REMOVAL OF PHARMACEUTICALLY ACTIVE COMPOUNDS IN ENVIRONMENTAL WATERS USING POLYMER INCLUSION MEMBRANES

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REMOVAL OF PHARMACEUTICALLY ACTIVE COMPOUNDS IN ENVIRONMENTAL WATERS USING POLYMER INCLUSION MEMBRANES

by

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DEDICATION

I dedicate this thesis to God almighty for his infinite mercies and protections. And to the memories of my late Dad and sister who passed on to the greater beyond during my PhD. I pray that God will forgive your sins and brighten your graves. To my mom and siblings for their support

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LIST OF SYMBOLS

K_{ow}	Octanol-water partition coefficient
D_{ow}	Octanol water distribution coefficient
S_w	Water solubility
K_H	Henry's law constant
K-1	Pseudo-first-order rate constant
pK_a	Acid dissociation constant
J	flux
k	Rate constant
COOH	Carboxyl group
cm	Centimeter
ºC	Degree Celsius
%	Percent
Kd	Distribution coefficients
ΔH^o	Enthalpy
ΔS^o	Entropy
Ea	Activation energy
B	Boltzmann's constant
g	Gram
R	Gas constant (J/Kmol)
H^+	Hydrogen ion
^-OH	Hydroxyl group
C_o	Initial concentration of adsorbate (mg/L)
C_t	Concentration in the feed phase at a given time.
J	Joules
K	Kelvin

KJ	Kilojoules
V	Voltage
L	Liter
Mg	Milligram
mL	Mililiter
mm	Millimeter
mM	Millimolar
µL	Microliter
M	Molarity
ng	nanogram
µg	microgram
N	Number of data points
nm	Nanometer
Log P	Partition coefficient
V	Volume
λmax	Wavelength of maximum absorbance

LIST OF ABBREVIATIONS

Aliquat 336	Tricapryl-methylammonium chloride
AgNPs	Silver nanoparticles
AAC	Adsorption on activated carbon
AOP	Advanced oxidation process
ATTs	Advanced tertiary treatments
B2EHP	Bis-2-(ethylhexyl) phosphate
BLM	Bulk Liquid Membrane
BOD	Biological Oxygen Demand
CAB	Cellulose Acetate Butyrate
CAP	Cellulose Acetate Propionate
CCD	Central Composite Design
CFMs	Chemically functionalised membranes
CIP	Ciprofloxacin
CTA	Cellulose triacetate
CTB	Cellulose Tributyrate
DBBP	Dibutyl butyl phosphonate
DCF	Diclofenac
DMA	Dimethacrylate
DNA	Deoxyribonucleic Acid
DNNS	Dinonylnaphthalene sulfonic
DOE	Design of Experiment
DOP	Dioctyl phthalate
DSC	Differential Scanning Calorimetry
ELM	Emulsion Liquid Membrane
EME	Electromembrane Extraction

EOCs	Emerging organic contaminants
EU	European Union
FP	Feed Phase
FTIR	Fourier transform infrared
HCl	Hydrochloric
HFP	Hexafluoropropylene
HPIM	Hollow polymer inclusion membrane
IEC	Ion Exchange Capacity
ISEs	Ion-selective electrodes
LLE	Liquid-liquid extraction
MSP	Membrane separation process
MW	Molecular Weight
NSAIDs	Non-Steroidal Anti-Inflammatory drugs
NaCl	Sodium Chloride
NPOE	2-nitro phenyl ether
OFAT	One factor at a time
PEG	Polyethylene glycol
PF	Preconcentration Factor
PIMs	Polymer inclusion membranes
PNEC	Predicted No-Effect Concentration
PVC	Polyvinyl chloride
PVDF	Polyvinylidene fluoride
SEM	Scanning electron microscope
SLM	Supported Liquid Membrane
SMZ	Sulfamethoxazole
SPE	Solid-phase extraction
SPR	Surface Plasma Resonance

SP	Stripping Phase
SUPRASs	Supramolecular Solvents
TBA	Tri-n-butylamine
TBP	Tri-n-butyl phosphate
TDA	Tri-n-decylamine
TDS	Total Dissolved Solid
TEM	Thermal electron microscopy
TGA	Thermal gravimetric analysis
THA	Tri-n-hexylamine
TOA	Tri-n-octyl amine
UN	United Nations
UNICEF	United Nations Children Funds
URTI	Upper Respiratory Tract Infection
US-EPA	U.S Environmental Protection Agency
UTI	Urinary Tract Infection
UV	Ultraviolet
WHO	World Health Organisation
WUC	Water Update Capacity
WWTPs	Wastewater treatment plants

LIST OF APPENDICES

PENYINGKIRAN SEBATIAN AKTIF FARMASEUTIKAL DALAM AIR PERSEKITARAN DENGAN MENGGUNAKAN MEMBRAN POLIMER TERANGKUM

ABSTRAK

Kehadiran sisa-sisa sebatian aktif farmaseutikal dalam persekitaran akuatik merupakan isu yang amat membimbangkan. Kemunculan, nasib dan potensi ketoksikan bahan cemar ini dalam media persekitaran yang berbeza telah mencetuskan minat di dalam komuniti sains. Ia telah ditemui dalam kepekatan yang berbeza-beza dari julat ng/L hingga mg/L dalam matriks persekitaran yang berlainan. Hasil daripada keterlarutan yang tinggi dan kemeruapan yang rendah, ia sering dijumpai dalam persekitaran akuatik dan loji rawatan air sisa (WWTP) yang merupakan takungan utama mereka. Walau bagaimanapun, WWTP konvensional tidak mampu menyingkirkan bahan cemar ini sepenuhnya semasa rawatan; oleh itu, terdapat keperluan untuk meneroka rawatan air sisa termaju yang lain untuk mengimbangi kekurangan WWTP konvensional. Dalam kajian ini, siasatan terhadap menyiasat penyingkiran bahan cemar degil seperti ciprofloxacin (CIP), sulfamethoxazole (SMZ), dan diclofenac (DCF) daripada air sisa menggunakan membran terangkum polimer (PIM) yang difabrikasi daripada polimer asas yang berbeza (polivinil klorida (PVC) dan selulosa. triasetat (CTA)), pembawa berbeza (bis-2-(etilheksil) fosfat (B2EHP) dan tricapril metilammonium klorida (Aliquat 336)), dan pemplastik berbeza (dioktil ftalat (DOP) dan 2-nitro fenil eter (NPOE)). Membran yang dihasilkan telah disiasat untuk sifat fizikokimia menggunakan TGA, SEM, TEM, FTIR, kapasiti pengambilan air dan kapasiti pertukaran ion. Pada keadaan optimum, CIP mempunyai 100%

kecekapan penyingkiran, 70% kecekapan pengangkutan dan 20.1 μm/s kebolehtelapan membran pekali. Begitu juga, SMZ mempunyai kecekapan penyingkiran sebanyak 100% dengan kecekapan pengangkutan 80% dalam 40 jam. Untuk meningkatkan pengangkutan SMZ, voltan luaran telah digunapakai melalui proses pengekstrakan elektromembran. Oleh itu, 100% SMZ berjaya diangkut apabila 50 V digunakan dalam masa 15 jam. DCF berjaya disingkirkan dengan 100% kecekapan penyingkiran dan pengangkutan menggunakan membran nanokomposit dalam masa 15 jam dengan pekali kebolehtelapan 48 μm/s. Kestabilan PIM yang dikaji adalah tertakluk kepada 10 -12 kitaran pemindahan jisim. PIM menunjukkan kestabilan yang baik dengan penurunan yang tidak ketara dalam kecekapan penyingkiran dan pengangkutan. Untuk tujuan ini, dapat disimpulkan bahawa penyingkiran CIP adalah lebih cekap menggunakan polimer PVC/B2EHP, manakala penyingkiran lengkap SMZ dipengaruhi oleh aplikasi potensi elektrik, dan aplikasi nanozarah Ag mempengaruhi penyingkiran lengkap DCF daripada air sisa alam sekitar. Maka, PIM boleh dipertimbangkan sebagai alternatif yang sesuai untuk rawatan bahan cemar degil dalam WWTP.

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ABSTRACT

The presence of residues of pharmaceutically active compounds in aquatic environments is a daunting issue of great concern. The occurrence, fate and potential toxicity of these contaminants in different environmental media have triggered the interest of the science community. They have been found in varying concentrations from ng/L to mg/L in different environmental matrices. As a result of their high solubility and low volatility, they are often found in the aquatic environment and the wastewater treatment plants (WWTPs) are their major reservoir. However, conventional WWTPs are incapable of removing these contaminants completely during treatments; hence, there is a need to explore other advanced wastewater treatments to compensate for the lapses of conventional WWTPs. In this study, an investigation on the removal of recalcitrant contaminants such as ciprofloxacin (CIP), sulfamethoxazole (SMZ), and diclofenac (DCF) from wastewater using polymer inclusion membranes (PIMs) fabricated from different base polymers (polyvinyl chloride (PVC) and cellulose triacetate (CTA), different carriers (bis-2-(ethylhexyl) phosphate (B2EHP) and tricapryl-methylammonium chloride (Aliquat 336)), and different plasticizers (dioctyl phthalate (DOP) and 2-nitro phenyl ether (NPOE)). The produced membranes were investigated for physicochemical properties using TGA, SEM, TEM, FTIR, water uptake capacity and ion-exchange capacity. At optimum conditions, CIP had a removal efficiency of 100%, a transport efficiency of 70%, and

a membrane permeability coefficient of 20.1 μm/s. Similarly, SMZ had a removal efficiency of 100% with a transport efficiency of 80% in 40 hours. To improve the transport of SMZ, an external voltage was applied through an electromembrane extraction process. Thus, 100% of SMZ was successfully transported when 50 V was applied within 15 hrs. DCF was successfully removed with 100% removal and transport efficiency using a nanocomposite membrane within 15 hrs with a permeability coefficient of 48 μm/s. The stability of the investigated PIMs was subject to 10-12 cyclic mass transfer. The PIMs demonstrated good stability with an insignificant decline in removal and transport efficiency. To this end, it was concluded that the removal of CIP was more efficient using PVC/B2EHP polymer, whilst the complete removal of SMZ was influenced by the application of electrical potential, and the application of silver nanoparticles influenced the complete removal of DCF from environmental wastewater. Thus, PIMs can be considered a suitable alternative for the treatment of recalcitrant contaminants in WWTPs.

CHAPTER 1

INTRODUCTION

1.1 Background of the study

Relevant world organisations such as the World Health Organisation (WHO), United Nations (UN), and United Nations International Children's Emergency Funds (UNICEF) have identified access to potable water for human consumption as a global existential challenge in this century (Vera Chamorro, 2019). The need for portable water increases with an increase in population due to the social-economic importance of water for the sustainability of every country. Consequently, this has led to unhealthy competition for potable water and unnecessary pressure on the aquatic environment (Garcia Rodríguez, 2016).

Water constitutes around 70% of the whole earth's crust, 2.5% of which is viewed as freshwater; notwithstanding, just 1% is accessible for human utilisation (Castro, 2007). Lack of consumable water for human utilisation and other domestic uses has for quite some time been distinguished as a societal menace in most developing and underdeveloped countries of the world. The European Union Parliament and Council on the security of groundwater contamination (Directive 2016/118/EC) distinguished groundwater as the biggest and most significant wellspring of freshwater in the European Union (Nogueira et al., 2019).

Anthropogenic activities like industrial processing, agricultural irrigation practice, urbanisation, and an increase in population contribute to freshwater scarcity. Although natural phenomena such as climate change have contributed tremendously to water scarcity; however, the rapid rate and magnitude of climate change have been

induced by various anthropogenic activities. Thus, it has been reported that water scarcity might increase geometrically due to an expected world population increase by 40-50 % in the next 50 years (Stewart et al., 2014). Hence, palliative measures would have to be put in place to cater to the expected increase in population and reduce pressure on the environment and available water bodies by providing alternative freshwater sources such as water reclamation and recycling, especially in agricultural practices like irrigation and other industrial water recycling (Cooley et al., 2013; Tian et al., 2017).

Wastewater treatment is an important approach to remediate the adverse effect of anthropogenic activities on freshwater availability. Several studies have reported the presence of toxic contaminants in treated and untreated water systems, which have the potential to cause adverse health effects. Therefore, concerted efforts have been made by the various water regulation authorities to continually review the processes of water treatments for human and ecological safety (World water council, 2009). However, conventional wastewater treatment plants (WWTPs) were designed only to remove biodegradable carbon compounds, phosphorus, nitrogen, and other microbial organisms. Hence, hundreds of toxic contaminants like emerging organic contaminants (EOCs) are still reportedly found in effluents of WWTPs, which are hazardous to human health and aquatic life (Reberski et al., 2022; Xing et al., 2018).

Pharmaceutically active compounds are contaminants that belong to the group EOCs. These chemical compounds have been ubiquitously used for different purposes, ranging from human health care, veterinary care, agricultural practices, industrial applications, and food preservatives (Couto et al., 2019). Pharmaceutically active compounds such as antibiotics, analgesics, beta-blockers, lipid regulators, anti-

inflammatory drugs, x-ray contrast media, and estrogens have been used globally to improve wellness and increase life expectancy in humans and animals. The consumption of these compounds is expected to increase in the coming years as a result of an increase in the ageing population and various improvements in health standards, especially in developing countries (Verlicchi et al., 2012). According to the US Food and Drug Administration, over 100 new pharmaceutical formulation and chemical entities were approved for clinical use in 2013 alone (Couto et al., 2019).

These contaminants enter the aquatic system through various sources like domestic sewage effluents, landfill leachates, industrial effluents, indiscriminate waste disposal, drain water, animal waste, and hospital waste (Karpińska and Kotowska, 2019; Lapworth et al., 2012a). As a result of their relatively high polarity and non-volatile nature, they are found in low concentrations (ng/L - μg/L) in environmental matrices. However, due to the continuous production, consumption, and discharge of these contaminants, there has been an upsurge in awareness of their occurrence, fate, and toxicity in different environmental compartments, especially the aquatic system. They have been reportedly found in varying concentrations in surface water, groundwater, seawater, and influents/effluents of water/wastewater treatment plants (Lee et al., 2019; Praveena et al., 2018). As a result of the paucity of information available on these contaminants, the toxicological effect on humans is not adequately understood. However, they have demonstrated the ability to cause severe damage to the aquatic environment, such as genotoxicity of aquatic organisms, development of resistance in the aquatic microbial community (Gwenzi et al., 2022; Taheran et al., 2016). Furthermore, they also cause endocrine conduit disturbance, brain damage, carcinogenic diseases, reproductive impairments, liver and lung damages, and

dysfunctional gene expression in an aquatic organism, which leads to the feminisation of some the aquatic organisms (Jackson et al., 2019; Tijani et al., 2013).

Unfortunately, the release of these compounds into the aquatic system has not been subjected to proper regulations (Lapworth et al., 2012). However, in September 2009, the U.S Environmental Protection Agency (US-EPA) released a final list (List-3) of unregulated pharmaceuticals and other EOCs with the potential to cause serious health hazards via drinking water (Joshi, 2017; Pedrouzo Lanuza, 2011). Furthermore, efforts have been made to control or ban the use of certain pharmaceuticals and endocrine-disrupting chemicals by different countries and relevant world organisations. Agencies such as the European Union Water Framework Directive and the US Food and Drugs Administration (US-FDA) gave a directive for evaluating and using certain drugs (Couto et al., 2018). Pharmaceuticals such as diclofenac have also been included in the European monitoring list by the EU Water framework directive (WFD-2000/60/EC) as a priority contaminant in surface water bodies (Stewart et al., 2014; Zenker et al., 2014). According to Couto et al. (2018), the occurrence of pharmaceuticals in the environment, their fate, human toxicity, and ecotoxicological effects may have been underestimated as a result of the complexity of the contaminants and their metabolites in the environment, coupled with the high cost of analysis, and the time and labour involved in the methods of monitoring these contaminants.

The WWTP remain the major reservoir of pharmaceuticals and other EOCs due to a large amount of pollutants coming from municipal/domestic, industrial, and agricultural effluents, which all converge at the WWTPs for treatment. Although, WWTPs are reportedly incapable of completely removing most highly soluble compounds such as pharmaceuticals, endocrine disruptors, and other EOCs because

they were not designed by default to completely remove contaminants in very low concentrations (ng/L - µg/L). Thus, their main goal is to separate large particles (biosolids) and remove nutrients and organic compounds in the order of g/L and mg/L concentrations. As a result of the inability of the conventional wastewater treatment plants to completely remove these contaminants, they are subsequently discharged into water bodies as a more complex parent or metabolite compounds found in a different concentration from the initial concentration at the point of influent (Yoon et al., 2010). In a study conducted by Sim et al. (2011), some contaminants were found in a higher concentration in the effluent than the concentration in the initial influent. It was attributed to various chemical interactions that led to the transformation of parent contaminants into more toxic conjugate/metabolite compounds, which are often found in higher concentrations.

As a result of the limitations demonstrated by the WWTPs, advanced tertiary treatments (ATTs) have been incorporated to compensate for the various lapses of the conventional treatment. Amongst the most frequently reported ATTs are adsorption on activated carbon (AAC), advanced oxidation process (AOP), and membrane separation process (MSP). Although the various advanced treatment techniques have reported significant improvement in the removal of pharmaceuticals than the conventional treatments, however, they also have their limitations, such as the cost of removing carbonaceous residue in ACC, cost of removing catalyst and agents of oxidation and mineralisation of contaminants in AOP, and cost of cleaning concentrated residues of contaminants from membrane surfaces in MSP. Hence, there is a need to explore other viable techniques such as chemically functionalised membranes (CFMs), otherwise known as liquid membranes (Garcia Rodríguez, 2016).

Polymer inclusion membranes (PIMs) are the most recent of all CFMs (Garcia-Rodríguez et al., 2015). They are made up of a base polymer, which serves as the mechanical strength of the membrane, and a carrier which serves as the mobile phase that aids the transport of contaminants from the feed solution to the stripping solution. A PIM sometimes also comprises a plasticiser which gives the membrane better flexibility and increases the solubility of the extracted adduct (M. I. G. Almeida et al., 2017). Amongst the most frequently used base polymers are thermoplastic elastomers such as poly(vinyl chloride) (PVC) and cellulose triacetate (CTA) (Maiphetlho et al., 2021). The choice of the carrier in PIM is dependent on the nature of the analyte(s) to be investigated, which is based on electrostatic interaction between the analyte and the carrier. An extensive review on different types of carrier and carrier-mediated transport was recently reported by Tajabadi and Ghambarian (2020). Several studies have reportedly used different types of plasticisers depending on their affinity for the base polymer, their dielectric constant, viscosity, volatility and cost (Maiphetlho et al., 2021). In addition, 2-nitrophenyl octyl ether (NPOE) and dioctyl phthalate (DOP) are a few of the most viable plasticisers reported (Baba et al., 2016).

As a result of several advantages such as low cost of fabrication, ease of preparation, high selectivity, good mechanical properties, and versatility, PIMs have been widely explored for the removal and monitoring of different heavy metals (Bonggotgetsakul et al., 2016; Kaya et al., 2016a; Suah & Ahmad, 2017), dyes (Ling & Suah, 2017a), nutrient (Almeida et al., 2016a), and organic molecules (Vera et al., 2018). However, only a few studies have investigated the use of PIMs for the removal of pharmaceutical compounds. In our previous study, we did a detailed review of the different applications of PIM for the remediation of pharmaceutically active compounds (Olasupo & Suah, 2020).

1.2 Problem statement

Residues of pharmaceutically active compounds have been found in different aquatic environments such as surface water and groundwater, as a result of the inability of the conventional WWTPs to remove them completely during wastewater treatments. Hence, the contaminants find their way back into water bodies that are meant for human and animal consumption. However, concerted efforts have been made to completely remove these recalcitrant contaminants through various advanced wastewater treatments such as the advanced oxidation process (AOP), membrane separation process (MSP), and adsorption on activated carbons (AAC), amongst others. But these contaminants are still reportedly found in water bodies; hence, there is a need to explore the use of other water treatment approaches.

Hence, this study is focused on synthesizing PIMs with different optimization and modifications for the complete removal of investigated pharmaceutically active contaminants from environmental samples such as river water and wastewater to compensate for the inadequacies of the conventional WWTPs and also serve as a useful alternative for the complete removal of these recalcitrant contaminants from our aquatic environments.

1.3 Hypothesis of the study

Different modifications of PIMs have been widely explored for the removal of environmental contaminants such as dyes, heavy metals, nutrients, pesticides amongst others in aquatic environments. However, there is very little known about the removal of pharmaceuticals and other EOCs from aquatic environments using PIMs. Thus, this study will potentiate the ability of PIMs made of different base polymers, carriers and plasticizers for the removal of investigated contaminants. Furthermore, the impact of

applied electrical potential in an electromembrane extraction of contaminants will be investigated. Finally, the influence of silver nanoparticles to form a nanocomposite membrane on the efficiency of PIM for the removal of contaminants from environmental wastewater samples would be substantiated.

1.4 Objectives of the Study

This study aims to develop a robust, cost-effective, less labour-intensive technique using PIM for the removal and preconcentration of pharmaceutically active compounds in aquatic environments as a potential water treatment technology for industrial application.

The specific objectives of the study are:

1. To prepare/synthesis PIMs with different base polymers, ionic liquids (carriers) and plasticisers for the removal of investigated pharmaceuticals (ciprofloxacin, sulfamethoxazole, and diclofenac) aqueous samples
2. To optimize the various fabricated PIMs for their applicability in the removal of investigated pharmaceuticals.
3. To investigate the impact of applied electrical voltage through electromembrane extraction for the removal and preconcentration of investigated pharmaceutical.
4. To synthesis, characterise, and investigate the impact of silver nanoparticles for the modification of PIMs and investigate the impact of the silver nanoparticles in the PIM performance (for removal and preconcentration of investigated contaminants.

1.5 Outline of the thesis

This thesis is divided into five chapters. Chapter 1 comprises the background of the study, which entails the general introduction, problem statement, research hypothesis, and objectives.

Chapter 2 entails the general literature review about pharmaceuticals, their sources, effect, physicochemical parameters, brief information about conventional wastewater treatment and other advanced water treatment technologies and a comprehensive review about polymer inclusion membranes (PIMs), their various composition and functions, and the various applications of PIMs.

In Chapter 3, the different materials and methodologies used in the synthesis and characterisation of PIMs used for the pretreatment of various investigated contaminants before instrumental analysis. This chapter is divided into three parts. Part 1 investigated the removal and transport of ciprofloxacin antibiotics using two PIM base polymers (PVC and CTA), two carriers (Aliquat 336 and B2EHP), and DOP as the common plasticiser for both PIMs. The various synthesis and characterisation of the optimum PIMs were elucidated in this part. Part 2 highlights the pretreatment and preconcentration of sulfamethoxazole antibiotics using PIM made of CTA, Aliquat 3336 and DOP through an electromembrane extraction process. The different composition, synthesis, characterisation and conditions for the electromembrane extraction process were mentioned in this section. Finally, part 3 elucidates the pretreatment of diclofenac using PIM made of CTA, B2EHP with NPOE and DOP as plasticiser through a preconcentration experiment. The synthesis, characterisation, and condition for extraction and transport of the contaminants were mentioned in this section using silver nanocomposite PIM.

Chapter 4 gives detailed results and discussion of the thesis. Similarly, this chapter is compartmentalised into three parts, like chapter 3. Each part discusses the synthesis of the membrane (PIMs) and their corresponding composition. Characterisation of the fabricated membrane was discussed in the sections to determine the physicochemical stability of the membranes. Subsequently, the different membranes were investigated for efficiency, such as permeability, flux, removal and transport efficiencies to determine the optimum membrane for subsequent optimisation experiments. Furthermore, the various optimisations experiments such as the effect of pH, initial concentration of the contaminants, time of experiments, type of stripping solution and the concentration of stripping solution were discussed elaborately here.

In chapter 5, the study's overall conclusion was drawn, and future recommendations were given to better the application of PIMs as a useful alternative to other advanced wastewater treatment towards actually the dreams of sustainable development goals (SDGs) of providing potable water to all by 2030.

CHAPTER 2

LITERATURE REVIEW

2.1 Pharmaceuticals

Pharmaceuticals are a group of chemical compounds used to diagnose, treat, alter or prevent abnormal health or dysfunctional conditions in humans and animals. They are known as the most important group of emerging organic contaminants (EOCs) due to their environmental impact, physicochemical properties and universality (Bunting et al., 2021). When ingested, they are not completely metabolised in human or animal systems; hence, they are excreted in urine or faeces as the parent compound, metabolites, and conjugate compound (Garcia Rodríguez, 2016). The vast array of pharmaceuticals often administered and used include analgesics (pain killers), antibiotics, anti-depressants, anti-diabetics, β-blocker, lipid regulators (anti-lipemic), anti-epileptics, and X-ray contracts media (Olasupo and Suah, 2020).

2.2 Pharmaceuticals studied in this work

2.2.1 Analgesics

Analgesics are the most commonly used pharmaceutical for relieving pains. Upon ingestion, they act on the peripheral and central nervous systems to alleviate all pains present in the body of humans and animals caused by various illnesses or diseases. Examples of these pharmaceuticals include acetaminophen, acetylsalicylic acid, and the common non-steroidal anti-inflammatory drugs (NSAIDs). Although acetylsalicylic acids are reportedly not found in environmental samples, their corresponding metabolites (salicylic acid) has been discovered in different types of aquatic system (Garcia Rodríguez, 2016; Li, 2014; Świacka et al., 2021). NSAIDs (e.g., ibuprofen,

ketoprofen, diclofenac, naproxen, indomethacin, and phenazone) are a group of analgesics with pain reduction, inflammation reduction, and temperature reduction (antipyretic) properties. They were one of the most commonly used drugs of self-prescription despite their health-damaging effect on the digestive system when over dozed (Świacka et al., 2021). The analgesic of interest in this study is diclofenac. DCF has been reported to be present in the aquatic system globally with a record of ecological effects on aquatic animals (Bonnefille et al., 2018). According to the Ministry of Health Malaysia (2014), DCF is ranked as one of the top three most used drugs in Malaysia, inexpensive and readily available in retail pharmacies, leading to self-medication and abuse (Praveena et al., 2018).

2.2.2 Antibiotics

Antibiotics are pharmaceutical compounds used for treating and preventing diseases in human and veterinary healthcare. They have been widely used to increase feed efficiency, improve growth in livestock, and various aquacultural practices. Their fate and transport have been studied in various aquatic environments (Kovalakova et al., 2020). Their primary function is to prevent the growth of microorganisms like viruses, fungi, or bacteria. However, the unregulated use and release of various antibiotics in effluents of wastewater treatments have become a daunting public health challenge due to increasing resistance to antibiotics by naturally occurring bacterial (Michael et al., 2013; Suzuki et al., 2017).

The major category of antibiotics are tetracyclines, macrolides, quinolones, sulfonamides, and others. Macrolides (e.g., erythromycin, roxithromycin, azithromycin, clarithromycin, josamycine, spiramycin, and tylosin) are basic and lipophilic molecules that are commonly used in human and veterinary treatment of diseases. They are known

to have a bacteriostatic ability, which implies that they do not necessarily kill bacteria like most bacterial antibiotic drugs. Still, rather they inhibit the growth and multiplicity of most bacteria. However, in some cases, such as the high concentration of macrolides, they can also act like bacteria. Tetracyclines (e.g., chlortetracycline, oxytetracycline, tetracycline, doxycycline, and minocycline) are polyketide molecules with amphoteric properties similar to sulfonamides. They are alternatively known as "broad-spectrum antibiotics" due to their vast therapeutic application, especially in treating infectious diseases and as growth enhancers in animal feed. Sulfonamides (e.g., sulfamethoxazole, sulfamethazine, sulfadiazine, sulfathiazole, and sulfaguanidine) are a group of synthetic antibacterial compounds, which are the first set of chemotherapeutic pharmaceuticals to be discovered. They are important growth-promoting compounds in veterinary, with prophylactic and therapeutic properties. They also function as an important competitive antagonist in the fight against bacteria with an amphoteric property (Gao et al., 2018). Fluoroquinolones (e.g., ciprofloxacin, enrofloxacin, and norfloxacin) are synthetic antibiotics that have been routinely used in clinical treatment globally. Unlike other bacteriostatic antibiotics, they can kill a bacterial (bactericidal) by preventing bacterial DNA synthesis. They are derivatives of 3-quinolonecarboxylic acid popular for the aromatic fluorine substitution at the C-6 position (Hu et al., 2020).

Antibiotics have been widely reported in different environmental matrices, especially in the aquatic environment (Suzuki et al., 2017). The antibiotics of interest in this study are ciprofloxacin and sulfamethoxazole, and they have been reported in some aquatic systems in Malaysia. The Malaysian Ministry of Health identified CIP as one of the five commonly used antibacterial drugs for the treatment of Upper Respiratory Tract Infection (URTI) and Urinary Tract Infection (UTI) in Malaysia (Praveena et al., 2018). Furthermore, URTI is one of the frequently treated infections in

Malaysian hospitals, and it accounts for about 51% of all infection cases. Subsequently, there has been a need for an antibiotic prescription, especially ciprofloxacin, for URTI treatment due to its effectiveness. In the coming years, an increased amount of CIP and other quinolinone antibiotics are expected to double in different environmental matrices due to the COVID 19 global outbreak, which is also an upper respiratory tract infection. Hypothetically, individuals with slight URTI symptoms would most likely do self-medication using CIP or other related drugs before getting tested for the pandemic virus. On the other hand, the use of SMZ has been banned in some countries of the world due to the sulphur component present in it. And the amount of SMZ has reportedly decreased in the aquatic system but is still reportedly found in the aquatic environment in Malaysia (Praveena et al., 2018).

2.3 Physicochemical properties

The bioavailability of pharmaceuticals in an environmental media is dependent on some physicochemical properties of individual compounds like water solubility (Sw), octanol-water partition coefficient (K_{ow}), octanol water distribution coefficient (D_{ow}), henry's law constant (K_H), an acid dissociation constant (K_a). These properties have demonstrated relevance in the mobility of pharmaceuticals in different environmental compartments (Meffe and de Bustamante, 2014). Furthermore, the distribution, occurrence, and fate of pharmaceuticals in the environment and their physicochemical properties depend on certain environmental parameters such as temperature, pH, redox potential, water and soil composition, and organic matter (de Andrade et al., 2018). The physicochemical properties of each pharmaceutical and the aforementioned environmental parameters at a given time are crucial factors determining the bioconcentration of pharmaceuticals in an aquatic environment.

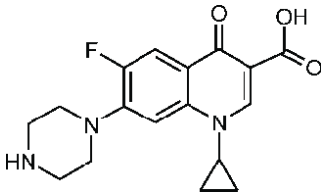
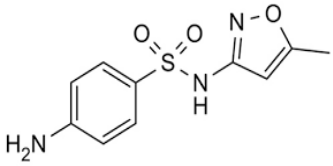
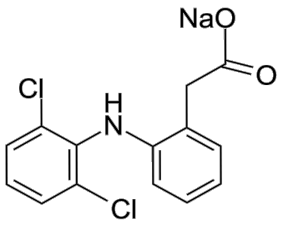
Generally, It has been reported by different authors that pharmaceuticals with K_{ow} < 2.5 are soluble in water; therefore, they are hydrophilic and polar (e.g., most antibiotics), while those with K_{ow} > 4 are more likely to be slightly soluble but regarded as hydrophobic; hence, the hydrophobic contaminants are more likely to adhere strictly to biosolids in wastewater treatments (de Andrade et al., 2018; Pal et al., 2010). The acid dissociation constant pKa, on the other hand, is the measure of an acid's strength for chemical reactions. It is expressed as the concentration of ionised compounds per concentration of unionised compounds (Zhang et al., 2014). Most antibiotic compounds have been reported to be ionisable and moderately soluble in water; therefore, they can occur as a charged or neutral molecule depending on the pH of their environment at a given time, while most analgesics are commonly anions in the pH range of 5-8 with lower tendency to be adsorbed on solid surfaces (Jansook et al., 2018; Zhang et al., 2014). The Henry's Law constant (K_H)is a critical determinant of contaminants' volatility. This partition coefficient is determined by the concentration of a compound in water to the concentration of the same compound in the air at equilibrium. Pharmaceuticals with a high K_H value would have a low water solubility value, low octanol-water partition value, and highly volatile. The K_H is also directly relative to the vapour pressure, molecular weight, and solubility of a pharmaceutical (Zhang et al., 2014). The physicochemical properties and structure of the investigated contaminants and some pharmaceuticals are illustrated in Table 2.1 and Table 2.2.

Table 2.1 Physicochemical properties of some pharmaceuticals.

Class of Pharmaceutical		Acronym	MW ($gmol^{-1}$)	Log Kow	pKa	Henry's coeff, air/water ($Pam3\ mol^{-1}$)
Antibiotics	Erythromycin	ERY	733.93	3.06	8.9	7.50×10^{8}
	Lincomycin	LIN	406.54	0.48	-	-
	Sulfamethoxazole	SMZ	253.27	0.48	5.5	3.91×10^{11}
	Sulfamethazine	SMT	278.33	0.9	7.4	-
	Ciprofloxacin	CIP	331.35	0.28	6/8.3	5.09×10^{19}
Analgesics/ anti inflammatory	Diclofenac	DCF	318.14	4.02	4.13	1.93×10^{10}
	Ketoprofen	KTP	254.3	3.12	4.45	8.67×10^{10}
	Ibuprofen	IBP	206.23	3.79	4.91	6.21×10^{6}
	Acetaminophen	ACT	151.17	0.27	9.4	2.63×10^{11}
	Naproxen	NPX	230.27	3.1	4.15	1.38×10^{8}

Data obtained from Sipma et al. (2010), Sahar et al. (2011), Hamid and Eskicioglu (2012), Sim et al. (2011), and Rivera-Jaimes et al. (2018).

Table 2.2 Structure and physicochemical properties of investigated pharmaceuticals in this study.

Group	Analyte	Structure	pKa	Log P
Antibiotic	Ciprofloxacin		pKa_1=6 pKa_2=8.8	0.28
	Sulfamethoxazole		pKa_1=1.85, pKa_2=5.6	0.89
Analgesic	Diclofenac		4.13	4.4

2.4 Occurrence and sources of pharmaceuticals

The aquatic environment remains the major reservoir for pharmaceutically active compounds due to their polarity in water. They are purportedly released into the aquatic environment from different sources like municipal sewage waste, hospital and industrial sewage systems, landfills, livestock, and various agricultural practices (Patel et al., 2019; Z. Yan et al., 2014). According to Lapworth et al. (2012), potential sources of pharmaceutically active compounds are categorised into point sources and diffused sources. Point sources such as industrial, hospital and municipal, and septic tank effluents contribute immensely to the load of pharmaceuticals and endocrine-disruptors in different environmental media, while non-point sources (diffuse sources) like runoffs from agricultural practices (animal waste and manure) and urban runoff from domestic wastes and various leakages from wastewater treatment plants also contribute to the amount of pharmaceuticals in the environment (Rivera-Jaimes et al., 2018).

The effluents from the various point sources are collected at the WWTP, where they undergo different treatments (physical, chemical and biological) before they are discharged into surface water bodies. At the same time, the non-point sources are often released into the groundwater aquifer, whilst others are attenuated naturally in the environment. Despite the concerted efforts by WWTPs to attenuate the pharmaceutical contaminant burden in the environments, they have been reportedly found in different environmental media such as in effluents of wastewater and surface water (Skees et al., 2018), in aquatic organisms (Núñez et al., 2017), groundwater (Yang et al., 2018), in plants (Madikizela et al., 2018), and biosolids like sewage sludge (Ekpeghere et al.,

2017). As a result of their solubility in water and low volatility, they are present in aquatic systems in extremely low concentrations, which makes sample preparation of pharmaceuticals a complicated one that requires efficient sample pretreatments and good instrumental analysis. Figure 2.1 illustrates the sources and possible routes of distributing pharmaceuticals, and endocrine-disrupting compounds in the environment, while Table 2.3 below highlights the occurrence of some pharmaceuticals and endocrine-disrupting compounds (ng/L) in some selected countries of the world relative to their sources.

2.4.1 Predictable No Effect Concentration (PNEC)

As a result of the varying concentrations of pharmaceuticals, endocrine disruptors, and other EOCs in different environmental matrices, the scientific community initiated the Predictable No Effect Concentration of an EOC, to check for potential toxicity of these contaminants in the environment. The Predictable No Effect Concentration (PNEC) is the concentration limit of a contaminant which serves as a threshold for determining potential effects in an ecosystem when exposed to such a contaminant. PNEC values are calculated by dividing the lowest no-observed-effect concentration (NOEC) for the most sensitive species in an environment by a safety factor. However, in the absence of NOEC value, PNEC values are estimated by determining the toxicity threshold, the lowest observable effect concentration, and minimal inhibitory concentration (Pal et al., 2010). In Table 1, of all of our investigated contaminants, residues of CIP have been found in concentrations beyond the acceptable PNEC concentration in surface water and wastewater in Asia and also in another wastewater in America; however other investigated contaminants are below the PNEC values.

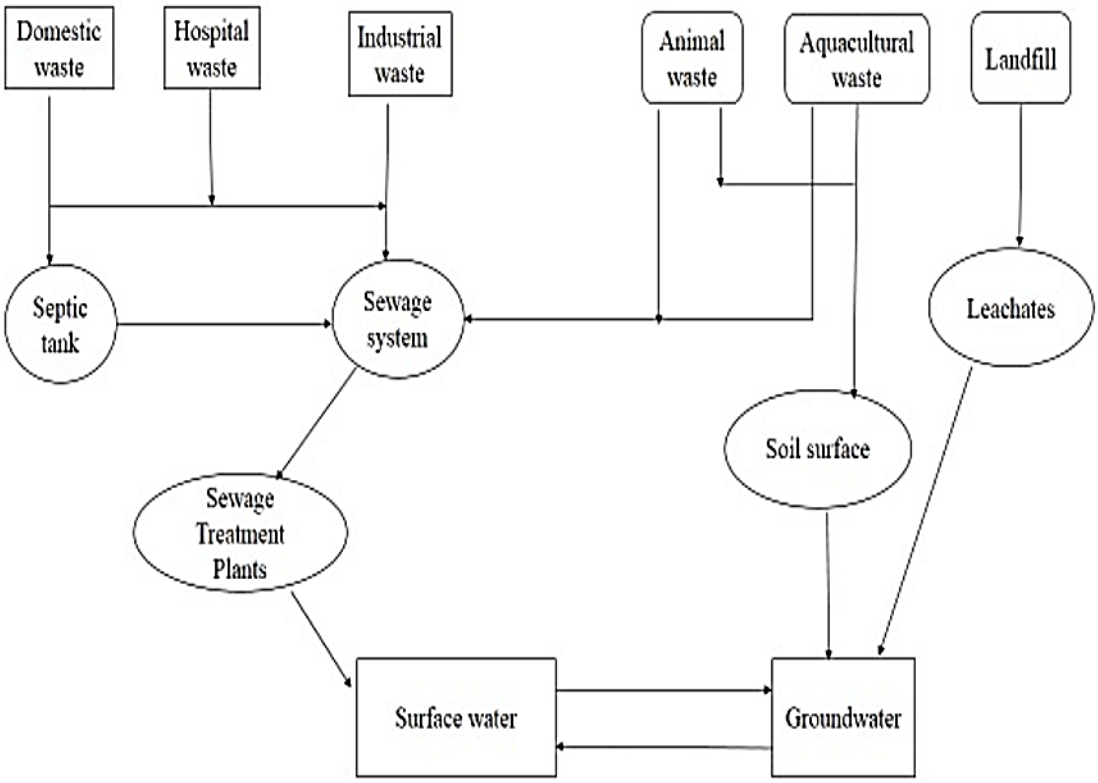


Figure 2.1 Schematic diagram of the different sources and occurrence of pharmaceuticals in the environment (Olasupo and Suah, 2020).

Table 2.3 Occurrence of some selected pharmaceuticals in the different aquatic environments around the world.

	Concentration (ng/L)									
	America			**Asia**			**Europe**			
Pharmaceuticals	WWTP	Surface water	Ground water	WWTP	Surface water	Ground water	WWTP	Surface water	Groundwater	Lowest PNEC (ng/L)
Analgesics/Anti-inflammatory										
Diclofenac	2363	1209		523	2.76		69.7	5.4	9.7	10000
Ketoprofen				58.2		4.1	458	3.4	2.8	15.6×10^{6}
Ibuprofen	1983	730		268.0	4.3	19.7	1596	5.5		5000
Acetaminophen	11600	3422	1890	51900	2.6	0.647	2463	14.7	10.3	9200
Naproxen	2600	3990	41900	12500	0.1	67.0	741	3.5	1.2	37000
Antibiotics										
Ciprofloxacin				246	112.40	0.519	221			20
Erythromycin				254.24	2.4	5.6	92.7			
Sulfamethoxazole	1143	173	170	2935.4	61.49	28.7	912	1.9	3.0	20000

Data compiled from Rivera-Jaimes et al. (2018), Skees et al. (2018), Fram and Belitz (2011), Kibuye et al. (2019), Schaider et al. (2014), Sim et al. (2011), Ashfaq et al. (2017), Chang et al. (2011), Yan et al. (2014), Praveena et al. (2018), Wee et al. (2019), He et al. (2018), Li et al. (2015), Peng et al. (2014), Lee et al. (2019), Santos et al. (2013), Vulliet and Cren-Olivé (2011), Teijon et al. (2010), Pal et al. (2010).

2.5 Impact of pharmaceuticals on the environment

Pharmaceuticals are ubiquitously present in different environmental compartments at a trace concentration ranging from ng/L to µg/L. The various natural attenuation processes and wastewater treatments have proven insufficient for removing pharmaceuticals in the aquatic environment due to their ability to resist various natural degradation and treatment processes. Hence, the continuous discharge of incompletely treated effluents from WWTPs to other aquatic environments like surface water has led to various ecotoxicological effects in the environment (Kar et al., 2018; Li, 2014). Thus, the direct toxicological effect of pharmaceutically active compounds on humans is poorly understood; however, the effect on aquatic life has been reported in different studies. Hence, special attention should be given to aquatic organisms feeling the direct impact of pharmaceutical accumulation in the aquatic environment, as they could also pose a potential risk to humans and other organisms across the food chain (Kar et al., 2018).

Most pharmaceuticals are soluble in water; therefore, aquatic organisms are the most susceptible to the toxicological effects of the contaminants. The effect of pharmaceuticals and endocrine compounds have been investigated in different species of aquatic organisms such as fishes, algae, mussels (Duarte et al., 2022; Gallego-Ríos et al., 2021; Johansson et al., 2014), and other non-aquatic organisms (Cuthbert et al., 2011; Plaza et al., 2022). Among the different aquatic organisms, fishes are the most studied for pharmaceutical exposure due to their direct link to other higher organisms in the food chain. The toxicological effect of pharmaceuticals like carbamazepine, triclosan, diclofenac, and ibuprofen have been widely studied in different species of fish. Li et al. (2011) reported on the acute toxicity effect of carbamazepine on juvenile

rainbow trout. The authors recorded a significant toxicological effect in different fish parts, especially in the antioxidant responses in tissues, blood, and liver.

Similarly, the effect of diclofenac, triclosan, and carbamazepine was investigated on Japanese Medaka's feeding behaviour and swimming speed for nine days. After the fifth day, sudden behavioural changes were recorded. According to the authors, changes in feeding habit was attributed to the combined effect of carbamazepine and diclofenac, while swimming speed was supposedly reduced due to carbamazepine and triclosan contamination (Nassef et al., 2010). However, pharmaceuticals like ibuprofen which belongs to the class of analgesics was experimentally reported to have no significant effect when exposed to fathead minnow and channel fish (Nallani et al., 2011). In some cases, the parent pharmaceutically active compounds were not detected in the aquatic organism; however, they were reported to have been metabolised into more harmful conjugate compounds found in higher concentrations. According to Michael et al. (2013), the concentration of metabolites of pharmaceuticals found in influents of WWTP was 2.5-3.5 times higher than the concentration of their various parent compounds. Thus, hydroxydiclofenac (an oxidative metabolite of diclofenac) was reportedly found in the bile of female rainbow trout subsequently causing severe damage to the intestinal tract (Dobrin et al., 2013; Mehinto et al., 2010). Also, the effect of steroid estrogenic hormones like 17-ET, a common contraceptive drug attributed to the feminisation of fishes and alteration of DNA at low concentration (Li, 2014).

Apart from the various fish species, the adverse ecological effects of pharmaceutically active compounds have also been investigated in algae. A high tolerance level to an antimicrobial agent like triclosan by periphyton microalgae and bacteria was reported by Johansson et al. (2014). Similarly, Vannini et al. (2011) in

their study reported the toxicological effect of carbamazepine and diclofenac on the chloroplast of the investigated algae, which subsequently affects the photosynthetic abilities of the alga community. Furthermore, ciprofloxacin, sulfamethoxazole, and erythromycin were reported to have caused toxic effects to the photosynthetic apparatus of algae (Liu et al., 2011). To this end, it is safe to assume that the presence of pharmaceutically active compounds in the aquatic system has compromised the survival of algae, hence leading to subsequent death in the algae community, which could, in turn, create problems to the ecosystem such as eutrophication and disruption in the food chain (Li, 2014).

The effects of pharmaceutically active compounds are not limited to aquatic organisms but also terrestrial animals. In a study conducted by Cuthbert et al. (2011), the effect of diclofenac was reported in the species of Gyps Vultures that are peculiar to South Asia. The authors linked the rapid extinction and depopulation of Gyps vulture in India to the residual amount of diclofenac found in carcasses of livestock consumed by the vultures. Carter et al. (2016) also investigated the effect of pharmaceuticals on soil organisms like earthworms. Their study investigated the uptake of some pharmaceuticals by earthworm and reported a potential exposure and toxicity of organisms higher in the food chain.

2.6 Treatments of pharmaceuticals in the aquatic system

2.6.1 Role of conventional wastewater system

The various processes that facilitate the removal of pharmaceuticals in WWTPs are influenced by the type of technology used for wastewater treatment, the characteristics of the wastewater, operational settings (sludge retention time), environmental parameter (temperature, dilution, and natural attenuation), and the

physicochemical properties of the contaminants (Garcia Rodríguez, 2016). According to research, the traditional processes implored in wastewater treatment are not designed to remove most pharmaceuticals and other EOCs (Verlicchi and Zambello, 2014). Thus, most pharmaceuticals still find their way into different environmental compartments, mostly aquatic environments (e.g., surface water and groundwater), even after wastewater treatments. Depending on the treatment process employed in conventional WWTP removal, the efficiency of removal of pharmaceuticals can range between 20-90 % after treatment (Murray et al., 2010). The removal of contaminants in conventional wastewater treatments involves various physical, biological, and chemical processes, respectively (Murray et al., 2010). In a typical conventional wastewater treatment plant, removing environmental waste involves three stages Primary, Secondary, and Tertiary treatments.

2.6.1(a) Primary treatment

The primary stage of wastewater treatment is a preliminary stage of filtration and separation of wastewater components based on sizes, otherwise known as the screening of larger objects, suspended solids, and organic matter. After a successful screening, solid materials are trapped, followed by subsequent sedimentation by gravity to remove suspended solids. The sedimentation process is aided by coagulation and flocculation, which involves the addition of metal salts to produce a chemical precipitate. Suspended solids are agglomerated to compact ball-like shape solid, followed by filtration and decantation (Khasawneh and Palaniandy, 2021; Spellman, 2013). In a typical primary treatment, pharmaceuticals and endocrine disruptors with log K_{ow} >4 have a high propensity to be adsorbed to biosolids, e.g., diclofenac, bezafibrate, gemfibrozil, ibuprofen, and estrogenic hormones and are removed by