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Compression characteristics of granulated materials. IV. The effect of granule porosity on the fragmentation propensity and the compactibility of some granulations *

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Summary

Eleven granulations of a common filler (lactose) and three granulations of a high dosage drug (dipentum) were produced by wet granulation with polyvinylpyrrolidone as binder in a high shear mixer. The agglomeration process was varied to produce granulations with varying granule porosity. The size fraction 500–710 μm was separated and characterised on binder content (lactose granulations), granule porosity and friability. The granule fragmentation during compaction was evaluated by measurements of the air permeability of the tablets. Finally, the diametral compression strength of tablets compacted from unlubricated granulations and lactose granulations lubricated with 0.5% by weight magnesium stearate at 150 MPa was measured. The results showed that the degree of granule fragmentation during compaction was related to the granule porosity before compaction. A granulation with a higher porosity had a higher fragmentation propensity, as evaluated by the permeametry measurements, and the tablet strength was less affected by magnesium stearate addition. The tablet strength correlated well with the degree of fragmentation, i.e. a granulation with higher degree of fragmentation gave tablets of a higher mechanical strength. These observations suggest that variations in compactibility, when the same formulation is wet granulated under different process conditions, can be explained by variations in granule porosity.

Introduction

Granulation of pharmaceutical powder mixtures is a common operation during tablet production to ensure, e.g. a good compactibility of the mass. The process conditions during the granulation can affect the physical properties of the granules which, in combination with the composition of the granulation, will govern the mechanical strength of the resultant tablets. In earlier papers in this series (Alderborn et al., 1987; Wikberg and Alderborn, 1990a,b), the importance of one such physical property, the propensity of the granules to fragment during compaction, has been discussed. The fragmentation propensity of the granules was evaluated by tablet air permeability mea-

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surements, i.e. the change in tablet permeability with compaction pressure. The term fragmentation was used to denominate a granule characteristic which was described as a collapse or a breakdown of the granule during the compression phase and this structural change of the granule affected the pore structure of the formed compact. A number of granulations of a high dosage drug and a common filler were produced by varying the conditions during the agglomeration phase, i.e. the amount and composition of the solvent for the binder. These variations affected the fragmentation propensity of the produced granules. It was found, that for a certain formulation the tablet strength was directly related to the degree of granule fragmentation during compression.

The effect of the process conditions during the agglomeration on the granule porosity have been studied extensively in the literature, e.g. the type and capacity of the mixer (Ganderton and Hunter, 1971; Hunter and Ganderton, 1973; Schaefer et al., 1986), impeller speed and design (Jaegerskou et al., 1984; Holm, 1987), process time and amount and composition of agglomeration liquid (Tapper and Lindberg, 1986; Riitala et al., 1988; Wikberg and Alderborn, 1990a). These agglomeration studies indicate for example that granule porosity shows a similar dependence of the composition of the agglomeration liquid as was found (Alderborn et al., 1987; Wikberg and Alderborn, 1990a) for the fragmentation propensity of the granules. This observation therefore suggests that the volume reduction characteristics of the granulation during the compaction can be affected by the porosity of the granules before compaction.

The relation between granule porosity and granule fragmentation was evaluated earlier for some lactose granulations (Wikberg and Alderborn, 1990a). There was a tendency for the degree of fragmentation to increase with an increased granule porosity, but these granule characteristics did not correlate well. For these granulations, the shape and surface characteristics of the granules varied markedly and it was suggested that these granule characteristics also influenced the granule fragmentation as well as the measurement of granule porosity. Furthermore, the range of granule porosity values produced by the granulation procedure was fairly narrow and it was concluded that the relation between granule porosity and granule fragmentation must be evaluated further.

Pharmaceutical granules usually consist of at least two components, i.e. a particulate substrate and a binder, which can be more or less well spread on the substrate particles. For granules produced of a certain substrate, a reduction in granule porosity will probably reduce the separation distance between the substrate particles (Chan et al., 1983). It seems reasonable that such a change in the packing characteristics of the substrate particles will be of importance for the particle-particle interactions and thus the mechanical properties of the granules, i.e. the response of a granule to a dynamic loading. A knowledge of how a variation in granule porosity affects the tableting properties of a granulation can increase the understanding of the volume reduction behaviour of a granulation and the mechanism of granule fragmentation. Furthermore, information on this relationship is also of practical interest to predict how changes in the process conditions can affect the tableting properties of a granulation. However, studies on this relationship have hitherto achieved limited attention in the literature although it has recently been reported (Millili and Schwartz, 1990) that for pelletized masses, a granulation with pellets of higher porosity gave higher tablet strength values compared to a mass consisting of pellets of lower porosity. The intention with this paper was therefore to study the effect of granule porosity on the fragmentation propensity and compactibility of some granulations. Granulations of a filler, lactose, and a high dosage drug, dipentum, were used as model systems.

Materials and Methods

Granulation

3.5 kg of lactose (α-monohydrate, 200 Mesh, DMV, The Netherlands, permeametry surface area approximately 0.39 m^2/g) was placed in the mixing bowl of a 25 l high shear mixer (Fielder PMAT 25, Fielder, U.K.) and dry-mixed for 2 min

to break down larger lumps. An amount of polyvinylpyrrolidone (Plasdone K 26/28, GAF, U.S.A) corresponding to 5% by weight of the dry granulation was dissolved in the binder solvent. The binder solution was sprayed on the powder mass with a spraying nozzle (Schlick, model 940, Germany) operating at an atomisation pressure of 1.5 kg/cm^2. The rate of liquid addition was controlled with a wing-type of pump (MPA 114/316, Telfa Jabsco AB, Sweden). All granulations were dried in a fluid bed dryer (Glatt, model TR 5, Germany) with an air inlet temperature of 25 °C for 20 min. Details concerning type and amount of binder solvent, rate of liquid addition, wet-massing time and impeller speed for the lactose granulations are given in Table 1 (E1-8, W1-3).

The dipentum (disodium 3,3′-azobis[6-hydroxybenzoate], Pharmacia AB, Sweden, permeametry surface area approximately 2.23 m^2/g) granulations were those as used in an earlier paper in this series (Alderborn et al., 1987). An amount of polyvinylpyrrolidone (Plasdone K 29/32, GAF, U.S.A.) corresponding to 5.7% by weight of the dry granulation was used. Three different granulations were produced by varying the type of binder solvent (Table 1, D1-3).

For all granulations, the size fraction 500–710 μm was separated by hand-sieving (Retsch, Germany) and used in all experiments. This size fraction was stored in a desiccator at 40% R.H. and room temperature for at least 7 days before any characterisation or tableting.

Primary characterisation of granulations

Binder content of granulations The amount of PVP in the lactose granulations was analysed (n = 2) according to the method earlier described (Wikberg and Alderborn, 1990a).

Granule porosity The porosity of the granulations (n = 3) was calculated from the apparent particle density, measured with an air comparison pycnometer (Beckman, model 930, U.S.A.) and the granule or effective particle density, measured with a mercury pycnometer as described earlier (Wikberg and Alderborn, 1990a).

Granule friability The friability of the granulations (n = 4) was initially measured with a flask-shaker with a relatively low shaking intensity

TABLE 1

Process conditions during the agglomeration

Denomination of granulation	Binder solvent	Amount of binder solvent (% v/wt)	Liquid addition rate (g/min)	Wet massing time (min)	Impeller speed (rpm)
E1	Ethanol	10	300	–	250
E2	Ethanol	18	300	–	250
E3	Ethanol	10	300	–	500
E4	Ethanol	18	300	–	500
E5	Ethanol	10	100	2	250
E6	Ethanol	18	100	2	250
E7	Ethanol	10	100	2	500
E8	Ethanol	18	100	2	500
W1	Water	10	300	–	250
W2	Water	10	500	–	250
W3	Water	10	1000 [a]	–	250
D1 [b]	Ethanol/water 60/40	15	180 [a]	0.5	250
D2 [b]	Ethanol/water 80/20	14	180 [a]	0.5	250
D3 [b]	Ethanol	15	180 [a]	0.5	250

[a] No atomisation.

[b] Wet- and dry-screened.

TABLE 2

Primary and volume reduction characteristics of granulations

Granulation	Binder content (% wt.)	Granule porosity (%)	Granule friability (%)	Slope [a] ($cm^2/(g\ MPa)$)	Area under the curve [b] ($(m^2/s) \times 10^8$)
E1	5.4	31.3	13	107	12.3
E2	4.9	15.6	12	58.1	50.5
E3	4.9	19.6	25	66.4	35.0
E4	4.9	15.3	6.6	59.3	66.8
E5	5.4	12.3	10	20.8	276
E6	5.0	12.3	7.1	31.1	157
E7	5.5	11.6	16	20.6	236
E8	5.0	13.3	4.6	32.4	135
W1	4.8	13.2	8.3	41.6	55.3
W2	4.9	13.7	6.5	48.0	55.8
W3	5.0	15.6	9.8	50.5	35.5
D1	–	15.9	1.0	23.8	125
D2	–	19.4	0.4	59.0	25.2
D3	–	25.1	0.3	180	13.4

[a] Calculated from the tablet surface area-compaction pressure profile.
[b] Calculated from the permeability coefficient-compaction pressure profile.

(Griffin and Tatlock, U.K.) as described earlier (Wikberg and Alderborn, 1990a). Subsequently, the friability was measured with a flask shaker with a relatively higher shaking intensity (BTL, Sweden).

Compaction and characterisation of tablets

Mixing with lubricant 10 g of the lactose granulations were mixed for 100 min with 0.5% by weight magnesium stearate (Ph. Eur., Apoteksbolaget AB, Sweden, permeametry surface area approximately 1.66 m^2/g) in a Turbula mixer (W.A. Bachofen, Switzerland) at 90 rpm.

Tensile strength and porosity of tablets Tablets were compacted from unlubricated and lubricated lactose granulations and from unlubricated dipentum granulations in an instrumented single-punch press (Korsch EK 0, Germany) at a maximum upper punch pressure of 150 MPa, as described earlier (Wikberg and Alderborn, 1990b). The tablets were compacted by driving the flywheel with the motor, i.e. the motor was started when the upper punch was at the extreme upper position, and the motor and flywheel were stopped when the upper punch left the die after the compaction.

The tablets were stored for at least 48 h in a desiccator of 40% R.H. and the diametral compression strength ($n = 10$) was then measured with an Erweka tester (Erweka TBH 28, Germany). Since all tablets showed approximately normal tensile failure, the tensile strength of the tablets was calculated (Fell and Newton, 1970). For the lactose granulations, a tablet strength reduction ratio was calculated, i.e. the quotient between the tensile strength of tablets compacted from masses with internal lubricant and the tensile strength of tablets compacted from masses without internal lubricant.

The total porosity of the tablets was calculated from the height and weight data of the tablets and the apparent particle density of the granules ($n = 10$).

Air permeability of tablets For each unlubricated granulation, five or six tablets were compacted by hand at a series of compaction pressures, i.e. 20–70 MPa (lactose granulations) or 30–70 MPa (dipentum granulations) by the instrumented press, as described earlier (Alderborn et al., 1985). In this case, the flywheel of the press was rotated by hand. The air permeability of the tablets was measured with a Blaine apparatus and

for each tablet the permeametry surface area (Alderborn et al., 1985) and a permeability coefficient (Wikberg and Alderborn, 1990a) were calculated.

Microscopy examination Photomicrographs of the upper tablet surfaces were taken with the aid of scanning electron microscopy (Philips SEM 525, The Netherlands) for tablets compacted at maximum upper punch pressures of 25 and 150 MPa for a number of granulations. The upper surfaces of the tablets were also inspected with a light microscope (Vanox Universal Research Microscope, Japan).

Results and Discussion

Effect of process variables during agglomeration on primary characteristics of granulations

Binder content of granulations The measured PVP content of the lactose granulations (Table 2) was generally close to the nominal value, i.e. 5% by weight. For two of the granulations, E1 and E3, produced with comparatively short process times, the first batches gave binder contents of 7.6 and 6.3% by weight, respectively. This is probably a result of a poor distribution of the liquid in the powder mass during the short process time although atomisation of the agglomeration liquid was used. Earlier experiments have indicated (Wikberg and Alderborn, 1990b) that the binder content can markedly affect the relation between granule fragmentation and tablet strength. The high binder contents for granulations E1 and E3 were therefore considered unacceptable. However, it was necessary to use such short process times during the agglomeration to obtain granulations with granules of comparatively high porosity. Two new granulations were therefore produced with the same process conditions but with a reduced binder concentration in the binder solution, i.e. a concentration corresponding to a final binder content in the dry granulation of 4% by weight. With this procedure, an acceptable binder content in the size fraction 500–710 μm of granulations E1 and E3 was obtained (Table 2).

Granule porosity The process conditions were varied during the agglomeration phase to produce a number of granulations with varying porosity (Table 2).

The composition of the binder solvent had a marked effect on the densification of the granules. For the lactose granulations, a change from ethanol to water as binder solvent, when the process conditions otherwise were equal, decreased the granule porosity from 31.2% (E1) to 13.2% (W1). The same effect was observed for the dipentum granulations, where a gradual increase in the amount of water in the binder solvent from 0% to 40% decreased the granule porosity from 25.1% (D3) to 15.9% (D1). A possible reason for this is that the type of binder solvent affected the surface tension of the binder solution, which can affect the densification of the granules during the agglomeration phase (Riitala et al., 1988).

For the lactose granulations, there was also a general trend that an increased process time and an increased impeller speed decreased the granule porosity, which can be predicted from the agglomeration literature (Jaegerskou et al., 1984).

When water was used as binder solvent (W1–3) the granule porosity decreased with a slower liquid addition rate, i.e. an increased process time. With ethanol as binder solvent, an increase in the amount of binder solvent markedly decreased the granule porosity at the higher rate of liquid addition. However, at the lower liquid addition rate, no effect was observed. Thus, it seems probable that for these granulations (E1–8), the total process time rather than the amount of agglomeration liquid governs the granule porosity.

An increase in the impeller speed lowered the granule porosity when the lowest amount of binder solvent and the shortest process time was used. When a higher amount of binder solvent and/or a longer process time was used, no effect of impeller speed was observed.

According to the literature, the effect of process conditions on the granule porosity depends on the nature of the primary particles, e.g. the particle size (Hunter and Ganderton, 1972; Jaegerskou et al., 1984). It seems that the lactose densified more easily during the agglomeration than the dipentum. A probable reason is that the lactose powder was of a larger particle size than the dipentum and therefore less cohesive.

Granule friability In some initial experiments, the friability of the lactose granulations was measured with the same flask-shaker (Griffin and Tatlock, U.K.) as used in an earlier study (Wikberg and Alderborn, 1990a). The friability values were generally below 4%, i.e. the granules generally exhibited a similar and, compared to the earlier experiences with the method, a high degree of resistance to attrition. It has been suggested earlier (Wikberg and Alderborn, 1990a) that the ability of granules to withstand the mechanical stress during the friability test is markedly influenced by the surface roughness of the granules. The friability results indicated that the granulations generally consisted of fairly smooth granules. It has been shown that drying of granulations in a fluid bed equipment can cause attrition of granules (Schaefer and Wørts, 1978) thereby probably smoothening the granule surface. This could explain why the granulations in this study showed a comparatively low friability.

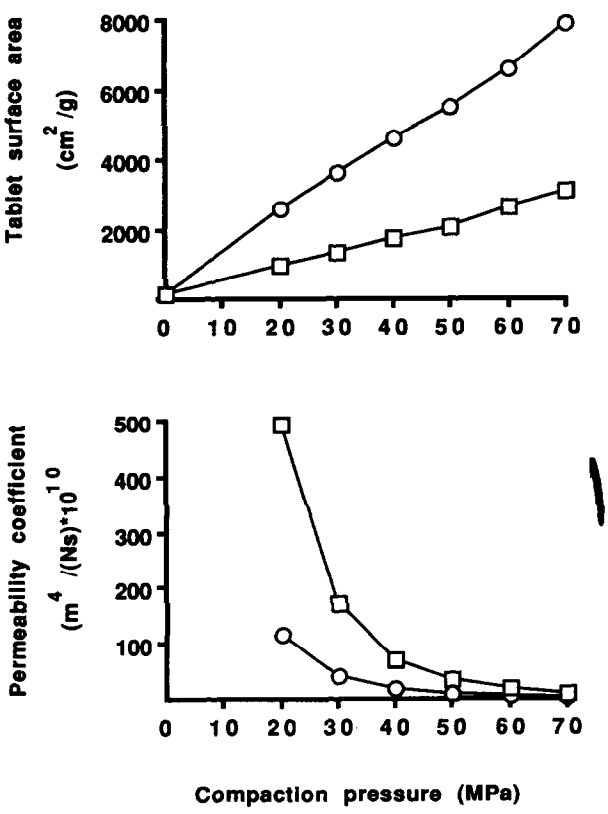

Fig. 1. The tablet surface area (calculated with apparent particle densities) as a function compaction pressure (upper panel) and the permeability coefficient as a function of compaction pressure (lower panel) for two lactose granulations. (○) Granulation E1; (□) granulation W1.

Wikberg and Alderborn (1990a) have suggested that granule fragmentation can be affected by the surface roughness of the granules and variations in granule surface texture between granulations can thereby affect the relation between granule porosity and granule fragmentation. Hence, the results from the friability measurements indicated that the granulations were suitable for a study on the relation between granule porosity and granule fragmentation. More on, to stress differences in granule friability between the granulations, the friability test was repeated with another flask-shaker (BTL, Sweden) with an increased shaking intensity. The friability data obtained are given in Table 2. A range of friability values was obtained for the lactose granulations but no general correlation to the measured granule porosity was found. This finding is consistent with earlier results (Wikberg and Alderborn, 1990a) that there is not necessarily a positive correlation between granule porosity and friability.

The dipentum granulations showed a low and similar friability. This, compared to the lactose granulations, low friability is probably due to the smooth surface and fairly regular shape of the dipentum granules which supports the assumption that the shape characteristics of the granules is of importance for the friability.

Effect of granule porosity on granule fragmentation during compaction

In Fig. 1 the tablet surface area and the permeability coefficient as a function of compaction pressure are presented for granulations E1 and W1, which are representative plots for all granulations.

The tablet surface area increased approximately linearly with compaction pressure within the pressure range used. As a measure of the degree of granule fragmentation during compaction, the slope of the profile was calculated with linear regression analysis and the slope values for all granulations are presented in Table 2. A high value indicates a high degree of fragmentation

(Wikberg and Alderborn 1990a). The calculation of the slope includes the value of the surface area of the granulations before compaction. The same surface area value was used as presented earlier for the same size fraction of a lactose granulation, i.e. 145 cm^2/g (Wikberg and Alderborn 1990a), as an approximate value for all granulations.

The permeability coefficient (P_c) can be seen as a measure of the total resistance to gas flow through the tablet and is a function of both the porosity and the surface area of the tablet. The value of P_c decreased in a non-linear way with compaction pressure (Fig. 1) and this relation was quantified by calculating the area under the curve (AUC) according to the trapezoidal rule (Table 2). A low AUC indicates comparatively impermeable tablets over the pressure range studied which indicates a high degree of granule fragmentation (Wikberg and Alderborn, 1990a). The value of P_c decreased most dramatically at the lowest pressures which means that the calculated AUC is influenced markedly by the air permeability at the lowest compaction pressures.

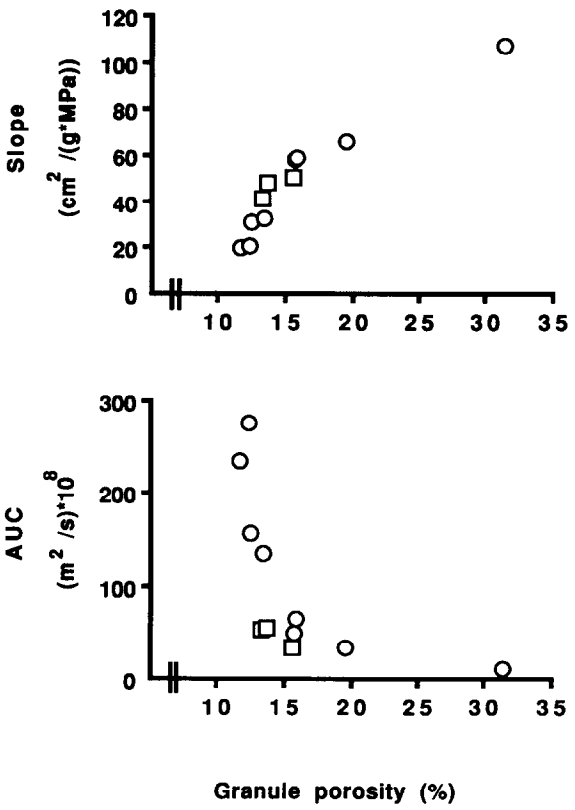

Fig. 2. The slope from the tablet surface area-compaction pressure profile (upper panel) and the area under the curve from the permeability coefficient-compaction pressure profile (lower panel) as functions of granule porosity. Lactose granulations. (○) Granulations E1–8; (□) granulations W1–3.

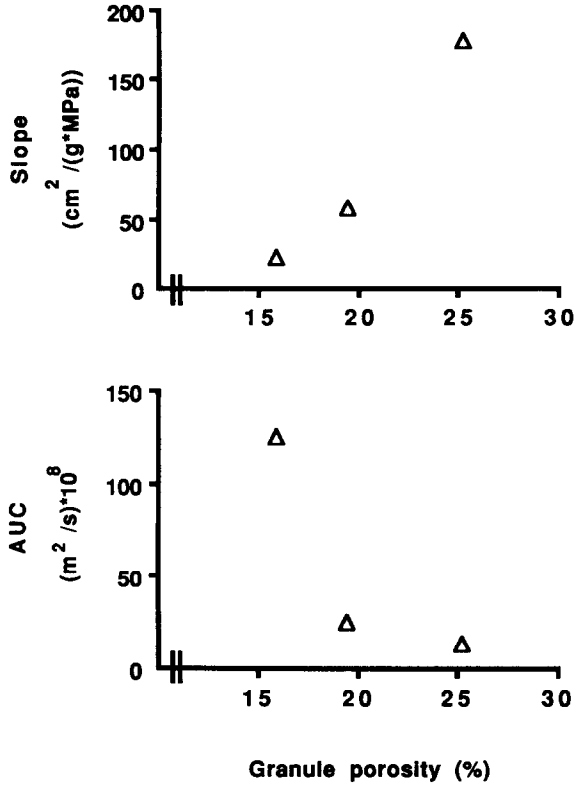

Fig. 3. The slope from the tablet surface area-compaction pressure profile (upper panel) and the area under the curve from the permeability coefficient-compaction pressure profile (lower panel) as functions of granule porosity. Dipentum granulations. (△) granulations D1–3.

The process conditions during the agglomeration affected markedly the volume reduction characteristics of the granules (Table 2). A comparison between the granule porosity and the granule fragmentation propensity results shows that these characteristics had a similar dependence of the variations in process conditions during the agglomeration. Thus, for both materials the different measures of granule fragmentation correlate well with granule porosity (Figs 2 and 3), i.e. an increased granule porosity changed the compression

behaviour of the granules towards a greater propensity to fragment. The total porosity of tablets of all granulations was generally similar (Table 3), i.e. differences in tablet permeability and tablet surface area are related to differences in the size characteristics of the tablet pore system rather than to differences in the tablet porosity. Thus, fragmentation of granules is associated with the formation of smaller pores between granules and an increase in the total surface area of the pore system. More on, the data indicates a similar degree of fragmentation for both lactose and dipentum in the same range of granule porosities although the particle size of the starting material was markedly smaller for dipentum than for lactose.

In Fig. 4a and b, photomicrographs of the upper surfaces of lactose tablets compacted at 25 MPa are shown. The tablets were made from granulations E1 (Fig. 4a) and E5 (Fig. 4b) which are granulations with a high and a low granule fragmentation propensity or granule porosity (Table 2). Assemblies or aggregates of primary particles which are separated by pores of varying size can be distinguished at the tablet surface. One can also notice cracks within parts of the granule. The observations indicate that the granules to some extent tend to keep their integrity during the compaction and that the tablet can be described as consisting of a number of small granules adhered to each other (Ganderton and Selkirk, 1970; Selkirk and Ganderton, 1970a,b). Especially for

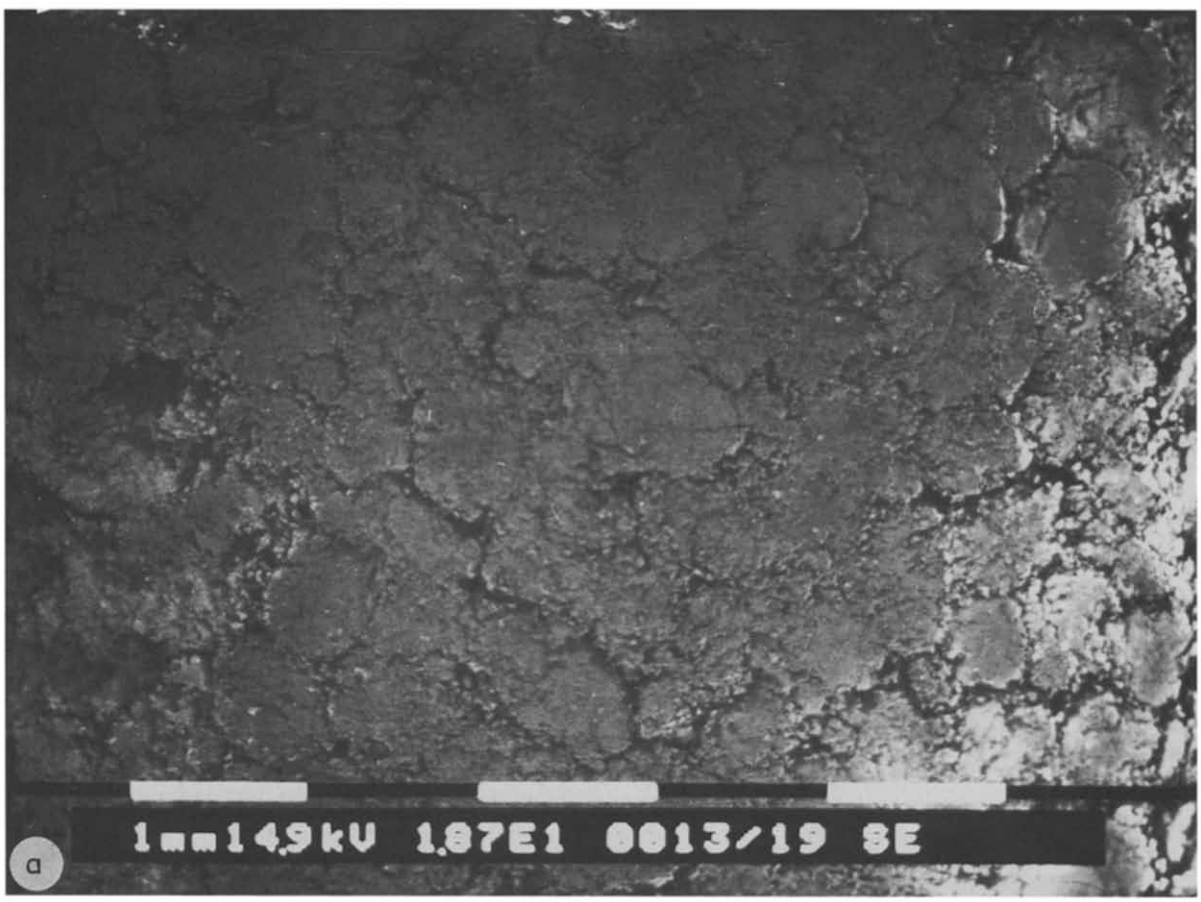

Fig. 4. (a) SEM-photomicrograph of the upper tablet surface of a lactose tablet compacted of granulation E1 at 25 MPa. (b) SEM photomicrograph of the upper tablet surface of a lactose tablet compacted of granulation E5 at 25 MPa.

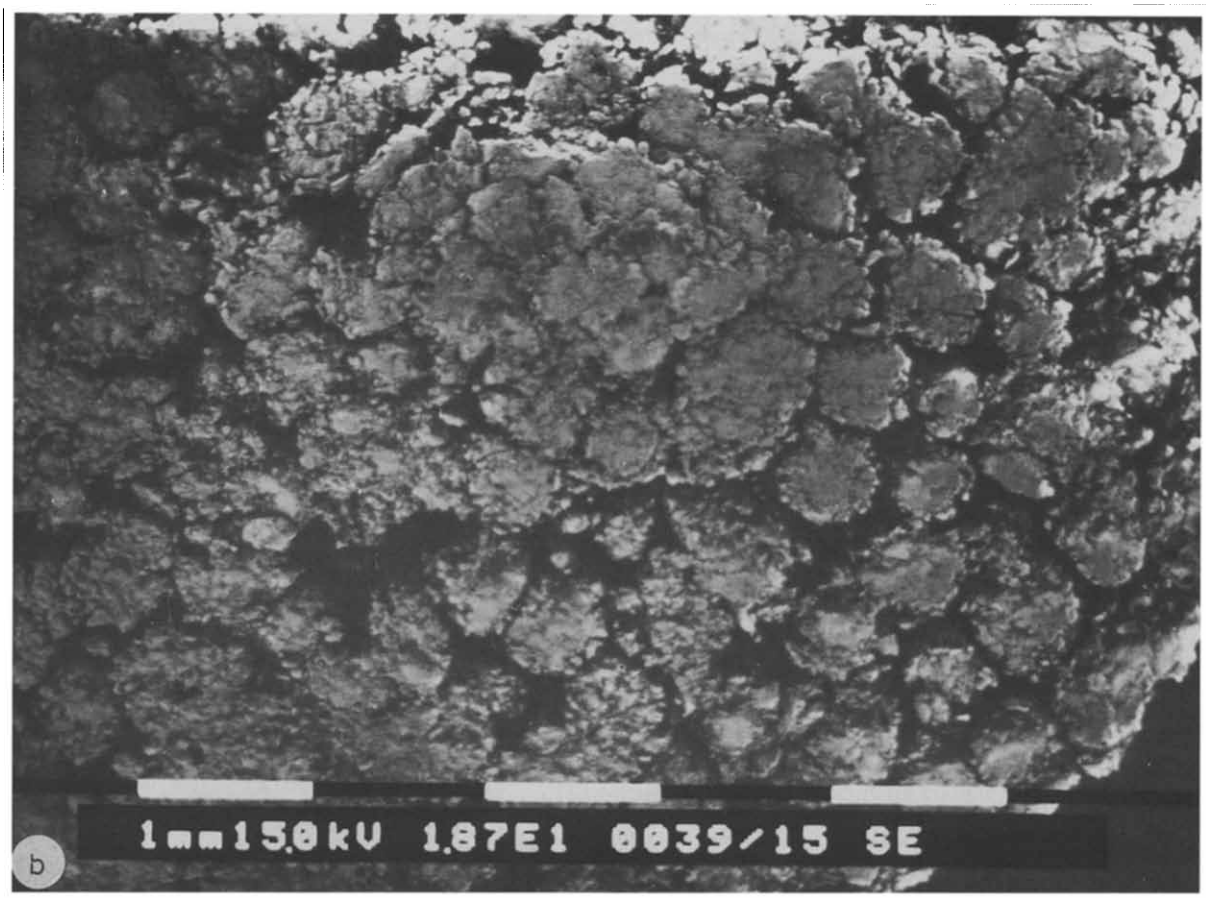

Fig. 4 (b).

tablets of granulation E5, which had comparatively low degree of fragmentation as evaluated by the permeametry method, the aggregates can be clearly distinguished and the pores between the granules are comparatively large. Thus, it seems that the pore structure of the tablet is related to the degree of breakdown of the original granule structure, which supports the concept that granule fragmentation leads to the formation of smaller inter-granular pores in the tablet and a reduced inter-granular separation distance.

For tablets compacted at 150 MPa, there was still a tendency for granules to be distinguishable at the surface of the tablet and that the pore structure was affected by the fragmentation propensity of the granules. However, the boundaries between the granules were generally more difficult to distinguish.

The examination by the light microscopy generally supported these observations for granulations of both substances.

The granules produced for this study are two-component aggregates where the binder is more or less well spread on the surface of the substrate particles and, to some extent, might form bridges between the particles. A number of interactions between surfaces are possible in such granules (Rowe, 1988). Cohesive attractions can occur between binder surfaces or between substrate particles and adhesive attractions can occur between the binder and the substrate particles. The granule porosity might affect both the cohesive and the

TABLE 3

Properties of tablets compacted at 150 MPa

Granulation	Total tablet porosity [a] (%)	Tensile strength (MPa)	Tensile strength of tablets with 0.5% wt MgSt (MPa)	Axial recovery [b] (%)
E1	16.0	2.64	2.32	6.0
E2	16.9	2.15	1.55	7.1
E3	16.0	2.20	1.83	6.0
E4	16.9	2.16	1.52	7.3
E5	16.7	1.68	0.96	7.0
E6	16.3	1.84	1.20	6.6
E7	16.9	1.57	0.85	6.6
E8	16.8	1.85	1.28	7.0
W1	15.1	1.91	1.45	5.7
W2	15.1	1.93	1.56	5.7
W3	15.4	2.03	1.66	5.9
D1	21.0	0.54	-	11
D2	21.6	0.72	-	10
D3	22.7	0.92	-	10

[a] Calculated from weight and height data using apparent particle density as measured by an air comparison pycnometer.
[b] Calculated from minimum height of tablet during compaction and height of tablet after 2 days storage at 40% R.H. and room temperature according to Armstrong and Haines-Nutt (1972).

adhesive attractions in the granule, e.g. the strength of the attraction between separated binder coated substrate particles due to an increased separation distance or the amount and size of binder bridges within the granule.

The observation that an increased porosity of the granules before compaction increased the granule fragmentation during the compaction indicates that the fragmentation propensity of the granules is related to the distance between the substrate particles. It seems therefore reasonable that fragmentation occurs by the creation of a failure plane between substrate particles in the granule. This failure can be a distinct, almost brittle fracturing of the granules or a shearing at the failure plane within the granule. The failure can probably be both adhesive and cohesive (Cutt et al., 1986; Mullier et al., 1987; Rowe, 1989a), i.e. a breakage of cohesive attractions between binder surfaces or a failure at the adhesive interface between the substrate and the binder. It is possible that both these attractions can be affected by the separation distance between the substrate particles within the granule.

A comparison between granule porosity and tablet porosity data (Tables 2 and 3) shows that the tablet porosity was similar or even lower than the porosity of the granules before compaction. This indicates that the granules also densified markedly during compaction. This densification might occur by a rearrangement of substrate particles, i.e. particles slide and shear in respect to each other.

Relation between fragmentation propensity and compactibility of granulations

Unlubricated granulations In earlier papers in this series (Alderborn et al., 1987; Wikberg and Alderborn, 1990b), a direct relationship between granule fragmentation and tablet strength has been found for both unlubricated lactose and unlubricated dipentum granulations. The different measures of the degree of granule fragmentation during compression, i.e. the slope and the AUC, correlated well with the mechanical strength of the tablets (Figs 5 and 6). A similar relation has also been found for compacts of crystalline lactose (Vromans, 1987). As discussed above, a tablet compacted with granulated materials can be described as an aggregate of granules of varying size. It seems reasonable that the largest pores and therefore the weakest attractions are between

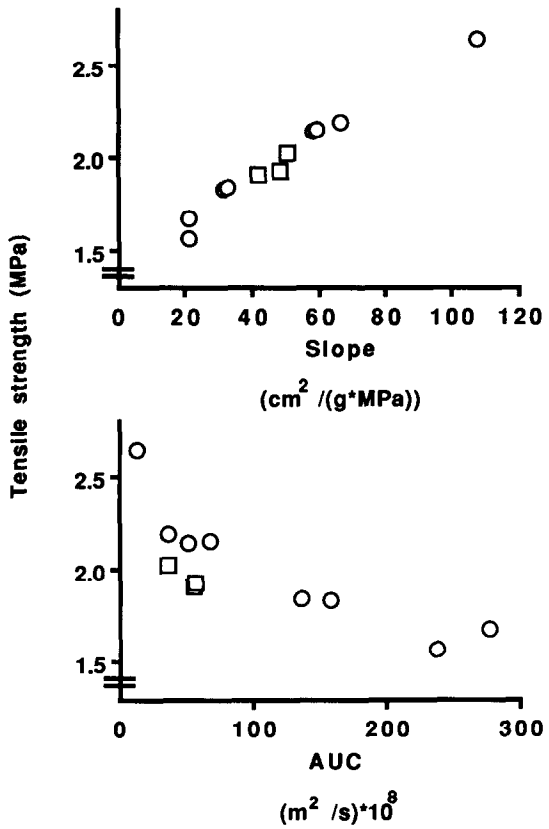

Fig. 5. Tensile strength of lactose tablets as a function of the slope from the tablet surface area-compaction pressure profile (upper panel) and the area under the curve from the permeability coefficient-compaction pressure profile (lower panel). Symbols as in Fig. 2.

rather than within the granules. The relationship between tablet strength and granule fragmentation indicates that the strength and the total area of the inter-granular attractions will be the main factor for the strength of the compact, i.e. the total attraction area and the separation distance between granule surfaces will be a function of the degree of granule fragmentation which will govern the tablet strength.

The strongest inter-granular attraction probably occurs between binder coated surfaces since the binder probably is more prone to deform plastically than the substrate particles and thereby can form larger areas of attraction. This indicates that the distribution of the binder within the granule before compaction as well as the mechanism of fragmentation during compaction are important for the effect of granule fragmentation on tablet strength. An optimal distribution of the binder on the substrate particles before compaction in combination with a cohesive failure between binder surfaces, could consequently be advantageous since this would give the largest fraction of binder coated surfaces exposed for inter-granular attraction relative to uncoated surfaces.

As can be seen from Figs 5 and 6, the lactose tablets are generally of higher mechanical strength than the dipentum tablets even if the degree of granule fragmentation is considered. This might be due to a higher total porosity of the dipentum tablets (Table 3) compared to the lactose tablets. This higher porosity can be a result of the greater

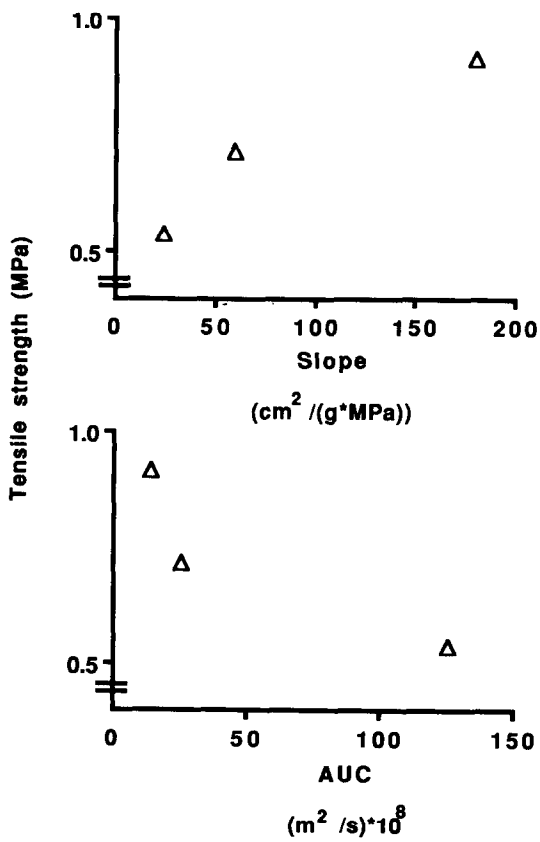

Fig. 6. Tensile strength of dipentum tablets as a function of the slope from the tablet surface area-compaction pressure profile (upper panel) and the area under the curve from the permeability coefficient-compaction pressure profile (lower panel). Symbols as in Fig. 3.

elastic recovery (Table 3) of the dipentum tablets during the ejection due to a greater elasticity of this material. However, it is also possible that the total ability of the mass to reduce in volume during the compression is generally lower for the dipentum granulations, which can result in a higher tablet porosity.

Another explanation for the general difference in tablet strength values is that the interaction between substrate and binder (Rowe, 1989b) might differ between lactose and dipentum. A different interaction can affect the spreading of the binder at the substrate particles during the granulation and the mechanism of fragmentation during compaction, e.g. the extent of cohesive or adhesive failure during compaction. Hence, the relative amount of binder which can be utilized for intergranular attractions can be different between the materials and affect the tablet strength.

Lubricated granulations The incorporation of magnesium stearate in a tablet mass is normally expected to decrease the tablet strength. The relative decrease in tensile strength for a certain material has been proposed to be dependent on the degree of fragmentation of the substrate particles (De Boer et al., 1978; Duberg and Nyström, 1982) provided a similar degree of surface coverage of magnesium stearate on the particles was obtained before compaction. The degree of surface coverage can be affected by the size, shape and surface texture of the particles, as well as the mixing conditions and the concentration of magnesium stearate (e.g. Vromans et al., 1988). In this study, the same size fraction of all granulations was used and the concentration of lubricant and the mixing conditions was kept constant. Furthermore, the friability measurements (Table 2) indicated similar surface characteristics of granules of all granulations and no general correlation to the granule porosity was found. It seems therefore reasonable to assume that the surface coverage of magnesium stearate on the granules was similar for all granulations used.

For the dipentum granulations, strength reduction ratios have earlier been presented (Alderborn et al., 1987). Granulation D1 and D2 showed similar and lower strength reduction ratios than granulation D3, i.e. the strength reduction correlated with the degree of granule fragmentation. It has to be pointed out that unfractionated granulations and a higher compaction pressure (300 MPa) were used in that study.

For the lactose granulations, the addition of magnesium stearate generally decreased the tablet strength (Table 3) and the reduction in tablet strength varied between 12% (E1) and 46% (E7). There was a general positive correlation between the tensile strength of tablets of lubricated granulations and the granule fragmentation propensity of the unlubricated granulations. However, the lubrication of the granulations stressed the importance of granule fragmentation for the tablet strength.

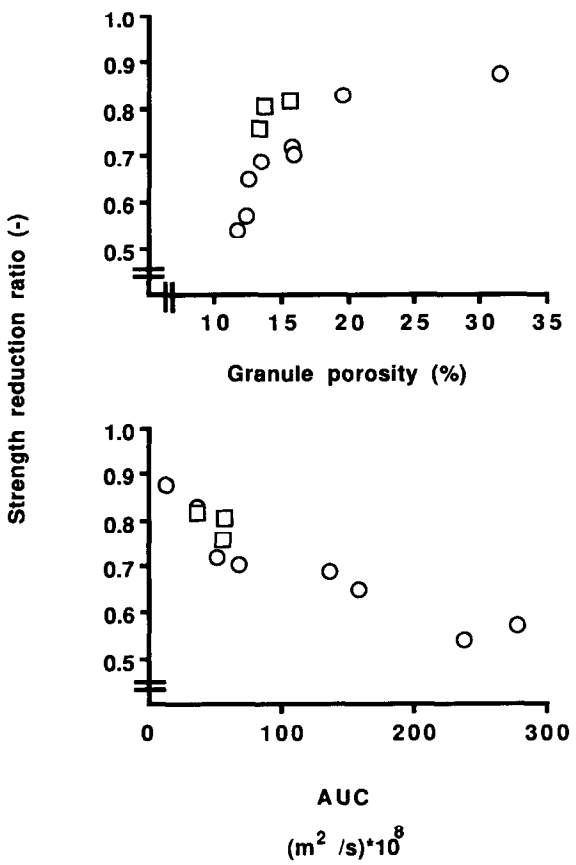

Fig. 7. The strength reduction ratio as a function of granule porosity (upper panel) and the area under the curve from the permeability coefficient-compaction pressure profile (lower panel). Lactose granulations. Symbols as in Fig. 2.

The strength reduction ratios for the lactose granulations correlated well (Fig. 7) with the porosity of the granules before compaction as well as the AUC, i.e. the degree of granule fragmentation during compaction. As discussed above, it is reasonable to assume that the surface coverage of the granules before compaction was similar for all granulations. Consequently, for the results in this study it is suggested that the differences in strength reduction ratios primarily were governed by differences in the fragmentation propensity of the granules. This means that fragmentation of the granules will lead to the formation of new surfaces exposed for inter-granular attraction. Thus, for a granule of higher fragmentation propensity, the ratio of magnesium stearate contaminated to uncontaminated surfaces will be lower and a higher strength reduction ratio will be obtained. However, it cannot be excluded that the degree of surface coverage might be affected by the porosity of the granules. It is possible that magnesium stearate, to some extent, can be pressed into large pores and surface cavities during the mixing procedure. A granule of higher porosity might have larger pores and larger surface cavities which can lead to a lower degree of surface coverage with the lubricant. This can then affect and stress the relationship between the strength reduction ratio and the granule porosity.

Conclusions

According to the literature (e.g. Ganderton and Selkirk, 1970; Selkirk and Ganderton, 1970a,b), the pore system of a tablet compacted of granulated materials can be subdivided in two categories: inter- and intra-granular pores. This duality of the pore structure means that such a tablet can be described as a large aggregate which consists of, or is built up of, a number of smaller granules. The results obtained in this study indicate that the fragmentation propensity of the granules will be of importance for the pore structure of the tablet. Fragmentation of granules will lead to the formation of smaller inter-granular pores, i.e. the separation distance between the granule surfaces within the tablet will be reduced. Granule fragmentation will also lead to an increase in the tablet surface area, i.e. the surface area of the inter-granular pores or the area of the external surfaces of the granules. Granule fragmentation is therefore associated with, firstly, the formation of an increased external surface area of the granules and, secondly, a decreased granule separation distance.

It was found that the porosity of the granules before compaction correlated to the degree of granule fragmentation during the compaction. This indicates that the separation distance between the primary particles within the granule is important for the granule fragmentation propensity. It is therefore suggested that the granule fragmentation occurs by the formation and propagation of a crack between the primary substrate particles or the formation of a shear plane between the substrate particles. The granules used were two-component aggregates and the substrate particles are probably more or less coated with a film of the binder, i.e. the failure during the fragmentation occurs either by the breakage of the cohesive binder-binder attraction or at the adhesive binder-substrate interface.

During the compression, the granules can, except from fragmenting, also respond to the load by deformation and densification (Rubinstein, 1976; Wikberg and Alderborn, 1990a). Furthermore, the substrate particles might to some extent fragment (Van der Zwan and Siskens, 1982). These phenomena can also affect the surface area and the pore structure of the formed tablet, i.e. the measured response of granule fragmentation used in this study. Consequently, all these phenomena can to some extent be included in a volume reduction characteristic which can be described as granule fragmentation. Fragmentation is therefore mechanistically more difficult to define for granulated materials compared to non-porous, crystalline materials.

The results in this study also confirmed earlier findings (Alderborn et al., 1987; Wikberg and Alderborn 1990b) that an increased granule fragmentation increased the tensile strength of the formed compact. It is therefore suggested that the inter-granular attractions within the tablet will be of decisive importance for the tablet strength.

Both the intensity and the area of the inter-granular attractions are probably related to the degree of granule fragmentation during the compaction.

The literature has frequently reported that the process conditions during a wet granulation can affect the compactibility of the granulation. The results in this study suggest that differences in compactibility between granulations of a certain formulation can be explained by differences in the porosity of the granules. This finding can thus be utilised to optimise a pharmaceutical granulation process and to explain problems during scale-up and production with respect to the compactibility of the granulation.

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