Compression Characteristics of Granulated Materials. VII. The Effect of Intragranular Binder Distribution on the Compactibility of Some Lactose Granulations

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Two sets of lactose–polyvinylpyrrolidone granulations (95:5) of different intragranular binder distributions were produced. The intragranular binder distribution was controlled by a two-step granulation procedure. The compactibility as well as the volume reduction behavior of the granulations was evaluated. Granulations with a more homogeneous distribution of binder in the granules generally produced tablets of a higher mechanical strength than granulations with a peripheral localization of binder. The tablet strength of the latter granulations was also comparatively more reduced by the addition of magnesium stearate. Thus, it is suggested that high granule porosity in combination with homogeneous intragranular binder distribution is advantageous for the compactibility of a granulation. The results of this study therefore contradict earlier suggestions in the literature regarding the preferred intragranular binder distribution.

KEY WORDS: tablet strength; compactibility; granulation; binder; intragranular binder distribution; volume reduction behavior.

INTRODUCTION

The compactibility of pharmaceutical granulations has been the subject of a number of papers in the literature. The effect of granulation processing and formulation factors as well as the importance of physical properties of individual granules was evaluated in relationship to the compaction characteristics of a granulation. Concerning the physical properties of the granules, the studies focused mainly on two granule characteristics, i.e., the porosity (e.g., Ref. 1) of the granules and the intragranular binder distribution (2).

Wikberg and Alderborn (1) found that for a series of granulations of the same composition, an increased granule porosity improved the compactibility of the granulations. By evaluating the volume reduction characteristics of the granules (1,3–5), it was found that an increased granule porosity changed the compression behavior of the granules toward an increased degree of fragmentation and deformation/densification during the compaction process. This change in volume reduction behavior affected the intergranular pore structure of the tablet which governed the strength of the compact. The results were explained by assuming that a tablet compacted of granules can be described as a large aggregate of small granules, i.e., granules tend to keep their integrity to a larger or smaller extent during the compaction process. The mechanical strength of the compact will then be governed by the attraction between these granules, which is related to the intergranular pore structure of the compact (1,6,7). Hence, during strength analysis of the tablet, a fracture plane is created between the granules within the tablet, and the strength of the tablet will thereby be governed by the sum of attractions in the fracture plane. With this model, also the effect of granule size before compaction for the mechanical strength of the tablet was explained (8).

Rue *et al.* (2) suggested that a peripheral localization of the binder within granules improves their compactibility. Their explanation was also based on the same assumption regarding the physical structure of a tablet, i.e., the tablet is built up of a large number of smaller granules. A peripheral localization of the binder within the granules would increase the relative amount of binder available for intergranular attractions in the compact compared to a situation where the binder is homogeneously distributed in the granules. Hence, tablets consisting of granules with a peripherally localized binder would possess a higher mechanical strength. However, this argumentation seems to assume that the granules will be more or less unaffected by the compaction procedure. This is not consistent with the observations by Wikberg and Alderborn regarding the changes in physical properties of granules which occur during the compression phase as discussed above. Thus, it appears that the statement of Rue *et al.* (2) regarding the effect of the intragranular binder distribution on compactibility needs to be reconsidered with respect to the effects of compression on the physical structure and appearance of the granules. In fact, the suggested order of granulation methods producing the most peripheral binder distribution in the granules, i.e., spray-drying > fluid-bed granulation > wet-massing, could be identical to the suggested order of granulation methods producing the most porous granules (9–11).

The intention of this paper was to study the effect of the intragranular binder distribution on the compactibility of some granulations by considering the volume reduction behavior of the granulations. Two different procedures were used to control the intragranular binder distributions, producing one set of granulations with a homogeneous distribution of binder in the granules and one set with the binder located peripherally. The granulations were made from a common filler, lactose, and a common binder, polyvinylpyrrolidone. Processing variables were chosen to give granulations of different porosity and therefore different volume reduction behavior. To increase the range of granule porosity, granulations were produced from two qualities of lactose of different particle size. The literature reports that smaller substrate particle sizes could produce granules of higher porosity (12) and tablets of a higher mechanical strength (13,14).

MATERIALS AND METHODS

Granulation and Coating

Two sets of four granulations, with a nominal binder

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content of 5% by weight, were produced. The strategy was to produce two sets of granulations with different intragranular binder distributions. For the set of granulations designated "U," all binder was added during wet-granulation so as to give a homogeneous binder distribution in the granules. For the other set, designated "C," 1% by weight of binder was added during wet-granulation and the remainder was added during a subsequent coating step so as to give a peripheral localization of binder. The ambition with the wet-granulation step was further to produce a granulation of a low and a high porosity for each lactose quality. Details concerning formulation and processing conditions are presented in Table I.

Three kilograms of lactose (α-monohydrate, DMV, The Netherlands) was wet-granulated, in either a planetary mixer (351, Bjørn Varimixer, Bjørn A/S, Norway) or a high shear mixer (251, Fielder PMAT 25, Fielder, U.K.). Two different qualities of lactose were used. For granulations designated "200" a 200-mesh quality was used (permeametry surface area, 0.39 m^2/g), and for granulations designated "450" a finer particulate quality, 450 mesh, was used (permeametry surface area, 0.57 m^2/g). The binder, polyvinylpyrrolidone (PVP; Plasdone K 26/28, GAF), was dissolved in water or ethanol and sprayed onto the powder mass using a spraying nozzle (Schlick, Model 940, Germany) operating at an atomizing air pressure of 1.5 kg/cm^2. The rate of liquid addition was 300 g/min and controlled with a wing-type pump (MPA 114/316, Telfa Jabsco AB, Sweden). After the liquid addition, the mass was further agitated for 2 min. The wet mass was thereafter pressed through a 2.0-mm screen using an oscillating granulator (Manesty Rotogran Mark III). All granulations were dried in a fluid-bed dryer (Glatt, Model TR 5, Germany) at an air inlet temperature of 25°C for 20 min.

The size fraction 710–1000 μm was then separated by hand-sieving (Retsch, Germany). This relatively coarse size fraction was chosen for further processing so as to minimize problems with fluidization and wall adhesion during the coating step. One hundred grams of this fraction was coated with PVP in a top-spray fluid bed (Strea 1, Aeromatic AG, Switzerland). The coating solution, 5% by weight of PVP in ethanol, was added at a rate of 15 g/min with an atomizing air pressure of 2 kg/cm^2. The temperature of the fluidizing air was 25°C. As the loss of binder was quite high (>40%), the coating had to be performed in two steps. For granulations of set U, no binder (i.e., only ethanol) was added.

Before any characterization or tableting, the granulations were stored in a desiccator at 40% RH and room temperature for at least 7 days.

Characterization of Granulations

Photomicrographs were taken with the aid of a scanning electron microscope (Philips SEM 525, The Netherlands).

The amount of PVP was analyzed ($n = 3$) according to the method described earlier (4). Fifty to one hundred milligrams of material was used for each analysis.

The granule porosity ($n = 3$) was calculated from the apparent particle density, measured with an air comparison pycnometer (Beckman, Model 930), and the effective particle density, measured with a mercury pycnometer (4). This nomenclature is in accordance with B.S. 2955:1958 (15).

The granule friability ($n = 3$–8) is expressed as the weight percentage of granules which, after treatment in a flask shaker (BTL, Sweden), passes through a 500-μm sieve (Veco, The Netherlands). The method has been described earlier (4).

The granule compressive strength is the force required to fracture a single granule ($n = 100$) during diametral compression (6). The granules were compressed at a rate of 0.5 mm/min using a materials testing machine (Model M30K, J. J. Lloyd Instruments Ltd., U.K.) fitted with a 50-N load cell. For this test, the size fraction 710–1000 μm was further differentiated with a ring gap sizer (FOA, Sweden) and the modal fraction 683–761 μm was used.

Compaction and Characterization of Tablets

Tablets were compacted, from both unlubricated and lubricated granulations, in an instrumented single-punch press (Korsch EK 0, Germany) at a maximum upper punch pressure of 150 MPa as described earlier (5). To lubricate the granulations, 10 g was mixed for 100 min with 0.5% by weight of magnesium stearate (Ph. Eur., Apoteksbolaget AB, Sweden) in a Turbula mixer (W. A. Bachofen, Switzerland) at 90 rpm. After compaction, the tablets were stored for at least 48 hr in a desiccator at 40% RH and room temperature and the diametral compression strength ($n = 10$)

Table I. Denomination of Granulations, and Formulation and Processing Conditions

Denomination of granulation	Quality of lactose	Mixer	Amount of binder solvent (% wt)	Type of binder solvent	Nominal amount of binder added (% wt)	
					During wet-granulation	During coating
200U1	200 mesh	High shear[a]	14	Water	5	—
200U2	200 mesh	Planetary[b]	18	Ethanol	5	—
450U1	450 mesh	Planetary	14	Water	5	—
450U2	450 mesh	Planetary	18	Ethanol	5	—
200C1	200 mesh	High shear	14	Water	1	4
200C2	200 mesh	Planetary	18	Ethanol	1	4
450C1	450 mesh	High shear	14	Water	1	4
450C2	450 mesh	Planetary	14	Water	1	4

[a] Impeller speed, 250 rpm; chopper speed, 3000 rpm.
[b] Impeller speed, 50 rpm.

was then measured with an Erweka tester (Erweka TBH 28, Germany). All tablets showed approximately normal tensile failure and the tensile strength of the tablets was calculated (16).

For each unlubricated granulation, six tablets were compacted by hand at a series of compaction pressures, i.e., 20–70 MPa, by the instrumented press as described earlier (17). The air permeability of these tablets was measured with a Blaine apparatus, and for each tablet the permeametry surface area (17) and a permeability coefficient (4) were calculated. From these data, the slope of the tablet surface area–compaction pressure profile was calculated with ordinary regression analysis. A starting surface area of 70 cm^2/g was used. This was based on measurements of the permeametry surface area of some uncompacted granulations according to Eriksson *et al.* (18). The area under the curve, AUC, of the permeability coefficient–compaction pressure profile was calculated according to the trapezoidal rule.

RESULTS AND DISCUSSION

Primary Characteristics of Granulations

General Appearance. The examination of the granulations by SEM (Fig. 1) showed no specific differences regarding the shape and surface characteristics between the granulations after the wet-massing step, i.e., they were all irregularly shaped, with fairly rough surfaces. However, after the coating step, the outer surfaces of granules from set C are smoothed out by a layer of binder. This binder layer could not be described as a continuous "film coating," but neither is the binder present in distinct and isolated lumps.

Binder Content and Intragranular Binder Distribution. The binder content after wet-granulation (Table II) were generally somewhat higher than the nominal amount of binder. The analyzed size fraction, 710–1000 μm, represents the coarser granules of each granulation and the comparatively higher binder content is probably the combined result of local overwetting and the coalescence mechanism of granule growth (19). After the coating step, granulations U and C were of approximately the same binder content (Table II).

In addition to the qualitative inspection of granules by SEM, the intragranular binder distribution was assessed quantitatively. We suggested earlier (4) that during a granule friability test, the granules are reduced in size mainly by attrition, i.e., removal of particles from the surface of the granule rather than breakage or fragmentation of the whole granule. A comparison of the binder content in the eroded material (i.e., <500 μm) and in the remaining granules (i.e., >500 μm) after such a friability test could therefore be expected to reflect the intragranular binder distribution.

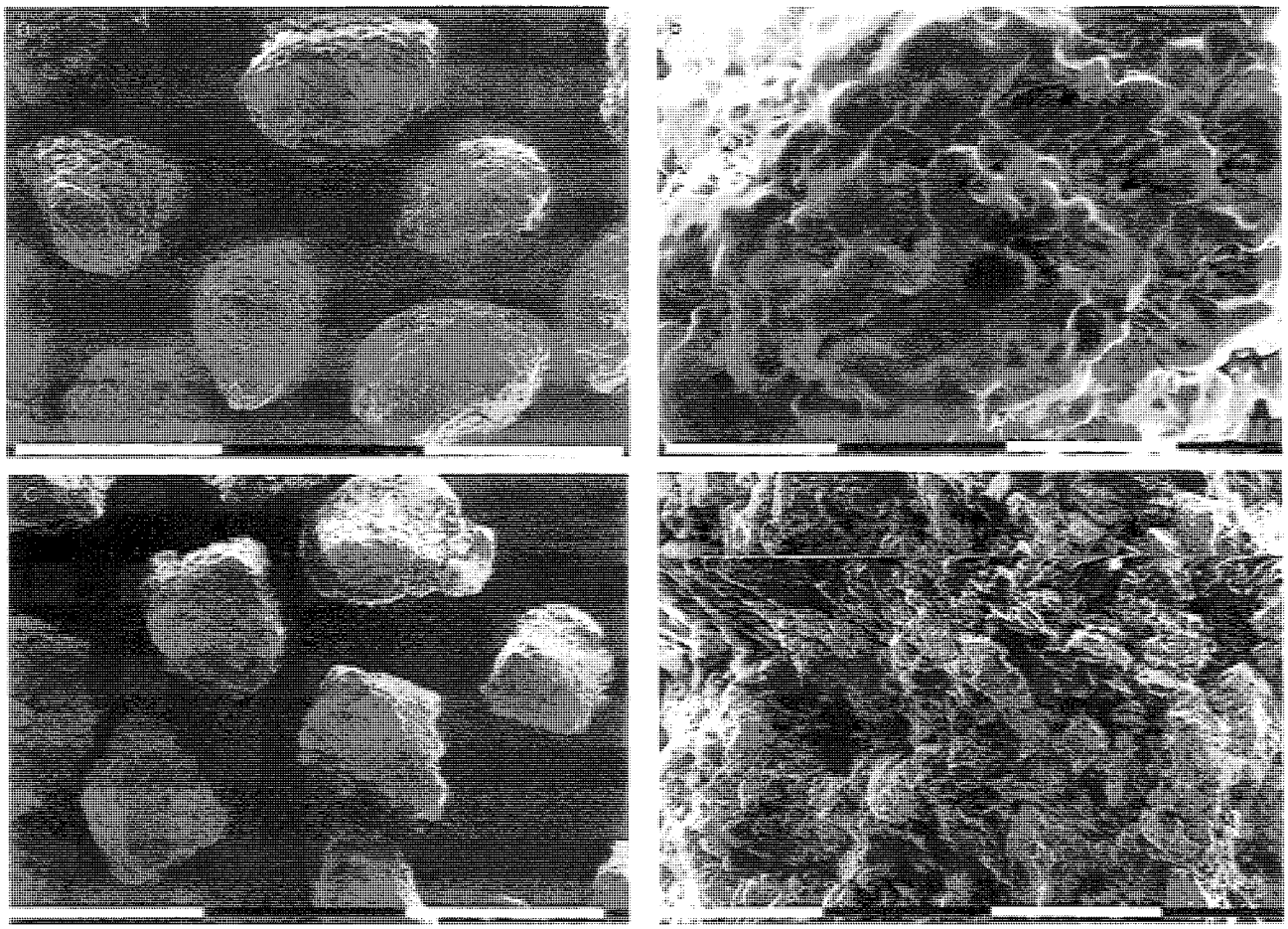

Fig. 1. SEM photomicrographs of granules from granulation 450C2 after the coating step (a, b) and from granulation 450U2 (c, d). The white bar denotes 1000 μm (a, c) or 100 μm (b, d).

Table II. Effective Particle Density, Apparent Particle Density, Calculated Porosity, Binder Content, Friability, and Compressive Strength of Granulations

Granulation	Effective particle density (g/cm^3)[a]	Apparent particle density (g/cm^3)[a]	Calculated porosity (%)[a]	Binder content (% wt)[a]	Friability (%)[b]	Compressive strength (N)[c]
200U1	1.30 ± 0.02	1.50 ± 0.01	13.7 ± 1.2	5.7 ± 0.1	8.3 ± 1.0	2.3 (0.6)
200U2	1.23 ± 0.01	1.51 ± 0.01	18.6 ± 0.8	5.5 ± 0.1	10 ± 1.7	1.7 (0.6)
450U1	1.15 ± 0.01	1.52 ± 0.01	24.5 ± 0.4	5.3 ± 0.1	9.7 ± 1.4	1.7 (0.6)
450U2	1.02 ± 0.02	1.52 ± 0.01	33.0 ± 1.3	5.4 ± 0.1	21 ± 2.4	1.0 (0.4)
200C1	1.18 ± 0.01	1.50 ± 0.01	21.3 ± 0.4	5.5 ± 0.1	7.2 ± 1.8	1.2 (0.3)
200C1[d]	1.22 ± 0.01	1.54 ± 0.01	20.9 ± 1.0	1.4 ± 0.1	—	1.2 (0.3)
200C2	1.14 ± 0.02	1.50 ± 0.01	24.0 ± 1.5	5.5 ± 0.2	27 ± 3.1	0.5 (0.2)
200C2[d]	1.13 ± 0.02	1.56 ± 0.01	27.7 ± 1.7	1.0 ± 0.1	—	0.4 (0.2)
450C1	1.02 ± 0.01	1.50 ± 0.01	31.9 ± 0.7	5.4 ± 0.1	29 ± 5.0	0.8 (0.2)
450C1[d]	1.01 ± 0.01	1.54 ± 0.01	34.7 ± 0.8	1.0 ± 0.1	—	0.6 (0.2)
450C2	1.01 ± 0.01	1.52 ± 0.01	33.2 ± 0.1	5.7 ± 0.1	14 ± 3.1	0.8 (0.2)
450C2[d]	1.02 ± 0.01	1.56 ± 0.01	34.5 ± 0.4	1.3 ± 0.1	—	0.6 (0.2)

[a] Mean ± SD; $n = 3$.
[b] Mean ± SD; $n = 3$–8.
[c] Median, interquartile range given in parentheses; $n = 100$.
[d] Measured on granulation before coating step.

The binder content in the two fractions from the friability test is presented in Fig. 2 for all granulations. For set U, almost the same amount of binder was found in the eroded material (<500 μm) as in the remaining granules (>500 μm). For set C, a higher amount of binder was found in the eroded material than in the remaining granules. Thus, both the qualitative and the quantitative evaluation indicates that for the first set of granulations (U), the binder was homogeneously distributed within the granules, while for the second set (C), a substantial fraction was localized at the surface of the granules.

Porosity and Mechanical Properties. The granulations of the more finely particulate lactose quality were generally of a higher porosity (Table II) compared to the coarser lactose quality, e.g., 450U2 vs 200U2 and 450C1 vs 200C1 (12). A lower granule porosity (Tables I and II) was obtained through using water instead of ethanol as binder solvent, e.g., 450U1 vs 450U2, and/or a combination of water as binder solvent and a mixer of higher agitation intensity, e.g., 200U1 vs 200U2 and 200C1 vs 200C2 (1,19). It was not possible to produce granulations of a lower porosity for set C.

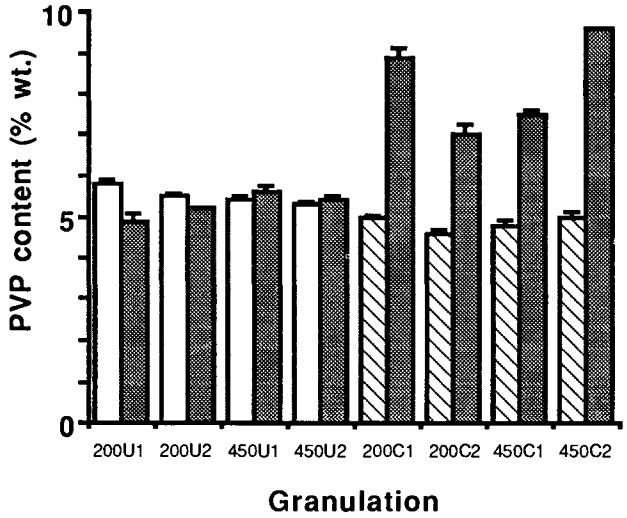

Fig. 2. The measured binder content in the two size fractions from the granule friability test. The error bars show the standard deviation of the mean ($n = 3$). (□) Size fraction >500 μm (set U); (▨) size fraction >500 μm (set C); (▩) size fraction <500 μm (sets U and C).

The calculated granule porosity was the same or somewhat lower after the coating step (Table II). The binder added during the coating step probably formed regions of comparatively higher relative density at the surface of the granules (Fig. 1), while the rest of the granule structure was unaffected.

The granules were generally considered to respond in a more brittle than ductile fashion when subjected to diametral compression, as they fractured instantaneously and without a preceding region of ideal plastic flow. For a certain combination of binder and substrate particles, an increased granule porosity reduced the compressive strength (Table II) of the granules, i.e., 200U1 vs 200U2, 200C1 vs 200C2, and 450U1 vs 450U2 (6). For granulations of series C, it appeared that application of binder on the surface of the granules did not affect the compressive strength of the granules to any particular extent, i.e., 200C1-2 and 450C1-2.

There was no general difference in friability between granulations of set U and those of set C (Table II), i.e., the binder layer at the surface of granules of set C did not improve the resistance against attrition. Earlier studies on lactose–PVP granulations (4) have shown that the amount and composition of binder solvent affect the granule friability, and in this study there was also a tendency for a higher friability when ethanol was used as binder solvent instead of water, e.g., 200U1 vs 200U2, 450U1 vs 450U2, and 200C1 vs 200C2. There is a slight trend for granules of a lower compressive strength to be of a higher friability.

Tableting Properties of Granulations

Volume Reduction Properties. The air permeability measurements of the tablets are presented in Table III. A

Table III. Slope of the Tablet Surface Area–Compaction Pressure Profile (Slope), Area Under the Curve of the Permeability Coefficient–Compaction Pressure Profile (AUC), and Tensile Strength of Tablets Compacted at 150 MPa

Granulation	Slope ($cm^2\ g^{-1}\ MPa^{-1}$)	AUC, ($m^2\ sec^{-1}$)10^8	Tensile strength ($MN\ m^{-2}$)[a]	
			A[b]	B[c]
200U1	41.4	84	1.73 ± 0.08	1.40 ± 0.05
200U2	61.0	49	2.13 ± 0.11	1.77 ± 0.06
450U1	90.7	25	2.29 ± 0.11	1.86 ± 0.08
450U2	112	15	2.48 ± 0.11	2.18 ± 0.06
200C1	63.8	28	1.80 ± 0.09	1.07 ± 0.05
200C1[d]	71.2	18	1.35 ± 0.05	
200C2	69.1	18	1.84 ± 0.05	1.27 ± 0.03
200C2[d]	87.4	8.8	1.32 ± 0.05	
450C1	105	12	2.03 ± 0.08	1.22 ± 0.04
450C1[d]	98.6	9.2	1.43 ± 0.08	
450C2	123	8.7	2.04 ± 0.08	1.08 ± 0.04
450C2[d]	113	7.9	1.53 ± 0.06	

[a] ±95% confidence interval for the mean.
[b] Tablets compacted from unlubricated granulations.
[c] Tablets compacted from granulation lubricated with 0.5% by weight magnesium stearate.
[d] Before the coating step.

higher slope value and a lower AUC reflect the formation of tablets of a higher surface area or a lower air permeability with the compaction pressure, i.e., tablets possessing a comparatively more closed pore structure (7). Within each set of granulations, compacts of a series of permeabilities were obtained with a somewhat larger gradient for set U. The granulations of the finer particulate lactose quality, i.e., 450 mesh, gave the highest slope values and the lowest AUCs.

Generally, a higher granule porosity (Table II) before compaction corresponds to a higher slope value and a lower AUC (Table III) (1). This finding can be accounted for by the effect of the porosity of the granules on their mechanical properties and thereby their volume reduction behavior during in-die compaction. Also in this study, there seemed to be a relationship between the porosity of the granules and their compressive strength (Table II). This result indicates that the differences in the pore structure of the compacts are, to a substantial degree, related to differences in the degree of granule fragmentation during compaction. However, there are some exceptions with respect to the relationship between granule porosity and granule strength, on one hand, and granule porosity and volume reduction behavior of the granulations, on the other, e.g., 450U1 vs 200U2 and 450C1 vs 200C2. This observation indicates that a decreased substrate particle size can promote the formation of a comparatively more closed tablet pore structure as a result of increased granule porosity, although the granules seem to be more resistant to fracturing. A possible explanation is that the granules produced from the finer particulate lactose quality can deform or become denser to a larger extent during compaction than granules of the coarser particulate quality.

Compactibility. Tablets compacted of granulations with a 1% wt binder content, i.e., set C before the coating step, generally showed the lowest tensile strength values (Table III). When the total amount of binder was increased to 5% wt, the tablet strength increased irrespective of the intragranular binder distribution. A comparison of the granulations of sets U and C showed that there was a tendency for tablets compacted from set U to be of a higher mechanical strength than tablets compacted from set C.

The model of a tablet compacted of granules discussed above suggests that an evaluation of the compactibility of granulations with different intragranular binder distributions must be related to the size characteristics or the surface area of the intergranular pores in the formed tablets. Consequently, in Fig. 3, the tablet strength is shown as a function of the slope (top) and the AUC (bottom) from the air permeability measurements. For granulations of set U, there was a tendency for an increased tablet strength with an increased tablet surface area or a reduced air permeability, which is in accordance with the earlier findings. However, for granulations of set C, no clear relationship was obtained, probably because these granulations had a similar volume reduction behavior. Furthermore, when the tablets of the two sets of granulations were compared with respect to the tablet pore characteristics, tablets compacted from set U were found to be stronger than tablets compacted from set C, i.e., a homogeneous distribution of binder in the granules before compaction improves the compactibility compared to a peripheral localization of binder in the granules.

The external surface of granules within the tablets could be equal to the surface of the substrate particles or it could, alternatively, be equal to the surface of a layer of binder which is situated on the substrate particles. Thus, within tablets compacted of such granules, three types of attractions between the granules can exist: two types of binder-related interactions (i.e., binder to binder and binder to substrate) and substrate-to-substrate interactions. It seems reasonable to assume that attractions which involve binder-coated surfaces form comparatively strong intergranular bonds, e.g., due to the comparatively higher propensity of the binder to deform plastically, and thereby both increase

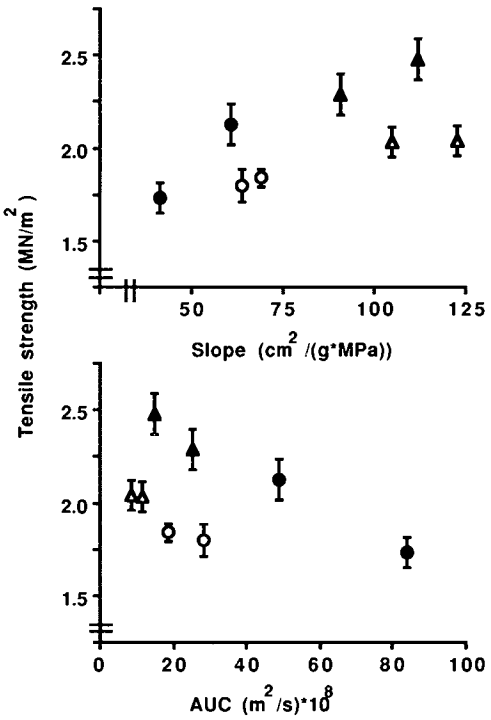

Fig. 3. The tensile strength of tablets compacted at 150 MPa from unlubricated granulations as functions of the slope of the tablet surface area–compaction pressure profile (top) and the area under the curve of the permeability coefficient–compaction pressure profile (bottom). The error bars show the 95% confidence intervals for the mean. (●) Granulations 200U1 and 200U2; (▲) granulations 450U1 and 450U2; (○) granulations 200C1 and 200C2; (△) granulations 450C1 and 450C2.

the interaction area and reduce the separation distance between the granules. Thus, in the following discussion it is assumed that the binder-related interactions are of decisive importance for the tablet strength and that the distribution of significant bonding zones between granules in the compact is a reflection of the binder distribution at the extragranular surfaces.

During the compression of granulated powders, new extragranular surfaces could have resulted from fragmentation and deformation/densification of the granules. Thus, the extragranular surfaces in the tablet consist of a substantial fraction of new surfaces created during compaction. If the binder is homogeneously distributed in the granule before compaction, all extragranular surfaces in the tablet will probably be of a similar composition. Hence, it is suggested that a homogeneous intragranular binder distribution before compaction will give binder interaction zones which are homogeneously distributed across the fracture plane within the compact. For tablets compacted from the granulations of set U and the uncoated granulations of set C, a similar type of homogeneous distribution of binder interaction zones in the fracture plane will be obtained. However, for tablets made from the granulations of set U, these zones will probably both be stronger and have a larger surface area, which will increase the total bonding capacity and hence the tablet strength.

For the granulations of set C, another type of distribution of binder interaction zones in the compact will probably be obtained as a result of the heterogeneous intragranular binder distribution before compaction. For these granulations, new extragranular surfaces will also be created, mainly of a composition similar to that of the extragranular surfaces in compacts made from the uncoated granulations of set C. However, extragranular surfaces will probably also exist within the tablet which correspond to the original extragranular surfaces, i.e., surfaces with a comparatively thick layer of binder. Thus, it is suggested that a peripherally located binder in the granules before compaction will result in a more heterogeneous distribution of binder interaction zones within the compact. This distribution is characterized by a fraction of binder interaction zones which forms comparatively weaker bonds and a fraction which forms comparatively stronger bonds. The net effect will be an increased mechanical strength compared to tablets made from the uncoated granulations of set C but a reduced mechanical strength compared to tablets made from granulations of set U. The types of distributions of the binder interaction zones in the fracture plane are schematically drawn in Fig. 4.

If this discussion on the mechanistics is valid, it can be concluded that a homogeneous distribution of binder within the granules promotes the compactibility. However, when the granules are unaffected by the compression procedure, i.e., nonfragmenting and nondeformable, a peripheral localization of binder within the granules will probably be advantageous for the compactibility. However, it is the experience of the authors that such granules are difficult to produce. Such granules are also less valid from a more general point of view since nonfragmenting granules will probably show poor compactibility compared to fragmenting granules and they will also be sensitive to additions, such as a lubricant (1).

The addition of a lubricant generally caused reduced tablet strength in these granulations (Table III). However, there is a tendency for the granulations of set C to be comparatively more affected by the lubricant addition, i.e., a reduction in tablet strength of 31–47% for granulations of set

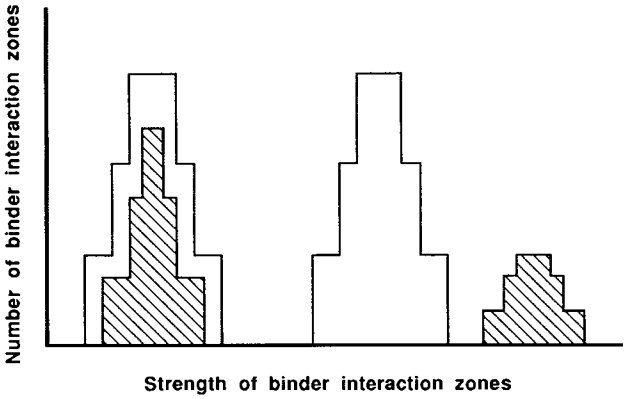

Fig. 4. Hypothetical types of distribution of binder interaction zones in the fracture planes of tablets compacted from three granulations of different binder contents and intragranular binder distributions but of similar volume reduction behavior. (□) Binder distributed homogeneously in the granules (low total binder content); (▨) peripheral localization of binder in the granules (high total binder content); (□) binder distributed homogeneously in the granules (high total binder content).

C compared to a reduction of 12–19% for granulations of set U. For the granulations of set C, the extragranular surfaces in the tablet which correspond to the original granule surfaces will probably be of vital importance for the tablet strength, as they constitute binder interaction zones with a higher bonding capacity. If these binder layers are covered with a lubricant before compaction, their interaction potential will be reduced and this could then have a dramatic effect on the tablet strength. Thus, a granulation with a peripheral localization of binder in the granules is probably more sensitive to lubricant addition.

The results of this study on the effects of intragranular binder distribution on compactibility contradict an earlier study on this relationship (2). However, Rue *et al.* did not consider the importance of the pore structure of the compact on the compact strength or the changes in physical appearance and structure of granules as a result of compaction. Thus, it is possible that the granulations used in those studies were generally almost nonfragmenting and nondeformable, which would account for the results obtained.

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