امتزاز دواء الميترونيدازول على سطح طين البنتونايت

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الخلاصة

يستعمل دواء الميترونيدازول (فلاجيل) كمضاد للأوالي و الأميبا المسببة لأمراض الأحشاء الطفيلية. أما البنتونايت فيستعمل في الطب كمضاد للإسهال وكعامل للانتشار و كمضافات للأدوية. إن التسمم بالجرعات الزائدة من الأدوية يعالج بواسطة المواد ألمازة مثل معلق الفحم المنشط الذي يمتز على سطحه الأدوية ويمنع امتصاصها لكن هذا المعلق غير مستساغ عادة من قبل المرضى. لذلك أجريت هذه الدراسة لتقدير قابلية طين البنتونايت للعمل كمادة مازة لدواء الميترونيدازول كبديل محتمل لمادة الفحم المنشط.

استخدمت تقنية المطيافية فوق البنفسجية لمتابعة الكميات الممتزة بعد مزج محلول الدواء مع طين البنتونايت. أعيدت التجربة عند أربعة درجات حرارية (١٢ و ٢٥ و٣٧.٥ و ٥٠ درجة مئوية) وذلك لقياس الدوال الثرموداينمكية (ΔH^o, ΔG^o, ΔS^o) *لعملية الامتزاز*.

اظهر تحليل النتائج أن هناك كمية قليلة فقط من الميترونيدازول هي قابلة للامتزاز وان الكميات الثرموديناميكية كانت كالأتي:

ΔH^o=18.68 KJ.mol^{-1}, ΔG^o=-10.03 KJ.mol^{-1} , ΔS^o=96.33 J.mol^{-1}.$^oK^{-1}$.

كما وجد ان كمية المادة الممتزة تزداد بزيادة حامضية المحلول.

إن عملية امتزاز الميترونيدازول على سطح البنتونايت هي عملية ماصة للحرارة مع قيم دوال ثرموديناميكية صغيرة. إن عملية الامتزاز تحفز بزيادة درجة الحرارة و زيادة حامضية المحلول.

مفاتيح الكلمات: الميترونيدازول - طين البنتونايت - التسمم – الامتزاز- الجرعات الزائدة- الدوال الثرموداينمكية ΔH^o- ΔG^o - $\Delta^o S$-.

ADSORPTION OF METRONIDAZOLE DRUG ON BENTONITE CLAY SURFACE

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Abstract:

Metronidazole drug (Flagyl) is widely used in as antiprotozoal drug in bowel parasitic diseases. Bentonite in medicine used as antidiarrheal, suspending agent, and as additives. Drug overdose may treated by adsorbents especially by activated charcoal suspension to prevent further absorption, but usually it is unacceptable to drink. Hence, an attempt was made in this work to estimate the ability of bentonite as adsorbent for metronidazole overdose *in vitro* as a possible alternative for activated charcoal.

UV-Visible spectrophotometry technique was used to follow the quantity adsorbed after incubation of bentonite with a known concentration of metronidazole solutions. The adsorption experiments were repeated at (12, 25, 37.5, and 50ºC) to measure the thermodynamical parameters (ΔH^o, ΔG^o, ΔS^o) of the adsorption process.

The results showed that, there are small amounts of metronidazole ready to adsorb on bentonite. The thermodynamic parameters values were (ΔH^o=18.68 KJ.mol^{-1}, ΔG^o=-10.03 KJ.mol^{-1}, ΔS^o=96.33 J.mol^{-1}.$^oK^{-1}$). The amount of the adsorbed drug was increased as the pH of the drug solution decreased.

It can be concluded that the adsorption of metronidazole on bentonite is endothermic process with low thermodynamic parameters values. The adsorption enhanced by increasing temperature and by increasing acidity of the medium.

Keywords: Metronidazole, clay, bentonite, pH, adsorption, drug overdose, thermodynamic, ΔH^o, ΔG^o, ΔS^o.

INTRODUCTION

Metronidazole drug (Flagyl) has antiprotozoal and antibacterial actions. It is used in the treatment of amoebic dysentery and amoebic liver abscess as well as for the eradication of *E.histolytica* from patients passing cysts [(1)]. It is still a standard antiprotozoal in the estimation of the activity of new antiprotozoal [(2)]. High doses of metronidazole taken accidentally or deliberately are toxic and the rapid treatment is necessary by different measures.

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 [(3)]. The term adsorption refers to the accumulation of atoms, ions or molecules (adsorbate) on a surface of a solid substance (adsorbent) [(4-5)]. 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 uses as physical antidotes in the treatment of acute poisoning by toxic substances and drug over dosages [(6-7)]. Activated charcoal was the most widely used solid surface as an antidote and to prevent further absorption of the drug, but it is usually unacceptable by patients because its color and taste [(8-9)]. Some clay materials were studied and found to possess similar surface properties to that of charcoal in the treatment of drug poisoning. Examples are kaolin [(10-11)], bentonite ([(12-13)] and attapulgite [(14)].

Bentonite used in the adsorption of aflatoxin and hence it is used as a component of the animal diet to prevent further absorption of aflatoxin if it is contaminate the food [(15)]. It is also used in the adsorption of different toxins [(16)], different herbicides in environment [(17)]. Montmorillonite showed adsorption ability of bacteria [(18)] and bacteriophage PBS1 of Bacillus subtilis but has no bacteriostatic and bactericidal effect [(19)]. Bentonite used in different agricultural formulations like the formula prepared for the slow release of Sulfosulfuron herbicide [(20)] and as a drug carrier [(21)].

Generally, adsorption is a natural process and usually 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 these factors are available in textbooks and references [(3, 4, 22)].

The term adsorption isotherm refers to the relation between the extent of adsorption (Qe) or (X/M) with the equilibrium concentration of the adsorbate in solution (Ce) at constant temperature. (X) is the amount of drug adsorbed in milligrams by (M) grams of the adsorbent [(23)]. Two main theories have been adopted to describe adsorption isotherms. The first, Langmuir adsorption isotherms which represented by the equation:

$$\frac{Ce}{Qe} = \frac{1}{ab} + \frac{Ce}{a} \qquad \text{.....(1)}$$

Where (a) represents a practical limiting adsorption capacity when the surface is fully covered with a monolayer of adsorbate, and allows the comparison of the adsorption performance, particularly in the cases where the adsorbent did not reach its full

saturation. The constant b is the equilibrium adsorption constant which related to the affinity of the binding sites [24].

The applicability of these equations on the adsorbent-adsorbate (solute) system assume the formation of one layer of adsorbate molecules on the surface while the Freundlich adsorption isotherm (equation) consider heterogeneity of the surface and the formation of more than one layer is probable. The linear form of Freundlich isotherm is:

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

Where k and n are Freundlich constants characteristics of the system, including the adsorption capacity and the adsorption intensity, respectively [22].

The process of adsorption from solution is more complicated than the corresponding process of gas adsorption on solid surface. The solvent effect and the complicated interaction between solvent molecules and drug molecules to be adsorbed has to be taken into account.

This work is concerned with the study of locally available bentonite clay as an adsorbent for the metronidazole drug from solution *in vitro* as a possible mean for the treatment of metronidazole poisoning.

Experimental:

(a) Clay Treatment:

The bentonite clay was collected from an open mine in Trifawi area and classified as bentonite contains about (75%) of its weight montmorillonite mineral. The analysis showed the chemical components of the bentonite expressed as weight per weight ratios are (SiO_2=54.66%, Al_2O_3=14.65%, MgO=6%, Fe_2O_3=4.88%, CaO=4.77%, SO_3= 1.2%, Na_2O=0.65%, and Loss On Ignition=12.56% in addition to other rare ions that were not analyzed. The clay was washed with excessive amounts of distilled water to remove any soluble materials, filtered and dried at 160° C for three hours and kept in an airtight container. The clay was grinded and sieved to a particle size of 75μm and then used in all adsorption experiments.

(b) Systematic procedure:

A volume of 10ml of eight different concentrations of each drug (5, 10, 20, 30, 40, 50, 80, and 100 mg/L) was shaken with 0.5g of bentonite adsorbent at a certain temperature in a thermostated shaker bath at shaking speed 60cycles/minute for two hours which is measured experimentally as a time needed for reaching the equilibrium state. After the equilibrium time is elapsed, the mixtures were allowed to settle and the clear liquids were centrifuged at a speed of 3000rpm for 20 minutes. Absorbencies were measured at the maximum wave length of metronidazole solution (320nm) using (Cintra5) U.V.-Visible spectrophotometer. Suitable dilution were made before measuring the absorbance in order to fit Beer–Lambert's limitation and then converted into absolute concentration readings through the calibration curve. The experiments were repeated at different temperatures (12, 25, 37.5, and 50ºC) to measure the thermodynamic parameters (ΔH^o, ΔG^o, ΔS^o). These experiments were also repeated using 0.1N HCl as a solvent of drug at 37.5ºC to simulate the acidity of stomach.

Results and Discussion:

Figure (1) showed the applicability of the linear form of Freundlich equation with high correlation coefficient value (r=0.949). The adsorption of the various antibiotics on the different antacids and other adsorbents in most cases obeyed the Freundlich adsorption isotherm [25].

The study of the adsorption process of metronidazole drug on bentonite clay 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 orientation of molecules towards the surface [26]. According to the Giles interpretation [27] for the adsorption isotherm shapes, the adsorption isotherm of bentonite molecules on the bentonite surface is of S3 type indicating the heterogeneity of the surface and the presence of different types of forces between the drug molecules and the surface active sites. The presence of multivalent, exchangeable cations on the clay surface diminishes interaction with the protonated form of drugs like tetracycline. Nonclay components such as calcite and dolomite increase the interactions of the zwitterionic and anionic forms of tetracycline with the clay [28]. In one study, the sorption interactions of three high-use tetracycline antibiotics (oxytetracycline, chlortetracycline, tetracycline) with montmorillonite were studied. The mechanism of adsorption were best described with a model that included cation exchange plus surface complexation of zwitterion forms of these compounds. Zwitterion sorption was accompanied by proton uptake, was more favorable on acidic clay, and was relatively insensitive to ionic strength effects. These results indicated that soil and sediment sorption models for tetracycline and other pharmaceuticals with similar chemistry, must account for solution speciation and the presence of other competitor ions in soil or sediment pore waters [29]. These findings may be applied for the adsorption of metronidazole drug on bentonite surface.

Different finding were recorded for the mechanism of the interaction of drug molecules with bentonite active sites. In one study, the adsorption of chlorpheniramine maleate by sodium montmorillonite was studied by X-ray diffraction and IR spectroscopy. The results indicated that the chlorphenirammonium ion penetrated into the interlayer space of montmorillonite, this increase was influenced, as was the amount adsorbed, by the pH, and the concentration of the chlorpheniramine maleate solution. The results showed that, the mechanism responsible for the interaction was cation exchange [30]. In another study, IR, X-ray diffraction, and absorption studies showed that digoxin is adsorbed onto montmorillonite by a reversible adsorption mechanism at pH=2 and 6. Degradation studies revealed that digoxin degradation is accelerated and the reason may attribute to the ability of the clay surface to concentrate both digoxin and protons and has a catalytic effect [31].

The data related to the effect of PH on adsorption isotherms of metronidazole on bentonite surface are shown in Figure (2) where a PH=1 was chosen to simulate the PH of the stomach fluid. The change in PH affects the solubility of adsorbate molecules which, in turn, affects its affinity towards the surface [32]. Hence, one can propose that the decrease in the solubility of metronidazole in a strong acidic medium leads to an increase in the tendency towards the surface. The interlayer spacing of montmorillonite

is very dependent on the external ionic strength [33]. Phenomenologically, strong water adsorption on surface is repressed by the addition of an electrolyte. Hence, replacing the metronidazole molecules by water molecules on the bentonite surface active sites might occur. Although the bentonite is able to remove heavy metals from aqueous solution [34-36], 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 and the adsorption quantity is little. It is still another possible mechanism reposes on catalytic activity of the bentonite clay that may enhance or inhibit the chemical transformation of different chemicals as shown in different papers [37].

In order to obtain a thermodynamical state of the adsorption process, the adsorption experiments were repeated at different temperatures (12, 25, 37.5, and 50ºC) to measure the thermodynamic parameters (ΔH^o, ΔG^o, ΔS^o).

The equilibrium constant (K) for the adsorption process at each temperature is calculated from division of the drug adsorbed on the bentonite surface on the quantity of drug present in solution:-

$$K = \frac{Qe * 0.5}{Ce * 0.01} \quad \text{----------(3)}$$

Where Qe is the amount adsorbed in (mg) per one gram of adsorbent, sometimes called (x/m) where (x) is the quantity in milligrams adsorbed by (m) grams of adsorbent. Ce is equilibrium concentration of the adsorbate expressed in mg/L. (0.5g) represent the weight of the clay that has been used and (0.01) represents the volume of the drug solution used in the adsorption process.

The change in free energy (ΔG^o) could be determined form the equation:-

$$\Delta G^\circ = -RT \ln K \quad \text{----------(4)}$$

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

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

$$\ln Xm = \frac{-\Delta H^\circ}{RT} + cons\tan t \quad \text{----------(5)}$$

Where Xm is the maximum uptake of adsorption at a certain value of equilibrium concentration (Ce) that was fixed for all temperatures. Plotting (InXm) versus (1/T) should produce a straight line with a slope = ($-\Delta H^o/R$) as shown in Figure (4).

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

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ \quad \text{----------} \ (6)$$

Figure (3) showed adsorption isotherms of metronidazole onto bentonite clay surface at four different temperatures. From this figure it can be concluded graphically the maximum quantities (Xm) adsorbed for each temperature at certain equilibrium concentration (say Ce=2mg/L). The natural logarithms of these Xm values were plotted versus the reciprocal of temperature to obtain the heat of adsorption from the graphic representation of vant Hoff's equation Figure (4). The thermodynamical parameters values are:

(ΔH^o=18.68 $KJ.mol^{-1}$, ΔG^o=-10.03 $KJ.mol^{-1}$, ΔS^o=96.33 $J.mol^{-1}.{}^oK^{-1}$).

Free energy change and entropy values were measured at 298ºK. These values are low and indicated a weak and nonspecific interaction between drug molecules and the active sites of bentonite clay surface.

The results of this work can be compared with other papers related to the adsorption of metronidazole and other drugs on bentonite in order to treat the drug poisoning or to obtain a drug formula with good characteristics. For example, in the context of the potential usefulness of clays in retarding the rate of release of adsorbed drugs, dissolution dialysis studies of the release of metronidazole from montmorillonite adsorbates have been conducted in an interesting research [38]. The goal was to develope a means for improving local gastrointestinal therapy of amoebiasis while concurrently maintaining efficacy in treating hepatic amoebiasis. A physical admixture of montmorillonite and metronidazole was also effective in inhibiting the rate of release of metronidazole. Upon increasing the pH to 7, the clay particles progressively deflocculated and the rate of release increased significantly. These findings confirmed the results of this research in that, the adsorption process is irreversible and the preferred direction of equilibrium is the desorption process depending on the obtained very low thermodynamical values of the adsorption process. It can be concluded that the mixture of metronidazole and bentonite has the ability to form a sustained release formula and the possible role of bentonite as adsorbent for the treatment of the metronidazole poisoning requires more investigation.

Conclusion: Adsorption of metronidazole on bentonite is endothermic process with very low thermodynamic parameters values. The adsorption enhanced by increasing temperature and with increasing acidity of the medium.

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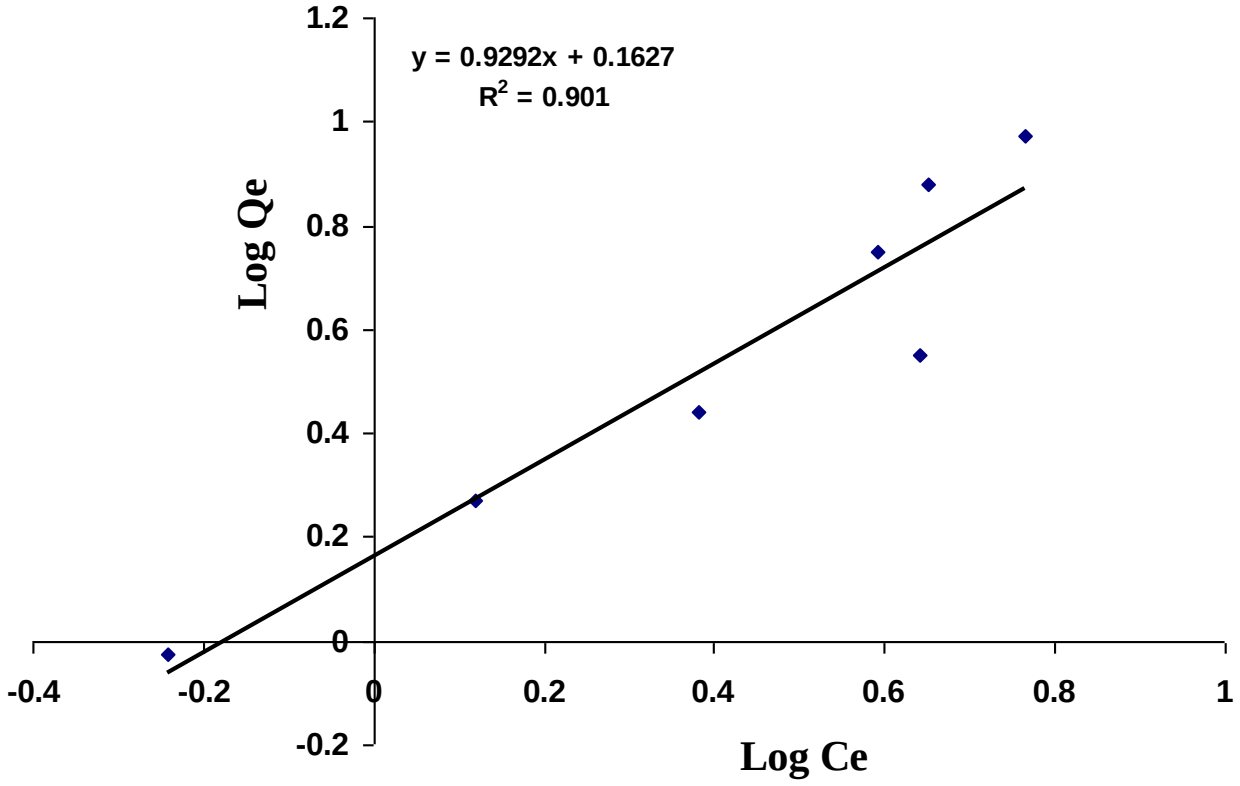

Figure (1): Linear form of Freundlich equation for the adsorption of metronidazole on bentonite.

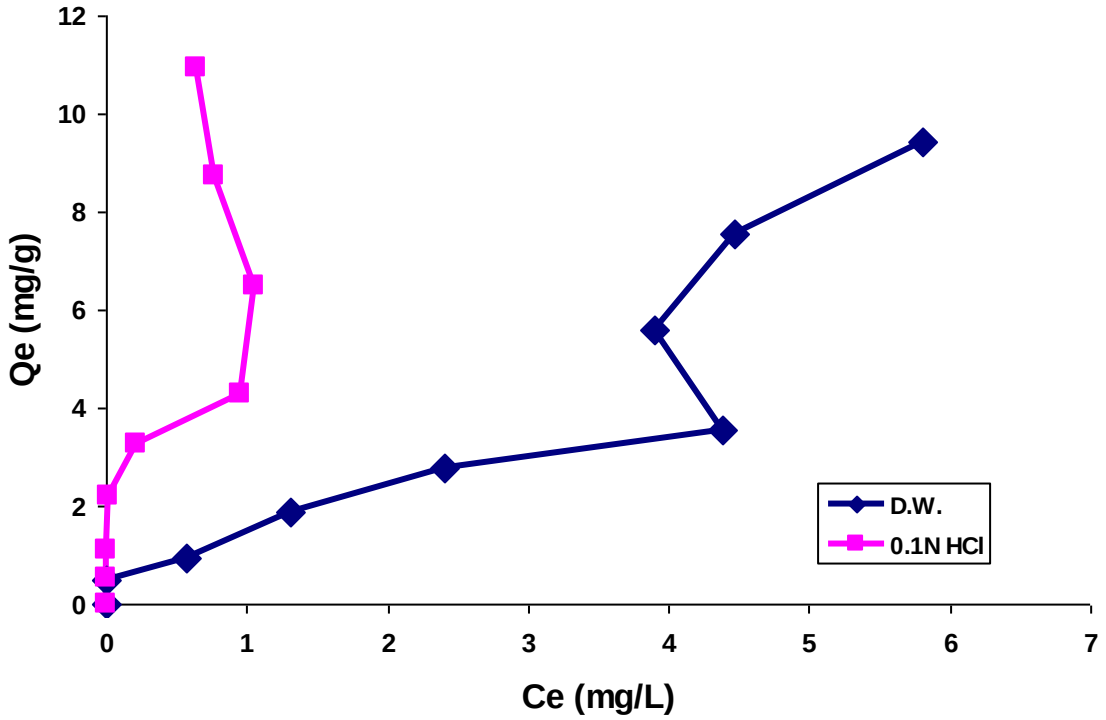

Figure (2): Adsorption isotherms of metronidazole in distilled water (D.W.) and 0.1N HCl on bentonite surface at 25ºC.

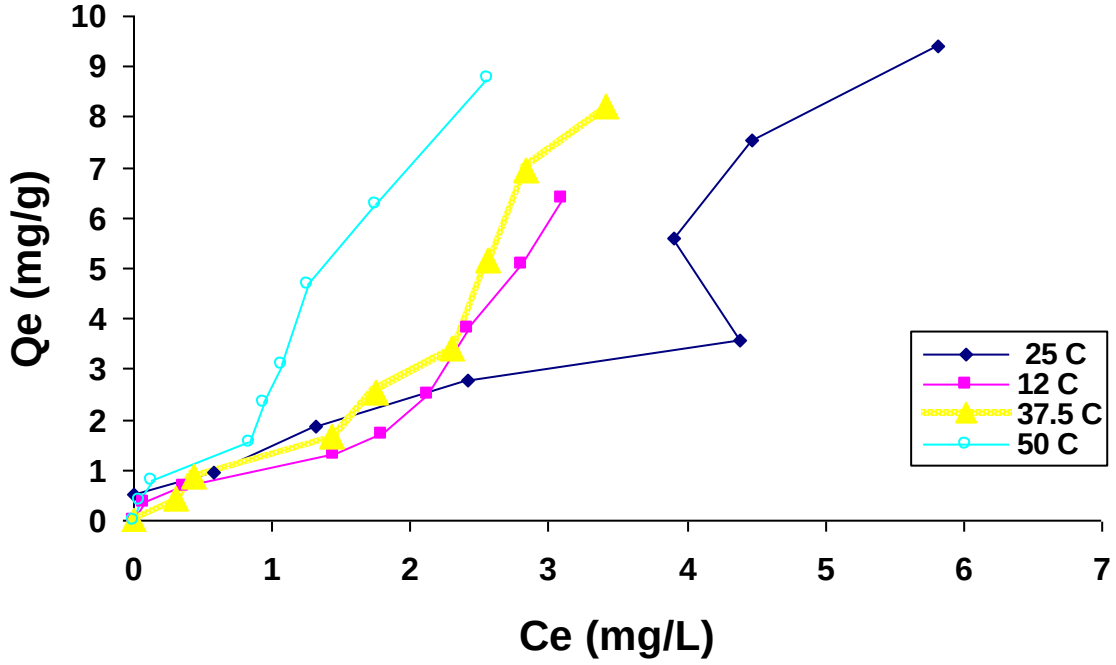

Figure (3): Adsorption isotherm of metronidazole on bentonite surface at (12, 25, 37.5, and 50ºC)

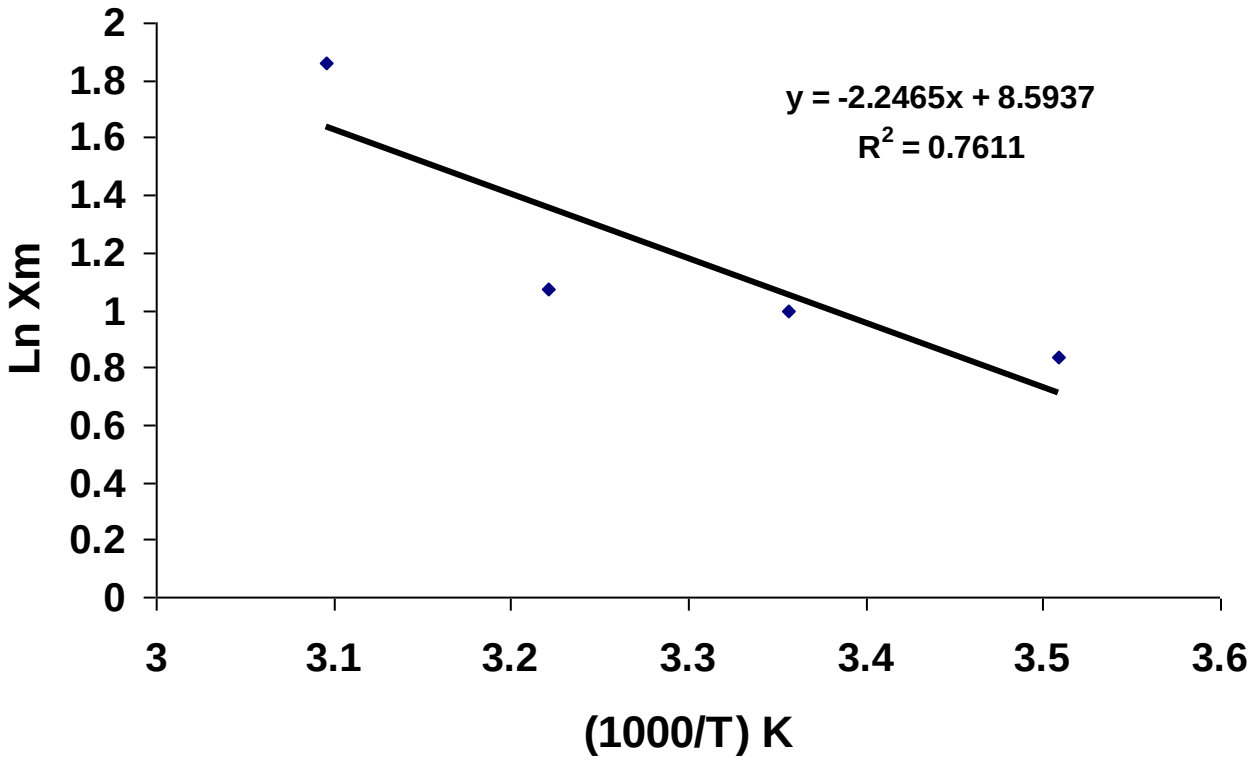

Figure (4):Graphic representation of the modified vantHoff's equation for the adsorption of metronidazole on bentonite at different temperatures.