

Absorption of moisture by sodium cromoglycate and mixtures of sodium cromoglycate and lactose

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The presence of up to about 15% w/w moisture has little effect on the tensile and shear properties of sodium cromoglycate and of 1:1 mixtures of sodium cromoglycate and lactose. Analysis of their adsorption and desorption isotherms using equations developed by Young and Nelson shows that this is because most of the moisture is absorbed into the interior of the sodium cromoglycate leaving little adsorbed moisture on the surfaces of the particles concerned.

A number of workers (Shotton & Harb 1966; Harwood 1969; Glushkov et al 1969; Eaves & Jones 1972a, b; Walton & Pilpel 1972) noticed that the presence of moisture in varying quantities could either increase or reduce the mechanical strengths of different powders. Their apparently conflicting findings can now be ascribed to the fact that moisture can be present in powders in three different physical states, Fig. 1a (Young & Nelson 1967a, b). It can form an adsorbed monomolecular layer; an adsorbed

Nelson (1967a, b) derived equations for describing the adsorption and desorption isotherms of powders and for calculating the amounts of moisture present in these different physical states.

They assumed that the presence of a second adsorbed layer of water would prevent the evaporation of water from the monomolecular layer beneath it. At equilibrium, the rate of condensation of water at the interface of these two adsorbed layers must be equal to its rate of evaporation. The monomolecular layer is subject to surface binding forces and diffusional forces, and these forces must be equal if it is to remain on the surface of the particles and not diffuse into their interior. Under adsorption conditions, the presence of a second layer of adsorbed moisture will cause an increase in the diffusional forces and will tend to move the water into the particles' interior. When the powder is dehydrated, this adsorbed moisture will remain inside the particles until the water in the monomolecular layer has evaporated.

Using the kinetic theory of gases, Young & Nelson (1967a, b) obtained the following expressions:

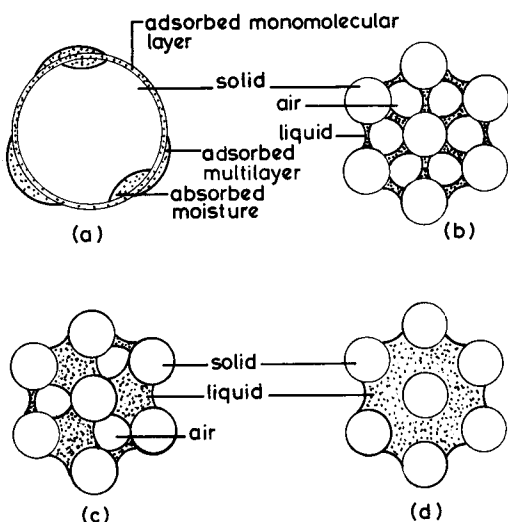


FIG. 1. Diagrammatic representation of different states of moisture (after Young & Nelson 1967a, b, and Newitt & Conway-Jones 1958).

multilayer which forms pendular, funicular or capillary bonds between particles, Fig. 1b, c, d (Newitt & Conway-Jones 1958); or moisture can be absorbed into the interior of the particles, Fig. 1a. Young &

$$\theta = \frac{RH}{RH + (1 - RH)E} \quad (1)$$

$$\psi = \theta RH \quad (2)$$

$$E = \exp \{-(q_1 - q_L)/(K_B T_e)\} \quad (3)$$

$$\beta = -\frac{E(RH)}{E - (E-1)RH} + \frac{E^2}{E-1} \log_e \frac{E - (E-1)RH}{E} - (E+1) \log_e (1-RH) \quad (4)$$

$$M_s = \frac{\rho_w V_m}{W_m} (\theta + \beta) + \frac{\rho_w V_a}{W_m} \psi \quad (5)$$

$$M_d = \frac{\rho_w V_m}{W_m} (\theta + \beta) + \frac{\rho_w V_a}{W_m} \theta RH_{max} \quad (6)$$

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

* Correspondence.

thick, β is the total amount of adsorbed moisture in a multilayer, q_1 is the heat of adsorption of water, q_L is the normal heat of condensation of water molecules, K_B is Boltzmann's constant, T_e is the absolute temperature, M_s and M_d are the moisture contents of the powder during adsorption and desorption conditions, V_m and V_a are respectively the volumes of the adsorbed and absorbed moisture, ρ_w is the density of water, W_m is the dry weight of the powder and RH and RH_{max} are the relative humidity and maximum relative humidity of the environment respectively.

In the present work, equations (1)–(6) have been used to calculate the amounts of moisture present in these three different physical states in samples of sodium cromoglycate and mixtures of sodium cromoglycate and lactose in order to account for their mechanical properties.

MATERIALS AND METHODS

Sodium cromoglycate (DSCG) was supplied by Fisons Pharmaceuticals Ltd in the form of a fine powder (1–5 μm) with an average particle size of 3 μm . One batch was physically mixed with an equal weight of lactose monohydrate of size range 5–160 μm to produce mixture M1. Another batch was physically mixed with an equal weight of lactose monohydrate of size range 40–60 μm to produce mixture M2. The degrees of mixedness (Rose 1959) were respectively 0.992 and 0.987 as measured by u.v. analysis of the DSCG at 238 nm.

Determination of adsorption and desorption isotherms

The powders were initially dried over phosphorus pentoxide in a desiccator at 20 °C. They were then divided and transferred to tightly closed desiccators whose different relative humidities at 20 °C were maintained by introducing dishes of the various saturated salt solutions listed in Table 1 (Winston & Bates 1960; Young 1967). The final moisture contents of the samples were determined by drying them

Table 1. Saturated salt solutions used to provide various humidity environments (after Winston & Bates 1960).

Saturated salt solution	Relative humidity at 20 °C
P_2O_5	0
$\text{LiCl} \cdot \frac{1}{2}\text{H}_2\text{O}$	15
$\text{CH}_3\text{COO} \cdot \text{K}$	20
$\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$	33
$\text{K}_2\text{CO}_3 \cdot 6\text{H}_2\text{O}$	44
$\text{Mg}(\text{NO}_3)_2 \cdot 2\text{H}_2\text{O}$	55
NaNO_2	65
NaCl	76
KCl	85

to constant weight in a vacuum oven (Townson & Mercer) at 105 °C over phosphorus pentoxide using 5 mm mercury pressure.

A similar procedure was followed for determining the desorption isotherms of the samples after initially equilibrating them over saturated potassium chloride (RH 85% at 20 °C).

Tensile and shear strength measurements

The tensile and shear strengths of the equilibrated powders, whose moisture contents had been determined as above, were measured with a Warren Spring tensile tester (Ashton et al 1964) and an annular shear cell (Carr & Walker 1967; Kocova & Pilpel 1972) respectively. During the measurements the environment was maintained at the same RH ($\pm 5\%$) as had been used for preparing each sample by means of a dehumidifier (Westair Dromatic).

RESULTS

Preliminary experiments showed that heating lactose monohydrate to 105 °C over P_2O_5 did not convert it to the anhydrous form. The free moisture contents of the samples were found to be less than 1% over a range of relative humidity of 0–85% at 20 °C.

Fig. 2a and b show the adsorption and desorption isotherms of DSCG and M1 at 20 °C; both powders exhibit hysteresis. In comparison, the lactose monohydrate did not exhibit hysteresis. It is seen from Fig. 2 that at each value of relative humidity, the moisture content of DSCG was higher than that of M1.

Because the quantities q_1 , V_m and V_a in equations (1)–(6) are not known and it is difficult to determine them experimentally, a combination of iteration and multiple regression techniques was used to fit the experimental data to these equations. This was done by the following procedure.

An assumed value of E was used to calculate θ , ψ and β using equations (1), (2) and (4). Rewriting equations (5) and (6) as

$$M_s = \bar{A}(\theta + \beta) + \bar{B}\psi \quad (7)$$

$$M_d = \bar{A}(\theta + \beta) + \bar{B}\theta RH_{max} \quad (8)$$

where $\bar{A} = \frac{\rho_w V_m}{W_m}$ and $\bar{B} = \frac{\rho_w V_a}{W_m}$

and using the experimental values of M_s and M_d and a multiple regression technique, the values of θ , ψ and β at various relative humidities were substituted into equations (7) and (8) to obtain the values of \bar{A} and \bar{B} and hence the theoretical values of M_s and M_d . The experimental and theoretical values of M_s and M_d were subjected to error analysis in which the

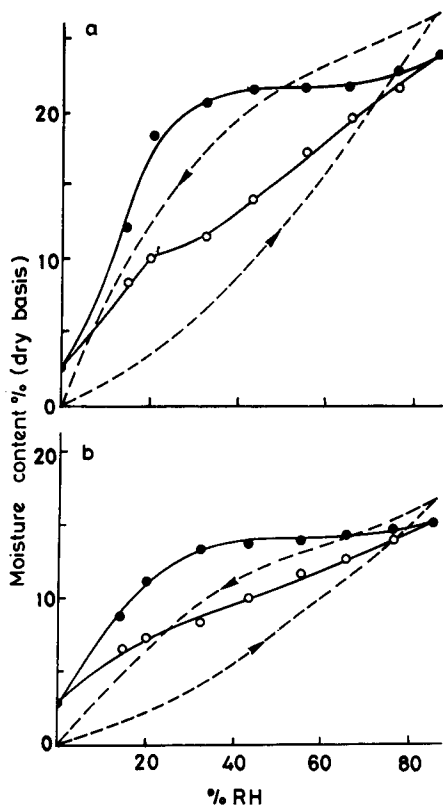


Fig. 2a. Moisture adsorption and desorption isotherms of DSCG at 20 °C. ○ adsorption isotherm, ● desorption isotherm; — observed value, - - - theoretical value.

Fig. 2b. Moisture adsorption and desorption isotherms of M1 at 20 °C. (Key as Fig. 2a).

sums of squares of deviation between them were estimated. This procedure was repeated using other assumed values of E until the highest correlation coefficient, given by

$$\text{Correlation coefficient} = \left[1 - \frac{\text{sums of squares of deviation of the theoretical values from experimental values}}{\text{sums of squares of deviation of the experimental values from their mean}} \right]^{1/2}$$

was obtained. In this way, the correct values of E, \bar{A} and \bar{B} for each powder were obtained.

These values are given in Table 2 and were then used to calculate the correct values of θ , ψ and β by employing equations (1), (2) and (4). From these values one could calculate the amount of moisture present as a monomolecular layer $\bar{A}\theta$, the amount of the adsorbed moisture $\bar{A}(\theta + \beta)$, the amount of adsorbed moisture $\bar{B}\psi$ during the adsorption cycle

Table 2. Values of E, \bar{A} , \bar{B} and correlation coefficient obtained from analysis of moisture adsorption and desorption isotherms.

	DSCG	M1
E	0.0005	0.0005
\bar{A}	0.006	0.0066
\bar{B}	0.617	0.387
Correlation coefficient	0.977	0.960

and the amount of absorbed moisture $\bar{B}\theta RH_{max}$ during the desorption cycle. The theoretical adsorption and desorption isotherms were then plotted by adding $\bar{A}(\theta + \beta)$ plus $\bar{B}\psi$ and $\bar{A}(\theta + \beta)$ plus $\bar{B}\theta RH_{max}$ respectively at different relative humidities. The plots are given in Figs 2a, b and show reasonable agreement with the experimental isotherms.

From these results it was possible to obtain the distribution of the moisture in the different samples at different relative humidities and some data are plotted in Fig. 3. It was found that during adsorption conditions at each relative humidity DSCG absorbed at least 15 times as much moisture as it adsorbed and M1, and therefore M2 which contained lactose monohydrate of a different particle size distribution, about ten times as much. This indicates that most of the moisture in these powders is located internally in the particles. It is also seen that in both cases, increasing relative humidity had a negligible effect on the amount of moisture in the form of a monomolecular layer, i.e. <0.1%.

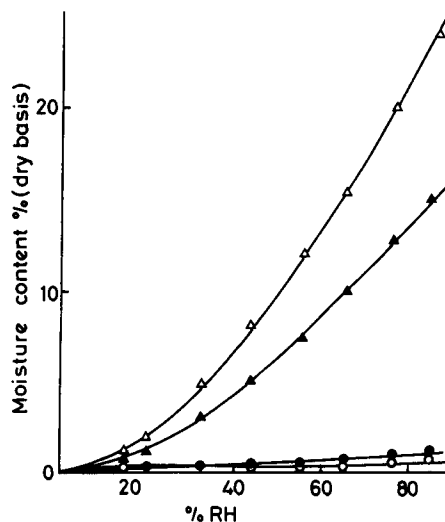


Fig. 3. Moisture distribution pattern in DSCG and M1 at 20 °C. Adsorbed moisture; ○ DSCG, ● M1; adsorbed moisture during adsorption conditions Δ DSCG, \blacktriangle M1; monomolecular moisture at <0.1% for both DSCG and M1.

It was found that when the logarithms of tensile strength of DSCG containing between 10 and 19% moisture; of M1 containing between 8 and 13% moisture and of M2 containing between 7 and 12% moisture were plotted against packing fraction, three straight line graphs were obtained with correlation coefficients of 0.932, 0.953 and 0.991 respectively. The results for M1 are shown in Fig. 4 and the scatter of the points was no greater than normally occurs when dry powders are being used (Farley & Valentin 1967; Eaves & Jones 1971).

The shear test results were plotted as graphs of shear stress versus compound normal stress (Williams & Birks 1967; Kocova & Pilpel 1972) and the values of the angles of internal friction (Δ) were obtained as illustrated in Fig. 5.

Table 3 lists the values of T at a selected packing fraction of 0.25 and of $\tan \Delta$ for DSCG, M1 and M2. It is seen that within the range employed in the present work, these mechanical properties of the powders were hardly affected by their moisture contents.

DISCUSSION

The analysis of the adsorption and desorption isotherms has shown that in DSCG and DSCG-lactose mixtures, hysteresis occurs and that most of the moisture is absorbed, i.e. located internally inside the particles. Since lactose monohydrate neither adsorbs nor absorbs moisture significantly,

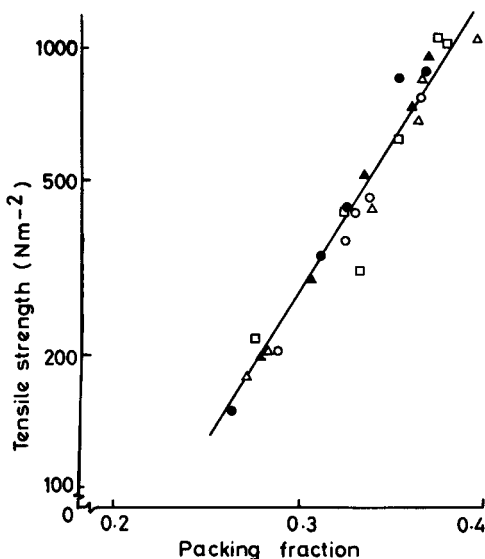


Fig. 4. Graph of log tensile strength against packing fraction of M1: moisture content %: \circ 8.5, \blacktriangle 9.4, \blacktriangle 11.0, \square 12.2, \bullet 13.0.

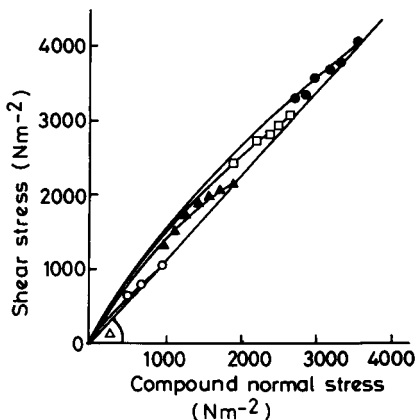
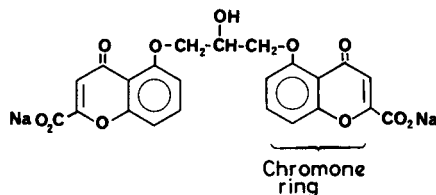


Fig. 5. Yield loci of DSCG at 14.0% moisture. Key: packing density: \circ 0.144, \blacktriangle 0.186, \square 0.189, \bullet 0.204.

nor exhibits any hysteresis, it may be inferred that both results are due to the DSCG which is known to have peculiar physical and chemical properties.

Several workers (Cox et al 1971; Champion & Meetan 1973; Hartshorne & Woodard 1973) have found that DSCG absorbs water from the atmosphere rapidly and that it accommodates up to nine molecules of water per molecule, depending on the environmental conditions, to form a series of solid solutions, before its crystal structure collapses at a relative humidity of 93% at 20 °C. In studying the molecular configuration of DSCG in the anhydrous state and in dilute solutions up to 3%, these workers noticed that the two chromone rings of the molecule remain coplanar. This is unexpected because the



glycerol bridge ($-\text{O}-\text{CH}_2-\text{CH}(\text{OH})-\text{CH}_2-\text{O}-$) between them is flexible and should permit them to rotate freely into other configurations. These workers therefore suggested that hydrogen bonds occur between water molecules and the carbonyl, carboxyl and hydroxyl groups of the DSCG molecules. These would stabilize a rigid coplanar configuration. Hamdrakas et al (1974) supported the likelihood of extensive hydrogen bonding by the observation that DSCG can accommodate six molecules of water in the three-dimensional space between the two chromone rings.

Hydrogen bonding would thus satisfactorily account for the rigid molecular configuration of DSCG, for its hygroscopicity and its tenacity for water to the extent that it cannot be completely dried even with phosphorus pentoxide. It would account for the present finding of considerable hysteresis between its moisture adsorption and desorption isotherms.

Table 3. Values of T at $\rho_F = 0.25$ and $\tan \Delta$.

Sample	Equilibration environment at 20°C (%RH)	Moisture content % (dry basis)	T at $\rho_F = 0.25$ ($N m^{-2}$)	$\tan \Delta$
DSCG	33	10.6	758	1.16
	44	14.0	733	1.16
	55	14.3	822	1.20
	65	18.9	789	1.21
	76	19.8	788	1.22
M1	33	8.5	97	1.06
	44	9.4	118	1.06
	55	11.0	116	1.03
	65	12.2	125	1.05
	76	13.0	116	1.05
M2	44	7.0	42	0.96
	55	8.3	38	0.96
	76	12.0	40	0.95

As the moisture content of DSCG and the DSCG-lactose mixtures is increased up to about 15% w/w, their tensile strengths and values of $\tan \Delta$ remain virtually unchanged (Table 3). This finding is uncommon although it has been reported to occur also with calcium phosphate (Eaves & Jones 1972b). As has been seen however (Fig. 3) most of the water is absorbed and the amount adsorbed on the surface of the particles remains approximately constant at about 0.8% throughout the range of humidity studied. As a result little change can occur in the number or strength of the surface bonds between particles. These are ultimately responsible for the mechanical properties of the powders and this could explain why T and $\tan \Delta$ for DSCG and its mixture do not alter significantly with relative humidity.

CONCLUSION

Analysis of the moisture distribution patterns in DSCG and DSCG-lactose mixtures shows that most of the moisture is located internally inside the particles. The small amount of moisture adsorbed on the surface of the particles is insufficient to affect the tensile and shear properties of these powders.

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REFERENCES

- Ashton, M. D., Farley, R., Valentin, F. H. H. (1964) *J. Sci. Instr.* 41: 763-765
- Carr, J. F., Walker, D. M. (1967) *Powder Technol.* 1: 369-373
- Champion, J. V., Meetan, G. H. (1973) *J. Pharm. Sci.* 62: 1589-1595
- Cox, J. S. G., Woodard, G. D., McCrone, W. C. (1971) *Ibid.* 60: 1458-1465
- Eaves, T., Jones, T. M. (1971) *Rheol. Act.* 10: 127-134
- Eaves, T., Jones, T. M. (1972a) *J. Pharm. Sci.* 61: 256-261
- Eaves, T., Jones, T. M. (1972b) *Ibid.* 61: 342-348
- Farley, R., Valentin, F. H. H. (1967) *Powder Technol.* 1: 344-354
- Glushkov, V., Karnaushenko, L., Platonov, P. (1969) 3rd Congress CHISA, section B4.3, Prague, Czechoslovakia, Sept. 15-20, 1969
- Hamodrakas, S., Geddes, A. J., Sheldrick, B. (1974) *J. Pharm. Pharmacol.* 26: 54-56
- Hartshorne, N. H., Woodard, G. D. (1973) *Mol. Cry. Liq. Cry.* 23: 343-368
- Harwood, C. F. (1969) Ph.D. Thesis, University of London
- Kocova, S., Pilpel, N. (1972) *Powder Technol.* 5: 329-343
- Newitt, D. M., Conway-Jones, J. M. (1958) *Trans. Inst. Chem. Eng.* 36: 422-442
- Rose, H. E. (1959) *Ibid.* 37: 47-64
- Shotton, E., Harb, N. (1966) *J. Pharm. Pharmacol.* 18: 175-178
- Walton, C. A., Pilpel, N. (1972) *Ibid.* 24: 10P-16P
- Williams, J. C., Birks, A. H. (1967) *Powder Technol.* 1: 199-206
- Winston, P. W., Bates, D. H. (1960) *Ecology* 41: 232-237
- Young, J. F. (1967) *J. Appl. Chem.* 17: 241-245
- Young, J. H., Nelson, G. H. (1967a) *Trans. Am. Soc. Agric. Eng.* 10: 260-263
- Young, J. H., Nelson, G. H. (1967b) *Ibid.* 10: 756-761