INVESTIGATION OF BENTONITE CLAY SURFACE AS A PHYSICAL ANTIDOTE IN ADSORPTION OF AMITRIPTYLINE-HCl, CHLORPROMAZINE-HCl AND CHLORDIAZEPOXIDE-HCl FROM SOLUTION

SAADOON A. ISA*, SAMEER M. JASSIM
AND HUSSEIN K.A. HUSSEIN,
DEPARTMENT OF CHEMISTRY AND BIOCHEMISTRY,
ALNAHRAIN COLLEGE OF MEDICINE,
ALNAHRAIN UNIVERSITY, BAGHDAD, IRAQ.
(*) TO WHOM CORRESPONDENCE IS TO BE MADE
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ABSTRACT:

A detailed study of adsorption from solution of amitriptyline-HCl, chlorpromazine-HCl and chlordiazepoxide-HCl on bentonite clay surface has been performed at variable conditions of temperature, pH and ionic strength. It is aimed in this work to explore the capability of this clay in treatment of poisoning by the mentioned drugs if taken in quantities higher than the usual doses. Quantities of drugs adsorbed have been determined by UV spectrophotometric technique. The sequence of adsorption in neutral media at 37.5 ℃ followed the order:

Amitriptyline-HCl > chlorpromazine-HCl > chlordiazepoxide-HCl.

The results were discussed in the light of Langmuir and Freundich adsorption isotherms. The usual basic themodynamic functions were estimated.

الخلاصة:

تضمن هذا البحث دراسة مفصلة لأمتزاز المركبات الدوائية أمتربتلين هيدروكلورايد و كلوربرومازين هيدروكلورايد وكلورديازيبوكساید هيدروكلورايد من محاليلها المائية على سطح طين البنتونايت. وكان هدف الدراسة هو معرفة قابلية سطح طين البنتونايت وفعاليته في معالجة حالات التسمم بهذه الأدوية إذا تم تناولها بجرعات عالية تفوق المقادير الاعتيادية. تم تعين كميات الأمتزاز بظروف مختلفة من درجة الحرارة و أس الهيدروجين pH والقوة الأيونيه بواسطة تقنية مطيافية الأشعة فوق البنفسجية. وقد وجد أن الأمتزاز في الوسط المتعادل بدرجة حرارة ٣٧.٥℃ يكون على وفق الترتيب:

أمتربتلين هيدروكلورايد > كلوربرومازين هيدروكلورايد > كلورديازيبوكساید هيدروكلورايد.

تم تفسير ومناقشة النتائج اعتماداً على نظريتي لانكماير وفريندلش للأمتزاز، وحسبت القيم الثرموديناميكية الاعتيادية لعمليات الأمتزاز.

INTRODUCTION:

Solids have the property of holding molecules, at their surfaces either from the gas phase or from solution; this property is quite marked in the case of porous and finely divided materials [1]. The term adsorption refers to the accumulation of atoms, ions or molecules (adsorbates) on a surface of a solid substance (adsorbent). The medical significance of some active surface materials arises from their high adsorption capability. The most important application of these materials in medicine is their use as physical antidotes in the treatment of acute poisoning by toxic substances and drug over dosages [2, 3]. Activated charcoal was the most widely used solid surface as an antidote and in drug adsorption [4-12]. Some clay materials were studied and found to possess similar characters to that of charcoal in the treatment of poisoning and drug adsorption. Examples are kaolin [13-17], bentonite[18-20] and attapulgite[21]. This work is concerned with the study of locally available bentonite clay as an active surface adsorbent for the drugs amitriptyline-HCl, chlorpromazine-HCl and chlordiazepoxide-HCl from solution in different conditions of temperature, pH and ionic strength.

The process of adsorption from solution is more complicated than the corresponding process of gas adsorption on solid surface. The solvent effect and the competition between solvent molecules and drug molecules to be adsorbed has to be taken into account. Generally, adsorption is a natural process and usually is accompanied by a decrease in free energy change and entropy of the system. There are a number of factors can influence the process of adsorption; the concentration of drug molecule, surface area of the clay, temperature, pH, ionic strength, solubility chemical state of both adsorbent and adsorbate molecules and the kinetic effect. Details of three factors are available in textbooks and references [22-31].

The term adsorption isotherm refers to the relation between the extent of adsorption (Q_e) or (x/m) with the equilibrium concentration of the drug in solution (C_e) at constant temperature. (x) is the amount of drug adsorbed in milligrams by (m) grams of the adsorbent[24].

Different isotherms of adsorption from solution on solid active surfaces have been classified by Giles and co-workers [32]. Two main theories have been adopted to describe adsorption from solution at constant temperature. The first, Langmuir adsorption isotherm, assumes that at equilibrium, only a mono layer of adsorbate molecules can occupy the energetically homogeneous active sites, on the surface[26,27] as represented by equation (1) :

$$\frac{C_e}{Q_e} = \frac{1}{ab} + \frac{C_e}{a} \qquad \ldots\ldots\ldots\ldots (1)$$

Where (a) and (b) are constants. If this theory is valid for a certain adsorption system, a straight line is obtained by plotting (C_e / Q_e) against C_e . Alternatively, the second theory known as Freundlich adsorption isotherm, considers the active adsorption centers having different potential energies (heterogeneous surface). More than one adsorption layer may develop according to this approach [1, 27, 33]. Freundlich isotherm is demonstrated by equation (2):

$$\log Q_e = \log k + \frac{1}{n} \log C_e \qquad \ldots\ldots\ldots (2)$$

Where (k) and (n) are empirical constants. Applicability of equation (2) is proved by linear plots of $\log Q_e$ versus $\log C_e$.

EXPERIMENTAL SECTION:

(a) Instruments

The instruments used in this study were: uv/vis spectrophotometers /Pye- Unicam PU- 8700 and PU- 8600 Philips, England., Cuvette / Quartz B.S. 3875. 1A, 10 mm F.O., Centrifuge machine / Hettich Universal (D-7200), Germany., Thermostated shaker bath / GFL (D-3006), Germany, PH meter / HM-73 , TDA Electronics Ltd., Electronic balance Sarturius Lab. L 420 B.W. Germany and Oven / Heraeus (D-6450) Hanau.

(b) Materials

Chemicals: HCl 36% w/w**,** sp.gr. (1.18) , BDH, England., NaCl and $MgSO_4$ 99.5% pure Fluka , Switzerland. Drugs: Amtriptyline HCl, Chlorpromazine HCl and Chlordiazepoxide HCl were obtained from (The State Enterprise for drug Industries and Medical Appliances), Samarra, Iraq (SDI). These drugs were pure and imported by (SDI) according to the British Pharmacopoeia. Sharp melting points were noticed for these drugs. Bentonite Clay: Obtained from (The General Company for Geological Survey and mining), Baghdad, Iraq. The clay was collected from (Trifawi) opened mine in the western desert, Iraq. The weight percentages of the clay components were: SiO_2 (54.7), Al_2O_3 (14.7), MgO (6.0), Fe_2O_3 (4.9), Na_2O (0.7), CaO (4.8), SO_3 (1.2), loss on ignition (12.6).

(c) Methodology

The clay was washed with excessive amounts of distilled water to remove the soluble materials, dried at 160 C^o for three hours and kept in an airtight container. The clay was ground and seived to a particle size of 75 μm and then used in all adsorption experiments. Wavelengths of maximum absorbancy (λ_{max}) were recorded for the drugs dissolved in aqueous media and found 256 nm, 328 nm and 329.5 nm for amtriptyline-HCl, chlorpromazine-HCl and chlordiazepoxide-HCl respectively. These values were utilized for quantitative estimation through the course of this research. Solutions of different concentrations were prepared by serial dilution for each drug. Absorbance values of these solutions were measured at the specified (λ_{max}) value for each drug. Calibration curves of absorbancy versus concentration of drug solutions were plotted. The concentration range that falls in the region of Beer-Lambert's law applicability was determined and then used for subsequent estimations. The time required for full saturation of bentonite surface at 37.5 C^o by each drug was determined by shaking 25 ml of 0.005M-drug solution with 0.5g of bentonite. The concentration of drug solution was determined spectrophotometrically at different intervals of time till no further uptake of adsorbate by the adsorbent as the time proceeds. The time needed to attain equilibrium was 1 hr, 2 hrs and 2.5 hrs for amitriptyline-HCl, chlorpromazine-HCl and chlordiazepoxide-HCl respectively.

(d) Systematic Procedure

A volume of 25 ml. of seven different concentrations of each drug (0.0250, 0.0200, 0.0150, 0.0100, 0.0050, 0.0025 and 0.0010 mole /l) was shaken with 0.5 g of bentonite adsorbent at a certain temperature in a thermostated shaker bath at shaking speed 60 cycles / min. After the equilibrium time is elapsed, the mixtures were allowed to settle and the clear liquids were centrifuged at a speed of 3000 rpm for 20 minutes. Absorbancies were measured at the (λ_{max}) value after making suitable dilution in order to fit Beer-Lambert's limitation and then converted into absolute concentration readings through the calibration curve.

RESULTS AND DISCUSSION:

The amount of drug adsorbed (adsorption uptake) at certain conditions of temperature, pH and ionic strength was calculated from equation (3):

$$Q_e \text{ or } \frac{x}{m} = \frac{V\,(C_o - C_e)}{m}$$

(V) Is the volume of solution in litres, (C_o) and (C_e) are the initial and equilibrium concentration of the drug in milligrams per litre. The weight of adsorbent (m) was taken equal to 0.5 g.

The adsorption uptake of amtriptyline-HCl, chlordiazepoxide-HCl and chlorpromazine-HCl at different temperatures (5, 20, 37.5 and 50 °C) from aqueous solutions on bentonite surface is shown in Figure 1.

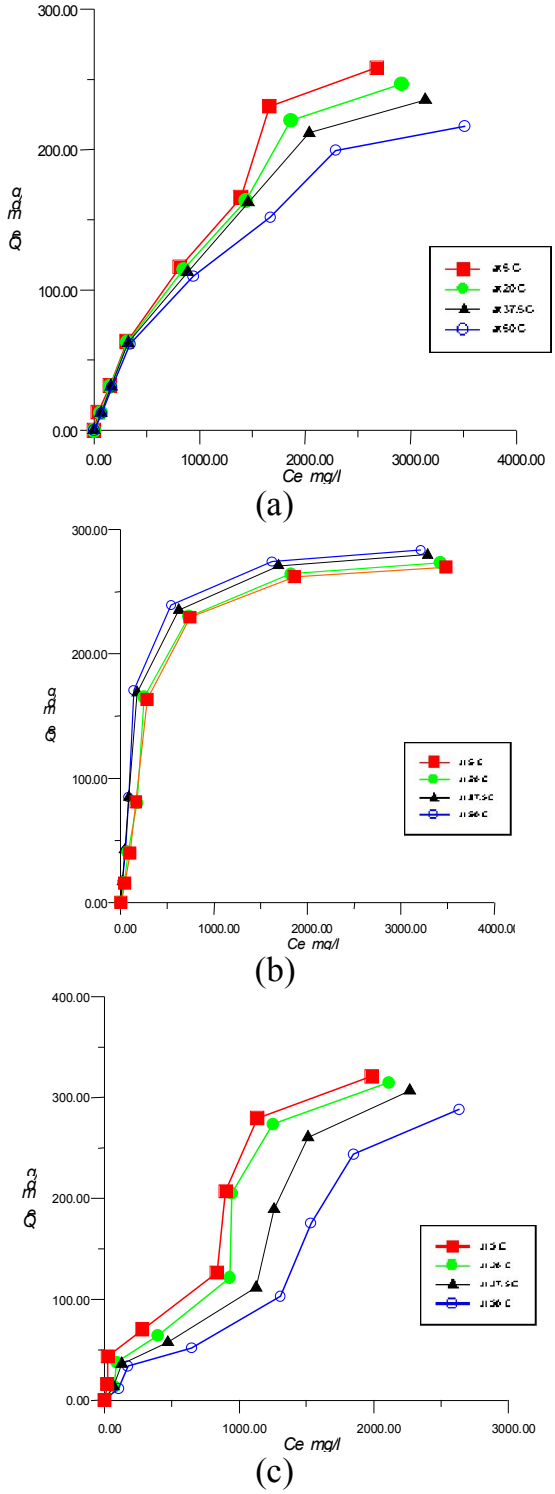

Figure 1: Adsorption isotherms of (a) amitriptyline HCl (b) chlorpromazine HCl (c) chlordiazepoxide HCl on bentonite at (5, 20, 37.5, and 50°C)

Adsorption of amitriptyline HCl and chlordiazepoxide HCl obeyed Freundlich adsorption isotherm as indicated by Figure 2,

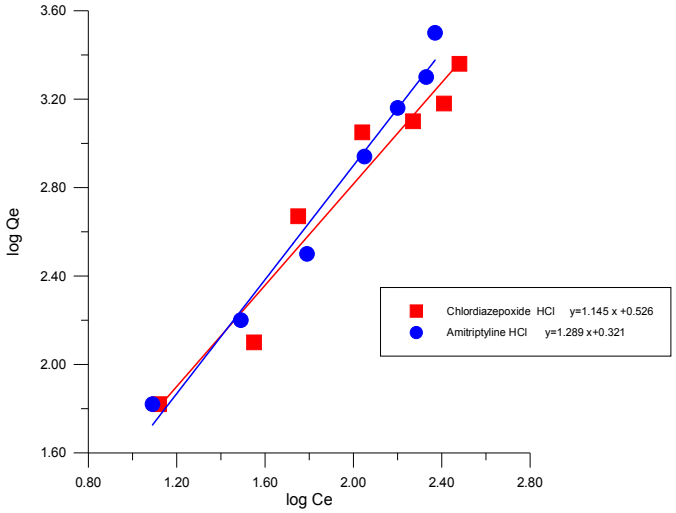

Figure 2: Freundlich lines of amitriptyline HCl and chlordiazepoxide HCl on Bentonite at 37.5° C

Whereas adsorption of chlorpromazine HCl on bentonite obeyed Langmuir isotherm as given by Figure 3.

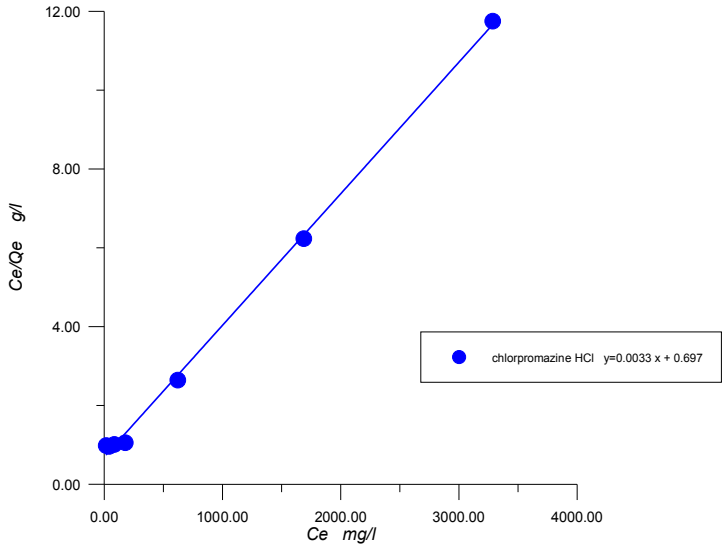

Figure 3: The linear form of the Langmuir equation of the adsorption of chlorpromazine on bentonite at 37.5 °C

The study of the adsorption process on bentonite requires taking the nature of the surface into consideration. Bentonite surface consists of small patches of various kinds of active sites which are different in physical and chemical nature or in the steric configuration [34]. Moreover, bentonite has a character of an ion exchange with the other ionized species and this affinity depends upon the size, valency and steric orientation of molecules towards the surface [35, 36].

The interpretation of the high adsorption capacity of bentonite has been estimated from X-ray diffraction studies[37] confirming the formation of more than one adsorbed layer on bentonite surface. The adsorption extent of the drugs on bentonite followed the order :

Chlordiazepoxide HCl > chlorpromazine HCl > Amitriptyline HCl

The highest affinity of chlordiazepoxide-HCl towards the surface may be interpreted as a result of the functional groups on the chlordiazepoxide-HCl molecule leading to an increase in polarization of molecule and subsequently increase the attraction between the surface and the adsorbed molecule. The chlorpromazine HCl adsorption isotherm obeyed the Langmuir equation. According to the Giles interpretation[32,38] for the adsorption isotherm shapes, the chlorpromazine HCl molecules could be oriented in the direction parallel to the surface and the area of connection will be great leading to a high attraction between chlorpromazine HCl molecules and the bentonite surface, while the attraction between amitriptyline HCl and the surface appeared with a lower level of magnitude.

Figure(4) shows the adsorption isotherm of amitriptyline HCl and chlordiazepoxide HCl at pH=1 ,which was chosen to simulate the pH of stomach fluid comparing the adsorption isotherm of chlordiazepoxide-HCl in figure(1,c) which was conducted at pH=7 with the corresponding isotherm in figure (4) .

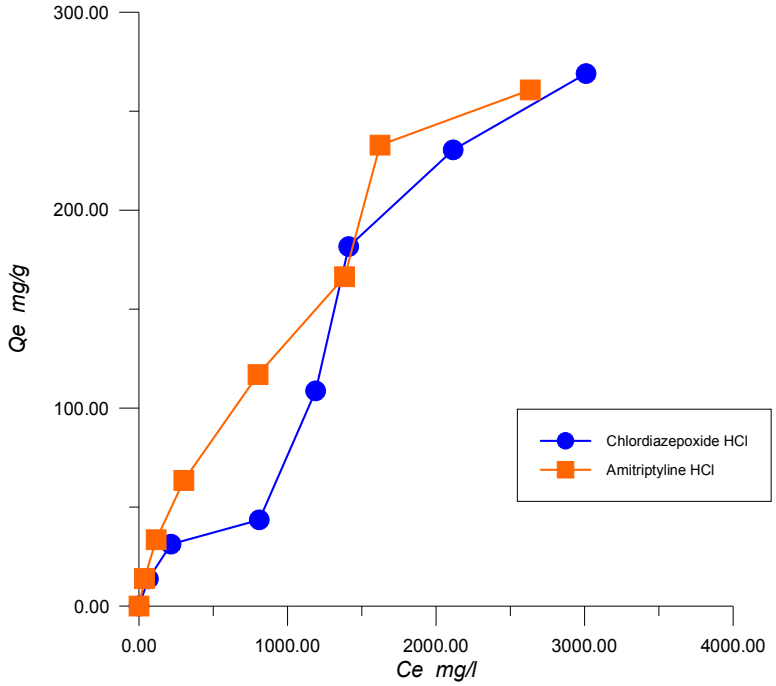

Figure 4: Adsorption isotherms of amitriptyline HCl and chlordiazepoxide HCl at pH=1 and temp.= 37.5 °C

At pH=1 shows that there is a decrease in adsorption at lower values of pH .the change in pH affects the solubility of adsorbate molecules which, in turn, affects its affinity towards the surface[39]. Hence, the increase in the solubility of chlordiazepoxide HCl in a strong acidic medium leads to a decrease in a tendency towards the surface. On the otherhand, for amitriptyline HCl drug ,the change in pH from 7[figure(1,a)]to pH=1 [figure(4)] cause an increase in adsorption of the drug on bentonite ,because amitriptyline-HCl is a lipophilic strong base[40], thus at low pH the solubility will decrease leading to an increase in the quantity adsorbed on the surface. The adsorption of chlorpromazine-HCl on bentonite at pH =1 is inapplicable due to the rapid oxidation of the drug molecule into phenothiazine-3-one derivatives or its cations in strong acidic medium[41].

Comparing the adsorption extent of the drugs on bentonite [figure(1) and that of figure (5)] in which 0.154 M of $MgSO_4$ and NaCl was used shows clearly that an increase in adsorption with

increasing ionic strength of the solution is evident . This effect is more significant in the case of chlorpromazine HCl than chlordiazepoxide HCl and amitriptyline HCl. This behaviour may be interpreted as follows: the solubility of ionic salts in water is usually higher than that of organic drug molecules, therefore, a competition between them to interact with the solvent molecules leads to an increase in the attraction between the clay surface and the drug molecules which in turn will decrease the solvent-drug interaction.

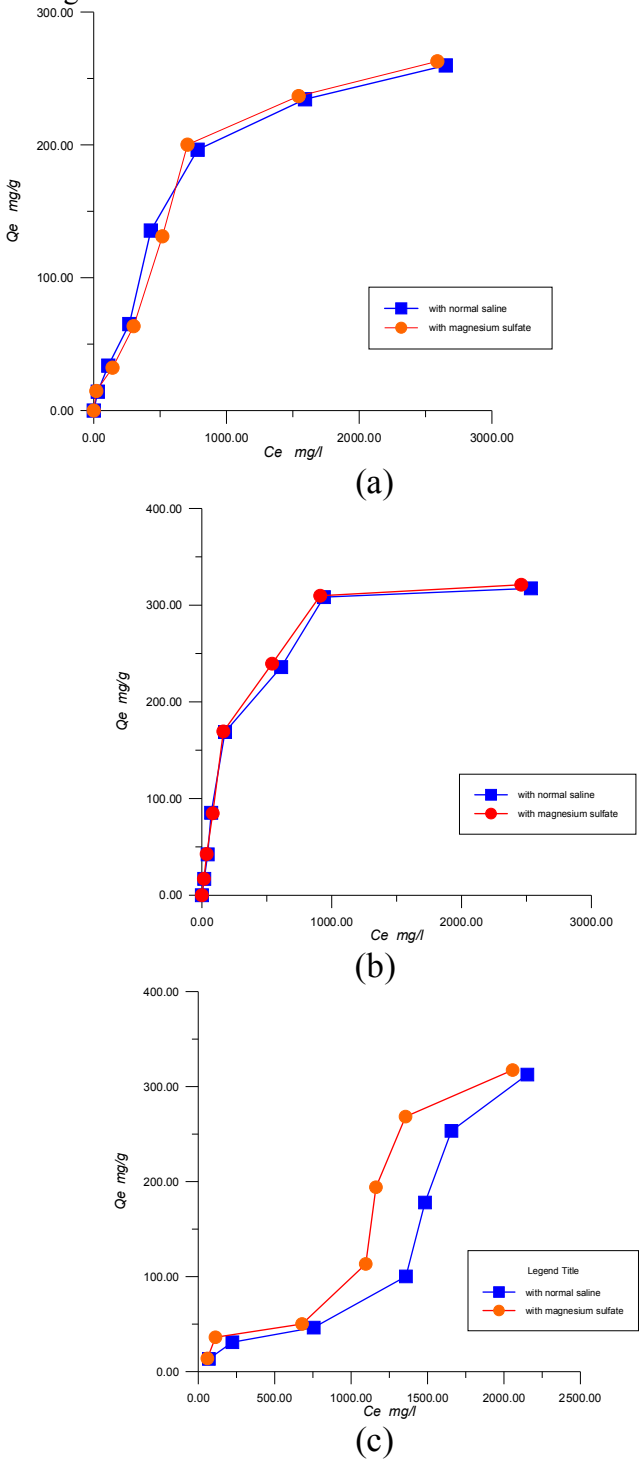

Figure 5: Adsorption isotherms of the (a) amitriptyline HCl , (b) chlorpromazine HCl (c) chlordiazepoxide HCl on bentonite using magnesium sulfate solution and normal saline at 37.5 ^{o}C

The interlayer spacing of montmorillonite is very dependent on the external ionic strength[42]. Phenomenologically, strong water adsorption on surface is repressed by the addition of an electrolyte. Hence, replacing the chlorpromazine HCl molecules the water molecules on the bentonite surface active sites might occur. Although the bentonite is able to remove heavy metals from aqueous solutions[43], there is no reason to suppose that the ionic exchange is taking place with sodium or magnesium ions because these ions are natural components of bentonite.

The equilibrium constant (K) for the adsorption process at each temperature is calculated from equation(4): -

$$K = \frac{Q_e * 0.5g}{C_e * 0.025l}, \qquad (4)$$

where Qe unit is in mg per one gram of adsorbent, i.e. (x/m) value. Ce unit is mg/l. (0.5 g) represents the weight of the clay that has been used and (0.025 l) represents the volume of the drug solution used in the adsorption process.

The change in free energies (ΔG) could be determined from the equation :-

$$\Delta G = -RT \ln K \qquad (5)$$

where R is the gas constant (8.314 J $mole^{-1}deg^{-1}$) and T is the absolute temperature.

The heat of adsorption (ΔH) may be obtained from the equation :-

$$\ln Xm = \frac{-\Delta H}{R\,T} + Constant \qquad (6)$$

Where Xm is the maximum uptake of adsorption at a certain value of equilibrium concentration (Ce) that was fixed for all temperatures of study[44]. Table 1 gives Xm values at different temperatures. Plotting (lnXm) versus (1/T) should produce a straight line with a slope =(-ΔH/R) as shown in Figure 6.

T(°K)	10^3/T (°K^{-1})	Amitriptyline HCl At Ce=1000 mg/l		Chlorpromazine HCl At Ce=1000 mg/l		Chlordiazepoxide HCl At Ce=1000 mg/l	
		Xm	LnXm	Xm	lnXm	Xm	lnXm
278	3.597	190	5.247	253	5.533	120	4.788
293	3.413	170	5.136	258	5.553	102.5	4.6299
310.5	3.221	160	5.075	266	5.583	77.5	4.35
323	3.096	140	4.942	273	5.6095	57.5	4.052

Table 1: Effect of temperature on the maximum adsorption of the drugs on bentonite

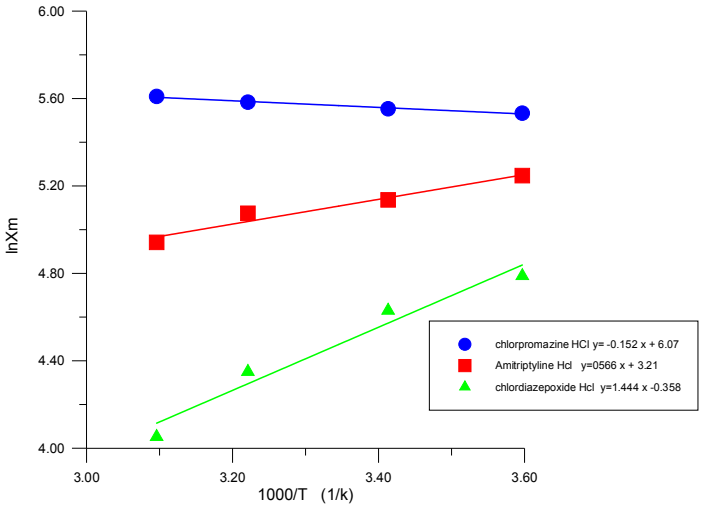

Figure 6: (lnXm) plotted against reciprocal absolute temperatures for the adsorption of the drugs on bentonite

The change in entropy (ΔS) was calculated from Gibbs equation:

$$\Delta G = \Delta H -- T\Delta S \qquad (7)$$

Thermodynamic functions (ΔG, ΔH, ΔS) of amitriptyline-HCl and chlordiazepoxide-HCl adsorption on bentonite were found to possess negative values indicating exothermic and spontaneous adsorption processes of these drugs (Table 2).

Drug	ΔH(kJ mole^{-1})	ΔG(kJ mole^{-1})	ΔS(J mole^{-1} ^{o}k^{-1})
Amitriptyline HCl	-4.706	-1.046	-11.79
Chlorpromazine HCl	+1.264	-1.374	+8.496
Chlordiazepoxide HCl	-12.005	-2.568	-30.394

Table 2: Values of thermodynamic functions for the adsorption of the drugs on bentonite at 37.5 ^{o}C

The adsorption of chlorpromazine-HCl on bentonite was found endothermic. This result agree with the previous experiments regarding endothermic adsorption process of chlorpromazine on different surfaces[45]. The higher TΔS product than the ΔH value in the basic equation ΔG=ΔH-TΔS will lead to a negative free energy change, i.e. the process is spontaneous. As one can notice, even a positive change in entropy (ΔS) may produce a negative ΔG value. The positive ΔS in the adsorption of chlorpromazine on bentonite could be viewed through the formation of less ordered adsorbed species on the surface. The status of the drug molecules on the surface is different in its configuration than that in solution.

CONCLUSIONS:

1. The clay was found to possess an appreciable adsorption capacity suggesting its probable use as an antidote in poisoning by the studied drugs. The clay may also be used as a stationary phase in chromatography technique.
2. The extent of drugs adsorption by bentonite followed the order: chlordiazepoxide HCl> chlorpromazine HCl > amtriptyline HCl.
3. Ionic strength was found to increase the drug uptake by the surface upon addition of MgSO4 and NaCl to the adsorption solution
4. The influence of pH = 1 showed an increase in amtriptyline HCl adsorption and a decrease in chlordiazepoxide-HCl uptake by the surface of bentonite.
5. Adsorption of amtriptyline HCl and chlordiazepoxide HCl on bentonite was found exothermic but chlorpromazine HCl adsorption appeared endothermic.

SUGGESTIONS FOR FURTHUR WORK:

1. A study of the adsorption of drugs from the surface of the clay at different conditions.
2. In vivo study to estimate the performance of bentonite as a physical antidote in the treatment of acute poisoning.

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