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Densification properties and compactibility of mixtures of pharmaceutical excipients with and without magnesium stearate

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Summary

Mixtures of a plastically deforming substance and a brittle one often lead to a positive interaction in the compactibility. It was observed that a deviation in the tablet strength from the linear interpolated value is often related to a similar deviation in tablet thickness. The densification properties of both the brittle and the plastic materials appeared to be of importance in this respect. Blends of different directly compressible filler binders with magnesium stearate resulted most often in negative interactions in compactibility. In some cases, however, a positive interaction was found. From the results it is speculated that the influence of magnesium stearate (used as a lubricant) on the binding properties of directly compressible materials is directly related to the densification behaviour of the filler binder. The negative effect of the lubricant on the binding properties is thought to be counteracted by the facilitated densification.

Introduction

The mechanism of consolidation and compaction of mixtures of materials has received little attention when compared with the studies performed on single materials. Moreover, the few studies reported in literature show no agreement. Tablet formulation would be facilitated if the properties of mixtures could be derived from those of the individual components. The compaction characteristics of blends have been found to be linearly related to the behaviour of the single materials (Humbert-Droz et al., 1983), but lack of proportionality has also been observed. Both positive and negative interactions have been reported in this respect (Lerk et al., 1974; Leuenberger, 1982; Jetzer et al., 1983; Sheikh-Salem and Fell, 1981, 1982). Fell and Newton (1970) were able to predict the tensile strength of tablets compressed from mixtures of various types of lactose when using approximately the same particle size. However, when the different forms of lactose were present in the same crystal, prepared either by spray drying or crystallization, this was not possible (Fell and Newton, 1971). Also in other studies (Newton et al., 1977; Cook and Summer, 1985), unpredictable tensile strength values have been obtained. Mixtures of dicalcium phosphate dihy-

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drate and phenacetin yielded stronger tablets than expected, the optimum composition being dependent on the pressure applied. The authors suggested (Newton et al., 1977) that the bonds between the different materials would be stronger than those between the individual materials. Moreover, it was observed that there existed large differences in porosity of tablets at a certain pressure.

More attention has been given to the tableting properties of mixtures of directly compressible filler binders with magnesium stearate, which is the most commonly used lubricant in pharmaceutical practice. Magnesium stearate is known to have strong negative effects on the binding properties of excipients, due to the formation of a lubricant film on the particle surface (Strickland et al., 1956; Bolhuis et al., 1975; Lerk et al., 1977). The extent to which compactibility reduces on lubrication depends on the consolidation properties of the material, the amount of magnesium strearate and the intensity and scale of mixing (Bolhuis et al., 1975; Lerk et al., 1977). It has been found that brittle materials were less susceptible to magnesium stearate than materials which deformed mainly plastically under load (De Boer et al., 1978). Subsequently the susceptibility of the binding properties of a substance has been proposed as a measure of the extent to which a substance fragments on compaction (Duberg and Nyström, 1982). Studies on the tableting properties of lactose (Vromans et al., 1988) revealed however, that this is not unambiguously true. This was underlined in a paper where it was argued that the film formation is unlikely to become complete when dealing with highly irregular particle surfaces and poorly flowing powders. There appeared to exist a relationship between the susceptibility to magnesium stearate and the bulk density for different types of lactose. Similar results have been obtained for 4 types of starch (Bos et al., 1987).

In the present paper an explanation is proposed for the interaction between two different filler binders on the basis of densification characterization and the influence of magnesium stearate on different materials is discussed.

Materials and Methods

The materials used were lactose (DMV, Veghel, The Netherlands), dicalcium phosphate dihydrate (Chemische Fabrik Budenheim, Budenheim, F.R.G.), amylose, potato starch (Avebe, Veendam, The Netherlands), microcrystalline cellulose (Avicel PH, FMC Europe SA, Brussels, Belgium), microfine cellulose (Elcema, Degussa AG, Frankfurt, F.R.G.; Sanacel 90, C.F.F., Mönchengladbach, F.R.G.) and magnesium stearate (Centrachemie, Etten-Leur, The Netherlands). Mixing of the excipients was performed in a Turbula mixer model 2P (W.A. Bachofen, Basle, Switzerland) at 90 rpm for 30 min. Compaction of 500 mg flat-faced tablets with a diameter of 13 mm was carried out using an hydraulic press (Paul Weber, Stgt. Uhlbach, F.R.G.). If necessary the die was prelubricated with magnesium stearate. Tablet strength and thickness were determined after a relaxation time of at least 15 min with a Schleuniger 4M tester (Dr. Schleuniger Productronic AG, Solothurn, Switzerland) and an electronic micrometer (Mitutoyo, Tokyo, Japan), respectively. The data given are the mean of at least 6 measurements. The theoretical porosity of a tablet compressed from a mixture was derived by first calculating the arithmetically expected thickness. Compressions for checking the Heckel equation were performed on a single punch tablet machine (Hoko KJ, Rijswijk, The Netherlands), instrumented with strain gauges to measure upper punch forces. The displacement of the upper punch was measured with an inductive displacement transducer (Philips type PR 9309). Upper punch displacement curves were recorded on an X-Y recorder (Hewlett Packard 7045A). A 13 mm diameter flat-faced punch and die system was used, being cleaned and then lubricated with magnesium stearate between compressions. Compaction occurred at a speed of 1 tablet/min, the die being filled with 500 mg of the required powder. The yield pressure was determined as the reciprocal slope of the linear section of the Heckel curve, which lay between 75 and 188 MPa in all cases, except for the pure plastic materials, in which case the range was 38–113 MPa. The values derived

from the Heckel plots are the mean of at least two measurements.

Results and Discussion

Mixtures of different excipients

One of the most important conclusions of the "studies on tableting properties of lactose" is that the compactibility of crystalline lactose is primarily determined by the surface area available in the tablet (Vromans, 1987; Vromans et al., 1987). This is illustrated in Fig. 1 where tablet strength is plotted vs tablet surface area as a linear relationship, being valid for several totally different types of crystalline lactose and several sieve fractions of α-lactose monohydrate. There are, however, some exceptions. For example, extremely small particle size fractions of α-lactose monohydrate exhibit relatively too low compactibilities (Fig. 1). It has been suggested that this is due to the poor densification properties of these samples (Vromans et al., 1987). At a pressure of 75 MPa, tablets of crystalline lactose normally exhibit porosity values of 17–22%. Tablets of the small particle size fractions of α-lactose monohydrate have values of 27.6% (1–8 μm) and 25.4% (8–16 μm), respectively. Clearly there must be a large effect of particle friction in the consolidation of the samples, preventing the large potential bonding surface area coming into close contact. Powder compressibility is obviously a very important parameter affecting tablet strength.

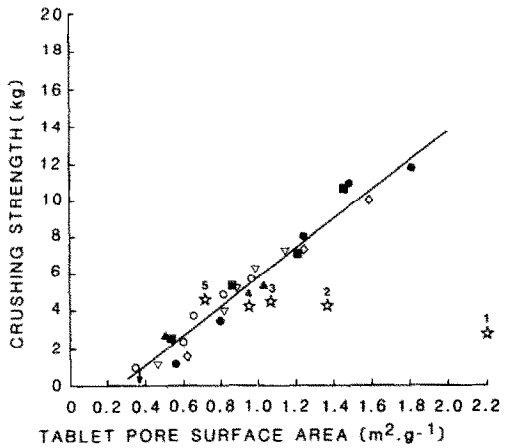

Fig. 1. Crushing strength of tablets compressed from different types of crystalline lactose at various compaction pressures, as a function of the tablet pore surface area, determined with mercury porosimetry (Vromans et al., 1987). (●), Anhydrous α-lactose 100–125 μm; (▲), crystalline β-lactose 100–125 μm; (■), roller dried β-lactose 100–125 μm; α-lactose monohydrate 32–45 μm (◇); 125-160 μm (▽); and 315–400 μm (○). The data of the α-lactose monohydrate samples indicated by numbered stars are obtained from tablets compressed at 75 MPa. (1), 1–8 μm; (2), 8–16 μm; (3) 16–24 μm; (4) 24–32 μm; and (5) 32–45 μm.

In Table 1, the values of crushing strength and thickness of tablets compressed at 150 MPa are given for blends of crystalline α-lactose monohydrate and microfine cellulose (Sanacel 90). Additionally, the values calculated by linear interpolation are given, which are derived from the data of tablets compressed from the individual starting materials. As can be seen, in all cases the tablet strength of the mixtures is higher than arithmeti-

TABLE 1

Porosity and crushing strength values for tablets of mixtures composed of 75% α-lactose monohydrate and 25% microfine cellulose, compacted at 150 MPa and yield pressures of the samples used

Particle size α-lactose monohydrate (μm)	Theoretical porosity (%)	Measured porosity (%)	Yield pressure lactose (MPa)	Yield pressure blend (MPa)	Lin. interpolated cr. strength (kg)	Measured cr. strength (kg)
1– 8	21.7	14.6	179	131	9.7	20.7
8–16	16.5	14.4	143	105	11.2	20.2
16–24	15.4	13.9	136	105	11.7	21.3
24–32	14.6	13.1	119	102	11.7	18.3
100 Mesh	12.5	11.4	115	101	9.3	11.0

The yield pressure and crushing strength at 150 MPa for the cellulose sample used are 64 MPa and 21.3 kg, respectively. Theoretical values are calculated using the data of tablets of the pure components.

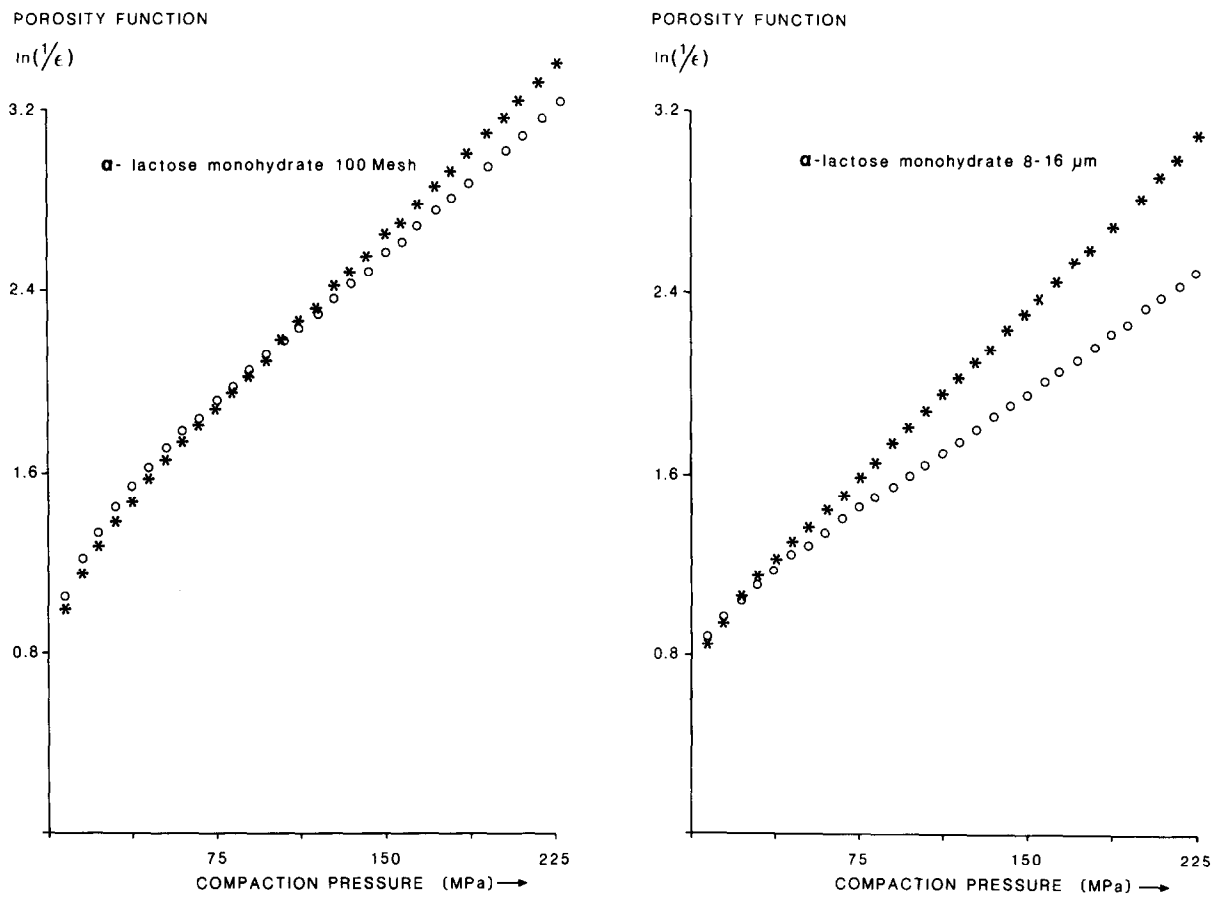

Fig. 2. Heckel plots of lactose samples without (○) and with (*) the addition of 25% cellulose (Sanacel 90).

cally expected. This effect tends to increase as the particle size of the lactose is decreased. Moreover, it goes parallel with the extent of densification; the smaller the particles, the more the densification is intensified, which is reflected in the values of tablet porosity and yield pressure. Apparently the cellulose part of the blends reduces the degree of particle interaction, thus facilitating consolidation. As a consequence, the large potential bonding surface areas (Fig. 1) can come into closer

TABLE 2

Porosity and crushing strength of tablets compressed at 150 MPa, crushing strength of mixtures with 25% microfine cellulose, the relative increase of the crushing strength and the yield pressure values of the starting materials and the blends

	Yield pressure starting material (MPa)	Yield pressure blend (MPa)	Porosity starting mat. (%)	Porosity blend (%)	Cr. str. starting mat. (kg)	Cr. str. blend (kg)	Incr. relative to start. mat
Amylose E	54	56	11.6	11.7	28.2 ± 1.0	20.5 ± 0.8	−0.27
Anhydrous α-lactose	122	113	10.1	8.7	13.7 ± 0.7	17.7 ± 0.9	+0.29
Roller-dried β-lactose	147	127	13.6	10.2	12.6 ± 0.5	19.8 ± 0.5	+0.57
Dicalcium phosphate dihydrate	342	228	23.6	21.6	6.4 ± 0.4	14.3 ± 0.4	+1.23

Values are means ± S.D.

contact. The effect is greatest in those cases where initially a bad densification existed.

Fig. 2 illustrates the Heckel plots of the starting materials and those of the mixtures for two lactose samples with Sanacel 90. Heckel plots have been used extensively for the characterization of powder compaction (Hersey and Rees, 1971; De Boer et al., 1978; Duberg and Nyström, 1982). The yield pressures of 100 mesh α-lactose monohydrate without and with cellulose are 115 and 101 MPa, while those of the 8–16 μm size fraction of α-lactose monohydrate are 143 and 105, respec-

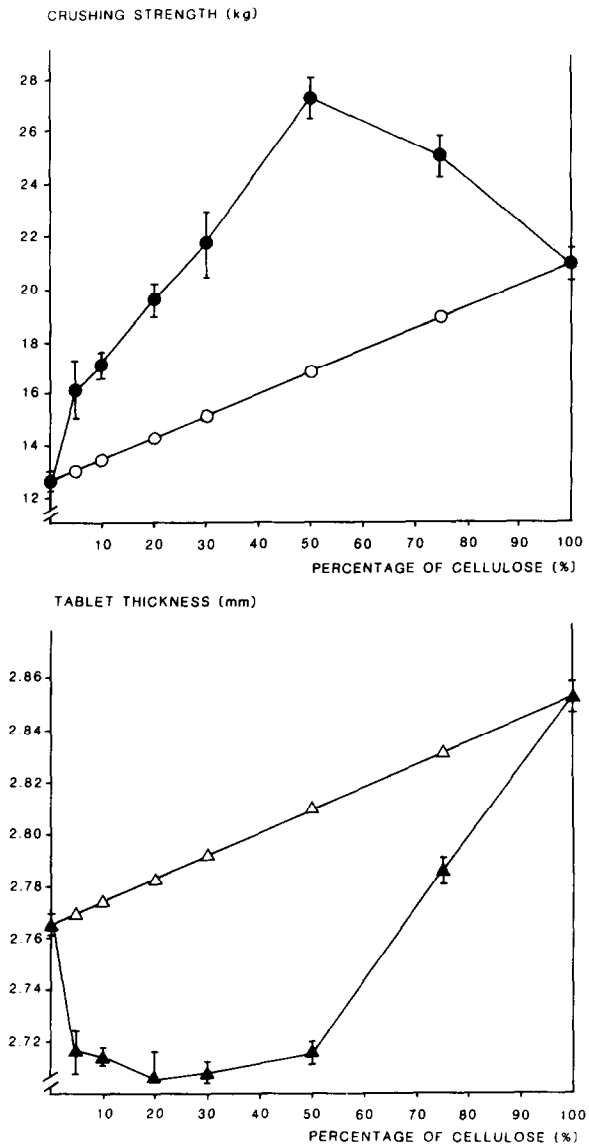

Fig. 3. Measured (●, ▲) and calculated (○, △) data of the crushing strength and thickness of tablets compressed at 150 MPa of mixtures of roller-dried β-lactose and cellulose (Sanacel 90) at different proportions.

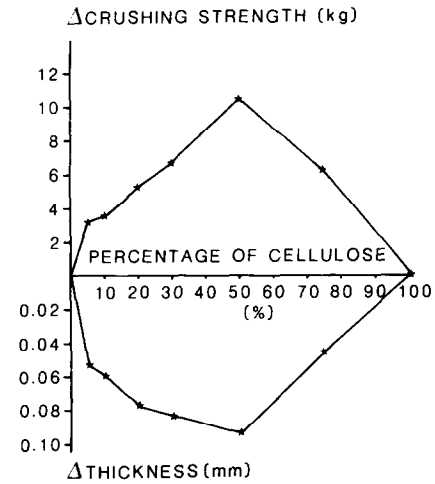

Fig. 4. Deviation of the measured crushing strength and tablet thickness from the calculated values for different mixtures of roller-dried β-lactose and cellulose (Sanacel 90).

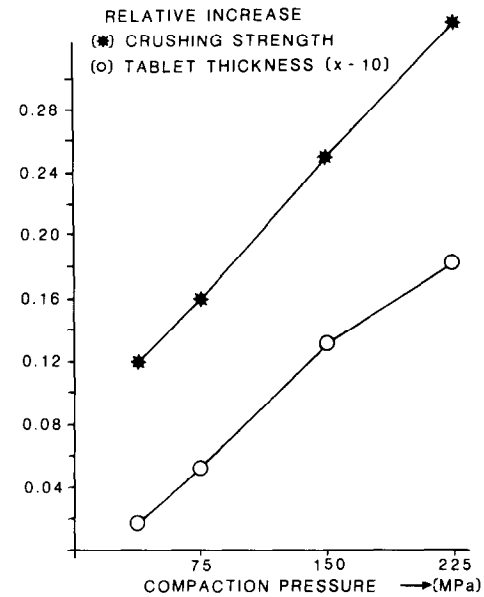

Fig. 5. Relative increase/decrease of the crushing strength and tablet thickness with respect to the arithmetically derived values of a mixture of roller dried β-lactose with 25% of cellulose (Elcema P050) as a function of the compaction pressure.

TABLE 3

Data of some plastically deforming samples and their 25% blends with 75% of roller-dried β-lactose

	Pure material		Blends			
	Tablet porosity (%)	Tablet strength (kg)	Theoretical porosity (%)	Measured porosity (%)	Theoretical cr. strength (kg)	Measured cr. strength (kg)
Elcema P050	12.8	14.5	13.0	11.8	13.1	15.7
Elcema P100	8.8	±56	12.3	11.3	±23.5	19.3
Elcema F150	10.6	±56	12.7	11.7	±23.5	18.9
Elcema G250	13.2	10.6	13.4	12.4	12.1	12.6
Avicel PH101	8.5	±65	11.9	11.4	±25.7	18.7
Avicel PH105	5.3	±80	11.5	10.1	±29.5	24.1
Sanacel 90	12.0	21.3	13.1	10.2	14.8	19.8
Amylose	12.6	25.9	13.2	11.4	15.9	14.8
Potato starch	10.9	7.4	12.8	7.2	11.3	18.8

The crushing strength and porosity of roller-dried β-lactose at 150 MPa are 12.6 kg and 13.6%, respectively.

tively. This confirms the observation that the consolidation of the fine lactose powder is intensified to a greater extent after addition of cellulose.

In Fig. 3 the crushing strength and thickness are plotted vs the ratio roller-dried β-lactose: cellulose for tablets compacted at 150 MPa. Roller-dried β-lactose (DCLactose 21) was chosen because of its relatively poor densification properties (yield pressure 147 MPa). As can be seen, the tablet strength of the blends are considerably higher than those of the individual components. To emphasize this, the arithmetically derived curve is also given. Similar considerations can be made regarding the tablet thickness, which demonstrates that the mixtures consolidate more intensely than expected by calculation. When the absolute differences between the measured and the calculated values are plotted (Fig. 4), it is apparent that the increased binding properties are related to the increased densification of the blends. Fig. 5 demonstrates the relative deviation from the arithmetically derived data for the crushing strength and the thickness as a function of the compaction load for the 25% cellulose blend. This again suggests a relationship between the compactibility and the compressibility. Moreover it is seen that the effect appears to depend upon the load applied.

Table 2 shows the data for mixtures of different pharmaceutical excipients containing 25% of microfine cellulose (Sanacel 90). Again it can be observed that poorly densifying materials are more prone to undergo a positive interaction comprising increased binding in relation to increased consolidation.

Table 3 shows the results from mixtures of roller dried β-lactose with different plastic materials. The different types of cellulose exhibit quite different compactibilities, which has also been shown by Doelker et al. (1987). Furthermore it is striking that the different types of Elcema have totally different compactibility properties. Rees and Rue (1978) found considerable interbatch variation in the compression characteristics of Elcema G250. Table 3 shows that addition of a plastic material to roller dried β-lactose has a rather unpredictable effect on the binding properties. For example, addition of Elcema P050 and G250 yields a positive interaction while mixing with the P100 and F150 types results in a negative (interaction) effect. An explanation for this might be that the tablet strength is limited by the weakest bond. When mixing roller dried β-lactose with a very strong binding substance, tablet strength will be limited by the lactose component, even when densification is intensified. Mixtures of two components with similar compactibilities will exhibit an increased binding capacity because of the lack of a definite weaker link. It is, however, also obvious, that the lactose, representing the largest amount of the bulk, forms the matrix of the tablet.

The degree of densification of this lactose part will therefore affect the tablet strength. Indeed there exists a tendency for the tablet strength to increase at decreasing porosity, with the exception of the potato starch blend. In this case the densification effect is extremely large.

Summarizing, it is found that a mixture of two excipients can exhibit unexpectedly high binding characteristics, which are most likely to be caused by the increased densification. The effect is the highest for poorly consolidating materials.

Mixtures with magnesium stearate

Fig. 6 shows the crushing strength of tablets compacted from blends of the same excipients as used in Table 2 with magnesium stearate (mixing time 30 min) at 150 MPa. Considerable differences exist between the properties of the materials. The compactibility of amylose is completely annihilated after the addition of 2% magnesium stearate. This is undoubtedly caused by the formation of the described lubricant layer. Further amounts of the lubricant give rise to an

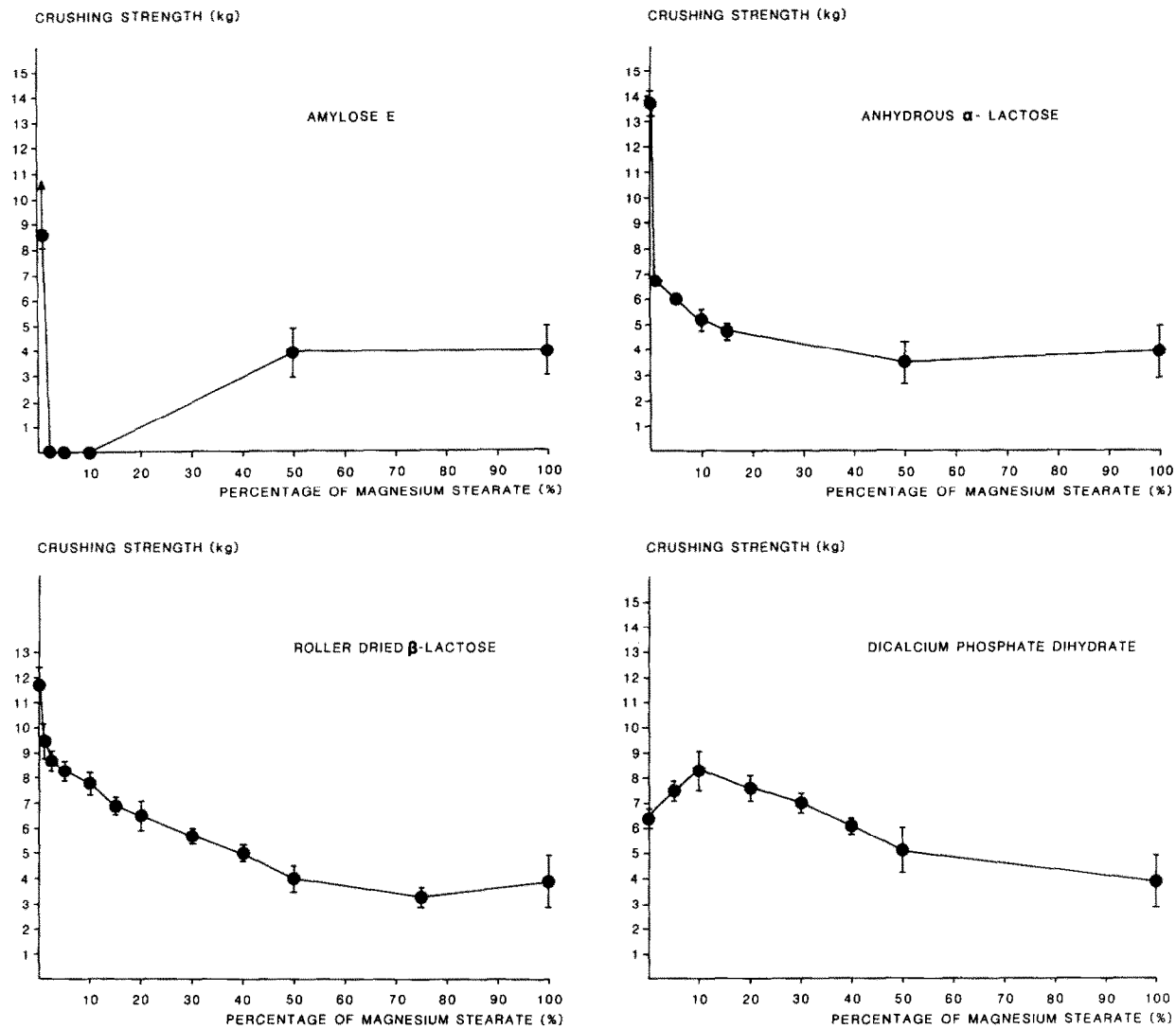

Fig. 6. Crushing strength of tablets compressed from mixtures of different excipients with magnesium stearate at 150 MPa.

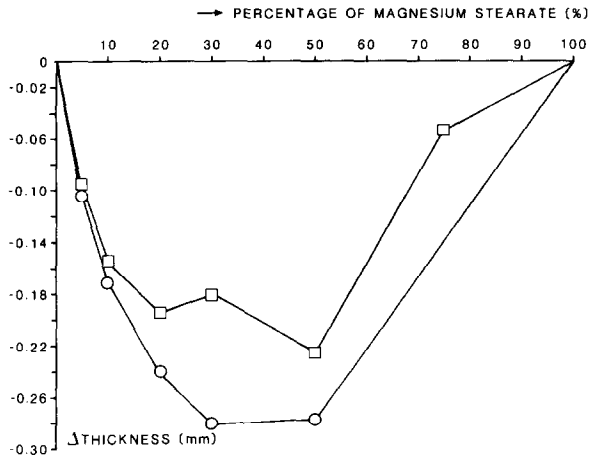

Fig. 7. Deviation of the measured tablet thickness from the calculated values for mixtures of dicalcium phosphate dihydrate (○) and roller-dried β-lactose (□) with magnesium stearate.

increase in tablet strength, until ultimately the value of magnesium stearate itself is reached. Cellulose and sodium chloride showed a similar behaviour. The binding capacity of anhydrous α-lactose is also considerably affected. The tablet strength is already halved after the addition of only 1% of magnesium stearate. However, on increasing percentages of the lubricant there remains a certain tablet strength. Roller-dried β-lactose shows a similar plot though it is relatively less sensitive. The tablets remain quite strong, even after the addition of 10% of magnesium stearate. In contrast, the tablet strength of dicalcium phosphate dihydrate does not decrease, but rather increases on addition of considerable amounts of lubricant, resulting in values which are even higher than the individual components. The only factor that could be responsible for the latter phenomenon is the facilitated densification of the substance. One has to notice in this respect that there is a parallel between the effect of magnesium stearate and the effect of cellulose (Table 2). In Fig. 7, the differences between the measured and the arithmetically derived thicknesses are given for tablets of dicalcium phosphate dihydrate and roller-dried β-lactose compacted at 150 MPa. Clearly an equivalent densification takes place when comparing this with the blends of roller-dried β-lactose with cellulose (Fig. 3). The difference is, however, that non-dried cellulose has good binding properties whereas magnesium stearate prevents the excipient from binding. Furthermore, in contrast to cellulose, the lubricant is situated as a film on the surface of the excipient particles. One might conclude from this, that materials with poor densification characteristics (high yield pressure values) apparently obtain extra tablet strength, induced by the facilitated densification due to lubrication, that can compete with the negative influence of magnesium stearate. Mixtures of the same excipients with dried (poor bonding) cellulose confirm this assumption (Fig. 8). Again the same sequence in susceptibility to the poor bonding additive is found. Dicalcium phosphate dihydrate exhibits an increase in crushing strength while anhydrous α-lactose and amylose demonstrate a negative interaction in binding capacity. Remarkably, anhydrous α-lactose seems to be more strongly affected by the dried cellulose than amylose. Probably an important reason for this is the fact that cellulose does not exhibit film formation.

The results obtained imply that mixtures which demonstrate an increased binding capacity because of facilitated densification should be sensitive to lubrication with magnesium stearate. Roller dried β-lactose (Fig. 3) and dicalcium phosphate dihydrate (Table 2) both are relatively unsuscepti-

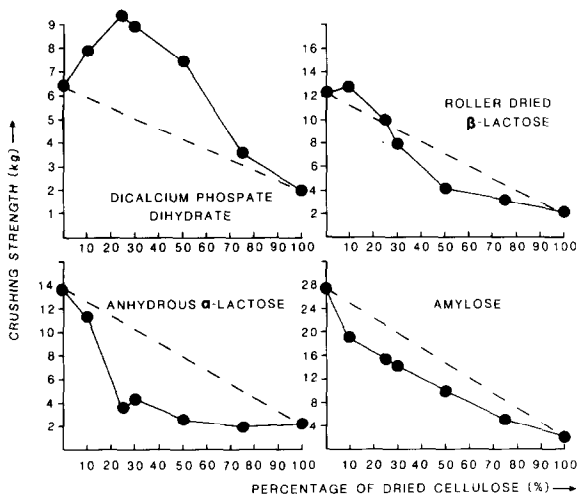

Fig. 8. Crushing strength of tablets compressed from mixtures of different excipients with dried cellulose (Sanacel 90) at 150 MPa.

TABLE 4

Yield pressure and crushing strength of tablets compacted at 150 MPa of roller-dried (r.d.) β-lactose and dicalcium phosphate dihydrate (dcp) and of mixtures of these materials with 25% microfine cellulose

	Yield pressure (MPa)	Crushing strength (kg)	Cr. strength lubr. 1% Mg. St. (kg)	Reduction ratio
Roller dried β-lactose 100%	147	12.6 ± 0.3	9.9 ± 0.5	0.79
R.d. β-lactose : cellulose 75 : 25	127	19.8 ± 0.5	8.5 ± 0.3	0.43
Dicalc. phosph. dihydr. 100%	342	6.4 ± 0.4	5.9 ± 0.5	0.92
Dcp : cellulose 75 : 25	228	14.3 ± 0.4	8.0 ± 0.4	0.56

Lubrication occurred by 30 min mixing with 1% magnesium stearate. The reduction ratio is the ratio between the crushing strength with and without lubricant addition. Values are means ± S.D.

ble to lubrication (Table 4). Addition of 25% of microfine cellulose results in an increase in compactibility, due to increased densification. However, these blends are very sensitive to lubrication, even though 75% of the lubricant-resistant component is present. The yield pressure of these samples is far lower than those of the starting materials, the cellulose increasing the densification of the brittle component. Therefore this advantageous property of magnesium stearate has less effect, and as a consequence, the negative effect on the binding becomes more pronounced.

From the foregoing results and previous literature reports (De Boer et al., 1978; Duberg and Nyström, 1982), it can be concluded that the consolidation properties of a material are of importance in the extent to which it is affected by lubrication with magnesium stearate. This means that, in principle, the susceptibility of a substance to magnesium stearate is not only a material property, but depends also upon its densification behaviour, which is also determined by e.g. the particle size and shape.

In conclusion, it is argued that the deleterious action of magnesium stearate on the binding properties of excipients is counteracted by the increased densification caused by the lubricant. This effect is the strongest for materials with poor densification properties.

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