Faculty of Graduate Studies

Fate of Pharmaceutical Compounds in Wadi Al Qilt Catchment Area

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مصير المركبات الصيدلانية في منطقة وادي القلط

By

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The findings, interpretations and conclusions expressed in this study do not necessary express the views of Birzeit University, the views of individual members of the MSc-committee or the views of their respective employers.

Dedication

To my parents

To my husband

To my lovely daughter "Sama"

To my sisters and brothers

To everyone who helped and supported me in my research

With love and respect

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I would like to express my deepest thanks and gratitude to my supervisor Dr. Nidal Mahmoud for his support, patience and guidance during the study period. It was my pleasure that I had such a supervisor in this research.

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Abstract

Recently, global concern has been raised to investigate the ecological system, were pharmaceutical pollutants affect negatively on aquatic life and underground water, researchers investigated main causes of its environmental impacts. Many Pharmaceutical compounds has been detected in wastewater samples in many areas. In Palestine, were wadi Al-Qilt catchment area has been affected by many pharmaceuticals. Upon that, this study investigated the occurrence of main pharmaceuticals in Al Qilt catchment area that affected underground water, in addition of reviewing information on sorption and transformation of three main pharmaceuticals, in addition to assessing the risks of these pharmaceuticals on public health. HPLC MS/MS analysis has been used to investigate the presence of these pharmaceuticals.

The Al-Qilt catchment is located in the West Bank on the western side of the Jordan Valley covering about 173 km^2; it is characterized by a steep relief with elevations in the range of 700 m.a.s.l in the western part to the range of -250 m.b.s.l in the eastern part. At Al-Qilt, there are about 96,935 inhabitants from Palestinian communities and Israeli colonies, they discharge about 14,000 m^3/d of wastewater and only about 30% of these quantities is treated, then it is mixed again with raw wastewater. Moreover, at Al-Qilt the rainfall is estimated by 600 mm/a in the west and it is 150 mm/a in the east area, which resulted of an average rainfall over the catchment is 400 mm/a. The long term observations of flow mainly for Al-Qilt springs range from 3.0 to 12.0 Mcm/a, and the continuous base flow for the Ras Al-Qilt spring of around 300 l/s (PWA, 2009).

In this study, sixteen pharmaceuticals were analyzed using HPLC method, namely: Phenacetin, Indomethacin, Diclofinac, Ibuprofen, Fenoprofen, Ketoprofen, Gemfibrozil, Fenofibrat, Fenofibrinsaure, Bezafibrat, Clofibrinsäure, Carbamazepin, Pentoxifyllin, Naproxen, Diazepam, Etofibrat. From all of those pharmaceuticals, only Ibuprofen, Diclofinac and Carbamazepne were detected in a considered concentrations, while the others were nil. These compounds are examples of pharmaceuticals that are released into the environment, all are marketed in the Palestinian market (pharmacies), private clinics, hospitals either for human veterinary use. Ibuprofen was detected only in the AWWTP inffluent in the first and second sampling time with a concentration of 300 ng/L and 1000 ng/L respectively and then disappeared in the other sampling stations because it was

eliminated after AWWTP. Diclofinac was detected in AWWTP influent in the two sampling time with a concentration of 310 ng/L in the first sampling time and 1450ng/L in the second sampling time. This concentration was decreased after treatment to 50ng/L and 225ng/L respectively. Then it was disappeared in Ras Al-Qilt and in Al Murashahat. On the other hand, Carbamazepine was detected in AWWTP influent with a concentration of 1995 ng/L in the first sampling time and then decreased respectively to become 1750 ng/L in AWWTP effluent, 1550 ng/L in wadi Mukhmas, 64 ng/L in Ras Al Quilt to reach a value lower than background in al Murashahat influent and effluent . The results revealed that the concentration of diclofinac and ibuprofen were below the background then there have no risk on al qilt catchment area, but the concentration of the carbamazepine in the second sampling time in Al Murashat influent and effluent was 48ng\L and 44ng\L respectively and this concentration was very low and near the background, then we can conclude that there are no risk of carbamazepine on drinking water in Al Murashahat station.

الملخص

في الآونة الأخيرة، ازداد الاهتمام العالمي بضمان الاتزان البيئي، فقد وجد بأن الملوثات الصيدلانية تؤثر بشكل سلبي على الحياة المائية والمياه الجوفية، مما استدعى العديد من الباحثين دراسة تأثيراتها البيئية. وقد تم الكشف عن العديد من تلك الملوثات الصيدلانية ضمن عينات مياه الصرف الصحي في مناطق عدة. وفي فلسطين، حيث يقع مستجمع وادي القلط والذي تلقى فيه مخلفات المستحضرات الصيدلانية. بناء على ذلك، هدفت هذه الدراسة التعرف على نسب وجود وتأثير الأدوية الرئيسية في منطقة مستجمعات وادي القلط على المياه الجوفية. فضلاً عن استعراضها لعمليتي الامتصاص والتحوّل لتلك الأدوية، والتعرف على خطورتها على الصحة العامة. وتم استخدام تحليل HPLC للتحقيق في نسب وجود هذه المركبات الصيدلانية.

يقع مستجمع وادي القلط في الضفة الغربية على الجانب الغربي من وادي الأردن والذي يغطي نحو 173 كيلومتر مربع، يتميز المستجمع بانحدار شديد يبدأ مرتفعات شديدة الانحدار يبلغ ارتفاعها نحو حدود 700 masl في الجزء الغربي ويصل إلى ما دون −250 mbsl أسفل مستوى سطح البحر في جزئه الشرقي. وفي وادي القلط يسكن حوالي 96,935 نسمة من التجمعات السكانية الفلسطينية والمستوطنات الإسرائيلية، وعليه يتم تصريف حوالي 14،000 متر مكعب من مياه الصرف الصحي، ويتم معالجة حوالي 30٪ فقط من هذه الكميات، ويتم إعادة دمجها مرة أخرى مع مياه الصرف الصحي الخام. علاوة على ذلك، يقدر معدل هطول الأمطار في وادي القلط نحو 600 مم في المناطق الغربية، ولا يزيد عن 150 مم في المناطق الشرقية منه، ويبلغ متوسط كميات هطول الأمطار السنوية في الوادي نحو 400 مم. وتجدر الإشارة إلى أن كمية تدفق المياه من الينابيع المتوفرة في المنطقة تتراوح ما بين 3−12 مليون متر مكعب سنوياً، أما كميات المياه التي تتدفق بشكل مستمر فلا تزيد عن 300 لتر/ثانية.

وركزت الدراسة الحالية على تحليل نسب وجود ستة عشر مركباً دوائيا وذلك باستخدام طريقة HPLC، وهي: Phenacetin, Indomethacin, Diclofinac, Ibuprofen, Fenoprofen, Ketoprofen, Gemfibrozil, Fenofibrat, Fenofibrinsaure, Bezafibrat, Clofibrinsäure, Carbamazepin, Pentoxifyllin, Naproxen, Diazepam, Etofibrat. وتوصلت الدراسة إلى وجود ثلاثة مركبات بنسب تستدعي الدراسة والبحث وهي Ibuprofen، Diclofinac و Carbamazepne. وتعد هذه الادوية من أشهر الأمثلة للأدوية التي يتم إطلاقها في البيئة الفلسطينية، ويتم تسويقها في الصيدليات والعيادات الخاصة والمستشفيات للاستخدام البيطري وللإنسان وتم الكشف عن Ibuprofen في المياه الداخلة الى محطة معالجة المياه العادمة في البيرة فقط في العينتين الأولى والثانيةوبتركيز بلغ 300 نانوغرام/لتر و1000 نانوغرام/لتر على التوالي، ولم يتم الحصول على أية نسب له في العينات الأخرى لأنه تم التخلص منه في محطة معالجة المياه العادمة في البيرة . كما تم الكشف عن

Diclofinac في المياه الداخلة الىمحطة معالجة المياه العادمة في البيرة وبتركيز 310 نانوغرام/لتر في العينة الأولى و1450 نانوغرام/لتر في الساعة الثانية لأخذ العينات. وقد انخفض هذا التركيز بعد العلاج ليصل إلى 50 نانوعرام/لتر و 225 نانوغرام/لتر على التوالي. ثم اختفى المركب في رأس القلط وفي منطقة المرشحات. من جهة ثانية، تم الكشف عن مركب Carbamazepin في وبتركيز بلغ 1995 نانوغرام/لتر في العينة الأولى ومن ثم انخفض التركيز ليصبح 1750 نانوغرام/لتر بعد منطقة المعالجة ضمن عينات النفايات السائلة، وبتركيز 1550 نانوغرام/لتر في منطقة وادي مخماس، وبتركيز بلغ 64 نانوغرام/لتر في منطقة رأس القلط للوصول إلى قيمة أقل من القيمة المسموح وجودها في المياه الداخلة والخارجة من منطقة المرشحات.لقد كشفت النتائج أن تركيز ال Ibuprofen و ال Diclofenac كان أقل من القيمة المسموح وجودها في جميع المحطات وبالتالي وجودهما لا يشكل خطرا على منطقة مستجمع وادي القلط.

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Abbreviations

PhACs	Pharmaceutically Active Compounds
PPCPs	Pharmaceuticals and Personal Care Products
CBZ	Carbamazepine
NSAIDs	Non Steroidal Anti-Inflammatory Drugs
JWTP	Jericho Water Treatment Plant
AWWTP	Al-Bireh Wastewater Treatment Plant
NSAIAs	Non-Steroidal Anti-Inflammatory Agents/Analgesics
NSAIMs	Non-Steroidal Anti-Inflammatory Medicines
OTC	Over-The-Counter
WHO	World Health Organization
COX-1	Cylooxygenase-1
COX-2	Cylooxygenase-2
CNS	Central Nervous System
CHF	Congestive Heart Failure
STP	Sewage Treatment Plant
PAC	Powdered Activated Carbon
PWA	Palestinian Water Authority
HPLC	High Performance Liquid Chromatography
UFZ	Water Research Center
SPE	Solid Phase Extraction
LOQ	Limits of quantification
MBR	Membrane Bioreactor
SRT	Sludge Retention Time
PPCPs	Pharmaceutical Personal Care Products
PEC	Predicted Environmental Concentration
PNEC	Predicted No-Effect Concentration
SSRI	Selective Serotonin Reuptake Inhibitor
API	Active Pharmaceutical Ingredients
m.a.s.l	Meter above sea level
m.b.s.l	Meter below sea level
Mcm/a	Million cubic meter per annual
m^3/d	Cubic meter per day

µg	Microgram
µg/l	microgram per liter
mg/l	milligram per liter
PCBS	Palestinian Central Bureau of Statistics
PWA	Palestinian Water Authority
RH	Relative Humidity
ARIJ	Applied Research Institute / Jerusalem
EPA	Environmental Protection Agency
MDH	Minnesota Department of Health

Chapter One

Introduction

1.1 Introduction

Recently, the occurrence and the fate of pharmaceutically active compounds in the aquatic environment have been recognized as one of the prominent environmental issues that have been affecting the ecological system (Dietrich *et al*., 2005; Kotchen *et al*., 2009).

Pharmaceutical compounds are any chemicals used for diagnosis, treatment, alteration or prevention of diseases **(**Thompson, 2005). Pharmaceutical products are used without taking into consideration their negative consequences on the environment in terms its high cost or effect. There are more than 100,000 types of chemicals are used in products and items either in households, industries or agriculture.

Pharmaceutical pollution is considered as one of the most modern issues which may put the environment in jeopardy **(**Kummerer, 2004). Most of pharmaceutical products are slightly transformed or even unchanged forms are disposed from the bodies of humans and livestock in the form of fluids causing critical damage to the ecosystem. This issue is still in the early phases of development in Palestine, where our conventional wastewater treatment plants are not capable of removing pharmaceuticals completely as drinking water treatment plants are not made particularly for eliminating Pharmaceutically Active Compounds (PhACs).

According to recent researches a variety of pharmaceuticals were identified in various water samples like health facilities of wastewater, pharmaceutical industries, wastewater treatment plant effluent, surface and ground water. Yu and his colleagues (2013) clarified the presence of some drugs in ground water and soil. Furthermore, drugs are poured down in sinks; flushed in the toilet, or disposed in the trash, without paying attention to their risks through landfills leachates that may reach to ground water (Yu *et al.,* 2013).

Although we need drugs for treatment of many diseases, it was found that they cause negative impacts on non-targets, environment, health and more. Therefore, negative

impacts can be mitigated through following scientific ways such as controlling random drugs used by the public, reducing distribution of physician free medical samples, sorting of solid waste, sewage recycling, upgrading sewage infrastructure, raising public awareness, nutrition and health maintenance, drug substitutes and research development.

Many studies show trace concentrations of pharmaceuticals in wastewater, various water sources and some drinking-waters. One these studies conducted by Andreozzi and his colleagues (2003) argues that the presence of humic substances hindered phototransformation of Diclofenac and Carbamazepine while nitrate enhanced the phototransformation rate of these compounds. Although, of the positive effect of phototransformation in the environment for reducing drug levels it can lead to formation of transformation product which are more stable and toxic than the parent compounds, e.g. the carcinogenic acridine is formed during phototransformation of Carbamazepine (Chiron *et al*., 2006).

In Palestine and Jordan, Marei and Tiehm (2007) studied the occurrence of pharmaceuticals in certain sites. The findings showed that target compounds of (Ibuprofen, Diclofinac and Carbamazepine) exist in an unneglegable amounts where it laid in the last resorts of wastewater catchment areas.

Locally, Diclofinac and Ibuprofen are used in pharmaceutical manufacturing products for human and veterinary sector, except Carbamazepine which is exclusively used for human, whether used through physician prescription or by the person himself. This is clear from my reviews to the Palestinian Ministry of Health data and many pharmacies. Regarding to the above mentioned reasons, this study will investigate the fate of some pharmaceuticals compounds (Phenacetin, Indomethacin, Diclofinac, Ibuprofen, Fenoprofen, Ketoprofen, Gemfibrozil, Fenofibrat, Fenofibrinsaure, Bezafibrat, Clofibrinsäure, Carbamazepin, Pentoxifyllin, Naproxen, Diazepam, Etofibrat), mainly Ibuprofen, Diclofinac sodium and Carbamazepine in drinking water.

1.2. Objectives

This research aiming at understanding the occurrences, fate and the transportation of some pharmaceuticals compounds (Phenacetin, Indomethacin, Diclofinac, Ibuprofen, Fenoprofen, Ketoprofen, Gemfibrozil, Fenofibrat, Fenofibrinsaure, Bezafibrat, Clofibrinsäure, Carbamazepin, Pentoxifyllin, Naproxen, Diazepam, Etofibrat), mainly Ibuprofen, Diclofinac sodium and Carbamazepine at wadi Al-Qilt catchment, and to identify their risk on public health and environment.

The specific objectives are:

1. To investigate the presence and measure the concentration of Phenacetin, Indomethacin, Diclofinac, Ibuprofen, Fenoprofen, Ketoprofen, Gemfibrozil, Fenofibrat, Fenofibrinsaure, Bezafibrat, Clofibrinsäure, Carbamazepin, Pentoxifyllin, Naproxen, Diazepam, Etofibrat in the wadis – mainly sewage waters- , springs ground waters, Jericho water treatment plant that supply drinking water to Aqbat-Jabr refugee camp.
2. To know the fate of the three main pharmaceuticals (Ibuprofen, Diclofinac and Carbamazepine) in Al Qilt cacthment area.
3. To identify the risk of these pharmaceuticals on public health.

1.3. Justification

In Palestine, there are many factories that manufacture pharmaceuticals, in addition to the existence of many governmental and specialized hospitals, where a lot of their wastes contain (Ibuprofen, Diclofinac and Carbamazepine) among others that have been thrown out in the environment. Despite the existence of these wastes in small quantities, long term disposure of them may result in significant environmental concentrations and consider being one of the most dangerous contaminant for the Palestinian environment (Alshouli, 2012).

Pharmaceuticals and PPCPs exist in Palestine via hospitals and drugs manufacture factories, where these compounds have been thrown as disposals in residential wastewater.

The findings of many researches showed that about (85%) of it portray the main source of influent to the plant. Since there is target PPCPs: Carbamazepine, Ibuprofen and Diclofinac may be found in septic tanks and consequently groundwater due to incomplete human metabolism and excretion into the waste stream or by disposal of unused medication in the toilet or down to sink, and not be completely removed during the wastewater treatment process, these compounds may be discharged into streams and land application sites, and therefore contaminate aquatic environment or persist in surface water, groundwater, and soil (Karnjanapiboonwong, 2010).

Carbamazepine (CBZ) has been frequently detected in study area among other active pharmaceutical ingredients (API) that has been used in relatively high volumes. Carbamazepine is a pharmaceutically active compound along with its metabolite Carbamazepine N-glucuronide while Carbamazepine-diol is not.

This study focused on sixteen pharmaceuticals that will be determined but three were found with significant concentrations: Ibuprofen, Diclofinac (non steroidal anti-inflammatory drugs (NSAIDs)) and its metabolites, and Carbamazepine because of their high consumption in Palestine, these pharmaceuticals are marketed in the Palestinian market (pharmacies).

Chapter Two

Literature review

2.1 Introduction

Palestine suffers from shortage of mineral water resources (streams, rivers), and water deteriorations of natural resources due to human activities. These activities include domestic or industrial wastewater, stone cutting, arbitrary dumping sites and urban runoff. These activities emit pollutants that reach to the nearest wadis. In West Bank, there are about 363 disposal sites to discharge these raw wastewater into the environment (ARIJ, 1999a), eight of them are located in wadi Al-Qilt catchment. The problem increases when people transform their septic tank by trucks into wadis, where it will also be mixed with urban run off during winter season. In wadi Al-Qilt catchment area there are 65,935 Palestinian people inhibit from cities, communities and refugee camps who live in West Bank, in addition to nearly 6,000 people who are living in Eastern Jerusalem. Furthermore, there are six settlement colonies estimated by 15,000 settlers living in the same area (PCBS, 2003).

Generally, weakness and ignorance of concern toward water treatment projects are noticed, for example RIJA argued that 30% of wastewater discharged in West Bank is treated efficiently, and 70% of the generated wastewater is discharged untreated to the environment 30% of total waste water which equals to 5,000 m^3/d is treated at Al-Bireh treatment station, but they remixed with raw wastewater from Qalandiah and Al-Ram with 3,000 m^3/d, all quantities continue running to downstream until eliminated completely (ARIJ, 2007).

The study will focus on pharmaceutical compounds that may found in A-Qilt catchment. It is worth mentioning that at this catchment area, there is only one pharmaceutical company (Al-Quds Pharmaceutical Company), where it disposes its medical waste in special ways, it uses ISO 14001 SYSTEM before they reach wastewater treatment system, that means medical waste is not the main source of pharmaceutical pollutant in the chosen wadi.

Wadi Al-Qilt is the main system in the area, its catchment area extends from Jerusalem and Ramallah in the west towards Jordan River in the east. The system of wadi Al-Qilt springs

is the main water source for filtration station(Al murashahat) where water transports from springs to the treatment facility through a 13km long open transportation canal. Al murashahat applying slow sand filters system and a chlorination unit is located in Aqbat-Jabr refugee camp which serves nearly 5,000 inhabitants. Sand filter beds at Almurashahat was covered with algal growth and there was an increase in the turbidity of treated effluent during storm weather flow.

The study conducted to provide information about wadi Al-Qilt drainage basin including types and possible sources of pharmaceuticals that may present in it. In order to investigate the presence of pharmaceuticals in wadi Al-Qilt catchment area, sampling stations were assigned along the path of the wadis, starting from Al-Bireh Wastewater Treatment Plant (AWWTP) path of the wadis starting to Al Murashahat inlet.

The most API that has been used in relatively high volumes and which has been frequently detected in the study area is Carbamazepine (CBZ).

In this study, many pharmaceuticals has been determined, measured and screened, where three of them have significant concentrations, Ibuprofen, Diclofinac (NSAIDs) and its metabolites, and Carbamazepine (anticonvulsant), where these pharmaceutical compounds consumed higher than others in Palestine and marketed in the Palestinian market (pharmacies) among others (Ministry of Health, 2013).

2.2 Definition of Non Steroidal Anti-Inflammatory Drugs (NSAIDs)

Non Steroidal Anti-Inflammatory Drugs (NSAIDs), are drugs with analgesic, antipyretic, and, in higher doses, with anti-inflammatory effects. The most common members of NSAIDs are Aspirin, Diclofenac, Ibuprofen, and Naproxen partly because they are available over-the-counter (OTC) drugs in many countries (Warden, 2010).

2.2.1 Ibuprofen

2.2.1.1 Definition

Ibuprofen is considered as one of common consumable global NSAIDs, with analgesic and antipyretic properties, which is an ionic acid derivative (Jacobs *et al*., 2011). It is the most consumed drug from the classification of the NSAIDs, where patients consume more than 70 million annual prescriptions in the world (Mendoza-Arriaga *et al*., 2010).

Ibuprofen is a pulp medicine in the World Health Organization (WHO), have an anti-platelet effect, though it is relatively mild and short-lived when compared with other anti platelet drugs. Half-life of Ibuprofen is (1.9-2.2) hours, with a molecular weight = 206.281 g/mol (Jarrar, 2003). In many areas, Ibuprofen trade names include (as Brufen, Motrin, Nurofen, Advil, and Nuprin). Figure (2.1) shows the chemical structure of ibuprofen.

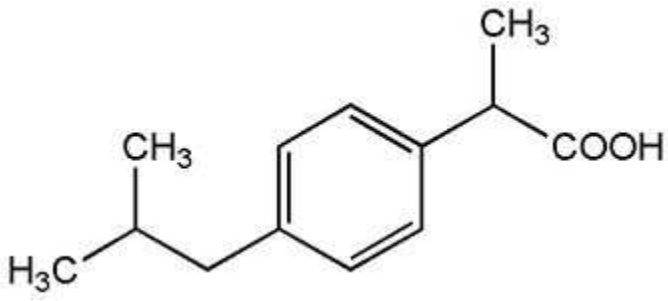


Figure 2.1: Chemical structure of ibuprofen

2.2.1.2 **History of Ibuprofen**

Ibuprofen was discovered in 1961 by Andrew RM Dunlop, and his colleagues as a form of propionic acid . It was developed at the Boots Company in the 1960s in the UK. The discovery was registered 1961. Ibuprofen was made available under prescription in 1969, while it had been approved in United States in 1974 (Rang *et al*., 1995).

2.2.1.3 Mode of Action

Ibuprofen is acting as inhibitor of both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) enzymes which leads to the inhibition of prostaglandin synthesis, which leads to analgesic and anti-inflammatory action of the drug (Rang *et al*.,1995).

2.2.1.4 Pharmacokinetics:

The absorbtion of ibuprofen occurr in gastrointestinal. It is extremely surrounded (90-99%) to plasma proteins and is largely metabolized to inactive compounds in the liver (mainly by glucuronidation). The rapid and full excretion of the inactive metabolites and a low amount of unchanged Ibuprofen occur by the kidney, with elimination of 95% of the administered dose in the urine during four hours of ingestion (Rang *et al*., 1995).

2.2.1.5 Medical Uses of Ibuprofen

In his study, Jarre mention that Ibuprofen is the most common NSAIDs, which used for both human and veterinary purposes . It used for the treatment of headaches, muscle aches, back aches, dental pain, menstrual cramps and arthritis.also Ibuprofen reduces fever and relieves minor aches and pain due to the common cold or flu, by the enzyme in the body that makes prostaglandins, and decreasing prostaglandins helps to reduce pain, swelling, and fever (Jarrar, 2003).

2.2.1.6 Ibuprofen Interactions

Matthieu shows that Ibuprofen can interact with an anticoagulants (including Warfarin),which increase risk of severe bleeding to fatal hemorrhage from the gastrointestinal tract. more over, it reduces the anti-hypertensive effect of beta-blockers and diuretics and this causes hyperkalemia in patientsv (Matthieu, 1992). Ibuprofen may increase bleeding time in patients treated with Zidovudine, and may also interact with probenecid, antidiabetic medicines and phenytoin (Hersh *et al.*, 2007).

2.2.1.7 Side Effects of Ibuprofen

The Adverse effects of Ibuprofen are rare (with non-prescription or short-term use of Ibuprofen), they may include **(**Al-Nasser, 2000):

- Gastrointestinal (heartburn, dyspepsia, loss of appetite, nausea, diarrhea and stomach pain),
- Central nervous system (CNS) (fatigue, dizziness, nervousness and headache),
- Hypersensitivity reactions (itching and skin rashes). Dermatitis and epidermal necrolysis have been reported with Ibuprofen, but very rarely,
- Photosensitivity (very rare cases),
- Cardiovascular (fluid retention and in some cases oedema) (rare effects at non-prescription doses),
- Allergic reactions (like itching, skin rash, swelling of the face, breathing difficulties).

2.2.1.8 Ibuprofen Effects on Ecosystem

The main route of ibuprofen entering surface waters is from wastewater treatment plant effluent, although a significant portion of ibuprofen is degraded in wastewater treatment (Buser *et al.*, 1999). Ibuprofen metabolites include hydroxy and carboxyibuprofen. Studies if Ibuprofen effect on aquatic life, like water plant called duckweed, *Lemna minor,* showed a declined ability to grow in an exponential decreasing manner. The effects on *Lemna* have been the most severe recorded to date. In a small ecosystem the loss of one organism could mean disaster to the whole food chain. With respect to human beings, there is an increasing concern as of prolonged use of ibuprofen, as it might cause gastrointestinal, cardiovascular, kidney, and brain conditions(Sirocki *et al.*, 2013).

2.2.3Diclofenac

2.2.3.1 Definition

Diclofenac sodium is phenyl acetic acid derivative. It is used as anti-inflammatory, analgesic and antipyretic for human and veterinarian treatment. The proper dose is 1.4 L/Kg. It surrounds to human serum proteins as per 99% . It spread into and out of synovial

fluid. Their removal occurr through urinary and biliary excretion of the glucuronide and the sulphate conjugates of the metabolite (Todd and Sorken, 2007).

Diclofenac act like anti-microbial drug and is under investigation for the treatment of tuberculosis. Diclofenac sodium is applied for pain relief in osteoarthritis, rheumatoid arthritis , ankylosing spondylitis and often used to treat chronic pain associated with cancer. When Diclofinac was taken in small doses daily there is an inhibition of the development of Alzheimer disease. It also acts as anti-uricosuric agent. Diclofenac is one of the most used drug, it was one of the first PhAc that could be detected in the aquatic environment (Buser *et al*., 1998).

Figure (2.2) shows the chemical structure of Diclofenac.

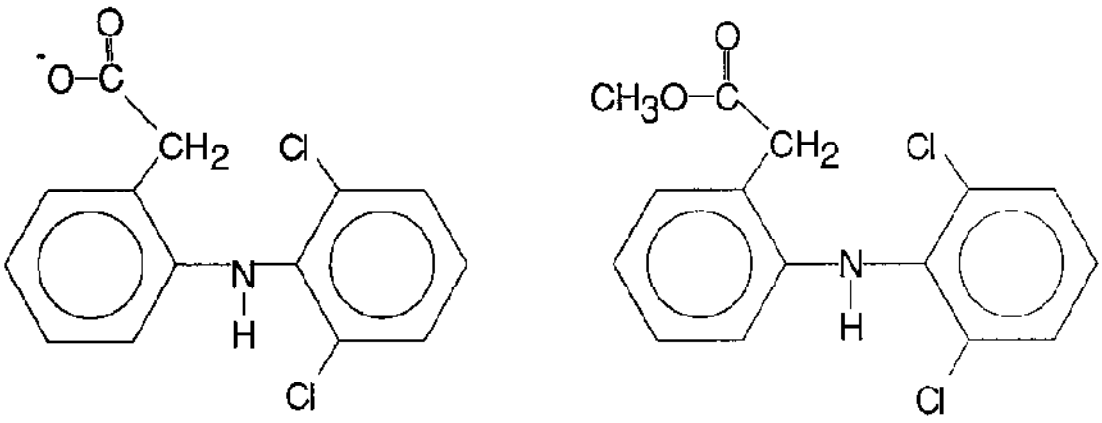


Figure 2.2: Chemical structure of Diclofenac

2.2.3.2 History of Diclofenac

The name "Diclofenac" derives from its chemical name: 2-(2,6dichloroanilino) phenylaceticacid. Ciba-Geigy (now Novartis) advances Diclofinac in 1973. It was first introduced in the UK in 1979. The usage of Diclofinac may be as sodium or potassium salt. Diclofinac is common drug and has a number of formulations.. The approval of OTC use is found in some countries for minor aches and pains and fever associated with common infections (Salmann, 1986).

2.2.3.3 Mode of action

Its action is similar to any NSAIDs. The Diclofinac acting as inhibition the enzyme, cyclooxygenase (COX), an early component of the arachidonic acid cascade, resulting in the reduced formation of prostaglandins, thromboxanes and prostacylin (McGettigan *et al.*, 2013).

2.2.3.4 Pharmacokinetics

The pharmacokinetics describes the absorption, metabolism, and excretion processes occurring in the body after the drug is administered. The kidneys and liver generally eliminate substances from the body, and data on the pharmacokinetics of diclofenac provides details as to which organ assumes primary responsibility for excretion and what medical conditions may hinder the process (Rahal *et al.*, 2008). Once absorbed, the body metabolizes, or breaks down the compound into metabolites and conjugates. These substances generally bind to proteins, particularly albumin. Through a diffusion process, diclofenac enters tissues that contain little to none of the drug. When tissue levels of the medication exceed levels in the bloodstream or the extracellular spaces, proteins carry the medication out of the tissues (KE and NM, 1997).

2.2.3.5 Medical use

Diclofinac is used for the treatment of pain, inflammatory disorders (musculoskeletal complaints, especially arthritis, rheumatoid arthritis, polymyositis, dermatomyositis, osteoarthritis, dental pain, TMJ pain, spondylarthritis, ankylosing spondylitis, gout attacks and pain management in cases of kidney stone sand gallstones), dysmenorrheal, and additional indication in the treatment of acute migraines. Diclofinac is used commonly to treat mild to moderate postoperative or post-traumatic pain, in particular when inflammation is also present, and is effective against menstrual pain and sendometriosis menstrual (Prasanna and Chandrashekar, 2010).

Diclofinac medicinal sample (eye drops: Voltaren-ophtha) are sold to treat acute and chronic nonbacterial inflammations of the anterior part of the eyes (e.g., postoperative states) .

2.2.3.6 Interactions

McGettigan and his colleagues clarify the mechanism of action of Diclofenac sodium is as same as other NSAIDs. it affects the enzyme, cyclooxygenase (COX), an early component of the arachidonic acid cascade by inhibition, leading to the reduced formation of prostaglandins, thromboxanes and prostacyclin. in other hand,McGettigan and his colleagues say: It is not completely understood how reduced synthesis of these compounds results in therapeutic efficacy (McGettigan *et al*., 2013).

2.2.3.7.Side effects

A serious side effect of Diclofinac such as (Solomon *et al.*, 2006):

- Gastro Intestinal complications
- weight gain, swelling in some organs like tongue urinating less than usual or not at all;
- jaundice (yellowing of the skin or eyes);
- Bruising, severe tingling, numbness, pain, muscle weakness;
- Neck stiffness, chills, and/or seizure (convulsions)
- Severe skin reaction- fever

2.2.3.8 Diclofenac effect on ecosystem

Diclofinac is poorly removed in treatment plants and thus is found in the effluents, and enters water bodies. In general Diclofenac is a pharmaceutical that entering aquatic environment and must be considered harmful for the ecosystem and there necessary to evaluate the occurrence of the parent compound and transformation products, as well as their ecotoxicological effect. Diclofinac is easily undergo phototransformation reactions in the environment and it is toxic to some vulture species. Diclofenac can be taken by fish with a concentration of (1µg\L) in the environment. Moreover, many studies have been shown that Diclofenac undergoes bioconcentration in fish (Hoeger, 2005).

2.2.4 Carbamazepine

2.2.4.1 Definition

Carbamazepine is an antiepileptic drug used to control seizures. It has been suggested as an anthropogenic marker in water bodies, and its major human metabolites, Carbamazepine diol (CBZ-DiOH) and Carbamazepine *N*-glucuronide (CBZ-*N*-Glu) (Zwiener *et al.,* 2003; Malarvizhi *et al.,* 2012).

Figure (2.3) shows the chemical structure of Carbamazepine.

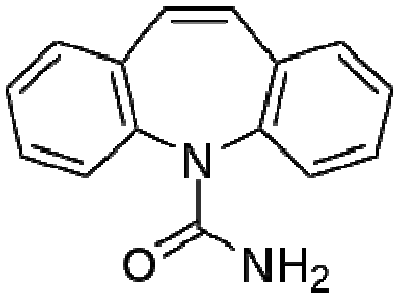


Figure 2.3: Chemical structure of Carbamazepine

2.2.4.2 History of Carbamazepine

Carbamazepineat was discovered by chemist Walter Schindler J.R. Geigy AG in Basel, Switzerland, in 1953 before its anti-epileptic properties had been discovered. Schindler synthesized drug in 1960. Firstly, Carbamazepine was marketed as a drug to treat trigeminal neuralgia (known as tic douloureux formerly). Carbamazepine has been used as an anticonvulsant in 1962 and as antiepileptic in the UK since 1965 to 1974. In 1971 Carbamazepine has approved in the USA. Drs. Hanaoka and Takezaki first used Carbamazepine to control mania in patients refractory to antipsychotics.

2.2.4.3 Mode of Action

The stabilizing of the inactivated state of Voltage-gated sodium channels, caused by CBZ which makes little of these channels ready to open. Then the influenced cells become less excitable until the drug dissociates. Carbamazepine has also been shown to potentiate GABA receptors made up of alpha1, beta2, gamma2 subunits. This may be relevant to its activity in neuropathic pain and manic-depressive illness (Granger *et al*., 1995).

2.2.4.4 Pharmacokinetics

Gastrointestinal tract is the site where Carbamazepine (CBZ) completely absorbed with the major amount of the dose being found in the urine (Table 2.1). The slow rate of excretion occur in the feces. Carbamazepine is also extensively metabolized in the body, as after oral administration 72% of it was found in the urine and 28% in the feces (Faigle and Feldman, 1976). Only 17% of the total usage of CBZ would be expected to enter the environment as CBZ, with 34% entering as the CBZ-DiOH or the *O*-glucuronide of CBZ-DiOH. The major metabolic pathways of CBZ are shown in Figure (2.4) (Faigle and Feldman , 1976).

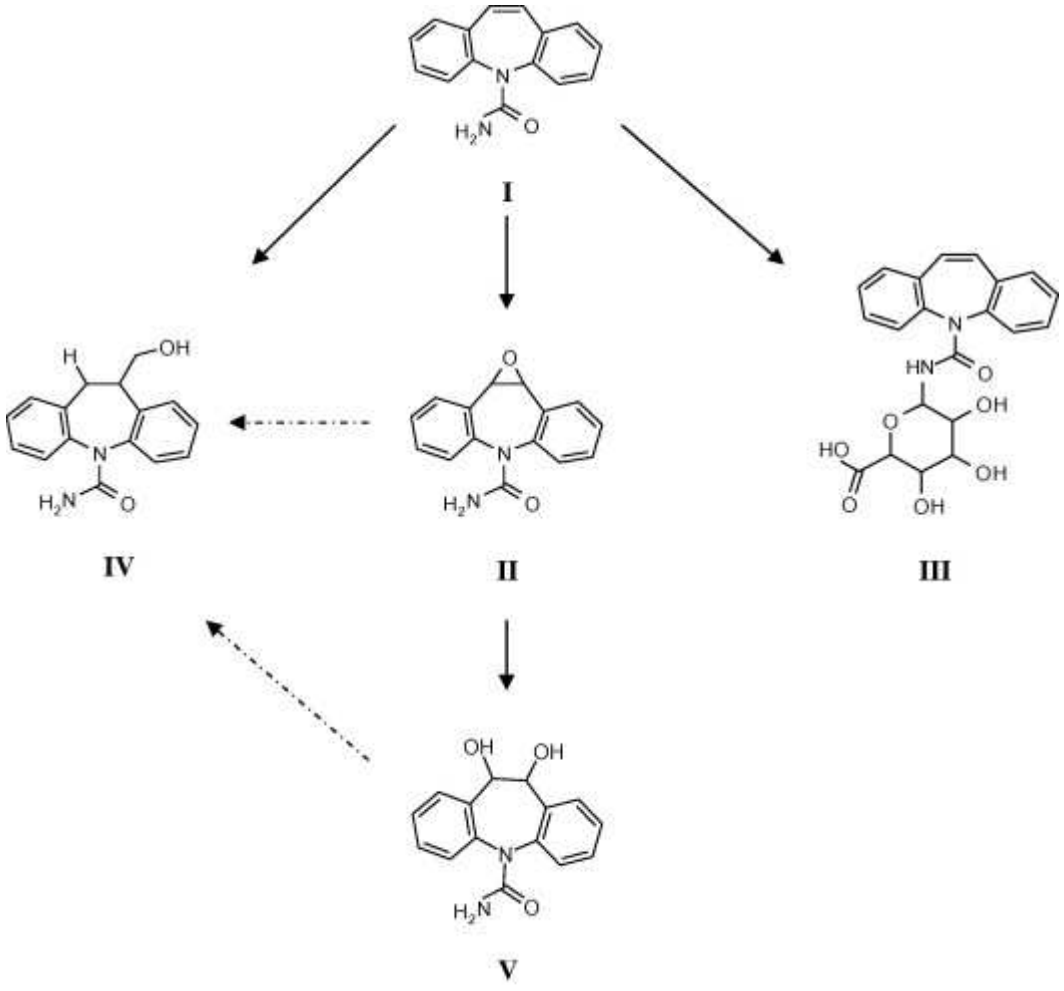


Figure 2.4: Carbamazepine metabolism (Zhang *et al*., 2008)

Biotransformation of CBZ via epoxidation and glucuronidation (I – CBZ; II – CBZ-EP; III – CBZ-*N*-Glu; IV – minor mono-hydroxy derivative of CBZ; V – CBZ-DiOH) (Faigle and Feldman, 1976).

2.2.4.5 Medical uses of Carbamazepine

Carbamazepine is used for the treatment of seizure disorders and neuropathic pain. Also it used as a second line treatment for bipolar disorder and along with antipsychotic agents in schizophrenia. In the United States, the FDA-approved indications are epilepsy (including partial seizures and tonic-clonic seizures), trigeminal neuralgia, and manic and mixed episodes of bipolar I disorder (Paul *et al*., 2011).

Carbamazepine has an effective and safe applications as lithium for the treatment of bipolar disorder, both in the acute and maintenance phases (Ceron-Litvak *et al*., 2009).

2.2.4.6 Interactions

Carbamazepine interacts with multiple drugs and warning should be used in joining other medicines with it. When phenobarbital, phenytoin (Dilantin), or primidone (Mysoline) then Lower levels of it is seen. Warfarin (Coumadin), phenytoin (Dilantin), theophylline, and valproic acid (Depakote, Depakote ER, Depakene, Depacon) were administrated with Carbamazepine there is a rapid metabolization occurr, while carbamazepine levels are increased when taken with erythromycin,cimetidine (Tagamet), propoxyphene (Darvon), and calcium channel blockers. The metabolism (destruction) of the hormones in birth control pills as well is increase by Carbamazepine and the effectiveness of birth control pills can be reduced because of it. Unexpected pregnancies have occurred in patients taking both carbamazepine and birth control pills. Concerning to Carbamazepine food interaction, grapefruit juice raises the bioavailability of Carbamazepine by inhibiting CYP3A4 enzymes in the gut wall and in the liver (Faigle *et al*., 1976).

2.2.4.7 Side Effects of Carbamazepine

Common side effects caused by Carbamazepine may include:

- Water retention, swelling, or difficulty breathing, which can be signs of CHF,
- High blood pressure (hypertension) or low blood pressure (hypotension),
- An irregular heart rhythm (arrhythmia),
- Yellowing of the whites of the eyes or skin (jaundice), which may be a sign of liver damage, including liver failure or hepatitis,

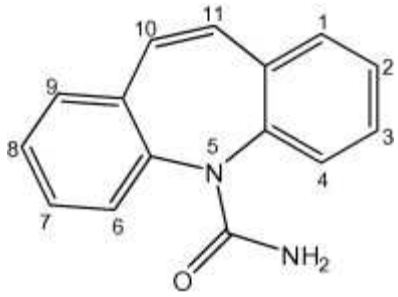
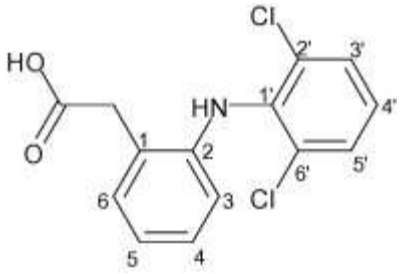
- Difficulty passing urine or a sudden, unexplained decrease in urine production (which can be a sign of kidney damage) (Diener *et al*., 1997)
- Low sodium levels in the blood (hyponatremia), which may cause symptoms such as: Loss of appetite, nausea or vomiting, irritability, ixcessive tiredness, confusion hallucinations, muscle weakness.

2.2.4.8 Carbamazepine Effects on Ecosystem

CBZ is considered as an anthropogenic marker of urban contamination because of its persistence (about 100 days) in effluent and surface waters (Clara *et al*., 2004 and Gagne *et al*., 2006). The most influenced animals by CBZ are small animals like fish and other invertebrate like (Mytilus galloprovincialis) (Ramesh *et al*., 2012)**.**

The exposure of fish to environmental pollutants show a variety of physiological responses, including affectation of blood balance, ion regulatory capacity and uptake and its relative transport of oxygen (Booth *et al*., 1988). The physical, chemical and pharmacological properties of Carbamazepine and Diclofinac are summarized in Table (2.1).

Table 2.1: Physical, chemical and pharmacological properties of Carbamazepine and Diclofinac (Zhang *et al.*, 2008)

	Carbamazepine (CBZ)	Diclofinac (DFC)
Pharmacology		
Structure, formula, CAS No. and molecular weight		
	$C_{15}H_{12}N_2O$	$C_{14}H_{11}C_{l2}NO_2$
	298-46-4	15307-86-5
	236.27 g mol^{-1}	296.16 g mol^{-1}
Usage	Analgesic, antiepileptic	Analgesic, anti-inflammatory
Water solubility	17.7 mg L^{-1} (25 °C)	23.73 mg L^{-1} (25 °C)
Log *P* (octanol–water)	2.45	–
Henry's Law Constant	1.09×10^{-5} Pa m^3 mol^{-1} (25 °C)	4.79×10^{-7} Pa m^3 mol^{-1} (25 °C)
p*K*a	Neutral	4.15[a]
Elimination half-life	25–65 h	2 h
Excretion	72% of oral dosage excreted in urine, 28% in faeces	Biliary excretion: 65% of oral dosage excreted in urine
Metabolites in urine (%of oral dosage)	CBZ, CBZ-epoxide, CBZ-diol, CBZ-acridan, 2-OH-CBZ, 3-OH-CBZ	DFC, 5-OH-DFC, 4′-OH-DFC, 3′-OH-DFC, 4′-5-diOH-DFC, 4′-OH-5-Cl-DFC, 3′-OH-4′-CH_3O-DFC
Dosage	Maintenance usually 800–1200 mg daily.	75–150 mg daily
Other Information	Autoinduction, i.e., long term applications increase its metabolism	Dermal applications available

2.3 Source of Pharmaceutical in Environment

In spite of all benefits of these drugs in the treatment of many diseases for human and animals, but the added to the environment in large quantities, through several sources that include (Moreno-González *et al*., 2014):

- Direct disposal at manufacturing.
- Excretion with urine and feces (wastewater).
- Drugs in animal manure.

Industrial wastewater may be possible source for contamination of surface water. The following figure (2.5) shows routes of the pharmaceuticals entering to the environment:

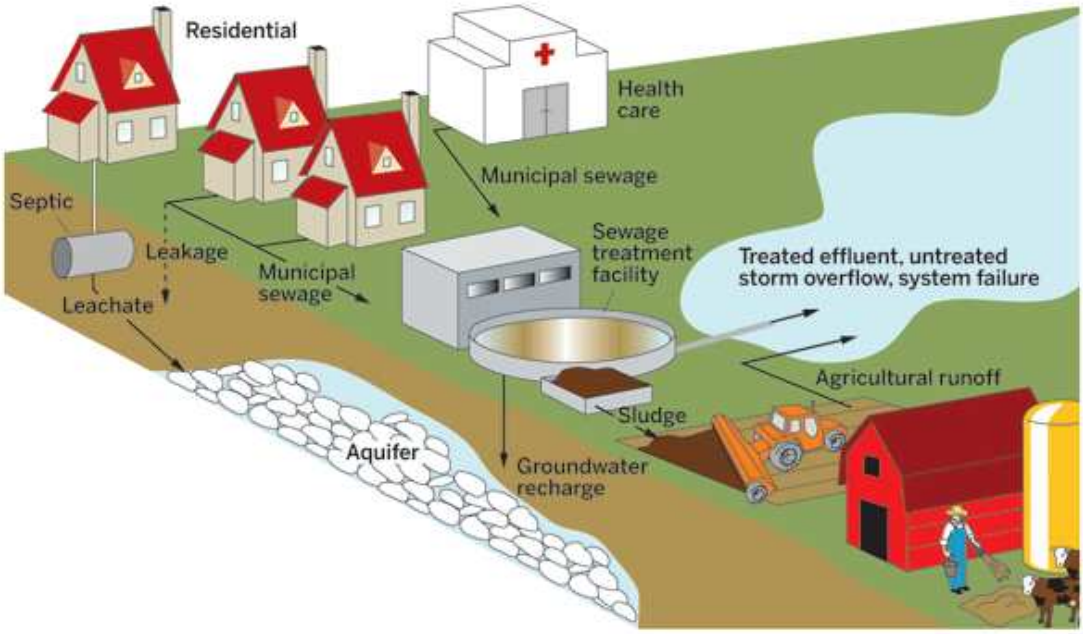


Figure 2.5: Drug flow Pharmaceuticals and their metabolites enter environment from homes, health care facilities, and farms (Halford, 2008)

The pharmaceutical administrated (consumed) by human after required action in the body get excreted with urine and feces as original compound, and usually as a number of metabolites. The environmental concerns stems because these Pharmaceuticals are not always adequately destroyed in the wastewater treatment plants **(**Dietrich *et al*., 2005), consequently they enter the surface water where they may affect aquatic life (Katarzyna *et*

al., 2007).Moreover, drinking water treatment plants are not specifically designed to remove PhAcs.

2.4 Removal in WWTP

The elimination of pharmaceutical compounds occurs in WWTPs in different mechanisms. The phototransformation is the important process which is used microorganism to mineralize pharmaceutical compounds into water and carbon dioxide, or degrade them into inactive form. As WWT process occur in open air, wastewater are exposed to sun light. In general, pollutants will be removed from water by stripping into air or by sorption onto sludge that is regularly discharged.

In Palestine, the WWTP use activated sludge processes.These processes do not remove pharmaceutical Compounds completely. Marie and Tiehm (2007) studied the emerging pollutants elimination processes applying membrane bioreactor and combination of MBR and Powdered Activated Carbon (PAC) technique and gained the following results in Table (2.2).

Table 2.2: Degree of elimination of four pharmaceutical substances (Bezafibrate, Carbamazepine, Ibuprofen, Diclofinac) by batch and column mechanism (Marei and Tiehm, 2007)

	Elimination according to Marei and Tiehm study.		**Elimination in Literature**	
Substance	Batch (effluent)	Column (20º)	observed	not observed
Bezafibrate	+ + +	+ + +	Joss *et al*.(2006); Quintana *et al*.(2005)	\
Carbamazepine	-	+	\	Clara *et al*.(2004); Schyett *et al*.(2006)
Ibuprofen	+ + +	+ + +	Joss *et al*.(2006); Zwiener *et al* .(2000); Smook *et al*.(2008)	\
Diclofinac	+ + +	+ +	Gonzalez *et al*.(2006)	Joss *et al*.(2006); Quintana *et al*.(2005)

*- no removl, + removal<50%, ++ removal 50_90%, +++ removal>90%

2.5 General description of Wadi Al Qilt drainage basin Study area

Study area of Wadi Al Qilt is illustrated in Figure (2.6).

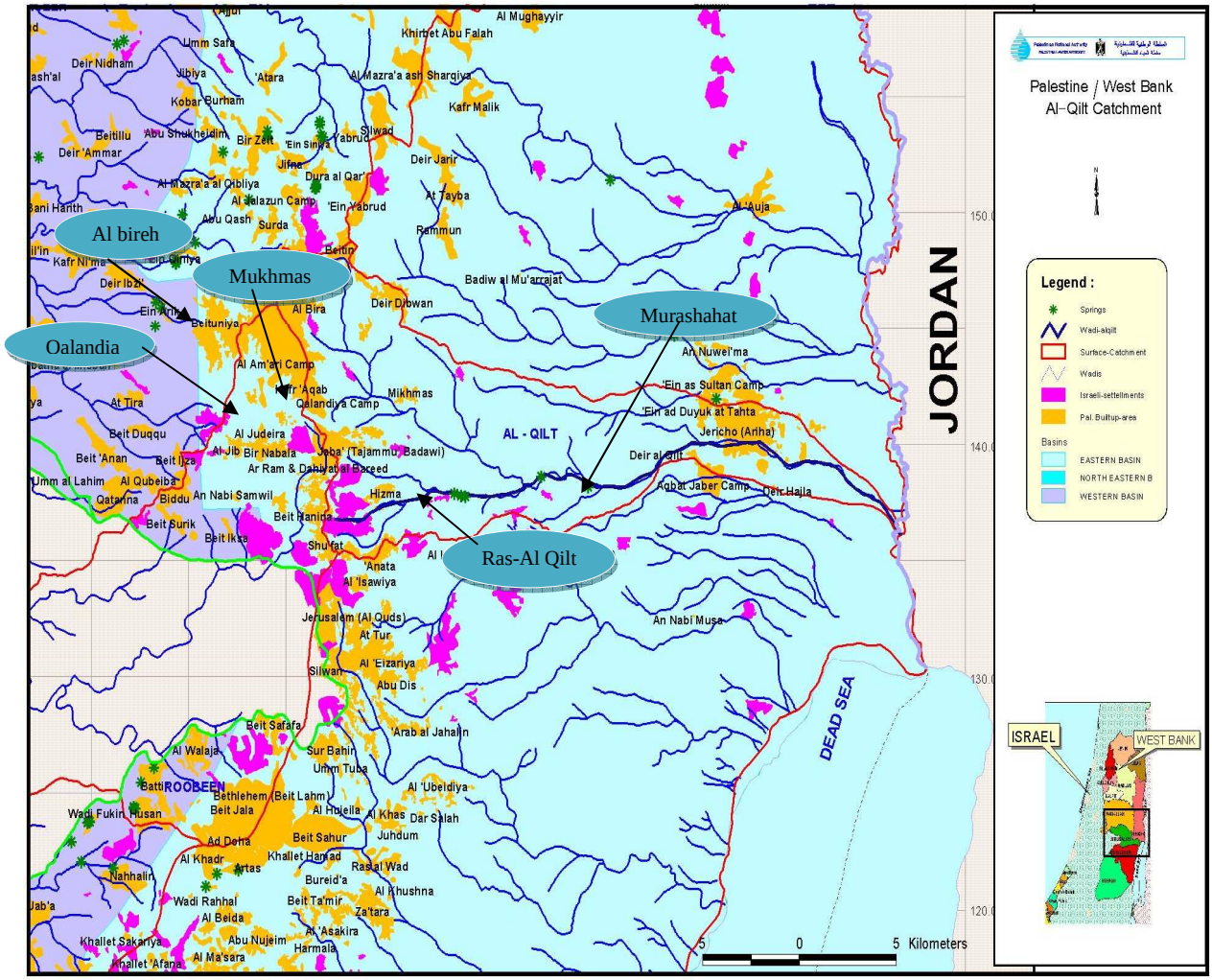


Figure 2.6: Al Qilt catchment area

2.5.1 Study area location

The study area is Wadi Al-Qilt cachment area (AWWTP, Mikhmas bridge, Al Qilt spring, Al Murashahat in aqpat jaber). Wadi Al-Qilt is situated in the east of the West Bank, including part of Ramallah, Al Bireh, Jerusalem and slopes down to Jericho with an area of 174 Km^2 (ARIJ, 2007).

2.5.2 Metrological Data

2.5.2.1 Population

Palestinian population living in the Wadi Al Qilt basin were estimated to be about 97,000 inhabitant (Al Bireh City (38200), Kafr O'qb (10000), Qalandia Camp (8800), Borqa (2240), Jaba' (3140), Mikhmas (1820), Al-Ram (24840), Hizma (5920), Anata (9340) and Beit Hanina(1345)).

2.5.2.3 Climate

The West bank is dominated by the Mediterranean climate with distinctive four seasons, with short wet period and longer dry period.

2.5.2.4 Rainfall

In Al-Qilt, the average rainfall over the catchment area is about 400 mm/year (PWA, 2009).

Chapter Three

Methodology

3.1 Personal communications and interviews

Meetings and personal communications with employee from the Palestinian Water Authority (PWA), some employee who work in the ministry of health and in the Jerusalem pharmaceutical company. The goal of this meetings was to renew the data, to identify other issues with the water resources that are not mentioned in the literature, as well as to collect data about the status of the pharmaceuticals in the study area.

3.2 Field Work

Field work and field surveys were basic modules in each aspect of this study, essentially to assure the data collected during the interviews, to know the existing water resources, limiting sampling stations and water sampling. Field visits were done to the study area. at November 2013 and April 2013. Because of the continual flow of water through wadis from AWWTP to water filtration plant(Al Murashahat), sampling stations were limited through Wadi Al Qilt, begining from AWWTP effluent (as it constitute the beginig flow in the drainage area), going through Wadi Al Qilt, ending with the effluent of Al Murashahat. Sampling frequency was variable according to the weather status.

3.3 Sampling Time and Site

Samples were collected at two different times in November 2012 during one days during wet weather in winter and the samples were collected again in April 2013 from the same stations and analyzed to make sure of the first result. 5 water samples were taken, from four stations (AWWTP, Mukhmas bridge, Al Qilt spring, Al Murashahat in Aqpat Jaber) (Figure 3.1). Distance between sampling stations (Figure 3.2).

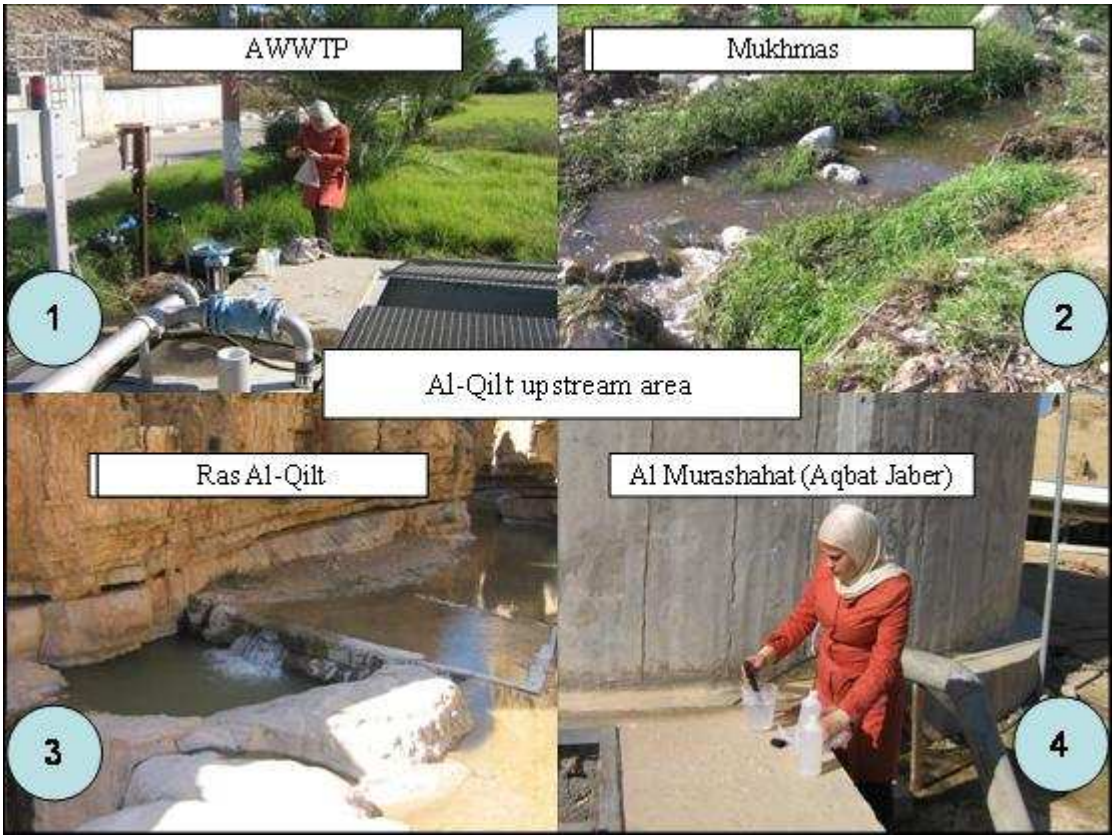


Figure 3.1: Wastewater sampling locations in Al-Qilt catchment

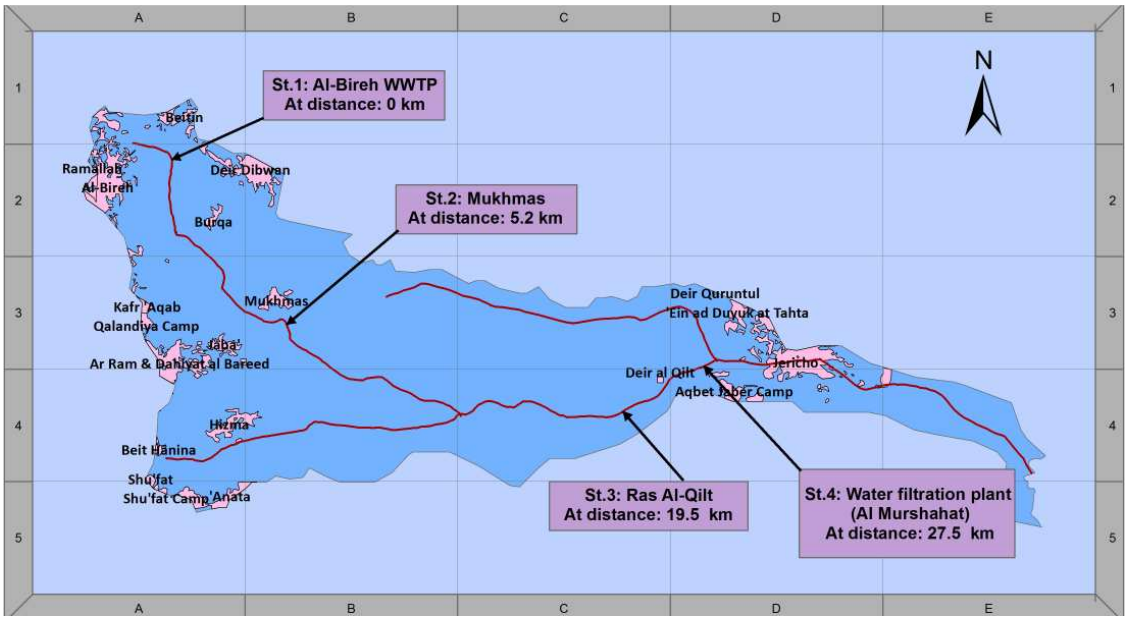


Figure 3.2:Distance between sampling stations

3.4 Field analysis and wet chemistry

The physical chemo-physical parameters such as electrical conductivity, total dissolved solid, pH and temperature were measured with suitable instruments at the field. Collecting data and the visit has been shown in Figure (3.2).

Figure 3.3: Measuring physical parameters in the water samples (pH, Temperature and TDS)

3.5 Samples Collection

The procedure for sample collection is critical so there is no difference in sample collection, which will lead to sample analysis. Below is a description of some important factors of sample collection to be concerned.

3.6 Samples Bottles

The samples were collected in HDPE bottles. These bottles are impact resistant, and provide a good moisture barrier**.** Sample bottles were filled and nearly 1 inch left empty of bottle rim. This will leave an air space in the sample bottle to allow for mixing of the sample in the laboratory.

3.7 Sample Volume

500 mL of sample is enough to be extracted through a SPE cartridge. Sample analysis include duplicates. Which need two separate sample bottles to evaluate sample collection reproducibility.

3.8 Preservative

A preservative should be used to prevent the decomposition for the analyte of interest. The samples were preserved using concentrated hydrochloric acid 4% to stop microbial activity.

3.9 Filtration

Filtration is important after sample collection to prevent bacterial growth. If the sample is not more turbid and filtration may decrease analyte recovery and, sample filtration was not applied. Instead, samples were analyzed within seven days, and samples were left to settle any particles (if any) for one hour before sample extraction.

3.10 Sample Storage

Samples were stored at 4ºC. The water samples should not be frozen during storage however should be cold enough to deter any algae formation or bacterial growth. Samples should also be away from excessive sunlight.

3.11 Water Analysis

The aim of water analysis was made to define the level of pharmaceutical pollution of water flux in wadi Al Qilt. This was achieved through measuring the following pharmaceutical compounds Phenacetin, Indomethacin, Diclofinac, Ibuprofen, Fenoprofen, Ketoprofen, Gemfibrozil, Fenofibrat, Fenofibrinsaure, Bezafibrat, Clofibrinsäure, Carbamazepin, Pentoxifyllin, Naproxen, Diazepam, Etofibrat using High Performance Liquid Chromatography (HPLC) in Water Research Center (UFZ), Magdeburg, Germany. Samples were acidified and preserved at 4ºC after collection until the analysis.

All compounds were pre-concentrated applying solid phase extraction (SPE) and analyzed by HPLC coupled with tandem spectrometry (MS/MS). SPE has an advantages which is relatively less solvent is used; suitable operation and good reproducibility (Laven *et al*., 2009). The pH of the samples was adjusted in the lab at extraction day. Before SPE conformable internal standards for all analytes were spiked into the samples and used for quantification. Limits of quantification (LOQ) were 10 ng L^{-1} in all case.

Cartridges were eluted with 10 mL acetone. After extraction, the elute was evaporated until dry and reforming with 50 mL methanol followed by 50 mL ultra pure water. The compounds were isolated by an Agilent 1100 HPLC (Agilent Technologies, Waldbronn, Germany) on a Luna C18 column (250 mm - 2 mm; 5 mm) (Phenomenex, Aschaffenburg, Germany). An API 2000 mass spectrometer (AB Sciex, Foster City, USA) was used for detection and quantification of CBZ (Lange *et al*., 2011).

Samples analysis based on Water and Wastewater Standard Methods (APHA, 2000), and based on "Deutsche Einheitsverfahren zur Wasser-, Abwasser- und Schlammuntersuchung". Specefic methods applied by the Water Research Center (UFZ), Magdeburg, Germany.

Chapter Four

Results and Discussion

4.1 General

In this study we analyzed sixteenth pharmaceutical compound in water samples and we get the following results in Table (4.1), Figure (4.1) (a.b.c.d.e.f.g.h.l)

Table 4.1: The Occurrence of Pharmaceuticals in Al Qilt Catchment Area

Pharmaceutical compound name	Sampling station name	Concentration of pharmaceutical compound	
		28/11/2012	15/04/2013
Ibuprofen	AWWTP inffluent	300ng/L	1000ng/L
	AWWTP effluent	<BG	<BG
	Mukhmas Wadi Quelle	<BG	<BG
	Ras Al Qilt Quelle	<BG	<BG
	Al Murashahat influent	<BG	<BG
	Al Murashahat effluent	<BG	<BG
Diclofinac	AWWTP inffluent	310ng/L	1450ng/L
	AWWTP effluent	50ng/L	225ng/L
	Mukhmas Wadi Quelle	100ng/L	70ng/L
	Ras Al Qilt Quelle	<BG	<BG
	Al Murashahat influent	<BG	<BG
	Al Murashahat effluent	<BG	<BG
Carbamazepine	AWWTP inffluent	1995ng/L	1450ng/L
	AWWTP effluent	1750ng/L	2000ng/L
	Mukhmas Wadi Quelle	1550ng/L	1995ng/L
	Ras Al Qilt Quelle	64ng/L	82ng/L
	Al Murashahat influent	<BG	48ng/L
	Al Murashahat effluent	<BG	44ng/L

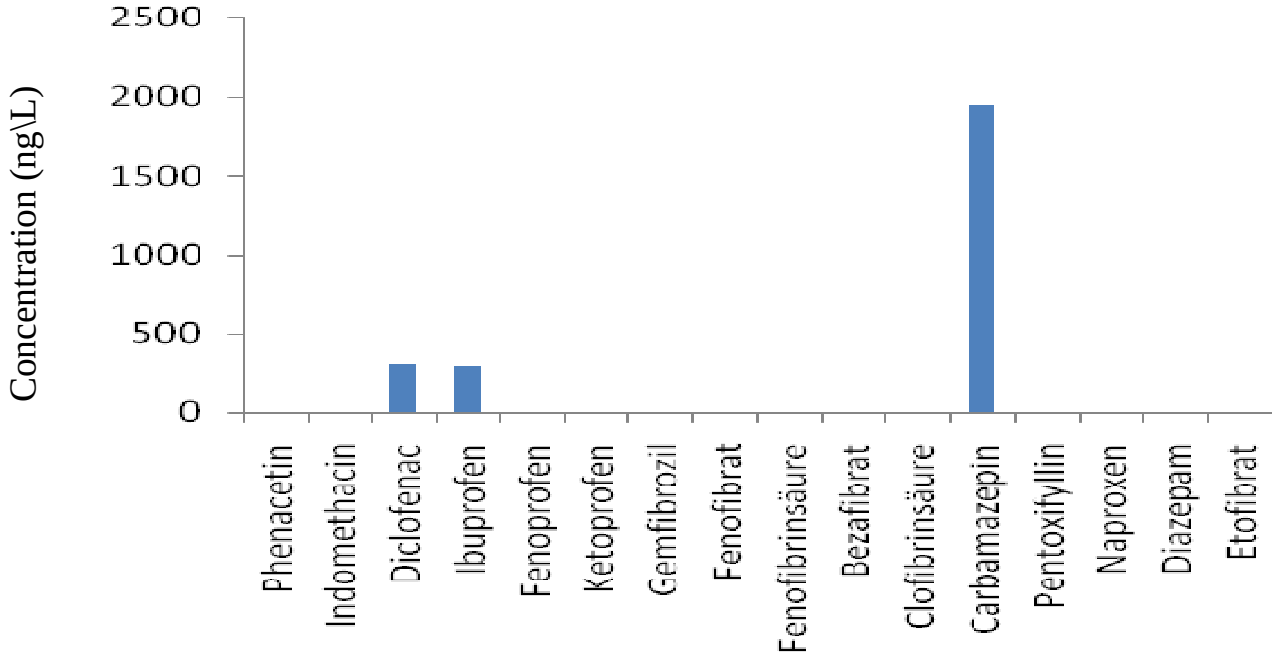


Figure 4.1.a: Concentration of pharmaceuticals in Al Bireh effluent in 28-11-2012

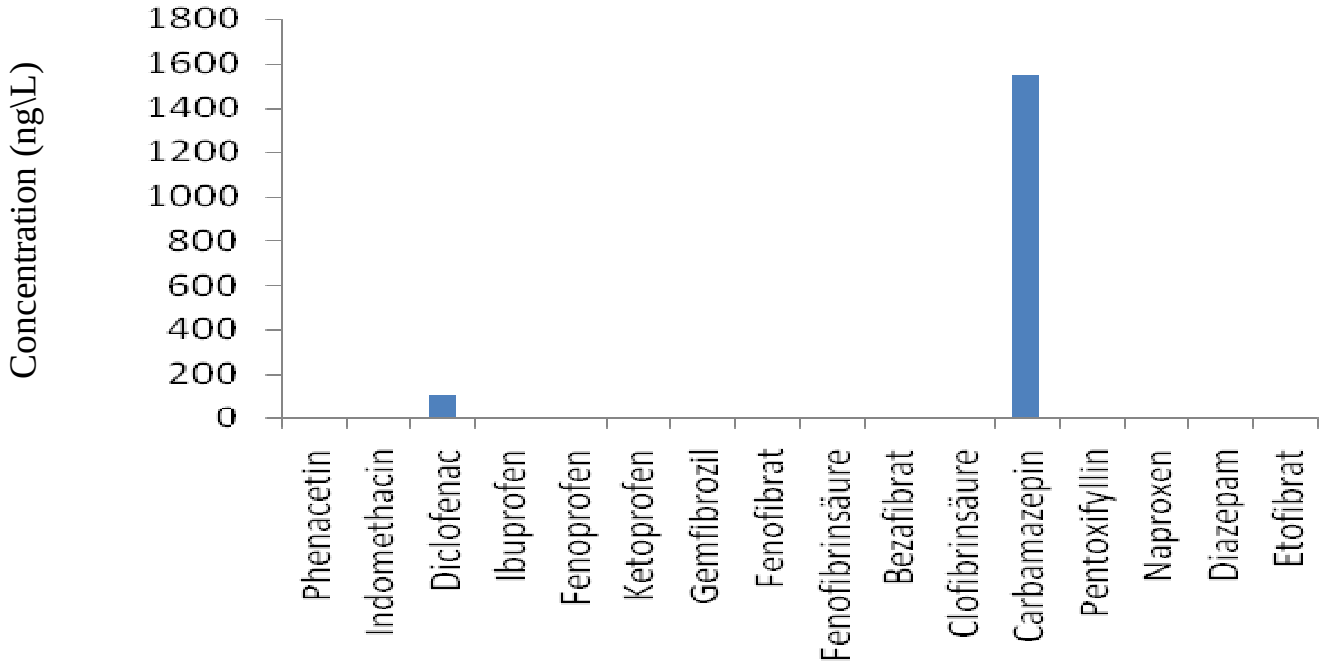


Figure 4.1.b: Concentration of pharmaceuticals in Mukhmas wadi in 28-11-2012.

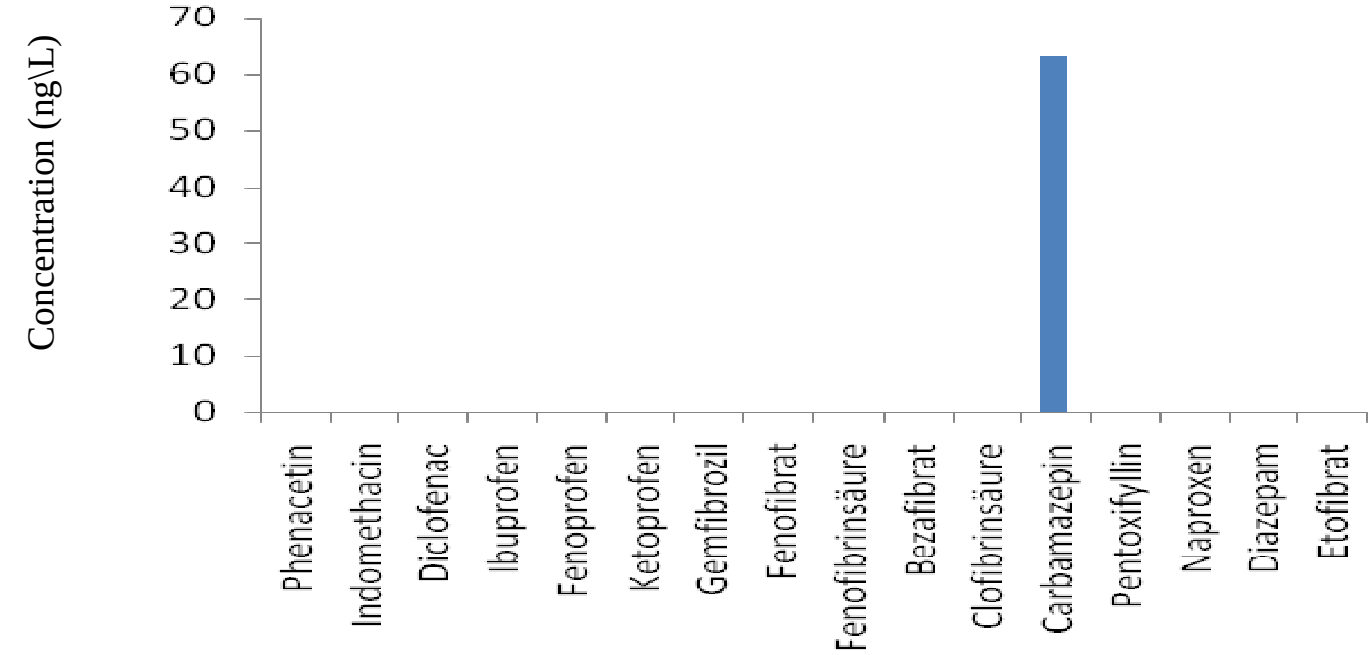


Figure 4.1.c: Concentration of pharmaceuticals in Ras Al Qilt in 28-11-2012

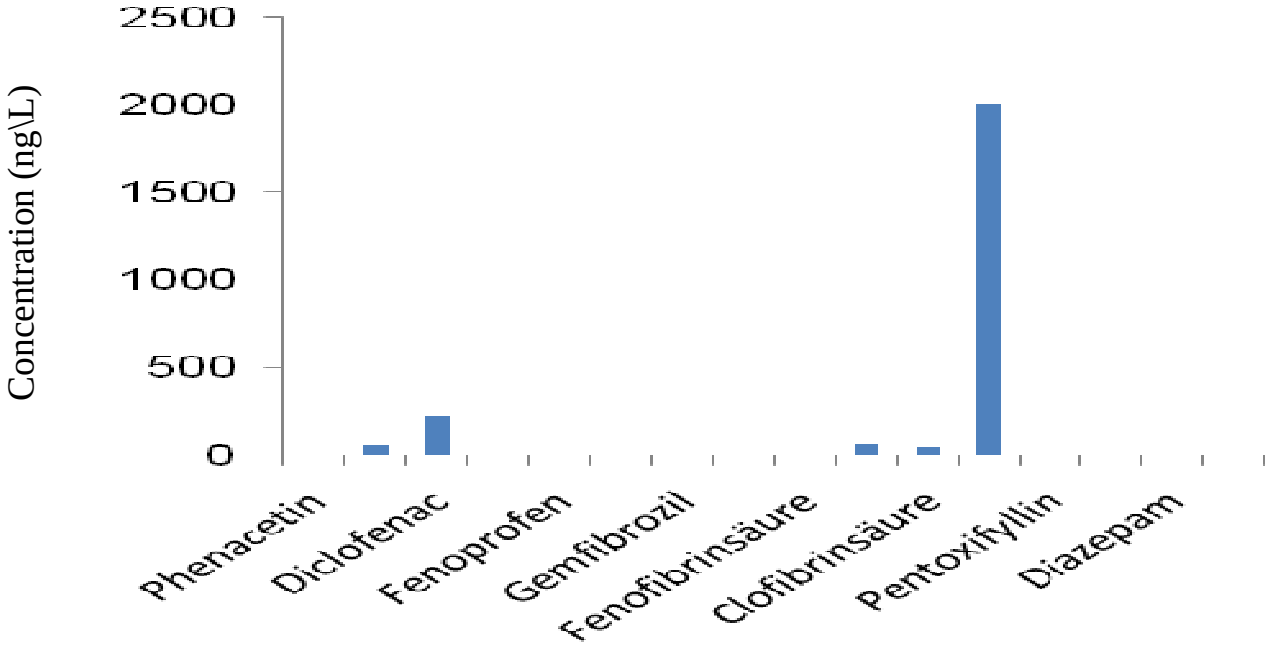


Figure 4.1.d: Concentration of pharmaceuticals in Bireh effluent in 15-4-2013

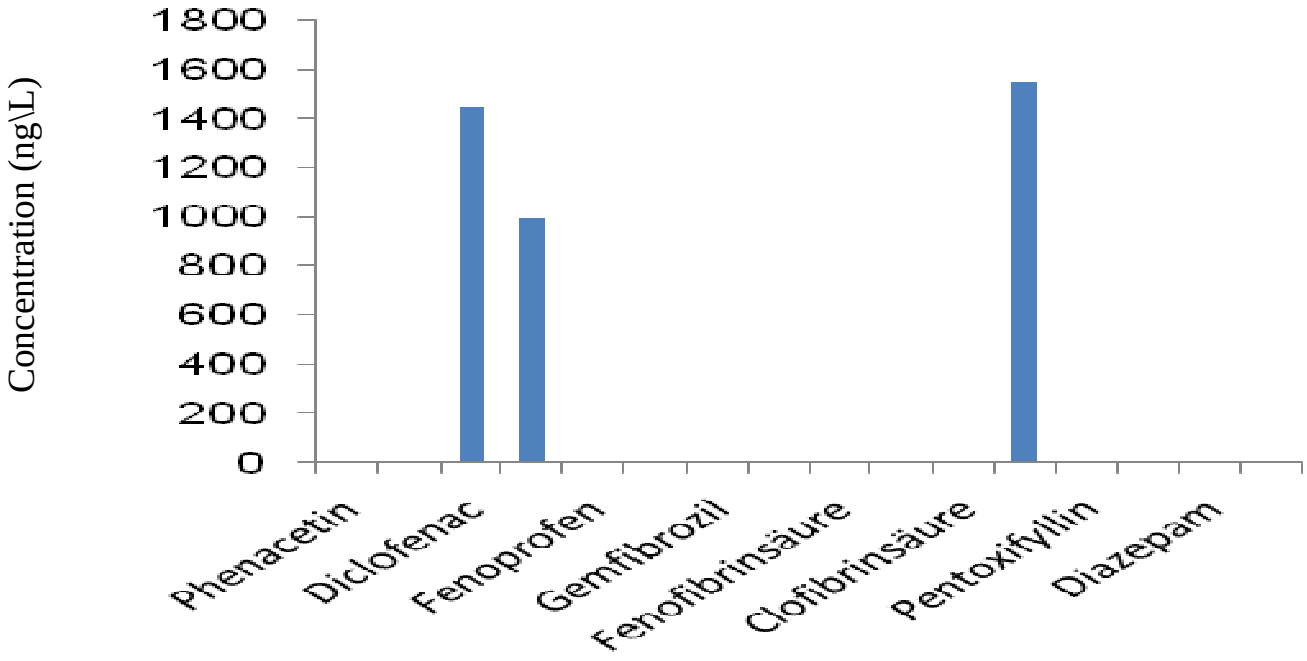


Figure 4.1.e: Concentration of pharmaceuticals in Al Bireh influent in 15-4-2013

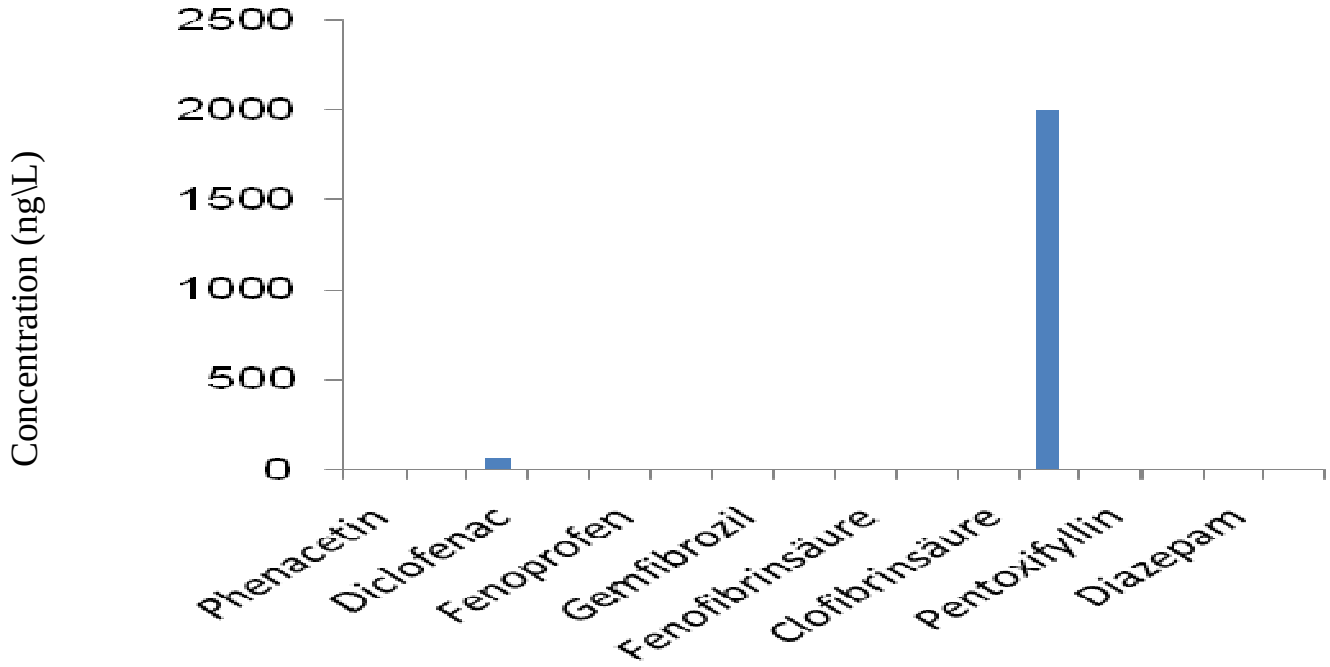


Figure 4.1.f: Concentration of pharmaceuticals in Mukhmas wadi in 15-4-2013

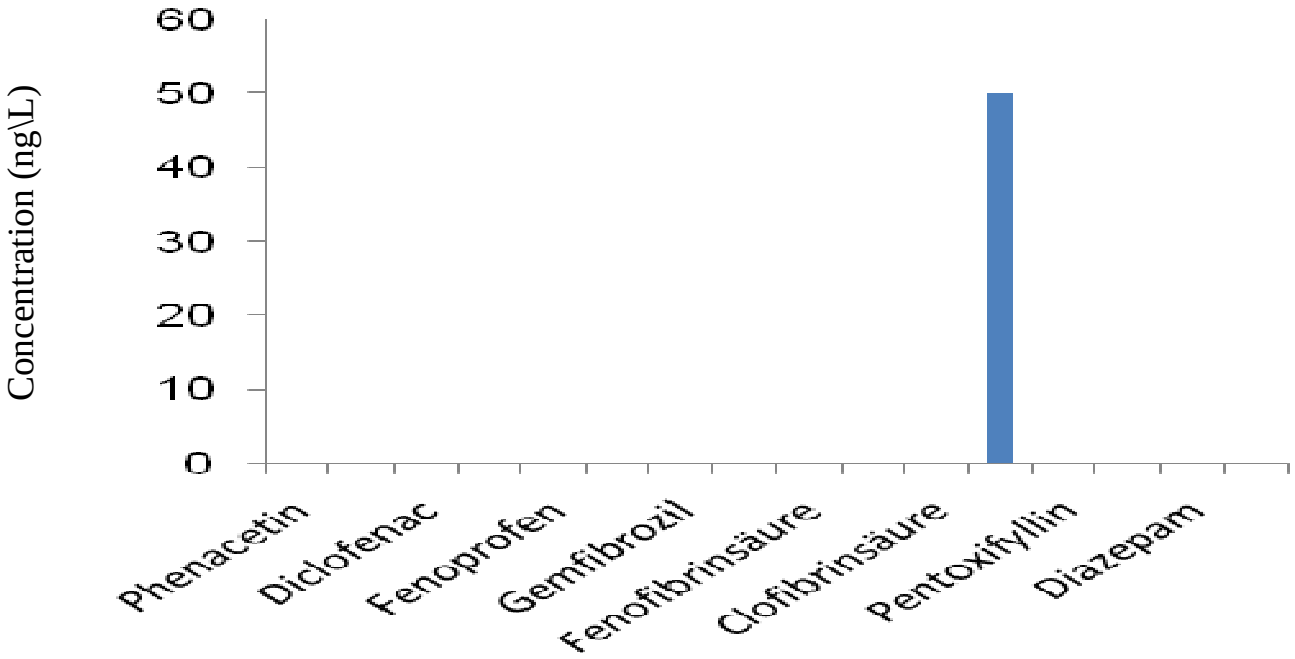


Figure 4.1.g: Concentration of pharmaceuticals in Ras Al Qlit in 15-4-2013

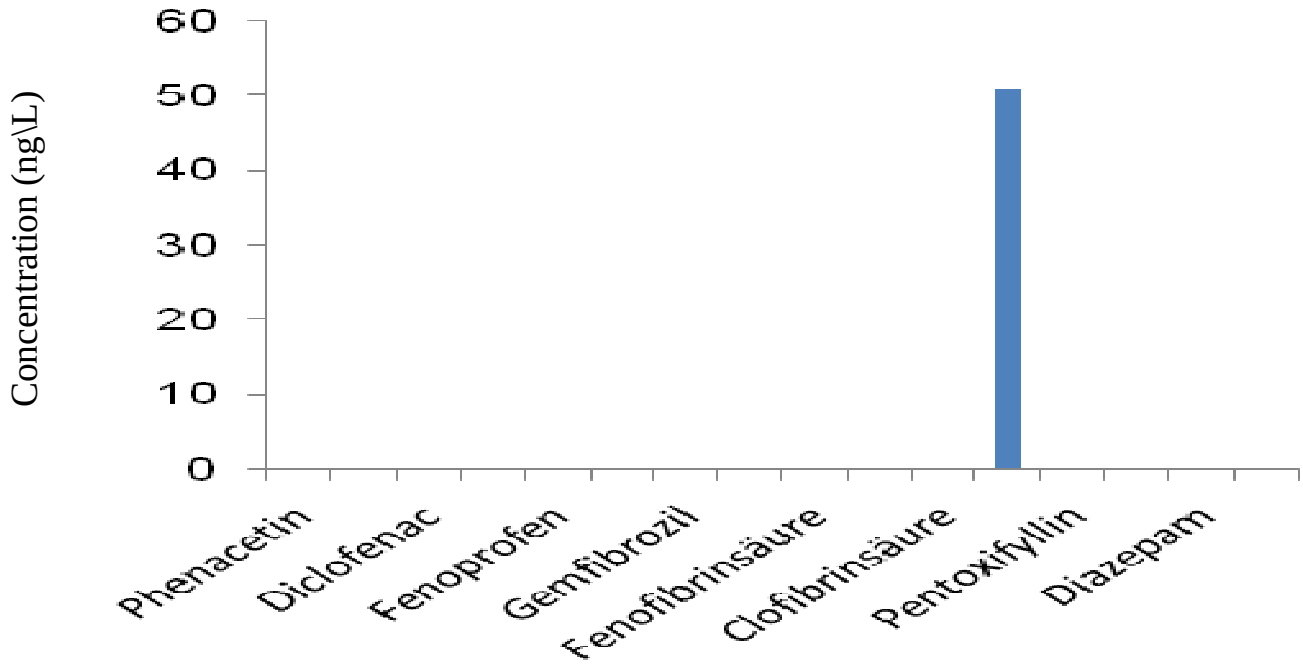


Figure 4.1.h: Concentration of pharmaceuticals in Aqpat Jaber drinking water before treatment in the water treatment plant in 15-4-2013

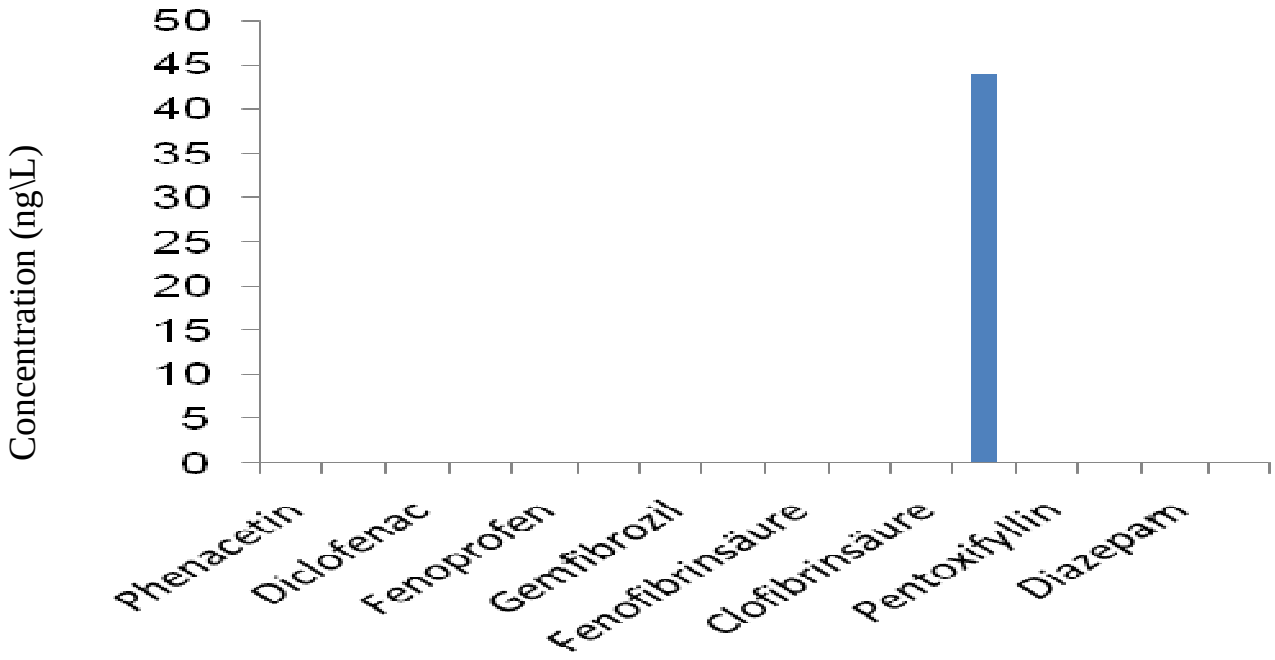


Figure 4.1.l: Concentration of pharmaceuticals in Aqpat Jaber drinking water after treatment in the water treatment plant in 15-4-2013

Sixteenth pharmaceutical compounds were analyzed in the water samples, namely Phenacetin, Indomethacin, Diclofinac, Ibuprofen, Fenoprofen, Ketoprofen, Gemfibrozil, Fenofibrat, Fenofibrinsaure, Bezafibrat, Clofibrinsäure, Carbamazepin, Pentoxifyllin, Naproxen, Diazepam, Etofibrat. In all of those, only Ibuprofen, Diclofinac and Carbamazepine were detected and the other are nil. The values of these compounds decreasing through the system (going from the first sampling station at the effluent of AWWTP to last sampling station in Murashahat) in decreasing the values of Ibuprofen, Diclofinac, Carbamazepine. This was due to the dilution process.

Moving from AWWTP to Al Murashahat, the highest values measured pharmaceutical compounds were registered for AWWTP effluent. The lowest values recorded downstream due to the dilution process through the wadis because of the discharge that come from Ein Fara, Ein Jumaiz, Ein Al-Ru'yan, Ein Al Fawwar and Ein Al Qilt springs into the wadis.

AWWTPs use activated sludge processes through which microorganisms are used for mineralization the pollutants into water and carbon dioxide.It is possible to remove the Pollutants from water by stripping into air or by sorption onto sludge that is discharged orderly. Some substances may be undergo photo-transformation process. Thus, the elimination of pharmaceutical residues in activated sludge processes includes four mechanisms: biotransformation, air stripping, sorption and photo-transformation (Zhang *et al*., 2008).

There are an absence of these compounds Phenacetin, Indomethacin, Ketoprofen, Gemfibrozil, Fenofibrat, Bezafibrat, Clofibrinsäure, Pentoxifyllin, Naproxen, Diazepam, Etofibrat in the four sampling station except Indomethacin also detected in the AWWTP with low concentration 60 ng/L below background and then it was disappear and then these compound is eliminated due to their biodegradability in water. The results revealed that there are three compounds with low concentrations present in the different sampling station, these compound are Ibuprofen, Diclofinac, Carbamazepine. These compounds have a high consumption rate in Palestine**.** Results showed variation in these compound concentration in the analyzed samples in different sample stations and it decrease with distance due to the dilution process to varying extent being which depend upon factors such as stream flow rate conditions and percentage of treated wastewater in the receiving water bodies**.** The results revealed the concentration of pharmaceutical compounds in the four stations. According to these results we saw that the presence of Ibuprofen only in the

AWWTP effluent in the first and second sampling time with a concentration of 300 ng/L and 1000 ng/L respectively and then disappeared in other sampling stations. Ibuprofen can remove in WWTPs for more than 90% (Schuman, 2008). Biotransformation is considered as a potential elimination pathway of ibuprofen. The metabolites of Ibuprofen can be removed efficiently, then it is not considered to be persistent. In the lake only the parent compound is determined and none of its metabolites (Buser *et al*. 1999).

Diclofinac was detected in AWWTP influent in the two sampling time with a concentration of 310ng/L in the first sampling time and 1450ng/L in the second sampling time. This concentration was decreased after treatment to 50ng/L and 225ng/L respectively. This mechanism of treatment can not eliminate pharmaceutical compounds completely**.** For Diclofinac, the elimination activity varies so much between different STPs in different studies. There is no elimination of Diclofinac in three Swiss STPs. (Tauxe-Wuersch *et al*., 2005). The average of elimination of diclofenac ranging from 17% (up to 75% (Stumpf *et al*., 1999; Ternes, 1998). Diclofinac is considered non-persistent in the environment, and decreases quickly in rivers (Bendz *et al.*, 2005) and lakes (Buser *et al*., 1998). Diclofinac is an Acid and found in the aquatic environment as an anion, which interpret a high solubility and very low volatilisation. Several studies were presented for monitoring the activity of elimination of pharmaceutical residues including Diclofinac and Carbamazepine. The results revealed that the activity of elimination of Diclofinac by WWTPs vary according to the study conducted by (Zhang *et al*., 2008). It revealed that the activity of elimination ranging from 0% up to 80%, but mainly in the way of 21–40% in wastewater treatment plants (Figure 4.1).

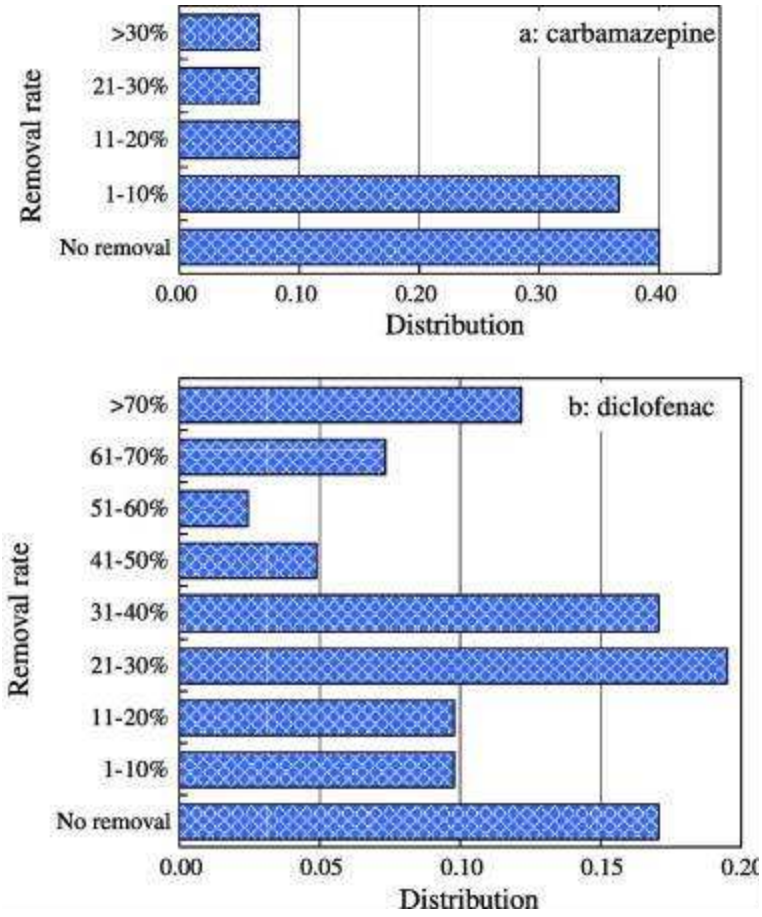


Figure 4.2: Removal efficiency distributions of Carbamazepine and Diclofenac in WWTPs (Zhang *et al*., 2008)

A study was conducted by (Quintana *et al.*, 2005) to investigate the biodegradation of Diclofenac by activated sludge. It shows that there are no transformation of Diclofenac over 28 days, neither when Diclofinac was the sole source of carbon (20 mg L^{-1}). Diclofenac shows poor biodegradation in batch elimination experiments using sludge from WWTPs and MBR, respectively. According to the result in Figure (4.1), the removal efficiency of Diclofinac could be up to 80% but for Carbamazepine was mostly below 10%. This variation might be that Carbamazepine is not biodegraded at low concentrations while biodegradation of Diclofinac may be possible under some conditions. The activity of elimination of these compounds is independent of the sludge retention time **(**SRT**)** (Clara *et al*. 2004; Kreuzinger *et al*., 2004).

Concentration of Diclofinac in wadi Mukhmas was increased in the first sampling time to 100ng/L due to mixing of not treated wastewater that come from Qalandia camp, then the

concentration of Diclofinac was disappeared in the last sample stations (Ras Al Qilt, Al Murashahat in Aqpat Jaber) which also showed that Diclofinac is not very persistent in the wadi Al Qilt, that it is rapidly degraded, most likely via direct photolysis when it is transported downstream .The main removal process of Diclofinac is Phototransformation (Tixier *et al*., 2003). The half-life of Diclofinac exposed to sunlight was less than 1 h (Zhang *et al.*, 2008). (Packer *et al.*, 2003) proved in their study that the presence of isopropyl alcohol, a radical quencher in Diclofinac is responsible for the rapid phototransformation of (Diclofinac in purified water, de-ionized water and Mississippi River water. In addition, Diclofinac having no large presence in groundwater to some extent due to its low mobility (Buser *et al*., 1999) . This study found a variation in the Diclofinac concentration in the two sampling period, the concentration of it is higher in the second sampling time than in the first sampling time in the AWWTP influent and effluent (1450 ng/L, 225 ng/L) respectively, may due to the seasonal variations in the consumption rate and elimination rates by humans and by WWTPs.

Carbamazepine was detected in AWWTP influent with a concentration of 1995 ng/L in the first sampling time and then decreased respectively to become 1750 ng/L in AWWTP efluent, 1550 ng/L in wadi Mukhmas, 64 ng/L in Ras Al Quilt to reach a value lower than background in al Murashahat influent and effluent. As we saw that Carbamazepine concentrations tend to decrease with increasing distance of the catchment area (Table 4.2).

Table 4.2: Distance between sample stations and the presence of pharmaceuticals in it.

Station name	**St.1 Al-Bireh WWTP**	**St.2 Mukhmas**	**St.3 Ras Al-Qilt**	**St.4 Water filtration plant (Al Murshahat)**
Distance from (Km)	0	5.2	19.5	27.5
Drug	Ibuprofen Diclofinac Carbamazepine	Diclofinac Carbamazepine	Diclofinac Carbamazepine	Carbamazepine

The measured concentration may decrease due to the dilution and flushing**.** The photolysis of Carbamazepine under sunlight irradiation occur at relatively low rate, therefore we can say this compound is persistent in surface waters. The measured concentration of Carbamazepine in the second sampling time was 1450 ng\L in AWWTP influent, 2000

ng/L effluent, 1995 ng/L in wadi Mukhmas, 82 ng/L in Ras Al Qilt, 48 ng/L in al Murashahat influent and 42ng/L in al Murashahat effluent. There are some variations in a concentrations between first and second sampling time. As we saw the concentration in AWWTP influent in the second sampling time was lower than the concentration in the first sampling time may be due to the decrease consumption of these pharmaceutical compound during this period, then the concentration of these compound increased in the AWWTP effluent. This increase might be because of a fast sorption of CBZ in the beginning than its desorption due to aging (decay, changing of structure of activated sludge enabling a better extraction of considered compound in the analytical method) of the activated sludge, or may be due to possible accumulation processes of degradates and parent compounds (Jimenez *et al*., 2011). Another interpretation is the daily concentration fluctuations during the sampling period (Clara *et al*., 2004). Or the separation of glucuronide conjugates of those pharmaceuticals by enzymatic processes in the treatment plant (Vieno *et al.*, 2005). So it is difficult to estimate the biodegradation of pharmaceutical residues since it is difficult to distinguish the bio-reduction from the separation increase.

Then, the concentration decrease in wadi Mukhmas with not significant value because of mixing of nontreated wastewater from Qalandia camp and Al Ram then decrease to 82ng/L in Ras Al Qilt and 48ng/L in JWTP influent due to the dilution and finally decrease to 42ng/L in JWTP effluent which is not significant amount because Carbamazepin is typically degraded with less than 10% during the wastewater treatment process. Most studies confirmed this issue. Properties of Carbamazepine may be the reason for its low elimination activity, thes properties include; first, it is resistant to biodegradation at low concentrations, secondly, it is hardly attached onto sludge (Nguyen,B., 2012).

Carbamazepine and Diclofinac, as discussed above, are examples of pharmaceutical compounds that have poor removal by WWTPs. These compounds have been determined in WWTP effluents, surface waters, groundwater and occasionally in drinking water, with succesive concentrations due to dilution and some removal processes as soil retention and phototransformation. Those compounds have been detected in WWTP effluents and in surface waters in some countries (Figure 4.2). There is a significant difference in the concentrations of these compounds among countries. This difference can be explained by the variation in the consumption rates of both pharmaceutical compounds in those

countries and due to the not enough investigations that carried out so far in the countries that do not have high concentration.

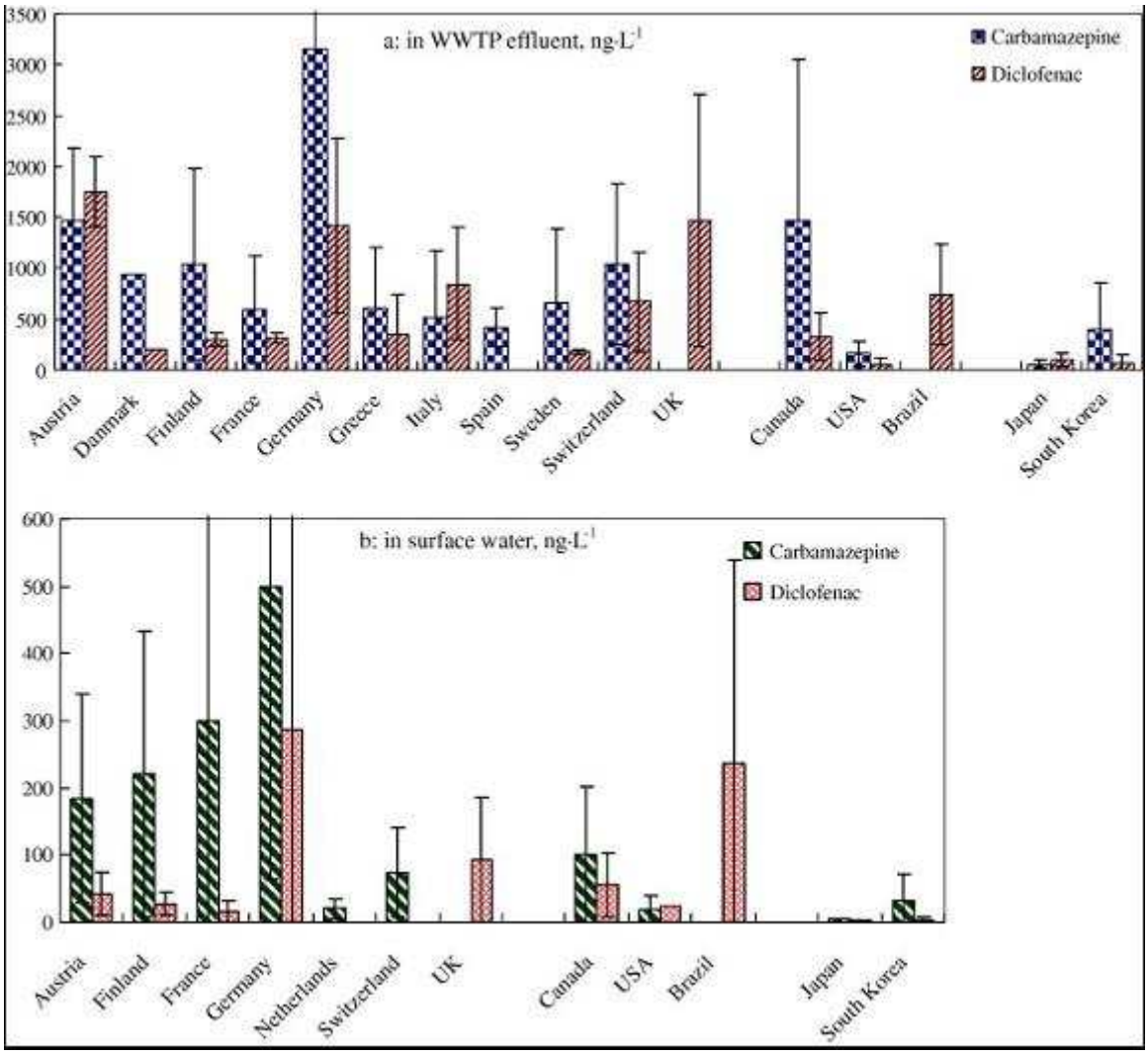


Figure 4.3: Average detected concentrations of Carbamazepine and Diclofinac in WWTP effluents (a) and surface waters (b) in some countries. Source (Zhang *et al*., 2008)

Because of the absence of functional groups that hydrolyze easily under environmental conditions in this compounds hydrolysis is not expected to be an important environmental fate process(Alshouli, 2012). It is possible for Carbamazepine to pass through an unsaturated underground zone and reach an aquifer. It was not degraded during its passage through underground/groundwater passage (Clara *et al*., 2004).

Andreozzi *et al*. (2003) showed in their study that presence of humic substances hindered phototransformation of Diclofinac and Carbamazepine while nitrate enhanced the phototransformation rate of these compounds. Although, of the positive effect of phototransformation in the environment for reducing drug levels it can lead to formation of transformation product which are more stable and toxic than the parent compounds, e.g. the carcinogenic acridine is formed during phototransformation of Carbamazepine.

Marei and Tiehm (2007) studied the occurrence of pharmaceuticals in Palestine and in Jordan in certain sites and gained a results similar with the results of this study for the target compounds (Ibuprofen, Diclofinac and Carbamazepine) (Figures 4.3 a and b),

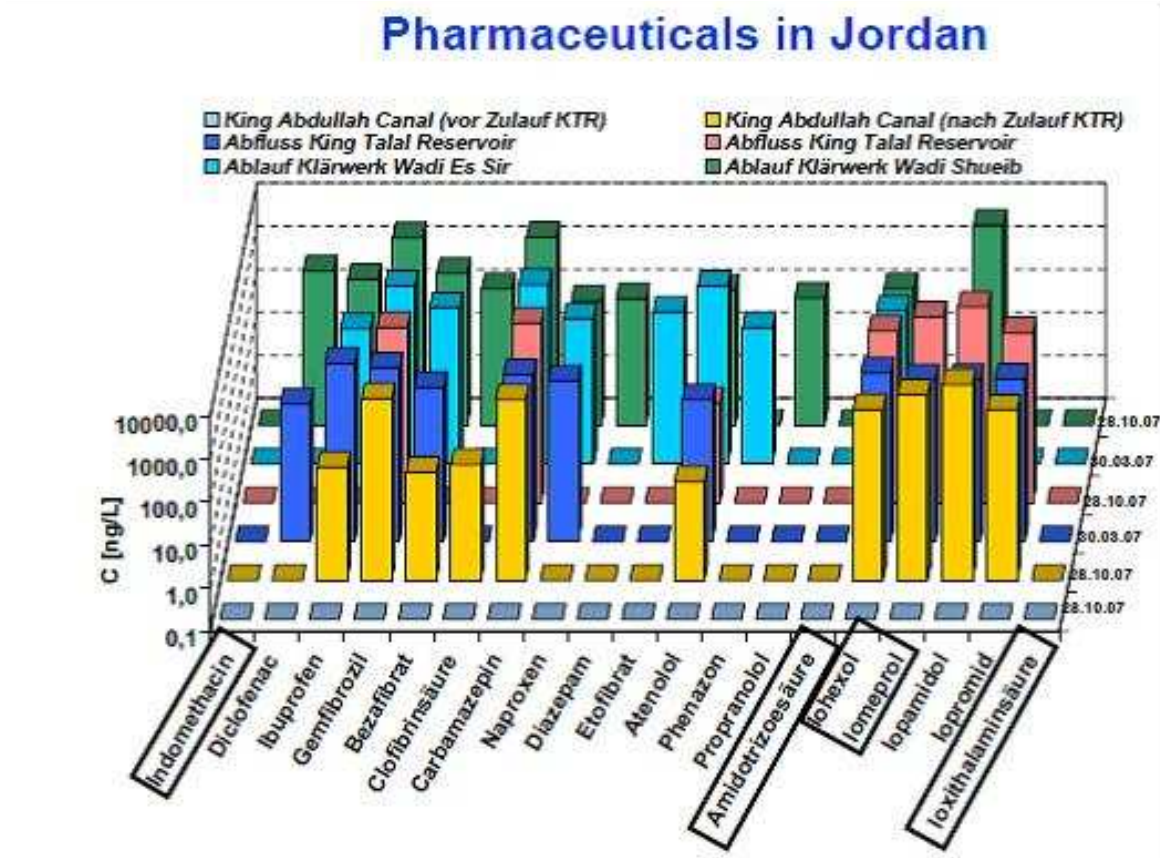


Figure 4.4a: Pharmaceuticals in Jordan (Marei and Tiehm, 2007)

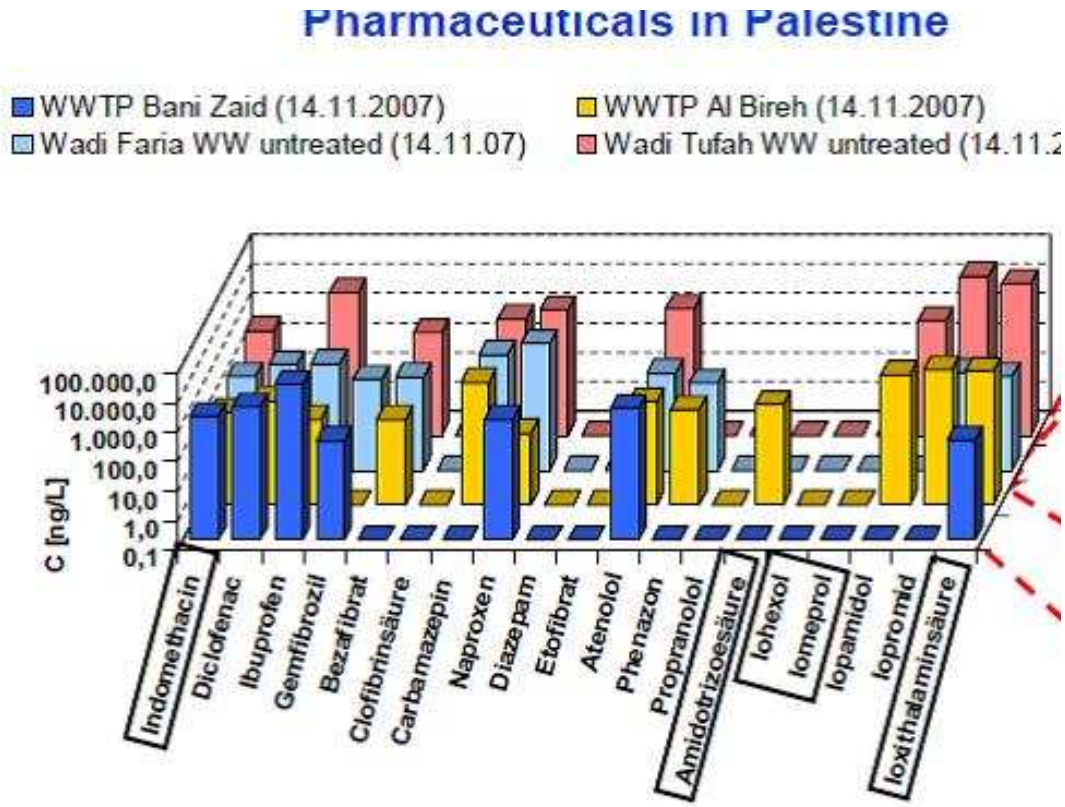


Figure 4.4b: Pharmaceuticals in Palestine (Marei and Tiehm, 2007)

4.2 Effect and Risk of pharmaceuticals

In this study we note that the target pharmaceuticals were decrease until to disappear in the last station except Carbamazepine that present all stations of the catchment area due to the previous reasons we mentioned that is first, it is resistant to biodegradation at low concentrations, secondly, it is hardly attached onto sludge. The Carbamazepine guidance value in drinking water is 40 ppb in MDH/USA. The highest concentration reported in the USA was 40 ng/l for meprobamate (Ferarri, 2004). The concentrations of pharmaceuticals in groundwater and surface water sources impacted by wastewater discharges are typically less than 0.1 µg/L, and concentrations in treated drinking-water are usually well below 0.05 µg/L (WHO, 2011). The effect of pharmaceuticals and their residues in aquatic environment are in most cases restricted to short term acute responses such as lethality in algae, invertebrates and fish (Webb, 2001). The chronic effects of pharmaceutical compounds are scarcely tested. To carry out accurate environment risk assessment, a long term exposures are essential . Elevated accumulation of Diclofinac in aquatic tissues were

reported, despite its low lipid solubility (Oaks *et al.*, 2004). The chronic effect of Ibuprofen could have interaction with estrogen homeostasis of Medaka fish (Han *et al*., 2005).

Table 4.3: Effects of ibuprofen, Diclofinac and Carbamazepine on various aquatic organisms at low pharmaceutical concentration (ng/L - µg/L).

Drug	**Effect**	**Concentration**
Ibuprofen	Significant decrease in activity of crustacean G. *pulex*	1 and 10 ng/L
	Toxic effects to microbial communities	10 µg/L
	Growth inhibition of duckweed L. minor, up to 25%	1,10,100 and 1000 µg/L
Diclofinac	Subtle sub cellular effects in fish	1 µg/L
	Renal lesions and alteration of gills in fish	5 µg/L
Carbamazepine	Slightly earlier maturation and reproduction of *Daphnia* and higher production of offspring	1 µg/L

According to the results of this study there is no comparison in the effect of ibuprofen because ibuprofen was disappear in WWTP. In case of diclofinac the concentration of it is below the concentration in the table above then there is no risk. In case of carbamazepine the concentration of it in this study was 1550ng\L and 1995ng\L in Mukhmas bridge in first and second sampling time and this concentration is higher than the concentration in the table above(1 microgram) and may cause a risk on small animals such as daphnia.In the Ras al Qilt and Al Murashat the concentration is below 1microgram then there is no risk.

Ferrari *et al*. (2003) studied the toxic effects of Diclofinac and Carbamazepine on algae, bacteria, fish and microcrustaceans. They reported that both Carbamazepine and Diclofinac had a relatively limited acute eco-toxicity on the tested organisms and chronic tests displayed higher toxicity than acute tests (see Table 4.4).

Table 4.4: Effects of ibuprofen, Diclofinac and Carbamazepine on various aquatic organisms at low pharmaceutical concentration. (Zhang *et al*., 2008)

	Acute toxicity EC_{50}	**Chronic toxicity NOEC**	**PNEC**
Carbamazepine	>13.8–81 mg L^{-1}	25–100 mg L^{-1}	0.42 μg L^{-1}
	1–10 mg L^{-1}		6.359 μg L^{-1}
	4.5–383.5 mg L^{-1}		
	75.1–502.6 mg L^{-1}		
Diclofinac	11.5– 22.7 mg L^{-1}	1–10 mg L^{-1}	116 μg L^{-1}
	1–10 mg L^{-1}		138.74 μg L^{-1}
	3.3–142.2 mg L^{-1}		
	90 ± 20 μg L^{-1} on zebra fish embryos.		
	68 mg L^{-1}	45 mg L^{-1}	
		1 mg L^{-1} on Daphnia magna and 1 μg L^{-1} on histopathological lesions	

EC_{50}: concentrations that cause 50% of effect.
NOEC: no observed effect concentration.
PNEC: predicted no-effect concentrations.

Pharmaceuticals in the environment have an effect on animal like birds such as vultures, raptors, cranes and owel. A study by Oaks *et al*. (2004) showed that the death of between 34 and 95% of the population of oriental white-backed vultures, was linked to the consumption of water contaminated with Diclofinac, a painkiller widely used by the human population that cause kidney failure and visceral gout in birds. In addition, it has also been found that detrimental effects may happen by the transfer of compounds within the food web.

Diclofinac is reported to negatively affect vulture populations in Southeast Asia (Pakistan, India, Bangladesh and Nepal), as it caused a severe Decline of vultures, after feeding themselves with domestic livestock and cattle, which were given Diclofinac (Oaks, 2004).

Old world vultures consume dead livestock that eat the carcass which having diclofinac in their body, as Diclofinac is used for treatment sick livestock in Asia. Dose of only 1 mg of these drug causes acute kidney failure and death within a few days. Many studies confirmed that ingestion of residues of the Diclofinac causes high mortality rate.

The impact of Diclofinac on the mortality, growth, and development of fish was studied by Svobodova *et al*. (2013). They reported that the exposure to Diclofinac at 3mg/L was associated with increased mortality, increased activity of glutathione S-transferase, and decreased activity of glutathione reductase.

4.3 Effect of target pharmaceuticals on groundwater

NSAIDs reach groundwater when municipal wastewater or biosolids are applied in soils then it may migrate through soils or be transformed in it ending into groundwater. CBZ has poor sorption and relative persistence which suggest that it may pose a high leakage risk for groundwater contamination when recycled for irrigation . Carbamazepine had the lowest concentration at the top soil layers which have the highest organic carbon content, which means that there is potential degradation of Carbamazepine in surface soils. Carbamazepine also showed significant accumulation from year to year (McLain and Williams, 2012). Soils may adsorb CBZ and making it to move slowly into groundwater (Williams *et al*., 2012). Carbamazepine and Diclofinac are classified as slow-mobile compounds in SOM-rich soil layers. They showed high mobility when introduced into SOM-poor soils, and their mobility increases significantly . Chemicals' characteristics (such as pK(a) values) and soil properties influence the mobility of NSAIDs in soil.According to the results of this study the concentration of Target compounds was below background and disappear in Ras Al Qilt and in Al Murashahat except carbamazepine which was near the background so it has no risk on it.

4.4 Conclusions

* Findings of this study show the following:

* Ibuprofen is detected only in the AWWTP effluent in the first and second sampling time with a concentration of 300 ng/L and 1000 ng/L respectively, and then disappeared in other sampling stations because it was efficiently removed in AWWTP.

* Diclofinac was detected in AWWTP influent in the two sampling time with a concentration of 310ng/L in the first sampling time and 1450ng/L in the second sampling time. This concentration was decreased after treatment to 50ng/L and 225ng/L respectively. Then it was disappeared in Ras Al Qilt and in Al Murashahat due to the photodegradation process.

* Carbamazepine was detected in AWWTP inffluent with a concentration of 1995 ng/L in the first sampling time and then decreased respectively to become 1750 ng/L in AWWTP effluent, 1550 ng/L in wadi mukhmas, 64 ng/L in ras al quilt to reach a value lower than background in al murashahat influent and effluent.

* Only Carbamazepine were detected in the Ras Al Qilt in the first and second sampling time and in Al Murashahat influent and effluent in the second sampling time, where the highest values were recorded for AWWTP effluent.

* The concentration of pharmaceutical compounds(Ibuprofen, Diclofinac, Carbamazepine) on Al Qilt catchment area are below background or near it, then they have no risk on groundwater and public health. According to the literature review it may have a risk on small animals as inertebrates and fish when it found in a concentration higher than the concentration that detected in this study with significant value and do not have a risk on human.

4.5 Recommendations`

To reduce the pharmaceutical environmental pollution, it is recommended to:

1. Back to alternative medicine and using herbs to reduce the pharmaceutical pollution, which they finished in the water.

2. Emphasis monitoring on pharmacies and inhibitthem from selling medicines randomly and without medical prescription.

3. Studies should be conducted for other chemical pollutants such as endocrine disruptor chemicals (EDC), hormone imposters, sex hormone pollution which distort the reproductive organs of animal life.

4. Interested ministries must be determine the responsibilities towards pharmaceuticals waste management in Palestine.

5. It must be apply more laws and regulations linked to pharmaceuticals waste management outside health care centers.

6. More researches in this regard should be carried out, further investigation into the fate of Ibuprofen, Diclofinac, Carbamazepinee in the environment which include:Degradation rates, local and global distribution, toxicity of it to understand their risk on water bodies and drinking water.

7. Further improvement and validation of the employed methods for the analysis of these pharmaceuticals in water.

8. Studying the effect of these pharmaceuticals on public health and environment in other places in Palestine. .

9. Disposal of expired pharmaceuticals by healthy way, and improve the methods of pharmaceutical removal in wastewater treatment plants.

References

Al Hirsh, I., 2010. The effect of antiprostaglandin COX1 & COX2 on nile tilapia fish growth rate mortality rate and sex reversal. Master thesis.Al quds university.

Ali, W., Hotzl, H., Wolfer, J., 1999. A hydrogeological study along Wadi Al Qilt between Jerusalem and Jericho, West Bank, *Water and Environment*. December, 1999: 5-11. Palestinian Hydrology Group, Palestine.

Al-Nasser, A., 2000. Ibuprofen-Induced Liver Mitochondrial Permeability Transition. Toxicology Letters, pages 213-218.

Alshouli, M., 2012. Wastewater Tracer Study Utilizing Carbamazepine, Triclocarban and Triclosan in the Philadelphia Waterway. Master Thesis. Drexel University.

ARIJ 1996a. Environmental profile/ Ramallah district, Applied Research Institute/Jerusalem.

ARIJ 1996b. Environmental profile/ Jericho District, Applied Research Institute/Jerusalem.

Applied Research Institute – Jerusalem ARIJ (2007) Status of environment in the West Bank Territories. Palestine.

Palestinian Water Authority (2009) Data Base and GIS units, West Bank, Ramallah.

Palestinian Central Bureau of Statistics (2003) Israeli Settlements in the Palestinian Territory, *Annual Report 2002*. Ramallah, West Bank, Palestine

Ministry of Health, 2013.Personal communication.

Bendz, D., Paxéus, N., Ginn T., Loge F., 2005. Occurrence and fate of pharmaceutically active compounds in the environment, a case study: Hörje River in Sweden, Journal of Hazardous Materials 122, 195-204

Bethany, H., 2008. Pharmaceuticals have been finding their way into our environment for a long time**,** but just what are they doing there,

Buser H., Boiger T., Müller M., 1998. Occurrence and Fate of the Pharmaceutical Drug Diclofinac in Surface Waters: Rapid Photodegradation in a Lake, *Environmental Science & Technology*. 32 (22), 188-192Daughton C.G

Buser, H., Poiger, T. and Muller, M. 1999 Occurrence and Fate of the Pharmaceutical Drug Diclofinac in Surface Waters: Rapid Photodegradation in a Lake; *Environ. Sci. Technol.*, *32* (22), 3449–3456

Buser, H., Poiger, T. and Muller, M.; 1999; Occurence and environmental behavior of the chiral pharmaceutical drug ibuprofen in surface waters and in wastewater; *Environ. Sci. Technol.* 33(15):2529.

Chane, P and Kung, H. 2009. Occurrence of Pharmaceuticals &personal care products along the West Prong littlePigeon River in east Tennessee USA, Published by *Journal Of Chemosphere*, 75,1281-1286.

Chiron, S., Minero, C. & Vione, D. 2006. Photodegradation processes of the antiepileptic drug carbamazepine, relevant to estuarine waters. *Environmental Science and Technology* 40(19), 5977–5983.

Clara, M., Strenn, B., Ausserleitner, M., Kreuzinger, N., 2004. Comparison of the behavior of selected micropollutants in a membrane bioreactor and a conventional wastewater treatment plant. *Water Sci. Technol*. 50, 29–36.

Clara, M., Strnn, B and Kreuzinger, N., 2006. Carbamazepine as a possible anthropogenic marker in the aquatic environment: investigations on the behaviour of Carbamazepine in wastewater treatment and during groundwater infiltration, Elsevier.

Cleuvers, M., 2004. Mixture toxicity of the anti-inflammatory drugs Diclofinac, ibuprofen, naproxen, and acetylsalicylic acid, *Ecotoxicology Environmental Safety*, 59, 309-315.

Cleuvers, M., 2003. Mixture toxicity of the anti-inflammatory drugs Diclofinac, ibuprofen, naproxen, and acetylsalicylic acid. *Ecotoxicol Environ Safety*, 59(3),309-15.

Hong, H., Kim, H., Park, K., Lee and Gu, M., 2007. Analysis of the effects Diclofinace has on Japanese medaka (Oryzias latipes) using real-time PCR, *Chemosphere*, 67(11): 2115-2121.

Dietrich, D., Prietz, A., 1999. Fish embryotoxicity an teratogenicity of pharmaceuticals, detergents, and pesticides regularly detected in sewage treatment plants effluents and surface waters. *T*oxicologist., 48(1-s): 151.

Dietrich, D., Webb, S., and Petry, T., 2005**.** Hot Spot Pollutants: Pharmaceutical in the Environment. *Toxico.l. Lett,* 131,1-3.

Fent, K., Weston, A., and Caminda. D., 2005. Ecotoxicology of human pharmaceuticals. *Aquat Toxicol,*76(2),122-59.

Fent, K., Weston, A., Caminada, D., 2006. Ecotoxycology of human pharmaceuticals, *Aquat.Toxicol*., 76, 122 – 159.

Gonzalez-Rey, M., Mattos, J., Piazza, C., Bainy, A., Bebianno, M., 2014. Effects of active pharmaceutical ingredients mixtures in mussel Mytilus galloprovincialis. *Aquat Toxicol,* 153,12-26.

Han, G., Hand Kim, S., 2005. Ecotoxicological risk of pharmaceuticals from wastewater treatment plants in Korea: Occurrence and toxicity to daphnia magna., *Environ Toxicol Chem*, 25(1), 265-71.

Hersh, E., Dem, M., Pinto, A., Paul A. Moore, P., 2007. Adverse drug interactions involving common prescription and over-the counter analgesic agents**.** Clinical Therapeutics. 29**,** 2477–2497.

Houeto, P., Carton, A., Guerbet, M., Mauclaire, A., Gatignol, C., Lechat, P., Jacobs, L., Fimmen, R., and Chin Y., 2011. Fulvic Acid Mediated Photolysis of Ibuprofen in Water, *Water Res.*, 45, 4449-4458.

Jarrar, A. 2003. Comparative Pharmacokinetic Study of Single Oral Dose of Ibuprofen in Health Volunteers for Palestinian, British and American Pharmaceutical Equivalents in Local Market, master Thesis.

Karnjanapiboonwong, A., 2010. Occurrence of Pharmaceuticals and Personal Care Products (PPCPs) at an effluent-dominated wastewater application site: Estrogens, Triclosan, and Caffeine. Texas Tech University, PhD Thesis.

Karnjanapiboonwong, A., Suski, J., Shah, A., Cai, Q., and Morse A., 2001. Occurrence of PPCPs at a Wastewater Treatment Plant and in Soil and Groundwater at a Land Application Site. Earth and Environmental Science., 216, Numbers1-4, 257-273.

Katarzyna, K-R., Ime A., and Mahmoud, N., 2007. Pharmaceutical Compounds In Environment.

Kostich, M and Lazorchak, J. 2007. Risks to aquatic organisms posed by human pharmaceutical use. Sci Total Environ., 389(2-3), 329-39.

Kotchen, M., Kallaos, J., Wheeler K., Wong C., and Zahller M. 2009. Pharmaceuticals in Waste Water: Behavior, Preferences and willingness to Pay for a disposal Program. *Journal of Environment Management*., 90,1476-1482.

Kummerer, K., 2004. Pharmaceutical in the Environment: Source, Fate, Effect, and Risk, 3rd edition**.**

Ramesh, M Malarvizhi, A., Kavitha, C., Saravanan, M., 2012. Carbamazepine (CBZ) induced enzymatic stress in gill, liver and muscle of a common carp, Cyprinus carpio. *Journal of King Saud University - Science***.,** 24, 179–186

Masset, D., 2012. Assessment of the health risks related to the presence of drug residues in water for human consumption: Application to Carbamazepine. *Regul Toxicol Pharmacol*., 62(1), 41-8.

Me´ndez-Arriaga, F., Esplugas, S., and Gime´nez, J., 2010. Degradation of the emerging contaminant Ibuprofen in water by photo-Fenton. *Water research*., 44, 589-595.

WHO, 2011. Pharmaceuticals in Drinking-water

Ministry of Health, Statistical report, (2013). Personal interview, (28\1\2014).

Mofazzeli, F., 2013. Three liquid-phase microextraction of Diclofinac and Ibuprofen from water samples prior to high performance liquid chromatography. *J. Mater. Environ. Sci.*, 4(5), 649-654.

Nassef, M., Kim, S., Seki, M., Kang,I., Hano, T, and Shimasaki, Y. In *ovo* nanoinjection of triclosan, Diclofinac and Carbamazepine affects embryonic development of medaka fish (*Oryzias latipes*). *Chemosphere.* 79(9), 966-73.

Nasser, A., 2000. Ibuprofen-Induced Liver Mitochondrial Permeability Transition. *Toxicology Letters*., 111(3), 213-8.

Oaks, J., Gilbert, M., Virani, M., Watson, R., Meteyer, C., 2004 . Diclofinac residues as the cause of vulture population decline in Pakistan. *Nature*. 2004 Feb; 427 (6975), 630-633.

Oppel, J., Broll, G., Löffler, D., Meller, M., Rombke, J., Ternes, T., 2004. Leaching behaviour of pharmaceuticals in soil-testing-systems: a part of an environmental risk assessment for groundwater protection. *Sci Total Environ.*, 328(1-3), 265-73.

Palestinian Central Bureau of Statistics (PCBS) 1999–2011. Jerusalem Statistical Yearbook. No. 1–13. Ramallah.

Rang, H., Dale, M., Ritter,J., 1995. Pharmacology, 3rd edition, pages 247, 635-641.

Salmann, A. 1986. The history of Diclofinac. *Am. J. Med*., 80(4B), 29-33.

Samhan, S., 2013. Occurrences and transport of trace metals in wastewater, sediment and soil. Case study Al-Qilt catchment, West Bank, Palestine, PhD Thesis, Karlsruhe University.

Schuman, E., 2008. Fate of human pharmaceuticals in biological treatment systems treating concentrated wastewater under various environmental condition. Msc thesis, Wageningen University.
,

Svobodova, Z., Stepanova, S., Praskova, E., Chromcova, L., Plhalova, L., Prokes, M., Blahova, J., 2013. The effects of Diclofinac on early life stages of common carp (Cyprinus carpio). 2013 May, 35(3), 454-60. Epub.

Stumpf, M., Ternes, A., Wilken, R., Rodrigues, S., Baumann, W., 1999. Polar drug residues in sewage and natural waters in the state of Rio de Janeiro, Brazil, Sci. Total Environ. 225 (1-2), 135 – 141

Tauxe-Wuersch, A., Alencastro, L., Grandjean, D., Taradellas, J., 2005. Occurance of several acidic drugs in sewage treatment plants in Switzerland and risk assessment, *Water Research*., 39, 1761- 1772Al-

Ternes, T., 1999. Pharmaceuticals and personal care products in the environment: agents of subtle change. *Environ Health Perspect*, 107-109.

Thompson, A., 2005. The Fate & Removal of Pharmaceuticals Sewage Treatment, ph.D Thesis, Cranfield University.

Todd, A and Sorken A., 2007. Long-Term Fate of Pharmaceuticals and Personal Care Production in the Environment, the World Health Organization (WHO).

ul Hassan, S., Yunus, S., and Latif, A. 2010. Study and improvement of methods for the determination of diclofinac sodium in pharmaceutical preparations, *Pak. J. Pharm*. ,20-23 (1 & 2): 7-10.

Walker, C., Watson, J., Williams, C., 2012 Occurrence of Carbamazepine in soils under different land uses receiving wastewater. Jul-Aug; 41(4),1263-7.

Wetzig, R. 2008. Removal of selected pharmaceuticals from sewage water by advanced treatment techniques.

Williams, C and McLain J., 2012.Soil persistence and fate of Carbamazepine, lincomycin, caffeine, and Ibuprofen from wastewater reuse., 41(5),1473-80.

Williams, M. 2007. The fate and effects of human pharmaceutical in aquatic environment. PhD, Thesis, University of Adelaide, Australia.

Wuersch, A., Alencastro, L., Grandjean, D., and Tarradellas, J., 2005. Occurrence of several acidic drugs in sewage treatment plants in Switzerland and risk assessment. *Water Research*., 39,1761–1772.

Yu Y, Liu Y, Wu L., 2013. Sorption and degradation of pharmaceuticals and personal care products (PPCPs) in soils. EPub, 2013 Jun; 20(6):4261-7.

Zhang, Y., Geiben, S, and Gal, C. 2008. Carbamazepine and Diclofenac: Removal in wastewater treatment plants and occurrence in water bodies, *Chemosphere***.,** *23***,** 1151–1161.

Zhi-Hua, L., Zlabek, V., Velisek, J., Grabic, R., Machova, J., Kolarova, J., Ping, L, and Randak, T., 2011 Acute toxicity of Carbamazepine to juvenile rainbow trout (Oncorhynchus mykiss): Effects on antioxidant responses, hematological parameters and hepatic EROD, *Ecotoxicol Environ Saf*., 74(3), 319-27.

Bethany, H. 2008 Pharmaceuticals have been finding their way into our environment for a long time, but just what are they doing there, *C & EN chemical engineering news*, 86, 08, 13-17.

Ceron-Litvoc, D., Soares, B., Geddes, J., Litvoc, J., de Lima, M. 2009. "Comparison of Carbamazepine and lithium in treatment of bipolar disorder: a systematic review of randomized controlled trials". *Hum Psychopharmacol*., 24 (1), 19–28.

Gonzalez-Rey, M and Bebianno, M. 2014. Effects of non-steroidal anti-inflammatory drug (NSAID) Diclofinac exposure in mussel Mytilus galloprovincialis, *Aquat Toxicol*., 148, 221-30.

Vieno, N., Tuhkanen, T. and Kronberg, L.; 2005; Seasonal variation in the occurence of pharmaceuticals in effluents from a sewage treatment plant and in the recipient water; *Environ. Sci. Technol*., 39, 8220

Martin-Diaz L, Franzellitti S, Buratti S, Valbonesi P, Capuzzo A, Fabbri E (2009). Effects of environmental concentrations of the antiepilectic drug carbamazepine on biomarkers and cAMP-mediated cell signaling in the mussel Mytilus galloprovincialis, *PMID*, 94(3):177-185.

Daghra.,G.2005. Treated Wastewater Impact on Al Qilt Catchment Area-Palestine.

Matthieu, L. 1992. Pharmacokinetic-Pharmacodynamic modelling of the analgesic effect of Ibuprofen and codeine, Doctor of Philosophy, PhD. Thesis, University of Florida, USA.

Laven *et al*., 2009. As cited in Lange.,F, Levc.,O, Ruck.,W, Brauch.,H, Graf.,C, Storck.,F, Scheurer.,M. 2011. Correlation of six anthropogenic markers in wastewater, surface water, bank filtrate, and soil aquifer treatment.

The Ministry of Health, Labour and Welfare 2006. "Diclofinac". Japanese Pharmacopeia. Prefectural office in Japan. 15th ed. 618.

Ferrari *et al*., 2003. as cited in zhang et al .2008. Carbamazepine and Diclofinac: Removal in wastewater treatment plants and occurrence in water bodies, Elsevier.

Mazumdar, K., Dutta, N., Dastidar, S., Motohashi, N., Shirataki, Y. 2006. "Diclofenac in the management of E. coli urinary tract infections". In Vivo 20 (5): 613–619.

Jacobs, L., Weavers, L., Houtz, F., Chin, P., (2012) .Photosensitized degradation of caffeine: Role of fulvic acids and nitrate, Chemosphere, Volume 86, issue 2, page124-129.

McGettigan., P, Henry D. 2013. Use of non-steroidal anti-inflammatory drugs that elevate cardiovascular risk. PLoS Med. 10(2):e1001388.

Marei.,A and Tiehm.,A. 2007. Managed Aquifer Recharge.

Monson, K and Schoenstadt. 2014. Diclofinac, emedtv, cited at:

"www:arithritis.emedtv.com", date: 13/4/2014.

Solomon, D., Avorn, J., Stürmer, T., Glynn, R., Mogun, H., Schneeweiss, S. 2006. "Cardiovascular outcomes in new users of coxibs and nonsteroidal antiinflammatory drugs: high-risk subgroups and time course of risk". Arthritis Rheum 54 (5): 1378–89.

Zwiener., C and Frimmel., F. 2003. Short-term tests with a pilot sewage plant and bio reactors for the biological degradation of the pharmaceutical compounds: ibuprofen, and diclofenac. Sci. Total Environ., 309, 201–211.

Ramesh., M., Malarvizhi., A., Kavitha., C., Saravanan, M. 2012. Carbamazepine (CBZ) induced enzymatic stress in gill, liver and muscle of a common carp, Cyprinus carpio, Journal of King Saud University – Science., 24, 179–186.

Granger, P. 1995. Modulation of the gamma-aminobutyric acid type A receptor by the antiepileptic drugs carbamazepine and phenytoin. Mol. Pharmacol., 47, 1189–1196.

Okuma, T., Kishimoto, A.1998. "A history of investigation on the mood stabilizing effect of carbamazepine in Japan". Psychiatry Clin. Neurosci. 52U (1), 3–12.

Al hellou.,F.2008. Spatial and Temporal Variation in the Hydrochemistry and Isotopic Composition of the Groundwater in the Jordan in Jordan Rift Valley.

Andreozzi, R., Marotta, R. & Paxéus, N. 2003. Pharmaceuticals in STP effluents and their solar photodegradation in aquatic environment. Chemosphere., 50(10), 1319-1330.

Chiron, S., Minero, C. & Vione, D. 2006. Photodegradation processes of the antiepileptic drug carbamazepine, relevant to estuarine waters. Environmental Science and Technology., 40(19), 5977–5983.

Sirocki.,A, Lanza.,R and Connors.,S. 2013. Removal of Ibuprofen from Drinking Water using Adsorption .

Warden, S. 2010. "Prophylactic Use of NSAIDs by Athletes: A Risk/Benefit Assessment". The Physician and Sports Medicine 38 (1): 132–138.

Faigle and Feldman, 1976). As cited in Bertilsson 1978. Clinical pharmacokinetic of carbamazepine.

Webb, S. 2001. A data based perspective on the environmental risk assessment of human pharmaceuticals II – aquatic risk characterization. In: Kummerer, K (Ed.). Pharmaceuticals in the environment, Sources fate, effects and risks, Springer-Verlag Berlin, Heidelberg, New York, 203-219.

Zwiener., C, and Frimme., F. 2000. Oxidative treatment of pharmaceuticals in water, Water Research, 34(6):1881.

Nguyen,B. 2012. Influence of membrane fouling on the removal of pharmaceutical.

Oehlmann.,J, Ternes.,T, Lçffler.,D, Nentwig.,G, Oetken.,M.2005. Effects of Pharmaceuticals on Aquatic Invertebrates.

Diener.,H, Timmann.,D, Wilhelm., H, Delcker.,A.1997. Side effects from increased doses neuropsychological and posturographic parameters of human.

Chandrashekar., K and Prasanna.,K. 2010. Analgesic and Anti-inflammatory Activities of the Essential oil from Cymbopogon flexuosus.

Hoeger., B, Kollner., B, Dietrich .,D and Hitzfeld. B.2005. Water-borne diclofenac affects kidney and gill integrity and selected immune parameters in brown trout (Salmo trutta f. fario).

Houeto., P, Carton.,A, Guerbet.,M, Mauclaire.,A, Gatignol.,C, Lechat.,P, Masset., D.2012. Assessment of the health risks related to the presence of drug residues in water for human consumption: Application to carbamazepine .

Tan.,S, Ng., W, Zhu.,J, Gersberg.,R, Hua.,T, Zhang.,D.2013. Carbamazepine and naproxen:Fate in wetland mesocosms planted with Scirpus validus.

Clara.,M, Strenn.,B, Kreuzinger.,N.2004. Carbamazepine as a possible anthropogenic marker in the aquatic environment: investigations on the behaviour of carbamazepine in wastewater treatment and during groundwater infiltration.

Tixier.,C, Singer., H, Oellers., S, Müller., S. 2003. Occurrence and fate of carbamazepine, clofibric acid, diclofenac, ibuprofen, ketoprofen, and naproxen in surface waters.

Gagne.,F, Blaise., André.,C.2006. Occurrence of pharmaceutical products in a municipal effluent and toxicity to rainbow trout (Oncorhynchus mykiss) hepatocytes.

Lange.,F, Levc.,O, Ruck.,W, Brauch.,H, Graf.,C, Storck.,F, Scheurer.,M. 2011. Correlation of six anthropogenic markers in wastewater, surface water, bank filtrate, and soil aquifer treatment.

KE,A., NM, D. 1997. Clinical pharmacokinetics of diclofenac. Therapeutic insights and pitfalls, lin Pharmacokinet., 33, 184-213.

Rahal, A., Kumar, A., Ahmad, A., 2008. Pharmacokinetics of diclofenac and its interaction with enrofloxacin in sheep, Research in Veterinary Science., 84, 452-456.