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The determination of equilibrium constants, ΔG, ΔH and ΔS for vapour interaction with a pharmaceutical drug, using gravimetric vapour sorption

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Abstract

The application of gravimetric vapour sorption (GVS) to the characterisation of pharmaceutical drugs is often restricted to the study of gross behaviour such as a measure of hygroscopicity. Although useful in early development of a drug substance, for example, in salt selection screening exercises, such types of analysis may not contribute to a fundamental understanding of the properties of the material. This paper reports a new methodology for GVS experimentation that will allow specific sorption parameters to be calculated; equilibrium constant (K), van't Hoff enthalpy change (ΔH_v), Gibbs free energy for sorption (ΔG) and the entropy change for sorption (ΔS). Unlike other reports of such type of analysis that require the application of a specific model, this method is model free. The analysis does require that over the narrow temperature range of the study ΔH_v is constant and there is no change in interaction mechanism.
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1. Introduction

Gravimetric vapour sorption (GVS) is a relatively straightforward method of analysis in which the change in mass of a sample is measured as a function of relative humidity or through sorption of organic vapours. Modern devices for such purposes are flow-through automated instruments that perfuse a carrier gas over a sample suspended from a micro-balance (Levoguer and Williams, 2003). Often the carrier gas is nitrogen but argon, oxygen and air have also been used. Critical to any type of meaningful analysis by GVS is the requirement that at each RH the mass of a sample being analysed should be at equilibrium with the environmental RH before the next RH step is progressed. Vapour sorption isotherms may then be generated by determining the equilibrium mass of a sample as a function of vapour partial pressure. It is common to apply specific models to the isotherm to determine thermodynamic parameters for the interaction of vapour with the material being analysed. There are several analytical models that are frequently applied to such isotherms (Brunauer et al., 1938; Sopade, 2001) in an attempt to determine the enthalpy change associated with adsorption as well as information about the surface area of the material. An

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intractable problem with the application of a specific model is that one is required to select a model that best fits the data. As often is the case, many different models can give perfectly satisfactory fits.

The application of a model free (see below) approach to data analysis provides a method for quantitative data interpretation without the requirement for model selection. In addition it will be shown that such a model free approach can provide thermodynamic information about the sorption process that may not be accessible from conventional analytical models. The method described here recognises that adsorption is exclusively exothermic and that sorption is an equilibrium condition. For a given vapour quantity (see below for reasons for employing vapour quantity, i.e. moles of vapour phase water in equilibrium with the moles of surface adsorbed water), the amount that is adsorbed will decrease as temperature is increased. If the quantity that is adsorbed, for a given constant total vapour quantity, is measured at several different temperatures, the equilibrium constant for the adsorption process can be calculated. Knowing the equilibrium constant at each temperature, and making the familiar assumption that ΔH is independent of temperature over the range studied (Price, 1998), the van't Hoff enthalpy change can be determined from the van't Hoff isochore. Applications of standard thermodynamic equations (Smith, 1990) allow calculation of ΔG and ΔS for sorption. As for all methods of analysis for sorption isotherms, the material must not change during the course of the experiment. Thermal analysis and spectroscopy was used to show the absence of amorphous material, intrinsic solubility experiments showed the polymorph chosen was the most stable form of the known forms and a cycling sorption experiment was performed to show that sorption was reversible. The cycling experiments showed no significant hysteresis, indicative of bulk sorption.

2. Theoretical method

The basis for the analysis is to derive equilibrium constants for the equilibrium between vapour phase water molecules and water molecules adsorbed onto a surface. This can be represented by the scheme

$$\text{Drug} + \text{Vapour} \Leftrightarrow \text{Drug} - \text{Vapour}$$

The equilibrium considers the total number of moles of water available from the vapour phase for adsorption and the actual number of moles adsorbed at the surface of a material (here the material is a drug substance). The number of moles of "free" water at equilibrium in the vapour phase is then equivalent to the total amount of vapour minus the amount of vapour adsorbed to the sample surface. The equilibrium constant for the adsorption/desorption process can be determined if both the total quantity of vapour and the quantity of that vapour that has adsorbed are known. The quantity adsorbed is measured by the GVS and is the change in mass from going from one level of vapour partial pressure to another level. The equilibrium constant is described by Eq. (1)

$$K = \frac{\text{moles}_{\text{adsorbed}}}{\text{moles}_{\text{total}} - \text{moles}_{\text{adsorbed}}} \tag{1}$$

Note that in Eq. (1), it is assumed that the activity coefficient of both vapour phase and adsorbed phase water are unity. $\text{Moles}_{\text{adsorbed}}$ is the amount of vapour adsorbed onto the surface of a material and $\text{moles}_{\text{total}}$ is the total amount of vapour available for adsorption. The latter can be found if the GVS experiment is performed at three different temperatures (Beezer et al., 2001). The temperatures chosen must meet the requirement such that

$$\frac{T_1 T_2}{T_1 - T_2} = \frac{T_2 T_3}{T_2 - T_3} \tag{2}$$

This condition is met when, for example, $T_1 = 298.150$, $T_2 = 310.150$, and $T_3 = 323.156$ K. For convenience the value of T_3 was set at 323.15 K. Providing this equality remains true, it can be shown (Beezer et al., 2001) that the ratio of equilibrium constants as described by Eq. (3) is also true

$$\frac{K_1}{K_2} = \frac{K_2}{K_3} \tag{3}$$

Substitution of the equilibrium constant in Eq. (3) for the expanded terms in Eq. (1) gives

$$\frac{\text{Ad}_{T_1}/(\text{moles}_{\text{total}} - \text{Ad}_{T_1})}{\text{Ad}_{T_2}/(\text{moles}_{\text{total}} - \text{Ad}_{T_2})} = \frac{\text{Ad}_{T_2}/(\text{moles}_{\text{total}} - \text{Ad}_{T_2})}{\text{Ad}_{T_3}/(\text{moles}_{\text{total}} - \text{Ad}_{T_3})} \tag{4}$$

Here Ad_{T_x} is the measured mass change of a sample determined at temperature T_x where x is 298.15,

310.15, and 323.15 K. From Eq. (4), the total quantity of water that are available for adsorption can be found

$$\text{moles}_{\text{total}} = -\text{Ad}_{T_2}\frac{(-2\text{Ad}_{T_1}\text{Ad}_{T_3} + \text{Ad}_{T_1}\text{Ad}_{T_2} + \text{Ad}_{T_3}\text{Ad}_{T_2})}{\left[\text{Ad}_{T_1}\text{Ad}_{T_3} - (\text{Ad}_{T_2})^2\right]} \quad (5)$$

Having obtained a value for $\text{moles}_{\text{total}}$, the equilibrium constant for a sample at a given relative humidity can be determined from Eq. (1).

This method requires that for each change in temperature, the total quantity of vapour that a sample is exposed to should be constant. The appropriate conditions can be determined from tables of vapour partial pressure as a function of temperature. In the experiment outlined in this paper water vapour was used and the partial pressures for each temperature determined from tables supplied by the National Physical Laboratory (National Physical Laboratory, 1996). For example, at 25 °C and 20% RH the water vapour will have a partial pressure of 634/3170 Pa. At 37 °C for the same water vapour quantity the partial pressure was calculated to be 634/6283 Pa (10% RH) and at 50 °C the partial pressure was calculated to be 634/12353 Pa (5% RH).

Providing the increase in mass of a sample exposed to a vapour is as a consequence of adsorption only, the derived equilibrium constant is independent of the surface area of the sample. Where the equilibrium constant is dependent on the surface area of the material it may be deduced that both adsorption and absorption processes are occurring. Note also that a cycling experiment (i.e. relative humidity is increased stepwise from 0 to 90% followed by stepwise relative humidity decrease back to the initial relative humidity) will demonstrate that adsorption has taken place where hysteresis was absent.

Having obtained the equilibrium constant at each temperature, the van't Hoff enthalpy change can be determined using the van't Hoff isochore, Eq. (6) (Smith, 1990; Price, 1998)

$$\ln\left(\frac{K_{T_1}}{K_{T_2}}\right) = -\frac{\Delta H^\circ}{R}\left(\frac{1}{T_1} - \frac{1}{T_2}\right) \quad (6)$$

where R is the gas constant. Note that the application of the van't Hoff isochore requires that the enthalpy change is independent of temperature and that the mechanism also remains constant (i.e. the process is adsorption only).

The Gibbs free energy at each temperature is accessible from Eq. (7), for example,

$$\Delta G_1^\theta = -RT_1 \ln(K_1) \quad (7)$$

And finally the entropy change for sorption at each temperature can be found using the Gibbs equation, for example,

$$\Delta G_1^\theta = \Delta H^\theta - T_1 \Delta S_1^\theta \quad (8)$$

3. Materials and methods

63.04 mg of a pure pharmaceutical drug substance, currently in development within GlaxoSmithKline, was studied at three temperatures, 298.15, 310.15, and 323.15 K in a GVS (Dynamic Vapour Sorption supplied by Surface Measurement Systems Ltd, 3, Marple Mews, Marple Way, London). Water was used as the sorption vapour and air was used as the carrier gas flowing at a rate of 200 ml min^{-1}. Each sample was initially left for 300 min at 0% RH before commencing the RH step change. The RH of the sample chamber was then increased stepwise in increments of 5%. At each RH step the experiment was left to progress until the differential of sample mass with

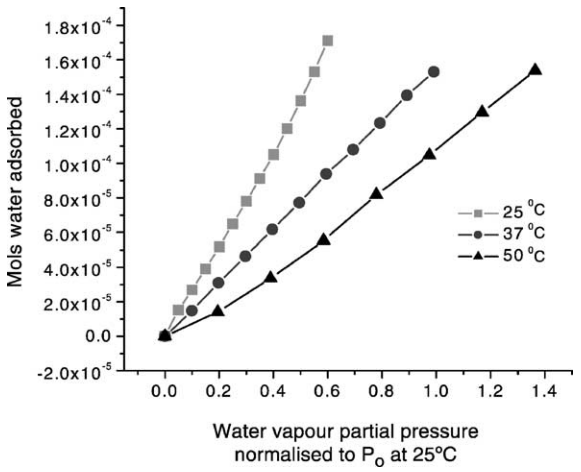

Fig. 1. A plot showing the isotherms derived from a GVS experiment for the pharmaceutical drug substance. The study was performed at three different temperatures and the water vapour partial pressures have been normalised to P_o at 25 °C.

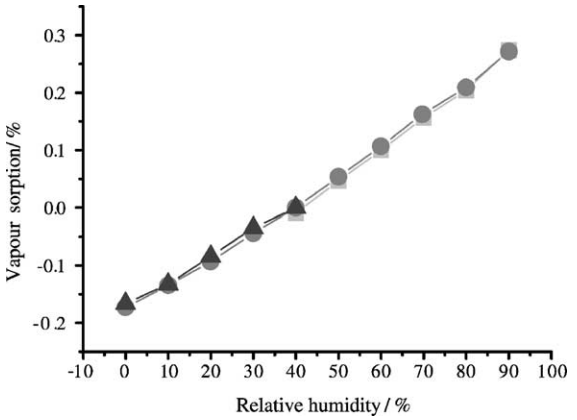

Fig. 2. An isotherm plot for the drug substance subjected to a cycling program of relative humidity, starting at 40%, increasing to 90% (□), decreasing to 0% (●) and then returning to 40% (▲). The incremental steps were 10%.

time (dx/dt) was at zero. The same sample was reused for each temperature to avoid surface area differences. Isotherms were then deduced from the equilibrium mass at each partial pressure. Fig. 1 shows a plot of the isotherms for each temperature where the x-axis is normalised to P_o (3170 Pa) at 25 °C. Sorption experiments were also performed over a wider range of relative humidity to determine sorption reversibility. Fig. 2 shows the sorption isotherms from 0 to 90% RH in steps of 10% and the results of the cycling experiment 0;90;0 RH range.

4. Results/discussion

From Fig. 1, isotherms were chosen that had a measured equilibrium mass for common vapour partial pressures, that is, 0.2, 0.4 and 0.6. In addition, an isotherm at 0.3 partial pressure was chosen and the mass change interpolated for the 50 °C data. Mass changes at each temperature and each relative humidity are shown in Table 1.

Using the values of mass change, shown in Table 1, the equilibrium constants for each partial pressure was calculated from Eqs. (1) and (5). A van't Hoff plot was then made by plotting $\ln K$ against $1/T$ which gave a linear plot of slope $-\Delta H/R$. Table 2 shows a summary of the equilibrium constants as well as the van't Hoff enthalpy changes for each partial pressure. Having obtained values for the equilibrium constant and van't Hoff enthalpy change, the Gibbs free energy and change in entropy were calculated and are summarised in Table 3.

A plausible explanation for the increasingly positive enthalpy change observed as the partial pressure of water vapour is increased, shown in Table 3, is as follows. At low partial pressure water molecules arrive onto an almost water free drug surface. As the drug surface becomes more populated with water molecules, water molecules arriving at the surface may interact with either the drug surface or with water molecules already present. What may be reflected in the values of the enthalpy change is that the enthalpy change for adsorption onto the drug surface is more negative than the enthalpy change for the condensation of water. At higher water vapour partial pressure water molecules arriving at the surface are more likely to condense with water molecules already present.

The value of the van't Hoff enthalpy change for the adsorption of water vapour was compared with the enthalpy change derived from a BET model for the sample run at 25 °C. The BET analysis was achieved using the method described by Pudipeddi et al. (1996) where individual isotherms at 5% RH increment were determined from 0 to 30% RH. A BET type equation (Pudipeddi et al.) was then fitted to give the values for the enthalpy change of vapour interaction as well as the amount of water molecules required to form

Table 1
A summary of the measured mass changes for the GVS study of the drug substance

Experimental temperature/K	Mass change at 0.2 P/P_o (mol g^{-1})	Mass change at 0.3 P/P_o (mol g^{-1})	Mass change at 0.4 P/P_o (mol g^{-1})	Mass change at 0.6 P/P_o (mol g^{-1})
298.15	5.324×10^{-5}	8.401×10^{-5}	1.055×10^{-4}	1.717×10^{-4}
310.15	2.821×10^{-5}	4.707×10^{-5}	6.055×10^{-5}	9.984×10^{-5}
323.15	1.411×10^{-5}	2.518×10^{-5}	3.333×10^{-5}	5.590×10^{-5}

The measured mass changes are expressed as moles of water per gram of drug substance.

Table 2
The derived equilibrium constants and van't Hoff enthalpy change for water adsorption onto the experimental drug substance

Water vapour partial pressure, normalized for P_o at 25 °C	K at 25 °C	K at 37 °C	K at 50 °C	Enthalpy change (kJ mol^{-1})
0.2	0.271	0.127	0.060	−48.3
0.3	0.244	0.123	0.062	−43.9
0.4	0.232	0.121	0.063	−41.8
0.6	0.220	0.117	0.062	−40.4

Table 3
A summary of the derived reaction parameters K, ΔH, ΔS and $\text{moles}_{\text{total}}$ for the GVS study

Water vapour partial pressure, normalized for P_o at 25 °C	Temperature (K)	$\text{Moles}_{\text{total}}$ (mol g$^{-1)}$	ΔG (kJ mol^{-1})	ΔS (J mol^{-1} K^{-1})
0.2	298.15	2.515×10^{-4}	3.3	−173.1
	310.15		5.3	−173.1
	323.15		7.6	−173.1
0.3	298.15	4.269×10^{-4}	3.5	−158.2
	310.15		5.4	−158.2
	323.15		7.4	−158.2
0.4	298.15	5.545×10^{-4}	3.2	−151.8
	310.15		5.4	−151.8
	323.15		7.4	−151.8
0.6	298.15	8.928×10^{-4}	3.9	−137.2
	310.15		5.5	−137.2
	323.15		7.3	−137.2

monolayer coverage on the drug surface, see Fig. 3. The results of this analysis gave a value of ΔH as $-47\,\text{kJ mol}^{-1}$ at 25 °C that compares well with the model free approach. However, it should be noted that the application of BET type equations to water vapour sorption of pharmaceutical type molecules is likely not to be reliable where water molecules condense as clusters rather than form monolayer coverage.

The entropy change shown in Table 3 reflects the increase in order of water molecules in the vapour phase when adsorbed onto the drug surface. There appears to be no temperature dependence of the entropy change over the small T range explored, however, the entropy change is dependent on the vapour partial pressure. This is presumably because water molecules adsorbing onto the drug surface have a larger entropy loss compared with water molecules condensing onto a surface occupied by water molecules and acting like bulk water.

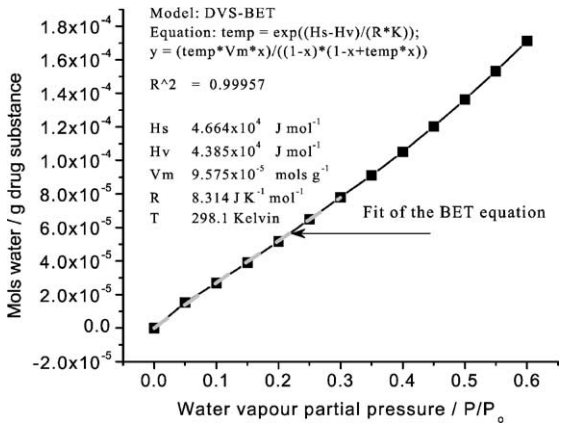

Fig. 3. The BET analysis for sorption isotherms at 25 °C. H_s is the enthalpy change for sorption, H_v is the enthalpy change for condensation of water, V_m is the amount of water for a monolayer coverage, R is the gas constant and T is temperature.

Table 4
The calculated apparent volume of water that that is at equilibrium with the drug surface as a function of temperature and water vapour partial pressure

Water vapour partial pressure, normalized for P_o at 25 °C	Temperature (K)	$Moles_{total}$ (mol g^{-1})	Volume (ml g^{-1})
0.2	298.15	2.515×10^{-4}	14.9
	310.15		15.6
	323.15		16.2
0.3	298.15	4.269×10^{-4}	25.5
	310.15		26.6
	323.15		27.8
0.4	298.15	5.545×10^{-4}	33.1
	310.15		34.6
	323.15		36.1
0.6	298.15	8.928×10^{-4}	57.3
	310.15		59.9
	323.15		62.5

4.1. Flow-through vapour sorption devices

All commercially available GVS instruments use a carrier gas to deliver a vapour to the sample in an open system. There is a holding device that holds a liquid form of the vapour of choice through which the carrier gas is passed. The carrier gas on passing through the liquid is saturated with the vapour. Mixing two vapour streams, one at 100% saturation and the other at 0% saturation provides the required partial pressure of vapour to be delivered. The carrier gas then passes through the apparatus and flows around the sample that is suspended from a micro-balance. On passing the sample the carrier gas exits through a vent. The velocity of the carrier gas passing by the sample is generally kept constant and in the range of 100 to 500 ml min^{-1}, depending on the make of instrument. It is therefore evident that not all of the vapour molecules carried through the system by the carrier gas are able to interact with the sample. The meaning of $moles_{total}$ in Eq. (1) is the number of moles of water in the vapour phase at equilibrium with the water molecules adsorbed onto the surface of the sample. By knowing the quantity of available vapour molecules that surround the sample it is possible to calculate a theoretical volume of vapour that is accessible to a sample in such experiments.

From tables of density of moist air (Dean, 1992) it can be found that the densities of air at 20, 10 and 5% RH at 25, 37, and 50 °C are 0.001165916, 0.001120715, and 0.001075536 g ml^{-1}, respectively. The density of dry air at these temperatures are 0.0011843, 0.0011383, and 0.0010924 g ml^{-1}, respectively. Subtraction of the moist air densities from the dry air densities gives the density contribution of the water vapour alone. These are 1.8384×10^{-5}, 1.7585×10^{-5}, and 1.6864×10^{-5} g ml^{-1}. Knowing the total amount of available vapour that can interact with the sample, $moles_{total}$, the volume that this water vapour would occupy can be determined. In each experiment at the three temperatures, the quantity of vapour was kept constant, as was the flow rate of the carrier gas. It is expected that the $moles_{total}$ would remain the same independent of temperature. Using the calculated value of $moles_{total}$ (see Table 3) the volume of surface accessible vapour molecules as a function of temperature was calculated and the data summarised in Table 4.

5. Conclusion

This method of analysis has been applied to the equilibrium of water vapour associated with adsorbed water on a solid drug during a vapour sorption experiments.

Results demonstrate that the process is adsorption and condensation only and the cycling experiments indicate there is no absorption occurring.

The basis of the analysis is to determine the quantity of water in the vapour phase that is at equilibrium with water molecules on the surface of a solid. This is achieved by measuring the quantity of water associated with the sample at three specific temperatures. The amount of water in the vapour phase can then be calculated in terms of a measurable parameter. In fact such measurements are not restricted to this type of sorption experimentation. For any process where there is an equilibrium and an associated measurable parameter, this method of analysis may in principle allow the calculation of an equilibrium constant. The method is truly model free (other than the constraint described early with conformity to the van't Hoff isochore) and can be used in addition too or instead of more traditional types of analysis where there is a significant complication of selecting an appropriate model for the analysis. For the example of vapour sorption outlined in this article, the method allows the calculation of additional interaction parameters not normally accessible using model-based approaches. However there is some overlap in the variety of constants that can be determined and so the method can be used to complement conventional methods of analysis. For example, the analysis of the water vapour interaction with the drug substance used in this study using a BET model indicates the vapour–drug interaction has an enthalpy change for adsorption of $-47\,\mathrm{kJ\,mol^{-1}}$. Interestingly the BET model was comparable with but not exactly the same as the model free method of analysis. This may be because in the application of the BET model one assumes water molecules are forming monolayer coverage on the drug surface within the boundary of the partial pressures chosen (i.e. 0–30% RH). The reality is more likely to be initial adsorption at low partial pressure followed by condensation at higher partial pressures. The model free approach indicates this is the case, adsorption at low partial pressures and condensation at higher partial pressures.

Calculation of the volume of surface accessible vapour molecules provides a measure of what exactly is at the surface of the sample, that is, the volume of vapour at equilibrium with the solid is not the same as the volume of vapour contained in the chamber of the instrument.

Paramount to the model free approach or indeed to any type of GVS analysis is the quality of the isotherms. Deciding on when the sample mass is at equilibrium with the environmental vapour pressure takes patience; one should not rush thermodynamics.

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