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Studies on direct compression of tablets II. The influence of the particle size of a dry binder on the mechanical strength of tablets *

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Summary

Tablets of free-flowing lactose, paracetamol, ascorbic acid and sodium chloride were compressed in an instrumented single-punch press. Five size fractions of methyl cellulose powder were added as binder. Increasing amounts of methyl cellulose increased the tablet strength of all materials. Small additions of coarse binder reduced the strength of sodium chloride tablets, however. The particle size of the binder was very important for the effect and fine fractions were considerably more effective. The effect of the particle size was smallest in lactose tablets, possibly due to the pronounced fragmentation of this material during compaction. Sodium chloride which did not fragment during tabletting was most affected by particle size variation of the binder. For paracetamol and ascorbic acid the tablet strength was directly related to the degree of surface coating obtained by the binder.

Introduction

Interest in the direct compression of pharmaceutical compounds into tablets has increased during recent decades (Milosovich, 1963; Mendell, 1972; Khan and Rhodes, 1973). Advantages that have been mentioned are the exclusion of such processes as agglomeration, drying and grinding, and the possibility of formulating water-sensitive compounds into tablets. In practice, however, the use of direct

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compression has been restricted mainly to formulations containing small proportions of the active ingredient, where the properties of the mixture is governed by the additives involved. If larger proportions of the active compound have to be used, it is often difficult to obtain sufficiently strong tablets. In such cases the compressibility can be improved by the addition of a binding substance. Binders added as dry powder are, however, generally less effective than when added as solutions.

Most excipients used in direct compression to improve the tablet strength have been relatively coarse materials (Bolhuis and Lerk, 1973; Lerk and Bolhuis, 1974; Stamm and Mathis, 1976), and are effective only in fairly high concentrations. Although it is reasonable to assume that smaller particles distributed efficiently in the tablet would be more effective, very little has been reported regarding the influence of the particle size on the binding properties.

Methyl cellulose is an effective binder in wet granulation and was therefore chosen as a model substance for the investigation of how a dry binder could improve tablet strength. Special interest was directed towards the use of very fine particle size fractions.

When studying the effect of additives to crystalline materials, it is also important to consider the deformation mechanisms during compaction. The degree of fragmentation seems to be especially important (de Boer et al., 1978). In this study we therefore used materials with different fragmentation tendencies during compaction.

Materials and methods

Materials

Methyl cellulose (A 15 premium, Dow Chemicals, U.S.A.). Four size fractions were obtained with the aid of an air classifier (100 MZR, Alpine, F.R.G.), see Table 1.

Lactose (α-monohydrate, crystalline, Svenska Mjölksocker, Sweden).

Paracetamol (crystalline, Bayer, F.R.G.).

Ascorbic acid (crystalline, Roche, Switzerland).

Sodium chloride (cubic crystalline, Kebo Grave, Sweden).

Methods

Projected surface area of the binder. With the use of a fixed pressure permeameter (Sub Sieve Sizer, Fisher Scientific, U.S.A.) the external surface areas were determined on 3 samples of each size fraction. From microphotographs the ratio between surface shape coefficient and projected area shape coefficient (Allen, 1975a) was estimated to be 4, and subsequently the projected surface area for each size fraction could be calculated (Table 1).

External surface area of the compounds. The external surface areas were calculated (Allen, 1975b) from the harmonic mean diameter by weight obtained by dry sieving and an approximate value of Heywood's surface-to-volume shape factor obtained by microscopy (Heywood, 1954) (Table 2).

Estimation of fragmentation propensity during compression. Mixtures of 0.1%

TABLE 1

SIZE CHARACTERISTICS OF METHYL CELLULOSE FRACTIONS

Size fraction [a] (μm)	Projected surface area (cm^2/g)
< 10	2983
10–20	1188
20–30	738
30–50	578
Raw material	662

[a] Obtained with an air classifier (Alpine 100MZR).

magnesium stearate and the 4 compounds, respectively, were compressed to tablets in an instrumented single-punch press (EK O, Korsch, F.R.G.) at 110 MPa. An axial tensile testing apparatus (Nyström et al., 1977) was used to strain the tablets until they broke and the tablet halves were subsequently photographed in a scanning electron microscope (SMU-3, JEOL, Japan) (Hardman and Lilley, 1970). Uncompressed samples of the 4 compounds were also photographed.

Addition of binder to the compounds

The amounts of binder in the mixtures were chosen to give ratios between the projected area of the binder and the external surface area of the compound in the range from 0 to 5. This ratio reflects both the weight and size relationships between binder and compound. A surface area ratio of unity indicates an amount of binder sufficient to form a monoparticular layer on the surface of the compound. The surface area ratios tested, were the same for all compounds, but the number of additions, varied slightly dependent upon the compaction properties of the materials. As an example of the relation between the surface area ratios and the corresponding weight amounts added, data for sodium chloride are presented in Table 3.

Mixing was performed in a Turbula Mixer (2 liters) for 100 min at a speed of 30

TABLE 2

PRIMARY CHARACTERISTICS OF THE COMPOUNDS

Compound	Sieve fraction (μm)	Density [a] (g/cm^3)	External surface area [b] (cm^2/g)
Lactose	180–500	1.52	153
Sodium chloride	180–500	2.17	70.5
Paracetamol	180–500	1.33	108
Ascorbic acid	250–500	1.69	142

[a] Measured with an air comparison pycnometer (mod. 930, Beckman, U.S.A.).

[b] Calculated from harmonic mean diameter by weight and Heywood's surface-to-volume shape factor.

TABLE 3

SURFACE AREA RATIOS BETWEEN THE BINDER AND COMPOUNDS

Binder fration (μm)	Percent binder added to sodium chloride:				
	1.50	2.36	5.71	9.81	14.6
<10	0.65	1.05	2.64	4.73	–
10–20	0.26	0.42	1.05	1.88	–
20–30	–	0.26	0.65	1.17	2.63
30–50	–	0.20	0.51	0.92	2.36
Raw material	–	0.23	0.58	1.05	2.06

rpm. This long mixing time was chosen to give a reasonably good de-agglomeration of the finest binder fractions (Nyström and Malmqvist, 1980), and it was verified with the aid of scanning electron microscopy that an adequate de-agglomeration had been achieved (Fig. 1). All mixtures were stored for at least 48 h at 20°C and approximately 45% RH, before compression.

Compression of tablets

Tablets were compressed with 1.13 cm flat-faced punches in the instrumented press at a rate of 30 rpm. The surfaces of the punches and the die were lubricated before compression with a 1 w/w % suspension of magnesium stearate in carbon tetrachloride. The tablet weight was 0.500 g, except for sodium chloride where it was 0.650 g. These amounts were individually weighed on an analytical balance and poured into the die. The compaction load was 110 MPa unless otherwise stated.

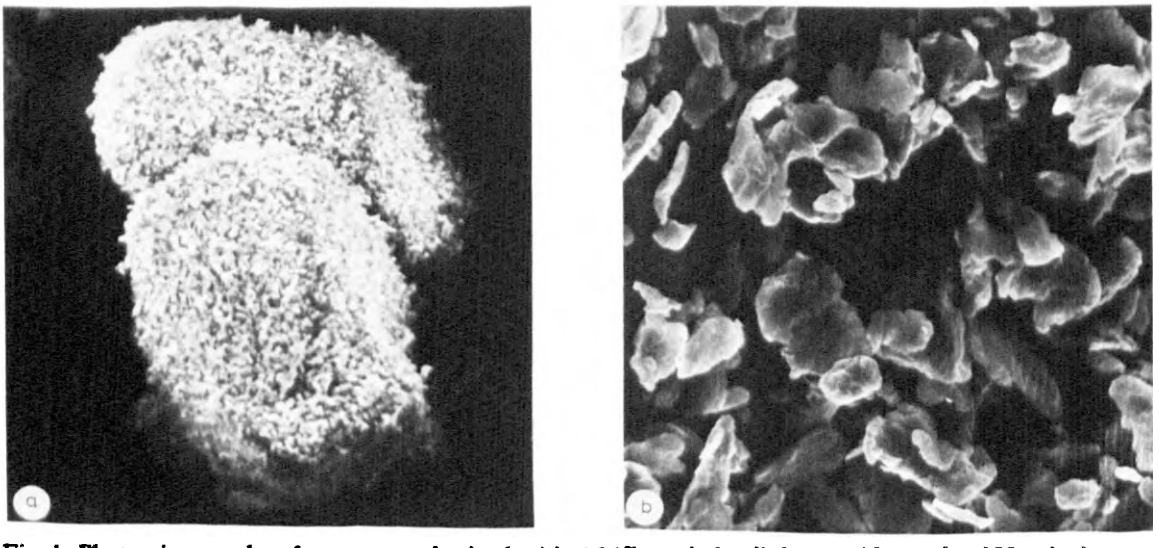


Fig. 1. Photomicrographs of paracetamol mixed with 4.24% methyl cellulose <10 μm for 100 min in a Turbula Mixer: a, low magnification; b, high magnification.

Measurement of tablet strength

The tablets were stored at 20°C, 45% RH for one week before being measured in a Heberlein diametral compression test apparatus (2E/205, Schleuniger, Switzerland). All tablets showed approximately normal tensile failure and the radial tensile strength was calculated according to Fell and Newton (1968). The mean values for ten tablets are given.

Results and discussion

Fragmentation propensity of compounds

Photomicrographs of the 4 compounds taken before and after compression are presented in Fig. 2. Lactose deformed to a large extent by fragmentation whereas no such effect could be observed for sodium chloride, which is in agreement with earlier findings (e.g. de Boer et al., 1978; Cole et al., 1975; Hersey and Rees, 1971). Both paracetamol and ascorbic acid appear to deform by fragmentation to a large extent.

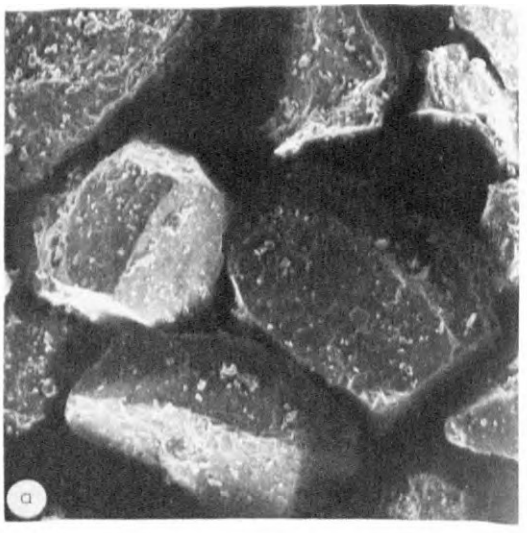
Effect of binder addition on tablet strength

Results from mixtures of paracetamol and 10% binder are presented in Fig. 3. The tablet strength increased with increasing compaction load for all of the binder fractions used. The particle size of the binder had a significant effect on tablet strength at all 3 compaction loads. In all the following experiments the compaction load was 110 MPa.

The tablet strength of lactose, paracetamol and ascorbic acid increased with increasing concentration of binder (Fig. 4). For sodium chloride, however, small additions of methyl cellulose decreased the mechanical strength, whereas an increase was found at high binder concentrations. For all compounds, a decrease in particle size of the binder resulted in tablets of higher mechanical strength. It seems, therefore, that not only the amount of binder is important, but also the degree of surface coating. In order to investigate if the latter was better correlated to the binding effect than the amount of binder, the tablet strength was plotted against the surface area ratio (Fig. 5). For paracetamol and ascorbic acid the results showed a reasonably good straight line correlation up to a surface area ratio of around unity (correlation coefficients of 0.961 and 0.904, respectively). Although the values for higher ratios are few, binder additions in excess of the amount needed for a monoparticular layer tend to have less effect on tablet strength.

The other two materials did not give a similar correlation. In lactose tablets the finest fraction had less effect than would be expected from the surface area ratios. Since this was not due to a poor de-agglomeration of the binder, it may be due to a different behaviour of lactose during compaction. The extensive fragmentation creates a large number of fresh, uncoated surfaces which may reduce the effects of added excipients as shown for lubricants by de Boer et al. (1978).

Sodium chloride, which does not deform by fragmentation, is more sensitive to the additions of lubricants (de Boer et al., 1978) and this was also the case for methyl cellulose additions. The correlation to the surface area ratio was poor, however.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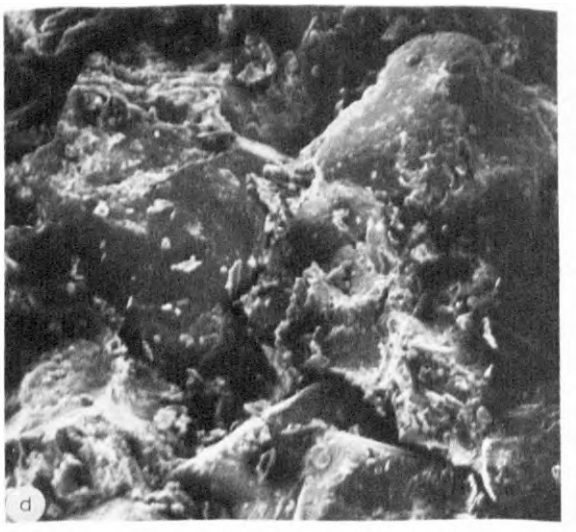
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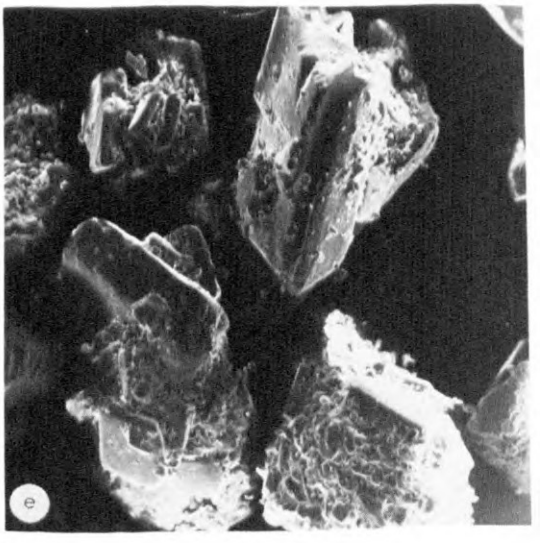
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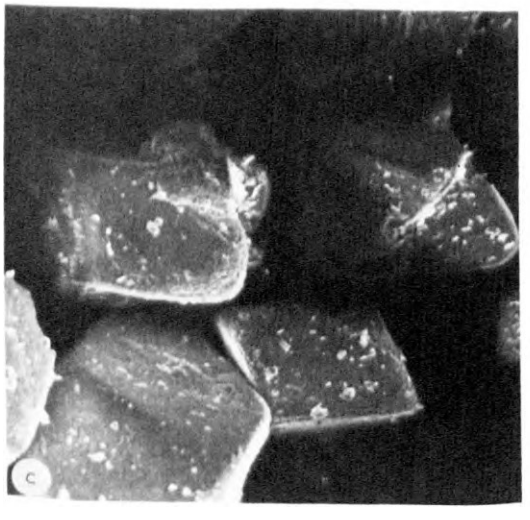
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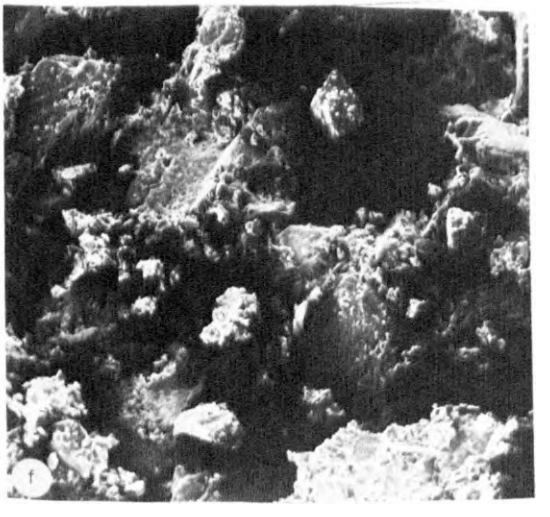
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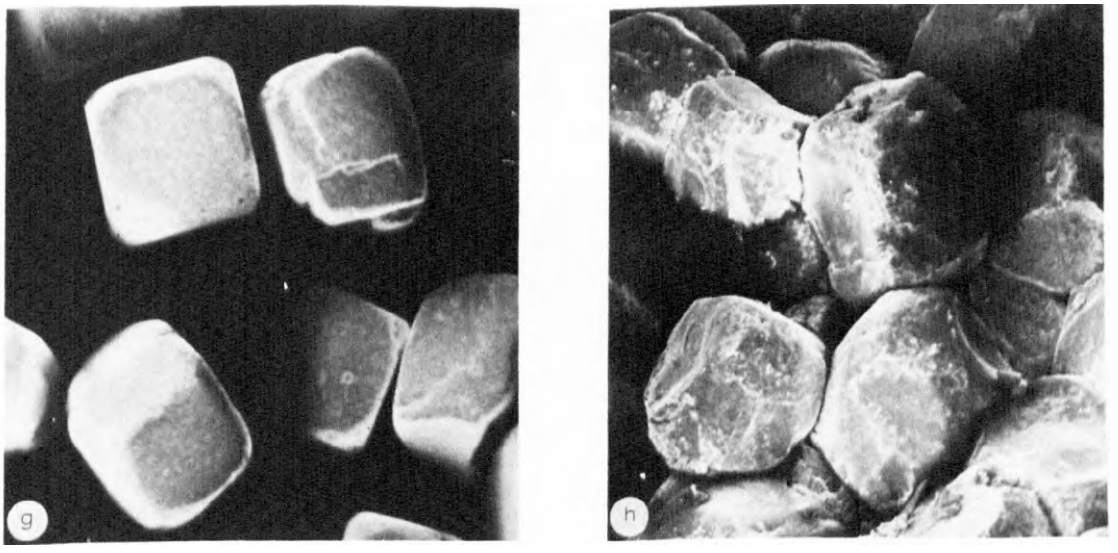

Fig. 2. Photomicrographs of compounds: a and b, lactose; c and d, paracetamol; e and f, ascorbic acid; g and h, sodium chloride, before and after compression, respectively.

Small additions of all fractions except the finest one decreased the bonding, which appears surprising as higher amounts increased the strength again. The finest fraction increased the strength considerably even at very low concentrations.

A plausible explanation for this behaviour is the elastic recovery of the sodium chloride tablets induced by the coarse fractions of methyl cellulose (see Table 4). The strength of the tablets is determined by the sum of all bonds in the tablet, i.e. between sodium chloride particles and between sodium chloride and methyl cellulose particles. The good tablet strength at high concentrations of the binder indicates that the latter type of bond is strong. Also the bonds between sodium chloride particles are fairly strong (see Fig. 4). The increased elastic recovery induced by the methyl

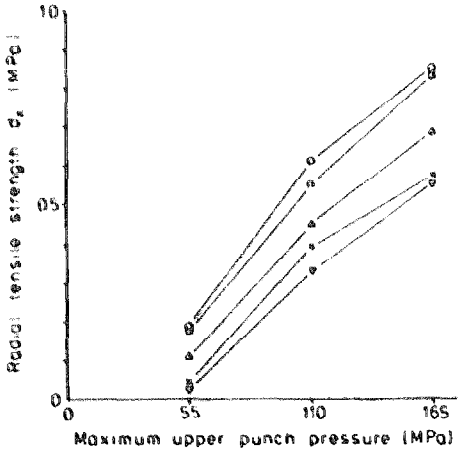

Fig. 3. Tablet strength of paracetamol mixed with 10% of the different methyl cellulose fractions at 3 different compaction loads: ○, < 10 μm; □, 10–20 μm; △, 20–30 μm; ▽, 30–50 μm; x, raw material.

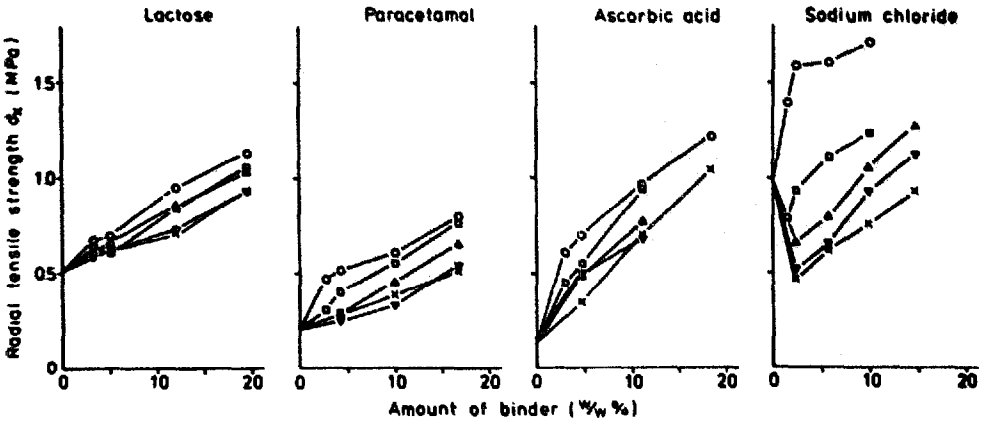

Fig. 4. Tablet strength of lactose, paracetamol, ascorbic acid and sodium chloride mixed with different amounts of methyl cellulose fractions: O, <10 μm; □, 10–20 μm; △, 20–30 μm; ▽, 30–50 μm; x, raw material.

celluiose particles reduces the number or the strength of these bonds and the resulting tablet is weaker. Not until the number of bonds including methyl cellulose is large enough will the tablet strength be improved by the addition of the binder. This can be achieved by increasing the concentration or reducing the particle size. Smaller particles will probably induce less elastic strain than bigger particles and the effect of the particle size is therefore pronounced.

In direct compression of larger amounts of an active compound, the addition of dry binders could be used to improve tablet strength. Especially when the interparticulate bonds between the compound crystals are weak, as in the case of ascorbic acid, a surface treatment with a finely divided binder could strongly improve the tablet strength. The mechanism of a binder like methyl cellulose is then to form

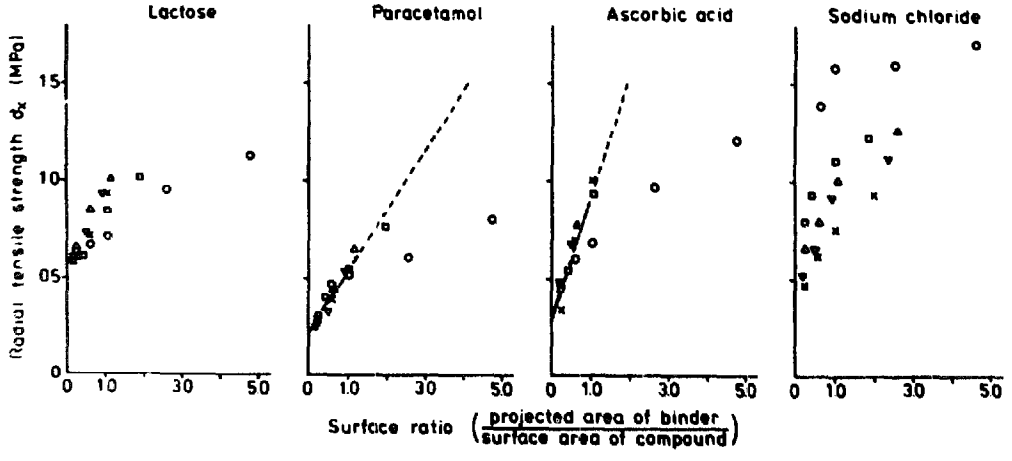

Fig. 5. Tablet strength of lactose, paracetamol, ascorbic acid and sodium chloride mixed with the different methyl cellulose fractions: O, <10 μm; □, 10–20 μm; △, 20–30 μm; ▽, 30–50 μm; ×, raw material, where the binder additions are expressed as surface area ratios.

TABLE 4

POROSITY OF TABLETS OF SODIUM CHLORIDE AND MIXTURES WITH 2.36% METHYL CELLULOSE COMPRESSED AT 110 MPa

Size fraction of methyl cellulose (μm)	Porosity [a] during maximum pressure	Porosity after 7 days	Elastic [b] expansion (%)
-	0.113	0.134	18.5
<10	0.114	0.134	17.5
10–20	0.115	0.138	20.2
20–30	0.121	0.148	22.2
30–50	0.119	0.149	24.8
Raw material	0.120	0.148	23.1

[a] Measured with the aid of an inductive displacement transducer.
[b] Mean values of 15 tablets.

stronger bonds between the particles in the tablet. The bonds should also be strong enough to allow the stress relaxation to occur without breakage. The larger the number of binder particles and surface coverage the stronger the resulting tablet will be. Apart from the particle size, the surface coverage will depend on the de-agglomeration of the binder and adhesion to the tablet particles. Fragmentation of the particles during the tablet compaction will also reduce the surface coverage.

Acknowledgements

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