International Journal of Pharmaceutics, 64 (1990) 35–43
Elsevier

IJP 02138

Studies on direct compression of tablets. XXIII. The importance of surface roughness for the compactability of some directly compressible materials with different bonding and volume reduction properties

P.G. Karehill, M. Glazer and C. Nyström

Department of Pharmaceutics, Uppsala Biomedical Center, Uppsala University, Box 580, S-751 23 Uppsala (Sweden)

(Received 21 February 1990)
(Accepted 27 March 1990)

Key words: Double-layer tablet; Axial tensile strength; Surface roughness; Bonding mechanism; Direct compression; Volume reduction

Summary

The axial tensile strength of double layer compacts prepared from a precompressed layer with varying surface roughness and a layer of material in powdered form, has been investigated for sodium chloride, Avicel ® PH 101, Sta-Rx ® 1500, latose, sucrose and Emcompress ®. The materials consolidating mainly by plastic deformation were all very sensitive to a decrease in the surface roughness of the pecompressed layer of the double-layer tablet. Presumably the plasticity of these materials is insufficient to produce high surface areas for bonding between the two layers. The fragmenting materials, lactose, sucrose and Emcompress ®, were relatively unaffected by the pretreatment of the first layer. This suggests that the surface area utilized for bonding by the fragmenting materials is large. For these materials a high bonding surface area between the particles in the tablet seems to be the primary requisite for a high tablet strength. The compact strength of the investigated materials is primarily dependent on intermolecular forces.

Introduction

Formation of a compact from a powder can be subdivided into several stages, namely, rearrangement of the particles followed by elastic deformation, plastic deformation and particle fragmentation (Duberg and Nyström, 1986). If these volume reduction mechanisms are to result in a permanent consolidation into a compact, then bonds must be formed between solid surfaces in the compact. Rumpf (1958) and Führer (1977) have proposed several bonding mechanisms in this context. For tablets, three types are normally considered: (a) solid bridges formed by e.g. a melting process or by recrystallization; (b) attractive forces active over distances, i.e. intermolecular forces (Karehill et al., 1990); (c) mechanical interlocking, depending on the shape of the particles. Bonding with solid bridges, in most cases, contributes less to the compact strength than bonding with intermolecular forces (Nyström and Karehill, 1986; Karehill et al., 1990; Karehill and Nyström, 1990). A prerequisite for the formation of a coherent compact is

---

Correspondence: C. Nyström, Department of Pharmaceutics, Uppsala Biomedical Center, Uppsala University, Box 580, S-751 23 Uppsala, Sweden.

that the surfaces should deform to such an extent that the combined effects of bonding with intermolecular forces and solid bridges are greater than the elastic component of the material. This can be expressed as the critical compaction pressure needed to form a compact.

The effective amount of surface area available for bonding is dependent on several material properties (Duberg and Nyström, 1985). Both the particle characteristics of the starting material and the changes caused by the volume reduction will be determining factors. In general, a decrease in particle size and an increase in particle surface roughness will result in stronger compacts. However, for some materials, e.g. coarse particulate sodium chloride, a decrease in particle size could result in a decreased compact strength (Alderborn and Nyström, 1982a). It is postulated that this material is able to form solid bridges, a bonding mechanism demanding interparticulate zones of high stress and friction and resulting in a minute bonding surface area (Nyström and Karehill, 1986). It has earlier been assumed that plastic deformation is the most effective means of producing a high bonding surface area. However, more recently it has been shown (Alderborn and Nyström, 1982b; Duberg and Nyström, 1985; Vromans et al., 1985) that increased fragmentation will result in increased compact strength, owing to a greater bonding surface area. The smaller fragments formed, however, should not possess a pronounced elastic component (e.g. Duberg and Nyström, 1986).

It seems that the final compact strength is a complex function of many material properties, inter alia particle size and shape of the starting material, volume reduction behavior and the dominating bond mechanism. Unfortunately the design of experiments to investigate these parameters separately, while all the others are held constant, is difficult. In the present study an attempt has been made to specifically study the importance of particle surface roughness on the compactability of some pharmaceutical materials. By using a model system comprising a double layer compact prepared from a precompressed layer with varying surface roughness and a second layer in powdered form, materials possessing different volume reduction mechanisms and different bonding mechanisms could be studied.

Experimental

Materials

Materials undergoing volume reduction mainly by plastic deformation or fragmentation but lacking a significant elastic component were selected. All materials were fractionated by dry sieving to obtain the fraction 212–250 μm. However, Avicel ® PH 101 was used as supplied or as a fraction < 10 μm obtained with the aid of an air classifier (100 MZR, Alpine, F.R.G.).

Sodium chloride (cubic crystalline, puriss, Kebo-Grave, Sweden). Sodium chloride is known to undergo volume reduction mainly by plastic deformation (Rees and Rue, 1978). Karehill et al. (1990) and Karehill and Nyström (1990) have proposed that coarse crystalline sodium chloride bonds by intermolecular forces together with a considerable proportion of solid bridges. The compactability has earlier been shown to be enhanced by an increase in particle size (Alderborn and Nyström, 1982a) and by particles with a more irregular shape and rough surface texture (Alderborn and Nyström, 1982b).

Avicel ® PH 101 (FMC, U.S.A.). The fragmentation of Avicel is limited and plastic deformation is believed to be the dominating volume reduction mechanism (Rees and Rue, 1978). The compact strength of Avicel ® PH 101 is attributed mainly to intermolecular forces (Karehill and Nyström, 1990) although mechanical interlocking may also contribute to the tablet bonding (Karehill and Nyström, 1990). Thus, the high compactability has been explained in terms of a high powder specific surface area, due to fine particles of high surface roughness (Karehill et al., 1990).

Sta-Rx ® 1500 (Colorcon Inc., U.S.A.). Sta-Rx ® 1500 is known to undergo volume reduction mainly by plastic deformation (Rees and Rue, 1978). This material binds predominantly by intermolecular forces (Karehill et al., 1990). Alderborn and Nyström (1982b) have reported that the unfractionated raw material consists of two different types of primary particles. The fraction < 125 μm consists of fairly smooth primary particles, while the larger particles have a more rough surface texture. The tablets produced from larger particles gave generally stronger compacts than those from the smaller fractions.

Lactose (α-monohydrate crystalline, CCF, Friesland, The Netherlands). Most types of lactose, including the α-monohydrate, undergo volume reduction by fragmentation and to a limited extent also by plastic deformation (Rees and Rue, 1978; Duberg and Nyström, 1982). A decrease in particle size also results in an increased compact strength. Lactose modifications possess different fragmentation tendencies and an increased compact strength is probably due to an increased bonding surface area (Vromans et al., 1985; Leuenberger et al., 1989). Lactose binds mainly by intermolecular forces. A small contribution by solid bridges could not be excluded (Karehill and Nyström, 1990).

Emcompress® (E. Mendell Co., Inc., U.S.A.). Emcompress is a granulated form of fine particulate dicalcium phosphate dihydrate with pronounced fragmentation tendency (Alderborn et al., 1985). The initial particle size only slightly influences the compact strength (Alderborn and Nyström, 1982a). A high particulate surface area is obtained, irrespective of the fineness of the starting material. The dominating bonding mechanism proposed by the authors for this material is bonding with intermolecular forces.

Sucrose (crystalline K5, SSA, Sweden). The material undergoes volume reduction mainly by fragmentation (Duberg and Nyström, 1982). The compact strength seems to be relatively unaffected by changes in particle size (Alderborn and Nyström, 1982a) and particle shape and surface texture (Alderborn and Nyström, 1982b). This material binds essentially by intermolecular forces.

Methods

Compaction

The specimens were compressed in an instrumented excenter press (Ek O, Korsch, F.R.G.), equipped with flat-faced punches and a die with a diameter of 1.13 cm. Before the compaction of the first layer, the die and the lower punch face were lubricated with a suspension of 1% w/w magnesium stearate in ethanol. Prior to the final compaction of the double layer tablet, only the face of the upper punch was lubricated. After manual filling of the die, each compression was conducted by starting the motor of the press when the upper punch was in its extreme upper position. Immediately after the tablet machine had reached its extreme lower position, the motor was stopped. This procedure gave an almost constant load rate, corresponding to a machine speed of 30 rpm. The first layer of the double layer tablet was compressed at 25–200 MPa. The maximum compression loads were within ±3% of the mean values presented.

After the first compaction, the compact (first layer) was left in the die while the lower punch was lowered and an equal amount of powder loaded into the die on top of the first layer. The lower punch was adjusted to give a compaction pressure of 200 MPa for the double layer compact. The amount of powder added was chosen to produce a height of 0.3 cm for the first layer and a total height of the double layer compact of 0.6 cm.

Strength characterization

Axial tensile strength was measured in an axial tensile test apparatus according to Nyström et al. (1977). Results presented are mean values of 10 determinations.

Microscopy

Photographs of the surface structure of the powder material and the first layer compressed at 50 and 200 MPa respectively were taken, using a scanning electron microscope (JSM U-3, JEOL, Japan).

Results and Discussion

Axial tensile strength

The axial tensile strengths for double layer tablets of all materials are presented in Figs 1 and 2. For all materials tested, an increase in pressure on the first layer of the double layer tablet resulted in a decrease in the axial strength.

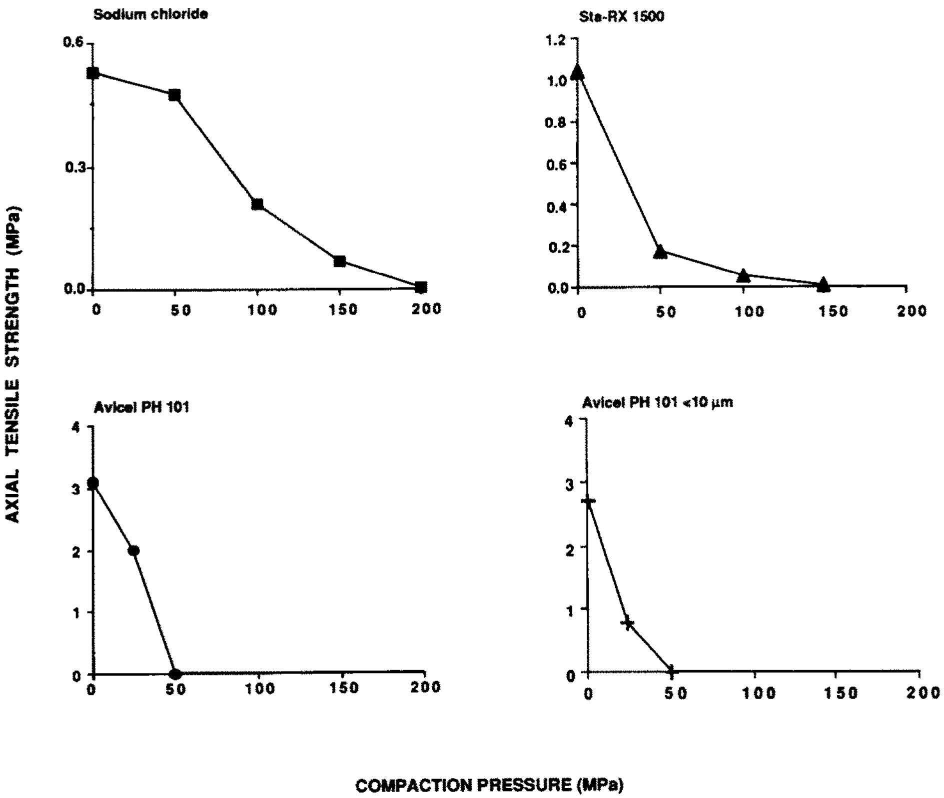

Fig. 1. The effect of compaction pressure of the first portion on the axial tensile strength of the double layer compact compressed at 200 MPa, for the plastically deforming materials.

All the plastically deforming materials (sodium chloride, Sta Rx ® 1500, Avicel ® PH 101 and Avicel ® PH 101 < 10 μm) failed in the contact zone between the first and the second layer of the double layer tablet, indicating that the bonding strength in the contact zone generally was lower than in the individual tablets. The materials consolidating mainly by fragmentation failed generally in the first layer of the double layer tablet, indicating that the bonding strength between the two layers was higher than that of the individual layers.

In Fig. 3, the percentage decrease in strength is plotted against the compaction pressure of the first layer of the double layer tablet for all materials tested. Avicel ® PH 101 and Sta Rx ® 1500 showed the greatest sensitivity followed by sodium chloride. The materials undergoing extensive fragmentation, i.e. Emcompress ®, lactose and sucrose are relatively insensitive to an increase in compaction pressure compared to the plastically deforming materials (Fig. 3).

Sodium chloride. The axial tensile strength for sodium chloride is presented in Fig. 1. At pressures of 50 MPa sodium chloride showed initially a minor decrease in axial tensile strength. Thereafter the strength decreased continuously down to zero.

The compact strength of coarse particulate sodium chloride is, according to our earlier studies, understood in terms of intermolecular forces and solid bridges (Karehill and Nyström, 1990; Karehill et al., 1990). Presumably the solid bridges are formed initially while the intermolecular forces arise as the surfaces move nearer, i.e. mainly in the vicinity of the solid bridges (Karehill and Nyström, 1990). If the surface asperities on the first layer of the double layer tablet are work hardened and

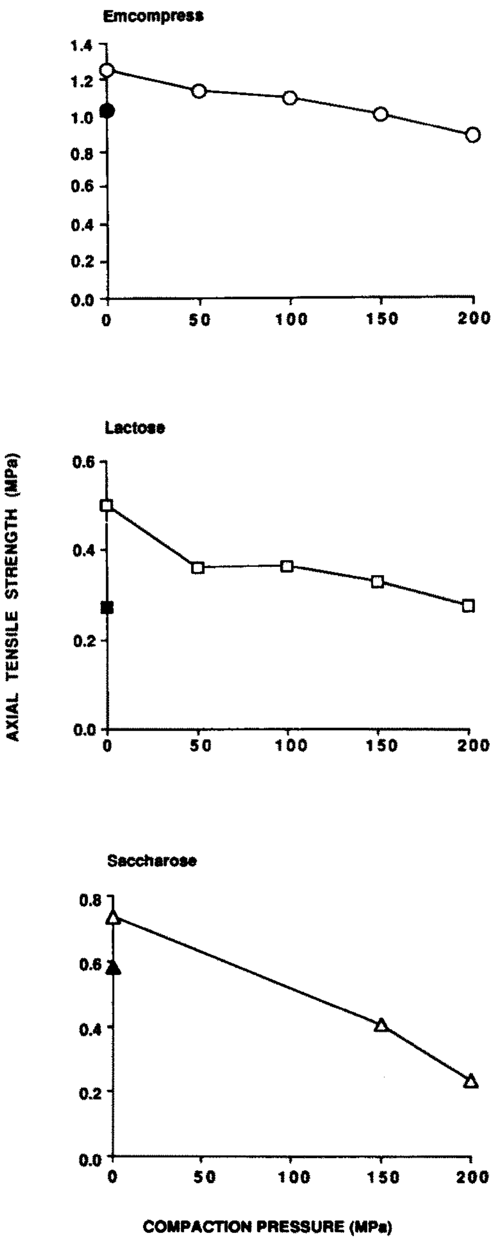

Fig. 2. The effect of compaction pressure of the first portion on the axial tensile strength of the double layer compact compressed at 200 MPa, for the materials undergoing volume reduction mainly by fragmentation. The strength of a single tablet compressed two times at 200 MPa is denoted by a filled symbol on the y-axis.

flattened out by compression then the ability of the second layer to form solid bridges will diminish. This reduction in bond formation should then be proportional to the applied pressure on the first layer for a plastically deforming, non fragmenting material. The slight initial decrease up to 50 MPa can probably be explained by fragmentation of the sodium chloride crystals (Down, 1983; Nyström and Karehill, 1986). The reduction in compact strength for sodium chloride is then primarily caused by a decrease in the proportion of solid bridges. If the ability to form solid bridges is lost then, the possibility that intermolecular forces will keep the two halves of the double layer tablet together must be considered. When the first layer is flattened out, the formation of intermolecular bonds will be dependent on the ability of the second layer to achieve close contact by plastic flow. The low axial strength obtained in this study for higher compaction pressures seems to contradict results reported for highly plastically deforming materials such as amorphous binders and polymer adhesives which show a high bonding ability to other materials. However, such soft solids adhere better because a hard solid is able to penetrate their surface establishing intermolecular forces over the whole surface area (Kendall, 1988). It is thus important to differentiate between excipients with a high and a low plasticity. Only materials that possess a very high degree of plastic deformation compared to sodium chloride can be effective in creating large interparticulate surface areas for bonding, when materials with a low degree of surface roughness are used.

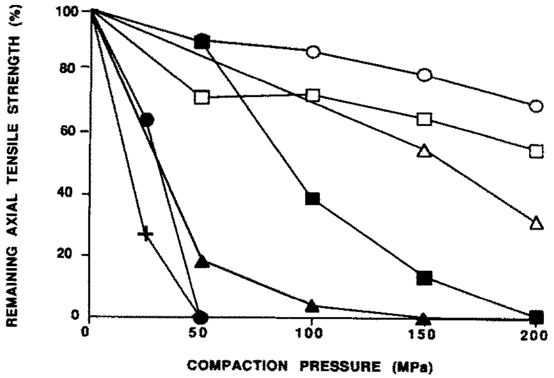

Fig. 3. The remaining axial tensile strength with the increase in compaction pressure of the first portion of the double layer tablet for all materials tested. Symbols as in Figs 1 and 2.

Avicel® PH 101 and Sta Rx® 1500. These materials bond predominantly by intermolecular forces, deform plastically and consolidate at relatively low loads, i.e. have a low yield pressure (Duberg and Nyström, 1982; Karehill et al., 1990; Karehill and Nyström, 1990). An important factor in the creation of strong intermolecular forces is the surface area available for bonding in the contact area of the double layer tablet. For plastically deforming materials, a large surface area and surface roughness generally give a greater bonding surface area and hence stronger compacts (Alderborn and Nyström, 1982a; Karehill et al., 1990).

The rather drastic decrease in axial tensile

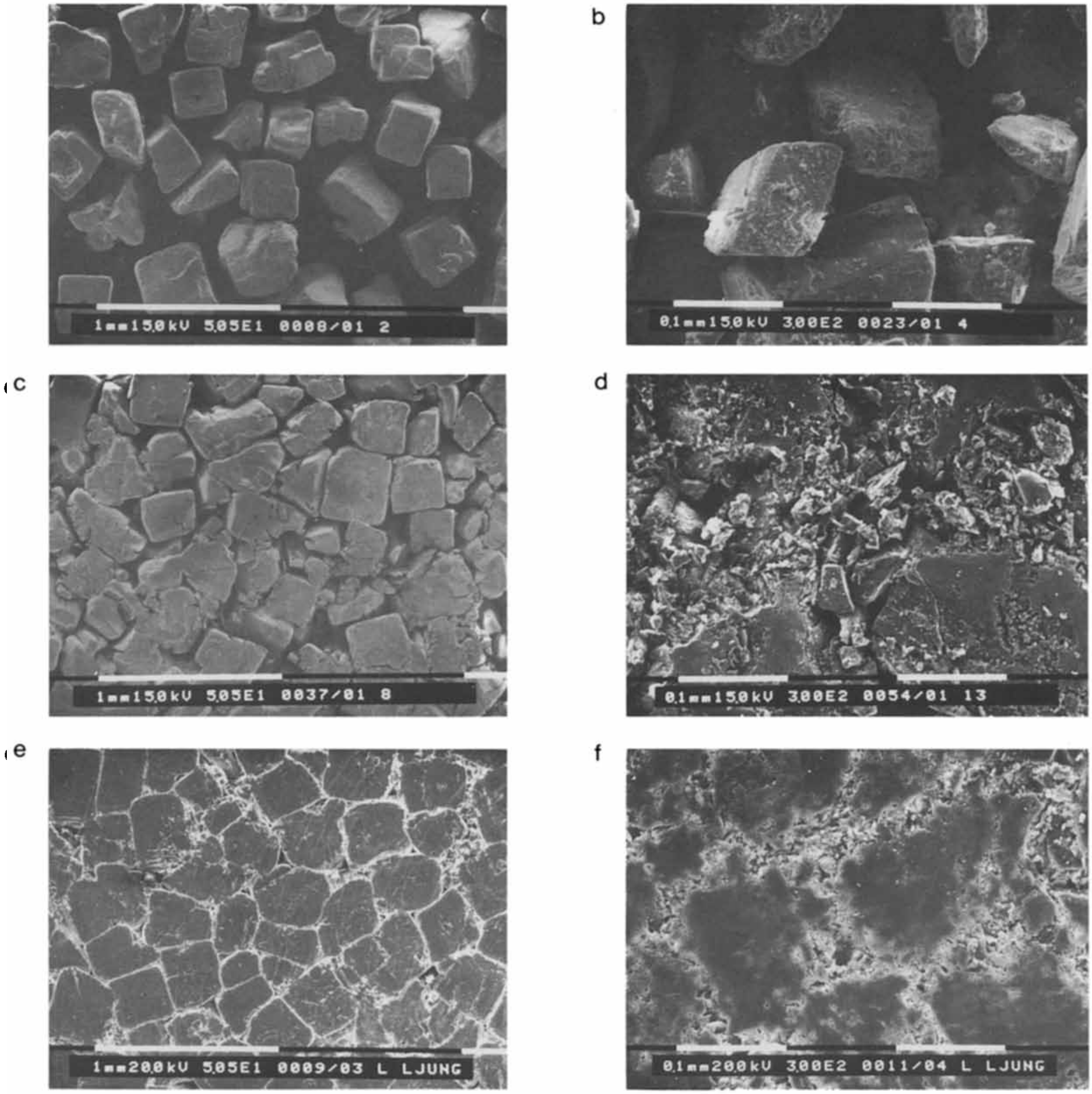

Fig. 4. Photomicrographs of the surface structure of powder materials (a and b) and the first portion of the double layer tablets compacted at 50 MPa (c and d) and 200 MPa (e and f) for sodium chloride and lactose, respectively.

strength with increased compaction pressure may, by analogy with sodium chloride, be related to the contribution by intermolecular forces. A finer fraction such as Avicel ® PH 101 and especially the fraction < 10 μm will form flatter surfaces than coarser materials when compressed at the same load. The intermolecular forces are considerably diminished owing to lack of surface roughness. For a coarse material such as Sta-Rx ® 1500, a higher compaction pressure is needed to eliminate the surface roughness compared to Avicel ® PH 101. However, as the surface asperities become less at higher pressures, the axial tensile strength of the double layer tablet decreases asymptotically to zero. For Avicel ® PH 101, it has been reported earlier that mechanical interlocking could contribute to the bonding (Karehill and Nyström, 1990). The results of the present study could also be interpreted similarly. The irregular Avicel ® particles will by compression of the first layer lose all the potential for hocking or shape related interactions between the particles.

Emcompress ®, sucrose and lactose. These fragmenting materials show a different pattern (Fig. 2) compared with the plastically deforming materials. A limited decrease in compact strength was obtained when low compaction pressures were applied to the first layer of the double layer tablet. At compaction loads equal to those applied to the double layer tablet (200 MPa), the strength after compaction was higher for the fragmenting materials than for the plastically deforming materials. These fragmenting materials bond predominantly by intermolecular forces. For coarse lactose and sucrose solid bridges may contribute to the compact strength (Ahlneck and Alderborn, 1989; Karehill and Nyström, 1990).

All double layer tablets of the fragmenting materials failed in the first layer of the double layer tablet. This means that bonding between the two layers is stronger than illustrated in Figs 2 and 3. Thus these materials were insensitive to a decrease in surface roughness and thus the surface area involved in intermolecular forces was large.

The large bonding surface area formed between the two layers is probably a result of pronounced fragmentation of the powder fraction added on top of the first layer. Additionally, it could not be excluded that also a limited micro fragmentation of the surface of the first layer could create larger zones of interparticulate attraction. It has been suggested that materials undergoing fragmentation followed by a plastic deformation of the smaller particles formed (Duberg and Nyström, 1986) are likely to form strong compacts. This is consistent with the result obtained by Duberg and Nyström (1982) that fragmenting materials generally form more homogeneous compacts than plastically deforming materials.

The relationship between the strength decrease in the first layer compared to the strength of the second layer and the zone between the layers was investigated by recompressing single compacts of all the fragmenting materials at 200 MPa. An amount of powder equal to the weight of the double layer tablet was added and compressed twice at a load of 200 MPa. The recompression data is denoted by filled symbols on the y-axis in Fig. 2.

All the single tablets compressed twice decreased in axial tensile strength (Fig. 2). This decrease was similar in absolute terms for all the investigated materials. A possible explanation for this decrease is elastic recovery upon the second compression of the first layer. This elastic recovery may promote the growth of cracks. Such effects have earlier been reported in studies of the well known capping phenomenon for elastically deforming materials (Hiestand et al., 1977; Von Parmentier, 1980). The first compression causes the formation of cracks whereas the second compression leads to a spreading of the cracks and a reduction in axial strength in Fig. 2.

Our results suggests that the slight reduction in double layer tablet strength for the fragmenting materials (Figs 2 and 3) is not due to a sensitivity for changes in surface roughness but rather an effect related to the magnification of the elastic component due to recompression.

Microscopical characterization of surface texture

Photomicrographs of the powder materials and surface of the first layer of the double layer tablets compressed at 50 and 200 MPa are presented for sodium chloride and lactose in Fig. 4. The materials were here chosen to represent the two main categories of volume reduction behaviour.

For both materials, the compact surface obtained at 200 MPa (Fig. 4e and f) appeared to be rather smooth, although a limited amount of small particle fragments could be seen for lactose. At 50 MPa (Fig. 4c and d) a less smooth surface texture is seen for both materials. Here, distinct gaps and even large interparticulate distances can be observed. Probably, this is the reason why sodium chloride at this pressure resulted in relatively strong double-layer tablets. The development of large zones of intimate contact is then not only a function of the plasticity of the material, but the relatively large sodium chloride particles also have the possibility to find position on the surface of the first layer facilitating a high interfacial surface area. Also, for the other materials a similar rough surface texture was found at low compression loads.

Obviously, the possibility to adapt to an adjacent surface is also dependent on the particulate fineness of the second portion. A decrease in particle size for the less fragmenting materials, bonding by intermolecular forces, ought therefore generally to result in stronger compacts.

The similarity in compactability behaviour of the two Avicel ® qualities was primarily due to that relatively flat surfaces were developed already at 25 MPa. However, it could also be a reflection of the fact that some type of mechanical interlocking plays an important role for Avicel ®.

The similarity in surface texture as characterized by microscopy, supports the idea that the marked difference in axial strength obtained between the two categories of materials, basically is due to a difference in effectiveness regarding the possibility to develop large zones of intimate contact to another surface in the neighbourhood. Only when the adjacent surface is relatively rough (as obtained for sodium chloride at 50 MPa) could particles of less-fragmenting materials in the second layer by rearrangement find a favourable position and thereby develop large bonding surface areas.

Conclusions

For the materials undergoing volume reduction, mainly by plastic deformation, a decrease in surface roughness of the first layer of the double-layer tablet, obtained by an increase in compaction load, resulted in a marked decrease in interparticulate attraction between the two layers. This was found for both sodium chloride which binds partly with solid bridges and for Avicel ® PH 101 and Sta-Rx ® 1500 which bind solely with intermolecular forces. However, for the easily fragmenting materials, the pretreatment of the first layer did not substantially influence these attractions.

Thus, volume reduction by fragmentation seems to be a more efficient means of producing larger surface areas that would promote interparticulate attraction in the compacts. This is especially valid for materials bonding with intermolecular attraction forces, i.e. probably the majority of pharmaceutical compounds and excipients. Vromans et al. (1985) have shown that fragmentation tendency is related to compact strength for several different lactose qualities. For fragmenting materials producing a large surface area, the compacts are generally stronger.

The so-called plastically deforming materials used in this study were all very sensitive to a decrease in the surface roughness of the first layer of the double-layer tablet, i.e. the plastic deformation of these materials was inadequate for the development of large zones of intimate contact between the layers.

It is debatable whether the term plastic deformation should be applied to all less fragmenting materials possessing varying degrees of plasticity. Many of the commonly used, amorphous tablet binders, with pronounced plastic deformation may provide an effective means of creating large interparticulate attraction surface areas. For most of the so called plastically deforming materials, possessing a moderate plasticity and bonding with intermolecular forces, it seems that a high external specific surface area is a prerequisite for high compactability. This is best achieved by using fine particle sizes or qualities with high surface roughness as reported earlier for Sta-Rx ® 1500 (Alderborn and Nyström, 1982a) and for sodium bicarbonate (Alderborn et al., 1988). It has also been suggested that the high compactability of Avicel ® PH101 is due to the large external specific surface area of the irregular particles (Karehill et al., 1990).

A large surface area and an irregular particle shape will probably promote all bonding mechanisms discussed. Fragmenting materials, normally bonding by intermolecular forces (Duberg and Nyström, 1985) do not seem to be severely affected by an increase in compression load, since the particles in the second layer can develop large bonding surface areas not only by particle rearrangement together with a limited plastic deformation, but also by extensive fragmentation. For the plastically deforming materials used in this study, the initially high surface roughness is effectively reduced after compression, with a subsequent reduction in intermolecular forces, the development of solid bridges (in e.g. sodium chloride), and mechanical interlocking.

The results of this study also suggest that a high fragmentation tendency of tabletting compounds and excipients will facilitate the formation of mechanically strong multilayer tablets. In practice, this is probably achieved by the use of granulated materials, i.e. materials that have a high fragmentation tendency.

References

Ahlneck, C. and Alderborn, G., Moisture adsorption and tabletting. II. The effect on tensile strength and air permeability of the relative humidity during storage of tablets of 3 crystalline materials. *Int. J. Pharm.*, 56 (1989) 143–150.

Alderborn, G., Börjesson, E., Glazer, M. and Nyström, C., Studies on direct compression of tablets. XIX. The effect of particle size and shape on the mechanical strength of sodium bicarbonate tablets. *Acta Pharm. Suec.*, 25 (1988) 31–40.

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

Alderborn, G. and Nyström, C., 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 (1982b) 147–156.

Alderborn, G., Pasanen, K. and Nyström, C., Studies on direct compression of tablets. XI. Characterization of particle fragmentation during compaction by permeametry measurements of tablets. *Int. J. Pharm.*, 23 (1985) 79–86.

Down, G.R.B., Localized particle fracture during compression of materials expected to undergo plastic deformation. *Powder Technol.*, 35 (1983) 167–169.

Duberg, M. and Nyström, C., Studies on direct compression of tablets. VI. Evaluation of methods for the estimation of particle fragmentation during compaction. *Acta Pharm. Suec.*, 19 (1982) 421–436.

Duberg, M. and Nyström, C., 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. Mfr.*, 6 (1985) 17–25.

Duberg, M. and Nyström, C., Studies on direct compression of tablets. XVII. Porosity-pressure curves for the characterization of volume reduction mechanisms in powder compression. *Powder Technol.*, 46 (1986) 67–75.

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

Hiestand, E.N., Wells, J.E., Peot, C.B. and Ochs, J.F., Physical processes of tableting. *J. Pharm. Sci.*, 66 (1977) 510–519.

Karehill, P.G., Alderborn, G., Börjesson, E., Glazer, M., and Nyström, C., Studies on direct compression of tablets, XX. Investigation of bonding mechanisms of some directly compressed materials by addition and removal of magnesium stearate. *Powder Technol.*, (1990) submitted for publication.

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

Kendall, K., Theoretical aspects of solid-solid adhesion. *Sci. Prog. Oxf.*, 72 (1988) 155–171.

Leuenberger, H., Bonny, J.D., Lerk, C.F. and Vromans, H., Relation between crushing strength and internal specific surface area of lactose compacts. *Int. J. Pharm.*, 52 (1989) 91–100.

Nyström, C., Alex, W. and Malmqvist, K., A new approach to tensile strength measurement of tablets. *Acta Pharm. Suec.*, 14 (1977) 317–320.

Nyström, C. and Karehill, P.G., Studies on direct compression of tablets. XVI. The use of surface area measurements for the evaluation of bonding surface area in compressed powders. *Powder Technol.*, 47 (1986) 201–209.

Rees, J.E. and Rue, P.J., Time-dependent deformation of some direct compression excipients. *J. Pharm. Pharmacol.*, 30 (1978) 601–607.

Rumpf, H., Grundlagen und Methoden des Granulierens. *Chem. Ing. Tech.*, 30 (1958) 144–158.

Von Parmentier, W., Warum deckeln Tabletten. *Pharm. Ind.*, 42 (1980) 752–756.

Vromans, H., De Boer, A.H., Bolhuis, G.K., Lerk, C.F., Kussendrager, K.D. and Bosch, H., Studies on tabletting properties of lactose. 2. Consolidation and compaction of different types of crystalline lactose. *Pharm. Weekbl. Sci.*, 7 (1985) 186–193.