Deanship of Graduate Studies

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Efficiency of Advanced Membrane Wastewater Treatment Plant towards Removal of Aspirin, Salicylic acid, Paracetamol and *p*-Aminophenol

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Efficiency of Advanced Membrane Wastewater Treatment Plant towards Removal of Aspirin, Salicylic acid, Paracetamol and *p*-Aminophenol

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Jerusalem – Palestine

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Dedication

This thesis is dedicated to the teacher of teachers, **Prophet Mohammad** -peace be upon him.

To my wonderful parents who sacrificed a lot for me to be what I am now. I am very grateful for their unconditional love, support and prayers. Thank you for instilling in me the desire to strive for the best.

A special dedication also goes out to my lovely sister, Sondos, for her love and support are always there when I need them the most.

Also, to all my dearest brothers and their families for their love, support and faith in me each day to succeed in my goals. Their friendship has taught me patience and confidence in myself and in others around me. And I am indeed blessed to have them in my life.

Also, I would like to dedicate my thesis to my beloved fiancé, Anan, for his love, motivation and inspiration.

Last but not least, I am dedicating this thesis to all those who believe in the richness of learning.

I owe everything I have achieved or will achieve to them. I hope that by obtaining my M.Sc. I can put smiles on their faces.

Fatima Ayyash

Declaration

I certify that the thesis submitted for the degree of master is the result 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: …………………………………………..

Fatima Shafiq Moussa Ayysah

Date: 6-6-2011.

Abstract

Efficiency of Advanced Membrane Wastewater Treatment Plant towards Removal of Aspirin, Salicylic acid, Paracetamol and *p*-Aminophenol

The membrane separation technology for wastewater treatment was studied to check its efficiency in removing pharmaceuticals, their degradation products, and their metabolites from wastewater. Aspirin and paracetamol were found to degrade in wastewater furnishing salicylic acid and *p*-aminophenol, respectively. The kinetics for the degradation reactions of both drugs (Aspirin and Paracetamol) were investigated in wastewater environment and both have shown first order kinetics with rate constants 0.845×10^{-8} Ms^{-1} and 1.0×10^{-8} Ms^{-1} at room temperature, respectively. These values are an order of magnitude larger than those obtained in pure water under the same conditions. The overall performance of the plant has shown complete removal of these compounds from spiked wastewater within the detection limit of the analytical method. The most effective components for removing those drugs within the plant were activated carbon adsorbent and clay-micelle complex. The adsorption isotherms for these compounds have been studied using both activated carbon adsorbent and newly developed adsorbent named clay-micelle complex. All studied isotherms were found to fit Langmuir isotherm. The Langmuir constant and the adsorption capacity were evaluated and discussed.

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First and foremost, I am thankful to **Almighty ALLAH** for granting me strength, wisdom, confidence and perseverance to carry out my M.Sc. thesis. Without him, none of this work would have been possible.

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List of Abbreviations

APIs	Active Pharmaceutical Ingredients
ASA	Acetylsalicylic acid
AST	Activated sludge treatment
BAC	Biologically activated sludge
BOD	Biological Oxygen Demand
CMC	Critical Micelle Concentration
COD	Chemical Oxygen Demand
Da; (g mol^{-1})	Dalton
DEET	N,N-Diethyl-meta-toluamide
EPA	Environmental Protection Agency
EDs	Endocrine disrupters
HCL	Hydrochloric acid
HF	Hollow Fiber
HPLC	High Performance Liquid Chromatography
HPMs	High-Pressure driven Membranes
$K_{o/w}$	Octanol-water Partition coefficient
kD	Kilodalton
kP	Kilopascal
LPMs	Low-Pressure driven Membranes
μm	Micrometer
M	Molarity; (mol L^{-1})
MEnA	Ministry of Environmental Affairs
MF	Microfiltration

MW	Molecular weight; (g mol^{-1})
MWCO	Molecular weight Cutoff
NAPQI	*N*-acetyl-*p*-benzo-quinone imine
NF	Nanofiltartion
Nm	Nanometer
ODTMA	Octadecyltrimethylammonium
OTC	Over the counter
OWCs	Organic Wastewater Contaminants
OPA	Orthophosphoric acid
PCPs	Personal Care Products
PDA	Photo Diode Arrays
PNA	Palestinian National Authority
POTWs	Public owned wastewater treatment plants
PPCPs	Pharmaceuticals and Personal Care Products
Ppm	Parts per million
Psi	Pound per square inch
PWA	Palestinian Water Authority
RO	Reverse Osmosis
SPE	Solid Phase Extraction
SPME	Solid Phase Microextrcation
STP	Sewage Treatment Plants
SW	Spiral Wound
TDS	Total Dissolved Solids
TSS	Total Suspended Solids
TOC	Total Organic Carbon

TOD	Total Oxygen Demand
UF	Ultrafiltartion
US EPA	United States Agency for Environmental Protection
USGS	United States Geological Survey
UV	Ultra Violet
UV/TiO$_2$	Ultra Violet/ Titanium dioxide
WHO	World Health Organization
WWTPs	Waste Water Treatment Plants

Introduction

Chapter One

Introduction

1.1 Background

In the Middle East, in general, and Palestine, in particular, water resources are very limited and currently a serious shortage problem exists [1-3]. This situation would be aggravated in the future since the water balance gap between the available water supplies and the water demand, as a result of population growth, rapid urbanization and industrialization associated with living standards improvement, will increase. This gap cause serious shortage of fresh water to be used in human purposes, agricultural, and other non-human purposes, Hence, water contamination and the production of large volume of wastewater are the expected results [3-6].

In Palestine, which is a semi-arid country, water is used for domestic, industrial, and agricultural purposes. Historically, agriculture plays an important role in Palestinian economy and life, and is the main water-consuming sector. The agricultural demand of water is estimated to be 70% of the total water
consumption, while 27% of water is used for domestic needs and only 3% is used for industrial sector [2, 4, 7]. The principal fresh water resources available to Palestinians include groundwater, surface water, and springs.

Additional water sources include rainwater harvesting. Groundwater and springs are the main source of fresh water in Palestine [1, 4, 7-8]. The West Bank aquifer system has three major drainage basins, the Western, the Northeastern, and the Eastern basins. The first two basins are shared between the West Bank and Israel. The Eastern basin falls entirely within the West Bank. Compared to groundwater, surface water is the minor importance in the West Bank. The only source of surface water in the area is the Jordan River; Palestinian access to fresh surface water from the Jordan River is almost zero because Israel's control of the flow of the river [1, 8].

Therefore, water must be used wisely and efficiently not only to control the consumptive use of water but also to reduce the wastewater flows. Due to the expected increase in volume of wastewater in combination with a serious problem from its disposal, treatment and recycling of wastewater is critical when looking for new sources of water in water-scarce regions (Figure 1-1). Hence, wastewater flows must be managed effectively to prevent pollution and to protect the environment from hazardous chemical and biological pollutants. The purpose of wastewater treatment is generally to allow human and industrial effluents to be disposed without causing a danger neither to human health nor to the environment.

The reuse of reclaimed wastewater in Palestine is a major priority, as confirmed by the Palestinian Water Policy recently adopted by the Palestinian Water Authority (PWA) and the Ministry of Agriculture [4, 7]. In addition, the Palestinian National Authority (PNA) has concern for the protection of the environment through the Ministry of Environmental Affairs (MEnA) [4].
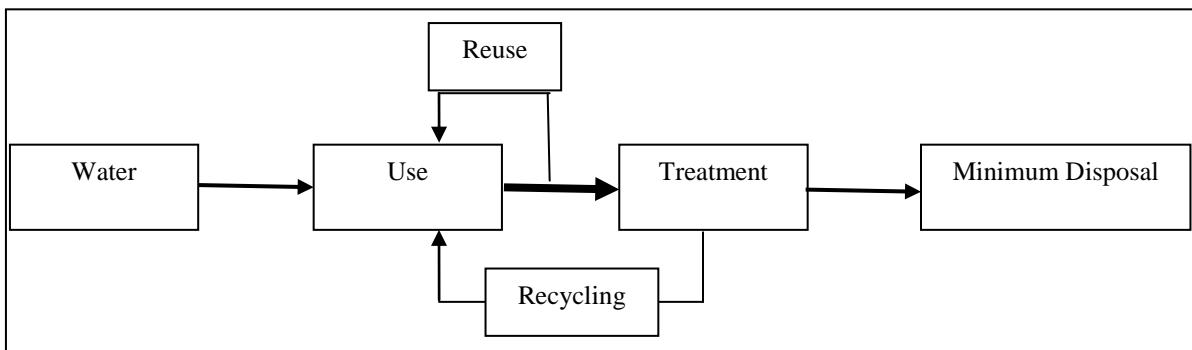
Figure 1-1: Future approaches of dealing with water.

1.1.1 Wastewater management in Palestine

Wastewater is one of the major sources of pollution that has serious adverse impact both on the environment and local residents. The wastewater sector status in Palestine is characterized by poor sanitation, different wastewater quality, insufficient treatment, and unsafe disposal of untreated or partially treated wastewater into the environment. Sewage collection networks in the West Bank are limited to major cities and to certain portions of these municipalities. Most of them are poorly designed and old [4, 9]. Therefore, the situation of the sewerage system is extremely critical [10]. Wastewater management in Palestine had been neglected for decades.

Meanwhile, wastewater management is a tool to maintain environmental integrity, promote health, and protect from diseases [11]. No comprehensive data on wastewater characteristics and amounts discharged are yet available [12]. The effectiveness of the existing urban sewage collection and treatment facilities is usually constrained by limited capacity, poor maintenance, process malfunction, poor maintenance practices, and lack of experienced or properly trained staff [13-14]. Generally, treated wastewater has a long history of applications and can serve many purposes for which fresh water is used, primarily in agriculture, and additional areas of applications, including industrial, and domestic if undergo suitable treatment [15]. To ensure sustainable and successful wastewater reuse applications, the following requirements must be fulfilled [16-17]:

1- The potential public health risk associated with wastewater reuse are evaluated and minimized.
2- The specific water reuse applications meet the water quality objectives.

Presently, raw or partially treated wastewater in many areas in Palestine is discharged to the wades where it is used for irrigation purposes. Several studies have shown that the reuse of treated effluents for irrigated agriculture is possible in most areas in Palestine. However these projects are still on the pilot-scale. In general, Palestinians farmers lack the proper experience in using this resource in a safe way [2-6, 12-14, 18-21]. The reuse of treated wastewater must be combined with strategies to prevent health risks and environment from pathogens, heavy metals, pesticides, personal care products (PCPs), pharmaceuticals and endocrine disrupters. Therefore, the Palestinian Water Authority (PWA), the regulator of water sector, has newly developed national guidelines based on recommended rules issued by the World Health Organization (WHO) to ensure protection of public health and the environment from the discharge of untreated or inadequately treated wastewater effluents [22-23].

Development of appropriate and sustainable sewage treatment technologies will help to preserve biodiversity, maintain healthy environment and save freshwater supply [7]. Among the different treatment systems now available worldwide, the main types of treatment plant are used in Palestine: (a) stabilization ponds for small communities [4-5]; (b) trickling filter [4-5];

(c) oxidation ditches [4-5]; and (e) activated sludge or extended aerated activated sludge for a large scale community [4-5]. Table 1-1 lists the current status of existing and planned wastewater treatment plants in the West Bank [4].

1.2 Thesis Objectives

The main goal of this research study is to investigate the performance of advanced treatment technologies which include integration between activated sludge process with ultra-filtration membranes (hollow fiber and spiral wound membranes), activated carbon adsorbent, micelle-clay filters, and reverse osmosis in terms of removal of aspirin (acetylsalicylic acid) and paracetamol (acetaminophen). The wastewater treatment plant located at Al-Quds University main campus in Abu-Dies is made from such integrations and samples will be taken from different compartments of this plant. Aspirin and paracetamol were chosen since both pharmaceuticals are widely consumed and are found to be frequently used medicines in Palestine.

The sub-goals of this research are:

• Identifying the most popular drugs prescribed in Palestine and preparing a ranking list of these drugs.

• Studying the stability of aspirin and paracetamol in pure water and in the presence of wastewater.

1.3 Thesis Outline

This thesis contains five chapters: Chapter 1 contains the introduction, Chapter 2 consists of literature review on pharmaceuticals present in wastewater, general information on wastewater and the technology used for its treatment, Chapter 3 reviews the materials and the methods used, as well as sampling and analysis, Chapter 4, 5 and 6 summarize the results and discussion, and Chapter 7 presents the conclusions and recommendations.

Table 1-1: Wastewater treatment plants (WWTP) in the West Bank (status and information) [4].

Name of T.P	Status of T.P	No. of population served by T.P * 1000 (year)	Capacity of T.P (mcm/year)	Funding Agency	Estimated cost for construction (million US$)	Technology
Nablus East	Planning phase	240(2021)	9.2	Germany KFW	25	Extended Aeration
Nablus West	Approved	225(2021)	9.0	Germany KFW	25	Extended Aeration
Salfit	Detailed study	24(2025)	2.3	Germany KFW	13	Extended Aeration
Jenin*	Rehabilitation is needed	13.5(1997)	0.5	Israel		Waste stabilization ponds
Al-Bireh	Constructed	40(2000)	1.1	Germany KFW	7	Oxidation Ditch
Tulkarem**	No study yet	223(2030)	7.5	Germany KFW	50	Extended Aeration Process
Abu-Dees	Feasibility study	26(2020)	1	Norway		Oxidation Ditch
Tafuh	Feasibility study	16	0.5	UNDP		Anaerobic Rock Filter
Halhul	Preliminary design	42(2020)	1.0	Not funded	5.5	Aerated Pond System
Birzeit area	Preliminary Study	28(1994)	1.2	Not funded	4.5	Imhoff tank and trickling Filter
Hebron	Planning stage	695(2020)	25.0	USA	45	Activated Sludge
Jericho	Preliminary Study	26 (2000)	1.2	Not funded		
Biddya	Preliminary Study	24 (2000)	1.1	Not funded	10.0	
Ramallah***	Feasibility Study	40 (North)	1.5	Not funded	7.0	Extended Aeration
		40 (South)	1.5		7.0	
Al-Ram	Preliminary Study	86.5(2000)	3.3	Germany KFW	11.0	Aerobic sludge Stabilization+ Activated Sludge
Total		**1789**	**66.3**		**210**	

 Note: *Old and non-functioning sewage treatment plant exists. **Currently rehabilitation of the sewage treatment plant takes place. *** Currently rehabilitation of the old sewage treatment plant takes place as a partial solution. (KFW: Kreditanstalt Fuer Wiederaufbau, T.P: Treatment Plant).

Literature Review

Chapter Two

Literature Review

2.1 Introduction

Wastewater contains a mixture of both organic and inorganic constituents. Its composition varies from time to time and place to place, basically depending on economic aspects, social behavior, type and number of industries located around the collection area, climatic conditions, water consumption, and the type and condition of the sewer system [17].

2.2 Definition of wastewater and its characteristics

Wastewater is defined as the liquid effluents which are discharged from a community after it has been contaminated by various ways. It is usually generated from residences, institutions, commercial, industrial establishments, and surface and ground water [17]. Wastewater consists of 99 percent water by weight and the remaining one percent includes suspended and dissolved organic and inorganic substances as well as microorganism [24]. The wastewater from residences, institutions, commercial places, and farms are referred to as domestic wastewaters [25]. Domestic wastewater, or "sewage", can also be divided into two groups; black-water which is basically wastewater from toilets (urine and etc.) and grey-water refers to the household wastewater which has not been contaminated by toilet waste and which originates from bathrooms and laundries. Grey-water constitutes the largest flow of wastewater [26]. Industrial wastewater generated from industries varies in flow and composition depending on the type of industries. A combination of domestic and industrial wastewaters often referred to as municipal wastewater [17, 24-27].

Wastewater is characterized in terms of its physical, chemical, and biological composition [28]. Physical parameters include total solid contents, particle size distribution, turbidity, temperature, conductivity, transmittance, density, color, and odor. Total solid contents are subdivided into total suspended solids (TSS) and total dissolved solids (TDS). Chemical

parameters associated with the organic content of wastewater include biochemical oxygen demand (BOD), chemical oxygen demand (COD), total organic carbon (TOC), and total oxygen demand (TOD). Inorganic chemical parameters include salinity, hardness, pH, acidity and alkalinity, as well as concentrations of ionized metals such as iron and manganese, and anionic entities such as chlorides, sulfates, sulfides, nitrates, and phosphates. Bacteriological parameters include coliforms, fecal coliforms, specific pathogens, and viruses [17, 28].

2.3 Overview of wastewater treatment

Wastewater treatment is the process of removing varying amounts of contaminants from wastewater, depending on the level and type of treatment they provide. Its objective is to optimize the benefits of wastewater as a resource of both water and nutrients, and to ensure protection of public health and the environment from the discharge of untreated or inadequately treated wastewater effluents [29]. Also, in wastewater reclamation and reuse, water quality requirements may call for reduction in suspended solids, total dissolved solids, pathogenic microorganism (i.e. bacteria, protozoan, and viruses), as well as selected constituents such as nitrates, chlorides, and natural and synthetic organic compounds [17].

2.3.1 Wastewater treatment plant process

Wastewater treatment process includes physical, chemical, and biological units to remove physical, chemical, and biological contaminants. Typically, wastewater treatment process (Figure 2-1) can be broken down into four basic steps: preliminary, primary, secondary, and tertiary. These treatments are to achieve different levels of contaminant removal. Primary and secondary unit operations and processes are called conventional wastewater treatment. After conventional wastewater treatment, tertiary (advanced treatment) treatment improves the quality of secondary wastewater and produces an effluent that can be used as a substitute of freshwater sources for household and industrial needs [17, 28, 30-31].

The initial steps are collectively known as preliminary treatment, in which oils, grease, fats and gross objects such as large objects, rags, and grit are removed through combination of screening and settling by gravity [17, 30]. Primary treatment involves partial removal of

suspended solids and organic matter found in wastewater by means of physical operations such as screening and sedimentation prior to biological treatment. Primary treatment acts as a precursor for secondary treatment. The secondary treatment is designed for removal of biodegradable dissolved and colloidal organics and suspended solids that have escaped the primary treatment by utilizing biological treatment processes. In secondary treatment unit, three types of technologies can be applied to break down organic material with agitation and aeration. These are: activated sludge process, trickling filters, and lagoon systems [17, 30]. The activated sludge process use a variety of mechanisms to utilize dissolved oxygen to promote the growth of a biological floc that substantially breaks down and removes organic material, then allows these solid flocs to settle out. Bacteria-containing ''activated sludge'' is continually re-circulated back to the aeration basin to increase the rate of organic decomposition [27, 32]. After primary and secondary treatment, several physical–chemical processes have been investigated as tertiary treatment of secondary effluents, including ozonation, photo-catalytic degradation of recalcitrant compounds (UV/TiO_2) [33], and adsorption [28, 31-32]. Tertiary treatment is often performed by a sequence of coagulation/flocculation, membrane filtration, and disinfection [31]. The effluents obtained from the combination of tertiary treatment processes are generally of good quality and can be used in different sectors: industry, agriculture, and urban consumption. This treated wastewater contains low concentrations of organic matter, inorganic ions (nitrates, sulfates and phosphates), and pathogenic microorganism which meets the requirements for the reuse criteria for wastewater so that it minimizes its potential negative impact on public health and to reduce environmental damage [31, 34]. Any settled solids (sludge) from any treatment process are given further treatment and undergone several options for disposal [17, 24]. Application of sewage sludge to agricultural land may be beneficial because it can improve and maintain productive soils which may enhance plant growth. In addition, the use of sludge as a fertilizer would decrease the amounts of chemical fertilizers needed in agriculture [17, 24, 35].

2.3.2   Membrane Filtration

Membranes filtration are frequently used for tertiary treatment of wastewater before discharge to surface water, recover materials in industry before they enter waste streams, and to treat waters for potable use [36]. Nowadays, membrane processes can play a key role in reducing water scarcity mainly in areas with scarce water supplies. These membranes are also increasingly being considered as essential additions to conventional water and wastewater treatment methods in anticipation of future demands for high standards and reduced environmental impact [31-40].

Membranes are semi-permeable barriers that are used to separate and remove constituents from a fluid stream ranging from large visible particles to molecular and ionic chemical species including bacteria, viruses, and other pathogenic microorganisms [17, 36]. In membrane separation process, the feed water is separated into a stream that can pass through the membrane, i.e., permeate and a fraction of feed that cannot pass through the membrane, i.e., the concentrate (Brine). Membrane process can be classified in terms of the size of the membrane pores or molecular weight cutoff (MWCO) which specifies the maximum molecular weight of a solute to be rejected, the separation mechanism, the nature of the driving force, the chemical structure and composition of membranes, and the geometry of construction [36]. A schematic representation of a membrane separation process is given in Figure 2-2.

2.3.2.1 Types of membranes

Most commercial membrane modules are manufactured in four configurations as spiral wound, hollow fibers, plate-and-frame, and tubular [41-42]. The principal types of membrane modules used for water and wastewater treatment are hollow fiber and spiral wound [17, 43]. In a hollow fiber element (Figure 2-3(a)), fibers made of porous polymer material are bundled together and sealed in a cylindrical pressure vessel. The feed flows into the module, the permeate flows into or out of the hollow fibers and is collected, while the retentate exits the module for further treatment [42].

As shown in (Figure 2-3 (b)), spiral wound elements consist of two flat membrane sheets separated by a thin, mesh-like porous support or spacer and are sealed on three sides like an envelope. The fourth side is fixed onto a perforated plastic center tube that collects the product water (permeate). The membranes are rolled up around the tube in the form of a spiral. Feed water is pumped through the layers and the product water (permeate) passes through the membrane into the permeate spacer and then is collected in the central perforated collection tube. The retentate exits from the feed spacers at the opposite end of the spiral sheet. Hollow fiber and spiral elements are used for microfiltration (MF), ultrafiltration (UF), and reverse osmosis (RO) [42].
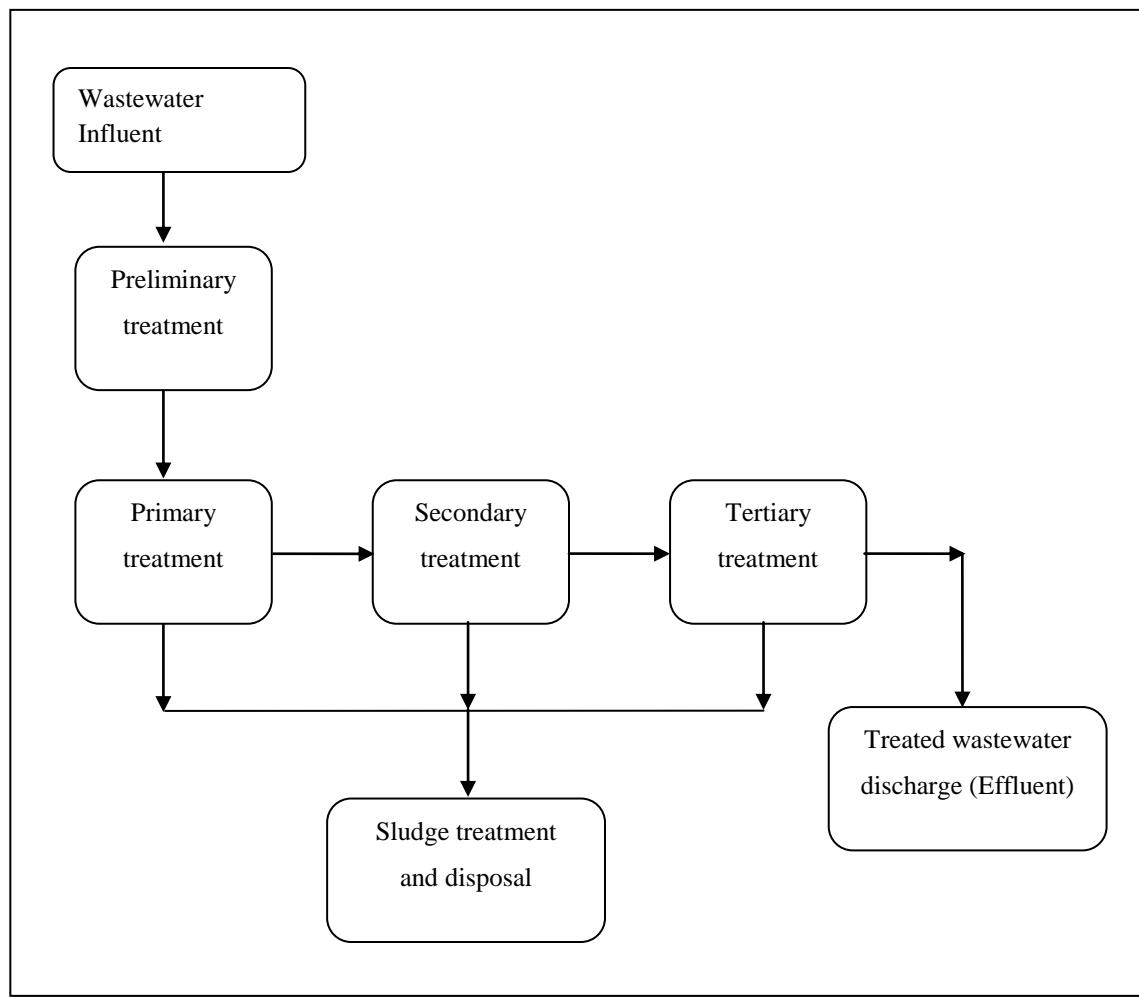
Figure 2-1: A schematic representation of a wastewater treatment classification.
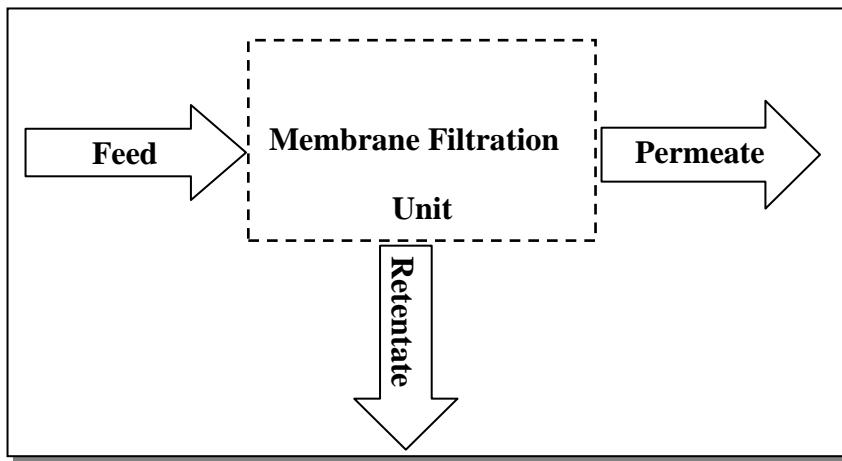
Figure 2-2: A schematic of operation of a membrane process.
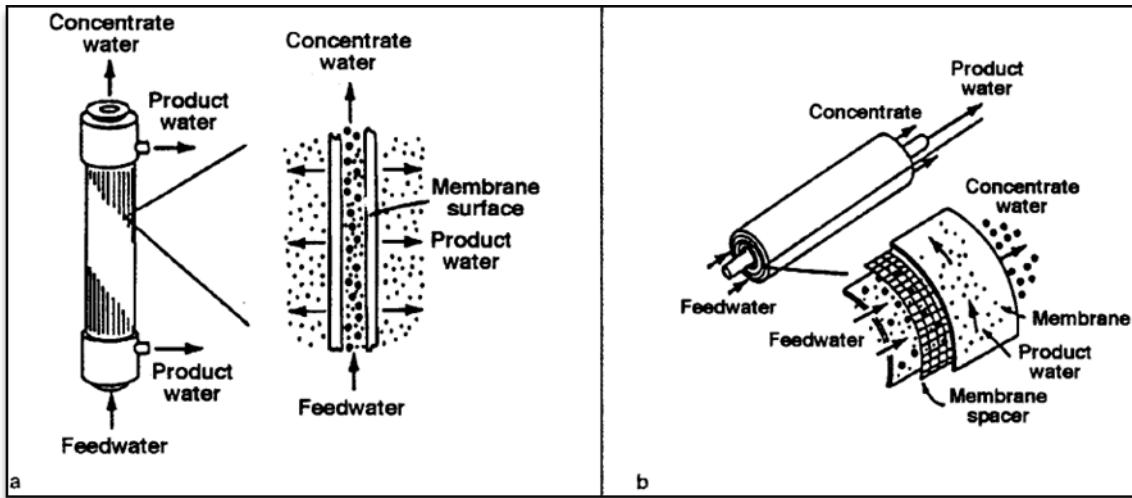
Figure 2-3: Hollow fiber **(a)** and spiral wound **(b)** modules [38].

The driving force for membrane process can be external pressure, electrical potential gradient, concentration gradient, or other driving forces [17, 36]. The most commonly used membrane systems in water and wastewater treatment are pressure-driven membranes, therefore, most of the discussion in this section focuses on them. Pressure-driven membrane processes are typically classified into four common categories depending on their pore size: microfiltration (MF), ultrafiltration (UF), nanofiltration (NF), and reverse osmosis (RO) [36, 38, 41-43]. The various pressures-driven membrane processes and their separation characteristics are shown in Table 2-1.

Table 2-1: Comparison of pressure-driven membrane systems

Parameters	Membrane system			
	Low-pressure membranes		High-pressure membranes	
	MF	UF	NF	RO
Product particle size (µm)	0.08 to 2.0	0.005 to 0.2	0.001 to 0.01	0.0001 to 0.001
Retained compounds	Very small suspended particles, some colloids, most bacteria	Organic compounds > 1000 Da, pyrogens, viruses, bacteria, colloids	Organic compounds > 200 Da, some dissolved solids (i.e. multivalent ions)	Ions, Organic compounds >100 Da MW
Operating pressure, psi	1 to 15	30 to 100	80 to 125	≥ 1,000

2.3.2.1.1 Microfiltration (MF) and Ultrafiltration (UF)

Low-pressure driven membranes (LPMs) include MF and UF which are typically operated under trans-membrane pressures of 100 pound per square inch (psi) or less (700 kPa). They are characterized by their ability to reduce turbidity, and remove suspended or colloidal particles *via* sieving mechanism. In wastewater reclamation, MF and UF are considered as a pretreatment step for RO and NF, so that fouling potential of the less permeable membranes is minimized and can be realized. MF have a pore size ranging between approximately 0.08-2.0µm, although there are exceptions, as MF with pores sizes of up to 10µm are available, with MWCO greater than of approximately 100 kD (D; g mol^{-1}). While UF pore size generally ranges from 0.005-0.2µm, with MWCO of approximately 10 to 100 kD. UF membranes are designed to remove dissolved macromolecules solutes from feed water, such as colloids, proteins, and carbohydrates. Therefore, UF offers higher removals efficiency than the MF; however, UF membranes do not remove ultra small substances such as sugar and salts [17, 36, 37, 41].

2.3.2.1.2 Nanofiltration (NF) and Reverse Osmosis (RO)

High-pressure driven membranes (HPMs) generally refer to NF and RO which are required for the removal of ultra-small dissolved contaminants via a softening or desalination mechanisms. NF also called "membrane softening" is designed for the removal of selected dissolved constituents from wastewater such as multivalent ions (i.e. calcium and magnesium) responsible for water hardness [17]. RO is used primarily for desalination, in which water is transferred through a dense membrane to retain salts and low molecular weight solutes [17, 36, 41]. Therefore, pushing water through membrane pores requires a higher operating pressure than MF and UF. The required operating pressure can range from less than 150 psi (1000 kPa) for some NF applications to more than 1,000 psi (7000 kPa) for RO. Commercially available HPMs employed in wastewater reclamation usually have small pore sizes ranging between approximately 0.01-0.001µm and 0.001-0.0001µm for NF and for RO membranes, respectively. With this ultra small pore size, the attainable range of MWCO levels is less than 100D for RO membranes and between 200 and 1,000D for NF membranes [16, 39].

Reverse osmosis, Figure 2-4, is the reversal of the natural osmotic process, accomplished by applying pressure in excess of the osmotic pressure to the more concentrated solution. This pressure forces the water through the membrane against the natural osmotic gradient, thereby increasingly concentrating the water on one side (i.e., the feed) of the membrane and increasing the volume of water with a lower concentration of dissolved solids on the opposite side (i.e., the filtrate or permeate) [17, 42].
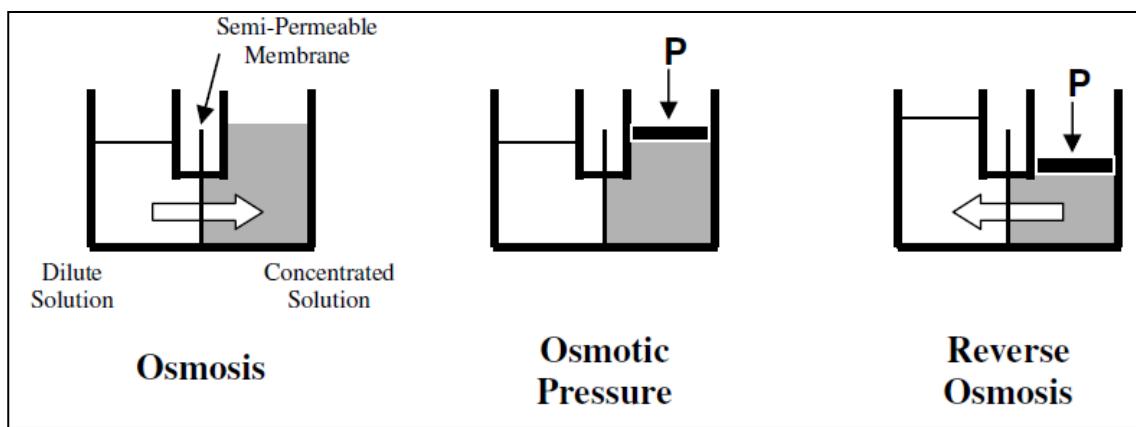
Figure 2-4: The principle of reverse osmosis process.

2.4 Occurrence of Pharmaceuticals in wastewater

In recent years, the occurrence of pharmaceuticals and personal care products (PPCPs) and their metabolites in the aquatic environment has been recognized as being an important part of the chemicals that are present in low concentrations in the environment. A variety of pharmaceuticals have been detected in many environmental samples worldwide. Their occurrence has been reported in sewage treatment plant effluents, surface water, seawater, groundwater, soil, sediment and fish [44-51].

2.4.1 Pharmaceuticals and personal care products (PPCPs) Background

Pharmaceutically active compounds (sometimes called active pharmaceutical ingredients or APIs) cover a wide-range of compounds with substantial variability in structures, function, behavior and activity, in which they are developed and designed to interfere with biological systems, and have an important role in diagnosis, treatment, prevention the disease, health conditions, or functions of human body and/or animals [44, 51]. These substances include both inorganic and organic compounds, although most of the modern pharmaceuticals are small organic compounds with a molecular weight below 500 Daltons. These chemicals are moderately water soluble as well as lipophilic to be bioavailable and biologically active [52]. Pharmaceuticals are produced and used in increasingly large volumes every year [53]. Examples of pharmaceutical compounds include antipyretics, analgesics, blood lipid

regulators, antibiotics, antidepressants, chemotherapy agents, and contraceptive drugs. Personal care products (PCPs) are defined as chemicals marketed for direct use by the consumer in order to alter odor, appearance, and touch without displaying significant biochemical activity (except over-the-counter, OTC, medications) and having intended end uses primarily on the human body (products not intended for ingestion with exception of food supplements) [44]. They include cosmetics, bath additives, shampoo, skin care products, oral hygiene products, hair sprays, sun screens, hair dyes, deodorants, perfumes, soaps, fragrances, veterinary drugs, insect repellents and lotions. The expectations of the amounts of these products will continue to increase due to the increase in the standards of living as reflected by the improvement in the health care system and longer life expectancy.

The term endocrine disrupters (EDs) refer, in general, to the synthetic chemicals and natural compounds that may affect the endocrine system (the communication system of glands, hormones, and cellular receptors) that control the body's internal functions [54]. Endocrine disrupters has recently attracted much attention since many of these disrupters cause negative reproductive and developmental health effects for the human or animals and its offspring [55-56].

2.4.2   Analytical methods

Although pharmaceuticals and endocrine disrupters have been detected in a wide variety of environmental samples including wastewater effluents, rivers, lakes, surface waters, groundwater and drinking water for decades, researchers have recently begun to quantify their levels in the environment due to the development of new analytical technologies that result in the detection of minute traces of pharmaceuticals and other organic chemicals [57]. These analytical methods have become sufficiently sensitive to identify and quantify their presence in wastewater treatment plant (WWTP) effluents, surface waters, drinking water, and ground water. Investigations carried out in many countries have detected more than 80 pharmaceuticals, their metabolites, and pharmaceuticals care products in aquatic environment at concentrations in the range of mg\l (ppm) to ng\l (ppt) levels [58-59]. Reported compounds include wide range of classes of pharmaceuticals: analgesics, anti-inflammatory compounds,

beta-blockers, lipid regulators, antiepileptics, antibiotics, X-ray media contrast agents, cytostatic agents, and contraceptives [59].

Because PPCPs and EDs represent structurally diverse classes of compounds, the different analytical methods have been used and applied for identification and quantification of these chemicals in water samples. The measurement of these compounds in water most commonly consist of an extraction of the chemicals from water, concentration of the resulting extract, and chromatographic separation by gas or liquid chromatography using high sensitivity detector. Due to the complexity of wastewater samples, the extraction techniques such as liquid-liquid and steam distillation have been used to extract these compounds from wastewater and water, however solid phase extraction (SPE) is the most common technique employed for sample enrichment. Variations of SPE include solid phase microextraction (SPME) and various on-line and automated SPE techniques [60-61].

2.4.3 Sources in the environment

After the administration, drug molecules are absorbed, distributed, metabolized, and finally excreted from the body. To be used safely most of the pharmaceuticals are designed in a way to undergo metabolism (enzymatic transformations) in organs such as liver, intestine, kidney, and lungs after they have achieved desired pharmacological effects. In most cases, pharmaceuticals are excreted as one or several metabolites. These metabolites are typically the result of either phase 1 or phase 2 metabolic reactions [62]. They excreted to the sewer system *via* urine and feces and reach WWTPs where they do not undergo further degradation to a satisfactory degree. Hence, WWTPs play a key role in the introduction of pharmaceuticals into the environment. Veterinary and human pharmaceuticals and their metabolites enter the environment by two main pathways. The first is *via* the effluents from wastewater treatment plants (WWTPs) (Figure 2-5). The second route by which pharmaceuticals can enter the environment is by the disposal of unwanted medicines and/or medications that have expired and ended in the sink/toilet or in household waste which subsequently are taken to landfill sites (Figure 2-5) [53]. Entry into the environment by this route is dependent on the habits of the society and level of education.

2.4.4   Physicochemical properties

The fate of organic substance, once released in the environment is determined by their physicochemical and biodegradability properties, water solubility, hydrophobicity and tendency to volatilize [63]. These properties will influence whether compounds will remain in the aqueous phase or adsorb to sewage sludge. The tendency for organic compounds to accumulate in sludge solids can be assessed using octanol-water partition coefficient K_{ow} (or log P). Table 2-2 shows the adsorption potential of organic substances depending on their K_{ow} values [64].

Table 2-2: Adsorption potential dependence on log K_{ow}.

Log $K_{ow} \leq 2.5$	Low sorption potential
$2.5 <$ Log $K_{ow} < 4.0$	Medium sorption potential
Log $K_{ow} \geq 4.0$	High sorption potential

2.4.5 Environmental occurrence, fate, and removal of PPCPs

Many scientific articles clearly document the release of PPCPs into the environment, and their presence in ground water, surface waters, and wastewater treatment plant effluents. Furthermore, the occurrence, fate and the concentration of these pharmaceuticals in the environments were also documented [44-51, 53, 55, 56]. Currently, intensive research is underway to investigate the effect of human and animal's medications on the environments. A brief summary of relevant studies in this field is outlined in the following paragraph.

A very comprehensive review is given by Daughton and Ternes about the occurrence, fate and causes of PPCPs in aquatic environment. Their study revealed that the most frequently PPCPs found in environmental sample are acetaminophen, acetylsalicylic acid, betaxol, bezafibrate, biphenylol, bisoprolol, carazolol, carbamazepine, and chlorophene [44]. Studies on tertiary wastewater treatment plant effluents and nearby wells and creeks in the Sequim-Dungeness area of northwest Washington detected 16 compounds in wastewater samples. These compounds are acetaminophen, caffeine, carbamazebine, cimetidine, codeine, cotinine

(metabolite of nicotine), diltiazem, hydrocodone, ketoprofen, metformin, nicotine, paraxanthine, salbutamol, sulfamethoxazole, trimethoprim, and estrone [58]. Kolpin *et al.* (2002) provided the first U.S nationwide reconnaissance of the occurrence of pharmaceuticals, hormones, and other organic wastewater contaminants (OWCs) in streams. The U.S Geological Survey (USGS) found 80% of the sampled streams contained organic contaminants, and the compounds most frequently detected were pharmaceuticals. The most frequently detected compounds are steroids (including cholesterol), nonprescription drugs (such as caffeine, nicotine metabolites, and pain relievers), triclosan (antiseptic), and DEET (*N,N*-Diethyl-*meta*-toluamide is the most common active ingredient in many insect repellents) [49].

Other Studies indicate that PPCPs are already harming wildlife at levels found in water and have shown a potential negative effects on fish, plants, algae, bacteria, earthworm, and dung invertebrates [57]. Example of negative impacts of EDs to aquatic organism is the contribution of synthetic estrogens, also known endocrine disruptors, to the feminization of male fish in waters receiving treated wastewater effluents [56, 65]. On the other hand, it was proven that drinking water contaminated by wastewater is a potential source of exposure to mammary carcinogens and endocrine disrupting compounds from commercial products, natural as well as pharmaceutical hormones. These contaminants are hypothesized to increase breast cancer risk [66]. Also, it has been reported that the effect of the pharmaceuticals and EDs on human body are: reduction of the amount of sperm, increase of the incidence of testicle and prostate cancers; and increased endometriosis [67].

Although concentrations of many pharmaceuticals residues in potable drinking water are so low that they do not pose high risks to human beings [68], the main concern is the chronic and/or synergistic effects of the "cocktail" of pharmaceuticals that humans have released to water-body. Some published reports raised issues related to the possible development of antibiotic-resistant bacteria upon exposure to untreated hospital and domestic sewage effluent [69], the genotoxic effects of some drugs [70], and endocrine disruption by therapeutically administered synthetic and natural hormones [48, 70-72].

Effluents from wastewater treatment plants can be considered as one of the most important sources of pharmaceuticals in the environment [44, 73-74]; therefore, the need for wastewater treatment technologies is required and plays an important role in removing pharmaceuticals and other contaminants [45]. Effective treatment technologies are also needed in order to ensure a safe use for reclaimed wastewater because Palestine suffers from an increase demand for water due to the rising population with very limited resources for water supply [1-3].

The methods of treatment used for the removal of pharmaceuticals from wastewater are the following [74-75]: (1) biodegradation: biological degradation (aerobic/anaerobic by micro-organisms) of drug substances leading to a reduction of the parent compounds and/or their metabolites during wastewater treatment. (2) Deconjugation: conjugates of organic compounds such as steroid hormones have been shown to be readily deconjugated in domestic wastewater and within sewage treatment plants (STPs) due to the large amounts of β-glucuridase enzyme present (produced by the fecal bacterium *Eacherichia coli*). It seems probable that gluconoride and sulfate conjugates of drug compounds will be degraded by the same process. The effect will be to increase the excreted contribution of the active drugs to sewage and effluents. (3) Partitioning: partitioning between the aqueous and organic biomass phases is a key component in determining the ultimate concentrations of organic pollutants. Compounds with high log P (lipophylic molecules) values are known to sorb to sludge, while substances with lower values are more likely to stay in the aquatic phase, depending on the individual compound, and substances sorbing to solids may also be remobilized if they are not strongly bound. (4) Removal during sludge treatment: drugs may also be degraded by abiotic process (hydrolysis) during sewage treatment processes. Many pharmaceuticals are not thermally stable and so might be expected to break down during processes such as composting due to heat (as well as chemical and biodegradation). (5) Photodegradation: several pharmaceutical compounds have been shown to degrade due to the action of sunlight. The most extensively studied of these compounds is the analgesic/anti-inflammatory drug diclofenac, which has been shown to degrade in the aquatic environment due to ultraviolet (UV) light.

Because of an incomplete elimination in wastewater treatment plants, residues of many toxic organic compounds, including pharmaceutical products, are also found in surface waters.

Advanced treatments have to be considered to overcome this problem. Several processes have been studied to remove pharmaceuticals from water. Researchers reported a significant efficiency of nanofiltration and reverse osmosis membrane filtration [74], advanced oxidation processes [72] and activated carbon adsorption [74-75].

In Palestine, this study is the first to report on the removal of pharmaceuticals by ultrafiltration membranes (hollow fiber and spiral wound), their adsorption by activated carbon and clay-micelle filters, and removal by reverse osmosis technology.
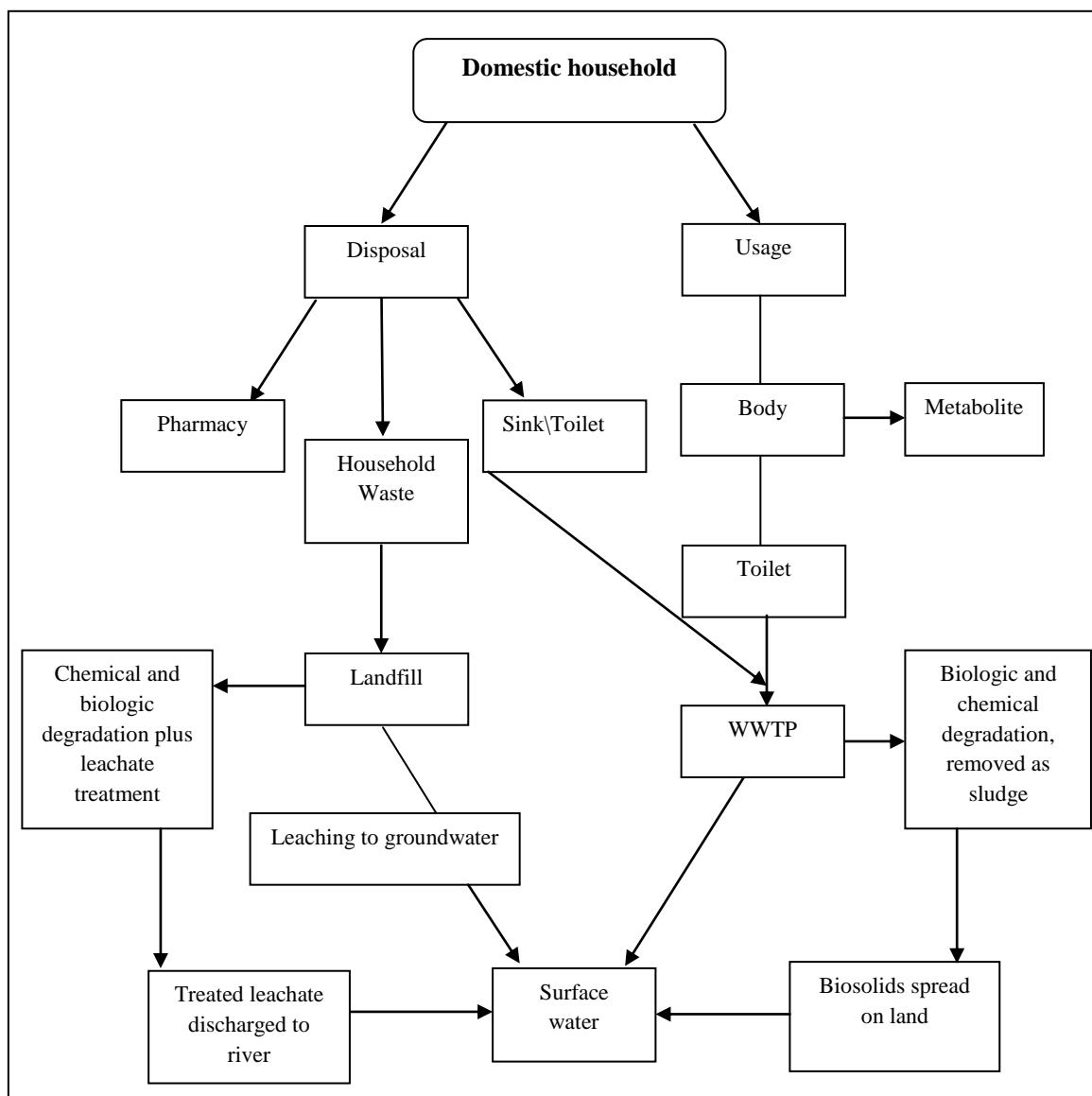
Figure 2-5: Pathways and fate of PPCPs from domestic households to the environment.

Experimental

Chapter Three

Experimental

This chapter is divided into four parts. The first one is concerned with the identification of the most popular drugs prescribed in Palestine. Part two describes the instruments, chemicals, and reagents that this study utilizes. The last two parts deal with specific preparation and analysis of aspirin and paracetamol.

3.1 Part One

3.1.1 Identification of the most popular drugs in Palestine

In the first stage of this study, we have evaluated the most popular drugs in Palestine by conducting a search on 7000 members of Kubat Holeim Klalit using "Omri" program. This program stores the medication files for all population in Israel and East Jerusalem [76].

3.2 Part Two

3.2.1 Instrumentation

3.2.1.1 High Pressure Liquid Chromatography

High Pressure Liquid Chromatography (HPLC-PDA) system consists of an alliance 2695 HPLC from (Waters: Israel), and a waters Micromass® Masslynx ™ detector with Photo diode array (PDA) (Waters 2996: Israel). Data acquisition and control were carried out using Empower ™ software (Waters: Israel). Analytes were separated on a 4.6 mm x150 mm C18 XBridge ® column (5 µm particle size) used in conjunction with a 4.6mmx20 µm XBridge ™ C18 guard column. Microfilter was used with 0.45µm (Acrodisc® GHP, Waters).

3.2.1.2 UV-Spectrophotometer

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

3.2.1.3 pH meter

pH values were recorded on pH meter model HM-30G: TOA electronics ™ was used in this study to measure the pH value for each sample.

3.2.1.4 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.

3.2.1.5 Description of Wastewater Treatment Plant (WWTP)

The wastewater treatment plant (WWTP) at Al-Quds University collects a mixture of black, gray, and storm water. The treatment plant consists of: a primary treatment (two stage primary settling basin), and a secondary (activated sludge with a hydraulic retention time of 16-20 hours, coagulation and chlorination) treatment. Then, the secondary effluent is introduced to the sand filter before entering the ultrafiltration membrane (Hollow fiber and Spiral wound). After the ultrafiltration process, the effluent is subjected to activated carbon column followed by a reverse osmosis (advanced treatment). Then, a blend of all effluents is used for irrigation. The ultra filtration process is made of two small scale membrane treatment plants with a capacity of 12 m^3 /day. The first UF unit is equipped with 2 x 4 inch pressure vessels with pressure resistance up to 150 psi. Each vessel holds two separation membranes (spiral wound with 20 kD cutoffs which is equivalent to 0.01 micron separation rate). The designed permeate capacity of the system is 0.5-0.8 m^3/h. This membrane can remove bacteria, suspended solids,

turbidity agents, oil, and emulsions. The second unit is equipped with two pressure vessels made from Vendor (AST technologies, model number 8000 WW 1000-2M) that houses the hollow fiber membranes with 100 kD cutoff (Vendor, AST technologies, Model no. 8000-WWOUT-IN-8080). The two units are designed to deliver 1.5m^3/h. The reverse osmosis (RO) membranes are made from thin film polyamide which consists of 1 x 4 inch pressure vessel made from composite material with pressure resistance up to 400 psi. The vessel holds two 4 inches special separation membranes (manufactured in thin film polyamide with pH range 1-11 models BW30-4040 by DOW Film Tec.). Membrane anti-scalent (Product NCS-106-FG, made of phosphate in water with active ingredient of phosphonic acid disodium salt) are continuously dosed to the RO feed at concentration of 4 ppm in order to prevent deposition of divalent ions. The system is designed to remove major ions and heavy metals. The designed RO permeate capacity of the system is 0.45- 0.5 m^3/h.

3.2.2 Chemicals and Reagents

Pure standards (>99 %) of aspirin, salicylic acid, paracetamol and *p*-aminophenol are commercially available (Sigma–Aldrich). Methanol and water are both HPLC grade and purchased from Sigma Aldrich. Magnesium sulfate and Charcoal were purchased from Sigma-Aldrich. Octadecyltriethylammonium clay-micelle complex (ODTMA) was obtained as a gift [77] from Professor Nir at The Hebrew University. High purity diethyl ether (>99%) was purchased from Biolab, Hydrochloric acid (37%), and orthophosphoric acid (OPA) were obtained from Riedel-De Haen. Tap water was filtered using 0.22μm filter.

3.3 Part Three

3.3.1 Methods (Aspirin and Salicylic acid)

3.3.1.1 Sample and standards preparation

(a) **Stock solution**: Stock solution was prepared by dissolving aspirin and salicylic acid standards in a mixture of methanol: water that adjusted to pH 3.45 in a ratio (45:55 v\v) to a concentration of 200 ppm for the use in (b).

(b) Calibration curves: A 500 ml stock solution of 1:1 mixture of aspirin and salicylic acid with a final concentration of 200 ppm was prepared in the same manner as for (a). The following diluted solutions were prepared from the stock solution: 1, 2, 3, 5, 10, 20, 40, 60, 100, 120, 140, and 160 ppm. Then, each diluted solution was extracted three times with ether. The ether extracts were combined, dried with anhydrous magnesium sulfate ($MgSO_4$), filtered and evaporated. For HPLC-PDA analysis, the dried residue after evaporated ether was dissolved with a mixture of methanol: water (adjusted to pH 3.45) (45:55 v\v) and was injected to the HPLC apparatus.

3.3.1.2 Kinetic studies on the stability of aspirin in pure water and wastewater

(a) Kinetic study on the stability of aspirin in pure water: For the hydrolysis reaction of aspirin in pure water, a 500 ppm solution was used. The reaction progress was followed by monitoring the disappearance of aspirin and the appearance of salicylic acid with time at (25° C) using the HPLC method.

(b) Kinetic study on the stability of aspirin in presence of wastewater: The same procedure as described in (a) was used for the hydrolysis of aspirin in the presence of wastewater. However, in this case water was replaced with a suspended wastewater in plain water at 25° C.

Samples at specific time intervals were taken. Then, the sample aqueous layer was extracted three times with ether. The ether extracts were combined, dried with anhydrous $MgSO_4$, filtered and evaporated. For HPLC-PDA analysis, the dried residue was dissolved in a mixture of methanol: water (adjusted to pH 3.45) (45:55 v\v) and was injected to the HPLC apparatus.

3.3.1.3 Liquid-liquid extraction

Liquid-liquid extraction procedure was applied to the diluted solutions (samples of calibration curve) and wastewater samples using diethyl ether solvent. Each 10mL of sample was extracted three times with ether. The ether extracts were combined, dried with anhydrous $MgSO_4$, filtered and evaporated. For HPLC-PDA analysis, the dried residue was dissolved in

10mL mixture of methanol: water (adjusted to pH 3.45) (45:55 v\v) and was injected to the HPLC apparatus.

3.3.1.4 Salicylic acid wastewater spiking and sampling

Sample of 60 g of salicylic acid was dissolved in a minimum amount of methanol and was poured immediately into the wastewater tank. Then, eight wastewater samples were collected from different locations of wastewater treatment plant (WWTP) (Figure 3-1). Samples were kept on ice during transportation to the laboratory. Once received, conventional wastewater parameters including total dissolved solids (TDS), temperature, and pH were measured then the samples were filtered and adjusted to pH ($<$ 2) by the addition of few drops of concentrated hydrochloric acid (HCl), and then stored at 4 ℃ until extraction. (See diagram in Figure 3-2).

3.3.1.5 Chromatographic conditions for the separation of aspirin and salicylic acid

All samples were analyzed using HPLC-PDA. The optimum HPLC conditions that was used for the analysis of salicylic acid are: a C-18 as the column, a mixture of water: methanol (water pH adjusted to 3.4 using dilute *o*-phosphoric acid) (55:45 v/v) as a mobile phase, a flow rate of 2 ml/ minute and a UV detection at a wavelength of 230 nm.

3.3.1.6 Adsorption studies of salicylic acid onto micelle-clay complex and charcoal

3.3.1.6.1 Sample and Standards preparation

(a) Stock solution: Stock solution was prepared by dissolving salicylic acid standard in distilled water of 500 ppm concentration, to be used in (b).

(b) Calibration curves: A 500 ml stock solution of salicylic acid with a final concentration of 500 ppm that was prepared in (a) used to prepare the following diluted solutions: 1 ppm, 2 ppm, 4 ppm, 6 ppm, 8 ppm, 10 ppm, 20 ppm,40 ppm, 60 ppm, 80 ppm, and 100 ppm. Then,

absorption of each solution was determined using UV-spectrophotometer at wavelength (λ_{max}) 296.6 nm.

3.3.1.6.2 Adsorption experiment

The salicylic acid was used as adsorbate. Stock solution of salicylic acid was prepared using filtered tap water. All working solutions were prepared by diluting the stock solution with filtered tap water. The amount of adsorbent (powdered activated carbon and clay-micelle complex) was 0.5 g in 100 mL of salicylic acid solutions with the concentration in the range of 100 to 400 ppm. The salicylic acid solutions were shaken at 250 rpm until the solutions have reached their equilibrium for 3 hours. Then, the samples were centrifuged and filtered. The equilibrium concentrations of unadsorbed salicylic acid in the supernatant solutions were measured by UV-visible spectrophotometer. Wavelength of 296.6 nm was used to analyze the concentration of salicylic acid. The mass of pharmaceutical (salicylic acid) sorbed, Q_e, was determined by mass balance as shown below:

$$Qe = \left[\left(\frac{Ci - Ce}{M}\right)\right] \times (Vt)$$

Where Q_e is the mass of pharmaceutical (salicylic acid) sorbed (mg g^{-1}); C_i is the initial concentration (mg L^{-1}); C_e is the equilibrium concentration (mg L^{-1}); M is the mass of adsorbent (g); and V_t is the total volume of liquid in sample (L).
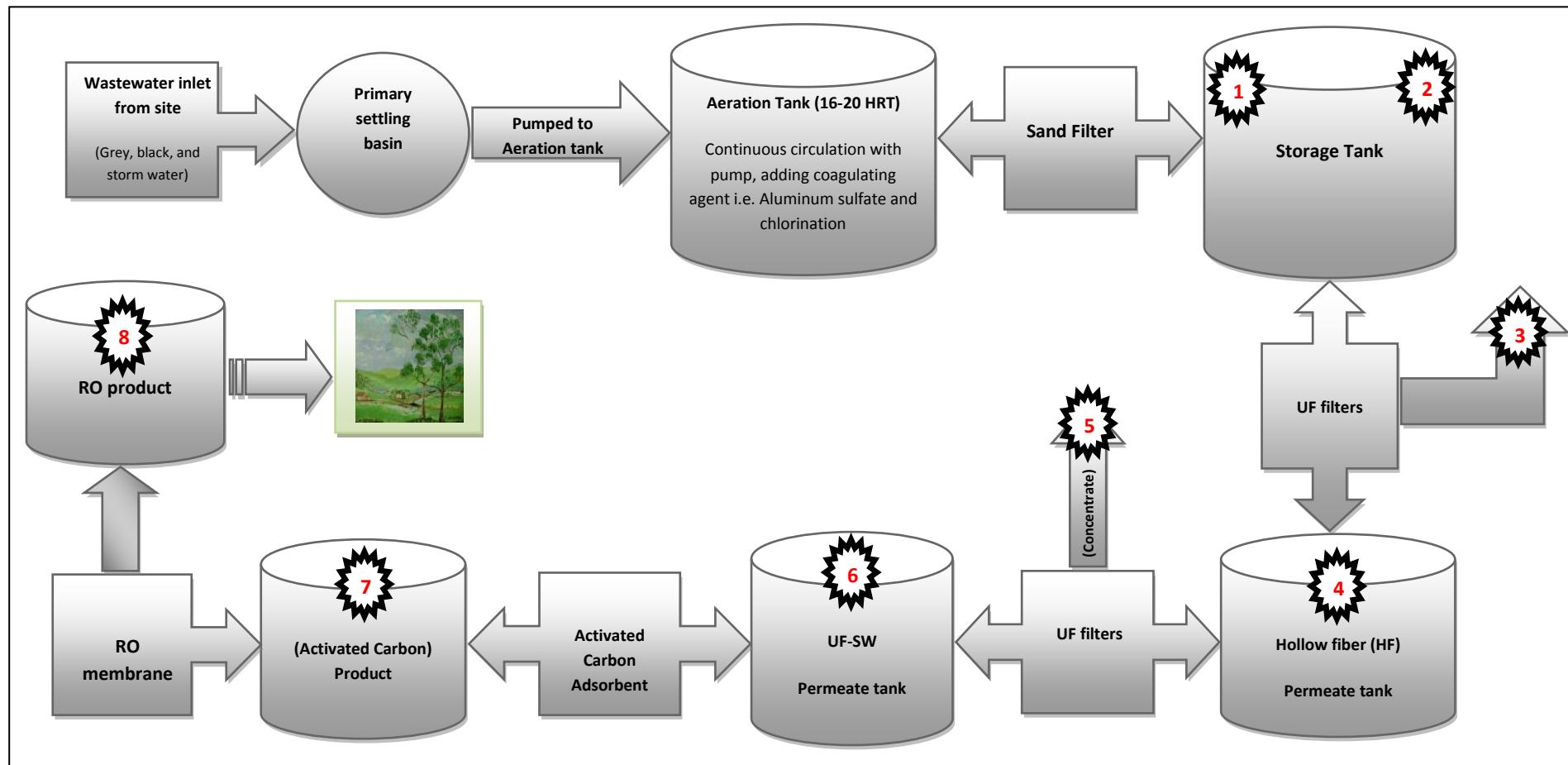
Figure 3-1: Flow diagram showing the process of wastewater treatment plant which consists of HF-UF filters (hollow fiber) and SW-UF (spiral wound), activated carbon and RO filters. The sampling locations in the plant are indicated by red printed Arabic numbers.
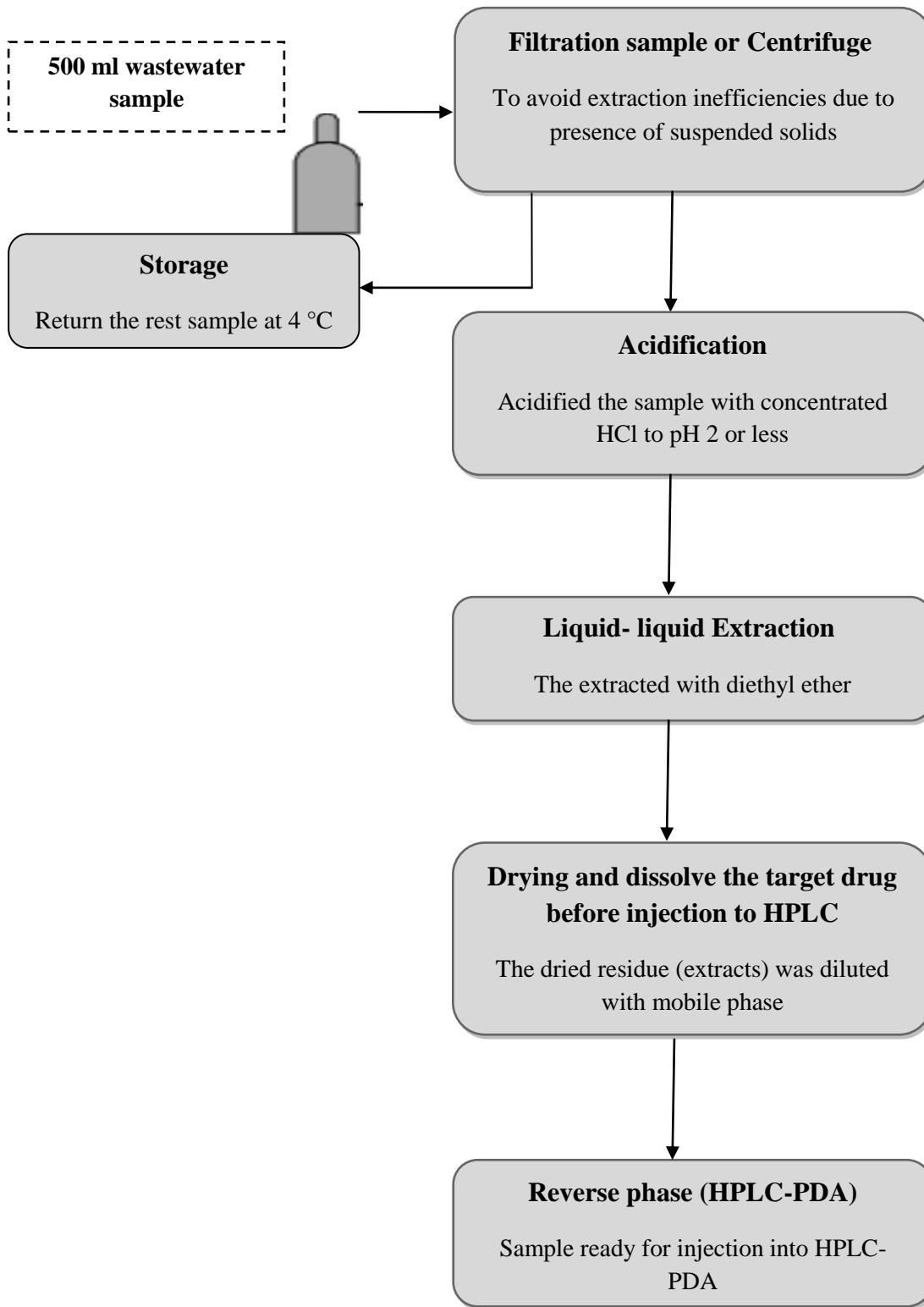
Figure 3-2: Schematic representation for the analysis process of salicylic acid, paracetamol, and *p*-aminophenol. (**Note:** paracetamol and *p*-aminophenol followed all steps without the acidification step).

3.4 Part Four

3.4.1 Methods (Paracetamol and *p*-aminophenol)

3.4.1.1 Sample and standards preparation

(a) **Stock solution:** Stock solution was prepared by dissolving paracetamol standard and *p*-aminophenol standard in acetonitrile and water that adjusted to pH 3.45 in a ratio (10:90) to a concentration 200 ppm to be used in (b).

(b) **Calibration curves**: A 500 ml stock solution of 1:1 mixture of paracetamol and *p*-aminophenol with a final concentration of 100 ppm was prepared in the same manner as for (a). The diluted solutions that were prepared from the stock solution are: 3 ppm, 5 ppm, 10 ppm, 20 ppm, 40 ppm, 60 ppm, 80 ppm and 100 ppm. Then, each diluted solution was extracted three times with ether. The ether extracts were combined, dried with anhydrous magnesium sulfate ($MgSO_4$), filtered and evaporated. For HPLC-PDA analysis, the dried residue after evaporated ether was dissolved with a mixture of water: acetonitrile (water adjusted to pH 3.45 using dilute *o*-phosphoric acid) in a ratio (90:10 v\v) and was injected to the HPLC apparatus.

3.4.1.2 Kinetic studies on the stability of paracetamol in pure water and wastewater

(a) **Kinetic study on the stability of paracetamol in pure water:** For the hydrolysis reaction of paracetamol in pure water, a 200 ppm solution was used. The reaction progress was followed by HPLC method.

(b) **Kinetic study on the stability of paracetamol in the presence of sludge:** The same procedure as described in (a) was used for the hydrolysis of paracetamol in the presence of wastewater. However, in this case water was replaced with a suspended sludge in plain water.

Samples at specific time intervals were taken. Then, the sample aqueous layer was extracted three times with ether. The ether extracts were combined, dried with anhydrous $MgSO_4$,

filtered and evaporated. For HPLC-PDA analysis, the dried residue was dissolved in a mixture of acetonitrile: water (adjusted to pH 3.45) (10:90 v\v) and was injected to the HPLC apparatus.

3.4.1.3 Liquid-Liquid extraction

Liquid-liquid extraction procedure was applied to the diluted solutions (samples of calibration curve) and wastewater samples using diethyl ether solvent. Then, 10 mL of each sample was extracted three times with ether. The ether extracts were combined dried with anhydrous $MgSO_4$ filtered and evaporated. For HPLC-PDA analysis, the dried residue was dissolved with 10 mL of a mixture of acetonitrile: water (adjusted to pH 3.45) (10:90 v\v) and was injected to the HPLC apparatus.

3.4.1.4 Paracetamol and *p*-aminophenol wastewater spiking and sampling

A sample of a mixture of 25 g of paracetamol and 25 g of *p*-aminophenol were dissolved in minimum amount of methanol and were poured immediately into the wastewater tank. Then, eight wastewater samples were collected from different locations of wastewater treatment plant (WWTP) (Figure 3-1). Samples were kept on ice during transport to the laboratory. Once received, conventional wastewater parameters including total dissolved solids (TDS), temperature, and pH were measured, the samples were filtered, and then stored at 4 ºC until extraction (See diagram in Figure 3-2).

3.4.1.5 Chromatographic conditions for the separation of paracetamol and *p*-aminophenol

The optimum HPLC conditions that was used for the separation of paracetamol and *p*-aminophenol are: C-18 as the separation column, a mixture of water: acetonitrile (water pH adjusted to 3.45 using dilute *o*-phosphoric acid) (90:10 v/v) as a mobile phase, flow rate of 1.0 ml/ minute and a UV detection at a wavelength of 247 nm.

3.4.1.6 Adsorption studies of parcetamol and p-aminophenol onto micelle-clay complex and charcoal

3.4.1.6.1 Sample and Standards preparation

(a) Stock solution: Each stock solution of paracetamol and *p*-aminophenol standard was prepared in a separated two volumetric flask by dissolving them in distilled water to a concentration 500 ppm that used in (b).

(b) Calibration curves: Each 500 ml stock solution of paracetamol and *p*-aminophenol with a final concentration of 500 ppm was prepared in (a) used to prepare the following diluted solutions: 1 ppm, 2 ppm, 4 ppm, 6 ppm, 8 ppm, and 10 ppm. Then, the absorption of each solution of paracetamol and *p*-aminophenol was determined using UV-spectrophotometer at wavelength (λ max) 243 nm and 195 nm, respectively.

3.4.1.6.2 Adsorption experiment

Paracetamol and *p*-aminophenol were used as adsorbate. Each stock solution of each one of adsorbate was prepared using filtered tap water. All working solutions were prepared by diluting the stock solution with filtered water. The concentrations of paracetamol and *p*-aminophenol were determined spectrophotometrically by monitoring the absorbance at 243 nm and 195 nm, respectively, where maximum absorbance was observed. All solutions were shaken with an electronic shaker at 250 rpm in 250mL conical flasks. In the adsorption isotherm tests, 0.5 g adsorbent was thoroughly mixed into 100 mL paracetamol solution in the range 200 to 700 ppm, while 0.5 g adsorbent was thoroughly mixed into 100 mL *p*-aminophenol solution in the range 10 to 100 ppm. After the flasks had been shaken for 3 hours, the solution was centrifuged for the separation of solid particles before spectrophotometric measurements of paracetamol and *p*-aminophenol. The mass of paracetamol and *p*-aminophenol adsorbed (Qe) was calculated in the same manner as in salicylic acid experiment (Section 3.3.1.6.2).

Results and discussion

Chapter Four

Identification of the Most Popular Drugs in Palestine

4.1 Introduction

Pharmaceuticals are used in large quantities throughout Palestine as prescription and non-prescription drugs and they reach the environment. So the application of advanced membrane wastewater treatment plant to ensure an efficient removal of these pharmaceuticals from wastewater is considered very important. Hence the current study has been carried out and it is considered as the first study in Palestine. It is anticipated that this study will be a stepping stone for conducting other studies which may be devoted to the investigation of (1) the occurrence, fate and the concentration of these pharmaceuticals once arrived wastewater; (2) the quantitative information on pharmaceuticals concentrations in WWTPs effluents and their removal; and (3) the effect of human and animals medications on the environment (i.e. environmental risk assessment) in Palestine.

4.2 Results and discussion

The data in Table 4-1 was obtained from a research on 7000 Kupat Holeem Klalit members residing in Israel and East Jerusalem. In this search, Omri program was utilized to evaluate the top twenty consumed drugs in the year 2009. This data is applicable also for the Palestinian population due to the similarity in the use of drugs in the two regions. Table 4-1 lists a wide range of pharmaceutical classes including analgesics, vitamin supplements, anti-inflammatory compounds, antibiotics, anti-hypertensive agents, hypoglycemic agents, and lipid regulators [76].

Table 4-1: List of the most top twenty consumed pharmaceuticals in Israel and East Jerusalem.

Drugs name Brand Name, (Generic Name), Dosage form	Uses
Vitacal®+ D (Calcium + vit D) Capsules	Calcium deficiency
Disothiazide® (Hydrochlorthiazide) Tablets	Diuretic
Metformin® (Metformin) Tablets	Anti-diabetic agent
Augmentin® (Amoxycillin + Clavulanic acid) Caplets	Anti-bacterial
Zinnat® (Cefixime) Tablets	Anti-bacterial
Micropirin®, Aspirin® (Acetylsalicylic Acid) Tablets	Anti-coagulant
Moxypen® (Amoxycillin) Syrup	Anti-bacterial
Fusid ® (Furosemide) Tablets	Diuretic
Tribemin ® (Vit B1, B2, B6) Tablets	Vitamin-B deficiency
Acamol® (paracetamol) Tablets	Anti-pyretic and pain killer
Ibufen® (Ibuprofen) Tablets	Anti-inflammatory
Ceforal® (Cephalexin) Capsules	Anti-bacterial
Normiten® (Atenolol) Tablets	Anti-hypertension
Omepradex® (Omeprazole) Capsules	Against stomach ulcer
Simvastatin® (Simvastatin) Tablets	Lowering cholesterol
Glibitic® (Glipizide) Tablets	Anti-diabetic agent
Optalgin® (Dyperone) Tablets	Anti-pyretic and pain killer
Enalpril® (Enalprilate) Tablets	Anti-hypertension
Bezafibrate® (Benzafibrate) Tablets	Lowering triglycerides
Amlodipine® (Amlodipine) Tablets	Anti-hypertension

Based on the above results, aspirin (acetylsalicylic acid, "ASA") and paracetamol (Acetaminophen) were chosen as examples for testing our methodology for removing pharmaceuticals from wastewater. Both pharmaceuticals are widely sold as an over-the-counter (OTC) and prescribed medications and therefore, they are anticipated to occur in wastewater influents. Some physicochemical properties of aspirin and its metabolite, salicylic

acid, and paracetamol, and its metabolite, p-aminophenol, are summarized in Table 4-2. Chapter 5 and 6 describes the fate of these pharmaceutical in wastewater and the efficiency of different wastewater treatment processes in removing them from environment.

Table 4-2: Physicochemical properties [78-79].

Properties	Aspirin	Salicylic acid	Paracetamol (Acetaminophen)	*p*-aminophenol
Structure	aspirin	salicylic acid	paracetamol	p-aminophenol
Chemical formula	$C_9H_8O_4$	$C_7H_6O_3$	$C_8H_9NO_2$	C_6H_7NO
Molecular weight (MW, g mol^{-1})	180.16	138.12	151.16	109.13
Water Solubility (mgL^{-1}), 25 ^{o}C	3000	2000	12742.7	15000
Log K_{ow}	0.46	1.19	0.46-0.89	0.04
pKa at 25 ^{o}C	3.49	2.98	9.5	5.75
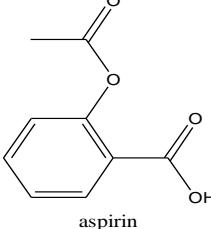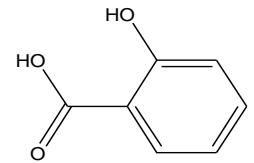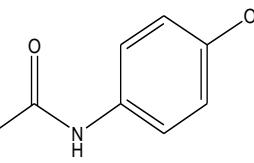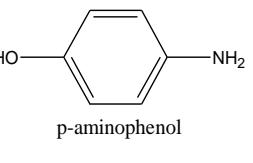
Chapter Five

Aspirin (Acetylsalicylic acid)

5.1 Introduction

Aspirin is a member of a family of chemicals called salicylates. It is chemically known as acetylsalicylic acid "ASA" and is commonly prescribed for its analgesic, antipyretic and anti-rheumatic actions. In addition, aspirin is used once daily in low doses, 75 mg and 100 mg, as prophylactic medicine for the prevention of blood aggregation [62]. The latter (blood aggregation) is the most common cause for heart attack among people over the age of 40. Aspirin is among the top twenty medicines that have been found to be frequently used in East Jerusalem due to its activity as a pain killer [76].

Aspirin is a white powder that is stable in dry conditions but is hydrolyzed to salicylic acid and acetic acid under humid or mist conditions (See Figure 5-1). Salicylic acid itself, which is derived naturally from willow tree bark, has also been used as an antipyretic since ancient times, and it is still used as an additive of some skin-care products and as a food preservative [59].
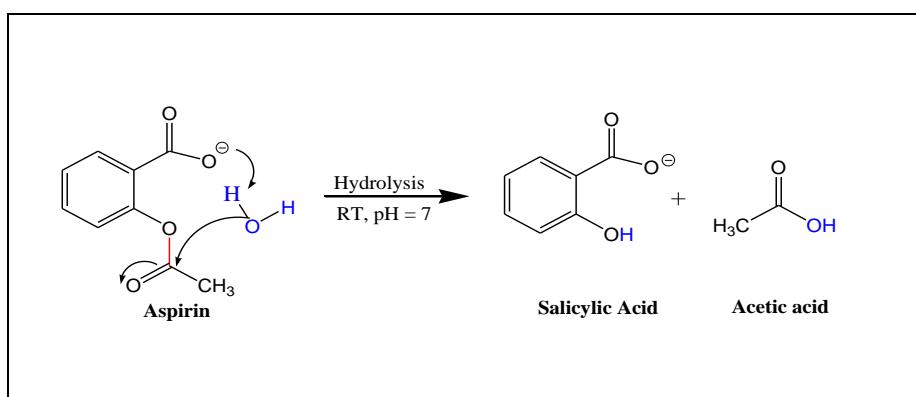
Figure 5-1: Hydrolysis of aspirin (acetylsalicylic acid) to salicylic acid and acetic acid.

When aspirin is ingested, it is quickly and effectively hydrolyzed to the major excretion product, salicylic acid. Then, salicylic acid is metabolized primarily to two major inactive

metabolites: salicyluric acid (75%) arises from conjugation of salicylic acid with glycine, and glucuronide ether and ester (15%) arises from conjugation with glucuronic acid. In addition to these metabolites, small amounts of gentisic acid (1%) metabolites resulting from *p*-hydroxylation mediated by cytochrome P450. These metabolites are then excreted in the urine. Only 5%-10% of a dose is excreted as free salicylic acid (See Figure 5-2) [80-81].

The occurrence of aspirin was reported in treated wastewater in many countries around the world. Nakada and coworkers, reported that aspirin had the highest concentrations among other pharmaceuticals, ranging from 470 to 19400 ngL^{-1} in the sewage treatment plants (STPs) influents in Tokyo, Japan, and were removed efficiently during primary and secondary treatments (> 90% efficiency) [82]. Terns and coworkers reported average concentrations of salicylic acid in public owned wastewater treatment plants (POTWs), which received influents from both domestic, municipal, and industrial sewage system 54 μgL^{-1} influents and in effluents of 0.5 μgL^{-1} [83].

The removal of salicylic acid (hydrolytic product of aspirin) has been studied by different research groups. Gagnon and coworkers studied the disinfection processes in terms of removing salicylic acid. They found that salicylic acid was eliminated at a rate greater than 50% at an ozone dose of 10 mgL^{-1}, and a higher rate (70%) was observed when 20 mgL^{-1} of ozone was used. The ozone technology is better than ultraviolet (UV) radiation in removing salicylic acid [84]. A high biodegradation of salicylic acid (>94%) during biologically activated sludge (BAC) process supported that salicylic acid was removed efficiently by BAC [85]. Whereas according to Heberer (2002b), there are several other sources of salicylic acid in sewage, besides to the active metabolite of aspirin. These sources such as the use of salicylic acid as keratolytic, dermatice or preservative of food are even more likely to be responsible for the occurrence of this compound in the aquatic environment [59].
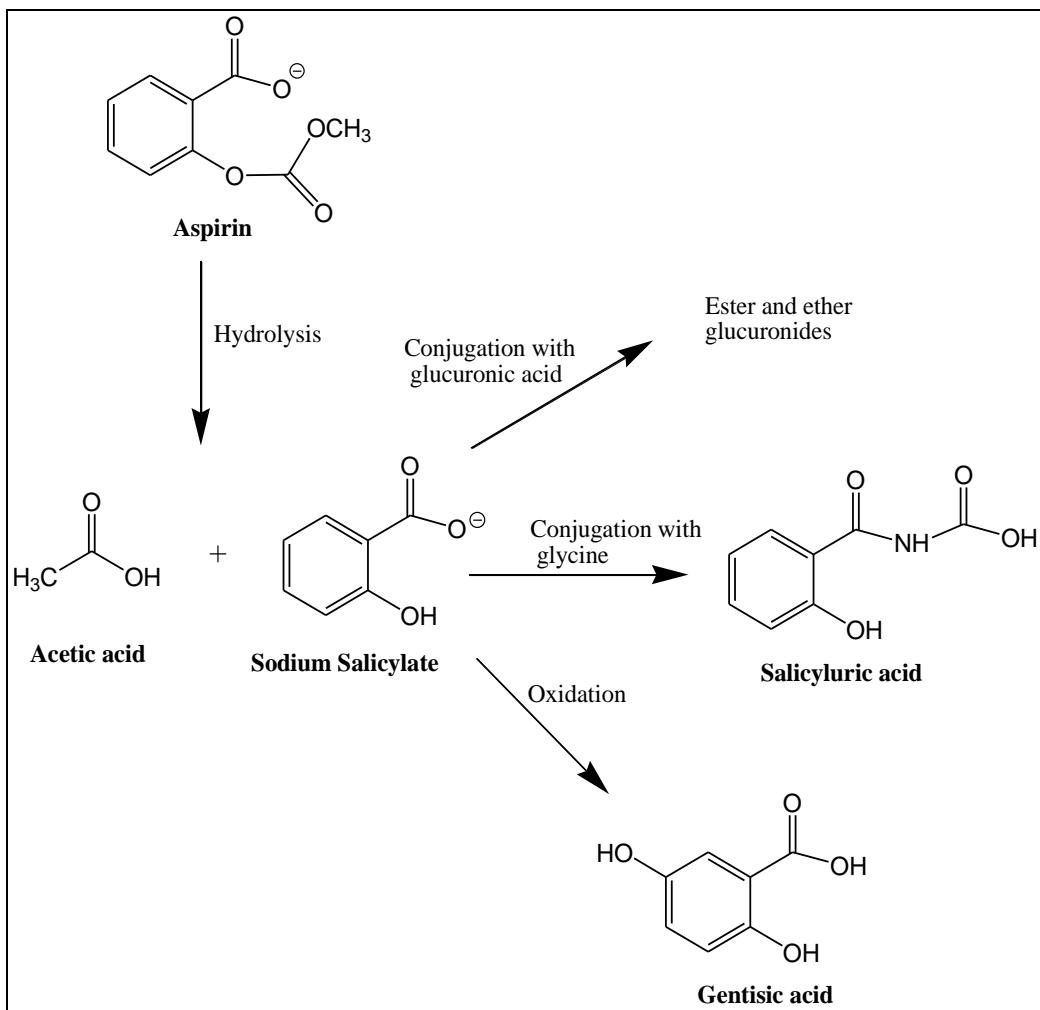
Figure 5-2: Major metabolism pathways for aspirin.

5.2 Calibration curve for Aspirin and Salicylic acid with extraction

The calibration curve was obtained by plotting peak area versus concentration and is displayed in Figures 5-3 and 5-4 (ten data points) for aspirin and salicylic acid, respectively. They showed excellent linearity with correlation coefficient (R^2) of 0.998 for aspirin and 0.999 for salicylic acid. This indicates that the method used is linear in the range of 0-200 ppm for both aspirin and salicylic acid.
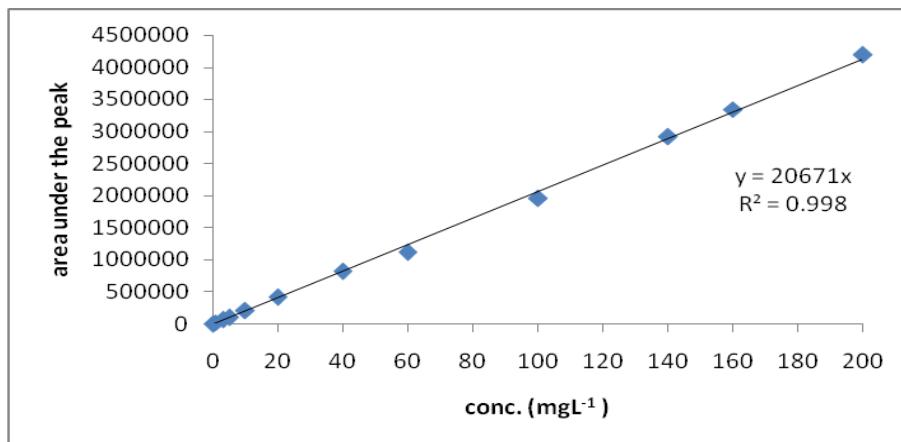
Figure 5-3: A calibration curve for Aspirin.
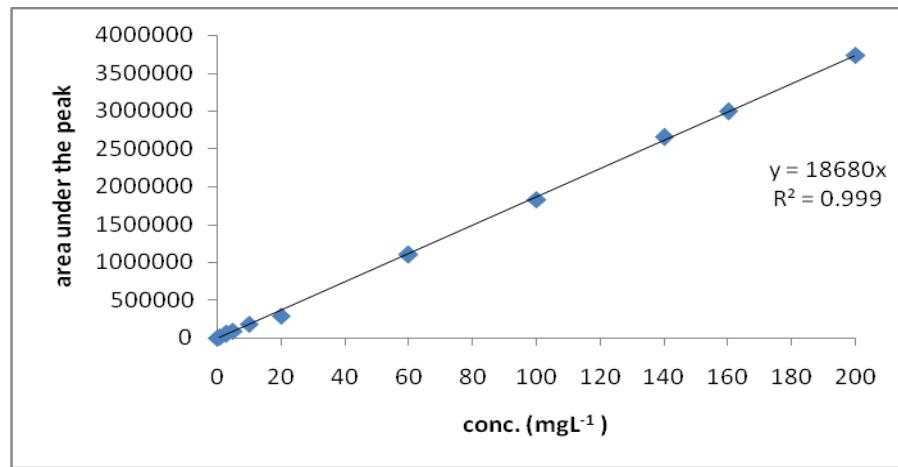
Figure 5-4: A calibration curve for Salicylic acid.

5.3 Kinetic studies on the stability of aspirin in pure water and wastewater

Since many pharmaceuticals might undergo degradation upon their standing in aqueous medium and wastewater environment, kinetic studies on aspirin in pure water and wastewater conditions have been undertaken. The kinetic results which were monitored by HPLC revealed that aspirin undergoes hydrolysis to salicylic and acetic acids (Figure 5-1). The rate of hydrolysis of aspirin is a function of temperature, amount of moisture present, and pH-dependent. Figures 5-5 and 5-6 display the HPLC chromatograms of aspirin hydrolysis in pure water after 5 days incubation at 25° C and of aspirin hydrolysis in the presence of wastewater

after 8 days at 25° C, respectively. The peak at retention time of 4.3 minutes belongs to aspirin and that at 5.5 minutes to the hydrolysis product, salicylic acid. The kinetic data was examined for linear relationship. A linear correlation with a high correlation coefficient (R^2) was found between ln [aspirin] (logarithms of aspirin concentration) and time. The correlation results obtained are illustrated graphically in Figure 5-7.

In pure water, the linear correlation between ln [aspirin] and time is shown in Figure 5-7 (blue points) where the correlation coefficient (R^2) was 0.9892. The rate constant for the hydrolysis of aspirin in pure water obtained from the slope of the plot in Figure 5-7 is 0.1104 s^{-1}. While the first order rate of the hydrolysis of aspirin in pure water is 0.357 x 10^{-8} Ms^{-1}. Similarly, kinetic study on the stability (hydrolysis) of aspirin in wastewater was conducted. The HPLC monitoring results for the hydrolysis of aspirin after incubation in wastewater for 10 days were examined for correlation-ship. The correlation of ln [aspirin] versus time gave a straight line with a correlation coefficient (R^2) of 0.9532 as shown in Figure 5-7 (pink points). The first order rate calculated from the slope of the curve gave a value of 0.841 x 10^{-8} Ms^{-1}.

The following calculations of the initial rate of hydrolysis of aspirin in pure water and wastewater further illustrate this point.

$$\text{Rate of first order reaction} = dC/dt = k\ [C]$$

Concentration of aspirin = weight of aspirin/Molecular weight of aspirin in 1 liter = 500 ppm = 0.5g ÷ 180 = 0.00278 M.

Initial Rate of the hydrolysis of aspirin in pure water at 25° C = 0.1104 x 0.00278 = 3.069 x 10^{-4} M day^{-1} = (3.069 x 10^{-4})M/(24 x 60 x 60) sec = 0.357 x 10^{-8} Ms^{-1}.

Initial Rate of the hydrolysis of aspirin in the presence of wastewater at 25° C = 0.2617x 0.00278 = 7.269x10^{-4} M day^{-1} = 7.269 x 10^{-4} M /(24 x 60 x 60) sec. = 0.841 x 10^{-8} Ms^{-1}.

The literature value for the rate constant for the hydrolysis of aspirin (Fersht and Kirby, 1967) at 39° C is 1.1 x 10^{-5} s^{-1} [86]. The initial rate at this temperature for the 500 ppm was equal to 0.29 x10^{-8} Ms^{-1}. This value is similar to that obtained in pure water and is significantly less than that in wastewater.
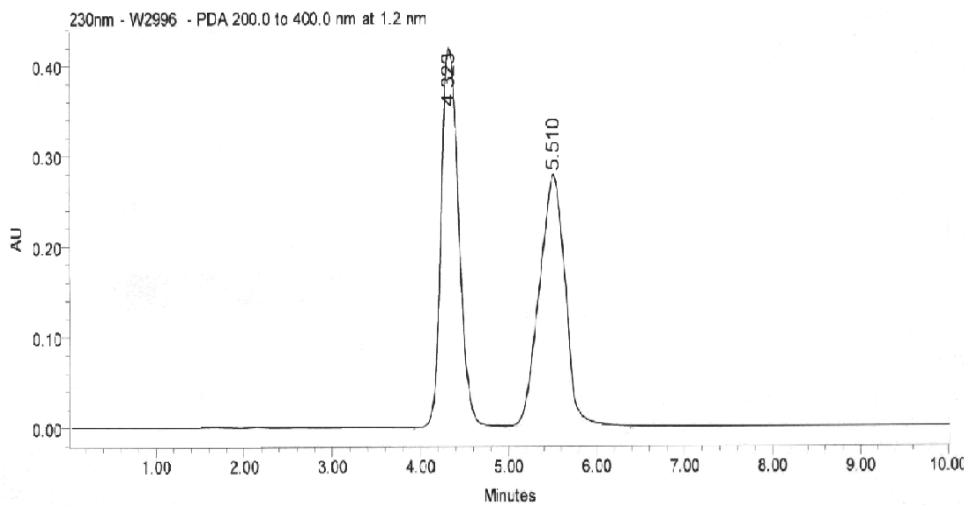
Figure 5-5: Chromatogram showing the hydrolysis of aspirin in pure water after 5 days.
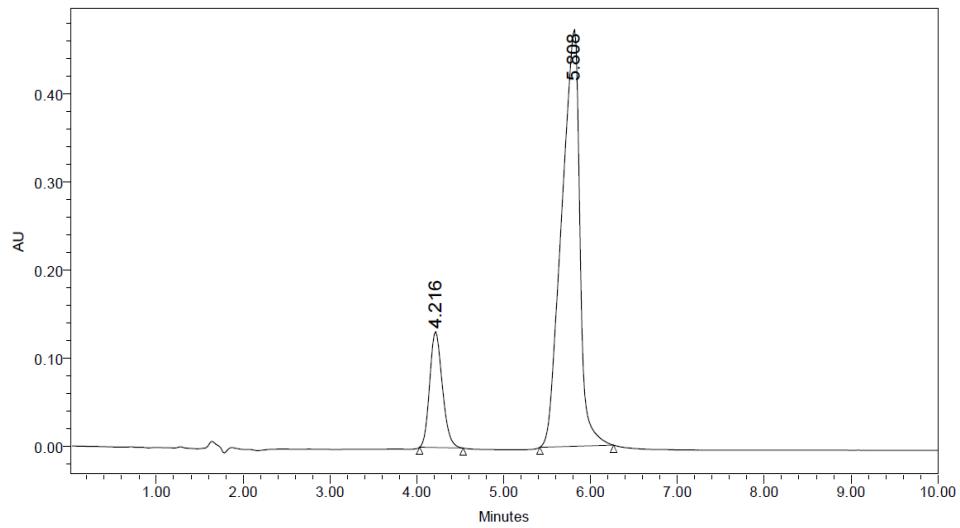
Figure 5-6: Chromatogram showing the hydrolysis of aspirin in presence of wastewater after 8 days.
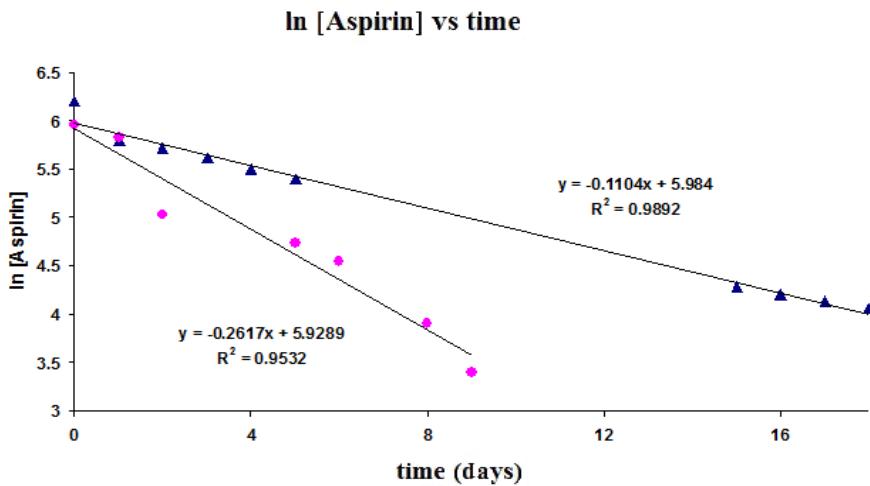
Figure 5-7: Plot of ln [Aspirin] vs. time (days). ▲ (Blue points) is for the hydrolysis of aspirin in pure water at 25° C and ● (pink points) is for the hydrolysis of aspirin in the presence of wastewater at 25° C.

Comparison of the hydrolysis reaction rate values in pure water and in wastewater solution (0.357×10^{-8} Ms^{-1} vs. 0.845×10^{-8} Ms^{-1}) revealed that the hydrolysis in wastewater proceeds at faster rate than in pure water. The accelerations in rate can be attributed to the content nature of the wastewater (consisting of variety of enzymes, bacteria and heavy metals) which can act as a catalyst for such reactions.

5.4 The efficiency of membranes and activated carbon adsorbent in terms of removal of salicylic acid

Since aspirin is not a stable chemical entity and undergoes a fast hydrolysis in the presence of wastewater, our goal was to find a suitable method for removing the aspirin hydrolyzed products, salicylic and acetic acids. It is known that acetic acid has a low boiling point and it is expected that within a short time of its formation will be evaporated. On the other hand, the solid non-volatile salicylic acid has to be removed by one of the well known filtration methods. Therefore, efforts in this research were concentrated on a membrane removal of the hydrolyzed product (salicylic acid) from wastewater samples rather than the removal of the parental drug (aspirin).

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The use of membranes for wastewater treatment, especially coupling the membrane systems with other technologies such as pretreatment using activated sludge treatment process and/or ultrafiltration membranes followed by the use of reverse osmosis technologies could be the most efficient method in treating wastewater and removing a variety of pharmaceuticals [87].

5.4.1 Salicylic acid wastewater spiking and sampling

60 gram of salicylic acid standard was dissolved in a minimum amount of methanol then poured into the wastewater treatment plant (WWTP). Eight wastewater samples were collected from different locations of the wastewater treatment plant located at Al-Quds University main campus at Abu-Dies using pre-cleaned 500 ml glass containers. Figure 3-1 illustrates the sampling points (s.p.) which are as follows: Blank sample "before the addition of salicylic acid sample" (s.p. 1); AST ultrafiltration "hollow fiber" (AST-UF-HF) influent (s.p. 2) and effluent (s.p. 4), Nirosoft ultrafiltration "spiral wound" (Nirosoft UF-SW) effluent (s.p. 6), activated carbon adsorbent effluent (s.p. 7), and reverse osmosis membrane effluent (s.p. 8). The eight samples were kept in an ice bath during transportation to the laboratory. Conventional wastewater parameters for the eight samples including total dissolved solids (TDS= 630 mgL^{-1}), temperature (27° C), and pH were measured (pH= 7.3), then the samples were filtered and adjusted to pH < 2 by the addition of a few drops of concentrated hydrochloric acid (HCL) to improve the recovery for the acidic drug (salicylic acid), and then the sample was centrifuged for 15 minutes to remove suspended materials prior to extraction of acidic drugs, and then stored at 4° C. The samples solutions were extracted by ether in order to clean up samples and this step is required in order to concentrate the target compound (salicylic acid) to a detectable level, and after evaporation were dissolved in mobile phase and analyzed by HPLC (see diagram in Figure 3-2). The results obtained are summarized in Table 5-1.

5.4.2 The efficiency of (UF-HF) and (UF-SW), activated carbon and RO membranes at the removal of salicylic acid.

Figures 5-8, 5-9, 5-10 and 5-11 display the chromatograms of salicylic acid after passing through UF-HF, UF-SW membranes, activated carbon adsorbent, and reverse osmosis, respectively. Table 5-1 shows the efficiency of the removal of salicylic acid during ultrafiltration by hollow fiber (UF-HF), spiral wound (UF-SW), activated carbon adsorbent, and reverse osmosis. Examination of the results listed in Table 5-1 reveals that the efficiency of the hollow fiber and spiral wound ultrafiltration process is more than 70% (samples No. 4 and 6) at the removal of salicylic acid in the effluent sample. The rejected salicylic acid was found and accumulated in the brine and concentrate of this machine. On the other hand, the efficiency for the removal of salicylic acid during activated carbon adsorbent is more than 98% (Sample No. 7).

The removal of salicylic acid from wastewater could rely on two types of processes which are based on mass transfer separtion accomplished by the transfer of mass from one phase to another (i.e. UF and RO membranes) and the sorption "i.e. adsorption" mechanism (activated carbon). It can be concluded that using a consequent system of the two types of UF membranes followed by activated carbon adsorbent is highly efficient to remove salicylic acid and hence there was no need to pass it through a reverse osmosis membrane.
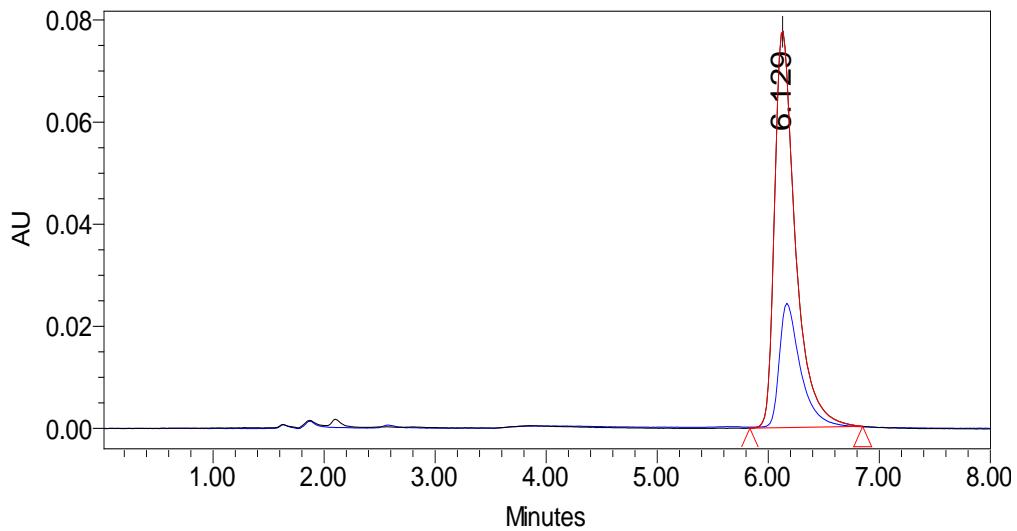
Figure 5-8: Chromatogram showing the initial concentration of salicylic acid and after running the HF-UF (it represents the concentration of samples number 2 and 4, "see Figure 3-1").
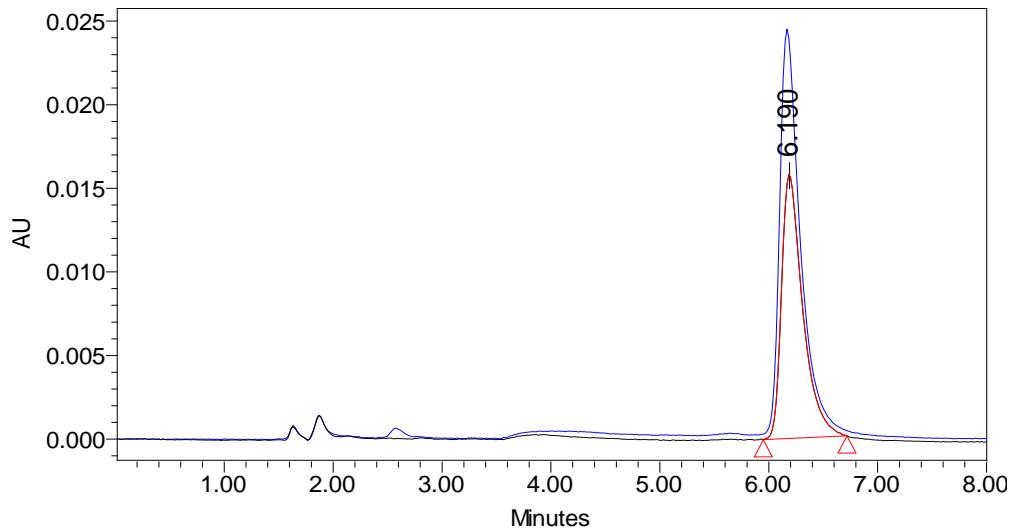
Figure 5-9: Chromatogram showing the concentration of salicylic acid before and after running the SW-UF (it represents the concentration of samples number 4 and 6, "see Figure 3-1").
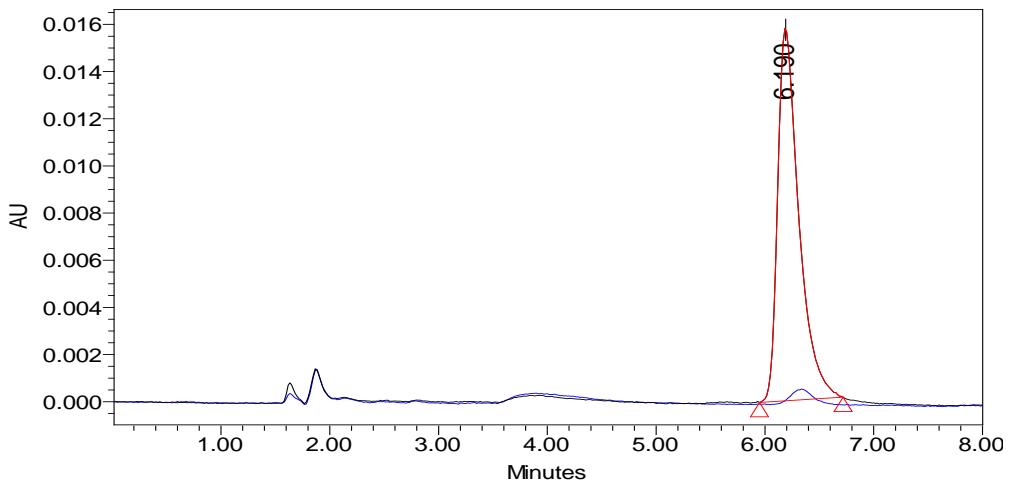
Figure 5-10: Chromatogram showing the concentration of salicylic acid after passing activated carbon adsorbent (it represents the concentration of samples number 6 and 7 "see Figure 3-1").
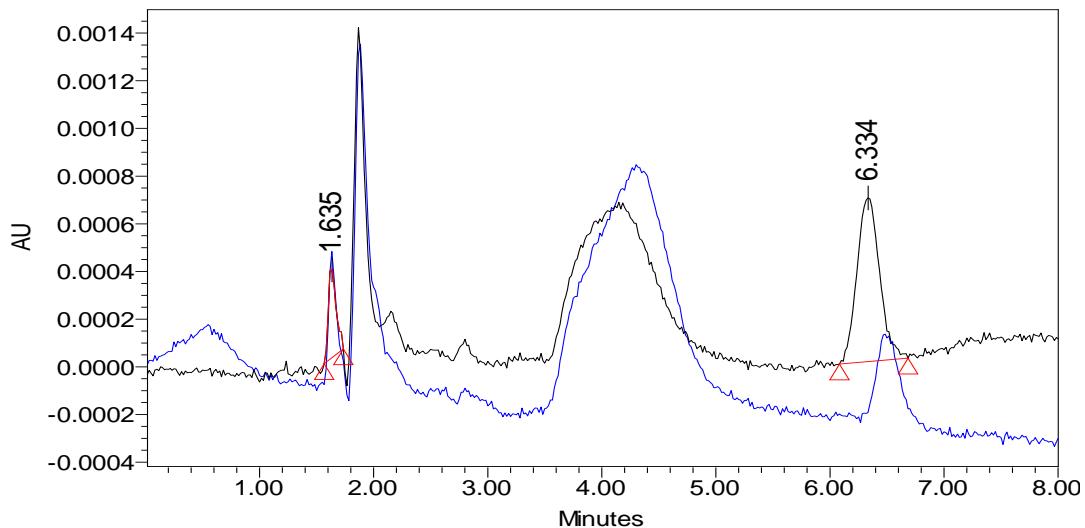
Figure 5-11: Chromatogram showing the concentration of salicylic acid before and after passing reverse osmosis (it represents the concentration of samples number 7 and 8 "see Figure 3-1").

Table 5-1: Performance of hollow fiber ultrafiltration (HF), spiral wound ultrafiltration (SW), activated carbon adsorbent, and reverse osmosis in terms of removal of salicylic acid from wastewater.

Sample location number (See Figure 3-1)	Name of sample location	Concentration of salicylic acid (mg L^{-1})
Sample No. 1	Blank (before addition 60 g of salicylic acid)	0
Sample No. 2	Initial concentration of salicylic acid before running wastewater treatment plant	54.30
Sample No. 3	Brine of AST (ultrafiltration-hollow fiber)	38.62
Sample No. 4	Product of AST (ultrafiltration-hollow fiber)	17.02
Sample No. 5	Nirosoft (ultrafiltration-spiral wound fiber) "concentrate"	14.43
Sample No. 6	Permeate of Nirosoft (ultrafiltration-spiral wound fiber)	11.42
Sample No. 7	Product of activated carbon adsorbent	0.50
Sample No. 8	Product of reverse osmosis	0.00

5.5 Adsorption studies of salicylic acid onto a clay-micelle complex and powdered activated charcoal

Adsorption mechanism depends on the physicochemical properties of the pharmaceutical and the aquifer media properties. Adsorption of salicylic acid onto a clay-micelle complex and pure activated charcoal adsorbents was investigated and described in this section.

5.5.1 Calibration curve for salicylic acid using uv-visible spectrophotometer

The calibration curve for salicylic acid was obtained by plotting absorbance of the drug versus its concentration, and is displayed in Figure 5-12. The results shown in the figure indicate an excellent linearity with a correlation coefficient (R^2) of 0.999 which indicates that the method used is linear in the range of 0-100 ppm for salicylic acid.

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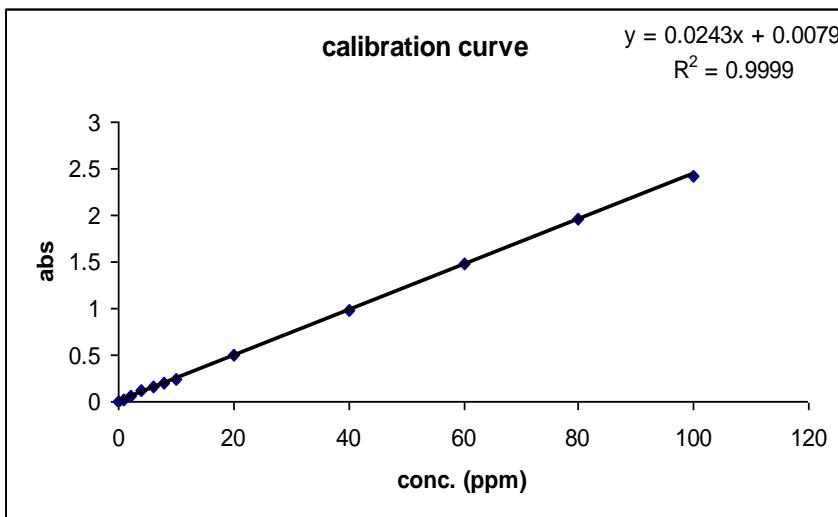
Figure 5-12: Absorbance versus concentration (mgL^{-1}) of salicylic acid (λ_{max} = 295nm).

5.5.2 Adsorption isotherm

A clay micelle complex is prepared by mixing a specific type of a clay mineral (montmorillonite) with a cationic surfactant. In this study, octadecyltrimethylammonium (ODTMA) (Figure 5-13) with a critical micelle concentration (CMC) value of 0.3 mM was employed for a complex formation. A certain mass of clay was introduced into a solution of ODTMA until reaching a concentration of $1*10^{-2}$ M then stirred for 24 hours. The complex was filtered and dried then mixed with excess sand [77].
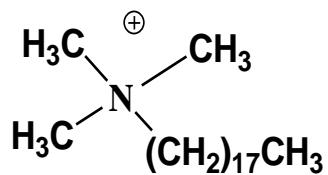
Octadecyltrimethylammonium (ODTMA)

Figure 5-13: Structure of Octadecyltriethylammonium (ODTMA).

Equilibrium relationships between adsorbents (i.e. clay-micelle complex and pure activated charcoal) and adsorbate (i.e. salicylic acid) are described by adsorption isotherms. The most common model for adsorption process is Langmuir adsorption isotherm. The latter is the most widely used for modeling equilibrium data and determination of the adsorption capacity [88]. Its linear form is represented by equation (1):

$$Ce/Qe = 1/(k \times Q\ max) + Ce/Q\ max \ldots\ldots\ldots\ldots\ldots\ldots Eq\ (1).$$

Where C_e is the equilibrium concentration of the pharmaceutical (salicylic acid) (mg L^{-1}); Q_e is the equilibrium mass of the adsorbed pharmaceutical (salicylic acid) per gram of complex (mg g^{-1}); k is the Langmuir constant; and Q_{max} is the maximum mass of pharmaceutical (salicylic acid) removed per gram of complex (mg g^{-1}) and it represents the adsorption capacity of the pharmaceutical onto adsorbents.

Tables 5-2 and 5-3 list the initial and final equilibrium concentrations of salicylic acid obtained from the adsorption test. Also, the tables include the fixed mass of the clay-micelle complex and activated charcoal used in the test. Figure 5-14 shows a linear correlation between the terms C_e/Q_e and C_e which indicates that the adsorption of salicylic acid onto the clay micelle complex and activated charcoal follows the Langmuir isotherm model.
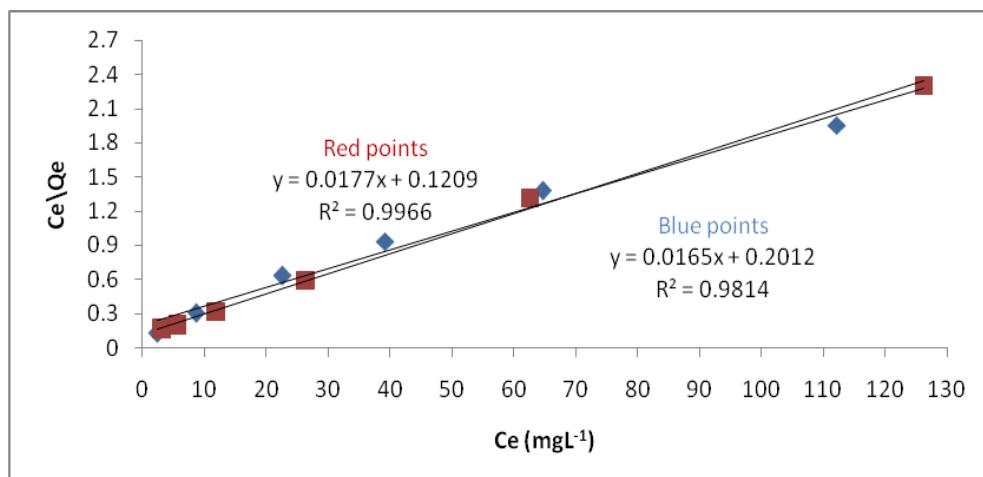
Figure 5-14: Langmuir isotherms for the removal of salicylic acid by a clay micelle complex (red point) and by powdered activated charcoal (blue points).

Q_{max} and k parameters for the removal of salicylic acid by the clay-micelle complex were determined from the slope and the intercept of (red points) shown in Figure 5-14. The calculated values of Q_{max} and k are shown in the following equations (2-3):

$$Slope = \frac{1}{Qmax} = 0.0177; \ Qmax = 56.49\frac{mg}{g} \ldots\ldots\ldots\ldots\ldots\ldots Eq \ (2).$$

$$Intercept = \frac{1}{(k \times Qmax)} = 0.1209; \ k = 0.1464 \ldots\ldots\ldots\ldots\ldots\ldots Eq \ (3).$$

Langmuir isotherm for the removal of salicylic acid by activated charcoal adsorbent was done in order to compare it with the efficiency for the removal by a clay-micelle complex. Blue points shown in Figure 5-14 describe the Langmuir isotherm for the removal of salicylic acid by charcoal. The calculated values of Q_{max} and k are shown in the following equations (4-5):

$$Slope = \frac{1}{Qmax} = 0.0165; \ Qmax = 60.60\frac{mg}{g} \ldots\ldots\ldots\ldots\ldots\ldots Eq \ (4).$$

$$Intercept = \frac{1}{(k \times Qmax)} = 0.2012; \ k = 0.0820 \ldots\ldots\ldots\ldots\ldots\ldots Eq \ (5).$$

Comparison between the calculated values of the Q_{max} for the adsorption of salicylic acid on the clay-micelle complex and activated charcoal reveals that both have comparable efficiency. However, since the quantity of the cationic surfactant in the clay-micelle complex is about three times smaller than the quantity of activated carbon in charcoal, so the adsorption efficiency of the clay micelle is much superior than activated charcoal. This complex by virtue of its positive charge with hydrophobic region is capable of binding negatively charged organic molecules and bacteria as well [77]. Meanwhile, from the results in Table 5-4, it can be observed that the activated carbon in charcoal has a higher capacity than the clay micelle complex in sorption of salicylic acid. This demonstrates that hydrophobic interactions are significant even for polar salicylic acid compound.

Table 5-2: Concentrations in equilibrium obtained for the adsorption test of salicylic acid onto the adsorbent clay-micelle complex used.

Conc. (initial) (mgL^{-1})	Mass (initial) (mg) per 100 ml	Conc. (final) (mgL^{-1}), (Ce)	Mass (final) (mg)	M initial - M final; (mg)	Qe (mg g^{-1}) = (M initial - M final) /0.5	Ce/Qe
100	10	3.17	0.31	9.68	19.36	0.16
150	15	5.55	0.55	14.44	21.66	0.19
200	20	11.97	1.19	18.80	37.60	0.31
250	25	26.48	2.64	22.35	44.70	0.59
300	30	62.51	6.25	23.748	47.49	1.31
400	40	126.11	12.61	27.38	54.77	2.23

Table 5-3: Concentrations in equilibrium obtained for the adsorption test of salicylic acid onto the adsorbent powdered activated charcoal used.

Conc. (initial) (mgL^{-1})	Mass (initial) (mg) per 100 ml	Conc. (final) (mgL^{-1}), (Ce)	Mass (final) (mg)	M initial - M final; (mg)	Qe (mg g^{-1}) = (M initial - M final) /0.5	Ce/Qe
100	10	2.45	0.24	9.75	19.50	0.12
150	15	8.62	0.86	14.13	28.27	0.30
200	20	22.65	2.26	17.73	35.46	0.63
250	25	39.18	3.91	21.08	42.16	0.93
300	30	64.61	6.46	23.53	47.07	1.37
400	40	112.14	11.21	28.78	57.57	1.95

Table 5-4: Langmuir adsorption parameters (k and Q_e), the square of correlation coefficient (R^2) of salicylic acid onto both adsorbents.

Pharmaceutical	Adsorbents	Langmuir sorption parameters		
		k	Q_{max} (mg g^{-1})	R^2
Salicylic acid	Clay micelle complex	0.15±0.0042	56.49±1.159	0.99±0.0022
	Powdered activated charcoal	0.08±0.0.0197	60.60±1.156	0.98±0.0021

Chapter Six

Paracetamol (Acetaminophen)

6.1 Introduction

Paracetamol was chosen for this study because it is widely used as an over-the-counter analgesic and antipyretic drug in Palestine. It is among the top twenty medicines that were found to be frequently used in East Jerusalem [76]. Also, it is heavily used all over the world [89].

Paracetamol is metabolized primarily in the liver into non-toxic products. Three metabolic pathways are notable as shown in Figure 6-1. Glucuronidation is believed to account for 40% to 60% of the metabolism of paracetamol. Sulfation (sulfate conjugation) may account for 20–40% [90]. N-hydroxylation and rearrangement, then Glutathione (gamma-glutamyl-L-cysteinylglycine: GSH) conjugation, accounts for less than 15%. The hepatic cytochrome P450 enzyme system metabolizes paracetamol, forming a minor yet significant alkylating metabolite known as NAPQI (*N*-acetyl-*p*-benzo-quinone imine). NAPQI is then irreversibly conjugated with the sulfhydryl groups of glutathione. All three pathways yield final products that are inactive, non-toxic, and eventually excreted by the kidney. In the third pathway; however, the intermediate product NAPQI is toxic. NAPQI is primarily responsible for the toxic effects of paracetamol [80].

Paracetamol has been found with a concentration of up to 6 mg L^{-1} in European sewage treatment plants (STP) effluents [49] up to 10 mg L^{-1} in natural waters in USA [91], and even more than 65 mg L^{-1} in the Tyne River, UK. Furthermore, according to a reconnaissance study of organic wastewater contaminants in USA waters, paracetamol was determined to occur at a frequency of 23.8% in surface water at a maximum concentration of 10 $\mu g L^{-1}$ [49]. Recently removal of aqueous paracetamol by electrochemical [92], ozonation, H_2O_2-UV oxidation, and semiconductor photo catalysis have been reported for degradation of paracetamol [93].
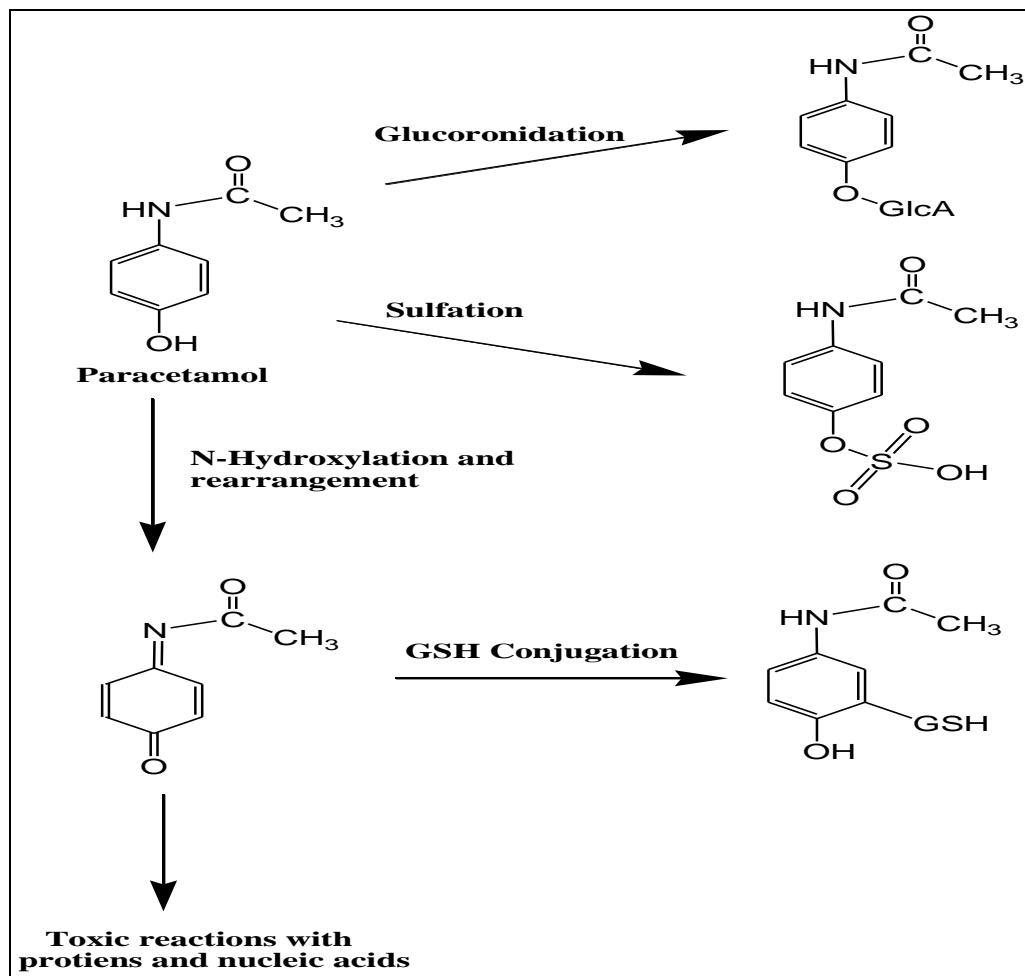
Figure 6-1: Metabolic pathways for paracetamol.

6.2 Calibration curve for paracetamol and *p*-aminophenol.

The calibration curve was obtained by plotting peak area versus concentration and is displayed in Figures 6-2 and 6-3 (seven data points) for paracetamol and *p*-aminophenol, respectively. The figures show excellent linearity with a correlation coefficient (R^2) of 0.997 for paracetamol and 0.986 for *p*-aminophenol. This result indicates that the method used is linear in the range of 0-100 ppm for both paracetamol and *p*-aminophenol.
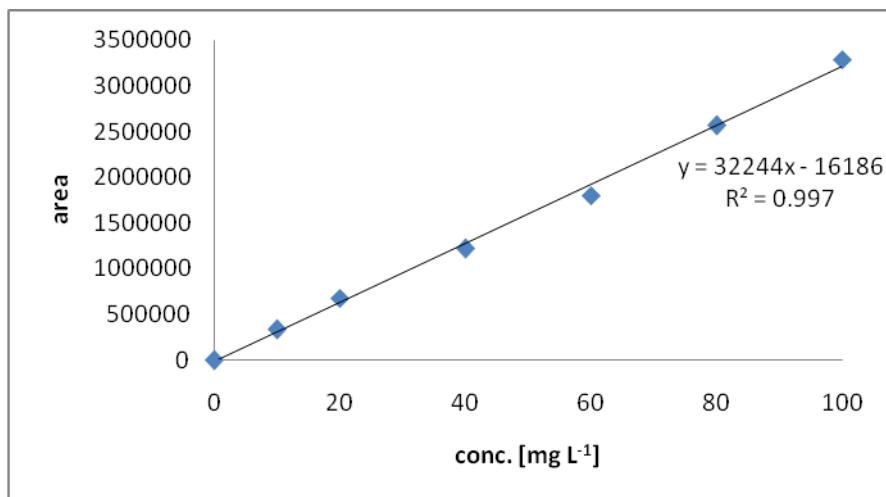
Figure 6-2: A calibration curve for paracetamol.
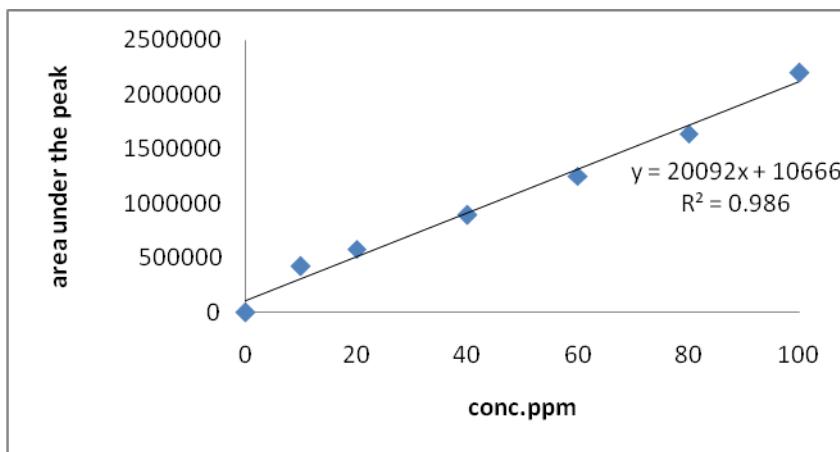
Figure 6-3: A calibration curve for *p*-aminophenol.

6.3 Kinetic studies on the stability of paracetamol in pure water and wastewater

Paracetamol is available in different dosage forms: tablet, capsules, drops, elixirs, suspensions, and suppositories. Its saturated aqueous solution has a pH of about 6 and is stable (half-life over 20 years), meanwhile under abnormal conditions (heat, pH, temperature, etc.) its stability decreases and it degrades slowly forming a mixture of contaminants, such as *p*-aminophenol and acetic acid, (Figure 6-4). This reaction could also be carried out by enzymatic cleavage or by microwave assisted alkaline hydrolysis of amide bond [90].
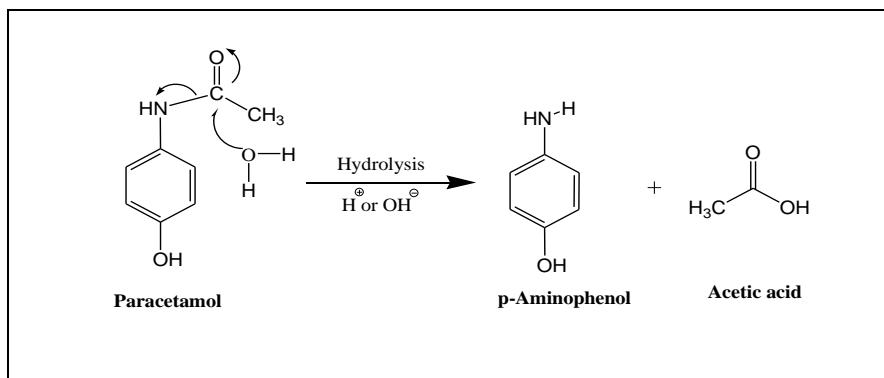
Figure 6-4: Hydrolysis pathway for paracetamol.

In a similar manner to that of aspirin, kinetic studies on paracetamol in pure water have been carried out at 25° C. The kinetic results which were monitored by HPLC revealed that paracetamol was very stable in pure water due to the high activation energy needed to break down the amide bond. No degradation products were observed after incubation for more than two weeks as presented in Figures 6-5 and 6-6.
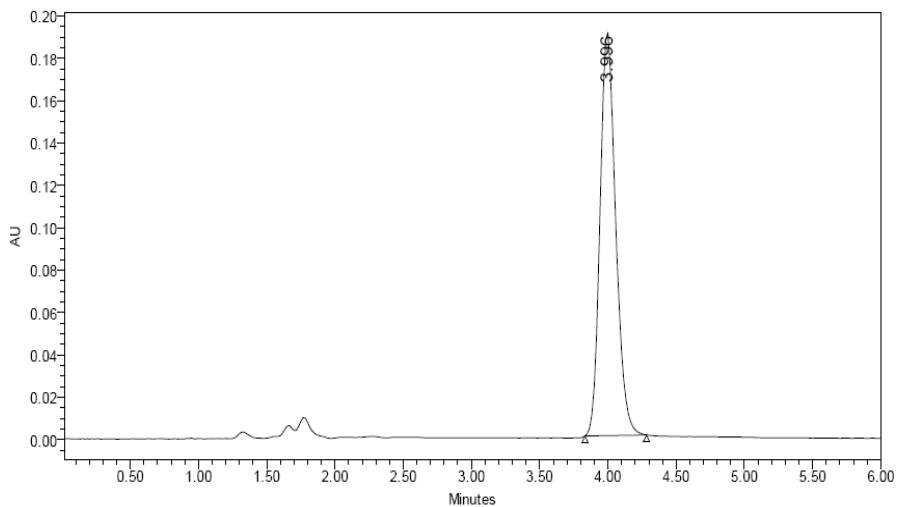
Figure 6-5: Chromatogram of paracetamol after 0 day of incubation in pure water.
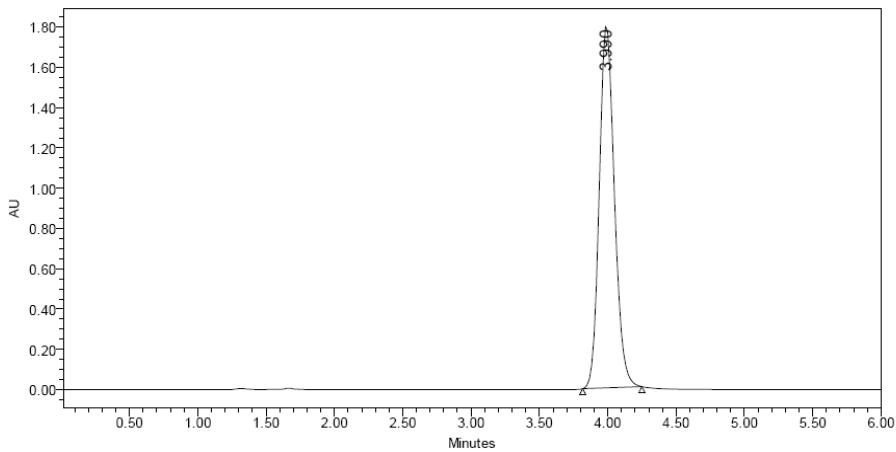
Figure 6-6: Chromatogram of paracetamol after 2 weeks incubation in pure water.

On the other hand, HPLC monitoring of a solution of paracetamol in the presence of wastewater gave a gradual disappearance of a peak characterized as the reactant at a retention time of 3.92 minutes and a gradual appearance of a new peak at a retention time of 1.97 minutes characterized as a degradation product. Figure 6-7 shows a representative chromatogram for the hydrolysis of paracetamol to products. Characterization of the compound that showed a peak at 1.97 minutes revealed that the hydrolyzed product of paracetamol is *p*-aminophenol. This result was supported by the fact that when a standard solution of *p*-aminophenol was injected to HPLC. Only one peak at a retention time of 1.97 minutes was obtained. Figures 6-7 and 6-8 display the HPLC chromatograms of paracetamol in wastewater after 2 days incubation at 25° C and the hydrolysis of paracetamol in presence of wastewater after 7 days at 25° C, respectively. The hydrolysis of paracetamol in the presence of wastewater can be attributed to the content nature of the wastewater (consisting of variety of enzymes, bacteria and heavy metals, etc.) which can act as a catalyst for the cleavage of the amide bond (Figure 6-4).

The kinetic data obtained from the HPLC monitoring (7 days) was examined for linear correlation. The correlation results indicates a linear correlation between ln [paracetamol] and time with a correlation coefficient (R^2) = 0.8855 (Figure 6-9).
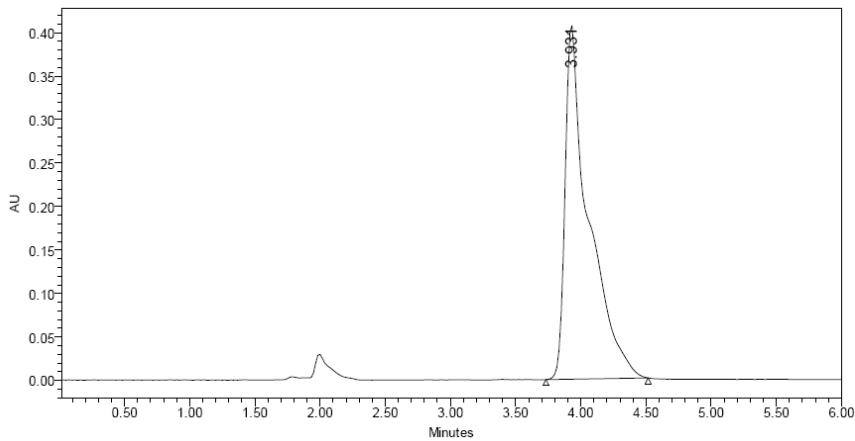
Figure 6-7: Chromatogram showing the hydrolysis of paracetamol after 2 days of incubation in presence of wastewater at 25° C.
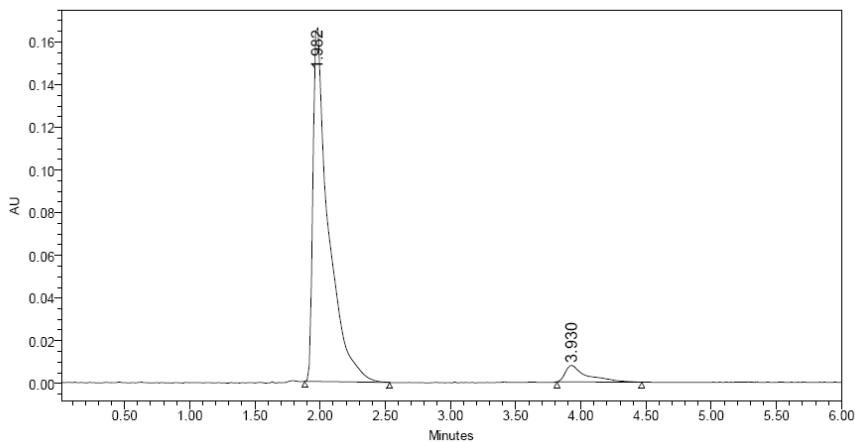
Figure 6-8: Chromatogram showing the hydrolysis of paracetamol after 7 days of incubation in presence of wastewater at 25° C.

The rate constant for the hydrolysis of paracetamol obtained from the slope of the plot in Figure 6-9 is 0.6529 s^{-1}. The initial rate of the hydrolysis of paracetamol in wastewater was calculated as follows:

Concentration of paracetamol = weight of paracetamol/Mw of paracetamol in 1 liter = 200 ppm = 0.20 g/151.1 = 1.323 x 10^{-3} M.

Rate of first order reaction = dC/dt = k [C].

Initial Rate of the hydrolysis of paracetamol in the presence of wastewater at 25°C = 0.6529 M x 1.3230 x 10^{-3}day = 8.6378 x10^{-4} M/day = 8.6378 x 10^{-4}M /(24 x 60 x 60) sec = 1.0 x 10^{-8} Ms^{-1}.
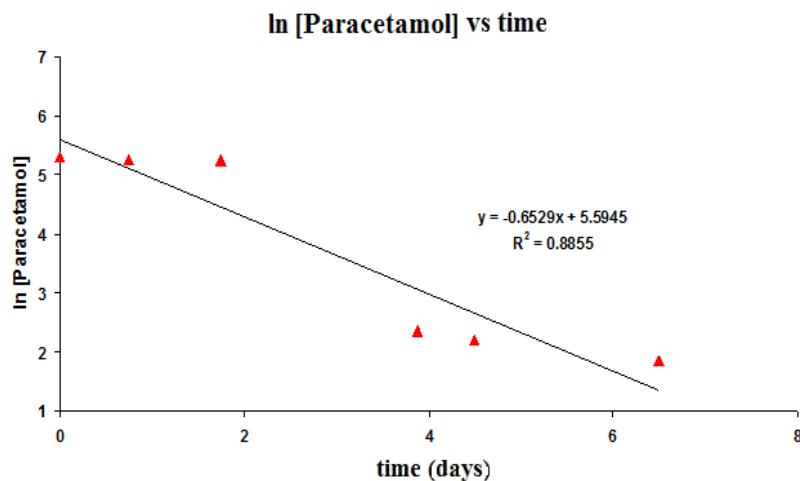
Figure 6-9: Plot of ln [Paracetamol] vs. time (days) for the hydrolysis of paracetamol in the presence of wastewater at 25° C.

6.4 The efficiency of membranes and activated carbon adsorbent in terms of removal of paracetamol and *p*-aminophenol

6.4.1 Paracetamol and its hydrolyzed product (p-aminophenol) wastewater spiking and sampling

Samples of 25 gram of paracetamol and 25 gram of its hydrolyzed product (*p*-aminophenol) were dissolved in a minimum amount of methanol and were introduced to WWTP. Then, eight wastewater samples were collected from different locations of WWTP located in Al-Quds University main campus at Abu-Dies using pre-cleaned 500 mL amber glass bottles. Samples from the sampling points 2, 4, 6, 7 and 8 (Figure 3-1) were collected for observing the membranes removal efficiency: ultrafiltration (hollow fiber and spiral wound), then followed by activated carbon and reverse osmosis membrane.

6.4.2 The efficiency of HF-UF (hollow fiber), SW-UF (spiral wound), activated carbon and RO membranes at the removal of paracetamol and p-aminophenol.

Since paracetamol was found to undergo hydrolysis to *p*-aminophenol when kept standing for long time in wastewater we sought to study the efficiency of the different membranes on the removal of both paracetamol and *p*-aminophenol. Figures 6-10, 6-11, 6-12, and 6-13 display the chromatograms of concentration of paracetamol and *p*-aminophenol after passing HF-UF , SW-HF membranes, activated carbon adsorbent, and reverse osmosis, respectively. While Table 6-1 summarizes the results of the efficiency of HF-UF, SW-UF, activated carbon adsorbent and reverse osmosis membranes in removing paracetamol and *p*-aminophenol. Inspection of the results listed in Table 6-1 indicates that the efficiency of the ultrafiltration process is more than 40% (samples No. 4 and 6) at the removal of paracetamol and more than 70% at that of *p*-aminophenol in the effluent samples. On the other hand, both the activated carbon adsorbent and the reverse osmosis membranes were significantly superior in the removal of paracetamol and *p*-aminophenol. In the case of acetaminophen a removal of 99% was observed by both membranes whereas a 100% removal was achieved when 4-aminophenol was tested (Sample No. 7 and 8).
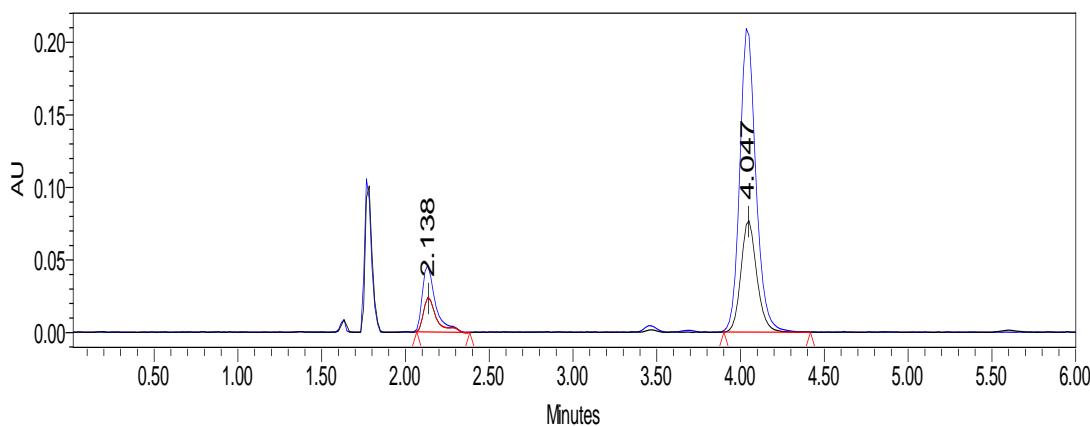
Figure 6-10: Chromatogram showing the initial concentration of paracetamol and *p*-aminophenol before and after running the HF-UF (it represents the concentration of samples number 2 and 4 "see Figure 3-1").
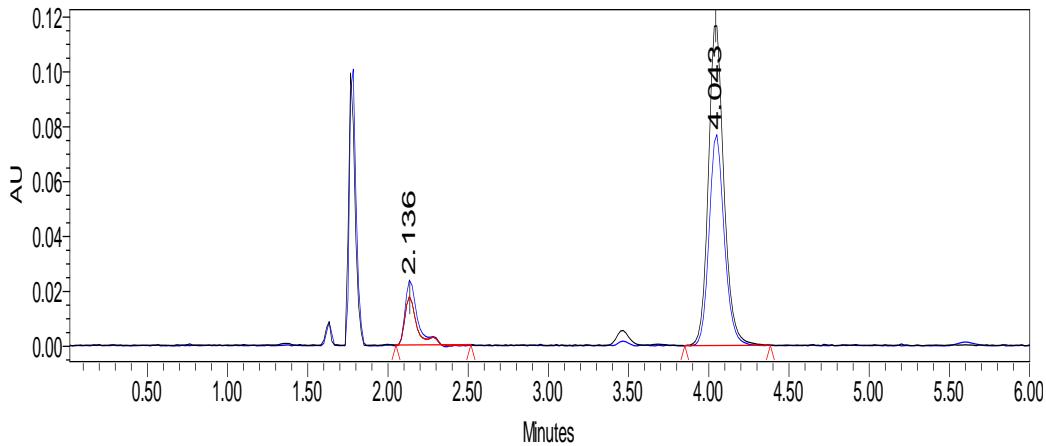
Figure 6-11: Chromatogram showing the concentration of paracetamol and *p*-aminophenol before and after running SW-UF (it represents the concentration of samples number 4 and 6 "see Figure 3-1").
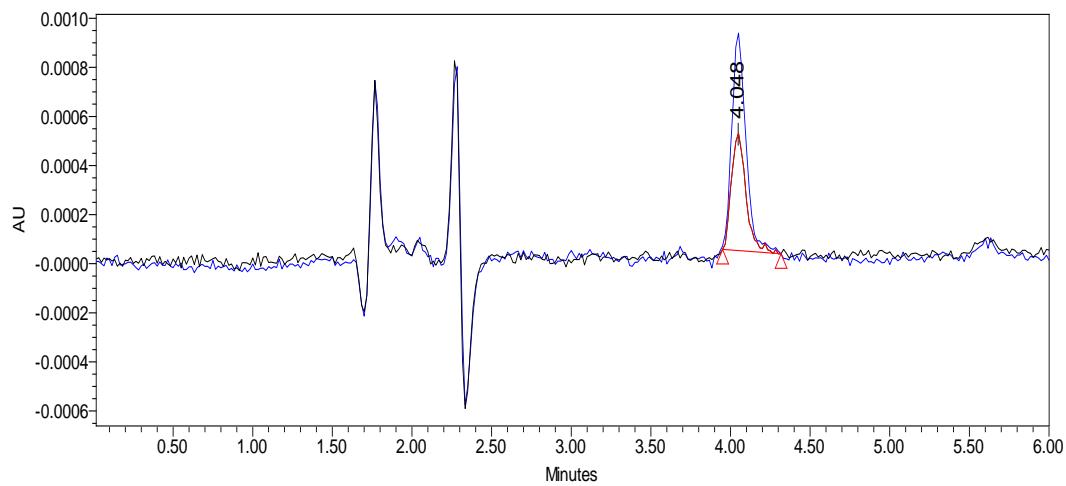
Figure 6-12: Chromatogram showing the concentration of paracetamol and *p*-aminophenol before and after passing activated carbon adsorbent (it represents the concentration of samples number 6 and 7 "see Figure 3-1").
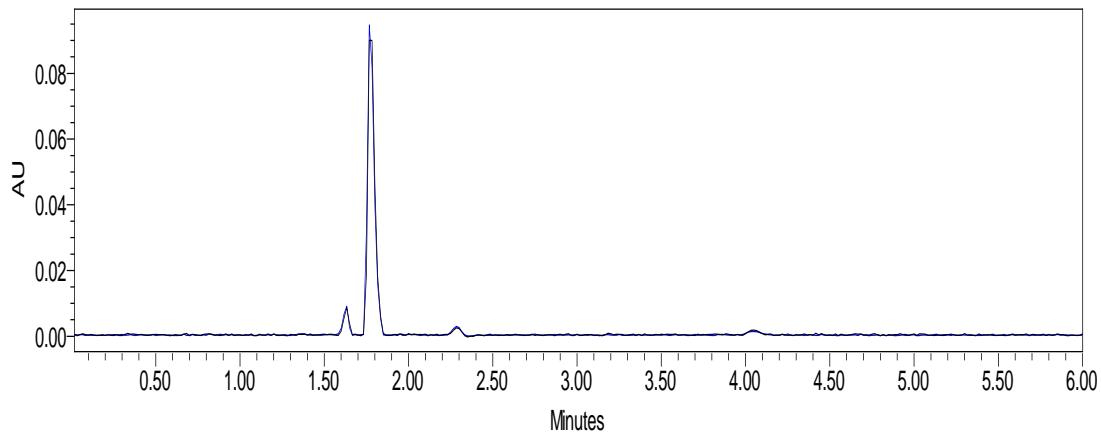
Figure 6-13: Chromatogram showing the concentration of paracetamol and *p*-aminophenol before and after passing Reverse Osmosis (RO) membrane (it represents the concentration of samples number 7 and 8 "see Figure 3-1").

Table 6-1: Performance of ultrafiltration hollow fiber (UF-HF), and ultrafiltration spiral wound (UF-SW), activated carbon adsorbent and reverse osmosis in terms of removal of paracetamol and *p*-aminophenol from wastewater.

Sample location No. (See Figure 3-1)	Sample location name	Concentration of paracetamol (mg L^{-1})	Concentration of *p*-aminophenol (mg L^{-1})
Sample No. 1	Blank (before addition of 25g paracetamol and *p*-aminophenol)	0	0
Sample No. 2	Initial concentration of paracetamol and *p*-aminophenol before running wastewater treatment plant	20.95	24.3
Sample No. 3	Brine of HF-Ultrafiltration	20.92	20.4
Sample No. 4	Product of HF-Ultrafiltration	12.47	6.87
Sample No. 5	SW-Ultrafiltration "concentrate"	11.84	5.22
Sample No. 6	Permeate of SW-Ultrafiltration	10.73	2.82
Sample No. 7	Product of activated carbon adsorbent	0.223	0
Sample No. 8	Product of reverse osmosis	0.01	0

6.5 Adsorption studies of paracetamol and *p*-aminophenol onto a clay-micelle complex and powdered activated charcoal.

6.5.1 Calibration curve for paracetamol using UV-visible spectrophotometer.

The calibration curve was obtained by plotting the absorbance of paracetamol versus its concentration and is illustrated in Figure 6-14. The Figure shows excellent linearity between the two variables with a correlation coefficient (R^2) of 0.998. This indicates that the method used is linear in the range of 0-40 ppm for both paracetamol.
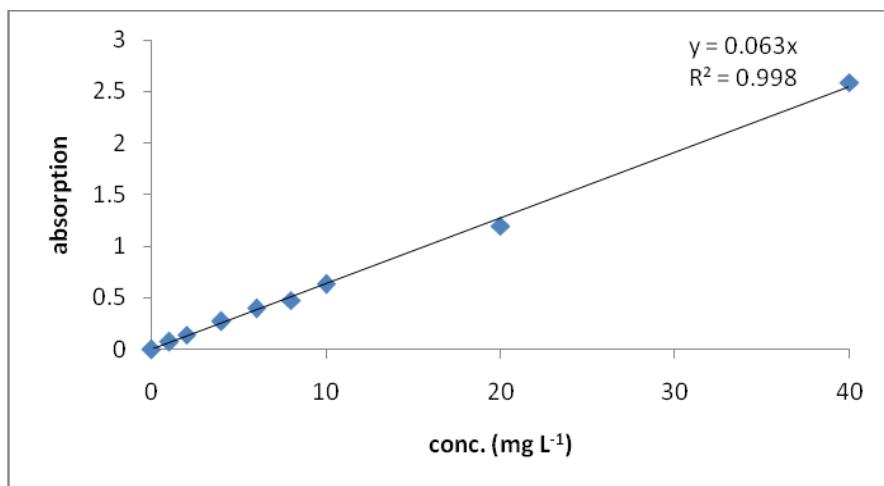
Figure 6-14: Absorbance vs. concentration (mg L^{-1}) of paracetamol (λ_{max} = 243nm).

6.5.2 Calibration curve for *p*-aminophenol using UV-visible spectrophotometer

The calibration curve was obtained by plotting the absorption of *p*-aminophenol versus its concentration and is illustrated in Figure 6-15. The figure indicates excellent linearity with a correlation coefficient (R^2) of 0.994.
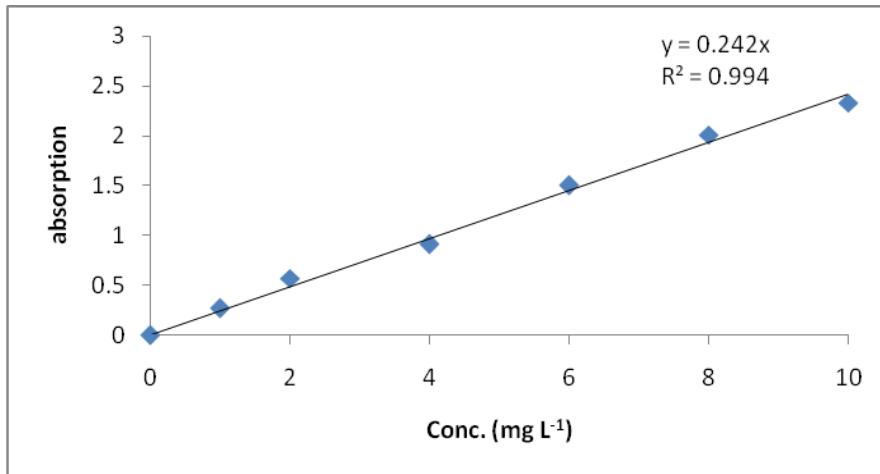
Figure 6-15: Absorbance versus concentration mg L^{-1} of *p*-aminophenol (λ_{max} = 195nm).

6.5.3 Adsorption isotherm

In a test similar to that conducted for salicylic acid, the sorption for the removal of paracetamol and its hydrolysis product *p*-aminophenol by a clay-micelle complex and powdered activated charcoal is well described by Langmuir adsorption isotherm as shown by the correlation of Ce\Qe versus Ce (Figure 6-16). Tables 6-2, 6-3, 6-4 and 6-5 list the initial and final equilibrium concentrations of both chemicals obtained from the adsorption test. Also, the tables include the fixed mass of the clay-micelle complex and powdered activated charcoal used in the test.

The sorption of paracetamol and *p*-aminophenol onto both adsorbents are well fitted with langmiur sorption isotherm since the correlation coefficients for the Langmuir sorption of paracetamol and *p*-aminophenol were found in the range of 0.9921-0.9968 (Table 6-6). The calculated Q$_{max}$ and k values for the removal of paracetamol by a clay-micelle complex are 185.185 mg x g^{-1}, 0.0325, respectively. The values for *p*-aminophenol are 15.33 mg x g^{-1} and 0.461, respectively. The Langmuir isotherms for the removal of both chemicals by powdered activated charcoal gave Q$_{max}$ values 129.87 mg x g^{-1} for paracetamol and 12.5 mg x g^{-1} for *p*-aminophenol and the calculated k values were 0.35 for paracetamol and 4.82 for *p*-aminophenol. Comparison of the calculated Q$_{max}$ values of both chemicals using a clay-micelle complex and powdered activated charcoal reveals that the former is more efficient than the later in removing paracetamol and *p*-aminophenol.
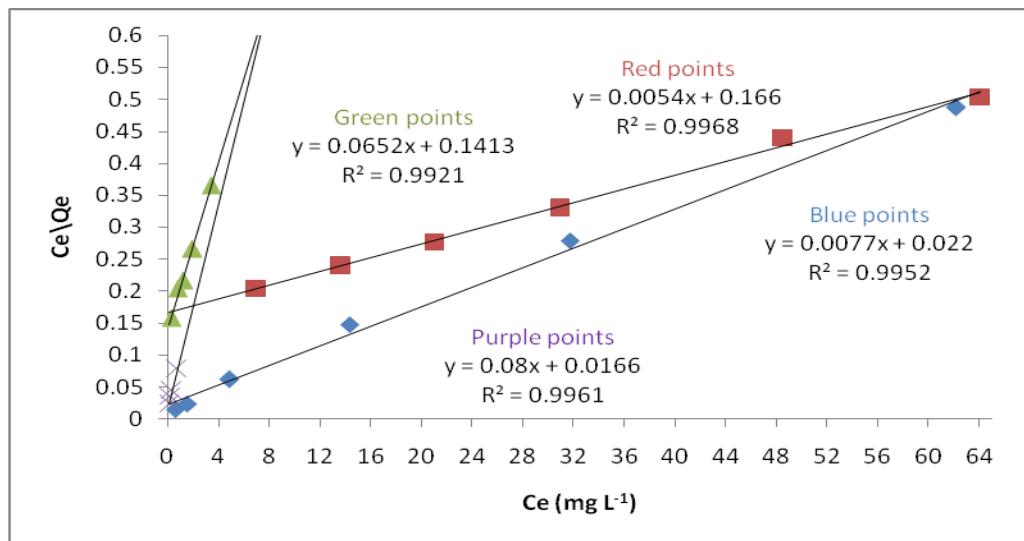
Figure 6-16: Langmuir isotherms for the removal of paracetamol and *p*-aminophenol by pure activated charcoal (blue points and purple points, respectively), and for removing paracetamol and *p*-aminophenol by a clay-micelle complex (red points and green points, respectively).

The results can be explained by the mean of physicochemical properties of the organic drug, that is, water solubility and octanol-water partition coefficient (K_{ow}). These properties can play a major role in the mobility of the drug in the subsurface adsorbents. The water solubility of paracetamol is 12,743 mg x L^{-1}, while that of *p*-aminophenol is 15,000 mg x L^{-1}. Moreover, *p*-aminophenol has a low log K_{ow} of 0.04, while that of the paracetamol is higher (0.46), as shown in Table 4-2. *p*-Aminophenol with low K_{ow} values tends to dissolve more readily in water than paracetamol, and thus tends to adsorb less. As a result, paracetamol shows greater sorption ability when compared to *p*-aminophenol in both adsorbents (Figure 6-16). In addition, it can be concluded that the adsorption of both chemicals onto activated charcoal surface is due mainly to dispersive forces causing the hydrophobic interaction between adsorbate and adsorbent. The hydrophobic part of pharmaceuticals tends to associate with the non-polar surface of activated carbon with the hydrophilic group directed toward the aqueous phase. Although the water solubility of these two pharmaceuticals is high, substantial sorption is still realized due to the hydrophobic part of both chemicals onto the non-polar surface of the activated carbon. The interactions caused by the affinity between polar and charged moieties of both organic compounds and a clay-micelle complex appear to play an important role in the sorption of those compounds onto this complex.

Table 6-2: Concentrations in equilibrium obtained for the adsorption test of paracetamol onto the adsorbent activated charcoal used.

Conc. (initial) (mgL^{-1})	Mass (initial) (mg) per 100 mL	Conc. (final) (mgL^{-1}) (Ce)	Mass (final) (mg)	M initial - M final (mg)	Qe (mg g^{-1}) = (M initial - M final) /0.5	(Ce)/(Qe)
200	20	0.60	0.060	19.93	39.77	0.014
300	30	1.58	0.15	29.84	59.68	0.02
400	40	4.90	0.49	39.50	79.01	0.062
500	50	14.32	1.43	48.56	97.13	0.147
600	60	31.73	3.17	56.82	113.65	0.27
700	70	62.18	6.21	63.78	127.56	0.48

Table 6-3: Concentrations in equilibrium obtained for the adsorption test of paracetamol onto the adsorbent clay-micelle complex used.

Conc. (initial) (mgL^{-1})	Mass (initial) (mg) per 100 mL	Conc. (final) (mgL^{-1}), (Ce)	Mass (final) (mg)	M initial - M final (mg)	Qe (mg g^{-1}) = (M initial - M final) /0.5	(Ce)/(Qe)
200	20	7.85	0.78	19.21	38.43	0.20
300	30	13.69	1.36	28.63	57.26	0.23
400	40	20.99	2.09	37.90	75.80	0.27
500	50	30.91	3.09	46.90	93.81	0.32
600	60	48.54	4.85	55.14	110.29	0.44
700	70	64.12	6.41	63.58	127.17	0.50

Table 6-4: Concentrations in equilibrium obtained for the adsorption test of *p*-aminophenol onto the adsorbent clay-micelle complex used.

Conc. (initial) (mgL^{-1})	Mass (initial) (mg) per 100 mL	Conc. (final) (mgL^{-1}) (Ce)	Mass (final) (mg)	M initial - M final (mg)	Qe (mg g^{-1}) = (M initial - M final) /0.5	(Ce)/(Qe)
10	1	0.30	0.03	0.03	0.06	0.15
20	2	0.78	0.07	1.92	3.84	0.20
30	3	1.24	0.12	1.75	3.51	0.21
40	4	1.94	0.19	3.80	7.61	0.26
50	5	3.40	0.34	4.65	9.31	0.36

Table 6-5: Concentrations in equilibrium obtained for the adsorption test of *p*-aminophenol onto the adsorbent activated charcoal used.

Conc. (initial) (mgL^{-1})	Mass (initial) (mg) per 100 mL	Conc. (final) (mgL^{-1}) (Ce)	Mass (final) (mg)	M initial - M final (mg)	Qe (mg g^{-1}) = (M initial - M final) /0.5	(Ce)/(Qe)
20	2	0.08	0.008	1.99	3.98	0.022
30	3	0.21	0.021	2.97	5.95	0.035
40	4	0.34	0.03	3.96	7.93	0.043
50	5	0.76	0.07	4.92	9.84	0.077

Table 6-6: Langmuir adsorption parameters (k and Qe), the square of correlation coefficient (R^2) of paracetamol and *p*-aminophenol onto both adsorbents.

Pharmaceuticals	Adsorbents	Langmuir sorption parameters		
		K	Q_{max} (mg g^{-1})	R^2
Paracetamol	**Clay micelle complex**	0.032±0.0062	185.18±9.714	0.99±0.0048
	Powdered activated charcoal	0.035±0.0.059	129.87±1.708	0.99±0.0014
p-aminophenol	**Clay micelle complex**	0.46±0.0550	15.33±0.216	0.99±0.0013
	Powdered activated charcoal	4.81±1.624	12.50±1.143	0.99±0.0039

Conclusions and Recommendations

Chapter Seven

Conclusions and Recommendations

7.1 Conclusions

In summary, the key conclusions from this study are:

• Both aspirin and paracetamol are not stable in wastewater conditions and they undergo a relatively fast hydrolysis to the corresponding hydrolysis products. Therefore, efforts should be concentrated on finding suitable methods for the removal of salicylic acid (aspirin product) and *p*-aminophenol (paracetamol product) rather than to focus on the parental drug.

• The efficiency of hollow fiber and spiral wound membranes at the removal of the pharmaceutical studied herein (paracetamol and aspirin) is not satisfactory (40-70%), whereas, the activated carbon, clay micelle complex and reverse osmosis membranes were completely efficient in removing both pharmaceuticals (about 100%). Hence, we conclude that a clay micelle complex and activated carbon filters can effectively remove pharmaceuticals of the kind described herein and there is no need to use more expensive methods such as a reverse osmosis membrane.

• Clay-micelle complex and powdered activated charcoal are considered to be effective methods for the removal of aspirin, paracetamol, and their degradation products from aqueous solution because both membranes characterized by a large surface area, micro-porous nature, high adsorption capacity, and easy availability.

7.2 Recommendations

The following recommendations are considered important regarding the efficiency of advanced membrane wastewater treatment plant towards the removal of pharmaceuticals in Palestine:

- Palestine, in particular, suffers from water shortage and poor water quality, so wastewater treatment and reuse as a reliable source of fresh water is essential to be adopted by the Palestinians to meet future needs in a sustainable way.

- The municipalities should construct wastewater treatment plants especially in industrial, agricultural, and hospital areas using advanced membrane technologies instead of traditional wastewater treatment pools. This is because it is efficient in terms of the removal of traces of pharmaceuticals.

- Further studies are recommended to be elaborated on the occurrence, fate, and concentration of pharmaceuticals. In addition more elaboration on the investigation of the effect of PPCPs on the environment (environmental risk assessment) and human risk assessment should be considered.

- Educating the general public in the Palestinian society on how the pharmaceuticals should be disposed in order to prevent their entry into the environment. This can be done by raising the awareness towards the household disposal of unused and expired pharmaceuticals.

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دراسة مدى كفاءة إستخدام تقنية الأغشية المتقدمة في محطة معالجة مياه الصرف الصحي في إزالة الأسبرين و حامض الساليسيليك "الصفصاف" والباراسيتامول وبارا-أمينوفينول

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المُلَخًَص:

يتناول موضوع هذا البحث دراسة تكنولوجيا الفصل الحاجزي بإستخدام الأغشية المتقدمة لمعالجة مياه الصرف الصحي (المياه العادمة) في فحص مدى كفاءتها في إزالة المواد الصيدلانية، وتحلل موادها والمواد الأيضية التابعة لها من المياه العادمة. وُجد أنّ الأسبرين والباراستيامول كلاهما يتحللُ في المياه العادمة وينتجا حامض الساليسيليك "الصفصاف" ومادة بارا- امينوفينول، على الترتيب. إنّ سرعة تفاعل تحلّل كلا الدوائين (الأسبرين و الباراسيتامول) في المياه العادمة تم فحصها ودراستها، ووُجد أنها من تفاعلات الدرجة الأولى بثابت مُعدّله مُساوٍ لِـ 10^{-8} * 0.845 مول/ثانية و 10^{-8} * 1.0 مول/ثانية في درجة حرارة الغرفة العادية، لكل منها على الترتيب. حيث إن هذه القيم كانت أعلى في المقدار من تلك التي تتحلل عليها في المياه النقية تحت نفس الظروف. وكذلك إن الأداء العام لمحطة معالجة المياه العادمة كان قد أظهر كفاءة واضحة في إزالة تلك المواد وبشكل كامل وضمن حدود الكشف بالمنهج التحليلي. وكانت المواد الأكثر فعالية وكفاءة في إزالة تلك العقاقير داخل محطة المعالجة هي مادة الكربون المنشط ذات السطح الماز (activated carbon adsorbent) ومادة مركب ميسل الصّلصال المعقد (clay-micelle complex). وكما وقد تم دراسة أيزوثرمات الإمتزاز(adsorption isotherms) لهذه المواد بإستخدام كل من الكربون المنشط ومادة إمتزاز مُطّورة حديثاً تُسمى مركب ميسل الصلصال المعقد. كل الأيزوثرمات التي تم دراستها وُجد بإنها تتطابق مع أيزوثرم لانكماير (Langmuir isotherm)، وكما إن ثابت لانكماير (Langmuir constant) وقابلية الامتزاز(adsorption capacity) تم تقييمها ومناقشتها هنا.

عمادة الدراسات العليا

جامعة القدس

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