

# Analysis of moisture sorption hysteresis in hard gelatin capsules, maize starch, and maize starch: drug powder mixtures

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Moisture sorption and desorption isotherms at 25 °C for hard gelatin capsules, maize starch and 50:50 mixes of maize starch: barbitone and maize starch: sodium barbitone have been measured. The sorption hysteresis observed in all four systems studied has been analysed according to the hypothesis of Young & Nelson (1967a) which distinguishes three locations for moisture—monolayer adsorbed moisture, normally condensed moisture and absorbed moisture. Hysteresis is explained by a separation of absorption and desorption isotherms for absorbed moisture and different patterns of moisture distribution are demonstrated in the four systems examined.

Knowledge of moisture sorption profiles of materials is necessary where controlled powder flow is critical. Moisture modifies the flow and mechanical properties of many powders (Pilpel 1971) as well as the processing of hard gelatin capsules (Bond et al 1970) as these exhibit optimal handling and mechanical properties when containing 14–16% moisture (Kellaway et al 1978). Moisture sorption is also a factor in the formulation of powder inhalation aerosols (Chowhan & Amaro 1977) and tablets (Jones 1977).

Moisture sorption hysteresis, that is a separation of moisture sorption and desorption isotherms, has been reported for magnesium trisilicate, bacitracin, sodium pentobarbitone, veegum, starch, procaine, gelatin, sodium cromoglycate: lactose blend and microcrystalline cellulose (Strickland 1962; Strickland & Moss 1962; Ito et al 1969; Bell et al 1973) but the origins are not well understood (Sing 1976). The moisture sorption profiles of some moisture sensitive pharmaceutical materials have been analysed to elucidate the mechanisms associated with hysteresis and investigate moisture distribution patterns.

## MATERIALS AND METHODS

The materials used were clear hard gelatin capsules, size no. 1 (Eli Lilly and Co., Basingstoke, U.K.), maize starch (Evans Medical Ltd., Liverpool, U.K.), barbitone and sodium barbitone (Hopkins and Williams, Chadwell Heath, U.K.). The physico-chemical properties of the materials, the preparation of the 50:50 maize starch: barbitone and 50:50 maize starch: sodium barbitone capsules of constant

porosity 50%, and storage of materials and filled capsules have been previously described (York 1980). Moisture contents were determined by drying materials to constant weight in a hot air oven at appropriate temperatures.

## RESULTS AND DISCUSSION

The moisture sorption and desorption isotherms for gelatin capsules, maize starch, maize starch: barbitone mixture and maize starch: sodium barbitone mixture all exhibit hysteresis (York 1980). Factors such as differences in advancing and decreasing contact angles between adsorbent and adsorbate, the role of surface pore shape and volume and the phenomenon of multilayer adsorption followed by capillary condensation in cylindrical pores have been proposed as possible explanations of the mechanisms of moisture sorption hysteresis, but none are completely satisfactory (Gregg 1961). In this study the experimental results have been tested against the theoretical relationships derived by Young & Nelson (1967a, b) who hypothesized three mechanisms by which water could be held (see Fig. 1). Moisture sorption hysteresis was explained thus: if a dry material is exposed to moisture, water molecules first adsorb onto the surfaces to form a monomolecular layer, which is subjected to both surface binding and diffusional forces, the latter tending to cause moisture transfer into the material. The diffusional forces exceed the binding forces as more water molecules adhere to the surfaces and moisture is transferred into the material. If the moisture vapour pressure is reduced, water molecules at the

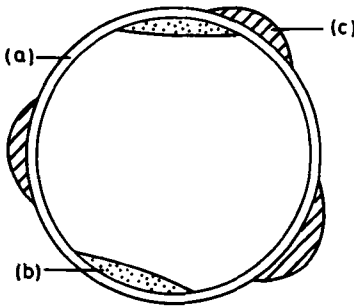


FIG. 1. Illustration of location of three types of moisture. (a) Monomolecular layer of water molecules bound to surface (termed monolayer adsorbed moisture). (b) moisture within material (termed absorbed moisture). (c) multimolecular layers of water (termed normally condensed water).

surface must be removed before diffusional forces pull moisture out of the interior of the material.

The relevant equations of Young and Nelson are as follows\*:

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

$$\phi = R\theta \quad (2)$$

$$\alpha = -\frac{ER}{E-(E-1)R} + \frac{E^2}{E-1} \ln \frac{E-(E-1)R}{E} - (E+1) \ln(1-R) \quad (3)$$

$$M_s = \frac{\rho V_m}{W} (\theta + \alpha) + \frac{\rho V \phi}{W} \quad (4)$$

$$M_d = \frac{\rho V_m}{W} (\theta + \alpha) + \frac{\rho V}{W} \theta R_m \quad (5)$$

\*  $\theta$  = fraction of surface of material covered by a monomolecular layer of water molecules.

$R$  = relative humidity

$E = \exp(-q_1 - q_L)/kT$

$q_1$  = heat of adsorption of molecules bound to surface of material

$q_L$  = normal heat of condensation of water molecules

$K$  = Boltzmann's constant

$T$  = absolute temperature

$\phi$  = fraction of surface covered by at least one or more layers of normally condensed moisture

$\alpha$  = total amount of normally condensed moisture measured in molecular layers

$M_s$  = total moisture content for sorption from the dry state

$M_d$  = total moisture content for desorption from a maximum relative humidity,  $R_m$

$\rho$  = density of water

$V_m$  = volume of moisture in the monomolecular layer

$W$  = mass of dry material

$V$  = volume of absorbed moisture at saturation

A combination of an iteration and multiple regression technique was used to fit the experimental data to the derived equations. Values of the exponential term,  $E$ , were assumed and using equations (1), (2) and (3) values of  $\theta$ ,  $\phi$  and  $\alpha$  were calculated. Equations (4) and (5) were then written as

$$M_s = A(\theta + \alpha) + B(\phi) \quad (6)$$

$$M_d = A(\theta + \alpha) + B\theta R_m \quad (7)$$

where

$$A = \frac{\rho V_m}{W} \quad \text{and} \quad B = \frac{\rho V}{W}$$

Then, with the experimental data and a multiple regression technique, values of  $A$  and  $B$  were calculated for each assumed value of  $E$ . In this way, unique values of  $E$ , and  $A$  and  $B$ , which minimized the sum of the squares between the computed and experimentally measured values of moisture content, were obtained. Computed values are listed in Table 1 together with correlation coefficients.

The experimentally measured sorption and desorption isotherms for the four systems studied are illustrated in Fig. 2 a-d (York 1980) together with the corresponding computed curves. The theoretical equations fit closely to experimental data with correlation coefficients greater than 0.988 (see Table 1), indicating the suitability of the hypothesis to examine the moisture sorption hysteresis of the materials under investigation.

Further analysis of data according to equations (6) and (7), using calculated values of  $\theta$ ,  $\alpha$  and  $\phi$  allows the pattern of moisture distribution to be

Table 1. Computed values of parameters  $A$ ,  $B$ ,  $E$  and correlation coefficients from equations 9 and 10\*.

	A	B	E	Correlation** coefficient
Hard gelatin capsule	0.0587	0.0572	0.033	0.991
Maize starch	0.0123	0.1199	0.148	0.988
Maize starch: barbitone mix	0.0088	0.0624	0.110	0.990
Maize starch: sodium barbitone mix	0.0174	0.0236	0.157	0.994

\* See text for definition of symbols.

\*\* Correlation coefficient estimated from the expression:

$$\left[ \frac{1 - \text{sum of squares of the deviations of calculated values from observed values}}{\text{sum of squares of deviations of the observed values from their means}} \right]^{\dagger}$$

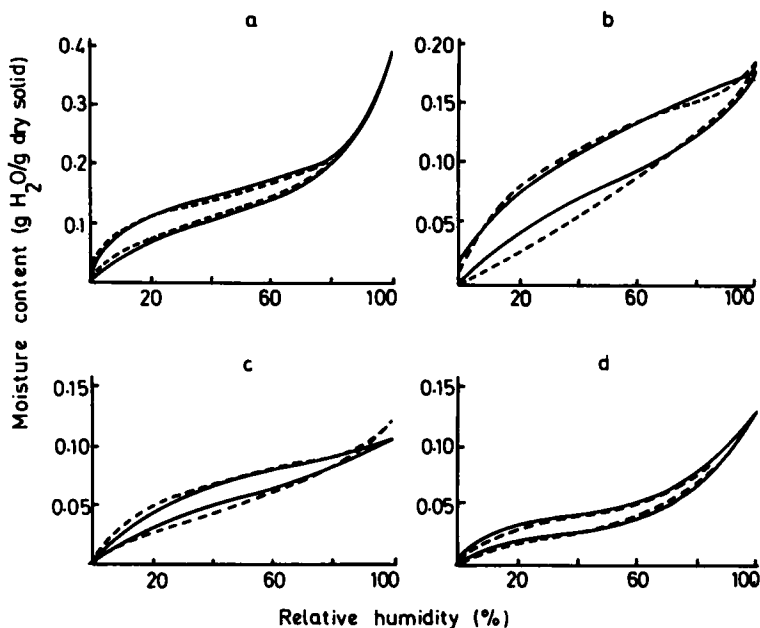


FIG. 2. Observed and computed moisture sorption and desorption isotherms at 25 °C. (a) Gelatin capsules. (b) Maize starch. (c) 50:50 maize starch:barbitone. (d) 50:50 maize starch:sodium barbitone. — Experimental data. - - - - Computed data.

demonstrated. Figs 3 and 4 show graphs of monolayer adsorbed moisture, normally condensed moisture and absorbed moisture versus relative humidity for the four systems examined.

The graphs for gelatin capsules in Fig. 3 indicate complete formation of the adsorbed monomolecular layer at 20% R.H., and moisture sorption hysteresis attributable to a separation of the absorption and desorption isotherms for the moisture located internally in the material. A linear relation between absorbed moisture and relative humidity is indicated between 25 and 100% R.H.

Above 80% R.H. the sorbed moisture is increasingly directed to form multilayers of condensed moisture, with the linear increase in absorbed moisture with increasing relative humidity maintained. At high moisture contents, gelatin films decrease in strength, attempt to contract and exhibit an increase in stress (Kellaway et al 1978). For gelatins containing more than 27% moisture, rubber-like viscoelasticity has been observed (Kellaway et al 1978). This rheological behaviour is attributed to the plasticizing effect of water (Eliassaf & Eirich 1960). The shrinking of films is thought to be associated with the change from glass-like to rubber-like viscoelastic behaviour, possibly caused by orientation effects and the formation of crystalline regions (Kellaway et al 1978).

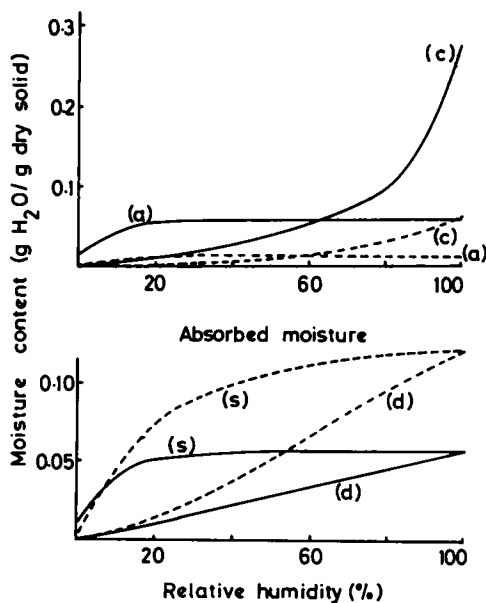


FIG. 3. Moisture distribution pattern for gelatin capsules and maize starch. — Gelatin capsules. - - - - Maize starch; (a) and (c) as in Fig. 1. (d) absorption from dried state and (s) desorption from saturation.

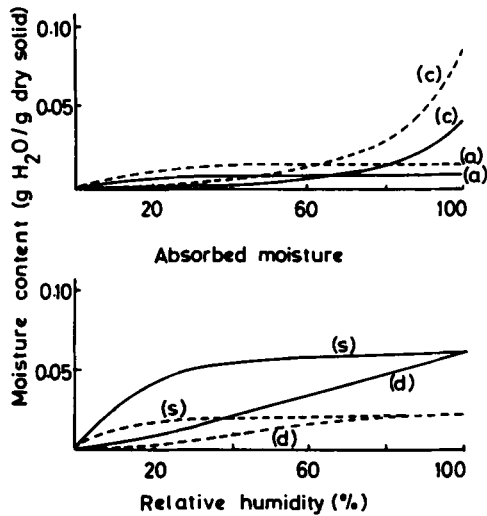


Fig. 4. Moisture distribution pattern for maize starch: drug mixtures. — 50:50 maize starch:barbitone. - - - 50:50 maize starch:sodium barbitone. Key for a, c, d, s as in Figs 1 and 3.

In contrast to the curves for gelatin capsules, the moisture distribution pattern for maize starch (see Fig. 3) indicates an increased proportion of moisture being held inside the starch grains (see Table 2). Normally condensed moisture remains minimal below 50% R.H. and rises to a maximum of 31.4% of the total moisture content present at 100% R.H., compared with 62.8% of absorbed moisture. Again, observed hysteresis is attributed to the separation of the absorption and desorption curves for absorbed water.

Collison (1968) has suggested that water molecules held internally penetrate the amorphous regions of the starch grains and form hydrogen bonds with free hydroxyl groups. The experimentally derived figure for monolayer and absorbed moisture of 13.1% (at

Table 2. Percentage moisture associated with monolayer adsorbed moisture, normally condensed moisture and absorbed moisture at 50 and 100% R.H. from sorption isotherms.

Monolayer adsorbed moisture		Normally condensed moisture		Absorbed moisture	
R.H. 50%	R.H. 100%	R.H. 50%	R.H. 100%	R.H. 50%	R.H. 100%
Hard gelatin capsules					
5.8 (46.4)*	5.8 (14.9)	4.0 (32.0)	27.6 (70.7)	2.7 (21.6)	5.6 (14.4)
Maize starch					
1.1 (15.3)	1.1 (5.8)	1.1 (15.3)	6.0 (31.4)	5.0 (69.4)	12.0 (62.8)
Maize starch: barbitone mix					
0.8 (19.2)	0.8 (6.8)	0.5 (11.5)	4.3 (38.2)	2.7 (69.2)	6.1 (55.0)
Maize starch: sodium barbitone mix					
1.5 (42.8)	1.5 (12.3)	1.0 (28.6)	8.5 (69.7)	1.0 (28.6)	2.2 (18.0)

\* Figures in parenthesis represent the amount of moisture associated with particular location as a percentage of total moisture content at stated relative humidity.

100% R.H.) is in close agreement with the 14% figure proposed for 'directly bound moisture' (Collison 1968). Shotton & Harb (1966) thought it likely that for maize starch the changes in cohesion they observed at different moisture contents were dependent upon the surface adsorbed moisture, that is the monolayer and normally condensed moisture, rather than a function of the total moisture content of the powder. This feature may also be applicable to other powders exhibiting moisture sorption hysteresis and materials absorbing moisture internally.

The two maize starch: drug mixes also exhibit hysteresis and contrasting moisture distribution patterns (see Fig. 4). The pattern for the maize starch and hydrophobic barbitone powder mix (barbitone powder—contact angle 70°; polarity index 0.36, York 1980) is similar to that observed for starch alone with absorbed moisture dominating the distribution. This is attributed to the hydrophilic starch powder acting as a sink for the moisture molecules at increasing relative humidities. For the mix containing the hydrophilic drug sodium barbitone (contact angle 41°; polarity index 0.96, York 1980) the water molecules are able to be distributed on the surface of the barbitone sodium particles, particularly at relative humidities above 85% (York 1980), as well as on the surface, and inside, the starch grains. As a result, competition for moisture molecules will exist and an associated decrease in absorbed moisture, for the starch, together with increased amounts of monolayer and normally condensed moisture compared with the starch: hydrophobic drug mix are observed (see Table 2). Thus, moisture distribution in the two powder mixes exhibits a different pattern which could account for the differences in permeability previously observed for powder beds prepared from these mixes (York 1980).

Long term open storage of filled hard gelatin capsules at high humidities has been reported to produce ageing and decreased rates of in vitro drug dissolution (Khalil et al 1974; York 1977, 1980).

Gelatin is known to exhibit typical reversible phenomena for moisture sorption hysteresis (Bell et al 1973). However, this behaviour was not observed when filled hard gelatin capsules containing either the maize starch: barbitone or maize starch: sodium barbitone mixes were cycled, after reaching weight change equilibria, between 33 and 75% R.H. conditions (see Fig. 5). In both cases, continued cycling produced a progressive loss in moisture from the gelatin capsules with the powder blends acting as a sink for it. A similar effect has been reported for hard

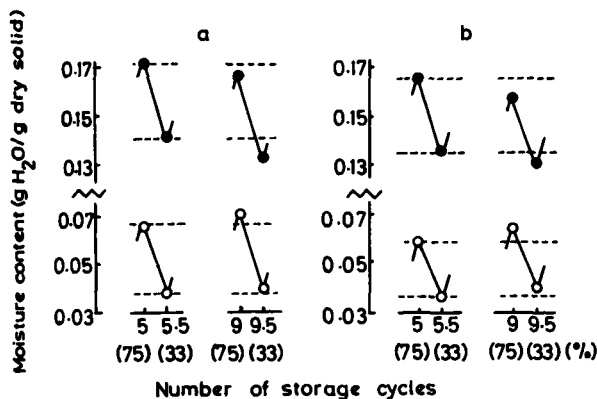


FIG. 5. Moisture content of gelatin capsule shell and encapsulated maize starch:drug mixture when cycled between 33 and 75% R.H. at 25 °C. (a) Capsules containing 50:50 maize starch:barbitone ○ Gelatin capsules ●. b. Capsules containing 50:50 maize starch:sodium barbitone ○. Gelatin capsules ●.

gelatin capsules containing a lactose/sodium cromoglycate blend (Bell et al 1973). Increases or change in the moisture content of hard gelatin capsules and drug substances can therefore occur even if the moisture contents of the component materials are stabilized before filling. Increase in moisture content of encapsulated materials could contribute to the reported ageing effects as well as causing other chemical and physical changes. Moisture loss from the gelatin shell would modify its mechanical properties (Kellaway

et al 1978) causing increased fragility which might lead to processing difficulties (Bond et al 1970).

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