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The effect of milling and addition of dry binder on the interparticulate bonding mechanisms in sodium chloride tablets

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Abstract

In sodium chloride compacts, it has been reported that particles within the tablet are held together both by weak distance forces and solid bridges. It was found that milling of the particles or addition of a dry binder appears to reduce the importance of bonding by solid bridges while increasing that of the weak distance forces. Such changes in the surface properties of the particles induced either by milling or addition of a dry binder will not only increase the surface area available for bonding but also increase the number of interparticulate contact points in the compact and, consequently, reduce the stress at each contact point. It is suggested that this reduction in the concentration of stress makes rearrangement of material at the particle surfaces, and thus the development of solid bridges, more difficult. Similarly, it is suggested that milling will increase the surface deformability of asperities on the sodium chloride particles which will also disperse the concentration of stress within the compacts. The changes in the properties of the particle surface also affect fracture propagation during the diametral compression test. If it is assumed that cracks mainly occur between particles, milling will probably increase the distance the fractures will run. © 1998 Elsevier Science B.V.

Keywords: Bonding mechanism; Dielectric constant; Dry binder; Liquid; Milling; Remaining tensile strength; Sodium chloride; Tablet

1. Introduction

Pharmaceutical compacts are held together by interparticulate bonds. Three different bonding types are commonly discussed in the literature: weak distance forces (e.g. van der Waals forces, hydrogen bonds and electrostatic forces), solid bridges and mechanical interlocking (Führer, 1977). Weak distance forces are believed to be the dominating bonding type for pharmaceutical ma-

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terials (Nyström et al., 1993). However, it is possible that solid bridges are created during the compaction of some materials. Interparticulate solid bridges consist of the same type of bonds that hold the molecules/ions together into a particle. The nature of these solid bridges is thus dependent on the chemical structure of the material (Olsson et al., 1996; Adolfsson et al., 1997). Mechanical interlocking may occur primarily in materials with a rough surface texture and/or irregular shape and is believed to be an important method of bonding in microcrystalline cellulose (Nyström et al., 1993). In addition to the type of interparticulate bonding, the area over which these bonds are active also affects the strength of pharmaceutical compacts.

It has been reported that the strength of the tablet depends on the original size of the tablet particles (Alderborn and Nyström, 1982b). Normally, a decrease in particle size results in an increase in surface area available for bonding and, consequently, increases tensile strength in the pharmaceutical compact. However, the new surfaces created cannot be utilised for establishment of interparticulate bonds in all materials. For example, sodium chloride, a material with plastic deformability characteristics (Nyström et al., 1993), has on the contrary been reported to show an increase in tensile strength with increase in particle size (Alderborn and Nyström, 1982b). This may be explained by the enhanced capacity for sodium chloride to develop strong interparticulate bonds during compaction, when larger particles (representing fewer interparticulate contact points) are used. Sodium chloride compacts are thus believed to be held together mainly by weak distance forces but also by solid bridges, the latter consisting of ionic bonds (Karehill and Nyström, 1990). Further, because of the relatively small distances between particles within the tablet when held together by solid bridges, powerful weak distance forces may develop in the neighbourhood of the ionic bonds. For extensively fragmenting materials, the initial particle size does not normally affect the tensile strength significantly (Alderborn and Nyström, 1982b).

For solid bridges to develop between particles, the material must have certain physicochemical and mechanical properties. When the volume reduction behaviour of a pharmaceutical material is studied, it is usually the bulk deformability of the material that is examined, using, for example, Heckel plots (Nyström et al., 1993). However, the surface deformability of the materials is also expected to affect the interparticulate interactions (Eriksson and Alderborn, 1995).

At a microscopic level, all particle surfaces have an irregular surface texture and high local stresses are probably created between these asperities in contact during compaction. Friction and high local stresses created during compression may result in hot spots within the compact, allowing melting or advanced diffusion of material to take place (Rankell and Higuchi, 1968; Jayasinghe et al., 1969/1970). This probably means that the crystal structure, and consequently the melting point of the material, affect the type of interparticulate bond that can develop during compaction. For solid bridges to develop between them, the distance between the particles must be small and the particles must orient correctly. When the particle size increases, the stress at each such interparticulate contact point when compacted also increases, and it is thus expected that an increase in particle size will favour creation of high energy centres in some materials. At high pressure, large stresses created by compaction are also expected to favour development of solid bridges during compaction, facilitating rearrangement of material at interparticulate contact points (Nyström et al., 1993).

When a crystalline material such as sodium chloride is milled, not only does the surface area of the powder increase but also many particles become cracked or develop defects (Hüttenrauch, 1977; Alderborn and Nyström, 1982a; Elamin et al., 1994). Thus, a more disordered surface structure created an increased mobility of the ions in the surface layer. This change will affect the volume reduction behaviour of the particles and the deformability of the surface layer of the particle will probably also increase (Hüttenrauch, 1977). The change in surface properties by milling will probably affect the interaction between particles under compaction. The disordered state is a high energy state and, over time, recrystallisation of the disordered structure may take place, but this

Table 1
Characteristics of the test materials

Material	Size fraction (μm)	Density[a] (g/cm^3)	Surface area (cm^2/g)
Sodium chloride (unmilled)	250–355	2.152 (0.000)	98.7 (1.1)[b]
Sodium chloride (milled)	250–355	2.152 (0.000)	122.1 (1.2)[b]
Microcrystalline cellulose	Raw material	1.547 (0.003)	7470 (390)[c]

Standard deviations are given in parentheses. Average values for at least two measurements are presented.
[a] The density was measured on the raw material
[b] Determined with a transient permeameter according to Eriksson et al. (1990).
[c] Determined with a Blaine apparatus.

transformation may be rather slow (Hüttenrauch, 1977; Alderborn and Nyström, 1982a).

When a fine particulate dry binder is added to a drug of coarse quality, the carrier particles will be covered by the binder. The addition of dry binder is normally expected to increase the tensile strength of a pharmaceutical compact compared with compacts of the pure carrier material (Nyström et al., 1982; Duberg and Nyström, 1985; Nyström and Glazer, 1985). Normally, the dry binder covering the drug particles increases and changes the nature of the surface area available for interparticulate bonds (Nyström et al., 1982). Addition of dry binder may also decrease the tensile strength if increased elasticity is induced and if relatively few interparticulate bonds survive the decompression phase.

If a compact of pure sodium chloride is held together by weak distance forces and ionic bonds, then the ionic bonds between tablet particles can probably penetrate the dry binder film around the sodium chloride particles and add additional strength to the compact (Duberg and Nyström, 1985). However, the binder particles may also prevent the sodium chloride particles making contact and becoming orientated correctly to allow creation of solid bridges (Nyström et al., 1982).

To study interparticulate bonding mechanisms in sodium chloride tablets, compaction and strength characterisation were performed in both air and liquid. The strength of a compact is expected to be reduced during compaction in liquid, because of the dielectric properties of the liquid (Karehill and Nyström, 1990; Luangtana and Fell, 1990; Olsson et al., 1996; Adolfsson et al., 1997). Therefore, since the liquid is believed to hinder development of interparticulate distance forces during compaction, the remaining tensile strength of the compact is assumed to be solely the result of solid bridges and/or mechanical interlocking.

The aim of this study was thus to evaluate the extent to which roughening or disordering the surfaces of particles (by milling or addition of a dry binder) will affect the interparticulate bonding mechanisms of coarse (250–355 μm) sodium chloride. The bonding properties were studied by compaction and strength characterisation of sodium chloride tablets in a liquid with a sufficiently high dielectric constant to nullify weak distance forces, and comparison of these data with results obtained by compaction of the tablets in air at normal room temperature and relative humidity.

2. Materials and methods

2.1. Materials

A size fraction of 250–355 μm was prepared from sodium chloride (crystalline, puriss, Kebo, Sweden). One fraction was prepared by dry sieving with ordinary laboratory sieves and the other was milled (original particle size >355 μm) with a mortar and pestle for approximately 5 min before dry sieving in order to obtain more irregular particles (Alderborn and Nyström, 1982a). The two preparation procedures resulted in different materials with varying surface areas (Table 1).

Ordered mixtures (Hersey, 1975) of the unmilled sodium chloride and the binder with a

typical particle size of 20 μm (microcrystalline cellulose; Avicel PH-105, FMC, Philadelphia, PA, USA) were then prepared. To obtain different degrees of surface coverage (surface area ratios of 0.2 and 1.0), the calculated amount of binder (Eq. (1)) was mixed in a Turbula mixer (W.A. Bachofen, Switzerland) for 100 min (Nyström et al., 1982; Nyström and Glazer, 1985). In order to evaluate the amount of binder needed to attain a certain surface coverage of the carrier particles (sodium chloride), the surface area ratio (R_S) was calculated (Eq. (1)), where $S_{carrier}$ is the weight-specific surface area (Table 1) of sodium chloride and S_{binder} is the weight-specific surface area of microcrystalline cellulose.

$$R_S = \frac{S_{binder}/4}{S_{carrier}} \quad (1)$$

The particle density (BS 2955, 1958) of the raw binder was measured with a helium pycnometer (Accupyc 1330, Micromeritics, USA). The powders were then stored at 40% relative humidity for at least 2 days before compaction (Nyqvist, 1983).

2.2. Methods

All the materials were compacted at 100, 150, 200 and 250 MPa with the aid of a hydraulic press (Apex, England), equipped with a piezo-electric crystal to register the compaction pressure. The compact thickness was held constant at 3.1 ± 0.2 mm and the compaction load was changed by varying the amount of material being compacted. Compaction was performed both in air at normal room temperature and relative humidity and in 1-butanol saturated with the material being compacted (in order to counteract dissolution of the tablet during compaction). The compacts were stored in the compaction medium for 2 days before testing their strength while still immersed in the compaction medium.

The tensile strength of the compacts was then calculated according to Fell and Newton (1970). The values presented are average values of at least eight (in most cases 10) tablets. When compacted in air, the tablets were stored at 40% relative humidity at least 2 days before strength characterisation. The ratio of tensile strength in air to tensile strength in butanol (expressed as a percentage) was used as a simplified measure of the amount of solid bridges present in the compact. Further details on the compaction procedure are reported in Karehill and Nyström (1990) and Olsson et al. (1996).

3. Results and discussion

3.1. Effect of milling on bond structure of sodium chloride compacts

When compacted in air, the tensile strength of compacts prepared from milled sodium chloride was greater than that of compacts prepared from the unmilled material (Fig. 1a). It is suggested that milling increased the surface area of the particles by creating more irregular shapes and the new surfaces thus formed allowed interparticulate bonding to take place (Alderborn and Nyström, 1982a). However, on its own, the moderate increase in surface area obtained by the milling procedure (Table 1) probably cannot explain the large increase in tensile strength (Fig. 1a). Disordering of the particle surface probably causes it to become more easily deformed (Hüttenrauch, 1977). This increased mobility of the surface structure may facilitate development of bonds over a large surface area (Eriksson and Alderborn, 1995).

The changes in surface properties induced by the milling procedure would also be expected to affect the fracture propagation properties. During diametral compression testing, it is believed that the fracture mainly propagates around the particles within the tablet rather than through them (Nyström et al., 1993). The length of the fracture within a compact of a certain tablet dimension is thus expected to be a function of factors such as porosity and bonding surface area (Gren and Nyström, 1996). These factors are in turn related to the shape and size of the particles within the tablet. At a macroscopic level, since the fracture has to find its way around the particles within the compact, and because of the relatively large particle size of sodium chloride particles, the fracture in these compacts will be quite long. It is sug-

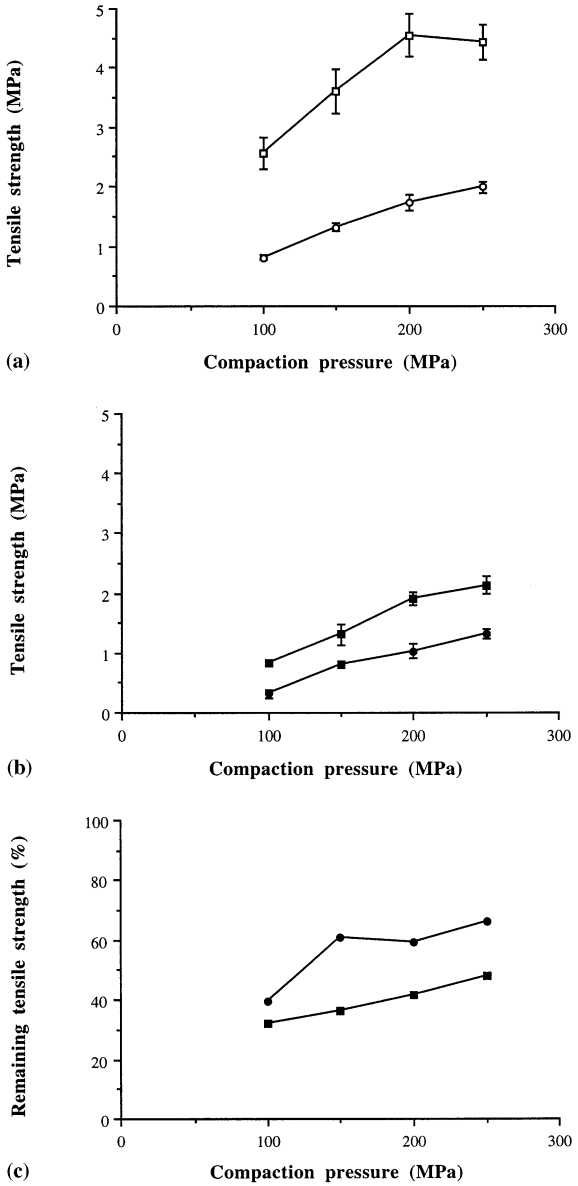

Fig. 1.

gested that at a microscopic level, the irregular shape and surface texture of the tablet particles created through the milling procedure (Table 1) will further increase the surface area where bonding may take place, and thus the distance the fracture must run: if the fracture tends to run mainly between these disordered structures, its length will probably increase. Hence, the asperities and irregular surface texture may create additional area where bonding can take place by reducing the amount of air within the fracture. For unmilled sodium chloride, the fracture is expected to be shorter since the shape and surface texture of the particles are expected to be more regular while the surface area available for bonding will be smaller.

The large decrease in tensile strength for compacts of the milled material when compacted in 1-butanol (Fig. 1b) indicates that the high tensile strength obtained at ambient condition is mainly due to weak distance forces, and not due to creation of strong ionic bonds between the particles. The high surface deformability of the milled sodium chloride particles probably makes it possible for the particles to get into close contact over large zones. An increase in compaction load will increase the remaining tensile strength of the system, indicating that an increased stress in the contact points will be utilised to create stronger bonds (Fig. 1c). However, the tensile strength of the compacts prepared from milled materials in air levelled off at 200 MPa, i.e. when the load was increased sufficiently, a limit was reached in the ability to form new bonds.

If surface deformability under pressure is too extreme, it may counteract the creation of solid bridges during compaction, because higher stresses may not be possible in the contact areas if the material is too deformable. Development of large stresses in contact zones are probably a prerequisite for formation of ionic bond between particles if the movement of solid material is not mediated by a solvent, by e.g. dissolution and recrystallisation taking place (Nyström et al.,

Fig. 1. Compacts of unmilled and milled sodium chloride (250–355 μm) compacted in different media. Confidence intervals for $p = 0.05$ are given in (a) and (b). (a) Tensile strength as a function of compaction pressure. Compaction and strength characterization performed in air at normal temperature and relative humidity for (○) unmilled sodium chloride and (□) milled sodium chloride. (b) Tensile strength as a function of compaction pressure. Compaction and strength testing performed in 1-butanol for (●) unmilled sodium chloride and (■) milled sodium chloride. (c) Remaining tensile strength (the ratio of tensile strength in 1-butanol to the tensile strength in air) plotted as a function of compaction pressure for (●) unmilled sodium chloride and (■) milled sodium chloride.

1993). Reduced stress concentrations might explain why fewer ionic bonds are created when milled sodium chloride is compacted, and why the strength of the compacts is due mainly to weak distance forces (Fig. 1c).

The activated surface state created by milling is a high energy state, resulting in unstable disordered regions. Over time, transformation to a more ordered surface structure should take place. Such crystallisation may result in the creation of ionic bonds between particles, but this transformation is believed to be slow (Alderborn and Nyström, 1982a; Elamin et al., 1994). Hence, in this study, it was assumed that the particles retained their disordered structure until the strength of the tablets was measured. Thus, the dominating bond type for milled sodium chloride tablet particles in this study appears to be weak distance forces.

3.2. Effect of addition of a dry binder on bonding structure of sodium chloride compacts

Addition of a dry binder to coarse sodium chloride particles will affect the tensile strength of compacts in different ways, depending on such factors as the size and amount of the dry binder particles added (Nyström et al., 1982; Nyström and Glazer, 1985). It has been suggested that the tensile strength of the mixture may best be increased by decreasing the size of the dry binder particles and ensuring a high degree of coverage of the carrier particles by the binder (surface area ratio 1.0) (Nyström et al., 1982). When compacted in air, an increase in the amount of dry binder added increased the tensile strength compared to

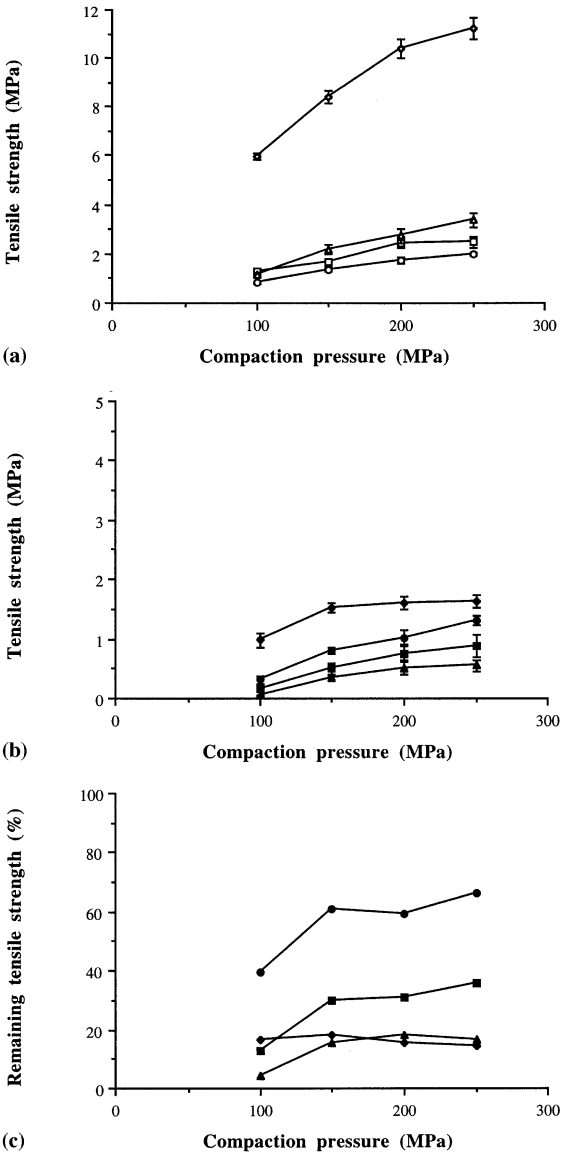

Fig. 2.

Fig. 2. Compacts of unmilled sodium chloride (250–355 μm), binary mixtures of sodium chloride particles (250–355 μm) and microcrystalline cellulose (raw material) compacted in different media. Confidence intervals for $p = 0.05$ are given in (a) and (b). (a) Tensile strength as a function of compaction pressure. Compaction and strength testing performed in air for (○) unmilled sodium chloride, (□) ordered mixture with microcrystalline cellulose, surface area ratio 0.2, (△) ordered mixture with microcrystalline cellulose, surface area ratio 1.0, and (◇) compacts of microcrystalline cellulose alone. (b) Tensile strength as a function of compaction pressure. Compaction and strength testing performed in 1-butanol for (●) unmilled sodium chloride, (■) ordered mixture with microcrystalline cellulose, surface area ratio 0.2, (▲) ordered mixture with microcrystalline cellulose, surface area ratio 1.0, and (◆) compacts of microcrystalline cellulose alone. (c) Remaining tensile strength (the ratio of tensile strength in 1-butanol to the tensile strength in air) plotted as a function of compaction pressure for (●) unmilled sodium chloride, (■) ordered mixture with microcrystalline cellulose, surface area ratio 0.2, (▲) ordered mixture with microcrystalline cellulose, surface area ratio 1.0, and (◆) compacts of micro crystalline cellulose alone.

sodium chloride (Fig. 2a). However, when compaction was performed in butanol, the binary mixtures resulted in the weakest tablets, and an increase in the amount of dry binder added actually decreased the tensile strength (Fig. 2b). Tablets of pure microcrystalline cellulose were included in this study as a control. These produced the strongest compacts in absolute terms in the different media surrounding the particles (Fig. 2a and b). When irregularly shaped agglomerates of microcrystalline cellulose (e.g. Avicel PH 101) are compacted, mechanical interlocking is believed to be an important bonding mechanism. Due to the small original particle size and consequently more regular shape of the microcrystalline cellulose particles included in this study (Table 1), mechanical interlocking is not however believed to be an important interparticulate bonding mechanism in this case (Adolfsson et al., 1997).

When the remaining tensile strength was calculated, it was seen that the mixture with a surface area ratio of 1.0 produced compacts with similar strength to those made of pure microcrystalline cellulose. This might indicate that the bonding structure is similar within these compacts (Fig. 2c). Thus, the compacts would be expected to be held together mainly by weak distance forces, since the remaining tensile strength is quite low, and the proportion of solid bridges produced between the sodium chloride particles during compaction for this mixture would be minute. This might be because the dry binder actually hinders development of the solid bridges by steric obstruction. Another possible explanation is that the dry binder counteracts creation of high local stress centres during compaction because of its high plasticity. When a lower amount of dry binder is added (surface area ratio 0.2), the remaining tensile strength increased (Fig. 2c). Thus, it may be assumed that the tensile strength is due mainly to weak distance forces but that solid bridges also play a role. If values for the remaining tensile strength of compacts with a low amount of binder are compared to those for milled sodium chloride (i.e. with a disordered surface structure), they are quite similar, which indicates that the bonding structure may also be similar for these compacts.

Table 2
Estimation of relative contribution of solid bridges (the ratio of tensile strength in 1-butanol to the tensile strength in air) calculated at a compaction pressure of 100 and 200 MPa

Material	Amount of solid bridges (%)	
	100 MPa	200 MPa
Sodium chloride (unmilled)	39	59
Sodium chloride (milled)	32	42
Sodium chloride (unmilled) and microcrystalline cellulose ($R_S = 0.2$)	13	31
Sodium chloride (unmilled) and microcrystalline cellulose ($R_S = 1.0$)	4.5	18
Microcrystalline cellulose (raw material)	16	15

3.3. Quantification of interparticulate bonding mechanism

When compaction was undertaken in 1-butanol (Karehill and Nyström, 1990; Olsson et al., 1996; Adolfsson et al., 1997), the remaining tensile strength was assumed to be a result of solid bridges (ionic bonding). In order to simplify the presentation of the data, the remaining tensile strength of tablets was also expressed in terms of proportion of solid bridges. Approximately 60% of the strength of the unmilled sodium chloride tablets was due to solid bridges at 200 MPa, while about 40% of the bonds in the milled sodium chloride tablets and 20% of those in the mixtures of sodium chloride and binder consisted of solid bridges (Table 2).

If the particles within the tablet are in close proximity due to bonding by ionic bonds (solid bridges), distance forces may be created in their neighbourhood (Karehill and Nyström, 1990; Nyström et al., 1993). The distance forces act over a relatively small interparticulate distance and will be quite strong since they probably will be less affected by the dielectric properties of the liquid surrounding the tablet particles. Thus, the distance forces may probably also contribute to the remaining tensile strength of the compacts.

The disordering of the surface structure of the sodium chloride particles seems to affect the bond

structure more at higher compaction loads than at lower. When higher compaction pressures were applied, the differences in tensile strength for the materials were more pronounced (Fig. 1c and Fig. 2c).

4. Conclusions

The tensile strength of tablets made of milled particles or with the addition of dry binder (i.e. with rough particle surfaces) was increased compared to untreated sodium chloride when compaction was carried out in air (Fig. 1a and Fig. 2a), but was decreased when compaction was carried out in 1-butanol (Fig. 1b and Fig. 2b). Milling or addition of a dry binder also reduced the value of remaining tensile strength (the ratio of tensile strength in 1-butanol to the tensile strength in air) if compared to unmilled sodium chloride (Fig. 1c and Fig. 2c).

(1) The surface properties of the particles are very important for the strength of a pharmaceutical compact, i.e. the condition of the surface will affect the interparticulate bonding type. It is suggested that when the crystalline surface was disordered by milling, the proportion of solid bridges formed during compaction decreased. It is possible that surface plasticity of milled sodium chloride was sufficiently high to prevent the melting or diffusion of solid material necessary for the formation of solid bridges.

(2) The amount of dry binder added in order to produce compacts of ordered mixtures affected the bonding structure within the compacts. Increasing the amount of dry binder added is expected to increase the number of weak distance forces and reduce the importance of solid bridges between sodium chloride particles. If the amount added is large enough, the surface properties of the core material become identical with those of the pure binder material.

(3) Disordering of the surface structure is also expected to affect the fracturing process during diametral compression. If the crack propagates mainly between the particles within the tablet, then the fracture length would be expected to be affected by changes in surface properties. If the fracture length is increased by milling and perhaps also by addition of a dry binder, the tensile strength of the compact would be expected to increase.

(4) It was assumed that an increase in the compaction load resulted in an increase in the number of solid bridges between sodium chloride particles during compaction. Large stresses created at interparticulate contact points are probably a prerequisite for solid bridges to form during compaction and this condition is fulfilled especially at high loads.

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References

Adolfsson, Å., Olsson, H., Nyström, C., 1997. Effect of particle size and compaction load on interparticulate bonding structure for some pharmaceutical materials studied by compaction and strength characterization in butanol. Eur. J. Pharm. Biopharm., in press.

Alderborn, G., Nyström, C., 1982a. Studies on direct compression of tablets III. The effect on tablet strength of changes in particle shape and texture obtained by milling. Acta Pharm. Suec. 19, 147–156.

Alderborn, G., Nyström, C., 1982b. Studies on direct compression of tablets IV. The effect of particle size on the mechanical strength of tablets. Acta Pharm. Suec. 19, 381–390.

BS 2955, 1958. Glossary of Terms Relating to Powders, no. 505. British Standard Institute, London.

Duberg, M., Nyström, C., 1985. Studies on direct compression of tablets XII. The consolidation and bonding properties of some pharmaceutical compounds and their mixtures with Avicel 105. Int. J. Pharm. Tech. Prod. Manuf. 6 (2), 17–25.

Elamin, A.A., Alderborn, G., Ahlneck, C., 1994. The effect of pre-compaction processing and storage conditions on powder and compaction properties of some crystalline materials. Int. J. Pharm. 108, 213–224.

Eriksson, M., Alderborn, G., 1995. The effect of particle fragmentation and deformation on the interparticulate bond formation process during powder compaction. Pharm. Res. 12, 1031–1039.

Eriksson, M., Nyström, C., Alderborn, G., 1990. Evaluation of a permeametry technique for surface area measurements of coarse particulate materials. Int. J. Pharm. 63, 189–199.

Fell, J.T., Newton, J.M., 1970. Determination of tablet strength by the diametral-compression test. J. Pharm. Sci. 59, 688–691.

Führer, C., 1977. Substance behaviour in direct compression. Labo-Pharma Probl. Tech. 25, 759–762.

Gren, T., Nyström, C., 1996. Compaction properties of melt coated coarse drug particles. STP Pharm. Sci. 6, 341–348.

Hersey, J.A., 1975. Ordered mixing: a new concept in powder mixing practice. Powder Technol. 11, 41–44.

Hüttenrauch, R., 1977. The mechanism of tablet forming—a new conception. Proc. 1st Int. Conf. Pharmaceutical Technology, vol. IV. APGI, Paris, pp. 114–120.

Jayasinghe, S.S., Pilpel, N., Harwood, C.F., 1969/1970. The effect of temperature and compression on the cohesive properties of particulate solids. Mater. Sci. Eng. 5, 287–294.

Karehill, P.G., Nyström, C., 1990. Studies on direct compression of tablets XXI. Investigation of bonding mechanisms of some directly compressed materials by strength characterization in media with different dielectric constants (relative permittivity). Int. J. Pharm. 61, 251–260.

Luangtana, M., Fell, J.T., 1990. Bonding mechanisms in tabletting. Int. J. Pharm. 60, 197–202.

Nyqvist, H., 1983. Saturated salt solutions for maintaining specified relative humidities. Int. J. Pharm. Tech. Prod. Manuf. 4 (2), 47–48.

Nyström, C., Glazer, M., 1985. Studies on direct compression of tablets. XIII. The effect of some dry binders on the tablet strength of compounds with different fragmentation propensity. Int. J. Pharm. 23, 255–263.

Nyström, C., Mazur, J., Sjögren, J., 1982. Studies on direct compression of tablets II. The influence of the particle size of a dry binder on the mechanical strength of tablets. Int. J. Pharm. 10, 209–218.

Nyström, C., Alderborn, G., Duberg, M., Karehill, P.G., 1993. Bonding surface area and bonding mechanism—two important factors for the understanding of powder compactability. Drug Dev. Ind. Pharm. 19, 2143–2196.

Olsson, H., Adolfsson, Å., Nyström, C., 1996. Compaction and measurement of tablets in liquids with different dielectric constants for determination of bonding mechanisms—evaluation of the concept. Int. J. Pharm. 143, 233–245.

Rankell, A.S., Higuchi, T., 1968. Physics of tablet compression XV. Thermodynamics and kinetic aspects of adhesion under pressure. J. Pharm. Sci. 57, 574–577.

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