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A coherent matrix model for the consolidation and compaction of an excipient with magnesium stearate

K.A. Riepma [a], H. Vromans [b] and C.F. Lerk [a]

[a] *Department of Pharmaceutical Technology and Biopharmacy, University of Groningen (The Netherlands) and* [b] *Organon International B.V., Oss (The Netherlands)*

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Summary

This paper reports that magnesium stearate sensitivity of brittle materials is not directly related to the degree of fragmentation during compression. A coherent matrix of magnesium stearate, created by the process of dry blending, is highly sustained during consolidation and compaction of the particulate system. Failure of the tablets happens therefore principally along the interfaces of the original excipient crystals. Fragmentation of the excipient particles occurs mainly within the areas surrounded by the magnesium stearate network and contributes therefore little to the crushing strength of the tablets.

Introduction

Studies on the consolidation and compaction properties of excipients are generally devoted to the single component only. However, pharmaceutical tablets are normally composed of several ingredients. In large scale tablet manufacturing, these powders are usually mixed with a lubricant before compaction in order to prevent the tablet from sticking to the die and to minimize wear on dies and punches. Magnesium stearate is probably the most commonly used pharmaceutical lubricant. However, next to its excellent lubricating action, magnesium stearate is notorious for its detrimental effects on several tablet properties, such as strength and disintegration time (Strickland et al., 1956). Bolhuis et al. (1975) showed that the effect of magnesium stearate on tablet strength is caused by the adhesion of a lubricant film upon the surface area of the substrate during the mixing procedure. The formation of the lubricant film around the particles was found to depend upon the amount of magnesium stearate used and the mixing time. The effect of magnesium stearate on the bonding properties of excipients was shown to depend upon their consolidation characteristics (De Boer et al., 1978). The bonding properties of definite plastically deforming substances were in some cases completely eliminated. Some fragmenting materials, however, showed to be quite insensitive to magne-

Correspondence to: C.F. Lerk, Dept of Pharmaceutical Technology and Biopharmacy, University of Groningen, Ant. Deusinglaan 1, 9713 AV Groningen, The Netherlands.

sium stearate admixing, which was explained to be due to the creation of clean surfaces during compression. Subsequently, the magnesium stearate sensitivity has been used to characterize the consolidation properties of materials. Duberg and Nyström (1982) used the strength reduction ratio (i.e., the ratio between radial strength of tablets with and without lubricant addition) as an indication for the fragmentation propensity of a substance. For several materials the method appeared to yield good results. However, in some cases the reduction ratio did not reflect the observed fragmentation propensity. In order to explain these observations, Vromans et al. (1988a) showed that factors other than fragmentation might affect lubricant sensitivity. They suggested that film formation of magnesium stearate on lactose powders was unlikely to become complete when dealing with highly irregular particle surfaces and poorly flowing powders. There appeared to exist a relationship between the sensitivity to magnesium stearate and the bulk density for different types of lactose. Similar results were obtained for four types of starch (Bos et al., 1991). In an other study, Vromans and Lerk (1988b) showed that the sensitivity of a substance to magnesium stearate is not only a material property, but also depends upon its densification behaviour, which is also determined by, e.g., the particle size and shape. The negative effect of the lubricant on the binding properties was thought to be counteracted by a facilitated densification.

This paper evaluates the effect of magnesium stearate lubrication on the compactibility of excipients with special attention to fragmentation behaviour. A coherent matrix model is introduced to explain magnesium stearate sensitivity of excipients on consolidation and compaction.

Materials and Methods

The materials used were sieve fractions (250–315 μm) of α-lactose monohydrate and roller

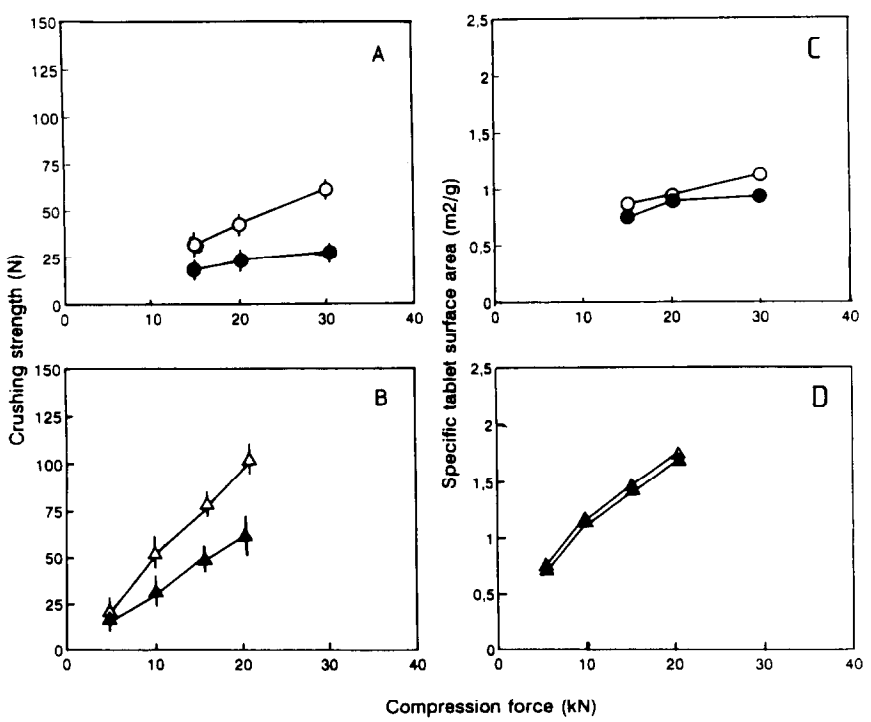


Fig. 1. Strength (a, b) and specific surface area (c, d) vs compression force of tablets compacted from unlubricated (open symbols) and lubricated (closed symbols) fractions (250–315 μm) of α-lactose monohydrate (○, ●) and roller dried β-lactose (△, ▲).

dried β-lactose, obtained from DMV, (Veghel, The Netherlands), dicalcium phosphate dihydrate from Chemische Fabrik Budenheim, (Budenheim, Germany), sodium citrate from Merck, (Darmstadt, Germany), decanoic acid from Janssen Chimica, (Beerse, Belgium), diethyl ether from Brocacef, (Maarssen, The Netherlands) and magnesium stearate from Centrachemie (Etten-Leur, The Netherlands).

All tests were performed at constant temperature (20 ± 1°C) and constant relative humidity (45 ± 5%). The powders were stored under these conditions for at least 2 days before mixing and compression.

All powders were mixed in a Turbula mixer model 2P (W.A. Bachofen, Basle, Switzerland) at 90 rpm for 60 min, regardless of whether or not magnesium stearate was present.

Lubricated and unlubricated powders were compacted at a rate of 2 kN/s into 500 mg flat-faced tablets with a diameter of 13 mm using a programmable hydraulic press (ESH Testing, Brierley Hill, U.K.).

Tablet strength was determined 30 min after compaction with a Schleuniger 4M tester (Dr Schleuniger Production AG, Solothurn, Switzerland). The presented data are the means of at least five tablets.

The specific surface area of the tablets was measured with a Quantasorp apparatus (Quantachrome Corp., Syosset, U.S.A.) using nitrogen as adsorbate in single point determinations. The tablets were stored 'immediately' after compaction in a nitrogen atmosphere to suppress sorption of moisture and subsequently transported to the apparatus (Riepma et al., 1992). No outgassing procedures were applied. The data are the means of at least four tablets.

Electron micrographs were recorded using a scanning electron microscope (Jeol JSM-U3, Japan). Prior to investigation, the samples were coated with gold, using a direct sputter technique.

Results and Discussion

Fig. 1 (a,b) shows the compactibility profiles of unlubricated and lubricated fractions (250–315 μm) of α-lactose monohydrate and roller dried β-lactose, respectively. As seen, lubrication results in a decrease in tablet strength at all compaction forces. This effect is slightly larger for tablets of α-lactose monohydrate than for tablets of roller dried β-lactose. Next, Fig. 1 (c,d) illustrates the specific surface area of the unlubricated and the lubricated tablets. The figures clearly demonstrate that no great difference exists between the specific surface area of the unlubricated and the lubricated tablets. This means that the extent of fragmentation, i.e., the consolidation, is almost unaffected by the presence of magnesium stearate.

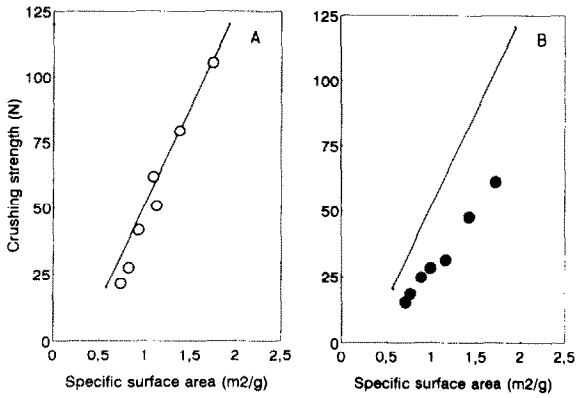


Fig. 2. Crushing strength vs specific surface area of unlubricated (a) and lubricated (b) tablets compressed with different forces from a fraction (250–315 μm) of α-lactose monohydrate and roller dried β-lactose, respectively. The line is similar to that reported earlier (Riepma et al., 1990).

In previous papers it has been demonstrated that surface area measurements could be applied to study compression and compaction behaviour of lactose. In this respect a relation between tablet strength and specific tablet surface area has been found (Vromans et al., 1985, 1987). Fig. 2a illustrates the relation between strength and specific surface area of the unlubricated lactose tablets from Fig. 1. The line in Fig. 2a is similar to that earlier reported (Riepma et al., 1990). As expected, the measured data fit the relationship found earlier. Fig. 2b shows the relation between strength and specific pore surface area of the lubricated lactose tablets, including the line from Fig. 2a. Fig. 2b clearly demonstrates that the data of the lubricated tablets deviate from the linear

TABLE 1

Specific surface area, extent of fragmentation and lubricant sensitivity ratio of tablets compacted at different forces from a fraction (250–315 μm) of α-lactose monohydrate and roller dried β-lactose, respectively

Fraction	C_f	S_t	$(S_t - S_p)/S_p$	LSR
α-Lactose monohydrate				
250–315 μm	0	0.08 (= S_p)	–	–
	15	0.76	8.5	0.38
	20	0.88	10	0.43
	30	0.96	11	0.56
Roller dried β-lactose				
250–315 μm	0	0.17 (= S_p)	–	–
	5	0.70	3.1	0.29
	10	1.15	5.8	0.39
	15	1.42	7.4	0.39
	20	1.68	8.9	0.42

C_f, compression force; S_p, specific powder surface area; S_t, specific tablet surface area; $(S_t - S_p)/S_p$, extent of fragmentation; LSR, lubricant sensitivity ratio.

relation. At any specific surface area the strength of the lubricated tablets is lower than that of the unlubricated tablets. It is obvious that there is a great difference in binding capacity. As a consequence, one should distinguish single-component tablets from multi-component tablets. Unlubricated tablets can be considered as homogeneous compacts in which all surface planes are equal in terms of bonding capacity. In contrast, lubricated compacts must be regarded as heterogeneous systems composed of clean surface planes and surface planes covered with a film of magnesium stearate.

The effect of magnesium stearate on the strength of the lactose tablets is further elaborated in Table 1. Table 1 presents the specific surface area, the degree of fragmentation, $(S_t - S_p)/S_p$, and the lubricant sensitivity ratio, LSR, of the lactose tablets at different compression forces. The degree of fragmentation, $(S_t - S_p)/S_p$, has been defined as the relative increase in surface area when compressing a powder blend with surface area S_p into a tablet with specific surface area S_t (Riepma et al., 1991). The LSR represents the ratio between the decrease in crushing strength of tablets due to mixing with lubricant and the crushing strength of unlubricated tablets (Bos et al., 1991). The data in Table 1 show for the two powder fractions an increase in specific surface area, and hence an increase in degree of fragmentation with increasing compaction force. Furthermore, Table 1 shows that, next to the compaction load, the degree of fragmentation of a lactose fraction depends on the type of lactose used. The sieve fraction of α-lactose monohydrate fragments to a larger extent than the fraction of roller dried β-lactose. With respect to the LSR, Table 1 shows that tablets of α-lactose monohydrate are slightly more sensitive to magnesium stearate admixing than tablets of roller dried β-lactose. In addition, the lubricant sensitivity of both lactose fractions increases with compaction load.

Earlier, several authors suggested that brittle behaviour of excipients would have favourable effects on the influence of magnesium stearate on the compactibility (De Boer et al., 1978; Duberg and Nyström, 1982). It has been proposed that during compaction of these excipients, lubricant-free surfaces would be created. According to this view, the originally present lubricant coated particle surfaces will be distributed at random within the compact, as illustrated in Fig. 3. As a consequence, the effect of a lubricant on the compactibility of an excipient would only be limited. However, considering Table 1, this model is not confirmed, i.e., the lubricant sensitivity is shown

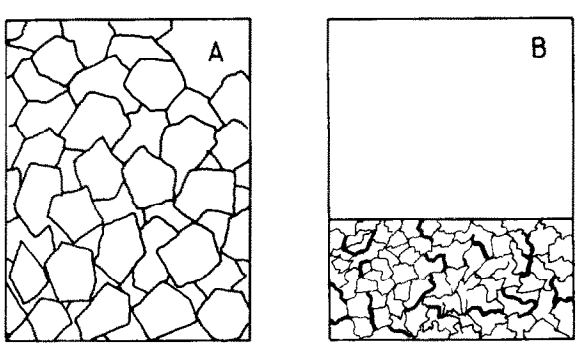


Fig. 3. Non-coherent matrix model. A coherent network of magnesium stearate (a), created by dry mixing the excipient with the lubricant, is interrupted by fragmentation and consolidation of the particulate system (b). The bold lines within the figure represent the magnesium stearate film upon the surface of the original particles.

not to be related to the degree of fragmentation. Obviously, the entire newly created surface area is not all available for bonding. This apparent behaviour could be explained if a significant part of the newly formed surfaces is contaminated with magnesium stearate. A possible mechanism has been proposed by Rubinstein and Moody (1985) and Fukumori and Carstensen (1983) who suggested that during compaction magnesium stearate migrates throughout the powder mass to the newly created surface areas.

The effect of magnesium stearate on the compactibility of three different excipients is shown in Table 2. In contrast to dicalcium phosphate dihydrate, α-lactose monohydrate and sodium citrate both exhibit a considerable reduction in tablet strength upon lubrication, whereas it is known that intensive fragmentation occurs during consolidation (Duberg and Nyström, 1982). In order to study the crushing of the tablets, scanning electron micrographs of tablet failure planes were taken. Fig. 4a and c shows tensile failure planes of unlubricated compacts of α-lactose monohydrate and sodium citrate, respectively. As observed, particles of the original size can be recognized. In fact, this confirms earlier findings of Butcher et al. (1974). Obviously, in spite of the intensive fragmentation occurring (Table 1), the initial particle characteristics are more or less preserved. In this respect, there is a great part of resemblance to earlier observations on the consolidation of granules (Riepma et al., 1993). In the latter study, it was shown that the primary characteristics of granules such as granule size were not eliminated during compaction. Therefore, it was concluded that the granules keep their integrity to some extent during the consolidation process.

Photomicrographs of the fractures of lubricated tablets of α-lactose monohydrate (Fig. 4b) and of sodium citrate (Fig. 4d) show that tensile failure occurs around the interfaces between the original crystals. Realizing that these surfaces are coated with magnesium stearate, it is suggested that a three-dimensional matrix of magnesium stearate is sustained during compression of the particulate system. Fragmentation of the excipient particles occurs within the areas surrounded by the magnesium stearate network (Fig. 5). Consequently, the strength of a compact is principally determined by the structure of a magnesium stearate matrix, created during the process of mixing the excipient with the lubricant. This model agrees with the findings of De Boer et al. (1978). They reported that original particles could be distinguished within tensile failure planes of lubricated tablets compacted from the plastically deforming subtances Amylose V and NaCl. This was explained by the absence of bonding between surfaces of original particles due to the presence of a magnesium stearate film.

Fig. 6 shows the fracture of a tablet compacted from dicalcium phosphate dihydrate mixed with 1% magnesium stearate. As seen in this photograph, no original crystals can be distinguished. Obviously, failure of the tablet takes place across the original particles, as has been reported by De Boer et al. (1978). Apparently, addition of the

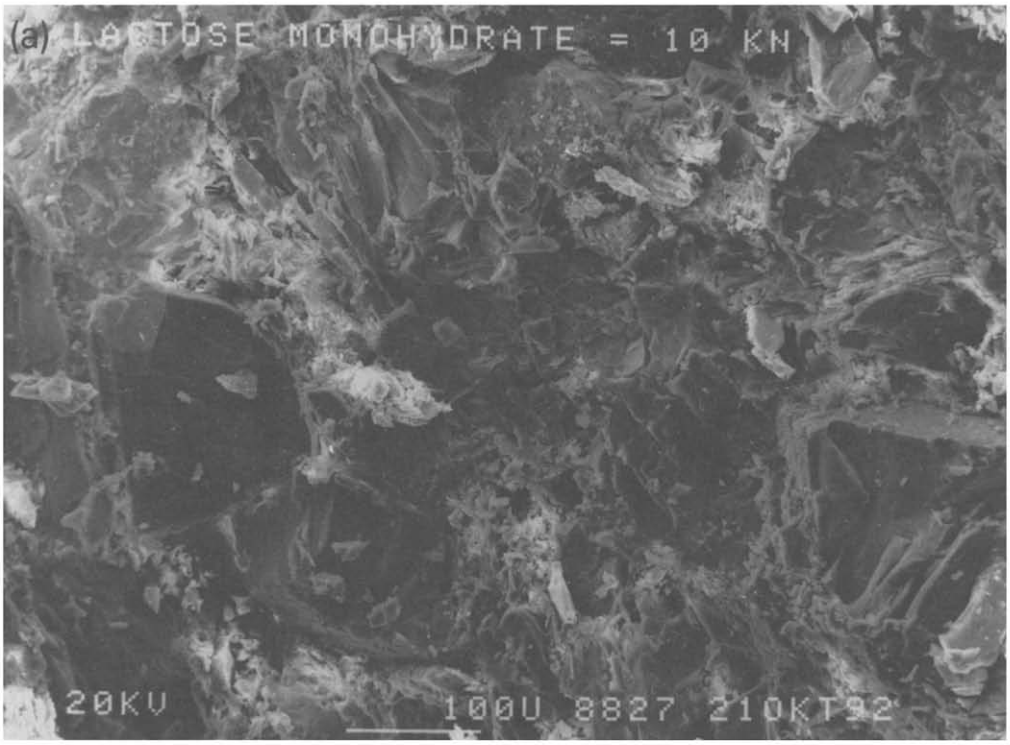
TABLE 2

The effect of lubrication with magnesium stearate (0.5%) and decanoic acid (0.5%), respectively, on the strength of tablets compacted at 20 kN from a fraction (250–300 μm) of several materials

Material	Magnesium stearate			Decanoic acid		
	Cs_u	Cs_l	LSR	Cs_u	Cs_l	LSR
α-Lactose monohydrate	42	24	0.43	42	21	0.50
Sodium citrate	23	5	0.78	23	11	0.52
Dicalcium phosphate dihydrate	32	29	0.09	32	16	0.50

Cs_u, crushing strength of unlubricated tablets; Cs_l, crushing strength of lubricated tablets; LSR, lubricant sensitivity ratio.

Fig. 4. Scanning electron micrographs of failure planes of tablets compacted at 10 kN from a fraction (250–300 μm) of α-lactose monohydrate (a, b) and sodium citrate (c, d), respectively. Tablets were compacted from unlubricated fractions (a, c) and from fractions lubricated with 1% magnesium stearate (b, d).


(a) LACTOSE MONOHYDRATE = 10 KN
20KV
100U 8827 21OKT92

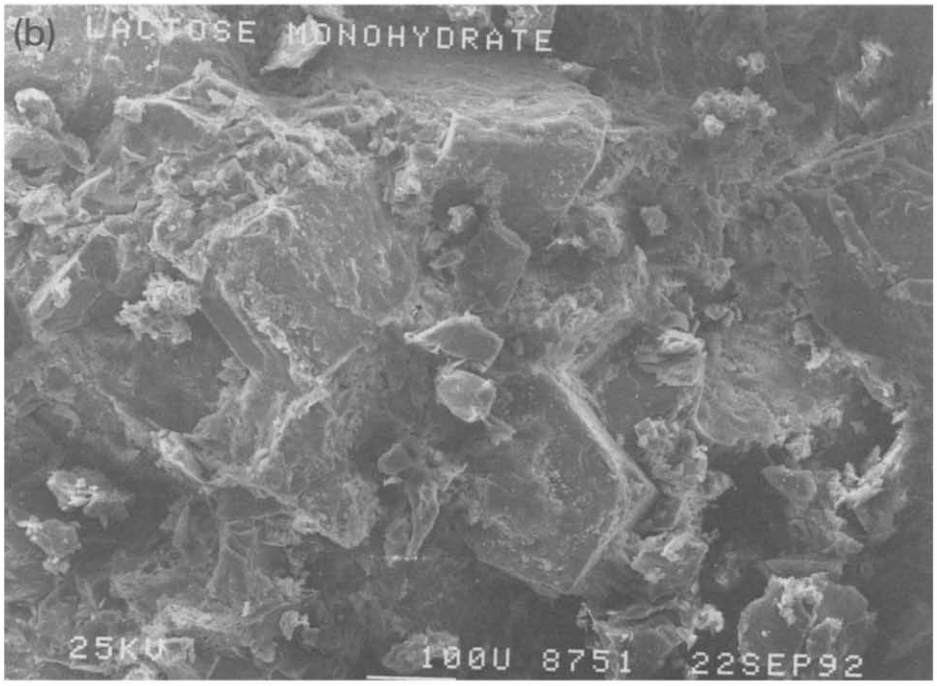
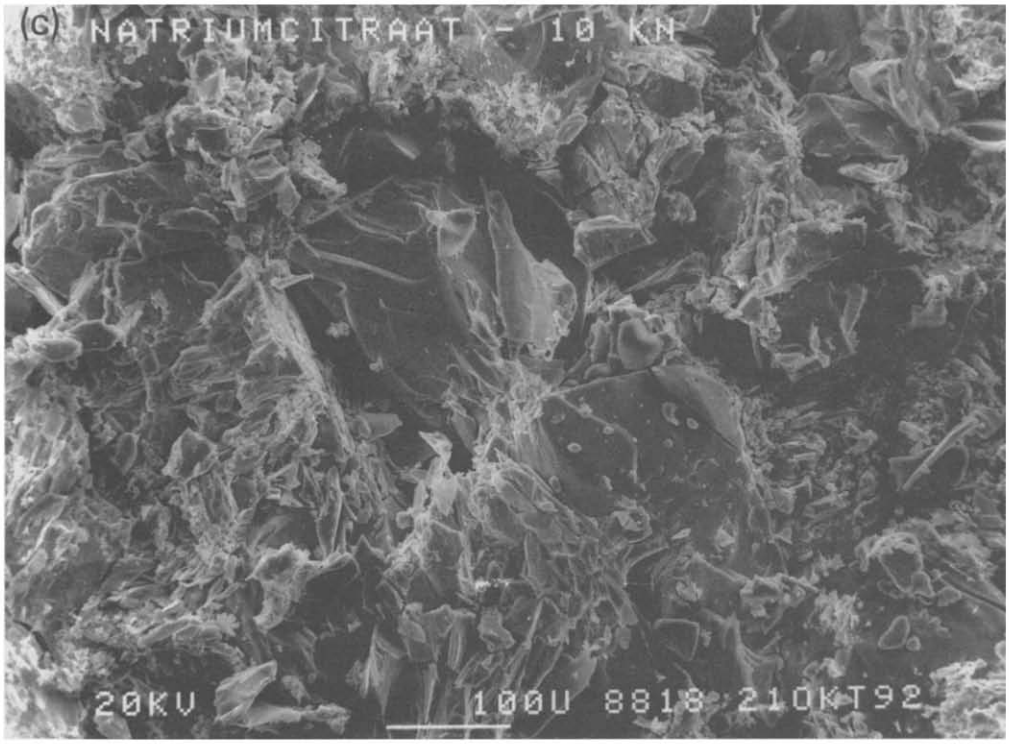

(b) LACTOSE MONOHYDRATE
25KV
100U 8751 22SEP92

Fig. 4(a,b).


(c) NATRIUMCITRAAT - 10 KN
20KV
100U 8818 210KT92

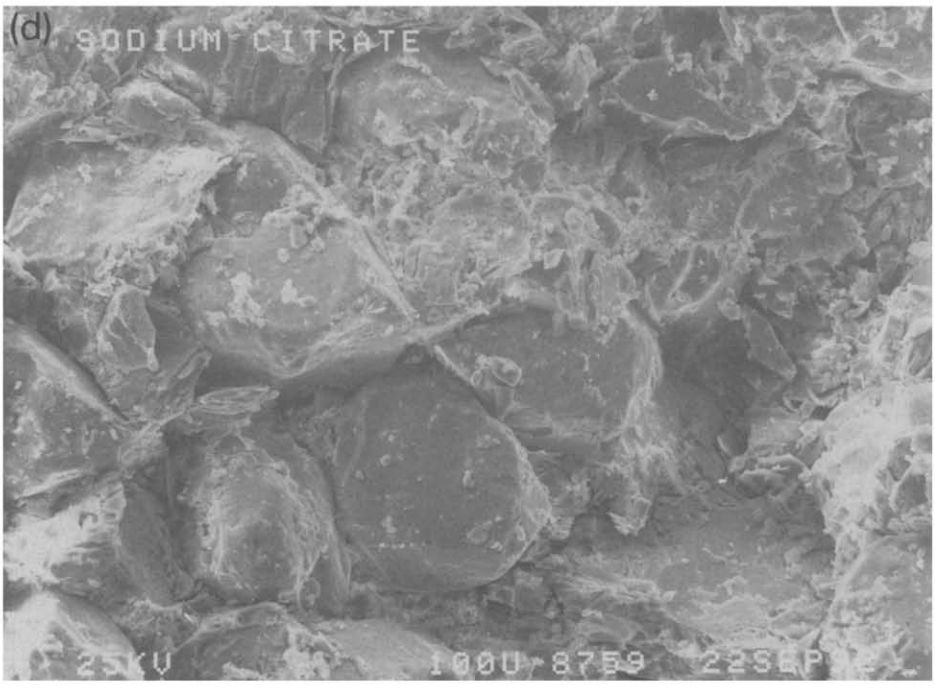

(d) SODIUM CITRATE
25KV
100U 8759 22SEP

Fig. 4(c,d).

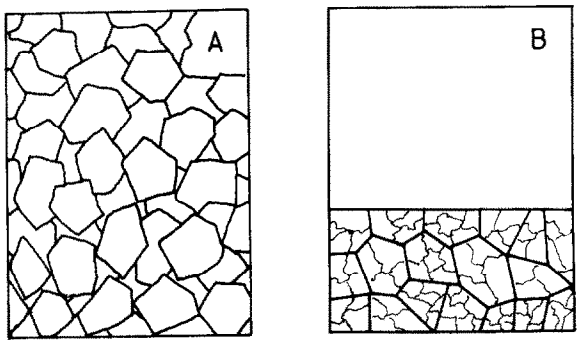


Fig. 5. Coherent matrix model. A coherent network of magnesium stearate (a), created by dry mixing the excipient with the lubricant, is sustained during the process of consolidation (b). Fragmentation occurs within the areas surrounded by the lubricant. The bold lines within the figure represent the magnesium stearate film upon the surface of the original particles.

lubricant does not lead to the formation of weak bonds between original particle surfaces.

From previous publications it is known that the lubricant sensitivity of a material depends, next to other factors, on the surface texture of the particles (Bolhuis et al., 1985; Vromans et al., 1985; Lerk and Sucker, 1988). Lerk and Sucker (1988) showed that during the mixing process of irregular shaped granule particles magnesium stearate formed a discontinuous layer around the particles of the granular excipient. Part of the magnesium stearate was trapped into the asperities and cavities and was therefore not available for the formation of a magnesium stearate film. Evidently no coherent matrix of magnesium stearate is formed. In order to assure the presence of a complete lubricant film, Vromans and Lerk (1988b) coated excipients with decanoic acid dissolved in diethyl ether. Table 2 demonstrates the effect of such a decanoic acid coating on the three materials under the present study. The data show totally different lubricant sensitivity ratios of the different excipients when dry-blended with magnesium stearate but almost equal lubricant sensitivities on liquid coating. This result endorses the determining effect of the presence of a coherent or non-coherent matrix of magnesium stearate within a particulate system. The very

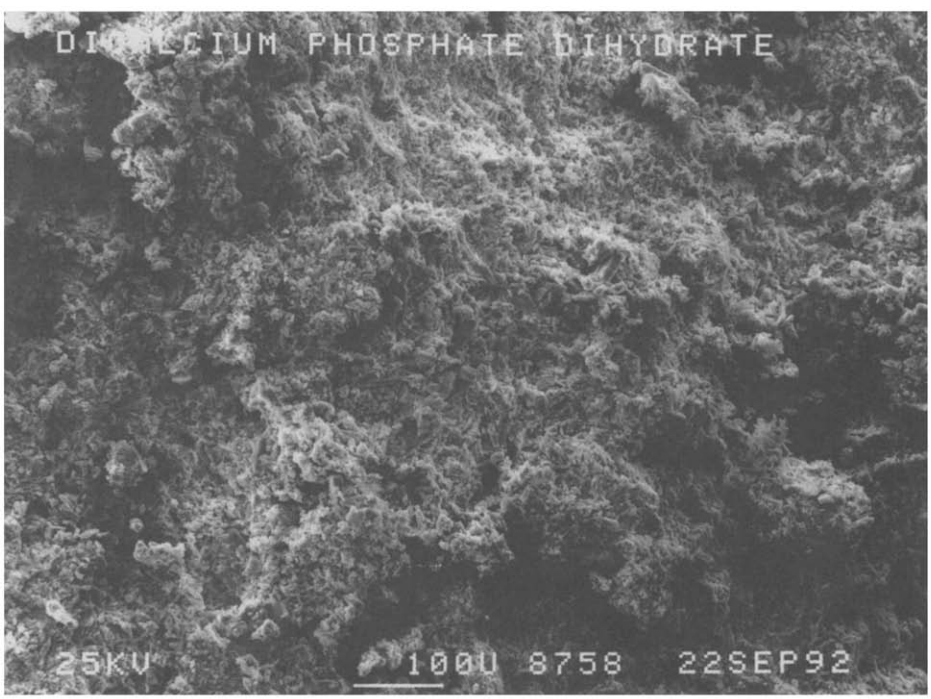


Fig. 6. Scanning electron micrographs of failure planes of tablets compacted at 10 kN from a fraction (250–300 μm) of dicalcium phosphate dihydrate. Tablets were compacted from fractions lubricated with 1% magnesium stearate.

irregular particle texture of dicalcium phosphate dihydrate particles, as compared to the relatively smooth crystal surfaces of α-lactose monohydrate and sodium citrate, prevents the formation of a continuous lubricant film on blending with magnesium stearate, and explains the low lubricant sensitivity of this excipient on direct compression.

The results presented so far demonstrate that magnesium stearate sensitivity of brittle materials is not directly related to the degree of particle fragmentation on compresssion. Lubricant sensitivity is principally determined by the creation of a complete or incomplete coating of the excipient by magnesium stearate during the process of dry mixing. A coherent matrix of lubricant is highly sustained during consolidation and compaction and results into failure of the tablets mainly along the interfaces of the original excipient particles. Fragmentation of the excipient particles within the areas surrounded by the lubricant network, with correspondingly increasing pore surface area of the tablets, therefore contribute only little to the crushing strength of the tablets.

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