Impact of Carbohydrate Constituents on Moisture Sorption of Herbal Extracts

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INTRODUCTION

Herbal medicines, including traditional Chinese medicines (TCMs) from plants, have been used worldwide for thousands of years in the prophylaxis and treatment of a variety of human diseases. Despite their long standing history and worldwide acceptance, it was not until recent years that the efficacy of certain herbal medicines has been scientifically proven in instances where conventional Western therapies have failed or have not been sufficiently effective (1). This latest development has generated substantial commercial interest in formulating medicinal herbs or their extracts into efficacious, safe, consistent, and stable herbal products, for which oral solid dosage forms (e.g. tablets, capsules, pellets) remain a popular choice.

Unlike Western medications, herbal extracts are normally taken in substantially higher doses to yield the desired effects. Thus, from a formulation standpoint, there is a need to incorporate a large quantity of the extracts into a single dosage unit. However, fulfilling this need would be extremely difficult if not impossible in view of the limited dosage unit size that can be used and the difficulty in handling and processing herbal extracts, which tend to be bulky and hygroscopic (2).

As has been well documented, residual water associated with drugs in the solid state can exert significant influences on the physical and chemical properties of the latter including chemical degradation, dissolution rate and compressibility (3–4). While the significance of this impact is well recognized in the herbal drug industry, the generally high hygroscopicity of herbal materials has never been systematically investigated, possibly due to the immense technical difficulties in analyzing their chemical constituents.

From a physicochemical perspective, the hygroscopicity of a material depends on its chemical composition and physical state. Carbohydrates, being a major constituent of plants and being soluble in the solvent system (water or water-ethanol mixture) commonly used for extracting active principles from herbs, are almost invariably present in crude herbal extracts. Depending on their hydrophilic nature and hygroscopic character, these carbohydrates may be responsible for the commonly observed moisture sorption tendency of herbal extracts. In addition, the complex composition of the extracts will likely hinder their crystallization during the drying process, thus rendering the dried materials amorphous. Based on thermodynamic reasoning, an amorphous solid possesses a high escaping tendency, fugacity or thermodynamic activity, and thus interacts readily with its external environment e.g. water vapour. Thus it can be envisaged that most, if not all, herbal extracts exhibit a significant propensity towards moisture sorption due to their lack of crystallinity. The objective of the present investigation was to determine the impact of carbohydrate constituents and their associated solid state changes on the hygroscopicity of herbal extracts. As a basis for explaining and quantifying hygroscopicity, two well-established sorption isotherm equations, namely the Brunauer-Emmett-Teller (BET) and Guggenheim-Anderson-de Boer (GAB) models, have been applied to data treatment in the present study.

MATERIALS AND METHOD

Materials

All crude herbal extracts (denoted by initials of their commercial names in Table 1) and raw herbs were supplied by Vita Green Products Co. (HK) Ltd. D-glucose (AR grade) was purchased from BDH. Phenol (AR grade) and 95.5% sulphuric acid (ACS certified) were obtained from BDH and Merck respectively. Dextran T10, T40, T70, T500 and T2000 were purchased from Pharmacia Biotech. Maltohepatose was obtained from Sigma. LiCl (11.15% RH), $KC_2H_3O_2$ (22.6% RH), $MgCl_2$ (32.73% RH), K_2CO_3 (43.8% RH), NaBr (57.7% RH), NaCl (75.32% RH), KCl (84.32% RH) and $BaCl_2$ (90.24% RH) (AR grade), used to create desired relative humidities in a closed system, were purchased from BDH. The samples were kept in glass weighing bottles (4 × 2.5 cm) and sorption experiments were conducted in airtight glass sorption containers (15 × 11.5 cm) inside an incubator (model 1535, Shell lab) set at 25°C.

Methods

Powder X-ray Diffraction

The analysis was conducted in a Rigaku RU-300 diffractometer using CuK_α X-rays. The samples were scanned from $2\theta = 10–40°$ at a speed of 1°/min.

Stepwise Fractionation of Low Molecular Weight Carbohydrate (LMWC) and High Molecular Weight Carbohydrate (HMWC) Content

Weighed sample (~50 mg) of each dried herbal extract was allowed to dissolve in 80% ethanol in water at 60°C for 1 hour. Precipitate was removed by filtration and dissolved in distilled water at 60°C for 1 hour. The resulting suspension was then filtered and the filtrate formed the HMWC fraction. The ethanol filtrate was gently heated to evaporate the etha-

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Table 1. Carbohydrate Contents, Fitted BET and GAB Parameters and Associated Statistics of the 13 Herbal Extracts

	Carbohydrate contents[b]		BET[b] (11.15–43.80 %RH)				GAB[b] (11.15–90.26 %RH)				
Extract[a]	LMWC	HMWC	W_m	C	RMS	r^2	W_m	C	K	RMS	r^2
HSW	60.43	5.08	7.469	7.319	0.331	0.961	8.837	4.587	1.000	0.934	0.999
(3)	(4.23)	(1.0)	(0.326)	(1.322)			(0.190)	(0.575)	(0.00225)		
JGL	36.9	14.65	5.692	69.628	0.763	0.783	7.089	12.768	0.952	1.207	0.995
(3)	(1.4)	(0.24)	(0.369)	(69.282)			(0.240)	(3.342)	(0.00564)		
WWZ	9.69	2.42	4.486	15.549	0.479	0.832	5.8778	5.775	0.994	1.046	0.997
(1)	(0.45)	(0.08)	(0.302)	(6.594)			(0.200)	(1.220)	(0.00389)		
JS	64.8	1.84	7.700	31.372	1.538	0.805	8.929	13.392	0.962	1.242	0.997
(3)	(0.58)	(0.07)	(0.485)	(21.777)			(0.259)	(3.280)	(0.00454)		
FA	6.09	4.47	4.231	146.971	1.529	0.488	5.236	13.566	0.994	0.995	0.999
(1)	(0.26)	(0.34)	(0.375)	(492.989)			(0.187)	(4.705)	(0.00435)		
SFS	63.54	5.69	5.578	3.068	0.304	0.931	6.702	2.379	0.980	0.614	0.998
(3)	(2.38)	(0.8)	(0.625)	(0.906)			(0.258)	(0.331)	(0.00425)		
DZ	37.38	0.79	6.670	3.959	0.720	0.905	8.951	2.123	0.982	0.887	0.999
(2)	(1.12)	(0.07)	(0.852)	(1.503)			(0.337)	(0.290)	(0.00396)		
BLC	51.6	1.84	6.021	17.171	0.708	0.855	6.860	9.877	0.972	1.108	0.996
(3)	(0.88)	(0.34)	(0.344)	(7.277)			(0.217)	(2.399)	(0.00449)		
YPF	50.15	16.43	7.633	3.717	0.468	0.947	8.478	3.168	0.961	0.456	0.999
(3)	(0.97)	(0.8)	(0.625)	(0.883)			(0.226)	(0.319)	(0.00352)		
LS	54.62	2.61	6.550	97.247	0.463	0.877	7.418	26.913	0.953	0.857	0.997
(3)	(1.08)	(0.1)	(0.212)	(94.910)			(0.181)	(8.968)	(0.00419)		
JS-VG	60.07	2.95	6.286	17.052	0.896	0.843	8.580	5.158	0.953	0.924	0.998
(3)	(6.29)	(0.06)	(0.371)	(7.008)			(0.274)	(0.781)	(0.00480)		
YQS	47.57	3.07	5.695	39.035	0.491	0.870	6.707	14.409	0.970	1.950	0.994
(3)	(1.05)	(0.38)	(0.266)	(23.225)			(0.271)	(5.771)	(0.00595)		
SWT	67.4	9.25	8.152	7.836	1.776	0.845	8.240	8.480	0.981	3.607	0.993
(3)	(2.96)	(0.69)	(0.727)	(2.987)			(0.369)	(2.727)	(0.0059)		
	n = 3[c]			n = 16[c]					n = 32[c]		

[a] Number of herbs in parentheses.
[b] Standard deviation in parentheses.
[c] n = the number of experimental data points (including replicates).

nol. Distilled water was added occasionally to prevent drying. The suspension was filtered and the resulting solution constituted the LMWC fraction.

Quantification of Carbohydrates (LMWC and HMWC)

To 1 ml of each carbohydrate fraction, 0.25 ml of 8% phenol solution and 2.5 ml 95.5% sulphuric acid were added. The solution was left at room temperature for 1 hour and then assayed colorimetrically at 490 nm. A calibration curve was constructed by repeating the above procedure using dextrose solutions at various concentrations. All determinations (expressed as % of dextrose equivalent) were performed in triplicate.

Validation of the Carbohydrate Fractionation Procedure

Weighed samples (~50 mg) of dextran T10 (MW = 10600), dextran T40 (MW = 37500), dextran T70 (MW = 69000), dextran T500 (MW = 464000), dextran T2000 (MW = 2000000) and maltoheptaose (MW = 1153) were allowed to dissolve in 80% ethanol in water at 60°C for 1 hour. Stepwise fractionation was closely followed and the amount of carbohydrates present in each fraction was assayed as described above. Virtually all dextrans with molecular weight greater than 10,600 were found in the HMWC fraction while all the maltoheptaose was recovered in the LMWC fraction.

Determination of Moisture Sorption Isotherms by Static Method

Accurately weighed samples (~ 0.1 g each) of the extracts were spread as a thin layer in weighing bottles and exposed over phosphorus pentoxide in a desiccator for at least 5 days at room temperature (~22°C). The bottles were weighed and transferred to the sorption containers containing saturated salt slurries at 25°C. The bottles with their contents were weighed every two days until the difference between two consecutive measurements was within 0.001 g (i.e. until equilibrium was reached). The initial moisture content of each extract was determined by weighing the sample before and after being dried in a forced air oven 100°C to constant weight. All determinations were made in quadruplicate. The sorption data were fitted to the Brunauer, Emmett and Teller (BET) and the Guggenheim, Anderson and de Boer (GAB) equations (Eqs. 1 and 2 shown below) using a non-linear iterative fitting regression programme (Sigmastat). Evaluation of the models was based on parameter estimates, r^2 and residuals statistics.

$$W = W_m C_B (P/P^0)/[(1 - (P/P^0)][(1 - (P/P^0) + C_B(P/P^0)] \quad (1)$$

where W is mass of vapor adsorbed at a particular relative pressure, P/P^0, W_m is theoretical amount of water corresponding to monolayer coverage of the surface, and C_B is an

equilibrium constant related to the affinity of sorbate adsorption.

$$W = W_m C_G K(P/P^0)/[(1 - K(P/P^0)][1 - K(P/P^0) + C_G K(P/P^0)] \quad (2)$$

where P, P^0, W, W_m and C_G are defined as above and K is a second equilibrium constant introduced to account for the intermediate state of water adsorption.

RESULTS AND DISCUSSION

Carbohydrate Contents

Thirteen crude herbal extracts (from either single herb or multiple herbs) displaying widely different propensities towards moisture uptake were employed in the present study, their selection being guided by the time taken by the extracts to transform to a gel-like state at room temperature (~22°C) and relative humidity (80%).

The herbal extracts generally exhibited a high LMWC content (Table 1). This was particularly so for those extracts prepared using a combination of three herbs (i.e. 36.9–67.4%). In comparison, the respective HMWC content was significantly lower (accounting for 0.79–18.15%) and varied considerably with the herbs and plant parts used.

Moisture Sorption Isotherms

All herbal extracts tested appeared non-crystalline (i.e. amorphous) as confirmed by an absence of peaks in powder X-ray diffraction. Consistent with their amorphous nature, these herbal extracts displayed substantial moisture uptake. All samples showed sorption isotherms with a progressively rising trend towards the high RH. This behaviour is commonly observed with food systems containing a large amount of carbohydrates and other small hydrophilic constituents (5). Presented in Fig. 1 are the moisture sorption isotherms of two representative samples, viz. HSW (highly hygroscopic) and JGL (poorly hygroscopic). The isotherms were distinctly different from one another in terms of the amount of water sorbed particularly at RH beyond 60% where dissolution was clearly discernable in most of the samples. With the exception of FA, all extracts displayed deliquescence, i.e. the extracts underwent phase changes from powder to gel and finally to a liquid form as they absorbed moisture continuously with increasing RH. The marked increase in moisture uptake by the extracts beyond 60% RH is probably due to the enhanced mobility and diffusion of the water molecules in the bulk brought about by the plasticizing effect of incorporated water (6,14).

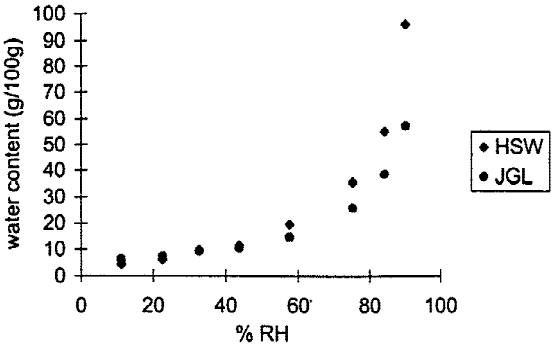

Fig. 1. Moisture sorption isotherms of HSW and JGL.

Data Analysis by Brunauer-Emmett-Teller (BET) and Guggenheim-Anderson-deBoer (GAB) Models

Of the various mathematical models that have been applied in moisture sorption studies, the BET and the GAB equations probably represent the most widely-used ones due to their relative simplicity and their ability to provide a mechanistic explanation for the sorption process. Other sorption models, notably the Flory-Huggins and Vrentas models which are based on polymer solution theories, have been strongly advocated in recent years for their suitability in interpreting water vapour absorption by amorphous solids which undergo concomitant physical changes (9). However, the application of these models requires the input of certain physicochemical parameters, which may not be readily obtainable or available, particularly for complex mixtures such as herbal extracts. For these reasons, only the GAB and BET models were considered in the present analysis.

The BET model was originally derived with reference to gas adsorption on crystalline surfaces, but has been applied to characterization of moisture sorption/absorption in amorphous materials. However, the validity of the latter application has been questioned since the equation does not take into account the plasticizing effect of water or any structural changes in the solid as water is absorbed. As has been extensively demonstrated, the equation generally fits moisture sorption isotherms well up to an RH of 40%. Since this RH probably corresponds to the limit where significant moisture absorption into the bulk and dissolution of the solid has not yet occurred, analysis of the isotherms up to this point may still prove useful in providing some insight into the sorption process at this low RH range. Thus, the present study has restricted the BET analysis to the RH range of 11.15–43.80 %. As shown in Table 1, the BET model fitted the data well for all samples (r^2 ~ 0.78–0.96) except FA which afforded an r^2 of 0.488. The relatively poor fit of data for FA is likely due to the lower moisture sorption of this poorly hygroscopic sample (W_m = 4.231) and the associated larger standard errors in the sorption data obtained in the low RH range. The parameter estimates for W_m were all statistically significant ($p<0.05$), but C exhibited a few statistically insignificant cases.

The GAB model, an extension of the BET model with one additional parameter, is widely considered to be complementary to the BET model in providing data analysis over the entire range of relative pressure. The equation was independently derived by Guggenheim and deBoer, and proposed by Anderson for use in characterizing water vapour absorption. Hence the model is commonly named GAB after these three investigators when applied to water vapour absorption. The additional parameter K in the GAB model was originally introduced on thermodynamic grounds to account for the intermediate state of vapour adsorption not being considered in the BET model. The GAB model reduces to the BET model when K = 1, i.e. when there is no difference in physical properties between the intermediate sorbate layer and the bulk liquid. However, in the case of water vapour absorption where structural changes of the sorbent may be involved, the original meaning of K becomes obscure although in relation to the BET model, K may be viewed as a correction factor for

the structural changes of the sorbent. Despite the controversy over the meaning of K, the GAB model has been found to afford an excellent fit for almost the entire sorption isotherm in many cases of interest including the tested amorphous samples in the present study. As indicated in Table 1, the GAB model afforded a remarkably good fit and highly adequate description of the data for all the extracts, as substantiated statistically by excellent r^2 (> 0.99), relatively small standard errors in parameter estimates and a lack of systematic pattern in the residuals.

For water vapour absorption, the common parameter, W_m, may be more appropriately viewed as the amount of water required to saturate the accessible binding sites both on the surface and in the bulk of the solid. In the present study, all the W_m values determined from the GAB model fitting displayed low standard errors and were relatively insensitive to error-related data variability, suggesting that W_m is a robust parameter and can be reliably used as a hygroscopicity estimator (Table 1). In comparison, the W_m derived from the BET analysis exhibited somewhat higher standard errors, which were still statistically acceptable. The correlation between W_m from either the BET or GAB model and the LMWC content was statistically significant ($r = 0.872$ for BET model and $r = 0.782$ for GAB model; $n = 13$; $p<0.05$) (Fig. 2(a)) while the HMWC content showed no correlation with the hygroscopicity estimator (Fig. 2(b)). This suggests that the LMWC may be an important contributing factor of the observed high hygroscopicity of the herbal extracts while the contribution of HMWC is not evident. The effect of LMWC content on moisture sorption at various RHs was further examined by correlating the water contents of the 13 extracts at each RH with their respective LMWC contents. The correlation coefficients at RH from 43.8% to 84.3% were statistically significant ($r = 0.67$–0.88; $n = 13$; $p < 0.05$), indicating that the impact of LMWC on moisture sorption was most evident within this RH range.

Since certain parameters in the GAB model (notably K) may account for the observed physical changes of the extracts, it would be of relevance to examine how these parameters may change with respect to incremental analysis of the isotherms from 60% RH onward where the extracts began to dissolve in the absorbed water. To this end, data of increasing RH range (i.e. 11.15–57.70% RH to 11.15–90.26% RH) were successively fit to the GAB equation. The resulting parameter estimates and associated standard errors are presented in Fig. 3.

For all herbal extracts except JGL and FA, the W_m values obtained from the incremental isotherm analysis increased to a maximum at the RH range of 11.15–84.32% and then decreased (Fig. 3(a)). The observed pattern of changes in W_m clearly indicates that the number of active binding sites in the samples, as reflected by the W_m values, are not invariant, and may depend on the physical properties of the sorbent. This point has been further substantiated by previous studies on samples showing hysteresis where the W_m values estimated from desorption data are normally higher than those from sorption data (15). This might be expected if the availability of the primary sorption sites had been increased by previous exposure of the sample to elevated RH, with subsequent increases in water sorption. The same argument may apply to the present situation in which dissolution of the extracts at high RH might have facilitated the exposure of the 'covered' active sites and the diffusion of moisture into the interior of the amorphous structure, resulting in an increase in W_m values. The 'unexpected' drop in W_m obtained at the full RH range (i.e. 11.15–90.26%) may be attributed to insufficient equilibration time being allowed for the samples concerned at 90.26% RH, resulting in an underestimation of their actual equilibrium moisture contents and hence W_m. This point has been supported by the observation that the W_m values determined for JGL and FA, which are less hygroscopic, only showed an upward trend, which may be explained

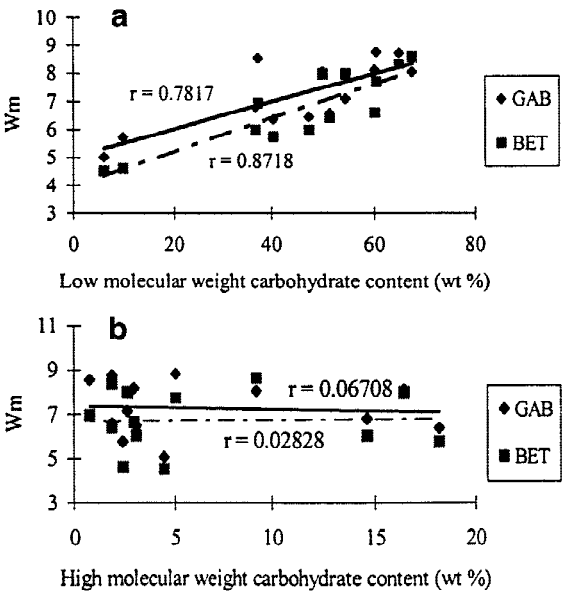

Fig. 2. Correlation between W_m values calculated from the BET and GAB models and the (a) LMWC and (b) HMWC contents of 13 extracts.

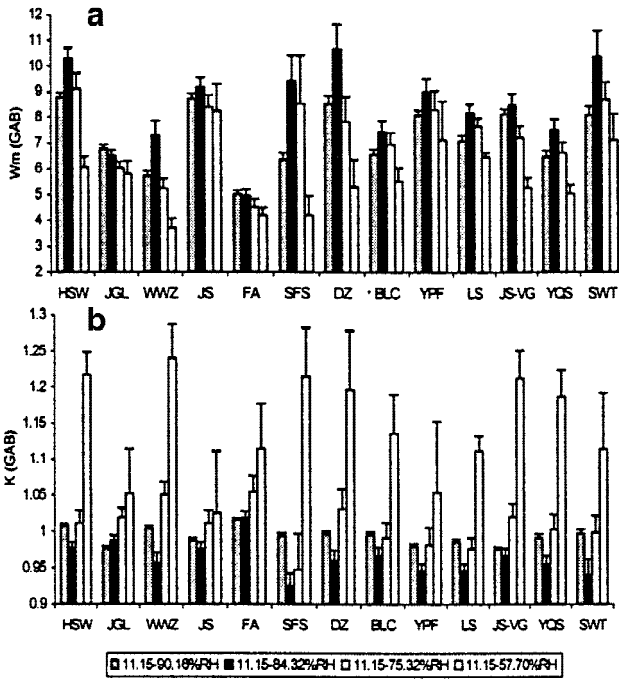

Fig. 3. Parameter W_m (a) and K (b) of GAB model of 13 extracts obtained from data at 4 different RH ranges.

by their ability to attain equilibrium in moisture sorption more readily.

The pattern of changes in K resulting from the above analysis mirrored that of W_m (i.e. a reverse trend). A consistently downward trend of K was observed for both extracts JGL and FA while for the rest of the samples, K dropped to a minimum at the RH range of 11.15–84.32% and rose thereafter (Fig. 3(b)). The initial decrease in K possibly reflects the change in physical state of the extracts from solid to liquid as the extracts started to dissolve in the absorbed water while the subsequent rise in K may be ascribed to the problem of inadequate equilibration with highly hygroscopic materials discussed earlier. Since the entire isotherms of the 13 extracts could all be fitted well to the model, one can speculate that K may serve as a correction factor for solid state changes occurring during water sorption.

Unlike W_m and K, the trend of parameter C is difficult to ascertain due to the high variability in its estimation (indicated by large standard errors) in a few BET analyses. The reasons for such isolated cases of high statistical uncertainty in parameter estimation remain unclear, but could be related to the model itself and/or to the spread and number of data points over the RH range being analyzed. Further investigation will be necessary to address this statistical problem as well as the physical significance of C, which has been widely used for quantitative and interpretative purposes in moisture sorption studies.

CONCLUSIONS

For moisture sorption on amorphous materials, the common parameter, W_m, in both the BET and the GAB models may be viewed as the amount of water required to saturate the accessible (energetically favorable) binding sites of the solid. Parameter K in the GAB model may be treated as a correction factor for the structural changes of the solid extracts as water is absorbed. In the present study, W_m has been statistically demonstrated to be a robust hygroscopicity estimator for the amorphous herbal extracts.

A significant correlation was found between the W_m values computed from model fitting and the LMWC contents of the herbal extracts, suggesting that the observed hygroscopicity of the extracts is largely contributed by the presence of LMWC. On the other hand, the HMWC did not appear to have any significant influence on the moisture sorption of the extracts since it showed negligible correlation with W_m. The impact of LMWC content on moisture sorption was most evident at intermediate RH range of 40–80%, as demonstrated by the statistically significant correlation between these two experimental parameters. That this RH range and the temperature (25°C) employed correspond to the normal storage and manufacturing conditions of herbal products probably explains why hygroscopicity of herbal extracts has been such a prevalent and poorly controlled problem in the herbal drug industry.

In view of the relative simplicity of the mathematical models involved and their ability to provide a mechanistic explanation for the moisture sorption process, the present approach may find wide applications in the assessment of hygroscopicity and related problems commonly encountered in the manufacture of herbal, pharmaceutical and food products.

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