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Review Articles

Pharmaceutical tablet lubrication

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Introduction

Three interrelated groups of tablet excipients are glidants, anti-adherents and lubricants. These are used in tablet production to promote granule flow, prevent powder adhesion to punch faces, and minimise die-wall friction, respectively (Rawlins, 1977; Lachman et al., 1976). Some confusion exists in the definition of a lubricant, as the word has also been used to encompass all three of the above properties, due to suitable materials often possessing more than one of glidant, anti-adherent and lubricant actions. However, for the purpose of this review a lubricant may be defined as a suitable material, a small amount of which, interposed between two rubbing surfaces will reduce friction arising at the interface (Strickland et al., 1960; Komarek, 1967).

An ideal lubricant should reduce friction effectively in small quantities with no adverse effects upon the formulation. It should be inert and cosmetically acceptable with respect to other dosage form ingredients. From a pharmaceutical viewpoint this usually means white and odourless but water-solubility may also be an essential requirement. The ideal lubricant should be unaffected by changes in process variables, consistent from batch to batch, readily available and cheap.

As yet there is no ideal lubricant material for pharmaceutical powders. This review intends to illustrate the materials available with a critical analysis of their suitability for use and potential for optimisation. Particular attention will be focussed on magnesium stearate, by far the most widely used pharmaceutical lubricant.

Frictional theories

Lubricants are used to reduce frictional forces during tabletting. A consideration of the mechanism of friction is therefore useful in subsequent discussion of the lubrication process.

Early frictional studies were recorded by Leonardo da Vinci, Amontons and Coulomb (Dawson, 1979). These led to the development of the basic laws of friction; that the frictional force is directly proportional to load and independent of the apparent area of contact between surfaces (Braithwaite, 1964) (Fig. 1).

The contact of surfaces through asperities and the role of adhesion were recognised by Bowden and Tabor (1964, 1967) in the development of the adhesional model for friction. This states that the real area of contact between touching surfaces is a small fraction of the apparent contact area and is

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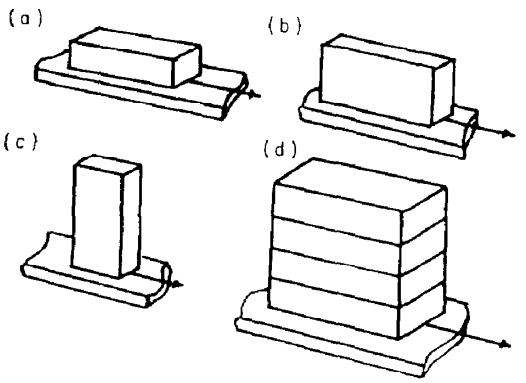

Fig. 1. Illustration of the two basic laws of friction. (a)–(c): friction is independent of the apparent area of contact between solids. (d): friction is proportional to the load between surfaces.

proportional to the perpendicular or normal load for plastically deforming solids. Thus:

$$N = KA \tag{1}$$

where N is the normal load, A is the real area of surface contact and K is a material parameter termed the flow pressure which is related to the hardness of the softer solid (Briscoe, 1982).

The frictional force is the summation of forces required to shear the welded adhesive junctions giving:

$$F = sA \tag{2}$$

where F is the frictional force and s is the shear yield stress of the weaker material. The coefficient of friction μ is then given by:

$$\mu = \frac{F}{N} \tag{3}$$

This model has been extended and modified (Bowden and Tabor, 1964) but nevertheless is directly applicable to the powder/die-wall interface during tablet compression and ejection (York, 1984).

Although basic frictional theory holds for a wide range of situations there are materials and conditions which show deviations from the general laws. For elastically deforming contacts:

$$A \propto N^x \tag{4}$$

where x is less than unity (Bowden and Tabor, 1967). Consequently the frictional coefficient may rise at low loads (Amuzu et al., 1976; Briscoe and Kremnitzer, 1979). Briscoe (1982) concludes that the laws of friction are working approximations whose effective use requires experience and subjective judgements.

Boundary lubrication

There are two main types of lubrication, hydrodynamic or fluid lubrication and boundary lubrication (Bowden and Tabor, 1967). In fluid lubrication the moving surfaces are completely separated by a lubricant layer and resistance to motion arises solely from the lubricant viscosity. Paraffin and mineral oils have been quoted as fluid lubricants for tabletting but boundary lubrication is much more common in pharmaceutical systems (Strickland, 1959; Strickland et al., 1960).

Boundary lubrication occurs when surfaces are separated by thin lubricant films. The friction is influenced by the underlying surfaces as the interfacial load is supported by the lubricant film and by minute junctions formed by substrate asperities which penetrate the lubricant layer (Fig. 2). The frictional force, F, is thus the sum of two terms:

$$F = A\left(\alpha S_s + (1-\alpha) S_L\right) \tag{5}$$

where α is the fraction over which substrate junctions are formed and S_s and S_L are the shear strengths of substrate and lubricant, respectively. Thus good boundary lubricants have a low shear

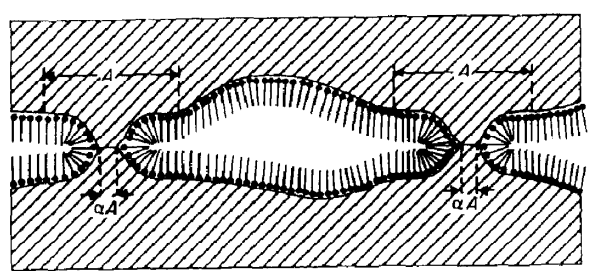

Fig. 2. Diagram showing boundary lubrication mechanism as demonstrated by Eqn. 5. (Bowden and Tabor, 1967).

strength and readily form a film hence reducing α, and are resistant to wear. This model forms the shear strength theory of lubrication (Bowden and Tabor, 1950, 1967) which is that most commonly accepted (Moody et al., 1981). Other proposals include laminar plate rolling (Train and Hersey, 1960), degree of surface and lubricant interaction (Allen and Drauglis, 1969) and antistatic action (Wolff et al., 1947; Gold and Palermo, 1965a and b).

Molecular arrangement of materials in a laminar structure has been reported as favourable for low shear strength. Graphite and molybdenum disulphide are typical examples (Bowden and Tabor, 1967) and a similar structure has been proposed for magnesium stearate (Muller, 1976, 1977c). In contrast, Buckley and Johnson (1972) suggest that this type of structure does not ensure lubricating properties and alternative modes of action for graphite have been suggested (Savage, 1948; Bollman and Spreadbough, 1960). Jentgen (1976) concluded that lubrication of solids could not be ascribed to any one material property, thermal and oxidative stability, chemical reactivity, mobility, strength and crystal structure all affecting lubricant performance.

Lubricant assessment

Early formulators probably evaluated lubricants by trial-and-error, but the development of instrumented tablet presses (Sixsmith, 1977; Marshall, 1983) had led to their extensive use in lubrication assessment. Comparatively few workers, however, have attempted to study lubricants in isolation from host powder systems.

Punch penetration tests have been used to evaluate the shear strengths of lubricant materials (Lewis and Train, 1965a; Lewis and Shotton, 1965) and extrusion forces have also been measured (Salisbury and Higuchi, 1960). A simple sliding test was used to investigate talc and magnesium stearate (Graham and Jenkins, 1952) and a similar concept led to the development of an empirical rotary lubrimeter (Levy and Schwartz, 1957).

Wall friction tests comparable to that developed by Jenike (1964) have found use in lubricant evaluation. Fukumori and Okada (1977) proposed static and kinetic frictional coefficients for pharmaceutical materials which were reduced by addition of 2% talc or magnesium stearate, due to a prevention of contact growth between the metal wall and substrate powder (Hirai and Okada, 1982). Strijbos (1977) showed that lubrication by stearic acid varied according to its film thickness in relation to host particles and metal surface roughness has been shown to be important in tests of this type (Jolliffe and Newton, 1982, 1983). Carstensen and coworkers (Carstensen et al., 1980; Fukumori and Carstensen, 1983) performed friction tests against paper surfaces or, glass (Roblot et al., 1985), to give comparative results of good reproducibility. Shear cells have also been used to study lubricants in isolation from host systems. A modified annular shear cell showed frictional differences between lubricant materials (Baichwal and Augsburger, 1985) and different magnesium stearate grades have been distinguished using a modified wall friction test (Miller et al., 1983; Miller and York, 1985b). Two coefficients were proposed – μ_a, the initial maximum friction coefficient and μ_b, the equilibrium dynamic coefficient of friction (Fig. 3). Studies of this type are important as they serve to bridge the gap in understanding between lubricant characterisation and lubricant behaviour in tablet production.

Early use of instrumented tablet presses for lubricant evaluation involved the measurement of maximum upper to lower punch force ratio or R value (Nelson et al., 1954; Strickland, 1959; Strickland et al., 1960). The better the force transmission in an axial direction the closer the R value becomes to unity. The R values of a number of lubricated granulations have been shown to increase with increased compression force (Lindberg, 1972; Delattre et al., 1976); to be pressure dependent even at constant tablet thickness (Holzer and Sjogren, 1978); and be unsuitable for distinguishing between well-lubricated granulations (Muller et al., 1982a). R value is thus of limited use and should only be employed for tablets with equivalent thickness and compaction pressures.

Many workers have used a measurement of compact ejection force to evaluate lubricants as

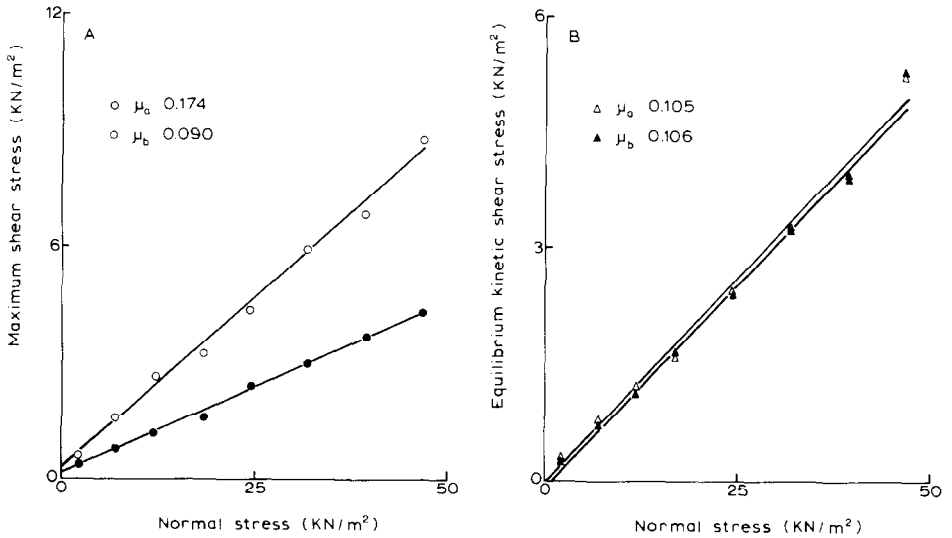

Fig. 3. Initial maximum, τ_a, and equilibrium kinetic shear stress, τ_b, against normal pressure for two magnesium stearate samples A and B. The slopes are μ_a and μ_b respectively (Miller and York, 1985a).

this corresponds more directly to actual tablet production (Hanssen et al., 1970; Juslin and Krogerus, 1971b; Delattre et al., 1976; Ward and Billington, 1979; Holzer and Sjogren, 1979; Al Shammat et al., 1979; Mitrevej and Augsburger, 1982; Holzer, 1983). Holzer and Sjogren (1978) stated the requirement for area compensated ejection force values used earlier for unlubricated systems (Rees and Shotton, 1969) and it has been suggested that ejection energy may be a better parameter for use in lubricant studies (Matsuda et al., 1976).

Another measurement used is that of residual force (Fuhrer et al., 1970; Hanssen et al., 1970; Suren, 1971; Muller et al., 1982b) which is the force remaining on the lower punch prior to the ejection of the compact. Holzer and Sjogren (1977), however, concluded that the measurement of an ejection parameter was preferable to a residual force as the former gave a better prediction of adhesional problems in tabletting.

Work originally done to evaluate frictional work during compression (De Blaey and Polderman, 1970, 1971; Jarvinen and Juslin, 1974; Ragnarrson and Sjogren, 1983a and b) has been adapted for use in lubricant studies (Kikuta and Kitamori, 1983, 1985). Holzer and Sjogren (1981a and b) extended the work of Al Shammat et al. (1979) and used the measurement of tabletting forces to derive die wall static (μ_1) and dynamic (μ_2) friction coefficients.

$$\mu_1 = (UPF - LPF)/DWFM \tag{6}$$

$$\mu_2 = EJF/DWFE \tag{7}$$

where *UPF* and *LPF* are the upper and lower punch forces, respectively, *EJF* is the tablet ejection force, *DWFM* is the maximum die wall force at compression and *DWFE* is the die wall force during tablet ejection. Limitations of this approach have been discussed (James and Newton, 1983; Fukumori and Carstensen 1983) and care must be taken to ensure samples have sufficient thickness to record a true radial force (Miller, 1984).

There are currently a wide range of methods available for the study of tablet compression (Jones, 1978; MacLeod, 1979; Krycer et al., 1982) and some of these have been adopted in lubricant investigations. A simple consideration of weight variation in tablet and capsule formulations was used to compare several lubricants (Caldwell and Westlake, 1973). Tablet crushing strength–com-

pression pressure profiles (Bossert and Stamm, 1980), plots of relative density against applied tabletting pressure (Lewis and Train, 1965b) and Heckel plots (York, 1979; Ragnarrson and Sjogren, 1984) have all found application in lubricant studies.

All methods of lubricant evaluation using tablet presses will be subject to machine, process and protocol variabilities and hence comparisons between studies is hazardous. The choice of technique will usually depend upon resource available and the purpose of investigation. With the advent of sophisticated compaction simulators (Hunter et al., 1976; Ho et al., 1979), enabling precise and variable machine control, it should be possible to obtain greater definition of important parameters for lubricant evaluation.

Lubricant materials

A wide range of compounds are available for use as pharmaceutical lubricants (Moody, 1981; York, 1984). A list of these materials is given in Table 1.

TABLE 1

List of lubricant materials

Group	Examples
Salts of fatty acids	aluminium stearate, calcium stearate, magnesium stearate, zinc stearate, sodium stearate, magnesium palmitate
Fatty acids, hydrocarbons and fatty alcohols	stearic acid, palmitic acid, stearyl alcohol, palmityl alcohol, liquid paraffin
Fatty acid esters	glyceryl monostearate, glyceryl mono- and distearate (Tegin515), glyceryl tristearate (Dynasan 118), glyceryl tripalmitate (Dynasan 116), glyceryl trimyristate (Dynasan 114), glyceryl tribehenate (Compritol 888), glyceryl palmito-stearic ester (Precirol), sorbiton monostearate, sodium stearyl fumarate (Pruv), saccharose monostearate (Sucrapen 5), saccharose monopalmitate (Sucrapen P)
Water soluble	sodium lauryl sulphate, magnesium lauryl sulphate, polyethylene, glycols, polyoxyethylene glycols, sodium benzoate, leucine, glycine, adipic acid
Miscellaneous materials	talc, polytetrafluoroethylene (Fluon, Teflon), fumaric acid, hydrogenated cotton seed oil (Sterotex, Lubritab) castor seed oil (Cutina HR)

Salts of fatty acids

The most common materials used as lubricants in the pharmaceutical industry are the metal soaps of which magnesium stearate is by far the most frequently employed. Molecules of this nature are thought to position with their hydrocarbon chains perpendicular to metal surfaces in a tightly packed manner preventing substrate contact (Buckley and Johnson, 1972). Such lubricants can be prepared in situ on a reactive metal surface (Pilpel, 1966) and provide better lubrication due to strong surface adhesion (Allen and Drauglis, 1969). The best lubrication has been reported for films which have high melting points and suitable shear properties (Rabinowicz and Tabor, 1951; Briscoe et al., 1973). As increased fatty acid chain length will increase the melting point but decrease "shearability" due to cohesion, magnesium stearate would appear to be a good compromise between the desired characteristics.

Magnesium stearate is usually used at a concentration of 0.5–1.0% w/w and possesses good anti-adherent and poor glidant properties in addition to lubricant action (Rawlins, 1977). It is a relatively cheap, non-toxic material (Final Safety Report, 1982) but commercially available supplies are chemically impure (Lien and Miller, 1948; Pilpel, 1971; Mroso et al., 1982; Holzer, 1983; Miller and York, 1985a) often containing a large percentage of magnesium palmitate. This batch variation extends to physical characteristics (Butcher and Jones, 1972; Hanssen et al., 1970) and may cause unpredictable problems in tablet formulations (Billany, 1981; Billany and Richards, 1982).

Magnesium stearate is a hydrophobic material (Lerk et al., 1976), along with all salts of this type, and hence has a negative effect on drug release from formulations (Lowenthal, 1972; Bolhuis et

al., 1975; Lerk and Bolhuis, 1977; Murthy and Samyn, 1977; Iranloye and Parrott, 1978; Soininen and Kuusivouri, 1980; Proost et al., 1983). Other disadvantages include a reduction of tablet strength (De Boer et al., 1978; Lerk et al., 1977; Bolhuis et al., 1975; Higuchi et al., 1953; Bolhuis and Lerk, 1977; Bolhuis et al., 1980) and interaction with some drugs including aspirin (Kornblum and Zoglio, 1967; Mroso et al., 1982; Li Wan Po et al., 1983).

Fatty acids, hydrocarbons and fatty alcohols

Juslin and Krogerus (1970, 1971a, b and c) studied a series of these three materials with carbon chain lengths C_{12}–C_{22}. Fatty acids were found to be generally better lubricants than hydrocarbons as fatty alcohols and increased chain length improved the efficiency of fatty acids and hydrocarbons.

The most commonly used material from this group is stearic acid. Usually used at a concentration of 0.5–2.0% w/w (Burlinson, 1968; Matsuda et al., 1976) it is also a chemically impure material (B.P., 1980) often containing a large percentage of palmitic acid. It is generally regarded as a poorer lubricant than magnesium stearate (Lachman et al., 1976) possessing some antiadherent properties (Mitrevej and Augsburger, 1982). Stearic acid has been shown to decrease tablet strength (Asker et al., 1975; Bolhuis et al., 1980; Jarosz and Parrott, 1984) retard drug dissolution and tablet disintegration (Levy and Gumtow, 1963; Lindberg, 1972; Nicklasson and Brodin, 1982), reduce tetracycline and chloramphenicol activity (Asker et al., 1973) and interact with aspirin (Maudling et al., 1968).

Fatty acid esters

A wide range of fatty acid esters have been examined as lubricants, usually in comparison with a commercial magnesium stearate batch. Various glyceride esters evaluated include glyceryl monostearate (Cid and Jaminet, 1971; Jaminet and Louis, 1968), glyceryl mono and distearate (Tegin 515), glyceryl tristearate (Dynasan 118), glyceryl tripalmitate (Dynasan 116), glyceryl trimyristate (Dynasan 114 and VP 114) (Stamm et al., 1977; Delattre et al., 1976), glyceryl tribehenate (Compritol 888) (Thomas et al., 1982) and glyceride fatty acid ester mixture (Boeson VP) (Bolhuis et al., 1980). A number of sugar esters have also been investigated. These include sorbiton monostearate (Strickland, 1959), sucrose monopalmitate and sucrose monostearate (Lindberg, 1972; Stamm et al., 1977). In general these materials show poorer lubrication than magnesium stearate or require an increased concentration up to 5% w/w in order to be as effective.

Two of the more commonly used fatty acid esters are sodium stearyl fumarate (Pruv) and a glyceryl palmitostearic ester of known composition (Precirol). Precirol was first reported by Jaminet and Hazee (1966) to give comparably stronger tablets, with faster disintegration than the use of magnesium stearate. However, lubrication in terms of tablet ejection force (Delattre et al., 1976; Bolhuis, 1980) and axial force transmission during compression (Paris et al., 1977) is inferior to magnesium stearate. Sodium stearyl fumarate has been recommended as a good alternative to magnesium stearate (Suren, 1971) with particle size a critical factor (Holzer and Sjogren, 1979). The effect of sodium stearyl fumarate on tablet disintegration as compared to magnesium stearate is subject to conflicting reports (Lindberg, 1972; Holzer and Sjogren, 1979). This may be a feature of magnesium stearate batch variation (Muller et al., 1982a) or other processing factors.

Water-soluble lubricants

The deleterious effect of magnesium stearate on tablet dissolution and the development of completely soluble effervescent tablets has led to the investigation of numerous materials for use as water-soluble lubricants.

Sodium and magnesium lauryl sulphates possess lubricating properties (Caldwell and Westlake, 1972, 1973; Osseekey and Rhodes, 1976) but are usually required at a higher concentration than magnesium stearate and have poorer anti-adherent properties (Salpekar and Augsburger, 1974).

Some polyethylene glycols (PEG) have been tried as water-soluble lubricants (Tsumura et al., 1972). The more frequently reported materials are PEG 4000 (Delattre et al., 1976; Strickland, 1959) and PEG 6000 (Stamm et al., 1977; Caldwell and Westlake, 1973) although PEG 1500 has been

investigated (Saleh et al., 1984). These materials always seem to be poorer lubricants than magnesium stearate and are required at concentrations up to 5% w/w within a formulation. Polyoxyethylene glycols are also water-soluble (Smilek et al., 1955) but were shown to be poorer lubricants than even PEG (Maly and Jaros, 1967; Maly, 1969).

A number of other materials tried as water-soluble lubricants include sodium benzoate (Cox, 1971), leucine and isoleucine (Shinozaki et al., 1971; Bolhuis et al., 1980), glycine (Saleh et al., 1984) and adipic acid (Hoss, 1970, 1971; Baker, 1971). These materials are used in a concentration of 2–10% w/w and provide relatively poor lubrication. Some sugar esters may be included as water-soluble lubricants at low concentrations and 0.25% sodium stearyl fumarate has been reported to provide a clear solution suitable for effervescent formulations (Saleh et al., 1984).

Miscellaneous materials

Talc is a hydrous magnesium silicate which has found some use as a tablet lubricant although it serves a better function as a glidant (Rawlins, 1977). Talc is not water soluble and may vary from batch to batch (Gold and Campbell, 1964). Used at a concentration of 1–5% w/w it has been shown to decrease tablet strength (Jarosz and Parrott, 1984; Asker et al., 1975) and drug dissolution (Lowenthal, 1972; Levy and Gumtow, 1963).

Polytetrafluoroethylene (PTFE) has been used in tablet lubrication at concentrations of 1–10% w/w (Hotko, 1967; Delattre et al., 1976; Sperandeo and De Marchi, 1976). It possesses a low coefficient of friction (James and Newton, 1983) low shear strength, high yield pressure and good compactibility (LaManna and Shotton, 1970; Shotton, 1972). Lubrication may be as good as magnesium stearate without impairing tablet strength or dissolution (Alpar et al., 1969; Conte et al., 1972). However, the nature of degradation products above its melting point of 250 °C have led to doubts over its toxicity (Alpar et al., 1969).

Many other compounds have been examined as lubricants. These include fumaric acid (Cox, 1970), surfactants such as Myrj (Maly and Jaros, 1967; Maly, 1969) and Brij (Smilek et al., 1955) and waxes exampled by hydrogenated cotton seed oil (Sterotex, Lubritab) and castor seed oil (Cutina HR) (Stamm et al., 1977; Bolhuis et al., 1980).

Lubricant characterisation and batch variation

The physical characteristics of a particular lubricant batch will be influenced by the chemical

TABLE 2

Some pharmacopoeial standards for magnesium stearate

	British 1980	United States 1980	Netherlands 1978	Nordica 1964	Italy 1972	Hungary 1970	Japan 1981	Europe 1983
Magnesium content	3.8 - 5.0 %	4.1 - 5.0 %	3.8 - 5.0 %	3.8 - 4.8 %	3.8 - 4.8 %	3.8 - 4.8 %	3.0 - 5.1 %	3.8 - 5.0 %
Solubility	Insoluble in water, ethanol and ether							
Ident. of acidified sample: Aqueous phase	Gives characteristic reactions of magnesium							
Ident. of acidified sample: Oily phase	f.pt. ≥52 °C	f.pt. ≥54 °C	f.pt. ≥52 °C	Titration of liberated acids	f.pt. ≥52 °C	m.p.t. 56-65 °C	m.p.t. ≥54 °C	f.pt. ≥53 °C
Loss on drying	≤6 % 100-105 °C	≤4 % 105 °C	≤6 % 1 g; 100-105 °C	≤7.5 % 0.2 g; 105 °C	≤6 % 100-105 °C	≤5 % 0.2 g; 105 °C	≤4 % 1 g P_2O_5, 4 h	≤6 % 1 g; 100-105 °C
Assay	Back titration of excess EDTA with $ZnSO_4$	Titration of acidified residue with EDTA	Back titration of excess EDTA with $ZnSO_4$	Back titration of excess H_2SO_4 with NaOH	Titration of acidified residue with EDTA	Titration of acidified residue with EDTA	Titration of acidified residue with EDTA	Back titration of excess EDTA with $ZnSO_4$
Other tests	Heavy metals Chloride Sulphate Zn stearate pH aq. extract Acid value of fatty acids	Lead Microbial limits	Heavy metals Chloride Sulphate Zn stearate pH aq. extract Acid value of fatty acids	Heavy metals Chloride Calcium Free fatty acids	Heavy metals Chloride Sulphate pH aq. extract Acid value of fatty acids Iodine value Iron Bulk volume	Heavy metals Sulphate pH aq. extract Calcium Arsenic H_2O extractive Free fatty acids	Heavy metals Arsenic	Heavy metals Chloride Sulphate pH aq. extract Acid value of fatty acids

composition and manufacturing process. Poor control over these parameters results in batch-variable products.

As boundary lubrication is related to surface coverage, lubricant powders are usually finely subdivided. Particle size reduction of sodium lauryl sulphate (Osseekey and Rhodes, 1976) and sodium stearyl fumarate (Holzer and Sjogren, 1979) have been suggested to improve lubrication. PEG is usually micronised (Tsumara et al., 1972) and a particle size range of 3–15 μm has been recommended for magnesium stearate (Muller, 1977b; Steffens et al., 1982).

Pharmacopoeial monographs, where available, tend to provide chemical restrictions whereas the bulk physical characteristics receive little or no attention. Table 2 compares several monographs for magnesium stearate. Physical characteristics can be an important consideration in lubricant materials and Butcher and Jones (1972) showed variation in particle densities, packing characteristics, sieving, shear and frictional properties for 5 magnesium stearate batches.

Many lubricant studies include little or no form of material characterisation. Of properties reported, surface area is one of the most commonly mentioned parameters, and this range greatly depending upon both the lubricant studied and the batch of a single material (Bolhuis et al., 1980; Holzer and Sjogren, 1981a). The surface area of magnesium stearate typically ranges from 1–16 $m^2 \cdot g^{-1}$ (Butcher, 1973; Buehler, 1978; Roblot et al., 1980, 1981; Moody, 1981; Holzer, 1983). Frattini and Simioni (1984) have proposed that magnesium stearate be added to formulations on a surface area rather than weight basis. This does not allow for potential surface area generation by shearing during mixing or tablet ejection. Also lubricant batches which have different solid-state characteristics (Miller and York, 1985a) do not show correlation between surface area and lubricity (Miller, 1984) because they have different inherent frictional quality (Miller and York, 1985b).

The moisture content of a lubricant powder may influence its physical characteristics and hence the subsequent lubrication effect. Magnesium lauryl sulphate has been shown to vary in moisture content from 9.7% to 19.3% (Caldwell and Westlake, 1973). Metal stearates made by a precipitation process will have moisture ranging from 2% for lithium salts to 12% for zinc (Pilpel, 1971). Magnesium stearate gives moisture values ranging from 0.6% to 7.5% (Buehler, 1978; Butcher, 1973; Holzer, 1983) for commercial samples and up to 10.2% for high purity materials (Steffens, 1978; Muller, 1977c).

The use of thermal analysis, X-ray and infra-red technique has enabled more fundamental characterisation of lubricant materials. Muller and coworkers (Muller 1977a, b, c; Muller et al., 1982a)

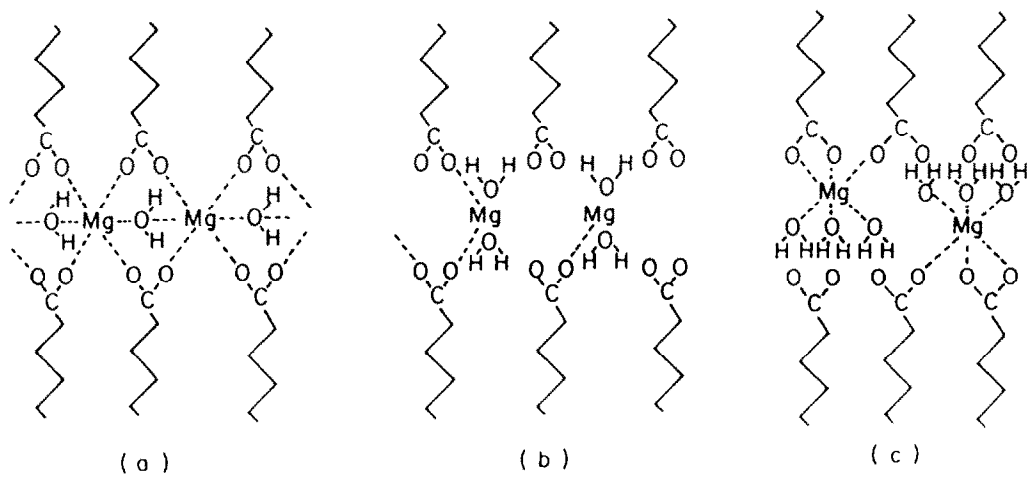

Fig. 4. Structures for magnesium stearate postulated by Muller (1977c). (a) monohydrate, (b) dihydrate; (c) trihydrate.

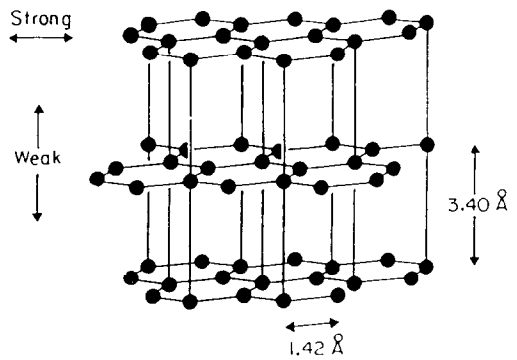

Fig. 5. Graphite structure with weaker bonding between lamellae (Bowden and Tabor, 1967).

identified different hydrated states of high purity magnesium stearate and hypothesized molecular arrangements for these (Fig. 4). The preferred form was considered to be the lamellar dihydrate structure which resists normal forces but shears readily when tangential forces are applied. A laminar or lamellar molecular arrangement was previously considered favourable for lubrication as shown in Fig. 5 for the graphite structure (Bowden and Tabor, 1967). However, this does not ensure lubricant properties (Buckley and Johnson, 1972) and PTFE exhibits lubrication without a lamellar structure (Bolhuis et al., 1980). The range of particle size and morphology shown by magnesium stearate (Fig. 6) illustrates the requirement for good material characterisation in lubricant studies.

Process and formulation effects

The effect of lubricant mixing time, concentration, speed, type of mixer and method of lubricant addition have all been shown to affect formulations. Magnesium stearate invariably produces the most deleterious effects (Bolhuis et al., 1980; Lindberg, 1972; Jaminet and Louis, 1968; Cid and Jaminet, 1971; Sperandeo and De Marchi, 1976).

Increased mixing time of magnesium stearate has been shown to reduce starch and lactose compact disintegration (Shah and Mlodozeniec, 1977; Bossert and Stamm, 1980), attributed to a reduced rate of water penetration (Ganderton, 1969). In strict terms, the critical factor is the rate of energy input during mixing as different speeds and types of mixer show different effects (Bossert and Stamm, 1980; Jaegerskou, 1981). The bioavailability of a paracetamol formulation (Soininen and Kuusivouri, 1980) and the in vitro dissolution of capsules (Murthy and Samyn, 1977) are also reduced by hydrophobic lubricant mixing. Sodium stearyl fumarate mixing has been shown to have little effect on formulation disintegration (Chowhan and Chi, 1986) and hydrophilic materials such as sodium lauryl sulphate may improve water penetration and reduce disintegration times (Levy and Gumtow, 1963) although this is not always the case (Osseekey and Rhodes, 1976; Marlowe and Shangraw, 1967). Interestingly, Huttenrauch (1977) has shown that pregrinding of lactose negates the effect of mixing time with magnesium stearate and this is related to increased surface activation of host particles enabling the mix to equilibrate rapidly. Hargreaves (1969) has reported that a small amount of magnesium stearate, below 0.1%, will actually improve tablet disintegration. Accelerated dissolution from capsules was found for magnesium stearate added to micronised rifampicin capsules (Nakagawa et al., 1980). This was attributed to a breakdown of cohesive drug agglomerates.

The effect of lubricant mixing on formulation dissolution is related not only to the hydrophobicity of the lubricant but to its tendency to form a film around host particles. Magnesium stearate has been demonstrated to form a hydrophobic film of low shear strength around host particles (Bolhuis and Lerk, 1977) which develops with time to give a molecular coverage (Bolhuis et al., 1975). Further studies (Lerk et al., 1977; Lerk and Bolhuis, 1977; Ragnarrson et al., 1979) have shown that subsequent mixing with colloidal silica disrupts the film, reducing negative effects of magnesium stearate but also its lubricating tendency. Lubricants may also affect the homogeneity of mixed powders. Lai and Hersey (1981) proposed a stripping mechanism for the observed deterioration of ordered mixes by magnesium stearate. However prednisone-starch/lactose granule ordered mixes have been shown to be unaffected by

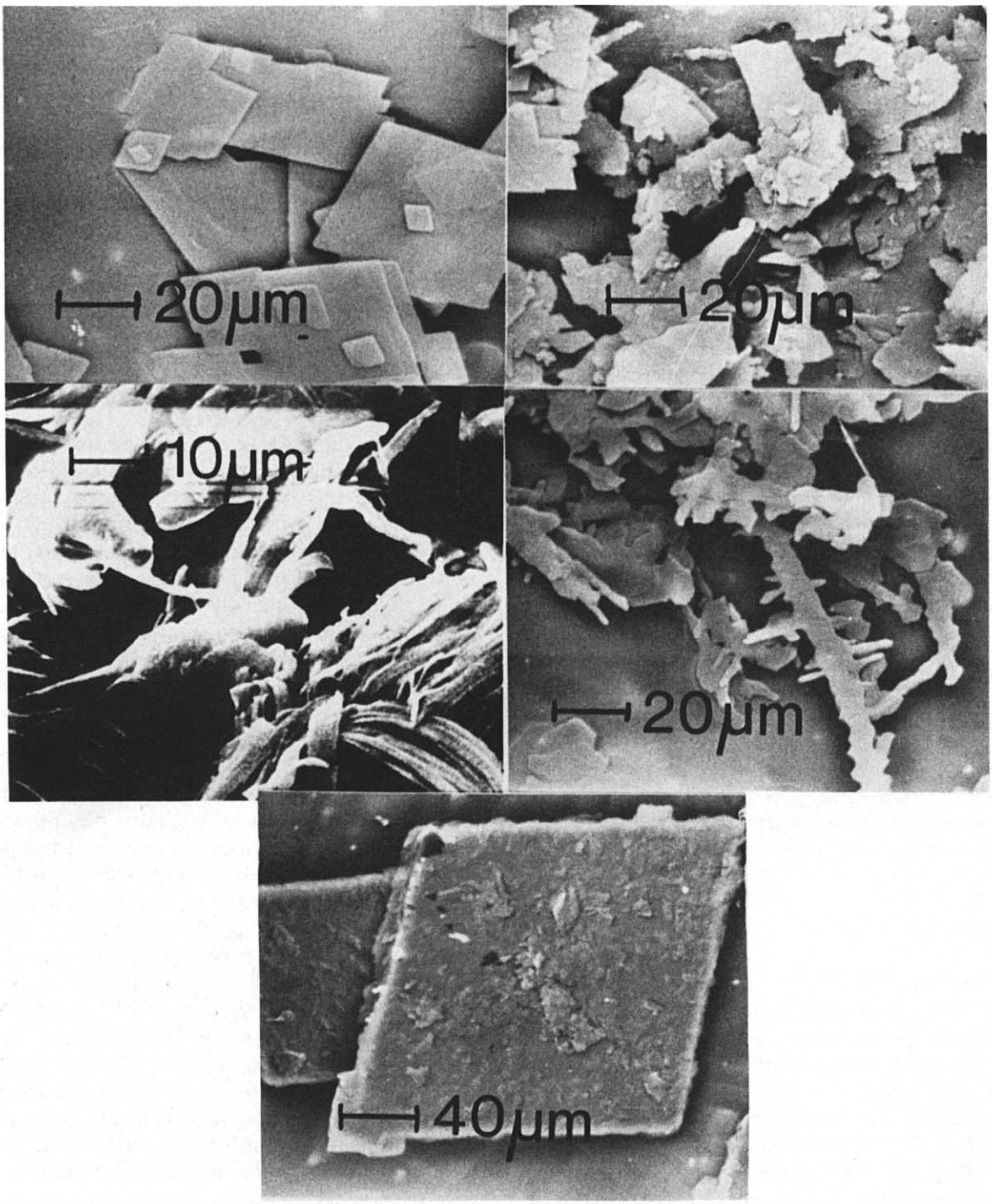

Fig. 6. Electron micrographs of different magnesium stearate batches illustrating a range of particle size and morphology (Miller and York, 1985a).

subsequent magnesium stearate addition (Stewart, 1981).

Shah and Mlodozeniec (1977) proposed a surface coveraged by lubricant particle adherance initially, followed by delamination to form a film around host particles which is usually discontinuous. The surface coverage of a magnesium stearate film has been estimated using dissolution (Nicklasson and Brodin, 1982; Johansson and Nicklasson, 1986) and film coat adhesion techniques (Rowe, 1983) to be 50–60% at a concentration of 5%. The development of X-ray microanalysis methods (Pintye-Hodi et al., 1981) has enabled elemental dot maps to be produced for metallic lubricant coverage, as shown in Fig. 7 (Miller, 1984). Roblot-Treupel and Puisieux (1986) have used this type of technique to demonstrate cavity filling by magnesium stearate on host particles.

The type of excipient has also been shown to affect the influence of lubricants on formulations. Delattre et al. (1976) showed that 0.1–2.0% magnesium stearate did not affect the dissolution rate of crystalline lactose tablets but decreased the dissolution rate of tablets containing Avicel PH101 and Aerosil 200. Magnesium stearate also reduced the disintegration (Bolhuis et al., 1981) and dissolution rate (Lerk et al., 1982; Proost et al., 1983) of tablets, including the slightly swelling disintegrant potato starch but not those containing a strongly swelling disintegrant, sodium starch glycollate. The effects are related to the tendency of excipients to create lubricant free surfaces during compaction by fragmentation or by swelling during dissolution. This phenomenon is also manifest in measurements of compact strength. Decreases in crushing strength of compacts have been attributed to weaker bonds resulting after compression between lubricant molecules rather than stronger host–host bonds (De Boer et al., 1978). Thus compact failure may occur around, rather than across, compressed particles (Shotton and Ganderton, 1961).

A wide range of lubricants have been assessed for their effect on compact strength (Jaminet and Hazee, 1966; Asker et al., 1975; Bolhuis et al., 1980; Jarosz and Parrott, 1984). Some typical results are shown in Fig. 8. In general, for hosts which consolidate by predominantly plastic mechanisms the tensile strength was reduced as the lubricant concentration was increased (Jarosz and Parrott, 1984). This was also true for the axial and radial work of failure (Jarosz and Parrott, 1982). For hosts exhibiting fragmentation consolidation the tensile strength of compacts was not proportional to lubricant concentration. Bolhuis et al. (1980) reported that lubricants without a laminar shear structure showed little effect on tablet crush-

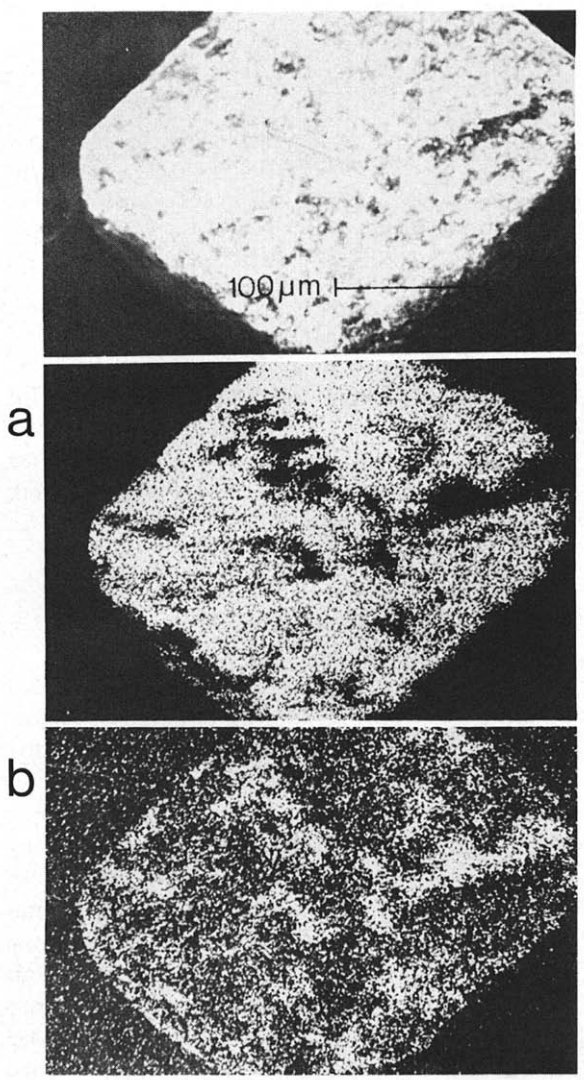

Fig. 7. Elemental dot maps of: (a) chloride and (b) magnesium for a blend of sodium chloride and 2% magnesium stearate (Miller, 1984).

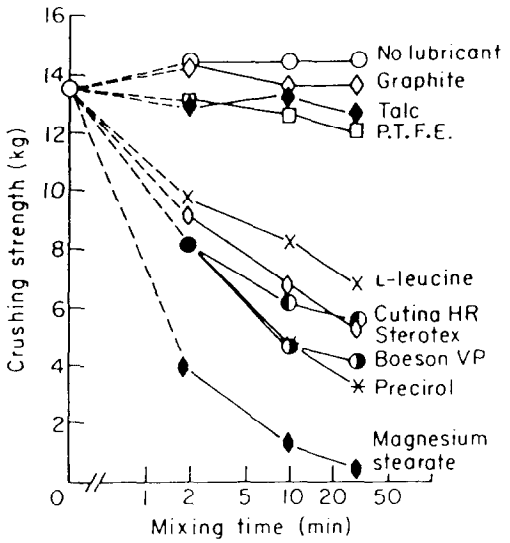

Fig. 8. Effect of mixing time on the crushing strength of tablets compressed from blends of 50% extra fine crystalline lactose, 25% starch 1500 and 25% Elcema G250 with 1% of various lubricants (Bolhuis et al., 1980).

ing strength. Examples of these Fig. 8 are PTFE (Lerk et al., 1977), talc and graphite which were proposed to act as lubricants by a roller bearing mechanism (Bollman and Spreadbough, 1960; Train and Hersey, 1960).

Lubricant selection and optimisation

From the discussion so far it is apparent that the lubrication process is a combination of factors involving the lubricant material, the formulation to be lubricated and the mechanical processes which result in the final dosage form. All of these may be considered in lubricant selection along with external influences such as cost, regulatory requirements and prior art, to produce a formulation with the desired characteristics. The optimal situation would be to have no lubricant at all, but few tablet formulations are self-lubricating.

The alkali metal salts of fatty acids, and magnesium stearate in particular, are the widest used lubricants, but occasions arise when they are unsuitable. Effervescent tablets usually require soluble ingredients and water-soluble lubricants are

TABLE 3

Typical properties given for lubricant materials by the Handbook of Pharmaceutical Excipients 1986

Material	Property	Typical value
magnesium stearate	density	1.03–1.08 $g \cdot cm^3$
	bulk vol	3.0–8.4 $ml \cdot g^{-1}$
	tapped vol	2.5–6.2 $ml \cdot g^{-1}$
	specific surface area	2.45–16.0 $m^2 \cdot g^{-1}$
stearic acid	bulk density	0.847 $g \cdot cm^{-3}$
sodium lauryl sulphate	density at 20 °C	1.07 $g \cdot cm^{-3}$
	melting point	204–207 °C
	moisture content	< 5%
zinc stearate	melting range	120–122 °C
	particle size	100% through 325 mesh
talc	bulk density	19–24 $lb \cdot ft^{-3}$
	tapped density	48–62.5 $lb \cdot ft^{-3}$
	specific gravity	2.7–2.8
	particle size	73–90% less than 2 μm
calcium stearate	shear strength	15.0 $kg \cdot cm^{-2}$
	particle size range	1.7–60 μm
	specific surface area	5.76–7.44 $m^2 \cdot g^{-1}$

available (Saleh et al., 1984; Stamm et al., 1977) but are usually less effective or require larger concentrations and are generally more expensive. Drug interaction reports with magnesium stearate include aspirin (Kornblum and Zoglio, 1967), tetracycline (Lee and Hersey, 1977) and digoxin (Khalil, 1978). A range of alternative lubricants are available (Table 1). Many of the more recent materials are glycerides or hydrogenated vegetable oils.

Lubricant action depends on both the frictional quality of the lubricant powder and the ability of this material to be present at the host powder/die-wall interface, which is the site of action (Miller et al., 1983). Lubrication can be improved by increasing either of these parameters. Knowledge of lubricant coating propensity has led many quality control laboratories to introduce surface area specifications for powder lubricants (York, 1984) and typical bulk characteristics appear in some modern excipient monographs (Katalog Hilfstoffe, 1974; Handbook of Phar-

maceutical Excipients, 1986), examples of which are shown in Table 3. However, in order to minimise adverse effects of lubricant materials it is desirable to have a reduced interfacial presence. This can be compensated for by improvement in the inherent frictional quality of the lubricant material (Miller et al., 1985; Miller and York, 1985b) and provides a fruitful area for further research. Observed variations in magnesium stearate batches (Hansen et al., 1970; Butcher and Jones, 1972) has led to studies with high purity materials (Steffens, 1978; Muller, 1977a, b and c; Muller et al., 1982a; Miller, 1984) and some understanding of the solid-state structural requirements for good inherent lubricity. The preferred lamellar dihydrate structure can be rapidly identified using thermal analysis techniques (Miller and York, 1985a). Extrapolation of this work to commercial samples (Steffens et al., 1982; Holzer, 1983; Columbo and Carli, 1984) could lead to the manufacture of improved magnesium stearate with reduced deleterious effects.

Batch variation in lubricant powders reflects a lack of control over raw materials and process in manufacture. Few producers of magnesium stearate supply predominantly to the pharmaceutical industry and hence show little interest in making materials to specifications other than chemical pharmacopoeial requirements (Table 2). The plethora of relatively new tablet lubricants stems from the willingness of suppliers to provide materials with a suitably low shear strength. Little or no consideration is given, however, to the solid-state structure of the powder which is also important in the lubrication process.

Formulations may be designed to function with excess lubricant, using excipients which consolidate with fragmentation (Delattre et al., 1976) and strongly swelling disintegrants (Proost et al., 1983) but this may be problematic and costly. A number of alternative techniques have been attempted to obtain adequate lubrication with reduced negative effects.

The influence of die-wall composition on lubrication has been investigated. Strickland (1959) found little difference between a range of metals but more recent studies have shown the importance of the metal surface finish on friction (Jolliffe and Newton, 1982, 1983; James and Newton, 1983). Modern tooling is often finished with highly polished chrome to minimise friction and wear. PTFE die linings and punch tips have been tried (Miller, 1967; Siegal et al., 1963) the latter with some success in effervescent tablet manufacture. The use of steel with lubricant inclusions (Hersey, 1972) proved unsuccessful at high pressures. The use of ultrasonic vibrations has also been considered (Komarek, 1967).

Alternative methods of lubricant addition have been considered. Early work by Nelson and others (Nelson, 1955; Nelson et al., 1955) considered spraying lubricant directly onto tablet tooling. This type of lubrication has also been achieved by compressing and ejecting a lubricant powder prior to die fill with an unlubricated formulation (Leal et al., 1962). This will alleviate problems of reduced compact strength (Church, 1984) but dissolution problems may remain (Nicklasson and Brodin, 1982). Lubricants incorporated into granulations gave poorer compact ejection and strength than those blended with granulations (Matsuda et al., 1976) whereas lubricants sprayed onto granules gave improved tablet ejection characteristics (Fekete et al., 1973). A recent innovation is the use of magnesium stearate in granular form (Johansson, 1984, 1985). Shear forces during the compression cycle probably cause the granules to lubricate the die wall adequately. However, little advantage is obtained over powder lubricants at the low concentrations required in pharmaceutical production. It has been suggested that reduction of the die-wall/tablet surface contact using deep curved punches may improve lubrication (Strickland, 1959) but die wall pressures are considerably greater serving to increase frictional forces with this tooling (Mechtersheimer and Sucker, 1986).

Optimisation of lubricant type and addition will require some means of assessment and these are discussed above. Future developments may include in process lubrication monitoring based on the decrease in mixer power consumption when lubricants are added to granulations (Schrank-Junghani et al., 1983). In the short term it would seem appropriate that quality control specifications include tests for properties such as surface

area, and water of crystallisation as well as thermal analysis profiles (Steffens et al., 1982) so that suitable materials can be selected. In the longer term, an understanding of the fundamental properties of a lubricant material can lead to the controlled manufacture of optimal batch-invariant products.

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