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Moisture sorption and tensile strength of some tableted direct compression excipients

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Summary

Moisture sorption and desorption isotherms, at 25°C, have been measured for some direct compression (DC) excipients and analysed according to the Young and Nelson equations and the GAB equation, which distinguish different physical forms of moisture. The mechanical characteristics, such as tensile strength and derived tableting indices (brittle fracture propensity and tensile strength isotropy) of compacts produced from the same DC excipients, have been determined after storage at various environmental relative humidities. The tensile strength reaches a maximum value and then begins to decrease when the moisture content is about double that corresponding to a tightly bound monomolecular layer. The changes in the mechanical characteristics have been explained by the combined effect of moisture on the interparticle and intermolecular forces.

Introduction

The interaction of water with powdered materials is a major factor in formulation, processing and product performance of solid pharmaceutical dosage forms, i.e., capsules, tablets etc. For the direct compression (DC) excipients, which provide the simplest possible approach to tablet manufacture, the moisture sorption and desorption isotherms are among the typical properties that have been tested and proposed as quality assurance specifications. Moisture can be present in powders in different physical forms: as adsorbed monolayers or multilayers on the surfaces of the particles, as normally condensed water on the surface, as physically absorbed water within the particles, or as 'strongly bound', chemisorbed water (York, 1981; Chan and Pilpel, 1983; Zografi and Kontny, 1986; Khan and Pilpel, 1987). For water-soluble substances, dissolution of the molecules at the solid surface (deliquescence) can also occur above a certain relative humidity which is defined as the critical relative humidity (RH_0) (Van Campen et al., 1983).

The presence and distribution of moisture in these various forms will depend on the chemical nature of the particulate material, its physical properties such as particle size and porosity, and on the ambient relative humidity which determines the equilibrium moisture content. To establish quantitative correlations between equilibrium moisture content and environmental relative humidity, several mathematical expressions

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have been proposed and those applied most extensively to pharmaceutical powdered materials are the GAB and the Young and Nelson equations (York, 1981; Chan and Pilpel, 1983; Zografi et al., 1983, 1984, 1988; Sadeghnejad et al., 1986; Zografi and Kontny, 1986; Malamataris and Dimitriou, 1990).

The GAB equation (Eqn 1) is a BET equation extended by Van der Berg according to the modifications developed by Guggenheim, Anderson and De Boer (Van der Berg, 1981):

$$\begin{aligned} W = {} & \{C_G \cdot K \cdot W_m \cdot (P/P_0)\} \\ & \times \{(1 - K \cdot P/P_0) \\ & (1 - K \cdot P/P_0 + C_G \cdot K \cdot P/P_0)\}^{-1} \end{aligned} \tag{1}$$

where W is the weight of water sorbed per gram of solid; W_m is the weight of water in the form of a monolayer, C_G and K are parameters related to the heat of sorption; and P/P_0 is the water vapour relative pressure. In contrast to the BET equation, the GAB equation involves the additional parameter K and takes into account a layer or layers of sorbed vapour, which may be taken up with a degree of binding intermediate to those of the monolayer and the bulk water taken up in a non-specific manner. The parameters K and C_G can be determined as:

$$K = B_1 \cdot \exp\left[\frac{H_L - H_m}{R \cdot T}\right] \quad \text{and}$$

$$C_G = D \cdot \exp\left[\frac{H_1 - H_m}{R \cdot T}\right]$$

where B_1 and D are constants; H_L is the heat of condensation; H_m is the heat of sorption of water sorbed in the intermediate layer, H_1 is the heat of sorption of water in the first sorbed monolayer; R is the gas constant; and T is absolute temperature.

The Young and Nelson equations (Eqns 2–6) were derived in order to describe the equilibrium water vapour sorption and desorption of biological materials, e.g., starch (Young and Nelson, 1967a,b). They distinguish three forms of moisture: a 'bound' or adsorbed monolayer on the surface, 'normally condensed' or external moisture, and 'absorbed' or internal moisture. The five Young and Nelson equations are as follows:

$$\theta = \frac{\mathrm{RH}}{\mathrm{RH} + (1 - \mathrm{RH}) \cdot E} \tag{2}$$

$$\psi = \mathrm{RH} \cdot \theta \tag{3}$$

$$\begin{aligned} \beta = {} & -\frac{E \cdot \mathrm{RH}}{E - (E - 1) \cdot \mathrm{RH}} \\ & + \frac{E^2}{E - 1} \cdot \log_e \frac{E - (E - 1) \cdot \mathrm{RH}}{E} \\ & - (E + 1) \cdot \log_e (1 - \mathrm{RH}) \end{aligned} \tag{4}$$

$$M_s = A \cdot (\theta + \beta) + B \cdot \psi \tag{5}$$

$$M_d = A \cdot (\theta + \beta) + B \cdot \theta \cdot \mathrm{RH}_{\max} \tag{6}$$

where θ is the fraction of surface covered by a monomolecular layer; ψ is the fraction of surface covered by a layer of water two or more molecules thick; β is the total amount of adsorbed moisture in a multilayer, M_s and M_d are the moisture contents of the powder during sorption and desorption conditions; and RH and $\mathrm{RH}_{\max}$ are the relative humidity and maximum relative humidity. A, B and E are parameters, unique to each material. $E = \exp[-(q_1 - q_L) \cdot \boldsymbol{k} \cdot T]$, where q_1 is the heat of adsorption of water molecules bound to the surface, q_L the normal heat of the condensation of water molecules, $\boldsymbol{k}$ Boltzmann's constant, and T the absolute temperature. $A = (\rho_w \cdot V_m)/W'_m$ and $B = (\rho_w \cdot V_a)/W'_m$, where V_m and V_a are the volumes of the adsorbed and absorbed moisture, respectively, ρ_w is the density of water and W'_m is the mass of dry material. $A \cdot \theta$ is the amount of moisture present as a monolayer, $A \cdot (\theta + \beta)$ is the externally adsorbed moisture and $B \cdot \psi$ is the amount of the internally absorbed moisture during the sorption cycle.

In the present work, Eqns 1–6 have been used to test the fit of moisture sorption-desorption data for some DC excipients and to calculate the fraction of moisture corresponding to different forms. The distribution of moisture in various forms could account for the differences in the tableting performance of the materials, and the physico-mechanical properties of the resulting tablets. The final aim therefore is to examine the possible correlations between the moisture distribution and the mechanical characteristics, such as tensile strength, brittle fracture propensity, tensile strength isotropy, and yield pressure of compacts produced from the same DC excipients after storage at various environmental relative humidities.

Materials and Methods

Materials

The following DC excipients were used as received from the suppliers: (a) cross-linked polyvinyl-polypyrrolidone (Polyplasdone XL, Fluka, Switzerland); (b) pregelatinized maize starch (Sta-Rx 1500, Colorcon Ltd, Indianapolis, IN, U.S.A.); (c) microcrystalline cellulose (Avicel pH 101, Vanderbilt, R.T. Co, Norwalk, CT, U.S.A.); and (d) dextrates in hydrated form (Emdex, Edward Mendell, New York, NY, U.S.A.).

Determination of moisture sorption and desorption isotherms

Samples of the DC excipients were dried over phosphorus pentoxide and then transferred to tightly closed desiccators at 25°C, and relative humidities of 11, 23, 33, 43, 52, 65, 75, 83 and 93%, achieved with saturated salt solutions (Callahan et al., 1982). After standing for 8 days, the equilibrium moisture contents were determined in triplicate to within $\pm 0.5\%$ by drying to constant weight in a vacuum oven (16 h at 60°C). The results yielded the sorption isotherms. A similar procedure was followed to determine the desorption isotherms, this time after initial equilibration over saturated potassium nitrate (RH 93% at 25°C).

Tablet preparation and testing

After the moisture sorption or desorption procedure, samples of each equilibrated DC excipient, of known moisture content, were formed into tablets in a hydraulic press. 500-mg samples of the equilibrated material were weighed in small glass vials and then stored in the same desiccators for more than 3 days, until they were compressed. The material was quickly transferred into a 13 mm diameter die with flat-faced punches, previously lubricated with a suspension of magnesium stearate in chloroform. Compression pressure from 20 to 100 MPa was applied for 10 s to the upper punch by lowering the hydraulic ram at a rate of 1.5 mm s^{-1}. Tablets were also made with a 1 mm diameter central hole, by using a suitably modified, 13 mm punch and die set (Ejiofor et al., 1986; Roberts and Rowe, 1986). The resulting tablets were weighed to the nearest 0.1 mg, their thickness and diameter were measured to the nearest 0.01 mm, and the packing fraction (P_f = bulk density/true density) of each tablet was calculated. The true particle densities of the excipients were measured using an air-comparison pycnometer (Beckman Mod. 930). From plots of the noted log reciprocal porosity ($= 1/(1 - P_f)$) vs applied pressure, values of the yield pressure (reciprocal slope, P_Y) and the packing fraction where the rectilinear part of the graph intersects the ordinate (parameter P_{fA}) were obtained (Heckel, 1961; Roberts and Rowe, 1985).

The diametral breaking strength for each of the tablets was determined immediately after preparation by using a JJ T30K material-testing machine (JJ Lloyd Instruments Ltd, Southampton, U.K.) operated at a cross-head speed of 50 mm min^{-1}. The results were converted to tensile strength according to the relationship used by Fell and Newton (1970). The brittle fracture index (BFI) was calculated by comparing the tensile strength values of tablets that contained a hole, T_0, and those that did not, T_s (Hiestand et al., 1977):

$$\mathrm{BFI} = \frac{T_s - T_0}{2T_0} \tag{7}$$

To determine the tensile strength isotropy, rectangular compacts measuring 12.5 × 6 mm by about 12 mm were formed in the hydraulic press, using a suitable punch and die set. The packing fraction of the compacts was calculated, and the maximum supported load (F) before they failed in bending was measured. The bending load was applied either co-directional or vertical to the plane of compression and the corresponding tensile strength (T_c and T_v) was calculated from the equation (Stanley and Newton, 1980): $T = 3Fl/2h^2b$, where l is the distance between the two lower supporting fulcrums; b the compact width; and h the compact height. The log of the ratio (T_c/T_v) was plotted against log T_c, and the gradient of the plots was specified as the tensile strength isotropy (Malamataris and Bourdakos, 1986).

Results and Discussion

The experimentally measured moisture sorption and desorption isotherms are illustrated in Fig. 1. It is seen that the isotherms exhibit hysteresis in decreasing order for Polyplasdone, Sta-Rx and Avicel. On the other hand, Emdex shows extensive moisture uptake after exposure to a relative humidity higher than 83%, which may be attributed to deliquescence (Van Campen et al., 1983). Under desorption conditions over phosphorus pentoxide (RH = 0), Emdex retains approximately 8% of moisture.

In order to analyse the sorption-desorption hysteresis, according to the hypothesis of Young and Nelson, a combination of iteration and multiple regression techniques was used, as described in detail by Young and Nelson (1967a,b), York (1981) and Chan and Pilpel (1983). Parameters A and B, describing Eqns 5 and 6, and parameter E were obtained from the experimental moisture sorption

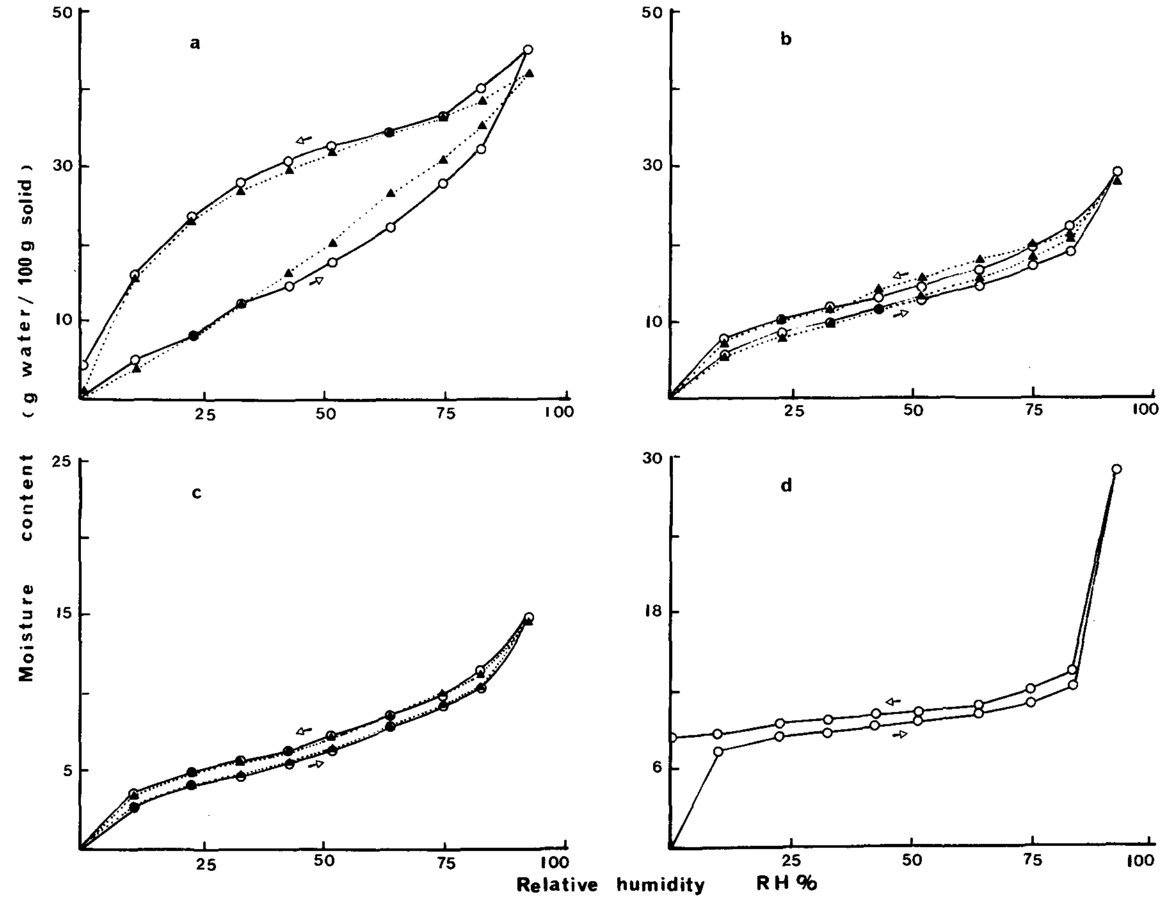

Fig. 1. Moisture sorption and desorption isotherms of: (a) Polyplasdone, (b) Sta-Rx, (c) Avicel and (d) Emdex (○——○, experimental; ▲------▲, computed data).

TABLE 1

Computed values of parameters in the Young and Nelson equations and fit of moisture sorption-desorption data

Excipient	E	A	B	(r)	Average deviation (%)	
					Sorption	Desorption
Polyplasdone	0.161	0.0287	0.3260	0.989	8.3	4.7
Sta-Rx	0.054	0.0654	0.0357	0.994	5.2	4.5
Avicel	0.075	0.0360	0.0143	0.998	2.2	2.6

and desorption data (M_s and M_d) for each DC excipient. They are given in Table 1 together with the highest correlation coefficient of the iteration and multiple regression.

By inserting the E values into the Eqns 2–4, the values of θ, ψ and β, respectively, were obtained. These values, according to Young and Nelson, yielded the amount of moisture present as a monolayer ($A \cdot \theta$), the amount of externally adsorbed moisture ($A \cdot (\theta + \beta)$), and the amounts of internally absorbed moisture during the sorption cycle ($B \cdot \psi$) and during the desorption cycle ($B \cdot \theta \cdot \mathrm{RH}_{\max}$). The theoretical sorption and desorption isotherms were then plotted by adding $A \cdot (\theta + \beta)$ plus $B \cdot \psi$ and $A \cdot (\theta + \beta)$ plus $B \cdot \psi \cdot \mathrm{RH}_{\max}$, respectively, at different relative humidities. The theoretical plots for the three DC excipients that exhibited significant and non-specific moisture uptake are included in Fig. 1. The average deviations of the theoretical from the experimental values are given in Table 1. For Emdex the validity of this curve-fitting procedure was very

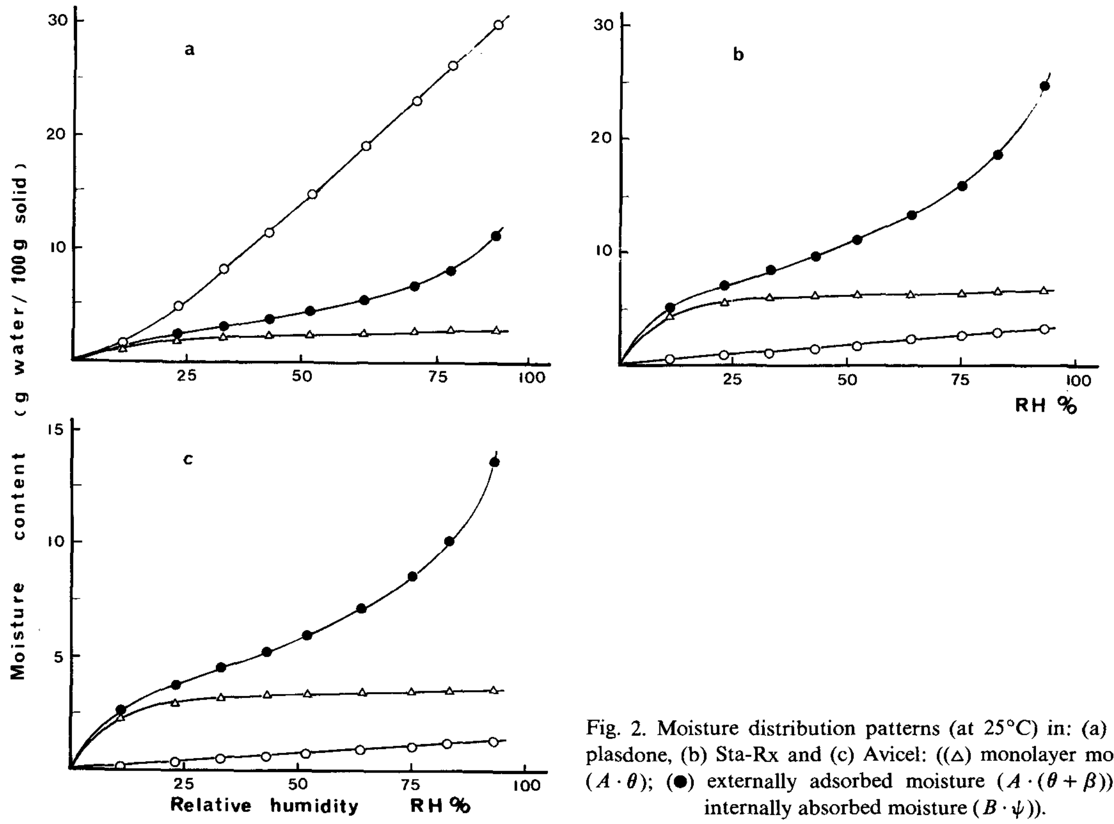

Fig. 2. Moisture distribution patterns (at 25°C) in: (a) Polyplasdone, (b) Sta-Rx and (c) Avicel: ((△) monolayer moisture ($A \cdot \theta$); (●) externally adsorbed moisture ($A \cdot (\theta + \beta)$); (○) internally absorbed moisture ($B \cdot \psi$)).

limited. A possible explanation for the latter may be the extensive moisture uptake at RH above 83% and the reduced mobility of water under desorption conditions over phosphorus pentoxide (RH = 0).

For the three DC excipients that followed the Young and Nelson model, the distribution of moisture in different forms at increasing relative humidity is demonstrated in Fig. 2. The graphs in Fig. 2 indicate that most of the moisture in Polyplasdone is located internally ($B \cdot \psi \gg A \cdot (\theta + \beta)$), while in the other two excipients the internally absorbed moisture ($B \cdot \psi$) is approximately 1/10 of the amount present as externally adsorbed moisture ($A \cdot (\theta + \beta)$).

As far as the analysis of the water-sorption data according to the GAB equation is concerned, polynomial regression analysis (2nd degree) was applied to obtain the parameters W_m, C_G and K. This was done by the following procedure. Eqn 1 was rewritten as:

$$\frac{P/P_0}{W} = \frac{1}{C_G \cdot K \cdot W_m} + \frac{C_G \cdot K - 2 \cdot K}{C_G \cdot K \cdot W_m} \cdot P/P_0 + \frac{K^2 - C_G \cdot K^2}{C_G \cdot K \cdot W_m} \cdot (P/P_0)^2 \qquad (8)$$

The experimental values of $P/P_0 \cdot W$ and P/P_0 were used to obtain the values of $1/(C_G \cdot K \cdot W_m)$, $(C_G \cdot K - 2 \cdot K)/(C_G \cdot K \cdot W_m)$, $(K^2 - C_G \cdot K^2)/(C_G \cdot K \cdot W_m)$ and hence the values of W_m, C_G and K. The parameters W_m, C_G and K, for all the DC excipients under investigation are listed in Table 2, together with correlation coefficients of the polynomial regression analysis and the average percent deviation of the theoretical from the experimental values. It can be seen from Table 2 that the fit of experimental data to the GAB equation is excellent, except for the case of Emdex which probably holds water in a specific manner, after the deliquescence at RH above 83%.

TABLE 2

Computed values of parameters in the GAB equation and fit of moisture sorption data

Excipient	W_m	C_G	K	(r)	Average deviation (%)
Polyplasdone	0.133	5.58	0.775	0.952	2.2
Sta-Rx	0.078	34.31	0.756	0.970	5.5
Avicel	0.042	18.07	0.763	0.988	3.4
Emdex	0.090	12.26	0.906	0.926 [a]	49.6

[a] RH $\leqslant$ 83%.

The values of the monomolecular water parameter (W_m), for the GAB equation, and the amounts of the monomolecular water ($A \cdot \theta$) at 93% RH, obtained from the Young and Nelson equations (Table 3), tend to be comparable for Sta-Rx and Avicel but not for Polyplasdone. W_m is very much higher than $A \cdot \theta$ in the case of Polyplasdone, and it seems to be equal to the total of externally adsorbed moisture $A \cdot (\theta + \beta)$ at 93% RH (see Fig. 2). For a further physically significant comparison of the GAB and Young and Nelson data, the values of enthalpy terms, $H_1 - H_L$ and $q_1 - q_L$ were calculated, since the parameter C_G is analogous to the E term. For this calculation it was assumed that B_1 and D are equal to unity. The results for the three DC excipients exhibiting significant sorption-desorption hysteresis are listed in Table 3 and show reasonable agreement. The discrepancy, referred to above, between the moisture distribution and the enthalpy terms for the case of Polyplasdone, might be an indication that the Young and Nelson model does not adequately describe the physical state of water vapour taken up by polymeric materials (Zografi et al., 1983).

The tensile strength results measured by diametral loading of tablets (intact or perforated) and by bending the rectangular compacts were found to fit the general equation:

$$\log T = A_1 \cdot P_f + B_1 \qquad (9)$$

with a highly significant correlation (> 0.95 for at least seven measurements over the range of pack-

TABLE 3

Comparison of values for monomolecular water and enthalpy terms obtained from the GAB and Young and Nelson equations

Excipient	W_m	$A \cdot \theta$ (at 93% RH)	$H_1 - H_L$ (kcal mol^{-1})	$q_1 - q_L$ (kcal mol^{-1})
Polyplasdone	0.133	0.028	1.169	1.081
Sta-Rx	0.078	0.065	2.259	1.728
Avicel	0.042	0.036	1.874	1.534

ing fraction, P_f, from 0.7 to 0.95) A_1 and B_1 are numerical terms which depend on the nature of the DC excipient, the relative humidity during storage and the type of tensile test employed.

The tensile strengths from diametral breaking of intact tablets prepared after storage of the DC excipients at different relative humidities either for the sorption or the desorption conditions were calculated for a fixed packing fraction, 0.9, by using Eqn 9. These values are plotted against the moisture content in Fig. 3.

It is seen that for Avicel and Emdex the tensile strength exhibits a small initial plateau and then decreases as the moisture content increases. On the other hand, for Polyplasdone and Sta-Rx the tensile strength initially increases, reaches a maximum, and then decreases. The tensile strength for sorption conditions is always higher than that of desorption, but only for the initial range of relative humidities (adsorption phase) (Fig. 3). At the higher relative humidities (absorption phase), the tensile strength for sorption conditions is either lower (Polyplasdone) or equal to that of desorption (Sta-Rx, Avicel, Emdex). The tensile strength maxima and the subsequent decrease occur at a higher moisture content for the desorption conditions but correspond to the same relative humidity for both sorption and desorption.

The above-mentioned observations may constitute evidence that the increase in tensile strength due to moisture content is caused by the externally adsorbed 'monomolecular' water (W_m or $A \cdot \theta$). This tightly bound water can be regarded as a part of the surface molecular structure of the particles, which facilitates the formation of interparticle hydrogen bonding (Zografi and Kontny, 1986; Khan and Pilpel, 1987) or increases the Van der Waals' forces, smoothing out the surface microirregularities and reducing the interparticle separation (Eaves and Jones, 1972).

The subsequent decrease in tensile strength with moisture content may be attributed to plasticising of the particles and weakening of the intra-particle bonds due to disruption of the forces between the molecules of the materials constituting the particles, especially in their surface (Khan and Pilpel,

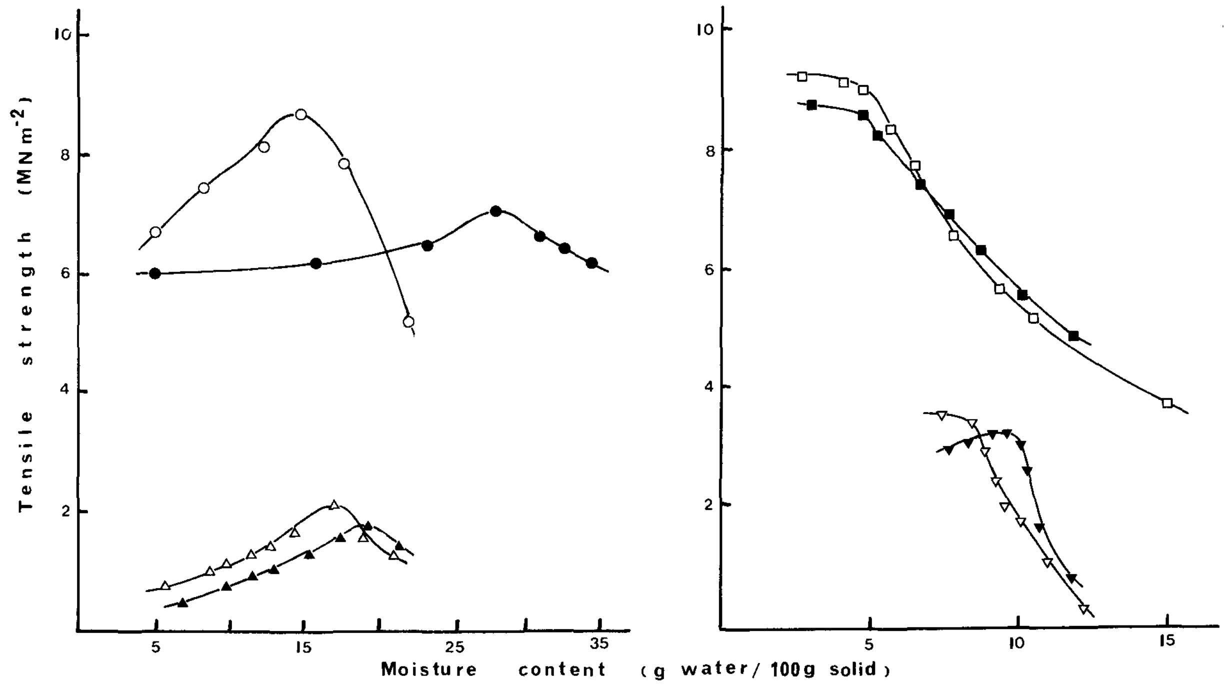

Fig. 3. Tensile strength from diametral breaking of intact tablets at $P_f = 0.9$. ((○) Polyplasdone; (△) Sta-Rx; (□) Avicel; (▽) Emdex under sorption and desorption conditions (closed symbols)).

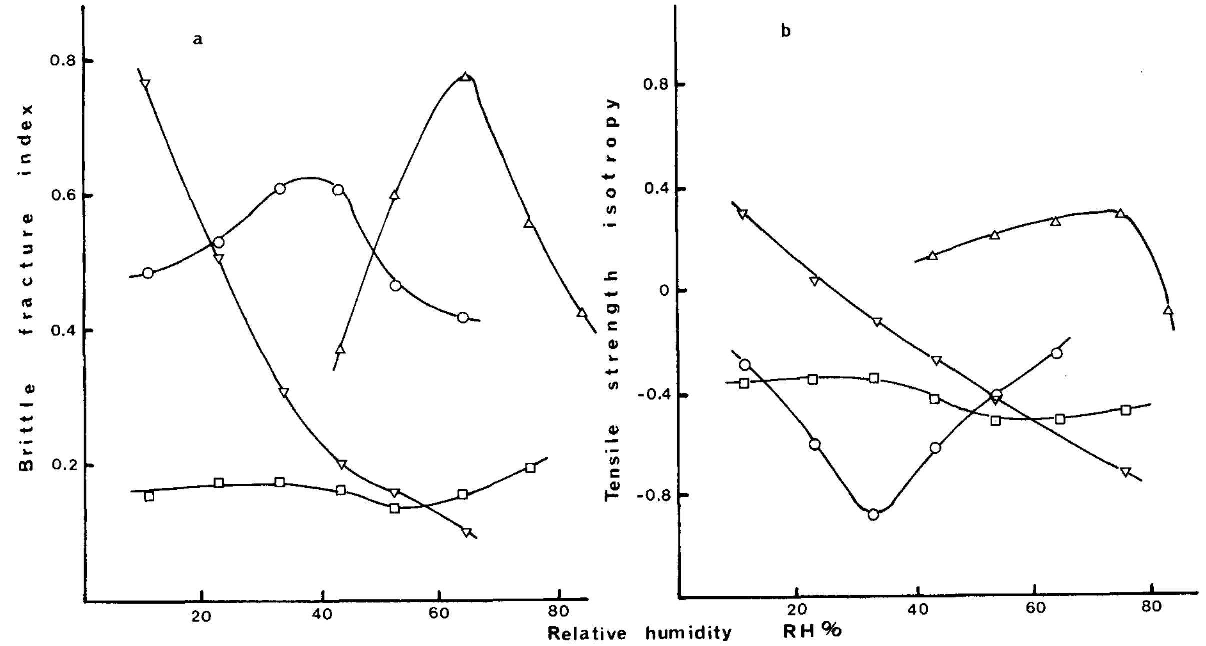

Fig. 4. Effect of ambient relative humidity during storage under sorption conditions on: (a) brittle fracture index, (b) tensile strength isotropy (symbols as in Fig. 3).

1987). The tensile strength maxima which were followed by a decrease in strength (Fig. 3) occurred at 0.06 g of water per g of dry Avicel, 0.15 for Polyplasdone, and 0.17 per g of Sta-Rx; these values are almost double the mean of the corresponding W_m and $A \cdot \theta$ values in Table 3.

Fig. 4a and b show the effect of relative humidity on BFI and tensile strength isotropy respectively. The curves in Fig. 4a and b are similar in shape and in relative position except for Polyplasdone. The extensive friction and adhesion observed during the preparation of the Polyplasdone perforated tablets may account for higher BFI values, and the position of the Polyplasdone curve

TABLE 4

Compression parameters (P_Y and P_{fA}) for the DC excipients after storage at different relative humidities

Relative humidity (%)	Polyplasdone		Sta-Rx		Avicel		Emdex	
	P_Y (MN m^{-2})$^{-1}$	P_{fA}	P_Y (MN m^{-2})$^{-1}$	P_{fA}	P_Y (MN m^{-2})$^{-1}$	P_{fA}	P_Y (MN m^{-2})$^{-1}$	P_{fA}
0								
11	194	0.54	204	0.55	117	0.48	105	0.51
23	171	0.58	200	0.61	113	0.49	101	0.55
33	137	0.61	167	0.62	111	0.52	92	0.55
43	91	0.52	160	0.66	110	0.57	86	0.55
52	57	0.29	139	0.67	102	0.59	79	0.52
64	46	0.24	103	0.65	100	0.64	76	0.52
75	[a]		66	0.59	94	0.66	67	0.52
83	[a]		53	0.59	92	0.68	[a]	
93	[a]		32	0.59	71	0.72	[a]	

[a] Very soft or weak tablets.

in Fig. 4a. For the different materials, the relative positions of the curves in Figs 3 and 4b are effectively reversed.

The above-mentioned similarities and reversed positions of the curves might be expected and possibly are related to the plasto-elasticity of the powders under investigation (Ejiofor et al., 1986). While elasticity is inversely proportional to the tensile strength, it is directly proportional to the BFI and the tensile strength isotropy.

The plasto-elasticity can be quantified as yield pressure derived from Heckel plots (reciprocal of slope, P_Y) which shows a continuous decrease with moisture content for all the DC excipients studied (Table 4).

The intercept of the Heckel plots, P_{fA}, shows continuous increase for Avicel but for Emdex, Sta-Rx and mainly for Polyplasdone it initially increases, reaches a maximum and then decreases. P_{fA} is a parameter of densification due to the slippage and rearrangement of particles (Roberts and Rowe, 1985) and indicates that moisture may act as a lubricant smoothing out the surface microirregularities, reducing the frictional force and facilitating particle rearrangement mainly at low concentrations when it is tightly bound as monolayer.

From the above-mentioned it is concluded that the changes in the mechanical strength of the tableted DC excipients studied, due to storage at different relative humidities, can be explained by a combined effect on the interparticle and intermolecular forces. The presence of 'tightly' bound 'monomolecular' water increases the interparticle bonding and the less tightly bound 'absorbed or bulk' water increases the plasticity and weakens the interparticle bonds. The tensile strength reaches a maximum value and then begins to decrease when the moisture content is about double that corresponding to a tightly bound monomolecular layer.

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