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Adsorption of Metamizole Sodium by Activated Carbon in Simulated Gastric and Intestinal Fluids

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Abstract: *In vitro* adsorption of metamizole sodium by activated carbon was studied at pH 1.2 and 7.5 in order to simulate gastric and intestinal fluids. In the first 5 minutes, more than eighty percent of the total adsorption occurred but the adsorption process achieved to the equilibrium in 1 hour. Time to reach equilibrium did not change with the changing pH, concentration of the adsorbate or the adsorbent amount. The equilibrium data followed the Langmuir model and therefore fitted to L-type in accordance with the Giles classification for adsorption isotherms. The maximum removal capacities of the activated carbon for metamizole sodium were calculated using Langmuir equation and found as 185.19 mg/g and 161.29 mg/g at pH 1.2 and 7.5, respectively.

Keywords: Adsorption, Metamizole sodium, Gastric fluid, Intestinal fluid, Dipyrone.

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INTRODUCTION

Metamizole sodium (MS), also known as dipyrone, is a pyrazolone derivative and represents analgesic and antipyretic activity. The molecular structure of MS is shown in Figure 1. It was withdrawn already in several countries due to its potentially fatal adverse effects. The most serious adverse effect of MS is agranulocytosis. Studies showed that MS overdose usually causes mild toxicity and occurs mainly at home by the oral route and in relation to a considerable number of suicide attempts. However, MS is still widely used as an over the counter preparation in adults and children in many countries (1). The use of MS during pregnancy and postpartum even exceeds the use of paracetamol in some of these countries. Studies report that metabolites of MS were found in the breast milk in concentrations similar to those in the maternal serum (2).

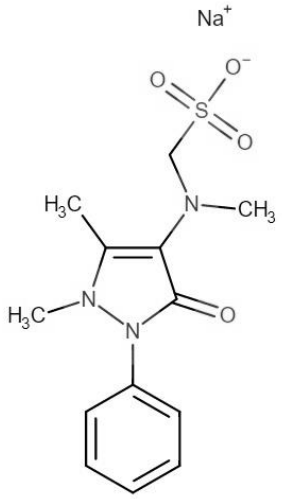


Figure 1: Chemical structure of MS (metamizole sodium).

Drug poisoning is a common and serious clinical problem. Because many drugs used do not have any specific antidote for the treatment of poisoning. If the specific antidote does not exist, gastrointestinal adsorbents are beneficial for the treatment of overdose or poisoning by preventing the further absorption of drug. Activated carbon is widely used as a gastrointestinal adsorbent and has been successfully applied in the cases of overdosing of many pharmaceuticals (3). Activated carbons are also commonly used in the industries relevant to water treatment, pharmaceutical and food as adsorbent materials due to their highly porous structure and large adsorption capacity. However, there are limited number of studies investigating the adsorption rate and capacity of activated carbon for a certain drug including the effect of pH on the adsorption (4-12). Nabais *et al.* have studied the adsorption of fluoxetine in activated carbons and activated carbon fibers at gastric and intestinal pH values and reported most of the materials tested have potential for treating potential fluoxetine intoxications (13).

In the literature, there was no study on the adsorption of MS on activated carbon or any other adsorbent. So, the objective of the current study was to explore the *in vitro* adsorption of metamizole sodium using commercial powder activated carbon in the simulated gastric and intestinal fluids. Adsorption studies were conducted at 37 °C (body temperature) using various contact times, adsorbent amounts and initial adsorbate concentrations. Data from the equilibrium studies were modeled by using Langmuir and Freundlich isotherm equations and adsorption capacities were calculated.

MATERIALS AND METHODS

Powdered activated carbon (PAC) was obtained from Merck. Surface and textural characterization of PAC used have been described in detail elsewhere (4). Briefly, the surface area and pH_{PZC} (PZC: point of zero charge) of PAC are 780 m^2/g and 9.5, respectively. MS was supplied by Sigma (≥98%).

The adsorption experiments were conducted in simulated gastric fluid (SGF) and simulated intestinal fluid (SIF). Stock solutions of MS were prepared in SGF (pH=1.2) which contains NaCl and concentrated HCl (pepsin omitted) and SIF (pH=7.5) which contains NaH_2PO_4 and NaOH (without pancreatin). All the solutions were prepared by using purified (MilliQ) water and used at once. 100 mL of MS solutions of a known concentration (10 to 100 mg/L) were shaken with PAC (25 to 250 mg) in glass containers at 37 °C for 1 hour using a thermostatic shaker with a water bath. Separation of the samples was done with microfilters (0.45 μm). Concentrations of MS in the samples were measured with a spectrophotometer (Shimadzu, UV-visible) at 225 nm. Concentrations of the samples were calculated using calibration curves prepared for MS. The same arrangement were used also for the kinetic experiments. Blank experiments (without adsorbent) were performed and all the experiments were repeated at least three times under identical conditions.

RESULTS AND DISCUSSION

In vitro adsorption of MS was performed in both SGF and SIF. In order to find the time to reach equilibrium, adsorption experiments were carried out using various shaking times. In the first 5 minutes, more than eighty percent of the total adsorption occurred but the adsorption process achieved to the equilibrium in 1 hour (Figure 2). The time to reach equilibrium did not change with changing pH, adsorbate concentration and the amount of adsorbent. So the adsorption of MS was carried out using 1 hour as shaking time at body temperature, 37 °C. The amount of adsorption (q, mg/g) was calculated as given below:

$$q = \frac{(C_0 - C_t)V}{w} \quad \text{(Eq. 1)}$$

C_0 shows the initial concentration of MS (mg/L) and C_t shows the concentration of MS (mg/L) at any time (t). V is the volume of MS solution used (L) and w is the mass of PAC (g).

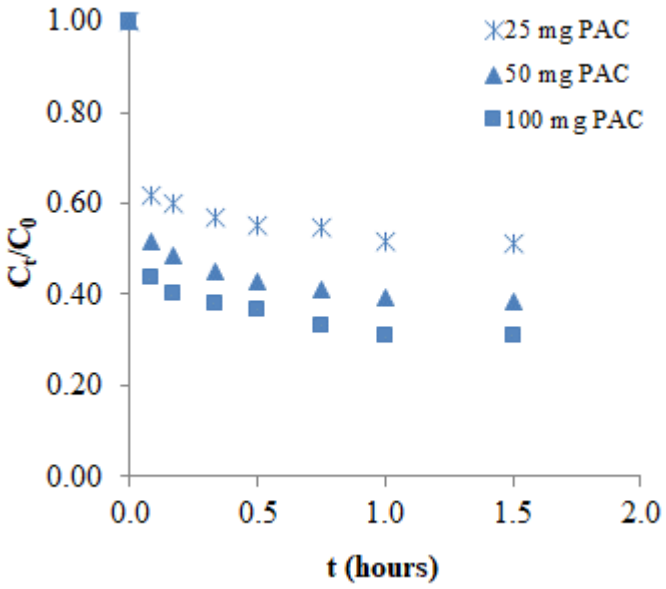


Figure 2: Effect of contact time on the adsorption of metamizole sodium (MS) on powder activated carbon (PAC).

Isotherm equations are used to model the interaction between the adsorbate and the adsorbent for the adsorption processes. Figure 3 and 4 are the Giles isotherms of MS on PAC at 37°C in SGF and SIF, respectively. The shapes of the isotherms in Figure 2 and 3 fit the L type in accordance with the Giles isotherm classification. L type means there is a high affinity between PAC and MS (14).

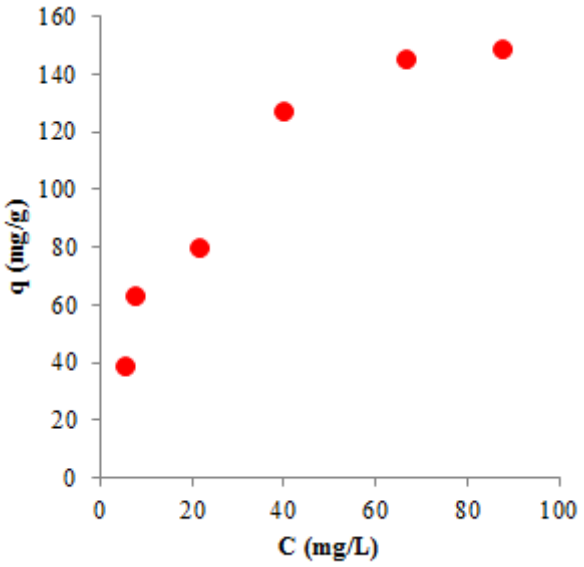


Figure 3: Giles isotherm for the adsorption of MS on PAC in SGF at 37°C.

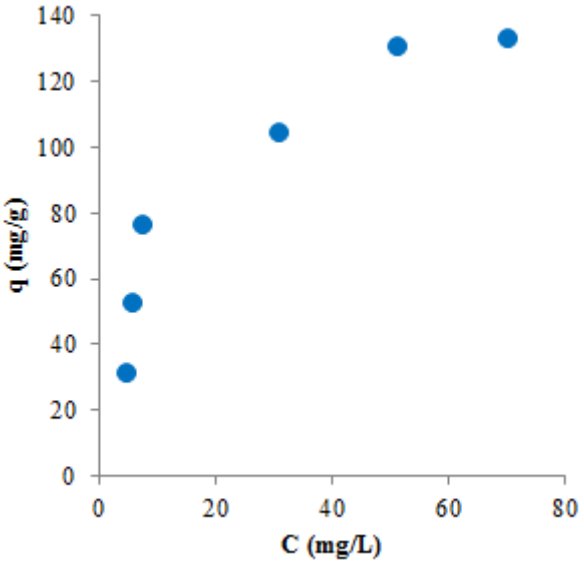


Figure 4: Giles isotherm for the adsorption of MS on PAC in SIF at 37°C.

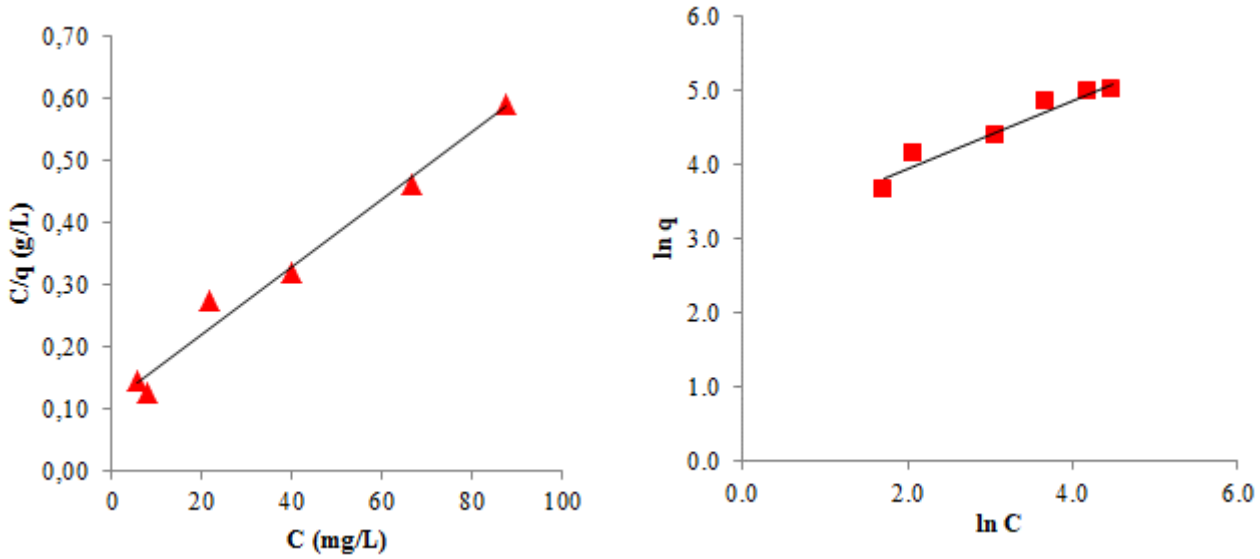
Data obtained from equilibrium experiments were modeled by using the Langmuir (Figures 5a and 6a) and the Freundlich (Figure 5b and 6b) isotherm equations. Langmuir (15) and Freundlich (16) isotherm equations in their linear forms are respectively shown below.

$$\frac{C}{q} = \frac{1}{Qb} + \frac{C}{Q} \quad \text{(Eq. 2)}$$

$$\ln q = lnk + nlnC \quad \text{(Eq. 3)}$$

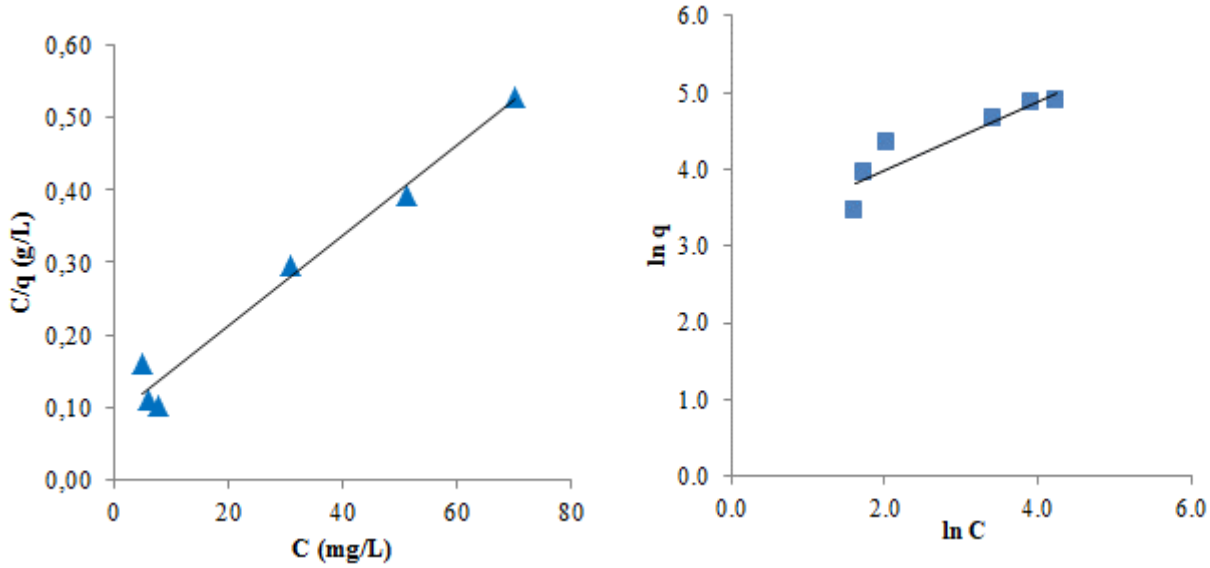
C shows the equilibrium concentration (mg/L); q shows the amount of adsorption at the equilibrium (mg/g); Q shows the maximum adsorption capacity (mg/g); b is the adsorption equilibrium constant (L/mg); k and n are Freundlich constants.

As seen in Table 1, the Langmuir model represents the adsorption of MS on PAC better than the Freundlich model. The Langmuir model indicates a localized adsorption with a monolayer coverage on the surface of the adsorbent where the adsorption heat is indepedent of the adsorbed amount of the material (17).



(a) (b)

Figure 5: Langmuir and Freundlich isotherms for the adsorption of MS on PAC in SGF at 37 °C.



(a) (b)

Figure 6: Langmuir and Freundlich isotherms for the adsorption of MS on PAC in SIF at 37°C.

Table 1: Isotherm parameters of the adsorption of MS PAC in SGF and SIF.

	Langmuir model			Freundlich model		
	Q (mg/g)	b(L/g)	R^2	n	k	R^2
SGF	185.19	0.05	0.981	0.47	20.16	0.945
SIF	161.29	0.07	0.976	0.45	21.95	0.839

pKa (Ka: acidity constant) is an important parameter that controls the dissociation of adsorbate and effects the adsorption. This effect is closely related to the solution pH. MS (pKa = -1.2) exists its anionic form in the solution (18). Another parameter which importantly effects the adsorption is the surface charge of the adsorbent which is PAC in this study (4). PAC is an amphoteric material and has a point of zero charge (pH_{PZC}) of 9.5 which means that the charge of the surface is positive at the working pH values, 1.2 and 7.5. But the net positive charge on the surface at the pH 7.5 is lower than the one at the pH 1.2 which is more closer to the pH_{PZC}. The maximum adsorption capacity obtained at the pH 1.2 (in SGF) is higher than the one obtained at the pH 7.5 (in SIF). The adsorption capacity of PAC decreased with the increasing pH which shows the main role of electrostatic attraction on the adsorption of MS. The adsorption of MS occurs related to the electrostatic attraction forces between the anionic MS molecule and surface of PAC charged positively.

Dispersive (dispersion) and electrostatic interactions are the types of interactions which rule the adsorption of aromatic compounds on activated carbons. Dispersive interactions between the π-electrons of the aromatic rings of MS molecules and those of the graphene layers of PAC may be also contributive in this process (5, 19-23).

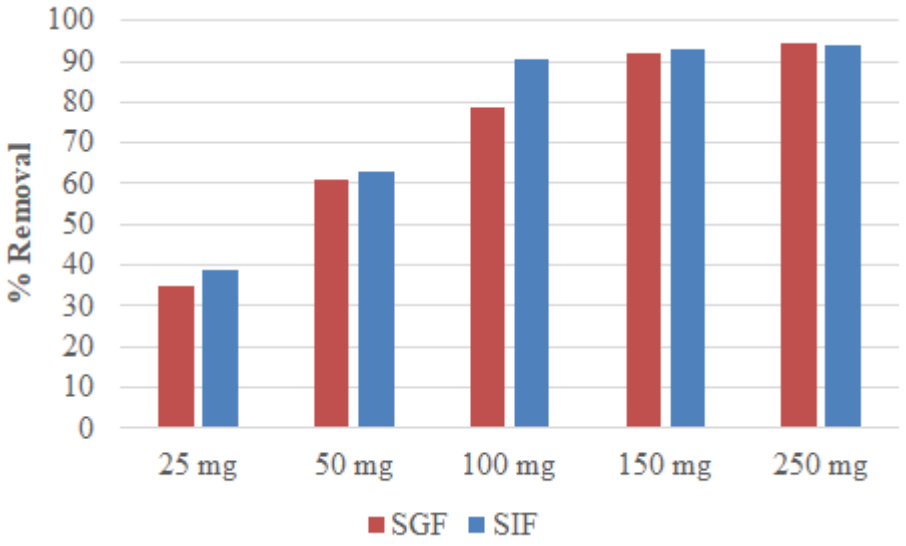


Figure 7: Comparison of % Removal of MS (metamizole sodium) for different amounts of PAC (powder activated carbon).

Figure 7 shows the effect of adsorbent amount on the removal of MS for various amounts of PAC. % Removal increases with an increase in the amount of PAC and stays almost constant at the adsorbent amounts higher than 100 mg. PAC used showed a high removal capacity for MS.

CONCLUSIONS

Adsorption of MS (metamizole sodium) on PAC (powder activated carbon) was studied in simulated gastric and intestinal fluids at body temperature. The adsorption process achieved to the equilibrium in 1 hour, but more than eighty percent of the total adsorption occurred in the first 5 minutes. The maximum adsorption capacities of MS on PAC were calculated using the Langmuir isotherm model. The maximum adsorption capacity of MS in the simulated gastric fluid was found to be 185.19 mg/g which is higher than the one obtained in the simulated intestinal fluid found to be 161.29 mg/g. The adsorption capacity increased with decreasing pH. These results indicate the role of electrostatic attraction in this prosess. Electrostatic interactions played the main role for the adsorption of MS on PAC with a possible contribution of π-π dispersion interactions. Taking into account the equilibrium time and the adsorption capacities of the PAC, it can be concluded from the above that the adsorption of MS on PAC is a fast process with a high removal efficiency. Results of the present study is important for the treatment of overdose or poisoning by preventing the further absorption of drug.

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