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BROMHEXINE HYDROCHLORIDE ADSORPTION BY SOME SOLID EXCIPIENTS USED IN THE FORMULATION OF TABLETS

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ABSTRACT

Adsorption isotherms of aqueous bromhexine hydrochloride (BHCl) were determined for activated charcoal, kaolin, elcema, avicel PH 101 and 102. The affinity of BHCl adsorption on charcoal was the highest followed by kaolin, avicel, elcema in a decreasing order. The pH alteration affected the adsorption on charcoal slightly. Adsorption by microcrystalline cellulose, and kaolin increased moderately with pH increase. The presence of sodium chloride enhanced the adsorption on all adsorbents used. The larger the particle size the lower the adsorption. Adsorption from mediums containing ethanol and glycerine was lower than the corresponding aqueous solution. The extent of adsorption by charcoal and cellulose showed little dependence on temperature within the range 20-46°. The standard thermodynamic functions, enthalpy, entropy and free energy were obtained. Adsorption on avicel proved to be favoured by both enthalpy and entropy, while enthalpy is the major driving force for adsorption on charcoal. Surface tension and conductivity measurements indicated that adsorption of BHCl may take place as a monomer.

INTRODUCTION

The selection of the proper excipients incorporated with certain drugs is a prerequisite for an effective formulation. Interactions between drugs and solid excipients always attracted the attention of formulators to avoid any damaging interactions. These may result from the dry mixing of various solids prior to further industrial processing, or from the interfacing between the drug solution and the solid excipients during manufacturing stages. Dry mixing of microcrystalline cellulose with alkoxyfuroic acid caused the decomposition of the latter. This degradation was evaluated and the reaction scheme was postulated[1]. Different microcrystalline cellulose materials were tested for their adsorption affinity for fluphenazine dihydrochloride and promethazine hydrochloride under different conditions of pH and ionic strength. The results showed that adsorption did not hinder the liberation of these drugs[2]. In addition, adsorption of some drugs co-administered in small doses with antiacids is cited in the literature. For example, the concomitant use of propranolol hydrochloride with commonly used antiacids may reduce the bioavailability of the drug[3]. The bioavailability of quinidine sulphate was decreased due to interactions with adsorbent, antiacids and antidiarrhoeal mixtures[4]. However, adsorption of the drugs on different excipients could be initiated in the early stages of the dosage form preparation, e.g., mixing and granulation.

As a part of preformulation study, this work was carried out to test the adsorption affinity of the bromhexine hydrochloride (B.P.) on some of the commonly used tablet excipients.

MATERIALS

Bromhexine Hydrochloride (BHCl) B.P. quality was obtained from the Jordanian Pharmaceutical Manufactųring Co. (JPM), Jordan. Avicel PH 101 and 102 are microcrystalline cellulose having 47 and 91 μ m as mean particle diameter, respectively, FMC, USA. Elcema G250 is a microcrystalline cellulose having 160 μ m as mean particle diameter, Degassa, FRG. Kaolin USP grade with mean diameter 4.2 μ m. Charcoal having 5.7 μ m as mean particle diameter, Merck, FRG. All reagents used were of analytical grade. Simulated gastric juice of pH 1.1 was prepared by dissolving 50G of glycine and 35G of sodium chloride in a 1000 ml of 0.1M hydrochloric acid. Buffer of pH 3.0 was made by dissolving 60 G of glycine and 48 G of sodium chloride in 1000 ml of 0.1 M hydrochloric acid.

A Pye Unicam Spectrophotometer (Sp 8-500 model), a pH meter (Kink), a conductivity meter (Phillips/ PW 9509), and a surface tensiometer (Kruss) were used.

METHOD

Adsorption Measurement: One hundred mililiter samples of BHCl solutions having concentrations in the range 3×10^{-3} to 2×10^{-5}M were added to charcoal (0.1G), kaoline (1G), elcema and avicel PH 101, or 102

(2G each). The mixtures were placed in stoppered conical flasks protected from light in a temperature controlled water bath shaker (20 ± . 5° C; and at 150 r.p.m.) At equillibrium, samples were withdrawn, centrifuged for 10 minutes at 2575 r.p.m. and filtered through a disc crucible discarding the first filtrate portion. The absorbance of the remaining filtrate was measured spectrophotometrically in duplicates at 313nm and 245nm. At these wavelengths, the Beer's Lambert law was followed in concentrations ranging from 4×10^{-5} to 3×10^{-3}M.

The influence of pH on adsorption was examined by pipetting 10ml of the simulated gastric stock solution of pH 1.1 or 3.0 into 100 ml volumetric flasks. Different volumes of aqueous 3×10^{-3}M BHCl solution were added, and the pH was adjusted with 0.1M HCl to 1.1 or 3.0 and the final volumes were made up to the mark. These solutions were separately added to conical flasks having weighed samples of the adsorbents and the same experimental procedure was repeated as described before.

The effect of sodium chloride on BHCl adsorption from solutions was examined by pipetting 10ml of 0.1M sodium chloride into 100ml volumetric flask. Different volumes of BHCl stock solutions containing 3×10^{-3} M were added and the volumes were made up to the mark with distilled water. Procedure for adsorption measurements was followed as described earlier.

The effect of temperature variation on adsorption of BHCl from solutions on charcoal and avicel PH 102 was investigated at 20°, 28°, 37° and 46°C. The same procedure for adsorption measurements was followed as described earlier.

The effect of different solvent systems on adsorption was studied by preparing one hundred mililiter of BHCl solution, (1mg/ml) in glycerine (20%), and propylene glycol (10%), and the volume was made up with distilled water to 100ml. Similar preparation was formulated, ethanol (12%). was added before the final volume was made up to a 100 ml with water. Ten mililiter of each preparation was diluted to 100ml and was added to charcoal, kaolin and avicel PH 101 and the adsorption was carried out as described before.

Treatment of Adsorption Data: The accepted method for describing adsorption at certain temperature from dilute solutions, is to plot the amount of the drug adsorbed on the adsorbent as a function of the drug concentration remaining in the mixture after equilibrium. Different shapes of isotherms are obtained and these could be differentiated according to the shape of their initial part of the curve[5]. The Langmuir is curvilinear characterizing most adsorption isotherms from dilute solutions. It indicates that the number of available sites for adsorption are the limiting factor. The linear form of the Langmuir adsorption isotherm is given by:

$$\frac{C_{eq}}{X/m} = \frac{C_{eq}}{X_m} - \frac{1}{X_m.b} \quad \text{.........................(1)}$$

Where: C_{eq} is the molar concentration of adsorbate after equilibrium with the adsorbent is established, X/m is the amount adsorbed per unit mass of adsorbent (in moles/g), X_m is the monolayer capacity (in moles/g), and b is a constant which is a measure of the adsorption affinity of solute towards the solid adsorbent.

A plot of $\frac{C_{eq}}{X/m}$ against C_{eq} would yield a straight line which has $\frac{1}{X_m}$ as the slope while $\frac{1}{X_m.b}$ is the intercept.

The experimental data on adsorption of aqueous BHCl solutions did fit the Langmuir isotherm up to the concentration 3X 10 M and within the temperature range of 20° to 46°C.

The thermodynamic parameters of adsorption were obtained from the following expression:

$$\ln \frac{X_m}{C_{X_m}} = \frac{\Delta H^o}{RT} - \frac{\Delta S^o}{R} \quad \text{...........(2)}$$

Where: X_m is the adsorption monolayer capacity in moles per kg,

C_{X_m} is the molar equilibrium concentration corresponding to complete monolayer formation, ΔH^o is the standard enthalpy of adsorption in KJ/mol , ΔS^o is the standard entropy of adsorption in J/mole , R is the gas constant and T is the absolute temperature.

The plots of $\ln \frac{X_m}{C_{X_m}}$ are rectilinear for both adsorbents used.

ΔH^o and ΔS^o could be obtained from the slope and intercept respectively.

However, ΔG^o was obtained for each temperature from the following equation:

$$\Delta G = - RT \ln \frac{X_m}{C_{X_m}} \quad \text{........(3)}$$

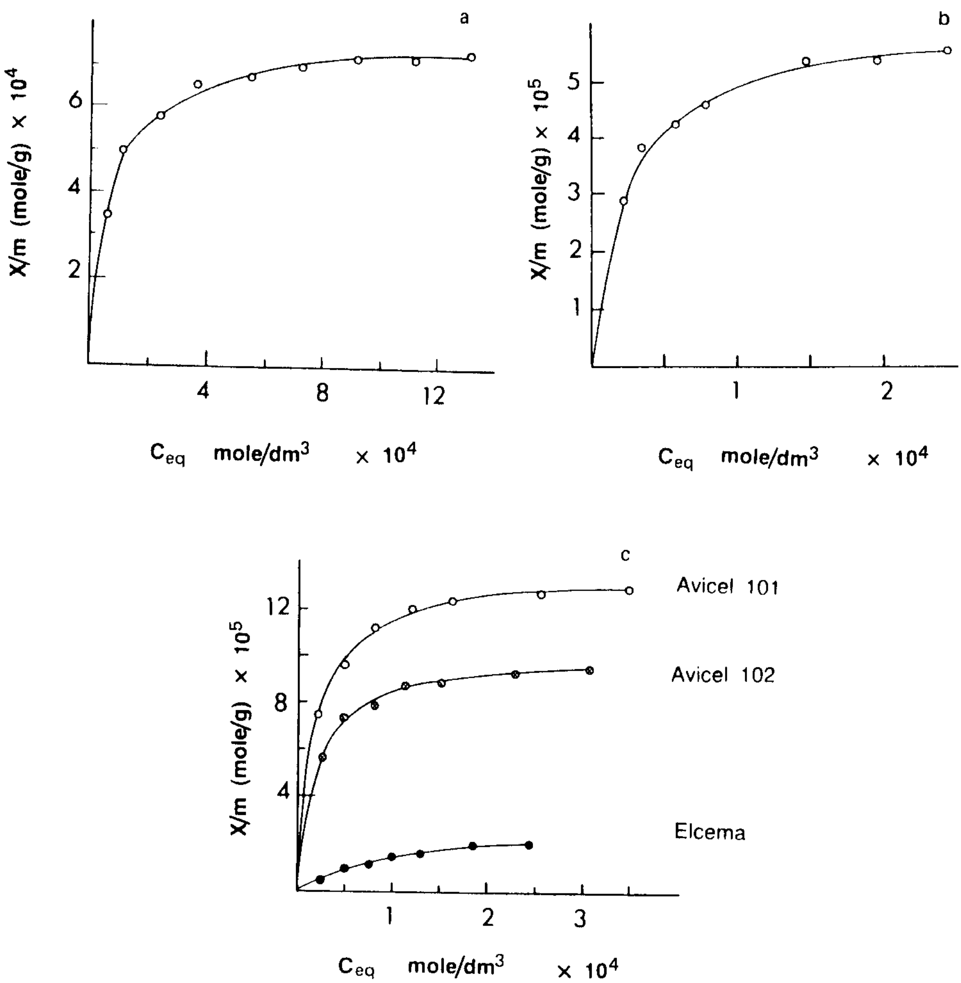


FIGURE 1

Adsorption Isotherms Of BHCl On Activated Charcoal (a), Kaolin (b), Elcema, Avicel PH101 And 102 (c) At 20°C.

Where: ΔG° is the standard free energy of adsorption.

From general thermodynamic considerations:

$$\Delta G^\circ = \Delta H^\circ - T\,\Delta S^\circ \qquad ......(4)$$

According to equation (4) ΔS° could be obtained from the slope of a plot of ΔG° against T, over a small temperature range.

Linear regression analysis was applied to obtain the absolute errors of all parameters of adsorptions.

TABLE 1

Summary Of Langmuir Constants For Adsorption Of BHCl By Activated Charcoal, Avicel PH 102 And Kaolin At 20.0°C

	Charcoal		Kaolin		Avicel PH 102	
Medium	X_m (M/g)×10⁴	bX_m	X_m (M/g)×10⁵	bX_m	X_m (M/g)×10⁴	bX_m
DDW	7.63±0.20	11.40±1.10	6.22±0.15	2.50±0.13	1.01±0.06	5.20±0.04
pH 3.00	7.00±0.16	5.42±0.31	3.14±0.06	0.27±0.01	0.11±0.01	1.15±0.01
pH 1.10	6.43±0.23	4.98±0.42	2.02±0.06	0.19±0.01	0.05±0.01	0.12±0.01
0.01M NaCl	14.30±0.10	19.00±1.40	10.10±0.50	3.63±0.45	1.30±0.08	0.24±0.04

N.B. DDW: Double Distilled Water

RESULTS

The adsorption isotherms of BHCl from aqueous solutions by charcoal, kaolin, elcema, avicel PH 101 and 102 are presented in figure 1 - a,b and c. The adsorption of BHCl by these adsorbents is fairly rapid and the equilibrium was attained after 3 hours for charcoal and 1 hour for each of the used adsorbents. The adsorption rises with equilibrium concentration till a point where no further adsorption would take place. The affinity of BHCl adsorption on charcoal was found to be the highest followed by kaolin, elcema, avicel PH 101 and 102 in a decreasing order. The experimental data were fitted into the linear form of Langmuir isotherm and table 1 presents the monolayer capacities and adsorption affinities for all systems studied at 20°C. Table 2 lists the data obtained for the three grades of cellulose as a function of particle size and pH. The linear plots for adsorption at pH 1.1 and 3.0 are shown in figure 2 - a, b and c. The pH alteration affected the adsorption on charcoal slightly. Adsorption by microcrystalline cellulose and kaolin increased moderately with pH increase. Figure 3 - a, b and c shows adsorption isotherms in the presence of sodium chloride which increased the adsorption on charcoal and kaolin. Such effect was not clear when avicel was used. Adsorption from solutions having different composition, of their solvent system, was lower than the corresponding aqueous solutions. Their adsorption functions are shown in table 3. Ethanol and glycerine reduced the affinity for adsorption. The standard thermodynamic functions were obtained from fitting the adsorption data at different temperatures into equations 2,3 and 4 . A typical plot of

TABLE 2

Summary Of Langmuir Constants For Adsorption Of BHCl By Different Grades Of Cellulose Used At 20.0°C

Cellulose grade	Average diameter (μ m)	DDW X_m (M/g)×10^5	DDW bX_m	pH 3.00 X_m (M/g)×10^5	pH 3.00 bX_m x10^2	pH 1.10 X_m (M/g) 10^5	pH 1.10 bX_m
Avicel 101	47	13.60±0.30	7.96±6.01	1.34±0.11	1.77±0.12	0.60±0.05	1.36±0.08
Avicel 102	91	10.10±0.30	5.17±3.80	1.14±0.08	1.49±0.07	0.50±0.04	1.22±0.07
Elcema	160	3.26±0.24	2.76±0.15	$< 10^{-2}$		$< 10^{-3}$	

ln $\frac{(Xm)}{C_{Xm}}$ against (1/T) is shown in figure (4) representing the adsorption on charcoal. The slope of this linear plot yielded the enthalpy of adsorption. The entropy of adsorption was obtained from the plot of ΔG^o against T as is shown in figure 5; the slope of the straight line is equal to $\Delta S^o/R$. The Gibbs free energy ΔG^o was obtained using equation 4 for each system at each temperature.

DISCUSSION

Bromhexine is rendered slightly soluble in water by the formation of the hydrochloride salt. The solubility of BHCl was determined by shaking an excess of the salt with distilled water at 20°C for 24 h and was found 3.75mg/ ml. The solubility is pH sensitive and in aqueous solutions having pH higher than 6, the base starts to precipitate. The surface tension of solutions ranging in concentrations between 4×10^{-4} and 8×10^{-3}M was measured. The lowering in surface tension of 10 m N m^{-2} below that of distilled water, indicates a slight surface activity. Unfortunately no further surface tension measurements were obtained at higher concentrations due to the insolubility of the drug. The area per molecule (a in A^{o2}) was obtained from the following relationship:

$$a = \frac{10^{23}}{L\,\Gamma} \qquad \text{.............................(5)}$$

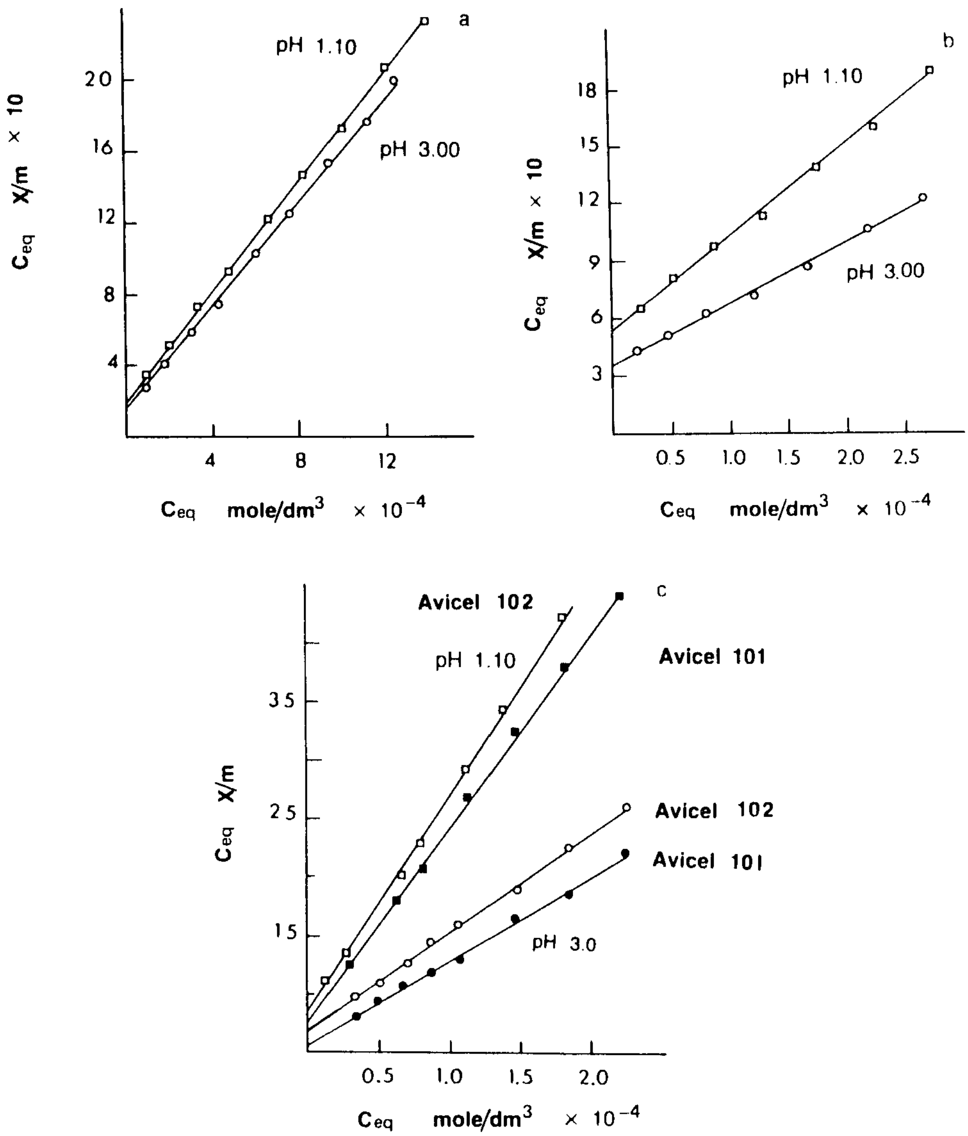


FIGURE 2

Linear Langmuir Plots At Two Different pH (1.1 and 3.0) Showing Of BHCl Adsorption On Activated Charcoal (a), Kaolin (b) And Avicel (c)

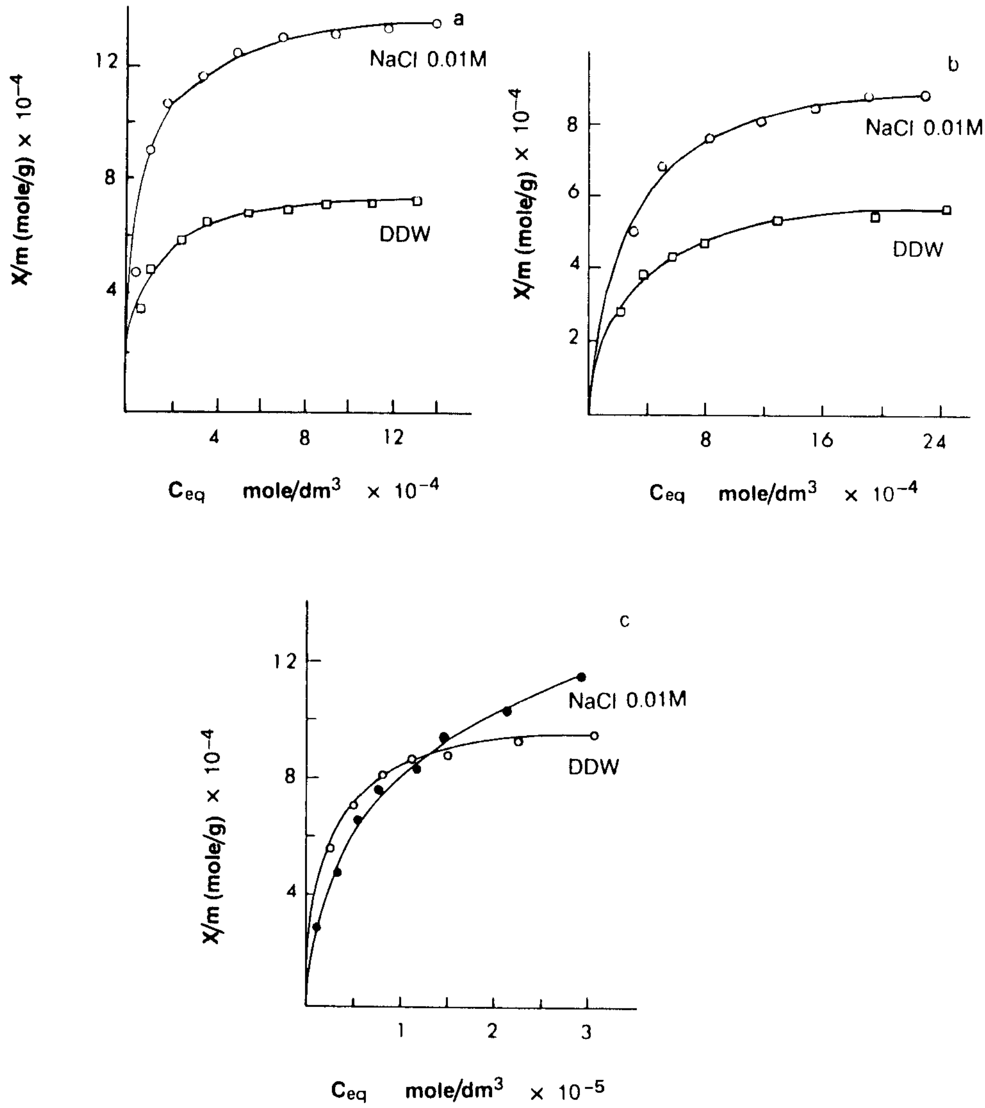


FIGURE 3

Adsorption Isotherms Of BHCl On Activated Charcoal (a), Kaolin (b), Avicel PH 101 At 20°C In The Presence Of 0.01M Sodium Chloride.

TABLE 3

Adsorption Of BHCl From Two Different Solutions Containing Ethanol And Glycerine On Activated Charcoal, Kaolin And Avicel PH 101

Adsorbent:	Charcoal		Kaolin		Avicel 101	
Concentration:	5.0×10^{-4}M		2.5×10^{-4}M		2.5×10^{-4}M	
	X/m (mMole/g)		X/m (mMole/g)		X/m (mMole/g)	
Medium: Formula	DDW	pH 1.10	DDW	pH 1.10	DDW	pH 1.10
I	1.5×10^{4}	1.1×10^{4}	1.0×10^{2}	2.2×10^{3}	1.8×10^{1}	3×10^{6}
II	1.0×10^{4}	8.3×10^{-3}	4.4×10^{3}	9.8×10^{4}	1.1×10^{3}	1×10^{6}

Where: L is Avogadros' number and Γ is the surface excess in mol/m², was calculated according to the Gibbs adsorption equation:

$$\Gamma = \frac{1}{4.606\, RT} \left(\frac{d\gamma}{d \log c} \right)_T \quad \cdots\cdots\cdots\cdots (6)$$

Where γ is the surface tension of BHCl solution in m N m^{-2}. R is the gas constant, T is the temperature in Kelvin degrees. C is the concentration

The area calculated per molecule was in the vicinity of 51 Å² indicating that the hexane ring of the bromhexine molecule is adsorbed at the interface. Specific conductivity measurements had no indication of micelle formation, which suggests that the drug is adsorbed in monomer form. The drug was sufficiently soluble to allow its adsorption up to an almost monolayer capacity.

The adsorption of BHCl on charcoal is illustrated in figure 1 a which shows a relatively higher affinity of BHCl to the predominantly hydrophobic charcoal surface. When the pH of the solution was raised from 1.1 to 3.0, the adsorption increased by almost 10%. A similar increase was also found when the pH was raised from 3.0 to 5.0. Charcoal exhibited an appreciable affinity towards the protonated and nonprotonated forms of the drug, with the latter having a slightly higher affinity. The addition of the electrolyte

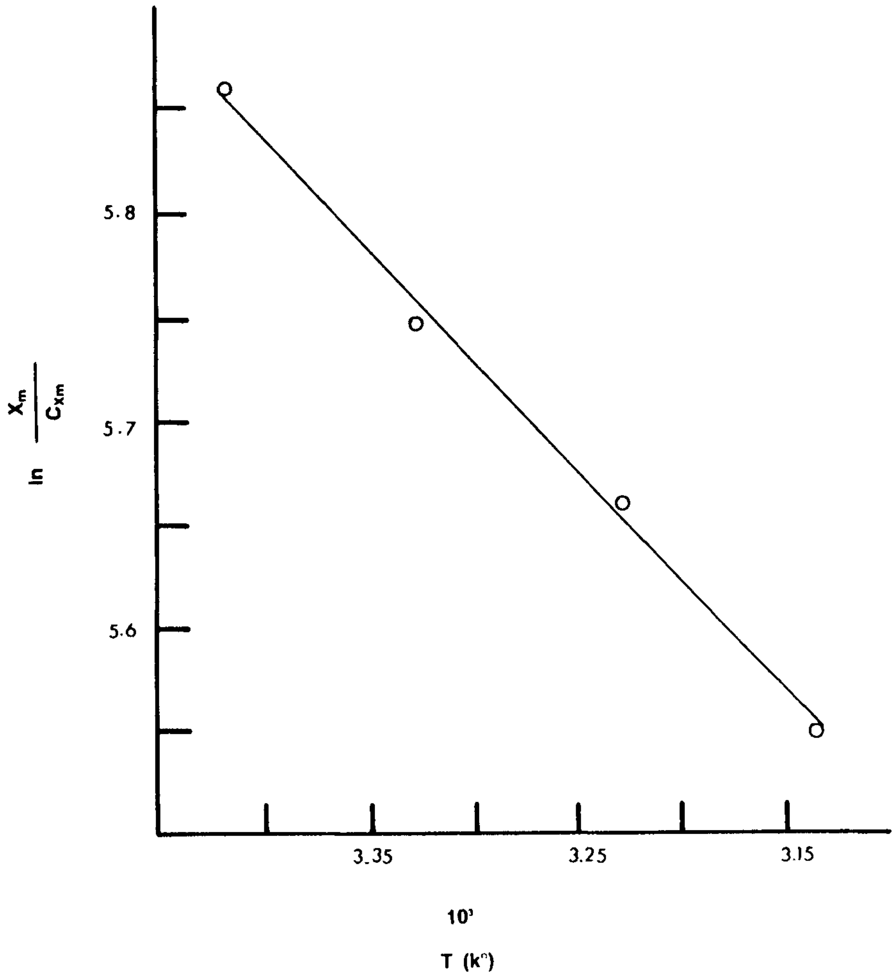
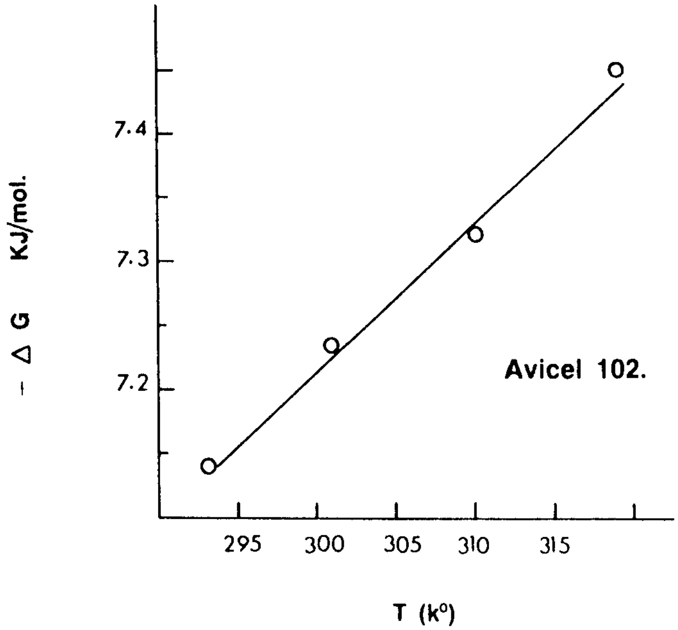


FIGURE 4

The ln $\frac{X_m}{C_{x_m}}$ Against $\frac{1}{T}$ For Adsorption Isotherm Of BHCl On Charcoal.

(sodium chloride) which changes the ionic strength raises the amount of BHCl adsorbed on the charcoal surface. This may be attributed to the suppression of BHCl solubility by the common ion effect[6], and the reduction of interionic repulsion between the protonated molecules permitting a closer packing at the double layer.

Kaolin is an alumino silicate, $Al_4\ Si_4\ O_{10}\ (OH)_8$, composed of two arrays of silicon-oxygen tetrahedra, and two dimensional arrays of



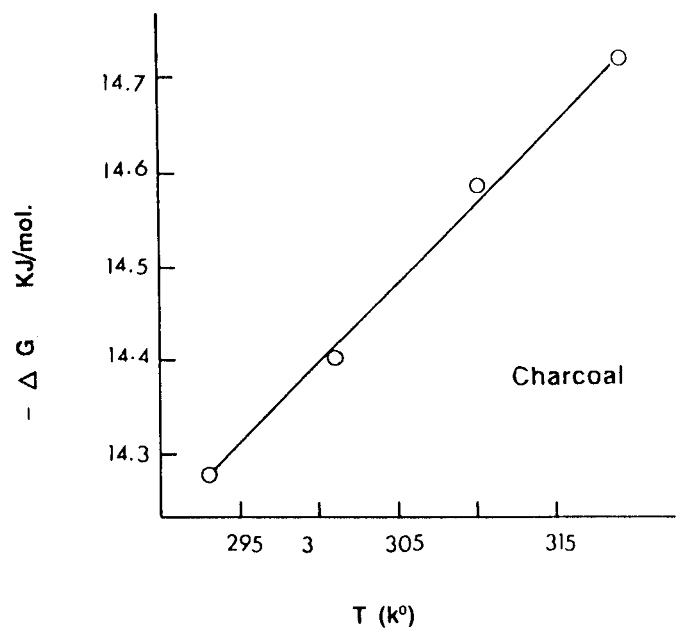


FIGURE 5

The Relationship Between ΔG And T For The Adsorption Of BHCl aluminum oxygen-hydroxyl octahedra. The detailed arrangement of atoms in what is known as clay sheets was described and discussed elsewhere[7]. Kaolin acquires a negative charge resulting from partial displacement of silicon (Si^{+4}) in the lattice by aluminum. The hydrophillicity of the kaolin surface is attributed to the distribution of hydroxyl groups through the clay sheet. BHCl was taken up by the kaolin surface from aqueous solutions in an appreciable manner. This may be due to adsorption occuring by an exchange of the protonated drug molecule with the counter ion present on the kaolin surface. A similar mechanism was suggested for adsorption of quaternary amines from solutions on kaolin and kaolin like materials[8]. Apparently, a change in pH affects both BHCl and kaolin. The lowering of pH enhances the solubility of the drug and diminishes the adsorption capacity of kaolin resulting in a lower uptake of the drug by kaolin. The addition of sodium chloride enhances adsorption. The mechanism of kaolin uptake of promazine from solutions with different sodium chloride concentrations was attributed to ion exchange, the effect on solubility and the physical properties of the adsorbents[8]. However, such mechanism was later argued and reffered to an increase in the negative charge on the clay surface. This is possibly due to the exchange of the divalent compensating cations present on the clay surface by the added sodium ions[9].

Cellulose has a structure of inter-linked D-glucose units, each having three uncombined hydroxyl groups. Each unit is ß -1,4 linked at a right angle to its neighbour. Carboxyl groups are formed by oxidation of hydroxyl groups on individual anhydroglucose units. These carboxyl groups have different degrees of ionization at different pH conditions. The pka value of these carboxyl group is in the vicinity of (4)[10]. It is apparent from figure 2 that the adsorption on microcrystalline cellulose increased with the increase in pH. At higher pH's, the negative charge on the cellulose surface is increased leading to a higher adsorption from BHCl solutions. At lower pH's the negative charge is suppressed and the adsorption is reduced. Accordingly, the adsorption forces could be electrostatic in nature. There is a little difference in the adsorption on cellulose in the presence of sodium chloride at low drug concentrations. At higher concentrations of the drug, adsorption increases in the presence of sodium chloride. It seems that sodium ions compete for the negatively charged surface at the lower concentrations of the drugs. When the drug concentration becomes high enough, adsorption increases due to the decrease in the solubility by the Cl-common ion effect.

It was possible to compare the effect of particle size variation of different grades of microcrystalline cellulose on adsorption table 2 . The smaller the particle size, the higher is the adsorption, due to the

TABLE 4

Thermodynamics Of Adsorption Isotherms For BHCl By Cellulose (Avicel 102) Over Temperature Range 20.0-46.0°C

T (C)°	$\ln \frac{X_m}{C_{Xm}}$		$-\Delta G^o$ (KJ mole^{-1})		$-\Delta H^o$ (KJ mole^{-1})		ΔS^o (J mole^{-1}. degree^{-1})	
	Charcoal	Avicel	Charcoal	Avicel	Charcoal	Avicel	Charcoal	Avicel
20.0	5.86	2.93	14.27	7.14				
28.0	5.75	2.89	14.39	7.23	9.1±0.9	3.4±0.4	17.7±1.7	12.6±1.4
37.0	5.66	2.84	14.59	7.33				
46.0	5.55	2.81	14.72	7.45				

enlargement of the solid surface area. This may suggest that microcrystalline cellulose having larger particle size is favoured in formulations of BHCl tablets to avoid significant adsorption of the drug.

Adsorption of BHCl from solutions containing different co-solvents was lower than the corresponding aqueous solutions. This may be due to the enhancement of the drug solubility, retarding its adsorption. Additionally, it is known that the introduction of ethanol and ethanol like substances would decrease the dielectric constant of the solvent system leading to a reduction in adsorption. However, charcoal proves to be a very efficient adsorbent and its use may be extended for the treatment of over dosage poisoning by BHCl.

The free energy of adsorption, ΔG^o, was negative for both adsorbents used indicating spontaneity of the adsorption process. The enthalpy of adsorption is negative as shown in table 4 indicating an exothermic process for adsorption on charcoal and avicel. Since ΔH^o is less than 25 KJ/mol adsorption is of a physical nature. The entropy changes associated with adsorption are positive in both cases suggesting that adsorption is favoured by enthalpy and entropy factors. The enthalpy contribution to the adsorption on charcoal is almost twice as much as the entropy contribution. Enthalpy and entropy contributed equally to the adsorption on avicel and to some what a lower extent than in charcoal. Adsorption on charcoal is more exothermic than avicel which may be attributed to the predominant hydrophobicity of BHCl and charcoal surfaces. The surface of avicel is hydrophillic consequently bonding forces between cellulose and BHCl are relatively low when compared with charcoal-BHCl forces. The increase in entropy of adsorption on charcoal is most likely related to an enhanced randomization of water molecules released from the adsorbent solid surface and BHCl. This randomization of water molecules occurs to a lower extent in cellulose, as a result of the higher hydrophillic character of cellulose compared to charcoal.

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