Drug Development and Industrial Pharmacy, 22(11), 1153-1160 (1996)

COMMUNICATIONS

Investigation of Water Adsorption on Ketotifen Fumarate by Inverse Gas Chromatography

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ABSTRACT

A gas chromatographic technique of elution by characteristic point has been used to study water adsorption on ketotifen fumarate in the temperature range 343–383 K. The entropy of adsorption, 50.10 kJ mol^{-1}, indicates a specific interaction between water and ketotifen fumarate. The isosteric heats of adsorption were viewed as a function of surface coverage, with the results indicating a strong adsorbate–adsorbate interaction.

INTRODUCTION

In pharmaceutical science, much effort has been dedicated to the problem of water interaction with pharmaceutical excipients or drug substances. On one hand, the efficacy of a drug can be severely limited for drugs having a low water affinity (1); on the other hand, some drug properties known to be modified by the association of solids with water (2) involve rates of chemical degradation, crystal growth, dispersibility and wetting, powder flow, lubricity, and powder compactibility (3,4). The ability to predict physical and chemical changes of a drug substance when it is associated with water is of essential importance for forecasting product stability (chemical, physical, and microbiological) (5). Water can be introduced into the drug substance or formulation through long exposure to an atmosphere containing water vapor or by a process which involves the use of water, for example, lyophilization, spray drying, aqueous film coating, wet granulation, or recrystallization (6).

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Measurements of properties such as the heat of sorption, freezing point, dielectric properties, and diffusion are performed to study the effects of water on solids. In some instances, valuable information can be gathered from the direct analysis of water content by methods such as Karl Fischer titration, x-ray crystallographic analysis, secondary ion mass spectroscopy, electron spectroscopy, thermal analysis, and inverse gas chromatography (IGC). Spectroscopic techniques are especially useful for analyzing surface chemistry; however, thermodynamic data about surface interaction cannot be easily clarified by these techniques. Techniques such as calorimetry, classical gas or vapor adsorption techniques (gravimetric or volumetric), and inverse gas chromatography are used to gain thermodynamic data about adsorbate–adsorbent interaction.

Gas chromatographic methods for studying adsorption phenomena have been well established and described (7–9). IGC has been extensively used to study many thermodynamic and kinetic properties of pure solid and liquid materials. The technique enables the investigation of adsorbate–adsorbent interaction, determining the amount and the nature of the active centers on the surface (10,11). Recently, the technique was applied to study various biophysical parameters related to structural characteristics of the DNA molecule (12), as well as thermodynamic parameters of adsorbed water on the surface of a set of Fractosils and Avicel PH 101® (13), and to characterize interaction between water and a hydrophobic microporous cyclic undecapeptide (cyclosporin A) (14). IGC represents a dynamic technique which offers numerous advantages over conventional static adsorption techniques. Measurements are rapid and accurate even at low surface concentrations, and temperature effects are easy to study. The ability to study both physisorption and chemisorption is of great importance for the study of catalytic processes.

The aim of this work was to apply IGC in characterizing water adsorption on ketotifen fumarate, which is known to be a nonporous solid material. Ketotifen fumarate is an antiasthmatic, marketed by Sandoz Pharma under the trade name Zaditen®.

MATERIALS AND METHODS

The laboratory-constructed gas chromatograph (thermal conductivity detection; helium carrier gas) used has been discussed in detail elsewhere (14,15). Prior to data acquisition by IGC, ketotifen fumarate was sieved. To secure a low pressure drop through a chromatographic column, only the fraction containing particle sizes of 25–40 μm was filled into a 35 × 0.3 cm i.d. stainless steel column. The column was conditioned for 24 hr at 383 K in a stream of helium, at a flow rate of 2 cm^3 min^{-1}. Peak areas were determined by cutting and weighing.

Surface area measurement by the Brunauer-Emmett-Teller (BET) method, with nitrogen as adsorbate at temperature of 77 K, was executed using the commercial instrument Quantasorb Jr. (Quantachrom). The scanning electron microscope used in this study was a Philips 515. Samples were gold sputter coated prior to examination to render them electrically conductive, and images were obtained using secondary electron detection. A diffraction pattern for ketotifen in a crystalline form of fumarate salt, Fig. 1, was obtained with an x-ray powder diffractometer model XPS2000, from Scientac Inc. (Santa Clara, U.S.).

Ketotifen fumarate was obtained from Sandoz Pharma (Switzerland) and its structure is shown in Fig. 2. After the adsorption studies were completed, the chromatographic column was emptied and the solid material was checked for possible degradation products employing a high-performance liquid chromatography (HPLC) method. No degradation products were detected.

Adsorbate Retention at Finite and Zero Surface Coverage

In the absence of kinetic factors inducing broadening of the adsorbate peak, and taking into account the carrier gas compressibility, the isotherm relating the amount of adsorbed material, q, corresponding to a particular partial pressure, p, can be calculated from chromatographic data through Eq. (1) and (2) given by Kiselev and Yashin (16). Thus

$$q = (nS_a)/(wS_p) \tag{1}$$

where w denotes the amount of adsorbent, S_p is the chart area under the peak when n moles of the adsorbate are injected, S_a is the chart area bounded by the diffuse profile of the chromatogram, the carrier gas front (as measured from a nonretained compound), and the peak height h. The partial pressure of the adsorbate in the gas phase is

$$p = (nshRT)/S_p jF_c \tag{2}$$

where s is the recorder chart speed, j is the James–Martin carrier compressibility correction factor, and F_c is the carrier-corrected flow rate.

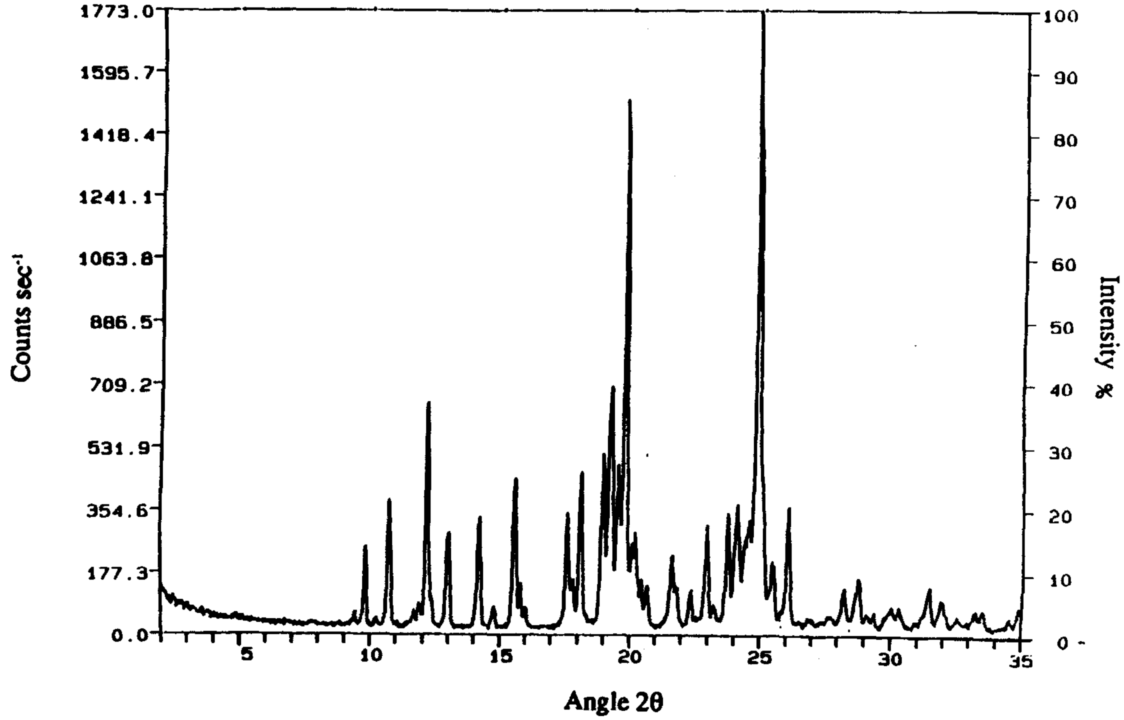

Figure 1. Diffraction pattern of ketotifen fumarate.

Isotherms provide important information about the surface chemistry of the solid, such as adsorbent surface area and porosity, as well as the thermodynamics and kinetics of adsorption (17). From the initial slope of the adsorption isotherm, the Henry's law region, the surface partition coefficient can be computed using the relation:

$$K_s = (qRT/pA_s)_{q\to 0} \qquad (3)$$

K_s is the slope of the isotherm at zero surface coverage ($q \to 0$) and is equal to the distribution coefficient of the adsorbate between the mobile phase and the stationary phase. A_s is the adsorbent specific surface area (m^2/g), and R is the gas constant. The thermodynamic data describing the adsorption process are easily obtained from the temperature dependence of K_s. The standard-state enthalpy of adsorption ΔH_A°, is attainable from the relation:

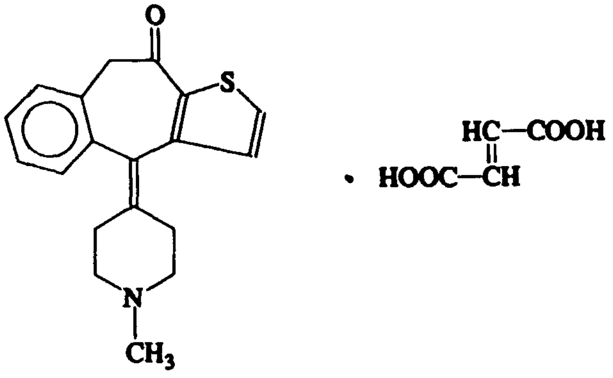

Figure 2. Structrue of ketotifene fumarate.

$$d(\ln K_s)/d(1/T) = -\Delta H_A^\circ/R \qquad (4)$$

under the assumption that ΔH_A° is temperature independent. Equation (5) describes the standard free energy change, ΔG_A°, for the isothermal adsorption of 1 mole of adsorbate.

$$\Delta G_A^\circ = -RT\ln(K_s p_{s,g}/P_s) \qquad (5)$$

where $p_{s,g}$ is a reference pressure (1.013 bar), while P_s is a reference two-dimensional surface pressure whose standard state is arbitrary. The usual value assigned to P_s is 0.338 mN m^{-1}, proposed by de Boer (18). The standard state entropy of adsorption, ΔS_A°, is calculated from the relation:

$$\Delta S_A^\circ = (\Delta H_A^\circ - \Delta G_A^\circ)/T \qquad (6)$$

DISCUSSION

To ensure that peak broadening is due sole to adsorbent-adsorbate and adsorbate-adsorbate interactions, several chromatograms obtained for different amounts of water injected into the column were overlaid. The profile of the chromatographic envelope, Fig. 3, confirms that the contribution of kinetic parameters to observed peak broadening was negligible and that effects due to nonideality were trivial in comparison to those due to nonlinearity (16).

Adsorption isotherms derived from chromatographic data at four different temperatures (343, 363, 373, and 383 K) are presented in Fig. 4. These adsorption isotherms are convex towards the adsorption axis, which indicates some specific interaction of water with the ketotifene fumarate surface. According to Brunauer's classification (19), the isotherms correspond to the type II isotherm. This type of isotherm is normally obtained with a nonporous adsorbent. The experimental data were fitted according to the Freundlich isotherm, Eq. (7), which is frequently more accurate than the Langmuir isotherm in the intermediate-pressure range:

$$q = kp^a \quad \text{or} \quad \log q = \log k + a \log p \qquad (7)$$

where k and a are constants, and are listed in Table 1.

The monolayer capacity, q_m, corresponding to the amount of water adsorbed by monolayer coverage on the solid surface, was reckoned from the adsorption data at 373 K using the BET method, Eq. (8):

$$p/[q(p^\circ - p)] = (1/q_mC) + (C - 1)p/q_mCp^\circ \qquad (8)$$

where p and p° represent the partial pressure of water in the column and the vapor pressure of water at column temperature, respectively, and C is an empirical constant. From the slope and intercept of the plot $p/q[p^\circ - p]$ versus p/p°, Fig. 5, a monolayer capacity of 1.04×10^{-4} mol g^{-1} and $C = 3.17$ were estimated. The specific surface area of 7.15 m^2 g^{-1} for ketotifene fumarate was computed from the monolayer capacity utilizing Eq. (9):

$$A_s = a_mNq_m \qquad (9)$$

where a_m denotes the area occupied by a water molecule (11.4×10^{-20} m^2) (20) and N is Avogadro's number. When nitrogen was used as adsorbate, a specific surface area of 1.23 m^2 g^{-1} was obtained. This difference is not surprising, since water vapor adsorption and nitrogen vapor adsorption seldom yield the same results for the specific surface area. The surface area determined by gas adsorption depends on the dimensions of the adsorbate molecule (e.g., its size and shape), as well as its orientation on the adsorbent surface. The area occupied by a nitrogen molecule, $a_m = 16.2 \times 10^{-20}$ m^2 (20), is 40% larger than the area engaged by a water molecule. The apparent surface area of a solid decreases with an increase in adsorbate size, due to the parallel decrease in geometric accessibility. This problem of "yardstick size" in determining surface area was addressed by Farin and Avnir (21).

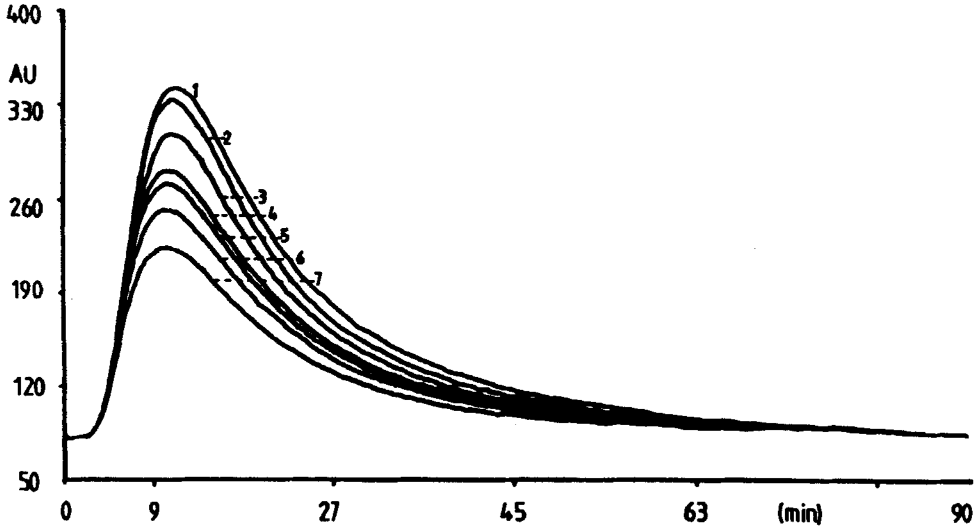

Figure 3. Chromatographic peaks obtained for various amounts of water injected onto ketotifen fumarate at 343 K: curve 1, 1.1 μl; 2, 1.0 μl; 3, 0.9 μl; 4, 0.8 μl; 5, 0.7 μl; 6, 0.6 μl; and 7, 0.5 μl.

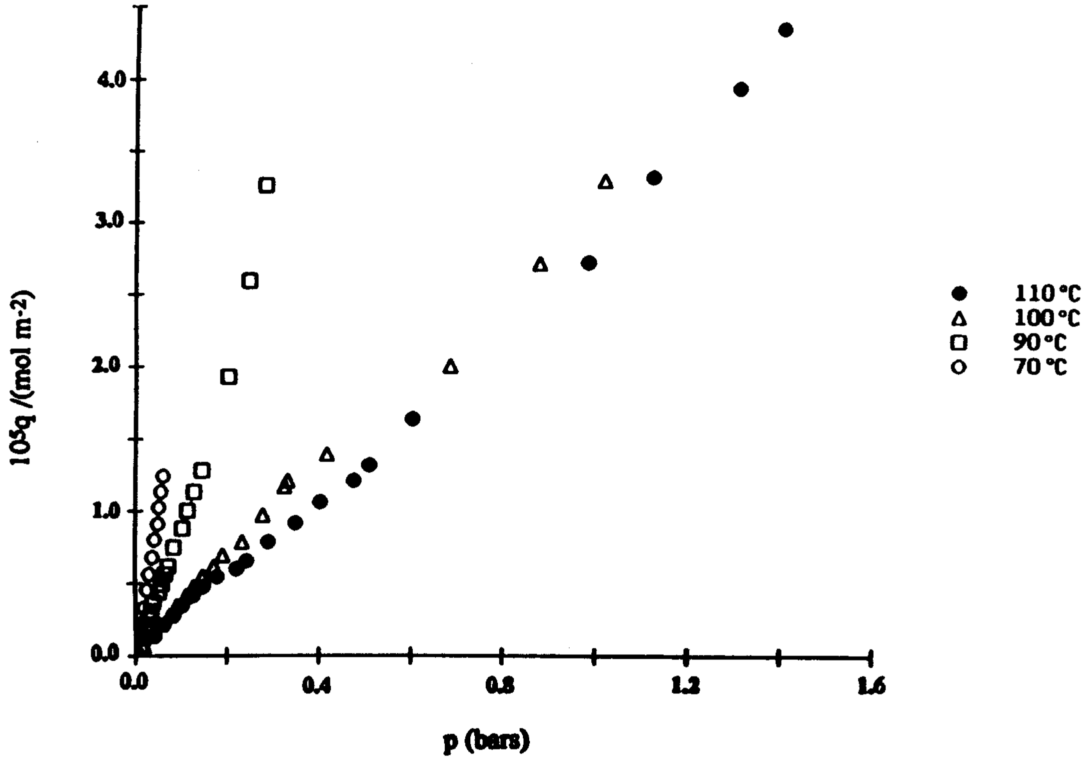

Figure 4. Adsoprtion isotherms (uptake vs. pressure) for water on ketotifen fumarate at four different temperatures.

In the case of a microporous adsorbent, the discrepancy in the surface area obtained with two different adsorbates could be explained by the sieving effect (14) or could be attributed to residual water frozen in many of the pores and surface irregularities of the solid at 77 K, the temperature utilized for nitrogen adsorption (22). Often, the area obtained using nitrogen as an adsorbate is an estimate of the external surface area of the solid, which may be relatively small compared to the total surface area.

Enthalpy of Adsorption

Enthalpy of adsorption is more relevant property than surface area for predicting solubility of the drugs in the solvents. More attention should be paid to this property and it should readily be available for predicting solubility of drugs in water.

Water partition coefficients at zero surface coverage, listed in Table 1, were calculated using Eq. (3). From their temperature dependence the standard enthalpy of

Table 1

Partition Coefficients (K_s, cm^3 m^{-2}), Constants of the Freundlich Isotherm (k, n), Standard Entropy of Adsorption (ΔS_A°, J mol^{-1} K^{-1}) and Standard Free Energy of Adsorption (ΔG_A°, kJ mol^{-1}) at 373 K

T, K	K_s, cm^3 m^{-2}	n	$k \times 10^3$	$-\Delta G_A^\circ$, kJ mol^{-1}	$-\Delta S_A^\circ$, J mol^{-1} K^{-1}
383	0.79	1.00	0.22		
373	1.20	1.01	0.25	18.26	88.0
363	2.45	0.92	0.56		
343	4.82	0.85	2.53		

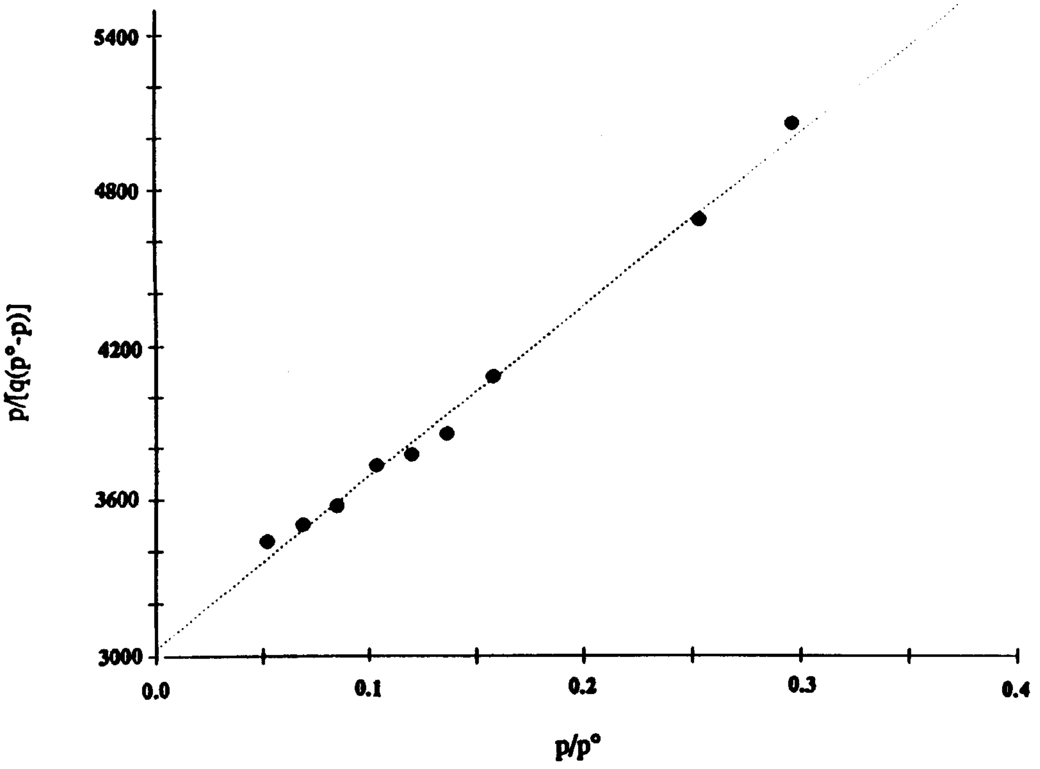

Figure 5. BET plot at 373 K.

adsorption, $-\Delta H_A^\circ$ = 51.09 kJ mol^{-1}, was computed. The enthalpy of adsorption at zero surface coverage represents sole adsorbent-adsorbate intermolecular interaction. Commonly, adsorption is accompanied by evolution of heat and by loss of a degree of freedom, since adsorbate molecules are more localized on the adsorbent surface than in the gas phase. In physical adsorption, which is a reversible process, the main binding forces are of the van der Waals type, and the enthalpy of adsorption corresponds roughly to the enthalpy of liquefaction of the adsorbate. This is only a rough estimate, since in most practical cases studied to date the enthalpy of adsorption is in fact substantially greater than the enthalpy of liquefaction. In our study the enthalpy of adsorption of water on the solid was higher than the enthalpy of condensation for water, $-\Delta H_{\text{con}}$ = 44 kJ mol^{-1} (23). The van der Waals interaction between a water molecule and a surface molecule of ketotifene fumarate is greater than the van der Waals forces between water molecules in the liquid phase.

The change in the standard entropy of adsorption, ΔS_A° = 88.0 J mol^{-1} K^{-1}, was greater than would be expected for the loss of a single degree of translational freedom for a water molecule, ΔS_t = 45.8 J mol^{-1} K^{-1} (14). This is a clear indication of a strong intermolecular interaction on the surface, and of the loss of more than 1 degree of freedom for the adsorbed water molecule upon adsorption on the solid surface.

Information concerning the magnitude of the heat of adsorption and its variation with coverage can provide useful knowledge about the nature of the surface and the adsorbed phase. The isosteric heats of adsorption were calculated from the experimental adsorption isotherms using the Clausius-Clapeyron equation. The isotherm method gives the isosteric differential heat, q_{st}, where $q_{st} = RT^2(\delta \ln p/\delta T)$, the differentiation being with respect to a constant amount adsorbed. The variation of q_{st} with surface coverage may be due to nonuniformity of the surface, lateral interactions of adsorbed molecules, or the heterogeneity induced in the adsorbent by molecules of adsorbate already adsorbed (this effect is negligible except in chemisorption) (24). It is difficult to assign the variation of q_{st} with surface coverage to only one of this effects. The dependence of the isosteric heat of adsorption, q_{st}, on the surface concentration q (mol g^{-1}) for the adsorption of water on ketotifen fuma-

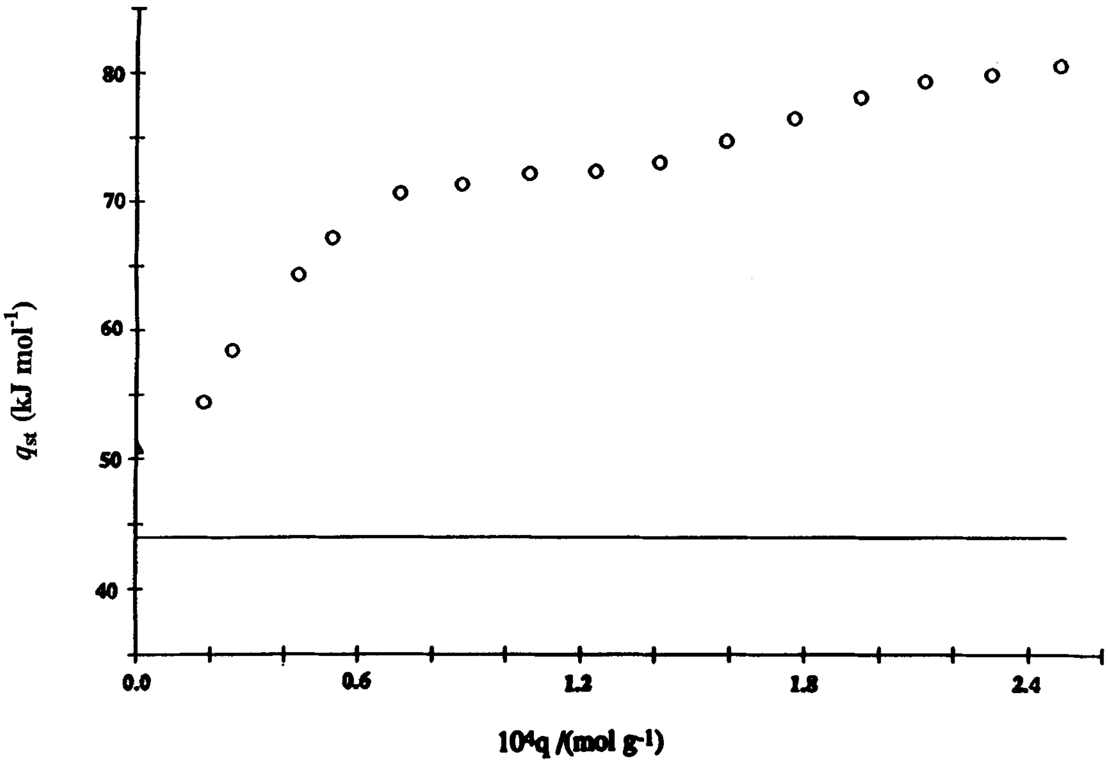

Figure 6. Isosteric heat of adsorption of water as a function of ketotifen fumarate surface coverage at 373 K. Filled triangle, $-\Delta H_A°$; horizontal line, molar heat of liquefaction q_{con} = 44 kJ mol^{-1}.

rate is presented in Fig. 6. The heat of liquefaction is also shown in Fig. 6 as a full line, while the triangle on the *y* axis represents the heat of adsorption at zero surface coverage. An increase in the isosteric heat of adsorption with surface coverage was observed. The initial adsorption occurred on the most active sites. As the pressure of the adsorbate was increased, adsorption developed on sites of less activity. An increase of the heat of sorption with surface coverage is commonly observed for the sorption of polar molecules on a homogeneous surface. This increase is attributed to the effect of intermolecular attraction forces.

CONCLUSION

The entropy of adsorption and the isosteric heats of adsorption indicate a specific interaction between water and ketotifen fumarate. The loss of more than 1 degree of freedom for the adsorbed water molecule on the solid surface, shown by the change in the standard entropy of adsorption (ΔS_A° = 88.0, Jmol^{-1} K^{-1}) is clear evidence of a strong intermolecular interaction on the surface.

REFERENCES

1. C. Ahlneck and G. Zografi, Int. J. Pharm., 62, 87 (1990).
2. J. T. Carstensen, Drug. Dev. Ind. Pharm., 14, 1927 (1988).
3. G. Zografi, Drug. Dev. Ind. Pharm., 14, 1905 (1988).
4. A. Nokhodchi, M. H. Rubinstein, H. Larhrib, and J. C. Guyot, Int. J. Pharm., 118, 191 (1995).
5. K. A. Riempa, B. G. Dekker, R. S. Jager, P. A. Elberse, and C. F. Lerk, Int. J. Pharm., 90, R.1 (1993).
6. W. A. Strickland, Jr., J. Pharm. Sci., 54, 31 (1962).
7. J. R. Conder and C. L. Young, *Physicochemical Measurements by Gas Chromatography*, Wiley, Chichester, 1979.
8. R. J. Laub and R. L. Pecsok, *Physicochemical Application of Gas Chromatography*, Wiley, New York, 1978.
9. D. R. Lloyd, *Inverse Gas Chromatograpy*, American Chemical Society, Washington, DC, 1989.
10. M. D. Ticehurst, R. C. Rowe, and P. York, Int. J. Pharm., 111, 241 (1994).
11. M. Jaroniec, R. Madey, and X. Lu, Sep. Sci. Technol., 26, 269 (1991).
12. G. K. Loukakis, E. G. Sideris, C. A. Kalfas, B. E.

Mazomenos, and A. A. Konsta, Top. Mol. Organ. Eng., 8, 45 (1991).
13. H. N-Tran, V. V. Nhuan, M. Buchmann, F. Sabra, P. Ruelle, and U. W. Kesselring, Drug. Dev. Ind. Pharm., 19, 1413 (1993).
14. N. M. Djordjevic, G. Rohr, M. Hinterleitner, and B. Schreiber, Int. J. Pharm., 81, 21 (1992).
15. N. M. Djordjevic, M. M. Kopecni, R. J. Laub, and S. Molonjic. Anal. Chem., 60, 1395 (1986).
16. A. V. Kiselev, and Ya. I. Yashin, *Gas-Adsorption Chromatography* (J. E. S. Bredley, translator), Plenum, New York, 1969, Chap. IV.
17. S. J. Gregg and K. S. Sing, *Adsorption, Surface Area and Porosity*, Academic Press, London, 1967.
18. J. H. De Boer, *The Dynamic Character of Adsorption*, Clarendon, Oxford, 1953.
19. S. Brunauer, *The Adsorption of Gases and Vapours*, Princeton University Press, Princeton, NJ, 1945, Vol. 1.
20. S. Brunauer, D. L. Kantro, and L. E. Copeland, J. Am. Chem. Soc., 80, 761 (1958).
21. D. Farin and D. Avnir, J. Phys. Chem., 91, 5517 (1987).
22. G. J. Young and F. H. Healey, J. Phys. Chem., 58, 881 (1954).
23. G. Bukton, A. E. Beezer, and J. M. Newton., J. Pharm. Pharmacol., 38, 713 (1986).
24. P. W. M. Jacobs and F. C. Tompkins, in *Chemistry of the Solid State,* (W. E. Garner, ed.), Butterworths, London, 1955, pp. 91-122.