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Moisture adsorption and tabletting. II. The effect on tensile strength and air permeability of the relative humidity during storage of tablets of 3 crystalline materials

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Summary

The effect of moisture adsorption on mechanical strength and air permeability of tablets during storage was studied. Three crystalline substances were used, two water-soluble (saccharose and sodium chloride) each represented by two size fractions and one practically insoluble (calcium hydrogen phosphate). Tablets were stored in a series of RH (33–100%) before measurement of tablet strength and permeability. Tablets were also stored for an additional period of time at a low RH whereafter the tablets were characterized again. For saccharose, an increase in RH during storage resulted in an increase in tensile strength up to a certain level and to a decrease in tablet surface area. This is probably a result of a rearrangement of molecules at the particle surfaces by the action of adsorbed water leading to a formation of solid bridges. A less pronounced effect was obtained for the finer fraction of sodium chloride, whereas no such effect was obtained for the coarser fraction and for calcium hydrogen phosphate. At high RH, the tablet strength decreased in most cases probably because condensed water disturbed intermolecular attraction forces between particles in the tablets. Storage at low RH of transferred tablets did not change the tablet strength or the tablet surface area, i.e. the tablets were at this RH unaffected by adsorbed moisture. Exceptions were transfer of saccharose and sodium chloride tablets from an RH in which the materials had begun to deliquesce. In these cases dissolved material crystallized in the tablet and the formation of solid bridges increased the tablet strength.

Introduction

In a previous study (Ahlneck and Alderborn, 1989) it was concluded that the relative humidity (RH) during storage of a powder before compaction had no or only a limited effect on the volume reduction properties for some unmilled, crystalline materials except at very high RH when 'condensed' water was present in the powder mass. However, the tensile strength was affected by adsorption of moisture during storage of the tablets. For materials of high solubility, an increase in tensile strength was found with increasing RH at low and intermediate RH, whereas no change was found for less soluble materials. At high RH there was a decrease in tensile strength for most materials. It was concluded that the effect of moisture on the tablet strength was governed by the adsorbed moisture during storage rather than by the amount of water present during compaction.

An *increase in tensile strength* with increasing RH during storage has been explained by two

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possible mechanisms. Firstly, adsorbed water could function as a surface restructuring medium leading to an increased amount of solid bridges (Ahlneck and Alderborn, 1989). Such an effect is then expected to occur at fairly low humidities, i.e., below the critical relative humidity (RH_0). The RH_0 is a characteristic of the solid and is the point above which adsorbed water assumes the character of a bulk solution or condensate (Van Campen et al., 1983). Although it is normally assumed that this point must be reached before adsorbed water can commence to dissolve a solid, it does not exclude the possibility that a change of the particle surface structure can occur below RH_0. Water vapour sorption below RH_0 has been shown to reduce the specific surface area, as measured by gas adsorption, for milled sodium chloride and sodium salicylate (Kontny et al., 1987). Also an increase in mechanical strength with RH for sodium chloride has been suggested to be a result of a restructuring of surfaces in the tablet (Lordi and Shiromani, 1984; Down and McMullen, 1985).

Another possible explanation for an increase in tensile strength is that immobile water layers sorbed at particle surfaces can enhance the particle–particle interaction. An adsorbed water vapour layer can according to this theory contribute in two ways to the strength of the interactions; a, tightly bound water vapour layers can be regarded as a part of the particles which reduces the interparticular surface distances and thus results in increased intermolecular attraction forces (Coelho and Harnby, 1978); b, adsorbed layers can touch or penetrate each other which will increase the attraction forces between neighbouring particles (Rumpf, 1962; Turba and Rumpf, 1964; Turner and Balasubramanian, 1974).

A *decrease in tensile strength* has been explained as a result of a formation of multilayers of water at the particle surfaces. Such layers may then disturb or reduce intermolecular attraction forces and thereby reduce the tablet strength (Kristensen et al., 1985; Ahlneck and Alderborn, 1989). For water-soluble substances deliquescence may occur at an RH above RH_0.

The aim of this paper was to study how storage of tablets in a series of relative humidities affects the tensile strength and the air permeability of tablets of 3 crystalline materials. The aim was also to discuss the mechanism(s) of the action of adsorbed water on the tablet strength.

Materials and Methods

Materials

Calcium hydrogen phosphate dihydrate (Calipharm, Albright & Wilson Ltd, U.K.) which is regarded as practically insoluble in water (B.P., 1988), i.e. it ought to be unaffected by moisture adsorption regarding dissolution or changes in particle surface structure.

Sodium chloride (crystalline puriss., Kebo-Grave, Sweden) which is freely soluble in water (B.P., 1988) and deforms plastically during compaction (Duberg and Nyström, 1982).

Saccharose (crystalline puriss., Kebo-Grave, Sweden) which is very soluble in water (B.P., 1988) and is expected to fragment to a larger extent during compaction (Duberg and Nyström, 1982). Thus, a larger specific surface area is created during compaction.

The materials tested show limited uptake of moisture at low and medium relative humidities. However, since they are hydrophilic some adhesion of water molecules to the particle surfaces is expected (Zografi, 1988). At high RH an increased water uptake has been reported (Ahlneck and Alderborn, 1989).

Methods

Preparation of powders

For sodium chloride the size fraction 180–250 μm was prepared by dry sieving. A fine particle size fraction, 20–40 μm, was prepared by milling in a pin disc mill (Alpine 63 C, Alpine AG, F.R.G.) and then classified with the aid of an air classifier (Alpine 100MZR, Alpine AG, F.R.G.).

For saccharose, the size fraction 125–180 μm was prepared by dry sieving. A fine particle size fraction, 20–40 μm, was prepared as described for sodium chloride.

Calcium hydrogen phosphate was used without any pretreatment of the material. The particle size was estimated to be < 20 μm by the use of scanning electron microscopy.

Storage of powder

The calcium hydrogen phosphate was stored in desiccators for not less than 5 days at 57% RH and room temperature before compaction. The fractions of sodium chloride and saccharose were stored at 0% and 33% RH, respectively, directly after sieving or milling before compaction. No materials could be compressed after prestorage at 0% RH because of friction problems during tabletting.

Compression of tablets

Tablets were compressed with 1.13 cm flat-faced punches in an instrumented tablet press (Korsch EK O, F.R.G.) at a maximum upper punch pressure of 75 MPa (sodium chloride and saccharose) and 50, 75 and 150 MPa (calcium hydrogen phosphate) at a machine speed of 30 rpm. The distance between the punch faces at the lowest position of the upper punch was in all cases 3 mm at zero pressure. The powder for each compact was individually weighed on an analytical balance and poured into the die. In this way, the compaction load could be kept within the interval ±3% of the nominal value. For saccharose and sodium chloride, external lubrication was performed with a 1% magnesium stearate suspension in ethanol. For calcium hydrogen phosphate a 5% magnesium stearate suspension in ethanol was used.

Storage of tablets

Tablets were measured for diametral compression strength and permeability (a) after storage in desiccators in a series of relative humidities by the use of saturated salt solutions (Nyqvist, 1983). For sodium chloride 33%, 40%, 57% and 75% RH were used, for calcium hydrogen phosphate 33%, 57%, 68%, 75%, 84%, 94% and 100% RH were used and for saccharose 33%, 57%, 75%, and 84% RH were used. Storage time was 7 days for sodium chloride and saccharose and 30 days for calcium hydrogen phosphate. (b) Tablets of sodium chloride and saccharose were stored as described above and then transferred to 33% RH for storage for another 7 days before measurements of diametral compression strength and permeability. (c) Calcium hydrogen phosphate tablets were first stored for 30 days at 100% RH and then transferred to 33% and 68% RH for additional storage during 30 days before measurements of diametral compression strength and permeability.

Characterization of tablets

The diametral compression strength was measured (Erweka TBH 28, F.R.G.) for tablets of each material and treatment. Also the weight and height were measured. The tensile strength of the tablets was calculated according to Fell and Newton (1970) as well as the tablet porosity. The results are mean of 10 determinations.

Measurements of the air permeability of tablets compacted at 75 MPa were performed with a Blaine apparatus equipped with a tablet holder adapter (Pharmatest, F.R.G.). The permeametry surface area and the pore diameter of the tablets were calculated according to Alderborn et al. (1985). The results are mean of 5 determinations. At high RH it was impossible to measure the permeability for calcium hydrogen phosphate, milled saccharose and sodium chloride probably because condensed water was blocking the flow of air through the tablets (Ahlneck and Alderborn, 1989). The surface areas of the finest qualities of the starting powders were also measured by permeability.

Results and Discussion

For *calcium hydrogen phosphate* tablets, there was no change in tablet strength with increasing RH except at 100% RH where the tablet strength decreased by approximately 50% (Fig. 1). The transfer of tablets from 100% RH to lower humidities gave for two compaction pressures the same tablet strength as for untransferred tablets stored below 100% RH. For the highest compaction pressure, the transfer gave a somewhat lower tablet strength. This was probably due to that the pore diameter for these tablets was small which results in a slow desorption and diffusion of water in the tablets (compare Table 1).

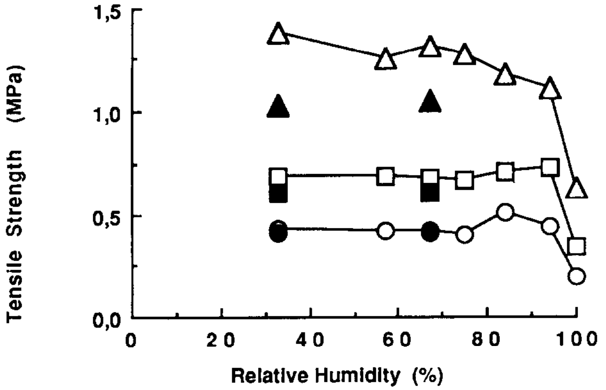

Fig. 1. The tensile strength of tablets of calcium hydrogen phosphate as a function of relative humidity. Tablets measured after storage at initial storage conditions, storage time 30 days (open symbols). Tablets measured after storage at 100% RH followed by transfer and storage at lower RH, storage time 30 + 30 days (closed symbols). △, 50 MPa ○, 75 MPa □, 150 MPa.

No major changes were found in permeametry surface area between the starting material and the tablet surface areas after storage of the tablets at selected RH (Table 1). Thus, no or only minor fragmentation occurred during compaction. Calcium hydrogen phosphate have in earlier reports (Duberg and Nyström, 1982; Ahlneck and Alderborn, 1989) been shown to fragment extensively during compaction. However, in those cases an aggregated quality of calcium hydrogen phosphate, Emcompress, was used.

The porosity of the tablets (Table 1) was not changed during storage at low and intermediate RH, but after storage at 100% RH the porosity decreased slightly. This was due to an increased tablet weight by water uptake. The porosity was re-established when tablets were transferred to 33% or 68% RH from 100% RH.

The results for calcium hydrogen phosphate indicate that water does not affect the interior structure of the tablets. Consequently, it seems reasonable that the decrease in tablet strength at the highest humidity is a result of a disturbance of intermolecular attraction forces between particles in the tablet. Consequently, for a porous specimen of relatively low porosity and high mechanical strength, there seems to be no positive effect of condensed water acting as liquid bridges between particles. However, this does not exclude that liquid bridges are an important bonding mechanism for agglomerates of lower mechanical strength.

Since no change in tablet strength below 100% RH was obtained, the results indicate further that thin layers of immobile adsorbed water do not affect the intermolecular attraction forces between particles for these tablets. A positive effect of such immobile adsorbed layers has been discussed. The results indicate that the suggestion (Turner and Balasubramanian, 1974; Coelho and Harnby, 1978) that thin layers of adsorbed moisture can "enlarge" particles and thereby increase intermolecular attraction forces can be questioned for tablets. Concerning the possibility for thin adsorption layers to touch each other and thereby increase interparticular attraction (Turba and Rumpf, 1962), it is probably related to the distance between particle surfaces. Although a very fine particulate material, giving relatively low pore diameters (Table 1), and a series of compaction pressures was used, no effect of adsorbed moisture on tablet strength was found. This finding is supported by results for other in water less soluble materials (Ahlneck and Alderborn, 1989). It seems therefore that such a bonding mechanism is of limited importance for pharmaceutical tablets. However, if very high compaction pressures are

TABLE 1

Tablet surface area, pore diameter and porosity for calcium hydrogen phosphate tablets compacted at 75 MPa

	RH [a] (%)	Surface area (cm^2/g)	Pore diameter (μm)	Porosity (%)
Powder		11000	–	–
Tablets stored at	33	13040 (180)	0.62 (0.05)	30.4
	57	11800 (390)	0.66 (0.01)	30.6
	75	11840 (470)	0.67 (0.02)	30.5
	100	n.m.	n.m.	29.4
Tablets transferred from 100% RH to	33	11550 (261)	0.66 (0.05)	30.5
	68	[a]	[a]	30.5

Standard deviations are given in parentheses; n.m., not measurable.

[a] Measurements were not performed for tablets stored at 68%, 84% or 94% RH.

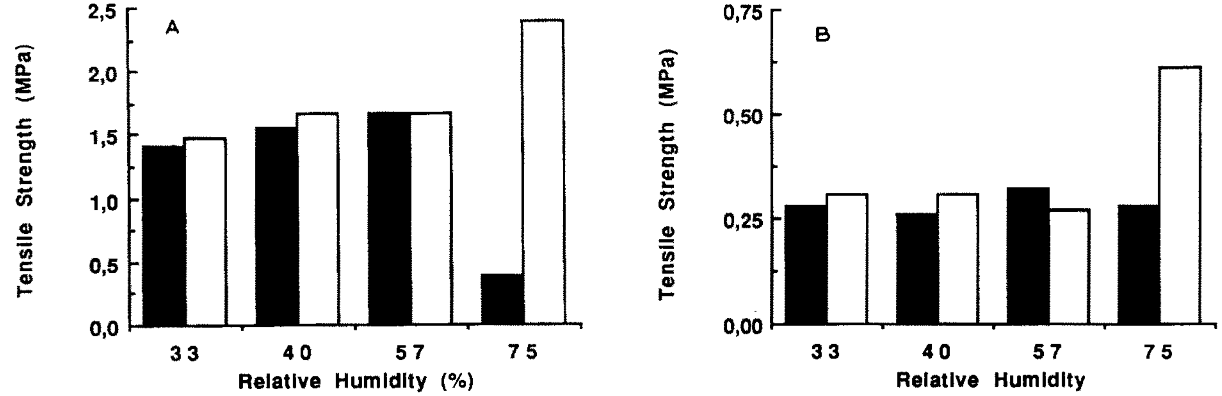

Fig. 2. A: the tensile strength of tablets of sodium chloride 20–40 μm as a function of relative humidity. Tablets stored at initial storage RH, storage time 7 days (closed columns). Tablets stored at initial storage RH and then transferred to 33% RH for additional storage, storage time 7 + 7 days (open columns). B: the tensile strength of tablets of sodium chloride 180–250 μm as a function of relative humidity. Tablets stored at initial storage RH, storage time 7 days (closed columns). Tablets stored at initial storage RH and then transferred to 33% RH for additional storage, storage time 7 + 7 days (open columns).

used, a bonding due to the touching of immobile layers cannot be excluded.

For *sodium chloride* the results for the effect of RH for the tablet strength are shown in Fig. 2. Generally, it seems that up to at least 57% RH no or only minor changes are found in tablet strength. There might be a small increase in tablet strength with increasing humidity for tablets of the finer particle size. This was also found in an earlier study (Ahlneck and Alderborn, 1989). At 75% RH, which is the critical relative humidity (RH_0) for sodium chloride, the tablet strength decreased markedly for the finer size fraction. This could be due to that at RH_0, condensation of water in the pores of the tablet occurs which can disturb intermolecular attraction forces and start to dissolve the solid. The fact that this only occurred for the finer size fraction is suggested to be due to the smaller pore diameter for these tablets.

For tablets transferred from the initial storage RH to 33% RH for additional storage, the same tablet strength as for untransferred tablets was obtained (Fig. 2). An exception were tablets originally stored at 75% RH for which an increased tablet strength was obtained when moved to 33% RH. This is suggested to be due to crystallization of deliquesced material during drying. The tablet strength is thereby considerably increased due to the creation of solid bridges.

As in the case of calcium hydrogen phosphate no change in porosity was obtained below RH_0 (Table 2). At RH_0 a decrease in porosity was obtained due to an increase in tablet weight by water uptake but the transfer to a lower RH re-established the porosity. Also the tablet surface areas and the pore diameters showed very little variations below 75% (Table 2). However, there was a tendency for a decreased surface area with increased RH. For sodium chloride the effect on tablet strength and surface area was thus limited

TABLE 2

Tablet surface area, pore diameter and porosity for sodium chloride (20–40 μm) tablets compacted at 75 MPa

	RH (%)	Surface area (cm^2/g)	Pore diameter (μm)	Porosity (%)
Powder		1490	–	–
Tablets stored at	33	1450 (88)	4.10 (0.21)	24.1
	40	1150 (13)	5.09 (0.07)	24.1
	57	1120 (30)	5.27 (0.14)	24.4
	75	n.m.	n.m.	22.7
Tablets transferred to 33% RH from	33	1610 (25)	3.67 (0.07)	24.4
	40	1570 (18)	3.82 (0.05)	24.5
	57	1540 (12)	3.87 (0.03)	24.2
	75	n.m.	n.m.	24.7

Standard deviations are given in parentheses; n.m., not measurable.

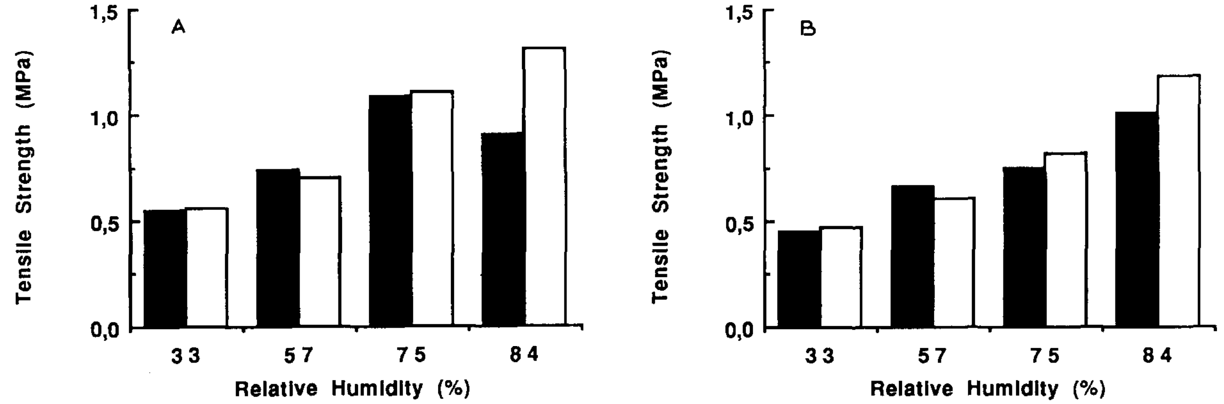

Fig. 3. A: the tensile strength of tablets of saccharose 20–40 μm as a function of relative humidity. Tablets stored at initial storage RH, storage time 7 days (closed columns). Tablets stored at initial storage RH and then transferred to 33% RH for additional storage, storage time 7 + 7 days (open columns). B: the tensile strength of tablets of saccharose 125–180 μm as a function of relative humidity. Tablets stored at initial storage RH, storage time 7 days (closed columns). Tablets stored at initial storage RH and then transferred to 33% RH for additional storage, storage time 7 + 7 days (open columns).

for storage below RH_0. The results on tablet strength are in agreement with an earlier report from our laboratory (Ahlneck and Alderborn, 1989) whereas a larger effect of moisture adsorption on tablet strength has been reported by others (Lordi and Shiromani, 1983; Down and McMullen, 1985). Especially Down and McMullen found a large increase in tablet strength with increasing RH up to 84% RH, i.e. well above RH_0 (75% RH).

For *saccharose* another pattern was obtained (Fig. 3). With increasing RH a marked increase in tablet strength was monitored in the whole range studied. However, for the finer fraction, a decrease in tablet strength was obtained at 84%. This was interpreted as a result of condensation of water as discussed for sodium chloride. Tablets which were transferred from the initial storage RH to 33% for additional storage (Fig. 3), gave generally the same tablet strength as for un-transferred tablets. An

TABLE 3

Tablet surface area, pore diameter, and porosity for saccharose (20–40 μm) tablets compacted at 75 MPa

	RH (%)	Surface area (cm^2/g)	Pore diameter (μm)	Porosity (%)
Powder		2820	–	–
Tablets stored at	33	4950 (155)	1.51 (0.06)	22.6
	57	4100 (118)	1.83 (0.08)	23.1
	75	2630 (68)	2.65 (0.08)	21.7
	84	n.m.	n.m.	18.7
Tablets transferred	33	4760 (222)	1.59 (0.09)	22.5
to 33% RH from	57	3660 (211)	2.03 (0.13)	22.4
	75	2520 (166)	2.79 (0.15)	21.5
	84	n.m.	n.m.	19.2

Standard deviations are given in parentheses; n.m., not measurable.

TABLE 4

Tablet surface area, pore diameter and porosity for saccharose (125–180 μm) tablets compacted at 75 MPa

	RH (%)	Surface area (cm^2/g)	Pore diameter (μm)	Porosity (%)
Powder		n.m.	–	–
Tablets stored at	33	1680 (75)	3.91 (0.19)	20.6
	57	1510 (59)	4.31 (0.21)	20.5
	75	1310 (58)	4.93 (0.24)	20.5
	84	872 (49)	6.98 (0.30)	19.7
Tablets transferred	33	1610 (83)	4.13 (0.21)	20.8
to 33% RH from	57	1540 (42)	4.29 (0.10)	20.8
	75	1330 (94)	4.91 (0.42)	20.5
	84	950 (34)	6.66 (0.24)	19.9

Standard deviations are given in parentheses; n.m., not measurable.

exception was found for tablets transferred from 84% RH, probably due to the same mechanism as for sodium chloride – a crystallization of material due to drying and thereby the formation of solid bridges. The fact that the transfer of tablets to a low RH did not reduce the tablet strength supports the discussion above that thin layers of adsorbed water do not affect the tablet strength. The increase in tablet strength with increasing RH ought then to be explained by another mechanism.

The porosity of the tablets was not changed during storage at low and intermediate RH, but after storage at 84% RH the porosity decreased (Tables 3 and 4). This decrease in porosity was due to a different reason than for calcium hydrogen phosphate and sodium chloride. For saccharose the decrease in porosity was primarily due to a decreased tablet height and the change was irreversible. We suggest that this is due to a dissolution or restructuring of parts of particle surfaces which leads to a more dense tablet.

The tablet surface area (Tables 3 and 4) was generally higher than for the starting powder which is due to fragmentation of particles. For both saccharose qualities there was a reduction in surface area with increasing RH.

Consequently, adsorbed moisture gave an increased tablet strength and a decreased tablet surface area and it seems that these characteristics are almost linearly related to each other (Fig. 4). It is therefore concluded that the change in tablet strength is a result of a change in the pore structure of the tablet. It may not be excluded that a smoothening of external particle surfaces can occur, resulting in a widening of the pores, which results in an increased permeability. However, it seems reasonable that such a change in the surface structure ought to produce a reduction in bonding surface area available for intermolecular attraction forces and thereby lead to a decrease in tablet strength (Vromans et al., 1985). Instead the increase in tablet strength can be explained as a result of the formation of solid bridges during a restructuring of the external particle surfaces, i.e. solid bridges represent a "stronger" bonding mechanism than intermolecular attraction forces in this case. It is interesting to note that for humidities below RH_0, the transfer of saccharose tablets did not result in an increased tablet strength which was observed for tablets of both saccharose and sodium chloride transferred from the highest humidities used, as discussed above (Figs. 2 and 3). The formation of solid bridges below RH_0 for saccharose seems therefore not to be a result of crystallization during drying of a saturated solution of the material. The formation of solid bridges might then be a result of a process which can be described as a rearrangement of molecules at the particle surfaces by the action of limited amounts of adsorbed moisture, i.e. water molecules act as a medium for restructuring the surface. Thus this process occurs although the point has not been reached where the state and thickness of the adsorbed water layers allow a dissolution of saccharose molecules.

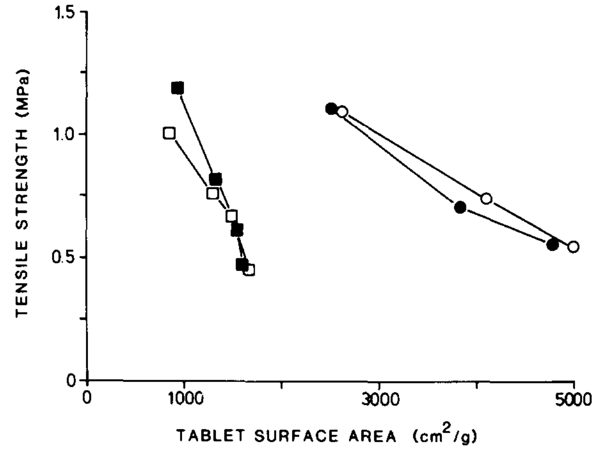

Fig. 4. Tensile strength as a function of air permeametry surface area for untransferred (open symbols) and transferred (closed symbols) saccharose tablets. ○, 20–40 μm □, 125–180 μm.

Although sodium chloride also is a highly water soluble material the same change in tablet properties as for saccharose tablets was not found. The observation that storage of saccharose tablets at 33% RH did not change the tablet strength (Fig. 3) indicates that a certain thickness of the adsorbed water layer is required for the rearrangement of molecules at the particle surfaces to take place. Although saccharose and sodium chloride in an earlier paper (Ahlneck and Alderborn, 1989) showed a similar water uptake at low and intermediate RH, it can not be excluded that the water layer locally is thicker for saccharose, i.e., clustering of water molecules (Zografi, 1988).

Alternatively, the limited increase in tablet strength for sodium chloride may be because the rearrangement is a function of storage time and that the time dependency varies between different materials, i.e. storage during a longer period of time would eventually increase the tablet strength also for sodium chloride. Also the pore size distribution in the tablets can be of importance. With greater distances between particles a creation of solid bridges might be more difficult. A comparison of mean pore diameters between sodium chloride and saccharose shows that the pore diameter is smaller for the latter. Another possibility is that saccharose during compaction undergoes an activation, due to fragmentation, and thus is more prone to be affected by adsorbed moisture during storage of tablets than sodium chloride.

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