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Influence of commercial and high purity magnesium stearates on sodium chloride and paracetamol DC granules during tabletting

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Summary

Tablets of standardised weight and dimension were prepared on an instrumented single-punch tablet machine, either from unlubricated samples or lubricated binary mixtures containing 0.5% w/w magnesium stearate of commercial or high purity grade. From dynamic compaction data, Heckel plots were constructed and critical parameters measured for comparison. The results indicated that sodium chloride consolidated primarily by plastic deformation and paracetamol DC by fragmentation and plastic deformation. The presence of magnesium stearate did not appear to alter deformation mechanisms, but, as expected, increased compression force transmission ratio, R, and reduced ejection force, EJF. Lubricant effects on yield pressure, P_y, and densification due to particle slippage, D_B, revealed differences between sodium chloride and paracetamol DC and results have been discussed in terms of inter-particulate rearrangement and crystalline slip-plane compaction. The crushing strength, CS, for tablets prepared from lubricated sodium chloride and paracetamol DC was reduced compared with unlubricated systems with a greater change for sodium chloride systems. Overall the high purity magnesium stearate was found to be as effective a powder lubricant as the commercial samples tested.

Introduction

Magnesium stearate, one of the most essential excipient components in a tablet formulation has been shown to impart or accentuate deleterious properties on the finished product (Higuchi et al., 1952/53; Shotton and Lewis, 1964; Ganderton, 1969; De Boer et al., 1978; Bolhuis et al., 1980). Despite these disadvantages magnesium stearate remains the most widely used lubricant in tablet manufacture in the absence of superior alternatives. At the same time the deleterious effects of magnesium stearate have been extensively studied (Strickland et al., 1956; Bolhuis et al., 1975; Lerk et al., 1977). In each case it has been suggested that the lubricants added as dry powder adhere to

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granules and form a coat around individual granules. The film formation of magnesium stearate on host particles has been studied by several workers (Bolhuis et al., 1975; Bolhuis and Lerk 1977; Hussain et al., 1988). Moreover, this hydrophobic magnesium stearate film on the host particles is implicated in the negative effects observed in tablet properties. In fact, recent work by Miller et al. (1985) has indicated that the magnitude of the negative effects can be related to the crystallographic and particulate properties of the powder lubricant.

The aims of this study were to examine the influence of commercial and high purity grades of magnesium stearate on paracetamol DC and sodium chloride compact formation and assess their effects on the critical compression parameters.

Experimental

Materials

The model host powders selected were sodium chloride (BDH Chemicals Ltd, Poole) and paracetamol DC (Hoechst Aktiengesellschaft, Frankfurt, Germany).

The magnesium stearate lubricants used were MSD (Durham Chemicals Ltd, Birtley, Durham), MSH (Hopkin and Williams, Chadwell Heath, Essex), MSJ (James M. Brown Ltd, Fenton, Stoke-on-Trent), MSM (Megret Ltd, N.E. Toxteth Dock, Liverpool), MSW (Witco Chemicals Ltd, Dronfield, Sheffield) and MSZ was prepared under acid conditions from high purity constituent materials and micronised (Hussain, 1988).

Mixing

Mixing of paracetamol DC, sodium chloride (250–425 μm) fraction with appropriate quantity of lubricant to produce 0.5% w/w concentration was carried out at 25 rpm in a perspex cube mixer of approx. 1850 ml volume. Each batch of 200 g of excipient and lubricant was mixed for a predetermined time interval and stored until required for tabletting.

Tablet studies and crushing strength (CS) measurement

The experimental powders were tabletted at 100 MPa (± 2 MPa) using a fully instrumented single-punch tablet machine (Type E2, Manesty Machines Ltd, Speke). Tablets of 12.7 mm diameter and 4 mm thickness, weighing approx. 500 mg (paracetamol DC) or 750 mg (sodium chloride) were prepared in a controlled environment (20°C and $40 \pm 5\%$ relative humidity).

Ejection force (EJF) and punch force transmission ratio (R), which is the ratio of maximum lower punch force to maximum upper punch force, were determined.

For determining tablet crushing strength (CS), a CT40 mechanical strength tester (Engineering Systems, Nottingham) was used. Tablet CS measurements were conducted 24 h after compact preparation. Since the tablets prepared were of constant diameter and almost identical thickness, the CS of tablets is reported throughout.

Results presented are the arithmetic mean of five compressions and tablet testing, together with standard deviations.

Compaction data analysis

Quantitative analysis of compaction data was carried out in accordance with the Heckel (1961a, b) equation:

$$\ln[1/(1-D)] = KP + A$$

where D is the relative density, i.e. apparent compact density/true density, K and A are constants, and P denotes the applied pressure.

The constant K in this equation has been demonstrated by Hersey and Rees (1971) to be equal to the reciprocal of the yield pressure, P_y. The compaction data were plotted according to the Heckel equation and the various parameters seen in Fig. 1 calculated.

Also, as proposed by Duberg and Nystrom (1986), attempts have been made to extend the application of the Heckel function and consider the decompression phase during load removal. These workers identified three distinct phases. In phase I, when the applied pressure is relatively low, volume reduction is thought to be enhanced

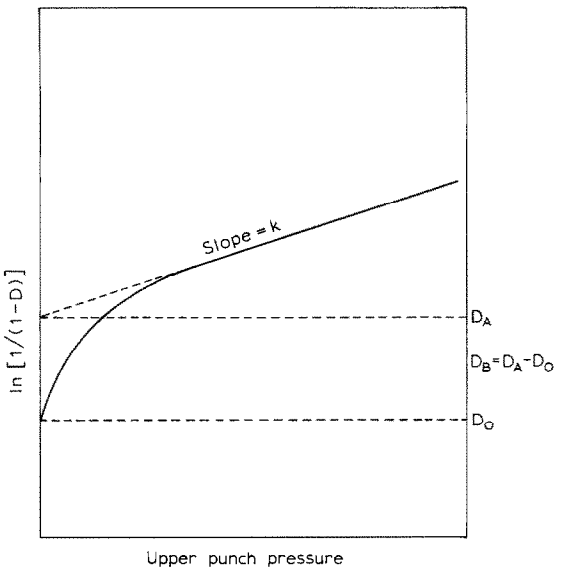

Fig. 1. Parameters which may be quantified from a typical Heckel plot.

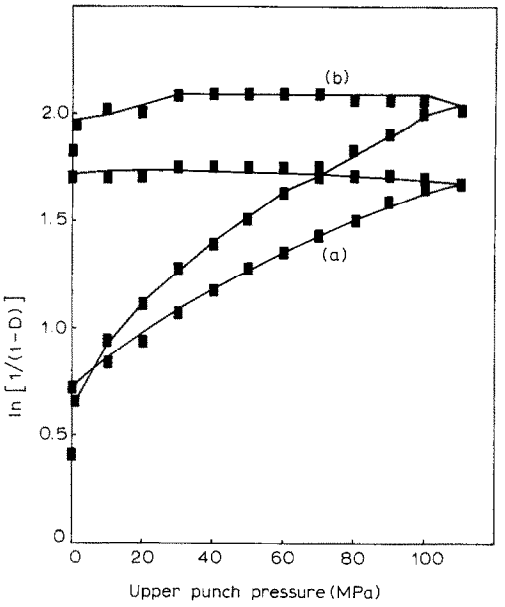

Fig. 2. Heckel plots of (a) sodium chloride and (b) paracetamol DC powders.

by particle fragmentation. Phase II usually shows a linear section denoting elastic and/or plastic deformation. The decompression region, represented by phase III, is approximately horizontal when no elastic deformation and recovery is present. Thus, in this study, effects of lubricants have been examined and compared by using this approach.

Results and Discussion

Lubricant effects on sodium chloride

Fig. 2a illustrates a representative Heckel plot for unlubricated sodium chloride during compression and decompression. Heckel plots for sodium chloride mixed with 0.5% w/w high purity magnesium stearate MSZ and all the commercial magnesium stearates were similar to those of Fig. 2a and are obtained for systems undergoing consolidation by plastic deformation (Duberg and Nystrom, 1986). Plastic deformation for sodium chloride has been previously demonstrated by Hardman and Lilly (1973). Thus, the small quantity of magnesium stearate caused no marked change to the general shape of the Heckel profile

TABLE 1

Compression. lubrication and crushing strength data for sodium chloride tablets unlubricated and lubricated with magnesium stearates (0.5 w/w%) and mixed for 30 min

Sample	P_y (MPa)	P_y [a] (UL = 100)	D_B	D_B [a] (UL = 100)	R	R [a] (UL = 100)	EJF (MPa)	EJF [a] (UL = 100)	CS (kg)	CS [a] (UL = 100)
UL	111.8 (1.4)	100.0	0.05	100.0	0.85 (0.002)	100.0	4.93 (0.10)	100.0	14.56 (2.82)	100.0
MSD	107.8 (3.3)	96.5	0.13	249.1	0.90 (0.002)	106.5	2.12 (0.05)	43.0	0.83 (0.13)	5.7
MSH	110.2 (3.5)	98.6	0.15	281.1	0.90 (0.001)	106.5	2.01 (0.06)	40.8	0.64 (0.24)	4.4
MSJ	105.5 (1.6)	94.4	0.13	241.5	0.90 (0.002)	105.9	2.16 (0.09)	43.8	0.98 (0.23)	6.7
MSM	111.7 (5.1)	100.0	0.14	258.5	0.88 (0.002)	104.3	2.41 (0.10)	48.9	0.75 (0.17)	5.2
MSW	104.2 (2.5)	93.2	0.13	237.7	0.91 (0.002)	107.0	1.72 (0.09)	34.9	0.48 (0.13)	3.3
MSZ	108.5 (5.7)	97.0	0.13	252.8	0.90 (0.005)	106.0	1.98 (0.13)	40.2	0.98 (0.09)	6.7

[a] Normalised data. UL, unlubricated; standard deviation given in parentheses; $n = 5$.

of unlubricated host and thereby the consolidation mechanism.

Values of the compaction parameters measured for sodium chloride tablets are listed in Table 1. Whilst P_y values show a small degree of scatter when comparing the various lubricated and unlubricated sodium chloride samples, the overall change is relatively small. These P_y values are nevertheless close to the 100 MPa value reported by Duberg and Nystrom (1986) for sodium chloride.

Comparison of the D_B values indicates an increase in particle slippage and rearrangement for the lubricated systems. Whilst the differences in the values within the lubricated mixes are small the normalised values indicate a possible rank order between the magnesium stearates.

During the tabletting of unlubricated sodium chloride, problems such as sticking to the punch and die or difficulty in ejection were not observed and an R value of 0.85 was calculated for the unlubricated material. As shown in Table 1, all lubricants produced a marginal improvement in this value. Detailed examination of the individual R values and the normalised values reveal differences between samples lubricated with commercial as well as between the high purity grade of magnesium stearate. It must be appreciated, however, that in terms of lubrication these R value differences are small.

The EJF has been widely used as a criterion for studying lubricants and lubrication (e.g. Patel and Guth, 1955; Lewis and Shotton, 1965). Data in Table 1 show that the EJF is markedly reduced for samples mixed for 30 min with 0.5% w/w concentration of the lubricants, and lubrication with MSZ appears to be as efficient as with the commercial lubricants.

The data in Table 1 also demonstrate that all lubricants decrease the CS of the tablets. The reduction in the tablet strength is marked and experimental values for lubricated tablets are extremely low. However, decreases of similar magnitude have been reported by Lerk et al. (1977), for STA-RX 1500 tablets blended with 0.5% w/w magnesium stearate. Holzer and Sjogren (1981) also observed sharp reductions in sodium chloride tablet strength after mixing with 0.5% w/w magnesium stearate and several other solid lubricants. Jarosz and Parrott (1984) suggested that the addition of magnesium stearate decreased the tensile strength of plastic materials because it interfered with bond formation during compression. Similarly, Bolhuis et al. (1975) concluded that the phenomenon of decreasing CS is caused by the formation of a lubricant barrier, interfering with the bonding between the particles. In this study the differences observed in the values of the CS caused by the various lubricants are small. However, the high purity material appears to have conferred marginally less negative influence on the strength of sodium chloride tablets.

Lubricant effects on paracetamol DC

The compaction of unlubricated paracetamol DC granules revealed minor sticking and adherence phenomena to the die wall but no such problems occurred with lubricated powders. In fact, during processing a general increase in the flow behaviour of lubricated granules was observed which was attributed to the adherence of the magnesium stearate to the granule surfaces.

A representative Heckel plot of unlubricated paracetamol DC is given in Fig. 2b, and profiles for the lubricated mixtures were essentially similar. The compression, decompression and relaxation phases are easily recognisable. The initial part of the compression cycle shows a non-linear consolidation at low compressional loads indicating granule fragmentation which is likely to be accompanied by slippage and rearrangement. This type of behaviour for paracetamol DC granules is attributed to primary paracetamol crystals fracturing and fragmenting in the aggregated form of granules under low loads. As the load is increased, a linear plot results indicating elastic and plastic deformation mechanisms. Unlike sodium chloride and its lubricated mixtures the decompression section of the cycle is non-linear. A well-defined curve is seen just prior to complete load removal. It is possible that an elastic recovery in this material may cause problems on ejection. A similar Heckel profile was reported by Duberg and Nystrom (1986).

Table 2 lists P_y, D_B, R, EJF and CS data for paracetamol DC and the lubricated mixtures. In

general, the lubricants did not affect D_B data. However, the paracetamol DC granules showed a larger D_B value (0.26) than sodium chloride (0.05), reflecting the different mechanisms of compaction for these two materials.

As expected, R values were markedly increased for lubricated systems compared to the unlubricated materials but were similar for the commercial and high purity samples. The mean EJF values recorded for the unlubricated paracetamol DC tablets were relatively high (12.55 MPa compared with 4.93 MPa for sodium chloride), emphasising the need for the lubrication of the granules. For samples mixed with lubricants for 30 min, this parameter was markedly reduced facilitating easy ejection of the compact. The unpredictable effects of the commercial magnesium stearates on the tablet strength are clearly demonstrated by the CS data for paracetamol DC tablets (see Table 2). CS has been reduced for all lubricated samples, with minimum deleterious effects observed for MSM and MSZ. Also, it may be noted that the lubricants have not reduced the tablet CS to the same extent as for lubricated sodium chloride tablets. Since the CS reflects inter-particle bonding and tensile fracture occurring on diametral loading of tablets, these CS results confirm the conclusions of De Boer et al. (1978) that magnesium stearate exercises a maximum effect on tablet for excipients that undergo complete plastic deformation.

Conversely, the bonding properties (and hence CS) of excipients which undergo complete fragmentation under pressure are relatively uninfluenced by magnesium stearate. Thus the effects of magnesium stearate samples on CS are consistent with the observed plastic deformation of sodium chloride on compaction and the fragmentation tendency of paracetamol DC granules during initial stages of compaction.

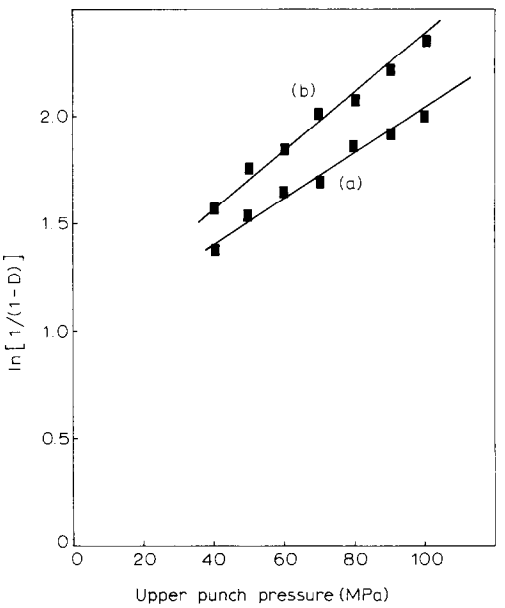

Fig. 3. Comparison of phase II of Heckel plots of (a) paracetamol, (b) paracetamol DC blended with 0.5% w/w MSH.

Lubricant effects on yield pressure (P_y)

Comparison of the linear sections of Heckel plots of the unlubricated and lubricated paracetamol DC Heckel plots showed that slopes for

TABLE 2

Compression, lubrication and crushing strength data for paracetamol DC tablets unlubricated and lubricated with magnesium stearates (0.5 w/w%) and mixed for 30 min

Sample	P_y (MPa)	P_y [a] (UL = 100)	D_B	D_B [a] (UL = 100)	R	R [a] (UL = 100)	EJF (MPa)	EJF [a] (UL = 100)	CS (kg)	CS [a] (UL = 100)
UL	96.9 (2.1)	100.0	0.26	100.0	0.73 (0.003)	100.0	12.55 (0.39)	100.0	9.55 (0.90)	100.0
MSD	90.9 (3.0)	93.9	0.27	101.5	0.82 (0.002)	112.6	5.93 (0.52)	47.3	6.49 (0.18)	68.0
MSH	74.4 (1.3)	76.8	0.25	93.9	0.86 (0.002)	117.3	2.83 (0.16)	22.6	8.29 (0.17)	86.8
MSJ	76.8 (1.3)	79.3	0.25	97.0	0.86 (0.003)	117.3	2.79 (0.11)	22.2	8.67 (0.25)	90.8
MSM	72.5 (4.8)	74.8	0.25	96.6	0.86 (0.002)	117.4	2.54 (0.86)	20.2	9.29 (0.30)	97.3
MSW	76.7 (3.9)	79.2	0.26	98.9	0.87 (0.003)	119.7	2.83 (0.29)	22.6	8.32 (0.22)	87.1
MSZ	78.1 (2.2)	80.6	0.26	100.4	0.86 (0.002)	117.7	2.69 (0.12)	21.4	9.26 (0.35)	97.0

[a] Normalised data. UL = unlubricated; standard deviation given in parentheses; $n = 5$.

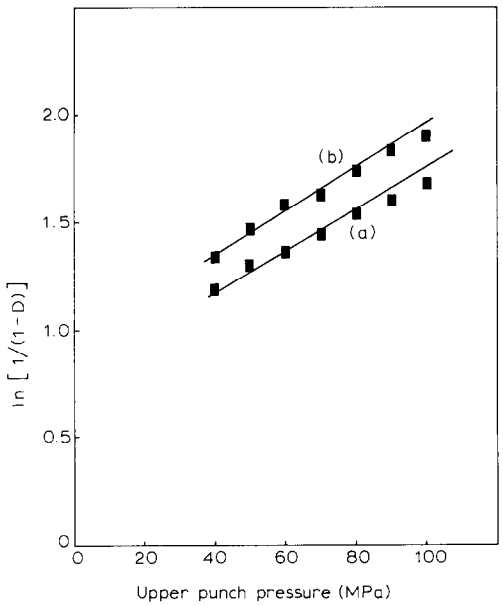

Fig. 4. Comparison of phase II of Heckel plots of (a) sodium chloride, (b) sodium chloride blended with 0.5% w/w MSH.

lubricated samples are displaced to higher density values and exhibit steeper slopes (see Fig. 3). In contrast, comparison of Heckel plots of sodium chloride and its lubricated mixtures indicate an upward and parallel movement of the plots for lubricated mixtures (see Fig. 4). Changes in the Heckel plots of lubricant blended (0.5% w/w magnesium stearate) excipients have been reported by De Boer et al. (1978), who found an upward and parallel displacement for lubricated dicalcium phosphate dihydrate, a material stated to consolidate by fragmentation. For amylose V, which was suggested to undergo plastic deformation, the upward movement for lubricated samples was associated with an increased slope. These observations are in contrast to data discussed above.

Thus, unlike the data for unlubricated and lubricated sodium chloride the P_y values for the paracetamol DC and its lubricated mixtures showed a decrease in P_y values. For example, P_y for paracetamol DC at 96.9 MPa falls to 78.1 MPa for MSZ lubricated mixture. Changes in P_y associated with the presence of magnesium stearate on paracetamol DC can be explained by extra-crystalline phenomena associated with the compaction mechanism of the granules. Fragmentation of primary paracetamol particles and breakage of inter-particle associations within the granules during compaction of lubricated mixtures create new and clean surfaces. The excess lubricant particles in the interstices in the bulk may then form lubricant films on the fragmented granules during particle movement following fragmentation, and compaction of these coated particles may register a lower P_y value. In contrast for sodium chloride predominance of intra-crystalline slip-planes rather than inter-particulate rearrangement during compaction is indicated since sodium chloride undergoes plastic deformation (Hess, 1978). Thus, as observed the presence of lubricant films on surfaces would not lead to major changes in P_y values.

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