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Compression characteristics of granulated materials. I. Fragmentation propensity and compactibility of some granulations of a high dosage drug

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Summary

Three granulations of a fairly water-soluble high-dosage drug, dinatrium 3,3′-azobis(6-hydroxybenzoate), were produced by intensive mixing with polyvinylpyrrolidone, dissolved in three liquids with different amounts of ethanol and water, as binder. The granulations were mixed with dry binders or with a lubricant and granulations and mixtures were compressed at 300 MPa and the tablet strength was measured. The tablet strength increased with increased amount of ethanol in the binder solution. The increase and decrease in tablet strength due to the addition of dry binder and lubricant, respectively, were also dependent on the amount of ethanol in the binder solution and indicated that the degree of fragmentation varied between the granulations. Heckel plots and tablet surface area–compaction pressure profiles confirmed the finding that the degree of fragmentation of the granules increased with increasing amount of ethanol in the binder solution. A good correlation between fragmentation propensity of the granulations and tensile strength of the tablets was found.

Introduction

In the production of tablets, an agglomeration procedure of drug and excipients prior to tabletting is very common. Consequently, different aspects of agglomeration and of properties of agglomerated materials have been extensively discussed in the literature. Among these publications also studies on factors influencing the ability of granulations to form coherent compacts have been presented, e.g. the effect of type and amount of binder (De Blaey et al., 1971; Doelker and Shotton, 1977; Chowan and Chow, 1981a and b; Alderborn and Nyström, 1984) and method of granulation (Rue et al., 1980; Ragnarsson and Sjögren, 1982) on the mechanical strength of the tablets. A number of these studies have also dealt with the behavior of the granulations during the compression, e.g. by studying porosity-pressure profiles (Chowan and Chow, 1981a and b) and force-displacement curves (De Blaey et al., 1971; Ragnarsson and Sjögren, 1982) and the relationship between granulation procedure, granulation

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characteristics and compactibility, i.e. the ability of the powder mass to form a compact of a certain strength, has also been discussed. However, compared to the amount of studies on the volume reduction mechanisms of crystalline materials as such or in two-component mixtures, little work has been done on the volume reduction behavior of agglomerated materials and its effect on the mechanical strength of the tablets.

Fragmentation of particles has been shown to be a common mechanism of volume reduction during direct compression of pharmaceutical materials (e.g. Alderborn et al., 1985a and b) and seems also be a factor of importance for the mechanical strength of tablets (De Boer et al., 1978; Alderborn and Nyström, 1982a; Nyström and Glazer, 1985; Vromans et al., 1985). Also for granulated materials, due to their nature, it seems probable that fragmentation is an important mechanism of volume reduction during compression and indications of fragmentation of granules have also been presented in the literature (Higuchi et al., 1953; Shotton and Lewis, 1964). It seems also that for granulated materials the degree of fragmentation during compression might be important for the obtained tablet strength. Doelker and Shotton (1977) report that the mechanical strength of the granules can affect the strength of the tablets. A varying granule strength might also result in a varying degree of fragmentation of the granules during compression. Another factor which has been suggested to affect the tablet strength is the distribution of the binder within a granule (Rue et al., 1980). However, it seems probable that if this hypothesis should be relevant, it requires a fairly low degree of fragmentation of the granules (Nyström and Glazer, 1985).

These observations indicate that fragmentation of agglomerated materials is important for the compact strength and is therefore a relevant mechanism of volume reduction to evaluate also for granulations. A simple way to obtain granules with differing compression characteristics might be to use binder solutions in which the drug has a varying solubility. One single binder can thereby be used, excluding the problem of the binding properties of the binder itself. The intention behind this work was therefore to study the volume reduction characteristics, especially the fragmentation propensity, and the compactibility of three granulations of a high dosage drug, made with binder solutions in which the solubility of the drug vary.

Materials and Methods

Materials

Dinatrium 3,3'-azobis(6-hydroxybenzoate) (Pharmacia AB, Sweden). The drug is a yellow fine-particulate powder and the particles are fairly regular in shape. It forms weak compacts and is prone to laminate or cap. Primary characteristics of the drug are given in Table 1.

Polyvinylpyrrolidone (Plastone K 29-32, GAF, F.R.G.).

Microcrystalline cellulose, two qualities (Avicel PH 102 and Avicel PH 105, FMC, U.S.A.).

Cross-linked polyvinylpyrrolidone (Polyplastone XL, GAF, F.R.G.).

Magnesium stearate Eur. Pharm. quality (FACI, Italy).

Methods

Granulation

Binder solutions were prepared by dissolving 150 g polyvinylpyrrolidone in 3 liquids, consisting of ethanol and water in the proportions 60/40 and 80/20% w/w and finally 100% ethanol. 400 g solvent was used except for the 80/20% mixture where 370 g was used.

TABLE 1

Primary characteristics of the drug

Density [a] (g/cm^3)	Specific surface area [b] (m^2/g)	Solubility in water [c] (%)	Solubility in ethanol [c] (%)
1.606	2.23	3	0.02

[a] Measured with an air comparison pycnometer (mod. 930, Beckman, U.S.A.).
[b] Estimated from permeametry data (Sub Sieve Sizer, Fisher Scientific, U.S.A.)
[c] Estimated by gravimetric analysis.

2500 g of the drug was mixed for 0.5 min in an intensive mixer (Diosna Pharmamix P25, Dierks and Söhne Maschinefabrik, F.R.G.). A binder solution was poured into the mixer during 3 min and the wet mass was mixed for 0.5 min. The granulation was then dried in a fluid-bed dryer (Glatt, F.R.G.) for 5 min, pressed through a 2.5-mm screen in an oscillating granulator (Frewitt MG 400, Switzerland), again dried in the fluid-bed dryer for 20 min and, finally, pressed through a 1.0-mm screen in the oscillating granulator.

The 3 granulations produced are denoted granulation I, II and III with increasing amount of ethanol in the binder solution.

Mixing

Each granulation was mixed for 30 min with one of the excipients at 90 r.p.m. in a 21 Turbula mixer (W.A. Bachofen, Switzerland). The fill volume in the mixing jar was approximately 65%. Compositions of the final masses are presented in Table 2.

Compression of tablets

Tablets of each composition were compressed at 300 MPa in an instrumented single-punch press (Korsch EK 0, F.R.G.). For each tablet, a certain amount of powder was weighed on an analytical balance and manually filled into the die, which was prelubricated (except for composition E) with a suspension of magnesium stearate in ethanol, 1% w/w. The tablet was then compressed at 30 r.p.m. with flat-faced punches with a diameter of 1.13 cm. The distance between the punch faces at the lowest position of the upper punch was in all cases 3 mm at zero pressure. The accepted variation in maximum upper punch pressure was ±5% of the nominal value.

TABLE 2

Compositions and denominations of granulation and mixtures

Material	Composition in % w/w				
	A	B	C	D	E
Drug	94.3	86.2	86.2	86.2	93.8
Polyvinylpyrrolidone	5.7	5.2	5.2	5.2	5.7
Avicel PH 102	–	8.6	–	–	–
Avicel PH 105	–	–	8.6	–	–
Crosslinked PVP	–	–	–	8.6	–
Magnesium stearate	–	–	–	–	0.5

Tablet porosity–pressure profiles

Three tablets of each granulation were compressed in the instrumented tablet press at 150 MPa according to the procedure described above. In addition to the registration of the upper punch force with strain gauges, the position of the upper punch was measured with an inductive displacement transducer during these compressions. The analog signals from the strain gauges and from the transducer were amplified and for every millisecond sampled with sampling hold units and then converted to digital form using a 12 bit A/D converter and, finally, stored on a floppy disk. Signals for upper punch force and displacement were sampled simultaneously, not sequentially, with different sampling hold units. The porosity of the tablets was then calculated with corrections for the elastic deformation of the punches and porosity–pressure functions, according to the Heckel equation (Duberg and Nyström, 1986), were plotted.

The Heckel profiles were evaluated in 3 ways (Duberg and Nyström, 1986). Firstly, by calculating the correlation coefficient of the profile with ordinary regression analysis in the pressure range 5–40 MPa. Secondly, by calculating the yield pressure, i.e. the reciprocal of the slope value, in the compression range 40–150 MPa. Finally, by calculating the elastic recovery of the compact during the ejection with the aid of the minimum porosity during the compression and the porosity at the time when the upper punch loses contact with the tablet. The elastic recovery was calculated as (ejection porosity − minimum porosity)/minimum porosity.

Tablet surface area–pressure profiles

For each granulation, approximately 10 tablets were also compressed by hand in the instrumented press at a pressure range up to 125 MPa. The compression procedure and the permeability measurement of the tablets as well as the equations used for calculating the tablet surface area have been presented earlier (Alderborn et al., 1985a).

With the aid of the tablet surface area–pressure results, the fragmentation propensity coefficient (C_{FP}%) was calculated (Alderborn and Nyström, 1985).

Mechanical strength of tablets

The tablets were stored for at least 24 h and the mechanical strength was then measured as radial and axial tensile strength. The diametral compression strength of 5 tablets of each composition was measured with an Erweka tester (Erweka TBH 28, F.R.G.) and the radial tensile strength was then calculated (Fell and Newton, 1970). The axial tensile strength of 5 tablets was also measured according to a procedure earlier described (Nyström et al., 1978).

Results and Discussion

Powder characteristics of granulations I–III are presented in Table 3. All granulations showed similar moisture content and granule size distribution and the distributions estimated in all cases showed an arithmetic normal distribution. However, there was a slightly increasing amount of fines in the granulations with increasing amount of ethanol in the binder solution. Microscopic examination of the granulations indicated a spherical shape and a smooth surface of the intact granules for all 3 granulations. The radial and axial tensile strength for tablets of all compositions and the strength isotropy ratios are presented in Table 4 (except for the composition with lubricant additions where only the radial tensile strength was measured). For the pure granulations, an increased amount of ethanol in the binder solution increases markedly both the radial and the axial tensile strength of the tablets. In all cases the addition of a dry binder increases the tablet strength while the addition of the lubricant decreases the mechanical strength. However, it seems that the relative increase, due to binder addition, and the relative decrease, due to lubricant addition, are continuously decreasing from granulation I to III. This observation is demonstrated in Tables 5 and 6 where the ratios between the radial tensile strengths with and without the addition of the dry binders (Table 5) and the lubricant (Table 6) are presented. For both types of ratios, the values closest to unity are shown by granulation III while the largest deviations from unity are shown by granulation I. Granulation II behaves as an intermediate. It has earlier been shown that the strength reduction due to lubricant addition (Duberg and Nyström, 1982) and the strength increase due to binder addition (Nyström and Glazer, 1985) are functions of the degree of fragmentation of the main compound. The results of the strength mea-

TABLE 3

Powder characteristics of granulations

Granulation	Water content [a] (%)	Median granule size [b] (μm)	Standard deviation [b] (μm)
I	1.0	605	200
II	0.8	555	195
III	0.9	555	210

[a] Loss on drying during 10 min in a moisture balance (Mettler LP 15 and PE 360, Mettler Instruments A.G., Switzerland).
[b] Estimated by dry sieving.

TABLE 4

Radial and axial tensile strength and isotropy ratio of granulations and mixtures

Composition	Radial tensile strength (MPa)	Axial tensile strength (MPa)	Isotropy ratio
I A	0.887	0.460	0.52
II A	1.387	1.006	0.72
III A	2.206	1.357	0.62
I B	1.158	0.555	0.64
II B	1.757	1.006	0.57
III B	2.467	1.580	0.64
I C	1.462	0.545	0.37
II C	1.963	1.153	0.58
III C	2.825	1.733	0.61
I D	1.319	0.675	0.51
II D	1.745	1.113	0.64
III D	2.488	1.787	0.72
I E	0.070	–	–
II E	0.136	–	–
III E	0.864	–	–

TABLE 5

Ratio between radial tensile strengths with and without dry binder

Granulation	Ratio between compositions		
	B/A	C/A	D/A
I	1.31	1.65	1.49
II	1.27	1.42	1.26
III	1.12	1.28	1.13

surements as summarized in Tables 5 and 6 therefore indicate that the degree of fragmentation varies between the granulations. Granulation III fragments most markedly, granulation I fragments to the lowest degree while granulation II shows intermediate fragmentation. The rather marked changes in compact strength due to the addition of an excipient indicate also that the degree of fragmentation of all granulations are fairly low.

From Table 5 it can also be noted that Avicel 105 gives higher values of the dry binder ratios than Avicel 102. This is probably due to the higher powder fineness of the former quality (Nyström et al., 1982; Nyström and Glazer, 1985). Worth noting also is that the cross-linked polyvinylpyrrolidone is, for these granulations, an equal dry binder compared to the microcrystalline cellulose concerning strength increase although it is mainly considered as a disintegrant.

The values of the strength isotropy ratio (Table 4) are fairly high for all 3 granulations, indicating that there is no tendency of capping for these tablets (Alderborn and Nyström, 1984). The value of the strength isotropy ratio has, except for being a capping index, earlier been shown to reflect the degree of fragmentation of the compound during compression (Duberg and Nyström, 1982; Alderborn and Nyström, 1982b). There are similar values of the isotropy ratio thereby indicating similar fragmentation behavior for the pure granulations. However, the variability in the isotropy ratio might be large and thereby make the results difficult to interpret concerning the degree of fragmentation.

TABLE 6

Ratio between radial tensile strengths with and without lubricant addition

Granulation	Composition ratio (E/A)
I	0.0789
II	0.0981
III	0.392

The evaluation parameters of the Heckel plots of granulations I–III are presented in Table 7. The values of the yield pressure and the minimum porosity during compression increase from granulation I–III which indicates that the ability of the granulations to reduce in volume, i.e. the compressibility, increases with decreasing amount of ethanol in the binder solutions. The ejection porosity increases also from granulation I to III resulting in a similar elastic recovery for all 3 granulations with a slightly higher value for granulation I. At the time of strength measurement, however, the tablets of all 3 granulations showed a similar porosity, i.e. 35.6%, 36.0% and 35.6% for granulation I, II and III respectively (compaction pressure = 300 MPa). Although these results are for tablets compressed at a higher pressure, a comparison of the porosity data indicates a marked increase in tablet porosity after the upper punch leaves the tablet. This might be the reason why the final tablet porosity does not reflect the differences in compressibility between the granulations shown by the Heckel plots.

The correlation coefficient (Table 7) decreases from granulation I to III. This latter observation supports the above findings that the degree of fragmentation increases from granulation I to III (Duberg and Nyström, 1982). To summarize, the results from the porosity–pressure profiles indicate that an increasing amount of ethanol in the binder solution gives granules which fragment to a larger extent during the compression. It will also give a powder mass which is less able to decrease in volume during the compression. This might be due to an increased degree of particle–particle interactions during the loading and thereby giving a less compressible mass.

The tablet surface area–compaction pressure profiles for granulations I–III are shown in Fig. 1. The slope of the profiles increases in the order granulation I–III, again indicating that the degree

TABLE 7

Evaluation parameters of Heckel plots for the granulations

Granulation	Yield pressure (MPa)	Minimum porosity (%)	Ejection porosity (%)	Elastic recovery (%)	Correlation coefficient
I	154	12.6	15.5	22.2	0.9908
II	165	13.9	16.8	20.9	0.9899
III	168	14.4	17.2	20.1	0.9878

of fragmentation of the granules is increasing with increasing amount of ethanol in the binder solution and thereby confirming the earlier observations. It can also be noted that the profiles deviate positively from a straight line which has also been found earlier (Alderborn et al., 1985a). This deviation, probably an error with the permeametry method, means that a numerical value of the slope, calculated with ordinary linear regression, is markedly dependent on the number of observations used in the calculation. This problem is reduced if the cube root of the tablet surface area is used instead of the absolute value. The slope from such a plot was therefore calculated, i.e. the fragmentation propensity coefficient, C_{FP}, (Alderborn and Nyström, 1985), in order to obtain a numerical value of the profile.

In Fig. 2, the fragmentation propensity of the pure granulations, expressed as the correlation coefficient from the Heckel plot and the C_{FP}(%) from the permeametry profiles, is plotted as a function of the tensile strength of the tablets. A decreased correlation coefficient and an increased fragmentation propensity coefficient correlates very well with an increased tensile strength of the compacts. This is especially notable for the radial tensile strength while the correlation with the axial tensile strength values is slightly weaker. This might be due to a higher variability in tensile strength values in the axial than in the radial direction. It seems therefore that the main parameter governing the tablet strength is the fragmenta-

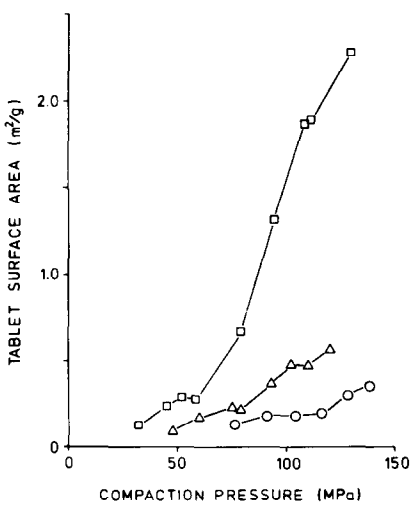

Fig. 1. Tablet permeametry surface area as a function of compaction pressure for granulation I (○), II (△) and III (□).

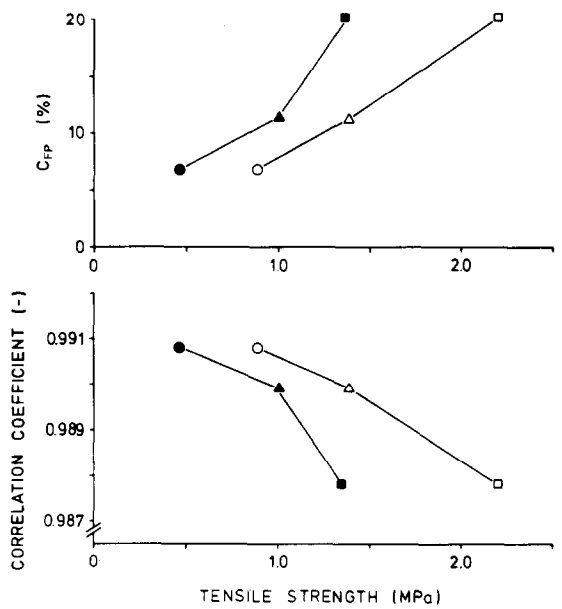

Fig. 2. Fragmentation propensity coefficient (C_{FP}) and correlation coefficient from the Heckel plot as a function of tensile strength of tablets compressed from granulation I (○), II (△) and III (□). Open symbols represent the radial and closed the axial tensile strength.

tion propensity of the granules during the compression rather than the ability of the powder mass to decrease in volume. The results might be explained by the phenomenon that the tablets obtained can be described as large agglomerates, consisting of a large number of small granules agglomerated together. This means that the attractions between the granules normally are weaker than the attractions within the granules. The failure of the tablet during strength measurement should then occur preferably around rather than across the grains. A fragmentation of the granules during compression will then give a larger number of small agglomerates in the compact and a larger number of possible contact points and thereby a larger total bonding surface area. Such contact points can consist of interactions between particles or surfaces of the drug but also of the binder. The fragmentation will probably give larger amounts of binder exposed on the surface of the granules, thereby giving the opportunity that a larger amount of binder can be used for adhering the granules to each other.

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