JPP Journal of Pharmacy and Pharmacology

JPP 2004, 56: 299–305

Received September 24, 2003
Accepted November 19, 2003
DOI 10.1211/0022357022827
ISSN 0022-3573

Effect of lubricant type and concentration on the punch tip adherence of model ibuprofen formulations

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Abstract

A model formulation, comprising ibuprofen and direct compression lactose (Tablettose 80) was used to assess the influence of two lubricants, magnesium stearate and stearic acid, on punch tip adherence. Lubricant concentrations were varied from 0.25% to 2% w/w. Formulations in the presence and absence of 0.5% w/w colloidal silica (Aerosil 200) were examined, to assess the influence of the glidant on the anti-adherent effects of the lubricants. Differential scanning calorimetry (DSC) was used to examine the effect of the lubricants on the melting temperature of ibuprofen. Tablets were compacted using a single punch tablet press at 10 kN using hard chrome-plated punches or at 40 kN using uncoated steel punches, tooling was 12.5-mm diameter in each case. The upper punch faces were characterized by obtaining Taylor Hobson Talysurf surface profiles. Following compaction, ibuprofen attached to the face was quantified by spectroscopy. At low concentrations of each lubricant, the levels of sticking observed were similar. Whilst sticking increased at magnesium stearate concentrations above 1%, sticking with stearic acid remained relatively constant at all concentrations. DSC revealed that the melting temperature of ibuprofen was lowered by the formation of eutectic mixtures with both lubricants. However, the onset temperature of melting and melting point were lowered to a greater extent with magnesium stearate compared with stearic acid. When using uncoated tooling at 40 kN, the deleterious effects of magnesium stearate on the tensile strength of the tablets also contributed to sticking. When using chrome-plated punches at 10 kN, the tensile strength reduction by the presence of magnesium stearate was less pronounced, as was the level of sticking.

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Introduction

Lubricants are added to pharmaceutical tablet formulations to reduce friction between the tablets and die wall during compaction and ejection. A lubricant may also prevent sticking to the die and punches and minimize wear (Zuurman et al 1999).

Magnesium stearate is the most widely used pharmaceutical lubricant (Miller & York 1988). However, the negative effect of the material on tablet strength is well known. During the mixing process, an adsorbed molecular film of magnesium stearate is formed around host particles (Bolhuis et al 1975). The deleterious effects of magnesium stearate are said to be smaller when using materials that fragment during compaction due to disruption of the lubricant film. Therefore, materials that plastically deform, such as microcrystalline cellulose (MCC), are more sensitive to the strength reduction caused by the presence of the lubricant (Bolhuis et al 1975; De Boer et al 1978). However, Riepma et al (1993) claimed that lubricant sensitivity was not related to fragmentation and that tablet strength was determined by the structure of a magnesium stearate matrix created during mixing. Other factors, such as surface texture of particles, might also be of influence (Vromans et al 1988; Riepma et al 1993).

The film formation of magnesium stearate on substrate particles during mixing can be influenced by the presence of a third component in the formulation. Lerk et al (1977) reported that the lubricating properties of magnesium stearate could be retained and its deleterious effects reduced by initial mixing with colloidal silica (Aerosil 200) and subsequent mixing, for a short period, with the lubricant. Similarly, Ragnarsson

et al (1979) stated that short, low intensity mixing of magnesium stearate achieved efficient lubrication. However, they reported that although the addition of Aerosil improved tablet strength, it reduced the lubricating efficiency of magnesium stearate.

Although magnesium stearate is ubiquitous in pharmaceutical tablet formulations its advantages over other lubricants in terms of sticking prevention are debatable. Mitrevej & Augsberger (1982) studied the adhesion of tablets to the lower punch in a rotary tablet press and reported that an increase in magnesium stearate and stearic acid concentrations reduced adhesion only at low compaction forces for both lactose and MCC. Magnesium stearate appeared to have greater anti-adherent properties in MCC blends. However, in lactose blends, the results of the two lubricants were comparable at low concentrations and at higher levels (1%) stearic acid appeared to be more efficient. In a study by Jarosz & Parrott (1984), magnesium stearate produced a greater reduction in strength of aspirin and lactose tablets than stearic acid, and capping of MCC tablets was more probable with the former. It was claimed that stearic acid could be used in concentrations of up to 8% with no effect on tensile strength of tablets made from brittle materials (Jarosz & Parrott 1984).

The aim of this study was to assess the influence of lubricant type and concentration on the sticking of ibuprofen to the upper punch face. Magnesium stearate and stearic acid were used and lubricant concentrations were varied between 0.25% and 2% w/w. The presence and absence of colloidal silica (Aerosil 200) in the formulations was studied to examine the influence of the glidant on the anti-adherent effects of the lubricants. Differential scanning calorimetry (DSC) was used to evaluate the effect of the lubricants on the melting temperature of ibuprofen.

Roberts et al (2003) examined the effects of surface roughness and chrome plating of the punch tip on the adherence of model ibuprofen formulations. A formulation of 69.5% ibuprofen, 29.5% lactose DC, 0.5% Aerosil 200 and 0.5% magnesium stearate exhibited high levels of adherence to the upper punch face during compaction. Particularly high levels were observed when hard-chrome plated punches were used at a compaction force of 10 kN or uncoated steel punches were used at 40 kN. The adherence problems observed when using the two different sets of tooling appeared to be due to different mechanisms. The primary formulation and compaction conditions that resulted in adherence problems were selected for this investigation to evaluate the influence of the type and concentration of lubricant used on the adherence of ibuprofen to the upper punch face.

Materials and Methods

Materials

Ibuprofen crystals (B.P.) were supplied by M & A Pharmachem (UK). The mean particle size of ibuprofen, determined by analysis using stainless steel laboratory test sieves (Endecotts, UK) and a model EVP1 mechanical sieve shaker (Endecotts UK), was 90 μm and the geometric standard deviation (σ_g) was 1.94. Tablettose 80, a commercially available direct compression grade of agglomerated α-lactose monohydrate, was supplied by Meggle GmbH (Germany). Colloidal silica (Aerosil 200, Degussa, UK), magnesium stearate (BDH, UK), stearic acid (VWR, UK) and 96% ethanol (Hayman, UK) were used as supplied.

Formulations

All formulations consisted of ibuprofen and lactose DC. The levels of magnesium stearate or stearic acid in the formulations were varied. When present, Aerosil 200 was added at 0.5% w/w. The content of each formulation used is shown in Table 1.

Scanning electron microscopy

Ibuprofen powder particles were examined using a JSM-840 Scanning Electron Microscope (Jeol, Japan) at $\times$ 200 magnification with an accelerating voltage of 20 kV. Before imaging, ibuprofen samples were coated for 5 min using an E5000 gold sputter coater (Polaron, UK).

Powder mixing

Ibuprofen, lactose and Aerosil (when present) were blended in a 500-mL glass jar using a tumbling powder mixer, consisting of a motor (Heidolph, Germany) and clamp, for 10 min at 40 rev min^{-1}. Following the initial blending stage, powder was sieved using a 1-mm aperture sieve (Endecotts, UK) to remove any agglomerates. The required amount of lubricant, magnesium stearate or stearic acid, was added and the formulation blended for a further 5 min.

Differential scanning calorimetry (DSC)

A differential scanning calorimeter (DSC 7, Perkin Elmer, UK) with automatic cooling facilities (Intracooler II, Perkin Elmer, UK) was used to determine the melting point of ibuprofen and to assess any effects of the lubri-

Table 1 Formulations used.

Component (%w/w)	Without Aerosil						With 0.5% w/w Aerosil					
Lubricant	0.25	0.5	0.75	1.0	1.5	2.0	0.25	0.5	0.75	1.0	1.5	2.0
Ibuprofen	69.9	69.75	69.65	69.5	69.25	69.0	69.65	69.5	69.4	69.25	69.0	68.75
Lactose	29.85	29.75	29.6	29.5	29.25	29.0	29.6	29.5	29.35	29.25	29.0	28.75

cants on the melting point. Scan rates of 10 °C min^{-1} and sample weights of 3–5 mg were used. Calibration was performed using indium and zinc samples and an empty DSC pan was used as reference. Pyris software was used to calculate onset temperature (extrapolated) and melting points.

Punch surface characterization

Surface profiles of the upper punch faces were obtained from a Taylor Hobson Form Talysurf 120 (Taylor Hobson, UK) as described by Roberts et al (2003).

Compaction

Tablets were compacted at 10 kN with 12.5-mm, flat-faced, chrome-plated punches or at 40 kN with 12.5-mm, flat-faced, uncoated tooling using an F3 single-punch tablet press (Manesty, UK) instrumented with strain gauges to measure upper punch compaction force. Strain gauges were connected, via a junction box (Bruel & Kjoer, Germany), to a chart recorder (SE120, ABB, UK). Target tablet weight was 400 mg. Each compaction run (i.e. running time of tablet press for each data set) was 1 min and production speed was 19 tablets min^{-1}.

Sticking quantification

Following each compaction run of 1 min, the upper punch was removed and the punch barrel was cleaned of any powder. Immediately, the punch face was immersed in 5 mL 96% ethanol and gently agitated to allow the surface powder to dissolve. The solution was analysed by spectroscopy at 264 nm using a diode array spectrophotometer (Hewlett Packard 845 2A) and the amount of ibuprofen (μg) attached to the punch face determined.

Statistical analysis

Results of the sticking quantification using the various formulation, punch and compaction force combinations were analysed using the Minitab statistical package. Analysis of variance was used to assess any significant ($P < 0.05$) differences in the levels of sticking observed.

Tensile strength

The tensile strength of tablets was assessed 24 h after ejection. Tablet dimensions were determined using a micrometer (Mitutoyo, Japan) and crushing strength was determined using a Pharmatron 6D tablet hardness tester (Dr Schleuniger, Germany). Tensile strength was calculated using the equation described by Fell & Newton (1968):

$$\sigma = 2P/\pi DT \quad (1)$$

where σ is the tensile strength (Pa), P is the crushing strength (kp), D is tablet diameter (mm) and T is tablet thickness (mm).

Results and Discussion

The SEM image of ibuprofen (Figure 1) shows the typical morphology of the acicular drug crystals used.

The Taylor Hobson Talysurf profiles of the hard chrome-plated and the uncoated steel upper punch are given in Table 2. Ra (mean of positive deviations) values for both punches were comparable. Although the Rt (maximum range) and Rz (mean of five highest peaks) values obtained differed slightly for the two sets of punches, both indicated good quality smooth surfaces with few imperfections.

Sticking of ibuprofen to the upper uncoated steel punch at a 40 kN compaction force is shown in Figure 2. Adherence levels were not reduced by increasing the concentration of magnesium stearate and as the lubricant concentration increased the amount of sticking increased significantly ($P < 0.05$), particularly at magnesium stearate levels above 1%. In a previous study (Roberts et al 2003), the high levels of sticking observed under these compaction conditions were attributed to the smooth surface of the punch face retarding the detachment of the tablet after compaction. DSC scans of the formulations

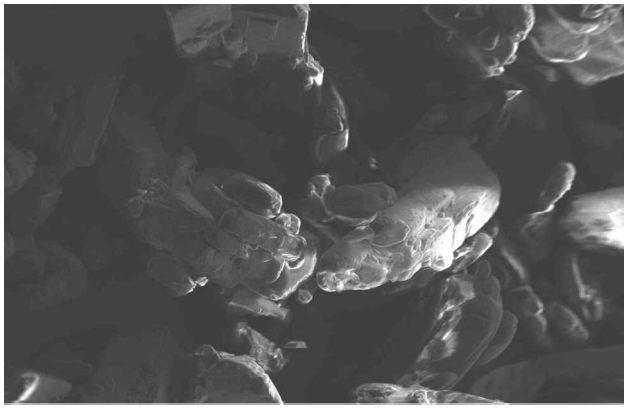

Figure 1 Scanning electron microscope image of ibuprofen particles at × 200 magnification.

Table 2 Taylor Hobson Talysurf 120 surface profiles of uncoated upper punch and chrome-plated upper punch faces.

Surface profile parameter	Uncoated steel punch	Chrome punch
Ra (mean of positive deviations, μm)	0.04 ± 0.02	0.05 ± 0.01
Rt (maximun range, μm)	0.44 ± 0.12	0.19 ± 0.03
Rz (mean of five highest peaks, μm)	0.20 ± 0.06	0.10 ± 0.01

Values are mean ± s.d., n = 5.

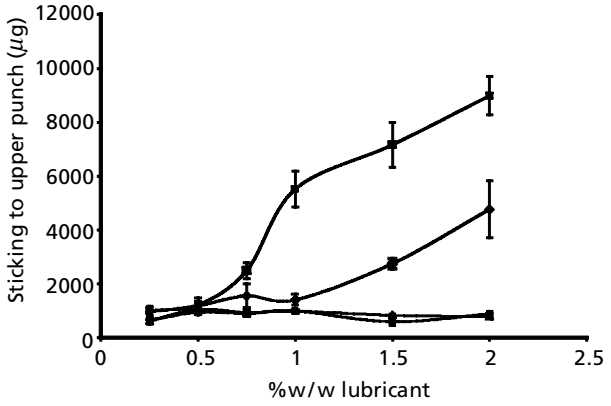

Figure 2 The effect of lubricant type and concentration in ibuprofen:lactose formulations, in the presence and absence of Aerosil 200, on sticking of ibuprofen to the upper punch face using 12.5-mm flat faced, uncoated steel punches at 40 kN. Key: magnesium stearate ■, magnesium stearate + 0.5% w/w Aerosil 200 ▲, stearic acid ●, stearic acid + 0.5% w/w Aerosil 200 ♦. Values are mean ± s.d., n = 5 for each data set.

(Figure 3) revealed that the melting point of ibuprofen had been lowered from 78 °C to 73.3 °C and that the onset of melting was lowered to 68.9 °C. The interaction between ibuprofen and the stearate lubricants, resulting in lowered melting point through formation of simple eutectics, was reported by Gordon et al (1984). It appears that the lowering of the onset of melting and the melting point of ibuprofen by around 5 °C resulted in an increase in the amount of adhesion to the upper punch during compaction. Bechard & Down (1992) reported that localized high temperature areas created by interparticulate friction could possibly attain the melting point of many compacted materials and compaction may induce temperature increases as much as 25 °C above ambient temperature. Similarly, Nürnberg & Hopp (1981) claimed that short-term increased temperature would suffice to melt the tablet surface causing concomitant changes in crystal structure. In powder mixtures with a low eutectic point comprehensive and inclusive melting will occur at the surface during processing. When the compressive force is removed rapid recrystallization will occur, which may cause adhesion to the compression tools. The smaller peak at around 50 °C on the DSC scan of the stearic acid formulation corresponds to the melting of the lubricant and also possibly to a small degree of ibuprofen melting. At the same point on the scan of the magnesium stearate formulation there is a slight inflection, again indicating a small degree of melting.

The tensile strength of tablets with magnesium stearate decreased as the levels of lubricant increased (Figure 4). This may be attributed to the reduction in inter-particulate bonding caused by the formation of a lubricant film around carrier particles (Bolhuis et al 1975; De Boer et al 1978; Duberg & Nyström 1982; Vromans & Lerk 1988). The increased sticking with increasing magnesium stearate levels correlated with the reduction in tablet strength caused by the magnesium stearate particles. As the bonds within the tablet were weakened by the presence of the lubricant they may have been broken more readily at the point of sticking (i.e. as the upper punch detaches from the tablet surface), resulting in adhesion to the punch face being greater than the cohesive forces within the tablet.

The inclusion of Aerosil with magnesium stearate resulted in lower sticking levels (Figure 2), and although an increase in sticking was observed with an increase in lubricant concentration at 1.5% and 2%, it was less pronounced. Aerosil has been reported to negate the reduction in bonding caused by magnesium stearate by coating the magnesium stearate particles themselves (Staniforth & Ahmed 1986). The presence of Aerosil reduced the deleterious effects of magnesium stearate, thus increasing tablet strength and lowering the adherence levels. An increase in sticking was still observed at higher lubricant concentrations due to the increased number of free mag-

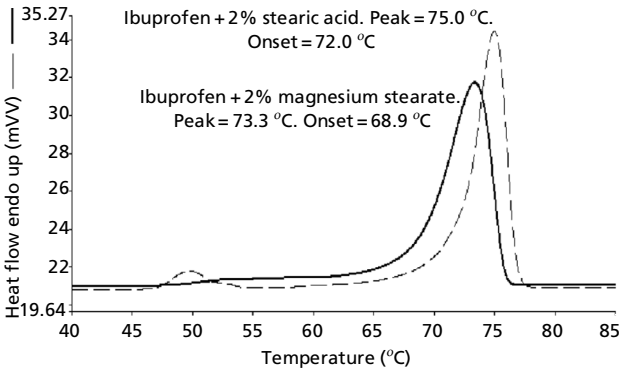

Figure 3 DSC scans of ibuprofen formulations containing 2% w/w lubricant. Scan rate of 10 °C min^{-1}.

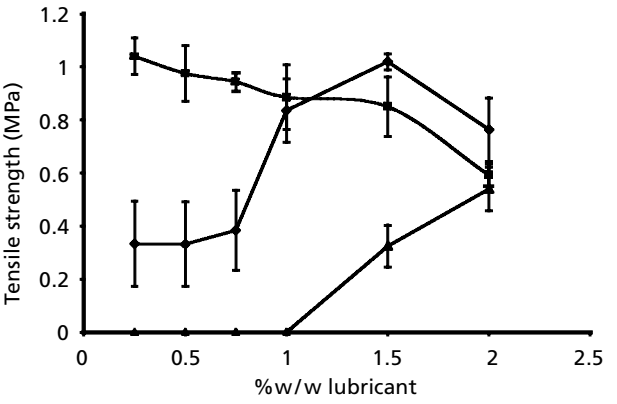

Figure 4 The effect of lubricant type and concentration in ibuprofen:lactose formulations in the presence and absence of Aerosil 200, on the tensile strength of tablets compacted using 12.5-mm flat faced, uncoated steel punches at 40 kN. Key: magnesium stearate ■, magnesium stearate + 0.5% w/w Aerosil 200 ▲, stearic acid + 0.5% w/w Aerosil 200 ♦. Values are mean ± s.d., n = 5 for each data set.

nesium stearate particles not enrobed by the Aerosil particles. The tensile strength data (Figure 4) would be expected to support this conclusion. However, the presence of 0.5% Aerosil at low levels of magnesium stearate (0.25–0.75%) resulted in capping and lamination of the tablets. It appears that this was due to the Aerosil particles enrobing the lubricant particles and preventing efficient lubrication during ejection. Capping and lamination of tablets occurs on ejection from the die due to the elastic recovery of the particles. Pedersen (1999) explained that on decompression elastic recovery occurs axially and the tablet is weakened, whilst on ejection, the recovery also occurs radially. The radial recovery is gradual as the tablet is ejected from the constraints of the die, which results in capping because of failure at the points of low density and bonding within the tablet. Sufficient lubrication would allow easier ejection from the die and reduce the problems of tablet failure. Ibuprofen is known to display high levels of elastic recovery during compaction (Rasenack & Müller 2002) and is prone to capping (Nokhodchi et al 1995). As the magnesium stearate concentration increased (1–2%) the tensile strength of the tablets improved and capping was not observed. This was possibly due to the increased number of free magnesium stearate particles, which were not enrobed by the Aerosil and could therefore facilitate ejection from the die. Therefore, although Aerosil may be able to reduce the negative effects of magnesium stearate it may also reduce the lubricating action of the material, especially when the Aerosil is present in greater or approximately equal quantities to the lubricant.

At 40 kN using uncoated steel punches (Figure 2), stearic acid produced marginally lower sticking levels than magnesium stearate at low concentrations (0.25–0.75%) and significantly ($P < 0.05$) lower sticking at higher concentrations (1–2%). The increase in sticking with increased magnesium stearate concentration was not observed with stearic acid. DSC scans of the stearic acid formulations revealed a lowering of the onset of melting and melting point of ibuprofen as seen with magnesium stearate. However, the onset of melting was 72.0 °C compared with 68.9 °C with magnesium stearate. It is possible that the higher onset of melting with stearic acid did not result in the increase in sticking observed with magnesium stearate. These results differed from previous reports (Gordon et al 1984), where stearic acid was found to reduce the melting point of ibuprofen more than other stearate lubricants.

Tablets compacted at 40 kN with uncoated steel punches, which included stearic acid as the lubricant, exhibited severe capping at all concentrations indicating that the lubricant was not as effective at reducing die-wall friction during ejection as magnesium stearate. Results for the tensile strength of these tablets is not shown in Figure 4 due to the capping of all tablets compacted. The presence of Aerosil improved the quality of tablets (i.e. reduced the occurrence of capping) at stearic acid concentrations of 1.5% and 2%. However, these tablets remained relatively weak and it was likely that the Aerosil improved the flow properties of the formulation, allowing better filling of the die rather than increasing the strength of the tablets. Capping and lamination can also be a result of entrapped air within the powder bed as well as elastic recovery (Pedersen 1999), and although this is not the fundamental cause of the problem, anything that obstructs the expression of air during compression will exacerbate capping (Armstong 1988). The improved die fill, resulting in less entrapped air between particles, combined with increased lubrication at levels of 1.5% and 2% stearic acid, was possibly why fewer tablets capped upon ejection from the die.

Sticking of ibuprofen to the upper punch using hard chrome-plated punches at a compaction force of 10 kN is shown in Figure 5. Adherence levels were not reduced by increasing the concentration of magnesium stearate and as the lubricant concentration increased the amount of sticking increased significantly ($P < 0.05$). Previously (Roberts et al 2003) the high levels of sticking observed under these compaction conditions were attributed to an electrostatic interaction between ibuprofen particles and the chrome surface of the punch face, which did not occur when using uncoated steel tooling. The lowering of the melting temperature of ibuprofen by magnesium stearate (Figure 3) is likely to have increased sticking to the upper punch. However, under these compaction conditions the reduction in tensile strength of the tablets due to the presence of magnesium stearate was less pronounced compared with the results at 40 kN using uncoated steel tooling. Therefore, the combined effect of weaker cohesion and lowered melting was less and the increase in sticking was not as great. When 0.5% Aerosil was included with magnesium stearate in the formulation, the same pattern of increased sticking with increased lubricant levels was observed. This supported the evidence that sticking to the chrome-plated punch at 10 kN was not exacerbated by a reduction in strength, as seen with the uncoated tooling at 40 kN. The presence of Aerosil, shown to negate

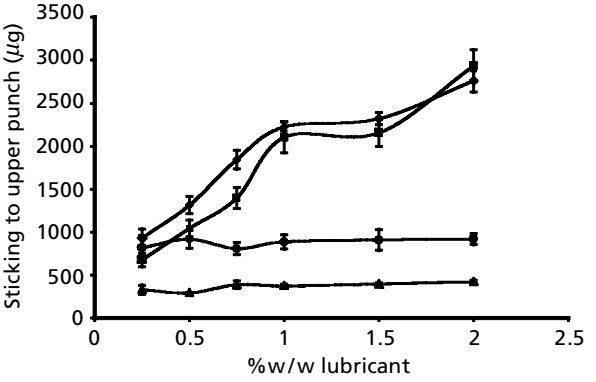

Figure 5 The effect of lubricant type and concentration in ibuprofen:lactose formulations, in the presence and absence of Aerosil 200, on sticking of ibuprofen to the upper punch face using 12.5-mm flat faced, hard chrome-plated punches at 10 kN. Key: magnesium stearate ■, magnesium stearate + 0.5% w/w Aerosil 200 ▲, stearic acid ●, stearic acid + 0.5% w/w Aerosil 200 ◆. Values are mean ± s.d., n = 5 for each data set.

the deleterious effects of magnesium stearate by the absence of a decrease in tensile strength (Figure 6), had no effect on sticking.

With chrome-plated punches stearic acid produced comparable sticking levels to magnesium stearate at low lubricant concentrations (0.25% and 0.5%). However, at higher concentrations, sticking remained relatively constant and the increase in sticking with increased lubricant levels, as seen with magnesium stearate, was not observed. This again may be attributable to the lesser reduction in melting temperature of ibuprofen by stearic acid compared with magnesium stearate (Figure 3). In comparison with stearic acid alone a reduction in sticking at all lubricant levels was seen when 0.5% Aerosil was included with stearic acid. This corresponded with the highest values of tensile strength (Figure 6). Therefore, the improvement in powder flow due to the presence of the glidant, the resultant better die-filling and stronger cohesion within the tablet resulted in reduced adhesion to the punch face.

Conclusion

Sticking of ibuprofen to the upper punch face during compaction was not reduced by increasing lubricant concentration. Increasing the concentration of magnesium stearate increased sticking whilst increasing the concentration of stearic acid had no effect on the problem. Both lubricants were found to lower the melting temperature of ibuprofen, but magnesium stearate caused a greater reduction in the onset temperature and melting point. This effect, combined with a reduction in the cohesive forces within the tablet due to the deleterious effects of magnesium stearate, caused an increase in sticking when using steel punches at 40 kN. The lesser effect of stearic acid on the melting temperature and tablet strength resulted in no change in the level of sticking with increased lubricant concentration. However, tablets including stearic acid exhibited capping at all concentrations, indicating poor facilitation of tablet ejection. When using chrome-plated punches at 10 kN, magnesium stearate had a lesser effect on tablet strength and resulted in a less pronounced increase in sticking. The presence of 0.5% w/w Aerosil reduced the negative effect of magnesium stearate on tablet strength at 40 kN when using steel punches, but may have also reduced the lubricating effect and resulted in ejection problems such as capping. The glidant also increased the strength of tablets with stearic acid compacted at 10 kN with the chrome-plated punches, resulting in lower levels of sticking.

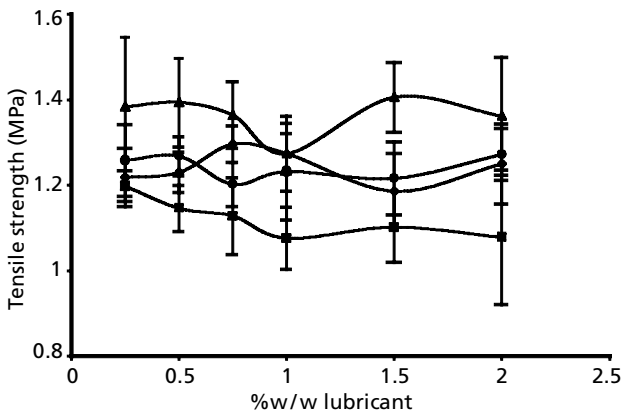

Figure 6 The effect of lubricant type and concentration in ibuprofen:lactose formulations, in the presence and absence of Aerosil 200, on the tensile strength of tablets compacted using 12.5-mm flat faced, hard chrome-plated punches at 10 kN. Key: magnesium stearate ■, magnesium stearate + 0.5% w/w Aerosil 200 ▲, stearic acid ●, stearic acid + 0.5% w/w Aerosil 200 ◆. Values are mean ± s.d., n = 5 for each data set.

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