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Detoxification from Paracetamol Using Charcoal-Micelles Complexes

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Detoxification from Paracetamol Using Charcoal-Micelles Complexes

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Jerusalem – Palestine

2017 / 1439

Dedication

This thesis is dedicated to my beloved mother, my lovely husband and my little son Jamal for their endless love, support and encouragement.

To my aunt Alia: because I owe it all to you. Many Thanks!

Declaration

I certify that the thesis submettied for the degree of master is the results of my own research, except where otherwise acknowledged, and that this thesis (or any part of the same) has not be submitted for a higher degree to any other university or institution

Signed:……..

Name: Alia Yousef Adel Qaddoumi

Date :17/12/2017

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 thesis we have investigated the efficiency of octadecyltrimethylammonium (ODTMA) micelles-activated charcoal complex that possesses a positive charge, a high surface area and a high affinity to capture paracetamol poisoning. Different physiological pH values were studied to evaluate the effect of pH on the removal of paracetamol by this adsorbent, effect of contact time and adsorption efficiency. The adsorption isotherm results demonstrate a best fit to Freundlich adsorption isotherm and adsorption kinetics follow a pseudo second order kinetics model. The results revealed that ODTMA charcoal micelles 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 ODTMA charcoal micelles complex can adsorb paracetamol in different forms at different pHs relative to charcoal, which renders the complex a better detoxificating agent than activated charcoal at physiological pH.

Acknowledgment

At the beginning and before anything I would like to thank god (Allah) for this success. As without his support, I would not have managed to accomplish this thesis.

I would like also to express my sincere gratitude to my advisor Prof. Rafik Karaman for the continuous support of my master thesis and related research, for his patience, motivation, and immense knowledge. His guidance helped me in all the time of research and writing of this thesis. I could not have imagined having a better advisor and mentor for my master thesis.

Besides my advisor, I would like to thank the rest of my thesis committee: Dr. Muhanad Qurie , Dr Mustaf Khamis , Ibrahim Ayyad for their insightful comments and encouragement, but also for the hard question which incented me to widen my research from various perspectives.

In this special day, I would like to thank all who supported me, encouraged and had the tolerance to wait for the success to be made.

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List of abbreviations

ODTMA: Octadecyltrimethylammonium bromide

Q max : The maximum mass of adsorbed paracetamol in mg per gram adsorbent.

Kf: Freundlich constant

Ce: Equilibrium concentration of paracetamol in mg L^{-1}

Qe : Equilibrium mass of adsorbed paracetamol

AM404 : N-arachidonoylaminophenol

GI : Gastrointestinal

Vd : Volume of distribution

NAPQI : N-acetyl-p-benzoquinone imine

CYP : Cytochrome P450

FHF : Fulminate hepatic failure

CMC : Critical micelles concentration

pH : Potential of hydrogen

rpm : Round per minute

CEC : Cation exchange capacity

Ppm: Part per million

Chapter One:

Introduction

1.1 Background

Paracetamol (*N*-acetyl-*p*-aminophenol; also known as acetaminophen) (figure 1.1) was first prescribed as an analgesic and antipyretic by Von Mering in 1893. In the 1940's Brodie and Axelrod confirmed its analgesic and antipyretic activity (Brodie, Lief et al. 1948). However, it has been gained popularity since 1949, after it was recognized that paracetamol is the major active metabolite of both acetanilide and phenacetin that were proved to be excessive toxic. Although paracetamol is a metabolite of both phenacetin and acetanilide but it does not share the renal or hematological toxicity of its precursors.

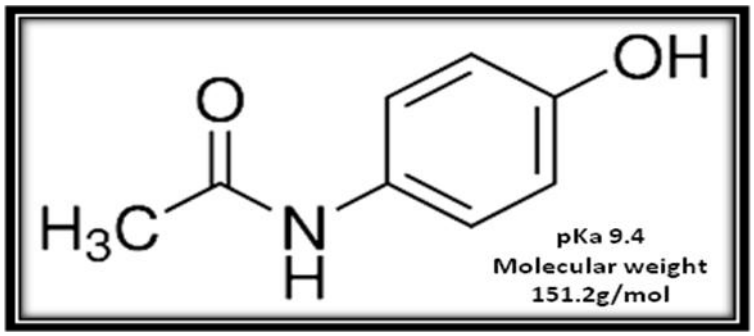

Figure 1.1 : structure of paracetamol

In the 1950 paracetamol has been a cornerstone of the management of mild to moderate pain and for the treatment of fever (Jahr and Lee 2010) and also first paracetamol product that combined with aspirin and caffeine was marketed in the same year.

Paracetamol is widely available, found in numerous products and in different dosage forms such as capsules, tablets, syrups, elixirs, drops and suppositories, also it is one of the most commonly used over-the-counter analgesics and in hundreds of prescription medications.

paracetamol one of the most commonly used oral analgesics and antipyretics. It has an excellent safety profile effective well tolerated when administered in proper therapeutic doses, but hepatotoxicity can occur after overdose or when misused in at-risk populations.

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(Jahr and Lee 2010).

1.2 Pharmacological effect and mechanism of action

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 inhibition of cyclooxygenase (COX), with a predominant effect on COX-2. Inhibition of COX enzymes prevents the metabolism of arachidonic acid to prostaglandin H_2, an unstable intermediate byproduct which is converted to pro-inflammatory compounds. In the central nervous system, inhibition of COX enzymes reduces concentrations of prostaglandin E_2, which lowers the hypothalamic set-point to reduce fever, and activation of descending inhibitory serotonergic pathways to produce analgesia (Anderson 2008, Jahr and Lee 2010).

While paracetamol shares the analgesic and antipyretic properties of other COX inhibitors such as aspirin and the non-steroidal anti-inflammatory drugs (NSAIDs), it does not

possess significant anti-inflammatory properties. Unlike aspirin, paracetamol does not inhibit thromboxane and, as a result, does not alter platelet aggregation.

Recent studies have suggested that paracetamol may work through additional mechanisms, including modulation of the body's endogenous cannabinoid system. One of the metabolites of paracetamol (*N*-arachidonoylphenolamine or AM404) inhibits the uptake of anandamide, increasing concentrations of endogenous cannabinoids. These substances can both modulate serotonergic descending pain pathways and lower body temperature. Other investigators have suggested that paracetamol produces direct inhibition of *N*-methyl-*D*-aspartate (NMDA) receptors, blocking substance P-dependent synthesis of nitric oxide through the *L*-arginine-nitric oxide pathway and reducing nociception. These proposed mechanisms are not likely exclusive; in fact, they may all be components of an interwoven series of responses to paracetamol administration (Anderson 2008, Jahr and Lee 2010).

1.3 Pharmacokinetic properties of paracetamol

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 (Forrest, Clements et al. 1982). Distribution is rapid with a volume of distribution (Vd) of about 0.9 L/kg and minimal protein binding at therapeutic concentrations (Forrest, Clements et al. 1982). 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. Approximately 85% of a therapeutic dose undergoes phase II conjugation to sulfated and glucoronidated metabolites that are eliminated by the renal. Of these two pathways, glucoronidation is predominant in adults, whereas sulfation predominates in children up to about 12 years of age. Up to 10% of paracetamol undergoes phase I oxidation to a reactive intermediate, *N*-

acetyl-para-benzoquinone imine (NAPQI) (Forrest, Clements et al. 1982, Gelotte, Auiler et al. 2007), which is normally conjugated with glutathione to nontoxic cysteine and mercaptuate metabolites. Cytochrome 2E1 is the primary cytochrome p450 (CYP) enzyme responsible for this oxidation(Gelotte, Auiler et al. 2007).

1.4 The mechanism of toxicity

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). The second theory, the oxidative stress in the cell and ultimately leading to its demise(Gibson, Pumford et al. 1996).

At supra-therapeutic doses of paracetamol (>4 g), sulfation becomes saturated with proportional increases in both glucoronidation and, more significantly, oxidation to NAPQI. Smaller proportions of paracetamol are eliminated unchanged in the urine and by ring oxidation to a catechol derivative (Figure 1).

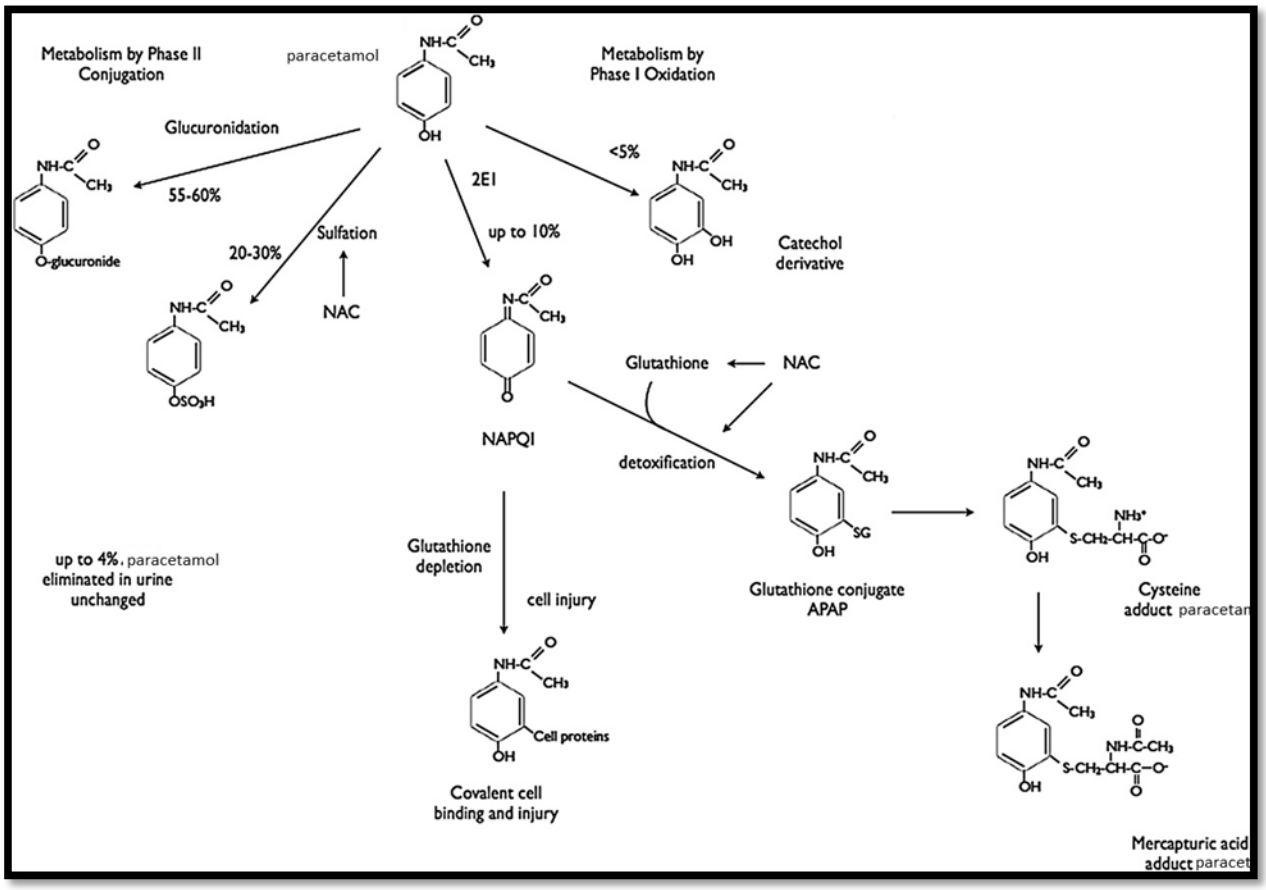

Figure 1.2 Metabolism of paracetamol

At toxic doses of paracetamol 150- 250 mg per kg, the continued production of NAPQI eventually results in the depletion of glutathione. Once glutathione stores have been depleted by about 70%, NAPQI binds to cellular proteins and leads to cell injury (Mitchell, Jollow et al. 1973). Glutathione depletion is only one of a cascade of intracellular events that includes mitochondrial oxidative stress, generation of reactive oxygen and nitrogen species, activation of stress proteins and gene transcription mediators, and mobilization of the liver's innate immune system. The balance between these numerous pathways ultimately determines whether there is recovery or cell death (Jones, Lemasters et al. 2010). Mitochondrial failure seems to be the terminal event heralding cell death (Kaplowitz, Shinohara et al. 2008). Although apoptotic pathways are activated, cell death is typically necrotic because mitochondrial failure precludes ordered cell death. The role of these various pathways in hepatocellular injury remains an area of active research.

Zone 3 hepatocytes, rich in CYP 2E1, are most susceptible to injury and this leads to the characteristic centrilobular pattern of hepatic necrosis seen with paracetamol. Patients on CYP2E1-inducing agents, such as ethanol, isoniazid, or St. John's wort, may be at an increased risk of toxicity because of increased NAPQI production, although there is no compelling data that this occurs at therapeutic dosages of paracetamol (Rumack 2002). Recommended maximum therapeutic dosages of paracetamol are 4 g daily in an adult and 50 to 75 mg/kg/d in children.

1.5 Treatment of paracetamol poisoning

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 (Singer, Carracio et al. 1995). Maximal liver injury typically peaks between 3 to 5 days with jaundice, coagulopathy, and encephalopathy (Rumack and Matthew 1975). Recovery or progression to FHF (Fulminent hepatic failure) 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 (Waring, Jamie et al. 2010)

1.5 Objectives

- To evaluate if the use of ODTMA-charcoal micelles complex could be optimized and rationalized compared with charcoal.
- To assess the efficacy of ODTMA-charcoal micelles complex in decreasing absorption of paracetamol from body in supra-therapeutic overdose compared with charcoal.
- To investigate the amount of ODTMA-charcoal micelles complex used in the clinical departments for gastrointestinal decontamination.
- Removal overdose of paracetamol in human body
- Investigate the removal efficiency by

1. different pH
2. Contact time
3. Application of different kinetic equations
4. Application of different adsorption isotherm

1.6 Thesis outline

The organization of the thesis and experimental approaches: the first chapter provides a comprehensive review of the paracetamol history, mechanism of action, pharmacokinetics and its overdose, the second chapter includes the literature review on ODTMA-charcoal micelles complex which is one of the effective routs of removal of paracetamol overdose. The third chapter includes materials, instrumentation and methods used in sampling, sample treatment and analysis. The fourth chapter includes results and discussion of the efficacy of ODTMA-charcoal micelles complex compared to activated charcoal. The fifth chapter includes conclusion. The sixth chapter is the references list.

Chapter Two:

Literature review:

Paracetamol poisoning is among the most common causes of medication related poisoning and death. It may occur following a single acute ingestion or through the repeated ingestion of supratherapeutic amounts. The evidence for all interventions for paracetamol overdose is weak. Activated charcoal, gastric lavage, ipecacuanha and *N*- acetylcysitine (as an antidote) are able to reduce absorption of paracetamol if started within one to two hours of paracetamol ingestion, but the clinical benefit is unclear. Activated charcoal seems to be the best choice if the patient is compliant.

Activated charcoal can absorb toxic substances in the gastrointestinal tract and prevent their absorption into the circulation. The adsorptive capacity of activated charcoal depends on many factors including physicochemical properties of activated charcoal, solubility and pH of toxic substances and presence of gastric content. (Physicochemical properties include particle size, pore size and surface area of the activated charcoal). No relevant evidence has been demonstrated for the clear influence of any single physicochemical property of activated charcoal on its adsorptive capacity. Charcoal can be derived from

many substances such as coconut shell, peat, lignite, and wood. Then, it is activated by heating in hot stream or air. The activation process causes the charcoal to become small size particles with an internal pore structure. Different kinds of activated charcoal, which are from different productions, have different physicochemical properties and different adsorptive capacity (Watson 1987, al-Shareef, Buss et al. 1990).

The British Pharmacopeia (BP) and the United States Pharmacopeia (USP) specify only that medicinal activated charcoal must meet standards for adsorption, contamination and purity. The surface area typically ranges from 950-2,000 m^2/g. Other physicochemical properties are not defined (Chyka, Seger et al. 2005).

Adsorption results from Van der Waals forces and adsorption of the solute (drug or poison) can occur if charcoal is sufficiently present. The poison or the drug ingested adheres to the surface of the activated charcoal and since the charcoal cannot be absorbed through the digestive tracts membranes, it passes out of the body eliminating the poisons with it.

Paracetamol is the most common drug poisoning over the world. Its toxicity is dose-dependent. Paracetamol at the dose of more than 150 mg/kg has been reported to have association with risk of developing hepatotoxicity. In clinical practice, plasma paracetamol concentration is the best predictor of its toxic severity.

In conclusion, of several studies the authors have demonstrated the efficacy of the activated charcoal in reducing gastrointestinal absorption of the supra-therapeutic dose of paracetamol. The activated charcoal is safe and should be administered early in treating human poison ingestion.

One of the studies was about 50 grams of the charcoal reduced paracetamol absorption by 56% if administered hour after a 3-gram dose of the drug, but only 22% if the activated carbon was administered 2 hours after ingestion. In another study, Green reported a

reduction in paracetamol (4 grams) absorption by 30.5% after an administration of 50 grams of activated charcoal 1 hour after the ingestion of the drug, and a 7.7% decrease in absorption was observed when the charcoal was administered 2 hours after the ingestion of the same amount of paracetamol (Green, Grierson et al. 2001). An interesting feature of this study was an analysis of the reduction in drug absorption plotted against the activated charcoal/drug ratio, which suggested that the optimal dose of activated charcoal may be much greater than the conventional 10:1 ratio. Another intriguing finding was that the reduction in drug exposure by activated charcoal was correlated with the drug's volume of distribution. This is not surprising since drugs with a large volume of distribution tend to be nonpolar and poorly water soluble, physiochemical characteristics that are likely to increase a compound's adsorptive binding to charcoal.

Recently Karaman's group have been engaging in studying the removal of a variety of commonly used drugs from waters by novel modified bentonite and activated charcoal; clay-micelles ODMTA complex and activated carbon-micelles ODTMA complex, respectively. The micelle-clay and micelle-activated carbon composites which were used in the drug's removal are positively charged have large surface area and include large hydrophobic domains. The organic cation, octadecyltrimethylammonium (ODTMA) has an alkyl chain of 18 carbon atoms; its critical micelle concentration (CMC) is 0.3 mM (Mishael, Undabeytia et al. 2002, Polubesova, Zadaka et al. 2006). 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 (Octadecyltrimethylammonium) as monomers (Figure 2).

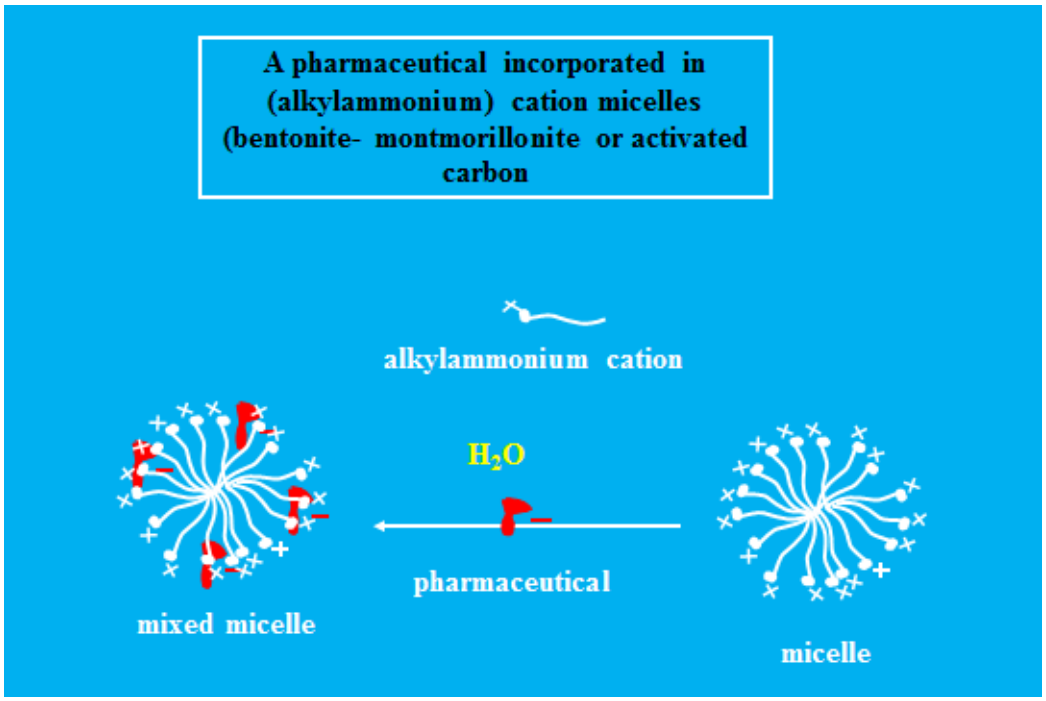

Figure 2.1 Adsorption of a drug or pharmaceutical on a clay mineral-micelle complex or activated carbon-micelle complex (Karaman, Khamis et al. 2012, Qurie, Khamis et al. 2013).

Using both micelle complexes they have already efficiently removed a variety of pharmaceuticals from water including: naproxen, diclofenac sodium, mefenamic acid, diazepam, amoxicillin, cefuroxime axetil and ibuprofen. Further, it was demonstrated that the removal efficiency of these modified adsorbents is much higher than that of bentonite and activated carbon. In addition, preliminary results of *in vitro* spiking of different pharmaceuticals such as metformin, paracetamol and aspirin in 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 (Karaman, Khamis et al. 2012, Qurie, Khamis et al. 2013)

Chapter Three:

Chemicals:

All chemicals were of analytical grade. The Octadecyltrimethylammonium (ODTMA) 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.

3.1 Instrumentation

UV-Spectrophotometer

The concentrations of samples were determined spectrophotometrically (UV-spectrophotometer, Model: UV-1601, Shimadzu, Japan) by monitoring the absorbance at λmaxfor each drug

3.2 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).

3.3 Centrifuge and Shaker

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

3.4 Dissolution apparatus

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

3.5 Methods

3.5.1 ODTMA charcoal complex preparation:

The micelles-carbon complex prepared by stirring 20mM of ODTMA with 10g/L charcoal for 72 h at 40 C . 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 min at 15,000g, supernatants were discarded, and the complex was lyophilized.

The effect of different pH's (1, 2, 5, 6.8, 7.4) on the adsorption of paracetamol onto powder activated charcoal

Stock solution and standard preparation

Stock solution was prepared by dissolving paracetamol standard in distilled water to concentration 500 ppm for the use in calibration curve

3.5.2 Calibration curve:

The following diluted solutions were prepared from the stock solution of paracetamol (500ppm, 250ppm, 200ppm, 100ppm, 50ppm, 25ppm,zero). The absorption of each solution was determined by using UV-spectrophotometer (λ max).

3.6 Sample preparing

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

The effect of different PH's (1, 2, 5, 6.8, 7.4) on the adsorption of paracetamol onto ODTMA charcoal micelles complex

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

The Effect of Contact Time on the percentage of paracetamol removed by the activated charcoal at different adjusted pH values (2, 4, 6, and 8).

3.7 Stock solution:

Stock solution was prepared by dissolving paracetamol standard in distilled water to concentration 100ppm for the use in calibration curve.

Sample preparing: adding 200 ml stock solution diluted to 50ppm in 250ml conical flask and shaken with an electronic shaker at 250rpm ,when the shaker start a sample is taken at zero time, after that 0.5 grams of activated charcoal added , every (0 ,5,10 ,20 ,40 ,80 ,160)minuets a sample was taken and filtered to detect the absorbance of paracetamol at 245nm.

The Effect of Contact Time on the percentage of paracetamol removed by the ODTMA-charcoal complex at different adjusted pH values

Stock solution was prepared by dissolving paracetamol standard in distilled water to concentration 100ppm for the use in calibration curve.

Sample preparing: adding 200 ml stock solution diluted to 50ppm in 250ml conical flask and shaken with an electronic shaker at 250rpm ,when the shaker start a sample is taken at zero time, after that 0.5 grams of ODTMA-charcoal complex added , every (0 ,5,10 ,20 ,40 ,80 ,160)minuets a sample was taken and filtered to detect the absorbance of paracetamol at 245nm.

3.8 Adsorption studies of paracetamol onto activated charcoal

Experiments were performed in 250 ml Erlenmeyer (conical) flasks containing 0.5 gram of activated charcoal, with diluted solutions (1000ppm, 500ppm, 200ppm, 100ppm, 50ppm, 30ppm, 10ppm) that were prepared from the 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 filtrated to detect the absorbance of paracetamol at 245nm.

Adsorption studies of paracetamol onto ODTMA micelles charcoal complex

Experiments were performed in 250 ml Erlenmeyer (conical) flasks containing 0.5 gram of ODTMA-charcoal complex, with diluted solutions (1000ppm, 500ppm, 200ppm, 100ppm,

50ppm, 30ppm, 10ppm) that were prepared from the 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 filtrated to detect the absorbance of paracetamol at 245nm.

Chapter four:

Results and discussion

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

4.1 Effect of different pHs values on the adsorption of paracetamol on to activated charcoal vs. ODTMA micelles charcoal complex

4.1.1 Calibration curve of paracetamol using UV-visible spectrophotometer at pH 1:

The calibration curve was obtained by plotting the absorbance of paracetamol versus its concentration in ppm at pH 1 (table 4.1) illustrated in figure (4.1). The figure shows excellent linearity between the two variables with correlation coefficient (R^2= 0.999).

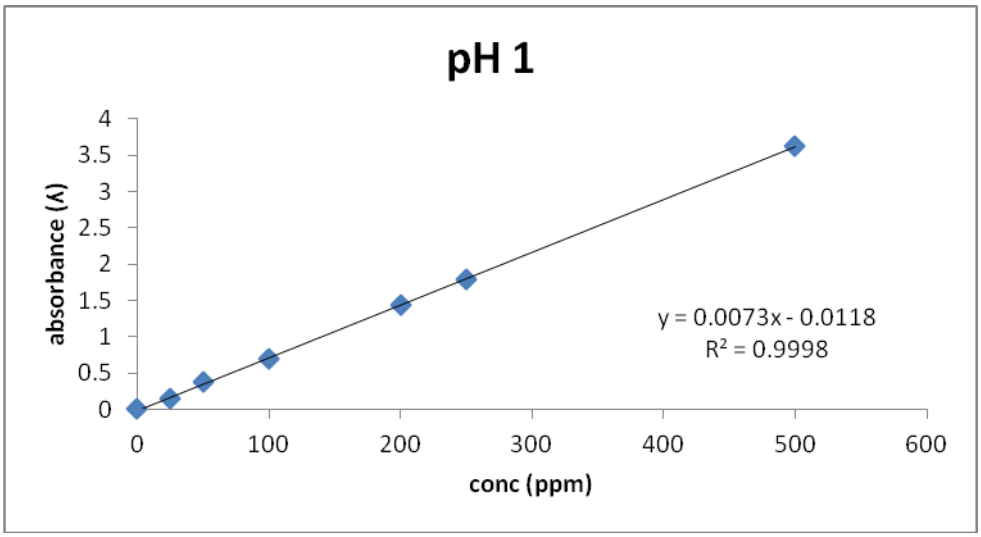

Figure 4.1 calibration curve of paracetamol using UV spectrophotometer at pH1.

4.1.1.2 The removal efficiency of paracetamol on to activated charcoal vs. ODTMA micelles charcoal complex at pH 1:

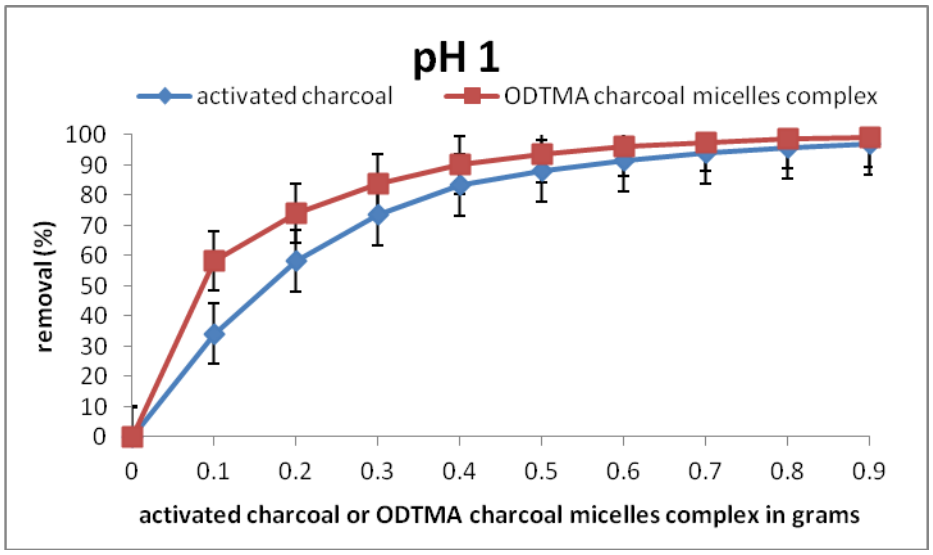

Figure 4.2: The effect of pH1 on the removal percentage of paracetamol on to activated charcoal vs. ODTMA micelles charcoal complex in grams, Initial concentration of paracetamol = 50 ppm, contact time = 4 h, temperature = 25.0 C°.

4.1.2.1 Calibration curve of paracetamol using UV-visible spectrophotometer at pH 2:

The calibration curve was obtained by plotting the absorbance of paracetamol versus its concentration in ppm at pH 2 (table 4.3) illustrated in figure (4.3). The figure shows excellent linearity between the two variables with correlation coefficient (R^2= 0.999).

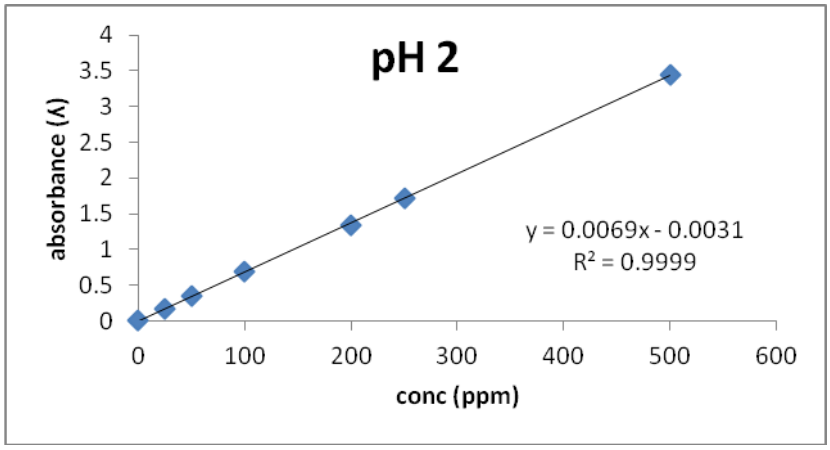

Figure 4.3 calibration curve of paracetamol using UV spectrophotometer at pH2.

4.1.2.2 The removal efficiency of paracetamol on to activated charcoal vs. ODTMA micelles charcoal complex at pH 2:

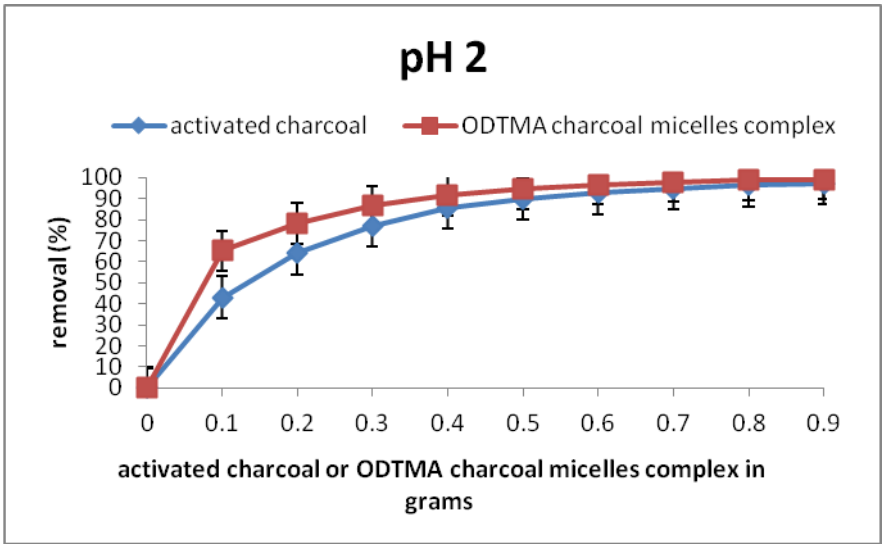

Figure 4.4 The effect of pH 2 on the removal percentage of paracetamol on to activated charcoal vs. ODTMA micelles charcoal complex in grams, Initial concentration of paracetamol = 50 ppm, contact time = 4 h, temperature = 25.0 C°.

4.1.3.1 Calibration curve of paracetamol using UV-visible spectrophotometer at pH 5.

The calibration curve was obtained by plotting the absorbance of paracetamol versus its concentration in ppm at pH 5 (table 4.5) illustrated in figure (4.5). The figure shows excellent linearity between the two variables with correlation coefficient (R^2= 0.999).

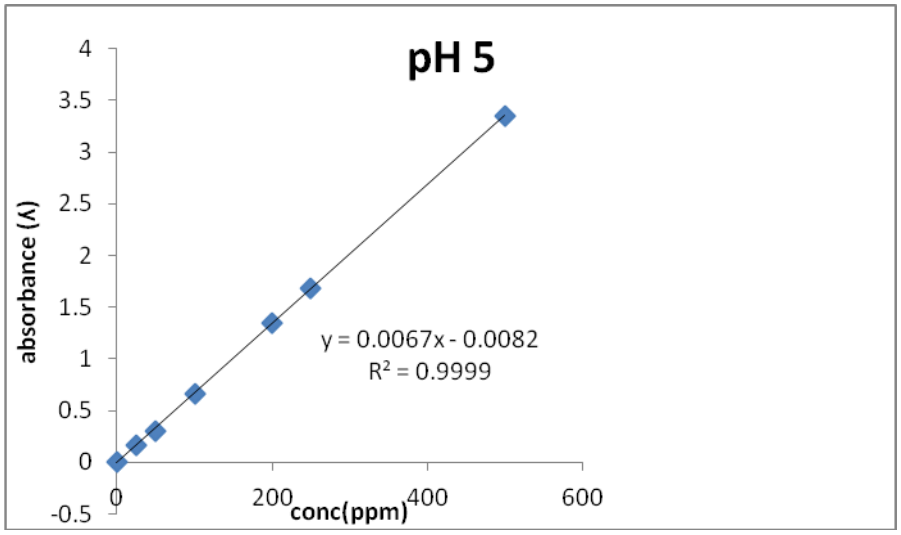

Figure 4.5 calibration curve of paracetamol using UV spectrophotometer at pH5.

4.1.3.2 The removal efficiency of paracetamol on to activated charcoal vs. ODTMA micelles charcoal complex at pH 5:

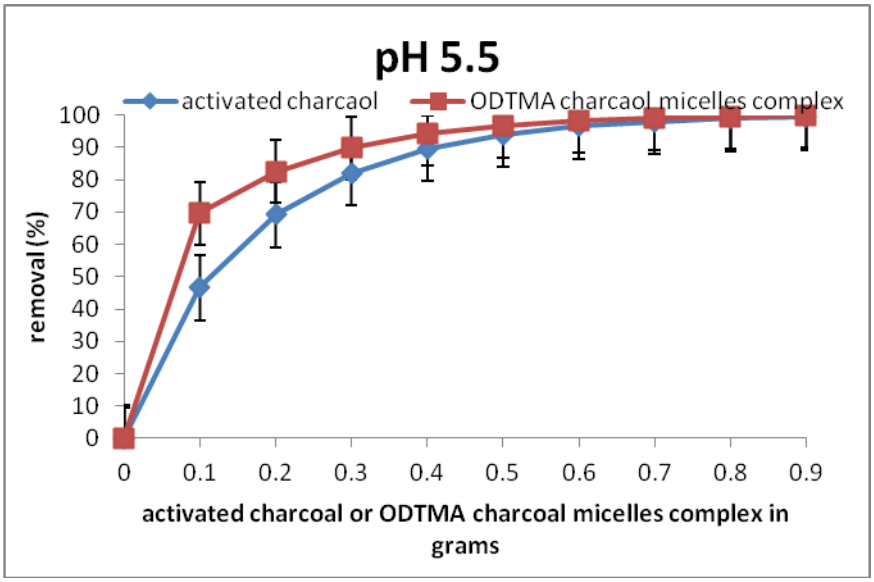

Figure 4.6 : The effect of pH 5 on the removal percentage of paracetamol on to activated charcoal vs. ODTMA micelles charcoal complex in grams, Initial concentration of paracetamol = 50 ppm, contact time = 4 h, temperature = 25.0 C°.

4.1.4.1 Calibration curve of paracetamol using UV-visible spectrophotometer at pH 6.8:

The calibration curve was obtained by plotting the absorbance of paracetamol versus its concentration in ppm at pH 6.8 (table 4.7) illustrated in figure (4.7). The figure shows excellent linearity between the two variables with correlation coefficient (R^2= 0.999).

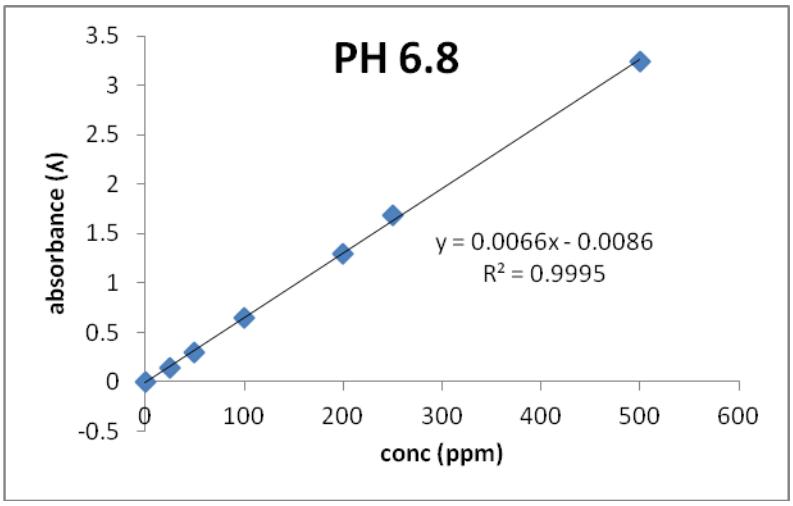

Figure 4.7 calibration curve of paracetamol using UV spectrophotometer at pH6.8.

4.1.4.2 The removal efficiency of paracetamol on to activated charcoal vs. ODTMA micelles charcoal complex at pH 6.8 :

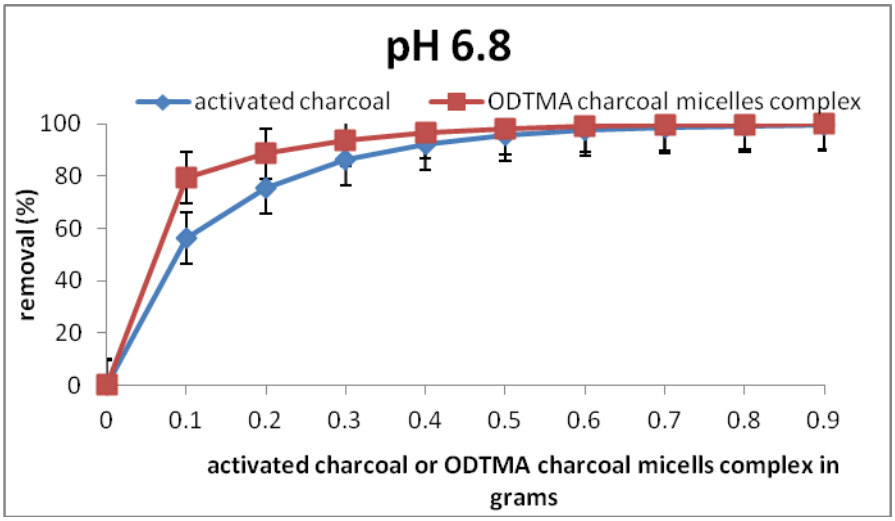

Figure 4.8 The effect of pH 6.8 on the removal percentage of paracetamol on to activated charcoal vs. ODTMA micelles charcoal complex in grams, Initial concentration of paracetamol = 50 ppm, contact time = 4 h, temperature = 25.0 C°.

4.1.5.1 Calibration curve of paracetamol using UV-visible spectrophotometer at pH 7.4:

The calibration curve was obtained by plotting the absorbance of paracetamol versus its concentration in ppm at pH 7.4 (table 4.9) illustrated in figure (4.9). The figure shows excellent linearity between the two variables with correlation coefficient (R^2= 0.999).

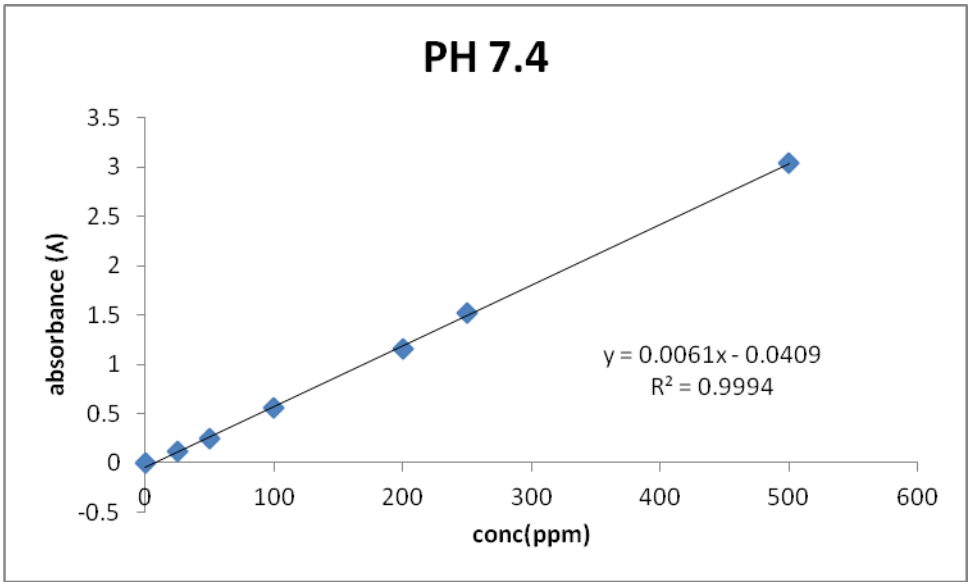

Figure 4.9 calibration curve of paracetamol using UV spectrophotometer at pH7.4.

4.1.5.2 The removal efficiency of paracetamol on to activated charcoal vs. ODTMA micelles charcoal complex at pH 7.4 :

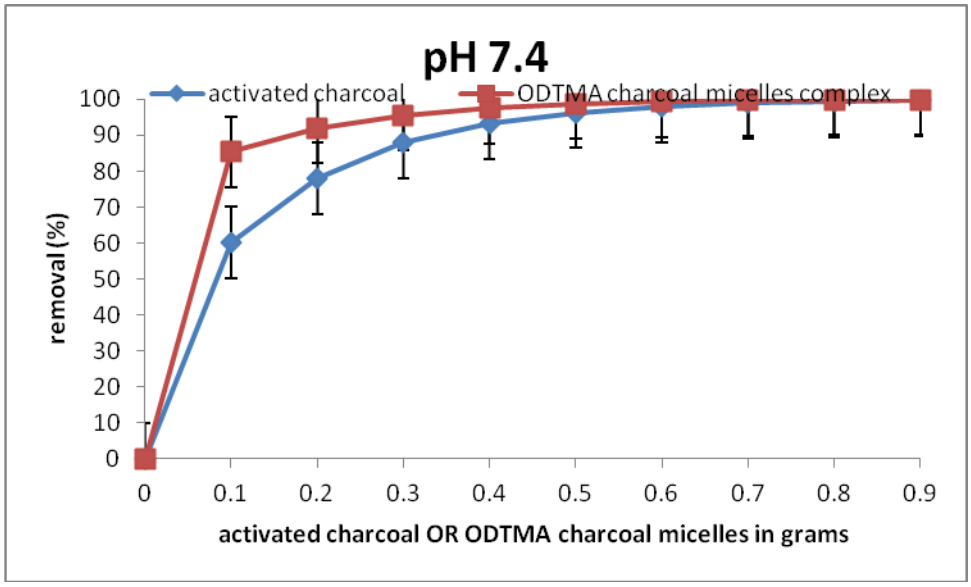

Figure 4.10 The effect of pH 7.4 on the removal percentage of paracetamol on to activated charcoal vs. ODTMA micelles charcoal complex in grams, Initial concentration of paracetamol = 50 ppm, contact time = 4 h, temperature = 25.0 C°.

Figures 4.12 and 4.11 display the results of the effect of pH and adsorbent dosage on the percent removal of paracetamol by activated charcoal and by ODTMA charcoal micelles complex. Inspection of these 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 ODTMA charcoal micelles complex, respectively. These results indicate that the complex is far more efficient in removing paracetamol than activated charcoal at all pH's

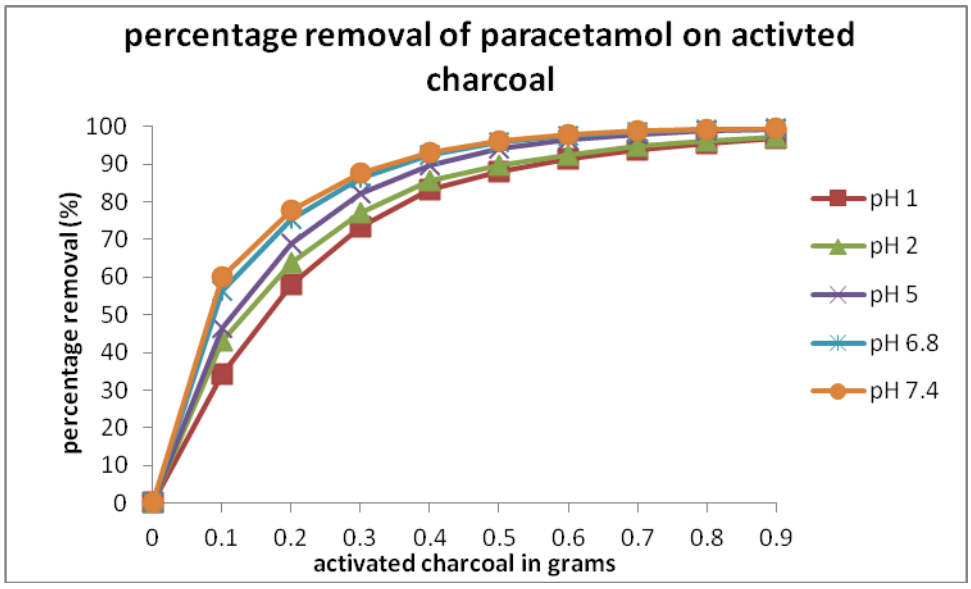

Figure 4.11 The effect of different pH values on the removal efficiency of paracetamol on to activated charcoal in grams Initial concentration of paracetamol = 50 ppm, contact time = 4 h, temperature = 25.0 C°.

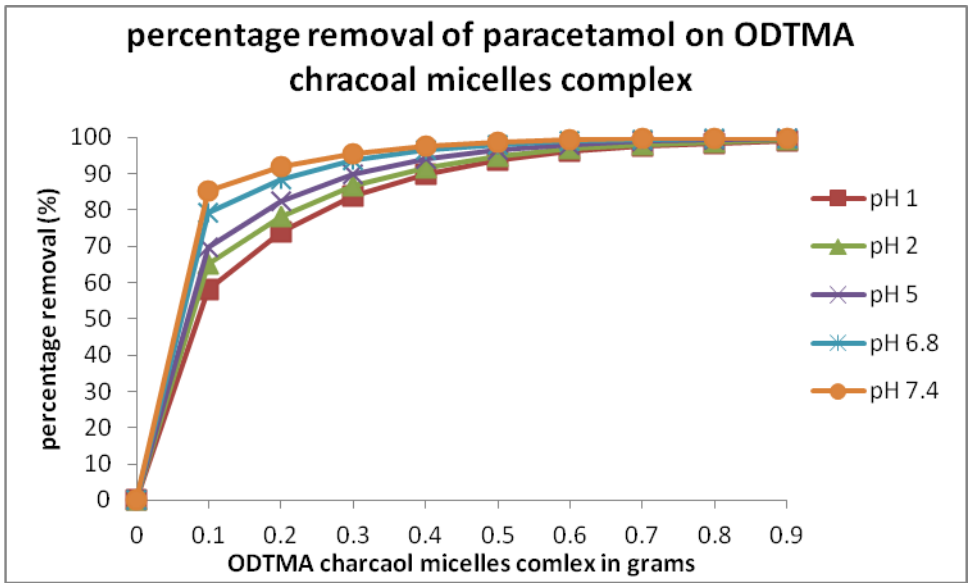

Figure 4.12: The effect of different pH values on the removal efficiency of paracetamol on to ODTMA micelles charcoal complex in grams Initial concentration of paracetamol = 50 ppm, contact time = 4 h, temperature = 25.0 C°.

At the optimum adsorbents dosage, figures, 4.11 and 4.12 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 degree of ionization which lead to the existence of different species at a given pH (Cristina Ferreira, M. Couto Junior et al. 2015) Weak electrolytes, such as paracetamol, can exist in both ionized (a base) and nonionized (an acid) forms dependening 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 (Boehm 1989).

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

Science pH 7.4 gives a better removal for ODTMA charcoal micelles complex, this can give another option instead of ingest activated charcoal or ODTMA charcoal micelles complex it can be used through hemodialysis and hemoperfusion these methods of choice for the rapid and efficient removal of selected drugs or poisons. Hemodialysis is a procedure in which the patient's blood is circulated extracorporeally over the surface of a semipermeable membrane. Low molecular weight solutes, including poisons and drugs, diffuse down a concentration gradient across the membrane into a standard or modified dialysis solution. Hemoperfusion refers to a procedure in which the patient's blood is percolated directly through a column or cartridge of activated charcoal or resin. Toxins are

removed from the blood by the direct adsorption of the drug onto the activated charcoal or resin.

Figure 4.10 display pH 7.4 which is the physiological pH of blood in human body, from 0.7 to 0.9 grams gives the highest percentage removal and also gives similar values approximately 99% to ODTMA charcoal micelles complex and 99% activated charcoal. Whereas the results from 0.1 to 0.6 gives a higher percentage removal in ODTMA charcoal micelles complex in contrast to activated charcoal, which means that ODTMA charcoal complex when used in a small amount such as 0.1 to 0.2 grams gives better removal (85 % and 94% respectively) than activated charcoal 0.1 to 0.2 in grams (60% and 78% respectively).

pH 6.8 is the physiological pH of intestine in human body, from 0.7 to 0.9 grams gives the highest percentage removal and also gives a similar values approximately 99% to ODTMA charcoal micelles complex and 99% activated charcoal. Whereas the results from 0.1 to 0.6 gives a higher percentage removal in ODTMA charcoal micelles complex in contrast to activated charcoal, which means that ODTMA charcoal complex when used in a small amount such as 0.1 to 0.2 grams gives better removal (79.40 % and 88.49% respectively) than activated charcoal 0.1 to 0.2 in grams (56.2% and 75.53 % respectively).

pH 2 is the physiological pH of gastric track in human body, from 0.7 to 0.9 grams gives the highest percentage removal and also gives a similar values approximately 99% to ODTMA charcoal micelles complex and 99% activated charcoal. Whereas the results from 0.1 to 0.6 gives a higher percentage removal in ODTMA charcoal micelles complex in contrast to activated charcoal, which means that ODTMA charcoal complex when used in a small amount such as 0.1 to 0.2 grams gives better removal (65.17 % and 78.36 % respectively) than activated charcoal 0.1 to 0.2 in grams (43.1% and 65.17% respectively).

Recently qarman group have been engaging in studying the removal of variety of commonly used drugs from waters first study was by using clay micelle complex (ODTMA) to remove cefuroxime axetil the removal was about 95.2%(Awwad, Al-Rimawi et al. 2015) and was achieved after three hours (Awwad, Al-Rimawi et al. 2015),second study by using micelle-clay complex (ODTMA) to remove Amoxicillin Trihydrate the removal was about 98.5% and was achieved after three hours(Awwad, Al-Rimawi et al. 2015), another study was by using clay micelle complex (ODTMA) to remove diclofenac the removal was 99% (Karaman, Khamis et al. 2012), last study also by using micelle-clay complex (ODTMA) to remove chlorpyrifos 90%(Karaman, Khamis et al. 2016) . Qaraman group used the ODTMA micelles – clay complex where as we used ODTMA charcoal micelles complex the results for removal efficiency shows approximately same percentage such like diclofenac but it show a superior efficiency when using ODTMA micelles charcoal complex to the removal paracetamol .Other groups also studied the removal of paracetamol using other adsorbant such as deried cellulose the percentage removal was 58.1% and activated charcoal 94.5% (Syed draman, Batra'azman et al. 2015), another group found that percentage removal of paracetamol was 96.6 % (hussain 2010), our results comparing to others show a superior efficiency of percentage removal with 99.9 % .

4.2. Kinetic studies

Figures 4.13 and 4.14 display the effect of contact time on the removal of paracetamol by activated carbon and ODTMA charcoal micelles complex, respectively. Inspection of these figures 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 min.

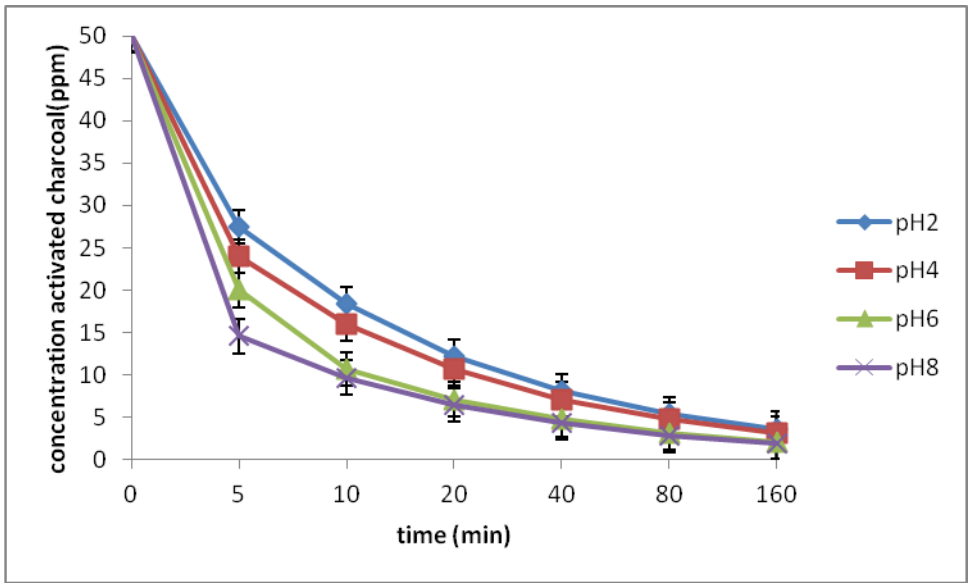

Figure 4.13 kinetic adsorption of paracertamol onto activated charcoal at different PH values (◊ pH 2, ▪ pH 4, Δ pH 6,× pH 8) . tempreture = 25.0 ˚ C and activated charcoal dosage = 0.5 g/L .

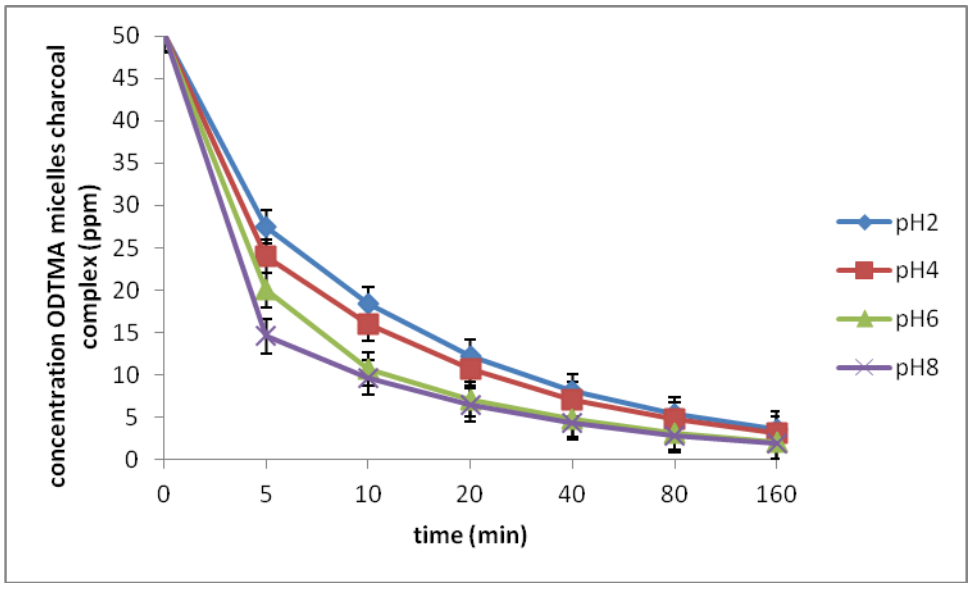

Figure 4.14 kinetic adsorption of paracertamol onto ODTMA micelles charcoal complex at different PH values (◊ pH 2, ▪ pH 4, Δ pH 6, × pH 8) . Temperature = 25.0 ˚ C and ODTMA micelles charcoal complex dosage = 0.5 g/L.

As the contact time increasing the concentration decrease showing an increase in the removal percentage, figure 4.13 and 4.14 represent the effect of contact time on both activated charcoal and ODTMA micelles complex.

The effect of contact time agreement with the previous results of batch experiment using different pH values shows a higher percentage of removal at pH 7.4, pH8 and also determines that ODTMA charcoal micelles complex better than activated charcoal.

To better quantify the kinetics of adsorption of paracetamol by the activated carbon and ODTMA charcoal micelles complex, tow kinetic models were applied. the pseudo first order model (Brunauer 1938)

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

in which *Qt* is the amount of adsorbate adsorbed at time *t*, *Q*e is its value at equilibrium and *k* is a constant.

the pseudo second order model (Temkin 1940).

4.2.1 Pseudo second order model

Our data were fitted to the pseudo second order model (Temkin 1940) as given in equation 1:

$$\frac{t}{qt} = \frac{1}{k2qe2} + \frac{1}{qe} * t$$

In which q_t *and* Q_e are the amount of adsorbate adsorbed at time t and at equilibrium, respectively. k_2 is the pseudo second order rate constant.

The regression coefficient (R^2) of this model was higher than that of the pseudo first order model which means the experimental data follow pseudo second order kinetics (Table 5).

Inspection of Table 4.5 reveals that the rate constant increases with increasing pH for both adsorbents. However, the rate of increase of ODTMA charcoal micelles complex is higher than that of activated charcoal, in accordance with our previous conclusion that ODTMA charcoal micelles complex in more effective as paracetamol detoxifying agent than activated charcoal.

The regression coefficient (R^2) of second pseudo order model was higher than that of the pseudo first order model which means the experimental data follow pseudo second order kinetics (Table 5).

Table 4.1 pseudo second order kinetic parameters of paracetamol on activated charcoal in comparison to ODTMA micelles charcoal complex at pH 2

PH 2		
adsorbent	activated charcoal	ODTMA micelles
time (minutes)	t/qt	t/qt
5	0.18	0.22
10	0.55	0.93
20	1.64	3.93
80	14.72	69.24

Table 4.2 pseudo second order kinetic parameters of paracetamol on activated charcoal in comparison to ODTMA micelles charcoal complex at pH 4.

PH 4		
adsorbent	activated charcoal	ODTMA micelles
time (minutes)	t/qt	t/qt
5	0.21	0.26
10	0.63	1.07
20	1.88	4.5
80	16.89	79.42

Table 4.3 pseudo second order kinetic parameters of paracetamol on activated charcoal in comparison to ODTMA micelles charcoal complex at pH 6.

PH 6		
adsorbent	activated charcoal	ODTMA micelles
time (minutes)	t/qt	t/qt
5	0.25	0.31
10	0.94	1.82
20	2.81	7.65
80	25.33	135.01

Table 4.4 pseudo second order kinetic parameters of paracetamol on activated charcoal in comparison to ODTMA micelles charcoal complex at pH 8.

PH 8		
adsorbent	activated charcoal	ODTMA micelles
time (minutes)	t/qt	t/qt
5	0.34	0.74
10	1.03	3.1
20	3.1	13.01
80	27.86	229.52

Table 4.5 the pseudo second kinetic parameters at different pH values

pH	k (ODTMA)	R^2 (ODTMA)	K (activated charcaol)	R^2 (activated charcoal)
2	0.9648	0.9822	0.2005	0.9915
4	1.1066	0.9822	0.23	0.9914
6	1.8821	0.9824	0.3454	0.9915
8	3.1982	0.9822	0.3795	0.9917

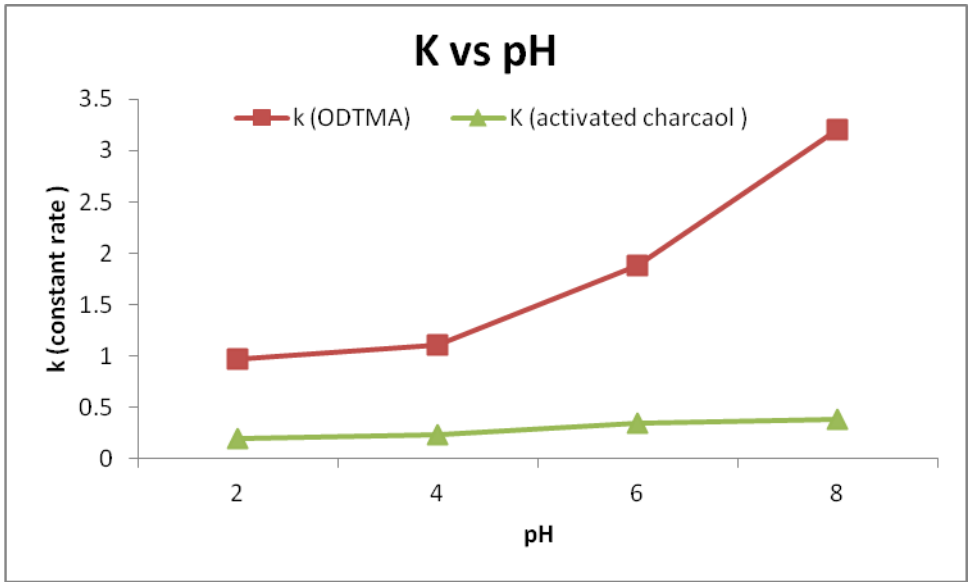

Figure 4.15 the dependence of K (constant rate) at different pH values.

The pseudo second order rate constant k2 obtained at pH 2 (0.9648 g mg–1h-1) was lower than at pH 4 (1.1066 g mg–1 h–1),at pH 6 (1.8821 g mg–1 h–1), at pH 8 (3.1982 g mg–1 h–1) indicating that the paracetamol adsorption was more efficient at pH 8 than other pH values, these results were for ODTMA charcoal micelles complex which show a superior results than activated charcoal pH 2 (0.2005 g mg–1 h–1) ,at pH 4 (0.23g mg–1 h–1),at pH 6 (0.3454g mg–1 h–1), at pH 8 (0.3795 g mg–1 h–1).

Difference between kinetic curves of pH 2, pH 4, pH6 and pH 8 are due to the pH influence in the ionization state of weak electrolytes of paracetamol pKa 9.38 and the charges that may appear in the carbon surface (Karaman, Khamis et al. 2016, Bernal, Erto et al. 2017).

FERREIRA et al (Cristina Ferreira, M. Couto Junior et al. 2015) worked on the removal of paracetmol on different pH values, in comparing results K(constant rate) using coconut activated charcoal was as the following pH 2 (0.002 g mg–1 h–1) at pH 6.5 (0.0018 g mg–1 h–1) (Cristina Ferreira, M. Couto Junior et al. 2015),our results were better and have a higher K which means more efficient .

Chang et al (Chang, Wan et al. 2015) also worked on paracetamol and its adsorption on granular activated carbon (GAC) K was 1.59×10^{-5} also show a low K and superior results for ODTMA charcoal micelles complex(Chang, Wan et al. 2015).

4.3 adsorption isotherms

4.3.1 langmuir isotherms:

The adsorption of paracetamol onto ODTMA micelles charcoal complex and activated charcoal analyzed by Langmuir isotherm equation (langmuir 1918) as shown below

$$\frac{Ce}{Qe} = \frac{1}{KQmax} + \frac{Ce}{Qmax}$$

Where

Ce: equilibrium concentration of paracetamol (ppm)

Qe: equilibrium mass of adsorbed selected pharmaceutical per gram of adsorbent (mg/g)

K: Langmuir affinity constant (L/mg)

Qmax: maximum amount of solute adsorbed per gram of ODTMA micelles charcoal complex, or activated charcoal (mg/g).

4.3.1.1 at pH 2:

Table 4.6 langmuir constant (Qmax & K) and correlation for adsoption isotherm of paracetamol onto micelles charcoal micelles complex and activated charcoal.

	absorbent	Q max (mg/g)	K (g/L)	R^2
paracetamol	ODTMA micelles complex	86.21 ± 1.48	0.0057 ± 0.001	0.9721
	activated charcoal	72.46 ± 1.20	0.0046 ± 0.001	0.9916

4.3.1.2 pH 4:

Table 4.7 langmuir constant (Qmax & K) and correlation for adsorption isotherm of paracetamol onto micelles charcoal micelles complex and activated charcoal

	absorbent	Q max (mg/g)	K (g/L)	R^2
paracetamol	ODTMA micelles complex	112.3 ± 1.14	0.0081 ± 0.003	0.7739
	activated charcoal	78.7 ±1.35	0.0042 ± 0.004	0.8835

4.3.1.3 pH 5.5:

Table 4.8 langmuir constant (Qmax & K) and correlation for adsorption isotherm of paracetamol onto micelles charcoal micelles complex and activated charcoal

	absorbent	Q max (mg/g)	K (g/L)	R^2
paracetamol	ODTMA micelles complex	75.18 ± 1.08	0.021 ± 0.009	0.7276
	activated charcoal	64.93 ± 0.76	0.010 ± 0.005	0.7882

4.3.1.4 pH 6.8:

Table 4.9 langmuir constant (Qmax & K) and correlation for adsorption isotherm of paracetamol onto micelles charcoal micelles complex and activated charcoal

	absorbent	Q max (mg/g)	K (g/L)	R^2
paracetamol	ODTMA micelles complex	128.2 ± 1.17	0.011 ± 0.07	0.8138
	activated charcoal	103.09 ±0.94	0.009 ± 0.003	0.8484

4.3.1.5 pH 7.4:

Table 4.10 langmuir constant (Qmax & K) and correlation for adsorption isotherm of paracetamol onto micelles charcoal micelles complex and activated charcoal

	absorbent	Q max (mg/g)	K (g/L)	R^2
paracetamol	ODTMA micelles complex	138.9 ± 1.25	0.022 ±0.006	0.8675
	activated charcoal	133.3 ± 0.99	0.084 ± 0.003	0.7729

4.3.1. 6 pH 10:

Table 4.11 langmuir constant (Qmax & K) and correlation for adsorption isotherm of paracetamol onto micelles charcoal micelles complex and activated charcoal

	absorbent	Q max (mg/g)	K (g/L)	R^2
paracetamol	ODTMA micelles complex	117.64 ± 1.61	0.003 ± 0.0005	0.6873
	activated charcoal	97.08 ± 1.53	0.002 ± 0.006	0.7168

4.3.1.7 Comparison between Qmax (maximum amount of solute adsorbed per gram of ODTMA micelles charcoal complex and activated charcoal (mg/g)) and different pH values (2, 4, 5.5, 6.8, 7.4, 10)

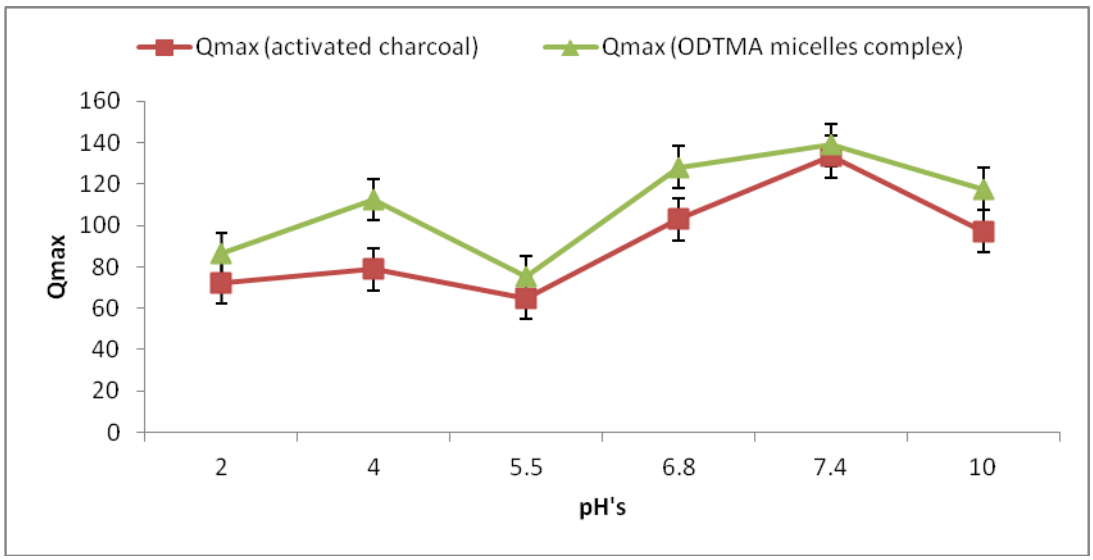

Figure 4.16 Comparison between Qmax (maximum amount of solute adsorbed per gram of ODTMA micelles charcoal complex and activated charcoal (mg/g)) and different pH values (2, 4, 5.5, 6.8, 7.4, 10) temperature = 25 C°

The parameter that best describe the adsorption capacity is Q max (langmuir 1918) (maximum amount adsorbed in mg/g) in figure 4.28 ,the highest Q max was at pH 7.4 (133 mg/g) for activated charcoal and (138 mg/g) for ODTMA charcoal micelles complex according to the batch experiment ,kinetic studies , Langmuir adsorption isotherm all show a better adsorption at pH 7.4 using ODTMA micelles charcoal complex .

Table 4.12 : Different studies were done to the maximum capacity adsorption (Qmax)

Adsorbent for paracetamol	Qmax (mg/g)
Granulated charcaol (*Temes et al*) (Ternes, Meisenheimer *et al.* 2002)	1.1
Granulated charcaol (*akatar et al*) (Akhtar, Amin *et al.* 2011)	1.32
Granulated charcaol (chang *et al*) *(Chang, Wan et al. 2015)*	3.82
Dend coconut activated charcoal Ferreira *(et al) (Cristina Ferreira, M. Couto Junior et al. 2015)*	
pH 2	80.6
pH 6.5	90.8
pH 11	62.9
Micelles clay complex (*qaraman et al) (Karaman, Khamis et al. 2016)*	47.17

The best Q max observed in ODTMA charcoal micelles complex at pH 7.4 (138 mg/g).

4.3.2 Freundlich isotherm

Freundlich adsorption isotherm (freundlich 1907)

The adsorption of paracetamol analyzed by freunlich isotherm equation (freundlich 1907):

$$logQe = logK + \frac{1}{n} logCe$$

Ce: equilibrium concentration of adsorbed (ppm)

Qe: equilibrium mass of adsorbed selected pharmaceutical per gram of adsorbent (mg/g)

K and n Freundlich parameter constant.

Adsorption of paracetamol is well described by plotting log (Qe) versus log (Ce) ,the correlation coefficient values R^2 obtained

4.3.2.1 at pH 2

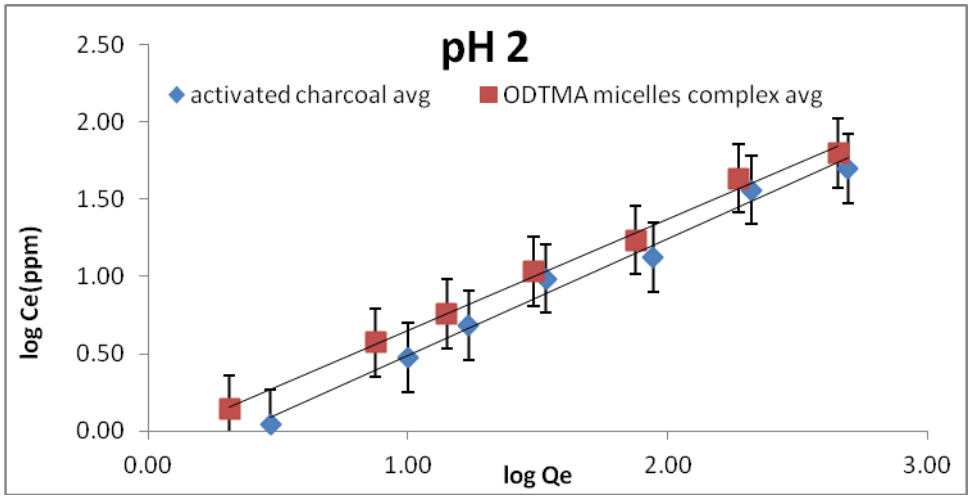

Figure 4.17 plot of freundlich isotherm for the adsorption of paracetamol onto micellecs charcoal complex and activated charcoal .contact time= 3 hours, tempreture = 25 C°and adsorbant 0.5 g/L

Table 4.13 freundlich constant (1/n & K) and correlation for adsoption isotherm of paracetamol onto micelles charcoal micelles complex and activated charcoal.

	absorbent	1/n	n	K	R^2
paracetamol	ODTMA micelles complex	0.7177 ± 0.02	1.38 ± 0.01	0.86 ± 0.013	0.995
	activated charcoal	0.7536 ± 0.03	1.33 ± 0.04	0.54 ± 0.03	0.9867

4.3.2.2 at pH 2

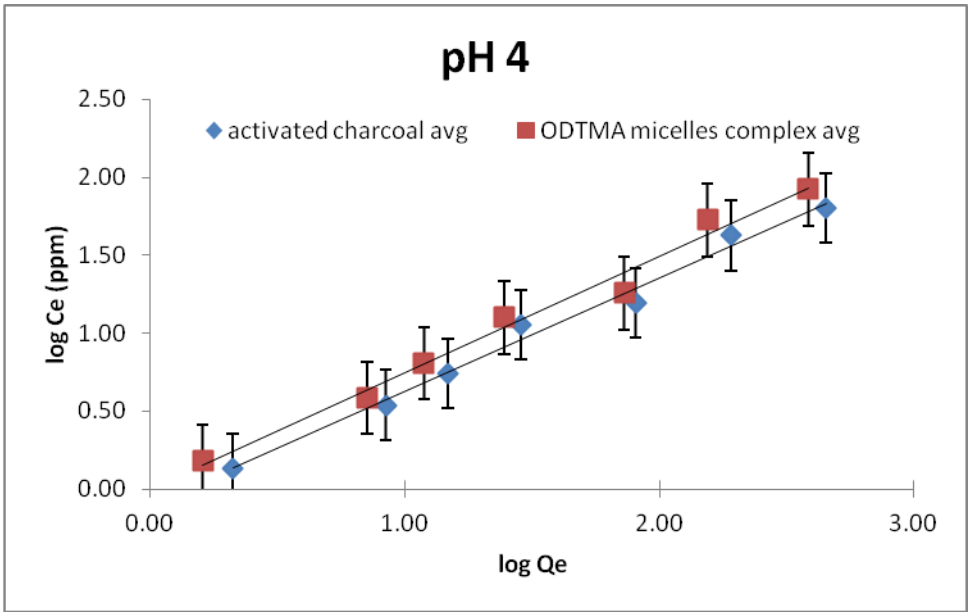

Figure 4.18 plot of freundlich isotherm for the adsorption of paracetamol onto micellecs charcoal complex and activated charcoal .contact time= 3 hours, tempreture = 25 C°and adsorbant 0.5 g/L

Table 4.14 freundlich constant (1/n & K) and correlation for adsoption isotherm of paracetamol onto micelles charcoal micelles complex and activated charcoal.

	absorbent	1/n	n	K	R^2
paracetamol	ODTMA micelles complex	0.75 ± 0.03	1.33 ± 0.09	1.00 ± 0.04	0.9853
	activated charcoal	0.73 ± 0.07	1.37 ± 0.08	0.79 ± 0.003	0.9884

4.3.2.3 at pH 5.5

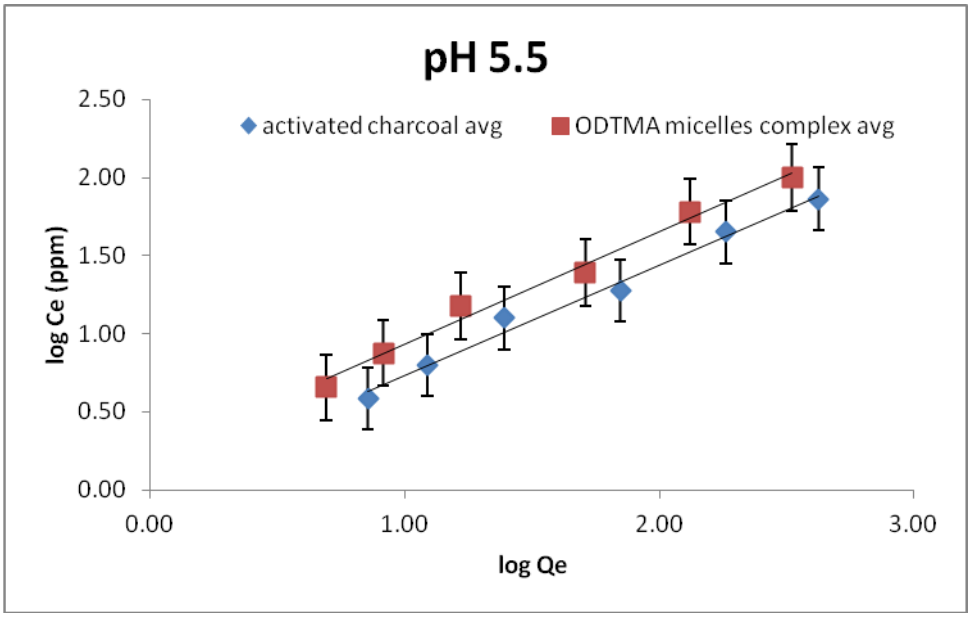

Figure 4.19 plot of freundlich isotherm for the adsorption of paracetamol onto micellecs charcoal complex and activated charcoal .contact time= 3 hours, tempreture = 25 C°and adsorbant 0.5 g/L

Table 4.15 freundlich constant (1/n & K) and correlation for adsoption isotherm of paracetamol onto micelles charcoal micelles complex and activated charcoal.

	absorbent	1/n	n	K	R^2
paracetamol	ODTMA micelles complex	0.72 ± 0.02	1.39 ± 0.08	1.62 ± 0.03	0.9883
	activated charcoal	0.71 ± 0.04	1.41 ± 0.1	1.06 ± 0.06	0.9876

4.3.2.4 at pH 6.8

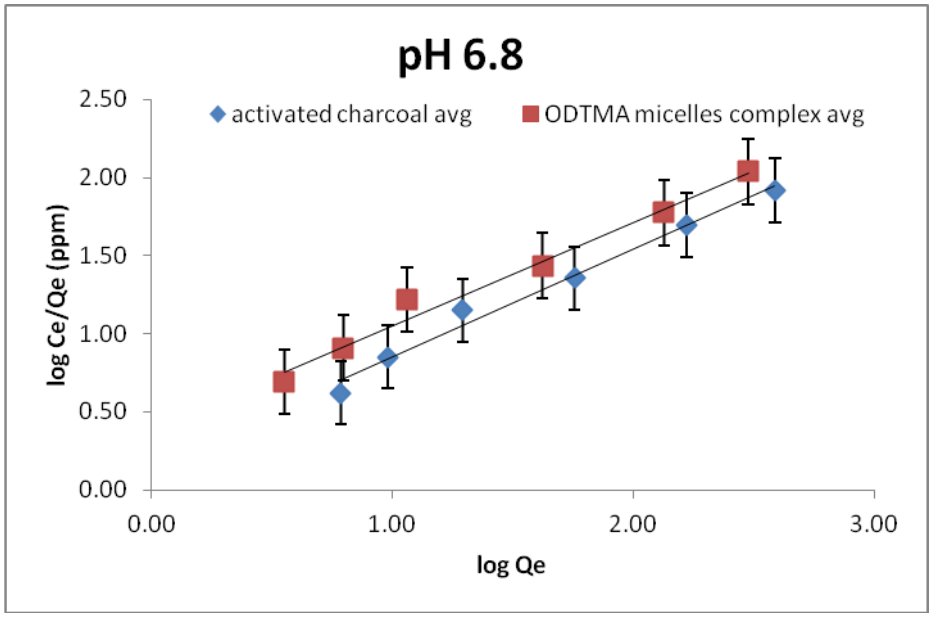

Figure 4.20 plot of freundlich isotherm for the adsorption of paracetamol onto micellecs charcoal complex and activated charcoal .contact time= 3 hours, tempreture = 25 C°and adsorbant 0.5 g/L

Table 4.16 freundlich constant (1/n & K) and correlation for adsoption isotherm of paracetamol onto micelles charcoal micelles complex and activated charcoal.

	absorbent	1/n	n	K	R^2
paracetamol	ODTMA micelles complex	0.66 ± 0.003	1.52 ± 0.06	2.47 ± 0.12	0.9838
	activated charcoal	0.69 ± 0.004	1.45 ± 0.06	1.44 ± 0.09	0.9853

4.3.2.5 at pH 7.4

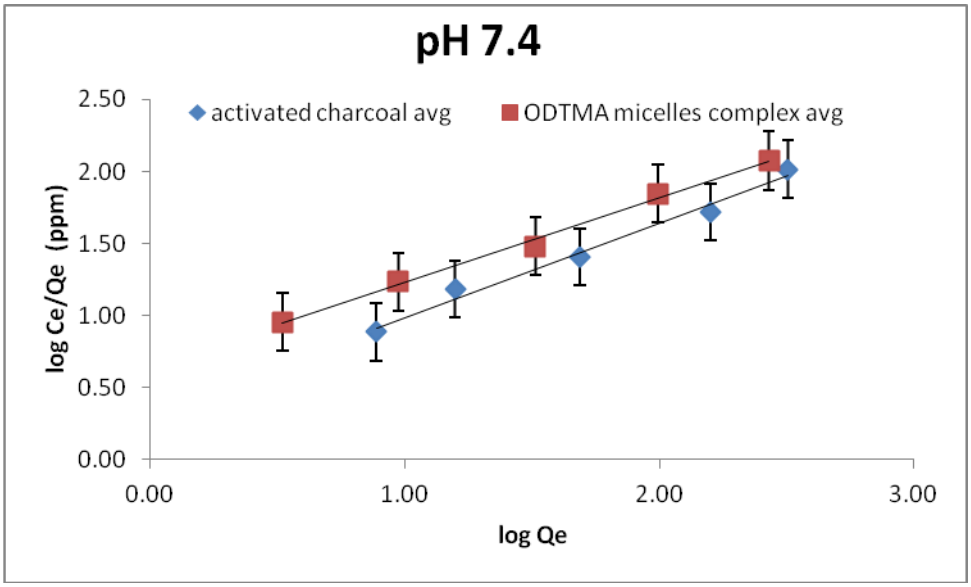

Figure 4.21 plot of freundlich isotherm for the adsorption of paracetamol onto micellecs charcoal complex and activated charcoal .contact time= 3 hours, tempreture = 25 C°and adsorbant 0.5 g/L

Table 4.17 freundlich constant (1/n & K) and correlation for adsoption isotherm of paracetamol onto micelles charcoal micelles complex and activated charcoal.

	absorbent	1/n	n	K	R^2
paracetamol	ODTMA micelles complex	0.59 ± 0.002	1.70 ± 0.07	4.4 ± 0.21	0.9949
	activated charcoal	0.65 ± 0.003	1.53 ±0.05	2.16 ± 0.09	0.9853

4.3.2.6 at pH 10

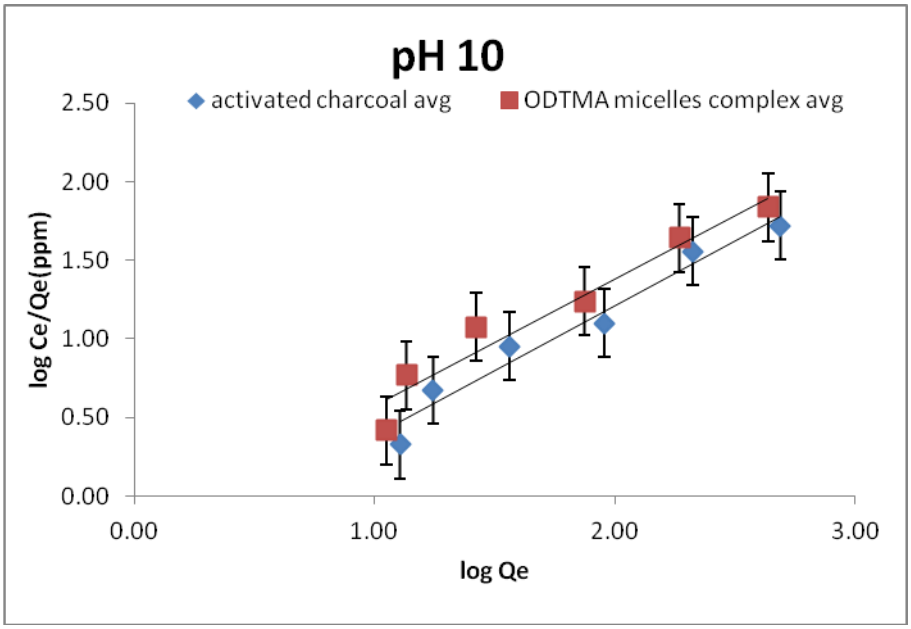

Figure 4.22 plot of freundlich isotherm for the adsorption of paracetamol onto micellecs charcoal complex and activated charcoal .contact time= 3 hours, tempreture = 25 C°and adsorbant 0.5 g/L

Table 4.18 freundlich constant (1/n & K) and correlation for adsoption isotherm of paracetamol onto micelles charcoal micelles complex and activated charcoal.

	absorbent	1/n	n	K	R^2
paracetamol	ODTMA micelles complex	0.83 ±0.003	1.20 ± 0.04	1.70 ± 0.21	0.9439
	activated charcoal	0.81 ± 0.006	1.23 ± 0.03	2.81 ± 0.31	0.9605

4.3.2.7 Comparison between n (freundlich parameter constant) and different pH values (2, 4, 5.5, 6.8, 7.4, 10)

The adsorption isotherms of paracetamol on both adsorbents are 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 below (Freundlich 1907):

$$Qe = KfCe^{1/n}$$

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 4.47 summarizes the results for each adsorbent together with the correlation coefficient (R^2).

Table 4.19: Comparison between K_f of activated charcoal and OMAC complex at different pH. T= 25.0 ^oC and adsorbent dosage 0.50 g

pH's	K_f(activated charcoal) (L/g)	R^2(activated charcoal)	K_f(ODTMA charcoal micelles complex) (L/g)	R^2(ODTMA charcoal micelles complex)
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

Fruendlich isotherm was derived theoretically (Yu Liu 2008) and the below equation was obtained.

$$Q_e = \frac{Q_{max}}{K} C^{1/n}$$

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} follow this trend. This is 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 4.20 summarizes the results for n as function of pH for the different adsorbent. These parameters indicate the extent of adsorption. According to equation, the higher the value of n, the less the extent of adsorption.

Table 4.20: Comparison between n of activated charcoal and OMAC complex as function of pH. T = 25.0 ˚C and adsorbents dosage 0.50 g.

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

The efficiency of adsorption is indicated by the value of n . Favorable adsorption is obtained when n is between 0.5 and 3 (Behnamfard and Salarirad 2009). Inspection of 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 are favorable at all pH values.

Table 4.21: A comparative table between Different studies used different adsorbent to compare our results with others

Adsorbent for paracetamol	K (ferundlich constant)	1/n
dend cocount activated charcaol *(Ferreira et al) (Cristina Ferreira, M. Couto Junior et al. 2015)*		
pH 2	2.58	0.28
pH 6.5	2.13	0.404
pH 11	1.22	0.422
micelles clay complex *(Karaman, Khamis et al. 2016)*	1.77	0.67

Kf for ODTMA charcoal micelles complex was 4.4 at pH 7.4 which gives best results than other groups.

Conclusion

The combined results revealed that ODTMA micelles charcoal 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 ODTMA micelles charcoal complex.

References:

Aburub, A. and D. E. Wurster (2006). "Phenobarbital interactions with derivatized activated carbon surfaces." J Colloid Interface Sci **296**(1): 79-85.

Akhtar, J., N. S. Amin and A. Aris (2011). "Combined adsorption and catalytic ozonation for removal of sulfamethoxazole using Fe2O3/CeO2 loaded activated carbon." Chemical Engineering Journal **170**(1): 136-144.

al-Shareef, A. H., D. C. Buss and P. A. Routledge (1990). "Drug adsorption to charcoals and anionic binding resins." Hum Exp Toxicol **9**(2): 95-97.

Anderson, B. J. (2008). "Paracetamol (Acetaminophen): mechanisms of action." Paediatr Anaesth **18**(10): 915-921.

Awwad, M., F. Al-Rimawi, K. J. Dajani, M. Khamis, S. Nir and R. Karaman (2015). "Removal of amoxicillin and cefuroxime axetil by advanced membranes technology, activated carbon and micelle-clay complex." Environ Technol **36**(13-16): 2069-2078.

Bernal, V., A. Erto, L. Giraldo and J. Moreno-Piraján (2017). Effect of Solution pH on the Adsorption of Paracetamol on Chemically Modified Activated Carbons.

blanchrad (1984). water res **18**: 1501.

Boehm, B. O. (1989). "surface properties of carbons. in structure and reactivity of surface." elsevier science publishers: 145-159.

Brodie, B. B., P. A. Lief and R. Poet (1948). "The fate of procaine in man following its intravenous administration and methods for the estimation of procaine and diethylaminoethanol." J Pharmacol Exp Ther **94**(4): 359-366.

brunauer (1938). "chem.soc." **60**: 309.

Chang, E. E., J. C. Wan, H. Kim, C. H. Liang, Y. D. Dai and P. C. Chiang (2015 .("Adsorption of Selected Pharmaceutical Compounds onto Activated Carbon in Dilute Aqueous Solutions Exemplified by Acetaminophen, Diclofenac, and Sulfamethoxazole." ScientificWorldJournal **2015**: 186501.

Chyka, P. A., D. Seger, E. P. Krenzelok, J. A. Vale, T .American Academy of Clinical, C. European Association of Poisons and T. Clinical (2005). "Position paper: Single-dose activated charcoal." Clin Toxicol (Phila) **43**(2): 61-87.

Cristina Ferreira, R., O. M. Couto Junior, K. Carvalho, P. Arroyo and M. A. Barros (2015). Effect of Solution pH on the Removal of Paracetamol by Activated Carbon of Dende Coconut Mesocarp.

Du, B., A. E. Price, W. C. Scott, L. A. Kristofco, A. J. Ramirez, C. K. Chambliss, J. C. Yelderman and B. W. Brooks (2014). "Comparison of contaminants of emerging concern removal, discharge, and water quality hazards among centralized and on-site wastewater treatment system effluents receiving common wastewater influent." Sci Total Environ **466-467**: 976-984.

ducker (1999). "adsorption of hexadeycaltrimethlammonium bromide to mica " **15**: 602-607.

Forrest, J. A., J. A. Clements and L. F. Prescott (1982). "Clinical pharmacokinetics of paracetamol." Clin Pharmacokinet **7**(2): 93-107.

freundlich (1907). "physik. chem." 385-740.

Gelotte, C. K., J. F. Auiler, J. M. Lynch, A. R. Temple and J. T. Slattery (2007). "Disposition of acetaminophen at 4, 6, and 8 g/day for 3 days in healthy young adults." Clin Pharmacol Ther **81**(6): 840-848.

Gibson, J. D., N. R. Pumford, V. M. Samokyszyn and J. A. Hinson (1996). "Mechanism of acetaminophen-induced hepatotoxicity: covalent binding versus oxidative stress." Chem Res Toxicol **9**(3): 580-585.

Green, R., R. Grierson, D. S. Sitar and M. Tenenbein (2001). "How long after drug ingestion is activated charcoal still effective "?J Toxicol Clin Toxicol **39**(6): 601-605.

hussain (2010). "Adsorption of paracetamol on activated charcoal in the presence of dextropropoxyphene hydrochloride, N-acetylcysteine and sorbitol." **29**(6.(

Jahr, J. S. and V. K. Lee (2010). "Intravenous acetaminophen." Anesthesiol Clin **28**(4): 619-645.

jayens (1991). "clay mineral type and organic compound sorption by hexadecyltrimethylammoniuom -exchanged clays

"soil SC **55**: 43-84.

Jones, D. P., J. J. Lemasters, D. Han, U. A. Boelsterli and N. Kaplowitz (2010 .("Mechanisms of pathogenesis in drug hepatotoxicity putting the stress on mitochondria." Mol Interv **10**(2): 98-111.

Kaplowitz, N., M. Shinohara, Z. X. Liu and D. Han (2008). "How to protect against acetaminophen: don't ask for JUNK." Gastroenterology **135**(4.1051-1047 :(

Karaman, R., M. Khamis, J. Abbadi, A. Amro, M. Qurie, I. Ayyad, F. Ayyash, O. Hamarsheh, R. Yaqmour, S. Nir, S. Bufo, L. Scrano, S. Lerman, S. Gur-Reznik and C. G.

Dosoretz (2016). Paracetamol biodegradation by activated sludge and photo-catalysis and its removal by a micelle-clay complex, activated charcoal and reverse osmosis membranes.

Karaman, R., M. Khamis, J. Abbadi, A. Amro, M. Qurie, I. Ayyad, F. Ayyash, O. Hamarsheh, R. Yaqmour, S. Nir, S. A. Bufo, L. Scrano, S. Lerman, S. Gur-Reznik and C. G. Dosoretz (2016). "Paracetamol biodegradation by activated sludge and photocatalysis and its removal by a micelle-clay complex, activated charcoal, and reverse osmosis membranes." Environ Technol **37**(19): 2414-2427.

Karaman, R., M. Khamis, M. Quried, R. Halabieh, I. Makharzeh, A. Manassra, J. Abbadi, A. Qtait, S. A. Bufo, A. Nasser and S. Nir (2012). "Removal of diclofenac potassium from wastewater using clay-micelle complex." Environ Technol **33**(10-12): 1279-1287.

Kowalczyk, P., A. P. Terzyk and P .A. Gauden (2001). "A Simple Method of the Determination of the Structural Heterogeneity of Microporous Solids." J Colloid Interface Sci **236**(2): 387-390.

Kowalczyk, P., A. P. Terzyk, P. A. Gauden and R. Leboda (2001). "The Characterization of Microporous Activated Carbons Utilizing a Simple Adsorption Genetic Algorithm (SAGA)." J Colloid Interface Sci **239**(2): 591-594.

lagaly (1982). "layer charge heterogeneity in vermiculties " **30**: 215-222.

lamont (1998). "surface - induced transformation for surfactant aggregates." **120**: 160-168.

langmuir (1918). "chem. soc." **40**: 1316.

menendez (1995). "on the difference between the isoelectric point and the point of zero charge of carbon." carbon cross ref **33**: 1655-1657.

Mishael, Y. G., T. Undabeytia, O. Rabinovitz ,B. Rubin and S. Nir (2002). "Slow-release formulations of sulfometuron incorporated in micelles adsorbed on montmorillonite." J Agric Food Chem **50**(10): 2864-2869.

Mishael, Y. G., T. Undabeytia, G. Rytwo, B. Papahadjopoulos-Sternberg, B. Rubin and S. Nir" .(2002) Sulfometuron incorporation in cationic micelles adsorbed on montmorillonite." J Agric Food Chem **50**(10): 2856-2863.

Mitchell, J. R., D. J. Jollow, W. Z. Potter, J. R. Gillette and B. B. Brodie (1973). "Acetaminophen-induced hepatic necrosis. IV. Protective role of glutathione." J Pharmacol Exp Ther **187**(1): 211-217.

Niranjan, S. K., S. M. Deb, A. Sharma, A. Mitra and S. Kumar (2009). "Isolation of two cDNAs encoding MHC-DQA1 and -DQA2 from the water buffalo, Bubalus bubalis." Vet Immunol Immunopathol **130**(3-4): 268-271.

Piccirillo, C., S. I. Pereira, A. P. Marques, R. C. Pullar, D. M. Tobaldi, M. E. Pintado and P. M. Castro (2013). "Bacteria immobilisation on hydroxyapatite surface for heavy metals removal." J Environ Manage **121**: 87-95.

Polubesova, T ,.D. Zadaka, L. Groisman and S. Nir (2006). "Water remediation by micelle-clay system: case study for tetracycline and sulfonamide antibiotics." Water Res **40**(12): 2369-2374.

Qin, Z., L. Bragg, G. Ouyang, V. H. Niri and J. Pawliszyn (2009). "Solid-phase microextraction under controlled agitation conditions for rapid on-site sampling of organic pollutants in water." J Chromatogr A **1216**(42): 6979-6985.

Qurie, M., M. Khamis, A. Manassra, I. Ayyad, S. Nir, L. Scrano, S. A. Bufo and R. Karaman (2013). "Removal of Cr(VI) from aqueous environments using micelle-clay adsorption." ScientificWorldJournal **2013**: 942703.

Rumack, B. H. (2002). "Acetaminophen hepatotoxicity: the first 35 years." J Toxicol Clin Toxicol **40**(1): 3-20.

Rumack, B. H. and H. Matthew (1975). "Acetaminophen poisoning and toxicity." Pediatrics **55**(6): 871-876.

Singer, A. J., T. R. Carracio and H. C. Mofenson (1995). "The temporal profile of increased transaminase levels in patients with acetaminophen-induced liver dysfunction." Ann Emerg Med **26**(1.53-49 :(

Syed draman, S. f., I. A. Batra'azman and N. Mohd (2015). Removal of paracetamol from aqueous solution by dried cellulose and activated carbon.

temkin (1940). "acta. physicochim." soc. **12**: 1501.

Ternes, T. A., M. Meisenheimer, D. McDowell, F. Sacher, H. J. Brauch, B. Haist-Gulde, G. Preuss, U. Wilme and N. Zulei-Seibert (2002). "Removal of pharmaceuticals during drinking water treatment." Environ Sci Technol **36**(17): 3855-3863.

Terzyk, A. P. (2001). "the influence of activated carbon surface chemical composition on the adsorption of acetaminophen (paracetamol) in vitro : part II " **177**: 23-45.

Waring, W. S., H. Jamie and G. E. Leggett (2010). "Delayed onset of acute renal failure after significant paracetamol overdose: A case series." Hum Exp Toxicol **29**(1): 63-68.

Watson, W. A. (1987). "Factors influencing the clinical efficacy of activated charcoal." Drug Intell Clin Pharm **21**(2): 160-166.

xu (1994). "cation exchange chemistry of hexadecyltrimethelammonium in a sub soil." **58**(1994.(

Y.S (2000). "sep. purification methods." **29**: 189.

Yu Liu, Y.-J. L. (2008). "Biosorption isotherms, kinetics and thermodynamics." Separation and Purification Technology **61**(3): 229-243.

Zadaka, D., S. Nir, A. Radian and Y. G. Mishael (2009). "Atrazine removal from water by polycation-clay composites: effect of dissolved organic matter and comparison to activated carbon." Water Res **43**(3): 677-683.

إزالة السموم من الباراسيتامول باستخدام مجمعات الفحم- ميسيلس

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الملخص:

يعتبر التسمم بالباراسيتامول من بين أكثر الأسباب شيوعا للتسمم بالموت والوفاة. قد تحدث بعد ابتلاع كمية كبيره مره واحده أو من خلال ابتلاع كميات كبيره على مراحل . الادلة على كل التدخلات للجرعات زائدة من الباراسيتامول ضعيفو لايوجد معلومات كافيه .منها الفحم المنشط، غسل المعدة، و إيبيكا وانها قادرة على الحد من امتصاص الباراسيتامول إذا بدأت في 1-2 ساعة من ابتلاع الباراسيتامول، ولكن الفوائد السريرية غير واضحه. ويبدو أن استخدام الفحم المنشط هو الخيار الأفضل إذا كان المريض متعاون .

في بعض الأحيان، هناك حاجة إلى جرعات متعددة من الفحم المنشط لعلاج التسمم الشديد. وفي حالة أخرى، فإن الكربون المنشط المستخدم الحالي لا يكفي لكبح العديد من الأدوية والسموم بكفاءة. ولذلك، هناك حاجة ملحة لابتكار أشكال معدلة من الكربون المنشط وغيرها من الممتزات مثل ODTMA charcoal micelles complex التي لديها شحنة إيجابية، و مساحة سطح كبيره وكفاءة عالية لالتقاط التسمم الباراسيتامول.

تم دراسة قيم درجة الحموضة الفسيولوجية المختلفة لتقييم تأثير درجة الحموضه على إزالة الباراسيتامول بواسطة هذا الممتزات وتأثير الزمني وكفاءة الامتصاص. نتائج إيسوثرم الامتزاز تثبت أفضل تناسب ل إيسوثرم فروندليتش الامتزاز والحركية الامتزاز اتباع الزائفة من الدرجة الثانية نموذج حركية. وكشفت النتائج ODTMA charcoal micelles complex يمكن أن تعزز إزالة السموم من الباراسيتامول في جرعات عالية في المعدة حتى في درجة الحموضة منخفضة مقارنة الفحم المنشط. وعلاوة على ذلك، تشير النتائج إلى أن ODTMA charcoal micelles complex يمكن امتصاص اراسيتامول في أشكال مختلفة في مختلف الدرجات الحموضه بالنسبة للفحم، مما يجعل من ODTMA charcoal micelles complexعامل أفضل من الفحم المنشط في درجة الحموضة الفسيولوجية.