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Research Article

Paracetamol Detoxification Using ODTMA Micelles-Activated Charcoal Complex

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Abstract

Paracetamol poisoning is among the most common causes of medication related poisoning and death. The evidence for all interventions for paracetamol overdose is weak. Activated charcoal, gastric lavage, and ipecacuanha are able to reduce absorption of paracetamol if started within one to two hours of paracetamol ingestion, but the clinical benefit is unclear. Therefore, there is a pressing need to invent modified forms of activated carbon and other adsorbents to treat paracetamol toxification. In this study we have investigated the efficiency of octadecyltrimethylammonium (ODTMA) micelles-activated charcoal (OMAC) complex that possesses a positive charge, a high surface area and a high affinity to capture paracetamol molecules. Various pHs were studied to evaluate the effect of pH on the removal of paracetamol by this adsorbent. The adsorption isotherm results demonstrate a fit to Freundlich adsorption isotherm and adsorption kinetics follow a pseudo second order kinetics model. The results revealed that OMAC complex can enhance the detoxification of paracetamol at high doses in the stomach even at low pH compared to activated charcoal. Furthermore, the results indicate that OMAC complex can adsorb paracetamol in different forms at different pHs relative to charcoal, which renders the complex a better detoxification agent than activated charcoal.

Keywords: *ODTMA Micelles-Carbon Complex; Paracetamol; Adsorption; Activated Charcoal; Poisoning; Detoxification*

Introduction

Paracetamol (N-acetyl-p aminophenol, acetaminophen) is cornerstone of the management of mild to moderate pain and for the treatment of fever [1], found in numerous products and dosage forms such as capsules, tablets, syrups, elixirs, drops and suppositories, also it is one of the most commonly used over-the-counter analgesics. However, the exact mechanism by which paracetamol exerts its analgesic and antipyretic effects remains to be defined. The primary mechanism of action is believed to be an inhibition of cyclooxygenase (COX), with a predominant effect on COX-2 [1,2].

Recent studies have suggested that paracetamol may work through additional mechanisms, including modulation of the body's endogenous cannabinoid system [1,2].

Paracetamol is rapidly absorbed from the gastrointestinal (GI) tract with peak concentrations achieved within 90 minutes of a therapeutic dose. The presence of food in the stomach may delay the peak but not the extent of absorption [3]. Its distribution is rapid with a

volume of distribution (Vd) of about 0.9 L/kg and minimal protein binding at therapeutic concentrations [3]. The half-life of paracetamol is 2.0 to 2.5 hours. With hepatic injury, the half-life is prolonged to more than 4 hours. Paracetamol undergoes extensive hepatic metabolism.

Overdose of paracetamol has been recognized in 1966 to cause fatal and nonfatal hepatic necrosis; it is suspected that even repeated therapeutic or slightly excessive doses can be hepatotoxic in susceptible individuals, such as alcoholics. Since that poisoning has become the most common cause of acute liver failure. The precise mechanism by which paracetamol causes cell death remains unknown, although there are two prevailing theories that are controversial. According to the first theory, there are biochemical reactions between the reactive and macromolecular cell components (protein, lipids, DNA). As per the second theory; the oxidative stress in the cell ultimately leads to its demise [4].

There are no specific findings early after an overdose of paracetamol. Early nonspecific symptoms are nausea, vomiting, abdominal pain, and malaise. Although these symptoms may improve over the first 24 hours, progressive hepatic injury may manifest as early as day 2 to 3 with right upper quadrant pain and tenderness. Liver enzymes typically start increasing within 24 to 36 hours after an overdose but may increase as early as 12 hours after a massive ingestion of paracetamol [5]. Maximal liver injury typically peaks between 3 to 5 days with jaundice, coagulopathy, and encephalopathy [6]. Recovery or progression to Fulminent hepatic failure (FHF) occurs over the following several days. Renal injury, oliguria, and acute renal failure are less commonly. Maximal renal injury lags beyond peak liver injury, and recovery is also more protracted. Isolated nephrotoxicity without hepatic injury rarely occurs [7].

The evidence for all interventions for paracetamol overdose is weak. Activated charcoal, gastric lavage, and ipecacuanha are able to reduce absorption of paracetamol if started within one to two hours of ingestion. Activated charcoal seems to be the best choice if the patient is compliant; sometimes multiple doses of activated charcoal are needed to treat severe poisoning. In other cases, the current used activated carbon is not sufficient to efficiently trap several drugs and poisons. Therefore, there is a crucial need to invent modified forms of activated carbon and other adsorbents such as ODTMA micelles carbon complexes that have positive charge, higher surface area and affinity to adsorb paracetamol upon poisoning.

Recently we have been engaged in studying the removal of a variety of commonly used drugs from waters by novel ODTMA modified bentonite and activated carbon-micelles complexes. The micelle-clay and micelle-activated carbon composites which were used in the removal of a variety of drugs are positively charged, have large surface area, and include large hydrophobic domains. The organic cation, ODTMA has an alkyl chain of 18 carbon atoms with critical micelle concentration (CMC) of 0.3 mM [8,9]. The micelles, which include several tens to about several hundred molecules, are in the nanometer range. It was shown by X-ray diffraction, electron microscopy and adsorption experiments that the material characteristics of the micelle-clay and micelle-carbon complexes are different from those of either an organo-clay or activated carbon, which were formed by adsorption of the same organic cation ODTMA as monomers [8-10]. Studies with both ODTMA clay and activated carbon-micelles complexes have demonstrated an efficient removal of variety of pharmaceuticals from waters. Among these drugs are spironolactone [11,12], diclofenac sodium [13], mefenamic acid [14], atorvastatin [11,12], amoxicillin [15], cefuroxime axetil [15] and dexamethasone [16]. Furthermore, it was demonstrated that the removal efficiency of these modified adsorbents is much higher than that of unmodified bentonite and activated carbon. In addition, preliminary results of *in vitro* spiking of different pharmaceuticals such as metformin, paracetamol and aspirin at a wide range of pHs mimicking that of physiological environments have revealed promising results for the use of these modified adsorbents in drug overdose and poisonings [13,17].

In the course of this study we have investigated the efficiency of OMAC complex towards the removal of paracetamol from a medium mimicking that of the physiological environments and compared it to that by naked activated carbon.

Materials and Methods

Chemicals

All chemicals were of analytical grade. The octadecyltrimethylammonium bromide was obtained from Sigma Aldrich. Paracetamol was obtained from Birzeit pharmaceutical company (Ramallah-Palestine).

Activated Charcoal (12 - 20 mesh) was obtained from Sigma (Sigma Chemical Company, USA). Deionized water was used to prepare all solutions.

Instrumentation

UV-Spectrophotometer

The concentrations of samples were determined spectrophotometrically (UV-spectrophotometer, Model: UV-1601, Shimadzu, Japan) by monitoring the absorbance at λ_{max} for each drug.

pH meter

pH values were recorded on pH meter model HM-30G: TOA electronics™ and on Cyberscan Electrodes (PC 300 Series) (EUTECH Instruments, waterproof series).

Centrifuge and Shaker

Labofuge®200 Centrifuge was used, 230 V 50/60 Hz. CAT. No. 284811; made in Germany. Pharmaceuticals solutions were shaken with an electronic shaker (Bigbill shaker, Model No.: M49120-26, 220-240 V 50\60 Hz.) at 250 rpm.

Dissolution apparatus

NTR-3000 dissolution tester was used (220VIØ 50.60) Hz, motor: 24W, heater: 500W, max temp 43°C.

ODTMA micelles-charcoal complex preparation

The micelles-carbon complex prepared by stirring 20 mM of ODTMA with 10g/L charcoal for 72h at 40oC. Under these conditions, most of the ODTMA was in micellar form, and most of the micelles as well as remaining monomers were absorbed by charcoal. Suspension was centrifuged for 20 minutes at 15,000 g, supernatants were discarded, and the complex was lyophilized.

Batch experiments and adsorption isotherm

Effect of pH and adsorbent dosage

50 milligram of paracetamol was dissolved in 1 Liter of water and adjusted to different pH's (1, 2, 4, 5.5, 6.8, and 7.4); this solution was poured into the dissolution apparatus. After operating the dissolution apparatus at 37 degrees different amounts of activated charcoal or ODTMA charcoal micelles complex were added, after 3 hours 1.5 ml of the solution was taken and filtered to determine the absorbance of paracetamol at 245 nm.

Effect of contact time

50 milligrams of paracetamol poured into 250 ml conical flask, shaken with an electronic shaker at 250 rpm, a sample was taken at zero time, after that 0.5 grams of activated charcoal was added, a sample was taken every (0, 5, 10, 20, 40, 80, 160) minuets and filtered to detect the absorbance of paracetamol at 245 nm.

Adsorption isotherms

Experiments were performed in 250 ml Erlenmeyer (conical) flasks containing 0.5 gram of activated charcoal or ODTMA charcoal micelles complex, with diluted solutions (1000 ppm, 500 ppm, 200 ppm, 100 ppm, 50 ppm, 30 ppm, 10 ppm) that were prepared from a stock solution of paracetamol. The conical flasks were shaken in an electric shaker for 4 hours at room temperature, and then the content of the flask was filtrated to determine the absorbance of paracetamol at 245 nm.

Results and Discussion

The removal of paracetamol by activated charcoal and OMAC complex were investigated under physiological conditions. The effect of pH, contact time, adsorption dosage and initial concentration on the adsorption efficiency were investigated. The following sections discuss the results of these investigations.

Effect of pH and adsorbent dosage

Figures 1 and 2 display the results of the effect of pH and adsorbent dosage on the percent removal of paracetamol by activated charcoal and OMAC complex. Inspection of these the two figures reveal that the optimum adsorption dosages at all pH's are 0.5 g/L and 0.2 g/L for activated charcoal and OMAC complex, respectively. These results indicate that the complex is far more efficient in removing paracetamol than activated charcoal at all pH's.

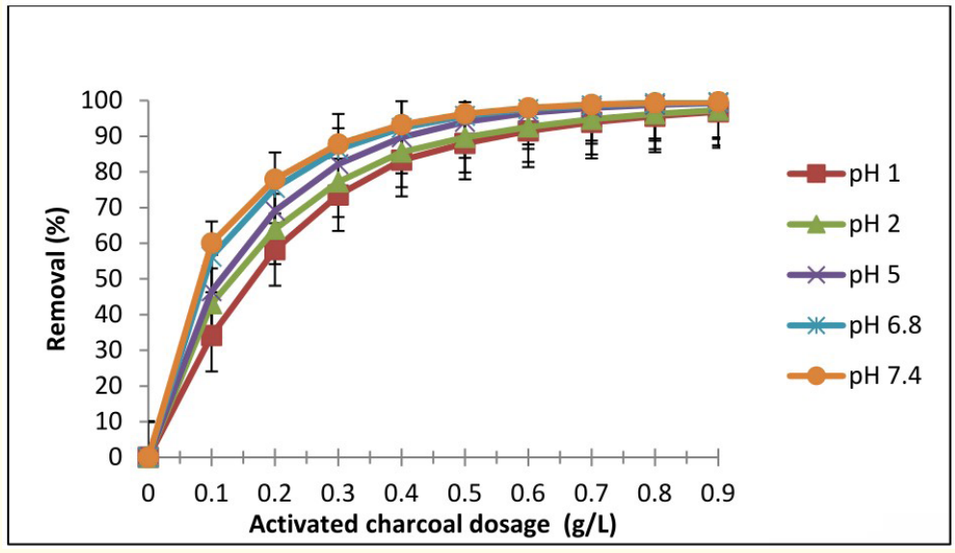

Figure 1: *Effect of pH and adsorbent dosage on the percent removal of paracetamol by activated charcoal. Initial concentration of paracetamol = 50 ppm, contact time = 4h, temperature= 25.0°C.*

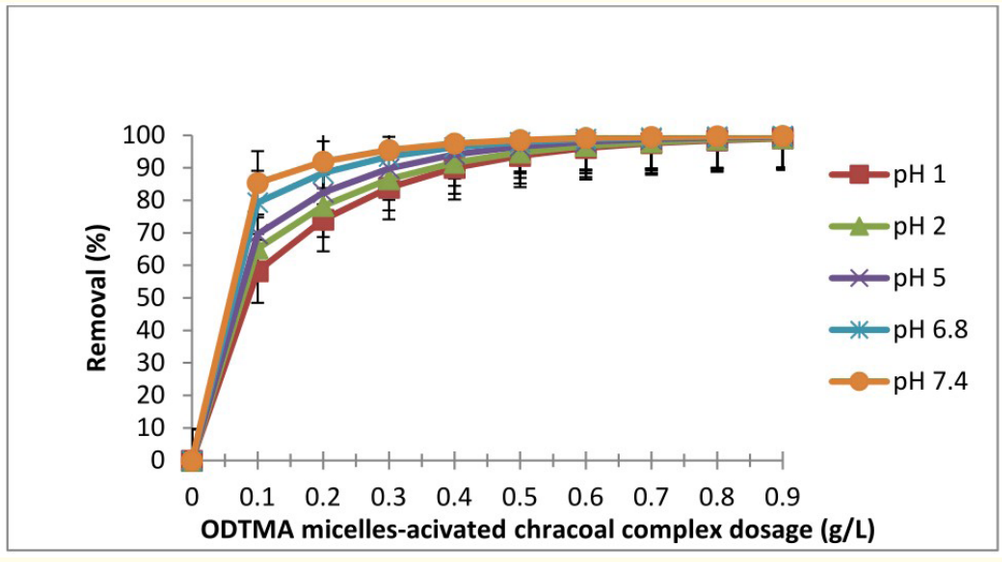

Figure 2: *Effect of pH and adsorbent dosage on the percent removal of paracetamol by OMAC complex. Initial concentration of paracetamol = 50 ppm, contact time = 4h, temperature = 25.0°C.*

At the optimum adsorbents dosage, figures 1 and 2 indicate that as the pH increases, an accompanied increase in the percent removal is observed. It is known that pH is one of the most important parameters that affect the percent removal of a given adsorbate by an

adsorbent. pH can affect both the surface charge of the adsorbent as well as the speciation of the adsorbate in solution. If the adsorbate is weak acid or weak base, the pH affects its ionization degree which leads to the existence of different species at a given pH [18]. Weak electrolytes, such as paracetamol, can exist in both ionized (a base) and nonionized (an acid) forms depending on the solution pH. The pKa value of paracetamol is 9.3 and hence, it can be concluded that at pH < 6, the acidic form is prevailing while at pH > 10, the basic form is the predominant one. At pH between 6 and 10, both forms coexist in solution and may interact with the surface of adsorbents. The interaction of each form with the adsorbent surface may favor or disfavor the adsorption process depending on the magnitude of the forces of attraction or repulsion [19].

As expected, pH 7.4 displayed the largest percent removal for both adsorbents. The lower adsorbent dosage at pH 7.4 for OMAC complex reveals that the forces of attraction between the ionized form of paracetamol and the surface are larger than those with activated charcoal. This is not surprising since the surface charge of the complex is positive, and coulombic attraction favors the adsorption process.

Effect of Contact Time

Figures 3 and 4 display the effect of contact time on the removal of paracetamol by activated carbon and OMAC complex, respectively. Inspection of figures 3 and 4 reveals that as pH increases, the rate of removal of paracetamol by both adsorbents increases. It can be concluded that the optimum contact time for both adsorbent is 160 minutes.

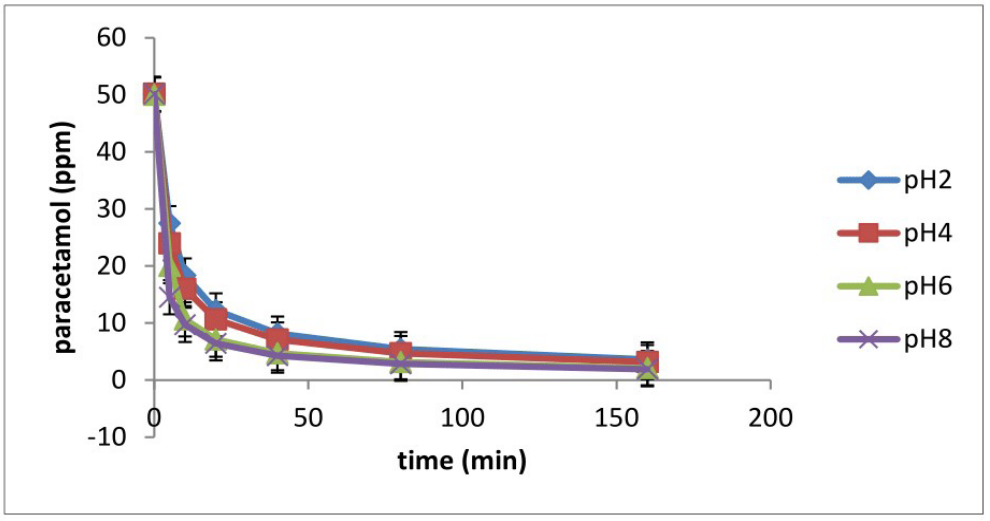

Figure 3: *Effect of contact time on the adsorption of paracetamol onto activated charcoal at different pH. Temperature = 25.0˚C and activated charcoal dosage = 0.5 g/L.*

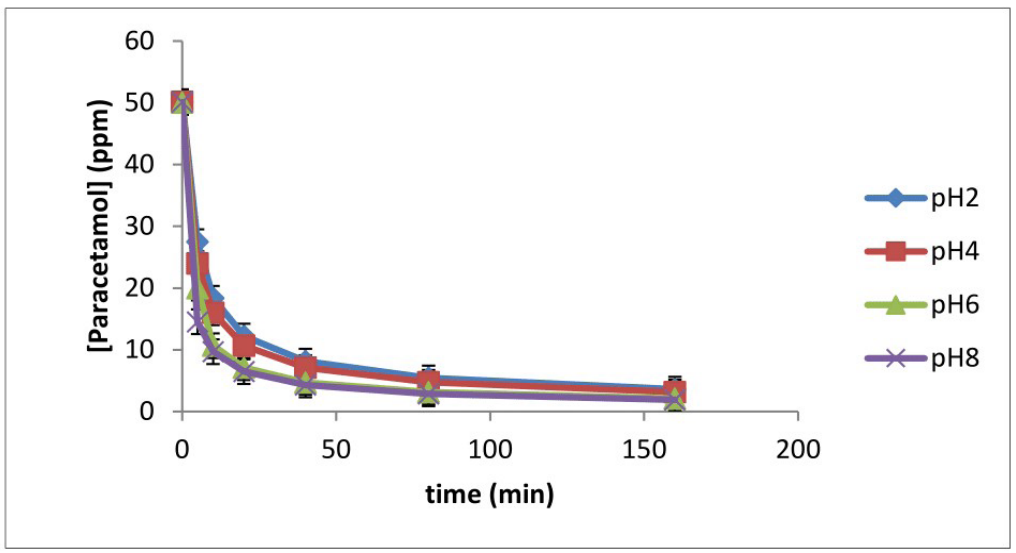

Figure 4: *Effect of contact time on the adsorption of paracetamol onto OMAC complex at different pH. Temperature = 25.0°C and OMAC complex dosage = 0.5 g/L.*

The results of the effect of contact time agree with the previous results of batch experiments. Both results show that at high pH, a higher percent of removal of paracetamol are obtained. Furthermore, these results support our pervious conclusion that OMAC complex is better detoxification agent than activated charcoal.

To better quantify the kinetics of adsorption of paracetamol by activated carbon and OMAC complex, two kinetic models were applied. These are the pseudo first order model [20] as a given in equation (1)

$$\frac{dQt}{dt} = K(Qe - Qt) \quad (1)$$

In which Qt is the amount of adsorbate adsorbed at time t, Qe is its value at equilibrium and k is a constant. and pseudo second order model [21].

Our data were fitted to the pseudo second order model [21] as given in equation (2)

$$\frac{t}{qt} = \frac{1}{k2qe2} + \frac{1}{qe} * t \quad (2)$$

In which q_t and Q_e are the amount of adsorbate adsorbed at time t and at equilibrium, respectively. k2 is the pseudo second order rate constant.

The regression coefficient (R2) of this model was higher than that of the pseudo first order model which means that the experimental data follows pseudo second order kinetics (Table 1).

Inspection of table 1 demonstrates that the rate constant increases with increasing the pH for both adsorbents. However, the rate of increase of OMAC complex is higher than that of activated charcoal, in accordance with our previous conclusion that OMAC complex is more effective as paracetamol detoxifying agent than activated charcoal.

Adsorption isotherms

Freundlich isotherm

The adsorption isotherms of paracetamol on both adsorbents were analyzed by both Freundlich and Langmuir models. Based on the linearity of the plots and R^2, the results were found to better fit Freundlich model than Langmuir model.

The Freundlich model is given by equation 3 [22]:

$$Qe = Kfce^{1/n} \quad (3)$$

Where C_e is equilibrium concentration of adsorb ate (ppm), Q_e is mass of adsorbate (mg) per mass of adsorbent (g) at equilibrium. K_f and n are Freundlich constants.

The model is tested by plotting log (Q_e) versus log (C_e). Table 2 summarizes the results for each adsorbent along with the correlation coefficient (R^2).

pH's	K_f (activated charcoal) (L/g)	R^2 (activated charcoal)	K_f (OMAC) (L/g)	R^2 (OMAC)
2	0.54	0.98	0.860	0.99
4	0.79	0.98	1.00	0.99
5.5	1.06	0.98	1.62	0.99
6.8	1.44	0.98	2.47	0.99
7.4	2.16	0.98	4.40	0.99
10	0.36	0.98	0.590	0.99

***Table 2**: Comparison between K_f of activated charcoal and OMAC complex at different pH. T= 25.0°C and adsorbent dosage 0.50g.*

Fruendlich isotherm was derived theoretically [23] and equation 4 was obtained.

$$Q_e = \frac{Q_{max}}{K} C^{1/n} \quad \text{---------- (4)}$$

This equation gives a physical meaning for K_f which indicates that it is directly proportional to Q_{max}. Inspection of table 2 reveals that K_f increases with increasing pH. Hence, it can be concluded that Q_{max} follows this trend. This can be explained on the bases of increasing the ion-dipole and electrostatic attraction between the ionized form of paracetamol and the surface of both adsorbents as pH increases.

Table 3 summarizes the results for n as function of pH for the different adsorbent. These parameters indicate the extent of adsorption. According to equation 2, the higher the value of n, the less the extent of adsorption.

PH	n	
	Activated charcoal	OMAC complex
2	1.33	1.38
4	1.37	1.33
5.5	1.41	1.39
6.8	1.45	1.52
7.4	1.53	1.7
10	1.23	1.2

Table 3: *Comparison between n of activated charcoal and OMAC complex as function of pH. T = 25.0˚C and adsorbents dosage 0.50g.*

The efficiency of adsorption is indicated by the value of n in equation 3. Favorable adsorption is obtained when n is between 0.5 and 3 [24]. Table 3 reveals that the values of n are all lower than 3 for both adsorbents. This indicates that the adsorption process for paracetamol on the two adsorbents is favorable at all pH values [25].

Conclusion

The combined results revealed that OMAC complex is an efficient adsorbent for paracetamol detoxification. The removal at various pH values showed a relatively large adsorption capacity, compared to activated charcoal. The large effectiveness and removal capacity is due to relatively strong interactions between the phenolic group of paracetamol and the positively charged OMAC complex.

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