DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 6(1), 15-33 (1980)

MIXING ACTION AND EVALUATION OF TABLET LUBRICANTS IN DIRECT COMPRESSION

G.K. Bolhuis, C.F. Lerk and P. Broersma

Laboratory for Pharmaceutical Technology

University of Groningen

Antonius Deusinglaan 2

9713 AW Groningen, The Netherlands

ABSTRACT

The effect of a series of modern lubricants during mixing on both lubricating action and binding properties of a direct compressible tablet formulation has been investigated and compared with the effect of magnesium stearate. Lubricants which gave the best lubricating action (magnesium stearate, hydrogenated vegetable oils and glycerides) caused the largest reduction in tablet strength with an increase in mixing time. When used in concentrations of 1%, the hydrogenated vegetable oils and glycerides tested gave about the same reduction of the ejection force as 0.5% magnesium stearate, but their effect on tablet hardness during mixing was

much smaller. This result was confirmed for three direct compressible tablet formulations, composed with different excipients, where magnesium stearate could be replaced advantageously by Boeson VP or Sterotex.

INTRODUCTION

In the production of tablets, lubricants are usually added to reduce the friction between tablet material and the die wall during compression and ejection of the tablet. Higuchi and co-workers (1-3) evaluated various materials as tablet lubricant and found that salts of fatty acids were best (3). Of those, magnesium stearate is perhaps the most widely used pharmaceutical lubricant. It is well known, however, that magnesium stearate can have a strong negative effect on both binding and disintegration properties of tablets and consequently on drug release and even in some cases -c.q.in aspirin tablets- on the drug stability. For this reason several new lubricants have been introduced in the last 10-15 years. Alpar (4) reported the succesful use of polytetrafluoroethylene as a tablet lubricant. The results showed it to be as equally effective as magnesium stearate when used in concentrations of 1 per cent, it did not, however, materially affect the disintegration time and the strength of the lactose tablets studied. Further work (5, 6) with aspirin sucrose and hexamine confirmed these properties. Hydrogenated vegetable oils such as hydrogenated cotton seed oil (Sterotex®) and hydrogenated castor oil (Cutina®HR) can be used as tablet lubricants. Sterotex

is claimed to be effective in concentrations of 0.2 - 1% for granulations and 1.5 - 3% for powder mixtures without influencing disintegration time and tablet hardness (7). Marlowe and Shangraw (8), however, found only slight differences in the dissolution rate of sodium salicylate from tablets, when 1% magnesium stearate was replaced by the same concentration of Sterotex. Similar results were found for aspirin tablets (9). Sterotex has, however, a favourable effect on the stability of aspirin tablets (10). Cutina HR is claimed to be effective in concentrations between 0.3 and 2.0% (11).

Another group of modern lubricants is formed by (mixtures of) glycerides. Jaminet and Hazée (12) introduced a glyceryl palmitostearate, marketed as Précirol®. The product is claimed to have both binding and lubricating properties simultaneously, when used in concentrations of 1-5% It was found that replacement of magnesium stearate by Précirol contributed considerably to the improvement of a number of properties of tablets (13, 14). A less well known mixture of glycerides, which can be used as tablet lubricant is Boeson® VP (15). It is effective in concentrations of 0.4 - 3% and is claimed not to have a negative effect on tablet hardness.

In several studies, comparative evaluations between magnesium stearate and modern lubricants such as polytetrafluoroethylene (P.T.F.E.), hydrogenated vegetable oils and glycerides were carried out. Paris (16) compared various concentrations of magnesium stearate, Précirol, Cutina HR and P.T.F.E. in granulations as well as in direct compressible tablet mixtures. The author found that the lubricating effect and the influence on tablet hardness were dependent on the nature and

the concentration of the lubricant and the formulation in which it was used. The best lubricating properties were obtained with 0.5% magnesium stearate, 1% Précirol or 0.5 - 1% P.T.F.E. Cutina HR gave less satisfactory results. Magnesium stearate and Précirol caused, however, a stronger decrease in tablet crushing strength than the other lubricants. Delattre et al (17) evaluated different lubricants in a direct compressible tablet formulation containing extra fine crystalline lactose (lactose E.F.C.) and microcrystalline cellulose (Avicel® PH 101). As both tabletting characteristics (lubricating coefficient, ejection force) and mechanical tablet properties (crushing strength) were strongly influenced by both the nature and the percentage of the lubricant, for each lubricant the minimum effective concentration was determined. The best overall properties found for Précirol and stearic acid were in concentrations of 1% and magnesium stearate in a concentration of 0.25%. Increase in lubricant concentration was, however, more critical when magnesium stearate was used. Due to the hydrophilic nature of the tablet excipient used, there was almost no difference in the effect of the lubricants on the disintegration time of the tablets. Stamm et al (18) compared the properties of magnesium stearate with various other lubricants under which glycerides, hydrogenated vegetable oils and P.T.F.E., using lactose E.F.C. as tablet excipient. The results of the effect of the lubricants on both lubrication and tablet properties showed that 0.25% magnesium stearate can often be replaced advantageously by for instance 4% Ste-otex, 2-4% Précirol or 4% P.T.F.E.

In all of the studies mentioned above, the influence of the mixing time of lubricants and excipients on the effect of lubricants on both lubrication and tablet properties was not taken into account. In previous work from our laboratory (19) it was found that the decrease of binding forces of direct compressible excipients is not only dependent on the concentration of magnesium stearate, but also especially on the intensity of the mixing procedure. The phenomenon was elucidated by the formation of a lubricant film upon the substrate surface of magnesium stearate molecules, which are sheared off from the magnesium stearate crystals during the mixing process. Studies with stearic acid and metal soaps of stearic acid showed that film formation is not only exhibited by magnesium stearate: all the lubricants decreased the crushing strength of tablets from direct compressible starch (STA-Rx® 1500) with an increase in mixing time of the blends (20). The results showed, in addition that the effect was dependent on both the nature and particle size of the lubricant. On the other hand, the binding between the particles was not affected by P.T.F.E. because this lubricant has no laminar structure and will not form a lubricant film during the mixing process.

The object of this study is the investigation of the effect of a series of modern lubricants such as hydrogenated vegetable oils and glycerides during mixing on both lubricating action and binding properties of direct compressible tablet formulations. The results

will be compared with the effect of magnesium stearate, in order to facilitate the choice of a proper lubricant in direct compression.

EXPERIMENTAL

Materials : The direct compressible excipients used were: microcrystalline cellulose N.F. (Avicel PH 101 and PH 102)[1], microfine cellulose (Elcema® G 250)[2], direct compressible starch (STA-Rx 1500)[3], amylose V[4], dicalcium phosphate dihydrate (Emcompress®)[5] and extra fine crystalline lactose (Lactose E.F.C.)[6]. The lubricants used were: magnesium stearate Ph.Ned. VI[7], talc Ph.Ned. VI[7], graphite[7], stearic acid (pharmaceutical quality)[8], polytetrafluoroethylene[9], Précirol-Ato-5[10], Sterotex[11], Boeson VP[12], Cutina HR[13] and l-leucine 99%[14]. The drugs used were: prednisone Ph.Ned. VII, micronized[15], phenobarbitone Ph.Eur.[16] and paracetamol Ph.Ned. VII[7]

METHODS

Particle densities were determined with an air comparison pycnometer[17] The specific surface by weight of the lubricants was determined by nitrogen adsorption[18].

Mixing of the blends of excipients with different lubricants was performed in a Turbula mixer[19] at 90 rpm. for the placebo tablets and in a 1-litre cubic tumbling mixer at 60 rpm. for the prednisone, phenobarbitone and paracetamol tablets. For both methods, the loading was about 20%. Before blending the lubricants were sieved through a 150 µm sieve.

If not stated otherwise, the blends were compressed to flat tablets using an instrumented single punch machine at a machine speed of 18 cycles/min. The instrumentation of the machine has been reported previously by Groenwold et al (21). Tablet diameter and tablet weight were 9 mm and 300 mg for the placebo tablets, 9 mm and 200 mg for the prednisone and phenobarbitone tablets and 13 mm and 715 mg for the paracetamol tablets, respectively. The compression force used was 20 kN. The data for the ejection force represent the mean of at least ten compressions.

In a preliminary test, placebo tablets were prepared by introducing manually a weighed quantity of 300 mg of the blend into a prelubricated 9 mm die of a compression device, mounted between the plattens of an instrumented hydraulic press. The samples were compressed at a compression force of 20 kN with a loading rate of 2 kN/s.

The crushing strength of the compacts was measured immediately after compression using a motorized Heberlein instrument. The data given are the mean of at least ten tablets. The friability of the tablets was determined in a Roche friabilator. Samples of 10 tablets were weighed, subjected to rotation for 5 minutes at 20 rpm. and then reweighed after careful dusting. The percentage of tablet weight loss was then calculated. The disintegration time of the tablets was determined using the USP XIX apparatus. The data given are the mean of the disintegration time of 6 individual tablets.

RESULTS AND DISCUSSION

In order to study the mixing action of different lubricants on both ejection force during compression and tablet crushing strength, a placebo mixture without lubricant containing 50% lactose E.F.C., 25% STA-Rx 1500 and 25% Elcema G 250 was prepared, from which tablets with sufficient crushing strength and ejection force could be compressed. As it was not possible to prepare tablets with some of the lubricants studied, using the eccentric press, the effect of mixing with lubricants on tablet hardness was studied in a preliminary test, using an instrumented hydraulic press and a loose, prelubricated die (figure 1).

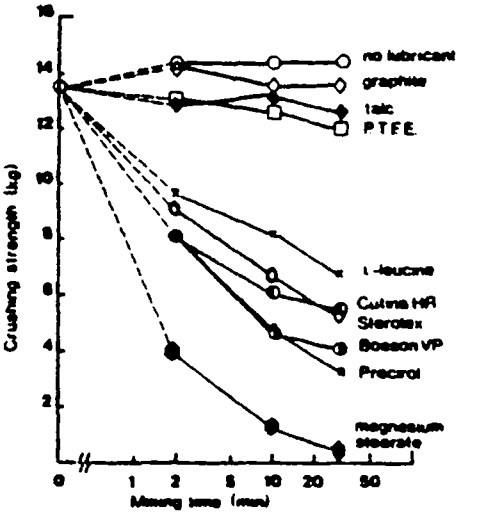

Figure 1.

Effect of mixing time on the crushing strength of tablets compressed from blends of 50% lactose E.F.C., 25% STA-Rx 1500 and 25% Elcema G 250 with 1.0% of various lubricants.

Figure 1 shows the effect of mixing time (log. scale) on the crushing strength of tablets, compressed from blends of the placebo mixture with 1.0% of various lubricants. The specific surface by weight of the lubricants used is given in table I. The figure shows that graphite, talc and polytetrafluoroethylene (P.T.F.E.) had little or no effect on the crushing strength of the tablets.

As could be expected from previous work (19), a strong decrease in crushing strength was found with magnesium stearate as tablet lubricant. Although the modern lubricants l-leucine, Cutina HR, Sterotex, Boeson VP and Précirol gave a strong decrease in crushing strength of the tablets with an increase in mixing time, the effect was less than the effect of magnesium stearate: after 2 minutes mixing the crushing strength decreased with about 10 kg for tablets wit

TABLE I

Specific surface by weight of the lubricants used.

Boeson VP	1.0 m^2/g
Cutina HR	1.2 m^2/g
graphite	6.4 m^2/g
l-leucine	1.8 m^2/g
magnesium stearate	14.3 m^2/g
polytetrafluoroethylene	2.0 m^2/g
Précirol	1.6 m^2/g
Sterotex	1.6 m^2/g
talc	3.3 m^2/g

magnesium stearate but with not more than about 5 kg for tablets with l-leucine, Cutina HR, Sterotex, Boeson VP or Précirol as lubricant. It should, however, be noted that the decrease-rate was found to be dependent on the particle size of the lubricant (20), so that the rank-order found refers only to the lubricants used.

Scanning electron micrographs have shown that all the lubricants tested, except P.T.F.E..have a laminar structure. This suggests that the lubricants which give a decrease in crushing strength during the mixing process are sheared off and form a lubricant barrier on the excipient particles, interfering with the binding, just as previously found for magnesium stearate (19, 20, 22). P.T.F.E. has no laminar structure and will not form a lubricant film during the mixing process (20). Talc and graphite have a laminar particle structure, but have no effect on tablet crushing strength. This may possibly be explained by the fact that their crystals show no layer lattice crystal slipping by shear but a roller mechanism (23, 24).

The efficacy of the lubricants was investigated by measuring the maximum force required to eject the tablets from the die i.e. the ejection force after compressing the blends on the eccentric press. Tablets without lubricant were prepared in the carefully cleaned die of the press, which was driven by hand. Table 2 summarizes the effect of mixing the placebo mixture with 0.5 or 1% lubricant on both crushing strength and ejection force. It can be seen that ejection forces lower than 300 N could only

TABLE 2

Effect of mixing with 0.5 or 1.0% lubricant on crushing strength and ejection force of tablets from blends containing 50% lactose E.P.C., 25% STA-Rx 1500 and 25% Elcema G 250.

Lubricant	Mixing time:2 min		Mixing time:10 min		Mixing time:30 min	
	Crushing strength (kg)	Ejection force(N)	Crushing strength (kg)	Ejection force(N)	Crushing strength (kg)	Ejection force(N)
no lubricant	11.0	670	11.0	670	11.0	670
0.5% graphite	a	a	b	b	b	b
1.0% graphite	a	a	12.4	1720	12.3	1660
0.5% talc	b	b	b	b	b	b
1.0% talc	b	b	b	b	b	b
0.5% P.T.F.E.	b	b	b	b	10.8	880
1.0% P.T.F.E.	11.5	340	11.9	370	10.8	340
0.5% l-leucine	b	b	b	b	b	b
1.0% l-leucine	b	b	b	b	b	b
0.5% Sterotex	8.2	620	5.6	560	5.0	450
1.0% Sterotex	7.3	170	4.0	130	3.7	120
0.5% Cutina HR	6.7	440	5.6	440	4.5	510
1.0% Cutina HR	5.9	300	4.0	250	3.7	200
0.5% Boeson VP	7.9	150	4.6	170	2.9	110
1.0% Boeson VP	7.8	190	2.7	<100	2.1	<100
0.5% Précirol	6.8	210	3.0	250	1.0	250
1.0% Précirol	4.4	110	2.2	<100	c	c
0.5% magnesium stearate	4.2	100	0.1	<100	0	<100
1.0% magnesium stearate	0	100	0	<100	0	<100

a= tabletting machine driven by hand, b= insufficient lubrication,

c= insufficient flowability .

be obtained with 1% Sterotex or Cutina HR and 0.5 - 1% of Boeson VP, Précirol or magnesium stearate. The results show that the ejection force hardly changes with an increase in mixing time. The lubricating properties of graphite, talc, P.T.F.E. and l-leucine were insufficient for the concentrations studied. Table 2 shows that the decrease in ejection force is roughly proportional to the decrease in crushing strength for each mixing time. It can be concluded that, with respect to both crushing strength and ejection force, 1% Sterotex and 0.5 - 1% Boeson VP gave the best results when mixed for a short period with the other vehicles.

The lubricants Sterotex and Boeson VP were then evaluated and compared with magnesium stearate in three direct compressible tablet formulations (table 3) with a low, a medium high and a high dose drug, respectively.

TABLE 3
Tablet formulations used.

Prednisone	2.5%	2.5%	Paracetamol	69.93%
Lactose E.F.C.	71.5%	72.0%	Avicel PH 101	29.72%
Avicel PH 102	25.0%	25.0%	Lubricant	0.35%
Lubriant	1.0%	0.5%		
Phenobarbiton	25.0%	25.0%		
Amylose V	20.0%	20.0%		
Emcompress	54.5%	54.0%		
Lubricant	0.5%	1.0%		

The tables 4 and 5 summarize the ejection force and tablet properties of prednisone and phenobarbitone tablets with 0.5% magnesium stearate, 1% Boeson VP or 1% Sterotex, respectively, as lubricant. The components without lubricant had been blended for 30 min. in the cubic tumbling mixer. The results show that an additional mixing time of 5 minutes with a lubricant was sufficient for obtaining a low ejection force. Longer mixing gave a corresponding decrease in crushing strength of the tablets, whereas the ejection force hardly changed.

TABLE 4

Effect of mixing with lubricant on ejection force, crushing strength, friability and disintegration time, respectively, of prednisone tablets.

Lubricant	Mixing time (min.)	Ejection force (N)	Crushing strength (kg)	Friability (%)	Disintegration time (s)
no lubricant[a)]	-	1750	9.5	<0.1	8
1% Boeson VP	5	190	8.7	<0.1	20
	15	190	8.4	<0.1	16
1% Sterotex	5	250	8.1	0.2	14
	15	300	7.4	<0.1	13
0.5% magnesium stearate	5	180	5.6	0.1	12
	15	150	4.7	0.5	20

a) tabletting machine driven by hand

In comparison with 0,5% magnesium stearate, 1% Boeson VP or 1% Sterotex gave less decrease in crushing strength, whereas the other tablet properties had hardly changed when compared with tablets containing magnesium stearate. Tables 4 and 5 show that with respect to both crushing strength and ejection force, the best results were obtained with 1% Boeson VP as lubricant.

TABLE 5

Effect of mixing with lubricant on ejection force, crushing strength, friability and disintegration time, respectively, of phenobarbitone tablets.

Lubricant	Mixing time (min.)	Ejection force (N)	Crushing strength (kg)	Friability (%)	Disintegration time (s)
no lubricant[a)]	-	1140	6.2	0.4	3
1% Boeson VP	5	< 100	6.0	0.5	210
	15	< 100	4.6	0.7	160
1% Sterotex	5	180	6.0	0.9	275
	15	180	4.1	1.2	170
0.5% magnesium stearate	5	< 100	4.1	0.6	180
	15	< 100	2.2	1.1	180

a) tabletting machine driven by hand.

The paracetamol formulation (see table 3) was originated from the F.M.C. Corporation with 0.35% stearic acid as lubricant (25). Comparison with the three other lubricants (table 6) shows that replacement of stearic acid by 0.35% of the other lubricants caused an even larger decrease of the ejection force. Addition of magnesium stearate had a very deleterious effect on crushing strength and friability, even when this lubricant was mixed for a short period with the other ingredients. The results show that Boeson VP and Sterotex caused not more than a small decrease in

TABLE 6

Effect of mixing with lubricant on ejection force, crushing strength, friability and disintegration time, respectively, of paracetamol tablets.

Lubricant	Mixing time (min.)	Ejection force (N)	Crushing strength (kg)	Friability (%)	Disintegrati time (s)
no lubricant[a)]	-	1140	10.1	1.2	30
0.35% stearic acid	5	480	10.5	1.2	32
	15	420	10.5	0.8	60
0.35% Boeson VP	5	300	9.5	0.7	19
	15	340	6.5	1.3	23
0.35% Sterotex	5	360	9.3	1.1	24
	15	340	8.8	0.8	23
0.35% magnesium stearate	5	350	3.3	3.1	21
	15	400	2.3	4.8	21

a) tabletting machine driven by hand

tablet hardness, when the mixing time was short. In comparison with stearic acid, these lubricants are advantageous with respect to both ejection force and disintegration time of the tablets.

CONCLUSIONS

Of a series of lubricants tested in a direct compressible system, all the lubricants except talc, graphite and polytetrafluoroethylene decreased the binding forces of the excipients with an increase in mixing time of the blends, just as previously reported for magnesium stearate. Hydrogenated vegetable oils, glycerides and magnesium stearate, which gave the lowest ejection forces, caused the largest reduction in tablet strength with an increase in mixing time. In concentrations of 1%, Sterotex, Boeson VP and Précirol gave about the same reduction of ejection force as 0.5% magnesium stearate, but -in spite of the higher concentrations, in which they were used- their effect on tablet hardness during mixing was much smaller. Examples of direct compressible tablet formulations show that it can be advantageous to replace magnesium stearate by Sterotex or Boeson VP. Good lubrication and tablet properties are obtained after a short mixing of lubricant with the blend of other tablet ingredients. In addition, the mixing time is less critical than when magnesium stearate was used.

FOOTNOTES

1. F.M.C. Corporation, American Viscose Division, Markus Hook, Pa., U.S.A.
2. Degussa, Frankfurt a. M., West Germany.
3. A.E. Staley Mfg. Co., Decatur, Illinois. U.S.A.
4. Avebe G.A., Veendam.
5. Edward Mendell Co., Inc., New York, U.S.A.
6. B.V. Hollandse Melksuikerfabriek, Uitgeest.
7. Lamers en Indemans, 's-Hertogenbosch.
8. Croda GmbH., Nettetal, West Germany.
9. B.D.H. Chemicals, Poole, England.
10. Etablissements Gattefossé, Saint-Priest, France.
11. Capital City Products Co., Columbus, Ohio, U.S.A.
12. C.H. Boehringer Sohn, Ingelheim a.R., West Germany.
13. Henkel & Cie. GmbH., Düsseldorf, West Germany.
14. Aldrich-Europe, Beerse, Belgium.
15. Nogepha, Alkmaar.
16. O.P.G., Utrecht.
17. Model 930, Beckman Instruments Ned. N.V., Amsterdam.
18. Perkin Elmer Sorptometer, model 212.
19. Model 2P, W.A. Bachofen, Basle, Switzerland.

REFERENCES

1. E. Nelson, S.M. Naqvi, L.W. Busse and T. Higuchi, J. Am. Pharm. Assoc., Sci. Ed. 43, 596 (1954).

2. W.A. Strickland, Jr., E. Nelson, L.W. Busse and T. Higuchi, Ibidem 45, 51 (1956).

3. W.A. Strickland, Jr., T. Higuchi and L.W. Busse, Ibidem 49, 35 (1960)

4. O. Alpar, J.J. Deer, J.A. Hersey and E. Shotton, J. Pharm. Pharmacol. 21, 6 s (1969).

5. A. La Manna and E. Shotton, Il Farmaco, Ed. Pr. 25, 689 (1970).

6. E. Shotton, Pharm. Ind. 34, 256 (1972).

7. A. Stamm and C. Mathis, Labo-Pharma no. 250, 61 (1976).

8. E. Marlowe and R.F. Shangraw, J. Pharm. Sci. 56, 498 (1967).

9. E. Cid and F. Jaminet, J. Pharm. Belg. 26, 360 (1971).

10. H. Delonca, J. Joachim, G. Joachim and A. Cantos, Il Farmaco, Ed. Pr. 30, 89 (1975).

11. Techn. bull. "Grundstoffe für die Pharmazie" Register 7, Henkel, Düsseldorf (1975).

12. F. Jaminet and A. Hazée, Pharm. Acta Helv. 41, 530 (1966).

13. F. Jaminet and G. Evrard, Ibidem 41, 601 (1966).

14. Techn. bull. Gattefossé, notice OL 0079 (1970) "Excipients pour formes galéniques sèches".

15. Techn. bull. Boeson VP, C.H. Boehringer Sohn, 126-5/780-EM.

16. J. Paris, thesis Paris (1974).

17. L. Delattre, J. Gillard, F. Jaminet and M. Roland, J. Pharm. Belg. 31, 497 (1976).

18. A. Stamm, A. Kleinknecht and D. Bobbé, Labo-Pharma no. 263, 215 (1977).

19. G.K. Bolhuis, C.F. Lerk, H.T. Zijlstra and A.H. de Boer, Pharm. Weekblad 110, 317 (1975).

20. C.F. Lerk, G.K. Bolhuis and S.S. Smedema, Pharm. Acta Helv. 52, 33 (1977).

21. H. Groenwold, C.F. Lerk and R.J. Mulder, J. Pharm. Pharmacol. 24, 352 (1972).

22. C.F. Lerk and G.K. Bolhuis, Pharm. Acta Helv. 52, 39 (1977).

23. W. Bollmann and J. Spreadborough, Nature (London) 186, 29 (1960).

24. D. Train and J.A. Hersey, J. Pharm. Pharmacol. 12, 97T (1960).

25. Techn. Bull. Avicel, PH 9, F.M.C. Corp. (1974).