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Paper

Effect of particle size and compaction load on interparticulate bonding structure for some pharmaceutical materials studied by compaction and strength characterisation in butanol

Åsa Adolfsson, Helena Olsson, Christer Nyström *

Department of Pharmacy, Uppsala University, Uppsala, Sweden

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Abstract

The remaining tensile strength (the strength of tablets in 1-butanol divided by the strength in air) was used as a simplified measure of bonding by solid bridges and/or mechanical interlocking. The remaining tensile strength is believed to provide information about interparticulate bonding structure. Weak distance forces appeared to play an important role in the bonding of all compacts. Bonding by mechanical interlocking has been suggested as a possible bonding mechanism for dicalcium phosphate dihydrate and microcrystalline cellulose. Solid bridges develop during compaction of sodium chloride tablets. Sodium bicarbonate and sodium chloride have similar chemical structures and volume reduction behaviour. However, due to the more complex intraparticulate chemical structure, solid bridges probably do not develop to a large extent in sodium bicarbonate compacts. Weak distance forces are probably the most important bonding mechanism for lactose and sucrose. Decreasing particle size and increasing compaction load appear to decrease bonding by mechanical interlocking in materials where this type of bond is possible. Increasing particle size and compaction load in sodium chloride compacts facilitates the development of solid bridges. However, the compaction load and particle size do not seem to have any major effect on the bonding structure in lactose and sucrose compacts. © 1997 Elsevier Science B.V.

Keywords: Bonding mechanism; Tablet; Dielectric constant; Liquid; Remaining tensile strength; Particle size; Compaction load; Volume reduction behaviour; Intraparticulate chemical structure

1. Introduction

The primary factors thought to determine the tensile strength of a pharmaceutical compact are the strength of the interparticulate bonds and the surface area over which these bonds are active [1]. The forces believed to hold tablet particles together in a pharmaceutical compact include distance forces, solid bridges and mechanical interlocking [2–4].

Weak long range distance forces are considered to be the dominant bonding mechanism for pharmaceutical materials. The strength of theses forces is affected by the type of material, the distance between the molecules or particles and the surrounding medium [5]. Van der Waals forces are probably the most common weak long range distance forces holding particles together, but hydrogen bonds may be important for some materials, e.g. lactose, sucrose and microcrystalline cellulose and might therefore add to the strength of a pharmaceutical compact considerably. Electrostatic forces are weak, probably not contributing to any large extent to the tensile strength of a pharmaceutical compact [1,6].

* Corresponding author. Department of Pharmacy, Uppsala University, Box 580, S-751 23 Uppsala, Sweden.

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Solid bridges may be defined as areas of true contact between particles, created by covalent or ionic bonds and/or weak long range distance forces that are active at a molecular or ionic level [7]. Solid bridges thus consist of the same types of bond as those occurring between molecules and ions within the powder particles. It has been claimed that advanced diffusion (i.e. transport of molecules or ions) or melting of material on tablet particle surfaces during and after compaction is assumed to create solid bridges. This type of restructuring of material may take place at temperatures far lower than the melting point of the material [4,8] and may be caused by strong forces created locally on the particle surfaces during compaction. For this to occur, the original size of the particles in the tablet must be fairly large and the material should not be too prone to fragmentation during compaction [1]. Contact areas at a molecular or ionic level (solid bridges) may also be created by recrystallisation or restructuring of the material on the particle surfaces. This rearrangement may be facilitated by the presence of a liquid [9,10].

Interparticulate bonding by mechanical interlocking is possible for some materials. Particles with a rough texture and irregular shape are probably more liable to bond by hooking or twisting [2–4]. Mechanical interlocking brings the particles into close proximity and facilitates the development of weak distance forces to further increase the tablet strength. Microcrystalline cellulose probably has the potential to bond by mechanical interlocking [1].

Obviously, the chemical structure of the material is important in determining which types of interparticulate attraction mechanism will be in force. The materials included in this study can be divided into three different groups according to their chemical structure.

(a) Firstly, the particles may consist of simple ions building up an ionic crystal structure, e.g. sodium chloride.

(b) Secondly, the ionic material may consist of more complex ions held together by covalent bonds, e.g. hydrogen phosphate. The hydrogen phosphate ions may also form ionic bonds with other ions, e.g. calcium ions, building up the chemical structure of, in this case, calcium hydrogen phosphate. In these more complicated materials, bonding with hydrogen bonds and van der Waals forces may also occur.

(c) In the third type of chemical structure, the material consists of molecules with intramolecular covalent bonds. The attractions between the molecules are van der Waals forces and hydrogen bonds. An example of such a material is sucrose.

In the study of bonding mechanisms, different methods of removing the interparticulate forces have been used. For example, it has been claimed that covering the tablet particles with magnesium stearate before compaction filters out the long range forces [1]. Compaction in liquid [6,7] or soaking the compacts after compaction [11,12] in liquids with different dielectric constants may also remove weak long range distance forces. An increase in the dielectric constant of the liquid would result in lower surface energy and thus reduction of the strength of the weak distance forces [7,12]. Thus, the tensile strength of a tablet compacted in liquid with a high enough dielectric constant should then be due to solid bridges and/or mechanical interlocking [6,7]. From two different studies carried out at our laboratory, it was concluded that a dielectric constant of 18 would filter out interparticulate weak long range distance forces without dissolving the materials included in this study. In these two papers [6,7] the theory behind strength reduction when compaction is performed in a liquid is discussed in more detail.

The aim of this study was to investigate the effect of chemical structure, volume reduction behaviour, particle size and compaction load on bonding structure, and further to evaluate the bonding mechanisms and the possibility of quantifying bonding type for some pharmaceutical materials. The bonding structure was studied by compaction and strength characterisation in butanol and in air.

2. Materials and methods

2.1. Test materials

The primary characteristics of the test materials are summarised in Table 1. Three size fractions (180–355 μm, 90–180 μm and 20–40 μm) of sodium chloride (crystalline, puriss, Kebo-lab, Sweden), dicalcium phosphate dihydrate (Emcompress® Edward Mendell Co. Inc., USA), lactose α-monohydrate (Svenskt socker AB, Sweden) and sucrose (crystalline, Svenskt socker AB, Sweden) were prepared. Two size fractions (90–180 μm and 20–40 μm) of sodium bicarbonate (crystalline, puriss, Kebo-lab, Sweden) were prepared. The finest size fraction (20–40 μm) was obtained by milling in a pin disc mill (Alpine 63C, Alpine AG, Germany), except for preparation of sodium chloride where a mortar grinder (Retsch, Germany) was used. In order to obtain the finer size fractions, air classification (Alpine 100 MZR, Alpine AG, Germany) was undertaken after milling. The coarser fractions were prepared manually by dry sieving of the raw material with laboratory sieves (Retsch, Germany). Microcrystalline cellulose (Avicel® PH101, FMC, USA) was used as the raw material was supplied.

2.2. Characterisation of test materials

The surface areas of the powders were characterised by permeametric methods [13,14] and the apparent

Table 1
Primary characteristics of the test materials

Material	Size fraction (μm)	Volume specific surface area (cm^{-1})	Apparent particle density (g/cm^3)
Sodium chloride	180–355	235 (3)[a]	2.152 (0.001)[c]
	90–180	436 (0)[a]	
	20–40	3168 (45)[b]	
Sodium bicarbonate	90–180	651 (4)[a]	2.214 (0.000)[c]
	20–40	4370 (17)[b]	
Dicalcium phosphate dihydrate	180–355	757 (10)[a]	2.341 (0.002)[c]
	90–180	1068 (49)[a]	
	20–40	5925 (185)[b]	
Lactose	180–355	392 (6)[a]	1.535 (0.001)[c]
	90–180	611 (2)[a]	
	20–40	3909 (138)[b]	
Sucrose	180–355	265 (1)[a]	1.588 (0.000)[c]
	90–180	532 (5)[a]	
	20–40	6937 (57)[d]	
Microcrystalline cellulose	*	5773 (69)[b]	1.571 (0.001)[c]

Mean values for two or three measurements are presented, and the corresponding standard deviations are given in parentheses
* Raw material used as supplied.
[a] Determined using a transient permeameter [11].
[b] Determined using a Blaine permeameter [10].
[c] Determined on the raw material using a helium pycnometer (Accupyc, 1330, Micromeritics, USA).
[d] Determined using a Fisher sub sieve sizer (Fisher Scientific Company, USA).

particle densities of all the materials were determined (Table 1). All powders were stored at 40% relative humidity [15] for at least 2 days before compaction. The liquid used for compaction and strength characterisation, 1-butanol with a dielectric constant of 17.8 [16], was of puriss quality (Kebo-lab, Sweden). A medium with such a dielectric constant was assumed to filter out distance forces effectively without causing any significant dissolution of the material during compaction and storage of compacts [6,7]. The dielectric constant of air was assumed to be the same as in vacuum, i.e. 1.0 [6].

2.3. Compaction and characterisation of tensile strength

The tablets were compacted in a hydraulic press (Apex, UK). The compaction pressure was registered using a piezoelectric crystal. Compaction was performed in a chamber specially constructed to allow the use of both 1-butanol and air [6]. Tablets were formed at three different loads, 100, 200 and 250 MPa, and the thickness of the compacts was in all cases adjusted to 3.0 ± 0.3 mm by varying the amount of material. Strength characterisation by diametral compression test (M30K, Lloyd Instruments, UK) was performed after 2 days storage in the same medium as used for compaction, and the radial tensile strength was calculated [17]. The liquid was saturated with solid material to prevent dissolution of the particles during compaction, storage and strength characterisation of the compacts.

2.4. Calculation of remaining tensile strength

The remaining strength was calculated as the ratio of tensile strength in butanol to tensile strength in air and was expected to be due solely to solid bridges and/or mechanical interlocking.

3. Results and discussion

3.1. Material for which the intraparticulate structure is formed by ionic bonds (sodium chloride)

An increase in particle size resulted in a decrease in tensile strength both in air and when compacted in liquid (Fig. 1a). A decrease in particle size will probably correspond to an increase in available bonding surface area, irrespective of the medium surrounding the tablet particles.

A reduction in particle size seemed also to result in a decrease in remaining tensile strength (Fig. 1b). For tablets produced from coarse sodium chloride, the load applied during compaction is concentrated at quite a small number of interparticulate contact points, i.e. large stresses will be created locally. This concentration of stresses is believed to facilitate diffusion or movement of material at particle surfaces, hence bonding by solid bridges is especially pronounced for the coarse fraction of sodium chloride (Fig. 1b). These results are consistent with those of Karehill et al. [22] but, in that

study, the effect of compaction pressure was not studied (all tablets were compressed at 150 MPa). This study indicates that the effect of particle size on the bonding structure of sodium chloride is also dependent on compaction load.

An increase in compaction load resulted in an increase in tensile strength for all particle size fractions studied (Fig. 1a). There was subsequently also an increase in remaining tensile strength with compaction pressure (Fig. 1b). However, at 200 MPa the remaining tensile strength seemed to have reached a plateau, especially for the two coarser fractions. When the compaction load is increased, the stress at the interparticulate contact points is expected to increase. However, a corresponding increase in remaining tensile strength did not occur, which may indicate that the higher energy

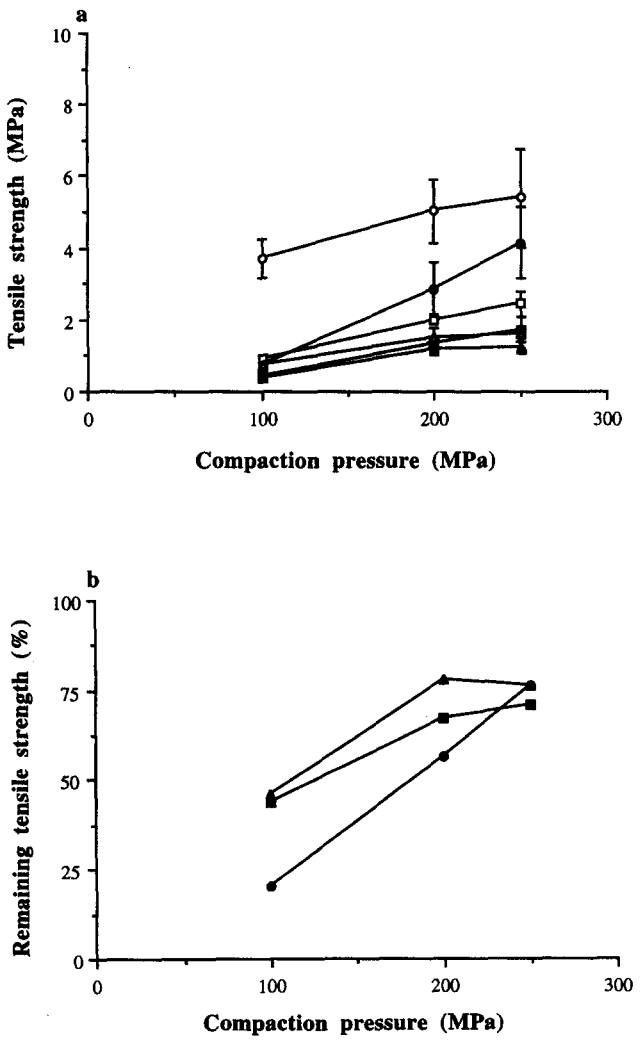

Fig. 1. (a) Tensile strength as a function of compaction pressure for sodium chloride of different size fractions compacted in 1-butanol (closed symbols) and in air (open symbols). (○) 20–40 μm, (□) 90–180 μm and (△) 180–355 μm. Confidence intervals for $p = 0.05$ are given. (b) Remaining tensile strength as a function of compaction pressure for sodium chloride compacts (●) 20–40 μm, (■) 90–180 μm and (▲) 180–355 μm.

concentration at the interparticulate contact points is not used to increase the number and/or the strength of the solid bridges. Generally, sodium chloride is considered to undergo volume reduction by plastic deformation, as described by the yield pressure value [18], but a limit for plastic deformation may have been reached. The development of more and/or stronger solid bridges may not have been possible when the load was increased if all available interparticulate contact points were already involved in bonding by solid bridges.

Another explanation for the levelling off in remaining tensile strength may be that when a coarse quality of sodium chloride is compacted at 250 MPa the particles will be in close proximity to each other and the surrounding liquid may be squeezed out. Thus, the filtering effect of the butanol may be reduced as the film surrounding the particles is removed. This effect may be more pronounced for coarse sodium chloride which normally forms compacts of a rather low porosity [7,18].

The simple ionic structure and the nonfragmenting properties of sodium chloride ought to favour creation of ionic bonds between particles during and after the compaction process. When the chemical structure of a material is quite simple it may be assumed that it is easier for the tablet particles to achieve the required orientation for creation of interparticulate ionic bonds [2]. The solid bridges in sodium chloride are likely to consist of ionic interparticulate bonds which form a continuous phase between the particles.

3.2. Materials for which the intraparticulate bonding structure is formed by ionic bonds and weak distance forces (sodium bicarbonate and dicalcium phosphate dihydrate)

3.2.1. Sodium bicarbonate

When compacted in air the tensile strength of the compacts of the finest size fraction was higher in absolute terms, but when compacted in liquid the strength was similar irrespective of particle size (Fig. 2a). The remaining tensile strength was low for both size fractions but lowest for the fine particulate size system (Fig. 2b), indicating that the dominating bond type between particles for all particle sizes is weak distance forces.

When sodium bicarbonate is compacted in air, the effect of compaction load on the tensile strength of the compacts is more pronounced than when compacted in liquid (Fig. 2a). The compaction load does not seem to have any significant effect on the remaining tensile strength, which seems to indicate that the reduced distance between particles does not result in strong bonds (Fig. 2b).

On the whole, sodium bicarbonate seems to have a limited ability to bond by solid bridges. This may be because the more complex chemical structure of bicar-

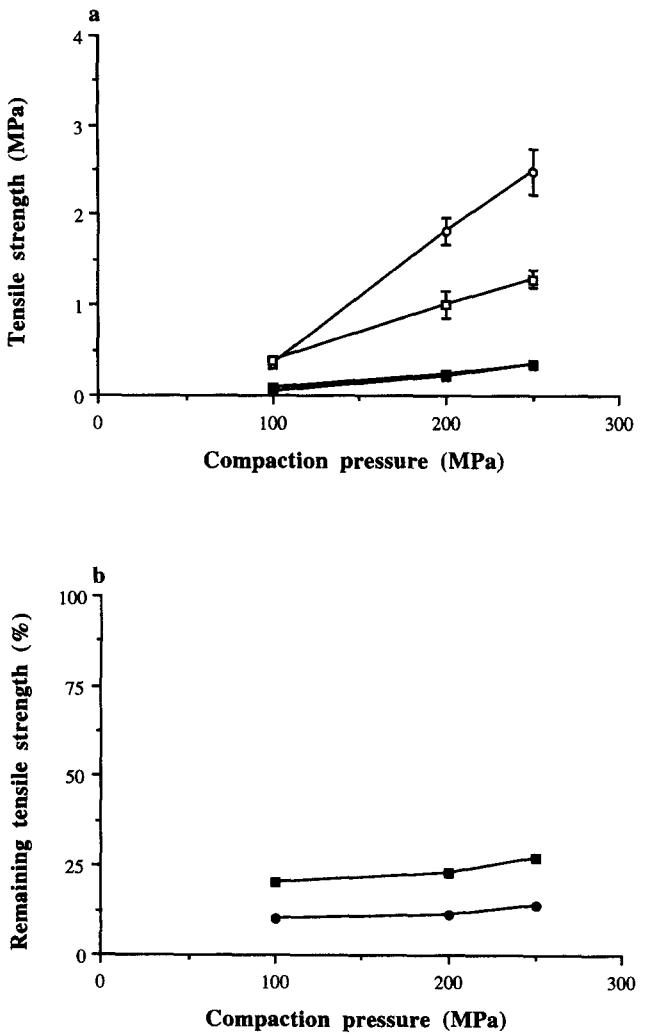

Fig. 2. (a) Tensile strength as a function of compaction pressure for sodium bicarbonate of different size fractions compacted in 1-butanol (closed symbols) and in air (open symbols). (○) 20–40 μm and (□) 90–180 μm. Confidence intervals for $p = 0.05$ are given. (b) Remaining tensile strength as a function of compaction pressure for sodium bicarbonate compacts (●) 20–40 μm and (■) 90–180 μm.

bonate ions tends to prevent the particles from approaching each other in such an orientation that solid bridges can easily be developed [2].

Another contributing factor may be that sodium bicarbonate does not deform plastically to the same extent as, for example, sodium chloride [18,19].

3.2.2. Dicalcium phosphate dihydrate

Generally, both an increase in compaction pressure and a decrease in particle size resulted in an increase in tensile strength with this substance (Fig. 3a).

In this study, the remaining tensile strength, irrespective of particle size, was higher than expected considering the fragmenting properties of the material (Fig. 3b). When a material undergoes extensive fragmentation during compaction, the required conditions for creation of solid bridges are probably not established. Energy supplied by compaction of powdered fragmenting materials will be transformed mainly to surface energy. Thus, energy will not be concentrated at interparticulate contact points, high local stresses will not be created and movement of material at interparticulate contact points will probably not take place.

The relatively high remaining tensile strength might indicate that dicalcium phosphate dihydrate bonds to a high degree by strong interparticulate bonds. Due to the fragmenting properties and the rather complex chemical structure of the material, bonding by solid bridges is not expected.

Dicalcium phosphate dihydrate consists of granulated primary particles. These agglomerates are expected to have a rough surface texture. Therefore, mechanical interlocking cannot be excluded [2–4] as a

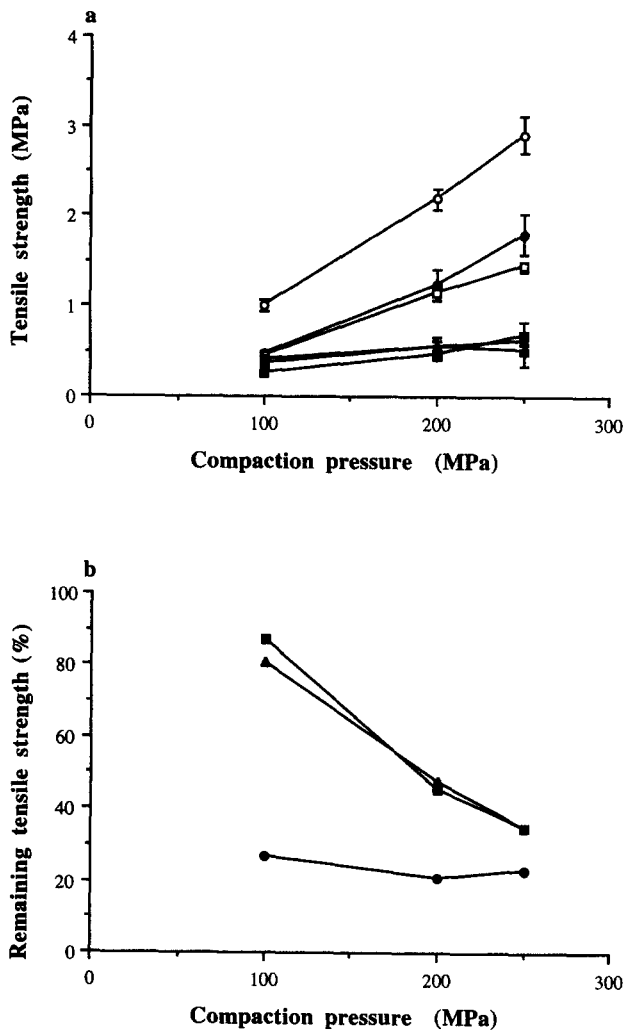

Fig. 3. (a) Tensile strength as a function of compaction pressure for dicalcium phosphate dihydrate of different size fractions compacted in 1-butanol (closed symbols) and in air (open symbols). (○) 20–40 μm, (□) 90–180 μm and (△) 180–355 μm. Confidence intervals for $p = 0.05$ are given. (b) Remaining tensile strength as a function of compaction pressure for dicalcium phosphate dihydrate compacts (●) 20–40 μm, (■) 90–180 μm and (▲) 180–355 μm.

possible interparticulate bonding mechanism. This explanation is supported by the effect of compaction pressure and particle size on remaining tensile strength, where a decrease in particle size or an increase in compaction pressure result in weaker interparticulate bonds (Fig. 3b). When the particle size of the material is reduced by milling, the agglomerates are fragmented. In this case, the primary particles produced are probably more regular in shape. When the compaction pressure is further increased, a larger number of primary particles are produced. This creation of more regular particles is expected to counteract bonding by mechanical interlocking.

Another, perhaps more probable, explanation for the high remaining tensile strength (especially at the lower compaction pressures) is that the absolute strength values both in air and in butanol are low and quite similar and the range of experimental results is quite wide (Fig. 3a). The ratio will then be sensitive to small changes in tensile strength, and the high remaining tensile strength at low pressures may be an artefact. Hence, due to the uncertainty in determination of the tensile strength, it is difficult to draw any general conclusions on the effect of particle size and compaction pressure on the bonding structure for this material (Fig. 3b).

The relatively complex chemical structure within the ions may also affect the interparticulate bonding structure, as discussed for sodium bicarbonate.

3.3. Materials for which the intraparticulate structure is formed by covalent bonds and weak distance forces (lactose, sucrose and microcrystalline cellulose)

3.3.1. Lactose

When compacted in air, an increase in tensile strength with a decrease in particle size was registered (Fig. 4). This increase could be explained by an increased surface area available for bonding [20]. Thus, the original particle size would appear to affect the tensile strength of lactose compacts.

The strength of the compacts in butanol was zero (or too small to measure with the equipment used), irrespective of particle size and compaction load (Fig. 4). Even though the particles will be in close contact when compacted at, e.g. 250 MPa, the liquid seems to be able to effectively screen off the interparticulate forces.

The results seem to indicate that the only bonding mechanism for lactose is weak distance forces, and that bonding by solid bridges is unlikely for α-lactose monohydrate particles.

3.3.2. Sucrose

As expected, when sucrose particles are surrounded by air during the compaction process, an increased load resulted in a corresponding increase in tensile strength.

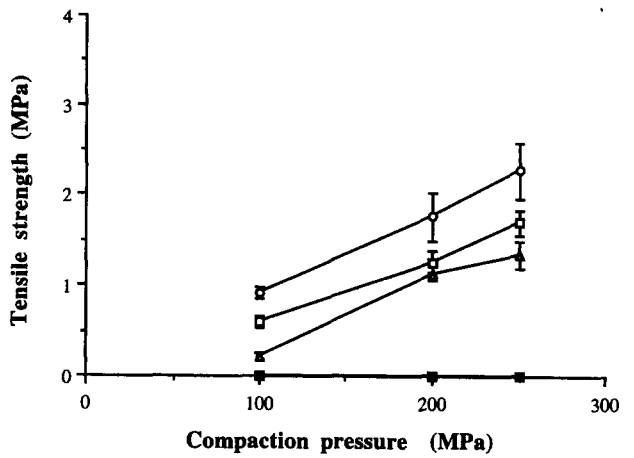

Fig. 4. Tensile strength as a function of compaction pressure for lactose of different size fractions compacted in 1-butanol (closed symbols) and in air (open symbols). (○) 20–40 μm, (□) 90–180 μm and (△) 180–355 μm. Confidence intervals for $p = 0.05$ are given.

A decrease in particle size also caused tensile strength to increase (Fig. 5).

When sucrose was compacted in butanol it was not possible to obtain any coherent compacts, i.e. the interparticulate bonds could not develop when the particles were surrounded by butanol during and after the compaction process, and consequently the remaining tensile strength was zero (Fig. 5). Neither the particle size nor the compaction load seemed to have any major effect on the remaining tensile strength of the compacts.

These results indicate that sucrose compacts are also held together by weak distance forces, which are effectively screened off by the liquid.

The similar behaviour of sucrose and lactose indicates that they bond with the same type of interparticulate attractions.

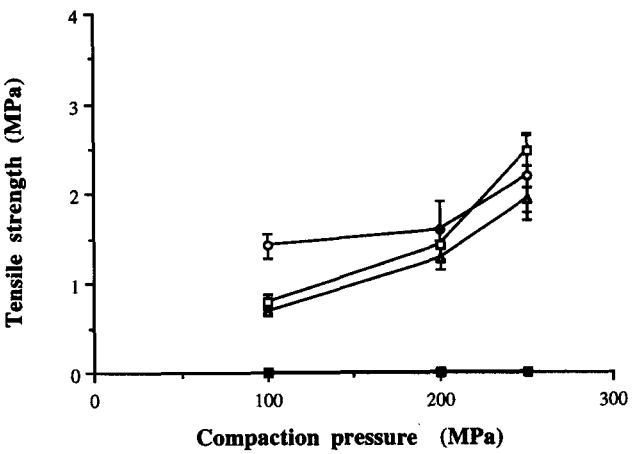

Fig. 5. Tensile strength as a function of compaction pressure for sucrose of different size fractions compacted in 1-butanol (closed symbols) and in air (open symbols). (○) 20–40 μm, (□) 90–180 μm and (△) 180–355 μm. Confidence intervals for $p = 0.05$ are given.

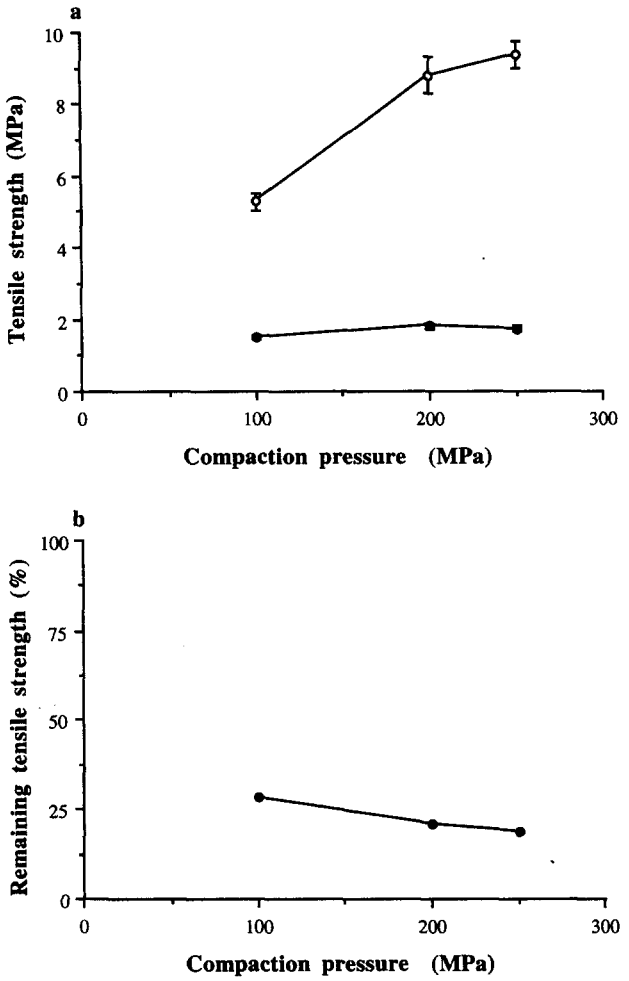

Fig. 6. (a) Tensile strength as a function of compaction pressure for microcrystalline cellulose raw material (○) compacted in 1-butanol (closed symbols) and in air (open symbols). Confidence intervals for $p = 0.05$ are given. (b) Remaining tensile strength as a function of compaction pressure for microcrystalline cellulose compacts of the raw material (●).

3.3.3. Microcrystalline cellulose

The effect of particle size on bonding properties was not studied, due to the narrow particle size range of the raw material.

An increase in compaction load affected the tensile strength of microcrystalline cellulose only when compacted in air. No effect of compaction load on tensile strength was detected when compacted in liquid (Fig. 6a). There was a tendency for an increase in compaction pressure to result in decreased remaining tensile strength (Fig. 6b). Due to the agglomerate structure of microcrystalline cellulose, fragmentation will take place during compaction and primary particles will be formed which will undergo further volume reduction by plastic deformation [21]. The primary particles are thus small and creation of a high energy centre will not take place since the load applied during compaction will be spread on a relative large number of interparticulate contact points.

If it is assumed that the remaining strength reflects the bonding type, it seems that when the load is increased weak distance forces will develop and/or the bonding surface area will be decreased (Fig. 6b). At lower loads the irregular shape and surface texture of the particles will also make it possible for the particles to bond by mechanical interlocking. When the compaction load is increased, it is believed that the particles will fragment or be flattened and will thus not be as irregular in shape and texture as before compaction. Consequently, bonding by mechanical interlocking may be reduced [22]. This may result in a decrease in remaining tensile strength (Fig. 6b).

The chemical structure of microcrystalline cellulose indicates that the main bonding mechanism for the particles might be van der Waals forces. However, hydrogen bonds are also expected to have an important role. These bonds will probably be influenced by the presence of butanol as discussed for lactose and sucrose. However, the remaining tensile strength does not decrease eventually to zero when compacted in butanol because of the hooking and/or twisting of particles.

3.4. Quantification of bonding type for some pharmaceutical materials

At each compaction load, a percentage value was calculated for the remaining tensile strength (Table 2). This value was assumed to reflect the amount of solid bridging and/or mechanical interlocking between tablet particles. Due to the variations in experimental data expressed as confidence intervals (Figs. 1–6), the actual number should be interpreted with caution, but it might be possible to make a quantitative comparison among or within materials, e.g. to study the effect of particle size and compaction load on bonding structure. Generally, the values are more reliable (especially for dicalcium phosphate dihydrate) at higher loads when the absolute values were larger.

4. Conclusion

By compaction and characterisation of the strength of pharmaceutical compacts in liquid and air, it is possible to obtain information about the bonding structure within the compacts. However, in order to properly evaluate the experimental data, knowledge of the chemical structure and volume reduction behaviour of the tested material is necessary.

(1) The intraparticulate chemical structure of the material appears to be of importance for the interparticulate bonding structure. A simple chemical structure seems to facilitate development of solid bridges during compression because it is easier for the particles to orientate in such a way that solid bridges can form.

Table 2
Remaining tensile strength (i.e. a simplified measure of bonding by solid bridges and/or mechanical interlocking in compacts) for different particle size fractions compacted at different loads

Material	Size fraction (μm)	Remaining tensile strength (%)		
		100 MPa	200 MPa	250 MPa
Sodium chloride	180–355	46	78	77
	90–180	44	68	71
	20–40	20	57	77
Sodium bicarbonate	90–180	20	23	27
	20–40	10	11	14
Dicalcium phosphate dihydrate	180–355	42	7	9
	90–180	51	34	28
	20–40	32	26	35
Lactose	180–355	0	0	0
	90–180	0	0	0
	20–40	0	0	0
Sucrose	180–355	0	0	0
	90–180	0	0	0
	20–40	0	0	0
Microcrystalline cellulose	Raw material	29	21	18

This is exemplified by sodium chloride. Materials held together by different types of bonds seem to have a more heterogeneous structure, i.e. it is more difficult for these materials to develop the same bonding structure between particles as occur within particles, i.e. solid bridges will not be created to any large extent.

(2) Another prerequisite for creation of solid bridges during compression seems to be that the material undergoes volume reduction by plastic deformation. If the material undergoes volume reduction mainly by fragmentation, large stresses at interparticulate contact points will not be created. The energy then supplied during compaction will mainly be transformed to surface energy due to the increase in surface area taking place.

(3) For the materials forming coherent compacts in butanol (except for materials which are believed to bond by mechanical interlocking), an increase in particle size seemed to cause an increase in remaining tensile strength. The stresses created during compaction are concentrated at a smaller number of contact points, which increases the possibility of forming solid bridges.

(4) An increase in compaction pressure also affects the bonding structure within the compacts. An increased load will increase the energy level at interparticulate contact points during compression. These increased stresses may facilitate movement of material by diffusion, i.e. increase the mobility of the material. This effect is most important for particles which undergo plastic deformation during compaction, e.g. sodium chloride.

(5) For materials consisting of irregularly shaped particles (agglomerates) it is suggested that a reduction in particle size and an increase in compaction pressure would make it more difficult for the particles to bond by mechanical interlocking. Smaller particles are probably more regular in shape and an increase in compaction pressure would then tend to fragment agglomerates or flatten irregularly shaped particles. Examples of such materials are dicalcium phosphate dihydrate and microcrystalline cellulose.

Acknowledgements

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