



Calculation of Diffusion Constants in a Pharmaceutical Powder using DVS

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Water sorption experiments were performed over a range of relative humidity values to elucidate bulk vapour diffusion coefficients for an amorphous pharmaceutical powder. The activation energy of diffusion was measured by performing experiments over a series of temperatures at a constant water vapour concentration.

Introduction

Vapour diffusion rates are of interest in a wide range of applications including: polymers, pharmaceuticals, flavours, and foods [1- 6]. This application note describes the measurement of water vapour diffusion coefficient and its activation energy of diffusion into an amorphous pharmaceutical powder by measuring water vapour sorption kinetics using a DVS instrument.

Theory

According to Fick's first law of diffusion, the transfer of solute atoms per unit area in a 1-dimensional flow can be described by the following equation

$$J = -D \frac{\partial C(x, t)}{\partial x} \quad (1)$$

where J is the particle flux, D is the diffusion coefficient, C is the concentration of the solute, x is the distance into the substrate, and t is the diffusion time. Using the conservation of mass relationship

$$\frac{\partial C}{\partial t} = - \frac{\partial J}{\partial x} \quad (2)$$

Fick's second law of diffusion describing non-steady-state mass transfer is obtained (3).

$$\frac{\partial C}{\partial t} = D \frac{\partial^2 C}{\partial x^2} \quad (3)$$

In the current DVS application measuring diffusivity in a powder, a spherical geometry is assumed, a constant diffusivity, and a constant source concentration resulting in the following equation in spherical coordinates

$$\frac{\partial C}{\partial r} = \frac{1}{r^2} \frac{\partial}{\partial r} \left(Dr^2 \frac{\partial C}{\partial r} \right) \quad (4)$$

With the additional boundary condition of $dC/dr=0$ at $r=0$, equation (4) has the following solution

$$\frac{M_t}{M_{inf}} = 1 - \frac{6}{\pi^2} \sum_{n=1}^{\infty} \frac{1}{n^2} \exp\left(-\frac{n^2 \pi^2 Dt}{r_p^2}\right) \quad (5)$$



where r_p is the particle radius [7]. For short times, equation (5) can be simplified to

$$\frac{M_t}{M_{\text{inf}}} = \frac{6}{r_p} \left(\frac{Dt}{\pi} \right)^{0.5} \quad \text{for } \frac{M_t}{M_{\text{inf}}} < 0.2 \quad (6)$$

or

$$\frac{M_t}{M_{\text{inf}}} = \frac{6}{r_p} \left(\frac{Dt}{\pi} \right)^{0.5} - \frac{3Dt}{r_p^2} \quad \text{for } \frac{M_t}{M_{\text{inf}}} < 0.8 \quad (7)$$

where M_t/M_{inf} is the ratio of the mass at a given time t and the mass at time equals infinity (equilibrium mass) [7]. For this application, equation (7) is used, because it is valid over a wider range of M_t/M_{inf} values.

If mass versus time values are measured for a powder exposed to a step-change in vapour concentration, bulk diffusion constants can be obtained. Initially, typically within a few minutes, there will be an increase in sample mass due to surface adsorption of the vapour. After this initial surface adsorption, absorption into the bulk can occur. Usually bulk absorption phenomenon is much slower than surface adsorption. Therefore, it is possible to take the time and mass at which surface adsorption stops as $t=0$ and $m=0$ and monitor the further increases in mass (M_t) due to diffusion of the vapour into the bulk. After long exposures to the vapour, bulk diffusion will cease and the sample will reach an equilibrium mass (M_{inf}). A plot of M_t/M_{inf} versus the square root of time is made and the data (up to $M_t/M_{\text{inf}}=0.8$) is fit to equation (7). The diffusion constants can then be obtained from the coefficients of the resulting second order polynomial.

The diffusion analysis requires a well-defined and monomodal particle size distribution. Ideally, the sample will have a narrow particle size range to ensure accurate and relevant diffusion coefficient results.

The temperature dependence of diffusion coefficients can be described by a simple Arrhenius-type expression, as illustrated in the equation below

$$D = D_o \exp \left[-\frac{E_D}{RT} \right] \quad (8)$$

where D_o is the pre-exponential factor, E_D is the activation energy of diffusion, R is the universal gas constant, and T is temperature [3]. Therefore, the activation energy of diffusion can be determined if diffusion coefficients under similar conditions are measured over a range of temperatures. Plotting the log of the diffusion coefficient versus reciprocal temperature will result in a straight line with a slope equal to $-E_D/R$.

Method

All experiments were performed on a DVS automated gravimetric vapour sorption analyser (Surface Measurement Systems Ltd., London). The DVS measures the uptake and loss of vapour gravimetrically using a SMS UltraBalance with a mass resolution of $\pm 0.1 \mu\text{g}$. The relative humidity around the sample was controlled by mixing saturated and dry carrier gas streams using mass flow controllers. The temperature was maintained constant, $\pm 0.1 \text{ }^\circ\text{C}$, by enclosing the entire system in a temperature-controlled incubator.

The investigated material is a spray-dried product provided by GSK. The drug was loaded into the sample pan and placed into the DVS instrument. Particle size analysis (Figure 1) indicates a monomodal particle size distribution with an average particle radius (r_p) equal to $9.1 \times 10^{-4} \text{ cm}$. Prior to being exposed to any water vapour the sample was dried at 0% RH for a minimum of three hours to remove any water present. Next, the sample was exposed to the desired relative humidity and the moisture uptake was measured. This was performed over a series of relative humidities at $25.0 \text{ }^\circ\text{C}$ and over a range of temperatures at 40% RH. A new sample was loaded prior to each experiment to eliminate any sample memory complications.

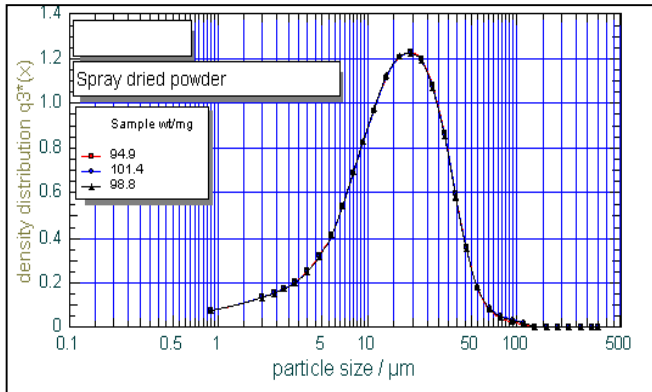


Figure 1. Particle size distribution of amorphous pharmaceutical powder.

Results

Figure 2 shows typical gravimetric data for the sample moisture uptake at 40% RH and 25.0 °C. As indicated by the equilibrium mass reached by $t=100$ minutes in Figure 2, the 180 minute drying period before exposing the sample to any water vapour is sufficient to completely dry the sample. Once exposed to the water vapour, there is a relatively large increase in sample mass due to surface water adsorption. This process is fast and is completed within 15 minutes. At this time, surface adsorption essentially ends and only water absorption into the bulk phase occurs. This is the mass ($M_t=0$) and time ($t_{adj}=0$) reference point from which the diffusion coefficients are calculated. As indicated by the slow rise in sample mass, bulk absorption continues slowly until an equilibrium value (M_{inf}) is reached by $t=1100$ minutes.

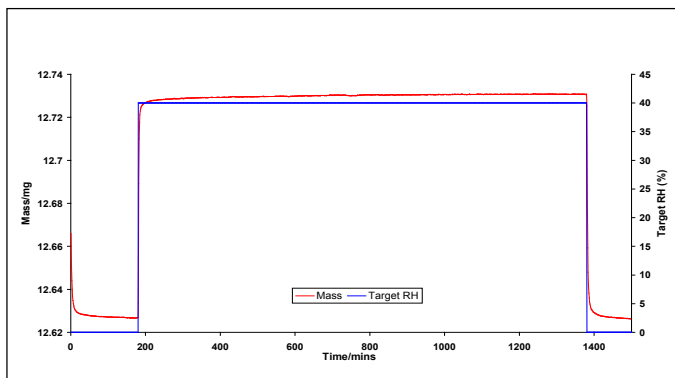


Figure 2. Kinetics of water sorption on an amorphous pharmaceutical powder.

Figure 3 shows the M_t/M_{inf} versus the square root of t_{adj} plot for the water vapour uptake experiment illustrated in Figure 2. The second order polynomial fit (solid line) and corresponding equation (as in equation 7) are also displayed in Figure 3. From the second order coefficient a value of $1.34 \times 10^{-11} \text{ cm}^2/\text{s}$ was obtained for the diffusion coefficient. The polynomial fit has a very good agreement with the experimental data, especially with M_t/M_{inf} values between 0.2 and 0.8. Repeated experiments indicate that the diffusion values under these conditions are reproducible ($\sigma=0.11 \times 10^{-11} \text{ cm}^2/\text{s}$).

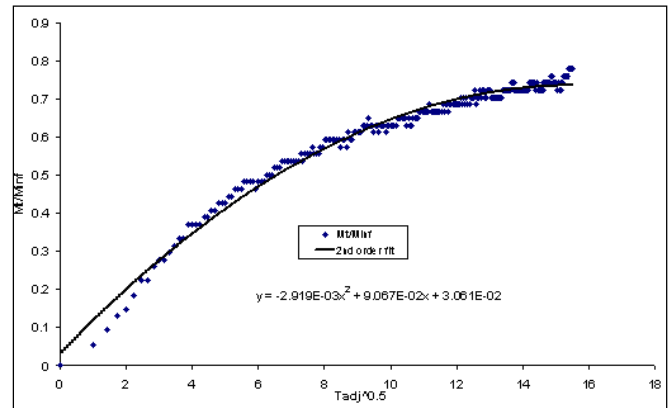


Figure 3. M_t/M_{inf} versus $T_{adj}/2$ values at 40.0% RH and 25.0 C.

Diffusion constants obtained over a series of humidities are displayed in Table 1. Each diffusion constant was measured on a new sample with an initial drying period at 0% RH for at least 180 minutes. As indicated in Table 1, the bulk diffusion coefficients increase with increasing humidity, which would be consistent with a concentration dependent diffusion coefficient. This diffusion phenomenon is not uncommon in moisture sorption systems.

Table 1. Bulk Diffusion constants at 25.0°C.

Target RH (%)	Diffusion Coeff. (cm ² /s)
20.0	2.77×10^{-12}
40.0	1.34×10^{-11}
60.0	5.41×10^{-11}

The activation energy of diffusion at 40.0% RH was obtained by performing a series of

diffusion experiments over a range of temperatures. Figure 4 displays the $\ln(D)$ versus $1/\text{Temperature}$ plot and the corresponding linear fit for diffusion values at 40.0% RH. The linear fit ($R^2=0.9995$) yielded an activation energy of 8.87 kJ/mol. For an activated process, 8.87 kJ/mol is relatively small, indicating that the diffusion process is dominated by flux over a concentration gradient over the temperature range studied. This relatively low activation energy also suggests a low barrier to water absorption for this powder.

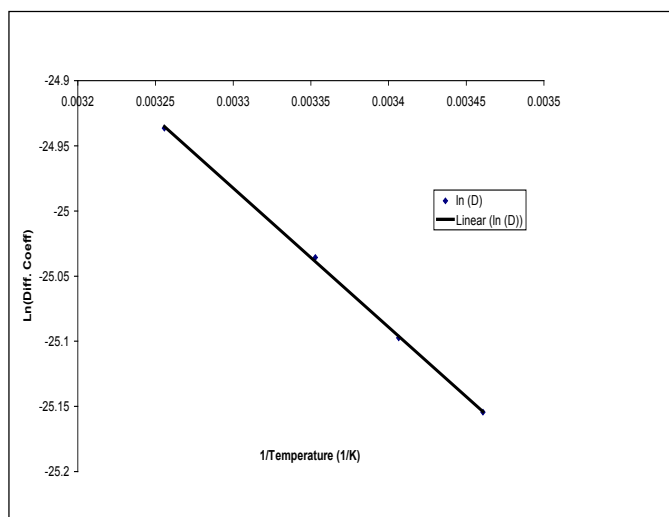


Figure 3. Activation energy of diffusion.

Conclusion

The above methodology outlines a method to determine bulk water diffusion constants and the activation energy of diffusion for an amorphous pharmaceutical powder. This same methodology can easily be expanded to other vapours and a wide range of powders capable of bulk absorption. Using the DVS Advanced Data Analysis add-in suite may facilitate rapid and reliable analysis of the experimental data.

References

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