Prediction of the Adsorption of Diazepam by Activated Carbon in Aqueous Media

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ABSTRACT: Adsorption isotherms for the diazepam-activated carbon system in simulated intestinal fluid (SIF), without pancreatin, and in SIF with different percentages of ethanol were determined as were the solubilities of diazepam in SIF and in SIF with different percentages of ethanol. The surface area of the activated carbon was also evaluated. The results from the experimental work provided information on the relationship between adsorption and solubility. An excellent logarithmic relationship was observed between the adsorption affinity and the solubility of diazepam in the ethanol-SIF mixtures. This relationship was explained by a linear relationship between the differential free energy of displacement and the differential free energy of solution. Excellent correlations were also observed between the amounts of diazepam adsorbed by activated carbon and the solubilities of diazepam in the ethanol-SIF mixtures. This relationship was used to predict the complete isotherm, which was in excellent agreement with the experimental work. © 2003 Wiley-Liss, Inc. and the American Pharmacists Association
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INTRODUCTION

The ability to conduct classical adsorption experiments can be severely limited by poor solubility of a test compound. This limitation is mainly due to limitations in analytical sensitivity and to the inaccuracies in weighing and transferring very small amounts of adsorbents. Accordingly, it is desirable to develop techniques to predict the adsorption isotherms of poorly water-soluble drugs in purely aqueous systems. This goal is likely to be achieved using miscible cosolvents, because these cosolvents should affect the extent of adsorption in a systematic manner.

Diazepam was selected as a model compound in this research for the following reasons. First, the solubility of the free base form of diazepam is very low. However, diazepam's solubility is just sufficient to allow the direct testing of the predictive method being developed. In simulated intestinal fluid (SIF) (without pancreatin), the solubility is <0.06 mg/mL at 37°C. Second, diazepam is quite stable at the chosen experimental pH of 7.5.[1] Third, it is a sufficiently weak base that it is unionized at a pH of 7.5. Therefore, changes in ionic strength are not likely to significantly affect the results. Finally, the carbonyl group on the seven-membered ring will likely hydrogen bond with the hydroxyl hydrogens on activated carbon. This belief is based on previous work[2–5] which indicates that compounds having a carbonyl group are likely to interact with the hydroxyl groups on the activated carbon surface. Bonding specificity justifies the use of a Langmuir-like equation, which is premised on the adsorption sites being homogeneous.

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The effect of decreasing aqueous solubility on adsorption from aqueous solutions has long been known.[6] Similarly, a regular increase in adsorption with increasing hydrocarbon chain length is usually observed when hydrocarbon adsorption occurs from aqueous media.[6] Hansen and Craig[7] observed the similarity of adsorption isotherms within a homologous series when isotherms were plotted as a function of reduced concentration (concentration at equilibrium divided by the solubility, or C_{eq}/solubility). Kolthoff et al.[8] also noticed that the adsorption of polymers onto substrates was markedly dependent on the solvent. Rubino et al.[9,10] have shown that co-solvent/water mixtures are useful for solubilizing diazepam.

Adsorption from Solution

Several models have been used to characterize the process of adsorption from solution, the most frequent being the Langmuir-like equation.[11,12] The original derivation of the Langmuir equation used a kinetic argument for the vapor/solid system. However, adsorption in a solution/solid system is not exactly analogous to adsorption in a vapor/solid system. The Langmuir equation has been derived for the solution/solid system using a thermodynamic (law of mass action) argument. In the current literature, the equation derived via the thermodynamic argument is usually referred to as the Langmuir-like equation. Although the Langmuir and Langmuir-like equations are identical in form, the Langmuir-like terminology alerts the reader to the potential for slight differences in the meanings of the modelistic parameters. The Langmuir-like equation is given below:

$$\frac{n_2^s}{m} = \frac{K_1 \cdot K_2 \cdot C_{eq}}{1 + K_2 \cdot C_{eq}} \qquad (1)$$

where n_2^s is the amount of solute adsorbed, m is the mass of adsorbent, K_1 is the capacity constant, K_2 is the affinity constant, and C_{eq} is the concentration of unadsorbed solute in the bulk solution at equilibrium. The Langmuir-like equation is based on several assumptions[11]: there are a fixed number of sites available for adsorption, the heat of adsorption is independent of surface coverage (all of the sites available for adsorption are energetically equivalent), the adsorbed phase is confined to a monolayer, there are no lateral interactions between adsorbate molecules, the adsorbate solution is dilute, there is no mixed film formation at maximum solute adsorption, and molecules of solute and solvent occupy equal areas on the surface.[12] The latter assumption has not been found to be critical.

The Partial Molar Free Energy of Solution

The partial molar Gibbs free energy, $\bar{G}$, of the solute at activity "a" in solution is given by

$$\bar{G} = \bar{G}^{\theta} + \mathrm{RT} \ln \mathrm{a} \qquad (2)$$

where, $\bar{G}^{\theta}$ is the standard partial molar Gibbs free energy of the solute in the solution. Butler[13] defined the standard state to be the condition of unit activity of the solute in a solution having the properties of an infinitely dilute solution ($a = x$). This standard state corresponds to the Henry's law-based mole fraction scale, for which $a = \gamma\ {}^*x$. This leads to

$$\bar{G} = \bar{G}^{\theta} + \mathrm{RT} \ln \gamma_x x \qquad (3)$$

where γ_x is the activity coefficient. The partial molar Gibbs free energy of the pure solute in solution, $\bar{G}^*$, relative to the Henry's law mole fraction standard state, is given by eq. 4:

$$\bar{G}^* = \bar{G}^{\theta} + \mathrm{RT} \ln \mathrm{a} \qquad (4)$$

The standard partial molar Gibbs free energy of transfer of the solute from the pure solid to the Henry's law mole fraction standard state in solution is $\bar{G}^{\theta} - \bar{G}^*$. This is shown in the following equation:

$$\Delta_{\mathrm{pure}}^{\mathrm{iso}} \bar{G}^{\theta} = \bar{G}^{\theta} - \bar{G}^* = -\mathrm{RT} \ln a_{x^*} \qquad (5)$$

where a_{x^*} is the mole fraction solubility. Because the solubility of nonpolar solutes in water is usually very low, the free energy of solution is positive when the standard state of the solute in solution is the hypothetical ideal 1 mol dm^{-3} solution.[14]

Differential Free Energy Change of Displacement

The differential free energy change of displacement can be calculated from the equilibrium constant using the following relationship:

$$\overline{\Delta G^{\circ}} = -\mathrm{RT} \ln K_{eq} \qquad (6)$$

The uncertainty in application of this equation is in the selection of the standard state for K_{eq}. Crisp[15] chose, as a standard state, the solute in solution at the point in which 50% of the surface is covered by the solute. By assuming that the

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