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THE EFFECT OF MAGNESIUM STEARATE ADMIXING IN DIFFERENT TYPES OF LABORATORY AND INDUSTRIAL MIXERS ON TABLET CRUSHING STRENGTH

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SUMMARY

It is generally known that hydrophobic lubricants such as magnesium stearate can have a strong negative effect on the binding properties of directly compressible filler-binders. It was found that the decrease in binding forces is not only dependent on the tablet ingredients and the lubricant concentration used, but especially on the mixing time and mixing procedure. Most studies were performed, however with small laboratory scale mixers. In order to evaluate the effect of magnesium stearate admixing in different types of laboratory-scale and industrial mixers, the decrease in crushing strength

was measured for a test formulation during mixing with the lubricant in different mixers. The formula used consisted of 90% α-lactose monohydrate 100 mesh, 9.5% microcrystalline cellulose and 0.5% magnesium stearate. The mixers used were two laboratory scale mixers: a 2 litre Turbula mixer and a 13 litre cubic mixer and five production scale mixers: a 45 litre drum mixer, 90 litre, 200 litre and 900 litre planetary mixers and a 1.000 litre V-shaped mixer, respectively. For the test formulation used, it was found that the effect of lubricant admixing on tablet crushing strength was strongly dependent on type, size and rotation speed of the mixer used.

When operated at the same rotation speed, the decrease in crushing strength was much faster for the large industrial mixers than for the small laboratory mixers. These differences were explained by differences in shear forces during the mixing process and the efficiency of the mixing procedure.

For the industrial mixers the decrease of the tablet crushing strength as an effect of lubricant admixing was mainly determined by the rotation speed and only to a small extent by the type and size of the apparatus. Moreover no effect of load could be observed between the mutual industrial mixers used.

For a prediction of the effect of lubricant admixing on tablet crushing strength in large mixers, efficient laboratory mixers, operating at high rotation speeds can be used. For this purpose a 2 litre Turbula mixer is a valuable tool in preformulation work.

INTRODUCTION

Magnesium stearate is an efficient lubricant, that is widely used in tablet formulations. It may, however, have negative effects on tablet strength (1, 2) as well as on disintegration rate (2) and drug dissolution (3). We previously found that the deleterious effect of using magnesium stearate was not only dependent on the tablet ingredients and the lubricant concentration used, but especially on the mixing time and mixing procedure (4 - 7). This effect was explained by the formation during the mixing process of a lubricant film. This film interferes both with particle binding during compaction and with water uptake of the tablets (4, 8). This film is a result of adhesion to the substrate particles of magnesium stearate molecules, which are sheared off mechanically from the magnesium stearate crystals during the mixing process (4). The distribution and film formation of magnesium stearate can be characterized as an ordered mixing process (9). The extent of film formation is dependent on the degree of mixing i.e. mixing time and mixing intensity (5, 10, 11).

In contrast to the effect of magnesium stearate on tablet properties, Ragnarsson and Hölzer showed that its lubricating efficiency was only slightly or not correlated to the mixing time (12, 13). They even found that a short mixing time, which results in a poor distribution of magnesium stearate, does not impair the lubrication efficiency of the lubricant (12, 11). For this reason, in practice short mixing times are used when magnesium stearate is mixed with other tablet ingredients.

The influence of magnesium stearate on tablet properties has been investigated using different types of mixers and different mixing conditions (5, 14, 15). In all of these studies, however, small laboratory mixers were used. Mixing large volumes with the lubricant when producing tablets on a production scale will increase mixing and shearing intensity. Moreover, it has been shown by Malmqvist and Nyström (16) that the rate at which an ordered mix is formed, increases strongly when the batch size is increased. Therefore, it may be expected that the formation of a magnesium stearate film during mixing tablet ingredients with the lubricant proceeds faster in large than in small scale mixers and will depend on the type of the mixer used and its rotation speed.

This means that the tablet properties also will depend on the type, size, load and rotation speed of the mixer.

There are, however, very few reports of the effect of the scaling up of the lubricant mixing process on the tablet properties. In one recent publication Johansson (17) studied the effect of mixing with magnesium stearate on both lubrication and tablet properties using three different sized double-cone mixers. The results showed that the lubricating effect was not affected considerably by an increase in batch size. On the other hand, the negative effect of the lubricant on the tablet properties was more pronounced.

Aim of this study was a comparison of the effect of 0.5% magnesium stearate on the crushing strength of tablets compressed from a directly compressible blend, when lubricant admixing was performed in different types and sizes of mixers, operating at various rotation speeds.

MATERIALS

As a test formulation for the determination of the lubricant sensitivity during mixing, a blend of 9.5% microcrystalline cellulose (Avicel[R] PH 101, FMC Europe SA, Brussels, Belgium), 90% α-lactose monohydrate 100 mesh (lactose Ph. Eur.; DMV, Veghel, The Netherlands) and 0.5% magnesium stearate Ph. Ned. VI (Breyer Chemie, Venlo, The Netherlands) was used. This combination of excipients was chosen because of the combination of excellent tableting properties (18) and the sensitivity of both microcrystalline cellulose and α-lactose monohydrate to lubricant admixing (19).

EXPERIMENTAL METHODS

Microcrystalline cellulose and lactose were mixed during 30 min in different laboratory scale or production scale mixers. The laboratory scale mixers used were a 2 litre Turbula mixer

Table I. Type, capacity, load and rotation speed of the mixers used

Mixer and capacity		Load	Rotation speed
Turbula	2 L	0.3 kg	45 rpm, 90 rpm
Cubic	13 L	6 kg	20 rpm, 60 rpm
Drum	45 L	20 kg	10 rpm
Planetary	90 L	25 kg	25 rpm, 42 rpm
Planetary	200 L	100 kg	26 rpm
Planetary	900 L	250 kg, 450 kg	10 rpm
V-shaped	1.000 L	300 kg	22 rpm

(model 2P, W.A. Bachofen, Basel, Switzerland), and a 13 litre cubic mixer (Servipharm, Zwijndrecht, The Netherlands). The production scale mixers were a 45 litre drum mixer (J. Engelsmann, Ludwigshafen, W-Germany), a 90 litre planetary mixer, a 200 litre planetary mixer and a 900 litre planetary mixer, (Mach. Collette, Wommelgem, Belgium) and a 1.000 litre V-shaped mixer (Mondelaers, Brussels, Belgium). The load and rotation speeds used are listed in Table 1. After the addition of 0,5% magnesium stearate, the mixing procedure was continued. If not stated otherwise, magnesium stearate was sieved through a 1 mm sieve before addition to the blend. After 1, 2, 4, 8, 15 and 30 min samples were withdrawn with a grain thief. When using the Turbula mixer, however, no samples were taken, but for every mixing time a separate blend was prepared.

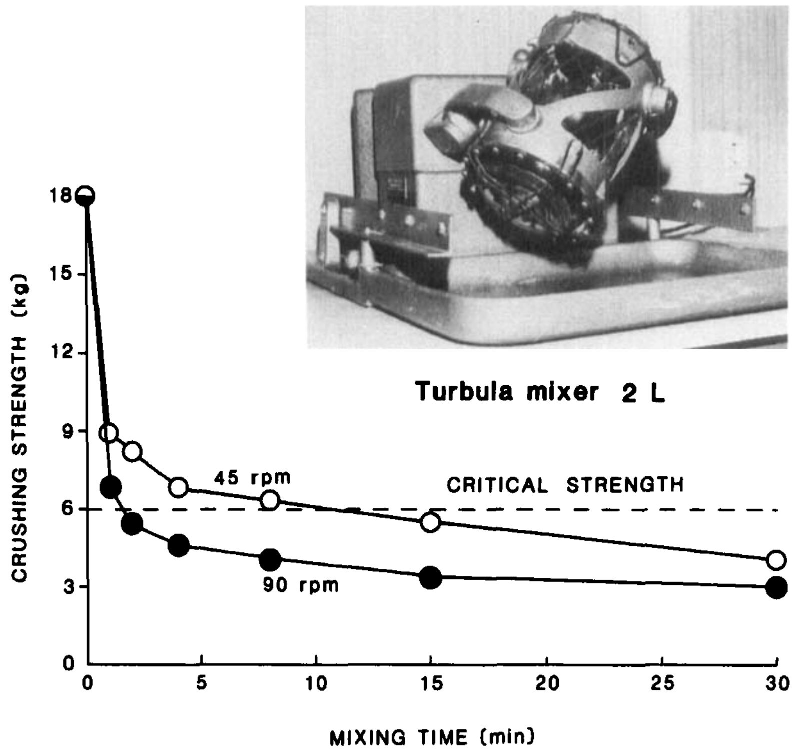

Figure 1

From the unlubricated blend and from the blends, mixed for different time periods with magnesium stearate, biconvex 9 mm tablets of 300 mg were compressed on a 6-station Korsch P.H. 106 rotary press (Korsch, Berlin, W-Germany) equipped with one die-and-punch assembly and five dummies. The compression load was kept constant for all the tablets prepared.

The tablet crushing strength was measured on a Schleuniger 4M apparatus (Dr. K. Schleuniger, Zürich, Switzerland). The data are given with a relative standard deviation and are the mean of 10 measurements.

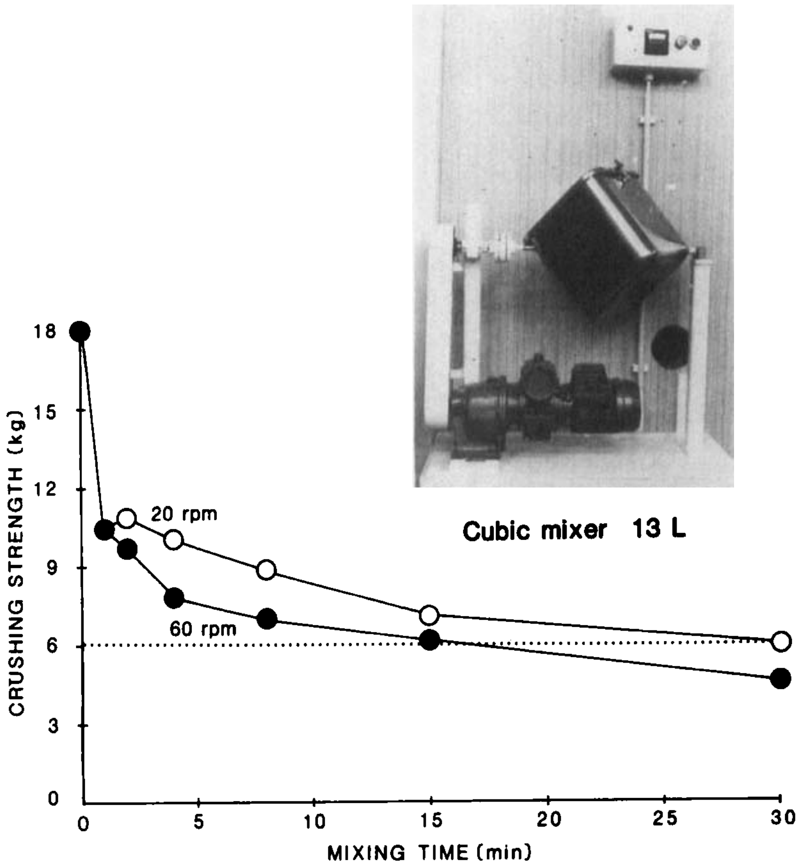

Figure 2

RESULTS AND DISCUSSIONS

Figure 1 shows the decrease in crushing strength of the lactose-microcrystalline cellulose tablets as a function of the mixing time with magnesium stearate for a 2 litre Turbula mixer at two rotation speeds. When a hardness value of 6 kg is arbitrarely chosen as a minimal acceptable level and the time after which the crushing strength falls below this level is defined as the critical mixing time, one can see that the critical mixing times were 1.5 min at 90 rpm and 10.5 min at 45

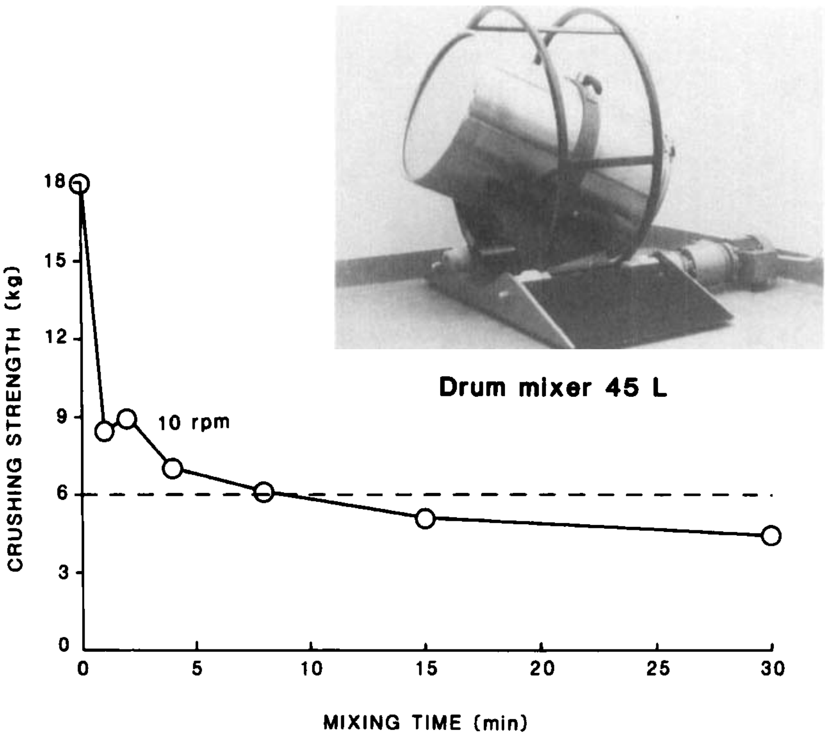

Figure 3

rpm. For a 13 litre cubic mixer (Fig. 2) these times were much longer: 17 min at 60 rpm and even 30 min at 20 rpm. For a 45 litre drum mixer at 10 rpm (Fig. 3), the critical mixing time was about 9 min. For a 90 litre planetary mixer (Fig. 4) a crushing strength of 6 kg was obtained after 2 min at 42 rpm and after 4 min at 25 rpm. For a 200 litre planetary mixer operated at 26 rpm (Fig. 5), the critical mixing time was 4 min and for a 900 litre planetary mixer at 10 rpm (Fig. 6) it was 8 min. Finally, for a 1.000 litre V-shaped mixer operated at 22 rpm (Fig. 7), the critical mixing time was 3.5 min.

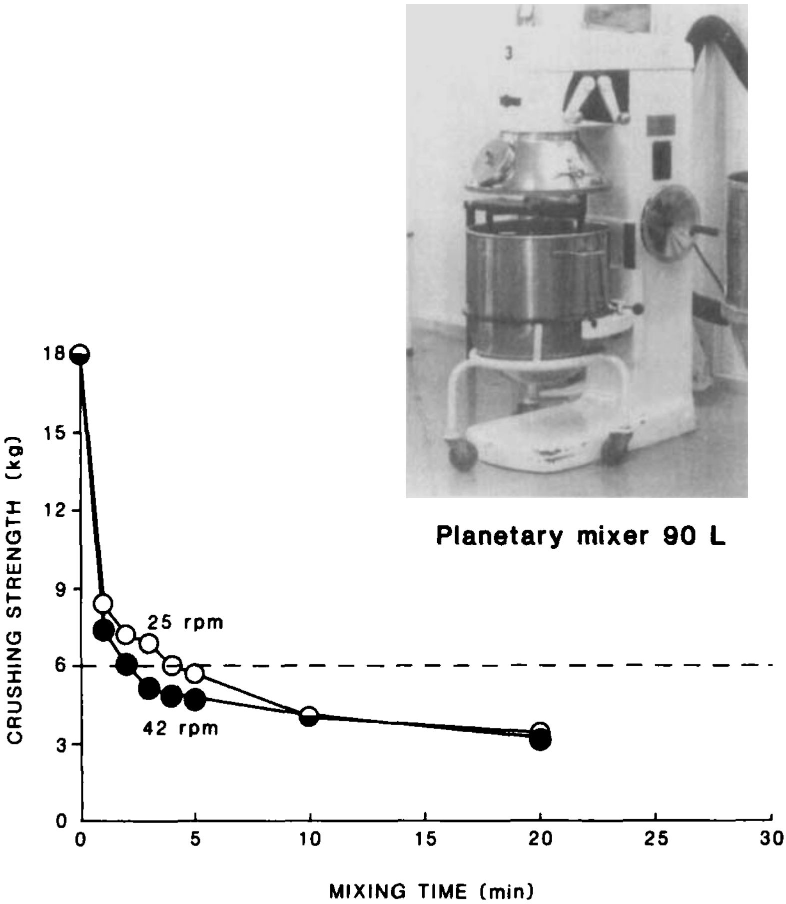

Figure 4

It can hence be concluded that he decrease in tablet hardness depends on both the type of the mixer and its rotation speed. In Table II, the lubricant sensitivity of the test formulation is depicted both as crushing strength half life and critical mixing time. Crushing strength half life is the time in which the crushing strength is halved from 18 down to 9 kg. The data in the Table indicate that the crushing strength half life depends less on both the type of the mixer and mixing

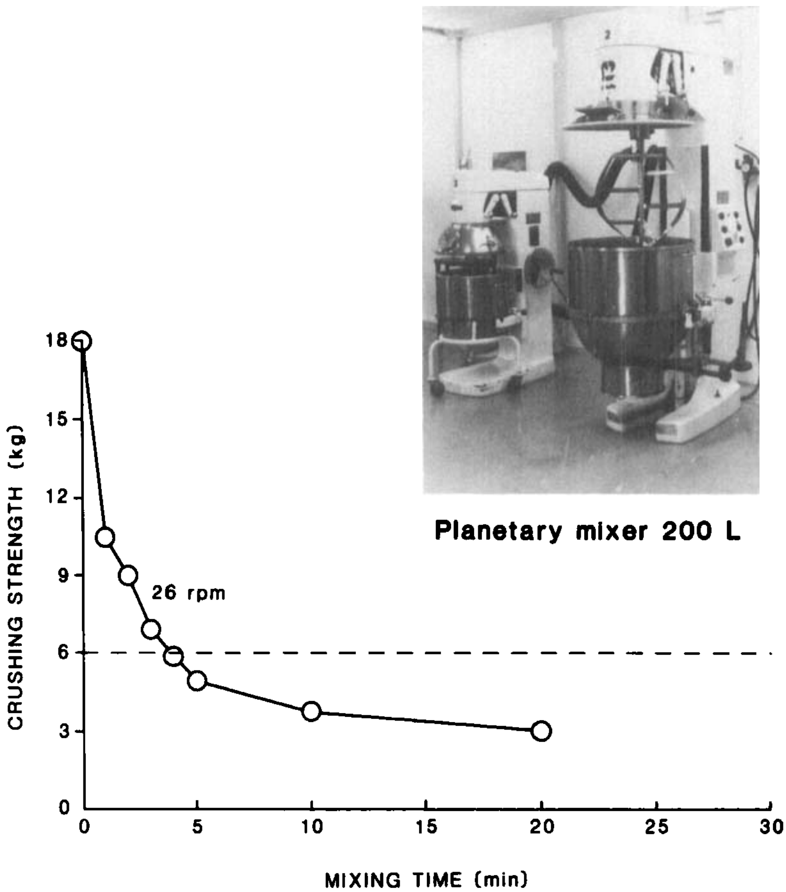

Figure 5

conditions than the critical mixing time does. Comparing the figures, it can be seen that for all the mixers and mixing conditions used, a decrease in crushing strength from 18 kg down to about 10 kg was found within the first minute of mixing. This steep decrease in crushing strength during the first stage of mixing indicates a rapid initial surface coverage with lubricant. This is a consequence of the fact that the film formation of magnesium stearate on base material can be

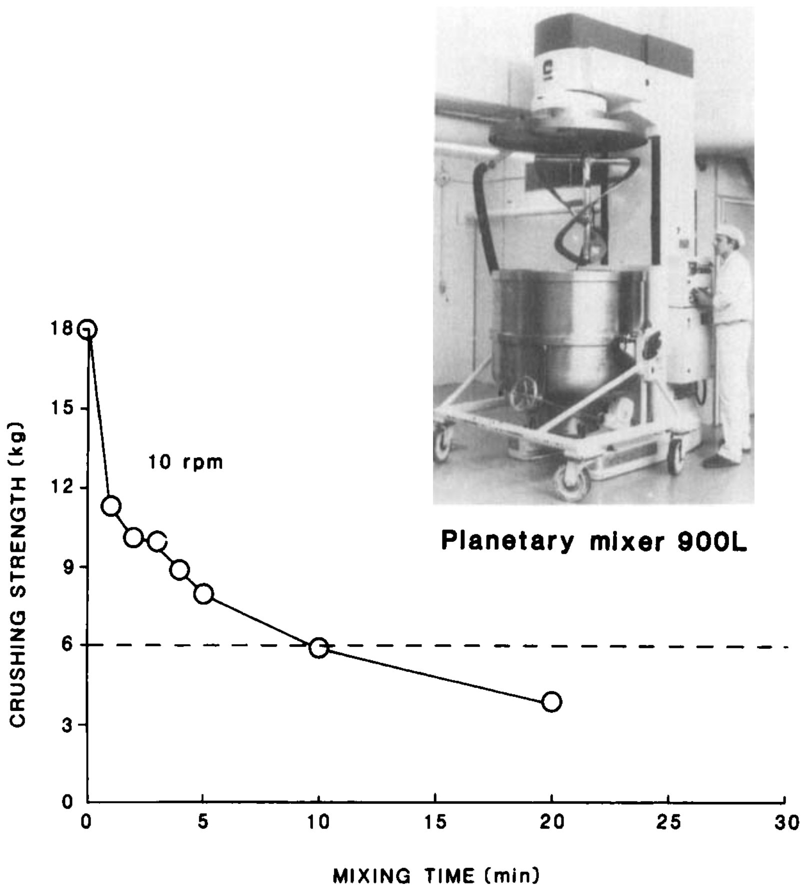

Figure 6

characterized by a Langmuir type adsorption process, (10, 20). The speed of the film formation on the excipient particles is affected by the size of the magnesium stearate particles (21, 11). This can be seen by comparing the effect of sieved and unsieved magnesium stearate in Figure 8. Using the unsieved lubricant, the magnesium stearate particles should desagglomerate first, before they can form a lubricant film upon substrate particles. As a result, the decrease in crushing strength is

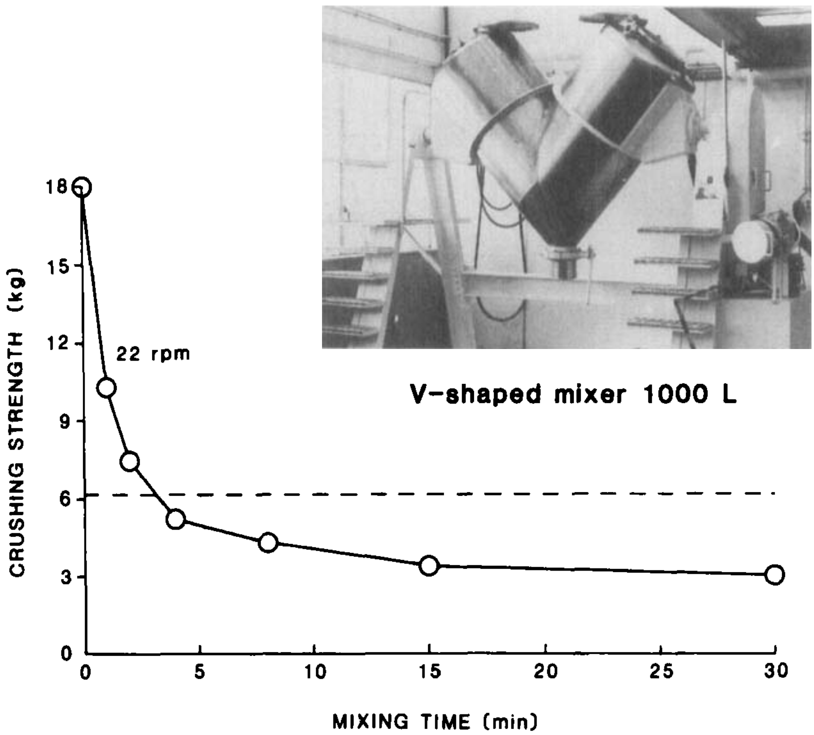

Figure 7

much slower when the magnesium stearate is not sieved before the mixing process. This result is consistent with the work of Johansson (22), who found less effect of magnesium stearate on tablet crushing strength, when the lubricant was used in a granular form.

Table II and the Figures 1 - 7 point to large differences in critical mixing times. In the Figures 9 and 10 the effect of different mixers, operating at about the same rotation speed are compared. For speeds between 20 and 26 rpm, it can be concluded from Figure 9 and Table II that the rate of decrease of tablet

Table II. Lubricant sensitivity with respect to crushing strength of the test formulation for different types of mixers

Mixer and capacity		Rotation speed	Crushing strength half-life	Critical mixing time
Turbula	2 L	45 rpm	1.0 min	10.5 min
		90 rpm	< 1.0 min	1.5 min
Cubic	13 L	20 rpm	8.0 min	30.0 min
		60 rpm	2.7 min	17.0 min
Drum	45 L	10 rpm	1.0 min	9.0 min
Planetary	90 L	25 rpm	1.0 min	4.0 min
		42 rpm	< 1.0 min	2.0 min
Planetary	200 L	26 rpm	2.0 min	3.8 min
Planetary	900 L	10 rpm	3.3 min	7.9 min
V-shaped	1.000 L	22 rpm	1.5 min	3.6 min

crushing strength during lubricant admixing was almost the same for the production-scale mixers, i.e. the 90 litre and 200 litre planetary mixers and the 1.000 litre V-shaped mixer, but was much slower for the 13 litre cubic mixer. A similar difference can be seen in Figure 10 between the 90 litre planetary mixer operated at 42 rpm and the 2 litre Turbula mixer operated at 45 rpm.

The differences in effect of lubricant admixing on tablet crushing strength between the small laboratory mixers and the

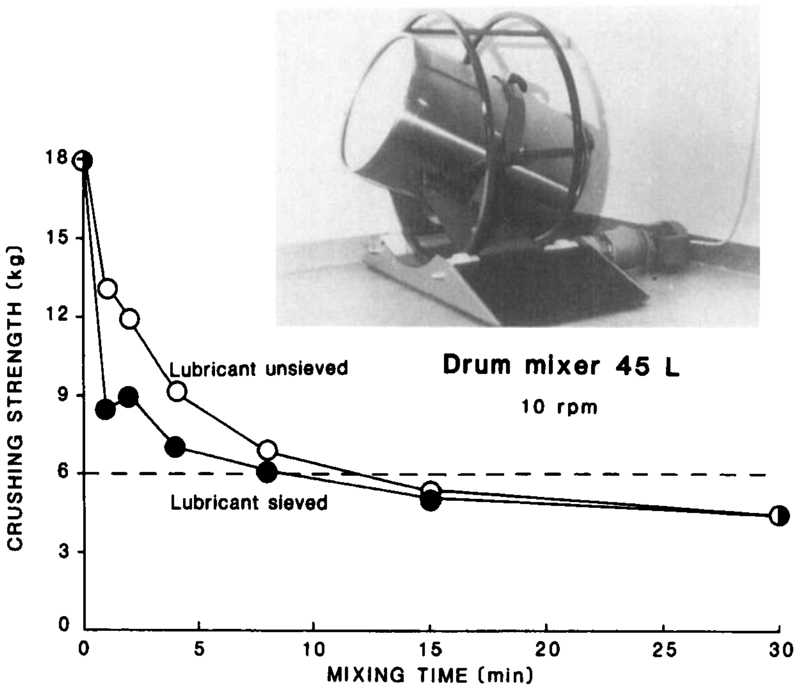

Figure 8

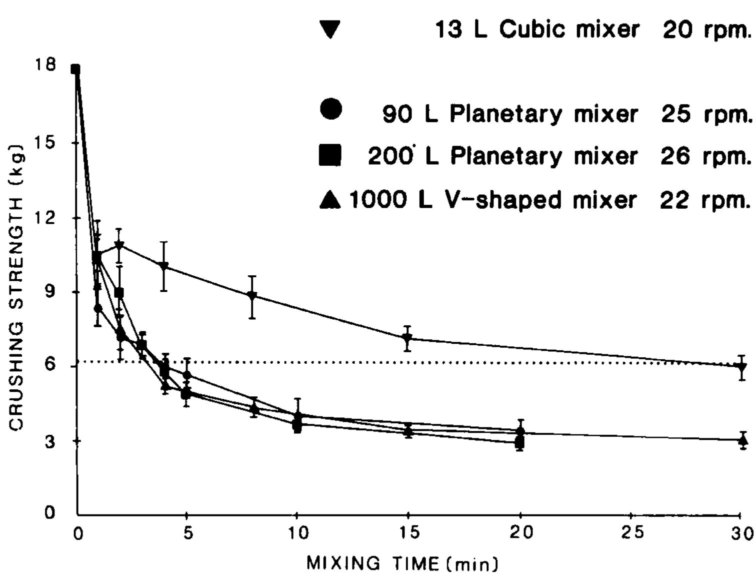

Figure 9

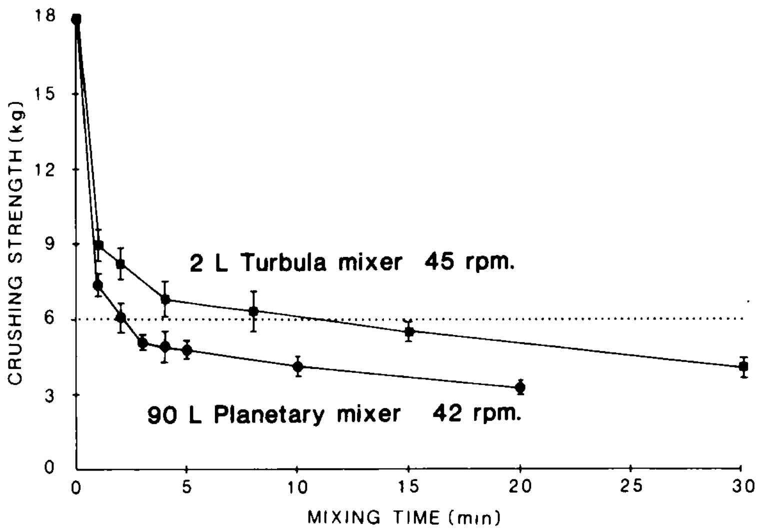

Figure 10

large industrial mixers, when operated at about the same rotation speed, will be caused by differences in shear forces generated during the mixing process and in the efficiency of the mixing procedure. In the industrial mixers, the load on the particles will be much greater than it is in the laboratory mixers. The increased load introduces larger shear forces during the mixing process. Large shear forces promote the shearing off of magnesium stearate molecules and the formation of an ordered mix of the lubricant on the substrate particles. For this reason the formation of a lubricant film and the subsequent decrease in tablet crushing strength proceed faster in large mixers than in small mixers.

The similarity in effect of lubricant admixing on tablet crushing strength of the production-scale mixers, operating at comparable rotation speeds (Figure 9) and the data of Table II indicate that for the large mixers used, the decrease of the crushing strength

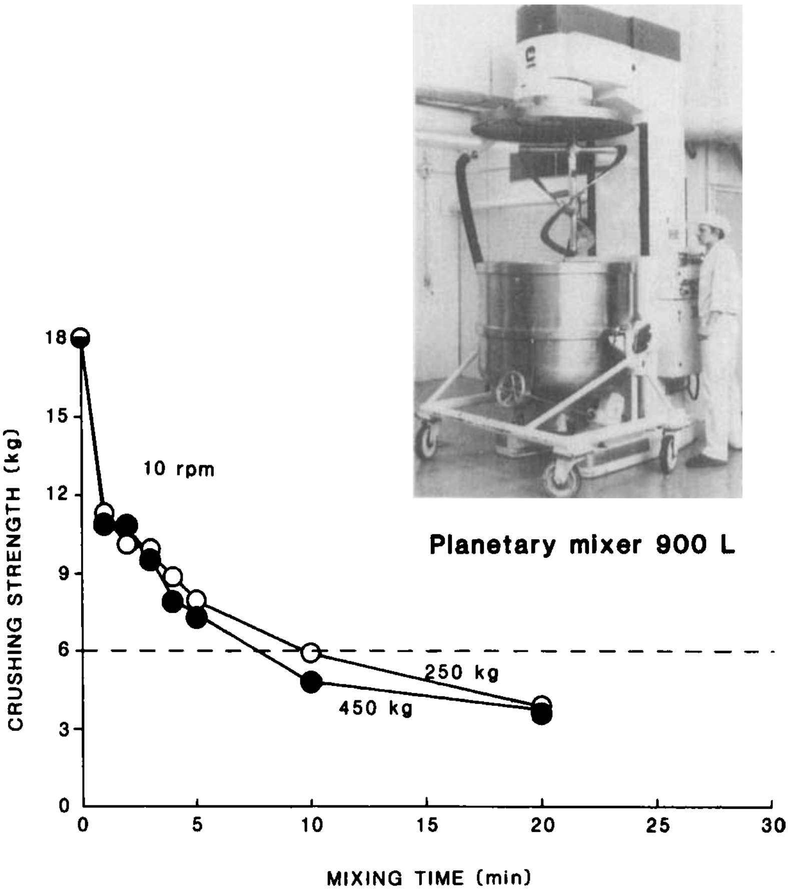

Figure 11

is mainly determined by the rotation speed and only to a small extent by the type and size of the apparatus. In contrast with the above mentioned effect of load between the small and the large mixers, no effect of load could be observed between the mutual industrial mixers used. This effect is supported by the observation that an increase of the load in the 900 litre planetary mixer from 250 kg to 450 kg caused only an insignificant effect on the decrease of the tablet hardness during lubricant admixing (Figure 11).

In order to obtain sufficient strength for tablets made with formulations that include lubricants, the lubricant mixing time should anyhow be shorter than the critical mixing time, but preferably as short as possible, because disintegration time (6), drug dissolution rate (7) and in-vivo adsorption rate (23) can be influenced negatively by a prolonged mixing with the magnesium stearate too. Therefore it is important to know the crushing strength-lubricant mixing time profiles for each industrial tabletting mixture in combination with the mixer used. These profiles can easily be determined by compressing samples, taken at selected time intervals during mixing with the lubricant.

In preformulation work, small laboratory mixers commonly are used for the determination of the lubricant sensitivity of tabletting blends. Therefore it is of interest to evaluate to what extent the preformance of a formulation in a small laboratory mixer is indicative of its performance in a large industrial mixer. Compared with the large mixers, for the small mixers much higher rotation speeds should be used to obtain the same rate of decrease in tablet crushing strength during mixing with lubricant. From Table II, it can be concluded that for the 13 litre cubic mixer an increase of the rotation speed from 20 rpm up to the maximum rate of 60 rpm is insufficient to simulate the effect in large mixers. On the other hand, with a 2 litre Turbula mixer, operating at high rotation speeds, a decrease in crushing strength similar to the decrease that will be found in production-scale mixers can be obtained. This is illustrated in Table II, where is shown that the critical mixing time in the Turbula mixer at 90 rpm has the same order of magnitude as that of the 90 litre planetary mixer at 42 rpm.

CONCLUSION

For the lactose/microcrystalline cellulose test formulation used, the effect of lubricant admixing on tablet crushing strength was strongly dependent on type, size and rotation speed of the mixer. The decrease in crushing strength was much faster for the large industrial mixers than for the small laboratory mixers when they operated at the same rotation speed. For the industrial mixers the decrease of the tablet crushing strength as an effect of lubricant admixing was more dependent on the rotation speed than on the type, size and load of the mixer. For a prediction of the effect of lubricant admixing on tablet crushing strength in large mixers, efficient laboratory mixers, operating at a high rotation speed can be used. For this purpose, the 2 litre Turbula mixer is a valuable tool.

REFERENCES

1. Strickland, Jr., W.A., Nelson, E., Busse, L.W. and Higuchi, T. 'The Physics of Tablet Compression IX; Fundamental Aspects of Tablet Lubrication'. J. Am. Pharm. Ass., Sci. Ed., Vol. 45, 1956, pp 51-55.
2. Shotton, E. and Lewis, C.J. 'Some observations on the effect of lubrication on the crushing strength of tablets'. J. Pharm. Pharmacol., Vol. 16, Suppl., 1964, pp 111T-120T.
3. Levy, G. and Gumtow, R.H. 'Effect of Certain Tablet Formulation Factors on Dissolution Rate of the Active Ingredient III: Tablet Lubricants'. J. Pharm. Sci., Vol. 52, 1963, pp 1139-1144.
4. Bolhuis, G.K., Lerk, C.F., Zijlstra, H.T. and De Boer, A.H. 'Film formation by magnesium stearate during mixing and its effect on tabletting'. Pharm. Weekblad, Vol. 110, 1975, pp 317-325.
5. Lerk, C.F., Bolhuis, G.K. and Smedema, S.S. 'Interaction of lubricants and colloidal silica during mixing with excipients; I. Its effect on tabletting'. Pharm. Acta Helv., Vol. 52, 1977, pp 33-39.

6. Bolhuis, G.K., Smallenbroek, A.J. and Lerk, C.F. 'Interaction of Tablet Disintegrants and Magnesium Stearate during Mixing I: Effect on Tablet Disintegration'. J. Pharm. Sci., Vol. 70, 1981, pp 1328-1330.

7. Lerk, C.F., Bolhuis, G.K., Smallenbroek, A.J. and Zuurman, K. 'Interaction of Tablet Disintegrants and Magnesium Stearate During Mixing II: Effect on Dissolution Rate'. Pharm. Acta Helv., Vol. 57, 1982, pp 282-286.

8. Van Kamp, H.V., Bolhuis, G.K., De Boer, A.H., Lerk, C.F. and Lie-A-Huen, L. 'The Role of Water Uptake on tablet Disintegration; Design of an improved method for penetration measurements'. Pharm. Acta Helv., Vol. 61, 1986, pp 22-29.

9. Bolhuis, G.K. and Lerk, C.F. 'Ordered mixing with lubricant and glidant in tableting mixtures'. J. Pharm. Pharmacol., Vol. 33, 1981, p. 790.

10. Shah, A.C. and Mlodozeniec, A.R. 'Mechanism of Surface Lubrication: Influence of Duration of Lubricant-Excipient Mixing on Processing Characteristics of Powders and Properties of Compressed Tablets'. J. Pharm. Sci., Vol. 66, 1977, pp 1377-1382.

11. Johansson, M.E. and Nicklasson, M. 'Investigation of the film formation of magnesium stearate by applying a flow-through dissolution technique'. J. Pharm. Pharmacol., Vol. 38, 1986, pp 51-54.

12. Ragnarsson, G., Hölzer, A.W. and Sjögren, J. 'The influence of mixing time and colloidal silica on the lubricating properties of magnesium stearate'. Int. J. Pharm., Vol. 3, 1979, pp 127-131.

13. Hölzer, A.W. and Sjögren, J. 'Evaluation of some lubricants by the comparison of friction coefficients and tablet properties'. Acta Pharm. Suec., Vol. 18, 1981, pp 139-148.

14. Roblot, L., Puisieux, F. and Duchêne, D. 'Etude de la lubrification par le stéarate de magnésium. Influence des proportions de lubrifiant et du procédé de mélange sur les charactéristiques des comprimés'. Labo Pharma Probl. Techn., Vol. 31, 1983, pp 843-847.

15. Bossert, J. and Stamm, A. 'Effect of mixing on the lubrication of crystalline lactose by magnesium stearate'. Drug Dev. Ind. Pharm., Vol. 6, 1980, pp 573-589.

16. Malmqvist, K. and Nyström, C. 'Studies on direct compression of tablets IX. The effect of scaling-up on the preparation of ordered mixtures in double-cone mixers'. Acta Pharm. Suec., Vol. 21, 1984, pp 21-30.

17. Johansson, M.E. 'The Effect of Scaling-up of the Mixing Process on the Lubricating Effect of Powdered and Granular Magnesium Stearate'. Acta Pharm. Technol. Vol. 32, 1986, pp 39-42.

18. Lerk, C.F., Bolhuis, G.K. and De Boer, A.H. 'Comparative evaluation of excipients for direct compression, II'. Pharm. Weekblad, Vol. 109, 1974, pp 945-955.

19. Bolhuis, G.K., Reichman, G., Lerk, C.F., Van Kamp, H.V. and Zuurman, K. 'Evaluation of Anhydrous α-lactose. A New Excipient in Direct Compression'. Drug Dev. Ind. Pharm., Vol. 11, 1985, pp 1657-1682.

20. Johansson, M.E. and Nicklasson, H. 'Influence of mixing time, particle size and colloidal silica on the surface coverage and lubrication of magnesium stearate'. Proceedings of the 5th Pharmaceutical Technology Conference, Harrogate, 1986, Volume 1, pp 217-225.

21. Bolhuis, G.K. 'Some aspects of the formulation and preparation of tablets with direct compressible excipients'. Thesis Groningen, 1978, pp 67-86.

22. Johansson, M.E. 'Granular magnesium stearate as a lubricant in tablet formulations'. Int. J. Pharm., Vol. 21, 1984, pp 307-315.

23. Proost, J.H., Bolhuis, G.K. and Lerk, C.F. 'The effect of the swelling capacity of disintegrants on the in vitro and in vivo availability of diazepam tablets, containing magnesium stearate as a lubricant'. Int. J. Pharm., Vol. 13, 1983, pp 287-296.