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Studies on direct compression of tablets. XIII. The effect of some dry binders on the tablet strength of compounds with different fragmentation propensity *

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Summary

Both fine and coarse fractions of Avicel PH 101, Avicel PH 105, methyl cellulose and polyvinylpyrrolidone were added to compounds with poor binding properties. The binding effect differed only slightly between the three binders tested, whereas a decrease in binder particle size effectively improved tablet strength. The effect of the binder additions was strongly dependent upon the fragmentation propensity of the compounds. The technique to cover the compounds with a fine binder resulted in stronger tablet for the compounds, which were less prone to fragment during compaction.

Introduction

When developing direct compression formulations of larger proportions of an active compound, it is often difficult to obtain sufficiently strong tablets. When only small amounts of excipients can be added, the compactability of the mixture is to a large extent governed by the compound itself.

It was earlier reported (Nyström et al., 1982), that a surface treatment with a finely divided methyl cellulose powder could strongly improve the tablet strength of some coarse crystalline compounds. It was shown that the improvement in tablet strength was dependent both on the amount and particle size of the binder but also

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on the bonding and consolidation properties of the compounds tested. The best effect was obtained when the compound particles were effectively covered by binder particles, i.e. using as small binder particles as could be adequately de-agglomerated during mixing. Furthermore it was concluded that fragmentation of the compound particles reduced the surface coverage and thereby limited the effect of the binder additions.

The strength of a powder compact is basically dependent on the main bond type involved and on the surface area over which the bonding acts (i.e. number of bond points). The bonding surface area is a complex function related to several parameters (Duberg and Nyström, in preparation). The size and shape of the powder particles, the consolidation behaviour and the elastic properties of the compacted particles seems to be of main importance (Alderborn and Nyström, 1982a and b).

In an earlier study (Nyström et al., 1982) it was discussed that the mode of action of a dry binder for increasing the tablet strength could be any of several: (a) to increase the number of bonds; (b) to produce a number of stronger bonds; (c) to produce a number of bonds that can withstand stress relaxation and the elastic recovery of the compound particles.

In that study, only one binder material (methyl cellulose) was tested. In this case it is of interest to investigate if different binders deliver bonds with large differences in mechanical strength. If so, the means of choosing the optimum binder should be considered. It is also of interest to further study the importance of the consolidation behaviour of the compound particles tested, and particularly the fragmentation propensity ought to be adequately characterized.

The intention of the present study was therefore to evaluate the effect of some binders, normally used in tabletting, and to test these on direct compression of some compounds with poor binding properties but with documented differences regarding fragmentation propensity during compaction.

Experimental

Materials

Binders. Avicel PH 101 (FMC, U.S.A.). Avicel PH 105 (FMC, U.S.A.). Methyl cellulose (A15 premium, Dow Chemicals, U.S.A.). Polyvinylpyrrolidone (Polyvidon K25, BASF, F.R.G.).

The binders were used as raw materials or as specific size fractions, obtained with the aid of an air classifier (100 MZR, Alpine, F.R.G.). Data for the binders used are presented in Table 1.

Compounds. Paracetamol (crystalline, Bayer, F.R.G.). Ascorbic acid (crystalline, Roche, Switzerland). Sodium bicarbonate (crystalline, Kebo Grave, Sweden).

Data for the compounds used are presented in Table 2. These compounds were chosen because of their poor bonding capacity and their difference in consolidation behaviour.

Methods

Projected and external surface area. The projected surface areas of the binder

TABLE 1

SIZE CHARACTERISTICS OF BINDERS

Binder	Size fraction [a] (μm)	Projected surface area [b] ($cm^2 \cdot g^{-1}$)
Avicel PH 101	< 10	2316
	30–40	729
	raw material	840
Avicel PH 105	raw material	2012
Methyl cellulose	< 10	2983
	30–50	578
Polyvinylpyrrolidone	< 10	2006
	30–40	448

[a] Obtained with an air classifier (100 MZR, Alpine, F.R.G.).
[b] Evaluated from permeametry data (Sub Sieve Sizer, Fisher Scientific, U.S.A.).

fractions and the external surface areas of the compounds were determined as described earlier (Nyström et al., 1982). The ratio between projected and external surface area is also here defined as the surface area ratio.

Fragmentation propensity of compounds during compression. The degree of fragmentation was here defined as the increase in tablet specific surface area as measured with a permeametry technique (Alderborn et al., 1982). The compounds were compacted at loads between 15 to 160 MPa (maximum upper punch pressure). Since the plots of surface area against compaction load showed acceptable straight line correlations and since the powder surface areas of the compounds were of the same order (Table 2), the slope values (in $cm^2 \cdot g^{-1} \cdot MPa^{-1}$) were used as a measure of fragmentation propensity.

Mixing of binder and compound. For each combination of compound and binder fraction, three different proportions were tested. In Table 3, these are presented as

TABLE 2

PRIMARY CHARACTERISTICS OF THE COMPOUNDS

Compound	Sieve fraction (μm)	Density [a] ($g \cdot cm^{-3}$)	Tablet strength [b] (MPa)	External powder surface area [c] ($cm^2 \cdot g^{-1}$)	Fragmentation propensity ($cm^2 \cdot g^{-1} \cdot MPa^{-1}$)
Paracetamol	180–500	1.33	0.15	108	46
Ascorbic acid	180–500	1.69	0.24	186	25
Sodium bicarbonate	125–180	2.16	0.18	219	4.6

[a] Measured with an air comparison pycnometer (mod. 930, Beckman, U.S.A.).
[b] Radial tensile strength of tablets compressed at 110 MPa.
[c] Calculated from harmonic mean diameter by weight and Heywoods surface-to-volume shape factor (Nyström et al., 1982).

low, medium and high binder additions in w/w%. Different additions were used for the respective compounds, due to their differences in density and external surface area (see Table 2). For the fine binder fractions, the high and medium addition corresponds to a surface area ratio of approximately 2 and 1, respectively. The low addition corresponds to a ratio of 0.5 for the fine binder fractions added to sodium bicarbonate, whereas the corresponding ratio for ascorbic acid and paracetamol is 0.7. However, the lowest addition was not tested for the Avicel fractions. The surface area ratios for all the coarser binder fractions were consequently lower than the ratios mentioned for the finer fractions. All the compound samples (approximately 50 g) were obtained with a spinning riffler (PT, Retsch, F.R.G.). Mixing was then performed in a Turbula Mixer (2 liters, WA Bachofen AG, Switzerland) for 30 min at a speed of 30 rpm. The long mixing time was chosen in order to break up the agglomerates of the fine binder fractions (Malmqvist and Nyström, 1984).

Compression of tablets. Tablets were compressed in an instrumented single-punch press at 110 MPa (maximum upper punch pressure) as described earlier (Nyström et al., 1982). However, here the tablet thickness was for all mixtures kept constant to 3 mm.

Measurement of tablet strength. The tablets were stored at 20°C, 45% RH for at least 48 h before being measured on diametral compression strength. The radial tensile strength was evaluated as described earlier (Nyström et al., 1982). The mean values for not less than 10 tablets are given.

Results and Discussion

Fragmentation propensity

The results from the permeametry measurements are presented in Fig. 1 and Table 2. The results show that paracetamol is most prone to fragment during compaction, while sodium bicarbonate has the lowest fragmentation tendency. Ascorbic acid behaves as an intermediate.

Effect of binder properties on tablet strength

Results from all mixtures are presented in Fig. 2, where the binder additions are expressed both as weight percentage and as surface area ratios. For all compounds,

TABLE 3

AMOUNT OF BINDER ADDED TO EACH COMPOUND

Compound	Addition of binder fraction (w/w%)		
	Low	Medium	High
Paracetamol	3.5	5.0	10
Ascorbic acid	5.8	8.5	16
Sodium bicarbonate	5.2	10	18

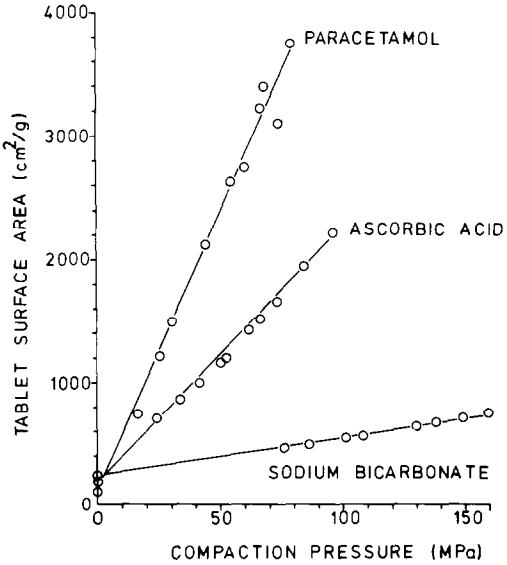

Fig. 1. Tablet surface area versus compaction pressure of the compounds as measured by permeametry.

the tablet strength increased with increasing concentration of binder but also with a decrease in binder particle size. The use of the fine fractions of methyl cellulose and polyvinylpyrrolidone almost doubled the tablet strength compared to the use of the coarser fractions. However, the use of the fine fraction of Avicel PH 101 gave a much lower effect on tablet strength than expected. The use of Avicel PH 105 gave results in better agreement with the other binders tested.

As obtained in an earlier study (Nyström et al., 1982), the use of surface area ratios gave a better correlation to the binding effect than using the amount of binder. The use of surface area ratios, therefore makes it easier to compare the binding effect of the different binders tested. The four binders, were all effective in improving the tablet strength of these poorly binding compounds. Concentrations, giving a surface area ratio up to unity, increased the tablet strength considerably, but above this level further additions were less effective.

For ascorbic acid, it was not possible to distinguish any main difference in the binding effect between the binders tested, with the possible exception of Avicel PH 101, < 10 μm. For sodium bicarbonate, the use of methyl cellulose resulted in slightly lower values than both Avicel and polyvinylpyrrolidone, whereas for paracetamol, the latter gave tablets of higher mechanical strength.

However, all the differences obtained are small. The results therefore indicate that there are no great differences in bond strength and bond type between the compounds and the respective binder tested. Regarding bond type, three bonding mechanisms are normally considered in literature.

(a) Strong bonds, e.g. ionic bonds created through sintering or cold welding of the primary particles (Führer, 1977).

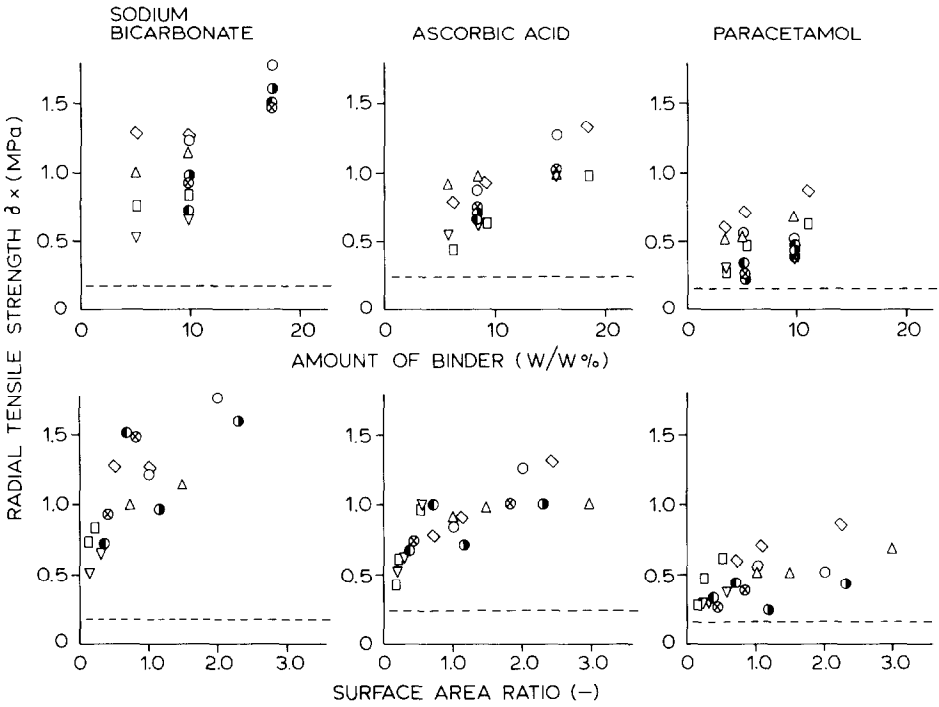

Fig. 2. Tablet strength of sodium bicarbonate, ascorbic acid and paracetamol mixed with different amounts of binders: ⊕, Avicel PH 101 <10 μm; ⊕, Avicel PH 101 30–40 μm; ⊗, Avicel PH 101 raw material; ○, Avicel PH 105 raw material; △, methyl cellulose <10 μm; ▽, methyl cellulose 30–50 μm; ◇, polyvinylpyrrolidone <10 μm; □, polyvinylpyrrolidone 30–40 μm. The dotted lines represent the tablet strength of the pure compounds.

(b) Weaker attraction forces, e.g. molecular forces of Van der Waals type or hydrogen bonds.

(c) Mechanical interlocking between irregularly shaped particles (Führer, 1977).

It is difficult to determine what kind of bond type is established between the compounds and the respective binder. The use of fine binder particles makes the presence of mechanical interlocking less probable. The relatively strong effect of small binder additions on tablet strength (Fig. 2) indicates that these attraction forces are relatively strong. However, considering the chemical structure of the binders tested, the possibility for establishing e.g. ionic bonds, seems to be small. Except for the possibility for non-specific attraction by induced dipole interaction (Van der Waals forces), all mixtures also have the possibility of establishing hydrogen bonds. In addition, the slightly better binding effect of polyvinylpyrrolidone could perhaps be explained by its hygroscopic nature, leading to an increased number of liquid bridges in the compacts.

The mechanism of the dry binder particles therefore seems to be to increase the total number of bonds. The deformable nature (plastic deformation) of these

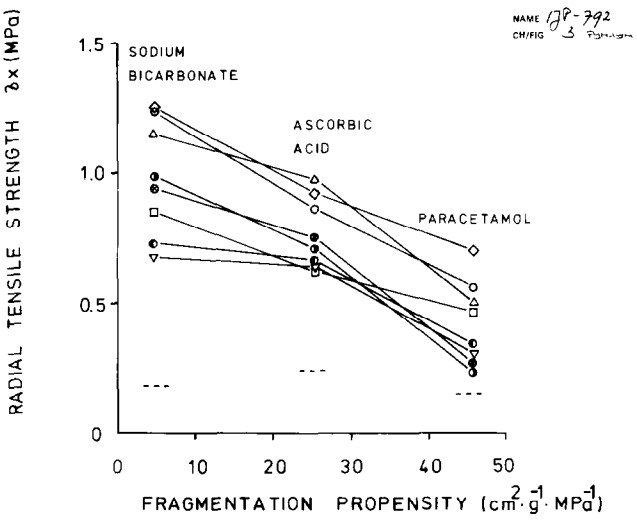

Fig. 3. Tablet strength of the compounds (rank ordered after their fragmentation propensity) mixed with medium additions of the binder fractions. Binder symbols, see Fig. 1.

particles also makes the bonds resistant enough to allow the stress relaxation and the elastic recovery to occur without breakage (Nyström et al., 1982).

Effect of compound properties on tablet strength

Results from the medium addition of the binder fractions to the compounds are presented in Fig. 3. Here the tablet strength values are plotted against the fragmentation propensity of each compound respectively. It is clearly shown that the fine binder fractions (giving an approximate surface area ratio of 1) increases the tablet strength more than coarser fractions (ratios of less than 1). The fragmentation propensity of the compound was very important for the effect of the surface treatment with the binders. The more the fragmentation, the less was the effect of the binder addition. As explained earlier (Nyström et al., 1982), extensive fragmentation of the particles during compaction creates a large number of fresh, uncoated surfaces, thereby reducing the initial surface coverage of the compound particles.

For sodium bicarbonate, which consolidates mainly by plastic deformation (Duberg and Nyström, in preparation) and not by fragmentation, the low tablet strength of the pure compound (Table 2) indicates that these particles are kept together by a relatively small number of weak attraction forces. The addition of a finely divided binder will then strongly increase the total number of bonds.

Pure paracetamol, which fragments extensively (Fig. 1), could be expected to produce strong tablets, since a large number of contact points are created. However, the low tablet strength of the pure compound (Table 2) implies that the compacted particles are partly elastic in their nature (Carless and Leigh, 1974; Travers and Cox, 1978) thereby reducing the number of remaining bonds in the ejected tablet. The addition of finely divided, plastically deforming particles, could therefore serve as a

means to increase the total number of bonds resistant to breakage. However, the extensive fragmentation of the coated compound particles, reduces strongly the effect of such binder additions.

Ascorbic acid particles show an intermediate fragmentation during compaction. The relatively low tablet strength (Table 2) indicates that as for paracetamol these attraction forces are relatively weak and not very resistant to stress relaxation and elastic recovery. The effect of an addition of fine binder particles will therefore be related to the fragmentation tendency of the compound particles.

Conclusions

The results in this study support our earlier findings that the effect of a dry binder is related not only to the amount but also the particle size of the binder used. The use of surface area ratios seems to be a useful means of expressing the addition of a dry binder. The ratio, which reflects both the weight and size properties of the binder, is well related to the binding effect. The effect of the different binders tested were surprisingly similar when the surface area ratios were kept constant. The results indicate that the binders tested act mainly by increasing the total number of bonds, while the bond strength and bond type is similar. Due to the deformable nature of the binder particles, these bonds are fairly resistant against stress relaxation and elastic recovery in the compact.

The effect of a surface treatment with a finely divided binder seems to be strongly dependent upon the fragmentation propensity of the compound. The technique is most suitable for compounds which are less prone to fragment during compaction.

To be able to use as small additions as possible, the binder should be very finely divided but still have the ability to de-agglomerate during mixing with the compound. Very few binder excipients are available today in such fine grades, but our experience with Avicel PH 105 suggests that this material could be an appropriate dry binder in direct compression formulations.

In order to evaluate the applicability of finely divided binders, it is important to include also lubricants and perhaps disintegrants into the formulations. Studies of such systems are under way at the department.

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