DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 19(17&18), 2143-2196 (1993)

BONDING SURFACE AREA AND BONDING MECHANISM – TWO IMPORTANT FACTORS FOR THE UNDERSTANDING OF POWDER COMPACTABILITY

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ABSTRACT

Two factors could be regarded as primary factors for the compactability of powders: the dominating bond mechanism and the surface area over which these bonds are active. Owing to considerable experimental difficulties, these factors have not been evaluated in any detail for pharmaceutical materials. Instead, more indirect, secondary factors are normally studied and used for correlations with tablet strength. Such secondary factors are particle size, shape and surface texture. Also the importance of volume reduction mechanisms, i.e. elastic deformation, plastic deformation and particle fragmentation have been studied in detail.

For the investigation of dominating bond mechanisms and estimation of the magnitude of the surface area of the solids involved in interparticulate attraction in compacts several pharmaceutical excipients representing both plastically deforming materials (sodium chloride, Avicel® PH 101, Sta-Rx 1500®, and sodium

bicarbonate) and fragmenting materials (lactose, sucrose, paracetamol and Emcompress®) have been used in a series of publications from our laboratory.

The bonding mechanisms discussed have been solid bridges, representing continous solid bridges between tablet particles, intermolecular forces, representing weaker attraction forces active over distances and mechanical interlocking, representing a bond type dependent on hooking and twisting of irregularly shaped particles. To characterize the dominating bond mechanisms, measurements of compact strength has been performed in media known to reduce bonding with intermolecular forces. The media used were liquids with different dielectric constants and films of magnesium stearate. The results establish that the intermolecular forces constitute the dominating bond mechanism for pharmaceutical materials. Bonding with solid bridges contribute to the compact strength only for coarse plastically deforming materials that can melt during compaction. Only for sodium chloride, of the materials tested, is there substantial evidence for the existence of solid bridges. Bonding with mechanical interlocking is a bonding mechanism of minor importance for most of the investigated materials with the possible exception of Avicel® PH 101.

The results indicate that the surface area utilized for bonding with solid bridges for sodium chloride as measured with gas adsorption is small in relation to the total surface area of the compact. For all the materials bonding with intermolecular forces, only a proportional relation between compact surface area and bonding surface area could be possible. By using permeametry surface area data, the surface specific compact strength was characterized and found similar for all materials bonding primarily with intermolecular forces. For such materials a large bonding surface area will thus be obtained if the surface area of the particles in the tablet is large. This could either be achieved by the use of materials that undergo extensive fragmentation or by the use of very fine particulate materials or qualities with pronounced surface roughness. It is suggested that most of the so called plastically deforming pharmaceutical materials often possess inadequate plasticity for the development of large zones that could take part in the interparticulate attraction by intermolecular forces.

INTRODUCTION

Stages in the Compaction Process

When a force is applied on a powder bed consisting of more or less non-porous particles, a number of mechanisms become involved in the transformation of the powder into a porous, coherent compact with a well-defined shape. A compaction process is normally described by a number of sequencial phases (1-3). Initially, the particles in the die are rearranged resulting in a closer packing structure. At a certain load, the packing characteristics of the particles or a high interparticulate friction between particles will prevent any further interparticulate movement. The subsequent reduction of compact volume is therefore accompanied by elastic and plastic deformation of the initial particles (4-7). Elastic deformation is a reversible, while the plastic is an irreversible deformation of the whole or a part of a particle. For many materials these particles are then fragmented. Fragmentation can be defined as a dividing-up of a particle into a number of smaller, discrete parts (8, 9). The particle fragment will then normally find new positions, which will further decrease the compact volume. When the applied pressure is further increased the smaller particles formed could again undergo deformation (3). Thus, one single particle may pass through one or several of these processes several times during a compression. As a consequence of the compression of the powder, particle surfaces are brought into close proximity to each other and interparticulate attraction or bonds will be formed.

The volume reduction processes consume energy (endothermal processes) and will normally increase the amount of particle surface area capable of forming interparticulate attraction forces. Bond formation is however, an exothermal process, thereby releasing energy (10). During ejection, when the load is reduced, many materials produce laminated (capped) compacts or results in compacts of pronounced low strength. These obervations indicate the importance of the elastic component of tableting materials.

To summarize, the following processes are involved in the compaction of a powder:

1. Particle rearrangement
2. Elastic deformation of particles
3. Plastic deformation of particles
4. Fragmentation of particles
5. Formation of interparticulate bonds

Examples of materials consolidating by plastic deformation are sodium chloride, starch and microcrystalline cellulose (8, 11, 12). Fragmenting materials are, for example crystalline lactose, sucrose and Emcompress® (8, 13-16). However, all materials possess both an elastic and a plastic component. The volume reduction mechanism which will dominate for a specific material is dependent on factors such as temperature and compaction rate. Lower temperatures and faster loading (17, 18) during compression will generally facilitate consolidation by fragmentation. Pharmaceutical materials normally consolidate by more than one of these mechanisms (3), which emphasizes the need for adequate characterization techniques.

Characterization of Volume Reduction Mechanisms

For metals and other materials possessing a high crystalline order or homogeneous structure, with low concentrations of crystal defects, pores or flaws, the relationship between material deformation and an increase in applied stress are well established. After an initial elastic deformation, the materials undergo plastic deformation and finally, if the stress is high enough, the material shows brittle behaviour and fragments.

However, most pharmaceutical materials, mainly organic compounds, exhibit consolidation properties far removed from this simple model. The main difference reported is that many materials seem to undergo particle fragmentation during the initial loading (8, 15, 19, 20) followed by elastic and/or plastic deformation at higher loads. This phenomenon could possibly be explained by considering the fairly complex particle structure of many pharmaceutical compounds. They often possess brittle behavior or consist of aggregates of primary particles or of highly

TABLE 1

Sequences of Volume-Reduction Mechanisms[a]

Expected mechanisms for metals[b]	Expected mechanisms for pharmaceutical materials[c]	Experimentally observed mechanisms for pharmaceutical materials[d]
	E_1: Elastic deformation of initial, weak particles	
	P_1: Plastic deformation of initial, weak particles	
	F_1: Fragmentation of initial particles into a number of smaller descrete particles of higher strength	F_1
E: Elastic deformation	E_2: Elastic deformation of smaller particles formed	E_2
P: Plastic deformation	P_2: Plastic deformation of smaller particles formed	P_2
F: Particle fragmentation	F_2: Fragmentation of smaller particles formed	

a Here not including particle rearrangement.
b Representing materials with low concentrations of crystal defects, pores and flaws.
c Representing materials with high concentration of defects.
d Utilizing, for example, porosity-pressure functions.

porous particles. These 'secondary' particles could then during the initial loading behave as mainly brittle units, with a negligible deformation ability, and produce a large number of smaller discrete particles. These particles, formed during compression, would then show elastic and plastic deformation, possibly followed by a final fragmentation, when the compression load is further increasesed (Table 1).

Several methods for the determination of volume-reduction mechanisms, both qualitatively and quantitatively, have been presented in the literature, e.g. scanning electron microscopy (8, 11, 15, 21), work measurements from force-displacement curves (22-25), the use of ratios from axial and radial tensile strength measurements (8, 14, 26), measurement of surface area changes by permeametry (9, 27, 28) and gas adsorption techniques (9, 27-31) and measurement of porosity changes during compression (19, 28-33).

In studies of pharmaceutical materials, the porosity function according to Heckel (19) has been used for the characterization of particle fragmentation and the degree of plastic deformation (20, 34). The porosity could then be measured either on the ejected compact or on the compact under load. By continuously recording the porosity changes during one compression cycle, the measurement could be made very rapidly. This technique also allows the characterization of materials with poor bonding capacity.

Heckel regarded compression of metal powders as analogous to first-order kinetics, where the pores are the reactant and the densification the product. The relation was described by the equation

$$\ln (1 / E) = KP + A \qquad \text{(Eqn 1)}$$

where E is the porosity and equivalent to 1-D, where D is the relative density, P the applied pressure, A a constant describing densification by particle movement and rearrangement and K is a measure of the ability of the compact to deform plastically.

The value of K was related by Heckel to the yield strength Y of the material by the expression $K = 1/3\ Y$ (19). Later, the reciprocal of K was defined as the yield pressure P_y (20). K and has been used to determine the deformation mechanisms of a material.

To be able to use the Heckel parameters to compare different substances and powder qualities, it is important to standardize the experimental conditions such as

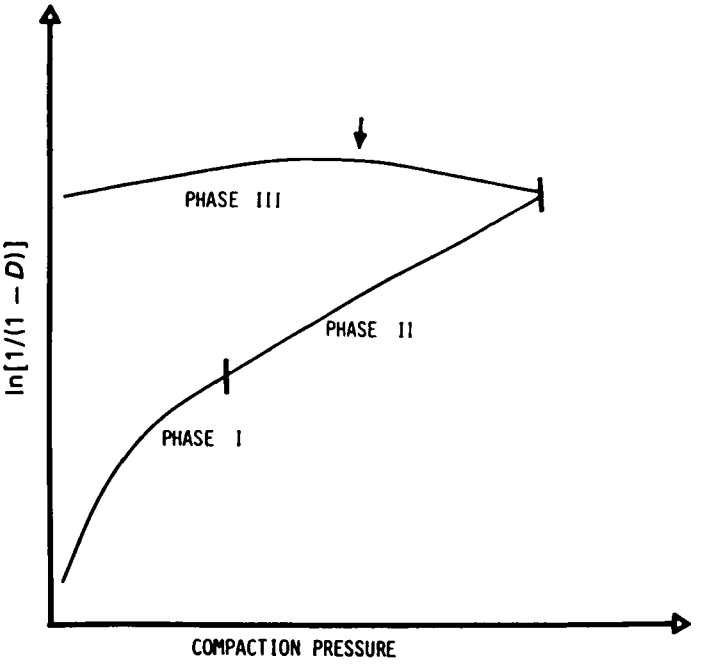

Figure 1. A compression cycle, evaluated using the Heckel function, separated into three phases to be used for the evaluation of volume-reduction mechanisms involved in compaction of pharmaceutical powders (From ref. 3).

tablet dimensions and speed of compaction (35). The elastic deformation of the punches must also be considered (19).

The question of when to measure compact porosity is also important. Heckel suggested measurements 'at pressure', since elastic recovery affects tablet volume after compression. There are two ways to accomplish this: either by compressing a number of tablets at different pressures and recording tablet thickness at maximum upper punch pressure (15, 36), or by continously recording tablet thickness and the corresponding pressure during a single compression cycle (8, 26, 37). The latter technique has the advantage of speed and requires less powder. A disadvantage is that the consolidation time is different at each pressure. This could result in a concave Heckel plot with positive deviation from a straight line for materials having pronounced time-dependent consolidation (8, 38).

Using porosity-pressure functions, where both the compression and decompression phase is analysed (3) (Fig. 1) it has been possible to classify pharmaceutical compounds according to their dominating volume reduction mechanisms. The following procedure has then been utilized. During phase I, when the applied pressure is relatively low, the porosity reduction could be strongly enhanced by particle fragmentation. The curvature of the plot could be evaluated as the deviation from a straight line and expressed as the correlation coefficient (CC) as described earlier (8, 15). The CC could then serve as a tool to quantify the fragmentation tendency. A linear curve is obtained for non-fragmenting materials. At higher pressures (phase II), elastic and/or plastic deformation are the dominating mechanisms. A low P_y-value should then indicate a high degree of plastic deformation (20). Since, for some materials, the density values 'at pressure' contain an elastic component, this could result in a false low P_y-value (26). During decompression (phase III), elastic properties of the particle could result in an increase in porosity. The elastic component as given by phase III has been calculated as the relative increase in porosity (ER) (3). The decompression curve should be approximately horizontal when no elastic deformation is present, i.e. the instantaneous elastic expansion of the tablet is negligible. Since phase III could give information about the elastic component, it seems possible to elucidate the contribution of plastic deformation during phase II. Another means to evaluate phase III could be to identify the time difference between maximum compression load and minimum porosity. This time-lag could be interpreted as a reflection of plastic deformation, i.e. plastic flow would not stop at maximum load, but continue over a time-period when the pressure is released.

The dominating volume reduction mechanisms for some pharmaceutical materials are summarized in Table 2. From the data it is clear that most materials show a complex behaviour and cannot simply be labelled as plastically deforming or brittle (undergoing fragmentation). The data also indicate that for a fragmenting material it is of major importance how the smaller particles formed will react on further densification during compression (3). Only when the smaller particles have a limited elastic component (e.g. Emcompress®, lactose and most binder granulations) (Fig. 2) the increase in surface area could effectively be utilized for bonding. When the elastic component is pronounced (e.g. phenacetin) (Fig. 3), elastic recovery after compression will strongly reduce the effective bonding surface area.

TABLE 2

Sequences of Dominating Volume-Reduction Mechanisms Determined for Some Pharmaceutical Materials

Materials	Mechanisms according to Table 1
Sodium chloride	P
Emcompress	$F_1 + P_2$
Sodium bicarbonate	P
Lactose	$F_1 + (E_2) + P_2$
Paracetamol	$F_1 + E_2 + P_2$
Phenacetin	$F_1 + E_2$
Aspirin	$F_1 + E_2 + P_2$

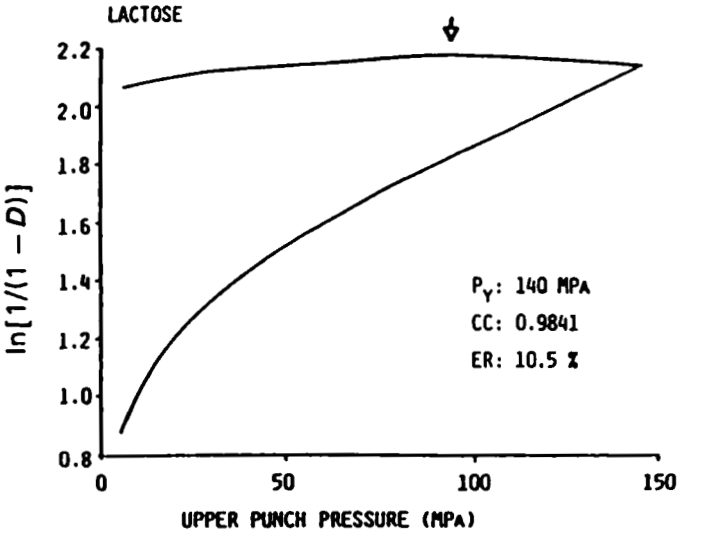

Figure 2. Heckel plot of lactose (From ref. 3).

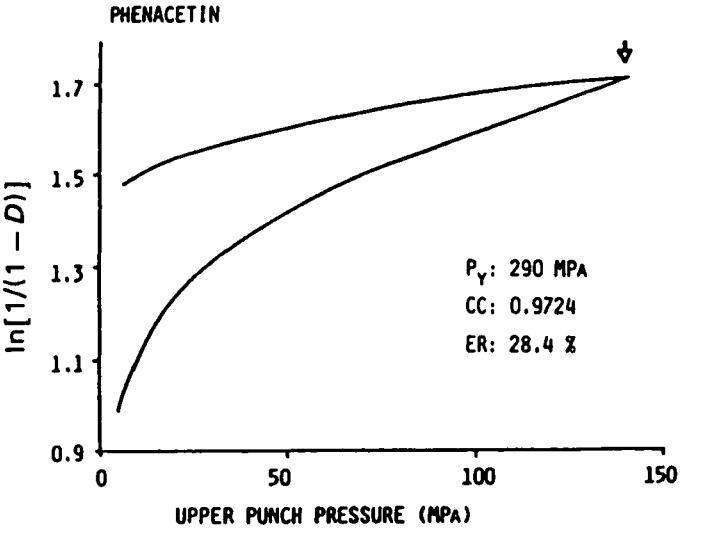

Figure 3. Heckel plot of phenacetin (From ref. 3).

Characterization of Particle Fragmentation

To estimate specifically the fragmentation tendency of a material during compression has been the object of several studies during recent years (8, 9, 15, 27, 28). In this context also several studies have been undertaken to investigate the importance of particle fragmentation for powder compactability (14, 15, 39-42). The results show that the degree of particle fragmentation is an important factor for the effect of additives (e.g. lubricants (15) and dry binders (39, 40) and variations in compound particle properties (e.g. size (42) and shape (41) on the tablet strength. In general a pronounced particle fragmentation seems to correspond to an increase in surface area potentially available for bonding and thus a high compactability, provided the elastic component is not pronounced (3). Consequently, several methods for estimating the fragmentation propensity of a substance have been purported. An adequate approach for characterizing fragmentation seems to be the measurement of the surface area of a material before and after compaction or the measurement of changes in tablet surface area with compaction pressure (8, 11, 28, 29, 43). Often the surface area of powders and tablets have been characterized by gas adsorption techniques. However, several problems seem to be related to the use of such techniques for studying particle

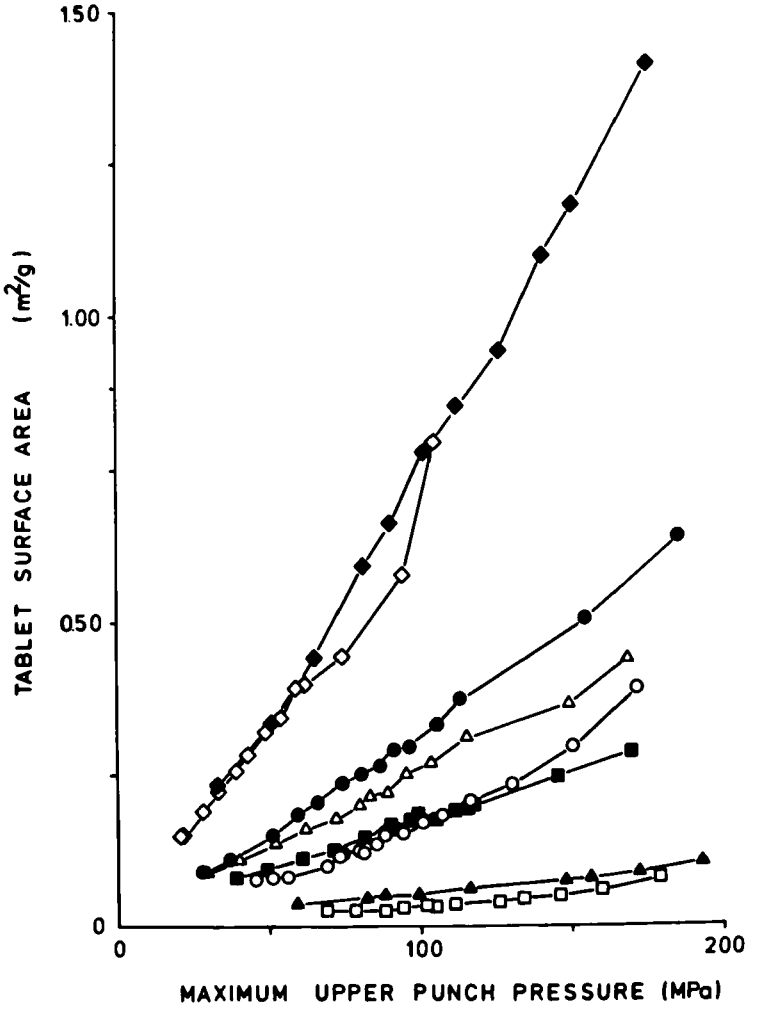

Figure 4. Specific surface area of sodium chloride (□), sodium bicarbonate (▲), saccharose (○), lactose (●), sodium citrate (■), ascorbic acid (△), paracetamol (◇) and Emcompress® (◆) tablets as a function of compaction pressure (From ref. 9).

fragmentation. The gas adsorption method estimates the total surface area of the specimen which makes it difficult to establish whether an observed change in surface ara is due to particle fragmentation or to other phenomena, such as the formation of cracks or opening of pores. Additionally, a very high initial total surface area due to, e.g., a high intra-particulate porosity may result in a smaller

increase in surface area than expected, although extensive fragmentation has taken place.

Since fragmentation here is defined as the formation of a number of smaller, discrete particles from an initial grain, it might be advantageous to use a permeametric method, which measures an external rather than a total surface area of the specimen. A method for estimating the specific surface area of tablets by permeametry has recently been presented (9, 27, 28). The results (Fig. 4) indicate the possibilities of using such a method for detecting particle fragmentation during compaction and to classify materials with respect to this property.

Although, many recent studies have shown that brittle materials undergoing extensive particle fragmentation generally results in a high tablet strength, provided the elastic recovery is limited (26, 44-49), it is still often claimed that plastic deformation represents an effective means of creating a large bonding surface area (50, 51).

Physical Description of a Tablet

The axial compaction of pharmaceutical powders results in anisotrope and inhomogeneous compacts or tablets, i.e. a tablet shows varying values of some characteristics, porosity, density (e.g. 52), bonding, mechanical strength in different directions and parts (Fig. 5).

For normal compaction pressures, not exceeding 300-500 MPa, the final compact porosity is in the range 1% to 25%, dependent on the powder compressibility. Two extreme models could be used to describe the distribution of this gas phase (Fig. 6). Firstly, the air could be regarded as a disperse phase of individual units incorporated in a solid continous phase (like a Swiss cheese). Then, the pores are to be considered as intra particulate pores in a large particle (the tablet). Secondly, the air could be regarded as a continous phase, in which solid particulate units are dispersed. In this case, the individual solid particles are separated by some distance and the tablet contains continous pores like a loose powder plug. Then the tablet can be penetrated by a flowing medium and characterized on e.g. permeability properties (28) and permeametry surface area (c.f. Fig. 4).

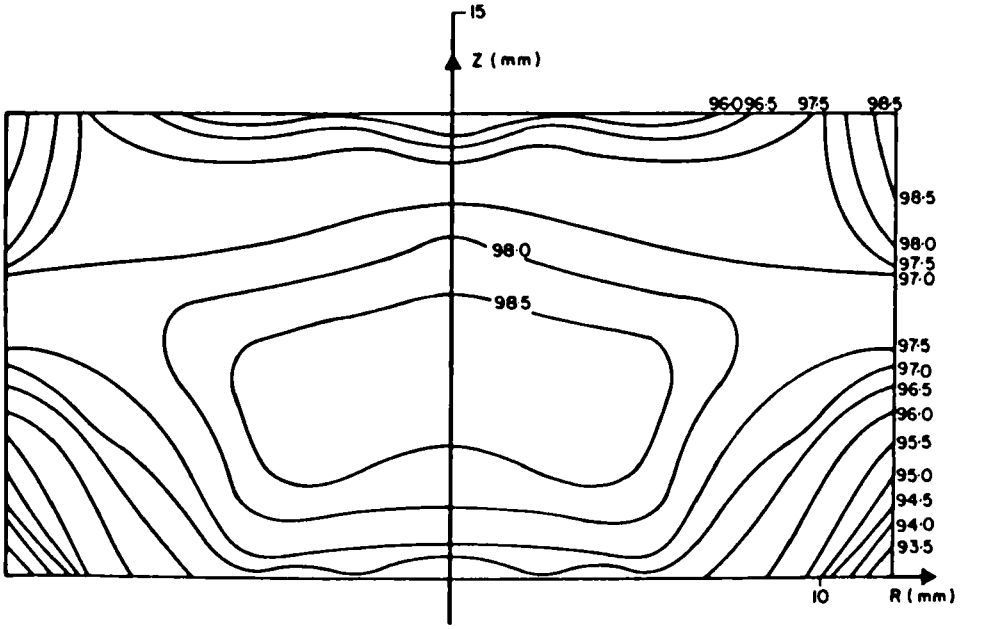

Figure 5. Density variation in the cross-section of a die compact (From ref. 52)

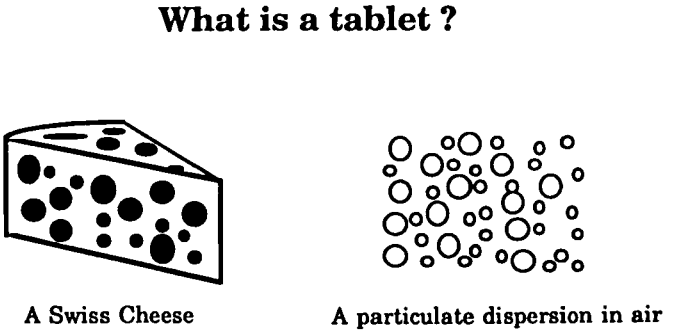

Figure 6. Models for describing the physical structure of a pharmaceutical tablet.

Which one of these extreme models that are most close to a correct description is largely related to the degree of compression and to the nature of the dominating bond type. If solid bridges easily can be formed due to melting, the first model may be relevant. This could be the case for some polymeric materials with a low melting temperature. However, for common tabletting materials strong evidence have been presented supporting the second model, as will be discussed below.

Primary and Secondary Factors for Tablet Strength

Two factors could be regarded as primary factors for the compactability of powders (14, 31, 36, 46-49, 53): the dominating bond mechanism and the surface area over which these bonds are active. Owing to considerable experimental difficulties, these factors have not been evaluated in any detail for pharmaceutical materials. Instead, more indirect, secondary factors are normally studied and used for correlations with tablet strength. Such secondary factors are particle shape, surface texture and particle size. The importance of volume reduction mechanisms, i.e. elastic deforamtion, plastic deformation and particle fragmentation have also been studied in detail.

Bonding Surface Area

The term bonding surface area, is often defined as the effective surface area taking part in the interparticulate attraction. In the case of solid bridges, the term corresponds to the true interparticulate contact area, while for intermolecular forces the term is more diffuicult to define. It can seldom be estimated from direct measurements of the surface area of the starting material. This is especially obvious for strongly fragmenting materials (30). Furthermore, in practice, many powders possess, in addition to their external visible surface area, an internal surface area. This internal surface ara is small for dense crystalline solids such as sodium chloride, but in porous bodies such as microcrystalline cellulose and Emcompress®, the internal surface area may be considerably greater than the external surface area (8).

Thus the bonding surface area, is a function of several secondary factors (26). Apart from the complex origin of a bonding surface area, this property is also

TABLE 3

Factors Influencing the Surface Area of Tablet Particles and the Bonding Surface Area in Tablets

Tablet particle surface area		Bonding surface area	
(before compaction)	(after compaction)	(during compaction)	(after compaction)
Particle size	Particle size	Particle size	Particle size
Particle shape	Particle shape	Particle shape	Particle shape
	Fragmentation	Fragmentation	Fragmentation
		Plastic deformation	Plastic deformation
		Elastic deformation	Elastic deformation
			Elastic recovery
			Friction properties
			Bond strength

difficult to exactly define. Consequently, experimental determinations are rare in literature. Instead of a direct measure of the bonding surface area, the secondary factors listed in Table 3 have been measured and used for the correlation to tablet strength (26).

Of special importance for the final bonding surface is probably the particle elasticity of the materials. This property is normally not measured, but the axial elastic recovery of the tablet is determined. Extensive particle elasticity could cause a drastic decrease in tablet strength, due to the breakage of interparticulate bonds, thereby reducing the bonding surface area (3).

Bonding Mechanisms

The general bonding mechanisms co- or adhering particles together have been classified by Rumpf to be of mainly five types (54):

1. Solid bridges (sintering, melting, crystallization, chemical reactions and hardened binders)

2. Bonding due to movable liquids (capillary and surface tension forces)
3. Non freely movable binder bridges (viscous binders and adsorption layers)
4. Attractions between solid particles (molecular and electrostatic forces)
5. Shape related bonding (mechanical interlocking)

This general classification has been widely accepted in the literature. In the case of compaction of dry, crystalline powders, it has been suggested that the mechanisms of importance could be restricted to class 1 and 4 (15) and perhaps also class 5 (55). However, it can not be excluded that the presence of liquids in a compact might be of significance for the tablet strength (53, 56). It can be discussed, though, if the change in tablet strength is due to an effect of liquid on the compressibility of the powder or on the nature of the particle-particle interactions.

However, the dominating bond types adhering particles together in compression of dry powders could for simplicity be limited to three types (55) (Table 4):

1. Solid bridges (due to e.g. melting).
2. Distance attraction forces (intermolecular forces).
3. Mechanical interlocking (between irregularly shaped particles).

The first type corresponds to strong bonds, where a true contact is established between adjacent particles. The second group could roughly be described as weaker bonds acting over distances.

The term, *intermolecular forces*, is used in this article as a collective term for all bonding forces that act between surfaces separated by some distance. Thus, the term intermolecular forces includes van det Waals forces, electrostatic forces and hydrogen bonding (57). The dominant interaction force between solid sufaces is the van det Waals force of attraction (58-60). This force operates both in vacuum, gas and liquid environment up to a distance of approximately 100 - 1000 Å. Hydrogen bonding is predominantly an electrostatic interaction and may occur either intramolecularly or intermolecularly (61). These bonds are of special importance for many direct compressible binders such as Avicel®, Sta-Rx 1500® and Lactose. Electrostatic forces arise during mixing and compaction due to tribo-electric

TABLE 4

Some Specifications of Bonding Mechanisms in Compacted Dry Powders

Type (-)	Dissociation energy (kcal/mol)	Separation distance at equilibrium (Å)	Maximum attraction distance (Å)
Solid bridges			
Convalent homopolar	50-150	<2	<10
Convalent heteropolar	100-200		
Ionic	100-200	<3	
Inter molecular forces			
Hydrogen	2-7	3-4	100-1000
van der Waals	1-10		
Electrostatic			
Mechanical interlocking			

charging. These electrostatic forces are neutralized with time by electrostatic discharging. For compacts stored at ambient relative humidity or in liquids, this is a relatively fast process owing to the high diffusivity of the charges in the liquid or the adsorbed liquid layers.

Solid bridges that contribute to the overall compact strength can be defined as areas of real contact, i.e. contact at an atomic level between adjacent surfaces in the compact. Different types of solid bridges have been proposed in the literature e.g. solid bridges due to melting, self diffusion of atomes between surfaces and recrystallization of soluble materials in the compacts (62-65). Solid bridges can be

detected by electrical resistivity measurements (66, 67). Electric conductance is found in compacts manufactured from metal powders or polycrystalline materials. Most of the electric conductance arises from valency vacancies and impurities in the crystal (67). The amount of electricity that travels between the different crystals in solid and liquid bridges is in the ideal case proportional to the area of real contact between the surfaces. Calculations of the contact area between metallic surfaces have indicated that the area of real contact is relatively small compared with the available geometrical surface area (66).

The term, *mechanical interlocking* is used to describe the hooking and twisting together of the packed material. It has been claimed (55) that materials bonding predominantly by this mechanism require high compression forces and have low compact strength and an extremely long disintegration time. However, a more limited description of this bonding mechanism is, that it is dependent on the shape and surface structure of the particles i.e. long needleformed fibres and unregular particles have a higher tendency to hook and twist together during compaction compared with smooth spherical ones.

AIM

The aim of the present article is to present the collective results from a series of publications from our laboratory (Studies on direct compression of tablets I-XXIII) concerning the mechanistical understanding of pharmaceutical powder compactability. Using several pharmaceutical materials and excipients with widely differing properties with respect to volume reduction behaviour, particle size, shape and porosity the objective was to develop a qualitative understanding of the primary factors involved in the formation of coherent compacts. In particular, emphasis will be placed upon the relevance and usefulness of estimating bonding surface area and bonding mechanisms.

EXPERIMENTALS

Materials

For the investigation of dominating bond mechanisms and estimation of the magnitude of the surface area of the solids involved in interparticulate attraction in

TABLE 5

Specifications of Test Materials According to Literature

Material	Dominating Volume reduction mechanism	Degree of surface roughness
Sodium chloride	Plastic deformation	Low
Sodium bicarbonate	Plastic deformation	Low
Avicel® 101	Plastic deformation (Fragmentation)	High
Sta-Rx 1500®	Plastic deformation	High
Lactose α-monohydrate	Fragmentation (Plastic deformation)	Low/Moderate
Sucrose	Fragmentation	Low
Paracetamol	Fragmentation Elastic deformation	Low
Emcompress®	Fragmentation	High

compacts several pharmaceutical excipients (Table 5) representing both plastically deforming materials (sodium chloride, Avicel® PH 101, Sta-Rx 1500®, and sodium bicarbonate) and fragmenting materials (lactose, sucrose, paracetamol, phenacetin, sodium citrate, ascorbic acid and Emcompress®) will be discussed in this article and have been used in a series of publications from our laboratory.

Compaction of Test Specimen

Compaction using excenter press. An instrumented single-punch press (Korsch EK 0, Federal Republic of Germany) equipped with flat-faced punches of diameter 1.13 cm, was used. The consolidation time for the investigated materials

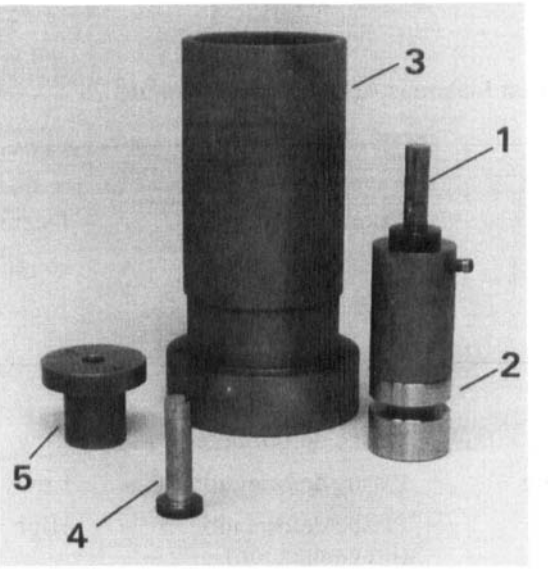

Figure 7. Tablet compression apparatur: (1) Upper punch, (2) Load cell, (3) Compression chamber, (4) Lower punch and (5) Die (From ref. 47)

is in the range of 100-200 ms. The different compression loads were obtained by varying the amount of powder in the die. Before each compaction, the die wall was normally prelubricated with a 1% magnesium stearate suspension in ethanol. The maximum compression loads were within ±3% of the mean values presented.

Compaction in liquids. Tablets were compressed in liquids in a specially designed apparatus manufactured of steel (Fig. 7) equipped with flat-faced punches of a diameter 1.13 cm (47).

The apparatus was filled with liquid to the top of the die. All liquids used in this study were preconditioned with the solid material prior to compaction to obtain a saturated solution. Excess liquid was then removed from the die with a pipette making it possible to add the powder in dry form. An amount of powder sufficient to give a compact height of approximately 0.3 cm at 150 MPa pressure was pured into the die. Liquid was then added to the apparatus to completely wet the powder mass. After one minute the upper punch was inserted in the die and the compression chamber was mounted in the hydraulic press. The upper punch

pressure was then raised to 150 MPa over ten seconds. This procedure gave two effects. Firstly, the liquid was able to leave the tablets when the load increased without disturbing the consolidation of the compact and, secondly, it increased the time for plastic flow in the tablet. Ejection of the tablet from the die was performed in the liquid by turning the die and applying pressure with the hydraulic press on the lower punch. The compact was not exposed to air during the compression and ejection phase since the compression chamber was completely filled with liquid. After ejection the tablets were removed and stored in the saturated liquid for 24 hours before the tensile strength was measured. The compaction procedure described was carried out in a ventilated safety box.

Characterization of Compact Strength

Characterization of radial and axial tensile strength. A Heberline diametral compression test apparatus (TBH 28, Erweka, Federal Republic of Germany) was used for all materials except for Avicel® PH 101. The compacts of Avicel® PH 101 was measured in a material tester (Overload dynamics, Overdyn, The Netherlands) (46-48). The radial tensile strength was then calculated from the obtained crishing strength data. Axial tensile strength was measured in an axial tensile test apparatus (49).

Characterixation of radial tensile strength in vacuum. A vacuum tensile strength tester was constructed (47) (Fig. 8). The tester was manufactured from a tube of stainless steel with two movable vacuum tigth end-plates. On each side of the tube two bellows were attached with vacuum tigth welding. Inside the bellows the tablet crushing device moved freely with a minimum of friction to transmit the force to the tablets in the tester. The force was manually transmitted to the crushing device by a traction wheel and measured with a piezoelectric crystal attached to the bellows. The tester could hold five compacts, stored in a sliding magazine. Prior to each measurement, the tablets were degassed for twenty-four hours or longer at a pressure of less than 10^{-4} mm Hg. For each material, ten tablets were measured in vacuum and ten in air in the apparatus. The radial tensile strength was then calculated.

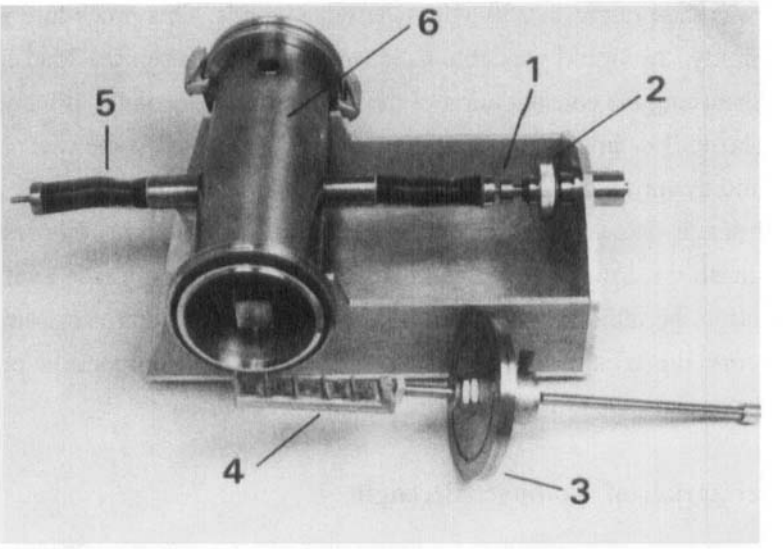

Figure 8. Vacuum tensile strength tester: (1) Load cell, (2) Traction wheel, (3) End plate, (4) Magazine, (5) Bellow and (6) Tube (From ref. 47).

Characterization of radial tensile strength in liquids. To measure the compact strength in liquids, a material tester (Overload dynamics, Overdyn, The Netherlands) was used (47). The radial tensile strength was then calculated.

Surface Area Measurements

Measurements of gas adsorption surface area. The specific surface areas of both powders and compacts were measured by low-temperature krypton adsorption in an Alfa-Mec 6E (Studsvik, AB Atomenergi, Sweden), with liquid nitrogen as coolant (68). The specific surface areas were calculated with the B.E.T. equation in the relative pressure range of 0.05-0.35 (28).

Measurement of permeametry surface area. A Blaine permeameter was used to measure the powder specific area of the test materials (31, 46-48). The apparatus and calculations are described elsewhere (28). For the coarse fractions of sodium

chloride and lactose, a powder plug with a diameter of 9.86 mm and a height of 100 mm was used (69). The surface area was calculated assuming pure viscous gas flow through the plug.

For the measurement of compact surface area a weighed amount of powder was put into a specially constructed die which was sealed with a plate according to Alderborn et al. (28). After compaction, the die containing the compact was connected to a Blaine permeameter. The compact surface area was calculated as described earlier (28), using terms for both viscous and molecular flow.

For tablets compressed in liquids (47), the die containing the specimen was stored at 30°C in a static-bed dryer for five hours. All compacts were stored at ambient relative humidity for at least 12 hours before the die was attached to the Blaine permeameter and measured in the same way as the compacts compressed at ambient conditions.

EVALUATION OF DOMINATING BOND MECHANISMS

Surface Specific Tablet Strength

Since solid bridges seem to be relatively strong bonds, while intermolecular forces are weaker, though acting over distances, a ratio between the compact strength and the surface area of the starting compound could perhaps be used to distinguish between the two bonding mechanisms (46).

The surface specific strength would then give a high value for a material bonding predominantly with solid bridges and a low value for a material bonding with long range forces as the dominating bond type. In Table 6 the compact strength is expressed in relation to the surface area of the respective materials.

The coarse sodium chloride qualities gave high values and iron, Sta-Rx 1500®, sodium bicarbonate, Avicel® PH 101 and sodium chloride <63 μm gave lower values. It is of special interest that the surface specific strength of Avicel® values is of the same order as the other materials in this group. This indicates that

TABLE 6

Surface Specific Radial Tensile Strength of Test Materials Compacted at 150 MPa

Material (-)	Radial tensile strength δ_x (kpa)	Powder surface area s (cm^2)	Surface specific tensile strength δ_x/s (kpa/cm^2)
Sodium chloride 425-500 μm	1150	44[a]	26.1
Sodium chloride 250-355 μm	793	68[a]	11.7
Sodium chloride <63 μm	2990	612[b]	4.9
Iron	1880	1490[b]	1.3
Avicel® PH 101	7330	1610[b]	4.6
Sodium bicarbonate 90-150 μm	571	503[b]	1.1
Sta-Rx 1500® 90-150 μm	514	358[b]	1.4

a Surface area of the amount of material corresponding to a tablet, as measured by gas adsorption.
b Surface area as measured by permeametry.

the high absolute tablet strength of Avicel® probably is caused by a high surface area taking part in the bonding.

The results indicate that all of the investigated materials are predominately bonding with long range forces, however, two of the materials i.e. sodium chloride 425-500 μm and sodium chloride 250-355 μm are also bonding with a significant contribution from solid bridges.

The use of Lubricant Films

The effect of mixing sodium chloride, iron, Avicel® PH 101, sodium bicarbonate or Sta-Rx 1500® with small amounts of magnesium stearate on

compact strength was investigated (47). The effect of removing magnesium stearate by soaking the compacts in an organic solvent was also studied in an attempt to regain the initial compact strength (47).

The main effect of the magnesium stearate film on compact strength is to reduce bonding with intermolecular forces. If intermolecular forces were the only bond type present and no fragmentation of the particles or rupture of the lubricant film occurred, a compact strength close to zero would be expected. For materials bonding with solid bridges, relatively high local stresses may be formed within the compact, as suggested for coarse sodium chloride (46). Such materials ought then to be capable of penetrating the lubricant film prior to the formation of solid bridges. The compact strength should level off at higher concentrations of magnesium stearate thereby ideally reflecting the relative contribution of solid bridges to the total compact strength.

The proportion of lubricant added to each test material corresponded to values above and below the theoretical amount required to form a mono-molecular coat on each material (34).

The plot (Fig. 9) of the rematining strength (%) against the weight of added magnesium stearate in relation to the compound surface area, shows that the radial tensile strength decreases for all materials with increasing amounts of magnesium stearate. This is in agreement with earlier reports (15, 34), where this effect was explained in terms of the formation of a molecular lubricant film around the compound particles.

At concentrations between 0.2-1 $\mu g/cm^2$, the compact strength levelled of and reached a constant value for all materials except Sta-Rx 1500®. This is in agreement with the lubricant concentration predicted to give a molecular film around the particles on the assumption that magnesium stearate corresponds to a molecular surface area of 400 m^2/g (34). This is equivalent to 0.25 μg magnesium stearate/cm^2 compound and is denoted by a dotted line in Fig. 9.

The results indicate that a shift in main bond type has taken place i.e. intermolecular forces have been filtered out by the magnesium stearate film and that

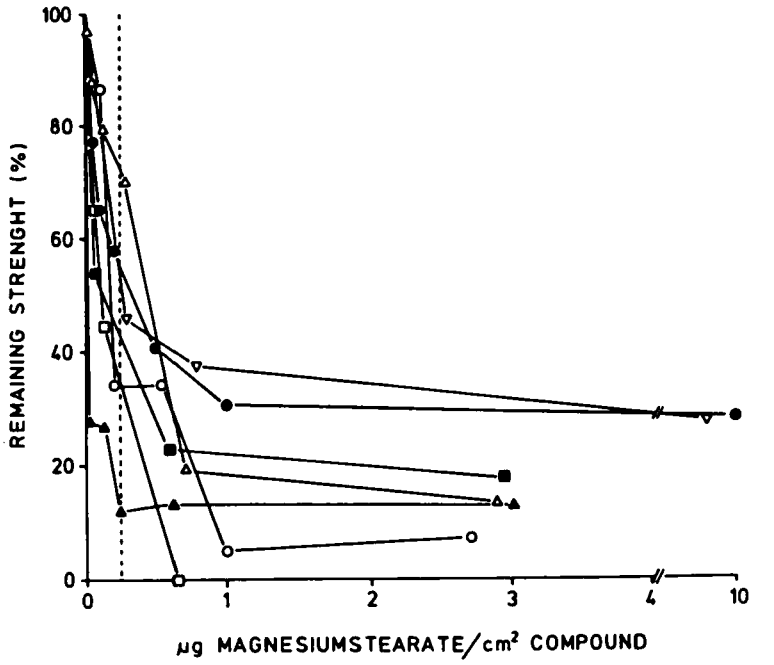

Figure 9. The effect of surface specific lubricant concentration on remaining strength. (△) Avicel® PH 101; (■) Iron; (○) Sodium chloride < 63 µm; (●) Sodium chloride 250-355 µm; (▽) Sodium chloride 425-500 µm; (▲) Sodium bicarbonate; (□) Sta-Rx 1500® (From ref. 46).

the dominating bond type involves solid bridges when the plateau has been reached. If this assumption is correct the relative contribution by solid bridges could be estimated.

The coarser fractions of sodium chloride appears to bond with a relatively high proportion of solid bridges, while for the other materials the contribution is less. However, for Avicel® PH 101 an incomplete surface coverage by the lubricant and a limited particle fragmentation can be expected which will influence the interpretation of the results. This assumption was supported by the fact that the constant level found for Avicel® PH 101 at 150 Mpa was absent when the material was compressed at 35 MPa. Then zero compact strength was obtained. According to Sixsmith (12) there is limited fragmentation tendency below 50 MPa. The level found for Avicel® PH 101 at 150 MPa is thus best explained by an incomplete

surface coverage with magnesium stearate after compaction due to fragmentation of the Avicel® PH 101 particles rather than solid bonds penetrating the surface film.

All lubricated tablets were then tested on soaking by immersing them in a mixture of isoamylalcohol and chloroform (1/1) for seven days. For all materials, soaking the unlubricated compacts resulted in little change in the mechanical strength, indicating that the solvent did not cause any specific interaction, such as dissolution followed by recrystallization. For all lubricated compacts except sodium bicarbonate the soaking procedure resulted in a reduction in the amount of magnesium stearate present in the compacts and with the exceptionof sodium bicarbonate, the lubricated compacts increased significantly in strength after the soaking (Fig. 10 and 11). Theoretically, if magnesium stearate functions as a filter for intermolecular attraction and thereby reduces the long range bonding forces, the compact strengths ought to be fully restored after saoaking, provided all lubricant is removed and that the proportion and degree of solid bridges have not been altered due to the admixing of the lubricant. However, the soaked compacts never attained the same strength as the unlubricated compacts. The most probable explanation for this is incomplete soaking of the specimens tested. For sodium chloride <63 μm (Fig. 10), the treatment resulted in an almost complete recovery of compact strength.

The results from the soaking experiments indicate that intermolecular forces, acting over distances, contribute substantially to the strength of the tested compacts. These forces could be filtered out by the addition of a film forming lubricant. However, this effect seems to be reversible in the sense that removal of the lubricant increases the strength again. Intermolecular forces thus constitute the dominating or only bonding mechanism for the investigated materials. Only for sodium chloride, is there substantial evidence for the existence of solid bridges.

Powder Compaction in Liquids with Different Dielectric Constants

If a surface is covered with a liquid, the liquid will act as a barrier for the adhesion forces and hence reduce the interaction between surfaces in close proximity. However, if more liquid condenses on the surface, liquid bridges may be formed between surfaces in close contact. These bridges are strong, and could

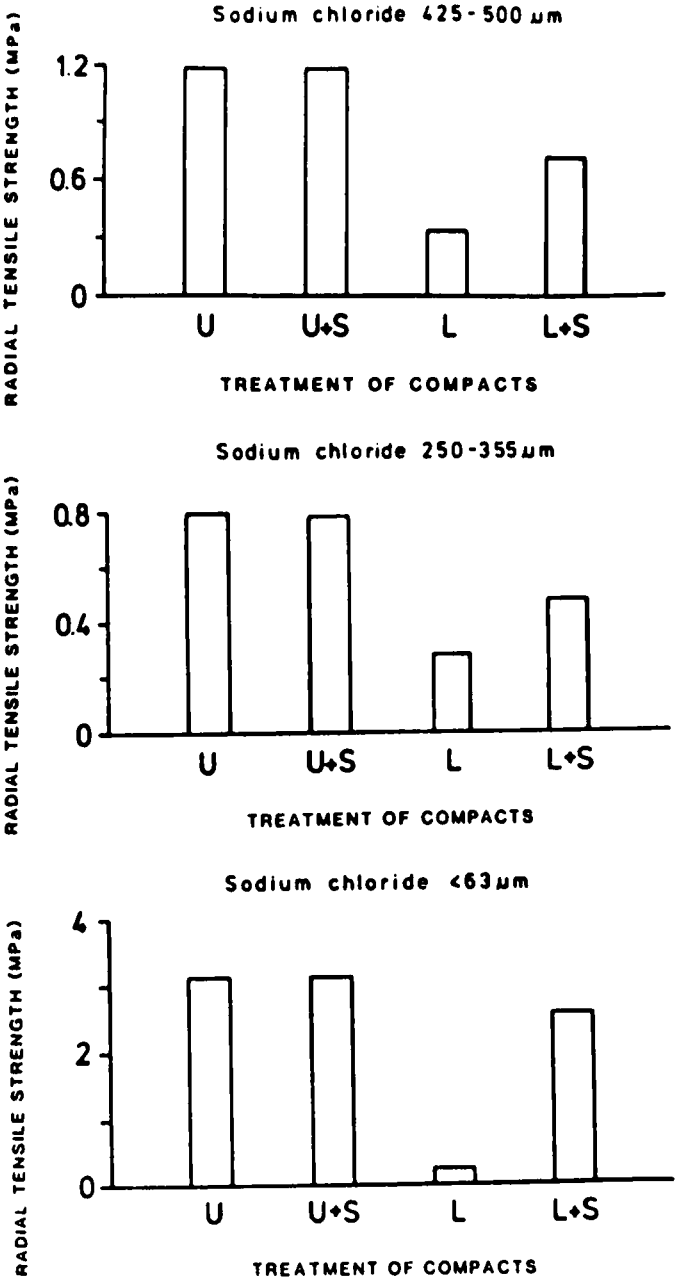

Figure 10. Radial tensile strength for unlubricated (U), unlubricated plus soaked (U+S), lubricated (L) and lubricated plus soaked (U+S) compacts of Sodium chloride (From ref. 46)

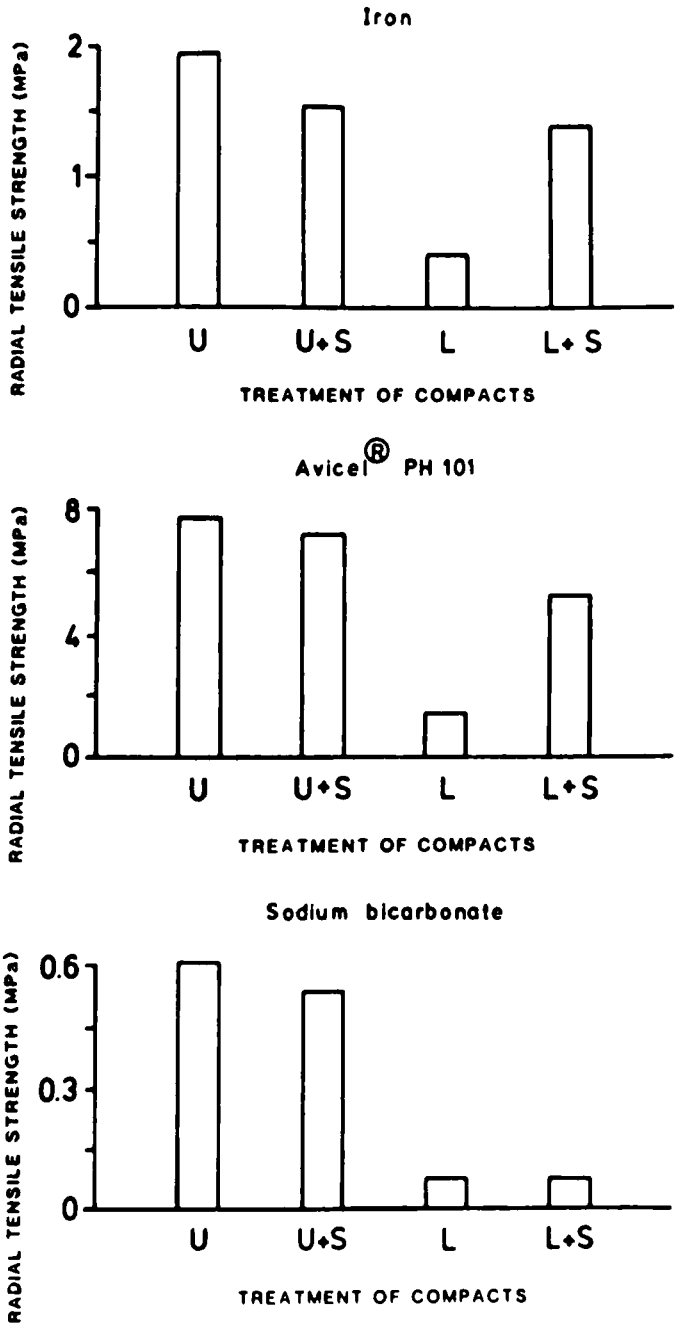

Figure 11. Radial tensile strength for unlubricated (U), unlubricated plus soaked (U+S), lubricated (L) and lubricated plus soaked (U+S) compacts of Iron, Avicel® PH 101 and Sodium bicarbonate (From ref. 46)

thus increase the compact strength. However, it should be noted that only the interfacial forces at the liquid-gas interface contribute to the bonding force between the grains. As soon as the liquid completely envelops the compact, all capillary bonding force vanishes (62).

Shirvinskii reported that the adhesion forces for a number of different particulate materials (silicon, aluminum and calcite) adhering to surfaces of silicon, quartz, teflon and steel, decreased with increasing dielectric constant for liquid binary media or along a curve with a minimum plateau value (70). The basic idea of this therory is that the forces interacting between surfaces in close contact are considered to be due to a fluctuating electromagnetic field. Because of the quantum mechanical fluctuations, this field is always present in the interior of a material medium, and it also extends beyond its boundaries. This theory is applicable to any material independent of its molecular nature (71, 72).

From the Hamaker and Lifshits theories some general conclusions related to the forces interacting in a medium between particles can be drawn:

a. The London-Van der Waals forces between two particles of the same material dispersed in a fluid are always attractive, provided there is no marked orientation of the fluid molecules. If the particles are of different composition, the resultant force may be repulsive in its nature (71, 73).
b. The London-Van der Waals forces between any two bodies in vacuum are always attractive (71, 73).
c. A decrease in London-Van der Waals forces with an increase in the dielectric constant of the medium could be expected (70, 71).

It seems, therefore, reasonable to determine the tablet strength for a number of pharmaceutical materials compressed in liquids with different dielectric constants, and to compare these strength values with the compacts strength values with the compact strength values obtained in both ambient air and in vacuum. The importance of solid bridges or mechanical interlocking in relation to bonding with intermolecular forces could then be obtained since these latter forces are at a minimum for liquids with dielectric constants of ten to twenty (70).

TABLE 7

Radial Tensile Strength Measured Under Ambient Conditions and in Vacuum of Compacts Prepared at 150 MPa

Material (-)	Tensile strength (MPa) [a]		Increase in tensile strength
	Ambient	Vacuum	(MPa)
Avicel® PH101	6.37 (0.81)	8.08 (0.73)	1.71
Sodium chloride coarse	1.01 (0.13)	1.28 (0.20)	0.27
fine	4.13 (0.56)	5.00 (0.56)	0.87
Lactose coarse	0.73 (0.08)	0.80 (0.10)	0.07
fine	1.03 (0.22)	1.40 (0.21)	0.37

[a] Standard deviations are given in parentheses.

Two plastically deforming materials sodium chloride, Avicel® PH101 and one material undergoing extensive fragmentation, lactose, were compressed both in air at ambient conditions and in liquids with different dielectric constants (47).

The use of liquids to reduce bonding with intermolecular forces has one important limitation for compounds easily soluble in water e.g., sodium chloride and lactose. The solubility of these materials increase drastically with increasing dielectric constant of the test liquids (74). A high solubility increases the risk that solid bridges and surface properties of the compact can change due to dissolution. This risk is difficult to grade and evaluate. However, for liquids with a dielectric constant below ten to twenty the solubility is limited and subsequently does not significantly affect the bonding properties of the tested materials (47). To further minimize dissolution, saturated solutions were used in this study.

The results (Table 7) showed that all investigated materials increased in radial tensile strength in vacuum. This was explained by the removal of condensed material, primarily water from the particle surfaces in the compact (75). Similar results have been reported for water absorption on degassed silica compacts (76). They found that the compact strength decreased proportionally to the surface coverage of water. This suggests that the strength increase in vacuum is primarily

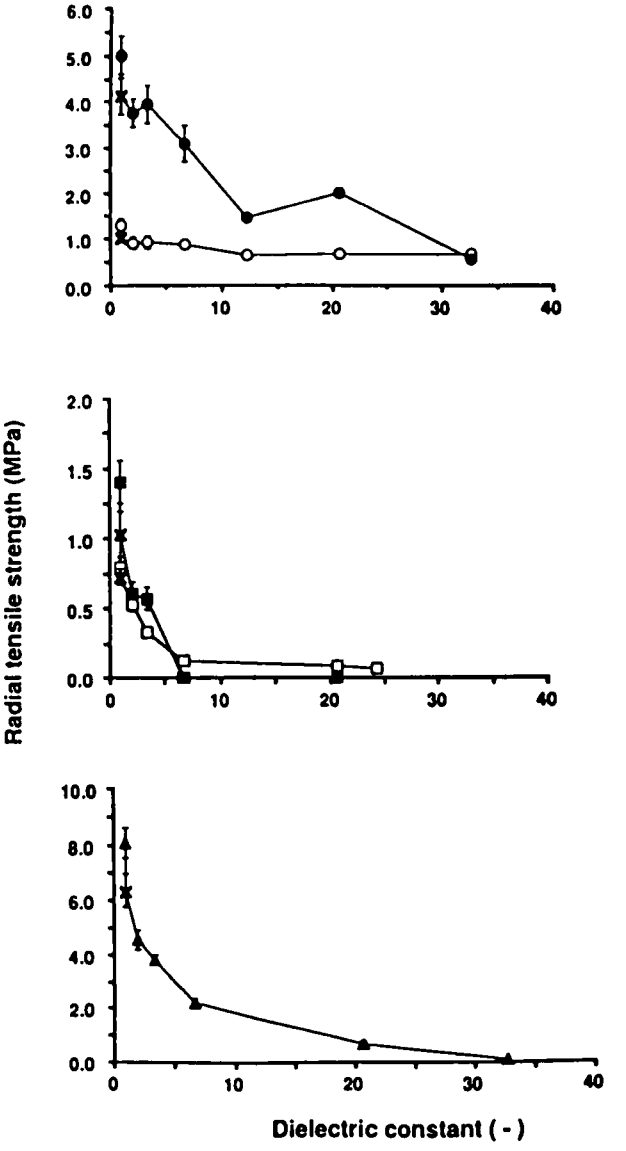

Figure 12. The effect of the dielectric constant of the test liquid on the compact strength. (○) Sodium chloride coarse; (●) Sodium chloride fine; (□) Lactose coarse; (■) Lactose fine; (▲) Avicel® PH101, compressed at 150 MPa. Error bars represent confidence intervals of the mean for 95% probability. For some of the result, precision is better than can be denoted in figure (From ref. 47)

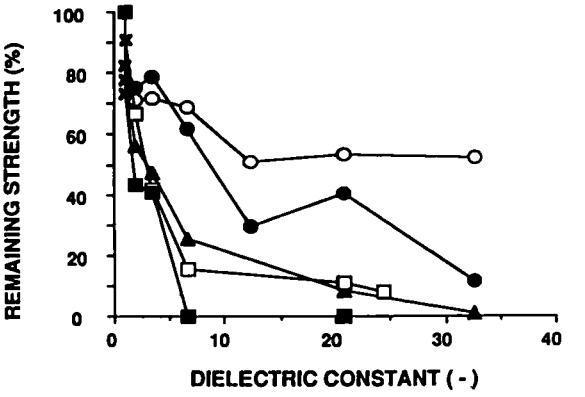

Figure 13. The remaining compact strength in liquids compaired with the radial tensile strength in vacuum. Compact strength in ambient surrounding is marked with X. Symbols as in Fig. 12 (From ref. 47).

caused by an increased surface interaction due to removal of adsorbed water vapor and surface contamination which act as a filter to reduce bonding with intermolecular forces (47). A completely clean surface correspond to a dielectric constandt of unity, i.e. maximal interaction between surfaces in close contact.

In Fig. 12 is the compact strength in liquids compared with the radial tensile strength in vacuum presented, and in Fig. 13 are the corresponding remaining strength values (%) given. Since the tensile strength of compacts prepared in air can be regarded as a starting point before transfer takes place to a vacuum or a liquid environment, the compact strength measured under ambient conditions is denoted by a different symbol (X) in the figure.

All materials decreased with increasing dielectric constant in the interval tested. This is similar to the results obtained above with small amounts of magnesium stearate (46). The formation of a plateau was above suggested to be typical for a material bonding with at least two different bond types, e.g. solid bridges and intermolecular forces (31, 46). When a stable plateau is obtained, the compact strength will in the ideal case be determined by solid bridges or mechanical interlocking alone.

It seems therefore that the results (47) for both size fractions of sodium chloride support the existence of solid bridges for this material. A similar result was obtained for coarse lactose compacts which also formed a plateau. Although lactose is described as a brittle material, the participation of plastic flow in the densification process has been reported (3). A limited contribution of bonding with solid bridges was therefor regarded as a possible explanation for the plateau for coarse lactose. For the fine fraction of lactose, no coherent compacts were formed when the liquid dielectric constant exceeded approximately seven, indicating that intermolecular forces is the only bonding mechanism for this size fraction.

Avicel® PH 101 showed a continuous decrease in tablet strength down to zero with increasing dielectric constant. Thus bonding with intermolecular forces seems to be the dominating bonding mechanism for this material.

EVALUATION OF BONDING SURFACE AREA

Relations Between Tablet Surface Area and Bonding Surface Area

For many materials it has been possible to relate an improved tablet strength to e.g. a decrease in particle size or a change to more irregulary shaped particles. It has also been claimed that materials which deform plastically bind better than materials undergoing elastic deformation or extensive particle fragmentation (50, 51). Plastic deformation are thus believed to be of special importance for the formation of a large bonding surface area (e.g. 55).

Some fundamental studies in the field of metallurgy (66) have indicated that the surface area taking part in the attraction between compact particles is relatively small, being only a minor fraction of the geometrical surface area available. Studies on pharmaceutical materials, using gas adsorption techniques, have, however, suggested that larger surface areas are involved (11, 29, 30,77). In these studies, a decrease in tablet surface area with compaction load has been regarded as a reflection of the surface area utilized for the bonding between particles.

With few exceptions, the relations between compaction load and measured tablet surface area presented in the literature are relatively complex (e.g. 29) (Fig.

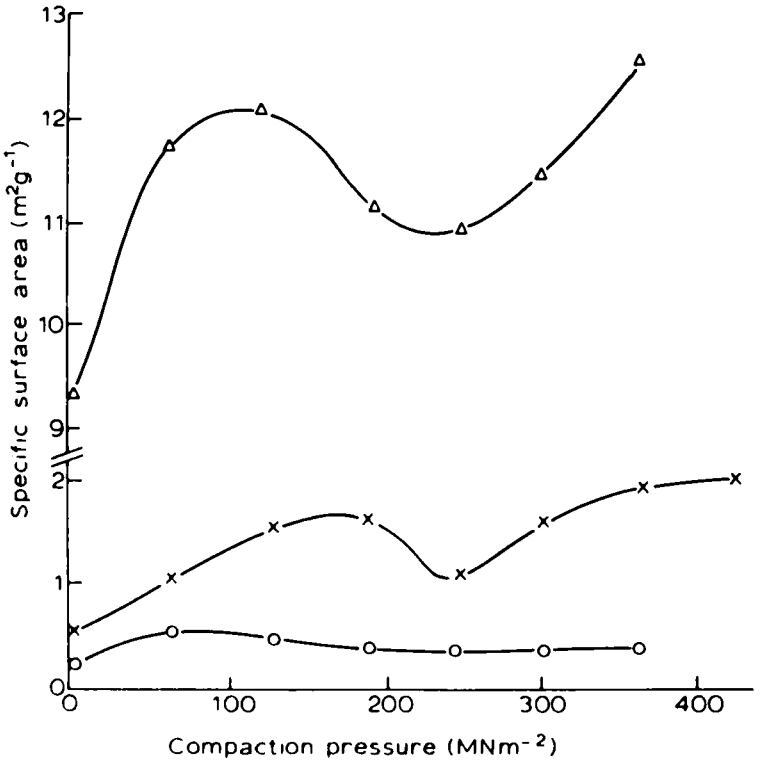

Figure 14. Specific surface area – compaction pressure profiles of sodium chloride (O), phenacetin (X) and magnesium carbonate (Δ) (From ref. 29)

14). Normally, an initial increase in tablet surface area with compaction load is recorded. This has been explained by a fragmentation of the compressed particles, resulting in the formation of new surfaces. With increasing compaction load, more dense compacts will be formed, bringing particle surface areas into closer proximity. The surface area available for the gas molecules will then be dependent upon the penetration capacity of the technique, i.e., mainly the size of the gas molecules used (31). For gases like nitrogen and krypton, that are normally used in these kind of studies, the molecules will only reach a fraction of the total tablet surface ara. Since the distances between solid surfaces needed for the development of bonds could be substantially smaller than the size of the gas molecules, only a part of the 'non-available' surface area may be utilized for bonding (11). Additionally, the use of porous materials and the possibility for pores and cracks to

be closed during compression may further complicate the evaluation of a bonding surface area (8, 28).

Using *gas adsorption* data the following relation has been applied to estimate the surface area utilized for bonding:

$$S_T = S_P + S_F - S_B \qquad \text{(Eqn 2)}$$

S_T: Tablet surface area as measured by gas adsorption
S_P: Surface area of uncompressed particles
S_F: New surface area created by fragmentation during compression
S_B: Surface area consumed for bonding

From the discussion above it is however obvious that such calculations involves to many uncontrolled factors, especially if porous, granulated materials are tested. These difficulties thus make the conclusion, that larger surface areas may be involved in pharmaceutical tablets, highly uncertain.

If however, solid non-porous materials, undergoing volume reduction mainly by plastic deformation without any tendency towards fragmentation are used, some kind of proportional relation between compact surface area and bonding surface area ought to be obtained. For iron powder and coarse particulate sodium chloride, two materials belonging to this group, this has been investigated at our laboratory (31).

The characteristics of both iron and sodium chloride compacts, compressed at increasing loads, are presented in Fig. 15. The compact strength increased approximately linearly for both materials tested. The minimum load at which coherent compacts could be obtained was about 100 and 50 MPa for iron and sodium chloride respectively. The slope of the linear part of the strength-pressure profile was approximately three times higher for iron than for sodium chloride, indicating that the iron powder was bonding with a stronger bond type or that the surface area utilized for bonding was higher. Assuming that the major bond types involved are unchanged with increasing pressure, it seems reasonable that an increase in strength is accompanied by a proportional increase in bonding surface

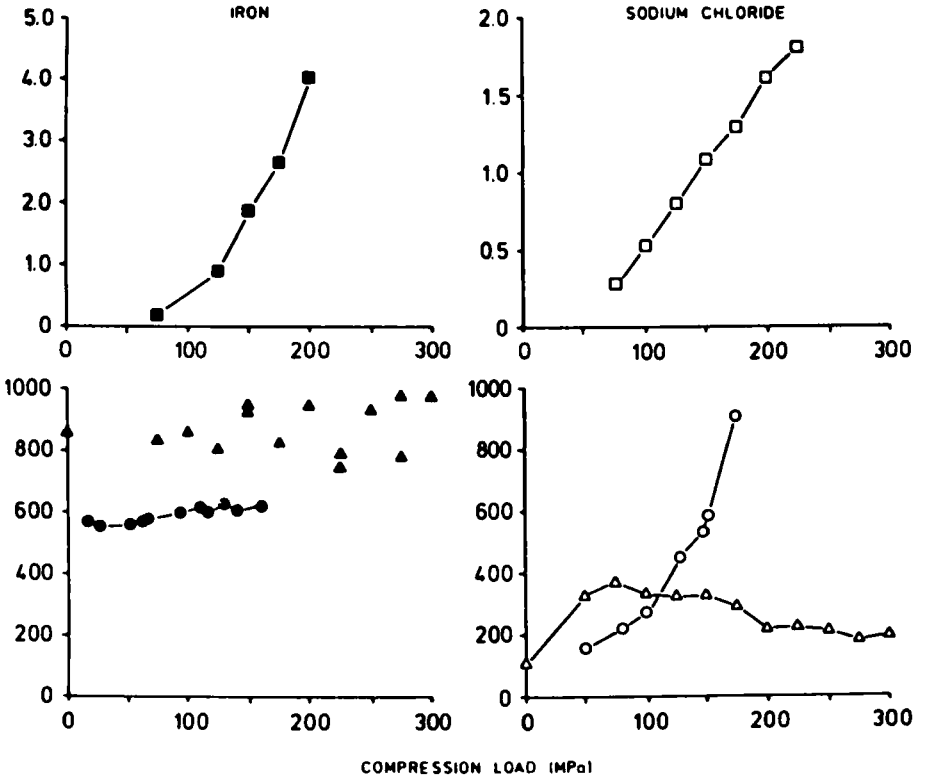

Figure 15. The effect of compression load on compact strength (□) and compact surface area as measured by gas adsorption (△) and permeametry (○), for iron (closed symbols) and sodium chloride (open symbols) (From ref. 31).

area. If the permeametry and gas adsorption techniques are capable of detecting such an increase in bonding surface area, results would be expected showing a decrease in compact surface area after 100 and 50 MPa for the two materials respectivley. However, for the iron compacts, the surface areas obtained by both permeametry and gas adsorption (Fig. 15) seem to be fairly constant with increasing pressure. For permeametry, even a slight increase was observed. It could, however, be questioned whether this is an artefact or not. In an earlier study (28), it was shown that measurements on powders compressed at relatively high loads could result in an overestimation of compact surface area. The surface areas measured by gas adsorption showed an appreciable variation, especially at high loads, making it difficult to draw firm conclusions. The result could not be

interpreted as giving a significant decrease in compact surface area with compression load, after 100 MPa. The relatively small difference in surface area obtained by the two techniques investigated supports the idea that the iron particles were essentially non-porous.

The lack of increase in permeametry surface area with increased compression load indicates that the iron particles were not significantly fragmenting during compression. The data obtained for the iron powder therefore indicate that the surface area utilized for interparticulate attraction is equal to or less than the precision of the surface area methods tested. Since it is reasonable to assume that these methods will tend to overestimate the bonding surface area (11) as discussed in the Introduction, the results imply that the bonding surface area in the iron compacts is very small (66).

The surface area profiles for sodium chloride (Fig. 15) show a different pattern. Initially, the permeametry surface area shows a moderate increase, whereafter an extensive increase is observed. Although the data obtained at higher pressures presumably correspond to an overestimation of the surface area (28), the results indicate that volume reduction of sodium chloride is accompanied by some tendency towards particle fragmentation. The surface area as measured by gas adsorption shows initially a higher increase with compression load than the corresponding data obtained by permeametry. This probably reflects the fact that cracks and pores were formed during compression. After approximately 75 to 100 MPa, the surface area decreases with an increase in compression load. This decrease in gas adsorption surface area could then be a reflection of an increase in bonding surface area. This means that sodium chloride particles bond with a significantly weaker bond type than the iron particles, resulting in weaker compacts but utilizing a larger surface area for interparticulate attraction, which subsequently is reflected in the decrease of gas adsorption surface area. This decrease could alternatively be interpreted as a sealing of cracks created. Considering the profiles obtained for the iron powder, the latter explanation seems more probable. The results therefore indicate that the bonding surface area for sodium chloride is relatively small.

In an attempt to vary the degree of bonding without changing the compression load and subsequently not affecting the fragmentation tendency or formation of cracks, mixtures of sodium chloride and varying amounts of magnesium stearate were compressed at 150 MPa. The effect of increasing additions of the lubricant on both compact strength and surface area for sodium chloride is presented in Fig. 16.

Using minute additions, the compact strength decreased strongly with increasing magnesium stearate concentrations. This is in agreement with results reported earlier (8, 15, 34), where this effect was explained in terms of the formation of a lubricant film around the compund particles. However, at additions in excess of approximately 0.005 wt.%, the compact strength levelled off and even the use of a relatively high concentration (0.05 wt.%) gave no further reduction in strength. Similar profiles have been obtained for silica compacts (76), where only a small amount of adsorbed water decreases the compact strength considerably, whereafter the strength remained fairly constant when the adsorption of water was further increased. The interpretation of the data obtained is as discussed above that two different bond types are involved in the interparticulate attraction (46, 47).

One bonding mechanism (e.g., molecular forces of Van der Waals type) is very sensitive for surface changes, while the other mechanism (e.g., solid bridges due to ionic bonding) could be established even in the presence of a lubricant film by, due to penetration by point irregularities. When a total surface coverage of sodium chloride particles by magnesium stearate is obtained, the latter bond type alone would determine the compact strength.

As evident from Fig. 16, the admixture of the different lubricant amounts did not affect the powder surface area as characterized by the gas adsorption technique. However, the gas adsorption surface area of the corresponding compacts showed a decrease with increased quantities of lubricant. This effect was not expected, considering the obtained decrease in compact strength, which was supposed to expose the surface area used for bonding (30). The result could probably be explained by a reduction in particle fragmentation and crack formation in the systems containing lubricant additions. Similar observations have been reported earlier (29) The results therefore indicate that the surface area used for bonding is relatively small, and masked by the surface area changes due to fragmentation and crack formation.

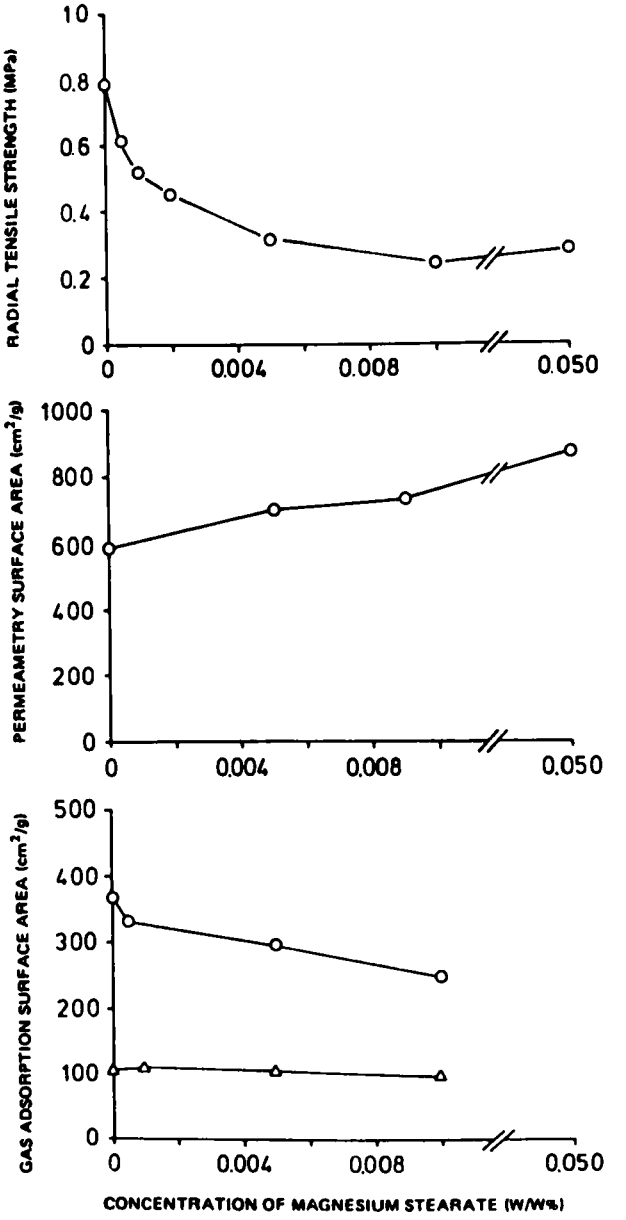

Figure 16. The effect of lubricant concentration on compact strength and surface area for sodium chloride, compressed at 150 MPa (From ref. 31).

The results obtained demonstrate the problems involved when investigating the compaction behaviour of pharmaceutical materials. Although sodium chloride in pharmaceutical studies (e.g. 8, 15, 29) normally represents a nearly ideal model substance (non-porous and consolidating by plastic deformation), it is evident from the results that sodium chloride must be classified as a complex substance with respect to its compaction behaviour. In contrast to the iron powder, sodium chloride particles undergo such changes during compression (fragmentation and formation of cracks and pores) that a simple monitoring of changes in surface area with pressure (Fig. 15) cannot unambigously be used for the evaluation of bonding surface area. Considering the even more complex nature of most pharmaceutical materials used in some reported studies (8, 11, 29, 30, 77) it is questionable whether the interpretations suggested, purporting relatively high bonding surface areas (11, 29, 30, 77), are justified solely on the basis of previously published experimental data.

The results in this study indicate that the surface area taking part in the interparticulate attraction for sodium chloride, as well as for iron powder, is small in relation to the geometrical surface area available. As discussed above it seems reasonable that the major bonding is facilitated by long-range forces (e.g., molecular forces of the Van der Waals type), thereby explaining why the two surface area techniques are not capable of detecting any substantial change in bonding surface area with changes in the different parameters tested.

Thus, a tablet which can be described as a dispersion of solid particles in gas phase where the individual particles are separated by some distance, can probably not be assayed on bonding surface area in any direct sense by surface area methods. The possibility to obtain a proportional relation between measured tablet surface area and the fraction of surface area participating in bonding is then probably limited to relatively simple test systems. Sofar, such relations have only been reported to a limited extent, e.g. for lactoses undergoing fragmentation during compression (45). In these studies, a unique relation was claimed to exist between compact strength and surface area as measured by mercury porosimetry (Fig. 17). It was also suggested that the obtained results indicated that the same bonding mechanism must be active in all types and size fractions of the lactoses tested.

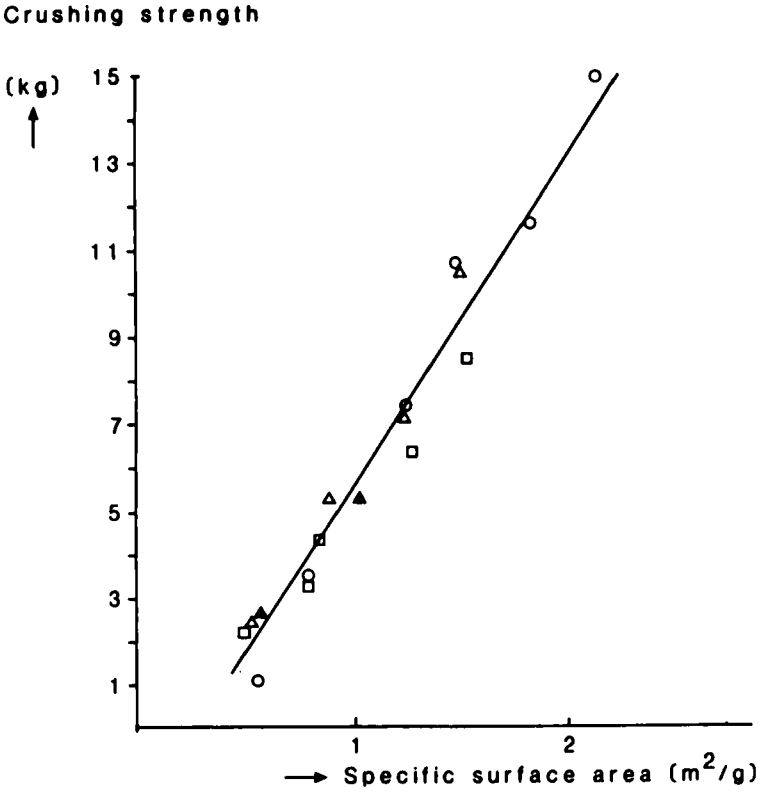

Figure 17. Crushing strength versus specific surface area for tablets compressed from different types of crystalline lactose; α-lactose monohydrate (□), anhydrous α-lactose (○), roller-dried β-lactose (△), crystalline β-lactose (▲) (From ref. 45).

However, it could be discussed whether mercury porosimetry is the best method to reflect the surface area of tablet particles, that potentially could participate in bonding since mercury porosimetry also monitors the surface area of intra particulate pores. Another approach is to use a permeametric technique. Several studies have demonstrated the usefulness of this technique for the characterization of external surface areas in tablets (e.g. 9, 27, 28, 40).

The Importance of Volume Reduction Mechanisms for Bonding Surface Area

The effective amount of surface area available for bonding is dependent on several material properties (26). Both the particle characteristics of the starting

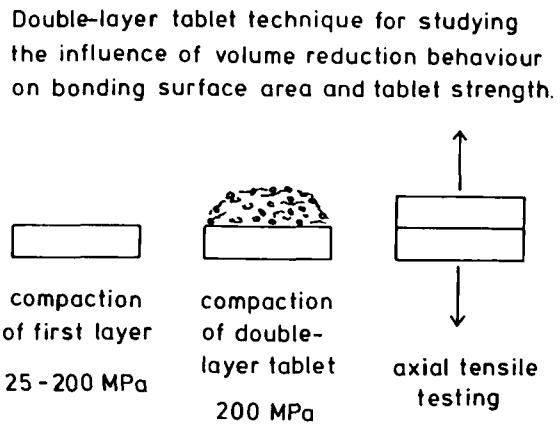

Figure 18

material and the changes caused by the volume reduction will be determining factors. The problems both to measure and also to define a bonding surface area have resulted in a great interest for more indirect, secondary parameters (Table 3). In this section, the influence of volume reduction meachnisms on bonding surface area and compact strength will be discussed.

To study the influence of volume reduction mechanisms on flattening of the surface roughness and the creation of bonding surface areas, a model system was developed (49) consisting of two layers that are compressed together to form a single tablet (Fig. 18). The first layer was precompressed at a compaction pressure of 25-200 MPa. Powder material was then added on top of the first layer and the lower punch was adjusted to give a compaction pressure of 200 MPa for the double layer tablet. The tablet strength was characterized by measuring the axial tensile strength according to Nyström et al. (78).

The axial tensile strength for double layer tablets of all materials are presented in Figs. 19 and 20. 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. 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

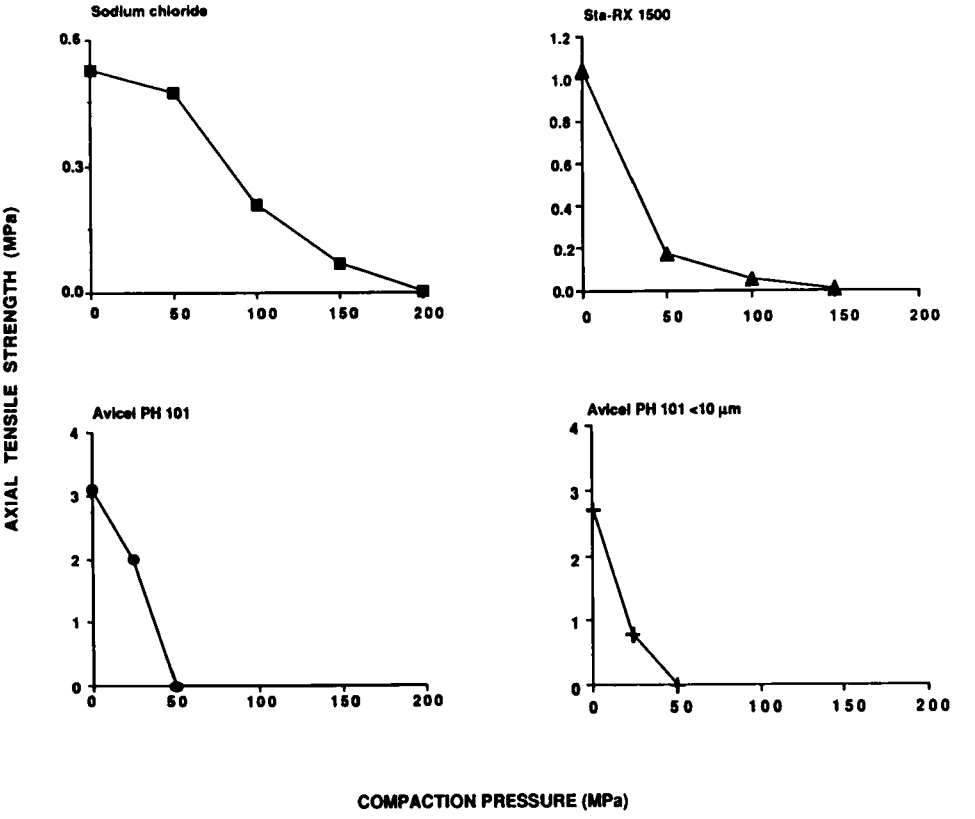

Figure 19. The effect of compaction pressure of the first portion on the axial tensile strength of the double layer compact compressed at 200 MPa, for the plastically deforming materials (From ref. 49).

zone generally was lower than in the intervidual layers. 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. 21, 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-Rx1500® 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

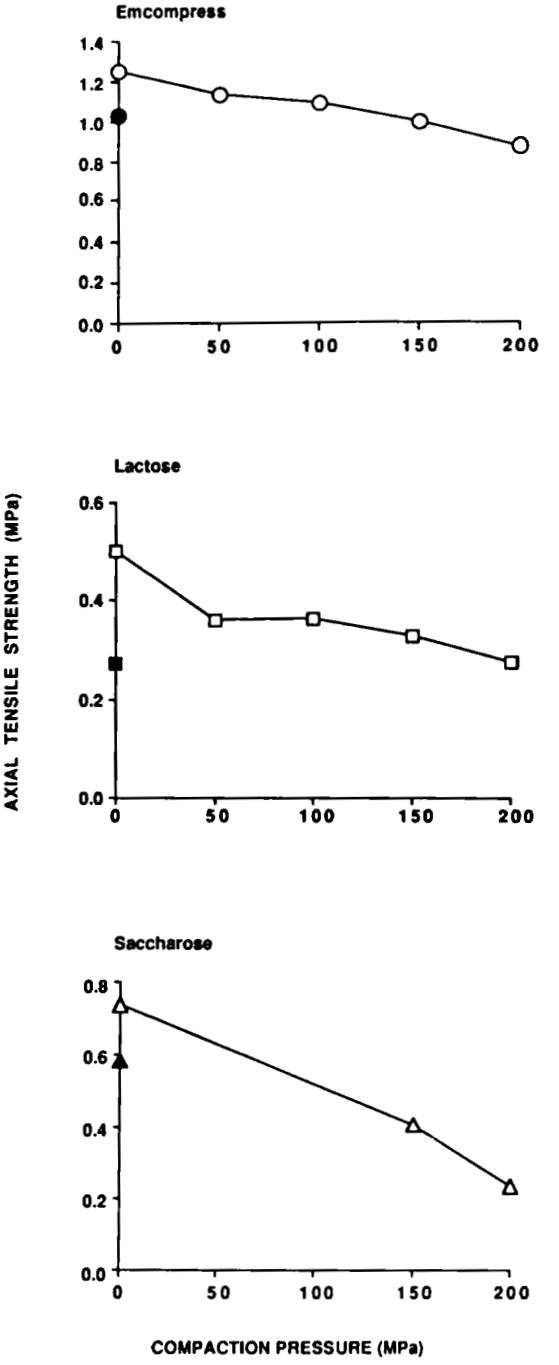

Figure 20. The effect of compaction pressure of the first portion on the axial tensile strength of the double layer compact compressed at 200 MPa, for the materials undergoing volume reduction mainly by fragmentation. The strength of a single tablet compressed two times at 200 MPa is denoted by a filled symbol on the y-axis (From ref. 49).

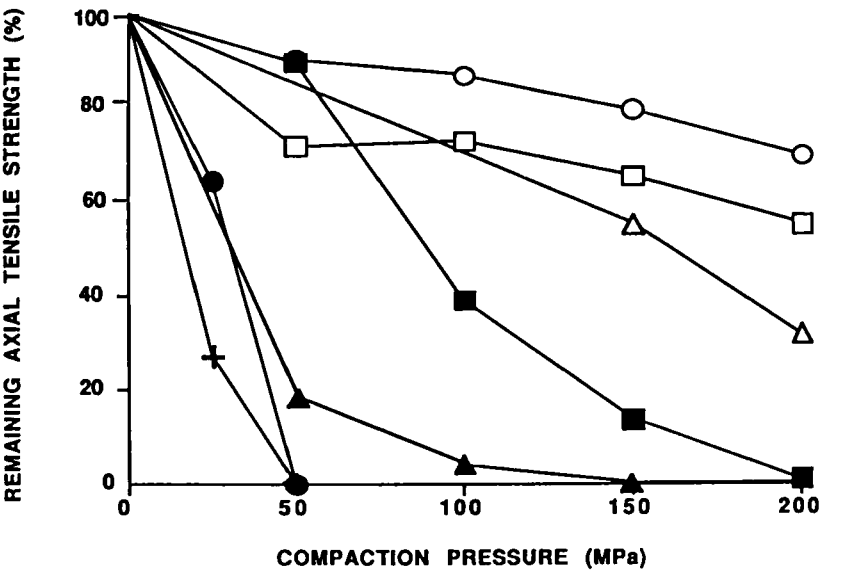

Figure 21. The remaining axial tensile strength with the increase in cmpaction pressure of the first portion of the double layer tablet for all materials tested. Symbols as in Figs. 19-20 (From ref. 49).

compaction pressure compared to the plastically deforming materials. 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 (45, 49). This is especially valid for materials bonding with intermolecular attraction forces, i. e. probably the majority of pharmaceutical compounds and excipients.

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 plasicity. 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® (14) and for sodium bicarbonate (79). It has also been suggested that the high compactability of Avicel® PH 101 is due to the large external specific surface area of the irregular particles (46).

A large surface area and an irregular particle shape will problably promote all bonding mechanisms discussed. Fragmenting materials, normally bonding by intermolecular forces (26) 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 reduced after compression, with a subsequent reduction in intermolecular forces, the development of solid bridges (in e.g. sodium chloride), and mechanical interlocking.

CONCLUSIONS

In this article, several pharmaceutical materials have been tested on volume reduction behaviour, dominating bond mechanism and to a limited extent bonding surface area. The following general conclusions have been suggested.

1. Intermoleccular forces constitute the dominating mechanism for pharmaceutical materials.
2. Then, a proportional relation between compact surface area and bonding surface area could in some cases be established.
3. The following material properties will in principle favour a high compact strength:
   * limited elastic deformation
   * high compact surface area
     - fine particulate starting materials
     - highly fragmenting starting materials
     - starting materials possessing high surface roughness
   * extreme plastic deformation (e.g. amorphous binders)

Classification of Tabletting Materials

It is believed that for materials undergoing extensive fragmentation, a large number of interparticulate contact points are created. The compaction load per unit area of such contact points will thereby be low. This indicates that mainly relatively weak attraction forces, acting over distances, can be formed. However, due to the large number of bonds or attraction zones, a relatively strong compact could be formed. For less fragmenting materials, a smaller number of contact points are formed, which then would result in strong compacts only if relatively strong interparticulate attraction forces, such as solid bridges, could be developed. This is probably the situation for compacts of coarse crystalline sodium chloride. If the material exhibit extensive plastic deformability, such as many amorphous binder materials, the number of weak distance forces would probably be much higher and thereby contribute significantly to the compact strength. Also materials having a rough surface texture ought to be capable of forming a relatively large number of weak distance forces, in spite of that such a material do not fragment extensively. If the powder being compressed consists of particles with both a rough surface texture and a pronounced plastic deformability, compacts of extremely high mechanical strength ought to be obtained, due to the large number of weak distance attractive forces developed. Microcrystalline cellulose (e.g. Avicel®) could be an example of such a material. A suggestion for how materials can be classified according to their compactability and its dependence on volume reduction and bonding properties is presented in Table 8.

An important parameter that will influence the final compact strength is the proportion of elastic deformation and consequently elastic recovery that will take place after compaction. By definition, so called plastically deforming materials show little elastic deformation. Thus for fragmenting materials, it seems important to distinguish between those where the smaller particles formed undergo mainly plastic deformation or elastic deformation. Most of the materials intended for direct compression have in common a minute elastic behaviour.

High tablet strength is thus primarily produced by materials possessing a low elastic component during consolidation and having a high bonding surface area that could develop intermolecular forces. To this group of materials belong fine

TABLE 8

Primary and Secondary Factors Affecting Compact Strength for Pharmaceutical Materials

Dominating volume reduction mechanism	**Low tablet strength**	**High tablet strength**	
	Small number of weak attractions (low bonding surface area and bonding predominantly with intermolecular distance forces)	Large number of weak attractions (high bonding surface area and bonding predominantly with intermolecular distance forces)	Small number of strong attractions (small bonding surface area and bonding both with intermolecular distance forces and solid bridges)
Plastic deformation	Not capable of forming solid bridges *e.g. Sodium bicarbonate*	Very fine particulate qualities e.g. *Fine particulate sodium chloride* Pronounced surface roughness e.g. *Avicel®* *Sta-Rx 1500®* *and milled qualities of materials* Very plastically deformable e.g. *amorphous binders*	Capable of forming solid bridges e.g. *Coarse particulate sodium chloride*
Fragmentation and plastic deformation	Non-existing	With a small elastic component e.g. *Lactose* *Emcompress®*	
Fragmentation and elastic deformation	With a large elastic component e.g. *Phenacetin* *Paracetamol*		

TABLE 9

Possible Advantages With Fragmenting Materials

- Less sensitive for variations in particle size and shape of starting materials
- Less sensitive for admixture of lubricants
- Less sensitive for load rate
- Less prone to undergo postcompaction strength changes by stress relaxation
- High compactability, provided the elastic component of smaller particles (fragments) formed is minute

particulate materials, milled materials and strongly fragmenting materials such as granulations. Excipients belonging to this group may produce a large bonding surface area in various ways e.g. the material can be highly fragmenting, very plastically deforming or exhibit a pronounced surface roughness.

Advantages of Using Fragmenting Materials

Some possible advantages for the use of materials with a high fragmentation tendency are presented in Table 9.

Several studies have shown that a pronounced material fragmentation will result in a reduced dependence on initial particle size, surface shape and texture, additive additions and load rate for the compact strength. In this article it has also been suggested that fragmenting materials in general will result in a high bonding surface area and compact strength, provided the elastic component of the material is limited.

Future Research

Future research in the field of powder compactability ought to be more focused on the characterization of bonding mechanisms and models for estimating the bonding surface area. A means of obtaining relevant information is probably to

directly characterize the behaviour of single primary particles. It is then of special interest to differentiate between bulk and surface behaviour. Also the importance of molecular mobility at particle surfaces and surface interactions with water is then of interest. Some studies on post compaction strength changes (48, 65, 80) are currently undertaken at our laboratory. To develop direct compaction of pharmaceutical materials, to a general formulation procedure, substantial efforts in the field of crystal engineering is demanded, especially regarding the task to decrease the elastic component of materials.

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