iGC SEA
Application
Note 214

The determination of the permeability and the activation energy of diffusion of drug powders by infinite dilution inverse gas chromatography (IGC)

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IGC SEA provides an easy and quick route for the determination of diffusion coefficients of solvents in powders and films. The determination of the diffusion coefficient in drug powders is performed by applying the van Deemter approach at infinite dilution. A measurement of this property at different temperatures also provides the activation energy for the diffusion process.

Introduction

The determination of diffusion coefficients of certain vapours in drugs can provide information about bulk absorption behaviour and is therefore an important parameter in drug formulation and manufacturing.

Conventional methods for measuring this property are static sorption methods. These techniques are time consuming and require a relatively large solvent concentration to observe a measurable effect. Inverse gas chromatography (IGC SEA) provides a fast and accurate utility for the determination of the solvent vapour diffusion in any required concentration range. IGC SEA has greater sensitivity compared to all other techniques and can measure sorption parameters even at the infinite dilution range.

IGC SEA has been applied in the past to both film and powder measurements. The original approach uses a transformation of retention data in the van Deemter equation [1]. This allows calculation of the stationary phase diffusion coefficient from the spreading of the elution profile. Pawlisch and Laurence [2] later developed a more accurate model for polymer films in capillary columns. Since this approach is not applicable for powders we used the van Deemter approach to obtain diffusion coefficients of octane and ethanol at different temperatures for an anti-obesity drug in this paper.

Theory

The bulk diffusion coefficient is calculated from a pulse IGC SEA experiment. An application of the van Deemter equation (Equation 1) requires symmetrical peaks, which occur at low concentrations (infinite dilution region). The van Deemter equation was originally derived for analytical chromatography and describes the dependence of the theoretical plate height *H* on the linear flow rate u [1].

$$H = A + \frac{B}{u} + C \cdot u \qquad (1)$$

A and *B* are constants representing the eddy diffusion and the molecular diffusion in the gas phase. The constant C describes all effects related to non-equilibrium behaviour. A more

detailed description of diffusion measurements at infinite dilution is given in [3].

By knowing the column geometry the linear flow rate u can be readily calculated from the experimental flow rate.

H is directly related to the peak width b (Equation 2).

$$H = \frac{L}{8 \cdot \ln 2} \cdot \left(\frac{b}{t_R} \right)^2 \qquad (2)$$

In this equation L represents the column length and t_R the gross retention time.

Assuming that the mass transfer resistance is due to the diffusion into the stationary phase (adsorbent) the permeability D_P can be calculated from the constant C. Equation 3 describes a simple relationship which assumes a sharp monomodal distribution of spherical particles.

$$C = \left(\frac{16}{\Pi} \right) \cdot \left(\frac{d^2}{D_P} \right) \cdot \left[\frac{k}{(1+k)} \right] \qquad (3)$$

Here d is the average particle size and k is the partition coefficient. The partition coefficient k is

$$k = \frac{(t_R - t_0)}{t_0} \qquad (4)$$

Method

Various columns (SMS standard column with 2mm ID and 30 cm length) were packed with the amorphous anti-obesity drug substance, provided by GlaxoSmithKline. The mean particle diameter was determined by High Resolution Laser Diffraction to be 18.20 µm. All sorption experiments were carried out on an SMS-*iGC* 2000. Measurements were done with octane and ethanol between 5 and 35 ml/min at 303, 308, 313 and 318 K.

Before measurement a pre-treatment was carried out for 10 h at a carrier gas flow rate of 10 ml/min at the measurement temperature. Methane was used as a tracer and helium as the carrier gas.

Calculations were performed by using the SMS-*iGC* Advanced Software v1.1 .

Results

Figure 1 shows a van Deemter plot at 303 K. The C-constant can be calculated from a fit of the van Deemter curve using Equation 1. Such a fit can either include a three parameter fit over the entire flow range or a linear fit at high flow rates since the second term of Equation 1 becomes negligible in the latter case.

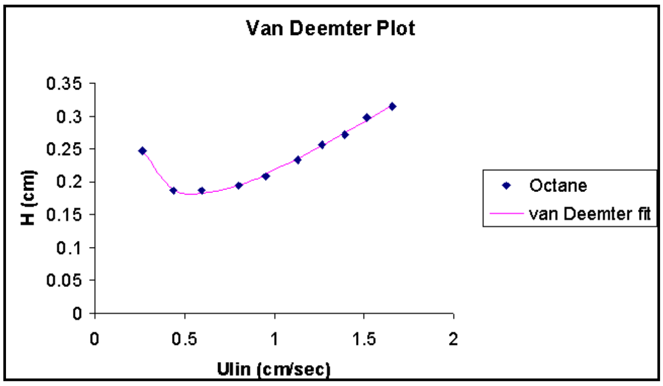

Figure 1. Van Deemter plot for the system octane / SB anti-obesity drug at 303 K (between 5 and 35 ml/min).

From the C-constant the diffusion coefficients can be computed using Equation 3.

Table 1 gives the obtained values for octane and ethanol.

Table 1. Diffusion coefficients for octane and ethanol on SB anti-obesity drug.

Probe molecule	Column temperature (°C)	D_P (cm^2/sec)
Octane	30.1	$4.12\cdot10^{-5}$
Octane	35.0	$4.96\cdot10^{-5}$
Octane	40.0	$5.19\cdot10^{-5}$
Octane	45.0	$6.86\cdot10^{-5}$
Ethanol	30.0	$8.12\cdot10^{-6}$
Ethanol	35.0	$8.48\cdot10^{-6}$
Ethanol	40.0	$9.21\cdot10^{-6}$
Ethanol	45.1	$1.07\cdot10^{-5}$

The values clearly indicate that the permeability of octane is higher than the permeability of ethanol. This could be due to the stronger interaction of ethanol with the hydrophilic material. Thus, polar molecules are retained more strongly and pass more slowly through the drug particles than non-polar probe molecules.

Using Equation 5 the activation energy of diffusion was calculated for octane and ethanol. Figure 2 shows the Arrhenius plot for ethanol.

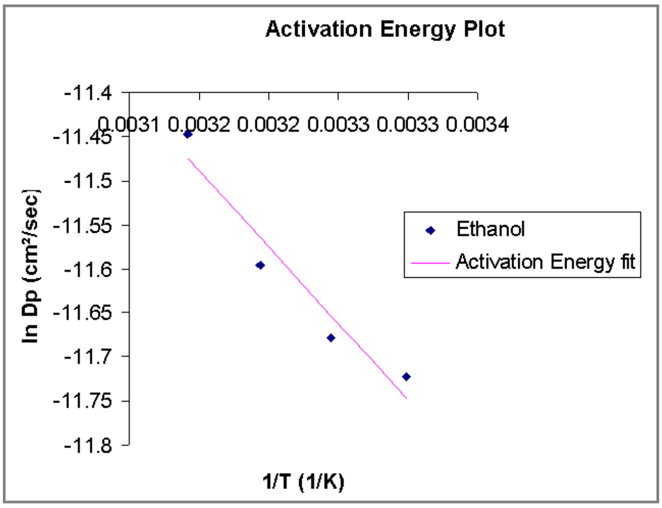

Figure 2. Arrhenius plot for the system ethanol / SB anti-obesity drug.

The activation energy for octane was 25.36 kJ/Mol and for ethanol 14.46 kJ/Mol.

A comparison with literature data is difficult in this case since very little IGC SEA work has been done on diffusion into drug particles. However, comparing these results with studies done with polymers the magnitude of the obtained diffusion constants seems to be rather high. For instance the value for octane in polyethylene powder is 1.4*10-8 cm2/sec at 303 K [4]. One explanation could be a much higher mobility of the probe molecules in the drug below its glass transition. Another reason could be the measurement of the particle size. Although the observed trend won't change the absolute numbers obtained alter significantly with the particle size. The value of 18.2 µm seems to be quite high for a sprayed-dried, amorphous material. Provided no recrystallisation took place prior the particle size distribution measurement, the value obtained may reflect a secondary rather than a primary particle size.

The magnitude of the calculated activation energies seems to be much closer to polymer values.

For instance activation energies for the dodecane diffusion through polyethylene-films are in the range of 9 kJ/Mol.

Conclusion

IGC SEA was demonstrated to be a fast and sensitive technique for the determination of diffusion coefficients and activation energies of diffusion in amorphous drug powders. In the current study a polar and a non-polar probe molecule were used for comparison. However, other probe molecules could provide even more valuable information for optimising drug formulation and manufacturing. An interesting study could be done with water to investigate storage stability.

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References

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