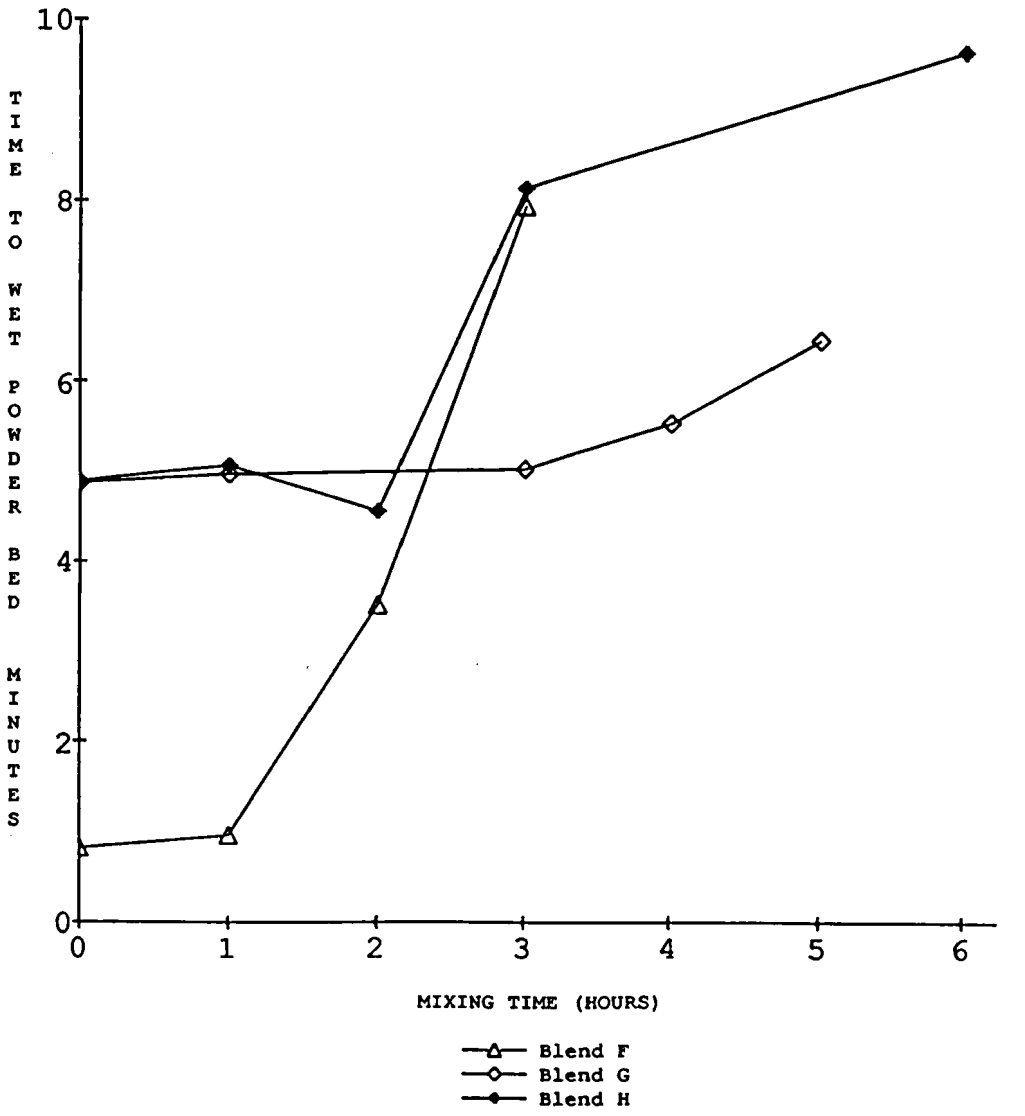

FIGURE 8

Effect of mixing time in a 2 litre Turbula on fluid penetration of capsule blends

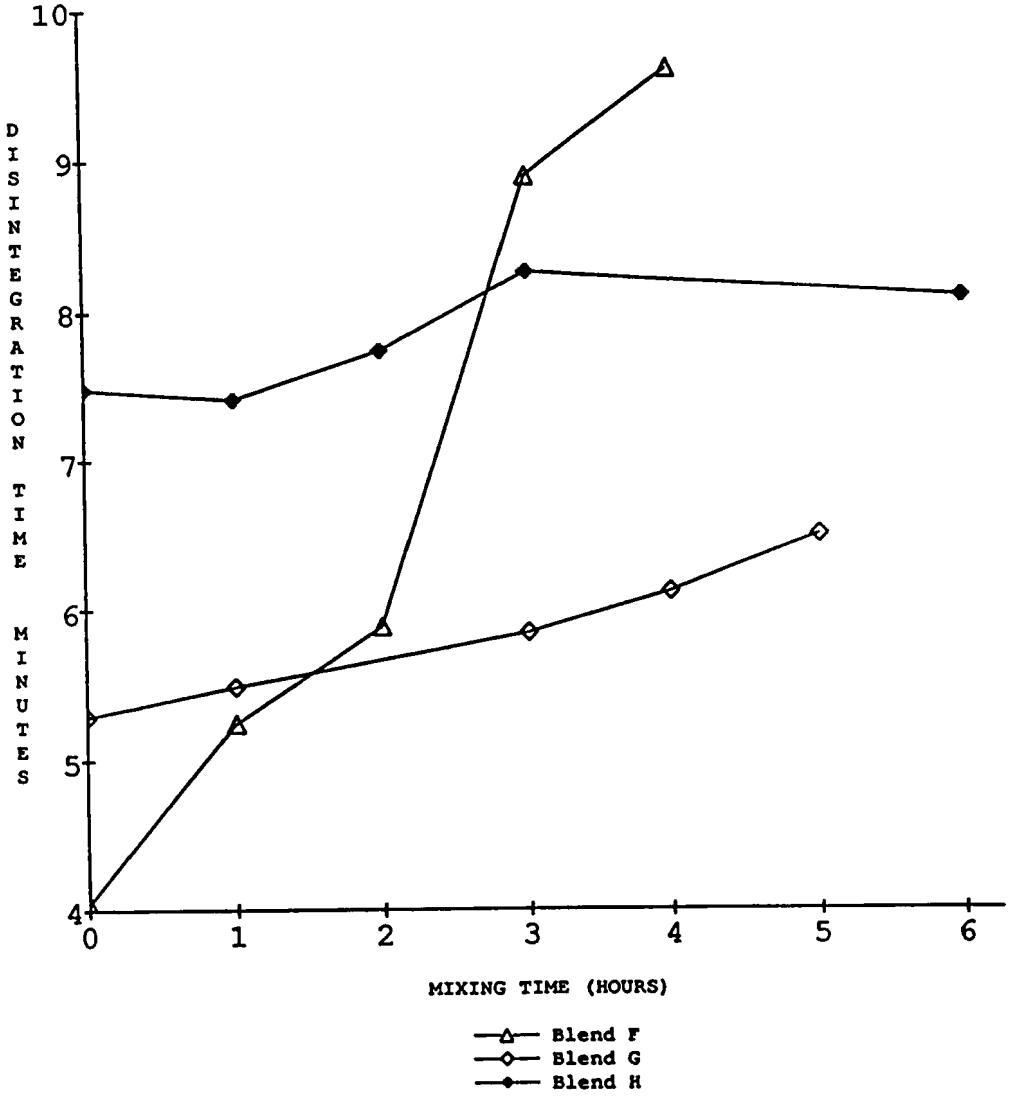

FIGURE 9

Effect of mixing in a 2 litre Turbula on disintegration of powder blends hand filled into capsules

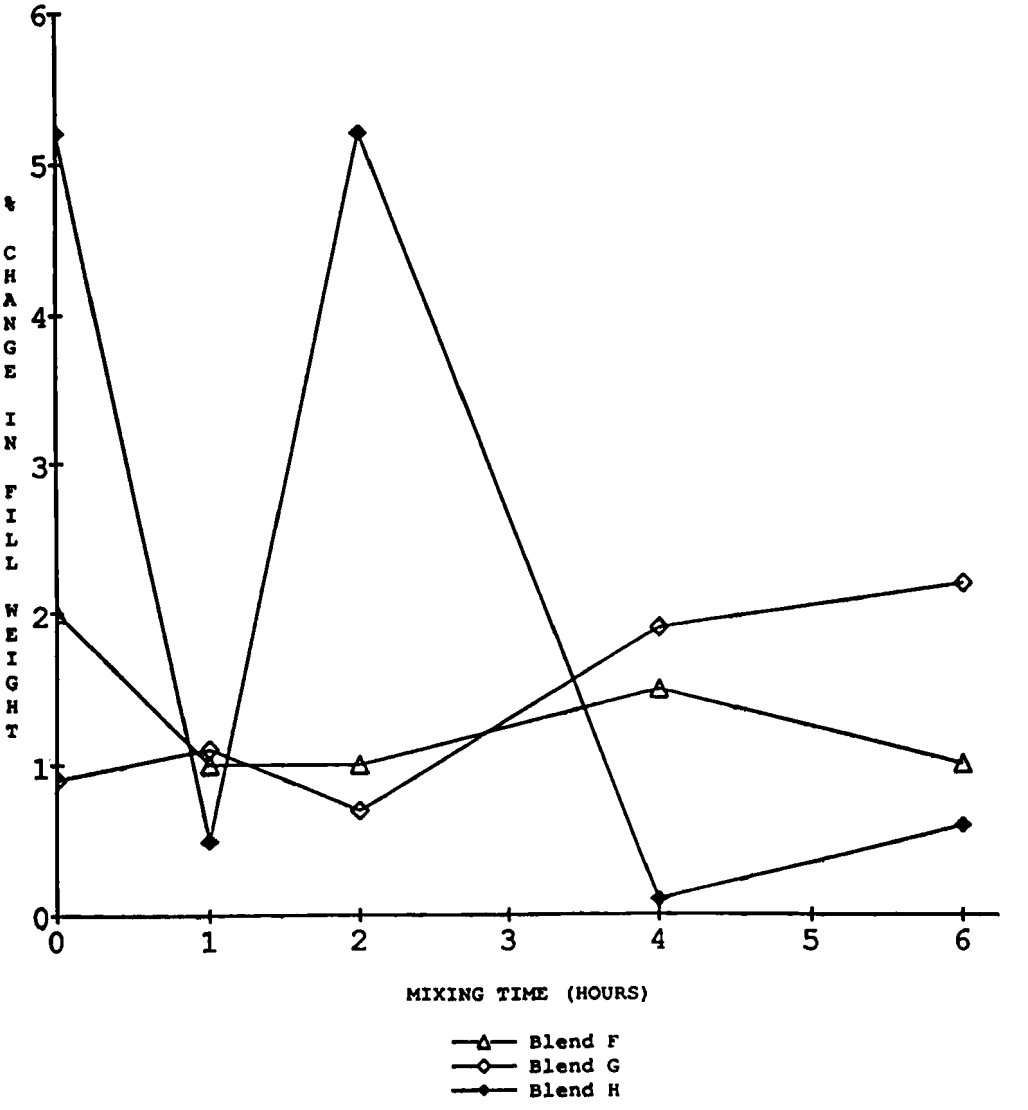

FIGURE 10

Effect of mixing time on weight uniformity of capsules during filling

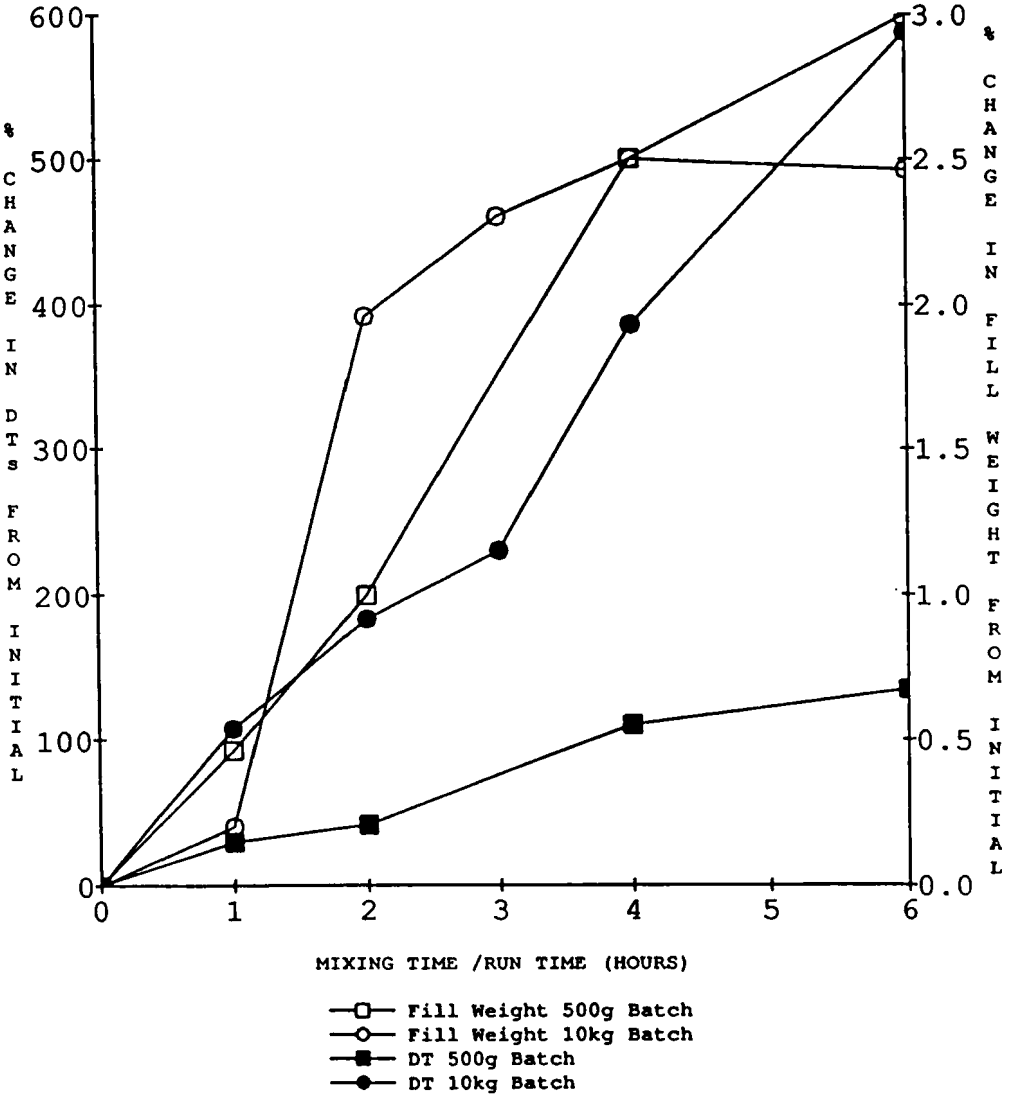

FIGURE 11

Comparison of the effect on encapsulation run time and Turbula mixing on disintegration and fill weight variation of 10 kg and 500 g batches of Blend F

Blend H did not change significantly with duration of mixing and is comparable with Blend G, its flow properties are unacceptable producing large fluctuations in capsule fill weight. In effect this blend flows too well. Examination of the results obtained demonstrate that these tests must be done in isolation - all of the parameters monitored must be investigated as a series to allow the selection of an optimum formulation.

(iv) Effect of Scale-up

To evaluate the validity of these small scale tests to blend performance on scale-up, the effect of encapsulation run time (on a Zanasi LZ64) and Turbula mixing on disintegration and fill weight variation of 10 kg and 500 g batches of Blend F were compared. The results are shown in Figure 11. There is a qualitative relationship between the changes induced by stressing in a Turbula T2C and the effect of long encapsulation run times on a dosator type machine.

The principal assumption made throughout this work is that mixing in the Turbula simulates stirring and agitation in the Zanasi LZ64 main hopper. However the Turbula could be "over-stressing" the powder blends highlighting changes in lubricity that may not be apparent when the blends are filled on the capsule machine. With Blend F this seems unlikely as the results obtained with these tests correlate well with the measured change in disintegration performance of a 10 kg batch. For Blend A, the stress tests show minimal change, confirming that the Turbula does not overstress the blends and therefore predicts changes in lubricity that may not be apparent until scale-up.

CONCLUSION

Magnesium stearate is an efficient lubricant, that is widely used in capsule and tablet formulations. However, it may have negative effects on blend properties, e.g. wettability, disintegration rate. The deleterious effect of magnesium stearate is not only dependent on the excipients and the lubricant concentration used, but greatly influenced by the kinetic energy and extent of mixing. During the mixing process lubricant particles adsorb on the excipient surface and with continued mixing distribute uniformly. Depending on input of energy this may be followed by delamination or deagglomeration (Shah & Mlodzeniec 1977). Such processes would result in maximum surface coverage. Once the adhered lubricant particles have delaminated the shear induced effects of continued mixing will not increase further. The nature and extent of surface coverage of the lubricant achieved by mixing will determine the strength or weakness of the consolidating forces and flow properties of blends. The extent of film formation is dependent on mixing time and mixing intensity (Lerk *et. al* 1977).

The purpose of this work was to develop small scale stress tests designed to pre-empt scale-up and long encapsulation runs on a Zanasi LZ64. Prolonged mixing on the Zanasi during encapsulation has been simulated on the Turbula T2C and shown to affect some formulations more than others. Attention is drawn to the large changes in blend performance induced by small changes in the formulation (Blends F, G and H).

In tumbling mixers the energy required to form an ordered mix is provided by shear forces within the blend (Bridgewater 1976). Our own work has shown that it is the kinetic energy input rather than the duration of mixing which is deleterious to certain capsule formulations (Figures 1 & 4). The

Turbula simulates the shearing energy of large scale blenders (Davison and Wells 1986). In general robust formulations, suitable for production, need to be unaffected by long lubrication times. Inclusion of brittle excipients, e.g. DCP may make powder blends more resistant to the adverse effects of "over-lubrication" (*cf.* Blends C & F), but the level is critical (*cf.* Blends G & H).

These generic stress tests have shown encouraging results and would seem to be applicable to early formulation development of capsule blends. Our results show that stressing in a Turbula T2C highlights changes in properties not only of diverse capsule blends (A-F) but also small differences in formulation (F, G & H). We have demonstrated that kinetic energy rather than extent of mixing is critical to emphasising changes in blend performance on scale-up. The predictive value of these tests is evidenced by the close correlation between changes in blend properties of a 500 g batch of Blend F stressed on the Turbula T2C (for 6 hours) and a 10 kg batch of the same formulation run on a Zanasi LZ64.

Studies are ongoing to examine the effect of glidant levels on stressed capsule blends as well as the capacity of formulations (shown by these stress tests to be robust) to incorporate high doses of poorly encapsulating drugs.

In conclusion, with low dose formulations or when the drug has little effect on blend lubricity (TBD), these stress tests facilitate the selection of capsule formulations for large scale manufacture.

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