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DOCTORAL THESIS

Evaluation of the occurrence, degradation, and ecotoxicological significance of pharmaceuticals as emerging contaminants of concern in wastewaters and surface waters of the urban area in Costa Rica.

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LIST OF ABBREVIATIONS

Abbreviation	Description
AC	activated carbon
ASP	activated sludge processes
AMR	antimicrobial resistance
AOPs	advanced oxidation processes
ARGs	antibiotic resistance genes
CCL	contaminant candidate list
CWs	constructed wetlands
D	diffusion coefficient of the analyte in the diffusive gel
DBL	diffusive boundary layer
DOC	dissolved organic carbon
DOM	dissolved organic matter
EC50	toxicity values for the median effective concentration
ECs	emerging contaminants
EDCs	endocrine-disrupting chemicals

E2	17β-estradiol
EE2	17α-ethinylestradiol
EPA	US Environmental Protection Agency
EU	European Union
Δg	diffusion layer thickness
GAC	granular activated carbon
GAM	Great Metropolitan Area
HLB	hydrophilic-lipophilic balance
HRMS	high resolution mass spectrometry
HRT	hydraulic retention time
Kd	solid-water distribution coefficient
Kow	octanol-water partition coefficient
LC50	toxicity values for the median lethal concentration
MT	17α-methyltestosterone
MBRs	membrane bioreactor systems
MLSS	mixed liquor suspended solids
NF	nanofiltration
NOM	natural organic matter
NSAIDs	non-steroidal anti-inflammatory drugs
o-DGT	organic-diffusive gradients in thin-films

PAC	powdered activated carbon
PCs	pharmaceutical contaminants
PEDOT	Poly(3,4-ethylenedioxythiophene)
pKa	negative log of acid dissociation constant
POCIS	polar organic chemical integrative sampler
PPS	polar passive samplers
PRC	performance reference compound
QSAR	Quantitative Structure-Activity Relationship
QTof-MS	quadrupole time of flight mass spectrometry
RO	reverse osmosis
ROS	reactive oxygen species
Rs	compound sampling rate
SPE	solid phase extraction
SRT	solid retention time
TWA	time-weighted average
USA	United States of America
UV254	ultraviolet light at 254 nm
WL	Watch List
WHO	World Health Organization
WTPs	water treatment plants

WWTPs wastewater treatment plants

DECLARATION OF AUTHENTICITY

I, Aura Ledezma Espinoza, student in the program of the Doctorado en Ciencias Naturales para el Desarrollo, declare that the doctoral thesis that I submit for its presentation and defense entitled "Evaluation of the occurrence, degradation and ecotoxicological significance of pharmaceuticals as emerging contaminants of concern in wastewaters and surface waters of the urban area of Costa Rica", evaluated by my thesis advisory committee integrated by PhD. Floria Roa Gutiérrez (thesis director), PhD. Charles Wong (advisor) and PhD. Luis Gerardo Chaves Barquero (advisor) is original, and that all sources used for its completion have been properly cited. I have not presented this material, in whole or in part, as a thesis at this or any other institution.

August 2023

Cartago, Costa Rica.

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«Si he llegado a ver más lejos que otros, es porque me subí a hombros de gigantes»

Isaac Newton

DEDICATION

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ABSTRACT

The widespread occurrence of pharmaceuticals in the environment has driven many countries to develop studies on pharmaceutical contamination and start monitoring programs to determine the baseline data of their water resources, strategies of water management and assessment of the environmental risks and potential exposure to human health and aquatic ecosystems. In this dissertation work, an insight of contamination levels with selected pharmaceuticals was first obtained from the analysis of impacted water systems that included the wastewaters of a hospital and a wastewater treatment plant, and the surface waters of the Virilla and Torres rivers from the Great Metropolitan Area in Costa Rica. Passive sampling with organic-diffusive gradients in thin-films (o-DGT) and quadrupole time-of-flight high resolution mass spectrometry was applied to detect and quantify time-weighted-average concentrations of pharmaceutical contaminants in the water samples from the urban sampling sites. Measured concentrations ranged from 0.012 to 3610 ng L^{-1} among the studied pharmaceuticals (atenolol, sulindac, levofloxacin, carbamazepine, sulfamethoxazole, sulfapyridine and sulfamethazine). All target molecules were ubiquitously detected in the surface waters and the wastewaters of the studied sites. In addition, a risk assessment was done of target pharmaceuticals for single parent compounds and mixtures in aquatic media. It was found that at concentration levels and exposure times analyzed in this study, sulfamethoxazole, levofloxacin and sulindac posed a potential risk to aquatic organisms. Overall, the results demonstrated the occurrence of varied class of pharmaceuticals during the long period of sampling, however additional monitoring studies are recommended to well-assess the actual effects of these compounds in the sampled urban waters. To our knowledge, this is the first study to assess the occurrence and risk assessment of sulindac on aquatic ecosystems using o-DGT passive sampling.

Second, in this research, a fundamental study on elucidation of kinetic behaviour and photodegradation pathways in water for sulindac direct photolysis was developed. A novel kinetic mechanism was proposed in which sulindac exhibits a consecutive reaction pathway, with pseudo-first order kinetics for rapid and reversible *Z* to *E* isomerization, to undergo after photoequilibrium, a second-order degradation of the isomers in the presence of the new photodegradation products. Two novel and major byproducts were identified, and the results demonstrated a greater persistence of sulindac at relevant environmental conditions of UV-A and pH 7, with a degradation pathway mainly photoinduced, enhanced by acidic

conditions. Furthermore, this chapter demonstrated an approach to carry out kinetic studies under challenging conditions.

The previous findings helped to better understand the fate and presence of selected pharmaceuticals in the aquatic matrices to define suitable treatment systems. A novel irradiated cellulose PEDOT composite was prepared as photocatalyst to remove pharmaceutical contaminants under ambient conditions. The I-Cell-PEDOT composite enhanced the photodegradation of sulindac and carbamazepine from neutral aqueous system under UV-A radiation, reaching photocatalytic removals of 89% for sulindac and 30% for carbamazepine within 7 h of treatment. The new treatment showed its potential to be used as an option for advanced removal processes of pharmaceutical pollutants from water sources.

Monitoring programs in natural and treater waters as well as fundamental studies on fate of pharmaceuticals and removal treatment technologies are needed to better understand the pollution situation in the aquatic environment, thus this research was aimed to generate knowledge about pharmaceutical contamination and its evaluation in waters impacted by urban activity in the Great Metropolitan Area of Costa Rica, to contribute to the decision making and sustainable water management for better protecting of the environment and public health.

KEYWORDS

Emerging organic contaminants; pharmaceuticals; o-DGT; passive sampling; risk assessment; photolysis; photocatalysis; gamma irradiation; PEDOT.

1. INTRODUCTION

Human life and natural ecosystems depend on the availability of clean water around the world. However, global development has increased anthropogenic pollution in aquatic environments, particularly with new classes of pollutants called emerging contaminants (ECs) (Xie et al., 2022). Broadly, these contaminants are defined as any synthetic or naturally occurring compounds not commonly monitored in the environment, largely unregulated, and that may cause adverse ecological and/or human health effects even at trace levels (X. Tong et al., 2022). Among these new pollutants, pharmaceuticals represent a major concern. Although the use of pharmaceuticals has benefited modern life, its continuous introduction in the environment has also resulted in the ubiquitous occurrence of active pharmaceutical ingredients in natural ecosystems at µg to ng per liter levels (Fent et al., 2006; Gogoi et al., 2018). Thus, initiatives to reduce the environmental pressure have been taken. Complementary approaches include first, finding solutions before the drugs are released into the environment by addressing the production, prescription, distribution, and use of medicines; and second, implementing actions once the pollutants are in the environment, such as monitoring, treatment, and remediation (Courtier et al., 2019).

Pharmaceuticals are essential in activities such as human and veterinary medicine, agriculture, aquaculture, and poultry industries. Nonetheless, their active pharmaceutical ingredients may pose a substantial risk to non-target organisms, particularly in aquatic media (Chaturvedi et al., 2021). Wastewater, surface run-off, and agricultural run-off can be a source of entry into the environment and contaminate drinking water supplies with these drugs in the form of parent compounds, metabolites and transformation products (Richardson & Kimura, 2017). Pharmaceutical contaminants (PCs) show wide variation in function, chemical structure, and physico-chemical properties, making it difficult to generalize their behaviour, persistence, or impact in the environment (Tahar et al., 2018). Some pharmaceuticals have been related to environmental effects such as bioaccumulation in the food chain (Puckowski et al., 2016), chronic impacts on biodiversity, endocrine disruption, and antimicrobial resistance (Comber et al., 2018; J. Xiang et al., 2018). Consequently, knowledge of the sources of contamination, concentrations in water bodies, and fate of drug residues are necessary to determine the toxic impact on exposed living organisms (Riva et al., 2019).

Regarding removal of pharmaceutical residues from aquatic matrices, increasing research on new robust and efficient treatments have been done to address environmental pressure from these contaminants. Pharmaceutical pollutants found in natural and urban waters differ widely in their physico-chemical properties, therefore an engineered system must include different approaches for treatment (K. Sharma et al., 2021). Conventional wastewater plants include a mixture of physical, chemical, and biological procedures, as well as sewage removal activities to eliminate insoluble contaminants and soluble pollutants (Rathi et al., 2021). However, those approaches are generally not designed to remove pharmaceutical residues from wastewater and surface and drinking water (Rodriguez-Narvaez et al., 2017), hence, hybrid systems that include biological and advanced methodologies have been developed to improve elimination (Carlson et al., 2013; Saidulu et al., 2021). Among those methodologies, advanced oxidation processes such as heterogeneous photocatalysis and Fenton-like processes, stand out as the most efficient to remove pharmaceuticals from water matrices (Nava-Andrade et al., 2021).

Many studies on pharmaceuticals in the environment have been conducted in high and middle-income countries. However, developing countries are running behind, trying mostly to identify and quantify pharmaceuticals in environmental samples (aus der Beek et al., 2016; K'oreje et al., 2016). Analytical and screening techniques for detection and quantification of pharmaceuticals in aquatic matrices represent a major challenge. Many difficulties include a high number of potential emerging pollutants with their relevant transformation products; changes in production of drugs, consumption and disposal; the occurrence and chronic effects at low environmental concentrations, and the corresponding need for sophisticated analytical methods with correspondingly low detection limits and high selectivity (Geissen et al., 2015)

Given the concerns about the potential harm of emerging pollutants to human health and wildlife across the globe, internationally recognized initiatives have been conducted to prioritize emerging pollutants that deserve monitoring or need to be banned. Among these efforts, the US Environmental Protection Agency (EPA) established guidelines to identify unregulated environmental contaminants in drinking water, and the European Union (EU) published priority substances and environmental quality standards for surface water (Zhong et al., 2022). Furthermore, the United Nations (UN) declared Sustainable Development Goals, aimed at taking actions on improving water and sanitation management (UN, 2015). Although information on emerging contaminants has been obtained mostly from high-

income regions, all reports contribute to the ability of decision makers around the world to define mitigation strategies for more sustainable water policy, health care, and environmental protection (Sousa et al., 2019).

According to the subjects above discussed, pharmaceuticals contaminants in aquatic media are the main goal of interest in this dissertation. This research focused on the study of the occurrence, transformation, potential risks and removal of targeted pharmaceutical residues as emerging contaminants in wastewaters and surface waters from the urban area in Costa Rica. Briefly, in this introduction chapter, topics related to the contamination with pharmaceuticals are presented for contextualization. Background on the main sources and fate of PCs is discussed to better understand their occurrence in aquatic environments. Potential ecotoxicological effects on non-target receptors that may result from chronic exposure to PCs are noted considering the bioactivity of parent drugs and their metabolites and transformation products. Details of some of the most recognized treatments for the removal of pharmaceuticals from water such as activated carbon adsorption, AOP-based technologies, and hybrid processes are included. Moreover, information on passive sampling and analytic techniques is addressed considering the high robustness, selectivity, and sensitivity needed to determine pharmaceuticals as polar contaminants in aquatic environments. Finally, brief examples of integrated actions among stakeholders from public, authorities and scientific community are presented as part of the holistic management that involves the pharmaceutical contamination in water sources.

1.1. SOURCES AND FATE OF PHARMACEUTICALS IN AQUATIC ENVIRONMENTS

Anthropogenic activities have contributed to the pollution of water with pharmaceutical active residues at concentrations generally in the ng L^{-1} and µg L^{-1} range (Sangion & Gramatica, 2016). In general, different therapeutic group of drugs are emitted into natural environmental waters from effluents of sewage treatment plants as the primary source. Other sources include the pharmaceutical industry for human, veterinary, and agriculture use, as well as hospital wastewater discharges, landfills, veterinary medicine run-off, livestock breeding, and septic systems (Destrieux et al., 2017; Fekadu et al., 2019). Particularly, septic tanks used in low-income regions remain as important sources of groundwater pollution, at locations where water tables are shallow and aquifers have high transmissivity (Lapworth et

al., 2012). A schematic view of the possible pathways and toxicological effects of PCs in the aquatic environment has been depicted in Figure 1.

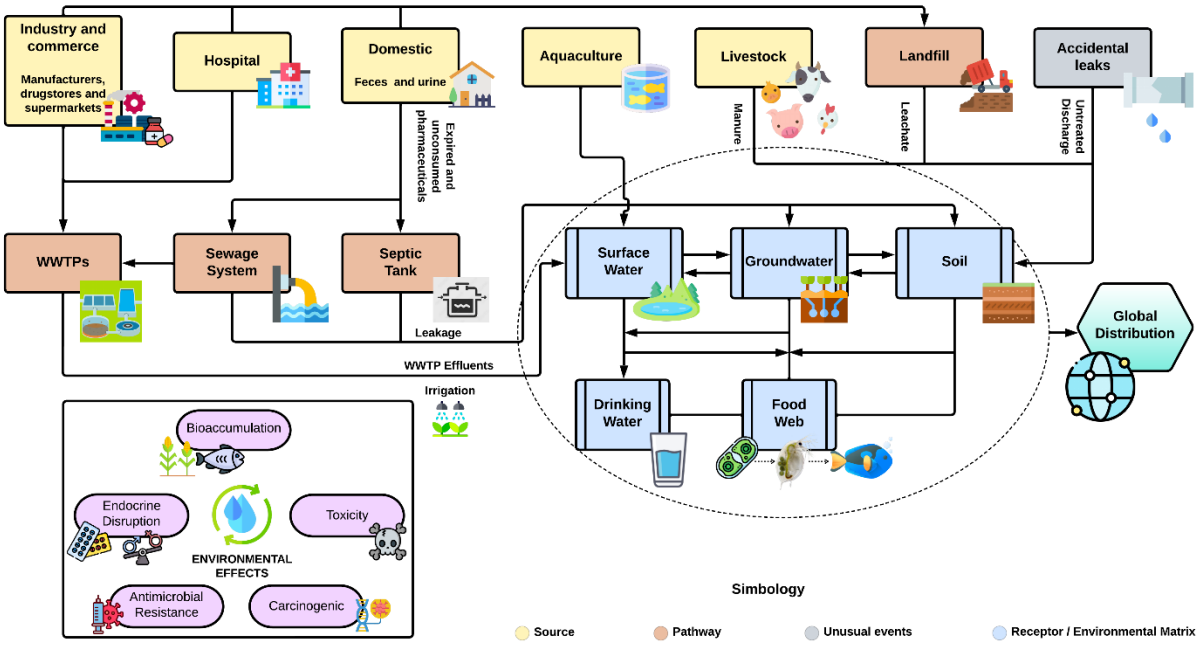

Figure 1. Potential sources, pathways, and toxicological effects of pharmaceuticals contaminants in the environment. (Own work).

The occurrence of these drugs and their transformation products are dependent upon various factors that include temporal and spatial variations. Differences in environmental occurrence could depend on persistence of the individual compound, production rate, type of waste received, direct discharge of residues, population size, excretion rate, water consumption per person and day, the size and efficiency of wastewater treatment plants (WWTPs), and climatic conditions like rainfall, temperature and sunlight (Kapelewska et al., 2018). Hence, to predict their environmental fate, is necessary to recognize the proper bioactivity, understand its biodegradability, conjugation, deconjugation, metabolic pathways, persistence, and sorption (Patel et al., 2019).

The fate of the pharmaceuticals in aquatic systems depends on their physico-chemical properties such as Kow (n-octanol water distribution coefficient), Kd (solid-water distribution coefficient), pKa (acid dissociation constant), solubility index and environmental factors such temperature, pH, salinity level, oxygen conditions, and humus content (Ebele et al., 2017;

Lapworth et al., 2012; Schwarzenbach, 2002). Many pharmaceuticals are polar and hydrophilic molecules (log Kow <5) with moderate solubility in water (Quesada et al., 2019). Many drugs are ionizable (e.g. acids, bases and zwitterions), and depend on the pH of the medium for degradation (Berthod et al., 2016), while others are non-ionizable and independent on the pH (Abou-Taleb et al., 2020; Tiwari et al., 2017). Mostly, these drugs have molecular mass ranges of 500/1000 Da and their complex structures may make degradation more challenging (K. Sharma et al., 2021).

After consumption, pharmaceuticals are metabolized within the body. Followed by their excretion into wastewaters, the parent drugs and metabolites (often excreted as non-conjugated and conjugated polar metabolites) undergo biological and chemical transformations (Fent et al., 2006; Rehman et al., 2015). Among these transformations, the most relevant mechanisms to control the fate of PCs in aquatic systems are biotransformation, sorption, and photolysis (Fent et al., 2006; Koumaki et al., 2015; Lapworth et al., 2012; Maculewicz et al., 2022; Pal et al., 2010). Three possible fates of the compounds in the environment and treatment plants include (1) complete mineralization to water and carbon dioxide via biological and chemical reactions, (2) sorption or retention upon the sediments or sludge, most often observed with lipophilic and difficult to degrade substances, and (3), transformation to more hydrophilic compounds and eventual discharge either as the parent compound or conjugate product into receiving waters (Fatta-Kassinos et al., 2011; Patel et al., 2019; Tijani et al., 2016).

The mobility of PCs in the environment and retention onto sediments or sludge is often based on the log Kow, Kd and pKa. For instance, compounds that remain in the aqueous phase tend to be more mobile through the WWTP and into nearby surface waters, while compounds held on sludge may end up in landfills or used as fertilizer, and may thus be a factor in terrestrial contamination (L. H. M. L. M. Santos et al., 2010). A simple approach suggests that usually pharmaceuticals with high log Kow (>5) tend to be more easily removed from aqueous matrix since are preferably sorbed to soils and sediments; while those compounds with low log Kow (<2.5) tend to remain in the water column (Christensen et al., 2022; Li, 2014; Patel et al., 2019). However, the behaviour of pharmaceuticals can be more complex than that, and sorption may be affected by factors such as the type and amount of organic matter in the particulate phase, interaction with inorganic surfaces such as clay minerals and ionization degree of compounds (Martínez-Hernández et al., 2014; Williams et al., 2006). At neutral pH, acidic pharmaceuticals, such as ibuprofen and

diclofenac, are in their negatively charged form, and therefore tend to occur mainly in the dissolved phase in the wastewater, while basic pharmaceuticals and zwitterions may be more sorbed to sludge, since at ambient pH values, natural organic matter (NOM) is negatively charged primarily due to the presence of carboxylic acid groups (Martínez-Hernández et al., 2014; Schwarzenbach, 2002). For example, atenolol, with low log Kow value, is not expected to adsorb greatly to the particles under the simple approach of Kow, but to dissociate in the aqueous phase (Couto et al., 2019), nevertheless it has been shown that the drug can be more sorbed onto a predominantly negatively charged sediment surface (Martínez-Hernández et al., 2014). In addition, even when the fluoroquinolone antibiotics ciprofloxacin and ofloxacin exhibit hydrophilic characteristics (log Kow <2.5), they are frequently found to have a high sorption potential onto sludge (Kd>500 L kg^{-1} MLSS), mainly attributed to electrostatic interactions (Tran et al., 2018).

Photolysis is a major abiotic transformation processes that may reduce concentrations of PCs in the environment and result in partial degradation or mineralization of these compounds (Challis et al., 2016). The extent of photodegradation depends on the intensity of solar irradiation, water depth, organic matter composition, eutrophic conditions, latitude, and seasonality (Ebele et al., 2017). The photochemical pathways that might take place in surface aquatic systems are divided in two mechanisms: direct and indirect photolysis. The principle of direct photolysis is the absorption of light at wavelengths present in sunlight (λ > 290 nm) by the compound (Koumaki et al., 2015). Meanwhile, indirect photolysis occurs when photosensitizers present in aquatic media, such as NOM, humic substances, and nitrate/nitrite absorb light and produce various reactive intermediates such as singlet oxygen ($^1O_2$), hydroxyl radical ($HO^\bullet$), peroxy radicals ($^\bullet OOR$), and DOM* (dissolved organic matter*), that subsequently react and transform the compound (Lee et al., 2014; Trawiński & Skibiński, 2016). Most non-steroidal anti-inflammatory drugs (NSAIDs) and endocrine-disrupting chemicals (EDCs) have been found to be photoactive due to their structural composition which allows them either to directly absorb solar radiation or indirectly react with radicals generated by the solar irradiation of photosensitizers in water (Koumaki et al., 2015).

Challis et al. (2014) described two major factors to predict direct photolysis: the rate of light absorption, and the quantum yield. The quantum yield is a characteristic parameter of each compound that denotes the fraction of the excited molecules of the compound that react by the absorption of a photon (Schwarzenbach, 2002), defining how efficiently a compound

degrades upon absorption of light (Lu et al., 2015). Quantum yield in many cases can be considered approximately wavelength independent, at least over the wavelength range of a given absorption band, corresponding to one individual electronic transition. (Schwarzenbach, 2002). Therefore, it serves as a much better predictor of direct photolytic fate when compared across studies than just rate constants and half-lives, which depend on the specific light conditions used (Challis et al., 2014). Basic direct photolysis experiments are conducted to obtain a (pseudo) first-order decay curve of the chemical in pure laboratory water using different light sources from which direct photolysis rate constants and half-life can be determined. More complex calculations are needed to determine values of quantum yields.

1.2. OCCURRENCE OF PHARMACEUTICALS IN WATERS

The occurrence of pharmaceutical pollutants has been extensively reported in freshwater ecosystems, wastewaters and even drinking water at concentrations ranging from ng L^{-1} to several hundred of μg L^{-1} (Bai et al., 2018; Eslami et al., 2015; González-González et al., 2022; Wilkinson et al., 2017). Although the marine environment is the last receiver of the continental contamination, it has not been investigated as much compared to freshwater systems (Branchet et al., 2020). In addition, most such scientific reports have been focused on North America, Europe, China, and India, leaving behind the countries of Africa, and Central and South America (Reichert et al., 2019).

The variations in the occurrence patterns of pharmaceuticals could be attributed to several reasons, including environmental and socioeconomic factors such as (i) human population size and distribution along with age distribution (demography), (ii) accessibility of health facilities (usage and consumption patterns and price regulations), (iii) the manufacturing sector's presence and size, (iv) available sewage treatment systems and their connectivity, (v) the environment in which effluents are received (natural attenuation processes), and (vi) availability and effectiveness of regulation guidelines (Khasawneh & Palaniandy, 2021; Patel et al., 2019).

The most commonly reported pharmaceuticals in drinking water and wastewaters include: fluoxetine, lipid-lowering drugs, antiacids, ciprofloxacin, diclofenac, steroids, antibiotics, analgesics, acid clorfibric blockers, anti-inflammatory drugs, stimulants, salicylic acid,

antidepressants, and propranolol (Khan et al., 2022). Among them, NSAIDs are predominant and widely reported in monitoring studies (Biel-Maeso et al., 2018; Ledezma-Espinoza et al., 2021), followed by the antibiotics and the antiepileptic carbamazepine, which has been pointed as the most detected drug in surface waters (Quesada et al., 2019).

PC concentrations consistently show the highest levels in wastewater and decrease from surface water to drinking water (Gomes et al., 2017; Tijani et al., 2016). Montes-Grajales et al. (2017) reviewed that 64 PCs were detected globally in WWTPs between 1996 and 2016, even in the Antarctic. Parida et al. (2021) summarized reports of selected PCs in influents of WWTPs worldwide, and noted that in Asia, the maximum reported concentrations for most of the PCs were obtained from South Korea and India, which included the antibiotic trimethoprim (162 000 ng L^{-1}), antiepileptic carbamazepine (21 600 ng L^{-1}) and the β-blocker atenolol (294 700 ng L^{-1}). The authors also added that a concentration greater than 620 000 ng L^{-1} of paracetamol was detected in Portugal and that atenolol was the most reported β-blocker in countries from Europe and Asia.

Yang et al. (2017) compiled studies in Spain that showed maximum concentrations in raw waters of WWTPs for sulfamethoxazole (149 ng L^{-1}), carbamazepine (215 ng L^{-1}), clofibric acid (20 ng L^{-1}), gemfibrozil (326 ng L^{-1}), 17α-ethinylestradiol (EE2, 97 ng L^{-1}), diclofenac (316 ng L^{-1}), and ketoprofen (250 ng L^{-1}). In another literature survey, Tran et al. (2018) reported geographic data from effluents of WWTPs. Concentrations of selected NSAIDs such acetaminophen, ketoprofen and naproxen reached highest levels up to 2570 ng L^{-1} (Asia), 62 000 ng L^{-1} (North America) and 33 900 ng L^{-1} Europe. Additionally, antibiotics were detailed such as trimethoprim (37 000 ng L^{-1}) in North America, and ofloxacin in Asia and Europe (>7000 ng L^{-1}). Moreover, Ebele et al. (2017) highlighted studies about wastewater reuse. The author mentioned that in Mexico, a study demonstrated the pollution of wastewaters for the irrigation with ibuprofen (742-1410 ng L^{-1}), naproxen (7270-13 600 ng L^{-1}), diclofenac (2050-4820 ng L^{-1}) and gemfibrozil (detected).

Regarding surface waters, Fekadu et al. (2019) concluded that the most measured PCs in Europe and Africa were the antibiotics sulfamethoxazole, clarithromycin and trimethoprim; the antiepileptic carbamazepine; the NSAIDs diclofenac, ibuprofen, naproxen, acetaminophen, ketoprofen, and the antidepressant venlafaxine. All compounds showed levels greater than the available ecotoxicity endpoints in both continents, and were considerably higher in African countries (by up to 20 000-fold) than those at European sites. Ebele et al. (2017) commented on the presence of glucocorticoids (a class of steroid

hormones) in a river from the United Kingdom, where their concentrations were found to be higher (30-850 ng L^{-1}) than those found for common estrogens such as EE2. According to the authors, glucocorticoids, which can be endocrine-disrupting pharmaceuticals at those concentrations, had the potential to have adverse effects to aquatic biodiversity. In addition, Li et al., (2014) consulted several studies to report the occurrence of high frequently detected PCs in rivers and canals from New Jersey and Canada. Carbamazepine (735 ng L^{-1}), naproxen (555 ng L^{-1}), sulfamethoxazole (170 ng L^{-1}), ciprofloxacin (77 ng L^{-1}) and trimethoprim (145 ng L^{-1}) were measured over recent years.

For ibuprofen, nationwide studies in the United States (USA), Europe, and Asia have reported high detection frequency, with concentrations ranging from 7 to 837 ng L^{-1} in groundwater in Taiwan, 92 ng L^{-1} in groundwater in Serbia, and up to 242 ng L^{-1}, 1320 ng L^{-1}, and 4.98 ng L^{-1} in surface waters from China, Portugal, and USA, respectively (Patel et al., 2019). Meanwhile, Yang et al. (2017) noted, based on studies in 14 countries across Europe, the Middle East, North America, and Asia, that the five most commonly reported PCs in groundwater, with their respective mean concentrations, were carbamazepine (5 µg L^{-1}, n = 23), sulfamethoxazole (252 ng L^{-1}, n = 15), ibuprofen (1.5 µg L^{-1}, n =14), caffeine (9.8 µg L^{-1} n = 14), and diclofenac (121 ng L^{-1}, n = 11). The authors also emphasized that according to a national survey of pharmaceuticals in the USA, sulfamethoxazole was one of the most frequently detected emerging contaminants (23%, n=47) in groundwater samples across 18 states.

Few studies have investigated the environmental occurrence in middle and low-income countries, most of them are conducted in high-income regions (Cristina et al., 2022). Developed countries contribute three to ten times higher (50 to 150 g), to the world-wide annual per capita consumption of drugs; hence, it can be expected that the raw sewage from these regions contains a larger amount of pharmaceutical compounds (Luo et al., 2014). Furthermore, high occurrence is exacerbated by inefficient sewage treatment processes. In Latin America, Brazil and Mexico have conducted most of the environmental monitoring work for contaminants of emerging concern, with pharmaceuticals being the most common pollutant groups noticed (de Oliveira et al., 2020). According to Peña-Guzmán et al. (2019), 17β-estradiol (E2) and EE2 were some of the most reported PCs in Latin America between 1999 and 2018. Within those investigations, the highest concentrations in urban water per country were diclofenac (103 ng L^{-1}, Uruguay), levothyroxine (54 980 ng L^{-1}, México), clorfibric acid (250 000 ng L^{-1}, Chile), ibuprofen (625 000 ng L^{-1}, Brazil), and

acetaminophen (46 600 ng L^{-1}, Colombia). Moreover, maximum concentrations of EE2 (798 ng L^{-1}) were reported in water treatment plants (WTPs), and ibuprofen (625 000 ng L^{-1}) was present in drinking water supplied by groundwater.

In another investigation, Botero-Coy et al. (2018) exemplified the inefficient removal of WWTPs in Colombia, were antibiotics such as ciprofloxacin, norfloxacin and azithromycin, and drugs for high pressure such as losartan and valsartan, remained at similar concentrations (> 1 ug L^{-1}) between influent and effluent wastewater. In Costa Rica, few studies have been conducted, among them, Spongberg et al., (2011) analyzed surface waters and coastal locations where it was found that drugs with the highest concentrations were doxycycline (74 µg L^{-1}), ibuprofen (37 µg L^{-1}), gemfibrozil (17 µg L^{-1}), acetaminophen (13 µg L^{-1}), and ketoprofen (10 µg L^{-1}). In another research, Causanilles et al. (2017) performed a qualitative screening of surface and wastewater samples in two municipal WWTPs in the country, and identified in all samples analyzed (12 in total), the presence of acetaminophen, atenolol and ibuprofen.

1.3. IMPACT OF PHARMACEUTICALS IN THE ENVIRONMENT

Widespread occurrence of PCs has raised awareness of scientists and health authorities worldwide to assess their ecological risk and human exposure. Due to the variety of drugs and factors that determine their fate in the environment and treatment facilities, it is necessary to prioritize specific pollutants according to factors such as consumption, biodiversity, occurrence data, and potential toxicity in each region.

Human and veterinary medicines are synthesized to act on a metabolic pathway for a specific organism, however their release into the environment expose them to non-target receptors that may result in chronic effects even at trace levels (Fent et al., 2006). Research to determine the ecotoxicological effects related to PCs on biodiversity has several challenges, some of them include developing appropriate methods for extraction and quantification of drugs in complex biological samples, analyzing potential adverse effects on various trophic levels of organisms, studying effects of mixtures of different therapeutic classes, which could lead to increased toxicity, and characterizing chronic effects at environmentally relevant concentrations of µg L^{-1} to ng L^{-1} (Destrieux et al., 2017; Mezzelani

et al., 2018). Usually experiments have focused on single drug effects, which can under- or over-estimate the actual environmental effects (Godoy et al., 2015).

The adverse effects of emerging contaminants on aquatic environments may be assessed through an ecological risk assessment (ERA), an iterative process based on two major elements of characterization of effects and characterization of exposure (EPA, 1998). ERA can help to evaluate systematically the chemical, eco-toxicological, and ecological risks in various environmental matrices by using, among others, chemical and biological techniques (Abbasi et al., 2022; H. Wang et al., 2021). Risk estimates for pharmaceuticals can be developed using the simplest quantitative approach of risk quotient (RQ), where typically, the ratio is expressed as an exposure concentration (in its simple form obtained from the environmental concentration of the contaminant) and divided by an effects concentration such as the predicted no-effect concentration (PNEC) for representative organisms (EPA, 1998; Mezzelani et al., 2018; H. Wang et al., 2021; Y. Xiang et al., 2021). In this manner, the ERA can be estimated by calculating RQ for the PCs and organisms of interest. Subsequently, RQ values are classified by low risk ($0.01 < RQ < 0.1$), medium risk ($0.1 < RQ < 1$), or high risk (≥ 1) (Papageorgiou et al., 2016; B. M. Sharma et al., 2019). In order to evaluate the ecotoxicological impact of chemicals on living organisms, different representative organisms are used, while pollutant effects on ecological indexes and community structure are included to assess ecological risks of exposure (Abbasi et al., 2022; EPA, 1998). The toxicity will be defined by parameters such as the type and stage of the organism, exposure time, temperature, and contaminant concentration (Khan et al., 2020). Usually, representative organisms include three trophic levels of the aquatic food web: primary producers such photoautotrophic bacteria (e.g., algae), primary consumers (e.g., daphnids), and secondary consumers (mainly fish) (H. Wang et al., 2021). The most extensively-used test for determining environmental toxicity based on the endpoint of mobility is the bioassay with the crustacean *Daphnia magna* (Khan et al., 2022), and the same organism is frequently applied in ecotoxicological tests with reproduction as endpoint that usually use organisms with a short lifecycle, since many other species such as fish and amphibian species, reproduce with longer lifecycles (e.g., only once a year), making reproductive tests more challenging (Schuijt et al., 2021).

Many studies have shown the global effects that PCs may produce on living organisms, ecosystems and ultimately, public health, even though their environmental concentrations (ng L^{-1} to ug L^{-1}) are at magnitude orders below therapeutic doses, and usually below

concentrations at which adverse effects have been found on non-target organisms (Corcoran et al., 2010; Schuijt et al., 2021; D. Yadav et al., 2021). Although continuous discharge over time, bioactivity, and ubiquity of PCs may contribute to potential adverse effects, these depend on the susceptibility of species. Several almost negligible effects have been found to occur from continuous exposure during the life cycle of aquatic organisms to sub-therapeutic drug concentrations, but these effects may slowly accumulate and manifest several generations later, disturbing the sustainability of aquatic organisms' populations (L. H. M. L. M. Santos et al., 2010). Susceptibility of species can be affected by the mode of action of drugs; taxonomic variation (leading to inadequacy in metabolic, excretory or detoxification systems); age, sex, population; direct and indirect (via food chain) exposition; and additive or synergistic effects from mixtures of pharmaceuticals (Arnold et al., 2014).

Adverse impacts include abnormal physiological processes and endocrine disruption, enlarged cancer incidence, increased antibiotic resistance by the presence of antibiotics and their metabolites, bioaccumulation of pollutants, antibiotic resistance gene (ARG) development, damage of genetic information (genotoxicity), and potential cumulative toxicity of combined pharmaceuticals (Couto et al., 2019; Giannakis et al., 2017; Gogoi et al., 2018; Khan et al., 2022; Li, 2014; Riva et al., 2019).

Xiang et al. (2021) discussed an ecotoxicological assessment of PCs on aquatic organisms for surface waters in China and reported that at maximum concentrations of more than 2000 ng L^{-1} found for ciprofloxacin, erythromycin and diclofenac, these drugs had potential high risk with a RQ > 10, while ibuprofen posed moderate to low risk to aquatic organisms. Furthermore, in other study, Parida et al. (2021) determined that ibuprofen at environmental concentrations higher than 5000 ng L^{-1} can pose a more severe threat, reaching a maximum RQ of 15.3 for algae. In the Ganges River, high and moderate risks were estimated on algae to PCs such as caffeine (RQ=49) and sulfamethoxazole (RQ=1.02), corresponding to the highest concentration found in the surface waters of 743 ng L^{-1} and 27.5 ng L^{-1} respectively for each drug (B. M. Sharma et al., 2019). Furthermore, Papageorgiou et al. (2016) calculated the RQs at three nutritional levels for NSAID diclofenac and the antibiotics trimethoprim and ciprofloxacin at the highest concentrations of 95.8, 591 and 2670 ng L^{-1} found in the effluent of a WWTP, and determined the potential high risk of diclofenac for chronic toxicity in fish and the high risk of all three drugs for acute toxicity, specifically ciprofloxacin for algae, trimethoprim for invertebrates and diclofenac for fish. In addition, Jurado et al. (2019) developed a research in Spain that revealed the high risk posed by

diclofenac against *Ceriodaphnia dubia* (RQ=21) and the medium hazard related to erythromycin for *Brachionus calyciflorus* (RQ= 0.46) at maximum concentrations in groundwater (>100 ng L^{-1}), which pointed out the need to establish drinking waters standards since groundwater is a major source to produce water for human consumption.

It is important to notice that even when the RQ approach is simple to be used for answering whether risks are high or low, it is subject to limitations that can contribute to the variety of results observed across studies, for instance: (a) threshold concentrations can be obtained from multiple reports in literature or derived for the actual study using ecotoxicological tests, (b) as was discussed before, different species exhibit differences in chemical sensitivity, but the method does not explicitly consider this uncertainty (e.g., extrapolation from tested species to the species or community of concern (c) exposure variability (spatial and temporal) is not usually quantified, leading to more common exposure point estimates (d) the method is not the best tool to predict secondary effects such as bioaccumulation or community interactions and (e) incremental quantification of risks cannot be used to quantify risk mitigation results (Abbasi et al., 2022; Arnold et al., 2014; EPA, 1998; Parida et al., 2021). Hence, some RQs will show risk and most of them will be no significant, thus complementary methods such as ecotoxicological tests, ecological monitoring, and modeling are needed to better predict the effects of contaminants on aquatic ecosystems (Schuijt et al., 2021).

The most studied analgesics with ecological effects are paracetamol, ibuprofen, naproxen, and particularly diclofenac. For instance, diclofenac has been reported to generate gill changes and kidney lesions in rainbow trout after the prolonged exposure to concentrations ranging from 1μg L^{-1} to 500 μg L^{-1} over a 28 day period; these sublethal toxic effects were supported by evidence of diclofenac accumulation in the liver, kidney and gills, suggesting that prolonged exposure to environmentally relevant concentrations of diclofenac can lead to chronic effects in some aquatic organisms (González-gonzález et al., 2022; Schwaiger et al., 2004). Even more concerned was the ~90% decline within 10 years registered in the 1990s of the Gyps vultures population in Pakistan and India, where mortality was caused by acute renal failure in vultures that ate animals treated with diclofenac, and consequently led to ban the veterinary use of the drug in the region (Lahti, 2012). In another report, it was found that prolonged exposure to ibuprofen at concentrations of 0.01, 1, and 100 μM significantly induced the cytochrome P450 enzyme (CYP) expression involved in the drug metabolism of *Cyprinus caprio* (common carp) hepatocyte cultures (Corcoran et al., 2012).

In addition, Santos et al. (2010) showed chronic toxicity impacts caused by commonly used antibiotics, in this case, the reproduction of the crustacean *D. magna* was affected when were exposed to levofloxacin and clarithromycin using toxicity values for the median effective concentration (EC50) of 340 and 40 μg L^{-1} respectively of each drug. Although these concentrations are higher than those usually found in the environment, the results may be employed as early warning indicators of the potential effects on the exposed organisms (Schuijt et al., 2021).

Furthermore, PCs can cause threats through their transformation products, metabolites, and mixtures. For instance, Diniz et al. (2015) investigated the exposure of adult zebrafish to parent compounds and UV photolysis byproducts of atenolol, ketoprofen and diclofenac, and found that through photolysis, the toxicity by atenolol and ketoprofen was reduced, while the transformation products of diclofenac were more toxic. In addition, acridine, a photobyproduct of carbamazepine, has been described as toxic, carcinogenic, and highly mutagenic to non-target organisms (Tijani et al., 2016). Moreover, an investigation compared the single and mixture effects of β-blocker metoprolol with carbamazepine, diclofenac and EE2 on life-history and morphological parameters over six generations of *D. magna* (Godoy et al., 2015). While body length of daphnids was decreased by metoprolol alone, it increased with the combined compounds (Godoy et al., 2015). Passananti et al. (2015) also described the ecotoxicity of etodolac, its photostable derivative and its irradiated mixture on algae, rotifers, and crustaceans and found mutagenesis and genotoxicity potential of the chemicals.

Endocrine disruption effects in aquatic ecosystems have been recognized over the last few decades. Endocrine-active compounds mimic, inhibit, and alter the hormones of the endocrine system, affecting reproduction, immunological protection, and health of water biota (Khan et al., 2022). Intersex condition has been used as a biomarker of endocrine disruption caused by estrogenic pollutants. This condition is determined by the presence of female germ cells within a predominantly male gonad (Grieshaber et al., 2018). Alterations in alligators, frogs, and fish have been reported around the world, and adverse effects such as abnormal sperm count, cancer, obesity and infertility are some of the major problems presented among humans (Kasonga et al., 2021; Tahar et al., 2018; Tijani et al., 2016). As an example, estrogens such E2 and EE2 (contraceptive pills) have been declared responsible for many harmful effects to wild aquatic species. Wang et al. (2021) summarized investigations that reported male feminization of the Indian frog *Euphlyctis cyanophlyctis,*

and induction of vitellogenin in male Murray rainbowfish at environmental concentrations of E2. The authors also mentioned the infertility of male fathead minnows (*P. promelas*) and decline of egg production related to EE2. Additionally, reduction of algal production and photosynthetic pigments of freshwater algae was found in compounds such estrogens, progesterones, and their mixtures (H. Wang et al., 2021). Furthermore, Puckowski et al. (2016) found additional harmful effects of E2 and EE2, such as the decrease of phytoplankton densities of *Conjugatophyceae*, increased cancer risk and infertility in male zebrafish, lower egg production in Japanese medaka (*O. latipes*), and adverse development of sea urchin embryos. In other laboratory and field research, vitellogenin induction has been widely reported as a highly specific marker of estrogenic endocrine disruption in fish, caused by exposure to environmental estrogens, in which production of the egg-yolk protein vitellogenin (normally occurred in mature female for reproduction), is significantly stimulated in male or immature female fish by exposure to exogenous E2 or estrogen mimics such EE2 at relevant environmental concentrations as low as 2 ng L^{-1} (Cheek et al., 2004; Harries et al., 1997; Kasonga et al., 2021; Mezzelani et al., 2018; Örn et al., 2003; Schultz et al., 2013).

Bioaccumulation of estrogens in fish tissues have been noticed even in urban waters. Teta et al. (2018) examined the widespread feminization of male tilapia potentially caused by environmental estrogens in urban waters of Zimbabwe. Ebele et al. (2017) observed a similar effect of feminization of wild fish residing in urban waters from UK. Moreover, in Costa Rica, a preliminary study reported problems on the reproduction of crocodiles from Palo Verde National Park, possibly related to the synthetic steroid 17α-methyltestosterone (MT) used in aquaculture around the area. The authors described switch sexes, resulting in males outnumbering females among hatchling crocs, regardless the temperature in the nest (Leslie, 2017).

Another significant risk about PCs in the environment is the development of antimicrobial resistance (AMR), a global concern that have been reported mainly in bacterial populations. Widespread use of antibiotics in human and veterinary medicine has been declared as the major reason for the spread of AMR (Anderson et al., 2015; Chaturvedi et al., 2021; Ohore et al., 2022; F. Wang et al., 2022). Conventional WWTPs are found unable to completely remove some antibiotics, drug-resistant pathogens and resistance genes from wastewater, which bacteria can pick up to create a (multi)resistant phenotype (Klatte et al., 2017). Moreover, septic tanks for disposal of sewage and leachate from solid waste landfills can contribute to the spread the problem (Koch et al., 2021; Pal et al., 2010) . To illustrate, the

presence of antimicrobial drugs such as antibiotics within biota and the occurrence of bacterial resistance genes have been noted (Reichert et al., 2019). Antibiotics such as ciprofloxacin, trimethoprim, erythromycin, and sulfamethoxazole were found in Australian wastewaters and later associated with the resistance of two naturally occurring bacterial strains found in the receiving water bodies (Ebele et al., 2017). Several pathogens resistant to different antibacterial drugs and responsible for serious infections have been widely reported. Among them, the most dangerous include *Mycobacterium abscessus, Mycobacterium tuberculosis, E. coli, Salmonella enterica,* and the so-called superbugs *Staphylococcus aureus* and *Vibrio cholerae* (Ahmad et al., 2018; Koch et al., 2021). Some of the examples of bacterial strains resistivity against various antibiotics include: fluroquinolones resistance in *E. coli*, non-typhoidal *Salmonella* and *Shigella*; methicillin resistance in *Staphylococcus aureus*; and rifampicin resistance in *Mycobacterium tuberculosis* (Chaturvedi et al., 2021; Tanwar et al., 2014). Furthermore, the β-lactam antibiotics have been noted as significant promoters of the development of antibiotic resistance (Koch et al., 2021), as it has been reported for cephalosporin resistance in *Klebsiella pneumoniae* (Tanwar et al., 2014).

Adverse effects of antibiotics and pharmaceuticals, in general, can also spread into the food web through additional pathways as irrigation with wastewaters, raw animal wastes, and by its application to promote growth and feed conversion efficiency in veterinary medicine and agriculture (Cheng et al., 2016; Ohore et al., 2022). Therefore, the resulting uptake of the drugs by animals and crops may lead to a potential exposure to pharmaceuticals through dietary intake (Ebele et al., 2017). In a review, Chaturvedi et al. (2021) outlined the presence in vegetables and fruits of oxytetracycline and streptomycin, two of the most used antibiotics in agriculture. The authors emphasized the risks associated with those compounds, including damage to the reproductive system, hormonal disequilibrium, abortion, and hemorrhage in livestock and even humans. Indeed, the European Union has prohibited the application of streptomycin and oxytetracycline in agriculture (Koch et al., 2021), but in other countries, both antibiotics are still permitted. Another research revealed traces of fluoxetine, diazepam, triclosan, carbamazepine and primidone in roots and leaves of lettuce, cucumber, pepper, and spinach, possibly absorbed by crops from irrigation with treated wastewater (Chaturvedi et al., 2021) . Parida et al. (2021) mentioned that bioaccumulation within biota of carbamazepine and atenolol can reach humans and may retard the growth of human embryonic stem cells. Additional examples included the use of the antibiotics tetracycline

and quinolone in salmon farming and the detection of ARGs in shrimps, cropland soils and harvest vegetables (Chaturvedi et al., 2021; Du et al., 2020; F. Wang et al., 2022)

According to the World Health Organization (WHO), AMR is one of the major public health threats worldwide. Thus, it has a priority to unify its approach *One Health* and recognize the connection between animals, humans, and environment for global health security (World Health Organization [WHO], 2021).

1.4. TREATMENT SYSTEMS FOR THE REMOVAL OF PHARMACEUTICALS

Climate change and global growing have scaled up the demand of clean water around the world. It is necessary to produce clean water for human consumption, to treat and reuse wastewaters, and to minimize pollution due to anthropogenic activities entering environmental matrices.

PCs are ubiquitous in the environment mostly due to their capability to resist treatment processes in the urban water cycle, which include water supply and wastewater decontamination. The removal success of the water treatments depends mostly on the chemical properties, the concentrations entering the facilities, and the technologies employed (de Jesus Gaffney et al., 2017). Generally, treatments for the abatement of ECs are classified into three categories: physical, biological, and chemical methods. For instance, physical treatments include adsorption and filtration, whereas biological processes comprise activated sludge, biological activated carbon, constructed wetlands, lagoons, and membrane bioreactor systems (MBRs). In addition, ozonation, advanced oxidation processes (AOPs), sonochemical, Fenton and photo-Fenton, and photocatalysis are the main advanced chemical processes applied for the elimination of trace organic pollutants in water (Shahid et al., 2021).

Traditional WWTPs are focused on the elimination of biodegradables, including carbon, nitrogen, and phosphorus compounds, nutrients, and microbiological organisms (Khasawneh & Palaniandy, 2021). In most countries, WWTPs have only primary and secondary levels of removal technologies. Tertiary treatments represent advanced methods that require more funding and expertise to be implemented, thus advanced engineered options are more frequently applied in developed nations (Collado et al., 2014; de Oliveira et al., 2020). In primary treatment, solids and liquids are separated by physical methods

such filtration, flocculation, coagulation and sedimentation, and PC removal is accordingly driven by the sorption to the resulting floc (Shahid et al., 2021). Secondary treatment is based on biological processes (i.e., aerobic and anaerobic systems) and typically is designed to remove organic matter and/or nutrients; in this stage PCs may also be biologically degraded to varying degrees by microorganisms, leading to mineralization or incomplete degradation (i.e., transformation products) (Choi et al., 2022; Mezzelani et al., 2018; Rodriguez-Narvaez et al., 2017; Tran et al., 2018). The water solubility, complex chemical structure, and polarity of the PCs may prevent conventional primary, secondary and even some tertiary methodologies, from completely removing these pollutants, resulting in typical elimination rates that could reach 20–50%, 30–70%, and >90% respectively for each treatment category. Therefore, advanced and integrated systems are necessary to complement and improve removal efficiency for PCs (Khan et al., 2022; Rout et al., 2021).

Some of the most prevalent and novel treatments for water sources remediation are discussed briefly in the following sections.

1.4.1. ACTIVATED CARBON ADSORPTION AS ESTABLISHED PHYSICAL TREATMENT FOR THE REMOVAL OF PHARMACEUTICALS

Adsorption by activated carbon (AC) has been a recognized technique for the elimination of ECs from water sources even at full-scale facilities. Factors such as a low cost of initial investment, unselective nature, and design and operational simplicity, contribute to this use (Akhtar et al., 2016). The potential of various adsorbents has been studied for the abatement of drugs from water based on their low-cost and efficiency, including those materials available in natural form, such as thermically treated materials and activated carbon (Quesada-Rodríguez et al., 2021; Quesada et al., 2019).

AC adsorption is a widespread method for purification of water from PCs. Decontamination of water matrix from several ECs have been reported to achieve up to 90% removal efficiency (Shahid et al., 2021). AC shows high porosity, adsorption capacity, and surface area, and it could normally be applied as powdered form (PAC) into a contact reactor, or as granular AC (GAC) in a packed bed filter, the latter being preferred. For both AC uses, the adsorption of pollutants is more efficient in water sources with low competing organic content (low dissolved organic carbon (DOC)) and could be monitored with the decrease of ultraviolet light at 254 nm (UV254) absorbance (Rizzo et al., 2019). The removal efficiency

of AC depends significantly on pH for ionizable compounds, the carbon structure of the raw material, and the AC dosage applied in the reactor (A. Yadav et al., 2021). Rodriguez-Narvaez et al. (2017) summarized a variety of removal efficiencies of PCs using AC with different carbon structures. An average removal of 80% were reported using GAC for levofloxacin, diclofenac, ibuprofen, trimethoprim, ciprofloxacin, erythromycin, carbamazepine, caffeine, and primidone, with a stronger adsorption (>90%) for clarithromycin. Nevertheless, adsorption in full scale applications has reported lower results for anthropogenic markers such carbamazepine and EE2, reaching 30% and 50%, respectively, with GAC (Rout et al., 2021). Apart from that, Rizzo et al. (2019) noted an adsorptive removal of primidone, sulfamethoxazole, and gabapentin of 80% using 2 g PAC/g DOC. Generally, a lower dose of PAC has been needed to achieve the same removal efficiency as GAC. Kårelid et al. (2017) demonstrated, in a pilot-scale investigation in three Swedish wastewater treatment plants, that treatment systems using a PAC dose of 15-20 mg L^{-1} or a larger GAC dose ranged from <28 to 230 mg L^{-1} achieved each, a 95% elimination for carbamazepine, clarithromycin and diclofenac, compounds that are currently discussed for regulation internationally (Kårelid et al., 2017).

In addition to efficiency, it is important to analyze the hazards of waste AC materials, application cost, and regeneration capacity of the adsorbents (Quesada et al., 2019). Rizzo et al. (2019) listed substantial advantages and disadvantages of AC adsorbents: (1) adsorptive removal with AC implies a lower energy consumption and no byproduct formation compared to chemical advanced technologies, but requires high energy consumption during the production of the AC, (2) exhausted AC with adsorbed trace contaminants must be disposed as hazardous waste, incurring additional expenses, (3) GAC can be regenerated and reused, with the respective energy demand, but PAC cannot, as it only can be recycled in biological treatment and eventually incinerated.

1.4.2. ADVANCED OXIDATION PROCESSES FOR THE REMOVAL OF PHARMACEUTICALS

Recently, AOPs have been considered as one of the most promising technologies for the removal of micropollutants from water and wastewater, with their high degradation rates and high mineralization efficiency (Rathi et al., 2021). AOPs consist broadly of aqueous phase oxidation methods based on the use of free radicals or highly reactive oxygen species such

as the hydroxyl radical ($HO^{\bullet}$), superoxide anion radical ($O^{\bullet}{}_2^-$), and alkoxyl radical ($RO^{\bullet}$), All these reactants have robust oxidation power and poor reactant selectivity, both of which allow for decomposition of the organic pollutants into simpler molecules. The $HO^{\bullet}$ radical has attracted the most attention because it features the specific advantages of high reactivity and oxidizing capacity (E^o = +2.8 V), in addition to a fast reaction with different chemical species with rate constants in the range of 10^6–10^9 $M^{-1}s^{-1}$ due to its generally non-selective behavior (Kanakaraju et al., 2018)

Different methods for AOPs include predominant ozonation (UV/O_3, O_3/ H_2O_2), UV-based oxidation (UV/H_2O_2, UV/TiO_2), Fenton and Fenton-like processes and photocatalysis, in addition to approaches emerging from areas such as electrochemical systems, ultrasonication, ionizing radiation, and other combined AOPs (Krishnan et al., 2021). From these**,** ozonation is the most widely used oxidation method; it has been considered as an established tertiary process in full-scale treatment to abate PCs in water and wastewaters, with the additional advantage of reducing some ecotoxicological effects such estrogenic activity (Kosek et al., 2020). Hydrogen peroxide and UV are generally applied to enhance ozone decomposition in the reaction media and increase the amount of HO• radicals, resulting in removal efficiencies greater than 90% for almost all types of PCs (J. Wang & Wang, 2016). Ozonation has been effective for removing antibiotics, β-blockers, lipid regulator metabolites, antiepileptic drug carbamazepine, and the natural estrogen estrone from wastewaters (Richardson & Kimura, 2017). Drugs such as ibuprofen, trimethoprim, gemfibrozil, caffeine, and diclofenac have been removed from wastewaters more effectively than conventional treatment using some AOPs scaled to a treatment plant, achieving significant removal rates through photocatalysis with TiO_2 (85-90%), Fenton processes (95-98%), and ozonation (>98%) (Rodriguez-Narvaez et al., 2017). In other applications, a pilot-scale experiment conducted for a water treatment plant under O_3/H_2O_2 and UV/H_2O_2 treatments resulted in the complete elimination of carbamazepine, fluoxetine, naproxen, and gemfibrozil, and the removal of diclofenac and ibuprofen by >97%, whereas atorvastatin had only 88% removal (Yang et al., 2017).

Photocatalysis is another AOP-based technology that has achieved effective elimination of multiple types of micropollutants from water sources. In the photocatalytic process, the light energy used to activate the catalysis and the assistance of oxidants such as H_2O_2, lead to the generation of various reactive oxygen species (ROS) that enhance the degradation rate of contaminants compared to photolysis alone (Dhangar & Kumar, 2020; Kanakaraju et al.,

2016, 2018). Heterogeneous photocatalysis based on the semiconductor titanium dioxide (TiO_2) is the most explored approach, and has advantages such as abundance, cost-effectiveness, physicochemical stability, and a nontoxic nature (Hazarika & Karak, 2016). The process by which TiO_2-based materials degrades contaminants is through the use of radicals formed from photoexcited electrons or photoinduced holes, or by direct oxidation from holes on the surface of the catalyst (Rizzo et al., 2019).

Innovative TiO_2-based photocatalysts applied at bench and pilot-scale have reported degradation rates of 99-100% for PCs such E2, EE2, carbamazepine, tetracycline, caffeine, and salicylic acid as well as some pesticides, without producing harmful byproducts (Athanasekou et al., 2018). Although the efficiency of photocatalysis with TiO_2 is promising to remove organic pollutants, some operational factors limit its performance. Among them, the most important include pH-dependency, the reduction of abatement rates by the presence of interferences such as dissolved organic matter, the separation of the catalyst particles from the treated water, and the energy cost involved in the UV sources (Rizzo et al., 2019). Further developments have been undertaken to improve the performance of photocatalysis and extend it to large-scale applications, especially in wastewater treatment. Those efforts include managing large water treatment capacity with energy autonomy and low operation cost, broadening the absorption of TiO_2-materials towards the visible region (UVA and sunlight), and employing hybrid systems with modified filtration membranes to overcome catalyst recovery issues (Athanasekou et al., 2018; Hazarika & Karak, 2016).

Nowadays, novel photocatalysis using conjugated polymers are on the rise, leading to materials with improved abilities to remove organic contaminants from water even under ambient conditions (Dhangar & Kumar, 2020; Taghizadeh et al., 2020). One of the most studied conducting polymers is poly(3,4-ethylenedioxythiophene) (PEDOT), which has attractive properties such as biocompatibility, thermal and chemical stability, high conductivity, low-cost, and elevated carrier mobility (Zamora-Sequeira et al., 2018). Kumar et al. (2021) described the removal (>99%) of metformin and other drugs using pure PEDOT and UV irradiation, without any co-catalyst. Ledezma-Espinoza et al. (2022) achieved higher elimination rates (>89%) for sulindac compared to direct photolysis by applying a composite of gamma irradiated cellulose and PEDOT under pH 7 and UV-A light. Both studies reported less time consumed (>50 h less) compared to traditional treatments such as direct photolysis.

In comparing and selecting oxidation treatments, important challenges must be considered. One relevant issue is the evaluation of scaling parameters for solar and lamp-driven AOPs and the challenge of comparing experimental conditions among different investigations. Results are highly dependent on the oxidant agent (type and dosage), the pH of the aqueous matrix, the chemical structure and initial concentration of the target pollutants, radiation source (wavelength and intensity) when it is present, and the efficient use of the radiation and exposure time (Rodriguez-Narvaez et al., 2017). Furthermore, although most advanced oxidation-based treatments are highly efficient, they all involve high operational and maintenance costs in energy consumption during use, and additional expenses for chemical reagents, catalyst fabrication or management of waste generation (Parida et al., 2021).

An additional concern about AOPs is the formation of byproducts as a consequence of the non-selectivity of highly reactive ROS (e.g., OH•), as these intermediates could retain the parent compounds' biological activity or even show more toxicity that the initial molecules (Fatta-Kassinos et al., 2011; Ma et al., 2014; Schwarzenbach, 2002). For instance, Kosek et al. (2020) observed a substantial increase in toxicity during the ozonation (O_3-TiO_2) of clofibric acid and the photocatalytic degradation of sulfamethoxazole by solar photo-Fenton processes. Moreover, in the production of potable water, ozone dose needs to be limited in the treatment of waters with high natural bromide (Br^-) concentrations, due to the potential formation of carcinogenic bromate (BrO_3^-) (Kosek et al., 2020). Up to now, significant production of toxic byproducts in full-scale WWTPs has been not evidenced, but the use of AOPs with post-treatment steps has been recommended to remove biodegradable transformation byproducts before the release of wastewaters into receiving water bodies (Kanakaraju et al., 2018; Kosek et al., 2020; Mirzaei et al., 2017).

Although isolated and combined AOP systems have demonstrated substantial elimination of trace pollutants, some drawbacks remain in their application as combined units, which include high operational costs as discussed above, the order of units in the coupled treatment is not clearly justified in most studies, there is a need to identify if intermediates resulting in coupled AOP treatments may show more or less environmental risk than the single AOPs and thus, a comprehensive understanding is needed for their practical application on a large scale (Kanakaraju et al., 2018; G. O. S. Santos et al., 2022). Hence, the combination of advanced oxidation degradation with other methods such biological and physical treatments has been suggested to be more cost-effective and to enhance the

elimination of trace pollutants (G. O. S. Santos et al., 2022), some examples of these applications are described below.

1.4.3. HYBRID TREATMENTS FOR THE REMOVAL OF PHARMACEUTICALS

Hybrid treatment processes have been employed to overcome the drawbacks in conventional and advanced treatments for water and wastewater purification. Integrated systems combine two or more existing technologies, such as physical and/or chemical processes with biological ones either simultaneously or sequentially, to achieve higher removal efficiencies (Shahid et al., 2021)

Of hybrid systems, MBRs are one of the most successful advanced biological systems used to eliminate ECs from water matrices. MBRs go beyond traditional activated sludge process (ASP) by combining membrane filtration and biological degradation (e.g., activated sludge). This technology generally has outstanding performance due to features such as longer solid retention time (SRT) that improves the biodiversity of microorganisms, maximizes sorption of contaminants by the smaller floc size and large surface area developed in the reactor and increases the growth of nitrifying bacteria, in addition to having the desirable features of stable biomass concentration, shorter hydraulic retention time (HRT) and less sludge production (Park et al., 2017; Saidulu et al., 2021; Tiwari et al., 2017). The application of MBR systems in hospital wastewater treatment has been reported as a common practice nowadays, showing significant removals (>81%) for PCs such ibuprofen, naproxen, atenolol, ofloxacin, acetaminophen, sulfamethoxazole, trimethoprim, and ciprofloxacin, although compounds such gemfibrozil and carbamazepine had lower removals (<40%) (Tiwari et al., 2017). Moreover, some disadvantages of MBR systems affecting their consideration in a full scale application include: the pollutants are not transformed, but only moved to a concentrated phase that later needs to be properly treated for final disposal; better removals for hydrophilic and more readily biodegradable compounds than for hydrophobic and biologically persistent contaminants (Rout et al., 2021); and additional operational limitations such membrane fouling, energy consumption, and cost of specialized membranes (Dhangar & Kumar, 2020; Rout et al., 2021). Therefore, to minimize those problems, the integration of MBRs with other physicochemical treatments is recommended.

Different tertiary systems such filtration membranes, ozonation, photocatalysis, adsorbents, Fenton oxidation, etc, are combined with MBRs to effectively remove hydrophilic and

hydrophobic micropollutants from water sources (Shahid et al., 2021). Typically, the average elimination of MBR-based embedded processes ranges from 90% to 95% (Parida et al., 2021), with systems combining a membrane bioreactor and a reverse osmosis/nanofiltration unit (MBR+RO/NF) being one of the most effective treatments for EC removal (Dhangar & Kumar, 2020). Some of the PCs effectively removed by MBR+RO/NF include carbamazepine, metoprolol, salbutamol, ofloxacin, propranolol, famotidine, erythromycin, lorazepam, clarithromycin, codeine, and diazepam (Rathi et al., 2021). Coupling treatment by MBR with oxidation by UV light at 254 nm is also one of the efficacious methods to eliminate (85–99%) hydrophilic and biologically persistent contaminants such as diclofenac and triclosan (Parida et al., 2021). Previous research examined a multi-stage system using MBR and a post-treatment of granulated activated carbon filter to remove PCs from hospital wastewaters, and demonstrated higher removals compared to the post-treatments of UV/H_2O_2 and ozonation, without generation of byproducts (Kosek et al., 2020). Another study, conducted in a full-scale WWTP, found that the application of a combined secondary treatment of the anaerobic-anoxic-oxic process with MBR facilitated an overall removal of 96% of 52 PCs such as metformin, paracetamol, caffeine, ibuprofen, and naproxen, and that residual drugs in the secondary effluent were removed more efficiently (>50%) with PAC as tertiary treatment, with the only exception being metformin (Choi et al., 2022). Meanwhile, Changotra et al. (2019) studied the remediation of pharmaceutical wastewaters from a pharmaceutical manufacturing unit using different Fenton´s methods as pre-treatment steps, including solar driven photo-Fenton followed by subsequent biological treatment, which resulted in an overall COD removal efficiency of >82% and the enhancement of the BOD5/COD ratio, which showed the improvement in biodegradability and reduction of organic load compared to single stage oxidation, either by Fenton or biological treatment, without any toxicity against the tested microorganisms *viz. P. aeruginosa, B. subtilis and E. coli*.

Alternative systems using biodegradation with photocatalysis show potential as cheap, environmentally friendly, and renewable ways to remove (>92%) compounds such atenolol, antipyrine, diclofenac, carbamazepine, hydrochlorothiazide, ketorolac, metoprolol, and sulfamethoxazole (Rathi et al., 2021). Hybrid treatments with constructed wetlands (CWs) at full scale have been suggested as promising low-cost solutions for wastewater purification, as they can eliminate PCs through primary mechanisms of phytoremediation, photodegradation and sorption with removals up to 99%, such as metformin, gabapentin,

caffeine, ibuprofen, ketoprofen, diclofenac, carbamazepine, naproxen, antibiotics, and antibiotic resistance genes (Hube & Wu, 2021). Crushed recycled glass as a novel CW substrate showed efficient removal of atenolol and metoprolol in a pilot-scale system, similar to traditional gravel and sand substrates, constituting a new approach that can be applied even in rural regions (Chaves-Barquero et al., 2021). Furthermore, multi-stage systems have proven to be efficient in mitigating EDCs, among them, promising results (>90%) for the removal of various compounds have been reported for MBR+ RO/NF, MBR+UV oxidation, flocculants + activated sludge + ultrafiltration (UF), combination of constructed wetlands, and UF + activated black carbon (Dhangar & Kumar, 2020).

Overall, although hybrid systems have provided effective options for water purification for contaminants such as pharmaceuticals, many challenges remain at the practical level. Today, only Switzerland has set a target of 80% total EC removal for WWTPs by using biological processes combined with ozonation to comply with the efficiency limits in full-scale facilities (Choi et al., 2022; Rout et al., 2021). Future work needs to promote sustainable technologies that can be applied on a commercial scale, to maximize EC removal at reasonable cost, to facilitate the detoxification of water sources, and to reduce the impact of ECs on the environment and public health.

1.5. SAMPLING AND ANALYTICAL TECHNIQUES FOR THE DETERMINATION OF PHARMACEUTICALS IN AQUATIC ENVIRONMENTS

Monitoring of emerging contamination by pharmaceuticals in waters is necessary to better assess their potential risks to the environment and public health, which is in turn needed to develop appropriate management strategies and future regulations. Critical steps in analytic strategies such as sampling, extraction, and quantitation should be adequately established to evaluate the actual impact of contaminants in specific water ecosystems.

Analysis methods with high robustness, selectivity, and sensitivity are required to determine multiple PCs at the same time in aquatic systems. Liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) is the most widely technology used to detect the presence of PCs in water (Kapelewska et al., 2018; Koch et al., 2021), as suggested for most PCs in the European Union's Watch List of the Decision 2015/495/EU (Sousa et al., 2019). This

advanced technology is essential since PCs are present in the environment as parent compounds, along with metabolites and transformation products with similar chemical structures, as well as other contaminants, all at low concentration levels of $\mu g\ L^{-1}$ and $ng\ L^{-1}$ (de Oliveira et al., 2020). Thus, for successful identification and measurement of the target molecules, instrumental confirmation of at least two MS/MS transitions and evaluation of their ion ratios are necessary to ensure the proper identification and quantitation of the compounds (EU, 2002). Non-targeted analysis and the use of sophisticated high resolution mass spectrometry (HRMS) instruments such as quadrupole time of flight (QTof-MS) mass spectrometers are important tools for wide screening of contaminants, determination of byproducts, and identification of suspect and non-target compounds; all of which help to understand processes such as transformation, partitioning, and transport of contaminants in the environment and to define and update the list of compounds to be examined according to the monitoring objectives (Branchet et al., 2020; Khan et al., 2022).

Before applying any instrumental technique to analyze a pollutant, proper sample collection and pretreatment steps should be applied. One of the most important steps is the selection of the optimal sampling technique, to account for the physicochemical properties of targeted substances, site configuration, and spatio-temporal trends (Mackeown et al., 2022). Different sampling approaches have been developed and applied for multiple forms of emerging contaminants in water. Common methods include the direct collection of water by automated or grab sampling, passive sampling and biomonitoring (Azcune et al., 2022).

Although traditional grab sampling is simple and low cost for short time trend investigations, some drawbacks are related to the method. For instance, it may require large volumes of sample to cleanup and concentrate, and exhaustive sample preparation protocols before instrumental analysis proceeds. It also only provides a non-representative concentration for the specific location and time where the sample was taken, which may not be representative of environmental contamination at that location over time (Söderström et al., 2009). As an alternative, passive sampling represents a more integrative approach, providing more representative levels of contaminant exposure through continuous *in situ* monitoring and time-weighted average (TWA) water concentrations, allowing for preconcentration of contaminants, improved detection limits, detection of episodic events, and simplicity and low cost sampling (Challis et al., 2016; Gong et al., 2018). Moreover, passive sampling is recommended for advanced environmental monitoring and prioritization of ECs, because the time-integrative method improves temporal representativeness of monitoring in water

resources with highly variable pollutant concentrations and allows a better assessment of chemical exposure and associated toxicity to aquatic organisms, including chronic effects (Brack et al., 2017; Zabiegała et al., 2010)

The theorical principle of aquatic passive sampling is based on the diffusion of the contaminant from the water to the receiving phase (the sampler), where the accumulation of the compound during the deployment time increases linearly following first-order kinetics, then continues with curvilinear kinetics and finally achieves an equilibrium partitioning phase. Net diffusion is caused by the difference in chemical activity of the compound in the two compartments (water and sampler) (Söderström et al., 2009; Taylor et al., 2020). Therefore, passive samplers can quantify analytes in two ways: the kinetic mode and the equilibrium sampling mode. For both ways, the chemical accumulates in the sampler with an uptake rate which depends on its own physicochemical properties, the device configuration, and the environmental conditions (Mackeown et al., 2022; Vrana et al., 2005).

Passive accumulation of polar compounds occurs through analyte adsorption to the sorbent used (Taylor et al., 2020). Polar passive devices typically operate in the kinetic sampling mode, where a contaminant uptake remains linearly proportional to the difference in chemical potential of the contaminant in the receiving phase (sorbent) over the whole deployment time (infinite sink behavior), without sorbent saturation (Vanryckeghem et al., 2021; Vrana et al., 2005; Zabiegała et al., 2010). In the kinetic mode, these samplers do not reach equilibrium with the surrounding environment within the sampling period, since the adsorption between the receiving phase and the polar contaminant occurs without an isotropic exchange thanks to the negligible release rate compared to the uptake rate (Söderström et al., 2009). These linear uptake passive samplers are considered time-integrative, as their high capacity to collect the target contaminants ensures the continuous enrichment of the compounds throughout the sampling period; additionally, for quantitative purposes, it is assumed that their sampling rate remains constant throughout the field exposure period, and that a linear relationship exists between the concentration of target analytes in the sample matrix and the amount of analytes extracted (Vrana et al., 2005; Zabiegała et al., 2010). Although kinetic integrative samplers is the most applied technology for polar passive sampling, some applications of equilibrium samplers have been reported recently, for example, Vanryckeghem et al. (2021) demonstrated the potential of a teabag equilibrium passive sampler using hydrophilic divinylbenzene sorbent for 2-week integrated

sampling of major therapeutic classes such as pharmaceuticals (e.g., trimethoprim and venlafaxine), steroidal hormones and personal care products.

The main polar passive samplers (PPS) employed for hydrophilic (log Kow<5) organic molecules such as pharmaceuticals include the polar version of Chemcatcher, POCIS (polar organic chemical integrative sampler), and o-DGT (organic-diffusive gradients in thin-films) (Challis et al., 2016; Gong et al., 2018). To retain water polar pollutants of a wide log Kow range, these samplers include appropriate receiving phases such Oasis HLB copolymer (hydrophilic-lipophilic balance, the most commonly used material), Sepra ZT, and C18 disks (Branchet et al., 2020). To operate, the devices act as time-integrative samplers working in the kinetic sampling phase (linear uptake) (Vanryckeghem et al., 2021), and provide TWA concentrations calculated from the mass of the analyte sampled, the compound sampling rate (Rs, theoretical volume of water sampled per unit time) and the exposure time, by applying first order kinetic models (Taylor et al., 2020).

Some drawbacks have been identified for the PPS. Generally, PPS must be calibrated in the laboratory or *in situ* to determine the Rs of each target analyte, since the uptake of the compound depends on its physicochemical properties, the device configuration and the site-specific environmental conditions to which the device is exposed, mainly flow velocity, biofouling, temperature, pH and salinity (Godlewska et al., 2021; Guibal et al., 2019).

The methods to correct differences between *in situ* and laboratory-derived Rs due to variations in environmental conditions for polar passive sampling are still in its early stages (Challis et al., 2016; C. E. Chen et al., 2012; Zabiegała et al., 2010). The performance reference compound (PRC) approach has been successfully used in passive sampling devices for hydrophobic analytes, but its application for polar compounds needs further investigation (Godlewska et al., 2021). In the PRC method, compounds that are not in the environment, such as isotopically labeled compounds, are spiked into the passive sampler before the deployment, to be released following first-order kinetics into the exposure media (Godlewska et al., 2021; Vrana et al., 2005). Equilibrium samplers used for non-polar compounds exhibit isotropic kinetics (similar rate constants) for both the release and the uptake of the analyte sampled, which allows to calculate the Rs of the analyte with the mass transfer kinetic data between the device and the environment (Söderström et al., 2009). Differences due to exposure conditions in Rs for analytes will be revealed by the same changes in the release of the PRCs, since they are carried out by the same molecular process (Godlewska et al., 2021). In polar passive sampling, in contrast, the analyte

accumulates by adsorption rather than by partitioning. Adsorption is often an anisotropic process, thus release of PRCs is limited and the approach is generally not useful for calibrating uptake rate and subsequent TWA calculation for various compounds (Branchet et al., 2020; C. E. Chen et al., 2012; Gong et al., 2018).

Because the Rs calibration is time consuming and expensive to optimize for each compound, an alternative approach often taken is to use Rs values obtained in the laboratory under generic exposure conditions, which poses uncertainties with regards to the estimation of TWA leading to relegation of the PPS as a semi-quantitative technique. Nevertheless, the overall information and advantages obtained from polar passive sampling as mentioned earlier (e.g., time-integrated data on environmentally relevant time scales with high spatial resolution, savings on time and cost compared to active methods, and in situ pre-concentration which improves detection limits at trace levels of organic contaminants) can help to understand pollutant dispersal, fluxes, and transport processes for target compounds, among others. These factors are important enough that such information may still be reliable and representative for environmental water monitoring, where associated uncertainties are reasonable within the large variation of concentrations for pollutants in the environment originated by factors such as heterogeneity of the sample, spatial and/or temporal change of contaminants, seasonal changes during exposure time (climatic conditions), and matrix effects during sampling (irreproducible deposits) (C.-E. Chen et al., 2013; Guibal et al., 2019; Zabiegała et al., 2010; Zhang et al., 2008).

Although POCIS is the most widely used PPS to develop field and lab scale environmental research (Godlewska et al., 2021; Mathon et al., 2022), and Chemcatcher technology has been studied more than o-DGT, it has been reported that o-DGT is a more quantitative sampling approach for environmental monitoring of polar ECs (C. E. Chen et al., 2020). The following comparations have been documented among the three samplers:

a. Regarding sensitivity, due to the larger sampler size, POCIS is preferred, followed by Chemcatcher and finally o-DGT (Mackeown et al., 2022). Chemcatcher and o-DGT have similar configuration, but the o-DGT shows lower Rs owing to much thicker diffusion layer and smaller exposure area; o-DGT sensitivity could be enhanced by increasing the exposure area (C. E. Chen et al., 2020; Guibal et al., 2019; Urík & Vrana, 2019).

b. POCIS and Chemcatcher devices feature greater dependence on site-specific environmental conditions than o-DGT (Gong et al., 2018; Harman et al., 2012; Söderström et al., 2009). For the later, the hydrogel diffusive layer controls analyte uptake, making the Rs for o-DGT less impacted by the hydrodynamic conditions and therefore more reliable (Challis et al., 2020; C.-E. Chen et al., 2013; C. E. Chen et al., 2012; Mackeown et al., 2022). The diffusive gel is thicker than the diffusive boundary layer (DBL), hence diffusion across the former takes longer, making it the rate-limiting step which can be controlled and reduces uncertainties caused by the differences in flow rate between laboratory and field conditions. Furthermore, temperature influence can be account through simple calculations of Rs using temperature-specific diffusion coefficients (Challis et al., 2016; C. E. Chen et al., 2012).
c. Generally robustness over pH was reported for o-DGT sampling (within 20% accuracy) (Guibal et al., 2019), although, some authors described discrepancies on the uptake rates that could be related to changes in analyte-sorbent interaction (H-bonding) due to analyte speciation (Stroski et al., 2018)
d. Effects of biofouling and flow rate on o-DGT uptake could be reduced with appropriate configuration of the sampler (thickness, sorbent, diffusive gel) (Branchet et al., 2020).
e. One of the greatest advantages of the o-DGT approach over Chemcatcher and POCIS, is that it allows to estimate Rs values based on a predictable diffusion-based model, without field calibration, showing average uncertainties within 27-33% (Challis et al., 2016, 2020; Gong et al., 2018; Mackeown et al., 2022).

From the above discussion, o-DGT samplers are a promising approach for sampling polar ECs such pharmaceuticals in aquatic environments.

The first o-DGT device was developed for antibiotics in 2012 (C. E. Chen et al., 2012) and was recently improved with modifications in diffusive and binding gels (Challis et al., 2020; Stroski et al., 2018; Urík & Vrana, 2019). Briefly, o-DGT is composed of a diffusive hydrogel overlying a binding hydrogel, and a protected prefilter could be present (Gong et al., 2018). A DBL is created on top of the diffusive gel at the water/sampler interface due to the change of diffusivity between phases and resistance, which result in increased viscosity at the surface of the sampler (Harman et al., 2012; Schwarzenbach, 2002; Söderström et al., 2009). Under these conditions, mass transfer from sampling environment (water) to the binding gel is governed by molecular diffusion, and can be modeled by Fick's first law of

diffusion (Guibal et al., 2019). Following previous field investigations that suggest that DBL contribution (δ) related to the influence of flow rate and biofouling on o-DGT uptake can be negligible, the TWA concentration from o-DGT sampling can be expressed by Eq. (1) (Challis et al., 2018):

$$TWA_{oDGT} = \frac{m\,\Delta g}{tDA} \quad (1)$$

where (m) is the mass of analyte that diffuses into the binding gel, (Δg) is the diffusion layer thickness, (D) is the diffusion coefficient of the analyte in the diffusive gel, (A) is the exposure area and t is the deployment time.

1.6. INTEGRATED APPROACHES FOR MANAGING PHARMACEUTICAL CONTAMINATION IN WATER RESOURCES

Actions to manage the pollution produced by pharmaceuticals in water sources is a major global concern (Barcellos et al., 2022; Geissen et al., 2015; Kidd et al., 2007; Okeke et al., 2022). Owing to the difficulties in detection, treatments, and potential risks detailed in previous sections, a holistic and complex strategy prioritizing preventive measures is needed to achieve sustainable results and reduce the problem (FOEN, 2019; Geissen et al., 2015; Klatte et al., 2017).

Several approaches have been used by authorities, international organizations, and governments, especially in developed countries, with short, medium, and long-term measures to prevent and mitigate contamination by human and veterinary pharmaceuticals. The main goal of the strategy should include a combination of public awareness and regulations that emphasize the management of the urban water cycle (UWC), the production of pharmaceuticals and user side, releases to the environment, occurrence in water sources, routine monitoring programs, and the application of fate and risk assessment tools that allow the development of sustainable water resource management with economic feasibility (Geissen et al., 2015; Peña-Guzmán et al., 2019). Some examples are presented from selected approaches founded in the literature.

1.6.1. TECHNICAL APPROACH

Technically specialized and multidisciplinary measures to reduce water pollution by PCs mainly include high-quality monitoring, sewage and water treatments, green chemistry, and risks assessment tools. The routine monitoring of ecological and chemical status is fundamental to determine the chemical condition of water bodies and the potential threats to aquatic species. It is essential to recognize the identities and properties of the PCs, their sources, pathways, sinks and their interactions in the surrounding environment (X. Tong et al., 2022).

Therefore, it is suggested that monitoring combine passive sampling and biota analysis at the scales of the water bodies of interest (e.g., river basin, estuarine, lake and/or coastal waters), including sediment extracts, to account for variations in discharges of receiving waters, sorption to sediments, and potential bioaccumulation, among others, and to provide the actual occurrence, distribution, trends and temporally representative concentrations of PCs in the examined environmental matrices (Azcune et al., 2022; Brack et al., 2017; Čelić et al., 2019; Geissen et al., 2015; Perez et al., 2022). This information may help to identify sources of contamination, potential impacts of direct wastewater effluents, and a broad range of cumulative effects for specific or general types of drugs and mixtures of PCs (Brack et al., 2017; da Costa Filho et al., 2022; Dan Liu et al., 2017).

Integrated and efficient assessment of chemical exposure and associated ecotoxicological effects are needed to understand the degree to which PCs are responsible for the deterioration of aquatic environments and to support the selection of priority drugs, a manageable and smaller group of PCs of high relative concern for the deployment of resources to conduct environmental and human health risk assessment, monitoring, abatement solutions, and regulatory initiatives (Destrieux et al., 2017; Fekadu et al., 2019).The European monitoring network NORMAN (NORMAN, 2005) has recommended a categorization/prioritization scheme that defines six categories of chemicals including pharmaceuticals, based on the environmental occurrence in surface waters and on PNECs, these categories include (1) priority regular monitoring; (2) watch list monitoring; (3) extension of the (eco)toxicological data set; (4) improvement of analytical methods; (5) extension of monitoring and (eco)toxicological data and, finally; (6) classification of compounds as non-priority for regular monitoring due to estimated low risks (Brack et al., 2017; Geissen et al., 2015). PNEC values available at NORMAN network database are

derived from experimental data and/or methods such as Quantitative Structure-Activity Relationship (QSAR) and read-across predictions (Brack et al., 2017).

QSAR and read-across methods (alone or combined) are widely used for predicting properties of chemicals and their mixtures for classification, hazard identification and hazard characterization in the absence of experimental toxicity data, which contribute to fill data gaps in ecological risk assessments (Chatterjee & Roy, 2022). Briefly, quantitative models based on QSAR are mathematical descriptions of the biological/toxicological activity of a group of chemical compounds using one or more of their physicochemical properties, that may be based on linear or non-linear relationships between the properties and the structural parameters (Benfenati et al., 2019). Meanwhile, read-across is another strategy that applies extrapolations on target molecules that have not been tested from available experimental data of structurally analogous chemicals, based largely on assumptions of similarity of chemical structures for prediction of the same endpoint (e.g., chemical toxicity) (Benfenati et al., 2019; Chatterjee & Roy, 2022; Helman et al., 2018). Overall, risk modeling tools can contribute to fill gaps in real typical sampling designs, using reasonable worst-case scenarios to predict seasonal variability, peak concentrations, hypothetical emissions, and effect of mitigation measures, which enhance the monitoring efforts and can provide quantitative relationships between the pollutants and the ecological status.

One of the initiatives that applies integrated approaches of new generation of monitoring and modelling tools is the SOLUTION project, an initiative that provides a framework for the assessment, prioritization and abatement of pollutants and mixtures to protect European waters, and to minimize ecological and human health risks, in direct support to the implementation of the WFD for water protection in Europe (Solutions Project, 2013). The project develops information on legacy, present and future chemicals, and mixtures posing a risk to water resources, contributing for the early detection and identification of harmful substances and the enhanced comprehension on chemical exposure and effects. The effects of emerging pollutants are provided based on approaches that include integrated models and databases for ecological assessment; predictions of environmental concentrations, fate, transport, toxicity and mixture effects; as well as ecological and human risk modelling, which additionally, may contribute for the assessing of abatement options and control measures in water resources for effective risk reduction (Bunke & Moritz, 2014)

The modernization of the WWTPs and the technologies for the efficient removal of PCs from water sources are needed with environmental and economic sustainability. Advanced

treatment methods that include hybrid approaches and the use of drug indicators such as ibuprofen and carbamazepine along with non-expensive methodologies for evaluating removal efficiency to reduces costs (such UV254 nm absorbance), are some of the suggested strategies that have also been practiced in leading countries such as Germany and Switzerland (Ahmed et al., 2021; Barcellos et al., 2022; Khasawneh & Palaniandy, 2021)

Green chemistry can be applied to develop environmentally benign compounds that involve reduced doses, maximization of metabolization, higher biodegradability, and reduced environmental effects without changing their functionality. Furthermore, green chemistry can be used to develop treatment technologies with low operational and implementation costs, that allow decentralization and efficient removals on a small or large scale, such as constructed wetlands (Barcellos et al., 2022)

Once data are known, the pharmaceutical life cycles should be recognized on a local scale to base future policies concerning the water quality management and for updating risk assessment initiatives (Peña-Guzmán et al., 2019).

1.6.2. COLABORATIVE APPROACH

This approach includes the action of multiple stakeholders developing networking, consensus, and awareness on the management of the PCs. Collaborative networking between technical, community, private and governmental sectors can reach initiatives to control and reduce the water pollution by PCs. Different agents can be part of the efforts, for instance NGOs, professional groups, community, academy, industries, hospitals, and health and commerce facilities. The goals of these initiatives can include promoting environmental voluntary actions and education campaigns, researcher training, spread of scientific knowledge and improvement of environmental practices (Barcellos et al., 2022).

One of the most successful examples of collaborative work is the NORMAN Project introduced in the previous section. This permanent international network is formed by reference laboratories, research centers, and related organizations that promotes the exchange of data, validation and harmonization in monitoring and biomonitoring for emerging contaminants such as pharmaceuticals and their degradation products, as well as various proven or suspected endocrine disrupting compounds. For instance, NORMAN provides results of prioritization, various databases of geo-referenced chemical occurrence,

data obtained with passive sampling, data on antibiotic resistance bacteria/ARGs in environmental matrices, results of ecotoxicity studies (experimental or predicted), and many others, for contributing to the early-warning system for those emerging pollutants and subsequent management and policy actions (Brack et al., 2012; NORMAN, 2005).

The Global Water Research Coalition (GWRC) is another example, a collaborative non-profit international organization that has specialized in water research. It is formed by members that are in charge of national research program addressing the urban water cycle. The coalition has classified several PCs as high-priority pharmaceutical products in water, such carbamazepine, naproxen, sulfamethoxazole, ibuprofen, gemfibrozil, atenolol, diclofenac, and erythromycin, with the aim to draw the attention to the pollutants and support decisions for the protection of the aquatic environment and the public health (Couto et al., 2019)

Countries in Europe, Australia, USA, Canada, and New Zealand, and recently Brazil, Colombia, and Mexico, have implemented the drug take-back strategy, a collaborative solution involving health professionals, education programs and community, with the aim of collecting disused household medicines and encourage individual habits and social awareness about the pharmaceutical wastes (Barcellos et al., 2022). Although is a popular strategy, little is known if the strategy actually works. Egan et al. (2017) reported results from permanent drug donation boxes and take-back campaigns developed in USA, and found that annually, disposed controlled medications represented only 0.3% of those dispensed. Another study in USA focused on the senior population (>65 years), identified that almost 11% of unused medication was disposed via drug take-back programs, whereas the majority was kept in a cabinet (55%), thrown in the trash (14%), or flushed down the toilet (9%) (Maeng et al., 2016). Whereas a survey conducted by Kamal et al. (2022) in three countries found that the main disposal method among the respondents were disposing in the toilet (35.4%) in USA; returned to the pharmacy in Italy (51.2%); and disposed the original container in the trash in Japan (82.7%). Hence, take-back has several challenges to overcome to act effectively, including: marginal capacity to mitigate the pollution due to the small portions of drug sales or prescribed being returned to disposal and reduced volume of drugs covered by the return option, undefined distribution of costs and responsibilities involved in the waste collection and treatment systems of pharmaceuticals, need of more promotion on professional guidance and educational programs to increase population adherence, and dependent efficiency on community awareness and legal regulation (Barcellos et al., 2022; A. Y. C. Tong et al., 2011). The latter show that better community-

level interventions for improving prescription efficiency and public awareness on appropriate disposal methods of drug residues are necessary to reduce environmental pollution (Maeng et al., 2016).

Furthermore, measures aimed at prevention and reduction in use can be promoted by health specialist and educational programs. Relevant actions are for example, to improve management and hygienic conditions in hospitals and livestock farming, avoid questionable prescriptions, and prioritize reduced therapeutic doses (particularly for antibiotics), support preventive health programs, label disposal instructions on medication packages and encourage take-back systems, offer periodic training to professionals, incentivize the redesign of pharmaceuticals towards environmentally-friendly drugs, raise awareness among patients and farm owners about the use of medications, apply manure fermentation to degrade veterinary drugs before discharging them into sewage, and promote technical processes to remove PCs from wastewaters (Klatte et al., 2017).

Another collaborative effort is The Global Green and Healthy Hospitals network, an international project created in 2011, formed by hospitals, health systems, and related health facilities with the objective to promote best organizational practices among the members, reduce the environmental impacts of medications, and improve public and environmental health ((GGHH, 2014). One of the main contributions of the GGHH network is the developing of guidelines and programs among its members on pharmaceutical pollution, aimed to prescribe appropriately the medications, educate patients and health workers and properly dispose of the pharmaceuticals; for example, in Australia and New Zealand the GGHH's practices are greatly promoted and hospitals need to embed regular pharmaceutical waste audits into ongoing practice, which include parameters such as: pharmaceutical contract tenders should include meaningful and accountable environmental impact criteria, hospitals should have comprehensive pharmaceutical waste programs in place, and the establishment of programs for the optimized use of antibiotics in hospitals established (Babb & Pruett, 2022; Carino et al., 2022).

Finally, the community can contribute significantly to prevent and reduce the domestic waste of pharmaceuticals, whether they are obtained over-the-counter or under prescription. Some actions include following the intended use and prescription of the medications, returning unused or expired medications at the proper collection points, avoiding disposal via toilet or sink, avoiding consumption of potential counterfeit drugs, participating in educational

campaigns, and adopting healthy practices such good nutrition and exercise (Barcellos et al., 2022).

1.6.3. REGULATORY APPROACH

This approach involves public policies, guidelines, directives, and measures launched by governments and authorities responsible for protecting the environment and public health. Legal and economic tools are used to establish mandatory emission limits, minimum technical standards in WWTPs, routine monitoring programs, information campaigns, and waste management practices, as well as prohibit or restrict the use of chemicals, support research, and induce synergies between the public and a wide range of stakeholders in the pharmaceutical chain, with results that tend to materialize in a long-term period (Barcellos et al., 2022).

The World Health Organization, the US Environmental Protection Agency and the European Commission are examples of the driving stakeholders that lead the efforts to improve public and environmental health (Beretta et al., 2014). In 2000, the European Union adopted the Water Framework Directive (WFD, 2000/60/EC) for the sustainable management, protection, and restoration of freshwater resources including groundwater bodies. This regulatory framework contains a priority lists of pollutants called Watch List (WL) that shall be monitored by the EU Member States, for which compound selection is based on high frequency of occurrence, potential risk to the aquatic environment or human health, and on the availability of analytical techniques and monitoring data (Khasawneh & Palaniandy, 2021; Krishnan et al., 2021). For these WL compounds, the concentration limits are defined in the Environmental Quality Standards Directive, and concentration data proceed from targeted high-quality monitoring of international routine programs used in risk assessment across water bodies (Geissen et al., 2015). Several pharmaceuticals have been listed in the WL since the beginning of the intervention, including antibiotics (erythromycin, clarithromycin, azithromycin), anti-inflammatory drugs (diclofenac, ibuprofen), hormones (estrone (E1), 17-β-estradiol (E2) and 17-α-ethinylestradiol (EE2)), and caffeine (Branchet et al., 2020; Couto et al., 2019; da Costa Filho et al., 2022; Sousa et al., 2018). The list is revised every 2 years, thus the new WL of priority substances for union-wide monitoring following the Decision 2020/1161 included amoxicillin, ciprofloxacin, sulfamethoxazole, trimethoprim, venlafaxine and O-desmethylvenlafaxine (human metabolite), among others

(Khasawneh & Palaniandy, 2021). Moreover, the presence of antibiotics in the new WL has the objective to collaborate in the action plan of the European Commission against antimicrobial resistance compounds (Khasawneh & Palaniandy, 2021; Reichert et al., 2019).

In the USA, another priority list of pollutants has been stipulated by law, in this case, to periodically monitor potentially hazardous substances in drinking water. Unsafe substances or high-status pollutants are listed by the EPA in the drinking water contaminant candidate list (CCL), to eventually determine whether to regulate the contaminants with a national drinking water regulation (Samal et al., 2022). Every five years the list is updated, recently in 2022 the last priorization was launched in the CCL5. Throughout the monitoring, some PCs such as erythromycin and hormones (estrone (E1), 17-β-estradiol (E2), 17-α-ethinylestradiol (EE2) and norethindrone) have been listed (EPA, 2022).

Other significant guidelines and regulations are issued by international organizations to control pharmaceutical contamination in the environment. For example, the WHO in 2012 recommended the minimum therapeutic dose (MTD) to assess the potential health risks of pharmaceuticals, and the Organization of Economic Cooperation and Development (OECD) advised governmental parties to take action to control the occurrence and effects of the PCs in the environment by five policies: (1) improving data about the occurrence, fate, and toxicity (for human and ecosystems) of PCs; (2) minimizing the pharmaceuticals residues produced by manufacturers (source-directed approach); (3) responsibly reducing the consumption of pharmaceuticals among farmers, patients, health professionals (use-oriented approach); (4) applying sustainable waste and wastewater treatments (end-pipe measures) and (5) adopting collaboration and a life cycle approach (Khasawneh & Palaniandy, 2021).

Countries such as Switzerland and Germany have taken the lead to implement specific regulations or voluntary actions on the removal of ECs from urban wastewater. Switzerland involved the public and stakeholders to institute the new Water Protection Act in 2016, a policy that establishes the upgrade of 50% of the national sewage systems with advanced treatments such as ozonation and AC to remove 80% of the country's proposed organic ECs used as indicator compounds (Barcellos et al., 2022). In addition, in 2018, the country approved the regular monitoring in surface waters of the PCs of atenolol, carbamazepine, diclofenac, sulfamethazine, and sulfamethoxazole (Khasawneh & Palaniandy, 2021). Similar initiatives, but as voluntary efforts, are carried out in Germany, where the federal states of Baden-Württemberg and North Rhine-Westphalia applied advanced treatments (ozonation and AC) for the abatement of ECs in wastewaters, aiming to reach mandatory

concentration limits in the near future; as well, the implementation of the Antimicrobial Resistance Strategy in the country reduced by over 32% (2014-2017) the consumption of antibiotics for livestock (Rizzo et al., 2019). Other countries that had implemented relevant measures to manage the issue of pharmaceuticals in the environment are Sweden, Netherlands, Australia, Spain, Canada, and South Korea (Kosek et al., 2020). Some of those measures are the monitoring of emissions and discharges of active pharmaceutical ingredients in European countries, developing of chain approach programs from source to end of the pipe in Sweden and Netherlands, introducing public collection schemes for unused pharmaceuticals in Australia, Spain and Canada, and employing non-target screening to detect, identify, and prioritize pharmaceuticals for water quality monitoring in South Korea (Khasawneh & Palaniandy, 2021).

The efforts detailed above demonstrate that the managing of the contamination with pharmaceuticals needs a holistic and adaptive approach, with the commitment of stakeholders, community, and governments to develop sustainable actions to protect efficiently the environment and public health.

2. OBJECTIVES AND HYPOTHESES

The following are the objectives and hypotheses of this research:

2.1. GENERAL OBJECTIVE

The overall aim of this dissertation was to evaluate the occurrence, degradation and ecotoxicological significance for aquatic ecosystems of three pharmaceuticals considered emerging contaminants found in waters impacted by urban activity in the Great Metropolitan Area of Costa Rica, to improve the knowledge on environmental protection and sustainable management of water resources.

2.2. SPECIFIC OBJECTIVES

1. To determine the occurrence of three pharmaceuticals contaminants of concern in wastewaters and surface waters of highly urbanized sites in the Great Metropolitan Area of Costa Rica.

2. To identify the potential risk of the target pharmaceuticals contaminants on the exposed organisms considering the toxicity data and the effect of at least one mechanism of environmental degradation.

2.3. HYPOTHESES

It is postulated that pharmaceutical contaminants can occur at concentration levels that lead to an environmental risk in aquatic ecosystems and whose toxicity could be potentiated by their mixture with other drugs and the tropical conditions in surface waters from the Great Metropolitan Area of Costa Rica.

3. OVERALL SYNTHESIS

3.1. GENERAL DESCRIPTION

This research focused on the study of the occurrence, transformation, and potential risks of pharmaceutical residues as emerging contaminants in waters of the urban area of Costa Rica. It brought the opportunity to create knowledge and developed work capacity in the study of novel anthropogenic contaminants in the country, by applying new techniques of monitoring, instrumental analysis, and interdisciplinary work. Fundamental topics are included in this dissertation as a guide to better comprehend such investigation, summarize information on the global problem of the pharmaceuticals as emerging contaminants, explain main routes of degradation, apply the theory of passive sampling as a reference tool to aquatic monitoring, discuss novel treatment technologies with potential to remove trace pollutants from surface and wastewaters, and explore sustainable actions for management of pharmaceutical contamination in aquatic media.

To develop these thesis, three main sections have been included. The first section describes the passive sampling with organic-diffusive gradients in thin-films conducted in urban waters of the GAM in Costa Rica, which included sources from a hospital, a large wastewater treatment plant, and the Virilla and Torres rivers which are some of the most polluted rivers in the metropolitan area. The study combined risk quotients, biotests with *D. magna* and the first evaluation of occurrences of target pharmaceuticals using o-DGT passive samplers. The occurrence of various pharmaceuticals in the sampling sites was confirmed, and

ecological risk assessment were conducted using the observed TWA concentrations, demonstrating the potential impact of these contaminants in the urban aquatic ecosystems. Additionally, the application of o-DGT demonstrated its performance for passive sampling of polar compounds, which helps to provide more representative data given the potential great variability of drug concentrations that has been observed elsewhere, at low cost and with the outstanding advantage of predicting time-weighted average integrated concentrations based on molecular structure of the compounds. These results can provide reliable scientific information to decision makers to define better strategies on awareness of community, monitoring programs, funding for advanced treatments, and future regulatory interventions.

The second section embraces a fundamental study of how a parent compound such as sulindac had complicated routes of transformation in the environment. Kinetics parameters, plausible mechanisms of inter-conversion, identification of byproducts and associated potential risks are reported. The information contributes to the understanding of how the impact of the pharmaceuticals may be found not only in the parent molecules but also in their transformation products and metabolites, which could lead to understanding major potential risks and underscore the difficulty to find effective technologies to their elimination from aquatic matrices.

The final section depicts the developing, characterization and application of a novel technology to remove pharmaceuticals from aquatic systems, showing the potential of a biopolymer to enhance the efficiencies of elimination of selected pharmaceuticals from water. This novel photocatalytic system is an ecofriendly approach and can contribute as an option for hybrid advanced treatment processes to remove micropollutants from water and wastewaters.

3.2. DISSERTATION OUTLINE

The results of this research are divided into three sections according to the following summary:

3.2.1. Pharmaceuticals in wastewaters and rivers in the urban area of Costa Rica: a first look at incidence, trends, and ecological risks using passive sampling.

An insight into contamination levels of selected pharmaceuticals was obtained in this work from the analysis of impacted urban waters that included effluent from a hospital and a WWTP, and surface water from two rivers. Passive sampling with o-DGTs and high-resolution mass spectrometry with isotope dilution were applied to identified PCs in the wastewaters and surface waters from the urban sampling sites. In addition, risk quotients and biotests were conducted to determine the potential risk on model organisms to similar concentrations levels found in the sampling sites. Manuscript to be submitted.

- **Journal**

Emerging Contaminants. Q1. Indexed in: Web of Science, Directory of Open Access Journals (DOAJ), Scopus. Publisher: KeAi Communications Co.

- **Reference**

Ledezma-Espinoza, A., Loaiza-Moss J., Ariza-Castro, N., Sánchez-Kopper, A., Challis, J. K., Romero-Blanco, E.G., Roa-Gutierrez, F., Chaves-Barquero, L. G., Rodríguez-Quesada, L., Pinnock-Branford, M., Luong K. H. & Wong, C. S. (2023). *Emerging Contaminants*. Manuscript to be submitted.

3.2.2. Photolysis of the nonsteroidal anti-inflammatory drug sulindac: elucidation of kinetic behaviour and photodegradation pathways in water.

The kinetic behaviour of sulindac under direct photolysis and ambient conditions was addressed in this paper. This work identified novel photoproducts of sulindac, proposed photodegradation pathways and provided novel and reliable kinetic parameters of its complex transformation following a mechanism of consecutive reactions. It is necessary to bring knowledge about the transformation of parent drugs under conditions that simulate those founded in the environment, to further investigate potential hazards to the aquatic ecosystems and efficient removal treatments.

- **Journal**

Environmental Science: Processes & Impacts. Q1. Indexed in: Web of Science, Scopus. Publisher: Royal Society of Chemistry.

- **Reference**

Ledezma-Espinoza, A., Challis, J. K., Roa-Gutierrez, F., Sánchez-Kopper, A., Castellón, E., & Wong, C. S. (2021). Photolysis of the nonsteroidal anti-inflammatory drug sulindac: elucidation of kinetic behaviour and photodegradation pathways in water. *Environmental Science: Processes & Impacts*, 23(9), 1405–1417. https://doi.org/10.1039/d1em00167a

3.2.3. Modified cellulose/poly(3,4-ethylenedioxythiophene) composite as photocatalyst for the removal of sulindac and carbamazepine from water.

A novel environmentally friendly composite was synthesized using gamma irradiated cellulose and PEDOT conductive polymer as a potential method for the abatement of pharmaceutically active contaminants in water. Promising results demonstrated the improvement in the photocatalytic removal of sulindac and carbamazepine drugs, and particularly showed the efficient of the system in removing sulindac from water comparing to the direct photolysis process.

- **Journal**

Environmental Technology & Innovation. Q1. Open Access. Indexed in: Web of Science, Directory of Open Access Journals (DOAJ), Scopus. Publisher: Elsevier B.V.

- **Reference**

Ledezma-Espinoza, A., Rodríguez-Quesada, L., Araya-Leitón, M., Avendaño-Soto, E. D., & Starbird-Perez, R. (2022). Modified cellulose/poly(3,4-ethylenedioxythiophene) composite as photocatalyst for the removal of sulindac and carbamazepine from water. *Environmental Technology & Innovation*, 27, 102483. https://doi.org/10.1016/j.eti.2022.102483

4. PHARMACEUTICALS IN WASTEWATERS AND RIVERS IN THE URBAN AREA OF COSTA RICA: A FIRST LOOK AT INCIDENCE, TRENDS, AND ECOLOGICAL RISKS USING PASSIVE SAMPLING.

Ledezma-Espinoza, A.[1], Loaiza-Moss J.[1], Ariza-Castro, N. [1], Sánchez-Kopper, A.[1], Challis, J. K.[2], Romero-Blanco, E.G., Roa-Gutierrez, F.[1], Chaves-Barquero, L. G.[1], Rodríguez-Quesada, L.[1], Pinnock-Branford, M.[3], Luong K. H.[4,5] & Wong, C. S.[6]

Manuscript to be submitted.

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ABSTRACT

This is the first study on occurrence and ecological risk assessments using passive sampling for pharmaceuticals in urban waters of Costa Rica. Organic-diffusive gradients in thin-films (o-DGT) passive samplers measured time-weighted average water concentrations of pharmaceuticals during the wet and dry seasons in the Great Metropolitan Area. Measured concentrations ranged from 0.012 to 3610 ng L^{-1} for atenolol, sulindac, levofloxacin, carbamazepine, sulfamethoxazole, sulfapyridine, and sulfamethazine, which were all detected in the surface waters of the Virilla and Torres rivers, and the wastewaters of a hospital and the major city's primary wastewater treatment plant. The highest concentrations were for atenolol (3610 ng L^{-1}) and carbamazepine (2290 ng L^{-1}) in wastewater influent, levofloxacin (1020 ng L^{-1}) in hospital wastewaters, and sulfamethoxazole in the Torres River (335 ng L^{-1}, upstream) and Virilla River (400 ng L^{-1}). Sulindac concentrations ranged from 38.2 to 672 ng L^{-1} in wastewaters and from 8.9 to 173 ng L^{-1} in surface waters. Higher concentrations were observed in the dry season, with a weighted annual average load for all detected pharmaceuticals of 19.6 kg discharged in wastewater effluent. Environmental risk assessment based on risk quotients showed that sulfamethoxazole posed a high potential risk to aquatic ecosystems, while ecotoxicity tests revealed that sulindac and levofloxacin posed adverse effects on crustaceous organisms under relevant environmental concentrations detected in this study. Our work may help to increase the confidence in the use of passive sampling to gather environmental monitoring data for improving the knowledge and management of pharmaceutical pollution.

1. INTRODUCTION

Pharmaceuticals are bioactive pollutants found ubiquitously in the environment mainly due to their incomplete removal from wastewater (Inostroza et al., 2017; Oulton et al., 2010; Verlicchi et al., 2012; Yang et al., 2017). Their presence may lead to prolonged exposure and may threaten aquatic ecosystems and human health (de Oliveira et al., 2020; Escher et al., 2011; Lei et al., 2015; Mezzelani et al., 2018). Adverse effects have been related to pharmaceutical pollution. These include abnormal physiological processes and endocrine disruption, enlarged cancer incidence, antimicrobial resistance, bioaccumulation, damage in genetic information, and potential cumulative toxicity of pharmaceutical mixtures (Couto et al., 2019; Gogoi et al., 2018; Khan et al., 2022; Riva et al., 2019). Moreover, even

significant effects have been reported at higher levels of the food chain, such as the collapse of several vultures species in India (1990s) due to kidney damage caused by feeding on cattle treated with diclofenac (Klatte et al., 2017).

Consequently, some international initiatives, such as the EU Water Framework Directive (WFD) with its Watch List for surface waters and the US Environmental Protection Agency with its Contaminant Candidate List for drinking water, have launched actions to prioritize, monitor, or regulate pollutants of emerging concern such as pharmaceuticals (Zhong et al., 2022). Passive sampling has been presented by the EU WFD and various researchers as a potential tool to advance monitoring and examine the fate and behaviour of polar compounds in aquatic systems (Allan et al., 2006; Barra et al., 2020; Brack et al., 2017; EU, 2009; Godlewska et al., 2021; Gong et al., 2018; Ji et al., 2022; Kot-Wasik et al., 2007; Kot et al., 2000; Křesinová et al., 2016). Many advantages have been reported for passive sampling over traditional grab sampling, including in situ time-weighted average (TWA) water concentrations of contaminants, to account for episodic changes in the environment, pre-concentration, cleaner samples, and cost and labor savings (Alvarez et al., 2004, 2007; Branchet et al., 2020; C. E. Chen et al., 2012; Harman et al., 2012; Huckins et al., 1990; Söderström et al., 2009; Taylor et al., 2020; Vanryckeghem et al., 2021; Vrana et al., 2005; Zabiegała et al., 2010). For monitoring polar compounds such as pharmaceuticals in aquatic environments, organic-diffusive gradients in thin-films samplers (o-DGT) are one of the most promising approaches (Challis et al., 2016; C.-E. Chen et al., 2013; C. E. Chen et al., 2012; Guibal et al., 2019). Several advantages of the o-DGT samplers over traditional polar samplers such as POCIS have been reported. For example, sampling rates for o-DGT are less impacted by the hydrodynamic conditions such as water flow rate, and can be predicted based on molecular structure of analytes of interest (Challis et al., 2016, 2020; C. E. Chen et al., 2020; Mackeown et al., 2022)

While studies have widely reported pharmaceuticals in the aquatic environment of developed countries of Europe, China, USA, and Canada (Couto et al., 2019; Rehman et al., 2015; Tran et al., 2018; Xie et al., 2022), there is still a gap of knowledge in developing countries such those from Central America, including Costa Rica (Causanilles et al., 2017; Cristina et al., 2022; Peña-Guzmán et al., 2019). Hence, passive sampling can be used as a reliable evidence-based tool to determine the occurrence and trends of aquatic contaminants, assess the removal efficacy of wastewater treatment operations for such contaminants, determine the risks posed by the presence of these contaminants on human

and aquatic ecosystem health, and develop sustainable actions for effectively and efficiently protecting the environment and public health in developing countries.

The present work provides a first look at the occurrence and seasonal variation of several target pharmaceuticals in the urban waters of the Great Metropolitan Area (GAM) of Costa Rica using passive sampling. The o-DGT passive sampler was employed to evaluate potential ecosystem exposure risks posed by these chemicals. To our knowledge, this is the first study in Latin America using o-DGT passive sampling as an environmental tool for monitoring and conducting comprehensive risk assessments of pharmaceuticals in aquatic environments.

2. EXPERIMENTAL SECTION

2.1. Target compounds

Target pharmaceuticals were selected as representatives of major therapeutic classes of β-blockers (atenolol), non-steroidal anti-inflammatory drugs (NSAIDs, sulindac), anticonvulsants (carbamazepine) and antibiotics (including the fluoroquinolone levofloxacin, and sulfonamides sulfamethoxazole, sulfapyridine and sulfamethazine). Selection criteria were based on the high annual consumption reported by health authorities, previous investigations on occurrence in Costa Rica (Causanilles et al., 2017; Spongberg et al., 2011), compounds targeted for removal initiatives of pharmaceuticals in hospital wastewater in the country (CCSS, 2021), and concern over potential adverse effects. Carbamazepine was highlighted due to its recognition as an anthropogenic marker of global water contamination (Clara et al., 2004; M. Kumar et al., 2022; Shahid et al., 2021), and sulindac (Kawabata et al., 2013; Ledezma-Espinoza et al., 2021) due to its limited data concerning the fate and behavior in the environment. The main properties of the studied pharmaceuticals are included in Table S1.

2.2. Chemicals and reagents

Standards for (*1Z*)-sulindac, (*1Z*)-sulindac-d_6, levofloxacin, and levofloxacin-d_8 were purchased from TRC (Canada). Atenolol, atenolol-d_7, carbamazepine, carbamazepine-$^{13}C_6$, sulfamethoxazole, sulfamethoxazole-d_4, sulfapyridine, sulfapyridine-d_4, sulfamethazine, and

sulfamethazine-$^{13}C_6$ were purchased from Sigma Aldrich (Costa Rica). All compounds were of >98% chemical purity and isotopically labeled standards were all of >99% isotopic purity. Methanol, formic acid, and water were LC-MS grade and were obtained from Sigma-Aldrich (Costa Rica), without further purification. Stock solutions were prepared in pure methanol.

Potassium chloride, magnesium sulfate heptahydrate, calcium sulfate dihydrate, and sodium hydrogen carbonate (all >99.0% purity) were obtained from Sigma Aldrich (Costa Rica).

The o-DGT devices used agarose diffusive gels (molecular biology grade) from Sigma Aldrich (Costa Rica) and binding gels made with agarose and OASIS™ HLB from Waters (Costa Rica).

2.3. Study sites

Samples were collected at sites representing likely significant point sources of water pollution with pharmaceuticals in the highly urbanized area of San José, in the GAM, which included a national hospital's wastewater discharge pipe into the city sewer system, and the largest city's wastewater treatment plant (WWTP) influent and effluent. In addition, sites along two polluted rivers in the GAM were monitored to evaluate contamination trends in receiving waters (Figure 1, Table S2).

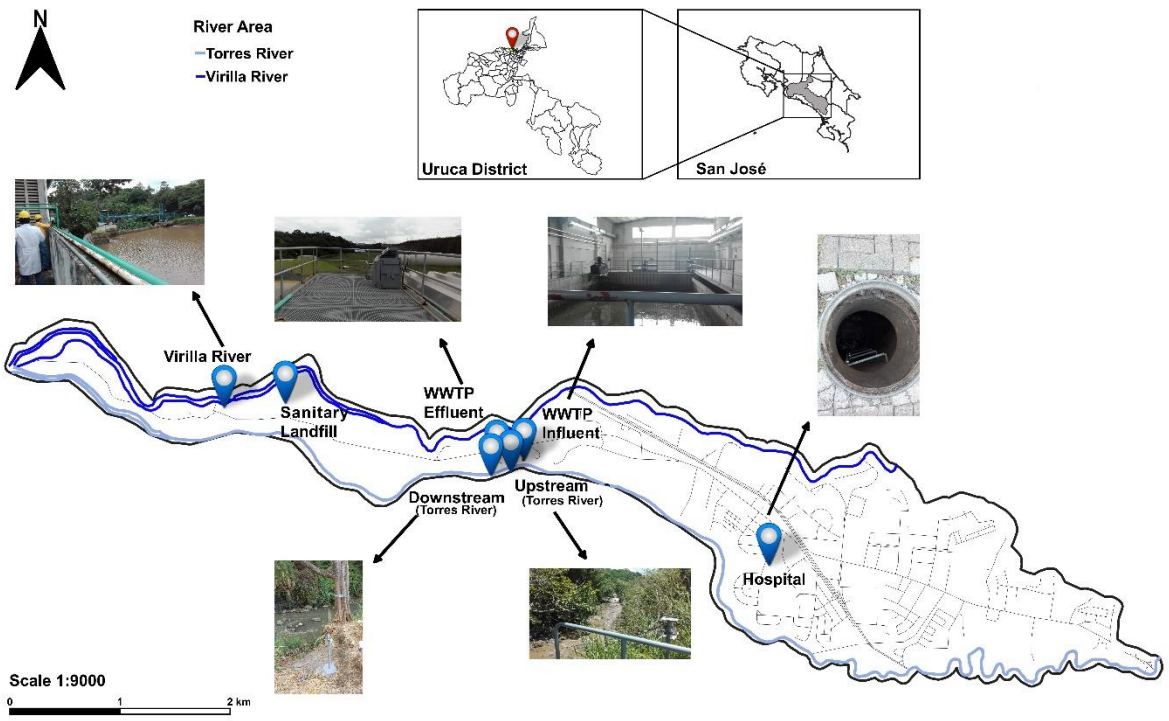

Figure 1. Locations of sampling sites at the hospital, WWTP (influent, effluent), upstream and downstream from the WWTP in the Torres River, and at the Virilla River. (Coordinates using CRTM05 projection)

The examined hospital has more than 500 beds for trauma and emergency medical services. It produces mixed wastewaters (average flow rate 11.9 L s^{-1}) from domestic and medical activities such as laundries, stormwaters, kitchens, drug laboratories, and toilets, which are discharged into the city pipe network systems after simple treatment processes, i.e., through gratings to screen out large material. In the hospital, there was no primary treatment prior to release the wastewaters into the city's sewage network during the time of the sampling campaigns for this research.

The WWTP is the largest facility in Costa Rica, serving over half of the estimated population of the GAM, and treating an average of 519 L s^{-1} (Mora-Aparicio et al., 2022). It receives combined stormwaters and domestic, hospital and industrial wastewaters, and provides treatment via screen- and grit-removal, degreasing and primary sedimentation (Mora-

Aparicio et al., 2022). Effluent is discharged into the Torres River; its micro-basin forms part of the Virilla River sub-basin (Alvarado García et al., 2020).

The Virilla River flows from the north-east of the Central Valley to the south-west Pacific region, where it merges with the Grande River and eventually drains into the Pacific Ocean (Alvarado García et al., 2020). The Virilla has an average flow rate oscillating between 20 to 80 m^3 s^{-1} from dry to rainy season (Waylen et al., 2016). It is surrounded mainly by urban areas in the GAM, and is heavily polluted from industrial activities, agriculture, household residues, wastewater discharges, livestock production, and landfill leachates (Mena-Rivera et al., 2018).

To evaluate the seasonal variation of pharmaceuticals, sampling campaigns were performed every two weeks, resulting in three consecutive sampling periods of fourteen days each for both, the dry (March 24 to May 5, 2017) and wet (June 16 to July 28, 2017) seasons, for a total of six deployment times (Table S2). o-DGT samplers were deployed at each site, at depths of 1.0-1.5 m. Water chemistry data was also collected (Table S3). Due to difficulties accessing the Torres, samplers upstream and downstream of the WWTP were only collected twice at these sites, once each during wet and dry seasons. Field blanks were exposed during retrieval and deployment of passive samplers.

2.4. Passive samplers

Preparation of o-DGT passive samplers followed Challis et al. (2016). Samplers used a binding gel with HLB (25 mg HLB, 1.5% AG, 0.75 mm thickness) and an outer diffusive gel of agarose (1.5% AG, 1.0 mm thickness) without an outer membrane, in a standard DGT plastic housing (DGT Research, Lancaster, UK).

After sampler retrieval, o-DGTs were disassembled, and binding gels processed by adding internal standards and extracting three times by sonication for 5 min with 3 mL methanol each. Extracts were combined, concentrated under vacuum to dryness, re-dissolved in 1 mL 1:1 methanol:H_2O, filtered through a 0.22 µm syringe filter into LC vials, and stored in the dark at −20 °C until analysis.

Water concentrations from sampler-accumulated chemicals (C_{oDGT}, ng L^{-1}) were calculated using the most common DGT equation (Eq. 1) (Challis et al., 2016):

$$C_{oDGT} = \frac{M_{oDGT}\Delta g}{DAt} \quad (1)$$

where M_{oDGT} is the mass of target compound accumulated in the o-DGT, Δg the diffusive gel thickness, A the sampler exposed area, t the deployment time, and D the gel diffusion coefficients. We estimated D (Challis et al., 2016) using Archie's law (Eq. 2):

$$D\left(\frac{cm^2}{s}\right) = \frac{3.3\ x\ 10^{-5}\varepsilon^m}{\sqrt[3]{M}} \quad (2)$$

where M is the molecular weight, and for 1.5% agarose diffusive gels, the porosity value (ε) is 0.98 and the Archie's Law exponent (m) is 2.

2.5. Analysis by high-resolution quadrupole time-of-flight mass spectrometry

Measurements were performed using a Xevo G2-XS quadrupole time of flight (QTOF-MS) mass spectrometer (Waters Corporation, Wilmslow, UK) coupled with an electrospray ionization source and an Acquity H-Class UPLC system. Detection was performed under positive ion mode (ESI+) and an optimized multiple reaction monitoring (MRM) acquisition method for mass monitoring over a range of 100 to 1000 Da, with mass resolution >50,000 FWHM. Experimental instrument parameters were 0.25 s scan time, 20 V sampling cone, 2.0 kV capillary, 100 °C source temperature, 400 °C desolvation temperature, 9 $L.h^{-1}$ cone gas flow, and 890 $L.h^{-1}$ desolvation gas flow. Data were processed using MassLynx™ V4.2. software. Chromatographic separation was achieved with an Acquity UPLC® BEH C18 column (1.7 µm, 2.1 mm×50 mm) (Waters Corporation, UK). Solvents for mobile phase were water (0.05% $v.v^{-1}$ formic acid) and MeOH (0.05% $v.v^{-1}$ formic acid). Samples were analyzed under gradient conditions (Table S4), 10 µL for injection volume, 40 °C and a flow rate of 0.3 mL min^{-1}. Analytes were quantified by isotope dilution (Table S5). Linearity (r^2) of calibration standards was >0.95 for all analytes.

Observed levels of all analytes were negligible in solvent, laboratory, and field blanks; measurements of DGT extraction recoveries for sulindac and levofloxacin (>85%) followed Challis et al. (2016), whereas reported recoveries for the remaining compounds were obtained from the same author (Challis et al., 2016).

2.6. Environmental risk assessment

2.6.1. Calculation of the environmental risk quotient (RQ)

Characterization of potential ecological risk of the target analytes to the aquatic environment was performed by calculating the risk quotients (RQ) for three trophic levels (e.g., algae, daphnids and fish). Values of RQ were calculated by dividing the maximum measured environmental concentration (MEC) by the predicted no-effect concentration (PNEC) (Afonso-Olivares et al., 2017; Khasawneh & Palaniandy, 2021). Chronic and acute RQs were calculated according to eq. 3 and eq. 4, using PNECs derived from (i) acute toxicity, determined by the lowest reported of EC_{50} or LC_{50} values and (ii) chronic toxicity, by using NOEC, both divided by an assessment factor (AF) determined as described in Papageorgiou et al. (2016). For those compounds with little to no ecotoxicology and risk assessment information on chronic and acute toxicities, such as sulindac and sulfapyridine, PNEC values were calculated using QSAR-predicted values, as those presented by NORMAN database (NORMAN, 2005). For acute toxicity, a standard value of 1000 was used as AF; whereas for chronic toxicity, AF varied depending on the number of trophic levels with long-term NOECs available: one long-term NOEC (AF = 100), two long-term NOECs in two trophic levels (50) and if long-term NOECs are available in the three trophic levels (AF = 10):

$$PNEC = \frac{EC50\ or\ LC50\ or\ NOEC}{AF} \quad (3)$$

$$RQ = \frac{MEC}{PNEC} \quad (4)$$

Target drugs were then classified into different levels of concern based on their RQ values (Kosma et al., 2014; Papageorgiou et al., 2016). A drug was classified as potential “high risk” when RQ ≥ 1, as “medium risk” for 0.1 < RQ < 1, and as “low risk” for 0.01 < RQ < 0.1.

2.6.2. Daphnia magna reproduction test

To the best of our knowledge, experimental toxicity data on *Daphnia magna* were not available for sulindac or its mixtures, therefore, ecotoxicity tests were performed on the aquatic model organism to measure the biological effects of individual exposure to sulindac and its mixture with two pharmaceuticals of interest (atenolol and levofloxacin). The biotest

were needed to address the biological effects in a direct manner and provide a link to chemical exposure, helping to unravel underlying adverse effects resulting from chronic exposure that are not detected with RQ approach. The combination of the ecotoxicological experiments and RQs is key to provide a more comprehensive and realistic assessment of the effects of the target pharmaceuticals to aquatic ecosystems and to establish priorities for further testing.

2.6.2.1. Test organisms

D. magna neonates (<24 h old) were obtained from the Laboratory of Ecotoxicology Studies at the Instituto Regional de Estudios en Sustancias Tóxicas, Universidad Nacional (Heredia, Costa Rica), and were kept in glass tubes during the execution of the assays.

2.6.2.2. Experimental design

Pharmaceutical treatment levels were chosen from passive sampling data. Solutions of sulindac, atenolol, and levofloxacin, and their mixtures, were prepared from stock solutions to a final concentration of 1000 ng L^{-1} in moderately hard reconstituted water (80 mg L^{-1} KCl, 2.5 g L^{-1} $MgSO_4 \cdot 7H_2O$, 1.2 g L^{-1} $CaSO_4 \cdot 2H_2O$ and 2 g L^{-1} $NaHCO_3$). Additionally, sulindac solutions of 500 ng L^{-1} and 2000 ng L^{-1} were prepared. In all cases, test media was supplemented with $1x10^8$ cells L^{-1} of both *Chlorella vulgaris* and *Pseudokirchneriella subcapitata*, 2 µg L^{-1} of both selenium and vitamin B12 and, a blended and filtered solution of 5.2 g L^{-1} *Saccharomyces cerevisiae*, 12.6 mg L^{-1} of fish meal and 1 mg L^{-1} of cereal as the food source for the test organisms.

The chronic toxicity test was performed following Test Guideline 211 (OECD, 2012). Neonates were raised in 75 mL test tubes with 50 mL of test medium, in a semi-static setup, with renewal of test media carried out three times per week. Each treatment group contained ten replicates, with one daphnid per test tube. A control group (in moderately hard reconstituted water) and a blank group (in moderately hard reconstituted water + methanol (<0,0001%)), were set up and supplemented with the food source. The number of neonates per daphnid were recorded, removed, and discarded every 48 h over the 21-day exposure.

Neonates were kept at 20±2 °C under a 16 h light and 8 h dark photoperiod. Water quality parameters such as dissolved oxygen and pH were monitored throughout the experiment.

Dissolved oxygen and pH were measured over the duration of the experiment, using a 5000 Dissolved Oxygen meter / 5010 BOD probe (YSI, SKU: 050022 and 050103) and Orion Star™ A211 Benchtop pH Meter (Thermo Fischer Scientific, Catalog number: STARA2110), with values ranged between 6.80 – 8.74 mg L^{-1} and 7.14 – 8.77, respectively. Conditions throughout the 21-day toxicity test are summarized in Table S6.

2.7. Statistical analysis

Statistical analyses for concentrations and loadings of pharmaceuticals obtained in water samples using o-DGT passive devices were achieved using the R programming language (r-project.org, 2022): the packages 'knitr' (version 1.4.2) and 'BSD'(version 1.2.1) were applied to determine the weighted and summarized two-sample Welch's t-test, while 'stats' (version 4.2.2) and 'agricolae' (version 1.3-5) were used to perform one-way ANOVA with Tukey's HSD test.

For toxicity tests, statistical analyses were performed using Minitab software (Minitab® 19 for windows, Minitab LLC, USA). Homoscedasticity for biotest on *D. magna* was checked using the Bartlett test and normality was checked on ANOVA residuals using the Anderson-Darling test. Group comparisons were performed using one-way ANOVAs and significance parameters were obtained using the Tukey post-hoc test.

Throughout, results in graphs and tables are presented as mean value ± standard deviation (SD), unless otherwise stated. Differences were considered statistically significant at $p < 0.05$.

3. RESULTS AND DISCUSSION

3.1. Sources, occurrence, and seasonal variation of pharmaceuticals

All seven target pharmaceuticals were detected in all samples from the examined wastewaters and surface waters along six seasonal campaigns at concentrations from 0.012 to 3610 ng L^{-1} *(*Fig. 2, Table S7). The specific contributions of the investigated sources for the target analytes are discussed below.

3.1.1. Pharmaceuticals in hospital wastewaters

Hospitals are “hot spots” for pharmaceuticals, and their generally untreated wastewaters have been evaluated as more toxic than that from WWTPs (J. Xiang et al., 2018; Xu et al., 2019). The types and amounts of pharmaceuticals in hospital wastewater often differ from

that in domestic and industrial activities (M. T. Khan et al., 2021; Luo et al., 2014). The investigated hospital in this work was a large-size health care structure (>500 beds) and its wastewaters resulted from the combination of stormwater, laboratory, laundry, toilets, and patient services, which flowed through preliminary treatments such a gating, and then were released into the municipal sewage to the examined WWTP. The hospital acted as a sub-source contributing to the WWTP with a ~ 2% of the facility´s discharge rate.

In the hospital wastewaters, all compounds (atenolol, carbamazepine, levofloxacin, sulfamethoxazole, sulfamethazine and sulindac) were 100% detected above their limit of quantitation (LOQ) (Table S5), except sulfapyridine, that was found at concentrations lower than the LOQ (0.21 ng L^{-1}) with 83% of detection frequency (Fig. 2a., Table S7). The antibiotic levofloxacin was the most dominant pharmaceutical in hospital samples with concentrations ranging from 104 to 1020 ng L^{-1}. This antibiotic is the (S)-enantiomer of the fluoroquinolone ofloxacin, the most commonly used fluoroquinolone broad-spectrum antibiotic in human and veterinary medicine, marketed in the form of racemic mixture, with (S)-ofloxacin being 8-128 times more active than (R)-ofloxacin against Gram-positive and Gram-negative bacteria (Y. Chen et al., 2022). As for the other compounds, the concentrations were also prominent, namely, atenolol (53 to 530 ng L^{-1}), carbamazepine (26 to 510 ng L^{-1}), sulfamethazine (0.5 to 30 ng L^{-1}), sulfamethoxazole (64 to 360 ng L^{-1}), sulfapyridine (<0.21 to 100 ng L^{-1}), and sulindac (87 to 159 ng L^{-1}) (Fig. 2a, Table S7). High concentrations were found during sampling M1 (3/24-4/7), the first sampling in the dry season, and were pronounced (>172 ng L^{-1}) for atenolol, sulindac, carbamazepine and levofloxacin. For all compounds no significant differences were found between concentrations detected in the dry and rainy season, although concentrations for all pharmaceuticals remained high through sampling M3 (4/21-5/5), which ended at the beginning of the rainy season and declined during rainy season in samplings M8 (6/30-7/14), and M9 (7/14-7/28) to values ranging from 160 (carbamazepine) to 0.7 ng L^{-1} (sulfamethazine). Since for hospital wastewater no treatment was applied except for gratings to screen out large material, those variations may suggest possible stormwater leaks into the sewage system with no significant overall dilution effect compared to what may occur in outdoor environments.

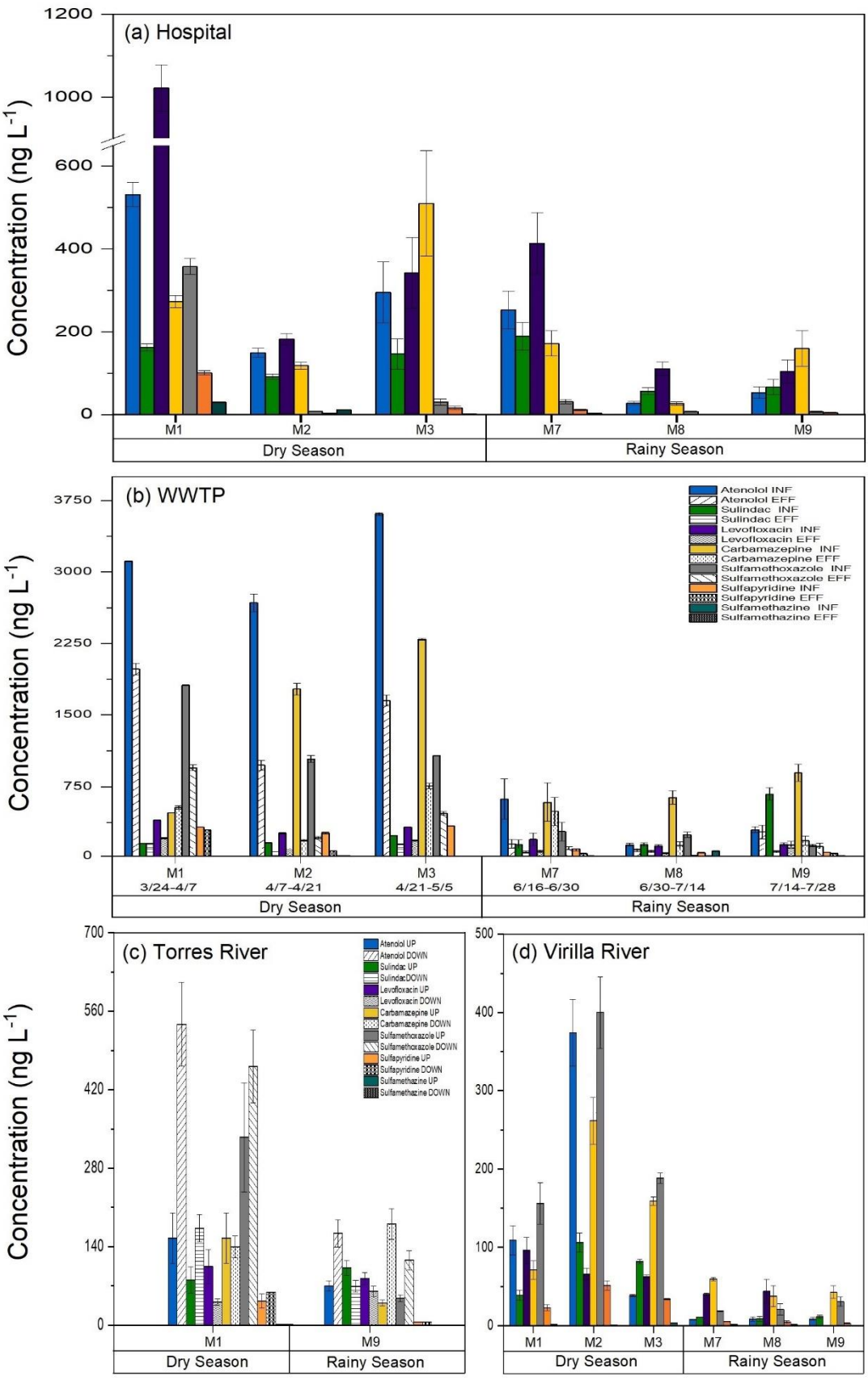
(a) Hospital
Concentration (ng L-1)
1200
1000
600
400
200
0
M1
M2
M3
M7
M8
M9
Dry Season
Rainy Season
(b) WWTP
Concentration (ng L-1)
3750
3000
2250
1500
750
0
Atenolol INF
Atenolol EFF
Sulindac INF
Sulindac EFF
Levofloxacin INF
Levofloxacin EFF
Carbamazepine INF
Carbamazepine EFF
Sulfamethoxazole INF
Sulfamethoxazole EFF
Sulfapyridine INF
Sulfapyridine EFF
Sulfamethazine INF
Sulfamethazine EFF
M1
3/24-4/7
M2
4/7-4/21
M3
4/21-5/5
M7
6/16-6/30
M8
6/30-7/14
M9
7/14-7/28
Dry Season
Rainy Season
(c) Torres River
Concentration (ng L-1)
700
560
420
280
140
0
Atenolol UP
Atenolol DOWN
Sulindac UP
SulindacDOWN
Levofloxacin UP
Levofloxacin DOWN
Carbamazepine UP
Carbamazepine DOWN
Sulfamethoxazole UP
Sulfamethoxazole DOWN
Sulfapyridine UP
Sulfapyridine DOWN
Sulfamethazine UP
Sulfamethazine DOWN
M1
M9
Dry Season
Rainy Season
(d) Virilla River
500
400
300
200
100
0
M1
M2
M3
M7
M8
M9
Dry Season
Rainy Season

Figure 2. Spatial and seasonal variation of target pharmaceuticals using o-DGT passive sampling over dry and rainy seasons (March to July 2017) reported in wastewaters of (a) Hospital and (b) WWTP influent (INF) and effluent (EFF), and surface waters of (c) Torres River and (d) Virilla River. Bars and errors represent means and standard deviation (n =3)

Most hospitals do not have on-site sewage-treatment plants to efficiently removed pharmaceutical residues, and are instead, connected directly to urban sewage systems, hence, there is likely to be a pronounced concentration of these residues in hospital wastewaters (aus der Beek et al., 2016). Our findings are in agreement with literature, reporting a more marked presence of compounds such as antibiotics and β-blockers in hospital effluents, compared with wastewaters from classical municipal sewage treatment plants (Verlicchi & Zambello, 2016). For instance, in a worldwide survey for 2018-2019, the highest occurrence in hospital wastewaters were reported for sulfamethoxazole and carbamazepine, with the highest concentrations of 1600 and 1900 ng L^{-1}, respectively (Hernández-Tenorio et al., 2022). Balakrishna et al. (2017) also reviewed high concentrations in hospitals effluents from India for sulfamethoxazole (81 μg L^{-1}), levofloxacin (81 μg L^{-1}), and ofloxacin (73 μg L^{-1}). Both review articles reported concentrations much higher than those found in our study for the same target compounds. Furthermore, frequently detected compounds such as fluoroquinolones, sulfonamides, and β-blockers were found in our work generally in relatively lower levels compared to other research studies. For example, Xu et al. (2019) reported concentrations of β-blockers including atenolol, up to 10 μg L^{-1} in hospital wastewaters from China, a higher value compared to the 5 ug L^{-1} found by the authors in the municipal WWTP close to the hospital, which showed that both places acted as sources of β-blockers in the environment. These values were higher than the concentrations of the investigated β-blocker drug obtained in our study. Other higher levels compared to our results were reported in Colombia, where the occurrence of pharmaceutical substances was studied in raw hospital wastewater samples, finding high levels for antibiotics such as norfloxacin fluoroquinolone (10.1 μg L^{-1}) and sulfamethoxazole (1.30 μg L^{-1}) and for the antihypertensive drugs such as irbesartan and losartan (0.03 to 7.65 μg L^{-1}) (Botero-Coy et al., 2018). Furthermore, in Mexico, hospital effluents were reported to have antibiotics such as sulfamethoxazole and ofloxacin at maximum concentrations ranged from 2100 to 35 500 ng L^{-1} (Brown et al., 2006). Last, the findings of our research are in agreement with previous results in Costa Rica, in which

sulfamethazine and sulfamethoxazole were detected in urban wastewaters influenced by hospital discharges (Spongberg et al., 2011).

Overall, to find antibiotics as the dominant drug class in the investigated hospital wastewaters raises concern because most of them are excreted via urine and feces into wastewaters and have been linked to the emergence of multi-drug-resistant bacteria and toxicity effects on aquatic organisms (Koch et al., 2021; Reichert et al., 2019; Tiwari et al., 2017; Yasojima et al., 2006). After human and animal administration, about 70% of fluoroquinolones are excreted out in unaltered form, in fact, levofloxacin has an excretion rate of 85%, which along with the presence of fluorine atoms (Table S1) that limit its microbial degradation and its water-soluble and moderately hydrophilic nature, facilitate its mobility throughout the water column, to eventually reach natural aquatic systems (Bhatt & Chatterjee, 2022; Yasojima et al., 2006). Among the effects, some fluoroquinolone drugs have been shown to exert genotoxic outcomes for the genetically modified bacterial strain *Salmonella typhimurium* (e.g., norfloxacin at 5000 ng L^{-1}) (Brown et al., 2006). Moreover, a synergetic interaction between clarithromycin and levofloxacin causing severe oxidative stress and inhibiting cell growth, was observed on the common bloom cyanobacterium M. *aeruginosa* (Wu et al., 2022), and multidrug-resistance in *Acinetobacter baumannii* has been detected under levofloxacin exposure (C. Zhang et al., 2023). In Costa Rica, scarce reports have identified concerns on antibiotics effects, such as different resistance mechanisms in *E. coli* strains with the extended-spectrum beta-lactamase phenotype, and presence of methicillin resistant *Staphylococcus aureus* on human and animal contact surfaces, likely related to inadequate wastewaters management (MS, 2018).

Although the studied hospital has a small discharge rate compared to the WWTP, our results confirmed the contribution that these medical wastewaters can pose to the environment with particular compounds such antibiotics, and consequently, the potential adverse impacts that may be associated (Barcellos et al., 2022; Chaturvedi et al., 2021; Klatte et al., 2017).

3.1.2. Pharmaceuticals in the WWTP

3.1.2.1. Temporal trends

In this work, during both seasonal monitoring campaigns, the highest concentrations of pharmaceuticals were detected in the influent and effluent of the WWTP (Fig. 2b, Table S7).

At the influent, the weighted average concentrations detected for atenolol, levofloxacin, sulfamethoxazole and sulfapyridine showed significant differences between the dry and rainy seasons, suggesting different consumption patterns of these compounds with seasonality, while for carbamazepine, sulfamethazine and sulindac no significant differences were observed. Seasonal maximum concentrations in the wet and dry terms were respectively 620 and 3610 ng L^{-1} for atenolol, 890 and 2290 ng L^{-1} for carbamazepine, 198 and 399 ng L^{-1} for levofloxacin, 50 and 6 ng L^{-1} for sulfamethazine, 280 and 1810 ng L^{-1} for sulfamethoxazole, 72.8 and 339 ng L^{-1} for sulfapyridine and 672 and 239 ng L^{-1} for sulindac. Taking water flow into consideration, seasonality was also evidenced by loading results. Pooled monthly loadings for most compounds (atenolol, levofloxacin, sulfamethoxazole, sulfapyridine and sulindac) were significantly higher ($p<0.05$) in the dry season, and atenolol was the compound with more prominent loads at most of the samplings. Differences between sampling seasons may be mostly due to attenuation by dilution and variations in therapeutic use and consumption patterns in the serviced population, e.g., carbamazepine is used for chronic ailments and thus it must be consumed regularly, while sulindac may be consumed more during wet season for flu symptoms. Moreover, regarding sulfamethazine, a widely used in veterinary medicine (García-Galán et al., 2012), the concentrations may have increased during wet season due to surface runoff from large adjacent areas to the WWTP, that likely introduced the contaminant excreted by animals to the wastewaters.

3.1.2.2. Occurrence in WWTP

All compounds were detected in both sites of the WWTP, with concentrations ranging from 1-3610 ng L^{-1} in influent and 0.034-1980 ng L^{-1} in effluent (Fig. 2b, Table S7). Atenolol had the highest concentration in both sites. Across samplings, a decreasing trend was observed between the influent and effluent concentrations with significant differences for most compounds (atenolol, sulfamethoxazole, sulfapyridine, and sulfamethazine), while carbamazepine, levofloxacin and sulindac displayed varied results. Details on occurrence data are discussed above.

3.1.2.2.1. Influent concentrations

For each compound, minimum and maximum influent concentrations were 140-3610 ng L^{-1} for atenolol, 476-2290 ng L^{-1} for carbamazepine, 128-399 ng L^{-1} for levofloxacin, 1-50 ng L^{-1} for sulfamethazine, 135-1810 ng L^{-1} for sulfamethoxazole, 33-339 ng L^{-1} for sulfapyridine, and 144-672 ng L^{-1} for sulindac (Fig. 2b, Table S7). Findings from this work were consistent with results reported elsewhere, for example, previous works stated the pseudo-persistence in the environment and resistance to biodegradation of atenolol, carbamazepine and sulfamethoxazole (Ebele et al., 2017; Nava-Andrade et al., 2021; Sousa et al., 2018), thus its occurrence in water sources is more likely. Table S8 summarize the concentrations of the investigated pharmaceuticals reported in influent and effluent waters of various WWTPs around the world, confirming that many of these substances are not effectively removed by conventional treatments usually applied in municipal facilities, as was evidenced in the present research.

Commonly prescribed atenolol was the compound with the highest influent concentration of 3610 ng L^{-1} among the studied drugs. In Costa Rica the β-blocker atenolol is widely prescribed (CCSS, 2015), it is used for the treatment of arterial hypertension, a highly prevalent chronic disease in humans (Steinbach et al., 2014), hence domestic wastewaters may be an important source of atenolol to the wastewaters of the investigated municipal treatment plant. Several reviews around the world have found consistently high concentrations of atenolol in the influents of municipal WWTPs from Europe, Asia, and North America, some of them with concentrations even higher than the reported in the current research. For example, Tran et al. (2018) reported significant higher concentrations of atenolol compared to the other β-blockers, with maximum values up to 2642 ng L^{-1} in North America, 33 106 ng L^{-1} in Europe and even 294 700 ng L^{-1} in Asia. Verlicchi et al. (2012) reported concentrations as high as 25 000 ng L^{-1} from 250 surveyed urban WWTPs, and Khasawneh & Palaniandy et al. (2021) reviewed similar high magnitudes in France (26 500 ng L^{-1}), India (2500 ng L^{-1}), Greece (2300 ng L^{-1}), USA (2440 ng L^{-1}) and Tunisia (1440 ng L^{-1}). The maximum concentration of atenolol exhibited in our study was higher than the maximum concentration (1700 ng L^{-1}) reported by Peña-Guzmán et al. (2019) for urban wastewaters in Latin America (including Brazil, Colombia and Costa Rica), higher than the 90 ng L^{-1} found by Rivera-Jaimes et al. (2018) in México and 3-fold higher than the maximum level (1700 ng L^{-1}) found by Elorriaga et al. (2013) in urban WWTPs from Argentina.

Carbamazepine concentrations measured in this research were lower than the maximum value (~ 22 000 ng L^{-1}) reported for developing countries such as India (Parida et al., 2021; Verlicchi et al., 2012), and in the same order of magnitude to the concentrations of 3700 ng L^{-1} globally reviewed by Luo et al. (2014), 2300 ng L^{-1} found in Argentina (Elorriaga et al., 2013), 3000 ng L^{-1} reported in Brazil (Pivetta et al., 2020) and 1900 ng L^{-1} found in Colombia (Cristina et al., 2022). Whereas the levels exhibited in this work were above the 380 ng L^{-1} in México (Rivera-Jaimes et al., 2018) and the concentration of 25 ng L^{-1} reported in Costa Rica during 2011 by (Spongberg et al., 2011), which suggested an increasing trend over time in the consumption of this psychiatric drug in the country.

Regarding the investigated antibiotics, out of the four target antibiotics, sulfamethoxazole was found with the greatest concentrations. Sulfamethoxazole is one of the most detected compounds worldwide (Yang et al., 2017). Our findings in influent wastewaters were lower than the concentrations of 54 830 ng L^{-1} reported in Kenya (K'oreje et al., 2016), 4200 ng L^{-1} in North America (Tran et al., 2018), 7190 ng L^{-1} in China (Gao et al., 2012) and 5980 ng L^{-1} in Perú (Nieto-Juárez et al., 2021); our levels were similar to the 2010 ng L^{-1} found in a conventional WWTP from México (Rivera-Jaimes et al., 2018) and slightly greater than the 729 ng L^{-1} recorded in Colombia (Botero-Coy et al., 2018).

The levofloxacin concentrations in the influent were in the range of other earlier studies, such as 250-981 ng L^{-1} in a global survey (Bhatt & Chatterjee, 2022), 307-981 ng L^{-1} in Japan (Yasojima et al., 2006), and 1080-1550 ng L^{-1} in Kenya (K'oreje et al., 2016). Other investigations have reported concentrations of ofloxacin (the racemic mixture with 50% levofloxacin) with worldwide values of 5100 ng L^{-1} (Verlicchi et al., 2012) and 1120 ng L^{-1} (Vargas-Berrones et al., 2020), and 390 ng L^{-1} (Brown et al., 2006) in Mexico. As was commented previously, fluoroquinolones such as levofloxacin are excreted mostly as parent compounds (>70%) and are recalcitrant towards conventional treatments, thus their presence in wastewaters is likely (Y. Chen et al., 2022).

The two remaining antibiotics (sulfamethazine and sulfapyridine) are widely used in veterinary medicine (K. L. Chen et al., 2017). In this study their concentrations showed maximum values in the influent up to 50 and 339 ng L^{-1} respectively. These sulfonamides have been reported in worldwide surveys and research studies of urban WWTPs at higher and similar levels than the observed in our work, for example, for sulfapyridine from 60 to 150 ng L^{-1} (Göbel et al., 2007) and up to 12 400 ng L^{-1} (Verlicchi et al., 2012) and for sulfamethazine with values ranged from 150 ng L^{-1} (Couto et al., 2019) to 1814 ng L^{-1} (Tran

et al., 2018). Runoff from areas around the WWTP and wastewaters from households could contributed to the concentrations found in the examined wastewaters. In Costa Rica, antibiotics are prescribed by private and public medical institutions, thus these marked levels of antibiotics may be related to the fact that the WWTP receiving wastewaters are influenced by other sources than the public hospital effluents presented in this work, such as wastewaters from households and private medical facilities connected to the municipal sewage system.

Regarding the NSAID drug class, data on environmental occurrence of sulindac are scarce (Ledezma-Espinoza et al., 2021). In this work the greatest concentrations were found in the influent of the WWTP (up to 672 ng L^{-1}), which was similar to the 644 ng L^{-1} reported in influents from China (Guan et al., 2016). The greatest concentration of sulindac was found in the sampling M9 (7/14-7/28) during the rainy season (Fig. 2b, Table S7), which probably may be related to more consumption due to seasonal ailments such as flu and the ease of obtaining the drug over the counter in the country. The presence in the aquatic environment of NSAIDs such as sulindac may raise concern about the adverse effects that its chronic exposure may cause, particularly to wild fish populations (Marmon et al., 2021), thus enhance the knowledge about their occurrence is a main issue.

3.1.2.2.2. Effluent concentrations

Pharmaceutical concentrations at the effluents depend on factors such as the removal efficiency of the WWTP, the physicochemical properties of the target drugs and the influent concentration levels, thereby result in composition profiles that are different from influents (Papageorgiou et al., 2016). In this study, all compounds detected in the influent were also present in the treated effluents at pronounced concentrations, with atenolol and sulfamethoxazole being the dominant compounds. Minimum and maximum concentrations in the WWTP effluent were 60-1980 ng L^{-1} for atenolol, 140-760 ng L^{-1} for carbamazepine, 29-210 ng L^{-1} for levofloxacin, 0.034-3.3 ng L^{-1} for sulfamethazine, 11-950 ng L^{-1} for sulfamethoxazole, 5.8-300 ng L^{-1} for sulfapyridine, and 38-150 ng L^{-1} for sulindac (Fig. 2b, Table S7).

Many studies informed on the inefficiency of conventional WTTPs to remove emerging compounds such as pharmaceuticals (Eniola et al., 2022; Sivaranjanee & Kumar, 2021; Tiwari et al., 2017; Yang et al., 2017), and the gap existent in the management of

pharmaceutical pollution between developed and developing countries (Barcellos et al., 2022; Peña-Guzmán et al., 2019). Concentrations found in the effluents are important to dimension the potential impact of the anthropogenic pollution to the environment and public health. Overall, the high effluent concentrations in the current study were in accordance with the data shown in other countries.

Our findings had a similar occurrence trend to the developing country of India, where atenolol, sulfamethoxazole, and carbamazepine were the most commonly detected drugs at higher concentrations in the effluents of WWTPs that treated predominantly the domestic sewage (Balakrishna et al., 2017). In the present study, atenolol showed a significant higher concentration in the effluent (1980 ng L^{-1}) compared to the other compounds, which was similar to the nationwide range (197-1500 ng L^{-1}) recorded in India by Balakrishna et al. (2017), but lower than the maximum values found in municipal WWTPs from other geographical regions, such as the reports of 14200 ng L^{-1} and 7602 ng L^{-1} for North America and Europe respectively (Tran et al., 2018), the reviewed values of 3700 ng L^{-1} (Verlicchi et al., 2012) and 7600 ng L^{-1} (Luo et al., 2014) and the concentration of 2772 ng L^{-1} for a municipal effluent from Korea (Behera et al., 2011). Lower concentrations of atenolol than those found in our research were recorded in Mexico (90 ng L^{-1}) (Rivera-Jaimes et al., 2018) and in a survey of urban effluents in Latin America with concentrations ranging from 38 to 277 ng L^{-1} (Peña-Guzmán et al., 2019).

Varied results have been reported for the remaining investigated compounds in conventional WWTPs around the world. For example, compared to our study, Nieto-Juárez et al. (2021) reported the effluent concentrations from a WWTP with primary treatment and found higher concentrations for sulfamethoxazole (up to 2360 ng L^{-1}) but lower levels for carbamazepine (90 ng L^{-1}), whereas Pivetta et al. (2020) recorded carbamazepine values between 244-3000 ng L^{-1} in effluent samples from Brazil. Although environmental occurrence data on the NSAID sulindac is limited, our study exhibited lower concentrations compared to the report (312 ng L^{-1}) in effluents from China (Guan et al., 2016). Moreover, regarding the remaining antibiotics investigated in this research, levofloxacin concentrations were lower to the maximum (400 ng L^{-1}) found in Japan by Yasojima et al. (2006). Sulfapyridine sulfonamide showed a higher value in this work compared to the 28 ng L^{-1} recorded in Spanish effluents (J. Wilkinson et al., 2017) but a lower result than the reported (493 ng L^{-1}) in China (Tamura et al., 2017). Meanwhile sulfamethazine concentrations in the present study were lower than 408 ng L^{-1} described in Korea (Behera et al., 2011). Antibiotics are of special interest

because of their potential impact on the spread and maintenance of antimicrobial resistance (Chaturvedi et al., 2021; Ohore et al., 2022), actually, Reichert et al. (2019) pointed out that the therapeutic class of antibiotics should be part of the priority list for monitoring in Latin America due to its high detection and potential antimicrobial resistance impact, therefore, improving knowledge about the emergence of antibiotics in developing countries such as Costa Rica is a matter of great concern.

3.1.2.2.3. Removal efficiency

There is an important scarcity of investigations reporting the spatial and temporal trends and removals of pharmaceuticals in Latin America compared to developed countries, in special for conventional WWTPs than usually include only primary and secondary treatments (Barcellos et al., 2022; Cristina et al., 2022; Hernández-Tenorio et al., 2022). In general, conventional WWTPs comprise a primary system of physico-chemical treatments and a secondary system with biological treatment formed by actived sludge (Rivera-Utrilla et al., 2013). The investigated WWTP in this study only applies primary treatment and it is the largest facility in Costa Rica, serving over half of the estimated population of the GAM, and treating an average of 519 L s^{-1} (Mora-Aparicio et al., 2022). In this facility, the combined wastewaters (stormwaters, domestic, hospital and industrial wastewaters) are treated via screen- and grit-removal, degreasing and primary sedimentation, and subsequently discharge into the Torres River (Mora-Aparicio et al., 2022).

By comparing the concentrations found in the influent with those obtained in the effluent, allowed us to roughly estimate the removal efficiency in the WWTP. No significant differences were identifiable for carbamazepine and sulindac in the dry season, and nor for atenolol, sulindac, and sulfamethazine during the rainy season. Findings demonstrated that removals were compound-specific, varying widely between negative and positive differences from influent to effluent. Overall, average removal efficiencies were 49% for atenolol, 53% for carbamazepine, 53% for levofloxacin, 50% for sulfamethazine, 59% for sulfamethoxazole, 50% for sulfapyridine, and 54% for sulindac. It must be noticed that during sampling M1 (3/24-4/7), carbamazepine concentration was observed to increase from influent to effluent.

The removal efficiency for the target pharmaceuticals in our study showed varied results compared to that of other countries as depicted in Table S8. For conventional WWTPs, the removal efficiency for emerging contaminants such as pharmaceuticals varies respectively in the range of 20–50% and 30–70% during the primary and secondary treatment steps, respectively (Rout et al., 2021). Previous research (Adeleye et al., 2022; Behera et al., 2011; Botero-Coy et al., 2018; Destrieux et al., 2017; Göbel et al., 2007; Guan et al., 2016; Luo et al., 2014; Nieto-Juárez et al., 2021; Pivetta et al., 2020) have also reported the challenges of conventional WWTPs to remove the same target compounds from this study. For example, low removal efficiencies were found for levofloxacin from 42% with primary treatment (Yasojima et al., 2006) to up 53% with conventional activated sludge process (Wu et al., 2022), whereas other investigation reported removals for atenolol of <28% and 64% in primary and secondary treatment respectively (Behera et al., 2011). Moreover, negative removals for carbamazepine have been documented widely, which may be explained considering that it is mainly excreted as its glucuronide metabolite, and the deconjugation of this compound in the sewage treatment process is plausible, leading to the increase of concentration in the effluents (Gurke et al., 2015; M. Kumar et al., 2022; Miao et al., 2005; Papageorgiou et al., 2016; J. Wang & Wang, 2016).

Furthermore, to assess the performance of the WWTP as a primary treatment facility, the variations of physicochemical parameters were consulted in literature. Mora-Aparicio et al. (2022) analyzed the removal of physicochemical and microbiological pollutants from the WWTP examined in the actual research during the operation years from 2015 to 2020, and reported significant removal of seven of the eight parameters analyzed, with the most representative removal percentages being the Total Suspended Solids (69%, TSS), Biochemical Oxygen Demand (52%, BOD), Chemical Oxygen Demand (50%, COD) and Fat, Oils and Grease (55%, FOG). In addition, the authors stated that the facility did not significantly remove nutrients such as phosphorus and nitrogen from the wastewaters (<20%), as it was expected for being a primary WWTP. Hence, in the investigated WWTP it was expected to observe that several pharmaceuticals can still be detected in relative high concentrations in influent samples, since the primary treatments are not designed to completely remove emerging contaminants such as pharmaceuticals (Choi et al., 2022). Overall, the performance of the full-scale system was in compliance with the regulatory levels for a primary WWTP based on the water quality parameters of TSS (<145 mg L^{-1}), BOD (<184 mg L^{-1}), COD (<460 mg L^{-1}) and FOG (Mora-Aparicio et al., 2022), nevertheless,

the results of pharmaceuticals showed the recalcitrant nature of the compounds and their inefficient removal in the WWTP with primary treatment.

The sedimentation/clarification process is the most common primary treatment, where large and coarse solids with sufficient density are removed by gravitational settling and fat/grease is skimmed from the top of wastewater (Adeleye et al., 2022; Gogoi et al., 2018). At this primary stage some pharmaceuticals may be removed by adsorption to settling particles or absorption into fat/grease floating on the wastewater surface (Adeleye et al., 2022). However, the polarity and high water solubility of pharmaceuticals as well as the pH dependence of ionizable compounds, reduce the removal effectiveness through physical processes that are applied such as filtration, flocculation and sedimentation (Ahmed et al., 2021; Lapworth et al., 2012; Luo et al., 2014; Yang et al., 2017). According to literature, poor sorption to the particles removed in this stage is expected due to the medium-high polar nature of the target compounds (Table S1) (Christensen et al., 2022; Li, 2014; Papageorgiou et al., 2016; Patel et al., 2019), and due to the effect of analyte ionization (neutral, positive, negative) on the extent of sorption-desorption processes (Behera et al., 2011; Berthod et al., 2016; K. L. Chen et al., 2017; Martínez-Hernández et al., 2014; Rivera-Utrilla et al., 2013; Tran et al., 2018). Regarding factors that may influenced sampling, it should be acknowledged that evidence for fouling was observed on most of the samplers at the effluent site and that temperature measurements were not possible to conduct, those are factors that can influence the sampling rates for the reported analytes and therefore the reported concentrations, as has been informed in earlier studies (Challis et al., 2016; C.-E. Chen et al., 2013; C. E. Chen et al., 2012; Gong et al., 2018; Ji et al., 2022; Perez et al., 2022; Vrana et al., 2005). Briefly, some studies suggest that fouling might increase the DBL thickness acting as an additional layer on the surface of the outer gel, or it may have interactions with the analyte, therefore, to reduce the effect, short-term deployments (<21 days) are recommended (Challis et al., 2016; C. E. Chen et al., 2012). Although to our knowledge, there is no reports of organic analytes detected in fouled diffusive gels, and little effect of fouling on organic DGT uptake have been informed during field deployments, significant fouling should be interpreted with caution (Ji et al., 2022), since more research is needed on this topic. Furthermore, the uncertainty associated with the temperature dependence of the diffusion coefficient have been also investigated previously (Challis et al., 2016; C. E. Chen et al., 2012). For instance, Challis et al. (2016) reported uncertainties due to fluctuating

water temperatures during deployments that reached roughly up to 12% per degree over a temperature range of 18°C between 5 and 23°C.

3.1.2.3. Mass loadings in WWTP effluent

To assess the impact of the WWTP to the load of pharmaceuticals into the Torres River, wastewaters from the effluent directly discharged in this river were analyzed. Average monthly loadings (Fig. 4, Table S7) at the WWTP were calculated for each season by multiplying the average daily water discharge in WWTP by the concentration of each pharmaceutical during each sampling period. Effluent loads were not statistically different between seasons for carbamazepine, levofloxacin, sulfamethoxazole, sulfapyridine and sulindac, but were for atenolol and sulfamethazine.

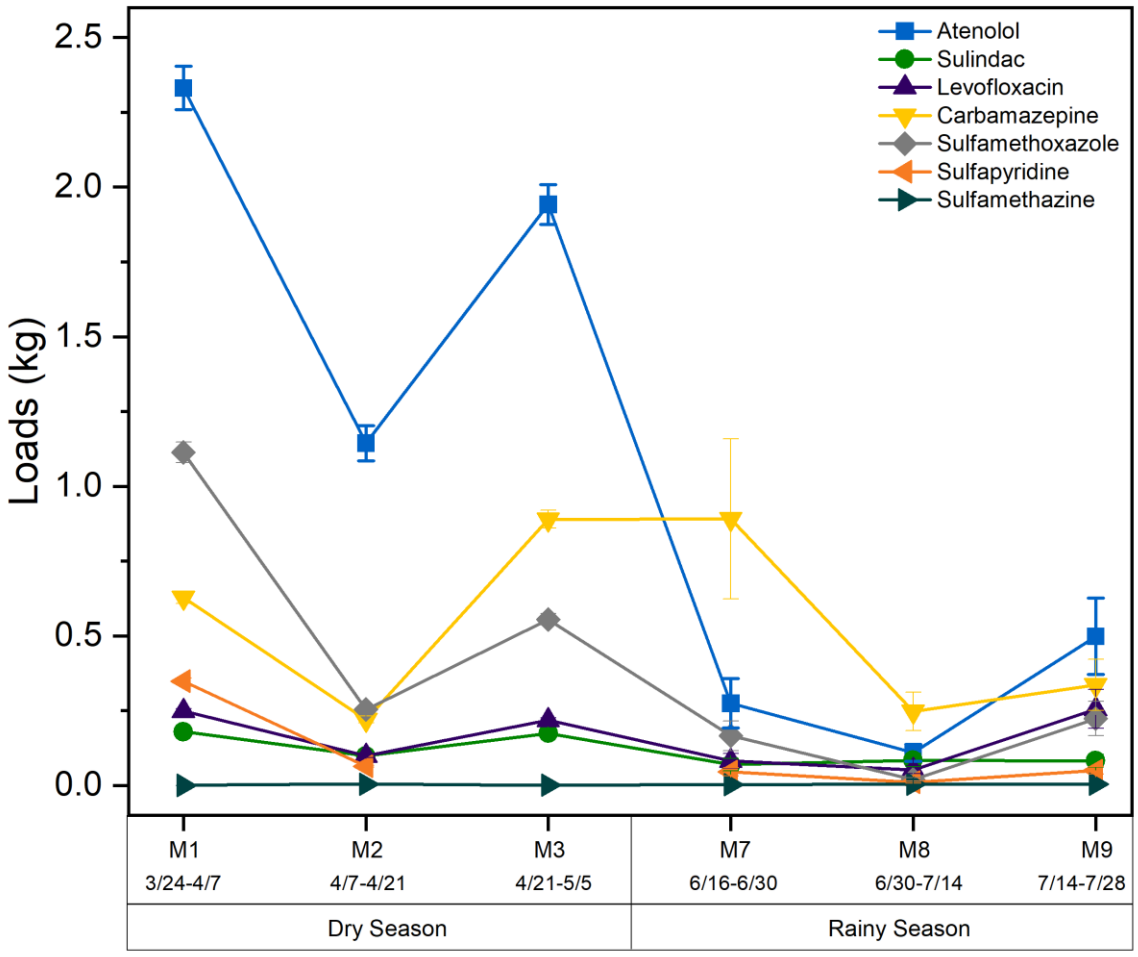

Figure 3. Monthly loadings of tested pharmaceuticals from the WTTP effluent directly discharged into the Torres River. Errors as SD.

Total monthly mass loads detected in the WWTP effluent were significantly higher (10.5 kg) in dry season than in the rainy season (3.5 kg) and resulted in a weighted annual average load of 19.6 kg for all detected pharmaceuticals discharged into the surface waters of the Torres River (Fig. 3). ANOVA analysis followed by Tukey comparisons were applied among loadings of different compounds at each sampling campaign, showing that among all compounds, atenolol consistently recorded the highest ($p>0.05$) monthly loadings at most of the sampling periods, except for M7 (6/16-6/30) and M8 (6/30-7/14), where carbamazepine was dominant. Pooled monthly loadings for the entire investigation were 6.3 kg for atenolol, representing a 45% of the total, followed by carbamazepine (3.2 kg, 23%), sulfamethoxazole (2.3 kg, 16%), levofloxacin (0.96 kg, 7%), sulindac (0.69 kg, 5%), sulfapyridine (0.52 kg, 3.7%) and sulfamethazine (0.02 kg, <1%).

The variation of the total loads for the pharmaceuticals can be justified by many factors including consumption, metabolized fraction, seasonal conditions (flow rate, temperature), kinetics, physicochemical properties such as log Kow and pKa and their degradation pathways, which can determine their fate, occurrence, and removal efficiencies (Gurke et al., 2015; Mezzelani et al., 2018; Paíga et al., 2016; Schwarzenbach et al., 2003; Sun et al., 2016). In general, atenolol and carbamazepine followed different trends, suggesting different sources and consumption habits among the investigated compounds. Both drugs are utilized to treat chronic illnesses (Nkoom et al., 2019; Steinbach et al., 2014), and in Costa Rica, both compounds are widely consumed either by prescription or over the counter.

As discussed earlier, atenolol displayed significant differences between concentrations of the influent samples for both seasons and significant greatest loads were found in the dry season, suggesting a seasonal behavior, contrary to expectations. The variability and great levels of atenolol might be related to its prevalence during wastewater treatment, accessible acquisition in the country, high consumption, and its high excretion rate as parent compound (up to 90%) (Bendz et al., 2005) (Table S1). Although in Costa Rica it is used as a continuous anti-hypertensive drug, it is chosen among other commonly prescribed β-blockers, and its prescription can change according to patient needs (Chaves, 2013). Furthermore, atenolol has a high reported national consumption in public facilities (2.16 ton) (CCSS, 2015), and

its occurrence may be affected by additional contributions during peak tourism that overlaps with dry season, which may lead to serviced population fluctuations. Previous studies have documented an increase in pharmaceutical concentrations due to the tourism season (Sharma et al., 2019; J. L. Wilkinson et al., 2017), and others have reported atenolol as the compound with the highest mass loads in wastewaters (Asia, 597-29.6 g/1000 in./day), justifying this value to the high release as unaltered compound of atenolol and its pseudo-persistency (Khasawneh & Palaniandy, 2021). Last, it is important to evaluate the contribution of the WWTPs with this drug class to the receiving waters, due to their potential impact on aquatic environment, since for example, previous investigations have associated β-blockers such as atenolol with sexual dysfunction in mammals, adverse effects on fish physiology and behaviour, and bioaccumulation in fish (Behera et al., 2011; Roberts et al., 2016).

Carbamazepine had a trend opposite to the rest of the compounds, with a greater load found in the sampling M7 (7/14-7/28) of the rainy season and no significant difference between the dry and rainy season at both influent and effluent sites, showing overall that the pharmaceutical displayed no seasonality and that its detection was in accordance with a drug for long-term treatment. This trend may be attributed to its specific prescription and continuous consumption for the control of chronic illness such as epilepsy and bipolar depression, and its stable structure that promotes its highly environmental persistence (Clara et al., 2004; C. F. Williams et al., 2006). Moreover, although excretion rate of carbamazepine as parent compound is minimal (<5%) (Table S1) compared to its metabolites (Pal et al., 2010), it was found as the second most widely consumed drug among the investigated pharmaceuticals (only after sulfamethoxazole), with an annual national public consumption of 2.92 ton (CCSS, 2015), those factors added to its high concentrations detected in wastewaters and its negative to lower removals in WWTP, may justify its constant presence during the entire period of sampling in this research.

The antibiotic and NSAID drug classes generally had similar loads during the six samplings, suggesting that their continuous inputs may have compensated for most of the variability due to transformations during wastewater treatment, dilution, excretion, and consumption patterns throughout both seasons (Fig. 4). Specifically, they showed varied consumption and excretion, i.e., levofloxacin (<1 ton, 86%), sulfamethazine (20%), sulfamethoxazole (3.2 ton, 39%) sulfapyridine (10%) and sulindac (2.9 ton, 50%), as well as different consumption patterns, namely, only antibiotics are consumed by prescription, but some of them are used

mostly in veterinary medicine, while sulindac is accessible over the counter and is used mostly for human seasonal illness. Moreover, it must be acknowledged that local public prescription rates reported here may not reflect the exact national trends, since the consumption over the counter and by private medical facilities was not considered in this research.

Overall, according to the therapeutic class, the pattern of contribution of mass loads was: NSAIDs< antiepileptics< antibiotics < β-blockers. Some relative rankings can be made among the compounds, for example, for those compounds that arrived at the WWTP principally in an unaltered form (>50%), i.e., atenolol, levofloxacin and sulindac, the relative rankings of drugs observed in wastewaters and load contributions agreed with the hypothesis that the greater their use, the greater their concentrations and loads (i.e., levofloxacin < sulindac < atenolol). While for those compounds more extensively metabolized (carbamazepine, sulfamethazine, sulfapyridine, and sulfamethoxazole) this trend was not observed. Carbamazepine was the main exception with the lowest excretion rate but consistently great loads during both seasons as discussed above. Whereas sulfamethoxazole with a greater excretion than carbamazepine and the highest consumption in the study, ranked at the third place for contributions to the effluent wastewaters, behind carbamazepine and atenolol. Similar to our findings, differences in pharmaceutical mass loadings have been observed in other countries due to a great variability of consumption, climatic conditions, contexts of water treatment, and applied sampling strategies (Papageorgiou et al., 2016). Hence, more frequent monitoring over the long term is needed to better characterize the pharmaceutical behavior at effluents or inputs to the effluent-receiving environment in the area. This information is relevant since effluent wastewater is one of the main sources of contamination to receiving surface waters (Bijlsma et al., 2021; Y. Xiang et al., 2021).

3.1.3. Pharmaceuticals in surface waters

3.1.3.1. Overall findings

Surface waters reflected the anthropogenic impact of the surrounding areas. All pharmaceuticals were detected in the Virilla River and the Torres River with concentrations ranging from 0.012 to 537 ng L^{-1} over the six sampling campaigns (Fig. 2b, Table S7). As

mentioned above, due to difficulties accessing the Torres, samples upstream and downstream of the WWTP were only collected twice, once each during wet and dry seasons. At time points when both rivers were analyzed (sampling M1, 03/24-04/07 and M9, 07/14-07/28), concentrations upstream in the Torres were generally greater than those at the Virilla, likely due to greater dilution from the larger volume of water in the latter. At these time points, sulfamethoxazole had the greatest values among the investigated compounds, with 335 ng L^{-1} at the upstream in Torres River and 156 ng L^{-1} in the Virilla, both during the dry season in sampling M1 (03/24-04/07). This antibiotic is used in both veterinary and human medicine (aus der Beek et al., 2016), with a lower cost compared to other antibiotic sub-groups such as macrolides (e.g., erythromycin) (Fekadu et al., 2019), which may contribute to its high consumption and concentrations found in the investigated surface waters. Although sulfamethoxazole is common in the water bodies (Cristina et al., 2022; Hughes et al., 2013; Verlicchi et al., 2012), its presence is of concern due to its potential to cause antimicrobial resistance strains (for example on *E. coli*) and harm to aquatic ecosystems (Reichert et al., 2019), which has led to its inclusion in the recently updated Watch List of European Union (Nieto-Juárez et al., 2021; Reichert et al., 2019). From the above, sulfamethoxazole may be considered as a good marker of anthropogenic pollution (such as discharges of domestic effluents) in the country´s receiving waters.

As for the sources of pharmaceutical residues, both rivers were possibly influenced by informal settlements, waste dump sites and industrial discharges considering the highly urbanization of the area, while directly for Torres River, the WWTP effluent discharge was identified as the main source of contamination.

The occurrence of the target pharmaceuticals at levels at least one order of magnitude lower than the observed effluent concentrations (Fig. 2) was likely due to hydrological variability and different degrees of natural attenuation mechanisms discussed in the literature (e.g., mostly likely river water dilution and rainfall, with potential contributions from direct and indirect photolysis, and to a lesser extent sorption onto suspended solids and sediments and/or aerobic biodegradation) (Luo et al., 2014). Although different degrees of attenuation may occur, it will depend on the physicochemical properties for each compound, diversity of river systems (physicochemical and biological parameters), environmental dynamic boundary conditions like temperature or solar radiation and other anthropogenic factors such as variable consumption patterns, diffusive sources of pollution and input cycle of WWTPs (Acuña et al., 2015; Cardinal et al., 2016; Glaser et al., 2020), that may even overlap the

degradation of the drugs by the natural mitigation processes, allowing its ubiquitous detection and pseudo-persistence among environmental compartments (Paíga et al., 2016). This shows the need to periodically monitor the concentrations of pharmaceuticals to better determine their occurrence and assess their potential risks on freshwaters ecosystems.

3.1.3.2. Torres River

In Torres River the sampling site upstream of the WWTP discharge was selected to investigate background concentrations of pharmaceuticals originated from other sources than the WWTP effluent. All target compounds were detected at the upstream of the WWTP in Torres River, being sulfamethoxazole the compound with the greatest concentration (335 ng L^{-1}). Maximum concentrations at the upstream of the Torres of the other drugs were 155 ng L^{-1} for atenolol and carbamazepine, 104 ng L^{-1} for levofloxacin, 1.1 ng L^{-1} for sulfamethazine, 43 ng L^{-1} for sulfapyridine and 102 ng L^{-1} sulindac (Fig. 2c, Table S7). Significant differences between concentrations in dry and wet seasons were identified for carbamazepine, sulfamethoxazole and sulfapyridine, and were not observed for atenolol, levofloxacin, sulfamethazine and sulindac. Furthermore, it should be noted that values decreased for all compounds except sulindac between dry (M1, 03/24-04/07) and rainy season (M9, 07/14-07/28), namely, sulindac had a concentration of 102 ng L^{-1}, greater than the 80 ng L^{-1} found in the dry season. These differences and unexpected seasonality behaviour of compounds such as carbamazepine, could be related to the residues contribution from diffusive sources in the area, environmental variability and the potency of the statistical analysis, the latter since due to poor site access, only one sampling at each season was conducted for comparisons. The increase in consumption of the NSAID sulindac could be plausible as more individuals are likely to be sick with the flu or other such ailments during rainy season and due to its easy purchase without a prescription.

The presence of drug residues has been documented in surface waters upstream from conventional WWTP elsewhere (aus der Beek et al., 2016; Peña-Guzmán et al., 2019; Roberts et al., 2016; M. Williams et al., 2013). In Portugal, the study of Paíga et al. (2016) found lower concentrations for carbamazepine (24.9-64.4 ng L^{-1}), higher levels for sulfamethazine (up to 67.4ng L^{-1}), no detection for sulfamethoxazole and sulfapyridine, and a pronounced presence upstream WWTP of NSAIDs (up to 1317 ng L^{-1}). In México another research recorded a maximum concentration of 16 ng L^{-1} for atenolol that was lower than

the value obtained in the present study, and greater values for carbamazepine (276 ng L^{-1}), sulfamethoxazole (348 ng L^{-1}), and NSAIDs (up to 4880 ng L^{-1}) (Rivera-Jaimes et al., 2018). While in surface waters from South Africa concentrations in the same order of magnitude were found for atenolol (156 ng L^{-1}), carbamazepine (157 ng L^{-1}), sulfamethoxazole (757 ng L^{-1}), and NSAIDs (224 ng L^{-1}) (Archer et al., 2017). Moreover, in Costa Rica, Causanilles et al. (2017) confirmed the presence of atenolol, sulfamethoxazole, sulfapyridine and NSAIDs upstream from the effluent discharge point of a municipal WWTP smaller than the investigated in the present study.

The high concentrations of pharmaceuticals detected upstream of the Torres River may be a result of diffusive sources such as direct inputs of raw or not effectively treated sewage from the highly populated communities not covered up by the WWTP, improper management or disposal of septic systems waste, run-off and leachates from the major landfill (serving ~1,5 million habitants) located in the surrounding area (Fig. 1). Furthermore, the relatively high concentration of sulfamethoxazole may be also explained by its high consumption among the population, in fact, it showed a consumption of 3.15 ton among the investigated compounds according reports of public facilities (CCSS, 2015). Similar routes of pharmaceutical pollution have been evidenced in other studies (Balakrishna et al., 2017; Kapelewska et al., 2018; Li, 2014; Martín et al., 2012; Verlicchi et al., 2012). Our assumptions were consistent with the study of Mora-Aparicio et al. (2022) which informed about the poor physicochemical water quality (based on the BOD_5, NH_3-N and dissolved oxygen) found in the river´s upstream during the period of 2015-2020, attributed to the possible discharges of raw wastewaters into the river, which justified the severe pollution in the river even before the WWTP installation and regardless of seasonality.

Downstream of the Torres River the pronounced presence of all investigated pharmaceuticals was also noted (Fig. 2c, Table S7). The compounds were detected in all water samples generally with greater levels in the downstream than those observed in the upstream, reflecting the impact by the WWTP discharges. Concentrations between dry and rainy seasons showed diverse results, being atenolol the predominant compound with values of 537 (M1, 03/24-04/07) to 164 ng L^{-1} (M9, 07/14-07/28), followed by sulfamethoxazole (462-116 ng L^{-1}), sulindac (173-70 ng L^{-1}), carbamazepine (140-180 ng L^{-1}), sulfapyridine (58.8-5.6 ng L^{-1}) and sulfamethazine (1.3-0.5 ng L^{-1}). Compared to our study, Paíga et al. (2016) found in downstream water samples of a municipal WWTP, lower results for sulfamethoxazole (43 ng L^{-1}), similar levels for carbamazepine (up to 214 ng L^{-1}), and

higher concentrations for sulfamethazine (up to 123 ng L^{-1}); while concentrations for NSAIDs reached up to 875 ng L^{-1} and sulfapyridine was not detected. In downstream surface waters from South Africa, Archer et al. (2017) recorded similar values than our work for atenolol (272 ng L^{-1}) and carbamazepine (280 ng L^{-1}), but higher results for sulfamethoxazole (1013 ng L^{-1}) and NSAIDs (up to 1113 ng L^{-1}). In México, Rivera-Jaimes et al. (2018) recorded lower values for atenolol (32 ng L^{-1}) and carbamazepine (59 ng L^{-1}) than those obtained in the present study, and greater values for NSAIDs (up to 3840 ng L^{-1}) and sulfamethoxazole (722 ng L^{-1}), additionally, sulfamethoxazole was also reported in a similar concentration (300 ng L^{-1}) to our results in México by Brown et al. (2006). Moreover, in Costa Rican surface waters, carbamazepine was detected with a maximum concentration of 82 ng L^{-1} in waters downstream of a large tourist area (Spongberg et al., 2011) and the presence of atenolol, sulfamethoxazole, sulfapyridine and NSAIDs was also confirmed downstream from the effluent of a municipal WWTP (Causanilles et al., 2017).

3.1.3.3. Virilla River

In the Virilla River (Fig. 2d, Table S7), six sampling events were conducted, resulting in 42 days of monitoring for each season. Concentration of pharmaceuticals ranged from 400 ng L^{-1} (sulfamethoxazole, M2 (04/07-04/21), dry season) to 0.012 ng L^{-1} (levofloxacin, M9 (07/14-07/28), rainy season). The maximum concentrations for the compounds were 374 (atenolol), 262 (carbamazepine), 96.2 (levofloxacin), 3.3 (sulfamethazine), 400 (sulfamethoxazole), 51.4 (sulfapyridine) and 106 (sulindac) ng L^{-1}. No significant differences were found between seasons for the concentrations of atenolol, carbamazepine, and sulfamethazine, but they were for levofloxacin, sulfamethoxazole, sulfapyridine and sulindac, with concentrations in the rainy season lower than those in dry season, which probably may be attributed to different consumption patterns for each pharmaceutical (for chronic or seasonal illness) and natural attenuation predominantly from dilution.

Relevant concentrations of pharmaceuticals in surface waters of urbanized areas have been reported globally (aus der Beek et al., 2016; Ebele et al., 2017; Hughes et al., 2013; Peña-Guzmán et al., 2019). To place our results in context especially on the compounds most studied worldwide, the concentrations of carbamazepine and sulfamethoxazole (Fig. 2d, Table S7) were below those reported by some reviews on a global scale. For example, in the review for Europe and Africa by Fekadu et al. (2019), sulfamethoxazole and

carbamazepine were found within the top ten most frequently detected compounds in both continents, with sulfamethoxazole levels among the highest ones (up to 53 828 ng L^{-1} in Africa), ~100 times higher than in the European natural waters, and carbamazepine reaching concentrations up to 559 ng L^{-1} (Europe). Additionally, our measurements were lower than the described in the global survey by aus der Beek et al. (2016), where sulfamethoxazole and carbamazepine were found nearly as often as the NSAID diclofenac (the most frequently detected drug in the review), with maximum concentrations of 8050 ng L^{-1} for carbamazepine and 29 000 ng L^{-1} for sulfamethoxazole (both in surface waters from Europe). In China, the highest concentrations for sulfamethoxazole (1484 ng L^{-1}) and sulfamethazine (654 ng L^{-1}) informed by Xiang et al. (2021) were lower than the levels reported in our work. Furthermore, compared to the maximum concentrations included in the review for Latin America by Peña-Guzmán et al. (2019) (one of the few surveys for the region), our measurements were higher than the reviewed for sulfamethoxazole (106 ng L) and lower compared to those for atenolol (5149 ng L^{-1}) and carbamazepine (36 920 ng L^{-1}). Additionally, the pharmaceutical concentrations in the Virilla River for sulfamethoxazole were similar to those found in Mexico (300 ng L) (Brown et al., 2006), but lower than in Peru (4600 ng L^{-1}) (Nieto-Juárez et al., 2021).

On the less studied compounds around the world, our results (Fig. 2, Table S7) were similar to the concentration described for levofloxacin (40 ng L^{-1}) by a Kenyan based study (K'oreje et al., 2016), and according to the same author, much lower than the reported value for sulfamethazine (630 ng L^{-1}). For sulindac, the maximum level found in our research was similar than the concentration reported (<148 ng L^{-1}) for a river in China (Guan et al., 2016). Regarding Costa Rica, our data agreed with the previous detection of atenolol (Causanilles et al., 2017), and compared to the study by Spongberg et al. (2011), our measurements resulted higher than those described for carbamazepine (82 ng L^{-1}) and sulfamethoxazole (56 ng L^{-1}) and were lower than the concentration reported for sulfamethazine (1626 ng L^{-1}). Overall, our results confirmed that the target pharmaceuticals of our study were ubiquitous in the investigated surface waters from the urbanized areas.

It is worth to acknowledge that the Virilla has been considered the river with the highest anthropogenic contamination in Costa Rica, with a land use mostly intended for industrial (11%) and urban purposes (48%), which receives approximately 67% of the national wastewater discharges (Mena-Rivera et al., 2018). At the surrounding area of the river, several potential sources of pharmaceutical pollution were identified. For example, there are

highly populated cities and several informal urban settlements particularly close to our sampling site, with most of the households not connected to the WWTP and using septic tanks to manage wastewaters. In addition, waste dumps are found in the riparian area, and upstream of our sampling spot, is located the largest municipal landfill of the GAM mentioned above (Fig. 1). Therefore, considering those key sources, the Virilla is likely prone to contamination with pharmaceutical residues from direct inputs and infiltration of raw wastewaters from households (probably the main cause of pollution) and industries, as well as leachate from the waste dumpsites and landfill nearby, which may lead to the pharmaceutical concentrations observed in our work.

When comparing the concentrations downstream of the Torres River with those of the Virilla River (at the time points where both rivers were sampled), lower levels were found in the Virilla for all compounds except sulfamethazine, regardless of seasonality (Fig. 2c and 2d, Table S7). Although the Virilla is not directly impacted by the effluents from the investigated WWTP, further downstream of our sampling point, the Virilla merges with the Torres River (Alvarado García et al., 2020), therefore the pharmaceutical contribution of the sewages connected to the WWTP eventually will reach the Virilla, exposing the aquatic ecosystems to this pollution.

It was expected that in the studied surface waters, some natural attenuation occurred during transport of the target compounds that may vary the concentrations to which the aquatic organisms were exposed. This natural attenuation is attributed to mechanisms that may occur in the environment such as phototransformation, biotransformation or sorption (Acuña et al., 2015; Challis et al., 2014; Fatta-Kassinos et al., 2011; Fono et al., 2006; Lin et al., 2006). Although the actual stream attenuation is challenging to estimate and data reported in literature are highly variable and scarce (Patel et al., 2019; Writer et al., 2013), some results from literature may help to contextualize it. For example, an attenuation up to 6.5% by photolysis was reported for carbamazepine in a field-based study (mean transit time of 2 h 10min and 3.65 km length from WWTP) (Glaser et al., 2020). Writer et al. (2013) found an in-stream attenuation efficiency (as half-life time) for carbamazepine up to 21 h, while Acuña et al. (2015) depicted an in-stream half-life for the same compound of 4.1 h, and for other compounds of 2.1 h (atenolol) and 5.8 h (sulfamethoxazole). In addition, other research described load reductions and attenuation rates (as % reduction and k (d^{-1}) respectively) at a river receiving WWTP discharges for carbamazepine (-8 %, -0.4 d^{-1}), sulfapyridine (-6%, -0.1 d^{-1}), and sulfamethoxazole (16%, 1.1 d^{-1}) (Aymerich et al., 2016). Laboratory

experiments under relevant environmental conditions have found a 16% removal of sulfamethoxazole after 11 days of exposure to light, and 33% removal by biodegradation after 58 days of exposure under aerobic conditions (Poirier-Larabie et al., 2016), and for sulindac, other study showed that isomerization was favored by direct photolysis, and that the parent compound and photoproducts were persistent (detected up >61 h) under neutral media and simulated sunlight conditions (Ledezma-Espinoza et al., 2021). Furthermore, atenolol was found relatively stable against direct sunlight, with relatively slow biodegradation (half-life > 24 h) in river water (Yamamoto et al., 2009) and resulted hydrolysis resistant but significantly photodegraded in the presence of dissolved organic matters and other natural water compositions (nitrate, bicarbonate and ferric ions) (Zeng et al., 2012). In addition, photolysis in natural waters have been identified as a major degradation route for sulfa drugs, NSAIDs and fluoroquinolones (Bonvin et al., 2013; Boreen et al., 2004; Challis et al., 2013, 2014; X. Tong et al., 2022; Van Doorslaer et al., 2014). Last, most notable fluctuations in attenuation seemed to be linked to dilution (as was observed in our work), and furthermore, to temperature changes in receiving waters, the later particularly associated with an increased microbial and biofilm activity due to increased water temperature (Wilkinson et al., 2017).

Finally, although only one stream sampling point was done in the Virilla River and *in situ* temperature measurements were not carried out due to access difficulties, our findings may help to refine further investigations on these particular issues, aiming to enhance knowledge about the occurrence linked to temporal and spatial changes, natural attenuation and sources of pharmaceutical pollution, to better understand the environmental risk that these contaminants may represent to the freshwater ecosystems in the area.

3.2. Environmental Risk Assessment

3.2.1. Risk quotients

Based on the maximum measured concentrations of the target pharmaceuticals found in our study (Table S9) and ecotoxicological data recovered from peer-reviewed literature and NORMAN database, PNEC concentrations and RQ values were calculated for the target compounds at the WWTP effluent and Virilla River (Table S10). Sulfamethoxazole presented the highest ecotoxicological risk in wastewater (RQ values from 1.1 to 7.9) and

surface water (RQ values from 0.44 to 3.3) (Table S10). In the WWTP effluent for acute toxicity (Fig. 4a), sulfamethoxazole was deemed a high-risk drug (RQ > 1.0) in crustaceans, cyanobacteria, and green algae, while the greatest RQs for medium risk (1 > RQ > 0.1) were identified for sulindac in fish, levofloxacin in crustaceans, carbamazepine in algae, and sulfapyridine in green algae. Furthermore, for chronic toxicity, the greatest values of RQs were found for sulfamethoxazole with high risk on algae and for levofloxacin and carbamazepine with medium risks for crustaceans. The RQ results for Virilla River are displayed in Fig. 4b. In the surface waters, only sulfamethoxazole posed a potentially high risk (RQ>1) toward crustaceans and algae for acute toxicity, while for chronic toxicity, a medium risk only for algae was obtained. Medium acute risks were found for sulindac in fish, carbamazepine in algae and levofloxacin in crustaceans, while for chronic toxicity, levofloxacin and carbamazepine were considered as medium risk drugs for crustaceans.

Previous studies have reported similar outcomes with high and medium risks associated with the target pharmaceutical in the present research (González-Pleiter et al., 2013; Küster et al., 2010; Liu et al., 2020; Merhabi et al., 2021; Rivera-Jaimes et al., 2018; Verlicchi et al., 2012; Yamashita et al., 2006; Zhou et al., 2022). For instance, in surface waters from Lebanon, high and medium risks were associated for carbamazepine (RQ ranged from 0.62 to 5.81) and ofloxacin (RQ up to 11.88) (Merhabi et al., 2021), while in Mexico, Rivera-Jaimes et al. (2018) reported high ecotoxicological risks for sulfamethoxazole in surface water (RQ up to 45) and even higher RQ values for wastewater effluents of a municipal WWTP (RQ up to 74).

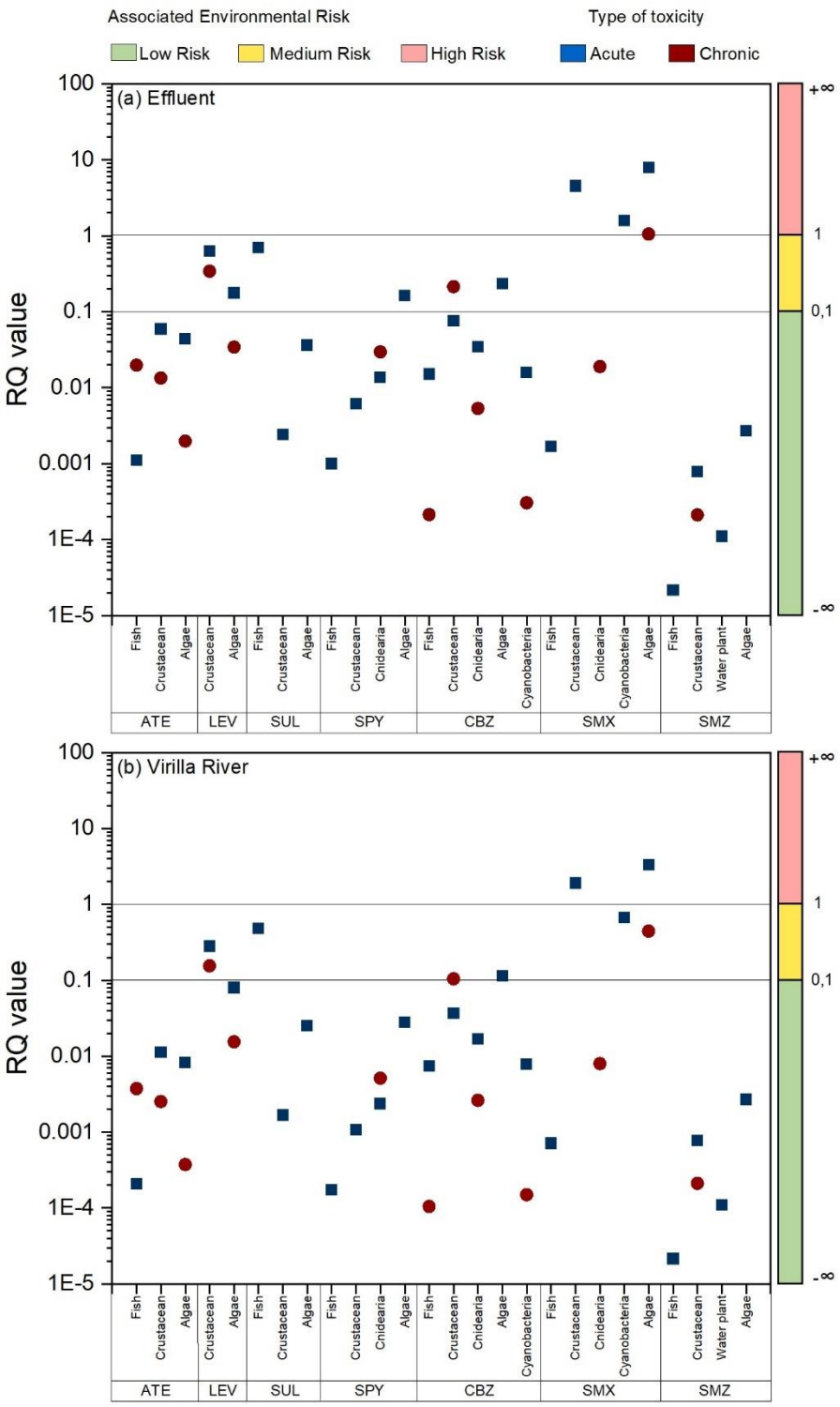

Figure 4. Risk Quotients (RQs) per taxa of different trophic levels associated to the target pharmaceuticals detected in the studied urban waters of WWTP Effluent and Virilla River.

Target compounds represented as ATE (atenolol), LEV (levofloxacin), SUL (sulindac), SPY (sulfapyridine), CBZ (carbamazepine), SMX (sulfamethoxazole) and SMZ (sulfamethazine).

Although most proposed priority pharmaceutical lists are based on methodologies that consider toxicity and occurrence data of pharmaceuticals in the environment, such as the RQ approach (aus der Beek et al., 2016; Fekadu et al., 2019; Khasawneh & Palaniandy, 2021; Verlicchi et al., 2012; Zhong et al., 2022), additional methods such as biotest, may help to link the chemical exposure scenario to adverse effects resulting from chronic exposure that are not detected with the RQ approach, especially for those compounds which toxicity information is scarce (EPA, 1998), as happened in our study, with the NSAID sulindac. This issue is addressed in the below section.

3.2.2. Effects on *Daphnia magna* reproduction.

Considering the high levels of consumption in the country, the environmental concentrations determined in this study and the information available on the potential adverse effects for aquatic ecosystems, atenolol, levofloxacin and sulindac were selected as representatives of their therapeutic classes, to further assess the biological effects *in vivo*. Sulindac was prioritized due to its lack of information on environmental occurrence and toxicity, and as part of the comprehensive analysis that our research has conducted to increase knowledge on its occurrence, fate and potential removal treatments (Ledezma-Espinoza et al., 2021, 2022). To the best of our knowledge, existing values on acute and chronic toxicity of sulindac for aquatic organisms are based on predicted toxicity thresholds derived from ECOSAR or NORMAN database, and there is no data derived from *in vivo* tests in peer-reviewed studies that help to provide a more realistic scenario of the environmental risk that sulindac and its mixtures may pose on aquatic ecosystems.

Atenolol was selected due to its exposure potential and previous reported potential hazards to some aquatic organisms. In our study, atenolol showed significant high loads for most of the samplings in the WWTP effluent and was found among the most dominant compounds in the investigated surface waters. Moreover, as discussed earlier, it has been reported that β-blockers such as atenolol may cause adverse effects on mammals and fish (Behera et al., 2011; Roberts et al., 2016). For instance, under an environmentally relevant concentration of 1 μg L^{-1} (lower than the greatest concentration found in our study), the long-term exposure

of rainbow trout juvenile fish to atenolol, affected the haematological and biochemical profile and vascular system of the fish, exhibiting higher lactate content in the blood plasma and reduced hemoglobin content compared with the control (Steinbach et al., 2014). Moreover, other β-blockers have been linked to harmful effects on aquatic organisms such as the decrease in heart rate of *D. magna* and the decrease of fecundity for *Oryias latipes* (Dzialowski et al., 2006; González-González et al., 2022; Huggett et al., 2002).

Regarding levofloxacin, it was found as the most prominent compound in the investigated hospital wastewaters, and as discussed previously, it belongs to the quinolone therapeutic class that has shown potential to produce antimicrobial resistant (Brown et al., 2006; Wu et al., 2022) and toxic effects on aquatic organisms such as algal species (Van Doorslaer et al., 2014; Xiong et al., 2020). Finally, a combination of these target drugs was assessed as it is common for aquatic organisms to be exposed to a mixture of pharmaceuticals and not only to an individual compounds, and to the possibility that potentially additive or synergetic effects of these compounds, when present in mixtures with other pollutants or chemical elements in water, may contribute to their environmental hazard (Acuña et al., 2015).

Chronic effects of the individual exposures and the mixture of the three pharmaceuticals (atenolol, levofloxacin and sulindac) were evaluated on the aquatic model organism *D. magna* (Fig. 5, Table S11). Since pharmaceutical concentrations in the present study were found up *to 3600 ng* L^{-1}*, a* concentration of 1000 ng L^{-1} was chosen as a representative environmental value for the purposes of performing the bioassays for the individual compounds and their mixture. Out of the three drugs, atenolol as isolated compound, showed no significant differences compared to the control on *D. magna´*s brood size, whereas significant effects were determined for sulindac and levofloxacin as individual compounds and for the mixture of the three target drugs (Fig 5a, Table S11). From these results, sulindac was the drug with the greatest daphnid reproductive toxicity, by reducing the brood size in 45.5% to 18.8 neonates per female. Additionally, due to its novelty, elevated consumption in Costa Rica and aiming to enhance the knowledge on potential sulindac toxicity to aquatic organisms, sulindac was also investigated at 500 and 2000 ng L^{-1}. All tested concentrations of sulindac exhibited a significant effect on *D. magna* brood size (Fig. 5b, Table S11), i.e., compared to control, sulindac solution at 500 ng L^{-1} reduced the brood to 27.3 neonates per daphnid (21% reduction), while at 1000 and 2000 ng L^{-1} it reduced the number of neonates to 18.8 and 19.40 per daphnid, respectively, reaching a 46% of decrease. Our results were consistent with the risks identified for levofloxacin and

sulindac individual compounds on aquatic organisms using the RQ approach (Fig. 4), and call attention to other possible adverse effects on aquatic ecosystems resulting from the long-term exposure of these individual compounds and their mixture with atenolol, as was evidenced in our biotests. It is worthily to highlight the significant effects found for sulindac at the 500 ng L^{-1} tested concentration, a concentration that was within the detected range for wastewaters (45.3-672 ng L^{-1}, Fig. 2b) and in the same order of magnitude of the maximum concentration detected for surface waters (173 ng L^{-1}, Fig. 2c and 2d) in the present study. To our knowledge, this is the first study to determine the potential harm effects of sulindac on aquatic organisms using environmental concentrations obtained by o-DGT passive sampling.

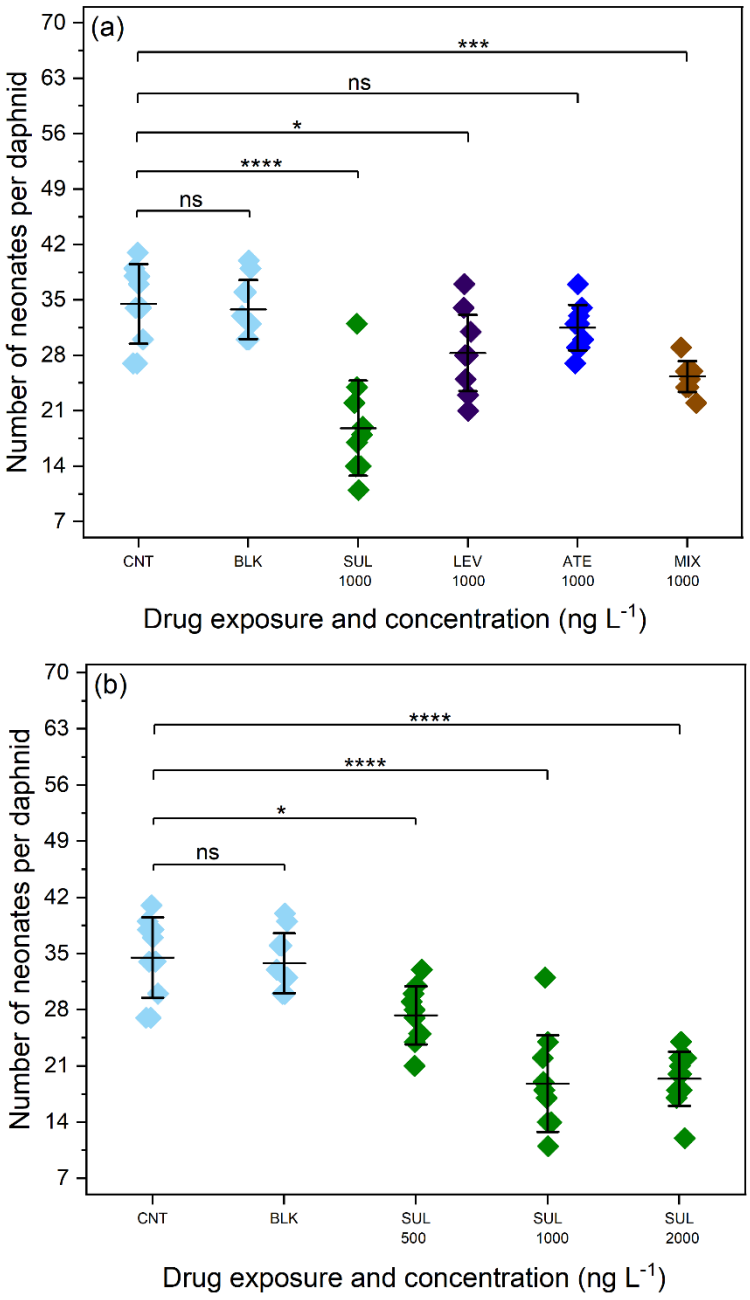

Figure 5. Chronic effects of sulindac (SUL), levofloxacin (LEV), and atenolol (ATE) on *Daphnia magna* reproduction. a) Test following the exposure to 1000 ng L^{-1} of SUL, LEV, ATE, and the combination of these three compounds (MIX, 1000 ng L^{-1} per compound) over 21 days. b) Test following the exposure to different concentrations of SUL (500, 1000 and 2000 ng L^{-1}) over 21 days. (CNT) and (BKL) correspond to control and blank, respectively. Each dot corresponds to number of neonates per replica and the bars represent the standard error (n = 10, except for MIX where n = 9). Significance levels (ns, *, **, ***, ****) obtained

using Tukey post hoc test are used to represent $P > 0.05$, $P \leq 0.05$, $P \leq 0.01$, $P \leq 0.001$ and $P \leq 0.0001$, respectively.

Overall, summarizing both, RQ screening and *D. magna* reproduction tests, the environmental monitoring of the high and medium -risk drugs found in this research such as sulfamethoxazole and levofloxacin and the poorly ecologically characterized compound of sulindac, should be a concern to investigate further in Costa Rica, and particularly for sulindac, further testing should be conducted to know better the potential harm of this drug on the exposed aquatic ecosystems.

4. CONCLUSIONS

The purpose of this work was to characterize the occurrence, trends and hazards of target pharmaceuticals in Costa Rican urban surface waters and wastewaters using o-DGT passive sampling. The antibiotic levofloxacin was the compound with the highest concentration in hospital wastewater, while atenolol was the dominant compound in the WWTP that received discharges from hospitals, households, and industries. Sulfamethoxazole was the prominent compound in surface waters of the Torres (upstream) and Virilla rivers, while sulindac revealed a continuous detection in wastewaters and surface waters from all sampling sites. Furthermore, the WWTP was not effective to completely remove the targeted drugs using the primary treatment. The temporal trends of concentrations and monthly loadings of the pharmaceuticals indicated that the examined hospital and WWTP were sources of these compounds into the monitored urban surface waters, and that untreated wastewaters and landfill leachate were other possible sources contributing to the studied systems. The RQ results showed that at concentration levels and exposure times analyzed in this study, sulfamethoxazole posed a high potential risk to the aquatic ecosystems, while bioassays exhibited the potential harm that sulindac and levofloxacin posed on crustaceous organisms. These findings can increase the confidence in the use of passive sampling in the country to gather environmental monitoring data on pharmaceutical pollution and to provide scientific information to decision makers to define strategies on awareness of community, monitoring programs, risk assessment and future treatment and regulatory interventions aiming to improve ecological and public health.

5. CONFLICTS OF INTEREST

The authors have no conflict of interest to declare.

6. AKNOWLEDGEMENTS

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8. SUPPLEMENTARY INFORMATION FOR CHAPTER 4.

Pharmaceuticals in wastewaters and rivers in the urban area of Costa Rica: a first look at incidence, trends, and ecological risks using passive sampling.

Author Contributions

Conceptualization: A. L.-E.; F. R.-G.; and C. S. W. Methodology: A. L.-E.; J. L.-M.; J. K. C.; N.A.C.; A. S.-K.; F. R.-G.; M. P.-B., C.-B., L.G., L. K. H. and C. S. W. Data curation: E.G. R-B, L.R.-Q. and J. L.-M. Data interpretation: A. L.-E.; J. L.-M.; J. K. C.; E.G. R-B, M. P.-B. and C. S. W. Writing original draft: A. L.-E.; J. L.-M; J. K. C. and C. S. W. Project administration:

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Table S1. Selected properties of the investigated pharmaceuticals.

Pharmaceutical	Formula	pKa	Log Kow	Excretion (%) (as parent compound)
Atenolol (β-blocker)	$C_{14}H_{22}N_2O_3$	9.6 [1]	0.16 [1]	90 [2]
Carbamazepine (antiepileptic)	$C_{15}H_{12}N_2O$	13.9 [3] (neutral drug)	2.45 [3]	<5 [3]
Levofloxacin (fluoroquinolone antibiotic)	$C_{18}H_{20}FN_3O_4$	5.19, 7.07 [4]	1.3 [4]	85 [5]
Sulfamethazine (sulfonamide antibiotic)	$C_{12}H_{14}N_4O_2S$	2.4, 7.4 [6]	0.89 [6]	20 [7]
Sulfamethoxazole (sulfonamide antibiotic)	$C_{10}H_{11}N_3O_3S$	1.7, 5.6 [8]	0.89 [8]	15-30 [1]
Sulfapyridine (sulfonamide antibiotic)	$C_{11}H_{11}N_3O_2S$	2.7, 8.3 [8]	0.35 [8]	10-20 [9]
Sulindac (NSAID)	$C_{20}H_{17}FO_3S$	4.7 [10]	3.4 [10]	50 [9]

References: [1] (Patel et al., 2019); [2] (Bendz et al., 2005); [3] (Pal et al., 2010); [4] (Van Doorslaer et al., 2014); [5] (Yasojima et al., 2006); [6] (Gao et al., 2012); [7] (Zulalian et al., 1984); [8] (Chen et al., 2017); [9] https://go.drugbank.com/ ; [10] (Ledezma-Espinoza et al., 2021)

Table S2. Information on geographical coordinates and sampling periods at the sampling sites of the Hospital, WWTP, Virilla river and Torres river [a]

Site	Coordinates CRTM05 X (m)	Y (m)	Sampling	Deployment/Retrieval date
Hospital	487179	1100506	M1	March 24 - April 7 (14 d)
			M2	April 7 – April 21 (14 d)
			M3	April 21 – May 5 (14 d)
			M7	June 16 - June 30 (14 d)
			M8	June 30 – July 14 (14 d)
			M9	July 14 – July 28 (14 d)
Virilla River	482169	1101964	M1	March 24 - April 7 (14 d)
			M2	April 7 – April 21 (14 d)
			M3	April 21 – May 5 (14 d)
			M7	June 16 - June 30 (14 d)
			M8	June 30 – July 14 (14 d)
			M9	July 14 – July 28 (14 d)
Upstream (Torres River)	484792	1101409	M1	March 24 - April 7 (14 d)
			M9	July 14 – July 28 (14 d)
Downstream (Torres River)	484607	1101351	M1	March 24 - April 7 (14 d)
			M9	July 14 – July 28 (14 d)
Influent (WWTP)	484910	1101463	M1	March 24 - April 7 (14 d)
			M2	April 7 – April 21 (14 d)
			M3	April 21 – May 5 (14 d)
			M7	June 16 - June 30 (14 d)
			M8	June 30 – July 14 (14 d)
			M9	July 14 – July 28 (14 d)
Effluent (WWTP)	484766	1101444	M1	March 24 - April 7 (14 d)
			M2	April 7 – April 21 (14 d)
			M3	April 21 – May 5 (14 d)
			M7	June 16 - June 30 (14 d)
			M8	June 30 – July 14 (14 d)
			M9	July 14 – July 28 (14 d)

(a) CRTM05 coordinates for sanitary landfill: (X= 482748 m, Y= 1101999 m).

Table S3. Water chemistry/quality data at the sampling sites of the Hospital, WWTP, Virilla river and Torres river [a]

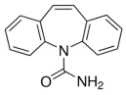
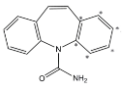
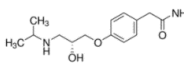
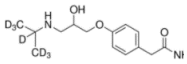
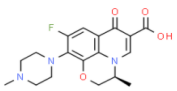
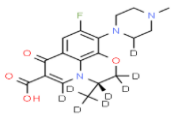
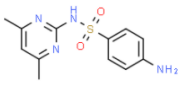
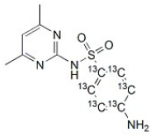
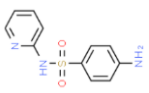
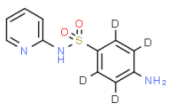
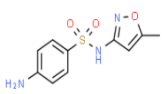
Site	COD (mg L^{-1})	TSS (mg L^{-1})	pH 25 °C (± 0.02)	Conductivity (µS cm^{-1})	Alkalinity (mg L^{-1})	Total Hardness (mg L^{-1})
Hospital	292 ± 14	70 ± 4	7.09	562 ± 15	327 ± 29	89 ± 16
Influent (WWTP)	344 ± 17	110 ± 34	6.41	729 ± 15	232 ± 20	80 ± 15
Effluent (WWTP)	394 ± 19	170 ± 34	6.35	676 ± 15	260 ± 23	85 ± 16
Upstream (Torres River)	43 ± 4	< 3	6.21	252 ± 1	71 ± 7	76 ± 15
Downstream (Torres River)	74 ± 6	50 ± 4	6.28	370 ± 1	39 ± 4	76 ± 15
Virilla River	46 ± 4	40 ± 4	6.91	472 ± 1	191 ± 17	176 ± 16

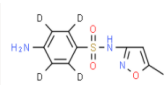
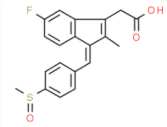
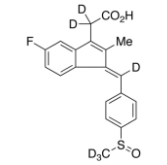
(a) Analysis performed on August 28, 2017. TSS: Total suspended solids. COD: chemical organic demand. Analysis following the Standard Methods for the Examination of Water and Wastewater.

Table S4: Gradient elution method for QTOF-MS Liquid Chromatography in sulindac analysis. Solvents were H_2O:0.05 % formic acid (A) and Methanol: 0.05 % formic acid (B).

Time (min)	Flow (mL min^{-1})	% A	% B
0	0.3	95	5
1	0.3	95	5
2.5	0.3	50	50
4.0	0.3	50	50
6.5	0.3	5	95
7.5	0.3	5	95
11.5	0.3	95	5

Table S5. Identification parameters of targeted pharmaceuticals by high-resolution quadrupole time-of-flight mass spectrometry (UPLC QTOF-HRMS) by Polarity (ESI+) and dynamic MRM method.

Compound name Therapeutic Class	Structure	Formula	Molecular ion (m/z)	Quantifier ion (m/z)	Qualifier ion (m/z)	Collision energy (V)	LOD	LOQ
Carbamazepine Anticonvulsants		$C_{15}H_{12}N_2O$	237.1028	194.0970	237.1028	15	0.0033	0.011
Carbamazepine-13C6		$_{13}C_6C_9H_{12}N_2O$	243.1229	200.1171	243.1229	15		
(R)-(+)-Atenolol β-Blockers		$C_{14}H_{22}N_2O_3$	267.1709	145.0677	190.0892	22	0.22	1.00
Atenolol-D7		$C_{14}D_7H_{15}N_2O_3$	274.2143	123.1530	145.0677	24		
Levofloxacin Antibiotics		$C_{18}H_{20}N_3O_4F$	362.1526	316.1496	344.1410	20	0.0038	0.012
Levofloxacin-d8		$C_{18}H_{12}D_8FN_3O_4$	370.2013	324.1983	352.1897	20		
Sulfamethazine Antibiotics		$C_{12}H_{14}N_4O_2S$	279.0916	186.0365	124.0885	20	0.057	0.19
Sulfamethazine 13C6		$C_6\ _{13}C_6H_{14}N_4O_2S$	285.1117	186.0365	124.0885	20		
Sulfapyridine Antibiotics		$C_{11}H_{11}N_3O_2S$	250.0650	156.0141	184.0904	10	0.066	0.21
Sulfapyridine-d4		$C_{11}H_7D_4N_3O_2S$	254.0896	160.0390	188.1153	12		
Sulfamethoxazole Antibiotics		$C_{10}H_{11}N_3O_3S$	254.0599	156.0141	108.0465	10	0.0031	0.011

Sulfamethoxazole-d4		$C_{10}H_7D_4N_3O_3S$	258.0850	160.0390	108.0465	13		
Sulindac NSAIDs		$C_{20}H_{17}FO_3S$	357.0961	233.0773	340.0943	20	0.042	0.14
Sulindac-d6		$C_{20}H_{11}D_6FO_3S$	363.1337	234.0835	346.1316	20		

Quantification by isotope dilution (Table S5) was conducted for o-DGT samples using the 2 mg L^{-1} internal standard mixture spiked in each sample prior to extraction to reach a concentration of 50 μg L^{-1} internal standard in the final 1000 μL extract. Calibration standards (ranging of 0.01-500 μg L^{-1}) were ran along with the samples (including field and lab blanks).

Table S6. Water quality parameters throughout the 21-day *D. magna* chronic toxicity study.

Day of Measurement	**D.2**	**D.4**	**D.7**	**D.9**	**D.11**	**D.14**	**D.16**	**D.18**	**D.21**
pH									
Control	7.83	8.02	7.7	7.52	7.67	8.27	7.75	7.8	8.15
Blank	7.22	7.45	7.88	7.66	7.90	7.82	7.83	7.67	7.83
LEV (1000 ng L^{-1})	8.24	8.75	8.60	8.42	8.51	8.38	8.68	8.67	8.59
SUL (500 ng L^{-1})	8.11	8.65	8.53	8.48	8.53	8.72	8.65	8.56	8.77
SUL (1000 ng L^{-1})	8.11	8.66	8.60	8.45	8.52	8.59	8.60	8.56	8.69
SUL (2000 ng L^{-1})	8.46	8.63	8.54	8.47	8.53	8.37	8.58	8.52	8.62
ATE (1000 ng L^{-1})	7.48	7.87	7.63	7.14	7.80	7.68	7.52	7.95	7.58
MIX (1000 ng L^{-1})	7.58	8.04	7.76	8.08	7.90	7.94	8.20	7.60	7.85
Dissolved Oxygen (mg L^{-1})									
Control	7.46	7.39	7.10	7.03	7.33	8.29	7.08	7.24	6.81
Blank	7.05	8.03	7.22	7.12	7.23	7.05	7.19	7.31	7.86
LEV (1000 ng L^{-1})	7.17	7.38	7.20	7.69	7.31	7.17	7.18	8.03	8.03
SUL (500 ng L^{-1})	7.43	7.09	7.48	7.70	7.28	7.08	7.15	7.95	7.99
SUL (1000 ng L^{-1})	7.57	7.19	7.21	7.56	7.24	7.16	7.04	7.89	7.89
SUL (2000 ng L^{-1})	7.68	7.12	7.20	7.51	6.90	7.01	7.09	8.11	8.08
ATE (1000 ng L^{-1})	7.14	7.22	7.44	7.02	8.74	7.43	7.27	7.34	7.29
MIX (1000 ng L^{-1})	7.05	6.80	6.86	7.06	7.44	7.06	7.39	7.13	6.92

Table S7. Concentrations of tested pharmaceuticals in the investigated urban waters [a] (Blank cells indicate that data was not investigated for the specific compound).

Compound - sampling	M1 March 24 - April 7		M2 April 7 – April 21		M3 April 21 – May 5		M7 June 16 - June 30		M8 June 30 – July 14		M9 July 14 – July 28	
	TWA (ngL^{-1})	Load (kg $month^{-1}$)	TWA (ng L^{-1})	Load (kg $month^{-1}$)	TWA (ng L^{-1})	Load (kg $month^{-1}$)	TWA (ng L^{-1})	Load (kg $month^{-1}$)	TWA (ng L^{-1})	Load (kg $month^{-1}$)	TWA (ng L^{-1})	Load (kg $month^{-1}$)
Effluent (WWTP)												
Atenolol	1980.9	2.331	972.3	1.144	1650.1	1.942	151.4	0.275	60.1	0.109	274.5	0.498
Sulindac	152.7	0.180	83.5	0.098	148.0	0.174	38.2	0.069	46.5	0.084	45.3	0.082
Levofloxacin	211.9	0.249	83.8	0.099	185.7	0.219	44.9	0.082	28.9	0.052	140.9	0.256
Carbamazepine	532.9	0.627	187.0	0.220	756.6	0.890	491.2	0.891	136.3	0.247	184.9	0.335
Sulfamethoxazole	946.1	1.113	215.6	0.254	471.7	0.555	91.3	0.166	11.2	0.020	123.2	0.223
Sulfapyridine	296.0	0.348	54.5	0.064	0.21		25.3	0.046	5.8	0.011	27.5	0.050
Sulfamethazine	0.034	0.00004	3.3	0.004	0.7	0.001	1.4	0.002	2.2	0.004	2.0	0.004
Influent (WWTP)												
Atenolol	3111.9		2677.2		3610.7		619.9		139.8		299.6	
Sulindac	156.3		160.5		239.3		143.5		144.1		672.1	
Levofloxacin	399.2		262.6		326.8		198.0		128.3		145.9	
Carbamazepine	475.9		1771.2		2292.9		585.6		637.2		890.4	
Sulfamethoxazole	1810.7		1037.1		1070.7		280.0		248.3		134.8	
Sulfapyridine	326.8		264.3		338.9		72.8		33.4		34.7	
Sulfamethazine	1.0		6.0		1.3		3.6		50.2		7.0	
Hospital												
Atenolol	531.2		149.4		295.1		252.8		27.3		53.1	
Sulindac	162.4		91.3		146.2		189.1		56.7		66.6	
Levofloxacin	1022.3		182.2		342.3		413.4		110.8		104.0	
Carbamazepine	272.5		118.1		510.1		172.0		26.5		159.6	
Sulfamethoxazole	357.2		7.5		30.3		30.9		7.2		6.4	
Sulfapyridine	100.6		3.2		15.9		11.1		0.21		4.4	
Sulfamethazine	29.7		11.5		2.2		2.7		0.5		0.7	
Virilla River												
Atenolol	109.0		374.1		38.4		7.9		8.3		8.7	
Sulindac	39.0		106.2		81.7		10.7		8.9		11.3	
Levofloxacin	96.2		65.9		62.3		40.2		43.6		0.012	
Carbamazepine	71.1		261.6		159.2		59.6		37.7		42.9	
Sulfamethoxazole	156.2		399.8		188.5		18.8		20.8		30.9	
Sulfapyridine	22.9		51.4		33.9		5.5		4.6		3.2	
Sulfamethazine	1.3		1.1		3.3		1.5		1.5		0.5	
Upstream (WWTP Torres River)												
Atenolol	155.1										70.0	

Sulindac	80.5										102.2	
Levofloxacin	104.3										83.2	
Carbamazepine	155.2										39.6	
Sulfamethoxazole	334.9										47.8	
Sulfapyridine	42.9										5.6	
Sulfamethazine	1.1										0.5	
Downstream (WWTP Torres River)												
Atenolol	536.5										163.5	
Sulindac	172.7										69.2	
Levofloxacin	41.5										60.5	
Carbamazepine	139.7										180.3	
Sulfamethoxazole	461.6										115.5	
Sulfapyridine	58.8										5.6	
Sulfamethazine	1.3										0.5	

(a) WWTP Flow: 454 L s^{-1} (dry season), 700 L s^{-1} (rainy season).

Table S8. Concentrations and removals of the selected pharmaceuticals in conventional WWPTs with primary and secondary treatments from different countries[a]

Compound	Influent ($ng\ L^{-1}$)	Effluent ($ng\ L^{-1}$)	Removal	Region and Observations	References
Atenolol	38.2-277 (116.23) average	3.69-140 (64.6) average	~ up to 44%	Latin American review	(Peña-Guzmán et al., 2019)
	0.1-33.1	0.13-7.60	0-85%	Worldwide review Korea, Spain, Switzerland, UK	(Luo et al., 2014)
	294 700 (Asia) 2642 (North America) 33 106 (Europe)	519 (Asia) 14 200 (North America) 7602 (Europe)	n.a.	Worldwide review	(Tran et al., 2018)
	11 239-5113 (7 801) average	5911-261 (2 772) average	<28% Primary treatment Up to 64.5 % Secondary treatment	Korea	(Behera et al., 2011)
Carbamazepine	37.7-167 (90.3) average	29.5-196 (108.51) average	n.a.	Latin American review	(Peña-Guzmán et al., 2019)
	WWTP B: 261-465 (282) average WWTP D: 442-3000 (597) average	244-429 (323) average 481-3000 (644) average	Negative	Brazil Primary treatment with Trickling filter	(Pivetta et al., 2020)
	73	78	Negative	Colombia Only Primary WWTP	(Botero-Coy et al., 2018)
	220	90	59%	Peru Only primary WWTP	(Nieto-Juárez et al., 2021)
	<0.04–3.78	<0.005–4.60	<0–62.3	Worldwide review China, EU-wide, Greece, Korea, Spain, UK	(Luo et al., 2014)
	127-43 (72) average	74-40 (55) average	Negative for Primary treatment 23% Secondary treatment	Korea	(Behera et al., 2011)
	n.a.	n.a.	29%	Spain	(Ortiz de García et al., 2013)
Levofloxacin	307-981 (552) average	189-400 (487) average	11% after primary, no degrease. 42% after secondary treatment	Japan	(Yasojima et al., 2006)
	n.a.	n.a.	2%	Spain	(Ortiz de García et al., 2013)
	470(ofloxacin)	110 (ofloxacin)	77%(ofloxacin)	Mexico	(Brown et al., 2006)
	n.a.	n.a.	53%	China	(Wu et al., 2022)

	1550	N.D	n.a.	Kenya WWTP3 only with primary treatment, operating through trickling filters	(K'oreje et al., 2016)
Sulfamethazine	174.4	47.2	73%	Mexico	(Brown et al., 2006)
	<LQ -343 (132) average	<LQ- 408 (114) average	13% Primary treatment <30% Secondary treatment	Korea	(Behera et al., 2011)
	230-570 ng/L	n.a.	-21 to -5%	Switzerland Primary treatment consists of a screen, an aerated grit removal tank, and a primary clarifier.	(Göbel et al., 2007)
Sulfamethoxazole	279-2050 (833.17) average	1.5-12 500	n.a.	Latin American review	(Peña-Guzmán et al., 2019)
	1389 Asia 4200 North America	562 ng L^{-1} Asia 1800 ng L^{-1} North America	n.a.	Worldwide review	(Tran et al., 2018)
	(230–570 ng/L).	n.a	-21 to -5% Primary treatment -138 to 60% Secondary treatment	Switzerland Primary treatment consists of a screen, an aerated grit removal tank, and a primary clarifier.	(Göbel et al., 2007)
	729	831	Negative	Colombia Only Primary WWTP	(Botero-Coy et al., 2018)
	n.a	n.a	1% (only primary treatment 50% (primary + secondary treatment)	Spain	(Ortiz de García et al., 2013)
	390	310	20%	Mexico	(Brown et al., 2006)
	729	831	Negative	China	(Guan et al., 2016)
	2100	2360	Negative	Perú Only primary treatment	(Nieto-Juárez et al., 2021)
	216-79;120	162-20;57	<28% Primary treatment 51.9% Secondary treatment	Korea	(Behera et al., 2011)
	<0.003-0.98	<0.003-1.15	<0-85.1	Worldwide review EU-wide, France, Korea, Spain, Sweden, Switzerland, UK, WB	(Luo et al., 2014)
Sulfapyridine	60-150	n.a.	-29 to 20% Primary treatment -107 to +72% Secondary treatment	Switzerland Primary treatment consists of a screen, an aerated grit removal tank, and a primary clarifier.	(Göbel et al., 2007)
Sulindac.	644	312	51%	China	(Guan et al., 2016)

(a) Data from Municipal WWTPs. Conventional treatment includes primary and secondary methods (conventional activated sludge system used as secondary treatment). n.a. (not available). ND (not detected).

Table S9. Maximum measured environmental concentrations (mg L^{-1}) for the seven drugs of interest in two sampling sites of the study: WWTP Effluent (Zone A) and Virilla River (Zone B).

Drug	Measured Environmental Concentrations (mg L^{-1})	
	WWTP Effluent (Zone A)	**Virilla River (Zone B)**
ATE	0.0019809	0.0003741
LEV	0.0002119	0.000096
SUL	0.0001527	0.0001062
SPY	0.000296	0.0000514
CBZ	0.0005329	0.0002616
SMX	0.0009461	0.0003998
SMZ	0.0000033	0.0000033

Table S10. Calculated PNEC (Predicted no-observed concentration) and RQ (Risk Quotient) values associate to chronic and acute toxicities for the targeted pharmaceuticals based on the measured environmental concentrations (Table ST) of two sampling sites of this study: WWTP effluent (Zone A) and Virilla River (Zone B).

Drug	Toxicity	Taxon	Species	Time	Endpoint	Conc. (mg L^{-1})	Reference	AF	PNEC (mg L^{-1})	RQ A	RQ B
ATE	Acute	F	*O. latipes*	96h	LC50	1800.00	Yamamoto et al. (2007)	1000	1.800000	0.00110	0.00021
		C	*C. dubia*	48h	EC50	33.40	Fraysse & Garric (2005)	1000	0.033400	0.05931	0.01120
		A	-	-	EC50	45.42	MEDISCA (2016)	1000	0.045420	0.04361	0.00824
	Chronic	F	*P. promelas*	21d	NOEC	1.00	Winter et al. (2008)	10	0.100000	0.01981	0.00374
		C	*D. magna*	21d	NOEC	1.48	Küster et al. (2010)	10	0.148000	0.01338	0.00253
		A	*P. subcapitata*	96h	NOEC	10.00	Yamamoto et al. (2007)	10	1.000000	0.00198	0.00037
LEV	Acute	C	*D. magna*	21d	EC50	0.34	Yamashita et al. (2006)	1000	0.000340	0.62324	0.28235
		A	*P. subcapitata*	96h	EC50	1.20	Yamashita et al. (2006)	1000	0.001200	0.17658	0.08000
	Chronic	C	*D. magana*	21d	NOEC	0.03	Yamashita et al. (2006)	50	0.000620	0.34177	0.15484
		A	*P. subcapitata*	96h	NOEC	0.31	Yamashita et al. (2006)	50	0.006200	0.03418	0.01548
SUL	Acute	F	*P. promelas*	96h	LC50	-	NORMAN	1000	0.00021962	0.69529	0.48356
		C	*D. magna*	48h	LC50	-	NORMAN	1000	0.06312225	0.00242	0.00168
		A	*S. capricornutum*	72h	EC50	-	NORMAN	1000	0.00422433	0.03615	0.02514
SPY	Acute	F	*P. promelas*	96h	LC50	-	NORMAN	1000	0.29595489	0.00100	0.00017
		C	*D. magna*	48h	LC50	-	NORMAN	1000	0.04820611	0.00614	0.00107
		A	*S. capricornutum*	72h	EC50	-	NORMAN	1000	0.00183029	0.16172	0.02808
		N	*H. attenuata*	96h	EC50	21.61	Quinn et al. (2008)	1000	0.02161	0.01370	0.00238
	Chronic	N	*H. attenuata*	96h	NOEC	1	Quinn et al. (2008)	100	0.01	0.02960	0.00514
CBZ	Acute	F	*O. latipes*	48h	EC50	35.40	Kim et al. (2007)	1000	0.0354	0.01505	0.00739
		C	*C. dubia*	48h	LC50	7.07	Lamichhane et al. (2013)	1000	0.00707	0.07537	0.03700
		A	*S. capricornutum*	72h	EC50	-	NORMAN	1000	0.00227578	0.23416	0.11495
		N	*H. attenuata*	96h	EC50	15.52	Quinn et al. (2008)	1000	0.015520	0.03434	0.01686
		CB	*S. leopolensis*	96h	EC50	33.60	Ferrari et al. (2004)	1000	0.033600	0.01586	0.00779

	Chronic	F	*D. rerio*	10d	NOEC	25.00	Lamichhane et al. (2013)	10	2.500000	0.00021	0.00010
		C	*C dubia*	7d	NOEC	0.03	Lamichhane et al. (2013)	10	0.002500	0.21316	0.10464
		N	*H. attenuata*	96h	NOEC	1.00	Quinn et al. (2008)	10	0.100000	0.00533	0.00262
		CB	*S. leopolensis*	96h	NOEC	17.50	Lamichhane et al. (2013)	10	1.750000	0.00030	0.00015
SMX	Acute	F	*O. latipes*	96h	EC50	562.50	Kim et al. (2007)	1000	0.562500	0.00168	0.00071
		C	*C. dubia*	7d	EC50	0.21	Isidori et al. (2005)	1000	0.000210	4.50524	1.90381
		CB	*S. leopoliensis*	-	-	-	NORMAN	10	0.000600	1.57683	0.66633
		A	*S. obliquus*	96	EC50	0.12	Xiong et al. (2019)	1000	0.000120	7.88417	3.33167
	Chronic	N	*H. attenuata*	96h	NOEC	5.00	Quinn et al. (2008)	100	0.050000	0.01892	0.00800
		A	*P. subcapitata*	96h	NOEC	0.09	Ferrari et al. (2004)	100	0.000900	1.05122	0.44422
SMZ	Acute	F	P. promelas	96h	LC50	-	NORMAN	1000	0.153133	0.00002	0.00002
		P	Lemna gibba	-	-	-	NORMAN	10	0.030000	0.00011	0.00011
		C	D. magna	21d	EC50	4.25	De Liguoro et al. (2009)	1000	0.004250	0.00078	0.00078
		A	S. obliquus	96h	EC50	1.23	Xiong et al. (2019)	1000	0.001230	0.00268	0.00268
	Chronic	C	D. magna	21d	NOEC	1.56	De Liguoro et al. (2009)	100	0.015630	0.00021	0.00021

Where: Taxon: F (Fish), C (Crustacean), A (Algae), N (Cnidiaria), P (Plant), CB (Cyanobacteria). AF (Assessment Factor). PNEC (Predicted no-observed concentration). RQ (Risk Quotient). Zone A (WWTP Efluent). Zone B (Virilla River).

Table S11. Daphnia magna chronic reproduction test as the mean number (± SD) of neonates per daphnid and percentage of brood reduction (%) after the exposure to levofloxacin (LEV: 1000 ng L^{-1}), atenolol (ATE: 1000 ng L^{-1}), sulindac (SUL: 500, 1000, and 1500 ng L^{-1}), and the combination of these three drugs (MIX: at 1000 ng L^{-1} each one), over 21 days. Adjusted p-values were obtained by comparing each treatment with the control.

Drug Exposure	n	Mean number of neonates per daphnid	Percentage of Brood Reduction	p-value
Control	10	34.50 ± 5.01	-	-
Blank	10	33.80 ± 3.74	2.03	0.9999
LEV (1000 ng L^{-1})	10	28.30 ± 4.81	17.97	0.0264
ATE (1000 ng L^{-1})	10	31.50 ± 2.88	8.70	0.7341
SUL (500 ng L^{-1})	10	27.30 ± 3.74	20.70	0.0051
SUL (1000 ng L^{-1})	10	18.80 ± 6.01	45.51	0.0000
SUL (2000 ng L^{-1})	10	19.40 ± 3.37	43.77	0.0000
MIX (1000 ng L^{-1})	9	25.33 ± 1.94	26.58	0.0002

References for supplementary information of chapter 4

a. References for Properties of target pharmaceuticals.

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5. PHOTOLYSIS OF THE NONSTEROIDAL ANTI-INFLAMMATORY DRUG SULINDAC: ELUCIDATION OF KINETIC BEHAVIOUR AND PHOTODEGRADATION PATHWAYS IN WATER

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ABSTRACT

Non-steroidal anti-inflammatory drugs are recognized widely as emerging contaminants. Sulindac has received additional attention as a prodrug in cancer treatment and because of its detection in drinking water and wastewaters. Nevertheless, there is limited knowledge about its kinetic behaviour and fate in the aquatic environment. In this work, the direct photolysis of sulindac, in which photochemical reactions were monitored and phototransformation products identified, was investigated under prolonged periods using UV-A and UV-B radiation and pH conditions (2 and 7) to evaluate the effect of the protonation state and the efficiency of the photolytic process. A novel kinetic mechanism has been proposed in which sulindac exhibits a consecutive reaction pathway, with pseudo-first order kinetics for rapid and reversible Z to E isomerization. Once photoequilibrium was reached, second-order degradation of the isomers in the presence of the

new photodegradation products was observed. Photochemical transformation was faster under UV-B irradiation and lower pH, which suggests greater persistence of sulindac at more relevant environmental conditions of UV-A and pH 7. Two novel major byproducts were identified, corresponding to the oxidative cleavage of the alkene exo to the indene system. The degradation pathway is mainly photoinduced, enhanced by acidic conditions and presumes the double bond as the most reactive site for the parent compound. Formed byproducts may sensitize the photolysis of sulindac by generating reactive intermediates such as triplet excited states and $^1O_2$. This research shows an approach for determining kinetics of compounds with challenging conditions, e.g., absorption from multiple electronic transitions, photoinduced products with unknown extinction coefficients and time-dependent concentrations, sensitized by photoinduced intermediates and speciation effects. Our work greatly improves our understanding of the degradation process of sulindac and will contribute to exposure assessments and treatment methodologies for this compound in impacted waters.

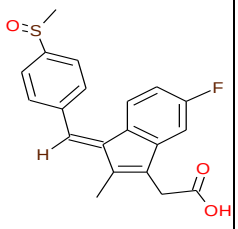
INTRODUCTION

Detection of many pharmaceutical residues in water bodies is a growing environmental concern worldwide.[1–3] Nonsteroidal anti-inflammatory drugs (NSAIDs) are extensively used as analgesic (pain-killing) and antipyretic (fever-reducing) drugs,[4] both clinically and over the counter.[5,6] They are among the most studied classes of emerging contaminants in monitoring studies.[7–9] The limited level of environmental legislation and the increasing evidence for potential chronic impacts, bioaccumulation, and effects in non-target organisms[10,11] make the study of NSAIDs in the aquatic environment highly relevant.[12]

The occurrence of NSAIDs has been widely reported in natural water bodies, wastewaters and even drinking water.[13–17] The presence of these drugs in the environment has been related to their inefficient removal during the sewage treatment processes.[18] Various nationwide studies summarized concentrations up to 210 ng L^{-1} in water treatment plants (WTPs),[4] high detection frequency reaching 1320 ng L^{-1} in surface waters[19,20] and levels up to 483 μg L^{-1} in wastewater treatment plants (WWTPs).[21,22] Particularly, concern about NSAID monitoring and adverse effects to the environment led to the inclusion of the painkiller diclofenac in the First Water Framework Directive Watch List as a priority substance.[23,24]

Many NSAIDs show potential in the treatment of cancer.[25] As such, one of the most effective and clinically used chemopreventive agent is the drug sulindac.[26] This compound belongs to a group of heterocyclic and arylic derivatives of acetic acid (Table 1) that is biotransformed *in vivo* to generate biologically active metabolites.[27] Few studies have investigated the environmental occurrence or photochemical fate of sulindac,[28] despite its increasing interest as a prodrug and subsequent increase in consumption, particularly in developing countries.[29] Among these studies, Kawabata et al.[30] reported a partial degradation of sulindac under natural sunlight, and its complete degradation with UV-C (254 nm). The authors also described marked toxicity on aquatic luminescent bacteria when sulindac was photo-exposed to UV-B (302 nm) irradiation.

Table 1. Chemical characteristics for sulindac.

Formula, CAS	Chemical structure	Monoisotopic Weight	Log P	pKa	Physicochemical characteristics [b]
$C_{20}H_{17}FO_3S$ 38194-50-2		356.08824 Da	3.42	4.5[a]	-Solubility (25°C): 3000 mg/L -Thermal stability (air atmosphere): up to 200°C

Data from https://www.drugbank.com/ [a 31], [b 27]

Several factors, including the specific structure of the compound, light absorption and physicochemical water conditions such as pH, must be considered in assessing the photochemical degradation of NSAIDs under natural conditions[32–37] or removal treatments.[38–42] However, from existing phototransformation studies in water for sulindac, there is no information about how specific functional groups are involved during degradation beyond isomerization, or how acid-base speciation may affect the kinetics of this ionizable compound. Particularly, specific kinetic parameters such as reaction quantum yields under simulated solar irradiation and potential photochemical transformation pathways under neutral and acidic conditions are still missing in the

literature. Therefore, simulated natural attenuation in water under variable pH conditions need to be investigated, and novel phototransformation products must be identified.

The objectives of this research were to evaluate the UV degradation of NSAID and prodrug sulindac under long irradiation exposure at different laboratory conditions of light (UV-B and UV-A) and pH (2 and 7), to elucidate direct photolysis kinetics, and to identify potential transformation mechanisms that yield photodegradation products. The results of this study could guide future screening in treatment systems and natural waters and improve our knowledge about the fate of sulindac and other compounds with similar structure or complex kinetics in the aquatic environment.

MATERIALS AND METHODS

Chemicals and Reagents

Standards for natural (1Z)-Sulindac and (1Z)-isotopic labeled compound (chemical purity >98%, isotopic purity d6 >99%) were purchased from TRC (Toronto, Canada). Pyridine (PYR, ≥99.9%) and p-nitroanisole (PNA, >97%) were supplied by Sigma–Aldrich (St. Louis, MO) and were used without further purification. Methanol and acetonitrile of LC-MS grade were purchased from Sigma-Aldrich (San José, Costa Rica). Solutions for direct photolysis and dark control were prepared using the same LC-MS grade water, provided by Sigma-Aldrich (San José, Costa Rica), buffered with di- and tri-basic potassium phosphate (K2HPO4, K3PO4, ≥98%, Sigma–Aldrich) and titrated (<1%) with dilute hydrochloric acid (HCl, Sigma Aldrich) solution to the desired pH value. Solvents for the liquid chromatographic analysis were prepared with LC-MS grade acetonitrile or methanol and buffered with formic acid (95%, Sigma-Aldrich).

Photolysis experiments

Batch photochemical reactor and irradiation sources.

Sulindac solutions were irradiated using a batch rotary Luzchem Photoreactor (model LZC-5b, Luzchem Research, ON, Canada). To perform separate experiments for each UV irradiation, the instrument was equipped with a UV-A lamp (LZC-UVAp, 315-400 nm, 49.425 mW*m^{-2}) and a UV-

B lamp (LZC-UVB, 280-315 nm, 39.39 mW*m^{-2}). Irradiation vessels were 10 mL cylindrical Pyrex tubes filtering wavelengths < ≈290 nm, with an irradiation path of L=1.33 cm.

Chemical actinometry system.

The p-nitroanisole/pyridine (PNA-Pyr) actinometer was used to evaluate the instrument´s photon flux, following procedures detailed in Challis et al.[36] with the updated quantum yield equation Φa= 0.29[pyr] + 0.00029 and reference data for the PNA standard molar absorption coefficient (ε_λ, M^{1-} cm^{1-}) described by Laszakovits et al.[43] Independent experiments were performed for each lamp (UV-A and UV-B), within 290-400 nm range, assuming a constant quantum yield (ϕa) over that interval. All irradiation experiments and dark samples used 7 mg L^{-1} PNA/PYR 0.01M, and were carried out simultaneously in triplicate at a constant temperature of 22°C. Sample analysis was done by the HPLC UV/VIS method described below.

The pseudo-first-order rate constant for the actinometer (kpa), related to each lamp, was measured in triplicate, and the value of ϕa=0.00319 was included to estimate the respective overall rate of light absorption (ka). For each wavelength (290-400 nm), the data for ka, the ε_λ of PNA from the literature,[43] and the wavelength-specific relative lamp emission from the manufacturer ($I_{\lambda m}$) were used to calculate actinometer-specific light absorption rates (ka,λ). The total incident light intensity for each lamp was then calculated by summing intensity (I_λ) over the wavelength range and including the experimental path length of the Pyrex tubes. The resulting incident light intensity allowed the calculation of the photon flux (290-400 nm) for the UV-A lamp of (3.43±0.07) × 10^{18} photons cm^{-2} s^{-1} and (2.04±0.02) × 10^{18} photons cm^{-2} s^{-1} for the UV-B lamp.

Direct photolysis for sulindac

Irradiation sources for UV-A (315-400 nm) and UV-B (280-315 nm) were selected to simulate absorption of the sunlight spectrum at pH 2 and 7, and to understand the effects of speciation on sulindac photolysis. To identify photoproducts and propose mechanistic pathways, experiments were performed at high concentrations to facilitate detection. Sulindac aqueous solutions were prepared at 7 mg L^{-1} using the appropriate potassium phosphate buffer (2 and 7). Irradiation experiments were carried out separately for each lamp (UV-A and UV-B) in Pyrex tubes. Solutions

of each pH were ran at the same time for each lamp UV source. Sampling (500 μL) was done periodically across at least two half-lives, surpassing 61 h total time. Dark samples were run in parallel. All experiments were performed by triplicate at 22°C, and analyzed by HPLC UV/VIS and UHPLC/ESI-QTof-MS as described below.

Analytical Methods

UV/VIS High performance liquid chromatography

Direct photolysis irradiated solutions were analyzed with a Dionex Ultimate 3000 UHPLC instrument (Thermo Scientific, MA, USA), equipped with an UV-Vis detector and a Dionex C18 (5 μm, 4.6×250 mm) column. Chromatography for sulindac was achieved isocratically with a mobile phase of 50:50 (v/v) water (0.05% v/v formic acid) and MeOH (0.05% v/v formic acid). Samples were run with a flow of 1 $mL \cdot min^{-1}$ at 25 °C. To limit light absorption over each single electronic transition of sulindac, detection was done at 326 nm for UV-A experiments and 285 nm for UV-B irradiations (UV-Vis spectra reported in Figure S1). Z-isomer was quantified using a calibration curve between 0.5 to 7 mg L^{-1} of non-irradiated Z-sulindac (R^2 = 0.9996). An estimate of E-isomer concentrations was achieved using the same calibration curve. Retention times were 5.77 min for Z-sulindac and 6.47 min for E-sulindac. To correct for overestimation of the E-sulindac concentration from different absorptivity of the two isomers, a molar absorptivity coefficient ratio ($\varepsilon_Z/\varepsilon_E$) was determined as described below.

PNA/PYR for actinometry was resolved using a Supelcosil LC-NH2 Amino Column (5 μm, 4.6×250 mm) and a 85:15 (v/v) mobile phase with water (0.05% v/v formic acid) and MeOH (0.05% v/v formic acid). Samples were monitored at 320 nm, with a constant flow of 1 $mL \cdot min^{-1}$ at 25 °C and a calibration curve of 2.0 to 9.2 mg/L PNA/PYR 0.01M.

Spectrum analysis for calculation of ratio molar absorptivity coefficients ($\varepsilon_Z/\varepsilon_E$)

Determination of molar absorptivity coefficient ratio ($\varepsilon_Z/\varepsilon_E$) of Z and E-sulindac isomers was achieved using a Thermo Scientific UV–Vis spectrophotometer, model Genesys 10S (Waltham, MA, USA). Photochemical experiments were conducted for solutions with three different concentrations (2, 7 and 10 mg L^{-1} of Z-sulindac) and two pH´s (2 and 7) for each irradiation lamp. The exposure period was 25 min and samples were taken at the zero and 25 min time points.

UV–Vis absorption spectra of each solution were recorded from 290 nm to 400 nm (Figure S1), using quartz cells with 1 cm path length. Calculations were made from the absorbance at λ_{max}=326 nm for each solution as detailed in ESI.

Time-of-flight mass spectrometry for non-targeted analysis.

To identify potential degradation products, irradiated solutions were analyzed with a Xevo G2-XS quadrupole time of flight (QTof-MS) mass spectrometer (Waters Corporation, Wilmslow, UK), equipped with Software MassLynx™ V4.1 and an electrospray ionization source coupled with an Acquity UPLC H-Class. Chromatographic separation of the photoproducts was undertaken with an Acquity UPLC® BEH C18 column (1.7 µm, 2.1 mm×50 mm) supplied by Waters.

The mobile phase consisted of water (0.05% v/v formic acid) and MeOH (0.05% v/v formic acid). The analyses were done under gradient conditions (Table S1), an injection volume of 10 µL, 40°C and a flow rate of 0.3 mL min^{-1}.

Mass spectrometry detection was performed by electrospray ionization under sensitivity-positive ion mode (ESI+) and a MSE centroid acquisition method, calibrated with Leucine Enkephalin, over a mass range of 50 to 1000 Da and mass resolution >50 000 FWHM. The instrument conditions included 0.5 s scan time, a ramp collision energy from 20 to 40 eV, 20 V sampling cone, 2.0 kV capillary, 130°C source temperature, 400°C desolvation temperature and 800 L h^{-1} desolvation gas flow.

The non-targeted analysis to identify potential photoproducts was performed by processing the UPLC-MSE raw data with Progenesis QI Software v. 2.4 (Nonlinear Dinamics from Waters, Wilmslow, UK). The final structures of detected byproducts, fragmentation patterns, and abundance during the different time points of the photochemical process were justified with data of isotopic similarity with a minimum value of 90%, mass error under 10 ppm and highest mean intensity across the degradation process. Abundance profiles for each compound are reported in ESI.

Kinetic Modeling

The behavior for sulindac under the different conditions of pH (2, 7) and irradiation sources (UV-A, UV-B) over time was fitted numerically to the solution of the differential equation model (equation system S4) that described the kinetic mechanism. Maple software (Maplesoft, Waterloo, Canada) was used to perform the fittings by numerical procedure of least squares, and to solve the differential equation model using the Runge-Kutta-Fehlberg method with fourth degree interpolation. Further details are found in ESI.

RESULTS AND DISCUSSION

Direct photolysis experiments under laboratory conditions

Sulindac, with a pKa of 4.5, could exist in aquatic media as a mixture of protonated (HS) and deprotonated (S) species. It absorbs radiation in environmentally relevant wavelengths with two observed electronic transitions at λmax = 325 nm and λmax = 285 nm (see UV-vis in ESI). The pH and UV irradiation conditions in this work were selected following previous criteria to include values of 2 pH units above or below the pKa, and to apply irradiation over individual electronic transitions for proper determination of quantum yields.[32] By using pH 7, deprotonated sulindac (S) was dominant (fraction f_S=0.997 > f_{HS} =0.003), while at pH 2, the neutral species prevailed (fraction f_{HS}=0.997 > f_S=0.003). Moreover, UV-A and UV-B light sources were selected to provide irradiation for each absorption band. In addition, the use of pH 7 and UV-A are relevant for the fate of sulind<ac in sunlit surface waters, while the pH 2 experiments helps evaluate acid-catalyzed processes in relatively acidic surface waters, reducing the complexity of speciation effects.

In our study, irradiated samples showed photolysis of the parent compound that was commercially available (Z-isomer), while the stability of dark samples indicated that hydrolysis and other abiotic transformation processes were negligible. Thus, our observed transformation was due to direct photolysis.

All experiments under UV light showed an isomerization reaction from Z to E species from the first irradiation period (3 min), whereas dark samples showed only the Z-isomer, indicating the occurrence of a photoinduced reaction. Further, both isomers were detected even after prolonged irradiation periods of 30 hours, along with other novel byproducts. Figure 1 shows the QTof-MS chromatogram for the photoproduct mixture generated after 30h of UV-A irradiation at pH7, with

mass spectra for the Z parent compound confirmed with the expected molecular ion [M+H]+ at m/z 357.0963 and the adduct of [2M+H]+ at m/z 713.1819. Z-Sulindac eluted at 6.3 min and the E-isomer at 6.5 min. Meanwhile, two novel compounds were observed with shorter elution times, around 3 min, suggesting photoproducts with greater polarity. The isomerization reaction observed in our work was in agreement with previous investigations that described partial degradation of sulindac after UV-A and UV-B irradiation up to 24 h,[30] and the isomerization of sulindac leading to the E-isomer as a first photoproduct.[28]

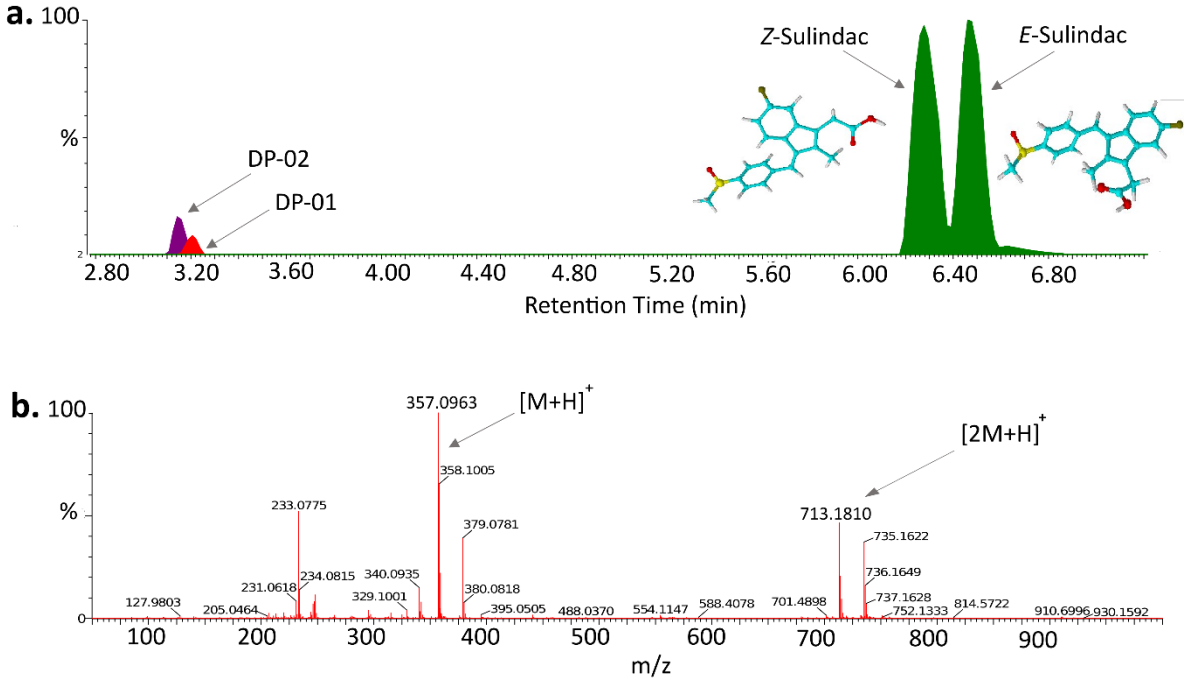


Figure 1. QTof-MS chromatogram trace of (a) sulindac photoproduct mixture generated after 30h of UV-A irradiation at pH 7 with (b) full scan mass spectrum for the Z-isomer identified.

According to Figure 2, degradation of sulindac using UV-A irradiation was pH dependent. For both pH conditions, a rapid transformation from Z to E-isomer was observed within the first 40 min (Figures 2a and 2c). At pH 2, the E-isomer peak increased in intensity over time, and eventually surpassed the parent compound signal at 25 min, whereas at pH 7, the Z-isomer had a greater intensity over E-sulindac along the entire irradiation period, until both isomers were completely degraded. Similar results were found for UV-B experiments (Figures S2 and S3). The latter

behavior suggests that isomer photoequilibrium is related to the pH. With a pKa of 4.5, sulindac is protonated at pH 2 and deprotonated at pH 7. The intensity observed for the two isomers indicates that E-isomer is more stable under acidic conditions, thus, protonated E-sulindac prevailed in acidic waters while anionic Z-sulindac was dominant in neutral natural systems.

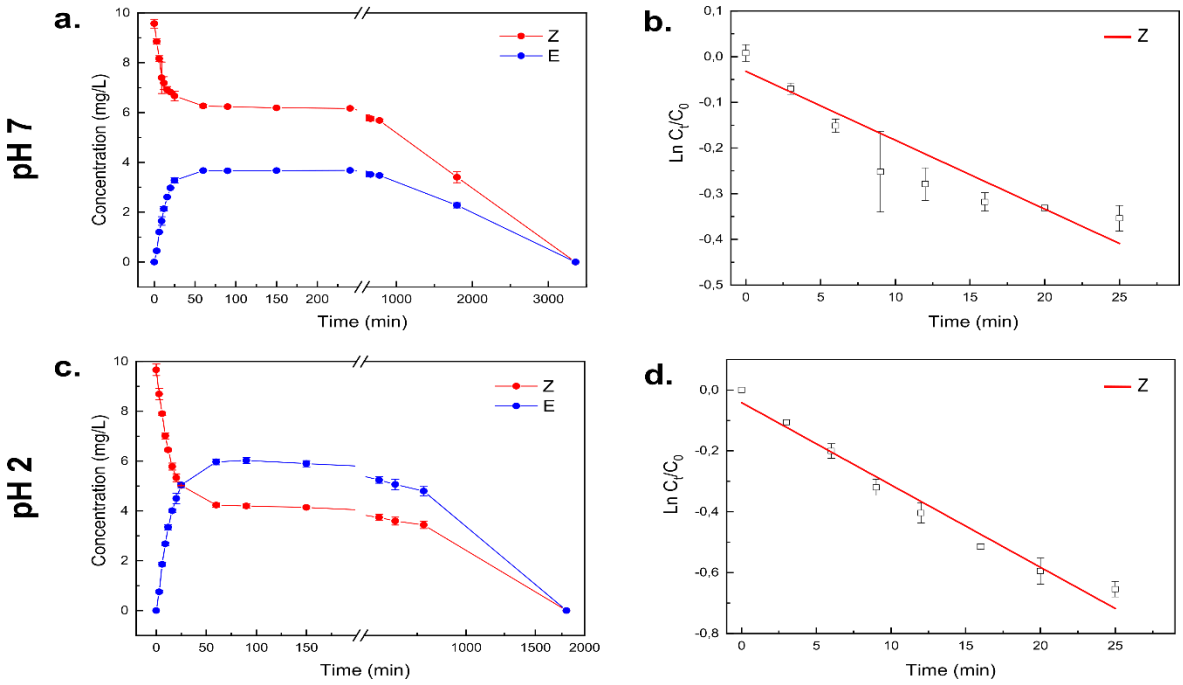


Figure 2. Time course profile for Z and E isomers concentrations, during the photolysis of Z-sulindac solutions in water under UV-A irradiation with (a) pH7 and (c) pH2 conditions. Figures on the right side represent pseudo first-order kinetics for Z-sulindac at early stage of treatment with same irradiation, under (b) pH7 and (d) pH2 conditions.

Early in irradiation (0-20 min, Figures 2b and 2d), the parent compound (Z-isomer) prevailed over its byproducts and photodegraded under pseudo first-order kinetics, indicating that isomerization occurred by a unimolecular process until equilibrium was reached at ~20 min. Within 40 min, one half-life was reached for all degradation experiments. After 40 min, a slower reaction was detected with a different kinetic behavior, suggesting an interaction of new byproduct compounds in the mechanism. A particular case of consecutive reactions has been reported with a similar behavior,

where initial rates follow first order kinetics over a relatively short time frame, and across the course of most of the reaction, a different kinetic order can be assessed.[44]

Rate constants (k_1), half-lives ($t_{1/2}$), and quantum yields (ϕc), which we report for the first time, were calculated for Z-sulindac (Table 2). Kinetics of each isomer could not be determined directly, as only the Z-isomer standard was readily available at the time of this study. Additionally, the E-isomer is not available without a substantial Z-isomer impurity (~5%).

Under the experimental design of this study, calculated quantum yields showed that the neutral form of Z-sulindac was more photoreactive than the fully deprotonated compound (Table 2). UV-B irradiated solutions reported the highest quantum yield of (1.70±0.04) x 10^{-3} at pH 2 compared to (9.6±0.4) x 10^{-4} at pH 7. Efficiency of photolysis using UV-A was higher at pH 2 with a quantum yield of (9.9±0.5) x 10^{-4}, decreasing to (5.7±0.2) x 10^{-4} at pH 7. As reported, the reaction quantum yield for the photolysis of sulindac is enhanced almost three times ($\phi_{pH2,\ UV\text{-}B} \approx 3\ \phi_{pH7,\ UV\text{-}A}$) by decreasing the pH and applying greater energy light with the UV-B lamp. Many organic compounds including some other pharmaceuticals also show pH-dependent photodegradation and toxicity changes linked to dissociation.[41,45–47]

Furthermore, for UV-A exposure, the half-life for Z-sulindac in pH 7 solution was 39.7 min, with a k_1 of (1.75±0.06)x10^{-2} min^{-1} (Table 2). Meanwhile, for the same light source at pH 2, Z-sulindac degraded faster with a half-life of 22.9 min (Table 2). Irradiation under UV-B light produced greater rate constants, ranging from (2.28±0.09) x 10^{-2} at pH 7 to (4.00±0.09)x10^{-2} min^{-1} at pH 2 (Table 2). It is worth highlighting that for the isomerization process, acidic conditions lead to half-lives that are nearly two-fold lower for pH 2 than for pH 7.

Table 2. Experimental rate constants (k_1), half-lives ($t_{1/2}$) and quantum yields (ϕ_c) for the pseudo first-order kinetic process of *Z*-sulindac direct photolysis under different exposure conditions.

Kinetic parameters	Irradiation source	
	UV-B	UV-A
$t_{1/2}$ (min)[a], pH 2	17.3 ±1.1	22.9 ±0.4
k_1 (min^{-1})[a], pH 2	(4.00±0.09) x 10^{-2}	(3.0±0.2) x 10^{-2}
ϕ[a,b], pH 2	(1.70±0.04) x 10^{-3}	(9.9±0.5) x 10^{-4}
$t_{1/2}$ (min)[a], pH 7	30.4±1.4	39.7±1.3
k_1 (min^{-1})[a], pH 7	(2.28±0.09) x 10^{-2}	(1.75±0.06) x 10^{-2}
ϕ[a,b], pH 7	(9.6±0.4) x 10^{-4}	(5.7±0.2) x 10^{-4}

[a]Errors represent standard deviation (SD). [b]Errors as SD, calculated through error propagation.

Kinetic mechanism using the approach of consecutive reactions.

Model description

Photochemical degradation modeling for sulindac was performed considering both the observed isomerization and the two pH conditions. As was shown in Figure 2 for UV-A irradiation, different order kinetics were observed and a similar trend was reported for UV-B irradiation experiments (Figure S2). These results can be related to consecutive photochemical reactions, which follow eqn (1) described below.[48]

$$A \underset{h\nu}{\overset{h\nu}{\rightleftharpoons}} B \xrightarrow{h\nu} C \qquad (1)$$

Previous studies have reported challenges in understanding consecutive reaction kinetics, which often include non-linear kinetics due to time-dependent concentrations of all components, and difficulty to isolate intermediates. Moreover, extinction coefficients of intermediates must be calculated.[48,49] In our work to overcome the lack of spectral information for E-sulindac, a molar absorptivity ratio for both isomers ($\varepsilon_Z/\varepsilon_E$ =0.85) was resolved as detailed in the ESI (equation system (S2)). This value suggests that the E-isomer absorbs radiation to a higher degree than the Z-isomer under the same source intensity and concentration, and hence, it can undergo to a higher

photo-reactivity. The ratio of 0.85 was applied to correct concentrations of E-sulindac for modeling calculations.

$$Z \rightleftharpoons E \qquad (2)$$

The following steps describe the photolytic degradation of sulindac (detailed in SI), where isomerization from Z to E-isomer is the first step (unimolecular), and the subsequent steps relate to the cleavage of both isomers due to irradiation (unimolecular and bimolecular reactions):

$$Z \xrightarrow{k_1} E \qquad (3a)$$

$$E \xrightarrow{k_{-1}} Z \qquad (3b)$$

$$Z \xrightarrow{k_2} P \qquad (3c)$$

$$E \xrightarrow{k_2} P \qquad (3d)$$

$$Z + P \xrightarrow{k_3} 2P \qquad (3e)$$

$$E + P \xrightarrow{k_3} 2P \qquad (3f)$$

In the above mechanism, P represents highly reactive products that with the E and Z isomers of sulindac yield to further degradation products. These P products could be photosensitizers or radicals that could be generated during the photochemical reaction. Nerveless for simplicity, regardless the chemical nature of the P products, their effect on the degradation kinetics of sulindac was expressed in the same way by the steps (3e) and (3f).

Validation of the model was assessed by criterion of goodness-of-fit and error analysis as detailed in ESI (Figure S4), which showed agreement between modeled concentrations and experimental findings for both isomers (Figure 3) under the irradiation and pH conditions tested.

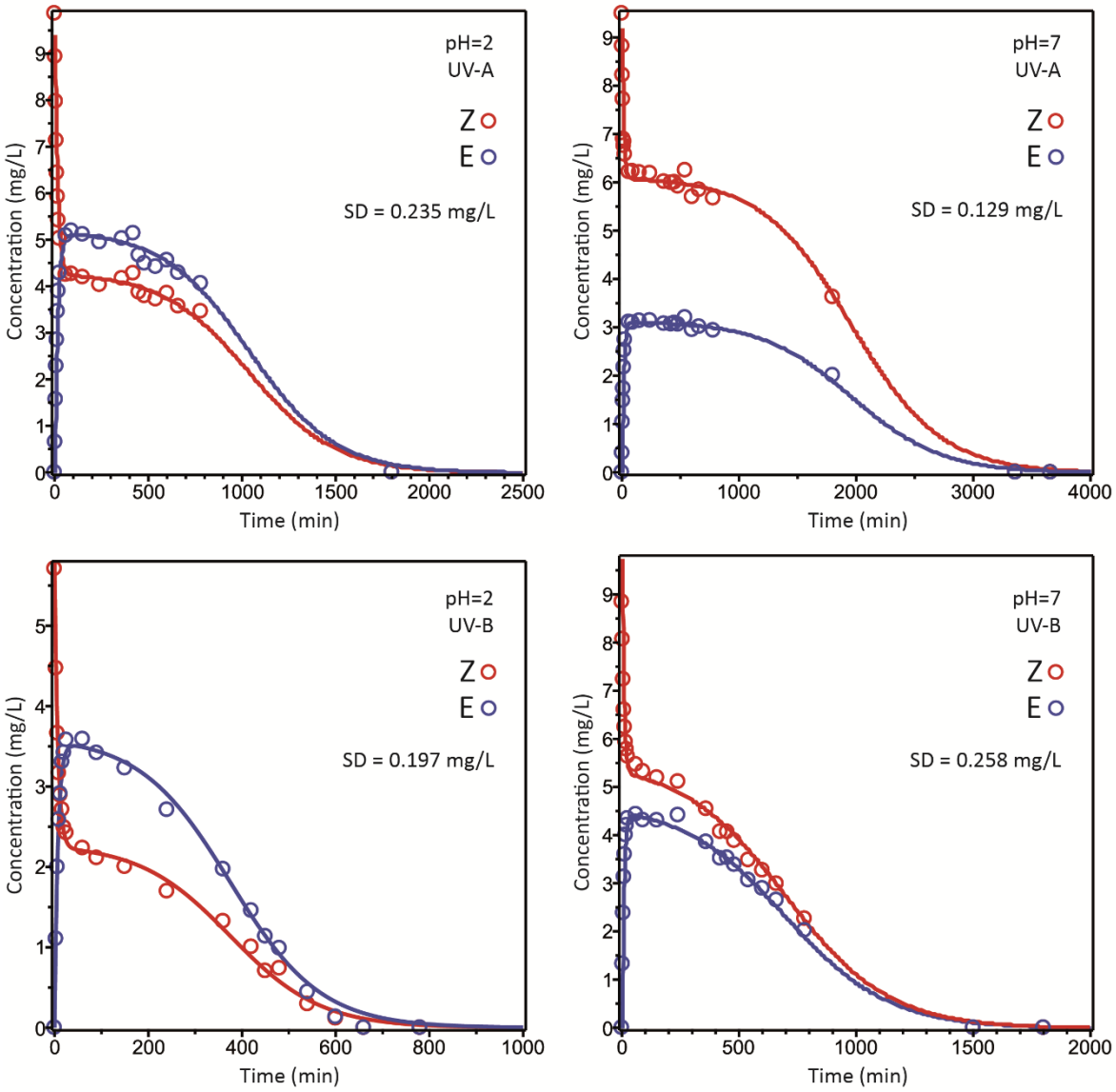


Figure 3. Time evolution fitting of kinetic experimental data (circles) to consecutive reaction model (continuous line) with first and second-rate constants for the photolytic degradation of sulindac under different conditions of pH and irradiation source. Standard deviations (SD) represent the maximum error of the regressions.

The estimated rate ($k_{i,i}$=-1,1,2,3) and equilibrium constants (K) from the model analysis are found in Table 3. For UV-B experiments, predicted rate constants were greatest at acidic conditions. The

predicted first-order rate constant k_1 was (6.2±0.1) x 10^{-2} min^{-1} at pH 7 to (8.6±0.8) x 10^{-2} min^{-1} at pH 2. While slower photolysis was observed under UV-A irradiation, the dependence on pH was consistent with a k_1 of (3.64±0.09) x 10^{-2} min^{-1} at pH 2 and (2.58±0.05) x 10^{-2} min^{-1} at pH 7. Experimental and modeled results of k_1 kinetic rate constants reported in Tables 2 and 3 can be compared to support the validity of the model.

Under UV-A irradiation, experimental and modeled values of k_1 were most similar with values of $k_1$exp=(3.0±0.2) x 10^{-2} min^{-1} vs $k_1$model=(3.64±0.09) x 10^{-2} min^{-1} at pH 2, and $k_1$exp=(1.75±0.06) x 10^{-2} min^{-1} vs $k_1$model=(2.58±0.05) x 10^{-2} min^{-1} at pH 7, and 21% and 47% of relative error respectively. For UV-B systems, value of $k_1$exp=(4.00±0.09) x 10^{-2} min^{-1} vs $k_1$model=(8.6±0.8) x 10^{-2} min^{-1} were obtained at pH 2 and $k_1$exp=(2.28±0.09) x 10^{-2} min-1 vs $k_1$model=(6.2±0.1) x 10^{-2} min^{-1} at pH 7, with corresponding relative errors of 115% and 172%. For the latter case, although more divergence was observed between model and experimental data, the model was still able to predict rate constants within <3-fold difference from experimental values. Lastly, for all systems, modeled and measured k_1 rate constants as well as modeled second order k_3 rate constants displayed a consistent trend with pH and light energy.

Table 3. Modeled rate constants and equilibrium constants for the photolytic degradation of *Z*-sulindac according to the proposed mechanism under the specific exposure conditions.[a]

Condition	k_1 (min^{-1})	k_{-1} (min^{-1})	k_2 (min^{-1})	k_3 ($(mg/L)^{-1}min^{-1}$)	$K = k_1/k_{-1}$
pH=2, UV-A	(3.64±0.09) x 10^{-2}	(2.9±0.1) x 10^{-2}	(4.0±1.0) x 10^{-5}	(4.8±0.4) x 10^{-4}	1.24±0.03
pH=7, UV-A	(2.58±0.05) x 10^{-2}	(5.0±0.1) x 10^{-2}	(2.3±0.6) x 10^{-5}	(2.6±0.2) x 10^{-4}	0.513±0.003
pH=2, UV-B	(8.6±0.8) x 10^{-2}	(5.4±0.6) x 10^{-2}	(1.9±0.4) x10^{-4}	(1.7±0.1) x 10^{-3}	1.60±0.04
pH=7, UV-B	(6.2±0.1) x 10^{-2}	(7.4±0.2) x 10^{-2}	(2.0±0.1) x 10^{-4}	(4.55±0.09) x 10^{-4}	0.840±0.003

[a]Errors represent SD.

The rate constants $k_1$and $k_{(-1)}$ were estimated when Z-sulindac parent compound prevailed. Both parameters were higher using UV-B irradiation than those with UV-A, irrespective of the pH of the medium, which implies faster interconversion between Z and E isomers under UV-B than UV-A. Furthermore, generation of the E-isomer is favored at pH 2 as evidenced by the equilibrium constant K reported in Table 3. The enhanced Z to E isomerization could be explained by the fact that the photoinduced isomerization mechanism could arise through the excitation of the alkene to a diradical excited state C•- C• to allow for the rotation necessary Z to E isomerization, followed by π bond formation with energy release to the ground state. Indeed, it is apparent from the 3D structure of sulindac (Figure 1) that the methyl sulfonyl phenyl group and the indene aromatic system are not in the same plane. The isomerization observed is likely facilitated by the molecule's highly conjugated system allowing both, resonance through the indene system, and easily excited π electrons. The acidic conditions at pH 2, in which the protonated carboxylic acid species dominates, could result in enhanced photoisomerization compared to neutral conditions (pH 7) because of the greater electron-withdrawing capability of the neutral species with higher photosensitivity compared to the deprotonated carboxylate present at pH 7. Early studies reported a similar withdrawing capability for alkene photoisomerization.[50]

The proposed isomerization mechanism and the slightly increased values of the acidic aqueous rate constants k_1 and $k_{(-1)}$ (Table 3) are consistent with the first steps for the photolytic degradation described in equation system 3 and the suggested electron withdrawal effect in sulindac. Finally, it was found that acidity did not have a scaling effect on the photodegradation of sulindac, as differences in pH did not lead to five-fold lower kinetic constants for pH 7 than for pH 2 (Table 3).

The kinetic results described in this work also agreed with the persistence of sulindac previously reported[28] and can be related to theoretical assumptions on the structural characterization of sulindac. Faizan et al.[51] described a small value (3.651 eV) for sulindac's HOMO-LUMO gap to predict low kinetic stability, high chemical reactivity and nonlinear properties with regards to its interaction with incident light. These observations are consistent with the fast isomerization reactions observed at the beginning of the photodegradation process, as even under UV-A irradiation (the lowest energy source applied), the conversion from Z to E-isomer began immediately (time=3 min). In a period of less than 40 min, it was possible to reach an equilibrium between the E and Z species. Overall, the present work revealed that across the ≈61h of exposure,

the process did not follow first order kinetics, and that generation of new products promote the photodegradation of both isomers (eq. (3e) and (3f)).

Degradation byproducts and transformation pathway under experimental conditions.

The identification of the photoproducts and pathways of transformation are important to assess exposure to different organisms. The present study applied long irradiation periods of ≈61 h facilitating the formation of additional byproducts beyond isomerization. The corresponding byproducts were not observed for the non-irradiated dark control samples.

The major degradation products DP-01 and DP-02 (Figure 1) were identified as probable structures resulting from the alkene cleavage in direct photolysis of the parent compound. According to the identification confidence level system proposed by Schymanski et al.[52] Our study was able to reach level 2 (i.e., proposed structure), in the elucidation for both byproducts. Assessment for both structures were supported with evidence of chromatogram data, diagnostic Qtof-MS fragments in experimental data and non-target identification reports from Progenesis QI.

As previously noted (Figure 1), after a period of 30 h of treatment under UV-A and pH7 exposure, a prevailing byproduct (DP-01) was identified with a higher polarity than the sulindac isomers. Sample analysis of the experiment after 30 h of irradiation (Figure 4a) gave an [M+H]+ ion at m/z=169.0330 detected at 3.21 min, that corresponded to a degradation product with a formula of $C_8H_8O_2S$. Major fragment ions of DP-01 were reported at m/z=141.9602 (C_7H_9OS, -CO) and 125.9873 (C_7H_9S, $-CO_2$), consistent with DP-01 being 4-(methylsulfinyl)benzaldehyde with a mass error of 7.34 ppm and 98.06% isotopic similarity. This product increased from 20 min to 30 h (Figure S5). The same compound was found under UV-B irradiation at pH7, but with a maximum mean intensity at 13 h instead of 30 h. The product was not detected under UV-B irradiation at pH 2 conditions. These observations are consistent with formation of DP-01 from oxidative alkene cleavage.

The second transformation product (DP-02) had an elemental composition of $C_8H_8O_3S$ (Figure 4b). The molecular ion [M+H]+ was detected at m/z=185.0275 and 3.16 min. Major fragment ions were m/z=168.0254 ($C_8H_8O_2S$, -HO), 151.0227 ($C_7H_4O_2S$, $-CH_5O$) and 105.0345 (C_7H_5O, $-CH_4O_2S$), consistent with 4-(methylsulfinyl) benzoic acid with a mass error of 6.74 ppm and 98.4%

isotopic similarity. DP-02 reached maximum abundance at 61 h and was also detected under UV-A irradiation at pH 2, but with maximum abundance at 56 h (Figure S5). It was not positively identified under UV-B irradiation. DP-02 is likely produced from further oxidation of the –CHO group in DP-01 to yield the corresponding byproduct 4-(methylsulfinyl) benzoic acid.

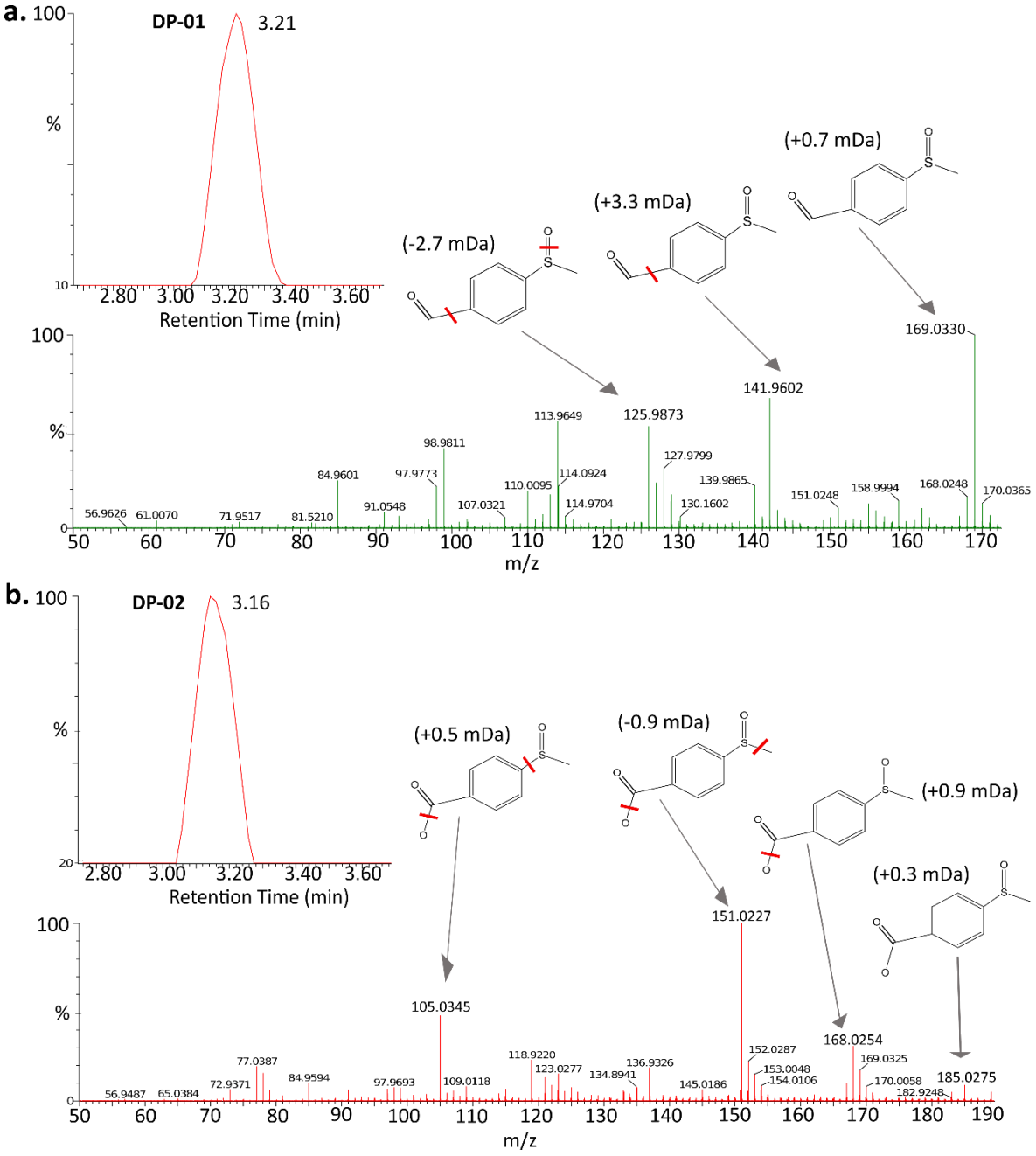


Figure 4. Mass spectrometry assignment of degradation products for sulindac direct photolysis in samples under UV-A and pH7 conditions, with a exposure of (a) 30 h to for DP-01 and (b) 61 h for DP-02, using extracted chromatograms for the molecular ion and MS^E high energy spectra for electrospray ionization in positive-ion mode (ESI+). Numbers in parenthesis indicate the error between measured and theoretical mass.

A photodegradation pathway (Figure 5) is proposed for the direct photolysis of sulindac. The alkene exo to the indene system could play a main role in the degradation process and is presumed to be the most reactive site of the Z-isomer. The E-sulindac isomer would undergo the same degradation process, leading to the same photoproducts as those of Z-isomer described above. Oxidative cleavage of the double bond (alkene) yield the two prevailing byproducts 4-(methylsulfinyl)benzaldehyde (DP-01) and 4-(methylsulfinyl) benzoic acid (DP-02). We speculate that DP-01 was produced via 2+2 cyclophotoaddition of singlet molecular oxygen to the alkene moiety in the sulindac parent isomers,[53] leading to a dioxoetane, which then can undergo an oxidative cleavage through a diradical intermediate54 to produce the corresponding carbonyl compounds, in this case, the (5-fluoro-2-methyl-1-oxo-1H-inden-3-yl)acetic acid) ketone and aldehyde, i.e., DP-01. Further oxidation of the aldehyde would yield the carboxylic acid (4-(methylsulfinyl)benzoic acid), i.e., DP-02. Although it was reasonable to expect the generation of the ketone, it is a highly reactive intermediate, thus direct evidence for its presence was inconclusive at the present time.

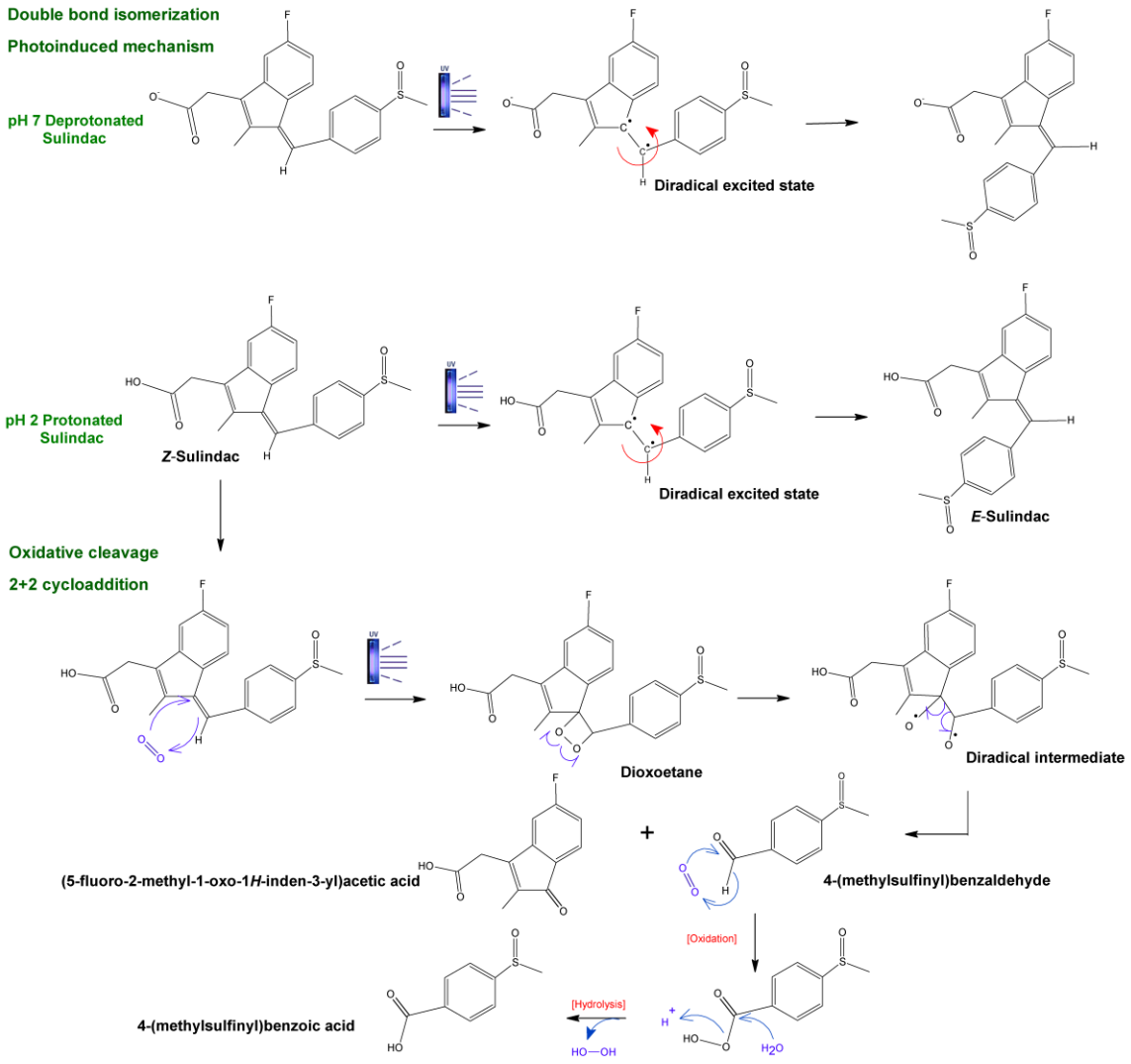


Figure 5. Proposed degradation pathway scheme of direct photolysis for sulindac and subsequent photoproduct transformations under experimental conditions. (E-sulindac isomer would undergo the same degradation process as Z-sulindac, scheme not shown).

Previous studies have reported that homolytic bond cleavage produces reactive radicals that could be involved in decomposition reactions with the original molecules, accelerating the degradations processes as more products are generated.[55] Zhang et al.[56] noted that gemfibrozil (GMF) underwent self-sensitized photolysis. The initial concentration-dependent photodegradation was

attributed to the involvement of singlet oxygen ($^1O_2$) initiated by the decarboxylated intermediates of GMF, that subsequently reacted with the parent compound and accelerated the photolysis.

We hypothesize that promotional effects on the photodegradation of sulindac could be attributed to degradation sensitized by DP-01 and DP-02 byproducts. Photo-induced intermediates DP-01 and DP-02 are ketone-type compounds with triplet-states that can generate reactive intermediates with triplet excited states, which subsequently produce $^1O_2$, a reactive oxygen species with high quantum yield.[56–60] These photochemically produced reactive intermediates may then facilitate the photolysis of sulindac in agreement with the kinetic model proposal included in this study. In this way, sulindac under UV irradiation and after reaching isomerization photoequilibrium proceeds through self-sensitized photolysis to reactive species via second-order kinetics. These results provide, for the first time, a novel insight of the effects of byproducts as sensitizers for the photodegradation of sulindac.

Prediction of aquatic toxicity with ECOSAR model

The Ecological Structure Activity Relationships Program (ECOSAR) of the United States Environmental Protection Agency (EPA) was used to predict the aquatic toxic potency of sulindac and its degradation products (Table S2). In silico toxicity prediction and physicochemical parameters were assessed through the general narcosis mechanism to standard test species (fish, daphnids and green algae). Phototransformation of sulindac can increase toxicity on some aquatic organisms. Among the species evaluated, daphnids showed greater sensitivity to chronic effects of Z-sulindac, DP-01 and DP-02 compounds than did fish and green algae. DP-01 aldehyde was categorized into a chemical class with excess toxicity and had the lowest predicted chronic concentration (0.67 mg L^{-1}). With regards to acute toxicity, Z-sulindac had the greatest effect to daphnid with 18 mg L^{-1} (LC50, 48 h). Future in vitro and in vivo testing should be addressed to more accurately evaluate the potential risks of sulindac and its photodegradation products in the aquatic environment.

CONCLUSIONS

A well-defined laboratory incubation experiment was conducted to investigate photolysis of sulindac under simulated conditions of relevance for aquatic ecosystems. Results indicated that sulindac's photochemical behavior is nonlinear. Upon exposure, the first half-life represents rapid Z to E isomerization following pseudo first order kinetics. Subsequent steps reported a second half-life dependence on concentration and formation of new byproducts, including an aldehyde and carboxylic acid, that could sensitize the photodegradation of sulindac by generating highly reactive intermediates, e.g., triplet excited states and $^1O_2$. This study reported the first experimental kinetic rates and quantum yields related to the consecutive reaction pathway for sulindac. Kinetic data showed that the parent compound underwent faster removal with UV-B radiation and lower pH.

Our work revealed the persistence of sulindac and its photoproducts under simulated sunlight conditions over periods longer than 61 h, with a dependence on pH. Our results improve our understanding of the photochemical fate of sulindac in environmental waters and may provide a guideline to treatment methodologies in engineered waters and exposure studies to aquatic organisms. Future work should aim to estimate the toxicity of parent and photoproduct mixtures in impacted aquatic systems.

AUTHOR CONTRIBUTION

Conceptualization: A.L.-E.; J.K.C. and C.S.W. Methodology: A.L.-E.; J.K.C.; A.S.-K. and C.S.W. Data analysis and interpretation: A.L.-E.; J.K.C.; F.R.-G.; A.S.-K.; E.C. and C.S.W. Modeling: E.C. Writing—original draft and revised manuscript: A.L.-E.; J.K.C.; F.R.-G.; A.S.-K.; E.C. and C.S.W. Project administration: A.L.-E. Supervision J.K.C. and C.S.W. Funding acquisition, A.L.-E.; F.R.-G. and C.S.W. All authors read and approved the final manuscript.

CONFLICTS OF INTEREST

The authors have no conflict of interest to declare.

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SUPPLEMENTARY INFORMATION FOR CHAPTER 5.

Photolysis of the nonsteroidal anti-inflammatory drug sulindac: elucidation of kinetic behaviour and photodegradation pathways in water

MATERIALS AND METHODS (ESI)

Table S1: Gradient elution method for Qtof-MS Liquid Chromatography in sulindac analysis. Solvents were H_2O:0.05 % formic acid (A) and Methanol: 0.05 % formic acid (B).

Time (min)	Flow (mL/min)	% A	% B
0	0.3	95	5
1	0.3	95	5
2.5	0.3	50	50
4.0	0.3	50	50
6.5	0.3	5	95
7.5	0.3	5	95
11.5	0.3	95	5

RESULTS AND DISCUSSION (ESI)

Direct photolysis experiments under laboratory conditions

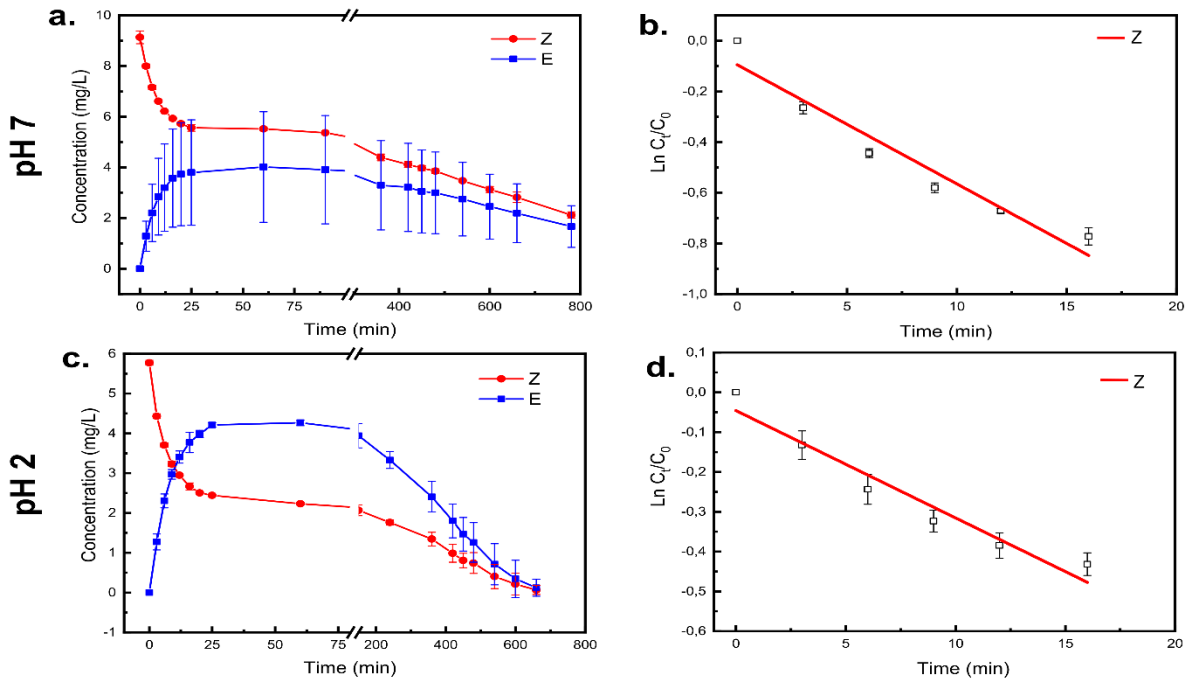

Figure S1. Time course profile for *Z* and *E* isomers concentrations during the photolysis of *Z*-sulindac solutions in water under UV-B irradiation with (a) pH7 and (c) pH2 conditions. Figures on the right side represent pseudo first-order kinetics for *Z*-sulindac at early stage of treatment with same irradiation under (b) pH7 and (d) pH2 conditions.

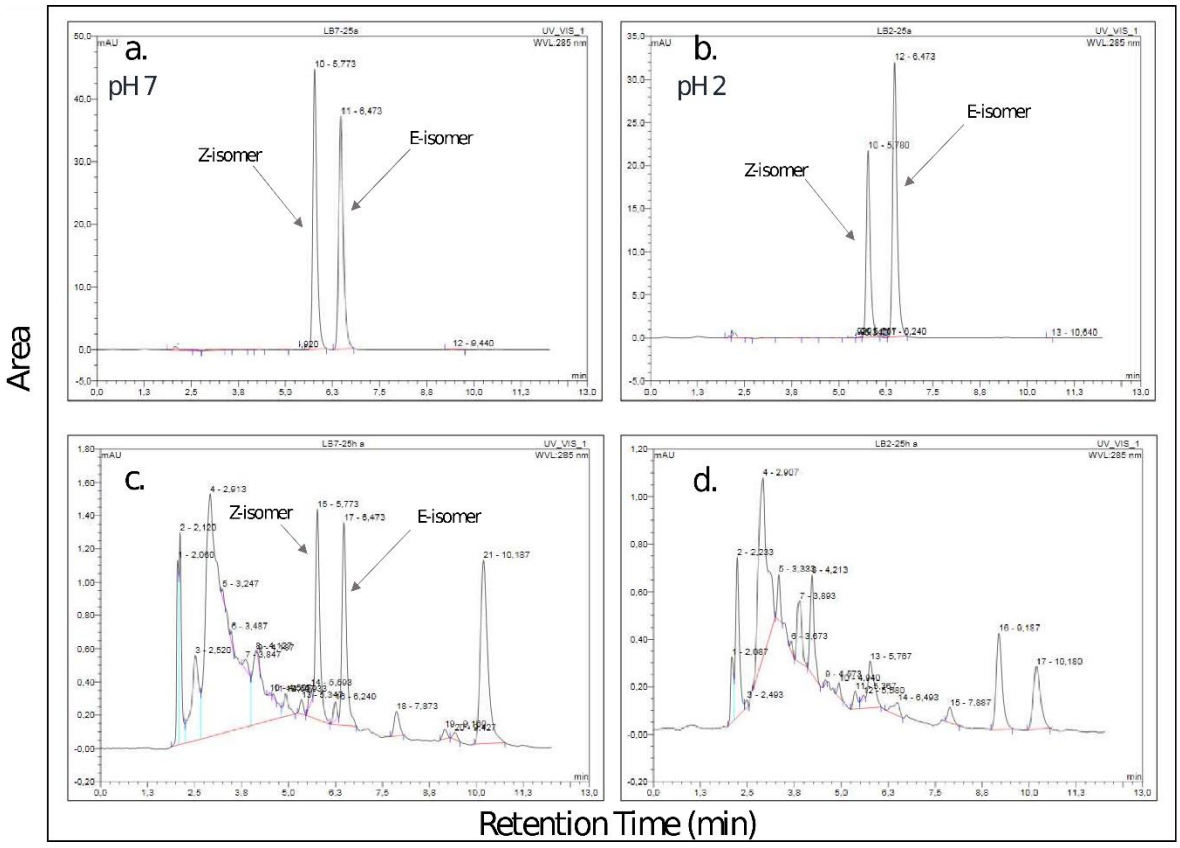

Figure S2. LC-UV/VIS trace for an isomeric photoproduct mixture of sulindac. generated with UV-B irradiation under conditions of (a) 25 min-pH 7. (b) 25 min-pH 2 and (c) 25 h-pH 7. Signals for isomers were no detected under (d) 25 h-pH 7 conditions ($\lambda_{detection}$ =285 nm).

Kinetic mechanism using the approach of consecutive reactions (ESI)

Model description

For simplicity. in the postulated mechanism (system equation 3). all the species are assumed to be in their neutral form. and P represents any degradation product. Stage 3b is the reversed isomerization of 3a. Reactions from 3a to 3d are unimolecular. and accordingly are considered as first order processes. Steps 3e and 3f involve bimolecular reactions of each isomer with any product P. generating additional products following second order reactions. Structural similarity among *E* and *Z* isomers support the assumption that steps 3c and 3d have the same first order

rate constant. k_2. The latter assumption additionally is used to estimate that steps 3e and 3f also take place with identical second-order specific rate constants. k_3.

Interpretation of model outputs are described below. Equation S4 provided the half-life of total sulindac concentration ($c_S = c_Z + c_E$) over time. depending on initial concentrations (eq. S5 and S6). The time variation of the total concentration of sulindac ($c_S = c_Z + c_E$) was fitted with the model equation S5 to calculate the specific rates k_2 and k_3. Further. fitted parameters were used to estimate $k_1$and k_{-1}.

Equation system S2. Calculation of molar absorptivity ratio sulindac isomers ($\boldsymbol{\varepsilon_Z/\varepsilon_E}$)

To calculate ($\boldsymbol{\varepsilon_Z/\varepsilon_E}$) ratio. absorbance *A* correspond to the wavelength of maximum absorption at the irradiation time (0 and 25 min). c_{Z0} is the sulindac concentration without irradiation (t=0). b is the pathlength. a is the error. and K is the equilibrium constant for the isomerization reaction. Measurements were made for three standard solutions with different initial concentrations of *Z*-sulindac (2. 7. and 10 mg/L) under each pH (2 and 7) and irradiation source (326 nm and 285 nm).

$$A = \varepsilon_Z\, bc_Z + \varepsilon_E bc_E + a \qquad (S2a)$$

$$\varepsilon_Z = \frac{A_0 - a}{b\, c_{Z0}} \qquad (S2b)$$

$$K = \frac{c_E}{c_Z} \qquad (S2c)$$

$$c_{Z0} = c_Z + c_E \qquad (S2d)$$

$$A = \frac{c_{Z0}\, K\, b\, \varepsilon_E}{K+1} + \frac{(A_0 - a)}{K+1} + a \qquad (S2e)$$

Differential equation model S4. Evaluation for the irradiation time dependence of the process according to the postulated mechanism (system equation 3).

$$\frac{dc_Z}{dt} = -k_1 c_Z + k_{-1} c_E - k_2 c_Z - k_3 c_Z c_P \qquad (S4a)$$

$$\frac{dc_E}{dt} = k_1 c_Z - k_{-1} c_E - k_2 c_E - k_3 c_E c_P \qquad (S4b)$$

$$\frac{dc_P}{dt} = k_2 c_Z + k_2 c_E + k_3 c_Z c_P + k_3 c_E c_P \qquad (S4c)$$

Where c_J represents the concentration of J as function of time and initial conditions are considered as $c_Z(0) = z_0$. $c_E(0) = 0$ and $c_P(0) = 0$. It is to be highlighted. that the system of differential equations S4 cannot be analytically solved (i.e. the mathematical functions of time for the concentrations cannot be expressed in explicit forms). However. the variation with time regarding to the total concentration of sulindac ($c_S = c_Z + c_E$) could be solved as an explicit function:

$$c_S = c_Z + c_E = \frac{z_0(z_0 k_3 + k_2)}{k_2 e^{t(z_0 k_3 + k_2)} + z_0 k_3}. \qquad (S5)$$

According to equation S5. the half-life of total sulindac depends on its initial concentration as follows:

$$t_{1/2} = \frac{1}{z_0 k_3 + k_2} \ln\left(\frac{z_0 k_3 + 2k_2}{k_2}\right). \qquad (S6)$$

Following the above analysis. the time variation of the total concentration of sulindac $c_S = c_Z + c_E$ was fitted with the model equation S5 to calculate the specific rates k_2 and k_3 through the Levenberg-Marquardt algorithm for non-linear regression. The fitted parameters were used for the numerical solution of the system of differential equations S4. The estimation of $k_1$and k_{-1} was achieved with a numerical procedure of minimization of squared residuals written in the software Maple for symbolic and numeric computation. The procedure was applied to fit the parametrized numeric solutions of the equation system S4. using the Runge-Kutta-Fehlberg method with fourth degree interpolant.

Validation of model

The model fitting was validated on criterion for goodness-of-fit and error analysis. Figure S3 illustrates the agreement between model and experimental findings. The standard deviation (SD) of the nonlinear regressions was considered to describe the maximum error for the model. According fitted model data for UV-A experiment at pH7. it can be stated that for a value of SD=0.129 mg/L. the maximum error in the modeled concentrations is predicted as 2SD=0.258 mg/L for 95% confidence. Therefore. the error of the regressions confirm the reliability of the proposed model to explain the experimental observations. Moreover. goodness-of-fit for each incubation system (Figure S3) showed that most of the modeled concentrations are similar to the experimental values. due all the points lining up close to the identity function (model=experimental). which indicates that the proposed kinetic model of consecutive reaction is valid and makes a reliable prediction of the sulindac degradation process induced by direct photolysis.

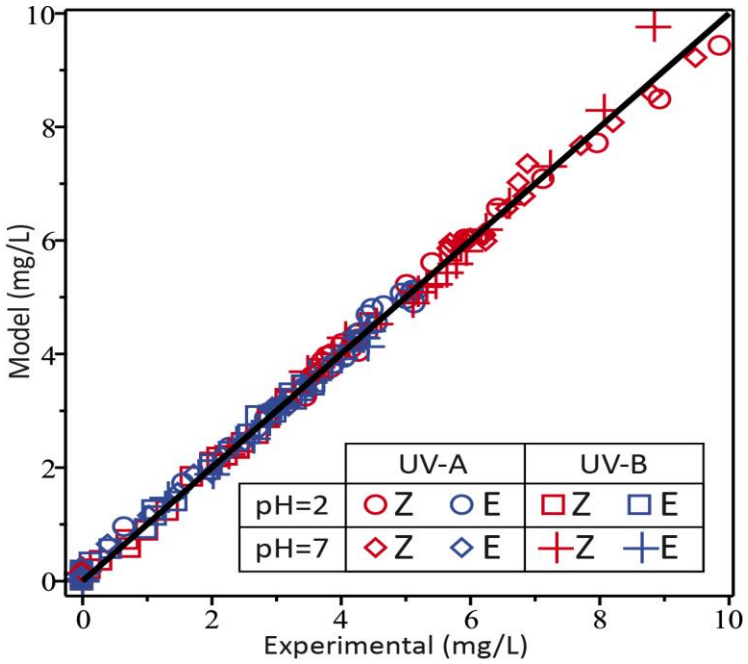

Figure S3. Modeled versus experimental concentrations of sulindac isomers. Modeled results from fitted differential equation system S4 following the proposed chemical mechanism of equation system 3. The black line represents the identity function (model=experimental).

Degradation byproducts and transformation pathway under experimental conditions.

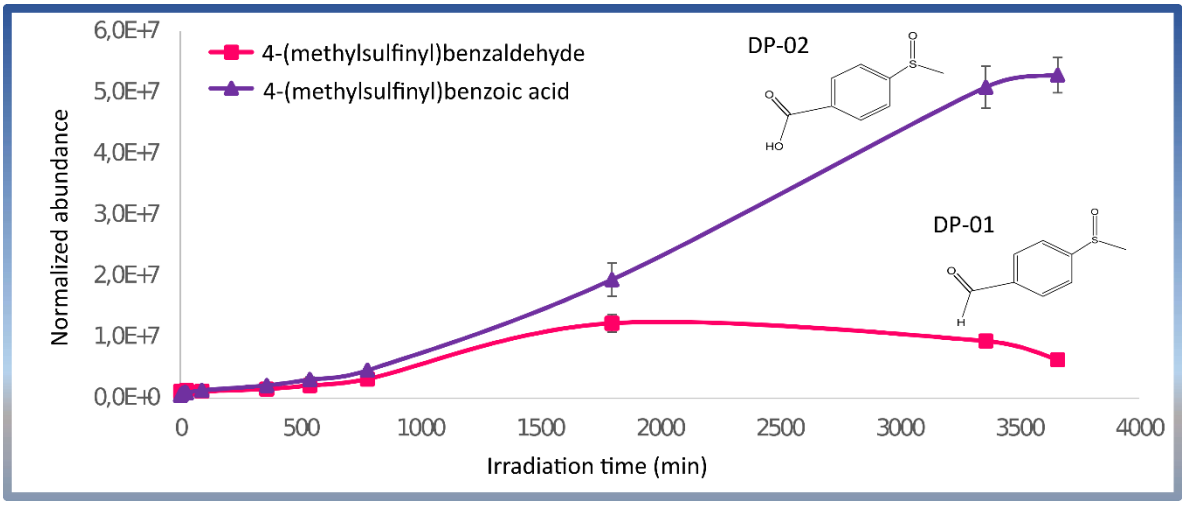

Figure S4. Monitoring of byproducts during sulindac photolysis by Qtof-MS compounds abundance profile under UV-A irradiation and pH 7 using Progenesis software. Data from replicates using average normalized abundance. standard deviations (SD) as errors. maximum fold Change>2 and Anova p-value≤0.05.

6. MODIFIED CELLULOSE/POLY(3,4-ETHYLENEDIOXYTHIOPHENE) COMPOSITE AS PHOTOCATALYST FOR THE REMOVAL OF SULINDAC AND CARBAMAZEPINE FROM WATER

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Abstract

Pharmaceutical compounds have been widely recognized as emerging contaminants around the world. Advanced oxidation processes using photocatalysts and ultraviolet radiation have been a successful integrated strategy for the removal of active pharmaceutical ingredients from polluted waters. In this research, an environmentally-friendly photocatalytic system operating under ambient conditions was developed. A conductive polymer composite was synthesized using

gamma irradiated cellulose as template and coated with poly(3,4-ethylenedioxythiophene). Gamma irradiation was applied as a green technology to functionalize cellulose, improving its stability in water and reducing its size. Our process proved to be a feasible technique to obtain stable particles in dispersion, confirmed by measuring their surface ζ-potential in water. The conductive polymer onto the composite catalyzed the photodegradation of highly persistent compounds sulindac and carbamazepine, showing outstanding catalytic effects within 7 hours of exposure under near ultraviolet (UV-A) light at pH 7. Removal efficiency of sulindac reached 89% and degradation of carbamazepine was 30% after pouring the composite into the photodegradative treatment. Similar results were achieved from mixture of both compounds. The composite reusability revealed that particle stability and photocatalytic activity were preserved even after repeating the degradation cycle. Our study showed a promising novel photocatalyst, synthetized through green technologies that can be used as a potential treatment for pharmaceutically active contaminants in water.

Keywords

Photocatalysis; Pharmaceutical compounds; Gamma irradiation; Conductive composite; Functionalized cellulose

1. Introduction

Drugs for human health and veterinary use allow the release of active pharmaceutical compounds (APIs) as emerging contaminants (ECs) to aquatic and terrestrial environments (Kleywegt et al., 2019; Kümmerer et al., 2019; Sousa et al., 2018; Tousova et al., 2017; Wilkinson et al., 2017). Parent compounds and their metabolites show non-biodegradable and pseudo persistence nature, resulting in poor degradation by conventional biological and chemical treatments (Kanakaraju et al., 2018). Considerable impacts on organisms exposed include microbial resistance, disturbance in endocrine systems and bioaccumulation in animals and plants (Chaturvedi et al., 2021; Dhangar and Kumar, 2020). Different removal efficiencies have been reported during the sewage treatment processes due to the different physicochemical properties of the pharmaceutical and the technology applied (Carlson et al., 2013; Eslami et al., 2015; Gurke et al., 2015; Mezzelani et al., 2018; Papageorgiou et al., 2016; Sun et al., 2016; Tran et al., 2018). Increasing attention is being drawn towards materials or composites (Ghosh et al., 2015a;

Serpone and Emeline, 2012) for photocatalytic solar-energy conversion to identify robust new methods for purification and environmental protection at lower cost and energy consumption in water. Table 1 presents a summary of peer-reviewed articles published in recent years on representative treatment technologies for emerging contaminants.

Table 1. Representative examples of recent removal technologies for treating emerging contaminants in water.

Treatment processes	Remarks	Removal of emerging contaminants (%)	References
Secondary biological processes (SBP)	Activated sludge processes (ASP) are the most used treatment in conventional wastewater treatment plants (WWTPs). High-rate SBP including constructed wetland, membrane bioreactors (MBR), moving bed biological reactor (MBBR), can increase removal efficiency. Some ECs exhibit toxicity to microorganisms, e.g., antibiotics. Disposal challenges for saturated sludges and concentrated phases. Processes depend on redox conditions. Long treatment times (days).	Median removal efficiency (<40%): codeine, metoprolol, propranolol, carbamazepine, sulpiride, sucralose, clorfibric acid, and crotamiton in full scale WWTPs across the globe. Many ECs show negative removals.	(Tran et al., 2018) (Gurke et al., 2015)

Activated carbon adsorption (ACA)	Powdered activated carbon (PAC) and granular activated carbon (GAC) are the major applications in WWTPs. The method depends on carbon structure of raw material, quality of water, seasonal variation, and dosage of the activated carbon. Struggles associated with dumping and renewing adsorbents.	GAC: diclofenac (>98%), carbamazepine (23%), propranolol (17 %), metoprolol (95%), sulfamethoxazole (90%), 17β-estradiol (>43%) and 17α-ethinylestradiol (50%) in full scale applications.	(Rout et al., 2021) (Yang et al., 2017) (Rodriguez-Narvaez et al., 2017)
Advanced oxidation processes (AOPs)	Include photo-Fenton, sonolysis, electrochemical oxidation, photocatalysis, ozonation, radiation, among others. Reactive oxygen or free radical species degrade pollutants to innocuous products. High removal efficiency up to mineralization. Some operational limitations for large-scale systems. Higher operating costs than conventional methods. Potential generation of more toxic byproducts.	Electrophotocatalytic oxidation (>99%): carbamazepine, atenolol, paracetamol, atrazine; amoxicillin (79%) and sulfamethoxazole (50%) in pure water. Solar photo-Fenton (>96%, 45 min): carbamazepine, ibuprofen, ofloxacin, flumequine and sulfamethoxazole from municipal WWTPs. Ozone/TiO_2 solar photocatalysis (60-80%): trimethoprim, atenolol and ofloxacin from synthetic effluent solution. TiO_2 photocatalysis (>90%): carbamazepine, aspirin, paracetamol, amoxicillin,	(Zhao et al., 2021) (Kanakaraju et al., 2018) (Richardson & Kimura, 2017) (Nava-Andrade et al., 2021) (Jing et al., 2013) (Pelaez et al., 2012)

	Efficacy could be affected by water composition.	diclofenac and ibuprofen from pure water. UV/H_2O_2 (60%–90%): diclofenac and ibuprofen, clorfibric acid, carbamazepine, and sulfamethoxazole from wastewater.	
Hybrid systems	Processes can include combination of BSP with AOPs, physical treatment units such as reverse osmosis (RO), nanofiltration (NF), and/or ultrafiltration (UF), etc. Much more efficient that individual methods in the removal of ECs. Economical cost and toxicity of byproducts are reduced. Persistent pollutants could be transformed into biodegradable intermediates. Optimal performance must be defined for each unit.	Increase of removal efficiency with MBR-membranes (RO and NF) hybrid system (i.e.,>98%): diclofenac, ibuprofen, naproxen, ketoprofen, acetaminophen, carbamazepine, gemfibrozil, atenolol and 17α-ethinylestradiol. Activated sludge + gamma radiation (100%): ibuprofen, carbamazepine, aspirin, clorfibric acid and diclofenac. UV/H_2O_2 + mixed bacterial inoculum: mineralization of tetracycline and carbamazepine from wastewater. Aerobic system + electro-Fenton (100%): recalcitrant furosemide and ranitidine. Aerobic system + ozone (100%): metoprolol and sulfamethoxazole.	(Saidulu et al., 2021) (Dhangar & Kumar, 2020) (J. Wang & Wang, 2016) (Rathi et al., 2021) (Olatunde et al., 2020) (Ahmed et al., 2021) (Monteil et al., 2019) (Ricky & Shanthakumar, 2022) (Parida et al., 2021)

	Semiconductor photocatalytic processes with TiO_2 and Xenon lamp: ofloxacin (100%)

Several authors reported that direct photolysis by natural or artificial light constitutes the dominant degradation mechanism for many pharmaceuticals (Challis et al., 2014; Couto et al., 2019; Musa and Eriksson, 2009; Rafqah and Sarakha, 2016). Key parameters may determine the final photodegradation performance including hydroxyl radical formation, UV light, water constituents, chemical structure of the pharmaceutical and acidity of the media (Al-Hajji et al., 2021; Challis et al., 2013; Kanakaraju et al., 2018; Poirier-Larabie et al., 2016).

Advanced oxidation processes (AOPs) like photocatalysis can promote the elimination of pharmaceuticals from water even under ambient conditions (Dhangar and Kumar, 2020; Serrano et al., 2019). Photocatalytic systems result in lower treatment times, can be applied using sunlight or near UV light for irradiation, tested under large pH range and easily monitored without elevate cost instrumentation for either one or both high temperature or high pressure operation (Gogate and Pandit, 2004; Taoufik et al., 2021). Titanium dioxide (TiO2) is currently the most widely used photocatalyst, even in the visible region (Asahi et al., 2001; Ghosh et al., 2015b; Grabowska et al., 2013; Hai et al., 2013; Kamat, 2012; Linic et al., 2011). Although oxide-based semiconductors have been widely reported as efficient photocatalysts, studies regarding photocatalytic activity of conjugated polymers are rising (Ghosh et al., 2015a; Katančić et al., 2020; Muktha et al., 2007; Yamini et al., 2022; Zia and Riaz, 2021). Poly(3,4-ethylenedioxythiophene) (PEDOT) is one of the most promising conducting polymers because of its excellent thermal and chemical stability, high conductivity, flexibility, low-cost, high transparency and elevated carrier mobility as well as biocompatibility (Hui et al., 2018; Zamora-Sequeira et al., 2018). Its photo and electrocatalytic properties under UV light and high degradation yields have been previously reported (Kumar et al., 2021; Shi et al., 2022; Zhang et al., 2022). The photoactivity is attributed to the formation of reactive oxidizing species (ROS) by the conductive polymer (Ghosh et al., 2015b; Kumar et al., 2021; Muktha et al., 2007; Zia and Riaz, 2021). PEDOT synthesized via-chemical oxidative

polymerization may provide an unprecedented potential as photocatalytic for water treatment (Ghosh et al., 2015a).

Cellulose is an ideal template to support some semiconductors because of its high hydrophilic nature, flexibility, permeability, thermal and chemically stability (Jayalakshmi et al., 2015; Zhang et al., 2017; Zhou et al., 2013). In addition, the biopolymer is a biodegradable and sustainable material, non-soluble, cheap and an abundant resource (Mohamed et al., 2015; Onwukamike et al., 2019; S. Wang et al., 2016; Wei et al., 2019; Zhou et al., 2013). To produce a continuous phase in water, the cellulose requires chemical modifications to generate functional groups that improve their stability (Feng et al., 2021; Siró and Plackett, 2010). Gamma radiation induces physical and chemical changes in polymers, being a feasible method either to produce materials or to tailor the properties according to the particular application (Benson, 2002; Driscoll et al., 2009; Santos-Rosales et al., 2021; Takács et al., 1999). From the molecular point of view, the gamma radiation induces several reactions like scission or crosslinking, depending on the experimental conditions and radiation dosage (Benson, 2002). Specifically, the gamma ionizing radiation leads to the degradation of the cellulose by the cleavage of the glycosidic bonds, generation of functional groups and reducing its size (Beck-Candanedo et al., 2005; Klemm et al., 2011). The resulted irradiated cellulose is a suitable template for the chemical deposition of PEDOT on the surface (Zamora-Sequeira et al., 2018).

Non-steroidal anti-inflammatory drugs (NSAIDs) and antiepileptic pharmaceuticals are some of the most studied classes as environmental pollutants in the aquatic media (Patel et al., 2019). Among them, two compounds of considerable interest are sulindac and carbamazepine (see table S1). Sulindac is prescribed to reduce inflammation and as one of the most effective and clinically chemopreventive agent (Mathew et al., 2018). Previous studies have reported its marked toxicity on aquatic luminescent bacteria (Kawabata et al., 2013) and its high environmental persistence at more relevant conditions of near ultraviolet (UV-A) light and pH 7 (Ledezma-Espinoza et al., 2021). Meanwhile, carbamazepine has been extensively described as a higher consumed anticonvulsant resistant to biodegradation (Gogoi et al., 2018), with degradation products that could be more toxic than the parent drug (Ding et al., 2017). It has frequently detected worldwide in aquatic matrices (Clara et al., 2004; Sui et al., 2015; Ternes, 1998; Tixier et al., 2003). Consequently, several strategies have been reported toward the elimination of carbamazepine

from water (Ali et al., 2018; Andreozzi et al., 2002; Ding et al., 2017; Donner et al., 2013; W. L. Wang et al., 2016).

In this study, an γ-irradiated cellulose PEDOT (I-Cell-PEDOT) composite was prepared from biomass using green methodologies to be evaluated in the removal of the emerging contaminants sulindac and carbamazepine from neutral aqueous media under UV-A irradiation. I-Cell-PEDOT composite was characterized and tested for the photocatalytic activity under UV light in water. To the best of our knowledge, this is the first research that describes the photodegradation of sulindac and carbamazepine catalyzed by I-Cell-PEDOT composite. The results may reveal the potential application of irradiated cellulose PEDOT (I-Cell-PEDOT) composites as photocatalysts for the remediation of pharmaceutical polluted waters.

2. Experimental section

2.1. Materials and reagents

Microcristalline Cellulose (Avicel®, PH101), 3,4-ethylenedioxythiophene (EDOT) (97%) and iron chloride (III) ($FeCl_3$) were purchased from Merck (San Jose, Costa Rica). Deionized water (18.2 Mohm-cm) was used in all the cellulose dispersion preparation. (1Z)-Sulindac (>98%) standard was supplied by TRC (Toronto, Canada) and carbamazepine standard was provided by Sigma-Aldrich (San José, Costa Rica). Solutions for photocatalytic experiments were prepared using LC-MS grade water obtained from Sigma-Aldrich (San José, Costa Rica) and buffered using di- and tri-basic potassium phosphate (K_2HPO_4, K_3PO4, >98%, Sigma–Aldrich) to the desired pH value. Methanol, formic acid (>95%) and isopropanol (IPA) of LC-MS grade were used for solvents in the liquid chromatographic analysis and were purchased from Sigma-Aldrich (San José, Costa Rica).

2.2. Cellulose dispersion preparation

The sample was prepared dispersing 2 g of cellulose in 25 mL of deionized water. The resulting suspension was subsequently sonicated (Q700, Ultrasonic Corporation, Danbury, CT, USA) for 1 min (20 W) to enhance the dispersion yield. The suspension was then centrifuged (IEC HN-SII, Damon LTD, Dunstable, Bedfordshire, England) during 4 min at 4000 rpm and room temperature,

then the supernatant was decanted and collected. This process was repeated up to 6 times until the supernatant turned turbid and it was identified as cellulose dispersion (Cell).

Cellulose dispersions (Cell) were placed in screw-cap glass vials (6 cm length and 1.5 cm in diameter) and irradiated using a gamma cell irradiator with a Cobalt-60 source (Ob-Servo Ignis, IZOTOP, Budapest, Hungary). The samples were exposed up to 300 kGy. The overall uncertainty of the absorbed dose rate was 2.4% for a 95% confidence level.

The resulting irradiated cellulose (I-Cell) was centrifuged (Sorvall LEGEND X1R, Thermo Scientific, Waltham, MA USA) at 10000 rpm during 10 min at room temperature and the supernatant was decanted and removed from the dispersion to be used as template in the polymerization of the conductive polymer.

PEDOT was synthesized onto cellulose by oxidative chemical polymerization of EDOT, adapted from a previous work (Starbird et al., 2014). The I-Cell sample was dispersed in an isopropanol solution of iron (III) chloride ($FeCl_3$) and kept overnight. The cellulose changed the color to orange due the Fe^{3+} interaction (I-Cell-Fe). EDOT (500 mg) was added to 10 mL iron-irradiated cellulose alcoholic dispersion at 30 °C. After 24 hours, a dark-blue powder (I-Cell-PEDOT) was obtained. The sample was then filtered and washed using methanol until the solution was colorless. The product was dried for 24 h in a vacuum oven (ADP 200C, Yamato-Scientific, Tokyo, Japan) at 60 °C and 85 kPa.

2.3. Template and composite characterization

Attenuated total reflectance-Fourier transformed infrared spectroscopy (ATR-FTIR) was conducted on a spectrometer equipped with an iATR accessory (Nicolet 380, Thermo Scientific, Madison, Wisconsin, USA) controlled with OMNIC v9.3.30 software. Dry samples were placed directly onto the diamond window (ca. 2 mg) without further preparation. Measurements were made in absorbance mode, in the 4000-600 cm^{-1} spectral range using 32 scans at a resolution of 4 cm^{-1}. Micro Raman spectroscopy was performed using a confocal Raman microscopy (WITec, GmbH, model Alpha300 R, Ulm, Germany) with a 532 nm excitation laser accumulating 120 scans. Thermogravimetric analyses (TGA) were carried out for commercial and irradiated samples in an SDT Q600 from TA Instruments (New Castle, Delaware, USA). A nitrogen atmosphere (100

mL.min^{-1}) was maintained during the analysis with a scan rate of 10 °C.min^{-1}, from room temperature to 700 °C in alumina cups (110 µL) (TA Instruments, New Castle, Delaware, USA).

Cellulose dispersions were characterized by dynamic light scattering (DLS) using a Zetasizer Nano (Nano ZS, Malvern Panalytical, UK) to evaluate the particle size and stability. A latex standard (DTS1235, Malvern Panalytical, UK) was employed to confirm the proper function of the equipment. All measurements were performed in purified water at 25 °C and at a 173° angle relative to the source. Values were calculated from the measurements performed in triplicate. The particle concentration was estimated using a Zetasizer Ultra (Nano ZS, Malvern Panalytical, UK) in a standard polystyrene cuvette.

The electrical resistance of the composites before and after the UV exposition was measured using a simple two-point probe configuration in a potentiostat (AUTOLAB, PGSTAT-302 model, Utrecht, Netherlands) (see fig. S1). A volume of the dispersed sample was poured in a self-fabricated gold electrode and dried in a vacuum oven (ADP-2000, Yamato-Scientific, Japan) for 12 hours. The resistance of each probe was obtained from the current-voltage curve (CV).

The sample topography was studied using an atomic force microscope (AFM) (NX10, Park Systems, Suwon, South Korea). An aliquot of the sample dispersion was poured onto a Mica substrate. Subsequently, it was dried using a stream of dry nitrogen (UAP, Praxair, San Jose, Costa Rica). The cantilevers used to obtain the image were Non-Contact PPP-NCHR probe (Park Systems Probes, Suwon, South Korea) with resonant frequency around 330 kHz and spring constant of 49 N.m^{-1}. The images were obtained using the software XEI (Version 1.0.7, Park Systems). The sample morphology was evaluated using scanning electron microscopy (SEM) TM 3000 (Hitachi, Tokyo, Japan), at 10 kV.

2.4. Photocatalytic experiments

Independent experiments were performed in 3 mg.L^{-1} aqueous solutions of sulindac (SUL), carbamazepine (CBZ) and the mixture of both compounds (Mix) at pH 7. The I-Cell-PEDOT aqueous dispersion was buffered also at pH 7 and prepared with 0.5 g.L^{-1} composite for all series of experiments. Pharmaceutical solutions along with I-Cell-PEDOT composite were irradiated during cycles of 7 h, using a batch rotary Luzchem Photoreactor (model LZC-5b, Luzchem

Research, ON, Canada). Cylindrical Pyrex tubes (10 mL) filtering wavelengths < ≈290 nm and with an irradiation path of L=1.33 cm were utilized as irradiation vessels. The instrument used an UV-A lamp (LZC-UVAp, 315-400 nm, 49.425 $mW.m^{-2}$) with a photon flux (290-400 nm) of (3.43 ± 0.07)×10^{18} $photons.cm^{-2}.s^{-1}$ (Ledezma-Espinoza et al., 2021). All photocatalytic experiments and control samples for adsorption and photolysis were carried out simultaneously by triplicate at 22 °C. Sampling (250 µL) for irradiation experiments was done periodically and all samples were analyzed by UHPLC/ESI-QTof-MS as described in the section 2.4.1.

I-Cell-PEDOT composite reusability was evaluated immediately after the first photocatalytic cycle treatment of 7 h, by spiking separately aliquots of sulindac, carbamazepine and the mixture of both compounds into the cylindrical Pyrex tubes with the remaining I-Cell-PEDOT dispersions. The same initial concentration for all the compounds and mixture (i.e., 3 $mg.L^{-1}$) was reached preserving the I-Cell-PEDOT particle concentration. Then, an additional 7 h photolytic cycle was completed under UV-A irradiation and pH 7.

2.4.1. Quantification by Time-of-flight mass spectrometry analysis

Irradiated solutions were analyzed using a Xevo G2-XS quadrupole time of flight (QTof-MS) mass spectrometer (Waters Corporation, Wilmslow, UK) with an electrospray ionization source and Software MassLynx™ V4.1, coupled with an Acquity UPLC H-Class. Chromatographic separation was resolved with an Acquity UPLC® BEH C18 column (1.7 µm, 2.1 mm×50 mm) supplied by Waters (Waters Corporation, Wilmslow, UK). Solvents for mobile phase were water (0.05% v.v-1 formic acid) and MeOH (0.05% v.v-1 formic acid). Samples were analyzed under gradient conditions (table S2), 10 µL for injection volume, 40 °C and a flow rate of 0.3 mL.min-1. Mass spectrometry detection was performed under sensitivity-positive ion mode (ESI+) and MSE centroid acquisition method over a mass range of 100 to 1000 Da, with mass resolution >50 000 FWHM. The experimental instrument parameters included 0.25 s scan time, 20 V sampling cone, 2.0 kV capillary, ramp collision energy from 20 to 40 V, 130 °C source temperature, 400 °C desolvation temperature and 800 $L.h^{-1}$ desolvation gas flow.

3. Results and Discussion

3.1. Cellulose template preparation

Diverse methodologies have been reported to treat cellulose and to improve its stability in water (Li et al., 2021; Siró and Plackett, 2010). Aiming for greener strategies, gamma radiation has been selected to functionalize dispersed micro-cellulose (MC) in water, followed by mechanical processes. The gamma irradiation effect on the cellulose (I-Cell) was evaluated measuring particle size, thermal stability and the oxidation degree (see figure 1).

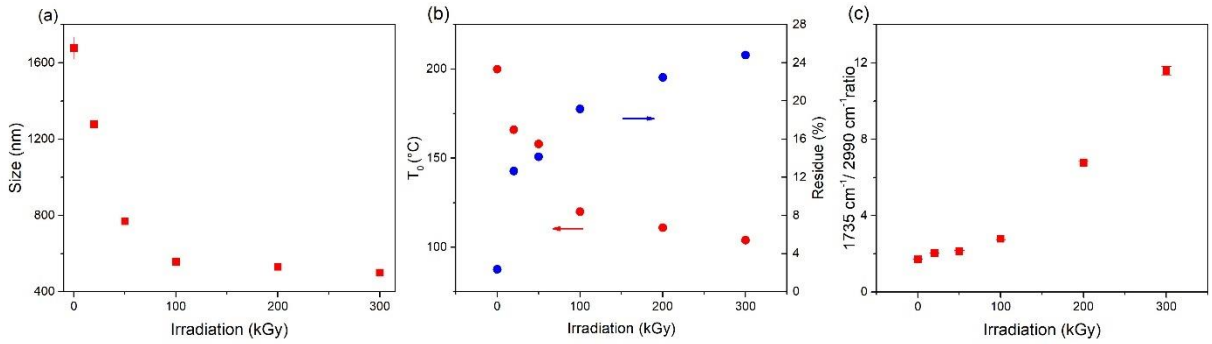

Figure 1. Effect of the gamma radiation on the cellulose irradiated at different dosages: (a) hydrodynamic particle size estimated by DLS, (b) initial degradation temperature (red squares) and residues (blue circles) obtained by TGA and (c) cellulose oxidation rate (1735 cm-1/2990 cm^{-1} ratio) by FTIR.

The observed trend for all properties confirmed that the gamma treatment modified the cellulose, decreasing the particle size (fig 1.a) and the initial degradation temperature (fig 1.b). The oxidation degree was followed by infrared spectroscopy (IR), studying a ratio of the C=O group (1735 cm^{-1}) signal normalized by the C-H stretching band (2990 cm^{-1}) (see fig. 1c and table S3 for more details regarding the cellulose spectra). Specifically, the MC dispersion and the highest (i.e., 300 kGy) irradiated cellulose sample (I-Cell) properties are contrasted in the figure 2.

The predominant reaction of cellulose polymers under gamma irradiation is the breakdown of the main chain due to oxidation process. Ionizing gamma radiation could cause formation of carbonyl groups of cellulose in the presence of oxygen that helps the breakdown of cellulose (Byun et al.,

2008; Choi et al., 2009) leading to the glycoside bond hydrolysis. Cellulose was broken down mainly into large fragments, promoting the loss of bound water from the chain and the alteration of the structure of the irradiated sample (Khan et al., 2006; Li et al., 2011). Then, due to the radiolysis, products that include RCHO, RCOOH, CO_2, CO and others were generated (see fig. 2a and 2d). With the breakdown of hydrogen bonds, free radicals appear and then the number of chains separated from cellulose increases with the irradiation dose, as it has been reported (Takács et al., 1999).

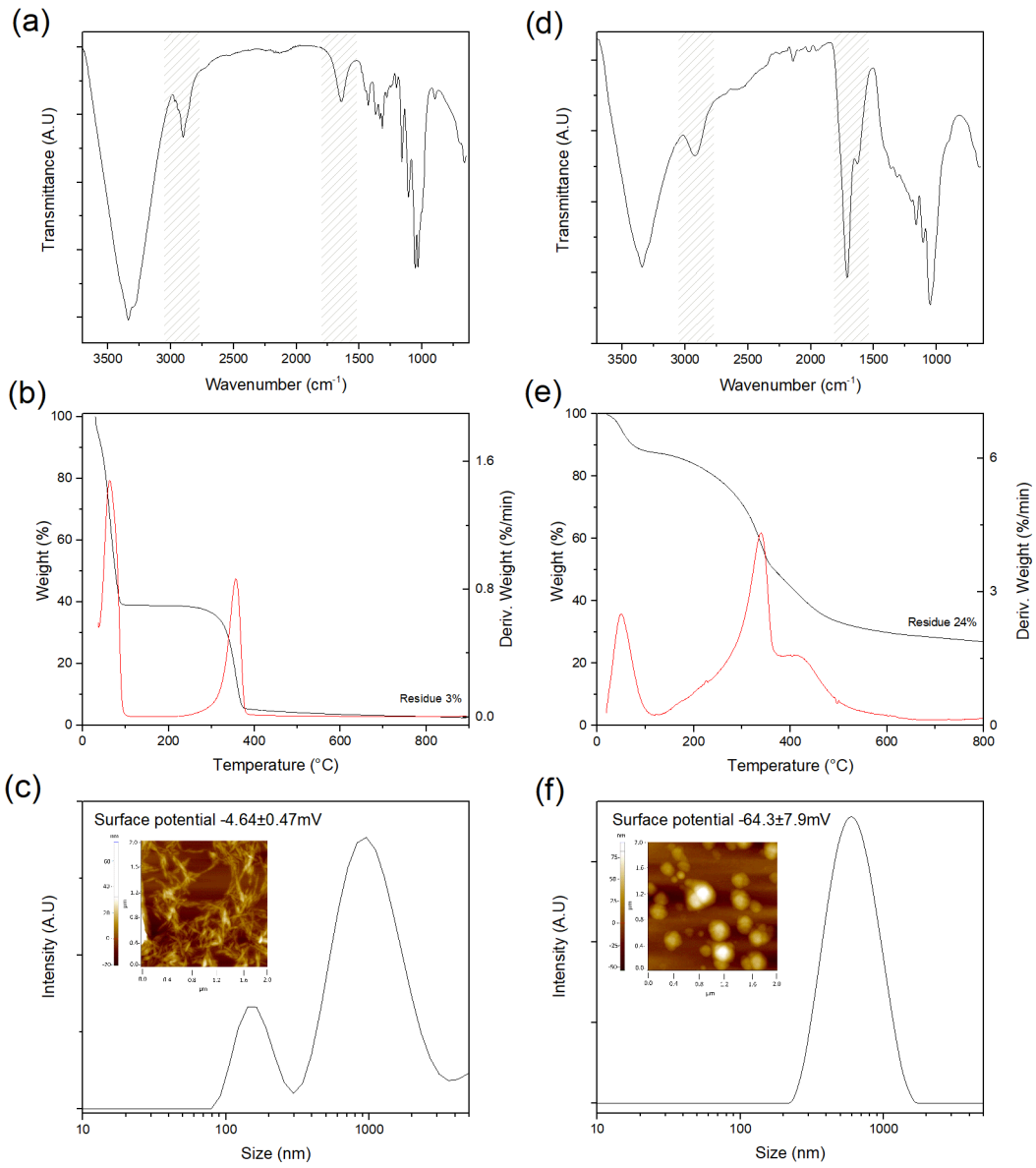

Figure 2. Characterization of the cellulose and irradiated cellulose particles modified to be used as template for the conductive polymer deposition. Characterization of the non-irradiated cellulose: (a) Infrared spectra, (b) Thermogravimetric analysis, (c) Size and ζ-potential in aqueous dispersion (Inset: AFM Topography). Characterization for the 300 kGy irradiated cellulose (I-Cell): (d) Infrared spectra, (e) Thermogravimetric analysis and (f) Size and ζ-potential in aqueous dispersion (Inset: AFM Topography).

Thermogravimetric analysis is a helpful technique to determine the thermal stability of materials as well as their compositional properties. The thermal stability of the non-irradiated and irradiated samples was followed by thermogravimetric analysis (table S4). Regarding the loss of mass, a first step of mass loss below 115 °C (see fig. 2b and 2e) was related to volatile components and physically absorbed water in the samples (W1), since it has been reported that dry biomass is stable up to 140 °C (Zapata et al., 2009). The second decomposition process (W2) around 300 °C was associated with cellulose degradation. In previous studies, the carbon-carbon bond between the structural units of the cellulose depolymerization was reported in the temperature range from 372 to 570 °C (W3) (Severiano et al., 2010). The later interaction takes place when the cellulose structure has absorbed enough energy to activate the division of the glycoside bond to induce the depolymerization (Aguiar et al., 2008). When the irradiation dose was increased, in the range of 100 to 300 kGy, the cellulose tended to show a lower degradation temperature compared to the non-irradiated substrate. The γ-irradiation promoted the rupture of the internal bonds of the cellulose, thus giving thermal degradation at lower temperatures (i.e., 110 °C) and an increase of the carbon residues.

The particle stability was studied by the superficial ζ potential in water. Values of ζ-potential over -30 mV are considered stable assuming that an electrostatic charge is the main stabilization mechanism at sub-micron size range (Hunter, 2013; Kind, 2000). Aqueous dispersion system provides a poor environment to stably disperse cellulose (ζpotential = -4.64 mV) because of the particle size and lack of functional groups. Meanwhile, cellulose functionalization leads to improve the I-Cell particle stability in water (ζpotential = -64.3 mV) (see fig. 2c and 2f). The overall data revealed that the gamma functionalization process tuned the cellulose thermal and physical properties compared to the untreated micro-cellulose (MC). Based on our results, the 300 kGy irradiated sample (I-Cell) was chosen as template for the conductive polymer chemical deposition.

3.2. Conductive polymer chemical polymerization and characterization

The selected I-Cell particles were added to a Fe^{3+} isopropyl alcohol solution (I-Cell-Fe^{3+}) as it has been previously reported (Starbird et al., 2014). An orange solid was obtained, then after the monomer was added, blue color particles confirmed the PEDOT synthesis. The obtained I-Cell-

PEDOT composite was dispersed in a neutral buffered aqueous media. The nominal concentration of PEDOT ($g.mL^{-1}$) is a broad way to evaluated the photocatalytic degradation performance. Therefore, a particle concentration of ca. 1.11×10^{9} $particle.mL^{-1}$ was determinate from a nominal I-Cell-PEDOT composite concentration of 0.5 $g.L^{-1}$. In order to provide more comparable results, the particle concentration was kept constant throughout all the experiments.

Zeta potential value of the precursor and conductive composite depends upon its composition, so, their dispersions stability is governed by their superficial charges. The dispersion stability of the precursor I-Cell-Fe3+ and the obtained I-Cell-PEDOT particles were confirmed using ζ-potential, with values of 40.90 and -32.20 mV, respectively. The positive value in the I-Cell-Fe3+ is due to the iron ions on the surface (Carlson and Kawatra, 2013). These results indicate that the I-Cell-PEDOT-Fe3+ and I-Cell-PEDOT particles are abundant in charged groups, enhancing their stability in neutral aqueous dispersion (Hunter, 2013; Kind, 2000). Additionally, the particle size (determined by DLS) of the I-Cell-PEDOT composite was around 350 nm (see fig. 3a), in the same size range of the template, suggesting that the composite replicates the shape of the template.

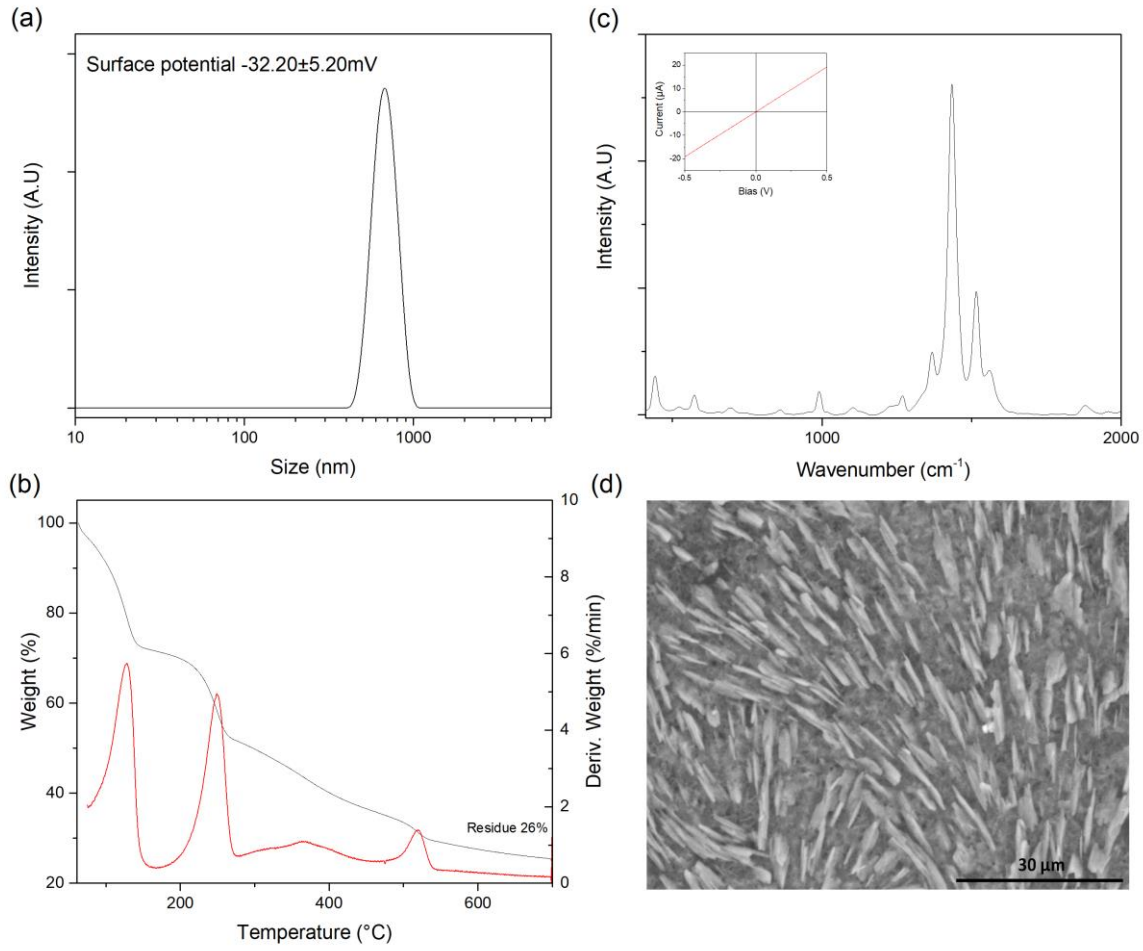

Figure 3. Characterization of the I-Cell-PEDOT composite: (a) Size and ζ-potential in neutral pH aqueous dispersion. (b) Thermogravimetric analysis, (c) Raman spectra (inset: CV curve using a bias voltage of 1 V) and (d) Low-magnification SEM image of the I-Cell-PEDOT particles.

Thermogravimetric analyses were performed to study the interactions among components in the composite (see fig. 3b). The initial decomposition temperature (onset) and ash content are affected by the reagents in the different steps of the synthesis. The I-Cell-PEDOT composite thermogram showed four distinct regions at 128, 249, 360 and 520 °C. The initial weight-loss may be associated to the water content in the material (Stefanidis et al., 2014). The initial degradation stage at 146 °C is related to the PEDOT degradation (Khalil et al., 2016; Starbird et al., 2014; Zamora-Sequeira et al., 2018). A thermal degradation at 360 °C is caused by modification of the

template structure to form products as pyrodextrins, followed by the selective dehydration and the cellulose depolymerization (Severiano et al., 2010; Starbird et al., 2014; Zamora-Sequeira et al., 2018; Zapata et al., 2009). Carbonaceous residues for the composite (ca. 26% w/w), after all the volatile products have been removed, (fig. 3b) showed similar values than the I-Cell template (24% w/w).

The electrochemical nature of the I-Cell-PEDOT composite was studied by Raman spectroscopy and resistance (CV curves) measurements. In table S3 are summarized the Raman signal assignments for the conductive polymer (PEDOT). As seen from figure 3c, the bands at 438, 700, 990 and 1260 cm^{-1} are respectively assigned to the C-O-C deformation, symmetric C-S-C deformation, oxyethylene ring deformation, and Cα-Cα inter-ring stretching (Hernandez-Suarez et al., 2019; Tran-Van et al., 2001). Particularly, the characteristic band at 1435 cm^{-1}, due to symmetric Cα=Cβ stretching is an indicative of a high-level conjugation in the structure of PEDOT (Hernandez-Suarez et al., 2019; Zamora-Sequeira et al., 2018). Hernandez et al. have reported that a characteristic band corresponding to the stretching vibration of Cα=Cβ becomes broad after electrochemical cycling, which could be associated to a change in the resonance structure of the PEDOT chain due to the polymer oxidation (Hernandez-Suarez et al., 2019). In our study, the band at 1425 cm^{-1} was narrowed, implying that PEDOT in cellulose matrix maintained its degree of conjugate groups, even after UV irradiation (see section 3.5). In addition, it has been reported that the PEDOT catalyst properties depend on its conductivity (Ghosh et al., 2015a). Thus, the electrically conductive behavior of the I-Cell-PEDOT composite was confirmed in bulk by the CV curve (fig. 3c inset).

Since the photocatalytic activity has been described to rely on the shape of conjugated polymer particles (Ghosh et al., 2015b; Yuan et al., 2019; Zia and Riaz, 2021), the composite morphology was observed by scanning electronic microscopy (see fig 3d). The composite showed analogous morphological features to the cellulose without gamma treatment. But the composite size distributions revealed remarked similarities with the template (I-Cell), according to the data obtained by DLS experiments. In our approach, the I-Cell-PEDOT composite size and morphology were determinate by the template (i.e., I-Cell), as it has been shown in the previous section 3.1. Thus, it is a viable technique to tune the catalyst size and shape by engineering the cellulose template.

3.3. Photocatalytic effect of the I-Cell-PEDOT composite on the removal of sulindac and carbamazepine from water under experimental conditions.

Photocatalysis activity in water treatment systems is determined by operational conditions such pH, light source, dispersion stability, pressure and temperature (Zia and Riaz, 2021). In our study, ambient conditions of 22 °C, room pressure and environmentally relevant UV-A radiation were selected as a more economical alternative for the removal of the pharmaceutical contaminants (Gogate et al., 2004). Furthermore, experiments were conducted at neutral aqueous media (pH 7), considering the acidity usually found in wastewaters (Luo et al., 2014; Quesada et al., 2019).

Although the dispersion stability of the system during the sunlight or UV light exposition may affect the catalytic properties (Kind, 2000), some studies lack of characterization on the particle stability or particle concentration (Ghosh et al., 2015b; Kumar et al., 2021). In our experiments, no sedimentation was detected even for long UV exposure periods (i.e., 7 h) and no adjustments of pH were necessary through all experiments. The dispersion stability was verified, since the composite particle showed surface potential values of -32.20 mV, that suggested the formation of a stable system (Lowry et al., 2016).

Regarding the I-Cell-PEDOT photocatalytic activity, it has been stated that due to the PEDOT band gap, less energy is required to promote an electron to the conduction band (Ghosh et al., 2015b; Yuan et al., 2019). Then, electronic transitions may occur at less energetic radiation. It is widely accepted that when the photocatalyst is irradiated, the semiconductor absorbs photons, and this phenomenon leads to the generation of charge carriers (Ghosh et al., 2015b, 2015a; Kumar et al., 2021). The photogenerated species may react with water or dissolved oxygen to produce reactive oxidizing species (ROS) to decompose pollutants into small molecules (Xiao et al., 2016). A large number of reactive species including holes and radicals (e.g., HO• and O_2•−) are involved in the photocatalytic oxidation process (Ghosh et al., 2015a; Ohtani, 2013; Zia and Riaz, 2021).

In this work, the photocatalytic activity of the I-Cell-PEDOT composite was evaluated by the degradation of pharmaceuticals sulindac (fig. 4a) and carbamazepine (fig. 4b). Removal efficiencies of the compounds and their mixtures were monitored up to 7 h using high-resolution liquid chromatography. It has been reported the persistence of parent compound and byproducts

of sulindac under UV-A irradiation in neutral waters up to 61 h (Kawabata et al., 2013; Ledezma-Espinoza et al., 2021). Furthermore, the sulindac double bond was proposed as the most reactive site for the parent compound in sulindac (Ledezma-Espinoza et al., 2021), which could be easily attack by the radicals HO• generated under I-Cell-PEDOT particle catalyst to lead a faster degradation. The I-Cell-PEDOT composite under UV-A light and pH 7 demonstrated a significant degradation of sulindac in a reduced time, reaching up 89% in only 420 minutes (fig. 4c), which offers an enhancing to the remediation process and reduces time consumption. To our knowledge, this is the first research that report the photocatalysis of sulindac by I-Cell-PEDOT composite. Slightly similar decomposition rate was observed for sulindac from the mixture with carbamazepine (fig. 4e), reaching 88%. Dark control experiments were performed with I-Cell-PEDOT particles along with the analytes in absence of UV radiation to measure the potential adsorption phenomena during our study. The dark experiments showed no degradation of the drugs. Meanwhile, direct photolysis in samples without I-Cell-PEDOT catalyst (fig. 4c, red squares) exhibited an insignificant removal compared to photocatalysis (fig. 4c, black squares).

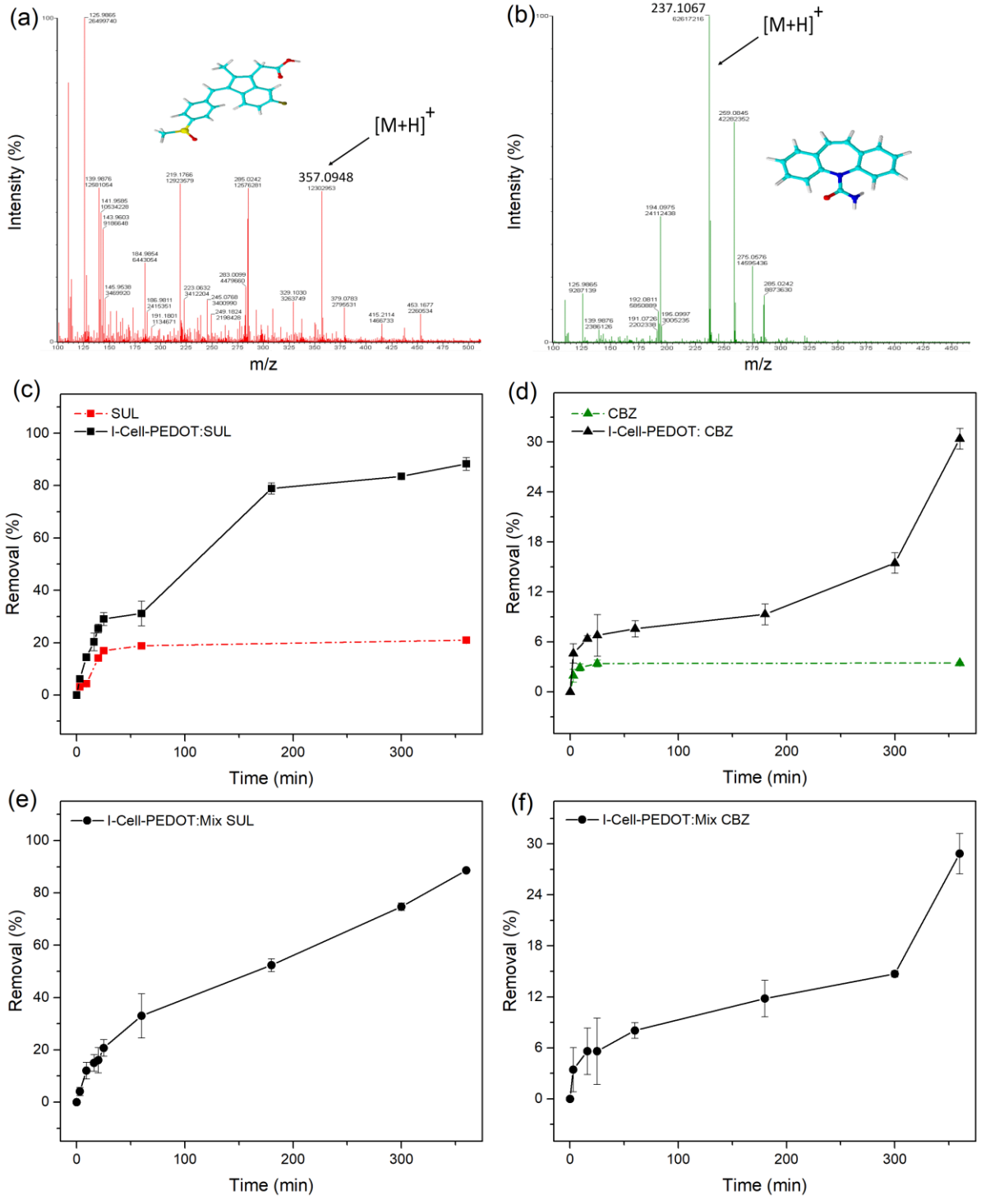
(a)
Intensity (%)
m/z
[M+H]+
357.0948
(b)
Intensity (%)
m/z
237.1067
[M+H]+
(c)
SUL
I-Cell-PEDOT:SUL
Removal (%)
Time (min)
(d)
CBZ
I-Cell-PEDOT: CBZ
Removal (%)
Time (min)
(e)
I-Cell-PEDOT:Mix SUL
Removal (%)
Time (min)
(f)
I-Cell-PEDOT:Mix CBZ
Removal (%)
Time (min)

Figure 4. Photocatalytic effect of I-Cell-PEDOT composite on pharmaceuticals UV-A degradation demonstrated with QTof-MS Full Scan mass spectra (MSE) at 5 h of treatment of (a) sulindac (m/z 357.0948) and (b) carbamazepine (m/z 237.1067), (c) sulindac removal with composite (black squares) compared to the system without composite (red squares), (d) carbamazepine removal with composite (black triangles) compared to the system without composite (green triangles), (e) sulindac removal from mixture with carbamazepine (black circles) and (f) carbamazepine removal from mixture with sulindac (black circles). (Conditions: UV-A radiation, initial concentration [C_0]=3 mg.L^{-1} for each drug, room pressure, pH 7 and 22 °C for all experiments). Degradation was not observed for the non-irradiated dark control samples (data not shown).

Photocatalytic degradation of carbamazepine by I-Cell-PEDOT composite showed lower degradation results than those for sulindac (fig. 4d vs fig. 4c). Degradation of CBZ by using UV-A irradiation without the catalyst resulted only in 3% of removal within 7 hours of treatment (fig. 4d, green triangles). Meanwhile, pouring I-Cell-PEDOT composite into the aqueous matrix increased the efficiency up to 30% (fig. 4d, black triangles). Similar attenuation effect was observed (29%) for carbamazepine from the mixture with sulindac (fig. 4f). Control experiments with I-Cell-PEDOT particles in the dark were also conducted for carbamazepine. The dark samples showed no significant degradation of the compound compared to the irradiated system. The high stability of the carbamazepine and its recalcitrant nature has been stated by some authors (Blum et al., 2017; Li et al., 2019). Previous studies have reported diverging results regarding the carbamazepine degradation under UV light (Ali et al., 2018; Kumar et al., 2021; Li et al., 2019; W. L. Wang et al., 2016), including half-lives of 884 h (37 days) in unfiltered river water (Blum et al., 2017). For all above, the degradation results obtained in our work confirmed the promising catalytic effect of the I-Cell-PEDOT composite. However, further research needs to be addressed to promote the fully degradation of carbamazepine using our I-Cell-PEDOT catalyst.

3.4. Reuse of the I-Cell-PEDOT composite under UV-A radiation

One of the key features of a photocatalyst for industrial applications is the potential reuse of the catalyst after repeating cycles of degradation reactions (Zia and Riaz, 2021). In this study, the I-Cell-PEDOT photocatalyst effect on the samples was confirmed since 98% of the sulindac and

9% of the carbamazepine were degraded after a second UV-degradation cycle (Table S5). In the reused I-Cell-PEDOT dispersion, a particle concentration was measured in the range of 1.34×10^{10} particle.mL^{-1}, a value that is acceptable as constant, considering the limitations of the technique for non-spherical particles (Austin et al., 2020; Caputo et al., 2021).

Furthermore, the dispersion stability and the electrochemical oxidation of the I-Cell-PEDOT composite were followed by ζ-potential and Raman spectroscopy in the reuse experiment, as seem in the figure 5. Raman spectroscopy did not show significant PEDOT polymer oxidation as it has been reported (Hernandez-Suarez et al., 2019; Zamora-Sequeira et al., 2018) (see fig. 5a and 5d) or changes in the particle size (fig. 5b, 5c, 5e and 5f) as result of a second UV-A radiation cycle. Although, the dispersion showed a decrease in the surface potential after of the reuse experiments (i.e., -29.90 and -20.10 mV, respectively), the surface potential provided moderately enough repulsive forces to be partially stable according to literature (Feng et al., 2021; Kind, 2000; Li et al., 2017).

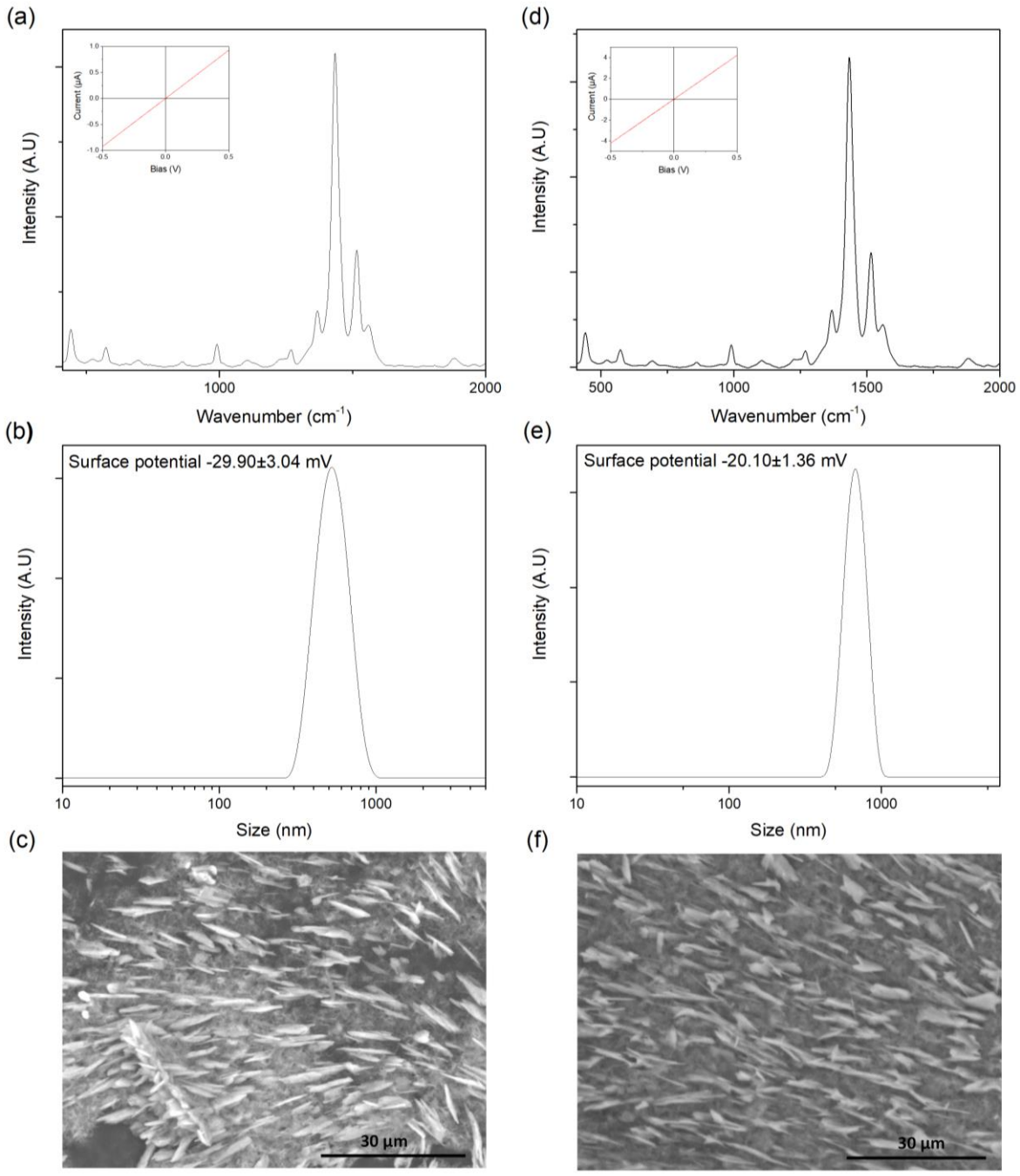

Figure 5. Characterization of the I-Cell-PEDOT composite of reuse experiments for the photocatalytic degradation of sulindac and carbamazepine after the first 7 hours UV-A irradiation

cycle: (a) Raman spectra (inset: CV curve), (b) size and ζ-potential in a neutral pH aqueous dispersion and (c) Low-magnification SEM image of the I-Cell-PEDOT particles; and after the second 7 hours UV-A irradiation cycle: (d) Raman spectra (inset: CV curve), (e) size and ζ-potential in a neutral pH aqueous dispersion and (f) Low-magnification SEM image of the I-Cell-PEDOT particles.

Our results revealed I-Cell-PEDOT photocatalyst as an innovative composite for practical applications in the treatment of impacted waters with pharmaceuticals pollutants at lower cost and energy consumption.

4. Conclusions

An irradiated cellulose PEDOT composite was successfully prepared applying green methodologies to be used as photocatalyst for the treatment of the emerging contaminants sulindac and carbamazepine under ambient conditions. The functionalization of the cellulose template was achieved using γ-irradiation, allowing a further chemical deposition of the conductive polymer (PEDOT). The surface ζ-potential of the obtained composite particles in water confirmed the dispersion stability during the treatment with a practically constant concentration. Our findings proved that I-Cell-PEDOT composite enhanced photodegradation of sulindac and carbamazepine from neutral aqueous system under UV-A radiation. Photocatalytic removals of 89% for sulindac and 30% for carbamazepine were reached within 7 hours of treatment. Similar degradation results were observed in mixtures of both compounds. The reuse of the composite as catalyst was confirmed with similar degradation efficiencies for each pharmaceutical component. Our work states the potential application of the I-Cell-PEDOT composites as a photocatalyst technology for the removal of pharmaceuticals from aquatic media and opens the possibility for further formulations in environmentally-friendly applications.

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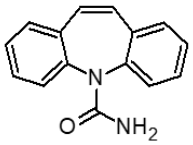
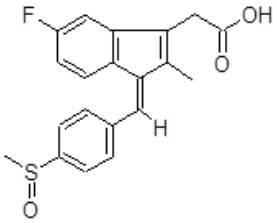
7. Supplementary information for Chapter 6.

Modified cellulose/poly(3.4-ethylenedioxythiophene) composite as photocatalyst for the removal of sulindac and carbamazepine from water

Chemical information on the targeted pharmaceuticals in the research.

Table S1. Chemical characteristics for sulindac and carbamazepine.

Name	Chemical formula	Chemical structure	Molecular weight ($g.mol^{-1}$)	Water solubility ($mg.L^{-1}$)	pK_a	Reference
Carbamazepine CAS 298-46-4	$C_{15}H_{12}N_2O$		236.27	18	13.9	(Puckowski et al., 2016)
Sulindac CAS 38194-50-2	$C_{20}H_{17}FO_3S$		356.41	3000	4.5	(Guerra et al.. 2016)

Composite electrochemical measurement set-up.

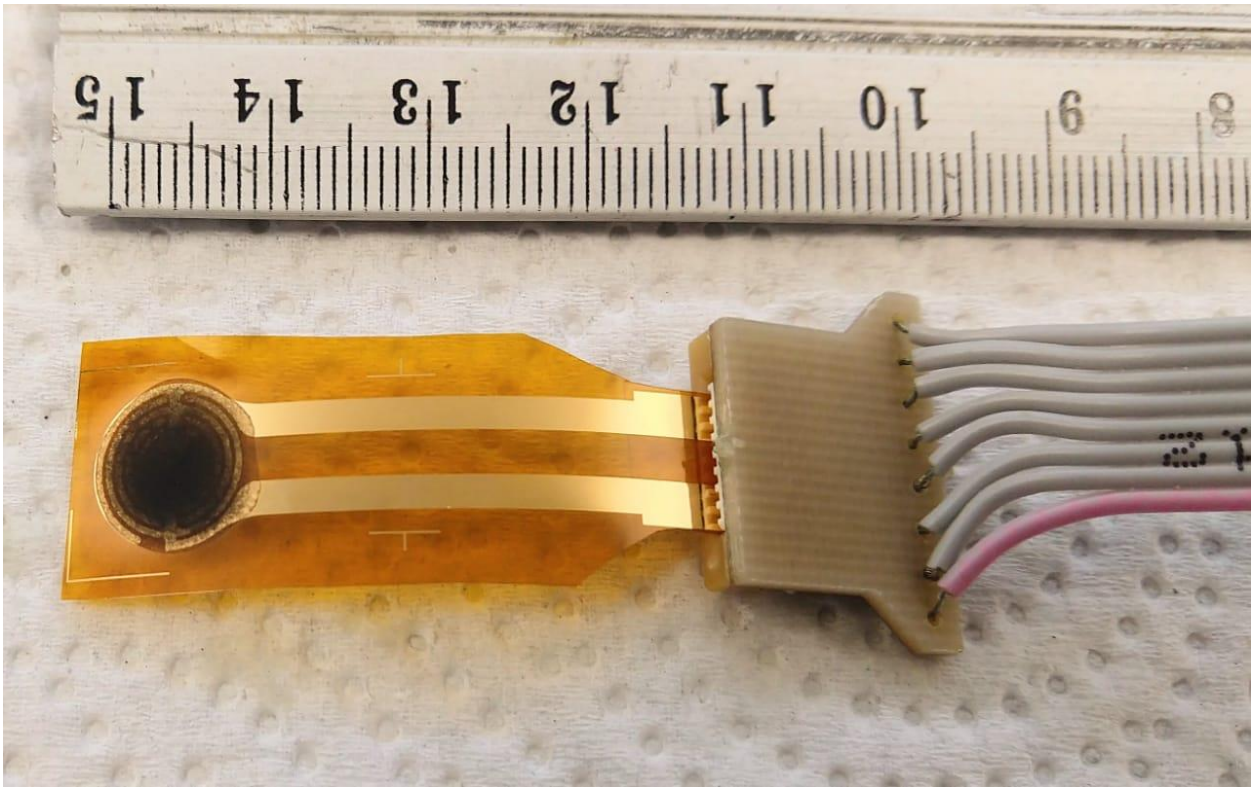


Figure S1: Self-made gold electrode used to obtain the resistance of the I-Cell-PEDOT particles. The sample was poured on the electrode and dry in a vacuum oven before testing.

Conditions for the analysis of sulindac and carbamazepine by time-of-flight mass spectrometry.

Concentration in each sample was calculated using the Software MassLynx™ (V4.1. Waters Corporation. Wilmslow. UK). Analyses of samples sets were conducted by running external calibration curves with 5 calibration standards for each compound ranging of 0.250 –3.0 mg/L along with the samples. Linearity (r2) for calibration curves was ≥0.99 over all analyses and both analytes.

Table S2: Gradient elution method for QTof-MS Liquid Chromatography in sulindac and carbamazepine analysis. Solvents were H_2O:0.05 % formic acid (A) and Methanol: 0.05 % formic acid (B).

Time (min)	Flow (mL min^{-1})	% A	% B
0	0.3	95	5
1	0.3	95	5
2.5	0.3	50	50
4.0	0.3	50	50
6.5	0.3	5	95
7.5	0.3	5	95
7.6	0.3	95	5
11.5	0.3	95	5

Effect of the gamma radiation doses on the cellulose particles.

The FTIR data showed absorption bands at 3330 and 2895 cm^{-1}. related to the hydroxyl (OH) and aliphatic (C-H) stretches. respectively. In addition. the peaks at 1645 cm^{-1} were assigned to stretch carbonyl group (C=O). according to previous reports (Takács et al.. 1999). The absorption signals around 1452 and 1320 cm^{-1} were assigned to the C-H flexion and the C-C stretch. The absorbance at 1740 cm^{-1} (stretching vibration C=O). formed by the oxidation of the polymer backbone (Takács et al.. 1999). normalized using the C-H band at 2924 cm^{-1}. In the irradiated samples. there is an increase in the carboxyl/aliphatic ratio as result of cellulose degradation (Takács et al.. 1999). The trend confirms oxidation of the cellulose due to the gamma radiation dose.

Table S3. IR Frequency bands assignments for cellulose structures and Raman signals for the PEDOT material (w: weak. m: medium and s: strong).

	Wavenumber (cm^{-1})		Activity	Approximate description of transitions	Reference
	Literature	Experimental	IR		
Cellulose	3400	3330	S	Hydrogen bond OH group	(Paşcalau et al.. 2012; Prasad et al.. 2006; Şen & Erboz. 2010; Takács et al.. 1999)
	2928	2924	W	CH stretching	(Paşcalau et al.. 2012; Prasad et al.. 2006; Şen & Erboz. 2010)
	1750	1740	M	C=O group	(Prasad et al.. 2006; Takács et al.. 1999)
	1646	1645	M	Polymer bound water	(Prasad et al.. 2006; Şen & Erboz. 2010)
	1432	1452		CH asymmetric deformation	
	1370	1320	W	C-C stretch	(Prasad et al.. 2006)
	1235	1227	S	C-C-O stretch	(Paşcalau et al.. 2012; Şen & Erboz. 2010)
	1160	1160	W	C-O-C (asymmetric stretching)	(Cirillo et al.. 2014; Prasad et al.. 2006) (Paşcalau et al.. 2012; Prasad et al.. 2006; Şen & Erboz. 2010)

	1150	-	-	C-O-C (asymmetric stretching)	(Matsuhiro & Rivas. 1993)
	1070	1060	S	Glycosidic linkage	(Matsuhiro & Rivas. 1993; Prasad et al.. 2006; Şen & Erboz. 2010)
	1040	1049	M	C-OH Bending vibration	(Matsuhiro & Rivas. 1993; Şen & Erboz. 2010)
	1034	-	M	C-O-C (cyclic ether) stretching vibration	(Paşcalau et al.. 2012; Prasad et al.. 2006; Takács et al.. 1999)
	Literature	**Experimental**	**Raman**		
PEDOT	2850	2851	-	Oxyethylene CH_2 symmetric stretching	(Tran-Van et al.. 2001)
	1565	1560	W	CH_2 bending	(Tran-Van et al.. 2001)
	1500	1500	W	Thiophene asymmetric $C_\alpha=C_\beta$ stretching	(Tran-Van et al.. 2001)
	1421	1442	S	Thiophene symmetric	(Hernandez-Suarez et al.. 2019; Tran-Van et al.. 2001)

				$C_\alpha=C_\beta$ stretching C-C stretching (symmetric) Benzenoid structure	
	1364	1377	M	Thiophene C-C stretching $C_\beta=C_\beta$ stretching	(Tran-Van et al.. 2001)
	1262	1270	W	Thiophene C–C inter-ring stretching	(Tran-Van et al.. 2001)
	1090	1025	-	Oxyethylene cycle deformation $C_\alpha=C_\alpha$ inter-ring deformation	(Tran-Van et al.. 2001)
	987	994	M	Oxyethylene ring deformation	(Hernandez-Suarez et al.. 2019; Tran-Van et al.. 2001)

	Wavenumber (cm^{-1})		**Activity**	**Approximate description of transitions**	**Reference**
	Literature	**Experimental**	**IR**		
	3400	3330	S	Hydrogen bond OH group	(Paşcalau et al.. 2012; Prasad et al.. 2006; Şen & Erboz. 2010; Takács et al.. 1999)

	2928	2924	W	CH stretching	(Paşcalau et al.. 2012; Prasad et al.. 2006; Şen & Erboz. 2010)
	1750	1740	M	C=O group	(Prasad et al.. 2006; Takács et al.. 1999)
	1646	1645	M	Polymer bound water	(Prasad et al.. 2006; Şen & Erboz. 2010)
	1432	1452		CH asymmetric deformation	
	1370	1320	W	C-C stretch	(Prasad et al., 2006)
	1235	1227	S	C-C-O stretch	(Paşcalau et al., 2012; Şen & Erboz, 2010)
Cellulose	1160	1160	W	C-O-C (asymmetric stretching)	(Cirillo et al., 2014; Prasad et al., 2006) (Paşcalau et al.. 2012; Prasad et al.. 2006; Şen & Erboz. 2010)
	1150	-	-	C-O-C (asymmetric stretching)	(Matsuhiro & Rivas. 1993)
	1070	1060	S	Glycosidic linkage	(Matsuhiro & Rivas. 1993; Prasad et al.. 2006; Şen & Erboz. 2010)
	1040	1049	M	C-OH Bending vibration	(Matsuhiro & Rivas. 1993; Şen & Erboz. 2010)

	1034	-	M	C-O-C (cyclic ether) stretching vibration	(Paşcalau et al.. 2012; Prasad et al.. 2006; Takács et al.. 1999)

	Literature	Experimental	Raman		
PEDOT	2850	2851	-	Oxyethylene CH_2 symmetric stretching	(Tran-Van et al.. 2001)
	1565	1560	W	CH_2 bending	(Tran-Van et al.. 2001)
	1500	1500	W	Thiophene asymmetric $C_\alpha=C_\beta$ stretching	(Tran-Van et al.. 2001)
	1421	1442	S	Thiophene symmetric $C_\alpha=C_\beta$ stretching C-C stretching (symmetric) Benzenoid structure	(Hernandez-Suarez et al.. 2019; Tran-Van et al.. 2001)
	1364	1377	M	Thiophene C-C stretching $C_\beta=C_\beta$ stretching	(Tran-Van et al.. 2001)

	1262	1270	W	Thiophene C–C inter-ring stretching	(Tran-Van et al.. 2001)
	1090	1025	-	Oxyethylene cycle deformation $C_{\alpha}=C_{\alpha}$ inter-ring deformation	(Tran-Van et al.. 2001)
	987	994	M	Oxyethylene ring deformation	(Hernandez-Suarez et al.. 2019; Tran-Van et al.. 2001)

In order to confirm the cellulose degradation. thermogravimetric analysis (TGA) were performed. The results of the non-irradiated and irradiated sample are shown in Table S3. Regarding the loss of mass in the TGA curves. the first step of mass loss below 115 °C is related to volatile components and physically adsorbed water molecules in the samples (W1). since it has been reported that dry biomass is stable up to 140 °C (Zapata et al.. 2009). The second decomposition process (W2). between 150 and 350 °C was associated with cellulose degradation. Up to 300 °C. the alkyl ether bonds are broken. Finally. the carbon-carbon bond between the structural units of the cellulose was split in the temperature range of 372 to 570 °C (W3). since the degradation of the cellulose is completed at around 360 °C. beginning with its depolymerization (Severiano et al.. 2010). This takes place when the cellulose structure has absorbed enough energy to activate the division of the glycosidic bond to induce the depolymerization (Aguiar et al.. 2008).

When the irradiation dose increases. between 100 and 300 kGy. the cellulose tends to show a lower degradation temperature compared to the non-irradiated substrate. The components of the cellulose sample gradually suffer chain breakage when the absorbed radiation dose reaches 100 kGy or higher. Similar effect was described regarding the relative degree of crystallinity (Henryk et al.. 2004) at that gamma dosage. The radiation promotes the rupture of the internal bonds of the cellulose. thus giving thermal degradation at earlier temperatures. Thus. it is assumed that the lower temperature range is due to the cleavage of a chemical bond such as glycosidic bonds. It is

observed that an increase in carbon residues for the samples is largely related to the decrease in hydrogen bonds and therefore to the dehydration generated in the material.

Table S4. Thermal behavior of cellulose exposed to different gamma radiation doses in water.

Gamma Radiation doses	Onset $_1$ (°C)	Δ W_1 (%)	Onset $_2$ (°C)	Δ W_2 (%)	Onset $_3$ (°C)	Δ W_3 (%)	Residue (%)
0	71.8	61.13	331.0	34.03	0	0	2.363
20	70.0	6.17	320.2	73.04	0	0	12.66
50	73.6	8.44	308.6	67.68	0	0	14.15
100	70.4	8.30	297.7	48.42	420.7	15.39	19.16
200	71.1	10.28	295.2	37.50	414.9	15.59	22.47
300	70.0	11.66	290.6	33.81	397.3	15.61	24.81

Analysis of sulindac and carbamazepine by time-of-flight mass spectrometry in the reuse test.

Table S5: Degradation of sulindac and carbamazepine analysis reusing I-Cell-PEDOT particles in dispersion. determinate by QTof-MS Liquid Chromatography.

Sulindac		**Carbamazepine**	
Time (min)	Removal (%)	Time (min)	Removal (%)
0	0± 0	0	0 ± 0
25	36.97 ± 3.09	60	2.93 ± 1.05
60	32.72 ± 4.84	420	9.44 ± 1.26
420	98.69 ± 1.26		

Reference for Chapter 6

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7. GENERAL CONCLUSIONS

7.1. This research aimed to enhance knowledge about pharmaceutical pollution in aquatic systems. By applying advanced methodologies which are recognized within the scientific community, the study developed comprehensive information about chemical characterization of target pharmaceuticals, behaviour, occurrence and potential risks in tropical waters, and offered solutions for remediation. Furthermore, this dissertation provided an insight of how other factors beyond environmental conditions such as available sanitation strategies and consumption patterns can lead to differences in the environmental occurrence of pharmaceuticals in urban waters of a developing country.

7.2. This study contributed to show the application of the o-DGT devices as sufficiently sensitive polar passive samplers for the environmental monitoring of pharmaceuticals in the urban superficial and wastewaters studied in our work. These devices are an alternative to traditional POCIS or Chemcatcher, with the advantages of reducing dependence on field conditions and lab or in situ calibration, as well as the ability to determine TWA concentrations based on the molecular structure of the target compounds. These features may help to promote monitoring research where funding is limited, especially for developing countries.

7.3. The occurrence of pharmaceutical contaminants of various therapeutic classes such as antibiotics, antiepileptics, nonsteroidal anti-inflammatory drugs, and β-blockers, was evidenced at all sampling sites during the extent of the monitoring study, demonstrating the contribution of anthropogenic sources to the pollution of urban waters in the GAM. Uncertainties associated with modeling water concentrations were reasonable within the large variation of concentrations for pharmaceuticals in the environment, based on the data set of this study. Results denoted representative information of the contamination based on occurrence, chemical transformation, sources of pollution, and seasonal variation of all these factors.

7.4. Risk assessment was done of target pharmaceuticals for single parent compounds and mixtures in aquatic media along with their detection by passive sampling. The results suggested that at concentration levels and exposure times analyzed in this study, sulfamethoxazole, levofloxacin and sulindac posed a potential risk to the aquatic organisms, thus, additional monitoring studies should be performed to well-assess the actual effects of these compounds and to support actions on prevention and remediation levels.

7.5. This work contributes to the scientific community with a significant knowledge about photochemical characterization of pharmaceuticals in water systems, by using tools to overcome kinetics determinations involving multiple challenges such as consecutive reactions, photoinduced products, time-dependent concentrations, and lack of spectral information of the generated intermediates. These applied strategies can also contribute to reduce limitations in laboratory experiments and to provide accurate and comparable data to other scientific studies.

7.6. The kinetic model and novel degradation byproducts, identified in the direct photolysis of sulindac, improved the understanding of its photochemical fate in aquatic systems. Thus, it can serve to develop prevention and treatment strategies to reduce its impact in water sources, and even more, to extend the experience and application to pharmaceuticals with similar degradation patterns.

7.7. These findings evidenced that is necessary to apply advanced technologies to remove emerging contaminants at trace levels from surface waters and wastewaters. Following this goal, the irradiated cellulose PEDOT composite developed in this research showed to be a promising photocatalytic system for the removal of pharmaceuticals from water, and an important contribution to the growing hybrid approach implemented in advanced process for treating emerging contaminants.

7.8. The results of this dissertation contribute to the call for actions of the Sustainable Development Goals, specifically to the goals of Good Health and Well-being (Goal 3) and

Clean Water and Sanitation (Goal 6) and draw attention to the challenges and holistic approach associated with the study and management of pharmaceutical contamination in water resources. It exposed the need for actions in terms of population awareness, monitoring, investment in efficient advanced treatments, and the urgency to promote collaborative work between stakeholders, scientists, community, and regulatory authorities, to define sustainable preventive and mitigation strategies that protect the environment and public health.

8. RECOMENDATIONS AND FUTURE WORK

The following are the recommendations identified from the lessons learned:

8.1. To improve spatial and temporal resolution, identify sources of pharmaceutical pollution, and prioritize pharmaceuticals of concern in natural waters, it is recommended to extend research on environmental monitoring to major strategic rivers, focusing on the river basin approach that combine passive sampling for water column and sampling of sediment and biota. A limitation of the present study was to have only one sampling site in the Virilla River, and in the upstream and downstream of the Torres River. Furthermore in the Torres, due to access conditions, only one sampling campaign was conducted for each climate season. Thus, it is necessary to increase in a strategic way, the sites and campaigns to obtain a more realistic scenario of the occurrence patterns, specific and diffusive sources of pharmaceutical contamination, and natural attenuation, among others. Moreover it is important to extend the research in the major WWTP of the GAM, including sites at different stages of treatment. At least, one study should be conducted in the country under this more comprehensive way. Some the conditions and potential sites for this study are suggested: a) Sites: Virilla River is the recommendation to be examined as a superficial water body, since the river´s upstream is used as a drinking water supply in the GAM, the downstream is influenced by the urban activity and it merges with the Torres River to drain into the Pacific Ocean. Definitely a sampling spot is needed upstream the landfill in the Virilla River. On the other hand, the major WWTP of the GAM investigated in this research

should be examined more extensively as the wastewater source, including additional sites for each treatment process. b) Monitoring: it can be done for two years at each climate season (dry and rain), using passive sampling with 2 weeks of deployment time and grab sampling to compare the water concentration results for the superficial and wastewaters samples. c) Prioritization of pharmaceuticals to study: it should be coordinated between different stakeholders including the academy, national entities for sanitation and public health such as Acueductos y Alcantarillados (AyA) and Caja de Seguro Social (CCSS). This strategy can help to get a better understanding of the stage of contamination, corresponding risks, potential accumulation in the aquatic food chain, among others, and facilitate the exploration of proper mitigation strategies.

8.2. To define the set of pharmaceuticals to study, it is suggested to consider national consumption, previous detection studies, those drugs that have been identified as priority compounds by international guidelines (e.g., Watch and CCL lists), and include recognized marker compounds of anthropogenic contamination, such as carbamazepine and caffeine, in addition, based on the current research, it is suggested to include atenolol and sulfamethoxazole. This prioritization may be considered in the update that is currently being addressed for the regulation of quality and reuse of wastewaters in Costa Rica, pointing those pharmaceuticals as *compounds under study*, which may promote national awareness.

8.3. Suspect and non-targeted screening could be applied to explore the occurrence of pharmaceuticals in different water sources. This approach could be especially useful to develop more efficient strategies for monitoring and remediation. Particularly this tool can contribute to further investigations of ARGs, by identifying in advance, those pharmaceutical contaminants that should be tested in the aquatic media and their connection with the resistance of the organisms.

8.4. Novel configurations of o-DGT samplers could be tested to improve sensitivity, such those that include a greater exposure area. Moreover, to prevent the degradation of agarose gels by organisms during the sampling period, polyacrylamide diffusive gels can be used as

recommended by (Stroski et al., 2018), additionally, a steel mesh could be placed covering the entire cage, which can serve as an effective physical protection against organisms and sediment particles, as recommended by Brazilian experiences (Federal University of Sao Paulo).

8.5. With regards to future laboratory work for those compounds that have not been calibrated (*i.e*., sulindac and levofloxacin), it is suggested according to the available budget, to carry out calibrations that consider the pH and temperature on the uptake of o-DGTs, for evaluating the influence of speciation on sorption considering the binding efficiency between protonated/deprotonated species and sorbent and the effects of high temperatures under tropical conditions.

8.6. This dissertation advances available data on fate and behaviour of sulindac in water systems, but such research is at an early stage. Investigation of photochemical transformation of the drug under field conditions should be addressed including direct and indirect photolysis experiments. As well, risk assessment should also be conducted on these photoproducts in aquatic environments.

8.7. The I-Cell-PEDOT photocatalytic system, developed in this research proved to be effective using gamma irradiated cellulose as a template and by applying the photocatalyst in dispersion form. Thus, for future investigations, the system can be tested under additional conditions such as: lower gamma doses, other mixtures of pharmaceuticals, and further formulations that include additional natural substrates. Furthermore, in the experimental design, the effect of parameters such as NOM and a real wastewater matrix should be considered to evaluate the performance of the photocatalyst under more realistic scenarios.

8.8. Further than the monitoring and prioritization recommendations discussed above, the experience of this research allows us to suggest some additional measures to improve the management of the pharmaceutical contamination in the country, such as:

a. It is recommended to establish a permanent network with members of the academy and health and sanitation authorities such as AyA, Ministerio de Salud, CCSS, SENASA

and MINAE. Thus, the network could promote initiatives on determining operational and logistic needs to achieve sustainable and relevant decreases on the occurrence of pharmaceuticals in the environment, highlight educational programs, funding strategies, preventive actions, and implement treatment technologies and scientific knowledge to support decisions. The collaboration between universities can help to reduce costs in acquisition of instruments and standards, increase the expertise in sophisticated methodologies for monitoring, quantification, and toxicity analysis, and contextualize the issue to the region of interest. Local collaborations with private stakeholders such as manufactures, and sanitation companies could improve the impact of the actions.

b. It is necessary to prioritize public awareness and preventive actions, thus a simple and familiar approach to do so could be the creation of a new category of Bandera Azul or include parameters in the program related to the responsible management of pharmaceutical residues. This could be implemented for instance in homes, schools, universities, hospitals, veterinary facilities, farms and pharmaceutical manufactures.

c. To promote the permanent funding for campaigns of disposal and treatment of pharmaceutical residues in national institutions that use/receive these compounds such as the CCSS and Ministerio de Seguridad Pública.

d. To implement at least a new full-scale or pilot project of advanced removal processes in municipal WWTPs that serve main cities in the country or in national hospitals, using the experience of the previous projects and with the collaboration of the academy to evaluate the performance and economic viability of the treatments.

e. A national authority related to public and environmental health could lead a proposal to review the actual status of the pharmaceutical pollution in the country, which also includes a list with minimum technical standards for sanitation including removal treatments that could be implemented and regulatory goals that can be achieved in a proper time.

8.9. This research meets the opportunity to be used as a reference for decision makers in the country to develop a comprehensive legislative process involving the public, stakeholders and decision makers. Nevertheless, It is important to acknowledged that the efficient management and any potential legislation on contamination with pharmaceuticals must

result from an iterative process based on realistic and sustainable informational, economic and legal instruments, which may promote a higher level of protection for aquatic environments and public health in the country.

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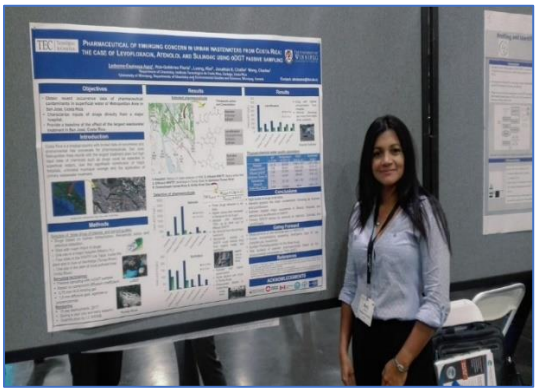
10.APPENDICES

10.1. APPENDIX A: ADDITIONAL SCIENTIFIC CONTRIBUTIONS.

10.1.1. Rodríguez-Quesada. L.. Ledezma-Espinoza. A.. Avendaño-Soto. E. D.. & Starbird-Perez. R. (2022). Characterization data of cellulose modified by gamma irradiation to be used as template in the synthesis of a photoactive composite for environmental applications. Data in Brief. 42. https://doi.org/10.1016/j.dib.2022.108277

10.1.2. Quesada-Rodríguez. J.. Ledezma-Espinoza. A.. Roa-Gutiérrez. F.. Romero-Esquivel. L.G.. 2021. Evaluation of pumice stone as an alternative low-cost adsorbent for atenolol removal. an emerging contaminant. Int. J. Environ. Sci. Technol. https://doi.org/10.1007/s13762-021-03391-2

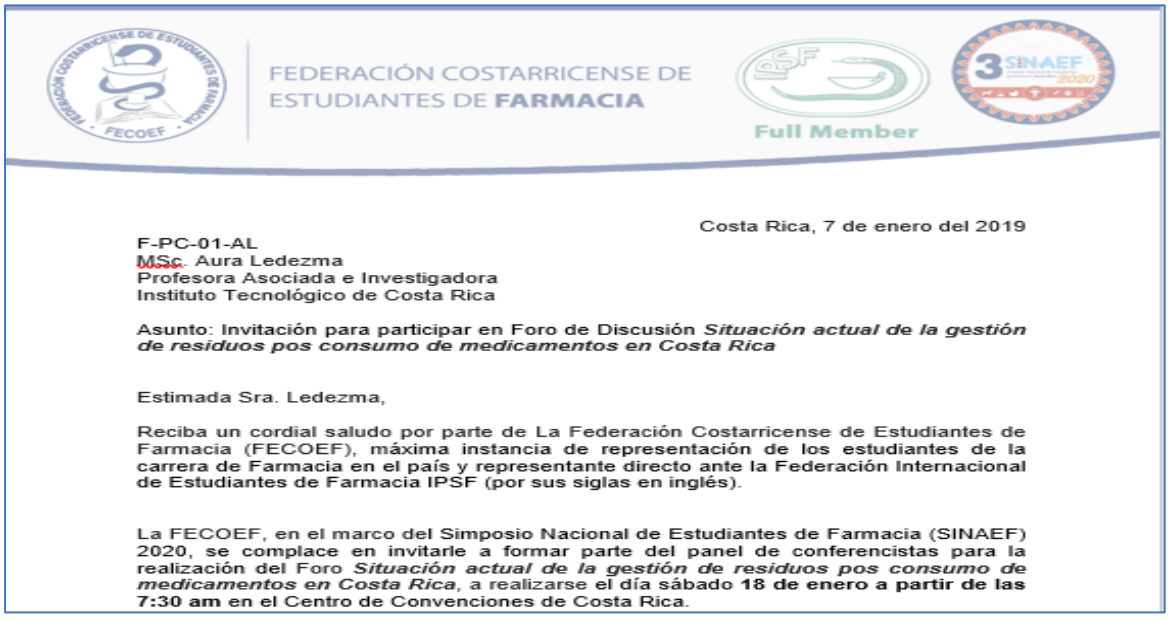
10.1.3. Attendance to SETAC Congress. November 2018. Sacramento. CA. USA.



Attendees: Charles Wong research group.

10.2. APPENDIX B: COLABORATIONS WITH STAKEHOLDERS AND PUBLIC.

10.2.1. Foro de Discusión: **Situación actual de la gestión de residuos posconsumo de medicamentos en Costa Rica**. La Federación Costarricense de Estudiantes de Farmacia (FECOEF). 18 enero 2019. Centro de Convenciones de Costa Rica.



FEDERACIÓN COSTARRICENSE DE ESTUDIANTES DE **FARMACIA**

Full Member

Costa Rica, 7 de enero del 2019

F-PC-01-AL
MSc. Aura Ledezma
Profesora Asociada e Investigadora
Instituto Tecnológico de Costa Rica

Asunto: Invitación para participar en Foro de Discusión ***Situación actual de la gestión de residuos pos consumo de medicamentos en Costa Rica***

Estimada Sra. Ledezma,

Reciba un cordial saludo por parte de La Federación Costarricense de Estudiantes de Farmacia (FECOEF), máxima instancia de representación de los estudiantes de la carrera de Farmacia en el país y representante directo ante la Federación Internacional de Estudiantes de Farmacia IPSF (por sus siglas en inglés).

La FECOEF, en el marco del Simposio Nacional de Estudiantes de Farmacia (SINAEF) 2020, se complace en invitarle a formar parte del panel de conferencistas para la realización del Foro ***Situación actual de la gestión de residuos pos consumo de medicamentos en Costa Rica***, a realizarse el día sábado **18 de enero a partir de las 7:30 am** en el Centro de Convenciones de Costa Rica.

10.2.2. Feria del Ambiente del Hospital México. Stand y exposición a la comunidad. 5 Junio 2019. San José. CR.

10.2.3. AyA: **Taller de Casos Especiales**: Contaminantes Emergentes. Plantel del AyA. Tres Ríos. Cartago CR. 10 julio 2019.

10.2.4. Conferencia Avance Nacional en Estudio de Contaminantes Emergentes. Secretaría Técnica de Coordinación para la Gestión de Sustancias Químicas. DIGECA-MINAE. 20 agosto 2019. San José. CR.

10.2.5. Conferencia Nacional para Comisiones Ambientales de la Caja Costarricense de Seguro Social (CCSS). Escuela de Química. 17 octubre 2019. Cartago. CR. Virtual y presencial.

Se contó con colaboración en la organización y realización de contactos del Profesor Carlos Calleja de la Escuela de Química. así como la asistencia especial de los estudiantes del Curso de Química Analítica para Ingeniería Ambiental.

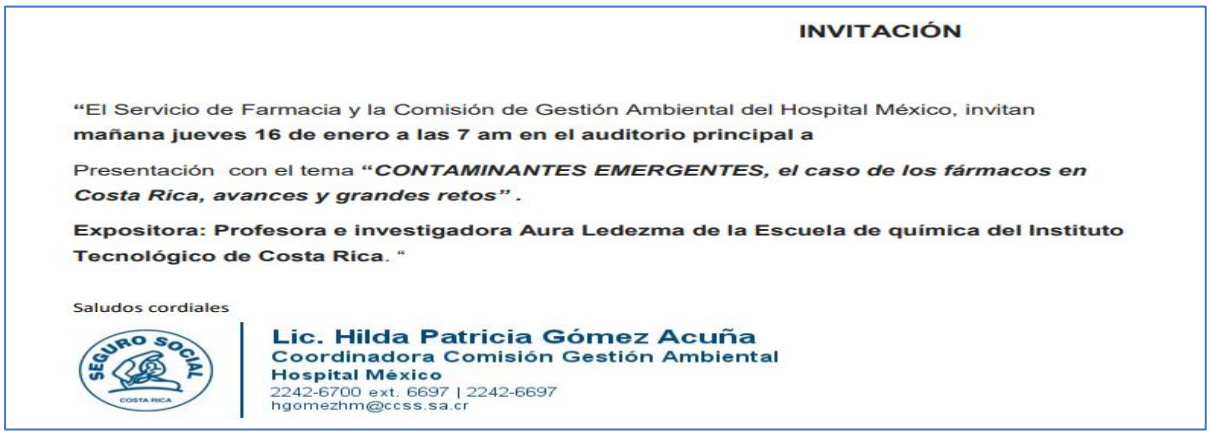
10.2.6. Conferencia de Concientización para Coordinadores de Comisiones Ambientales CCSS. 01 noviembre 2019. Centro Guillermo Padilla Castro.

Este grupo representa a los coordinadores que trabajan bajo la supervisión de la subárea de gestión ambiental de la CCSS. y se encargan de supervisar las ejecuciones de actividades ambientales como presentación de PGAI para Hospitales. Clínicas y áreas de salud. incluyendo los EBAIS.

10.2.7. Conferencia de concientización para Directores de Áreas Rectoras de Salud Central Sur del Ministerio de Salud. 15 de noviembre 2019. **Colegio de Médicos**. San José. C.R.

Se expuso los resultados de la investigación en el "Consejo de Gestión Local". una reunión que se realiza de manera mensual con los directores de las Áreas Rectoras de Salud; en este caso los directores de la Región Central Sur del Ministerio de Salud. (San José). Los directores tienen poder de decisión y seguimiento sobre actividades como la revisión y cumplimiento de normativas sobre la gestión adecuada de aguas residuales.

10.2.8. Exposición para **Programa de Educación Continua** del Personal de Servicio de Farmacia y Enfermería en cooperación con Comisión de Gestión Ambiental. **Hospital México**. 16 enero 2020. San José. CR.



INVITACIÓN

"El Servicio de Farmacia y la Comisión de Gestión Ambiental del Hospital México, invitan **mañana jueves 16 de enero a las 7 am en el auditorio principal a**

Presentación con el tema ***"CONTAMINANTES EMERGENTES, el caso de los fármacos en Costa Rica, avances y grandes retos"*** .

Expositora: Profesora e investigadora Aura Ledezma de la Escuela de química del Instituto Tecnológico de Costa Rica. "

Saludos cordiales

Lic. Hilda Patricia Gómez Acuña
Coordinadora Comisión Gestión Ambiental
Hospital México
2242-6700 ext. 6697 | 2242-6697
hgomezhm@ccss.sa.cr

10.2.9. Exposición de resultados y concientización en actividad declarada de interés institucional por la CCSS y UCR: **V Conferencia Hacia una agenda de servicios de salud verdes y sostenibles en Costa Rica.** 6 noviembre 2020. Virtual. Participación según memorando CGA-198-2020.

V Conferencia
Hacia Una Agenda de Servicios de Salud Verdes y Saludables en Costa Rica
Contaminantes emergentes y su impacto en la salud pública en el contexto del COVID-19

Organizado por la Facultad de Medicina de la Universidad de Costa Rica y el Comité de Gestión Ambiental del Hospital Nacional de Niños.

Declarada de Interés Institucional en la UCR según oficio R-156-2020
Declarada de Interés Institucional en la CCSS según oficio GM-DDSS-1582-2020

AGENDA

- Fecha: 06 de noviembre 2020
- Horario: 8:00 a.m. a 1:45 p.m.
- Modalidad virtual

HORARIO	ACTIVIDAD
8:00 a.m.	Acto inaugural y saludo de las instancias de la Universidad de Costa Rica y la Caja Costarricense de seguro Social
8:15 a.m.	Tema: Generalidades del COVID-19, experiencia sector salud Expositora: Dra. Olga Arguedas Arguedas, Directora General Hospital Nacional Niños
9:15 a.m.	Tema: Formulación anticuerpos equinos contra el SARS-CoV-2 Expositor: Dr. Alberto Alape Girón, Instituto Clodomiro Picado
10:15 a.m.	Receso
10:30 a.m.	Tema: Contaminantes emergentes experiencia en Costa Rica Expositora: Dra. Aura Ledezma Espinoza, Instituto Tecnológico de Costa Rica
11:30 a.m.	Tema: Gestión de Residuos durante la pandemia Expositora: Licda. Alejandra Fernández Sánchez, Soluciones Químicas Integrales S.A.
12:30 p.m.	Tema: Guía para la gestión de compras sostenibles en salud Expositora: Marcela Medina Galaz
1:30 p.m.	Despedida- cierre

*Cada expositor dispondrá 50 minutos para exponer y 10 minutos de preguntas.

10.2.10.Semana Mundial De Concientización Sobre El Uso De Los Antimicrobianos. Organizador SENASA. Conferencia el 19 noviembre 2020. Virtual.

Agenda de la Semana Mundial de concientización sobre uso de los Antimicrobianos 2020

Servicio Nacional de Salud Animal MAG · COSTA RICA

Miércoles: 18 Noviembre	Charlas	Expositores
9:00 a 9:30 am	Palabras de apertura y bienvenida	SENASA, FAO y OIE
9:30 am a 11:00 am	Plan Nacional de Lucha contra la RAM	Dra. Marlen Arce, Ministerio de Salud
1:30 pm a 3:00 pm	Plan Pecuario Estratégico y Operativo de Lucha contra la RAM	Dra. Hellyn Fernández, SENASA
Jueves: 19 Noviembre	**Charlas**	**Expositores**
8:30 am a 10:00 am	Apoyando a los países en la lucha multisectorial contra la Resistencia a los Antimicrobianos. (Preguntas y Respuestas)	Dr. Alejandro Dorado y Dr. Armando Hoet, FAO Internacional Dr. Aitziber Echeverría, PNUMA Internacional
1:00 pm a 2:30 pm	Fármacos como contaminantes emergentes en el ambiente.	Dra. Aura Ledezma, Instituto Tecnológico de Costa Rica (TEC)
3:00 pm a 4:30 pm	Conceptos básicos de las medidas de bioseguridad	Dr. Arturo Méndez, Cámara Nacional de Avicultores de CR
Viernes: 20 Noviembre	**Charlas**	**Expositores**
8:30 am a 10:30 am	Estrategia Integral del Buen Uso de Antimicrobianos en Finca/Granja desde un enfoque Salud de Hato.	Dr. Danilo Montero, Instituto Nacional de Aprendizaje (INA)
1:30 pm a 3:30 pm	Fundamentos de la Vigilancia Basada en riesgo	Dr. Fernando Sampedro, Consultor experto FSP EEUU
5:00 pm a 6:00 pm	Uso racional de Antimicrobianos en Ganado Bovino Lechero.	Dr. Gonzalo Carmona, Universidad Técnica Nacional
Lunes: 23 Noviembre	**Charlas**	**Expositor**
9:00 am a 9:45 am	Rol de los organismos internacionales impulsando la Vigilancia de la RAM en los sistemas agropecuarios para evitar un impacto negativo en el comercio	Dra. Ericka Calderón, IICA
10 am a 10:45 am	Problemas Asociados a la Resistencia Antimicrobiana y su Relación con la Agricultura y la Cadena Agroalimentaria	Dr. Armando Hoet, Profesor/ Universidad del Estado de Ohio
1:30 pm a 3:00 pm	Análisis de Riesgos de la Resistencia a los Antimicrobianos en el uso de antimicrobianos utilizados en animales de producción.	Dr. José Luis Rojas, Investigaciones Fármaco-veterinarias S.A.
3:30 pm a 5:00 pm	Buenas Prácticas en el uso de medicamentos en producción porcina.	Dr. Alberto Armocida, VETANCO-Argentina
Martes: 24 Noviembre	**Charlas**	**Expositores**
8:30 am a 10:30 am	Alternativas de gestión de los desechos de antimicrobianos en sector pecuario.	Dr. Gustavo Sáenz, Punto Seguro
1:30 am a 3:00 pm	Actualización de Normativa del uso de antimicrobianos Contexto Regional e Internacional.	Dr. Federico Luna, SENASA-Argentina
3:00 pm a 3:30 pm	Cierre del evento	SENASA

"Maneja con cuidado los antimicrobianos"

Enlace único para la Sala Teams:

Unirse a reunión de Microsoft Teams

Más información sobre Teams | Opciones de reunión

Unirse con un dispositivo de videoconferencia

142800591@t.plcm.vc Id. de conferencia VTC: 1186842936

Con la colaboración de:

Organización de las Naciones Unidas para la Alimentación y la Agricultura · OIE Organización Mundial de Sanidad Animal · ONU programa para el medio ambiente · Ministerio de Salud · The Ohio State University College of Veterinary Medicine · Cámara Nacional de Productores de Leche · IICA · Punto Seguro · Vetanco · ina Instituto Nacional de Aprendizaje · FSP · TEC Tecnológico de Costa Rica · Investigaciones Fármaco veterinarias S.A. · senasa

10.2.11.Conferencia Para Semana De La Resistencia De Los Antibióticos. 22 noviembre 2019. **Hospital de Niños**. San José. CR.

CONFERENCIA:

CONTAMINANTES EMERGENTES

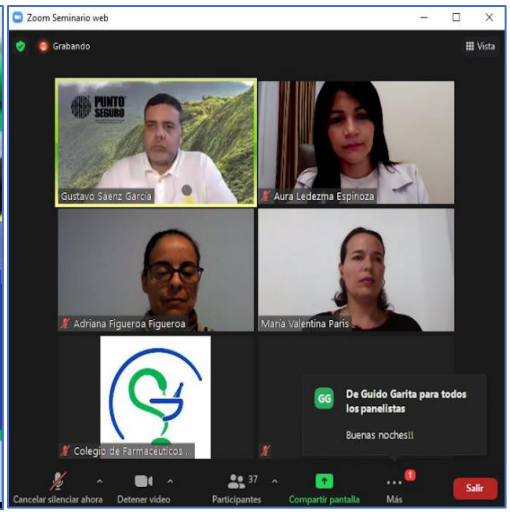
"El caso de los fármacos en Costa Rica: avances y grandes retos"

- Expone: MLGA. Aura Ledezma Espinoza, Instituto Tecnológico de Costa Rica
- Fecha: Viernes 22 de noviembre
- Hora: 7:00 a.m.
- Lugar: Auditorio Dr. Roberto Ortiz Brenes

HOSPITAL NACIONAL DE NIÑOS "Dr. Carlos Sáenz Herrera" Centro de Ciencias Médicas de la CCSS

comité gestión ambiental HOSPITAL NACIONAL DE NIÑOS

10.2.12. Seminario web Zoom: **Impacto Ambiental del Desecho Inadecuado de Medicamentos. Colegio de Farmacéuticos**. 24 marzo 2021. Costa Rica.



10.2.13. Presentación en Sesión de **Comité de Vertido de Aguas Residuales para actualización de Reglamento de Aguas Residuales.** con potencial inclusión de contaminantes emergentes.

10.2.14. Cooperación con entidades de saneamiento y salud para el desarrollo de proyectos sobre contaminantes emergentes.

Los conocimientos adquiridos en esta investigación doctoral han permitido la colaboración con entes tomadores de decisión sobre la temática de los contaminantes emergentes. a raíz de la necesidad nacional de establecer líneas de monitoreo ambiental y planes de remediación a un futuro con inversión de recursos para tecnologías avanzadas de tratamiento. Las actividades se realizaron dentro del quehacer del Centro de Investigación CEQIATEC de la Escuela de Química del TEC. con la cooperación de los Profesores PhD. Nancy Ariza y PhD. Andrés Sánchez. A continuación. se muestran los proyectos asociados:

i. Proyecto AyA 2020-2021: Monitoreo de contaminantes emergentes por método de muestreo pasivo en un sistema de tratamiento de agua potable del Instituto Costarricense de Acueductos y Alcantarillados (AyA)"
ii. Proyecto CCSS 2022: Monitoreo de Parámetros Fisicoquímicos. Microbiológicos y Micro Contaminantes en el Sistema de Tratamiento de Aguas Residuales de Hospital San Vicente de Paul.
iii. Proyecto CCSS 2022-2023: Monitoreo de Parámetros Fisicoquímicos. Microbiológicos y Micro Contaminantes en el Sistema de Tratamiento de Aguas Residuales del Hospital San Rafael de Alajuela".