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Studies on direct compression of tablets. XXII. Investigation of strength increase upon ageing and bonding mechanisms for some plastically deforming materials

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Summary

Strength increase as a function of time has been measured for tablets of five plastically deforming materials. The addition of small amounts of magnesium stearate was also tested for all materials in this context. The effect of ageing was evaluated by measuring the radial tensile strength immediately after compression and again after 2 days storage. The contribution of bonding with intermolecular forces as compared to bonding with solid bridges capable of penetrating the lubricant film was evaluated. Stress relaxation resulting in increased areas of interparticulate attraction was suggested to be a common denominator for strength increase in the unlubricated compacts. Solid bridges contributed to the strength increase upon ageing only for sodium chloride. Bonding with intermolecular forces seems in general to be the dominating bonding mechanism for the investigated materials.

Introduction

Tablet strength depends on a large number of both material and processing parameters. Normally, it is difficult to evaluate the tablet mechanical strength in terms of bonding mechanisms.

According to Rumpf (1962), particles can be kept together by a number of mechanisms. For pharmaceutical tablets Führer (1977) has proposed three major interparticulate bonds: solid bridges, intermolecular attraction forces and mechanical interlocking. Bonding with solid bridges is dependent on surfaces coming in real

contact, while intermolecular forces can be described in a simplified manner as weak forces which attract particles separated by a large distance compared with chemical bond distances to each other (Nyström and Karehill, 1986; Karehill et al., 1990; Karehill and Nyström, 1990).

Earlier studies on pharmaceutical materials at our laboratory (Nyström and Karehill, 1986; Karehill et al., 1990; Karehill and Nyström, 1990) have shown that intermolecular forces are normally the dominating bond mechanism. Coarse fractions of sodium chloride, which is a commonly used material in tableting studies, seem to be an exception here, i.e. solid bridges appear to play an important role for sodium chloride. In the earlier studies, use was made of the sensitivity of intermolecular forces to changes in the media between attracting particles. In two studies (Nyström and

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Karehill, 1986; Karehill et al., 1990), the addition of a lubricant film to the test particles was used to reduce the strength of intermolecular forces, since it was assumed that the effect on solid bridges was much less pronounced. Another means to gain information about dominating bond mechanisms in pharmaceutical compacts could be to study changes in compact strength as a function of time.

Strength increase as a function of time has been frequently reported for sodium chloride (e.g. Rees and Shotton, 1970). Ageing time is defined as the time between compaction and compact characterization (Nyström and Karehill, 1986). Several different methods such as changes in sound emission and in permeametry surface area have been utilized for the investigation of strength increase upon ageing (Rue and Barkworth, 1980; Nyström and Karehill, 1986). The conclusion from the sound emission study was that the strength increase was directly proportional to the number of emitted sounds. This indicates that significant increase in compact strength could be due to surfaces moving in closer proximity to each other. When monitoring the changes in permeametry surface area with strength increase in sodium chloride compacts, no surface area changes were detected. This could be explained if the initial strength was due to bonding with both intermolecular forces and solid bridges, followed by a time-dependent increase in strength mainly due to a continuous formation of intermolecular forces. This latter bonding mechanism would then be active over a relatively long distance and at the same time be very sensitive to changes in the distance between the surfaces, thus resulting in an almost constant compact permeability during the ageing period, when these bonds are established.

By comparing the change in strength with ageing for both unlubricated and lubricated materials it may be possible to characterize the relative contribution of solid bridges and intermolecular forces respectively, to the change in tablet strength. For a compact prepared from a plastically deforming non-fragmenting material, which is completely coated by a lubricant film, solid bridges penetrating the film can be regarded as the dominating bonding mechanism (Bowden and Tabor, 1950; Karehill et al., 1990). Strength in-

crease as a function of ageing for such lubricated materials will then primarily be due to an increased bonding by solid bridges.

The objective of this study was thus to investigate the extent to which strength changes in some pharmaceutical compacts upon ageing are caused by formation of solid bridges or intermolecular forces. A further aim was to obtain more information about dominating bond mechanisms in pharmaceutical compacts in general.

Experimental

Materials

Materials undergoing plastic deformation, and thus possessing a low degree of fragmentation during compaction, were chosen as test substances.

Sodium chloride (cubic crystalline, puriss, Kebo-Grave, Sweden) was fractionated by dry sieving to obtain the fractions 425–500 and 250–355 μm . From the fraction 250–355 μm a finer size fraction ($< 63 \mu\text{m}$) was prepared by milling the material in a pin disc mill (Alpine 63 C, F.R.G.). Iron (powder, puriss, Kebo-Grave, Sweden) was used as supplied.

Sodium bicarbonate (puriss, Ph. Eur., Kebo-Grave, Sweden) was fractionated by dry sieving to obtain the fraction 90–150 μm .

Sta Rx[®] 1500 (Colorcon Inc., U.S.A.) was fractionated by dry sieving to obtain the fraction 90–150 μm .

Avicel[®] PH 101 (FMC, U.S.A.) was used as supplied.

Magnesium stearate (Ph. Nord) was used as supplied. This lubricant represents an additive known to reduce compact strength (De Boer et al., 1978).

The primary characteristics of test materials are presented in Table 1.

Methods

Density

The density was measured with an air comparison pycnometer (model 930, Beckman, U.S.A.). Results presented are mean values of three determinations.

TABLE 1

Primary characteristics of test materials

Material (-)	Density ^a (-)	Specific surface area ^b (cm ² /g)	Magnesium stearate ^c concentration (% w/w)
Avicel PH 101	1.54	3490	-
Sodium chloride < 63 μm	2.17	925	0.005
Sodium chloride 250-355 μm	2.17	100	0.01
Sodium chloride 425-500 μm	2.17	65	0.1
Sodium bicarbonate 90-150 μm	2.16	797	0.02
Sta Rx 1500 90-150 μm	1.46	760	0.05
Iron	7.86	850	-

^a Measured with an Air Comparison Pycnometer Model 930 (Beckman, U.S.A.).

^b Measured with a Blaine permeameter according to Alderborn et al. (1985).

^c Amount lubricant admixed, prior to characterization of strength increase in lubricated compacts.

Specific surface area

A Blaine permeameter was used as described by Alderborn et al. (1985). The powder samples were compressed to a powder plug in a metallic adapter connected to the Blaine apparatus. The specific surface area was calculated as described earlier (Alderborn et al., 1985), using terms for both viscous and molecular flow. For the two coarsest fractions of sodium chloride, powder plugs with a diameter of 9.86 mm and a height of 100 mm were used (Eriksson et al., 1989). The calculation of surface area was then based on the assumption of a pure viscous gas flow through the plug. Results presented are mean values of three determinations.

Admixing of magnesium stearate

Small amounts of magnesium stearate were mixed with the powders (50 g) in a Turbula mixer at 90 rpm (W.A. Bachofen, Switzerland) for 3000 min. The long mixing time was chosen in order to ensure the adequate deagglomeration of the lubricant, and also to cause attrition of the magnesium stearate primary particles in order to obtain a molecular film around the compound particles (Bolhuis et al., 1975; Karehill et al., 1990). Magnesium stearate was added in amounts sufficient to provide an approximately monomolecular coat for each test substance, as described earlier (Karehill et al., 1990). For all materials and size fractions the additions ranged between 0.005 and 0.25% w/w (Table 1), corresponding to 0.25-1.0

μg magnesium stearate per cm² test material (Karehill et al., 1990).

Powder compression

All powders and powder mixtures were stored for not less than 2 days at 20°C and 40% relative humidity. Compacts were then made in an instrumented single punch press (Korsch Ek 0, F.R.G.) using flat-faced punches with a diameter of 1.13 cm.

Before each compaction by motor, the die and punch faces were lubricated with a suspension of 1% w/w magnesium stearate in ethanol. The powder for each tablet was weighed on an analytical balance and the die was then filled manually. Each compact was prepared by starting the motor when the upper punch was in its extreme upper position. Immediately after ejection the motor was stopped and the compact collected. This procedure gave an almost constant load rate, corresponding to a machine speed of 30 rpm and a consolidation time of approx. 150 ms. All specimens were compacted at 150 MPa.

Characterization of compact strength

After compaction, the height of the tablet was measured before strength characterization. The time between compaction and initial strength characterization was thus 10-15 s. The clock was started when the upper punch was in its lowest position and stopped when the tablet was crushed in the diametral compression test apparatus.

Tablets of all materials were also stored for 2 days at 20 °C and 40% relative humidity before compact characterization. This storage procedure has special importance since the relative humidity has been shown to influence the compact strength for sodium chloride tablets (Down and McMullen, 1985; Ahlneck and Alderborn, 1989a,b).

All compacts were measured for crushing strength in a Heberlein diametral compression test apparatus (TBH-28, Erweka, F.R.G.). Since all compacts showed approximately normal tensile failure, the radial tensile strength was calculated (Fell and Newton, 1970). Results presented are mean values of at least 10 determinations.

Results and Discussion

The tablet tensile strengths for pure as well as lubricated compounds are summarized in Figs 1 and 2.

For two of the materials tested, iron and Avicel® PH 101, no significant ($P < 0.05$) strength increase as a function of ageing could be detected for either unlubricated or lubricated samples.

Strength increase upon ageing for unlubricated materials

The highest strength increase for sodium chloride, in absolute terms, was obtained for the fraction $< 63 \mu\text{m}$, followed by the fractions 425–500 and 250–355 μm . This is in good agreement with the rank order of the total compact strength of these sodium chloride fractions.

Sodium bicarbonate showed a major increase as a function of ageing. However, the absolute strength was low, indicating that interparticulate attraction is related to a weak bond type.

Sta-Rx® 1500 showed a similar pronounced increase for the unlubricated material with time.

For two of the materials, iron and Avicel® PH 101, no significant increase in strength was monitored. These materials gave tablets of relatively high strength. However, this does not appear to be a prerequisite for the absence of strength increase upon ageing, since the finest fraction of sodium chloride also produced a high tablet strength.

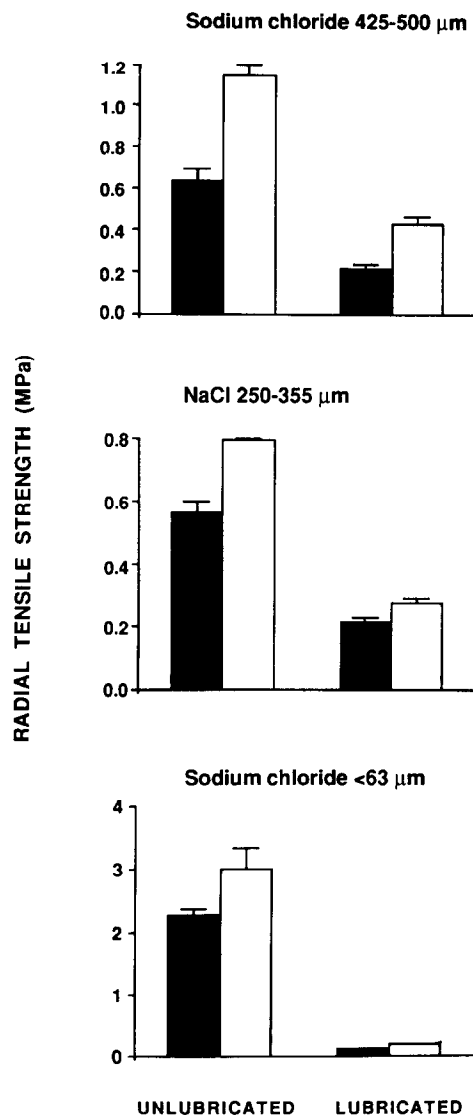


Fig. 1. Tablet tensile strength of unlubricated and lubricated fractions of sodium chloride. Compact strength measured directly after compaction (closed columns) and after 2 days storage (open columns). Error bars represent confidence intervals of the mean for 95% probability.

Lordi and Shiromani (1984) have found that the crushing strength increased with ageing, e.g. for the case of sodium chloride compacts stored at elevated humidities. The increase reached a maximum value in the region of deliquescence and then decreased. This phenomenon has been suggested to be caused by recrystallization (Down

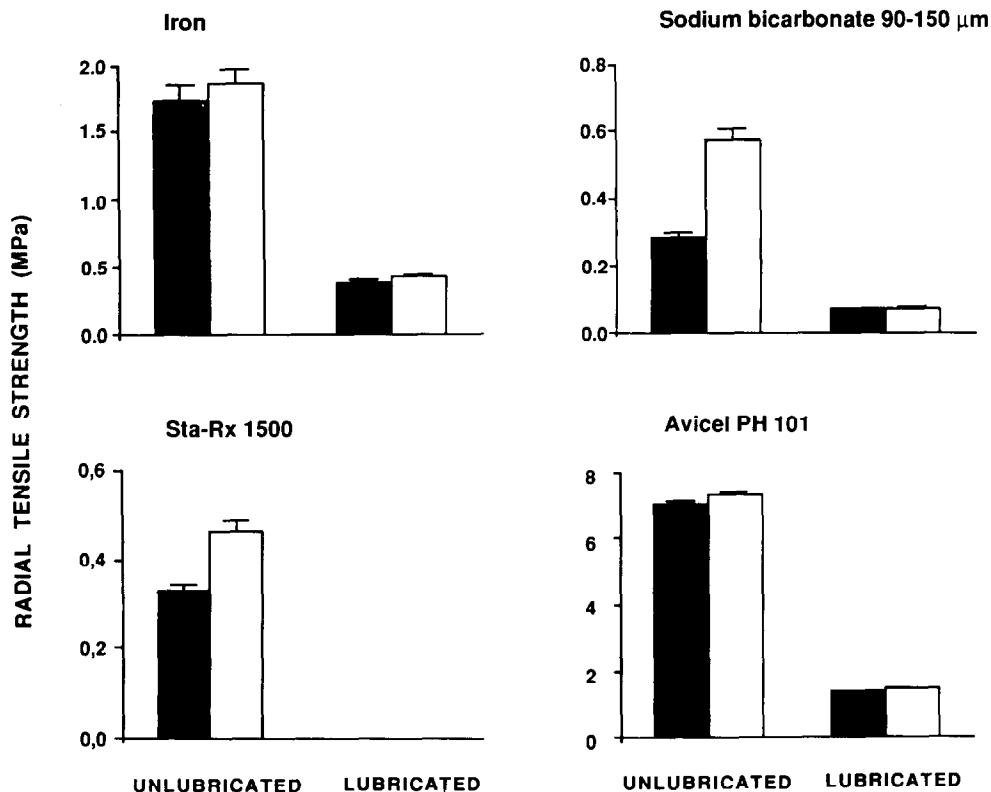


Fig. 2. Tablet tensile strength of unlubricated and lubricated fractions of iron, sodium bicarbonate, Sta-Rx[®] 1500 and Avicel[®] PH 101. Symbols as in Fig. 1.

and McMullen, 1985) or molecular rearrangement (Ahlneck and Alderborn, 1989b) of the material which is readily soluble in water. The crushing strength of sodium chloride was relatively unaffected up to approximately the same relative humidity as used in this study, i.e. 40% (Down and McMullen, 1985). The materials used in this study have different solubilities in water. Iron, Sta-Rx[®] 1500 and Avicel[®] PH 101 are insoluble in water. Sodium bicarbonate and the three fractions of sodium chloride are highly soluble in water. It seems therefore that the results obtained in this study are not primarily related to interactions with water.

Since all the materials used were chosen to represent plastically deforming rather than fragmenting materials, differences in volume reduction mechanisms do not appear to provide a rea-

sonable explanation for the different behavior of iron and Avicel[®] PH 101 from the rest of the test materials.

However, a possible prerequisite for strength increase is a time-dependent stress relaxation as proposed by Rees and Shotton (1970). For both sodium chloride (Rees and Shotton, 1970; Rue and Barkworth, 1980) and Sta-Rx[®] 1500 (Rees and Rue, 1978) an increase in strength with ageing has been shown to be due to stress relaxation within the compacts. By means of plastic flow of tablet particles, surfaces are brought into closer proximity, thereby increasing interparticulate attraction. On the other hand, a minute stress relaxation has been demonstrated for iron at room temperature, whereas at high temperatures it may show large stress relaxation although the load is equivalent (Ford and Alexander, 1963). From this

point of view, iron ought to exhibit very little strength increase as a function of ageing, as was indeed found in this study.

A relatively limited stress relaxation has been reported for Avicel® PH 101 also (David and Augsburg, 1977). Although no direct measurements have been conducted on sodium bicarbonate, it has been reported to possess similar volume reduction behavior to sodium chloride (Duberg and Nyström, 1986). Thus, plastic flow induced by stress relaxation after ejection seems to be a reasonable prerequisite for strength increase upon ageing when no water-related effects are at hand (Nyqvist et al., 1981). Furthermore, the phenomenon does not seem to be restricted to any specific bonding strength or mechanism of the tablet when newly formed. The increase in strength is found in both weak and strong compacts as well as in materials bonding with solid bridges (sodium chloride), and with intermolecular forces (e.g. Sta-Rx® 1500) (Karehill and Nyström, 1990; Karehill et al., 1990).

Comparison between unlubricated and lubricated materials and possible mechanisms responsible for strength increase upon ageing

The differential increases in tablet strength, in absolute terms, for both unlubricated and lubricated materials are presented in Fig. 3.

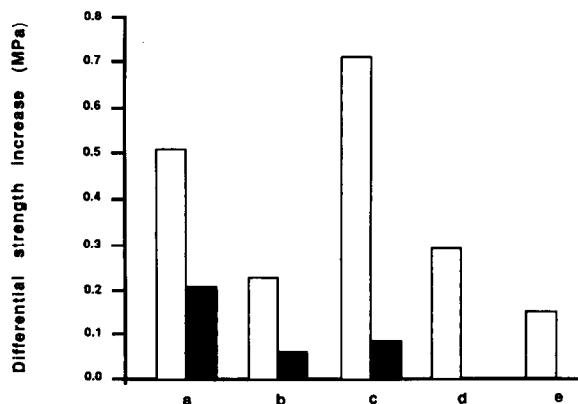


Fig. 3. Differential strength increase for unlubricated (open columns) and lubricated (closed columns) tablets. (a) Sodium chloride 425–500 μm; (b) sodium chloride 250–355 μm; (c) sodium chloride < 63 μm; (d) sodium bicarbonate; (e) Sta-Rx® 1500.

Sodium chloride

A somewhat different order was found for the lubricated sodium chloride fractions as compared to the unlubricated samples as shown in Figs 1 and 3. For sodium chloride > 63 μm the addition of lubricant resulted in a pronounced reduction in compact strength, irrespective of the measuring time. Consequently, the absolute change in strength as a function of time was much less than for the unlubricated system. However, the monitored strength increases for all lubricated fractions (Fig. 3) indicate that particulate sodium chloride is able to form bonds despite the magnesium stearate film. This could be explained if sodium chloride during strength increase upon ageing formed solid bridges penetrating the lubricant film. This is in good agreement with results from an earlier study where the bonding mechanisms for these three fractions were evaluated (Karehill et al., 1990). It was then concluded that intermolecular forces is the dominating type of bond for the unlubricated compacts. For the lubricated sodium chloride compacts it was concluded that bonding with solid bridges is the dominating bonding mechanism.

Sodium bicarbonate

The increase in strength monitored for the unlubricated sample is absent for the lubricated powder (Figs 2 and 3). This suggests that bonding with solid bridges plays a minor role for this material. This is probably due to the crystallographic structure of the material. It consists of long one-dimensional chains of HCO₃ (Greenwood and Earnshaw, 1984) and bonding with solid bridges is not likely to occur.

Sta-Rx® 1500

No significant increase in strength was achieved for the lubricated compacts of Sta-Rx® 1500 (Figs 2 and 3). The explanation is probably the same as for sodium bicarbonate, i.e. in the unlubricated compact only intermolecular forces are present and these are totally excluded by the lubricant film.

The explanation for the differences in strength increase with ageing for unlubricated as well as lubricated fractions is thus suggested to be the

relative contribution of different bonding mechanisms. The strength increase could then be bonding with both solid bridges and intermolecular forces in different proportions. The strength increase for the unlubricated compacts is assumed to be caused by both bonding mechanisms. However, bonding with intermolecular forces is thought to be filtered out by the lubricant in the lubricated compacts and an increased compact strength with ageing is considered to be due to bonding with solid bridges penetrating the lubricant film. The validity of these assumptions depends on a total surface coverage by magnesium stearate at the contact points and the establishment of bonding with solid bridges, even in the presence of a lubricant film, by protrusions penetrating the film. The first prerequisite is discussed in some detail in a previous paper (Karehill et al., 1990). The possibility of forming continuous molecular films by a dry mixing process is supported by several independent studies (e.g. Bolhuis et al., 1975; Pintye-Hódi et al., 1981). The latter prerequisite is normally fulfilled for surfaces separated by a boundary lubricant such as magnesium stearate at high loads, i.e. the film breakdown and the surface protrusions penetrate the film and make contact (Bowden and Tabor, 1950). Another factor of importance is that these contact points are regarded as being formed initially in the compaction process and then develop continuously during the ageing period.

From the data in Fig. 3, it can be seen that the two coarse sodium chloride compacts have approx. 30–40% solid bridges. The fine particulate sodium chloride has approx. 10% bonding ascribed to solid bridges, indicating that the strength increase for sodium chloride upon ageing depends on bonding with solid bridges as well as intermolecular forces. Values close to zero were obtained for both sodium bicarbonate and Sta-Rx[®] 1500.

In principle, it cannot be excluded that the incorporation of a magnesium stearate film could reduce the stress relaxation to a varying degree for the materials tested. Rees and Rue (1978) investigated the stress relaxation for sodium chloride, Sta-Rx[®] 1500, anhydrous lactose, Elcema and Emcompress with and without magnesium

stearate. For most materials the lubricant seemed to have little effect on stress relaxation. The main difference was seen for sodium chloride which showed less total stress relaxation when the compact contained lubricant. In the present study, the only material that retained an increase in strength upon ageing after lubrication was sodium chloride. Thus, it seems unlikely that a reduction in stress relaxation could be proposed as the explanation for the obtained results.

General bonding mechanisms for test materials

By evaluation of strength increases in both unlubricated and lubricated materials, it seems possible to obtain a fairly good characterization of the bonding mechanisms taking part during ageing. From these data some interpretations could also be made regarding general bonding mechanisms for the test materials.

For sodium bicarbonate and Sta-Rx[®] 1500 the magnesium stearate film seems mainly to function as a medium that reduces bonding with intermolecular forces. The bonding mechanism responsible for strength increase upon ageing and for the compact strength in general for both these materials seems thus to be intermolecular forces.

The strength increase for sodium chloride upon ageing is due primarily to changes in two main bonding mechanisms i.e. bonding with intermolecular forces and solid bridges. Bonding with solid bridges is enhanced here by local plastic deformation at the points of contact which probably play an important role as anchor points for additional bond formation, caused by intermolecular forces. The results for the unlubricated sodium chloride fractions indicate that, for this compound, the strength increase upon ageing may be influenced by the same bonding mechanisms responsible for the compact strength at equilibrium. Bonding with intermolecular forces is, according to this, the dominating bonding mechanism. The contribution of solid bridges is substantial for all three fractions, but the relative importance is decreased with a decrease in particle size. As has been discussed in previous papers, it seems likely that the absolute amount of surface area taking part in solid bridges is relatively small but constant and

independent of particle size (Karehill et al., 1990; Karehill and Nyström, 1990). This latter suggestion is supported by the similarity in differential strength increase found for the lubricated compacts (Fig. 3).

For two of the materials, iron and Avicel® PH 101, no significant changes in compact strength were obtained and consequently no conclusions are possible from this study regarding general bonding mechanisms for these materials.

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