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Compression characteristics of granulated materials
II. Evaluation of granule fragmentation during compression by tablet permeability and porosity measurements

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Summary

Lactose was granulated with 5% (w/w) polyvinylpyrrolidone as a binder with a wet massing–screening procedure. Fourteen granulations were produced by using different amounts and types of solvent for the binder during the agglomeration procedure. After the granulation, the size fraction 500–710 μm was separated from each granulation for investigation. The granules were characterised on water and binder content, and granule porosity and friability. Both the porosity and friability of the granules were affected by the process conditions. However, there was no correlation between these parameters, which indicates that one surface property of the granule, i.e., the ability to withstand attrition, can be different from the overall granule strength. The volume reduction behaviour during compaction was evaluated by measuring tablet permeability and tablet porosity as a function of compaction pressure. The results indicate that the granules became denser at low compaction pressures. It is therefore difficult to use the changes in porosity with compaction pressure as a measure of the degree of granule fragmentation during compression. The tablet permeability as a function of compaction pressure varied among the granulations which indicates that the ability to break down during compression, i.e., the granule fragmentation, varied. It is suggested that changes in tablet permeability with compaction pressure can be used as a measure of this property. The difficulty of defining the intergranular pore space in the tablet will affect the calculation of the tablet surface area. However, the results indicate that in the pressure range used for the permeametry measurements, the total porosity is probably fairly close to the intergranular pore space. Thus, it is suggested that surface area–compaction pressure profiles give a reasonable estimate of the degree of granule fragmentation during compression.

Introduction

During the production of tablets, the drug and excipients are often granulated before tabletting. The granulation process is used to ascertain a tablet mass with adequate properties, e.g., regarding compactibility, i.e., the ability of the powder to form compacts of a certain mechanical strength (Leuenberger, 1982). The compactibility of a granulation is affected by formulation parameters but also by their volume reduction properties (Alderborn et al., 1987).

It has been suggested (Van der Zwan and Siskens, 1982) that a number of processes are involved in the volume reduction of a granulation

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during compaction, i.e., rearrangement, deformation and fragmentation of the granules but also rearrangement, deformation and fragmentation of the primary particles within the granules. Both deformation (Carstensen and Hou, 1985) and fragmentation (Selkirk and Ganderton, 1970) of the granules have been discussed as relevant volume-reduction mechanisms. However, it seems that the characterisation of volume reduction mechanisms for pharmaceutical granulations as well as its relation to the compactibility of the mass have not achieved great attention in the literature.

The quantification of fragmentation of particles during direct compression of tablets has been discussed in the literature. As indirect measures, the changes in tablet strength due to addition of lubricants (Duberg and Nyström, 1982; De Boer et al., 1978) and dry binders (Nyström and Glazer, 1985) have been used. Also the ratio between the axial and the radial tensile strength of tablets has been suggested to reflect the degree of particle fragmentation (Duberg and Nyström, 1982). Both these methods can be regarded as fairly rough techniques, i.e., it is difficult to make detailed interpretations regarding the degree of fragmentation. Furthermore, for the strength reduction and strength improvement ratios the mixing quality of the powder mass, i.e., the surface coverage of the main compound with the excipient, is probably critical (Vromans et al., 1988). The surface coverage is probably affected by, e.g., the particle characteristics of the main compound, i.e., the particle shape and surface texture.

Another indirect measure of particle fragmentation can be obtained by following the changes in tablet porosity with compaction pressure according to the Heckel function (Heckel, 1961). It has been suggested that the deviation from linearity in the early compression phase (De Boer et al., 1978; Duberg and Nyström, 1982), i.e., up to 40–50 MPa, is related to the degree of particle fragmentation.

As a more direct approach for characterising fragmentation, tablet surface area as a function of compaction pressure has been estimated. The tablet surface area has been measured by gas adsorption (e.g., Hardman and Lilley, 1973; Alderborn et al., 1985), mercury intrusion (e.g., Vromans et al. 1985) and air permeability (e.g., Alderborn et al., 1985) techniques. The calculation of the slope of the tablet permeametry surface area–compaction pressure profile has hitherto proved to be a simple and reliable method for quantifying particle fragmentation.

Granules are often irregular particles with a rough surface texture and the use of strength reduction and strength improvement ratios are thereby probably often difficult to apply for granulated materials. Thus, the measurements of tablet permeametry surface area and tablet porosity as a function of compaction pressure seem to be more interesting alternatives. However, granules are porous aggregates, and the use of both tablet porosity–pressure profiles and tablet surface area measurements might be difficult due to problems of defining the porosity of the space between the granules in the tablet in relation to the intragranular porosity.

The aim of this study was therefore to discuss the possibility to estimate granule fragmentation by permeametry and porosity measurements of tablets. As model materials, a number of lactose granulations were produced in a planetary mixer by varying the amount and composition of the solvent for the binder. The variations in process conditions were based on literature reports that the type of binder solvent (Alderborn et al., 1987) and the amount of agglomeration liquid (Guyot et al., 1987) can affect the compactibility of granules.

Materials and Methods

Granulation

1 kg of lactose (α-monohydrate, Ph. Eur., Pharm. Lactose, AB Svenskt Mjölksocker, Sweden, specific surface area approximately 0.22 m^2/g) was granulated with polyvinylpyrrolidone (K-25, Roth, F.R.G.) solutions (Table 1) by wet massing in a 7l planetary mixer (Kenwood A717C, U.K.). Fourteen granulations of the same composition (95 wt% lactose, 5 wt% binder) were produced. The lactose was mixed at 75 rpm, and the binder solution was gently poured into the mixing bowl at an approximate rate of 75 ml solvent/min.

After the liquid addition, the moistened mass was agitated further at approximately 105 rpm for 5 mix. The mass was then forced through a 2.0 mm screen in an oscillating granulator (Manesty Rotogran Mark III, U.K.) and tray-dried at room temperature overnight. Finally, the dried mass was forced through a 0.8 mm screen in the oscillating granulator. To minimise influence of granule size, the size fraction 500–710 μm was prepared from the granulations by hand sieving (Retsch, F.R.G.). This size fraction was stored in a desiccator at 40% R.H. and room temperature for at least 2 days before any characterisation or tabletting.

Primary characterisation of granulations

Moisture and binder content of granulations. The moisture content before compaction is expressed as percentage weight loss after storage in a desiccator with P_2O_5 for 7 days ($n = 3$). 1.5 g of granules was used for each analysis. The amount of PVP in each granulation was determined by a spectrophotometric method (Müller, 1968) and is expressed as per centage of the total dry weight of the granulation ($n = 3$). 100 mg granules was used for each analysis.

Intragranular porosity. The porosity of the granules ($n = 3$) was calculated from the material density (often reffered to as the 'true' density), measured with an air comparison pycnometer (Beckman, model 930, U.S.A.) and the granule density, measured with a mercury pycnometer according to Strickland et al. (1956). For the measurement of granule density, approximately 2.5 g of granules was placed in the pycnometer and degassed to a pressure of 80 mmHg. The pycnometer was filled with mercury and the pressure raised to 740 mmHg. The volume of the granules was determined and the granule density calculated.

Granule friability. 500 mg of granules was placed in a 100 ml vessel which was shaked with a flask shaker (Griffin and Tatlock, U.K.) at highest intensity for 10 min. The treated granules were then placed on two precision sieves (Veco, Holland) with sieve openings of 500 and 360 μm. The sieves were vibrated on a mechanical sieve shaker (Retsch, F.R.G.) for 30 s. Granule friability ($n = 4$) is here expressed as the weight percentage of the treated granules passing the 360 μm sieve.

Measurement of tablet porosity during compression

The changes in total tablet porosity with compaction pressure during compression up to 150 MPa, i.e., 'in die' measurements, was followed according to the Heckel equation ($n = 3$). The procedure and the equipment used have been presented earlier (Duberg and Nyström, 1986; Alderborn et al., 1987). The Heckel profile was evaluated in two ways: Firstly, by calculating the correlation coefficient with ordinary regression analysis in the pressure range 2–50 MPa. Secondly, by calculating the reciprocal of the slope value in the pressure range 40–130 MPa, i.e., the so-called yield pressure.

Air-permeability measurements of tablets

For each granulation, six tablets were compacted by hand at a series of compaction pressures (15–80 MPa) and the air permeability of the tablets was measured with a Blaine apparatus in the same manner as described earlier (Alderborn et al., 1985).

The permeability data were treated in two ways. Firstly, for each tablet a permeability coefficient was calculated. This coefficient relates the flow rate through the specimen to the pressure head during the measurement, i.e.:

$$\frac{\mathrm{d}V}{\mathrm{d}t \cdot A} = P_\mathrm{c} \cdot \frac{\Delta P}{L} \tag{1}$$

where V is the volume of air flowing through compact (m^3); t the time for air flow (s); A the cross-sectional area of compact (m^2); ΔP the pressure drop across the compact ($\mathrm{N/m}^2$); L the height of compact (m); and P_c the permeability coefficient (m^4/Ns).

The permeability coefficient (P_c) can thus be seen as a measure of the resistance against gas flow through the compact. In this study a Blaine apparatus was used, and Eqn 1 for this transient permeameter becomes;

$$\frac{a \cdot \mathrm{d}h}{A \cdot \mathrm{d}t} = P_\mathrm{c} \cdot \frac{2\,h \cdot \partial \cdot g}{L} \tag{2}$$

where a is the cross-sectional area of manometer arm (m^2); h the height above the equilibrium position of the liquid in the manometer arm (m); ∂ the density of the manometer liquid (kg/m^3); and g the gravitational constant (m/s^2).

After integration between the start and stop points on the manometer arm (h_2 and h_1) and rearrangement, Eqn 2 becomes:

$$P_c = \frac{\ln(h_2/h_1) \cdot L \cdot a}{A \cdot t \cdot 2 \cdot \partial \cdot g} \tag{3}$$

Secondly, for each tablet, the weight specific surface area was calculated with the Kozeny-Carman equation corrected for slip flow as described earlier (Alderborn et al., 1985).

For one of the granulations (E4) also the air permeability surface area was measured before tabletting. This was done according to a permeability method for coarse powders as described elsewhere (Eriksson et al., 1990). This surface area (145 cm^2/g) was used as an approximate measure of the starting surface area for all granulations.

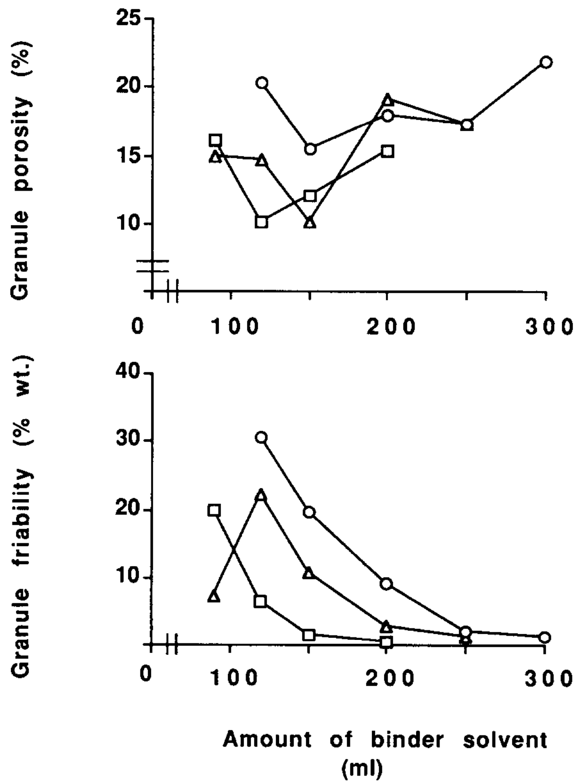

Fig. 1. Granule porosity (upper panel) and friability (lower panel) as a function of amount of binder solvent used during the granulation process. Symbols: □, W1–4; △, WE1–5; ○, E1–5.

Results and Discussion

Primary characteristics of granules

Binder content. The binder and moisture contents of the granules are given in Table 1. The binder content of the granules were generally slightly above the nominal value, i.e., 5% (w/w). However, for the granulations produced with the lowest amount of liquid with ethanol/water and ethanol as binder solvents (WE1, E1 and E2) comparatively high amounts of binder were found. This is probably a result of poor distribution of the liquid in the powder mass during the agglomeration which could be due to the relatively low agitation intensity of the mixer and the properties of the agglomeration liquid used, e.g., concerning the viscosity (Wells and Walker, 1983).

Moisture content. The measured moisture content of the granules was in the range of 0.7 to 1.1% (w/w). However, the amount of water in the dried granules did not appear to be related to the amount or composition of binder solvent used during the granulation process. Furthermore, no relation was found between the content of the binder and the measured moisture content of the granules. Thus, it is reasonable that the variation in measured moisture content can be seen as a fairly small and random variation.

Granule porosity. The granule porosity as a function of volume of binder solvent is presented in Fig. 1. The range of porosities is fairly small for the different granulations. The ethanol granulations were generally more porous than the others. It has earlier been found (Riitala et al., 1988) that the surface tension of the agglomerating liquid can affect the densification of the agglomerates during the wet massing. The surface tension of the binder solution is expected to decrease with an increased proportion of ethanol in the binder solvent (Wells and Walker, 1983) which can explain the relatively high granule porosity values for the ethanol granulations.

For all three solvents, the granule porosity initially decreased but with an increased amount of agglomeration liquid the porosity increased. The relation between granule porosity and the amount of agglomeration liquid has been studied earlier (e.g., Ganderton and Hunter, 1971; Jaegerskou et al., 1984; Tapper and Lindberg, 1986). It seems to be a common observation that the granule porosity decreases with an increased amount of agglomeration liquid. Thus, the granulations produced in this study did not follow this expected relation between granule porosity and amount of agglomeration liquid. The granulations were produced by a traditional wet granulation procedure, i.e., both wet and dry screening steps were used. It seems possible that the density of the wet agglomerates can be increased also by the screening procedure and the final granule density should thereby be a function of densification during both wet mixing and wet screening. During the extrusion of wet masses in a laboratory ram extruder with one extrusion opening, it was found (Jerwanska et al., 1990) that an increased proportion of liquid in the mass during the extrusion increased the porosity of the extrudates. The wet screening process is similar to an extrusion process and it can thereby be assumed that with an increased amount of agglomeration liquid, the densification during the wet screening was reduced. This assumption can then explain the observation that for the majority of the granulations the granule porosity increased with an increased amount of agglomeration liquid.

The method for the estimation of the granule porosity used here probably gives a fairly rough estimate of the porosity because a distinction between intragranular pores and surface irregularities cannot be made. This is probably valid especially for granules with a rough surface structure. When a fairly low intrusion pressure is used, it seems reasonable that for granules with a rough surface structure the granule porosity can be overestimated. Microscope examination (Philips SEM 525, Holland) indicated that a lower amount of agglomeration liquid gave a rougher granule surface, i.e., especially for these granules there might be a tendency for an overestimated porosity.

It can also be pointed out that an increased amount of agglomeration liquid decreased the binder concentration in the liquid which might change the viscosity of the liquid (Riitala et al., 1988). It cannot be excluded that such a change can also affect the density of the agglomerates.

Granule friability. The granule friability was measured as an estimate of the strength of the granules. A direct measure of the compression strength of granules seems difficult due to their irregular shape. Reports on such measurements (e.g., Lindberg et al., 1974) have given very variable results for mechanical strength which are difficult to interpret. In Fig. 1, the granule friability is presented as a function of volume of binder solvent.

The granule friability generally decreased with an increased amount of agglomeration liquid. A break in this relation was found for the granules produced with the lowest amount of agglomerating liquid for the water/ethanol system (WE1). Here an unexpectedly low friability was observed.

TABLE 1

Amount and composition of solvents for the binder and moisture and binder content of the granulations

Denomination of granulation	Composition of solvent	Amount of solvent (ml)	Moisture content (% wt.)	Binder content (% wt.)
W1	Water	90	0.72	5.27
W2		120	1.00	5.20
W3		150	1.02	5.38
W4		200	1.06	5.39
WE1	Water/ ethanol (50:50)	90	0.95	6.63
WE2		120	1.11	5.33
WE3		150	0.77	5.42
WE4		200	0.68	4.97
WE5		250	0.76	5.00
E1	Ethanol	120	1.05	6.38
E2		150	0.90	6.30
E3		200	0.78	5.30
E4		250	0.74	5.15
E5		300	0.72	5.67

An increased amount of binder in granules has earlier been shown to reduce the friability (Rubinstein and Musikabhumma, 1978; Cutt et al., 1986). It is therefore suggested that the low friability of granules in the WE1 granulation is a result of an increased binder content (Table 1).

The results in Fig. 1 show that both the granule porosity and the granule friability are affected by the amount of agglomeration liquid used during the wet massing. It seems reasonable that the particle–particle interactions in the granule are related to the granule porosity, i.e., a decrease in the porosity should give an increased granule strength. However, a comparison of the porosity and the friability data (Fig. 1) shows that instead there was a tendency for an inverted relationship between these characteristics. At the lower amounts of agglomeration liquid both the porosity and the friability are reduced. However, the friability continued to decrease and reached fairly low values while the porosity increased. It seems therefore that the ability of granules to withstand attrition, i.e., friability, is not necessarily related to the porosity, i.e., a measure of the bulk strength, of the granules.

Granule attrition probably occurs through removal of particles from the surface of the granule rather than breakage or fragmentation of the whole granule. The granule is thereby continously reduced in size by an erosion process, i.e., the friability is a measure of the strength of the exposed surface of the granule. From the microscope examination it was concluded that the most friable granules had comparatively rough surface structures. It seems reasonable that the outer particles of a rough surface are more loosely adhered to the other particles and can thereby be removed relatively easily. However, the lack of correlation between porosity and friability might also be explained by assuming that there is a gradient in strength properties within the granules, i.e., the porosity is related to some mean strength in the granule while the strength at the surface of the granule might be higher.

There could be several reasons for the existence of such a strength gradient. Firstly, the exposure time to the liquid during the drying of the granules will probably vary within the granule. The surface of the granules will have the longest exposure time and the opportunity for some densification of the surface or the formation of crystal bridges between the particles is thereby increased. Secondly, it has been pointed out (Ridgway and Rubinstein, 1971) that the dissolved binder can migrate in the granule during the drying. This migration will then result in a gradient of binder within the granule and thereby probably give a strength gradient. In both explanations it appears that the strength gradient can be affected by the amount of liquid in the granule.

Generally, a change in composition of the solvent which increases the solubility of lactose, i.e., an increased proportion of water in the liquid, results in a reduced granule friability (Wells and Walker, 1983). The increased solubility of lactose in the agglomeration liquid can probably facilitate the formation of lactose bridges between the particles due to crystallisation of dissolved lactose during drying, especially at the surface of the granule. Furthermore, it can not be excluded that the migration of binder can be affected by the type of binder solvent, resulting in differences in the concentration of binder at the granule surface.

Evaluation of granule fragmentation

Air permeability of tablets. The air permeability of tablets was measured at a series of compaction pressures between 15 and 80 MPa. The lower pressure level was chosen to ascertain the formation of coherent compacts while the fairly low upper level was chosen to minimize errors during the calculation of the tablet surface area (Alderborn et al., 1985).

As a measure of the permeability of the tablets, a permeability coefficient was calculated. This coefficient is a measure of the resistance against gas flow through the tablet and is thereby related to both the surface area and the porosity of the specimen. In Fig. 2, the permeability coefficient for three granulations as a function of compaction pressure are presented. The permeability coefficient generally decreased with increased compaction pressure but in a non-linear way. The permeability decreased markedly initially but levelled out with increased pressure and seemed to asymptotically reach an impermeable specimen.

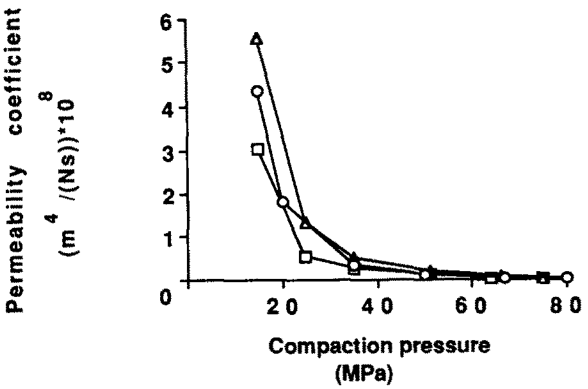

Fig. 2. Permeability coefficient as a function of compaction pressure for granulations produced with 200 ml of binder solvent. Symbols: □, W4; △, WE4; ○, E3.

The decrease in permeability is probably a result of both a decreased porosity of the tablet and of a reduced mean pore size in the tablet due to granule fragmentation.

The presented profiles in Fig. 2 are representative of all the granulations concerning the relation between permeability and compaction pressure. As a measure of the change in permeability with compaction pressure, the area under the curve (AUC) for the pressure range 20–70 MPa was calculated with the trapezoidal rule. The AUCs for all granulations as a function of volume of binder solvent are presented in Fig. 3. The AUC decreased for all three solvent systems with increased amounts of binder solvent, i.e. the mean resistance against gas flow through the compacts, over the pressure range studied, increased with increased amount of binder solvent. Tablets of the water/ethanol granulations generally had the highest permeability while the tablets from the other granulations had lower permeability. The results thereby show that the change in pore structure with compaction pressure varied among the granulations, which indicates that the propensity of granules to collapse or fragment varied. Fragmentation will reduce the size of the pores in the tablet and result in a low permeable specimen (Ganderton and Selkirk, 1970; Selkirk and Ganderton, 1970).

Characterization of particle fragmentation by permeametry has been done by following the changes in tablet surface area with compaction pressure. According to the literature, it seems that granules tend to keep their integrity to some extent during compaction, i.e., the tablet can be described as a large aggregate of small granules (Selkirk and Ganderton, 1970; Seager et al., 1981). It seems thereby probable that the total porosity of the tablet is a function of the porosity both between and within the granules. It also seems reasonable that during the permeability measurements the air is flowing mainly or totally in the intergranular space because it is reasonable to assume that the largest pores are found between rather than within the granules, at least at relatively low compaction pressures. The correct porosity value in the permeability equation should

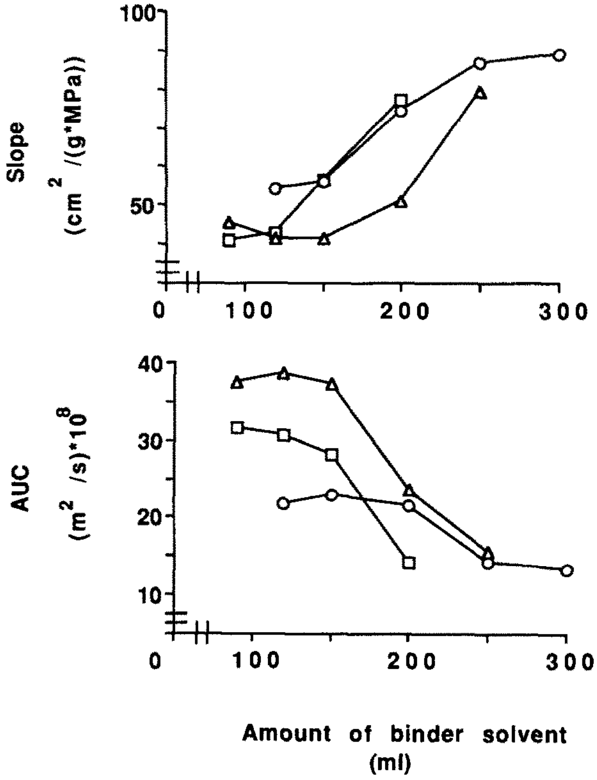

Fig. 3. The slope from the tablet surface area (calculated with material densities) compaction pressure profile (upper panel) and the area under the curve from the permeability coefficient–compaction pressure profile (lower panel) as a function of amount of binder solvent used during the granulation for all granulations. Symbols as in Fig. 1.

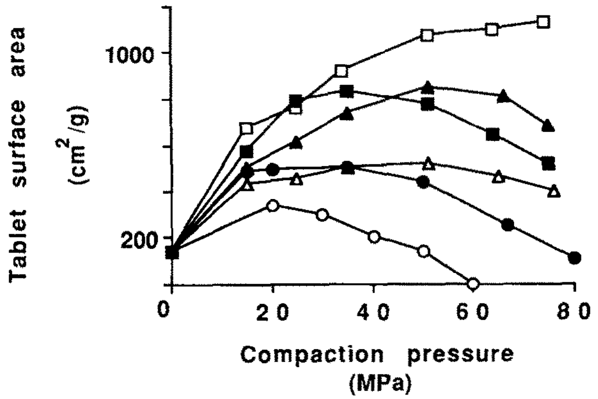

Fig. 4. Tablet surface area, calculated with the granule densities, as a function of compaction pressures for some granulations. Symbols; □, W2; ■, W4; △, WE2; ▲, WE4; ○, E1; ●, E3.

consequently be the intergranular porosity of the tablet. However, this porosity is difficult to estimate. The tablet surface area was therefore calculated from the permeability data in two ways: firstly, by using a tablet porosity calculated from the granule density, i.e., it is assumed that the density of the granules are not changed during the compaction; and secondly, by using a tablet porosity calculated from the material density of the granules. If it is assumed that granules tend to keep their integrity during compaction, the latter porosity will probably overestimate the flow porosity which will result in an overestimated tablet surface area.

In Fig. 4, the tablet surface area values calculated from granule density values as a function of compaction pressure are presented for six granulations. The surface area at zero compaction pressure, i.e., the surface area of uncompacted granules, was measured with an air permeability method for coarse powders. This was done for one granulation (E4) which can be considered to be representative for all masses used in this study. The surface area–compaction pressure profiles varied among the granulations. However, there was a general tendency that the tablet surface area increased initially, but with increased compaction pressure the curves levelled out and in many cases also decreased markedly. Earlier experiences concerning the relation between tablet surface area and compaction pressure have shown that these characteristics are almost linearly related to each other for non-porous materials in the pressure range used here. The unexpected levelling out or decrease in tablet surface area obtained for these materials can be explained by assuming that the granules became denser during the compression. The porosity used for air flow will then be underestimated and the surface area also underestimated. The calculated tablet porosities showed generally low values and, furthermore, were in some cases negative, i.e., it was not possible to calculate the tablet surface area. This supports the theory that the granules during compression became, in many cases markedly, denser. The fact that granules became denser even at low compaction pressures means that the tablet surface areas are more or less underestimated throughout the range of compaction pressures. The initial increase in tablet surface area must then be a result of fragmentation of the granules.

The values for the total porosity of the tablets, i.e., calculated from the material density, also indicated that the granules became denser during the compression. The tablet porosity decreased with compaction pressure non-linearly and was similar for all granulations. In the pressure range used, the total tablet porosity was in the range 20–35%. This is in agreement with porosity data for crystalline, non-porous materials such as lactose and saccharose compressed in this pressure range and is fairly close to the porosity of the granules before compression. This indicates then that the granules increased in density already at low compaction pressures, i.e., below 20 MPa. Thus, the use of material density values probably gives a better representation of the intergranular pore space during the calculation of the tablet surface area than does the density of the granules before compression.

In Fig. 5, the tablet surface area, calculated by using the total tablet porosity, is presented as a function of compaction pressure for three granulations. The tablet surface area increased linearly with compaction pressure and the profiles are representative for all granulations. Consequently, the shape of these profiles is in accordance with earlier experiences on the relation between tablet permeametry surface area and compaction pres-

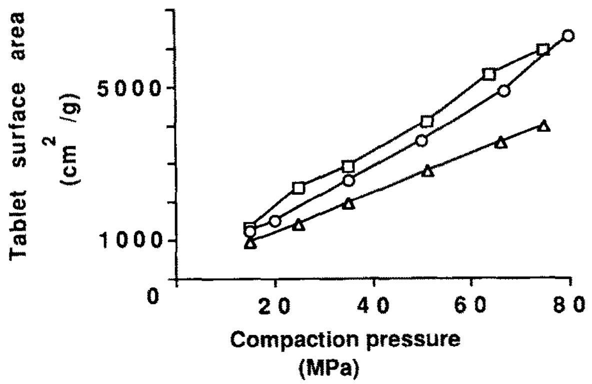

Fig. 5. Tablet surface area, calculated with the material densities, as a function of compaction pressure for granulations produced with 200 ml of binder solvent. Symbols as in Fig. 2.

sure which also suggests that these profiles give a reasonable estimate of the changes in tablet surface area with compaction pressure and thus reflect the fragmentation behaviour of the granules. However, one can notice that there is a dramatic increase in surface area with compaction pressure in Fig. 5, and that the tablet surface area can reach higher values than the surface area of the lactose powder before granulation. This supports the earlier discussion that the surface areas of the tablets are overestimated probably depending partly on an overestimation of the effective porosity of the tablet, i.e., the porosity of the pores in which the air mainly flows.

Because of the good linearity of the profiles, they were quantified by calculating the slopes of the lines in the pressure range 0–70 MPa. The slope values for all granulations as a function of volume of binder solvent are also presented in Fig. 3. The surface area–compaction pressure slope increased for all three solvent systems with an increased amount of binder solvent. Also the type of binder solvent affected the slope but in a less pronounced way: Tablets from the ethanol granulations gave generally the highest slope values followed by the water and the water/ethanol masses. However, as a general comment it can be pointed out that the differences in slope values were generally fairly small, i.e., there appears to be little difference in degree of granule fragmentation among the granulations.

A comparison between slope and AUC values shows that these measures showed a similar dependence on the type and amount of binder solvent. It seems therefore that a decreased tablet permeability generally corresponds to an increased specific surface area of the tablet. In Fig. 6, the surface area is plotted as a function of the permeability coefficient for each individual tablet. The two parameters seem to correlate to each other, i.e., changes in both the permeability coefficient and the tablet surface area, calculated from material density values, with compaction pressure reflect the same characteristic of the granules.

To summarize, the permeability results indicate that the process conditions during the granulation can affect the volume reduction behaviour of the granules during compaction. This difference in volume reduction behaviour can be seen as different air permeability properties of the tablets, i.e., different granulations result in tablets with different pore structures, i.e., more or less permeable tablets. A low tablet permeability is due to the formation of a less open pore structure in the tablet. The formation of such a pore structure is probably a result of a breakdown or a collapse of the granules, which can be described as granule fragmentation. A decreased permeability corresponds generally to an increased tablet surface area. Thus, both the change in tablet surface area and tablet permeability with pressure can thereby be used as measures of the propensity of the

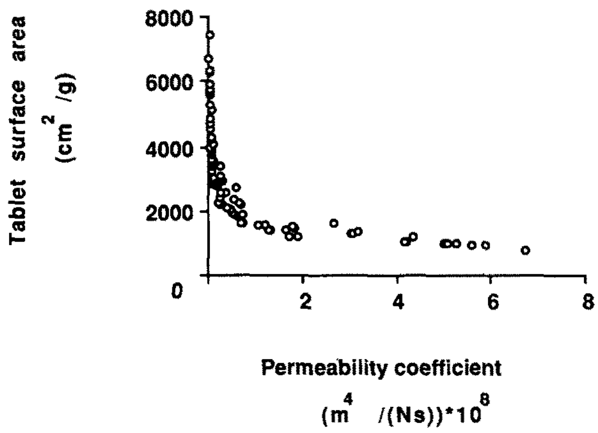

Fig. 6. The tablet surface area as a function of the permeability coefficient for each individual tablet of all granulations.

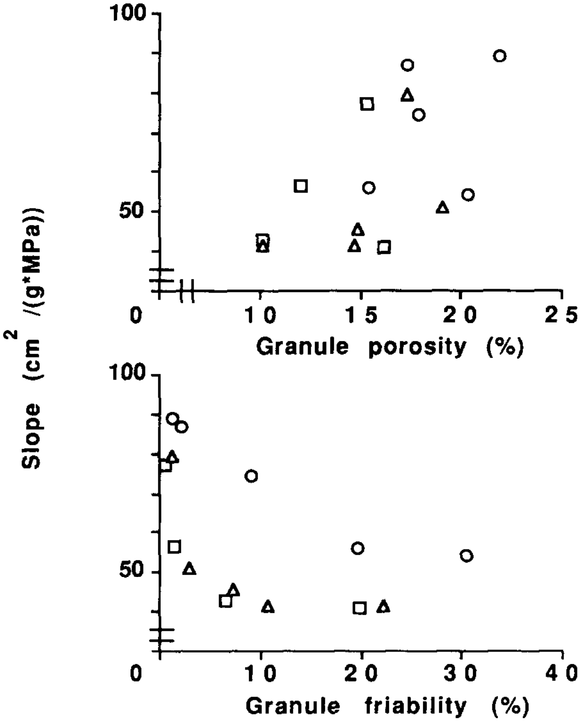

Fig. 7. The slope from the tablet surface area (calculated with material densities) compaction pressure profile as a function of granule porosity (upper panel) and granule friability (lower panel) for all granulations. Symbols as in Fig. 1.

granules to fragment during compression. However, it is worth pointing out that in both cases, the measures are rough estimates of granule fragmentation.

The porosity and the friability of the granules were also affected by the type and amount of binder solvent and in Fig. 7 the surface area-pressure slopes are presented as a function of granule porosity and friability. Because of the inverted relationship between these characteristics there was a tendency for an increased degree of fragmentation with increased porosity and decreased friability. It seems probable that the degree of granule fragmentation is related to the interactions between the primary particles in the granule, i.e., in some way related to the mechanical properties of the granules. It is thereby reasonable to assume that the porosity of the granules is of importance for the degree of granule fragmentation. However, it is also possible that the surface properties of the granule can affect the degree of fragmentation and thereby affect the relationship between slope and porosity, e.g., a rough surface can increase the degree of fragmentation or a tough skin around the granule can prevent fragmentation. However, none of these parameters correlated well with the permeability data and the relationship between granule fragmentation and granule porosity will be studied further later.

Porosity-pressure profiles. A number of equations intended to relate volume changes with pressure during compression have been presented (Kawakita and Lüdde, 1970). Although originally developed for metallic powders, the Heckel equation (1961) appears to be the most common in the pharmaceutical literature. Heckel described the compaction of powders as a first order reaction, with the pores of the bulk as the reactant and the alteration in density of the bulk as the product. However, the first part of the profile often deviates from linearity. This deviation was suggested by Heckel to be the result of particle movement and rearrangement. However, it has also been claimed that this deviation from linearity is related to the degree of particle fragmentation during compression (De Boer et al., 1978; Duberg and Nyström, 1982) and can consequently be used as a measure of the degree of fragmentation. The second part of the profile, i.e., above approximately 50 MPa, is often linear and thereby in agreement with the equation. The reciprocal of the slope of this line has been used as a measure of the compressibility of the material (Duberg and Nyström, 1986).

The correlation coefficient (cc.) from the interval 2–50 MPa and the reciprocal of the slope value from the linear part 50–130 MPa, often referred to as the 'yield pressure', are presented in Fig. 8. The correlation coefficient, i.e., deviation from linearity, was affected by both the volume and the composition of the binder solvent used during the agglomeration. Generally, the more liquid used during the agglomeration the lower the correlation coefficient. Further, the granulations where water was used as solvent gave lower correlation coefficients than the water/ethanol mixture granulations, which in turn gave lower correlation coefficients than the pure ethanol granulations.

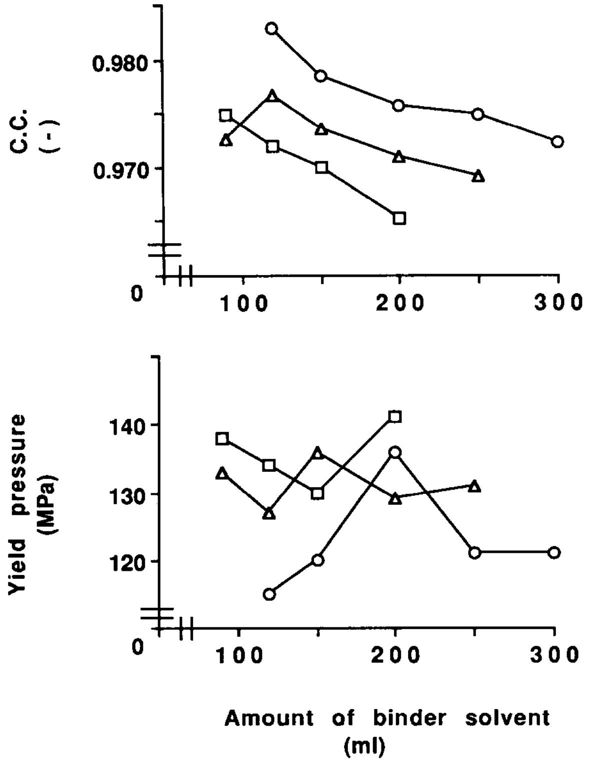

Fig. 8. The correlation coefficient (c.c.) (upper panel) and the yield pressure (lower panel), calculated from the Heckel profiles, as a function of amount of binder solvent used during the granulation for all granulations. Symbols as in Fig. 1.

The yield pressure values showed little variation among the granulations. There is a small tendency that the granulations where ethanol was used as agglomeration liquid show somewhat lower values than the others.

According to some of the above discussed studies, the c.c. reflects the degree of fragmentation during compaction. However, the Heckel results generally did not correlate well with the permeametry results. The lack of correlation found here between permeametry and porosity–pressure profiles might be explained in different ways.

Carstensen and Hou (1985) linearised the initial curved region of Heckel plots by using granule density in the calculations instead of the commonly used true density and proposed that the pore space between the granules is the reactant in the Heckel equation for granulated materials. Thus, the density value of the starting material markedly affects the calculated c.c. However, as discussed above, it seems that the granules also became denser to some extent during the compression, i.e., the porosity within the granules is changing during the compression, and this might also affect the curvature of the profile and thereby the c.c. values. Just to simply use the granule density before compaction in the Heckel equation can consequently be questioned for materials that alter density during a compaction.

It has also been suggested (Heckel, 1961; York, 1978) that the initial deviation from linearity can be affected by particle rearrangement. If the ability of the granules to slide past each other and thereby rearrange in the die varied between the granulations, e.g., due to differences in surface characteristics, this can probably also affect the lack of correlation with the permeametry data.

It can thereby be concluded that it is difficult to interpret the c.c. results obtained from the Heckel plots concerning degree of fragmentation when granulated materials are compressed. However, in an earlier study (Alderborn et al., 1987), tablet permeametry surface area data and Heckel c.c. results agreed with each other concerning degree of granule fragmentation during compression. The results indicated that there were large differences in the degree of fragmentation among the granulations. It is thereby possible in that case that the degree of fragmentation governed the c.c. value and masked differences in degree of densification or rearrangement among the granulations.

It is interesting to note that there seemed to be a correlation between the c.c. value and the granule friability (Fig. 9), i.e., a higher friability resulted in a higher c.c. from the Heckel profile. If the c.c. values primarily reflect differences in granule densification or rearrangement, the results indicate that such effects can be affected by the surface properties of the granules, e.g., a tough skin around the granules or a rough surface can prevent the densification of the granule or affect the possibility of granules sliding past each other. There seemed not to be any correlation between the c.c. values and the granule porosity.

It was also suggested that alterations in the granule density occurred mainly at low pressures

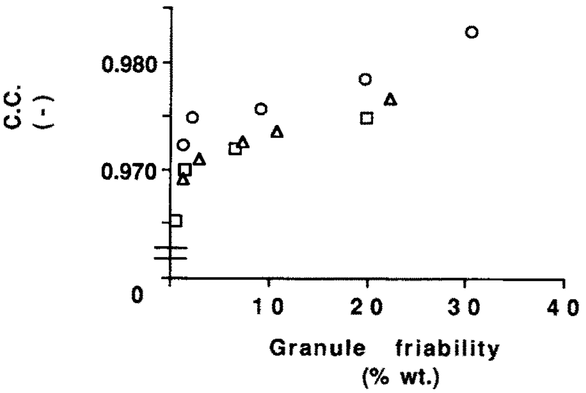

Fig. 9. The correlation coefficient (c.c), calculated from the Heckel profiles, as a function of granule friability for all granulations. Symbols as in Fig. 1.

which can indicate that the so called yield pressure values are more useful in the study of compaction behavior of granules. However, the value is a measure of the ability of a powder to reduce in volume during a dynamic loading. This compressibility is probably affected by a number of factors, such as elastic and plastic deformation of particles and the intensity of the particle–particle interactions in the powder mass. It seems therefore difficult to use the yield pressure as a measure of the degree of granule fragmentation. Furthermore, it cannot be excluded that some alteration of granule density can proceed up to high compaction pressures and thereby also affect the value of the yield pressure.

Conclusions

During compaction of granulated materials there are indications in the literature that granules to some extent tend to keep their integrity, i.e., the tablet can be described as consisting of a number of granules adhered to each other. This observation indicates that the air in a tablet, i.e., the porosity, is distributed both within and between the granules. However, during a dynamic loading it seems that both densification and fragmentation of granules are important volume reduction mechanisms. The distribution of air in the tablet, i.e., the distinction between intra and intergranular porosity, will thereby be difficult to measure. This problem will then affect the possibility of estimating the degree of granule fragmentation during compression by tablet permeability and tablet porosity data as a function of compaction pressure.

The results indicate that the lactose granules used in this study became denser at low compaction pressures and the total tablet porosity at pressures above 20 MPa is similar to that of tablets of non-porous, fragmenting powders. It seems therefore reasonable that during the calculation of tablet permeametry surface areas, the total porosity of the tablet can be used as a reasonable estimate of the intergranular porosity. The data indicated further that granules fragment during compression and this fragmentation propensity can be estimated by following the changes in tablet permeability or permeametry surface area with compaction pressure.

The evaluation of the porosity–pressure profiles did not agree with the permeability measurements concerning degree of granule fragmentation. It is suggested that either the granule densification or the granule rearrangement affected the porosity–pressure data and this method may therefore be questionable if the data to be interpreted regarding granule fragmentation.

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