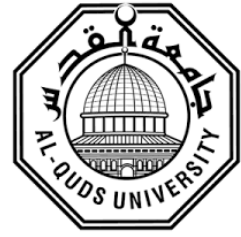


Deanship of Graduate Studies

Al-Quds University



**Assessment of some selected pharmaceutical residues
from Wastewater Treatment Plant in Palestine**

By:

Mohammad Sobhe Samhan

M.Sc. Thesis

Jerusalem - Palestine

1445 - 2024

Assessment of some selected pharmaceutical residues from
Wastewater Treatment Plant in Palestine

Prepared by:

Mohammad Sobhe Samhan

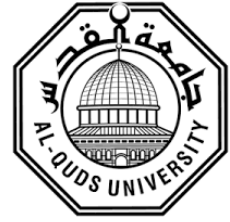
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A thesis submitted in partial fulfillment of requirements for the
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Thesis Approval

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Jerusalem – Palestine

1445– 2024

Dedication

With the grace of Almighty Allah, I write this expression of gratitude on the occasion of obtaining my Master's degree. I dedicate this achievement to my parent, who have been an inexhaustible source of support and inspiration at every stage of my journey.

I extend my heartfelt thanks to my brothers and sister for their unlimited support and constant encouragement, which played a significant role in achieving this milestone. Moments of joy and challenging times were made easier thanks to their warm presence.

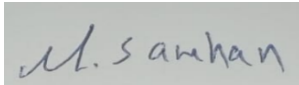
On this occasion, I express special thanks to my dear friends who have been an integral part of my journey. A word of gratitude to all of you for always being there to provide support and motivation.

Declaration

I Certify that this thesis submitted for the degree of Master of Water Science innovations studies is the result of my own research, except where otherwise acknowledged, and that this thesis (or any part of the same) has not been submitted for higher degree to any other university or institution.

Mohammad Sobhe Samhan

Signature

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First and foremost, of all, thank Allah, the most merciful, for all the power and knowledge I was endowed with, which helped me to do this research.

"I dedicate this thesis to my beloved parents, who have provided me with endless love, support, and encouragement throughout my academic journey. Your sacrifices and unwavering belief in me have made this achievement possible.

To my dear sisters and brothers, who have been my closest companions and confidants, I am grateful for your companionship and understanding. Your support has been a source of strength and motivation for me.

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Mohammad Sobhe Samhan

Abstract

Sewage Treatment Plants (STPs) around the world, including those in Palestine, are typically not designed to remove micro-pollutants such as pharmaceuticals. This can lead to STPs being a significant source of pharmaceutical contamination in the environment, including surface waters, coastal waters, and ground waters. The presence of these compounds, combined with their potential adverse ecological effects, makes them a problematic pollutant. A study was conducted to analyze the distribution of pharmaceutical residues in five conventional STPs of varying sizes in Palestine. The study also aimed to evaluate the effectiveness and potential of treatment processes such as activated sludge and conventional wetlands, as well as advanced treatment processes called Nature-based Solutions (NbS) and Wetland systems, which can be used as post-treatment secondary treatment steps to complement existing STP configurations. The study found significant variability in the removal of pharmaceuticals in the five STPs. The targeted pharmaceuticals were Atenolol, Carbamazepine, Caffeine, Cotinine, Erythromycin, Lidocaine, Metronidazole, Paracetamol, and Ranitidine. The removal of pharmaceuticals in the Al-Bireh treatment plant ranged from 0% for Lidocaine to 99.9% for Caffeine. In the Nablus treatment plant, the removal of pharmaceuticals ranged from 5.5% for Lidocaine to 99.8% for Caffeine. In the Misilya treatment plant, the removal of pharmaceuticals ranged from 47.5% for Ranitidine to 100% for Caffeine. In the Al-Aroub treatment plant, the removal of pharmaceuticals ranged from 19.6% for Erythromycin to 91.0% for Metronidazole. In the Kharras treatment plant, the removal of pharmaceuticals ranged from 16.4% for Atenolol to 91.8% for Metronidazole. The study found that STPs show only moderate removal of pharmaceuticals at best, and that the conventional treatment processes applied cannot achieve satisfactory removal of pharmaceuticals. Although the literature presents optimization measures that can enhance pharmaceutical removal in conventional processes, it still does not result in effective removal of pharmaceuticals. In

conclusion, this study highlights the importance of implementing advanced treatment processes such as NbS and Wetland systems as post-treatment steps in existing STP configurations to improve the removal of pharmaceuticals. Further research is needed to optimize these treatment processes and to better understand the ecological effects of pharmaceutical contamination in the environment.

Keywords: Pharmaceuticals, removal, sewage treatment plants (STPs), NbS and Wet Land treatment.

تقييم بعض المخلفات الدوائية المختارة من محطة معالجة مياه الصرف الصحي في فلسطين.

إعداد: محمد صبحي سمحان

إشراف: أ. د. جواد حسن شقير

الملخص

إن محطات معالجة مياه الصرف الصحي في جميع أنحاء العالم، بما في ذلك تلك الموجودة في فلسطين، ليست مصممة عادةً لإزالة الملوثات الدقيقة مثل الأدوية. يمكن أن يؤدي ذلك إلى أن تصبح محطات معالجة مياه الصرف الصحي مصدرًا مهمًا للتلوث الدوائي في البيئة، بما في ذلك المياه السطحية والمياه الساحلية والمياه الجوفية. إن وجود هذه المركبات، بالإضافة إلى آثارها البيئية الضارة المحتملة، يجعلها ملوثًا مثيرًا للمشاكل.

أجريت دراسة لتحليل توزيع المخلفات الدوائية في خمس محطات معالجة مياه الصرف الصحي التقليدية بأحجام مختلفة في فلسطين. هدفت الدراسة أيضًا إلى تقييم فعالية وإمكانات عمليات المعالجة مثل الحمأة المنشطة والأراضي الرطبة التقليدية، بالإضافة إلى عمليات المعالجة المتقدمة التي تسمى *Nature-based Solutions* و *Wetland systems*، والتي يمكن استخدامها كخطوات معالجة ثانوية بعد المعالجة. لاستكمال تكوينات محطات معالجة مياه الصرف الصحي الموجودة.

وجدت الدراسة تباينًا كبيرًا في إزالة المستحضرات الصيدلانية في محطات معالجة مياه الصرف الصحي الخمس. وكانت الأدوية المستهدفة هي أتينولول، كاربامازيبين، الكافيين، الكوتينين، الأريثروميسين، ليدوكائين، ميترونيدازول، باراسيتامول، ورائيتيدين. وتراوحت نسبة إزالة المواد الصيدلانية في محطة معالجة البيرة من ٠٪ لليدوكائين إلى ٩٩.٩٪ للكافيين. وفي محطة معالجة نابلس، تراوحت نسبة إزالة المواد الصيدلانية من ٥.٥٪ لليدوكائين إلى ٩٩.٨٪ للكافيين. وفي محطة معالجة المسيليا، تراوحت نسبة إزالة المواد الصيدلانية من ٤٧.٥٪ للرائيتيدين إلى ١٠٠٪ للكافيين. وفي محطة معالجة العروب، تراوحت نسبة إزالة المواد الصيدلانية من ١٩.٦٪ للأريثروميسين إلى ٩١.٠٪ للميترونيدازول. وفي محطة معالجة خاراس، تراوحت نسبة إزالة المواد الصيدلانية من ١٦.٤٪ للأتينولول إلى ٩١.٨٪ للميترونيدازول.

وجدت الدراسة أن معالجات محطات معالجة مياه الصرف الصحي تظهر فقط إزالة معتدلة للمستحضرات الصيدلانية في أحسن الأحوال، وأن عمليات المعالجة التقليدية المطبقة لا يمكن أن تحقق إزالة مرضية للمستحضرات الصيدلانية. على الرغم من أن الأدبيات تقدم تدابير التحسين التي يمكن أن تعزز إزالة المستحضرات الصيدلانية في العمليات التقليدية، إلا أنها لا تزال لا تؤدي إلى الإزالة الفعالة للمستحضرات الصيدلانية. في الختام، تسلط هذه الدراسة الضوء على أهمية تنفيذ

عمليات المعالجة المتقدمة مثل Nature-based Solutions وWetland systems كخطوات ما بعد العلاج في تكوينات محطات معالجة مياه الصرف الصحي الحالية لتحسين إزالة المستحضرات الصيدلانية. هناك حاجة إلى مزيد من البحث لتحسين عمليات المعالجة هذه وفهم الآثار البيئية للتلوث الدوائي في البيئة بشكل أفضل.

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List of Abbreviations

- AFD: Agence Française de développement (“French development agency”)
- AMR: Antimicrobial resistance
- AL: Aerated Lagoons
- APIs: Active Pharmaceutical Ingredients.
- BMBF: Bundesministerium für Bildung und Forschung
- BOD: Biochemical Oxygen Demand
- CAS: Conventional Activated Sludge
- CBZ: Carbamazepine
- COD: Chemical Oxygen Demand
- CoV-19: Coronavirus disease of 2019
- CEC: Contaminants of Emerging Concern.
- CEC: Critical Environmental Concentration
- CW: Constructed Wetlands
- CWWTP: Conventional Wastewater Treatment Plant
- DO: Dissolved Oxygen
- DCL: Diclofenac
- EAAS: Extended Aeration Activated Sludge
- EDCs: Endocrine-Disrupting Compounds
- EE2 :Ethinyl Estradiol
- ERY: Erythromycin
- EU: European Union
- GHG: Greenhouse Gas
- HWE: House Water Environment
- IBP: Ibuprofen
- KFW: Kreditanstalt für wiederaufbau (“reconstruction credit institute”)
- LC-MS/MS: Liquid Chromatography – Mass Spectrometry/ tandem Mass Spectrometry
- MBR: Membrane Bioreactor
- MP: Micro Pollutants

NbS: Natural Base Solution

NSAID: Non-Steroidal Anti-Inflammatory Drug.

ng/L or g: Nano gram per liter or gram

NO_3^- : Nitrate

OECD: Organization for Economic Co-operation and Development

O&M: Operation and Maintenance

PDA: Photodiode array

PE: Population Equivalent

PhCs: Pharmaceuticals

PhACs: pharmaceutically active compounds

PPCPs: Pharmaceuticals and personal care products

pH: Potential of Hydrogen

PWA: Palestinian Water Authority

QC: Quality Control

RBC: Rotating Biological Contactors

SDGs: Sustainable Development Goals.

STPs: Sewage Treatment Plants.

SPE: Solid Phase Extraction

SPs: Service Providers

SS: Suspended Solids

ST: Septic Tank

SSFCW: Subsurface Flow Constructed Wetland

TF: Trickling Filter

TN: Total Nitrogen

TP: Treatment Plant

TSS: Total Suspended Solids

TWW: Treated Wastewater

UPLC-MS/MS: Ultra-Performance Liquid Chromatographic-tandem Mass Spectrometry

U.S: United States of America

UV: Ultraviolet

WW: Wastewater

WB: Word Bank

WWT: Wastewater Treatment

WWTP: Wastewater Treatment Plant

Chapter One : Introduction & Background

1.1 Introduction

According to the World Bank reports (WB, 2018) ,approximately 2.3 billion people worldwide lack access to basic sanitation services, with around 892 million of those practicing open defecation. Although significant progress has been made since 1990 (with over 2.2 billion people gaining access to improved toilets or latrines), sanitation services remain one of the most off-track Millennium Development Goals (MDGs). Currently, only 68% of the global population has access to basic sanitation, and only 39% have access to safely managed sanitation (which includes containment, safe collection and conveyance, treatment, and end-use/disposal). Moreover, 72% of people in Sub-Saharan Africa and 50% of the people in South Asia lack access to basic sanitation services. The world missed the MDG target for sanitation by nearly 700 million people.

In recent decades, there has been significant progress in modernizing the pharmaceutical manufacturing process, primarily aimed at improving the flexibility and robustness of the process to address drug demand issues. However, extensive research has been conducted on pharmaceutical pollutants in the environment, which can end up in the environment through medical, industrial, or household waste. Pharmaceutical compounds, particularly when mixed, can pose a threat to aquatic ecosystems, causing acute and chronic toxicity to aquatic organisms and unfavorable effects on human health. These concerns arise not only from direct exposure to harmful molecules but also from indirect effects associated with their transportation along the food chain, particularly in relation to agriculture or fish consumption.. (Carolin, Kumar, Joshiba, & Kumar , 2020)

Pharmaceutical residues for human use (PhCs) represent a class of organic micro-pollutants that are prevalent in aquatic ecosystems. The presence of these compounds, particularly when found in mixtures, can pose significant risks to aquatic organisms, leading to both acute and chronic toxicity. Moreover, PhCs can have detrimental effects on human health, with concerns arising not only from

direct exposure to harmful molecules but also from indirect exposure through the food chain. Specifically, the consumption of contaminated agricultural products or fish can pose potential health risks to humans, highlighting the need for effective monitoring and mitigation strategies to address PhCs in the environment. (Palli, et al., 2019).

Policy Highlight

PhCs play a crucial role in human and animal health; however, their residues are emerging as a significant concern for environmental and human health when they enter freshwater systems. For instance, PhCs residues have been linked to reproductive toxicity and increased risks of breast or prostate cancer in humans, and the overuse of antibiotics is contributing to the global antimicrobial resistance (AMR) crisis. Without appropriate action, the situation is expected to worsen due to the growing use of PhCs, driven by economic growth, aging populations, advancements in healthcare, and increased livestock and fish production. To address this issue, policy responses are essential to bridge the science-policy gap by guiding cost-effective reduction measures for PhCs in the environment and associated risks to human and ecosystem health. A life-cycle approach that incorporates a policy mix of source-directed measures is required to effectively manage PhCs across their entire life cycle. This approach involves several policies within the water sector and is critical for addressing the widespread occurrence of PhCs in aquatic environments across the globe. Active Pharmaceutical Ingredients (APIs) have been detected in soils, biota, sediments, surface water, groundwater, and drinking water worldwide, highlighting the urgent need for effective PhCs management strategies Figure 1. (Bernhardt, Rosi, & Gessner, 2017)

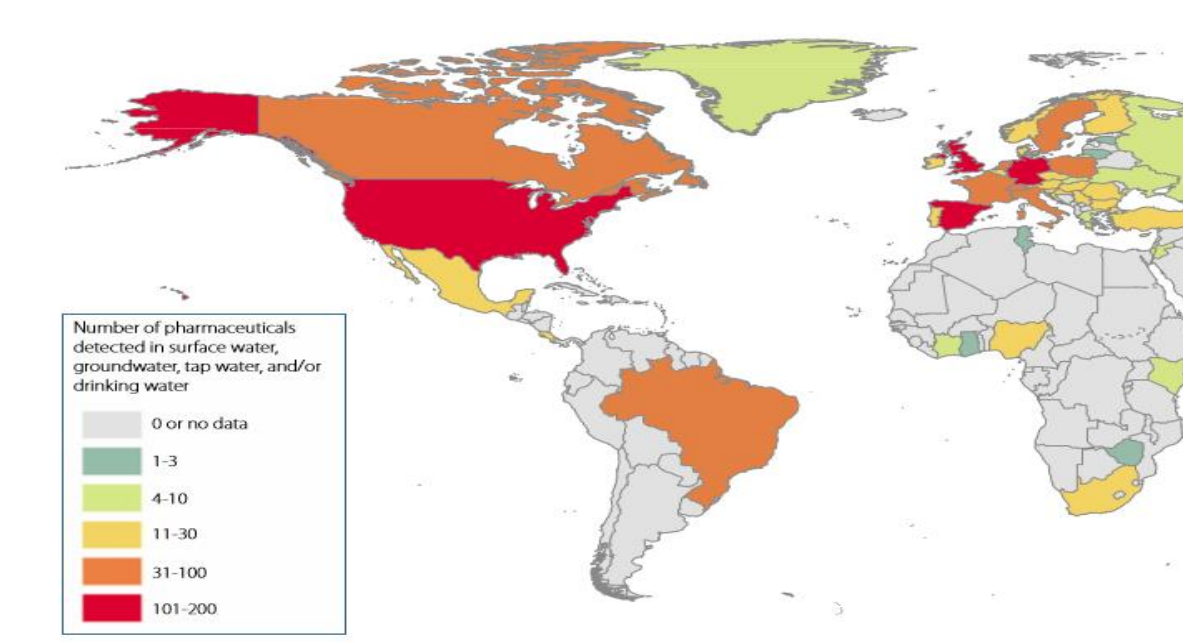


Figure 1: Numbering of PhCs detected in surface water, groundwater, tap water, and/or drinking water (Bernhardt, Rosi, & Gessner, 2017)

Pharmaceutical residual such as antidepressants, hormones, antibiotics, analgesics, anticonvulsants, and antipyretics are only a few of the many pharmacological chemicals taken across the world. For example:

1. (CBZ) is an anticonvulsant used to treat various types of seizures and pain resulting from trigeminal neuralgia that are widely utilized by the public and are among the most regularly prescribed and used pharmacological agents globally due to their great efficacy. (Hassen Khazri, 2019). CBZ physiochemical properties of hydrophobicity and net-charge of zero have made it to be resistant to solubility in aquatic mediums rendering it a mobile agent. CBZ and Diclofenac (DCL) recognized among the most frequently reported PhCs on a global scale. (Tim aus der Beek, 2016).
2. Ibuprofen (IBP), a widely used Non-Steroidal Anti-Inflammatory Drug (NSAID), has found its way into the environment through the excretion of both its active form and metabolites. As a result, it has become a notable pharmaceutical contaminant in WW. This research will explore the

environmental implications of IBP in WW and discusses potential strategies for its removal before reuse according to national or international guidelines.

3. Erythromycin (ERY) is an antibiotic medication commonly used to treat various bacterial infections. It's important to note that the use of ERY should always be under the guidance of a healthcare professional, who will consider the specific infection, its cause, and the patient's medical history when determining the appropriate treatment. Additionally, as with all antibiotics, it's crucial to complete the full course of treatment as prescribed, even if symptoms improve, to prevent the development of antibiotic resistance. In the contemporary pharmaceutical landscape, a substantial repertoire of approximately 2000 distinct APIs is extensively employed within the pharmaceutical industry. ERY, a naturally occurring macrolide antibiotic, is frequently employed in clinical practice for the treatment of a diverse spectrum of bacterial infections. The presence of antibiotics, including ERY, in the environment is primarily a consequence of human utilization, characterized by their persistence through excretion and subsequent dissemination into terrestrial ecosystems and aquatic effluents. Furthermore, the contamination of environmental reservoirs with ERY can be attributed, in part, to its introduction via agricultural activities or environmental ecosystem extended from the poultry and livestock breeding sectors Ma et al. (2020) (Hongrui Ma a, 2020) and Yu et al. (2021) (Han Yu a b, 2021). ERY have consistently reported concentrations in water and WW that exceed typical baseline levels. This recurrent and elevated occurrence underscores the urgent imperative of developing effective strategies for the removal of ERY residues from WW (Jodeh, et al., 2021).

4. Famotidine is a widely used histamine-2 receptor antagonist used to treat conditions such as gastric ulcers and gastroesophageal reflux disease. As with many medications, a portion of famotidine is excreted by individuals and disposed of in WW, entering WWTP before it is eventually released back into the environment. The use of famotidine poses several risks to WWTP and aquatic ecosystems. One major concern is the potential for the medication to persist in the environment after passing

through WWT processes. Because famotidine is highly resistant to degradation, it can pass through these systems and enter water sources, potentially affecting aquatic organisms and ecosystems. Another issue is the effect of famotidine on microbial communities within WWTP. Studies have shown that famotidine can alter the composition of microbial communities and their activity. This disruption can have a significant impact on the efficacy and efficiency of WWT processes, potentially leading to lower quality treated water. (Durán-Álvarez J. C., Prado, Zanella, Rodríguez, & Díaz, 2023).

5. Diclofenac (DCL) the toxic effects PhCs exert on environmental life form recognized after the near extinction of vultures in Pakistan during 2000-2003. The implicated PhCs found to be DCL, which led to fatal renal disease. This PhCs gained entry to the food chain by the administration to prey vulture's feed. CBZ physiochemical properties of hydrophobicity and net-charge of zero have made it to be resistant to solubility in aquatic mediums rendering it a mobile agent. (Oaks, et al., 2004) CBZ and DCL recognized among the most frequently reported PhCs on a global scale (Tim aus der Beek, 2016). These APIs encompass a diverse array of pharmaceutical classes, many of which have witnessed significant escalation in sales. Engineered to manifest specific physiological mechanisms of action and exhibit robust resistance to inactivation until they achieve their intended therapeutic outcomes, PhCs inherently possess the potential for eliciting deleterious ecological consequences. Predominantly administered through oral ingestion, the rates of absorption are subject to considerable variance contingent upon the specific compound, ranging from as low as 20% to an approximate 80%. While absorb compounds may undergo metabolic transformations within the human body, a significant proportion of PhCs remain incompletely metabolized and are ultimately excrete via urine and feces. (Bermúdez, Sánchez, Díaz, Poyatos, & Martín-Pascual, 2023).

The United Nations Sustainable Development Goals (SDGs) and the European Green Deal strategy, among other initiatives, are formulate with the overarching aim of safeguarding both public health

and ecosystems against the adverse effects of chemical substances, including pharmaceuticals, while concurrently addressing and mitigating their negative impacts. The presence of PhCs and specific chemical compounds, coupled with the associated hazards they pose to human health and the environment, has already been the subject of extensive research and scrutiny. A pivotal and indispensable element in realizing these objectives is the rapid and precise identification of such substances, encompassing the capacity to pinpoint their sources and track the pathways through which they propagate. In the context of in-situ risk assessment, it is imperative to develop environmentally sustainable and efficient detection tools that can supplant conventional and time-consuming chromatographic analyses. (Pierpaoli, et al., 2021)

Upon entry into Sewage Treatment Plants (STPs), this effluent laden with pharmaceutical residues and their metabolites undergoes a complex fate. It may undergo degradation, persist in a dissolved or suspended state in the aqueous phase, or bind to sludge or bio-solid. The extent of pharmaceutical degradation within the STP is contingent upon the physicochemical properties of the individual compounds.

After this, the environment heavily investigated for the presence of different PhCs and possible access sources as follows. PhCs can gain access to the environment (soil and water) in several anthropogenic routes:

1. Direct disposal of pharmaceutical WW into receiving environment (from different facilities or any health care setting).
 2. Use of PhCs in Aqua Culture for example fish.
 3. Animal PhCs-rich manure utilized for crops production and surface run-off with rain events,
 4. Treated municipal and industrial WW discharged into surface water, and the use in agriculture.
- (Haller, Müller, McArdeU, Alder, & Suter, 2002), (Larsson D. J., 2014), (You & Silbergeld, 2014), (Mohan, Bashir, Mohan, Kumar, & Kaur , 2023).

Moreover; IBP, are subject to near-complete degradation, typically exceeding 90%, while others, exemplified by CBZ, exhibit minimal removal rates, typically ranging from 4% to 8%. This discrepancy in removal efficiency is primarily attributable to the limitations inherent in conventional WWT processes. (Mathias & Hägglund, 2021).

CBZ is a pharmaceutical drug commonly prescribed for epilepsy, and trigeminal neuralgia, and as an antidepressant. It consistently been identified as the most frequently detected pharmaceutical compound in WWTPs, with the highest observed effluent concentration reaching 18.5 µg/L. Studies have revealed that CBZ can accumulate in aquatic organisms within the aqueous phase and inhibit acetylcholinesterase activity in the brains of fish. Additionally, CBZ exhibits dose-specific effects with variations among individuals, potentially leading to adverse reactions such as seizures, central nervous system toxicity, dizziness, sleepiness, and headaches, even when taken at recommended dosages. CBZ known for its resistance to biodegradation owing to its hydrophilic properties, chemical stability, and the presence of strong electron-withdrawing groups. Considering the growing demand for CBZ, its concentration in sewage sludge is, anticipate increasing in the future. CBZ is likely to affect Anaerobic Digestion (AD) processes before entering natural water bodies (Yang, et al., 2023).

CBZ is currently consumed on a global scale in substantial quantities, with a noteworthy surge from 742 tons in 1995 to 1214 tons in 2015. Following its oral administration, approximately 72% is subject to absorption within the human body, with subsequent metabolism reaching levels as high as 99%. The residual fraction is subsequently excreted into the sewage system. CBZ exhibits minimal proclivity for biodegradation, photodegradation, or volatilization, rendering it an apt subject for investigations pertaining to the degradation of (CEC). Furthermore, CBZ has served as a valuable indicator of contamination in water and WW effluents, contributing to the assessment of water quality and the monitoring of emerging environmental concerns. (Feijoo, Kamali, & Dewil, 2023).

IBP, a pharmaceutical compound identified as one of the constituents found in WW. This widely used medication is a non-prescription pain reliever employed to alleviate various discomforts, including aches, fever, and pains, and it is also recognized for its anti-inflammatory properties. The presence of IBP and other PhCs in domestic WW predominantly arises from human excretion and the disposal of expired or unused medications into sewage systems. Additional sources of IBP in WW may include discarded drugs deposited in landfills and inadequately treated effluents from pharmaceutical industries (AL Falahi, et al., 2021).

Approximately 15% of the therapeutic dose of IBP is excreted from the body without undergoing any alteration, while about 26% is eliminated as hydroxyl-IBP and 43% as carboxy-IBP after metabolic processes. Notably, these metabolites are even more toxic than the parent compound. Owing to the continuous release of IBP into the environment, it has emerged as one of the most prevalent pharmaceutical residues in effluents from WWTP, sewage sludge WW. It was detected at concentrations of up to $95 \mu\text{g L}^{-1}$, 208 ng g^{-1} , and $92 \mu\text{g L}^{-1}$ in various European, American, and Asian countries. The removal of IBP through processes such as solar photolysis, biodegradation, and conventional WWTP treatments involving activated sludge, sedimentation, and filtration, is notably insufficient, achieving at most an 85% reduction from the influent load. Consequently, this pharmaceutical compound found in surface water at concentrations of up to $0.4 \mu\text{g L}^{-1}$ and in drinking water at levels of up to $1.3 \mu\text{g L}^{-1}$. This presence raises concerns regarding ecotoxicity and potential risks to both the aquatic ecosystem and human health due to use for agriculture or from sea fish. IBP is identified as a carcinogenic substance and a non-steroidal endocrine-disrupting drug. Furthermore, IBP has been associated with deformities in the kidney, liver, and gills of the fish species *Clarias gariepinus*, highlighting the multifaceted ecological and health-related concerns associated with its presence in the environment. (Brillas, 2022)

Existing Technology of WWTP in West Bank - Palestine.

Despite the slow progress in the WWT sector, 18 WWTPs implemented out of 32 WWTPs proposed on the Palestinian Water Authority (PWA) priorities according to the yearly report 2021.

According to PWA, 2017 report the most dominant technology in the West Bank is Activated Sludge (ASS) using different types of type technologies regardless of the plant's size or the number of people served as follow: Aerated Lagoons (AL), Rotating Biological Contactors (RBC), (CW), Membrane Bioreactor (MBR) and Trickling Filter (TF). Table A summarizes the under operation WWTPs in the West Bank according to Eng. Adel Yasin the general director of planning in PWA. (Yasin, 2022)

Table 1: Under operation West Bank's WWTPs Ref Eng. Adel Yasin, 2022

| No. | WWTP | Design capacity | Types of technology |
|-----|-------------------|-------------------|--|
| 1 | Al-Bireh | 50,000 -70,000 | Activated sludge process |
| 3 | Kharras | 1,900 -2,500 | Primary settling (Imhoff tank), CW (vertical + horizontal) |
| 4 | Saeer Al Aroub | 8,000 -15,000 | Activated sludge process (EAS) |
| 5 | Misilya | 4,000 -7,500 | CW (French hybrid configuration) (vertical + horizontal) |
| 6 | Nablus West | 110,000 – 135,000 | Primary settling Activated sludge process, |

In particular, relevance to the southern European region, exemplified by Spain, is the heightened utilization of analgesics and anti-inflammatory pharmaceuticals. Consequently, WW and sludge samples originating from these areas' manifest discernible concentrations of specific PPCPs. Notably, salicylic acid and IBP have surfaced as the principal compounds characterized by the

highest documented concentrations within the matrices of WW and sludge. The identification of these prevalent PPCP residues underscores the imperative for focused scientific inquiry and targeted mitigation strategies, directed toward the resolution of these burgeoning environmental challenges. (Pérez-Lemus, López-Serna, Pérez-Elvira, & Barrado, 2022).

In recent years, there has been a notable surge in the advancement of analytical methodologies designed for the quantification of PPCPs within environmental matrices, with a specific focus on substrates such as sewage sludge. This phenomenon is evident in a comprehensive literature review authored by Pérez-Lemus and colleagues. (Petrie, Youdan, Barden, & Barbara, 2016). Pérez-Lemus and associates reported that, according to their literature review, the primary technique employed for the analysis of PPCPs within environmental matrices is Liquid Chromatography-tandem Mass Spectrometry (LC-MS/MS). This choice is attributed to the method's exceptional versatility, sensitivity, and selectivity. (Evans, Davies, Lubben, & Kasprzyk-Hordern, 2015).

In the context of sample pre-treatment, it is noteworthy that ultrasound-assisted extraction (UAE) is widely favored when conducting determinations of PhCs within solid environmental matrices, particularly sewage sludge. UAE stands out for its ease and expeditious nature of sample preparation, alongside its capability to curtail the customary demand for substantial volumes of organic solvents. (Petrie, Youdan, Barden, & Barbara, 2016).

A healthy environment is as healthy as its smallest components can get to sustain its normal function. This is jeopardized as pharmaceutical (PhCs) pollutants of different sources are frequently found with different toxicities influences various life forms of different classes of therapeutics is indispensable for human and veterinary purposes, by which they are continuously being introduced into the environment. (Pereira, Silva, Laranjeiro, Lino, & Pena, 2020)

These chemical substances typically detected in surface water at concentrations ranging from nanograms per liter (ng L^{-1}) to micrograms per liter ($\mu\text{g L}^{-1}$), categorizing them as emerging

pollutants. Notably, even after undergoing WW treatment, pharmaceutical residues persist, exerting detrimental effects on human and animal health when present in natural water samples. WWTPs serve as critical components of the environmental management framework, tasked with the purification of WW to mitigate the detrimental impacts of diverse pollutants and ensure the preservation of a high quality of life for all biotic entities. WWTPs intricately engineered to effectively eliminate particulate matter and reduce the levels of heavy metals, bacterial populations, and other pathogenic microorganisms within the treated effluent.

Pharmaceutical residues represent a ubiquitous presence in water bodies, including surface water, groundwater, and coastal waters worldwide. Predominantly, the primary source of pharmaceutical residues in the environment is WW. These pharmaceutical compounds are typically detected in concentrations ranging from (ng/L) to micrograms per liter ($\mu\text{g/L}$), classifying them as Micro Pollutants (MP). Notably, a comprehensive study delved into the prevalence of MP in effluents from 90 distinct STPs across Europe, uncovering the presence of 125 out of 156 screened compounds. Similarly, multiple investigations have attested to the existence of pharmaceutical residues in effluent waters in Sweden. Consequently, the effluents from STPs emerge as a prominent source of PhCs in aquatic ecosystems. The presence of pharmaceutical residues in the environment typically follows a trend of diminishing concentrations from WW to freshwater resources. This phenomenon is primarily attribute to the compounds' natural attenuation processes, influenced by factors such as biotransformation, photolysis, sorption, volatilization, and dispersion.

Furthermore, the presence of PhCs in the environment linked to the development of antibiotic resistance in bacteria, raising concerns regarding potential threats to public health. Consequently, there is a compelling imperative for continued efforts to develop strategies aimed at reducing pharmaceutical contamination in our water systems (Mathias & Hägglund, 2021).

Source of Pharmaceutical Residues in the WW.

Drugs go through numerous steps after entering the body, including absorption, distribution, metabolism, and elimination. During metabolization, the residual quantity is expelled into WW, either intact as a parent chemical or transformed as metabolites... (Dogan , Płotka-Wasyłka , Kempieńska-Kupczyk, Namieśnik , & Kot-Wasik, 2019).

Medications reach the environment mostly through patient usage, where they can flow through our bodies and into rivers. Pharmaceutical manufacture and incorrect disposal of leftover prescriptions lead to pharmaceutical trace levels in rivers, lakes, soils, and, in certain situations, drinking water. Pharmaceutical dangers in the environment must be recognized, reduced, and controlled even at such low quantities. 88% of pharmaceutical compounds enter the environment through patient usage (directly), 2% through trash created by pharmaceutical companies' factories, and the remaining 10% through discarded medicine. (Astrazeneca, 2022).

1.2 Problem Statement

In Palestine, the pharmaceutical residuals are not considered for monitoring and guidelines for reuse purposes. This research will highlight the concentrations of pharmaceutical residuals in domestic of the WWTP. In parallel, this will be related to standardization and guidelines used in Palestine if available. In Palestine the technology's use in WWTP is different this research will focus on the efficacy removal of the PhCs in WW.

1.3 Study Justification

The study on pharmaceutical residues in WWTPs in Palestine is justified by the need to address emerging contaminants that can harm the environment and human health. Pharmaceutical residues, especially antimicrobial ones, can contribute to Anti Microbial Resistance (AMR), a significant global health concern. There is a lack of guidelines for monitoring and managing pharmaceutical

residues in Palestine, and this study can help fill that gap by providing data on their concentrations in WWTP effluent and evaluating existing standardization and guidelines. The study will also assess the efficacy and sustainability of different technologies for removing pharmaceutical compounds (PhCs) from wastewater, which can inform policymakers and stakeholders in Palestine about the best management practices for pharmaceutical residues.

1.4 Study Goal

To identify and quantify various pharmaceutical compounds present in the Wastewater Treatment Plant (WWTP).

To analyze the distribution and behavior of these pharmaceuticals during the treatment process, providing data on their occurrence, persistence, and transformation patterns.

To evaluate the effectiveness of the current treatment methods in removing the detected pharmaceuticals, and to suggest potential improvements for enhanced removal and minimized environmental impact.

This study will contribute to a better understanding of the distribution of pharmaceuticals in WWTPs and provide valuable information for optimizing treatment processes and reducing the environmental risks associated with pharmaceutical pollution.

1.5 Study Question

This study answers the following research question:

What is the current state of WWTP technology in Palestine, and how does it compare to international standards?

What is the effectiveness of the various existing STP configurations in eliminating specific pharmaceuticals and biocides?

How can the current WWTP technology be optimized to effectively remove PhCs prior to water reuse, in accordance with Palestinian standards and guidelines?

Chapter Two: Literature Review

2.1 Pharmaceutical Residues in Treated Wastewater: Impacts on Crop Production and Soil Quality in Agricultural Reuse.

Pharmaceutical residues, which are the remaining traces of drugs and medications, can be introduced into the environment via multiple routes, including patient excretion, improper disposal, and inadequate removal during wastewater treatment processes. These residues have gained attention due to their potential hazards to both human and environmental health. Pharmaceutical residues are classified as contaminants of emerging concern (CEC) because they have the ability to infiltrate surface water and groundwater systems, thereby posing risks to aquatic life and human health. The presence of PhCs in surface water and groundwater, as well as terrestrial ecosystems, can lead to the uptake of PhCs by wildlife, with the potential for bioaccumulation. This can ultimately result in human exposure through various pathways, such as drinking water and the consumption of contaminated plant crops, fish, and dairy products. Therefore, it is crucial to monitor and manage the occurrence of pharmaceutical residues in the environment to mitigate their potential risks to human and ecological health. (Kostich, 2023).

On the other hand; using treated wastewater (TWW) in agricultural reuse is becoming an increasingly popular solution, given the current water scarcity issues worldwide. Agricultural irrigation is one of the primary applications for TWW reuse, as it offers an alternative water supply for farmers and reduces their dependence on freshwater resources. Additionally, TWW provides a reliable source of nutrients and other elements that are essential for plant growth. A 2020 study published in the *Journal of Environmental Management* investigated the effects of TWW irrigation on crop production and soil quality in agricultural fields. The researchers found that using TWW for irrigation had positive effects on crop yield and quality, soil fertility, and water use efficiency. Their findings suggest that the agricultural use of TWW can be a sustainable and cost-effective solution for water-scarce regions. (Kakwani & Kalbar, 2020).

The Critical Environmental Concentrations CEC: As previously mentioned, pharmaceutical occurrence and adverse effects make them problematic. In addition, many animals have similar target molecules to those that pharmaceuticals interact with in humans. (Gunnarsson, Jauhiainen, Kristiansson, Nerman, & Larsson, 2008). This raises the need for prioritizing substances to include in screening campaigns as well as for producing useful risk indicators. A possible tool for doing this is by using Critical Environmental Concentration (CEC) to calculate the surface water concentrations that are expected to have pharmacological effects in fish. The calculation of this concentration is based on literature data for human potencies and a predicted value for bioconcentration in fish based on lipophilicity. (Fick, Lindberg, Tysklind, & Larsson, 2010).

The existence of pharmaceutical residues in treatment wastewater (WW) exerts discernible effects on crops. These residues, originating from the effluent discharge of TWW into agricultural irrigation systems, can induce diverse consequences that impact crop growth, soil health, and potentially, human health through the food chain.

WWTP is recognized as the main source of PhCs in the environment. (Larsson D. J., 2014), (Feng, et al., 2020) Figure 2. Moreover; WWTPs designed to remove organic and some in-organic pollutants before the effluent is discharged into the receiving body. PhCs of any class were not removed in the process and their presence and effect in TWW were noticed. Where surface water is the end recipient for TWW effluents. (Vajda, et al., 2008), (You & Silbergeld, 2014).

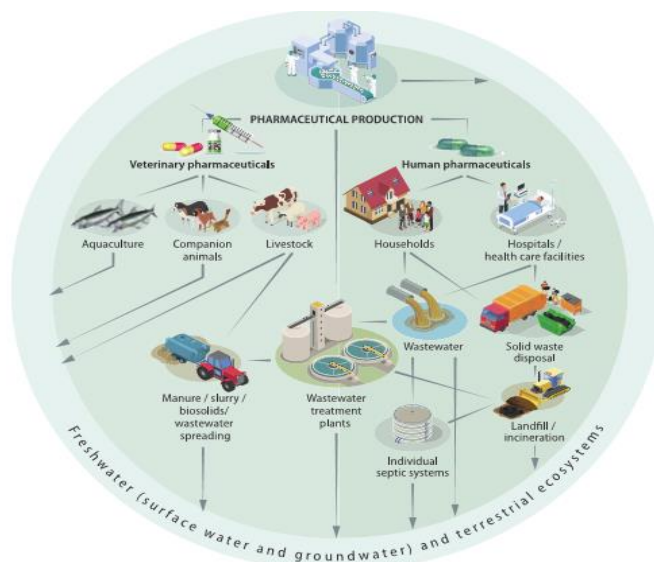


Figure 2: The introduction of antibiotics into the environment and the direct and indirect human exposure to pharmaceutical residues. (Serwecińska, 2020)

Figure 2 displays how pharmaceuticals have gained special attention after their detection in nature. Their delivery into the environment is via different anthropogenic routes. Domestic WW, animal manure, aquaculture, industrial and municipal WW. The cycle continues for human indirect exposure through contaminated water, crops and food-animals (Serwecińska, 2020).

On the other hand; Crops cultivated in soil- or irrigated with reclaimed water or contaminated surface water are found to uptake such crops from the soil. In previous studies, several researchers investigate the fate and occurrence of Ph.Cs. such as pharmaceutical pollution of water resources in pharmaceutical pollution of water resources by Sahar *et al* 2019, in Nakivubo wetlands and Lake Victoria, Kampala, Uganda for Carbamazepine (CBZ), Trimethoprim and Diclofenac (DCL) was found to have accumulated in the soil of wetlands and yam roots. Moreover, the Eco toxicity is concentration dependent. For example, toxicity in inhibiting the growth rate of *P. subcarinate* was observed at a concentration of 10.4 mg/L while 6 mg/L of DCL is sufficient for the same effect. (Dalahmeh, Björnberg, Elenström, Niwagaba, & Komakech, 2020)

A study conducted by Smith et al. (Smith), delved into the repercussions of pharmaceutical residues in TWW on crops. The investigation underscored concerns regarding the potential accumulation of these residues in soil and their subsequent absorption by plants. The research revealed the persistence of specific pharmaceutical compounds in the soil, posing a latent risk of bioaccumulation in crops over prolonged periods. Moreover, the research conducted by Jones et al. (Jones), investigated the translocation of pharmaceutical residues from irrigation water to crops, emphasizing the imperative need for a comprehensive understanding of the fate and transport mechanisms of these compounds in agricultural environments. The study elucidated that certain PhCs could undergo absorption by crops, thereby prompting inquiries into the safety of consuming such crops and the potential for adverse effects on human health.

The removal of pharmaceutical residues from water and WW is an area of active research and development. Various methods, including sorption onto solids and WWT systems, were explored to address the challenge of managing PhCs in water. (Matamoros & Toor, 2016). (Mouele, et al., 2021). The entry of pharmaceutical residues into the environment and their potential impact on ecosystems and human health has prompted regulatory and research efforts to better understand and mitigate this issue. Efforts made to assess the risks posed by pharmaceutical residues and to develop policies and technologies to minimize their presence in the environment. (Kostich, 2023)

The concentrations of dexamethasone, azithromycin, and ivermectin were observed to be elevated in sewage originating, exhibiting factors of 3.48, 3.52, and 2.55, respectively, compared to levels detected in municipal wastewater. Within the effluent of the Atotonilco Wastewater Treatment Plant (AWWTP), responsible for treating approximately 60% of Mexico City's sewage, famotidine was not detected. In this effluent, concentrations of indomethacin, dexamethasone, azithromycin, and ivermectin were 78.2%, 76.7%, 74.4%, and 88.1% lower, respectively, than those observed in the influent. The presence of Pharmaceutical and Personal Care Products (PhACs) in both treated and

untreated wastewater poses a medium to high environmental risk, particularly considering the reuse of Mexico City's wastewater for irrigation in the Mezquital Valley. In this region, PhACs were found in irrigation canals at levels below those recorded in Mexico City during monitoring. Conversely, famotidine, indomethacin, and dexamethasone were absent in surface water resulting from wastewater infiltration through soil in the Mezquital Valley, while azithromycin and ivermectin sporadically appeared in surface water samples collected throughout 2021. Utilizing an optimized risk assessment employing a semi-probabilistic approach, the prioritization of PhACs was established as ivermectin > azithromycin > dexamethasone > famotidine > indomethacin. (Durán-Álvarez J. , Prado, Zanella , Rodríguez, & Díaz, 2023).

The importance of water as a vital component of life underscored in recent decades, with increased utilization in domestic, agricultural, and industrial sectors leading to water quality degradation. The discharge of diverse and toxic pollutants from various industries has raised significant concerns. The heightened focus on emerging contaminants, particularly Pharmaceutical Compounds (PCs), is attributed to their adverse impacts on the ecosystem. In Asian countries such as India, Bangladesh, and China, the rapid growth of pharmaceutical industries and drug consumption is observed. Effluents from pharmaceutical manufacturing industries are known to enter domestic WW sewers, natural water streams, soils, sediments, and plants. Reports indicate that effluents from pharmaceutical industries in Asian countries contain elevated levels of antibiotics compared to other regions. Notably, antibiotics have garnered increased attention due to their role in the evolution of Antibiotic-Resistant Bacteria (ARB) and Antibiotic-Resistant Genes (ARGs), which pose threats to aquatic ecosystems and human health. The presence of ARB and ARGs in water bodies shown to have significant implications. These findings highlight the need for effective WW management and the mitigation of pharmaceutical residues to safeguard the environment and public health. (Golbaz, et al., 2011).

2.2 Source of Pharmaceutical Residues in the WW.

Drugs go through numerous steps after entering the body, including absorption, distribution, metabolism, and elimination. During metabolization, the residual quantity is expelled into WW, either intact as a parent chemical or transformed as metabolites... (Dogan , Płotka-Wasyłka , Kempnińska-Kupczyk, Namieśnik , & Kot-Wasik, 2019).

Medications reach the environment mostly through patient usage, where they can flow through our bodies and into rivers. Pharmaceutical manufacture and incorrect disposal of leftover prescriptions lead to pharmaceutical trace levels in rivers, lakes, soils, and, in certain situations, drinking water. Pharmaceutical dangers in the environment must be recognized, reduced, and controlled even at such low quantities. 88% of pharmaceutical compounds enter the environment through patient usage (directly), 2% through trash created by pharmaceutical companies' factories, and the remaining 10% through discarded medicine. (Astrazeneca, 2022).

2.3 Pharmaceutical Compounds in Wastewater Treatment Plants in Palestine: A Review of Concentrations and Removal Efficiency.

The potential of PhCs to cause a cascade of health impacts is particularly relevant in Palestine, where WWT is found at varying degrees of treatment levels. Recent findings under research indicate that concentrations of Endocrine-Disrupting Compounds (EDCs) in Palestinian TWW are found at minimis levels. In contrast, earlier studies indicate the presence of antibiotic residuals in high concentrations in effluents and receiving waters. Intermittent analyses in research also highlighted the significant prevalence of Pharmaceuticals and personal care products (PPCPs) in effluents, with PPCP indicator chemicals measured in relatively high concentrations—an order of magnitude higher than the EDCs monitored.

For instance, the micro-contaminants measured in research with the highest concentration in the effluents released by Palestinian WWTPs were carbamazepine, a common drug used to treat epileptic seizures and nerve pain (2.8micrograms/liter) Figure3. The results confirm earlier studies showing considerable concentrations of antibiotics in a water table region, where monitoring wells placed to assess the long-term impact of WW irrigation. (USAID, 2022).

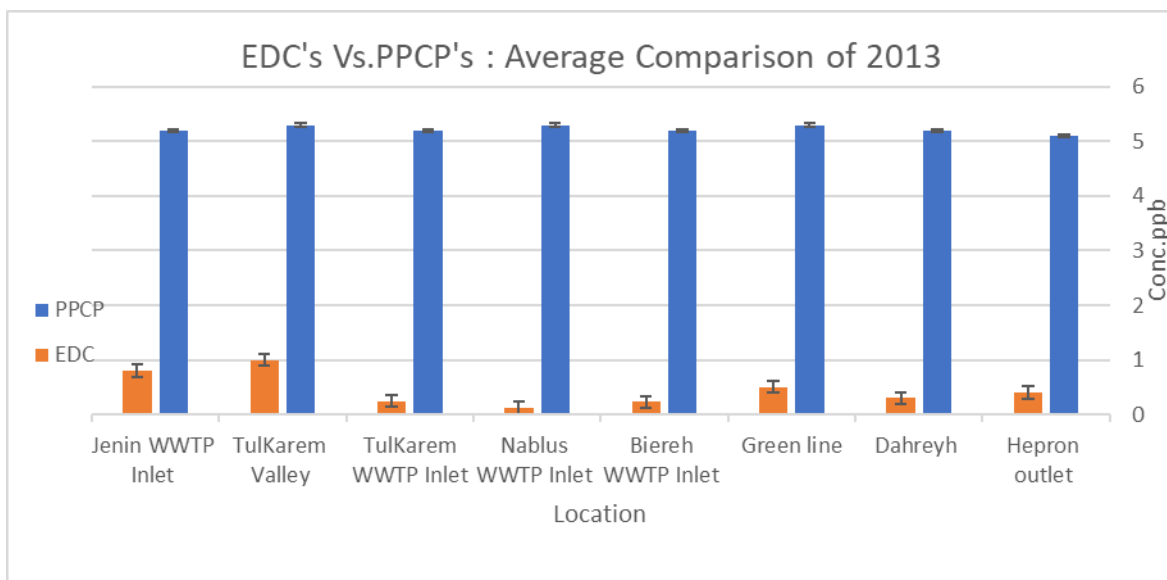


Figure 3:Maximum Concentration of PPCPs versus EDCs in Palestine Sampling Sites. (USAID, 2022)

findings from a previous study at the Palestinian El-Bireh WWTP, as presented in Figure 3 are comparable: notwithstanding seasonal differences, there is a significant reduction in EDC concentrations after treatment as compared to more modest effectiveness in removing PCs, Carbamazepine, and Bisphenol. The maximum concentration of PhCs and EDCs from WWTP in West Bank. The concentrations of PCs are typically 2 to 3 orders of magnitude greater if compared to USAID studies in 2022. (USAID, 2022)

The study found that WWT in Palestine foundvarying degrees of treatment levels. Recent studies indicate that concentrations of EDCs in Palestinian TWW are found at de minimis levels. In contrast, earlier studies indicate the presence of antibiotic residuals in high concentrations in effluents and receiving waters. Intermittent analyses in previous studies also highlighted the significant prevalence

of PhCs in effluents, with PPCP indicator chemicals measured in relatively high concentrations order of magnitude higher than the EDCs monitored. For instance, the micro-contaminants measured in the previous study with the highest concentration in the effluents released by Palestinian WWTPs were carbamazepine, a common drug used to treat epileptic seizures and nerve pain (2.84 micrograms/liter). (USAID, 2022)

USAID, 2022 underlying regulatory message to emerge from the recent of endocrine disrupting chemicals in Israeli WWTP that recycling effluent does not appear to pose a significant risk from EDCs if the sewage is treated. By way of contrast, PPCPs appear to be much more persistent throughout the sewage treatment process Figure4.

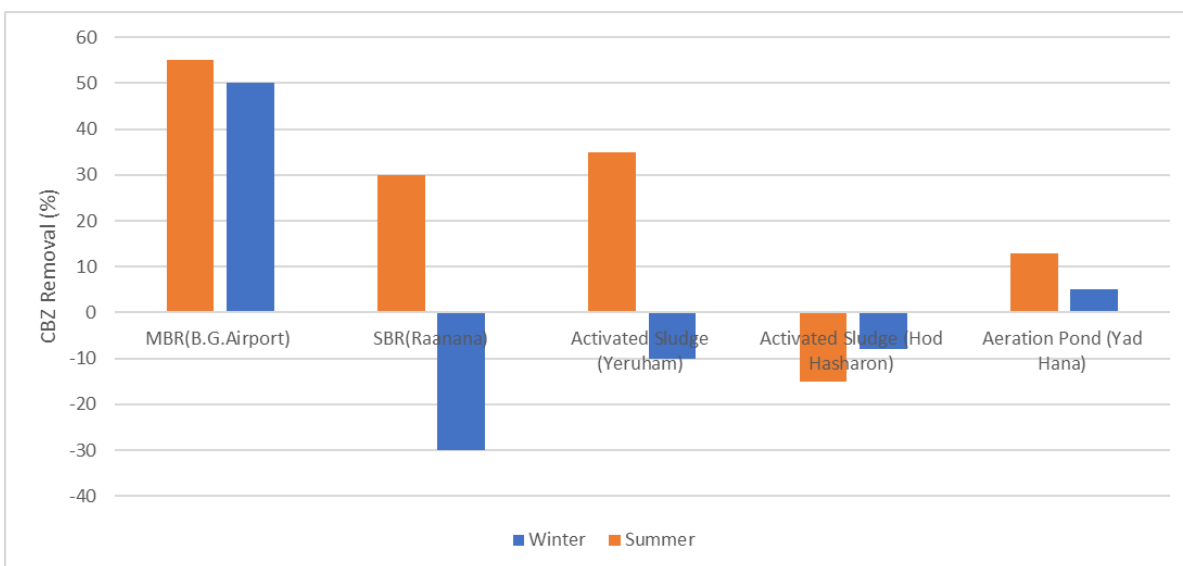


Figure 4:Carbamazepine (CBZ) Removal by different technology. (USAID, 2022)

Perhaps the most notorious pharmaceutical in the water environment is Ethynyl Estradiol (EE2), which is widely used as an oral contraceptive. In 1999, the first report documenting EE2 occurrence in U.S. surface waters was published. (Snyder, et al., 1999). More importantly, the occurrence of both the synthetic estrogen EE2 and the endogenous estrogen 17β-estradiol (E2) in U.S. WW effluents was subsequently identified as putative contaminants linked to reproductive ailments in fish (SNYDER, 2001). Due to reports of ecological effects, some investigators (Caldwell, et al.,

2008) have argued that proper environmental measurements of hormones such as EE2 may be required at sub-Nano gram per liter (ng/L) levels, presenting significant analytical challenges. However, it is important to note that endogenous steroid hormones generally occur at far greater concentrations than synthetic ones because all living creatures excrete hormones as part of their natural cycle.

In the early 1970s, the U.S. EPA serendipitously discovered and subsequently published the first report specifically addressing PhCs in WW effluents (Burnham, et al., 1972) . In 2008, the Associated Press released a series of stories related to the discovery of PhCs in U.S. drinking waters. These reports culminated in a hearing called by the U.S. Senate Subcommittee on Transportation Safety, Infrastructure Security and Water Quality. Experts from the federal government and the private sector seemed to have paradoxical responses when questioned on the relevance of PhCs in U.S. drinking water. However, one consistent outcome of the hearing was the clear message that some U.S. politicians and the public were genuinely interested in U.S. drinking water quality and those additional studies to determine prevalence of occurrence and impacts to human health would be necessary. A more comprehensive follow-on study published in 2009, which demonstrated the nation-wide occurrence of PhCs in U.S. drinking waters. The Maximum Residue Limit (MRL) is defined as the highest concentration of a contaminating metabolite resulting from the use of a veterinary medicinal product, which may be legally permitted or recognized as acceptable in or on a food Table 2. (Benotti, et al., 2009).

Table 2: Concentration of PhCs in U.S. Drinking water.

| Compound | MRL (ng/l) | Max.(ng/L) | Drinking Water (n=18) | |
|------------------------|------------|------------|-----------------------|----|
| | | | Med.(ng/L) | # |
| Meprobamate | 0.25 | 42 | 5.7 | 14 |
| Phenytoin | 1 | 19 | 6.2 | 10 |
| Atenolol | 0.25 | 18 | 1.2 | 8 |
| Carbamazepine | 0.5 | 18 | 6 | 8 |
| Gemfibrozil | 0.25 | 2.1 | 0.48 | 7 |
| Sulfamethoxazole | 0.25 | 3 | 0.39 | 4 |
| Fluoxetine | 0.5 | 0.82 | 0.71 | 2 |
| Diazepam | 0.25 | 0.33 | 0.33 | 1 |
| Progesterone | 0.5 | 0.57 | 0.57 | 1 |
| Estradiol | 0.5 | <MRL | <MRL | |
| Ethinylestradiol | 1 | <MRL | <MRL | |
| Atorvastatin | 0.25 | <MRL | <MRL | |
| Diclofenac | 0.25 | <MRL | <MRL | |
| Estrone | 0.2 | <MRL | <MRL | |
| Naproxen | 0.5 | <MRL | <MRL | |
| Norfluoxetine | 0.5 | <MRL | <MRL | |
| o-Hydroxy atorvastatin | 0.5 | <MRL | <MRL | |
| p-Hydroxy atorvastatin | 0.5 | <MRL | <MRL | |
| Risperidone | 2.5 | <MRL | <MRL | |
| Testosterone | 0.5 | <MRL | <MRL | |
| Trimethoprim | 0.25 | <MRL | <MRL | |

Since the past two century, many WWT technologies have been developed for WW treatment, the widely used is the CAS (Kalbar, Karmakar, & Asolekar, 2012), other technologies have been developed that employ various treatment processes, both aerobic and anaerobic Figure 5.

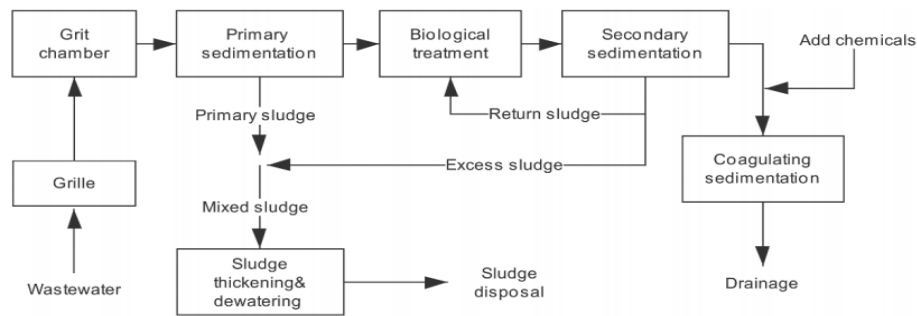


Figure 5: Flow chart of common WW and sludge (WW&S) treatment. (Kalbar, Karmakar, & Asolekar, 2012)

2.4 Available theoretical background of WWTP in Palestine.

Based on what level of treatment we need to treat the WW, there are three main treatment stages, as follows:

- Primary treatment:

It achieves treated water to some extent of treatment level, based on mechanical and physical processes like screening and grit removal.

The removal rate of Biochemical Oxygen Demand (BOD) is only (30% to 40%) and SS is (50% to 60%) in primary treatment (Tchobanoglous, Burton, & Stensel, 2003).

- Secondary treatment:

This treatment level considered the main treatment process, as it removes the highest percent of organics. (Gupta, Ali, Saleh, Nayak, & Agarwal, 2012).

Secondary treatment processes can remove up to 90 % of the organic matter in WW by using biological treatment processes (EPA, 2004).

This stage of treatment is mainly divided into two categories:

- 1- Suspended growth biofilm: Activated sludge, AL ...etc.
- 2- Attached growth: TF, RBC...etc.

- Tertiary treatment:

There is some remaining pollutant after the biological process in WWTPs. Therefore, the step of treatment can make further removal of pollutants e.g., P, N, and other biodegradable organic pollutants.

2.5 Available technologies in Palestine:

1. The (CWWTP) is a facility comprising multiple unit processes, typically involving seven to ten steps to provide potable water for consumption. The process encompasses the collection, purification, and concentration of water before assessment. Water sourced from various outlets, and supplementary pumps utilized to convey the water to the dedicated purification system. Conventional treatment plants employ diverse materials to aid in the filtration process, encompassing substances ranging from sand to granular activated carbon. Subsequently, the treated water undergoes disinfection to furnish pollutant-free water for the populace and commercial entities within the specific municipality or township, this requires larger areas such as ponds. (What is Conventional Water Treatment Plant, 2020). Nablus WWTP is an example for the traditional WWTP necessitating substantial space and entailing higher construction and operational expenses in comparison to natural systems.

2. Membrane technology in WWTP involves the use of various membrane processes such as microfiltration (MF), ultrafiltration (UF), Nano filtration (NF), and reverse osmosis (RO). These membrane processes are designed to remove contaminants and particulate matter from WW, providing a high level of purification. The use of membranes allows for the separation of pollutants from water, contributing to the production of cleaner effluent for discharge or reuse purposes.

Additionally, membrane technologies offer an efficient and advanced approach to WWT, enhancing the overall quality of treated water and meeting stringent regulatory requirements for environmental protection and public health. (Ezugbe & Rathilal, 2020).

3. Post-treatment technologies:

The Natural base Solution (NbS) at Saer Hebron is a type of subsurface flow-constructed wetland (SSFCW) as shown in Figure 6. NbS consists of a bed of graded stone media with an influent at one end of the bed of stone and an effluent collection device. At the opposite end of the bed to collect and discharge the treated effluent from the bed. Vegetation in the form of plants strategically placed on the surface of the bed of stone used (MENA, 2022).

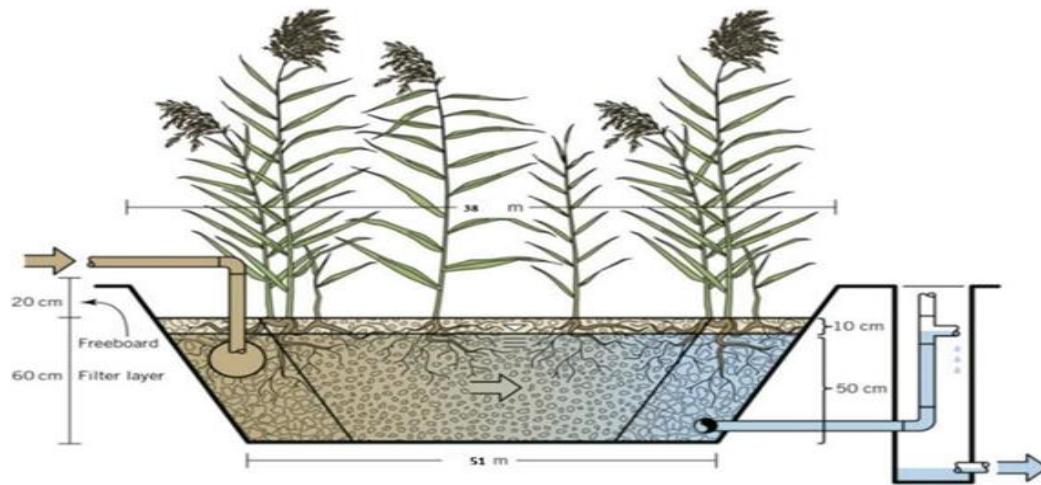


Figure 6: The NbS is a type of a (SSFCW)

The (Al-Aroub)-Saer NbS constructed in 2022 is and expected to increase the organic removal included the pharmaceutical residual in the future Figure 7.



Figure 7: Sear (Al-Aroub) WWTP as post-treatment for Secondary treated WW from Arroub camp.

The (Al-Aroub)-Saer WWTP-NbS as post-treatment for secondary treatment consist of Vertical Flow Constructed Wetland Vertical Flow Constructed Wetland is a plant-filtered wetland, with water draining below it. Water flows vertically through the filtration layer to the bottom of the basin where it is collected in a drainpipe. The important difference between horizontal and vertical wetlands is not just the direction of the path but the other conditions as well. When water is injected into the wetland at irregular intervals (from 4 to 10 times per day), the filter goes through saturated and unsaturated phases, resulting in distinct stages of aerobic and anaerobic conditions. As the filter emptied, air was sucked into it, allowing oxygen to flow through the pores of the filter material. The filter medium serves as a solids filter; a stable surface for bacteria to attach to, a foundation for plants, and the top layer is cultivated. The plant permitted to grow deep and wide rootsto infiltrate the filter media. Plants release a little quantity of oxygen into the root zone, where aerobic bacteria proliferate and breakdown organic materials. Nonetheless, the primary function of vegetation is to maintain the permeability of the filter medium and to create a conducive habitat for microorganism development. Microorganism communities absorb breakdown nutrients, and organic materials. By pushing, the microorganisms into a starving phase between dosage injection stages, biomass

overgrowth minimized and porosity enhanced. (Eawag Swiss Federal Institute for Water Science and Technology, 2022)

3.1 Misilya has WWTP discharges 150 m^3 per day buildup area of 20 dunums and has a capacity of up to 5000 P.E. In addition, the total area around the WWTP used for irrigation, is about 50 10 dunums. The TWW discharged into the wadis, around 25-40% of this TWW is used for irrigation and the quality of the WW effluent meets the Palestinian Standards Institute (PSI) 742-2003 effluent criteria. (PWA, PWA Data Base, 2018).

The reclaimed water is used for restricted and unrestricted irrigation in agriculture. The crops that irrigated without barriers are such as fodder crops, forestry that have no contact with the public.

The Misilya WWTP constructed during the years 2017, 2018, and commissioned in the end of the year 2018. The original outlet of the Misilya WWTP was an “infiltration trench”. Part of the treated water infiltrates in the “infiltration trench” and another part flows into nearest Wadis, Figure 8.



Figure 8:Aerial view for Misilya WWTP. (Council, 2022)

However, the efficacious in their designated functions, demonstrate limited proficiency concerning the removal of PhCs and Personal Care Products (PPCPs), leading to the discharge of treated effluents into aquatic ecosystems that may still significant quantities of these chemical entities.

In particular, relevance to the southern European region, exemplified by Spain, is the heightened utilization of analgesics and anti-inflammatory pharmaceuticals. Consequently, WW and sludge samples originating from these areas manifest discernible concentrations of specific PPCPs. Notably, salicylic acid and IBP have surfaced as the principal compounds characterized by the highest documented concentrations within the matrices of WW and sludge. The identification of these prevalent PPCP residues underscores the imperative for focused scientific inquiry and targeted mitigation strategies, directed toward the resolution of these burgeoning environmental challenges. (Pérez-Lemus, López-Serna, Pérez-Elvira, & Barrado, 2022).

In recent years, there has been a notable surge in the advancement of analytical methodologies designed for the quantification of PPCPs within environmental matrices, with a specific focus on substrates such as sewage sludge. This phenomenon is evident in a comprehensive literature review authored by Pérez-Lemus and colleagues. (Petrie, Youdan, Barden, & Barbara , 2016).Pérez-Lemus and associates reported that, according to their literature review, the primary technique employed for the analysis of PPCPs within environmental matrices is Liquid Chromatography-tandem Mass Spectrometry (LC-MS/MS). This choice is attributed to the method's exceptional versatility, sensitivity, and selectivity. (Evans, Davies, Lubben, & Kasprzyk-Hordern, 2015).

In the context of sample pre-treatment, it is noteworthy that ultrasound-assisted extraction (UAE) is widely favored when conducting determinations of PhCs within solid environmental matrices, particularly sewage sludge. UAE stands out for its ease and expeditious nature of sample preparation, alongside its capability to curtail the customary demand for substantial volumes of organic solvents. (Petrie, Youdan, Barden, & Barbara , 2016).

A healthy environment is as healthy as its smallest components can get to sustain its normal function. This is jeopardized as pharmaceutical (PhCs) pollutants of different sources are frequently found with different toxicities influences various life forms of different classes of therapeutics is

indispensable for human and veterinary purposes, by which they are continuously being introduced into the environment. (Pereira, Silva, Laranjeiro, Lino, & Pena, 2020)

These chemical substances typically detected in surface water at concentrations ranging from nanograms per liter (ng L^{-1}) to micrograms per liter ($\mu\text{g L}^{-1}$), categorizing them as emerging pollutants. Notably, even after undergoing WW treatment, pharmaceutical residues persist, exerting detrimental effects on human and animal health when present in natural water samples. WWTPs serve as critical components of the environmental management framework, tasked with the purification of WW to mitigate the detrimental impacts of diverse pollutants and ensure the preservation of a high quality of life for all biotic entities. WWTPs intricately engineered to effectively eliminate particulate matter and reduce the levels of heavy metals, bacterial populations, and other pathogenic microorganisms within the treated effluent.

Pharmaceutical residues represent a ubiquitous presence in water bodies, including surface water, groundwater, and coastal waters worldwide. Predominantly, the primary source of pharmaceutical residues in the environment is WW. These pharmaceutical compounds are typically detected in concentrations ranging from (ng/L) to micrograms per liter ($\mu\text{g/L}$), classifying them as Micro Pollutants (MP). Notably, a comprehensive study delved into the prevalence of MP in effluents from 90 distinct STPs across Europe, uncovering the presence of 125 out of 156 screened compounds. Similarly, multiple investigations have attested to the existence of pharmaceutical residues in effluent waters in Sweden. Consequently, the effluents from STPs emerge as a prominent source of PhCs in aquatic ecosystems. The presence of pharmaceutical residues in the environment typically follows a trend of diminishing concentrations from WW to freshwater resources. This phenomenon is primarily attribute to the compounds' natural attenuation processes, influenced by factors such as biotransformation, photolysis, sorption, volatilization, and dispersion.

Furthermore, the presence of PhCs in the environment is linked to the development of antibiotic resistance in bacteria, raising concerns regarding potential threats to public health. Consequently, there is a compelling imperative for continued efforts to develop strategies aimed at reducing pharmaceutical contamination in our water systems (Mathias & Hägglund, 2021).

Chapter Three: Materials & Methods

3.1 Area of Study

In this study, we focused on the main WWTPs situated in the West Bank, as depicted in the accompanying map. Our objective was to gain a comprehensive understanding of the distribution and behavior of these WWTPs within the region. Figure 9

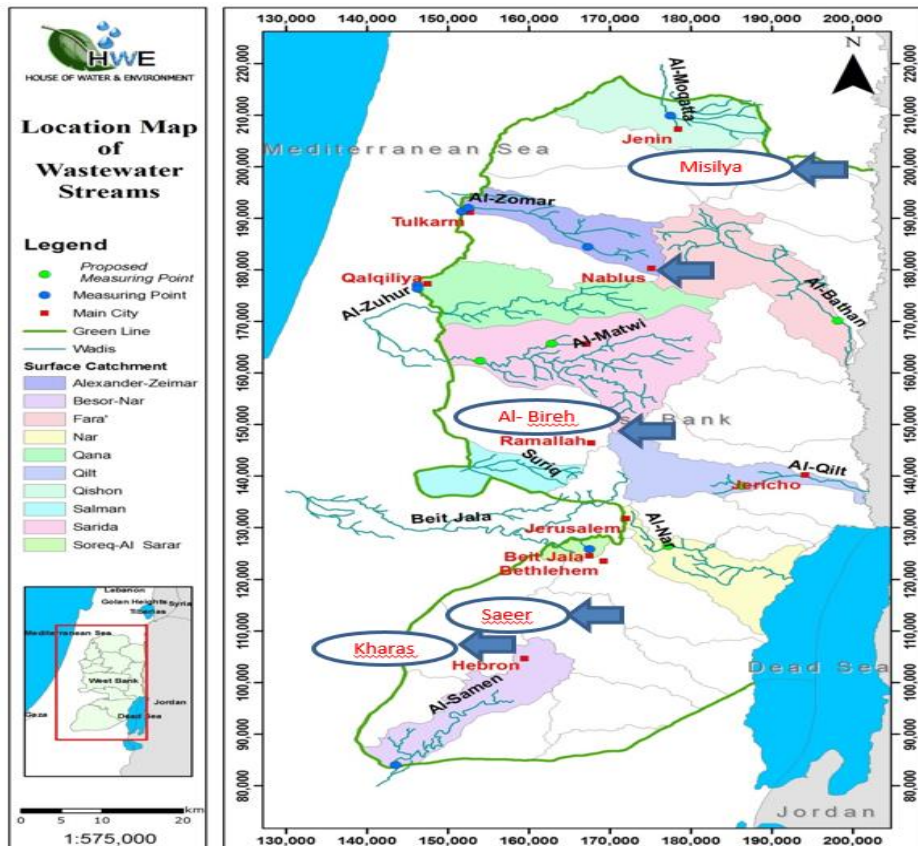


Figure 9: Location of WWTP and sampling point with surrounding communities Palestine\West Bank- Palestine map. (Environment, 2020)

• Al-Bireh WWTP:

Located in South East Al Bireh city serving 93% of Al Bireh City, Am'ari Camp, Qaddura Camp, and Al Awdeh Camp, it started operation in 2000, producing daily treated water around 5750m³. The construction budget allocated from Kreditanstalt für wiederaufbau (“reconstruction credit institute”) KfW, Garman. The plant designed for the 2020 horizon serves around 50 000 Population Equivalent (PE). Extended Aeration Activated Sludge (EAAS). Aerobic sludge digestion, thickening, belt filter

press for dewatering. Then mixed with solid waste and transported to the Zahret Al-Fenjan sanitary landfill. (Group, 2018).

- **Nablus Governorate (Nablus Western WWTP):**

It has been working since Nov 2013 and serves around 120,000 PE, producing a daily average of treated water of 14,000 m³. It is Conventional Activated Sludge (CAS) plant, which provides nutrients carbonaceous, nitrogen, and phosphorous removal, sludge stabilization, and anaerobic digestion. Later on, filtration and chlorination unit processes installed as part of reuse pilot projects funded by KFW. Current flow treated at the plant is 11,000 m³/day. (AbuJaffal, 2020).

- **Jenin Governorate (Misilya WWTP).**

It is located in Misilya village, Jenin district. It started operation in 2019, producing daily treated water of around 120m³. The construction cost allocated from Agence Française de développement (AFD). The plant designed for 2025 horizon serves around 3,635 PE. A Low cost WWTP. Vertical and Horizontal Constructed Wetlands (CW) and storage ponds provides nutrient removal (C, N, P removal). Sludge accumulates and is removed every 15-20 years. (Group, 2018).

- **Hebron Governorate (Saer and Kharras WWTP).**

- **Saer WWTP:** Located in North Hebron city between Saer and Al-Aroub refugee camp serving Al Aroub Camp and Shuyoukh Al Aroub, it started operation in 2016, producing daily treated water around 1500m³. The construction budget was allocated from Spanish Cooperation, Spain.

The plant designed for the 2035 horizon serves around 8000PE. Activated Sludge. Screening (4 mm); Preliminary treatment; Biological reactor; Secondary Clarifier; Sludge thickener; Sand filters; Disinfection. Then transported to the Al-Menyah sanitary landfill. (Group, 2018).

• **Kharras WWTP:** Located in West-North Hebron serving Kharras village, it was starting operation in 2022, producing daily treated water around 1100m³. The plant designed for 2035 horizon serves around 9000PE. Activated Sludge. Screening (4 mm); Preliminary treatment; Biological reactor; Secondary Clarifier; Sludge thickener; Sand filters; Disinfection. (PWA, PWA Report (Kharras WWTP), 2022).

3.2 Sample Collection

Samples were collected from the inlet and outlet of the of WWTP, at each sampling location using the 500 mL basin and cord included in the water sampling pack Figure 10 (A). The collection can occur from the bank or mid-course of the treated or untreated WW. The basin was rinsed three times with WWTP domestic water at each site before sample collection. Water samples are collected in duplicate from the sampling basin Figure10 (A) into 20 mL amber glass vials Figure 10 (B) using a plastic syringe Figure 10 (C) equipped with a GFF (0.7µm pore size) glass microfiber syringe filter Figure 10 (D) the syringe rinsed once with the collected water before aspirating the sample water.

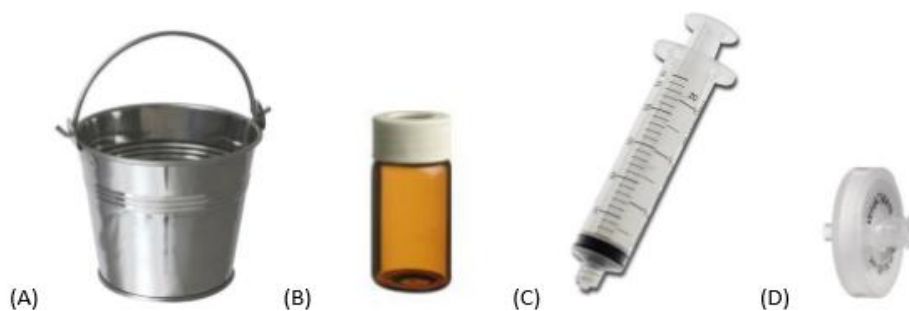


Figure 10: Sampling equipment in the collection kit including: (A) 500ml sampling basin , (B) The water sample vials, (C) syringe , (D) syringe filters.

Prior to discharging the water sample from the syringe. Prime the filter before collecting any water samples and rinse each collection vessel with filtrate. If more water needed in the syringe, un-screw the syringe filter and aspirate more water from the collection basin. Discharge 10 mL of filtrate into both amber glass vials per sampling site. Use the water collected in the sampling basin for both samples. Only one syringe and syringe filter needed per sampling location (use one filter for both of the vials at each location). Once collected, samples kept cold in the provided Styrofoam coolers using the ice packs until they reach the lab where they froze at -20°C. Sample collection should be complete on one day.

3.3 Sample preparation and extraction

The extraction process starts after collecting the sample then we make a centrifuge at 4000rpm for 10 min to decolorize the color of the sample. Then take the supernatant and make extraction on the SPE by pouring in the cartage and filtrate the sample by the pump. After the filtration we make elution by the minimum amount of Acetonitrile (5ml) then collect the elution in an amber vial in the refrigerator at 4°C before we analyze the LC-MS/MS.

3.4 Instrument use: LC-MS-MS

The separation of compounds was done using the AB-Sciex 5500 Qtrap (LC-MS-MS) equipped with Luna Omega polar C18 embedded column (100 mm*3.0 mm, particle size of 3µm). Gradient elution mode is considered in the following order: eluent A is 5mM ammonium formate and 0.1% formic acid, and eluent B is Acetonitrile and 0.1% formic acid. The initial mobile phase conditions started with 98:2 A/B for 1min then a linear gradient pattern was used to reach a ratio of 70:30 A/B at 3min, and then the ratios changed to reach 50:50 A/B at 6min. Before returning to the initial conditions, the last ratio was maintained for 10minutes. The flow rate was set at 0.6mL/min and the injection volume of 5 µL.

Multiple Reaction Monitoring (MRM) conducted with AB-Sciex 5500 Qtrap equipped with an electrospray ionization interface, using the positive-ion mode (Santa Clara, CA, USA). Instrument control, data acquisition, and quantitation were run using analyst software. Setting the drying gas temperature at 350°C, the capillary voltage of 4.0kV, drying gas flow of 12L/m, and the nebulizer pressure of 40 psi.

3.5 Chemicals

All chemicals including all reference materials and labeled standards for antimicrobials and PhCs are obtained from Sigma–Aldrich (St. Louis, MO, USA). Solvents used in sample preparation were of high-grade purity (OPTIMA, Fisher Scientific, St. Louis, MO, USA). See **Appendices H**.

3.6 Quality Control (QC)

Two quality control samples are required from each sampling.

3.6.1. A field blank- This QC will enable an evaluation of any method-derived pollution or interference. One field blank was made on sample collection day using the same sampling protocol as used for real water samples used for domestic purposes (i.e., filtration through a syringe filter) except with 10mL of LC-MS-MS grade water. The required amount of LC-MS-MS grade water shipped in a labeled amber glass vial Figure 10 along with a field blank syringe and syringe filter Figure 10.

3.6.2. A spiked quality control- This QC will enable a determination of the extent to which the target PhCs degrade during shipment. A glass vial containing 10 ng of each pharmaceutical (prepared as a mixed spike dried onto the bottom of the vial) shipped with each sampling kit. A second vial will contain 10 mL of LC-MS-MS grade water. On the day of sample collection, we will pour the 10 mL HPLC-grade-water sample into the vial labeled ‘Spiked Quality Control’ yielding an aqueous mixture of all target PhCs at 1000 ng/L. This QC should be stored frozen.

3.7 Accompanying Environmental Data

Some environmental data is needed to enable comparisons of pharmaceutical concentrations between sites. These data should include photographs, flow, water temperature and pH on the day of sampling, COD, BOD, TOC and Solids. Ideally, these data collected from each sampling location at the time of sample collection. However, if flow measurements area reading collected from the nearest flow gauge or a long-term average flow obtained from WWTP control.

3.8 Challenges for determination of PhCs in the WW.

PhCs are excreted at a much lower level than they are consumed, whether as a parent molecule or as metabolites. Mass spectrometers, which typically have higher sensitivity than conventional detection systems and can analyze at lower concentrations. Many methods for analyzing drug molecules in WW samples developed. The majority of them used liquid chromatography in conjunction with tandem mass spectrometry. Trace-level drugs, such as illegal drugs and drugs used to treat rare diseases, necessitate more selective and sensitive analysis methods.

For Pharmaceutical residual, the Solid-Phase Extraction (SPE) followed by LC-MS-MS Figure 11, for the selective isolation and concentration of analyses from complex matrices, encompassing aqueous solutions, soil substrates, and biological fluids. Its widespread application is particularly pronounced in the analytical scrutiny of pharmaceutical residues within aqueous systems. SPE offers a refined and specific means to extract and concentrate pharmaceutical compounds from diverse environmental samples, enhancing the precision and sensitivity of analytical methodologies. The systematic application of SPE contributes significantly to the advancement of scientific understanding regarding the presence and ramifications of pharmaceutical residues in environmental matrices. (Kafeenah, Osman, & Bakar, 2018), (Sadutto & Picò, 2020). The technique involves passing a liquid sample through a solid sorbent material, which selectively retains the analysts of

interest. The sorbent is then washed to remove unwanted matrix components, and the analytes are eluted from the sorbent using a solvent that is compatible with the subsequent analytical method. (Campíns-Falcó, et al., 2012).

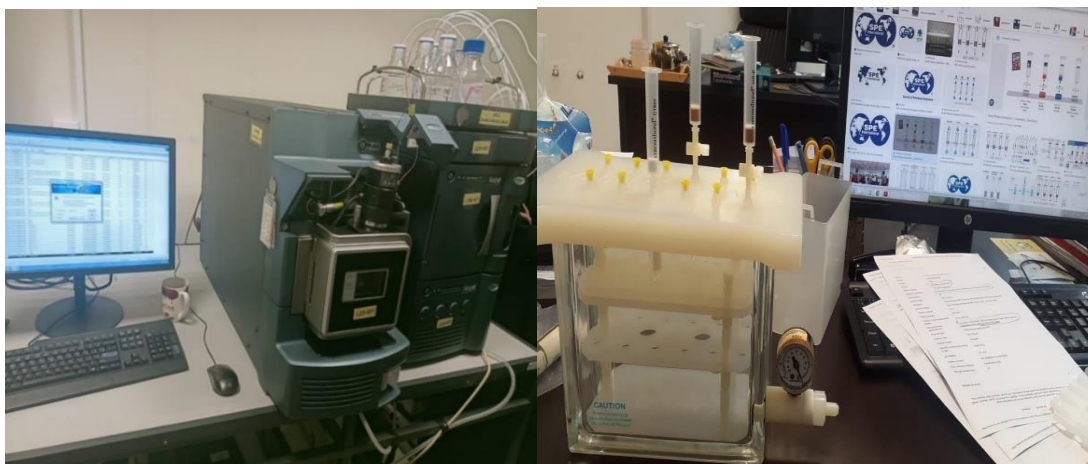


Figure 11: LC-MS-MS at Al-Najah University followed by Solid Phase Extraction (SPE) at Al-Quds Public Health Society.

Disk SPE is a type of SPE that uses a disk-shaped sorbent material. It is used to determine multi-class pharmaceutical residues in tap water and hospital WW. (Kafeenah, Osman, & Bakar, 2018), (Sadutto & Picò, 2020). In one study, a new clean-up and pre-concentration method based on disk SPE was developed to determine multi-class pharmaceutical residues covering a wide range of polarities in water systems, prior to ultra-performance liquid chromatographic-tandem mass spectrometry (UPLC-MS-MS) analyses. (Kafeenah, Osman, & Bakar, 2018). The method was found to have good recovery values and intra-day precision for tap water, effluent, and influent WW. Other types of SPE used in the analysis of pharmaceutical residues in water systems. For example, a study used SPE cartridges filled with biomass-based sorbents to quantify PhCs in aquatic environments (Stratulat, Sousa, Calisto, & Lima, 2023) .

Chapter Four: Results and Discussion

4.1. Occurrence of pharmaceuticals

Samples of wastewater collected from the five WWTP studied, a total of 9 pharmaceuticals were detected above their respective LOQ in at least three samples Table 3. Results of the influent Atenolol, Carbamazepine, Caffeine, Cotinine, Erythromycin, Lidocaine, Metronidazole, Paracetamol and Ranitidine pharmaceuticals compounds detected in all samples. Interestingly, the compound with the highest average concentration was caffeine with $229.060\mu\text{g/L}$ at the influent of Nablus WWTP followed by Paracetamol with $60.418\mu\text{g/L}$ at the influent of Al-Bireh WWTP.

The Atenolol, Carbamazepine, Caffeine, Cotinine, Erythromycin, Lidocaine, Metronidazole, Paracetamol and Ranitidine pharmaceuticals compounds were present in all samples including pharmaceutical classes hypertension drugs, Statins, Antihistamines, Psychometrics', Antidepressants, Stimulants, Antibiotics, and Analgesics. Table 3.

The detection of pharmaceuticals in a screening study, such as the one conducted in this research, is influenced by several factors. Firstly, local consumption patterns have been demonstrated to have a relatively strong correlation with the concentrations detected in wastewater influents. Other factors, including excretion rates, water consumption, STP size, environmental persistence, and site-specific removal efficiencies, also affect the concentrations of pharmaceuticals in both influent and effluent streams.

Additionally, rainfall and precipitation have been shown to dilute influent waters, leading to lower detected concentrations during the sampling period. During the sample collection for this study, some of the STPs were experiencing high flow conditions, which may have affected the detectable concentrations.

The most frequently detected drug class in effluent wastewaters in this study was hypertension drugs.

Table 3: The Concentration of PhCs in WWTP November of 2023 as Avarege

| Compound | Sample Type (Avg) | Al-Bireh | Nablus | Misilya | Al-Aroub | Kharras |
|----------------------|-------------------|----------|---------|---------|----------|---------|
| unit | | (µg/L) | (µg/L) | (µg/L) | (µg/L) | (µg/L) |
| Atenolol | Influent | 0.065 | 4.796 | 6.676 | 2.130 | 1.854 |
| | Effluent | 0.046 | 0.055 | 2.202 | 1.196 | 1.550 |
| Carbamazepine | Influent | 0.567 | 2.212 | 2.825 | 0.805 | 0.976 |
| | Effluent | 0.399 | 0.150 | 1.287 | 0.380 | 0.550 |
| Caffeine | Influent | 156.203 | 229.060 | 176.203 | 5.835 | 4.304 |
| | Effluent | 0.165 | 0.550 | 0.895 | 1.861 | 3.861 |
| Cotinine | Influent | 2.650 | 11.050 | 15.196 | 3.973 | 6.517 |
| | Effluent | 1.141 | 1.441 | 4.405 | 1.309 | 2.315 |
| Erythromycin | Influent | 0.150 | 0.210 | 0.140 | 0.051 | 0.030 |
| | Effluent | 0.070 | 0.090 | 0.071 | 0.041 | 0.015 |
| Lidocaine | Influent | 0.140 | 0.365 | 0.513 | 0.146 | 0.758 |
| | Effluent | 0.145 | 0.345 | 0.188 | 0.106 | 0.545 |
| Metronidazole | Influent | 0.444 | 0.658 | 1.080 | 0.980 | 0.881 |
| | Effluent | 0.351 | 0.485 | 0.340 | 0.088 | 0.072 |
| Paracetamol | Influent | 60.418 | 50.407 | 54.299 | 3.729 | 47.790 |
| | Effluent | 22.023 | 19.235 | 24.277 | 1.203 | 20.215 |
| Ranitidine | Influent | 5.210 | 3.320 | 4.045 | 0.179 | 2.472 |
| | Effluent | 3.211 | 1.320 | 2.124 | 0.088 | 1.171 |

In addition the removal efficacy of the detected as influent and effluents inthe wastewaters studied was summarized in Table 4.

Table 4: % of removal of the PhCs of the TWW

| Compound | %Removal Al-Bireh | %Removal Nablus | %Removal Misilya | %Removal Al-Aroub | %Removal Kharras |
|---------------|-------------------|-----------------|------------------|-------------------|------------------|
| Atenolol | 29.2% | 98.9% | 67.0% | 43.8% | 16.4% |
| Carbamazepine | 29.6% | 93.2% | 54.4% | 52.8% | 43.6% |
| Caffeine | 99.9% | 99.8% | 100% | 68.1% | 91.0% |
| Cotinine | 56.9% | 87.0% | 71.0% | 67.1% | 64.5% |
| Erythromycin | 53.3% | 57.1% | 49.3% | 19.6% | 50% |
| Lidocaine | 0% | 5.5% | 63.4% | 27.4% | 28.1% |
| Metronidazole | 20.9% | 26.3% | 68.5% | 91.0% | 91.8% |
| Paracetamol | 63.5% | 61.8% | 55.3% | 67.7% | 57.7% |
| Ranitidine | 38.4% | 60.2% | 47.5% | 50.8% | 52.6% |

Moreover: the removal efficacy for the the most detected drug ineach wastewaters studied was summarized in Figure 12.

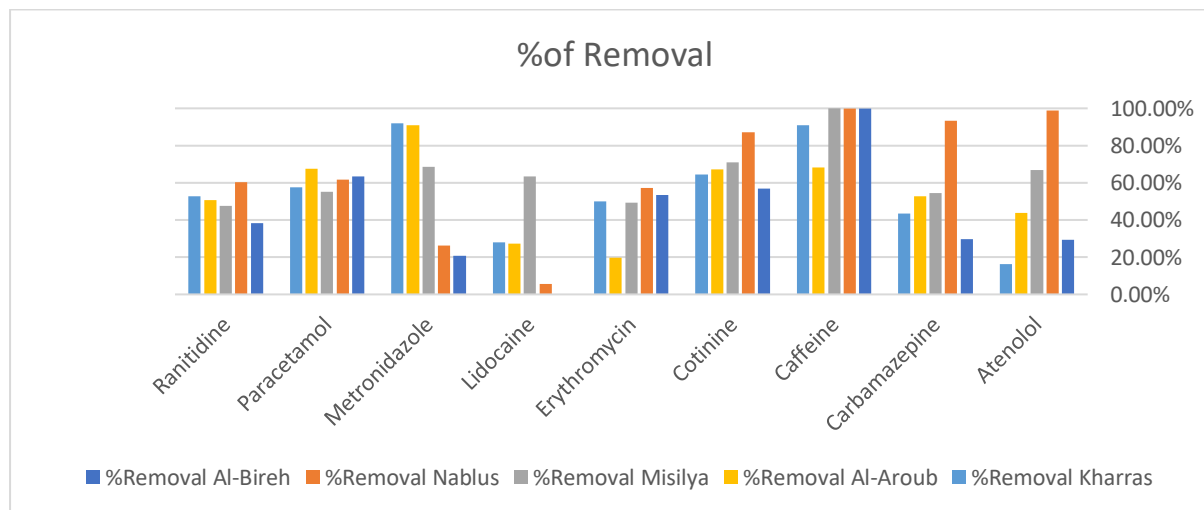


Figure 12: The removal efficacy for the most detected drug in each WW investigated

4.2.Results& Discussion

The subsequent table outlines the typical parameters assessed for the influent and effluent streams of the five wastewater treatment plants (WWTPs) under examination. These parameters are commonly measured to evaluate the performance and effectiveness of the WWTPs in removing pollutants and improving water quality. The table includes parameters such as pH, TSS, BOD, COD, Fecal Coliforms among others. By monitoring these parameters, it is possible to determine the efficiency of the treatment processes and ensure compliance with regulatory standards for wastewater discharge.

Kharras WWTP

Table 5: The main parameters for Kharras WWTP

| Test | Result (Effluent) |
|-------------------------------------|-------------------|
| BOD₅ | 20.4 mg/l |
| COD | 62.6 mg/l |
| Total suspended solids (TSS) | 8 mg/l |
| Fecal Coliforms | TMTC/100ml |
| pH | 6.65 |
| Dissolve Oxygen (DO) | 5.3 mg/l |
| Total Dissolved Solids (TDS) | 810 mg/l |

Saer WWTP

Table 6: The main parameters for saer WWTP

| Test | Result (Influent) | Result (Effluent) |
|------------------------------------|---------------------|---------------------|
| BOD₅ | 442 mg/l | 138 mg/l |
| COD | 904 mg/l | 297 mg/l |
| Total Suspended Solid (TSS) | 392 mg/l | 104 mg/l |
| Fecal Coliform | 4.8*10 ⁵ | 8.3*10 ³ |

Table 7: The main parameters for Al-Bireh WWTP

| Test | Result (Influent) | Result (Effluent) |
|------------------------------------|--------------------------|--------------------------|
| BOD₅ | 454 mg/l | 14 mg/l |
| COD | 1109 mg/l | 52 mg/l |
| Total Suspended Solid (TSS) | 462 mg/l | 12 mg/l |
| pH | 7.66 | 7.51 |
| Total Dissolved Solid (TDS) | 850 mg/l | 782 mg/l |
| Conductivity | 1801 μ S/cm | 1587 μ S/cm |

Table 8: The main parameters for west Nablus WWTP

| Test | Result (Influent) | Result (Effluent) |
|------------------------------------|--------------------------|--------------------------|
| BOD₅ | 543 mg/l | 12 mg/l |
| COD | 687 mg/l | 38 mg/l |
| Total Suspended Solid (TSS) | 118 mg/l | 0 mg/l |
| pH | 7.76 | 7.69 |
| Conductivity | 1438 μ S/cm | 1360 μ S/cm |

Table 9: The main parameters for Misilya WWTP

| Test | Result (Effluent) |
|------------------------------------|--------------------------|
| BOD₅ | 20 mg/l |
| Total Suspended Solid (TSS) | 30 mg/l |
| Fecal Coliform | 1000 MPN/100ml |
| pH | 6-9 |

In the previous tables shows the main parameters of each WWTP, Wastewater treatment processes are designed to remove or reduce various contaminants, including organic and inorganic materials, nutrients, and solids. The concentration of these contaminants is often measured using parameters

such as COD (chemical oxygen demand), BOD (biochemical oxygen demand), pH, TSS (total suspended solids), and TDS (total dissolved solids).

COD and BOD are measures of the amount of oxygen required to oxidize organic matter in wastewater. High COD and BOD values indicate a high concentration of organic matter, which can be challenging to treat. Pharmaceutical compounds in wastewater can contribute to high COD and BOD values, as they often contain organic matter that can be difficult to break down.

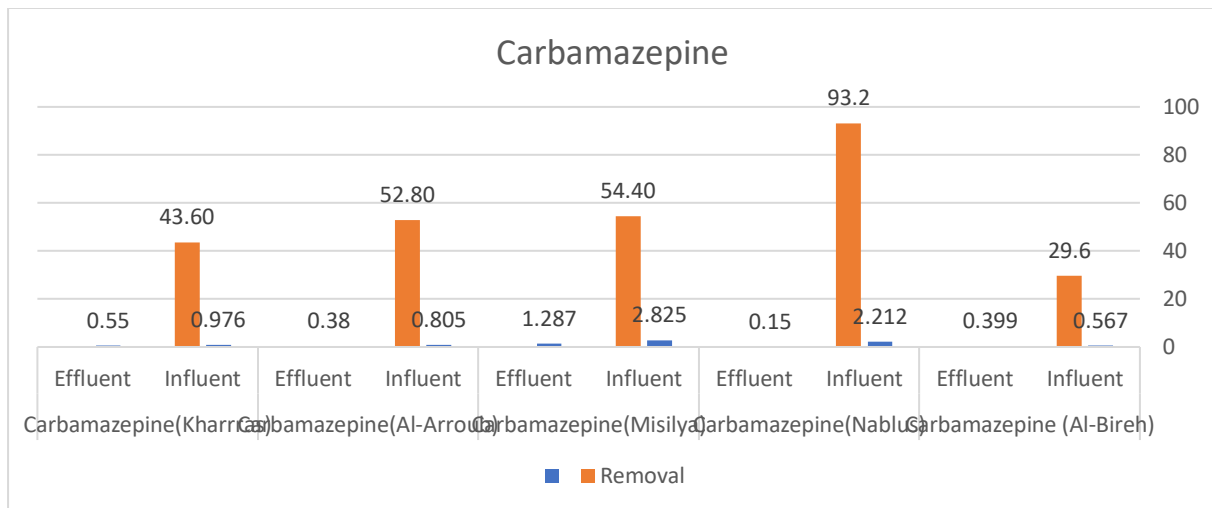
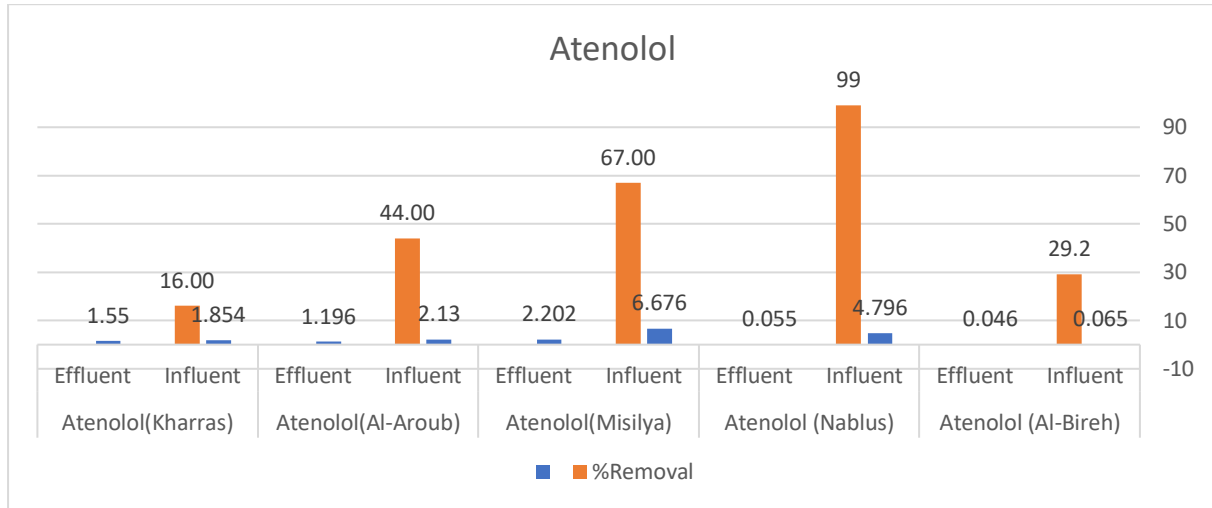
pH is a measure of the acidity or alkalinity of a solution, and it can affect the efficiency of wastewater treatment processes. For example, some treatment processes, such as biological treatment, work best at a specific pH range. Pharmaceutical compounds can affect pH values, as some of them are acidic or basic in nature.

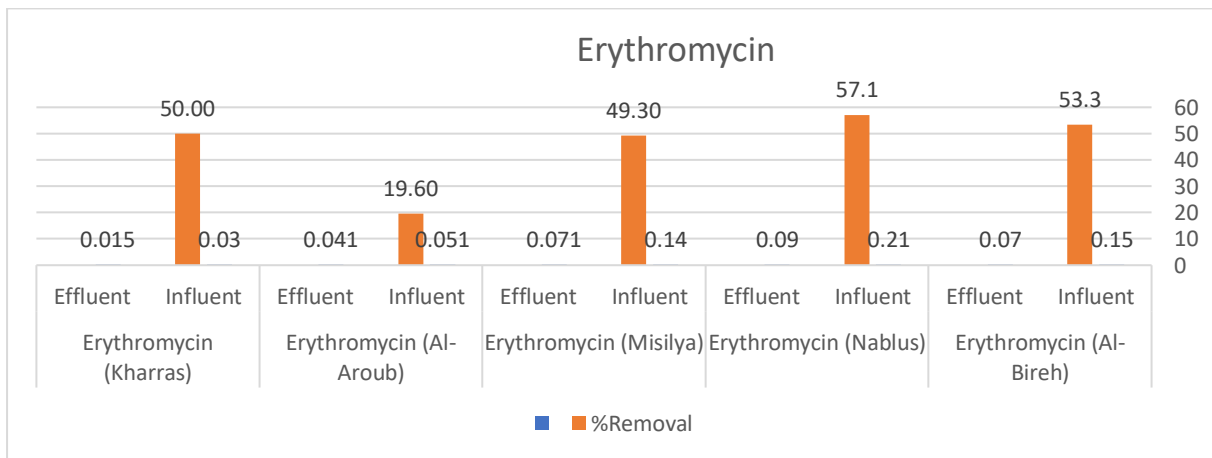
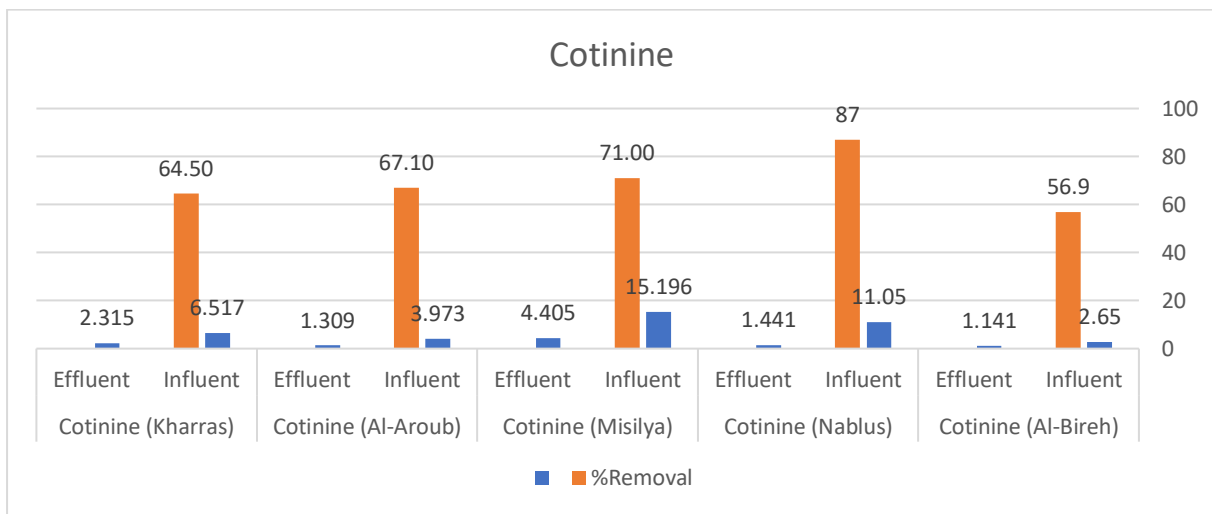
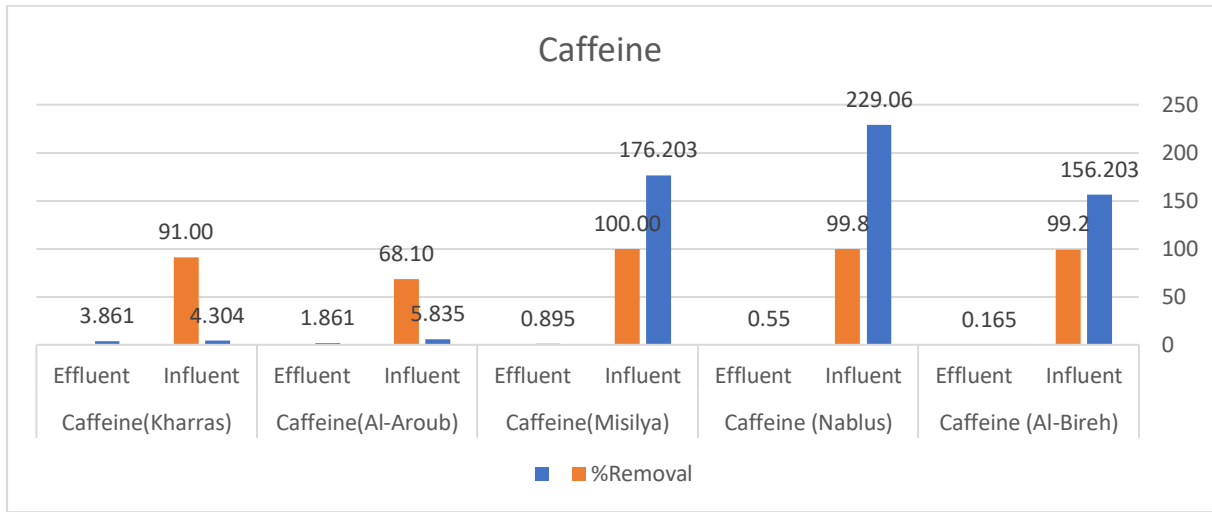
TSS and TDS are measures of the amount of solids in wastewater. High TSS and TDS values can indicate a high concentration of suspended or dissolved solids, which can affect the clarity and quality of the treated water. Pharmaceutical compounds can contribute to high TSS and TDS values, as they may contain solids that are difficult to remove during treatment.

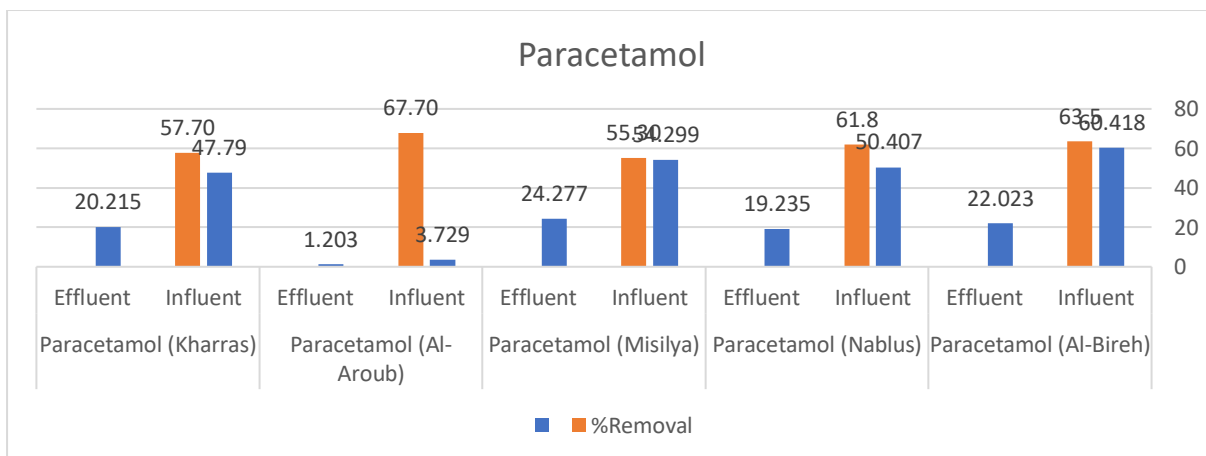
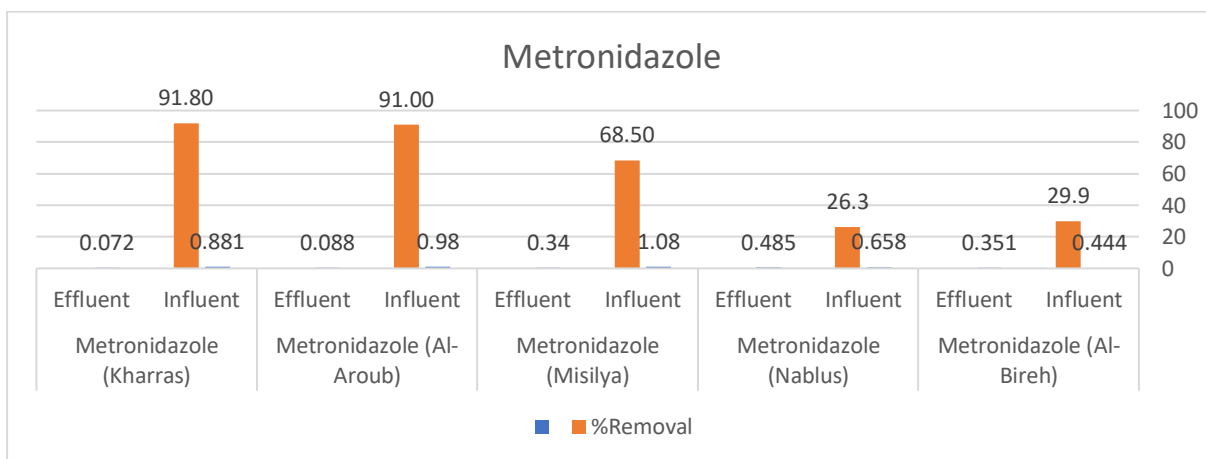
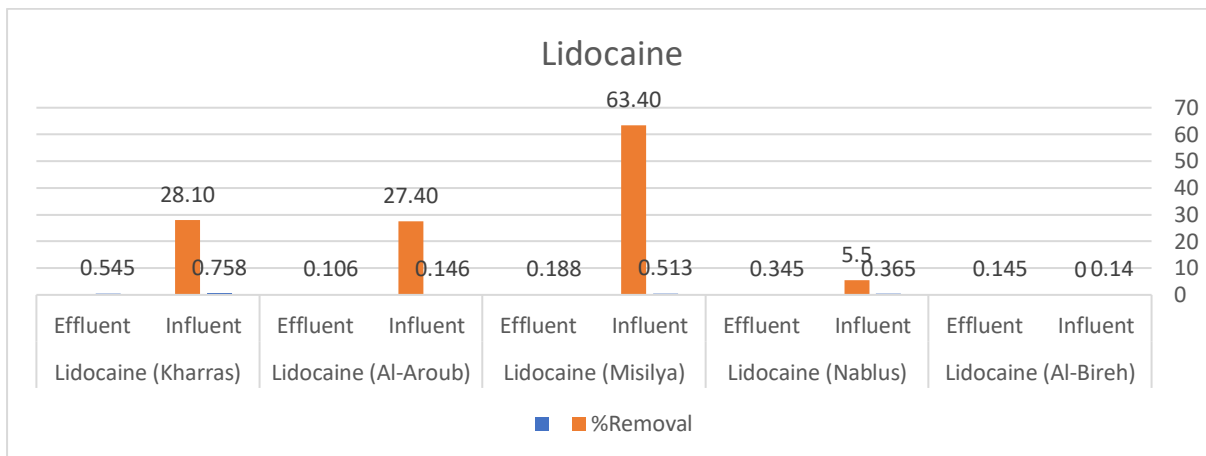
In summary, pharmaceutical compounds in wastewater can affect various treatment parameters, including COD, BOD, pH, TSS, and TDS. It is essential to monitor these parameters regularly to ensure that the wastewater is treated effectively and meets the required discharge standards.

The study found significant variability in the removal of pharmaceuticals in the five STPs. The targeted pharmaceuticals were Atenolol, Carbamazepine, Caffeine, Cotinine, Erythromycin, Lidocaine, Metronidazole, Paracetamol, and Ranitidine. The removal of pharmaceuticals in the Al-Bireh treatment plant ranged from 0% for Lidocaine to 99.9% for Caffeine. In the Nablus treatment plant, the removal of pharmaceuticals ranged from 5.5% for Lidocaine to 99.8% for Caffeine. In the Misilya treatment plant, the removal of pharmaceuticals ranged from 47.5% for Ranitidine to 100% for Caffeine. In the Al-Aroub treatment plant, the removal of pharmaceuticals ranged from 19.6%

for Erythromycin to 91.0% for Metronidazole. In the Kharras treatment plant, the removal of pharmaceuticals ranged from 16.4% for Atenolol to 91.8% for Metronidazole. In the following figures we summarized the concentrations as influents and effluents in relation to wastewater treatment plant investigated Figure 13.







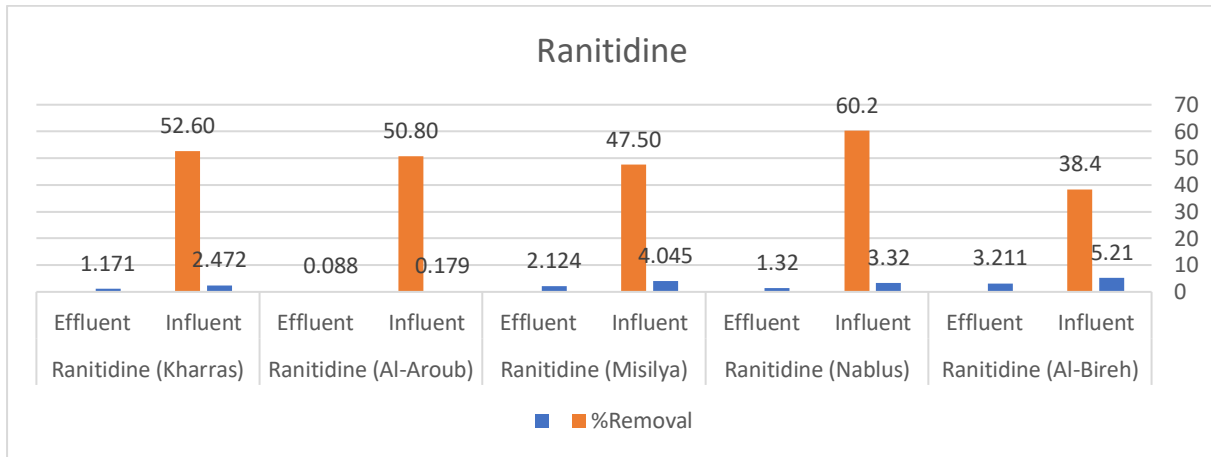


Figure 13: The Concentration of each pharmaceutical residual as influant and effluent vs WWTP

4.3. Comparison between this study and previous study

In Palestine, the receiving water bodies are significantly impacted by pollutants derived from the discharge of raw and TWW. WWTPs play a critical role in protecting the environment by removing a significant portion of pollutants, including pharmaceutical residuals. However, WWTPs must maintain high performance levels at all times, despite experiencing hourly, daily, and seasonal fluctuations. The removal efficiency of WWTPs is influenced by the variations in input qualities and quantities, while the output effluent must consistently meet the required standards.

From the region (Jordan), the concentrations of PhCs and PPCPs detected in the influent of the As-Samra WWTP were higher compared to those in the Wadi Al-seer WWTP. This disparity may be attributed to the larger population served by the As-Samra WWTP. It is well established that the consumption levels of PPCPs are contingent on the size of the population. The total population served by the As-Samra WWTP is estimated at approximately 2.3 million, whereas the population served by the Wadi Al-seer WWTP is significantly lower (with a total population of about 181,212 in Wadi Al-seer city). Among the PPCPs, the highest concentrations in raw WW samples were observed for caffeine, acetaminophen, 1,7-dimethylxanthine, cotinine, and carbamazepine. Caffeine

exhibited the highest estimated concentration, followed by acetaminophen and the caffeine metabolite 1,7-dimethylxanthine.

This observation is unsurprising, given the widespread availability and usage of caffeine and acetaminophen over the counter Table 10. (Al-Mashaqbeh, et al., 2018).

Table 10: the influent concentration (ppb) of pharmaceuticals residue in major WWTP in Jordan and Palestine.

| Compound | As-samre | Wadi-Al-seer | Al-Bireh | Nablus | Misilya | Al-Aroub | Kharras |
|----------------------|----------|--------------|----------|--------|---------|----------|---------|
| 1,7-Dimethylxanthine | 7.47 | 5.90 | NA | NA | NA | NA | NA |
| Acetaminophen | 28.7 | 0.135 | NA | NA | NA | NA | NA |
| Amphetamine | <0.005 | <0.005 | NA | NA | NA | NA | NA |
| Caffeine | 182.5 | 30.0 | 156.203 | 229.06 | 176.203 | 5.835 | 43.041 |
| Carbamazepine | 1.54 | 0.554 | 0.567 | 2.211 | 2.825 | 0.802 | 0.979 |
| Cimetidine | <0.005 | <0.005 | NA | NA | NA | NA | NA |
| Cotinine | 4.67 | 0.059 | 2.65 | 11.05 | 15.196 | 3.973 | 6.516 |
| Diphenhydramine | <0.005 | <0.005 | NA | NA | NA | NA | NA |
| MDA | <0.005 | <0.005 | NA | NA | NA | NA | NA |
| MDMA | 0.018 | <0.005 | NA | NA | NA | NA | NA |

Pharmaceuticals that comprise a significant proportion of an STP's total pharmaceutical load can significantly impact the calculation of overall removal efficiency. Therefore, it is crucial to exercise caution when interpreting results, such as those presented in this study. The average total removal of problematic pharmaceuticals in the studied STPs is notably higher compared to a previous study conducted in Palestinian WWTPs Table 10.

The removal efficiency of pharmaceuticals in the studied WWTP exhibited variability in the sum of the investigated compounds. The STPs demonstrated relatively low removal rates, with less than 30% removal observed. Specifically, the highest total removal of pharmaceuticals was achieved by Al-Bireh and Misilya for Caffeine, with removal efficiencies of 99.9% and 100%, respectively.

However, when excluding the impact of Atenolol, the total removal range was significantly reduced, ranging from 16.4% to 98.2%. (Jelic, et al., 2011).

Moreover, some compounds can be presumed to be enclosed in feces and organic matter when entering the STP and later released during treatment. Further, sampling procedures and sampling representativity might also have influenced the observed removal efficiencies. (Jelic, et al., 2011)

When it comes to the conversion of transformation products, it has been previously been known to occur for compounds such as diclofenac and carbamazepine. (Luo, et al., 2014)

Transformation products and metabolites can be least as active as their parent compound and therefore to evaluate STP efficiency the occurrence of these products and their pathways should be investigated. (Jelic, et al., 2011)

Several factors can affect the removal efficiency of pharmaceuticals in STPs. For example, the pharmaceutical's ability to biodegrade, to volatilize, adsorb to sludge and physicochemical properties have all known to influence removal efficiencies. Additionally, the specific treatment processes that are applied in an STP can also affect removal efficiencies. Some examples of process factors are temperature, pH conditions, Hydraulic Retention Time (HRT) and Sludge Retention Time (SRT), *Kosma et al.* (Kosma, Lambropoulou, & Albanis, 2014), reported decreased removal during colder temperatures and winter months. In the case of pH, it can affect the sorption behavior of some compounds but is generally not a major influence in the narrow pH range that many STPs operate in. Additionally, there have been improvements in the removal of some pharmaceuticals when operating at long HRTs and SRTs. It is possible that some of these factors also contribute to the differences seen between the studied STPs. Firstly, when it comes to what treatment processes used, all studied STPs applied a chemical treatment step and two STPs, also applied a biological treatment step. The literature states that applying conventional chemical treatment has little or negligible effect on pharmaceutical removal (Luo, et al., 2014). Biological treatment on the other hand gives more

options for pharmaceutical removal. This can occur through either biodegradation or sorption, it might also occur through volatilization, but only to a small degree. Biological treatment works best on substances that have a high affinity to sludge or are readily biodegradable. This, however, only includes a few substances, for example Paracetamol and Carbamazepine, while for instance antibiotics Erythromycin in general and NSAID Paracetamol show low ability to biodegrade (Luo et al. 2014). Substances that mainly are present in the sludge phase are few. However, the partitioning between the sludge phase and water phase varies between compounds. To be certain of how well a STP has managed to remove a substance, sludge samples should analyze as well, which was not done in the present study. The biological treatment step applied in Al-Bireh and Nablus was the Activated Slaged process, which is proposed to have some advantages over Conventional Active Sludge (CAS). The advantage comes from its ability to facilitate older sludge ages and more mature bacterial communities that are important for the removal of some micropollutants. The CAS also makes it possible to have compartments with different redox conditions which in turn favors the removal of certain micropollutants (Luo et al. 2014). Previous studies have shown increased removal of micropollutants when compared to CAS to varying degrees. Despite previous results, no clear improvements in total pharmaceutical removal have been seen in this study between the STPs that applied biological treatment and those that did not. Both STPs that applied biological treatment, in this case of Misilya CWL, showed positive removal when excluding. However, it should be noted that apart from the previously mentioned reasons that affect removal efficiencies and negative removal, operational parameters can also influence the performance of the CAS treatment. In conclusion, it is possible that these factors also can be a reason for the absent improvement in removal at the STPs that utilized biological treatment. Treatment in septic tank system mainly occurs through the settling of solids, sorption, and anaerobic biodegradation. Therefore, treatment in a septic tank is more likely to remove substances with high affinity for sludge such as substances

with low water solubility. Most pharmaceuticals are present in both phases to some degree, however, pharmaceuticals that mainly partition to the sludge phase are fewer than those that partition mainly to the water phase. Additionally, previous studies have shown that different redox conditions can affect the degradation of pharmaceuticals. Some pharmaceuticals experienced improved removal under anaerobic conditions and some impaired, while other were recalcitrant regardless of redox conditions (Luo et al. 2014). The high removal achieved in Nablus STP with avg. removal for all pharmaceuticals is 65.5% can therefore be at least partly connected to the physicochemical properties of the pharmaceuticals and the operational parameters of the applied processes, as previously mentioned.

Table 11: Comparison between India, Jordan and Palestine WWTPs concerning the influent concentration of PhCs ($\mu\text{g/L}$).

| Compound | India | Jordan | Palestine * |
|----------------------|---------------|----------------|----------------|
| 1,7-Dimethylxanthine | 7.400-19.000 | 5.909-7.467 | – |
| Acetaminophen | 4.500-86.800 | 0.135-28.741 | – |
| Amphetamine | 0.238-4.700 | <0.005 | – |
| Caffeine | 0.016-102.840 | 30.004-182.460 | 5.835- 229.060 |
| Carbamazepine | 0.022-8.200 | 0.554-1.538 | 0.567 – 2.825 |
| Diphenhydramine | 0.0348-0.144 | <0.005 | – |
| MDA | 0.0592-0.440 | <0.005-0.018 | – |
| MDMA | 0.023 | 0.0115 | – |

*This study

According to Mashaqbeh, 2018 study since he compared the pharmaceutical residual concentrations in WWTP at India and Jordan. Table 11.

Chapter Five: Conclusions & Recommendations

5.1 Conclusions

The studied STPs show only moderate removal of pharmaceuticals at best, and that the conventional treatment processes applied cannot achieve satisfactory removal of pharmaceuticals. Although the literature presents optimization measures that can enhance pharmaceutical removal in conventional processes, it still does not result in effective removal of pharmaceuticals. This study has evaluated the suitability CW and NbS as a complimentary secondary treatment process. The results in this study have shown significantly improved pharmaceutical removal in CW and NbS, running under non-optimized conditions when compared to the conventional processes in the studied STPs. Previous studies have already showed that CW and NbS is a less energy and cost-effective. CW and NbS leads to less harmful by-product formation as well as shorter treatment time and higher efficiency of removal for resistant micropollutants.

5.2 Recommendations

1. Develop a comprehensive guideline for the monitoring and management of pharmaceutical residues in treated wastewater (TWW) in Palestine, with a particular focus on agricultural reuse. This guideline should be informed by current scientific evidence and international best practices.
2. Conduct a detailed investigation into the occurrence and distribution of pharmaceutical residues in the Sun spring of Nablus and Al-Qilt, with a focus on the potential overlap

between these springs and drinking water sources. This study should employ state-of-the-art analytical techniques and incorporate a rigorous risk assessment framework.

3. Recognize that the upgrading of wastewater treatment plants (WWTPs) with new technologies is a necessary but not sufficient step in addressing the issue of pharmaceutical compounds (PhCs) in water. These technologies are limited by their removal efficiencies, high capital investment and operation costs, and increased energy consumption. Moreover, they do not capture diffuse sources of pharmaceutical pollution, such as those from agriculture and aquaculture. Therefore, a holistic and integrated approach is required, encompassing multiple strategies and interventions across different sectors and stakeholders.
4. Solid-phase extraction (SPE) is a highly efficient method for collecting and detecting pharmaceuticals in various matrices. This technique exploits the affinity of solutes in a liquid mixture to a solid packing, allowing for the separation and purification of analytes of interest from undesired components. By passing the sample through a small column containing a stationary phase, SPE enables the retention of desired analytes, which can then be eluted and collected using an appropriate solvent. This method offers several advantages, including high sensitivity, selectivity, and speed, making it an ideal choice for pharmaceutical analysis. Furthermore, SPE can be used to isolate analytes from a wide range of matrices, including urine, blood, water, and animal tissue, and is particularly useful for detecting trace amounts of pharmaceuticals in complex samples. Overall, SPE is a powerful tool in the field of pharmaceutical analysis, enabling the efficient collection and detection of pharmaceuticals in various instruments.

Appendix

Appendix A: SMART project:

In Palestine and according to PWA research projects they organize for fieldwork and analysis in cooperation with local universities in the following research project:

SMART project: Pharmaceutical fate and availability in Wadi Al Qilt and PWA related projects

SMART 2006-2013 concerning the Pharmaceutical Studies Figure 13.

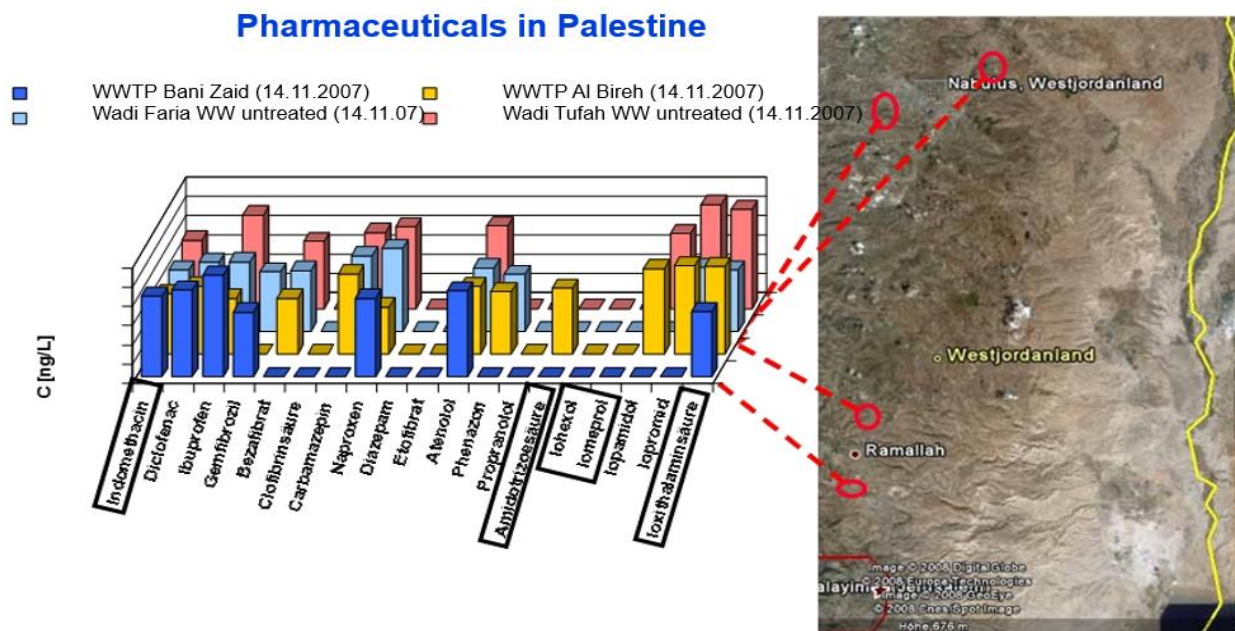


Figure 14: Sampling for PhCs. Al-Qilt, Bani Zaid, Al-Faraa catchments SMART project 2007-2009

SMART project funded by Bundesministerium für Bildung und Forschung (BMBF), Germany, and the research aims:

1. Investigate the occurrence and availability of Indomethacin, DCL, Ibuprofen, Ketoprofen, Gemfibrozil, Fenofibrat, Bezafibrat, Clofibrinsäure, Carbamazepine, Pentoxifyllin, Naproxen, Diazepam and Etofibrat.
2. Study the fate and biodegradation of the main PhCs available at the Al Qilt catchment area.
3. Identify the risk of these PhCs on public health.

4. Organize for student “Fate of Pharmaceutical Compounds in Wadi Al Qilt Catchment Area- Jericho”. This data used by Nihal Fkhaida 2009, Birzeit University / Results for the master study summarized in Table 14

Table 12: Nihal Fkhaida main results for the targeted PhCs, 2009

| Phc compound in ng\L | AWWTP influent | | | <u>Mukhmas Wadi</u> | | | Ras Al Qilt | | | Al Murashahat influent | | |
|----------------------|----------------|-------------|------------|---------------------|---------------|-----------|---------------|---------------|-----------|------------------------|---------------|-----------|
| | 2012/02 | 2013/04 | BG | 2012/02 | 2013/04 | BG | 2012/02 | 2013/04 | BG | 2012/02 | 2013/04 | BG |
| Phenacetin | <BG | <BG | 200 | <BG | <BG | 50 | <BG | <BG | 50 | <BG | <BG | 40 |
| Indomethacin | <BG | 60 | 200 | <BG | <BG | 50 | <BG | <BG | 50 | <BG | <BG | 40 |
| Diclofenac | 310 | 1450 | 200 | 50 | 225 | 50 | 100 | 70 | 50 | <BG | <BG | 40 |
| Ibuprofen | 300 | 1000 | 200 | <BG | <BG | 50 | <BG | <BG | 50 | <BG | <BG | 40 |
| Fenoprofen | <BG | <BG | 200 | <BG | <BG | 50 | <BG | <BG | 50 | <BG | <BG | 40 |
| Ketoprofen | <BG | <BG | 200 | <BG | <BG | 50 | <BG | <BG | 50 | <BG | <BG | 40 |
| Gemfibrozil | <BG | <BG | 200 | <BG | <BG | 50 | <BG | <BG | 50 | <BG | <BG | 40 |
| Fenofibrat | <BG | <BG | 200 | <BG | <BG | 50 | <BG | <BG | 50 | <BG | <BG | 40 |
| Fenofibrinsäue | <BG | <BG | 200 | <BG | <BG | 50 | <BG | <BG | 50 | <BG | <BG | 40 |
| Bezafibrat | <BG | <BG | 200 | <BG | <BG | 50 | <BG | <BG | 50 | <BG | <BG | 40 |
| Clofibrinsäure | <BG | <BG | 200 | <BG | <BG | 50 | <BG | <BG | 50 | <BG | <BG | 40 |
| Carbamazepin | 1995 | 1450 | 200 | 1550 | 1995 | 50 | 64 | 82 | 50 | <BG | 48 | 40 |
| Pentoxifyllin | <BG | <BG | 200 | <BG | <BG | 50 | <BG | <BG | 50 | <BG | <BG | 40 |
| Naproxen | <BG | <BG | 200 | <BG | <BG | 50 | <BG | <BG | 50 | <BG | <BG | 40 |
| Diazepam | <BG | <BG | 200 | <BG | <BG | 50 | <BG | <BG | 50 | <BG | <BG | 40 |
| <u>Etofibrat</u> | <BG | <BG | 200 | <BG | <BG | 50 | <BG | <BG | 50 | <BG | <BG | 40 |

Appendix B: STREAM project:

PWA project in cooperation with Al-Quds Public Health Society (AQPHS) and York University. Under Global Monitoring of PhCs STREAM / University of York in cooperation with PWA and AQPHS for sampling campaign at the project named: “Laying the basis for a joint national policy to promote safe and productive use of irrigation with TWW” Appraisal of risks to agricultural crops and to the environment in the Palestinian Authority 2019. The researchers use York University Protocol of sampling and analysis from 1/11/2018-25/11/2018 according to the following methodology from 10 Wadis Figure 13.

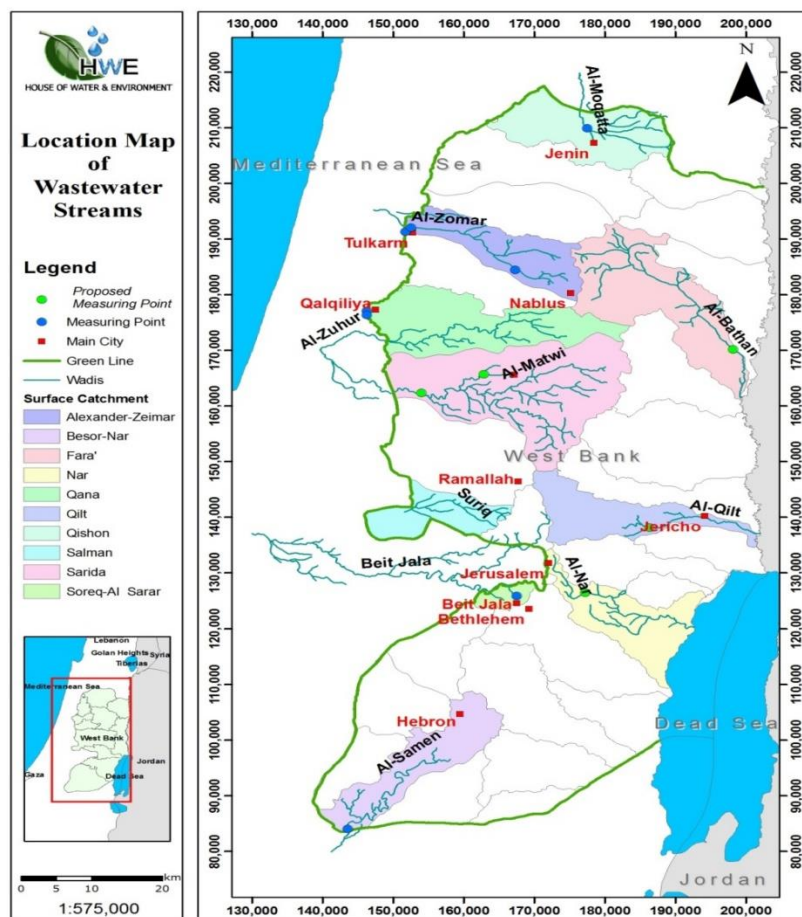


Figure 15:Hous Water Environment (HWE) location map of WW stream according to catchment 2020.

1. Sample preparation protocol for river water and WWTP sample collection University of York- January 2018
2. This document outlines a sample collection protocol to obtain 3x10 mL replicates of filtered river or WW samples in the field.
3. Sample collection and sample preparation will require two people to carry out the 'clean hands' and 'dirty hands' duties.
4. After the water sample has been retrieved use a 20 mL Luer lock syringe (Sigma Aldrich reference Z248037-1PAK) to draw up 15 mL of sample.
5. Attach a 0.7 μm Luer lock syringe filter (Fisher Scientific reference 11344794) to the syringe and run through 5 mL of sample to prime the filter. The filtrate is waste and does not need to be collected.
6. Filter the remaining 10mL and collect filtrate in an amber glass vial (Sigma Aldrich reference CRMA20-EPAVCSA).
7. Repeat steps 4-6 for two additional samples collected from the same site. In total there should be 3 x 10 mL samples collected per site. The same syringe and filter can be used for each site. Using the supplied sticky labels, label each replicate with: location of sample collection, date and replicate number.
8. Place 3 x reps in a plastic bag and label the bag with site details and sampling date.
9. Freeze samples immediately. This will ideally be flash freezing using dry ice, however, if dry ice is not available, then place samples between freezer packs in the field and freeze at -20oC upon returning to laboratory.
10. At the next site please repeat the process using a new syringe and filter to generate 3 x 10 mL replicate samples per site.

11. Blanks consisting of High-Pressure Liquid Chromatography (HPLC) water only need to be prepared once each month at collection points for the influent, effluent and the samples (i.e., three blanks). At these sites 15 mL HPLC water is run through a 0.7 μm filter following the same steps as for the composite samples to generate 3 x 10 mL samples. A new syringe and filter are required for each triplicate set of samples.
12. Shipment and analysis organized between AQPHS and PWA.

The Global Monitoring of PhCs Residual (2020), the PhCs are an essential component of a healthy society and their use is ubiquitous across the world. Over recent decades, much research has been conducted elucidating their concentrations and fate in surface waters. However, limited, if any, data reported for many parts of the world. Furthermore, inter-study variables including sample collection, storage and ultimate analytical quantification hinder the ability to compare data between individual studies. This project aims to establish a snapshot view of pharmaceutical concentrations in freshwater rivers across the globe. Here we will significantly reduce the impact of key inter-study variables by:

1. Adopting the same approach to site selection project-wide;
2. Adopting the same sample collection method across all study-sites;
3. Use of quality controls to monitor the effects of sample integrity over the variable shipment durations from each partner institution to the University or PWA lab;
4. Use of field blanks from every partner to evaluate sampling campaign-specific contamination and matrix interference, and
5. Use of one validated: High-Pressure Liquid Chromatography-tandem Mass Spectrometry (HPLC-MS/MS) method to accurately and specifically quantify 40 PhCs in all of the project's samples using one instrument and at one time.

Together, this unified methodology will enable a robust comparison between pharmaceutical concentrations in the aquatic environment of up to three laboratories at the country. A network at national level will also be connected which could develop future collaborative work.

Sampling Site and field measurements:

The Sample preparation protocol for WWTP sample collection Ref: University of York- January 2018.

1. Five water samples taken, from five stations at each catchment.
2. The physical chemo-physical parameters such as electrical conductivity, total dissolved solid, pH and temperature measured with suitable instruments at the field.
3. Chemical analysis, major, nutrient and pharmaceutical parameters.
4. Samples Bottles: The samples collected in High Density Polyethylene HDPE bottles.
5. Sample Volume: 500 mL of sample is enough to extract through a SPE cartridge.
6. Preservative: samples preserved using the sodium thiosulfate.
7. Sample Storage: Samples were stored at 4°C.





Figure 16:sampling site and sample preservation .

Appendix C: Sample preparation protocol for WWTP sample collection Ref: University of York- January 2018

This document outlines a sample collection protocol to obtain 3x10 mL replicates of filtered WW samples in the field. Sample collection and sample prep. will require two people to carry out the 'clean hands' and 'dirty hands' duties.

1. Please complete a log during each sampling campaign detailing the location, replicate number and date of each sample.
2. Each person should wear gloves and change these between sample collections at the different sites.
3. The person nominated 'dirty hands' will handle/open the sample collection vessel to enable the 'clean hands' person to carry out the sample prep.
4. After the water sample has been retrieved, the person nominated 'clean hands' will use a 20 mL Luer lock syringe (Sigma Aldrich reference Z248037-1PAK) to draw up 15 mL of sample.
5. Attach a 0.7 μm Luer lock syringe filter (Fisher Scientific reference 11344794) to the syringe and run through 5 mL of sample to prime the filter. The filtrate is waste and does not need to be collected ('clean hands').
6. Filter the remaining 10mL and collect filtrate in an amber glass vial (Sigma Aldrich reference CRMA20-EPAVCSA).
7. Repeat steps 1-4 for two additional samples collected from the same site. In total there should be 3 x 10 mL samples collected per site. The same syringe and filter can be used for each site ('clean hands'). Using the supplied sticky labels, label each replicate with: location of sample collection, date and replicate number.
8. Place 3 x reps in a plastic bag and label the bag with site details and sampling date.

9. Freeze samples immediately. This will ideally be flash freezing using dry ice, however, if dry ice is not available, then place samples between freezer packs in the field and freeze at -20°C upon returning to laboratory.
10. At the next site please repeat the process using a new syringe and filter to generate 3 x 10 mL replicate samples per site.
11. Blanks consisting of HPLC water only need to be prepared once each month at collection points for the influent, effluent and the river samples (i.e., three blanks per month). At these sites 15 mL HPLC water is run through a 0.7 µm filter following the same steps as for the composite samples to generate 3 x 10 mL samples. A new syringe and filter are required for each triplicate set of samples.
12. For return shipment to the Universities labs: Place properly labelled samples in an insulated shipping container and wrap each sample with protective padding to prevent breakage.
13. Samples should be frozen prior to shipment and returned with icepacks in the cooler to slow thawing.

AppendxD: PhCs in the environment are a challenge to manage for the following reasons:

1. PhCs are design to interact with a living system and produce a response at low doses, which makes them of environmental concern even at low concentrations.
2. PhCs are design to be stable in order to reach and interact with target molecules, their constant use leads to continuous release into the environment at rates exceeding degradation rates.
3. Conventional Wastewater Treatment Plants (CWWTP) are not designed to, nor do they fully, remove PhCs from WW. Furthermore, veterinary PhCs used in agriculture and aquaculture can enter water bodies directly or via surface runoff (diffuse pollution).
4. PhCs in the environment could be long-term, potentially occurring via multiple exposure routes, and involving mixtures of substances.

Appendix E: Fact and figures

1. About 4,000 APIs are being administered worldwide in prescription medicines, over-the-counter therapeutic drugs and veterinary drugs. (Vogiatzi, Jacobson-Dickman, & DeBoer, 2014).
2. PhCs administered to humans or animals are excreted via urine and feces, with 30 to 90% of oral doses generally excreted as active substances (Yang, CUI, Xiao, Gandomi, & Karamanoglu, 2013).
3. Extremely high pharmaceutical concentrations (in the order of mg/l), have been detected in industrial effluents and recipient streams in China, India, Israel, Korea and the USA. (Larsson D. G., 2014).
4. In the United States, it is estimated that about one-third of the four billion prescription items annually become waste. (Schumock, Stubbings, Li, Matusiak, & Vermeulen, 2018)
5. Projected growth rate of the pharmaceutical industry: 6.5% per year by 2022. (Alpizar, et al., 2019)
6. Projected increase in antibiotics administered to livestock animals in feed: 67% worldwide by 2030 (from 2015 levels), much of this increase will come in emerging economies. (Van Boeckel, Brower, Gilbert, & Laxminarayan, 2015).
7. In Germany, pharmaceutical usage is projected to increase by 43-67% by the year 2045 (from a baseline of 2015). An ageing population is thought to be the main driver (Christina Fitzmaurice, 2017)
8. An estimated 10% of pharmaceutical products have a potential environmental risk. (Küster & Adler, 2014)
9. In the United Kingdom, Ethynylestradiol, diclofenac, ibuprofen, propranolol and the macrolide antibiotics are present at high enough concentrations in the effluent of 890 WWTP

(13% of all plants) to cause adverse environmental effects in surface waters. (Comber, Gardner, Sörme, Leverett, & Ellor, 2018).

Appendx F: Organization for Economic Co-operation and Development (OECD) recommendations on end-of-pipe measures. Pharmaceutical life cycle stages: collection and disposal, and WWT and reuse. (Development, 2020)

End-of-pipe measures should only be used in complementary to source-directed and use-orientated measures. An over-emphasis on upgrading WWTP infrastructure is not a sustainable, optimal use of limited resources.

1.Ensure value-for-money in investments in WWTP upgrades through evaluation and prioritization.

Consider trade-offs.

2. Factor in financing needs and cost-recovery mechanisms for capital, and operation and maintenance (O&M) costs of WWTP upgrades.

3.Ensure appropriate collection and disposal of waste pharmaceuticals. Educate and engage with health professionals, veterinarians, consumers and farmers to raise awareness about inappropriate disposal of unused medications.

4.Promote best practices on the use and disposal of bio-solids (which may include toxic transformation products) following WWT.

Appendix G: A selection of policy instruments to control PhCs in the environment. (Development, 2020)

1. In the United Kingdom, the poultry industry has successfully reduced unnecessary antibiotic use – whilst increasing meat production – with a voluntary antibiotic stewardship programmed.
2. The United States has national regulations on the disposal of hazardous pharmaceutical waste in the health sector.
3. Germany has developed an environmental checklist for veterinarians and farmers with the aim of reducing the use and release of veterinary PhCs to the environment.
4. Sweden has a ‘Wise List’ of recommended PhCs for the treatment of common diseases that takes into account environmental impacts when comparing medications that are equally safe and equally suitable for the medical purpose.
5. Korea uses suspect and nontarget screening to identify and priorities PhCs for water quality monitoring.
6. Switzerland has a nationwide tax to fund the upgrade of 100 WWTP with new technologies to reduce PhCs in water bodies.
7. Australia has a national pharmaceutical collection and disposal programmed, with retail pharmacies commonly acting as collection sites.

Appendx H: Chemicals:

5M ammonium format, 0.1% formic acid, Acetonitrile, Methanol.

Table 13: Appendices I : CEC values according to sweden sewage treatment plant*

| <i>Pharmaceutical</i> | <i>CEC (ng\l)</i> |
|-----------------------|---------------------------|
| <i>Carbamazepine</i> | <i>346496</i> |
| <i>Paracetamol</i> | <i>2.4*10⁷</i> |
| <i>Caffeine</i> | <i>-</i> |

(Mathias & Hägglund, 2021)*

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