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ASPECTS OF PHARMACEUTICAL TRIBOLOGY

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INTRODUCTION

Pharmaceutical tribology may be defined as the study of friction as it affects the performance of excipients and drugs in the production and use of medicines. Pharmaceutical tribology is therefore concerned with studying the efficiency of formulation additives such as glidants, anti-adherents and lubricants and with process equipment and conditions which modify frictional effects. The work presented here is related to an investigation of some formulation and process changes on anti-adherent and lubrication effects on compaction of model powders.

Some mechanisms involved in producing friction have been described by Clayton[1]. Initially, friction was attributed totally to Coulomb friction, a mechanical resistive force created by interlocking surface asperities (fig 1a). Work has to be done to

deform or fracture one of the asperities so that movement can continue; the work done is the frictional work. Friction has also been attributed to adhesion forces and Schnurman[2] has suggested an electrostatic component of friction which may account for certain "stick-slip" frictional phenomena. The actual mechanism of friction may be a combination of all those mentioned, but Bowden and Tabor[3] have explained the laws of friction using only adhesion theory and showed that an effective lubricant acts by reducing shear strength at the interface between a compact and the die wall, reducing the coefficient of friction and hence the frictional force at a given load.

Reducing the coefficient of friction has a number of advantages such as reducing the work required to compact the powder and perhaps more importantly, reducing the work done in ejecting the tablet. Picking and sticking of material to metal tooling surfaces may in part be attributed to ineffective lubrication[4]. An increase in the coefficient of friction at the die wall will result in useful work being lost as heat during compaction. This causes liquid flow of low melting point lubricants such as oils or waxes producing a double effect: firstly, this may be the principle mode of action of these materials as lubricants, melting producing a fluid film between solid surfaces (fig 1c); secondly however, the probability of sticking or picking is increased in these materials. Fluid film formation is one of two main mechanisms of lubrication of solids used in tablet compaction, the other being boundary lubrication.

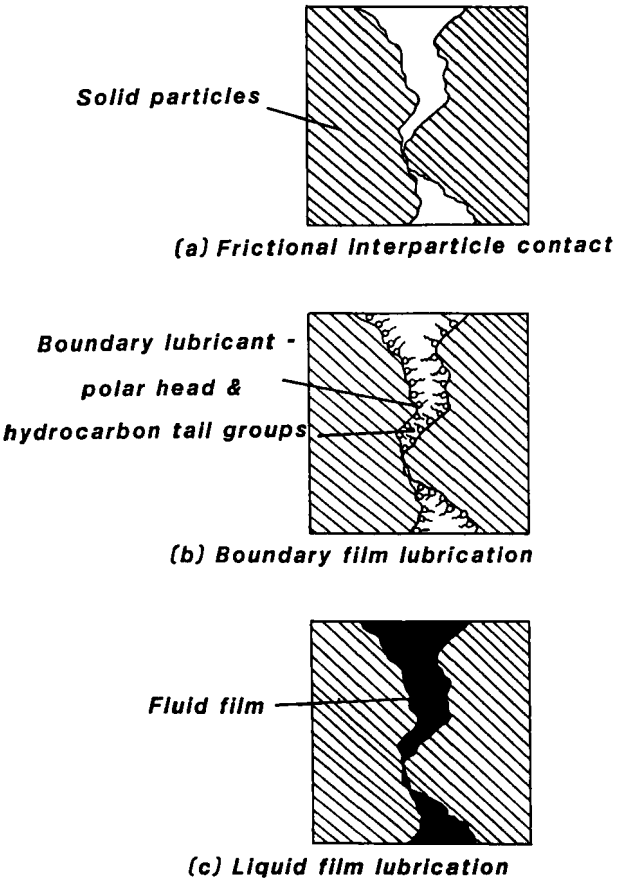


Figure 1

According to Freeman[6], for a boundary lubricant to be effective it must have a low shear strength and secondly must adhere readily and firmly to interacting surfaces. Many common boundary lubricants were compared by Strickland et al[7], including magnesium stearate, sodium lauryl sulphate and zinc stearate - all of which have amphiphilic activity. Moody et al[8], suggested that the polar portions of the molecules adhere to the metal and powder/granule

surface as shown schematically in fig 1b. Boundary lubricants are generally more effective than fluid film forming lubricants such as paraffin, distearin, beeswax etc; the activity of these materials being linked to their viscosity[6].

It is widely accepted that one of the boundary lubricants, magnesium stearate, is the most effective anti-friction excipient used in tablet compaction. Magnesium stearate exists in two pseudo polymorphic forms: a trihydrate acicular form and a dihydrate lamellar form; the lamellar form possesses the greatest lubricant activity[9].

However, magnesium stearate has a number of disadvantageous secondary effects on the performance of tablets. As a result of its hydrophobic nature, magnesium stearate can cause an increase in disintegration times and a reduction of dissolution rates. Shah et al[10] found that two other boundary lubricants, sodium stearyl fumarate and glyceryl behenate, had a less deleterious influence on dissolution rates than magnesium stearate. Magnesium stearate is also known to significantly reduce the work of failure of tablets such as those containing microcrystalline cellulose; the effect being much greater than with other lubricants[11,12]. In addition, magnesium stearate has been found to cause a marked loss of drug homogeneity in tablets as a result of destabilization[13,14]. It has been suggested that the deleterious effects of magnesium stearate result from its exceptional

lubricant activity. Lubrication is a surface effect and hence lubricant efficieny will be related to the efficiency of powder and metal surface coating. It is known that magnesium stearate can form a continuous hydrophobic film around particles; the effect being especially pronounced after prolonged mixing[12].

One approach to reducing the deleterious effects of magnesium stearate may be to increase its affinity for the die wall. Tingle[15] has shown that freshly-cut surfaces of metal are not effectively lubricated by fatty acids; he found that water and oxygen are usually essential environments for good boundary lubrication. In the present study, four approaches to maximising lubricant activity and minimizing secondary effects have been investigated. These can be sub-divided into (a) formulation modifications: (i) substitution of magnesium stearate with other lubricants (ii) addition of magnesium stearate action modifying excipients and (b) process modifications (i) pre-treatment of die walls by phosphation (ii) removal of magnesium stearate or other lubricants from the bulk formulation using electrostatic deposition (Electro-lubrication).

MATERIALS

Emcocel, Lot 5114, Manufactured by Finnish Sugar Company for Edward Mendell Co Inc, USA and Europe.

Emcompress, Edward Mendell Co Inc.

Ferrous Chloride, BDH Chemicals Ltd, UK.

Leucine, Forum Chemicals Ltd, Redhill, UK.

Magnesium Stearate, Lot 4586292G, BDH Chemicals Ltd, UK.

Orthophosphoric acid 88%, Lot 104, Fisons plc, Loughborough, UK.

Potassium dihydrogen orthophosphate, Lot 1089242, BDH Chemicals Ltd, UK.

Zinc Chloride, BDH Chemicals Ltd, UK.

Zinc Oxide, BDH Chemicals Ltd, UK.

Compitrol 888, Lot 2373, Gattefosse, France.

Tabfine S100I, Lot 34304114, Manufactured by Finnish Sugar Company for Edward Mendell Co Inc, USA and Europe.

Lubritab, Edward Mendell Co Inc.

Potassium chloride, Fisons plc, Loughborough UK.

Aerosil 200, Degussa AG, Frankfurt FRG.

Explotab, Edward Mendell Co Inc.

METHODS

(a) (i) Substitution of Magnesium Stearate with Other Lubricants

Tablets were compressed under power using a reciprocating tableting machine (type F3, Manesty Machines, Liverpool). The maximum punch forces during compaction and the ejection forces exerted on the lower punch were measured using load cells (type 9031, Kistler Instr., Switzerland). The output signal was fed through a charge amplifier (type 5054A) via a fast A/D converter into a microcomputer (BBC model B, Acorn Ltd, UK) where the data was processed and printed. Mixtures were produced containing either a brittle excipient, Emcompress or a ductile excipient,

Emcocel together with one of the following lubricants: magnesium stearate, sodium stearyl fumarate, Leucine, Lubritab and Compitrol.

(a) (ii) Factorial Analysis of Quinary Mixes

Eight different formulations of quinary mixes were prepared according to a 2^3 factorial design (table 2). Firstly, a binary mix was prepared from the main excipient (Tabfine S100I) and the model drug potassium chloride in a 0.5% w/w conc. Subsequently, the ternary (added magnesium stearate), quaternary (added colloidal silica) and the quinary component (added sodium starch glycolate) were mixed using a metallic stirrer and a mortar in a premixing stage followed by mixing for about 1 minute using a cube mixer at 300 rpm. Before starting the experiment, materials were conditioned in a dessicator containing $MgCl_2$ salt solution for 48 hours. The sucrose-based excipient was sieved using a 710 m sieve and the powder undersize was used for the experiment. Magnesium stearate was sieved using a 90 m sieve to break up any agglomerates, whereas colloidal silica was treated using a pestle and mortar to break up agglomerates. Explotab (sodium starch glycolate) was used as received from the supplier. The effects of three factors (components), ie magnesium stearate (A), colloidal silica (B) and sodium starch glycolate (C), on physical stability of the quinary mix were studied at two levels for each fator (table 1). Table 2 shows the various combinations for the eight trials used for experimentation. It also shows the calculation

TABLE 1

An Outline for the Factorial Design

Factor	Value (Concentration %)	
	Low Level -	High Level +
A (Magnesium Stearate)	0.25	1.00
B (Colloidal Silica)	0.5	2.00
C (Sodium Starch Glycolate)	2.00	4.00

matrix for a 2^3 factorial design, with the following combinations of factors A, B and C at two at two levels: (1), a, b, ab, c, ac, bc, abc. In these combinations (1) refers to all factors at their low level, (a) refers to the experiment with factor A at the high level and B and C at low levels, etc. Physical stabilities of different mixes examined, were represented using the coefficients of variation (CV%) of the potassium ion content determined for 20 samples as mentioned before. Each formulation in the experiment was examined, at least twice. Thus the CV% was calculated using at least 40 samples for each formulation during vibrated or non-vibrated conditions.

The choice of the factors to be included in the experiment is a consequence of the experimental objective. Factors or components selected for this experiment represent, in addition to the model drug and the principle excipient, a lubricant, a glidant

TABLE 2

A Calculation Matrix for the Experiment

Key: A Magnesium Stearate
B Colloidal Silica (Aerosil 200)
C Sodium Starch Glycolate (Explotab)

Factor Combination	Experimental Factor Level[a]			Level of Interactions			
	A	B	C	AB	AC	BC	ABC
(1)	-	-	-	+	+	+	-
a	+	-	-	-	-	+	+
b	-	+	-	-	+	-	+
ab	+	+	-	+	-	-	-
c	-	-	+	+	-	-	+
ac	+	-	+	-	+	-	-
bc	-	+	+	-	-	+	-
abc	+	+	+	+	+	+	+

a: - Factor at low level; + Factor at high level
b: Multiply signs of factors to obtain signs for interaction terms

In combination (eg AB at (1): = (-) x (-) = (+)

and a disintegrant. As mentioned above, the use of a factorial design can reveal any existing interaction. The effect of factors usually pass a maximum. It is therefore to be recommended that the difference between the levels of the factors should not be too large, otherwise any interaction occuring might be overlooked. According to the matrix in table 2, the value for the effect of each factor or interactions can be obtained.

(b) (i) Pre-treatment of the Die Walls by Phosphation

Freeman[16] described the use of phosphates and oxalate coatings to increase the adhesion and life of other solid lubricants. The phosphate coating also shows some lubricant activity in that, "The layer is relatively friable and so facilitates running-in, more over it is thick enough to make a high finish" Clayton (1).

The use of a phosphate coating in lubrication or as a lubrication aid may be possible by coating the die, using a method described by Amundsen [17].

Placing the die in an aqueous solution of dihydrogen phosphate will coat the metallic surface with a layer of adherent phosphate. The composition of the solution will determine whether the layer is crystalline or amorphous.

A crystalline layer is deposited using an acidic solution of the zinc or magnesium dihydrogen phosphate, and the ions of the metal to be treated. During phosphating a double exchange reaction takes place.

$$2H^+ + Fe^0 \longrightarrow Fe^{2+} + H_2 \qquad \text{equation 1}$$

$$Zn(H_2PO_4)_2 \rightleftharpoons Zn^{2+} + 2H_2PO_4^- \qquad \text{equation 2}$$

$$H_2PO_4^- \rightleftharpoons HPO_4^{2-} + H^+ \qquad \text{equation 3}$$

$$HPO_4^{2-} \rightleftharpoons PO_4^{3-} + H^+ \qquad \text{equation 4}$$

$$3Fe^{3+} + 3Zn^{2+} + 5PO_4^{3-} \rightleftharpoons Zn_3(PO_4)_2 + Fe_3(PO_4)_3 \qquad \text{equation 5}$$

$$Fe^{2+} + 2H_2PO_4^- \longrightarrow Fe(H_2PO_4)_2 \qquad \text{equation 6}$$

Equation 1 shows the acidation of the metal surface, equation 2 the equilibrium in which the zinc dihydrogen phosphate exists, equation 3 and 4 show how the phosphate ion is created which acts in 5, equation 5 shows the creation of the phosphate salt and the dihydrogen phosphate salt in equation 6. The iron reacting in both these cases may either be free ions in solution or acidized on the die wall.

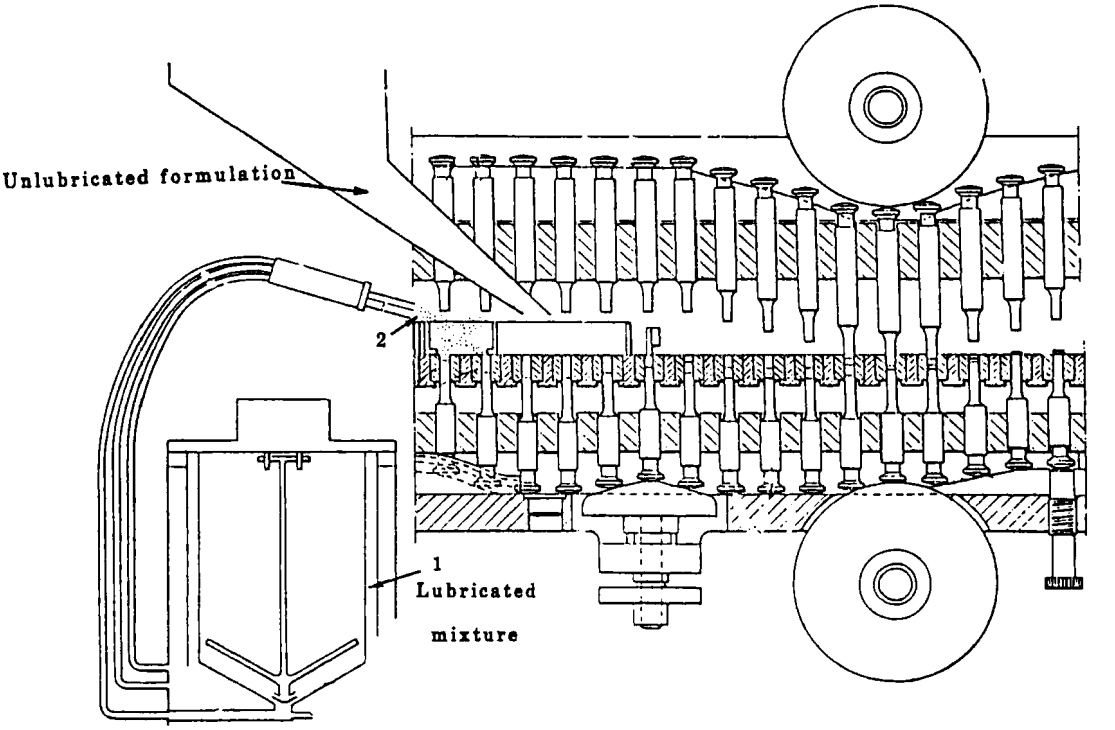
A stock phosphating solution was prepared by dissolving 5.5g of zinc oxide in 11.7 cm^3 of phosphoric acid in a 50 cm^3 volumetric flask. 30g of zinc chloride and 2.5g of Iron II chloride were weighed and washed into the 50 cm^3 volumetric flask, together with 19 cm^3 of distilled ater. The flask contents were agitated overnight using a magnetic stirrer and the resulting stock solution was made up to volume with distilled water. 10 cm^3 of stock solution was diluted to 250 cm^3 using distilled water. 150 cm^3 of this solution was heated to 55°C in a beaker using a heating mantle. A die was thoroughly cleaned using acetone and

then immersed in the heated phosphating solution for 15 minutes. After this time it was removed, rinsed with water and allowed to cool. The die surface was examined using electron microscopy and x-ray energy dispersive analysis together with a similar unphosphated die. The lubricant activity of the phosphated die was compared with that exerted by added lubricants: Leucine and Compitrol using Emcocel or Emcompress as the principle excipient of the formulations.

(b) (ii) Electro-lubrication

A newly researched and patented method of applying tablet lubricants allows formulations to be compacted in the absence of "internal" lubricant. Magnesium stearate, or any other lubricants are applied "externally" to the formulation and in this way, the very beneficial effects of lubricants like magnesium stearate can be used without having to accommodate the adverse effects described above. The way in which lubricants such as magnesium stearate can be applied externally and need not be added to the rest of the drug formulation is by using electrostatic deposition of lubricant particles on punch faces and die walls.

Fig 2 shows the general layout of an electrostatic lubrication system attached to a rotary tableting machine. The magnesium stearate or other lubricant is blended with other fine components of the formulation to its normal lubricant concentration of say, 0.5 - 1.0%. This lubricant blend is fed



204

Figure 2- Schematic representation of electrostatic lubrication system

into the lubricant hopper (fig 2, £1). From here the lubricant is blown in air suspension past an electrostatically charged needle (fig 2, £2) and the charged dry particle spray is directed into a specially sectioned-off area at the very front of a modified feed frame. Under these conditions, the charged powder is attracted to earth at the die wall and on the upper and lower punch faces. This now-lubricated station of tooling passes into the second part of the feed from where the unlubricated formulation is fed in.

The rest of the tableting process is essentially similar to that of a normal rotary tableting machine.

RESULTS AND DISCUSSION

(a) (i) Substitution of Magnesium Stearate with Other Lubricants

Figures 3 and 4 compare the difference in ejection forces for various alternative tablet lubricants to those for magnesium stearate. The data shows that none of the alternative lubricants were as effective in reducing ejection forces as magnesium stearate. Although sodium stearyl fumarate was found to produce acceptably low ejection forces in tablets made from either Emcocel or Emcompress, some of the other lubricants showed different efficiencies for the brittle excipient compared with the ductile excipient. Notably, it appears from this data that Leucine has a greater benefit when used as a lubricant for ductile formulations, than when included in more brittle formulations. This difference in performance of Leucine may result from formation of new surfaces through fracture of brittle materials during compaction. It could be hypothesized that Leucine is unable to adequately coat these surfaces and therefore the coefficient of friction rises. Whereas, in ductile materials plastic deformation occurs, so that deforming surfaces could be assumed to carry the Leucine with them as a near continuous coating. Leucine has a melting point of 294^{o}C and acts as a boundary lubricant. However, the converse situation exists for fluid film-forming lubricants, such as the low melting point oils, Lubritab and Compitrol. In these cases, creation of high coefficients of friction in brittle materials as

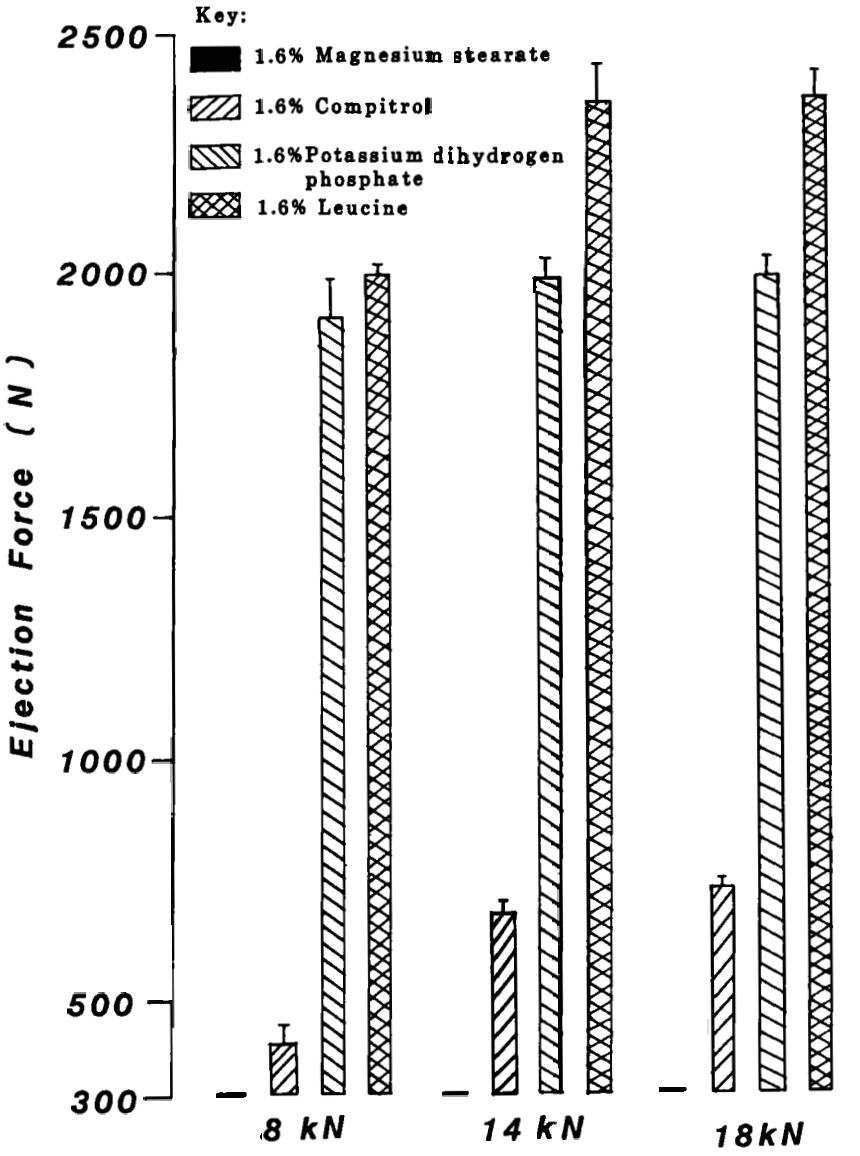


Figure 3A- A comparison of lubricant efficiency at different compaction forces for a model ductile powder- Emcocel

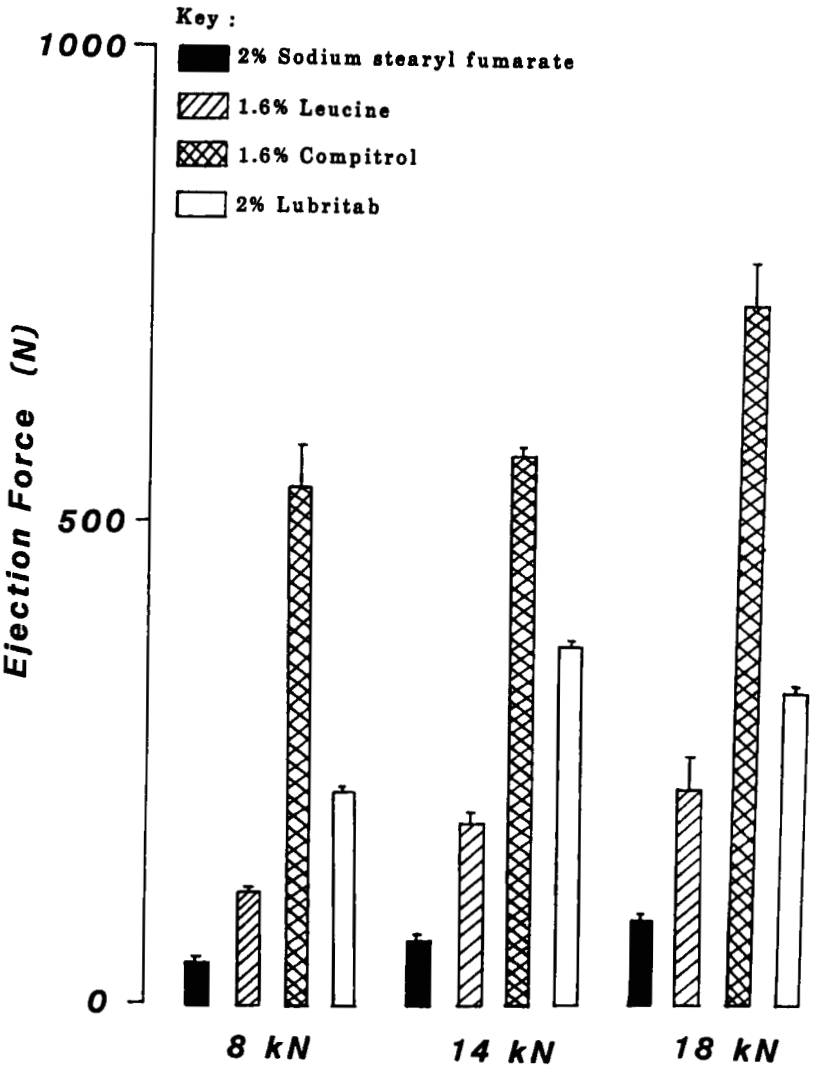


Figure 4A- A comparison of lubricant efficiency at different compaction forces for a model brittle powder- Emcompress

they fragment, creates localized heating and favours lubricant melting. Thus for this type of alternative lubricant, brittle formulations may be more efficiently lubricated than ductile formulations (figs 3 and 4).

(a) (ii) Factorial Analysis of Particle Interactions in Quinary Mixes

The main effects of different factors and their interactions are presented in table 3. Fig 5 shows the relationship between the coefficient of variation (CV) used to indicate physical stability (resistance to drug segregation) and different fomulations in vibrated and non-vibrated conditions. The effects of magnesium stearate, colloidal silica and soidum starch glycolate on the physical stability of the quinary system are summarized in figs 6, 7 and 8. These diagrams are used for the intpretation and visualization of the main effects of the factors and their interactions. For example, in fig 6 labelled magnesium stearate, any effect and interaction may be assessed visually by comparing the slopes of the lines (B- C-) and (B- C+) as well as comparing the slopes of the lines (B+ C-) and (B+ C+) in both non-vibrated and vibrated conditions. Dotted lines represent the main effect which is the average of all data at low and high levels of the factors in each diagram. The fact that these lines are not parallel indicates dependency or interaction of these factors (ie colloidal silica and sodium starch glycolate) with magnesium stearate. On the other hand, parallel lines indicate

TABLE 3

Non-Vibrated System

Results and Analysis[a] for the Factorial Experiment
(Run in Duplicate)

Source of Variation	CV% Exp 1	CV% Exp 2	df	Effect	Sum of Squares	b F Value
(1)	7.730	7.035	1	95.82	1147.68	-
a	18.430	19.430	1	30.90	119.350	64.63**
b	7.240	10.650	1	7.06	6.230	3.37
ab	13.580	17.520	1	11.34	16.074	8.71*
c	9.970	5.890	1	-5.5	3.780	2.043
ac	19.040	15.650	1	-5.7	4.060	4.157
bc	7.470	9.240	1	-3.74	1.750	0.948
abc	11.478	11.580	1	-1.14	0.162	0.087
Residual			8			
Total (n-1)			15			

Key: a Analysis of variance depends on Yates' method
b Significance level based on 1 and 8 df

F .01 1,8 = 11.26 }
F 0.025 1,8 = 7.57 } From F - Distribution Tables
F 0.05 1,8 = 5.32 }

** P < 0.01
* P < 0.025

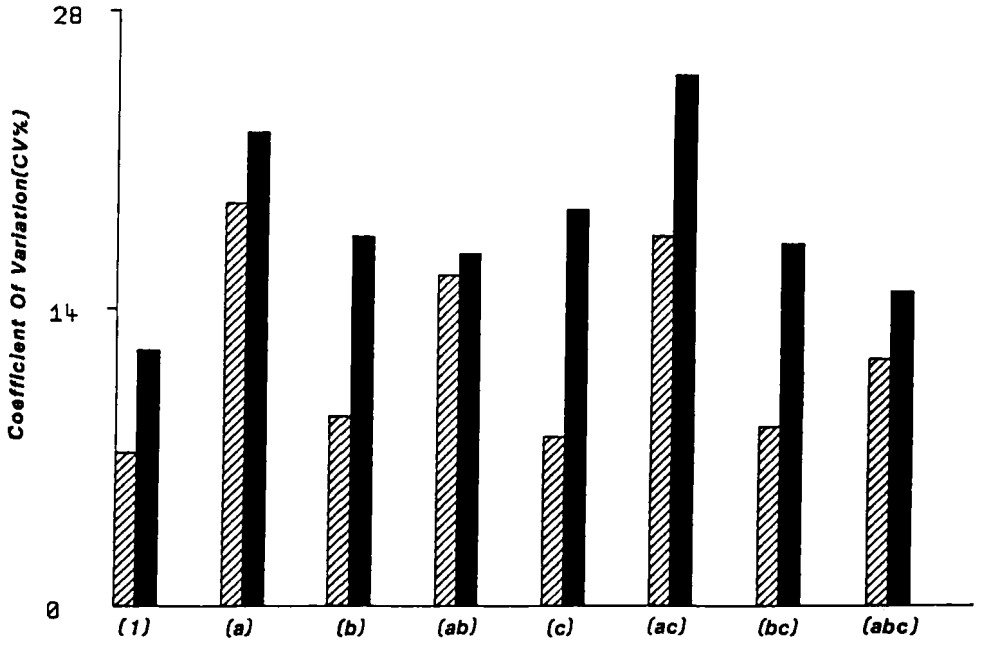


Figure 5- Relationship between CV% & different formulations at vibrated & non/vibrated conditions

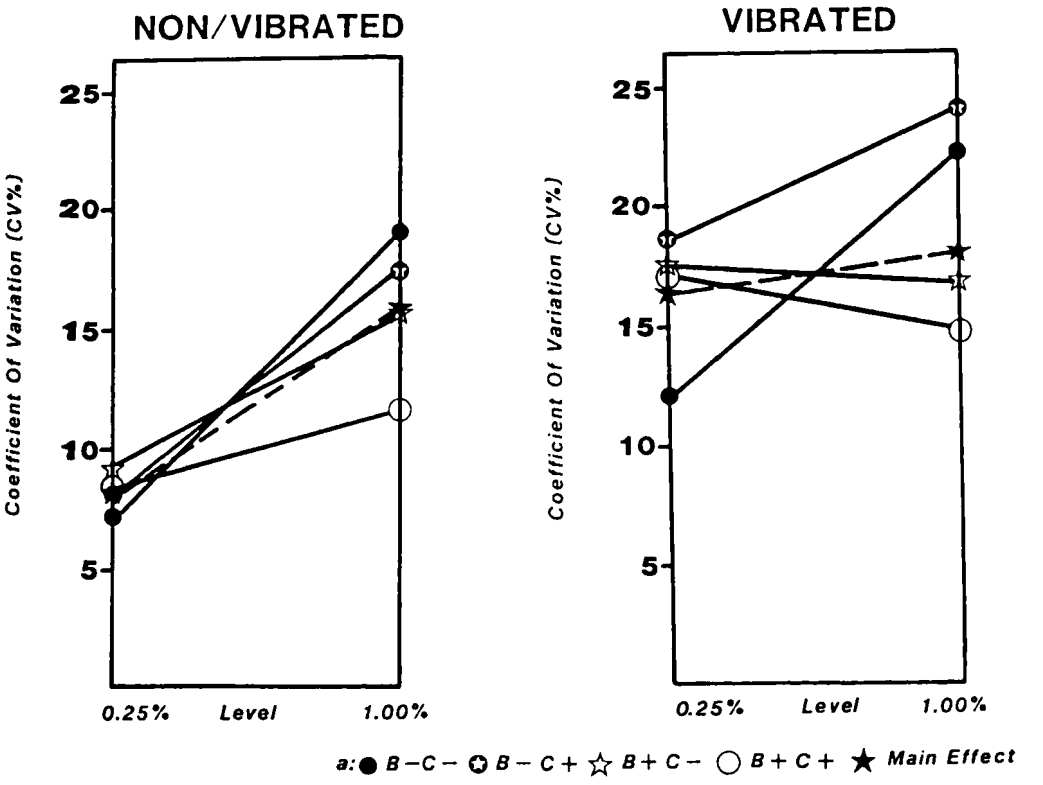


Figure 6- Magnesium Stearate

TABLE 4

Vibrated System

Results and Analysis[a] for the Factorial Experiment
(Run in Duplicate)

Source of Variation	CV% Exp 1	CV% Exp 2	df	Effect	Sum of Squares	F Value[b]
(1)	12.51	11.57	1	143.19	2562.90	-
a	23.61	20.79	1	13.35	22.28	7.71*
b	15.95	18.79	1	-12.23	18.70	6.47*
ab	13.27	19.76	1	-19.55	47.78	16.53*
c	19.65	17.53	1	6.95	6.04	2.08
ac	22.58	27.17	1	-5.25	3.45	1.19
bc	15.71	18.14	1	-11.51	16.56	5.73*
abc	13.86	15.51	1	2.49	0.78	0.27
Residual			8			
Total			15			

Key: a Analysis depends on Yates' method
b Significance level based on 1 and 8 df

* $P < 0.05$

$F_{0.01\ 1,8} = 11.26$
$F_{0.025\ 1,8} = 7.57$
$F_{0.05\ 1,8} = 5.32$

lack of any interaction of dependency. This may be seen when a comparison is made in fig 8 labelled sodium starch glycollate, between non-vibrated and vibrated conditions. In the non-vibrated conditions, lines are approximately parallel, which indicates minimum interaction berween magnesium stearate or colloidal silica

TABLE 5

Main Effects and Interactions

Components/Condition	Non-Vibrated	Vibrated
Magnesium Stearate	+ 7.725%	+ 3.37%
Aerosil 200	- 1.765%	- 3.057%
Explotab	- 1.375%	+ 1.737%
Mag. Stearate/ Aerosil 200	- 2.835%	- 4.887%
Mag. Stearate/ Explotab	- 1.425%	- 1.31%
Aerosil 200/ Explotab	- 0.935%	- 2.88%
Mag. Stearate/ Aerosil 200/ Explotab	- 0.285%	+ 0.6225%

The overall average effect = (11.97%) non-vibrated

(17.90%) vibrated

with sodium starch glycolate; put another way - it shows that the effects of magnesium stearate and colloidal silica are both independent of sodium starch glycolate. During vibration (fig 8) the lines are no longer parallel and even cross each other, this indicates a greater interaction between magnesium stearate or colloidal silica and sodium starch glycolate. In fact the

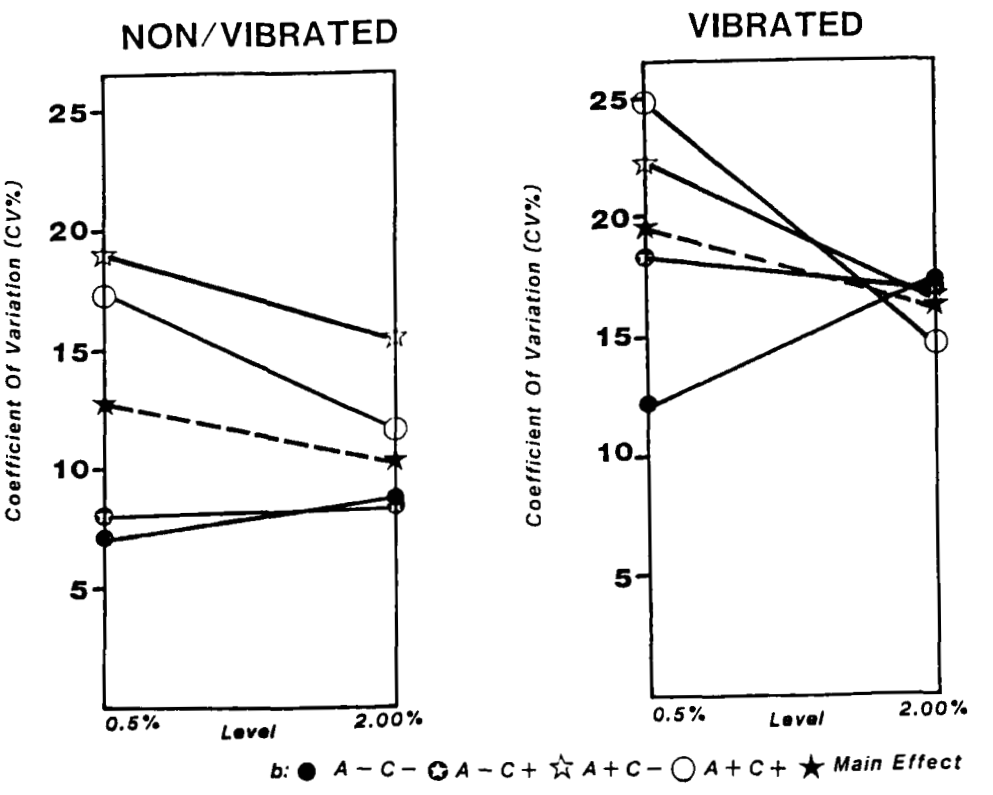


Figure 7- Colloidal Silica (Aerosil 200)

colloidal silica/sodium starch glycolate interaction was found to be statistically significant ($P < 0.05$), which results in an improvement in physical stability of the quinary mix. Other figures can be interpreted in the same manner when investigating main effects and interactions. More information may be obtained from these figures, for example, in fig 6 labelled magnesium stearate, if factor B (colloidal silica) is equal to 0.5% and factor C (sodium starch glycolate) equals 2%, an increase in concentration of magnesium stearate from 0.25% to 1.00% results in

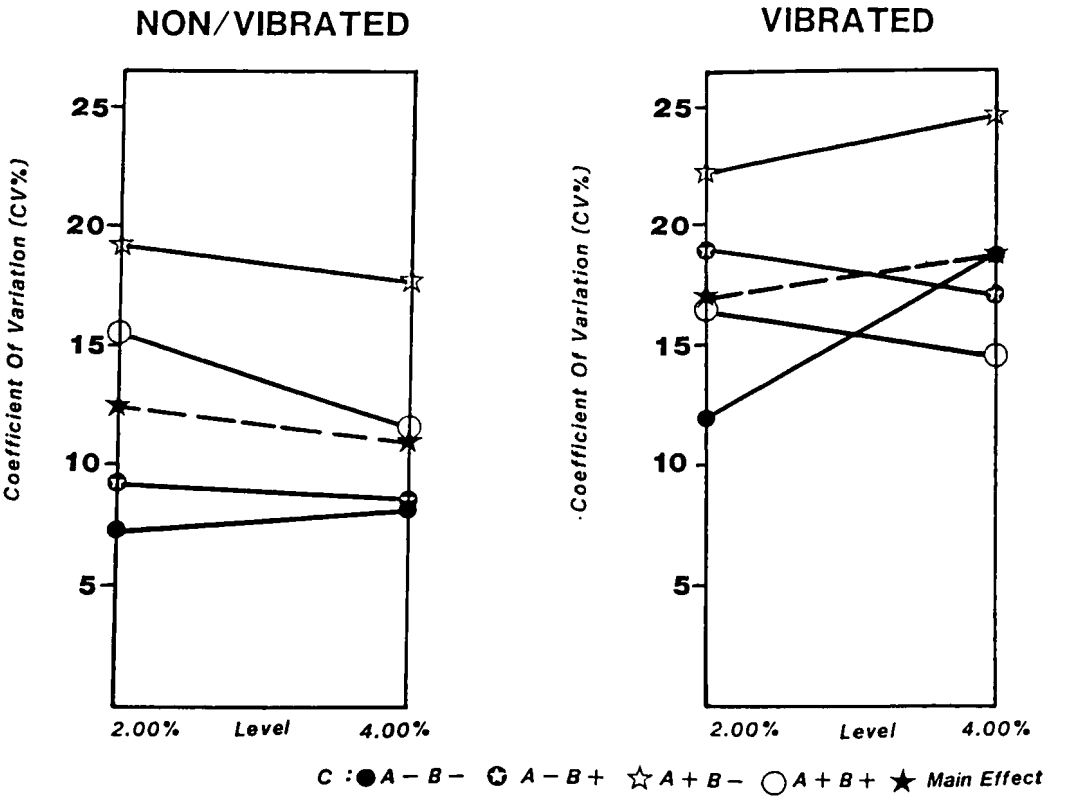


Figure 8- Sodium Starch Glycollate (ExplotAB)

an increase of CV% from 7.23% to 18.93%, in the non-vibrated system. In a vibrated system the corresponding change in CV% was from 12.04% to 22.20% (ie mean values of combination (1) and (a) in tables 4 and 5).

Tables 4 and 5 show the main results of the experiment in both non-vibrated and vibrated conditions, as well as analysis of variance of a 2^3 factorial experiment run in duplicate. An interesting feature of table 4 is that it shows the highly

significant effect of magnesium stearate dominating any effect of colloidal silica which appears insignificant during non-vibrating flow conditions. However, after vibration (table 5), a significant effect of the colloidal silica was observed. It seems that vibration reduces the dominating effect of magnesium stearate and hence allows a significant interaction of colloidal silica to occur. In both conditions magnesium stearate/colloidal silica interactions were shown to be significant which results in an improvement in the physical stability of the quinary mix. According to the present study, magnesium stearate showed a significant destabilizing effect on the homogeneity of the quinary mix. In contrast, colloidal silica showed a significant re-stabilizing effect. Sodium starch glycolate has an indirect re-stabilizing effect through an interaction with colloidal silica.

The effect of colloidal silica and perhaps to a lesser extent, sodium starch glycolate in reducing the deleterious effects of magnesium stearate, results from enrobement of the lubricant by other particles[13]. Such enrobement restricts spreading of the magnesium stearate prior to compaction, but during the compaction event, high shear forces exist close to the die wall causing the magnesium stearate to be exposed thereby producing lubrication. This hypothesis is supported by other data which shows that enrobement of magnesium stearate with colloidal silica restores tablet strengths and prevents loss of homogeneity, without compromising lubricant efficiency[14].

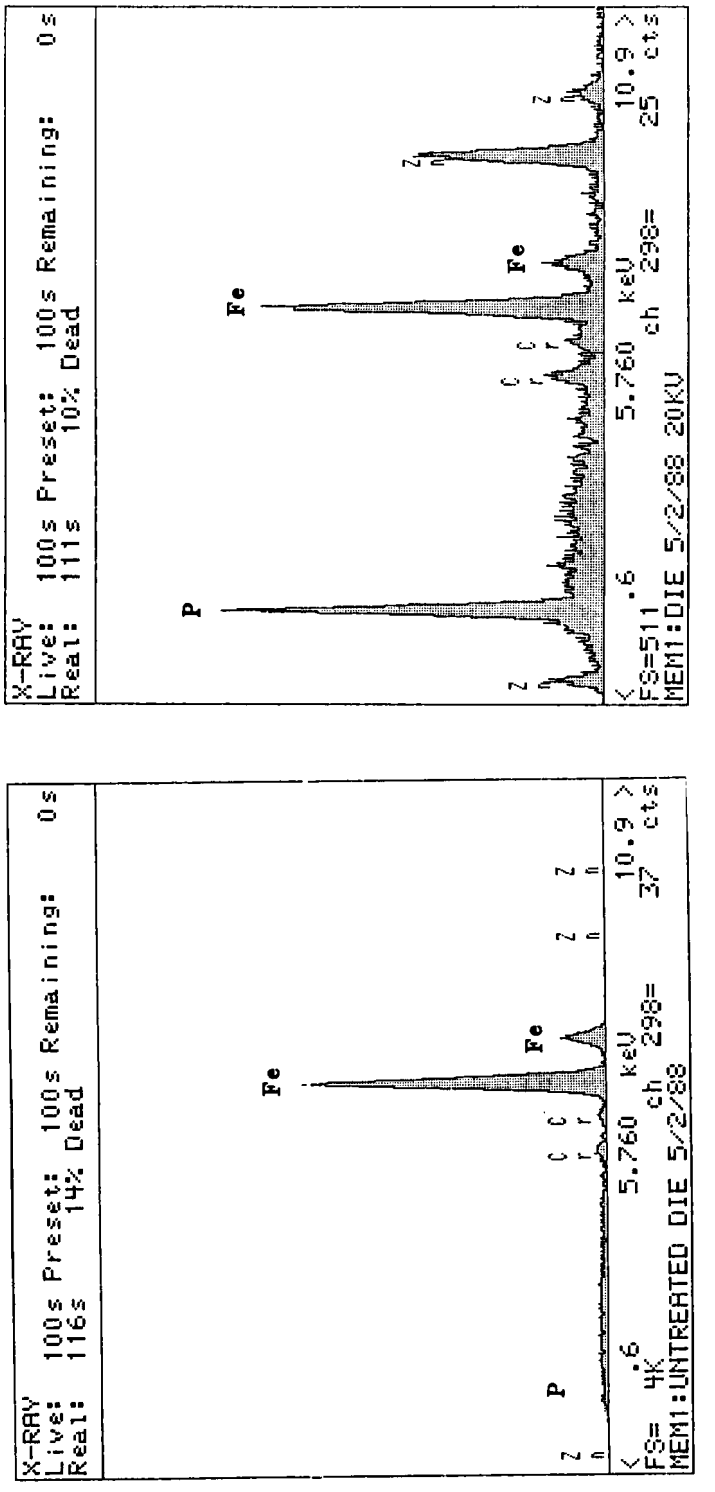


Figure 9- X-ray energy dispersive analysis of 2 tablet die surfaces

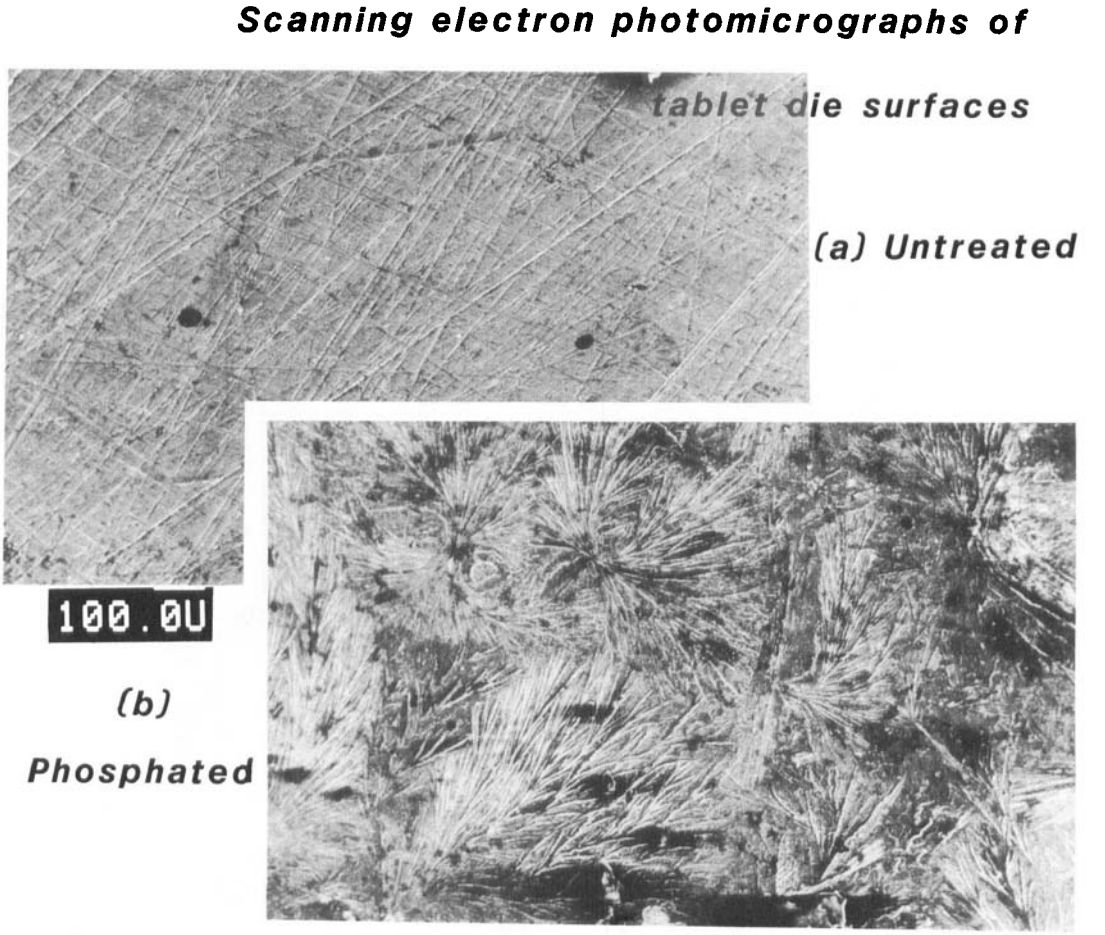


Figure 10

(b) (i) Pre-treatment of Die Walls by Phosphation

X-ray energy dispersive microanalysis of die wall surfaces shows that phosphation causes both phosphor and zinc to be deposited on the die (fig 9a,b). The phosphor is most probably present as the phosphate or dihydrogen phosphate and the zinc as the zinc phosphate salt, as suggested by equations 5 and 6 above.

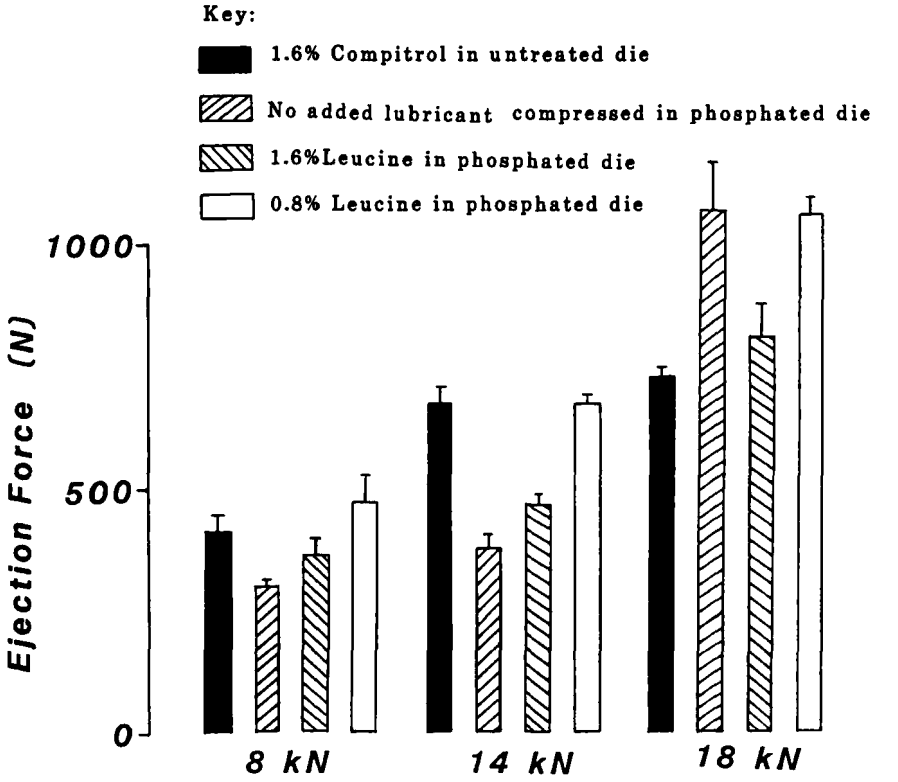


Figure 11- Effect of phosphating tablet dies on lubrication of Emcocel

X-ray dot mapping of the die wall surface showed that both zinc and phosphor ions were homogeneously distributed and electron micrographs of the surface (fig 10b) showed that phosphor was deposited by surface crystallization. Fig 11 shows that at 8 and 14kN compaction forces, the phosphorylated die exerted a greater lubricant effect on Emcocel than did the added lubricants, Compitrol using an unphosphorylated die. These results show that phosphorylation produces a friction-reducing effect between powder

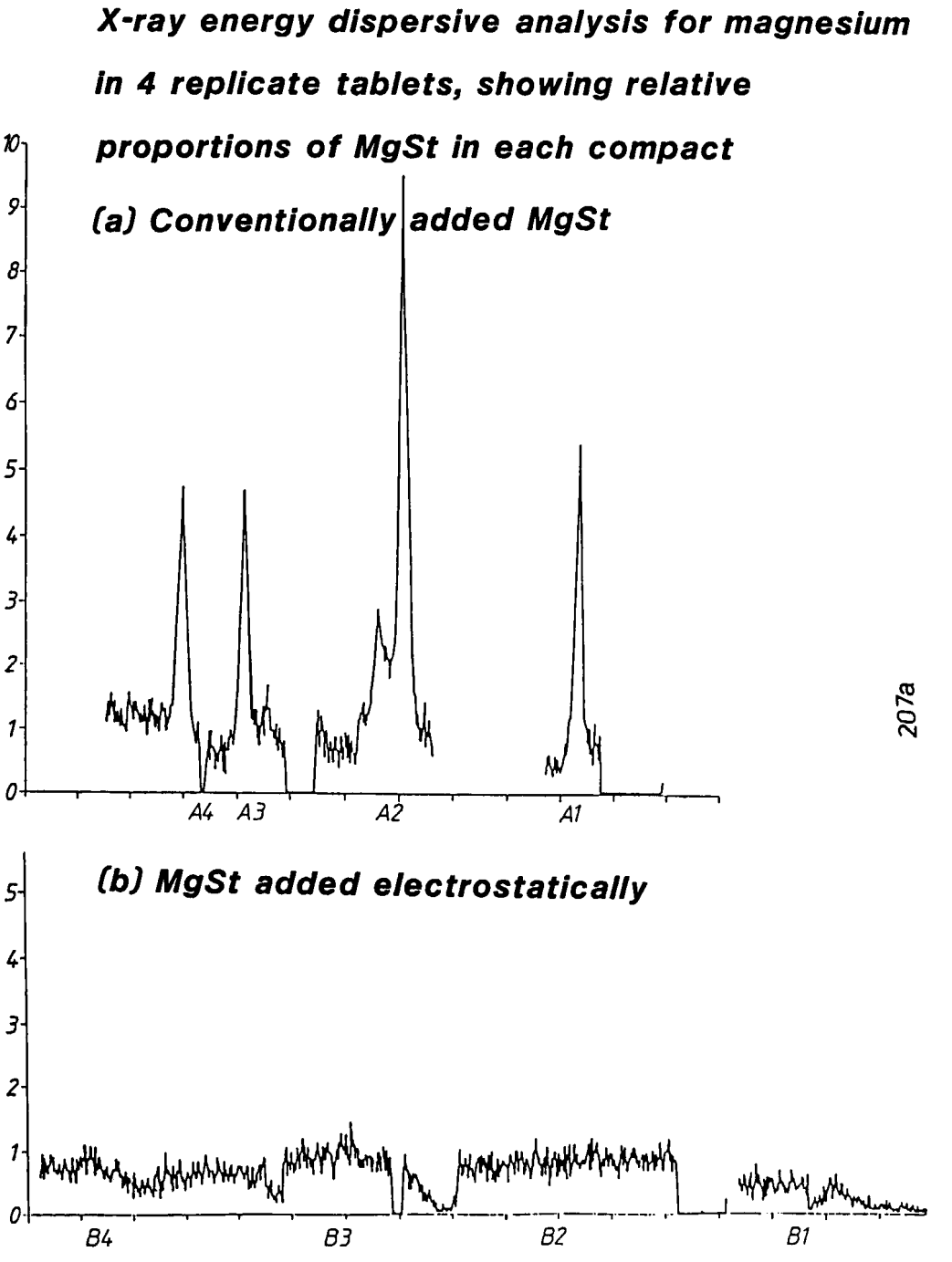


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Figure 12

and die wall. However, the deposited phosphate layer is black and may be friable on prolonged tablet production (although no evidence of exchange onto tablet surfaces was found in this study).

(b) (ii) Electro-lubrication

It was found that applying magnesium stearate externally using electrostatic deposition, produces tablet which contain only trace quantities of magnesium stearate. Fig 12a shows an energy dispersive x-ray analysis of four conventional tablets. In each case the x-ray energy peak corresponds with that for magnesium, and the area under the curve shows the proportion of magnesium stearate. Fig 12b shows the equivalent energy dispersive x-ray analyses for four tablets produced using electrostatic deposition of magnesium stearate. The magnesium concentrations are within the background noise of the analysis method.

Because only a fraction of the normal concentration of lubricant such as magnesium stearate is present in each tablet, hydrophobic lubricants such as magnesium stearate can be solubilized using a small concentration of surfactant in formulations which are to be used as soluble or effervescent tablets. In this way, the benefits of magnesium stearate can be fully utilized without concern for adverse effects, including those associated with use in soluble or effervescent formulations. It has been found that strengths can be virtually doubled, without any alteration to the tablet formulation

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