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Anti-inflammatory drugs analysis in a wastewater sewage treatment plant and surface water in semiarid climate

Análise de anti-inflamatórios em uma estação de tratamento de esgoto e água superficial em clima semiárido

Renatha Michelly Sabino dos Santos[1], Raquel Ferreira do Nascimento[2], Elizabeth Amaral Pastich Gonçalves[1], José Adson Andrade de Carvalho Filho[2], Guillaume Francis Bertrand[3,4], Daniella Carla Napoleão[2], Jaime Joaquim da Silva Pereira Cabral[5], Anderson Luiz Ribeiro de Paiva[2]

ABSTRACT

This work aimed to analyze the presence of four common molecules (diclofenac, dipyrone, ibuprofen, and paracetamol) in the Ipojuca River, in the stretch of Caruaru municipality (Brazil), and in a wastewater treatment plant that discharges treated water to the river. Collections were conducted for three months at each point during April, May, and June. The samples were collected in three repetitions (sample, replica, and triplicate). Through Pearson's correlation, the correlation between ibuprofen and diclofenac concentration and rainfall in the region was also verified. These drugs were detected in 100% of the samples, with concentrations between 7.4–548.2 and 81.8–231.8 $\mu g.L^{-1}$, respectively. Paracetamol and dipyrone were not detected. The observed high concentrations are due to the high consumption of drugs and the low rate of sewage collection in the municipality. Both analyzed drugs — ibuprofen and diclofenac — had insignificant correlation results with rainfall (-0.022 and -0.071, respectively). Regarding the drugs in the WWTP, the treatment consisting of anaerobic followed by aerated lagoons showed efficiency ranging from 35.9 to 93.6% in the removal of diclofenac. The removal of ibuprofen was higher in April (86.6%), but in the other two months, it did not prove to be efficient, evidencing the need to implement more adapted technologies in the removal of drugs combined with the network expansion for sewage collection in the region. A study with longer time monitoring is needed to understand the rainfall effect on drug concentration in the river.

Keywords: domestic effluents; drugs; effluent treatment; water quality; urban rivers; emerging contaminants.

RESUMO

Este trabalho teve como objetivo analisar a presença de quatro moléculas comuns (diclofenaco — DC, dipirona — DP, ibuprofeno — IBU e paracetamol — PAR) no rio Ipojuca, no trecho do município de Caruaru (Brasil), e em uma estação de tratamento de esgoto (ETE) que despeja água tratada no rio. Foram realizadas coletas mensais, por três meses, para cada ponto durante os meses de abril, maio e junho. As amostras foram coletadas em três repetições (amostra, réplica e triplicata). Por meio da correlação de Pearson, verificou-se também a correlação entre a concentração dos fármacos e a pluviometria da região. DC e IBU foram detectados em 100% das amostras, com concentrações de 7,4–548,2 e 81,8–231,8 $\mu g.L^{-1}$, respectivamente. PAR e DP não foram detectados. As altas concentrações observadas devem-se ao alto consumo de fármacos e ao baixo índice de coleta de esgoto no município. Ambos os medicamentos analisados (IBU e DC) tiveram resultados de correlação insignificantes com a precipitação (-0,022 e -0,071, respectivamente). Com relação aos medicamentos na ETE, o tratamento em questão, constituído por lagoas anaeróbicas seguidas de aeradas, apresentou eficiência variando de 35,9 a 93,6% na remoção de DC. A remoção do IBU foi alta no mês de abril (86,6%), mas nos outros dois meses não se mostrou eficiente, demonstrando a necessidade de implantação de tecnologias mais adaptadas na retirada de drogas, aliada à ampliação da rede de coleta de esgoto na região. Um estudo com maior tempo de monitoramento é recomendado para compreender o efeito das chuvas na concentração dos fármacos no rio.

Palavras-chave: efluentes domésticos, medicamentos, tratamento de efluentes, qualidade de água, rios urbanos, contaminantes emergentes.

[1]Universidade Federal de Pernambuco – Caruaru (PE), Brazil.
[2]Universidade Federal de Pernambuco – Recife (PE), Brazil.
[3]Université de Franche-Comté – Montbéliard, France.
[4]Universidade Federal da Paraíba – João Pessoa (PB), Brazil.
[5]Universidade de Pernambuco – Recife (PE), Brazil.

Correspondence address: Anderson Luiz Ribeiro de Paiva – Avenida da Arquitetura, s/n – Cidade Universitária – CEP: 50740-550 – Recife (PE), Brazil. E-mail: anderson.paiva@ufpe.br

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Introduction

Emerging contaminants (ECs) are a relevant category of pollutants present in wastewater that need appropriate treatment and degradation (Nagarajan et al., 2023). For pollutants in which new sources of contamination are discovered, new paths for the contaminants, new methods of detection, and treatment development are considered emerging (El-Kalliny et al., 2023).

With recent advances in techniques and analytical instruments, it has been possible to detect levels and traces of various ECs in the environment, including surface water, groundwater, wastewater, drinking water, sediments, soil, and even in some organisms (Wang et al., 2017). The presence of these compounds in aquatic matrices is a serious threat to the environment and humans (Shanmuganathan et al., 2023).

Several substances are classified as ECs, such as pharmaceuticals, personal care products, hormones, illicit drugs, nanomaterials, sucralose and surface sweeteners, pesticides, brominated flame retardants, siloxanes, dioxins, by-products from water disinfection processes, microplastics, and algal toxins, among others (Richardson and Kimura, 2017). Among ECs, the pharmaceutical market deserves to be highlighted, as it has expanded worldwide in recent decades, both in quantity and variety of new active molecules (Montagner et al., 2017), whose impact and influence on the ecosystem and public health are not well understood and defined.

Pharmaceuticals include all drugs for human and veterinary use consumed with or without medical prescription. Among the most sold are analgesics and antipyretics and those for continuous use such as lipid regulators, contraceptives and antidepressants. Among pharmaceuticals, nonsteroidal anti-inflammatory drugs (NSAIDs) belong to a category of analgesic medication that reduces pain, fever, and inflammation. Its three main therapeutic actions can be described as anti-inflammatory, analgesic, or antipyretic (Koumaki et al., 2017; Mlunguza et al., 2019). Self-medication combined with the ease purchasing of pharmaceutical products can result in an increase in the concentration of these substances in the environment. The main entry routes for pharmaceutical compounds into the ecosystem are effluents and discharges resulting from WWTP, as a significant proportion are not metabolized in the human body and end up present in excreta (Kumar et al., 2023).

As an example, the anti-inflammatory diclofenac has been found in surface waters in South Africa at 1.1–1.2 $\mu g.L^{-1}$ (Sibeko et al., 2019), in Germany at 1.9–2.1 $\mu g.L^{-1}$ (Schmidt et al., 2018), in Pakistan at 5.0–116.0 $\mu g.L^{-1}$ (Hanif et al., 2020) and in Brazil at 19.0–193.0 $\mu g.L^{-1}$ (Veras et al., 2019). As for paracetamol, in Midwest Brazil, Américo et al. (2012) detected a concentration of 130–1,877 $\mu g.L^{-1}$.

In some specific places, even higher concentrations are found in domestic effluents, as can be seen in the work by Palli et al. (2019), who detected a concentration of 1,038–3,429 $\mu g.L^{-1}$ of diclofenac in effluents from Italy. Ibuprofen concentrations of 233–236 $\mu g.L^{-1}$ were detected in Brazil (Floripes et al., 2018), 34–168 $\mu g.L^{-1}$ in Spain (Gómez et al., 2007), and 2.8–25.4 $\mu g.L^{-1}$ in Greece (Kosma et al., 2010).

In this context, pharmaceuticals have been the subject of studies in the environmental sciences since chronic exposure, indirectly through water consumption from certain contaminated sources can lead to serious health problems even in low concentrations. The pharmaceutical groups — antineoplastics, hormones, antidepressants, antibiotics, analgesics, anti-inflammatories, antipyretics, and lipid regulators — present in the water, can lead to adverse effects on human health, such as cell damage, endocrine disruption, infertility, behavioral changes, antibiotic resistance, and changes in blood pressure, among others (Batt et al., 2017; Montagner et al., 2017). In addition, chemical substances present in medicines can be transformed into other potentially more toxic substances (Pinto et al., 2014).

Given this background, the objective of this work was to evaluate the presence of four NSAIDs — diclofenac (DC), dipyrone (DP), ibuprofen (IBU), and paracetamol (PAR) — in the surface waters of the Ipojuca River and in a WWTP in the city of Caruaru, whose receiving body is the mentioned river, both located in a semiarid region in the state of Pernambuco (PE), Brazil. In addition, we aimed to verify through Pearson's correlation, the correlation between pharmaceuticals concentration and rainfall in the region. The results found herein can be used to support public decision-making in the management of water resources, public awareness campaigns, and investments in sewage treatment technologies capable of removing these pollutants.

Methodology

Study area

The Ipojuca River has an extension of about 320 km, with its sources in the Serra do Pau D'arco, municipality of Arcoverde (PE). The river basin is located between the parallels 8º09'50" and 8º40'20" south latitude, and the meridians 34º57'52" and 37º02'48" west longitude of Greenwich (CONDEPE-FIDEM, 2005). It is predominantly oriented in a West-East direction, with its fluvial regime being intermittent, becoming perennial from its mid-course, near the city of Caruaru (SRHE, 2010; APAC, 2020).

The municipality of Caruaru, capital of the central Agreste, concentrates 41% of the population of the 12 municipalities with headquarters in the Ipojuca River basin. The Agreste region, where 70% of the basin is located, has a rainy period from February to July, with maximum rainfall during April and May (SRHE, 2010; COMPESA, 2016). Figure 1 shows the map of land use and occupation of the Ipojuca River basin, highlighting the municipality of Caruaru, the studied stretch.

The main potential sources of pollution in the Ipojuca River basin are industrial effluents, untreated domestic sewage, and solid waste released into the open, in addition to the indiscriminate use of pesticides (SRHE, 2010). The section of the Ipojuca River studied herein crosses the city of Caruaru, where approximately 57% of the population is not served by a sewage collection network (SNIS, 2021).

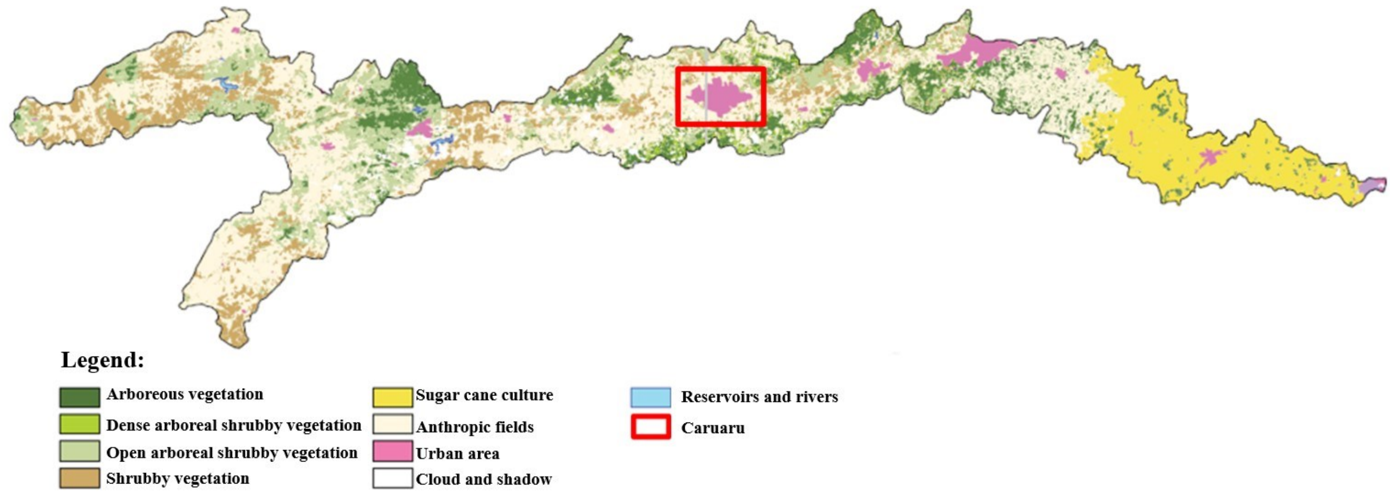

Figure 1 –Land use and occupation in the Ipojuca River basin, highlighting Caruaru, in Pernambuco.

In December 2019, the Ipojuca River Basin Committee (COBH-Ipojuca), through Resolution No. 01/2019, based on CONAMA Resolution 357/2005 (Brasil, 2005), approved the classification of water bodies of that basin, leaving the stretch of the Ipojuca River analyzed in this work classified as class 3. Fresh water classified in this category can be used for supplying human consumption, after conventional or advanced treatment; irrigation of tree, cereal, and forage crops; amateur fishing; secondary contact recreation; and watering of animals.

The wastewater treatment plant under study is the Rendeiras WWTP located in Caruaru (Figure 2), responsible for treating 40% of the city's sewage and rejecting the treated effluent in the Ipojuca River (SNIRH, 2019). Planned to serve a population of 148,000 inhabitants, this plant was designed to operate with an average sewage flow of 253 $L.s^{-1}$ and a maximum flow of 450 $L.s^{-1}$ (ANA, 2017). During this work (April to June 2019), the Rendeiras WWTP was operating between 45 and 60% of its capacity. The raw effluent arrives at the station through pumping, being submitted to an initial grating for the separation of coarse material, and operating with the following treatment lines: rectangular channel type desanders; anaerobic treatment through upflow anaerobic sludge blanket (UASB) reactors; aerobic treatment through an aerated lagoon with membrane diffusers; sedimentation pond; and final polishing pond (ANA, 2017). Table 1 shows the hydraulic detention time (HDT) of each treatment step performed in the WWTP.

The nominal design flow of the WWTP is 250 Ls^{-1} and the total HDT is approximately 6.58 days (COMPESA, 2019). During the study, as the WWTP operated at approximately 50% of its capacity, the estimated flow was 125 $L.s^{-1}$.

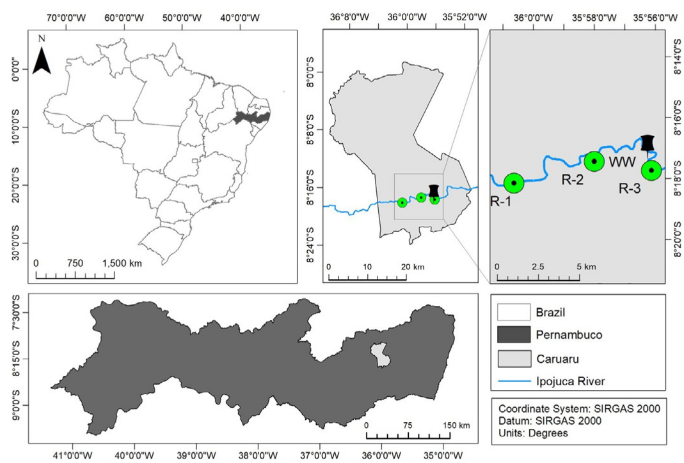

Figure 2 – Location of collection points.

Table 1 – Hydraulic detention time for the treatment steps of the wastewater treatment plant.

Treatment step	HDT (h)
UASBs	8
Aeration tank	6
Facultative lagoon	48
Polishing pond	96

Source: COMPESA (2019).
HDT: hydraulic detention time; UASB: upflow anaerobic sludge blanket reactor.

Characterization of the rainfall regime and assessment of the basin concentration

The study of the pluviometric regime was carried out based on the historical series of rainfall station 211, located in Caruaru and monitored by APAC, the Pernambuco Water and Climate Agency, with the objective of characterizing the pluviometric regime of that municipality. The period of analysis was 20 years, from 2000 to 2019. These data were used to calculate the basin time of concentration.

Sample collection and drug analysis

In order to understand which are the hydrological and environmental factors constraining the pharmaceuticals distribution along with the effluent collection-treatment-restitution continuum, the choice of monitoring points (Figure 2) followed a range of conditions: 1) points upstream and downstream of the city, aiming to assess the impact of the urban perimeter on the concentration of drugs in the river (R-1 and R-3); 2) points upstream and downstream of the city's WWTP outfall (R-2 and R-3), aiming to assess the impact of WWTP on the anti-inflammatory drugs concentration in the river; and 3) affluent and WWTP effluent points (WW-1 and WW-2), aiming to evaluate the drug removal efficiency in the station. A summary of the conditions is found in Table 2.

To evaluate the concentration of NSAIDs in the domestic effluent as well as the potential for removal of these contaminants by the WWTP, samples from the WWTP's affluents and effluents were collected. The collections were conducted at each point during the months of April, May, and June, on a monthly basis, in three repetitions (sample, replica, and triplicate). Samples were collected and stored in previously cleaned amber flasks, and transported in a thermal box containing ice, and then stored at 7°C in the laboratory.

In the laboratory, the compounds were extracted using solid phase extraction (SPE). The methodology for extracting and concentrating the analytes under analysis in this work followed the validation by Napoleão et al. (2018) for the drugs DC, DP, and PAR. For IBU, the analysis followed the methodology by Monteiro et al. (2018).

The quantification and identification of the drugs were carried out using high-efficiency liquid chromatography equipment coupled to ultraviolet spectrometry (HPLC/UV) by Shimadzu, equipped with an ULTRA C18 column operating in reversed-phase (5 µm; 4.6 × 250 mm) and UV-visible detection (SPD-20A) for wavelengths equal to 285 nm. The mobile phase used was composed of a solution of water acidified with 10% acetic acid and acetonitrile in a volumetric ratio of 65:35. The oven temperature of the equipment was maintained at 40±1°C with a flow rate of 0.700 $mL.min^{-1}$ and a pressure of 53 $kgf{\cdot}cm^{-2}$.

The wavelength used for the detection of chromatographic peaks was 254 nm and the detection of each drug was based on their respective retention times, being 6.5 minutes for DC and 4.2 minutes for PAR and DP (Veras et al., 2019). The wavelength used for the IBU was 223 nm, with a retention time of 5.8 minutes (Monteiro et al., 2018). For the validation of the chromatographic method under study, the limit of detection, limit of quantification, and precision were analyzed and determined. Precision analysis was performed based on the coefficient of variance (Table 3).

The efficiency of DC, DP, PAR, and IBU removal (E) by WWTP was based on the average values of drug concentrations found in the raw effluent and in the treated effluent and calculated from Equation 1.

$$E = \frac{(C_o - C_f)}{C_o} \quad (1)$$

In which,
C_o: initial concentration
C_f : final concentration

Statistical treatment — Pearson's correlation

In order to evaluate the trends, variability, and relationship between rainfall and the concentration of drugs in the water, Pearson's correlation was used (with statistically significant variation $p<0.05$). The coefficient (r) varies between -1 and +1, with the signs indicating the direction of the correlation (positive or negative), and the value suggesting the strength of the relationship between the variables.

Table 3 – Limit of detection, limit of quantification, and coefficient of variance used in the detection method of pharmaceutical compounds.

Drug	LD ($mg.L^{-1}$)	LQ ($mg.L^{-1}$)	CV (%)
DC	0.19	0.74	2.89
DP	0.24	0.72	2.19
PAR	0.36	1.12	4.08
IBU	5.33	16.15	1.56

LD: limit of detection; LQ: limit of quantification; CV coefficient of variance; DC: diclofenac; DP: dipyrone; PAR: paracetamol; IBU: ibuprofen.

Table 2 – Characteristics of the sampling points on the Ipojuca River and the wastewater treatment plant.

Sampling points	Description	Geographic coordinates	
		Latitude	Longitude
R-1	Upstream of urban area of Caruaru	8°18'9.68" S	36°00'37.73" W
R-2	Inserted in the urban area of Caruaru and upstream from Rendeiras Wastewater Treatment Plant	8°17'26.85" S	35°57'59.64" O
WW-1 and WW-2	Sewage treatment station	8°16'59.16" S	35°56'14.87" O
R-3	Downstream of the urban area of Caruaru from the wastewater treatment plant	8°17'49.40" S	35°56'11.67" W

Regarding the magnitude of the correlation coefficient, values up to 0.3 were considered weak; between 0.4 and 0.6, moderate; and above 0.7, strong (Paranhos et al., 2014).

All the statistical treatments of the Person's correlation, including the previous treatment of standardization and scaling, were performed in the R software. Even with a small number of data, it is proposed to apply the correlation as an indicator to be evaluated.

Results

Characterization of the rainfall regime

Based on the accumulated monthly rainfall values from the Caruaru's pluviometric station, in the period between 2000 and 2019, the average reference value was calculated at 47 nm. This value was then considered the limit for classifying the months as dry or rainy. Figure 3 shows the monthly average precipitation, the annual average of the historical series from the analyzed station, and the variation in precipitation relative to the reference average of 47 mm, calculated for the rainfall station 211.

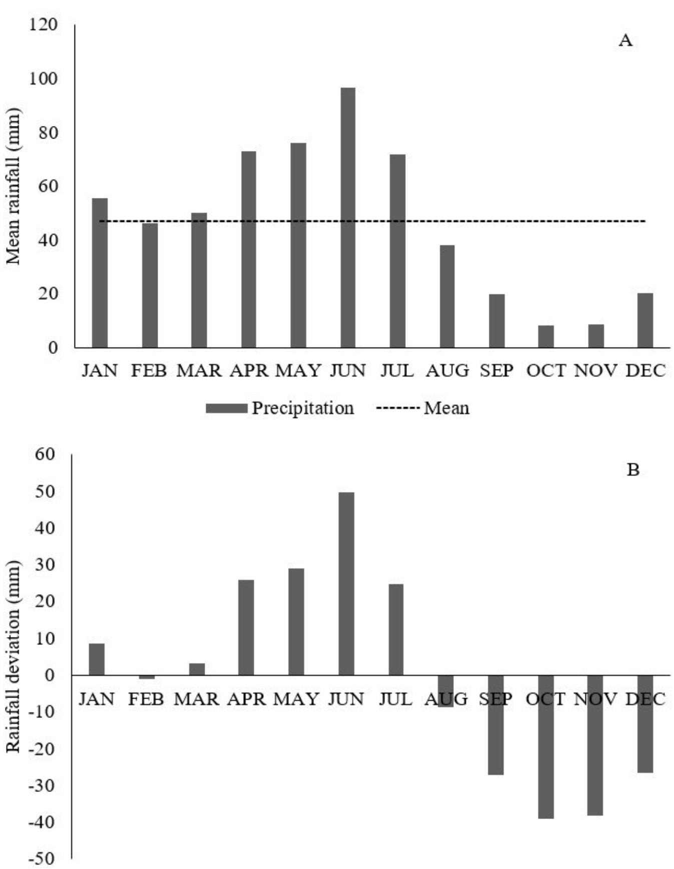

Figure 3 – Average monthly rainfall of the historical series (2000–2019) in station 211 in Caruaru (A) and rainfall deviation in relation to the reference average (B).

In 2004, there was an isolated event in January, where the accumulated rainfall was 316.7 mm. Due to this index, when the rainfall deviation was performed in relation to the average reference value for this station, January was considered as a rainy month. However, in the analysis of the historical series, the average of the other indexes for this month was 41.9 mm, below the average reference value. Thus, it was decided to allocate January to the dry period, as classified by Souza et al. (2020). Therefore, the months from March to July were classified as belonging to the rainy period and the other months of the year, to the dry period.

Figure 4 reveals the rainfall index and average rainfall of the study period (2019 to 2020). Station 211, in Caruaru, had the highest rainfall in April, with 133.7 mm. Despite being considered a rainy month, May had a rainfall index below the average for the analyzed period. October, November, and December presented rainfall below 10 mm, configuring what was already analyzed by the historical series, as dry months. January and August, despite being classified as dry months, presented values above the average rainfall for the analyzed period.

Basin concentration time

The basin concentration time of the Ipojuca River was calculated according to the modified Kirpich equation (Equation 2), taking into account the point, the slope, and the length of the source of the main river, up to the last point of analysis in this work. For the calculus application, the data utilized from the Ipojuca River basin were: the basin area in square kilometers (7,455 km²); the river length in kilometers (104.3 km); the height of the source in meters (1,135 m); the height of the last point in meters (340 m); and the height difference between the source and the last point, expressed in meters (ΔH=795 m) (SRHE, 2010).

$$tc = 85.2.\left(\frac{L^3}{H}\right)^{0.385} \tag{2}$$

The concentration time obtained was 2.22 days for the Ipojuca River basin. Therefore, the accumulated rainfall data of the three days prior to the collection days were observed for the analysis of the drug data.

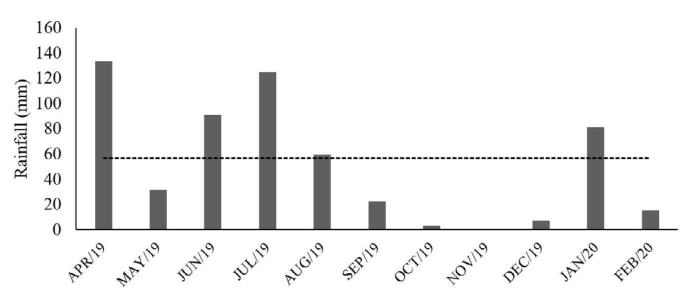

Figure 4 – Monthly rainfall index of station 211, in Caruaru, during the study period (2019–2020).

These were used in statistical correlation analyses to examine the contribution of rainfall to medication dilution. Table 4 shows the accumulated monthly rainfall for the Ipojuca River, according to the calculus of concentration time.

Drugs detected in the Ipojuca River

In the analyzes of water from the Ipojuca River, DC and IBU were found in 100% of the samples. PAR and DP drugs were not detected or were below the HPLC quantification limit, except for point R-1, in April, when the PAR concentration was 0.8 $\mu g.L^{-1}$ (Table 5).

Among the drugs studied, DC had the highest concentration, reaching a value of 548.2 $\mu g.L^{-1}$. This drug is known as the most administered analgesic in the world (Carvalho Filho et al., 2022) and is frequently detected in aquatic matrices (Hanif et al., 2020). Similar results were observed by Rivera-Jaimes et al. (2018) in the Apatlaco River in Mexico, where DC was detected in 100% of the samples.

The second most abundant pharmaceutical was IBU reaching a concentration of 195.3 $\mu g.L^{-1}$. DC and IBU are some NSAIDs most frequently detected in aquatic matrices (Hawash et al., 2023).

The concentrations identified in the present study are outstanding, especially DC (7.4 to 548.2 $\mu g.L^{-1}$) when compared to other studies. Praveena et al. (2018) detected DC in the surface waters of the Lui, Gombak, and Selangor rivers, in Malaysia, at average concentrations of 0.00276, 0.00484 and 0.00430 $\mu g.L^{-1}$, respectively. Osorio et al. (2012) detected the presence o/f DC in the Llobregat River, Spain, in a range from 0.0004 to 0.7850 $\mu g.L^{-1}$. In an extensive review article, Rastogi et al. (2021) found concentrations of NSAIDs in surface water bodies below 1 $\mu g.L^{-1}$; only 17.24% of the 29 evaluated documents presented a concentration greater than 1 $\mu g.L^{-1}$ for DC. To our knowledge, only a few studies reported concentrations in a similar range of magnitude in surface waters. In Córrego da Onça, located in the municipality of Três Lagoas, Mato Grosso do Sul, the highest concentration of DC (8.25 $\mu g.L^{-1}$) was observed at a point downstream of the WWTP (Américo-Pinheiro et al., 2017). Veras et al. (2019) found DC in the Beberibe River, in the metropolitan region of Recife (PE), at a maximum concentration of 193 $\mu g.L^{-1}$, which is close to the lowest value encountered in the present study. Other studies in Brazil found concentrations lower than 1 $\mu g.L^{-1}$ (Montagner and Jardim, 2011) in water samples from the Pinheiros and Anhumas streams, at 0.096 and 0.115 $\mu g.L^{-1}$, respectively, in the city of Campinas, São Paulo. In the Iguaçu River, in Curitiba municipality, Paraná, the DC concentration was 0.285 $\mu g.L^{-1}$ (Kramer et al., 2015).

This excessively high DC concentration is consistent with the fact that the Ipojuca River is located in a semiarid region, with high evapotranspiration (Table 6) and intermittent rivers with low average flows of 3.18 m^3/s (Silva and Galvíncio, 2011) — conditions that reduce the self-purification capacity of rivers and concentrate pollutants.

The IBU concentration found in the present study ranged from 81.8 to 195.3 $\mu g.L^{-1}$, being quite high when compared to other studies, which can also be attributed to the low self-purification capacity and intermittence of rivers in the region. In a study by Rivera-Jaimes et al. (2018), in the surface waters of the Apatlaco River, in Mexico, IBU was observed in 78% of the analyzed samples with concentrations from 0.184 to 1.106 $\mu g.L^{-1}$. Mandaric et al. (2018) detected IBU at a maximum concentration of 2.660 $\mu g.L^{-1}$ in the surface waters of

Table 6 – Average temperature, rainfall, and evaporation in the Ipojuca River basin from 1962 to 2018.

Month	Temperature (°C)	Rainfall (mm)	Evaporation (mm)
April	23.3	128.6	96.1
May	22.3	114.1	86.2
June	21.0	120.0	70.3

Source: Modified from Medeiros (2020).

Table 4 – Accumulated rainfall, according to the concentration time of the Ipojuca River basin.

Month	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC	JAN	FEB
Year	2019									2020	
Cumulative rainfall (mm)	4.0	0.0	47.8	5.0	11.5	0.0	0.2	0.0	0.0	0.0	0.0

Table 5 – Concentration of drugs at sampling points on the Ipojuca River.

Drug ($\mu g.L^{-1}$)	April			May			June		
	R-1	R-2	R-3	R-1	R-2	R-3	R-1	R-2	R-3
DC	548.2	8.1	341.1	7.4	100.5	54.2	24.7	360.7	9.9
DP	<LQ	ND	ND	ND	ND	ND	ND	ND	ND
PAR	0.8	ND	<LQ	<LQ	<LQ	<LQ	<LQ	<LQ	<LQ
IBU	86.8	116.0	105.3	81.8	195.3	231.8	111.7	172.7	130.5

DC: diclofenac; DP: dipyrone; PAR: paracetamol; IBU: ibuprofen; LQ: limit of quantification; ND: not detected.

the Ebro River, in Spain. Osorio et al. (2012) found IBU concentrations in the Llobregat River, Spain, between 0.0027 and 0.8680 μg.L^{-1}. In Brazil, this drug was detected in the Santos Hydrographic Basin, in the state of São Paulo, with concentrations of up to 2.090 μg.L^{-1} (Pereira et al., 2016).

In a bibliographic survey carried out by Wang et al. (2017), with studies published in 29 countries distributed in America, Asia, Europe, and Oceania, IBU was the most detected NSAID in the environment. The high consumption of IBU was evidenced by its occurrence in water. In this study, 75% of all 139 publications involved IBU, which is the most frequently studied NSAID. This NSAID substance's huge global consumption by the population could be explained by its popularity. In 2000, 58 tons of IBU were consumed in Poland, and 162 and 300 tons in England and Germany, respectively. In Brazil, in 2018, the IBU occupied the sixth position in the ranking of active principles with the largest quantities of presentations marketed in Brazil (between 50 and 100 million units) (ANVISA, 2018), which can be justified by the absence of mandatory medical prescriptions for purchase in the country.

Regarding PAR, the drug was detected only at the R-1 point, and at a much lower concentration (0.800 μg.L^{-1}) than that of the other NSAIDs analyzed. In Brazil, low PAR concentrations in surface waters were also found by Lopes et al. (2016), in Camorim, Arroio Pavuna, Grande, and Arroio Fundo rivers, located in the state of Rio de Janeiro, in concentrations ranging from 0.009 to 0.014 μg.L^{-1}. PAR occupies the 14th position among the most consumed drugs in Brazil, ahead of DC, which occupies the 15th position (ANVISA, 2018). However, when it is free in the environment, PAR has a biodegradability of 57% (Henschel et al., 1997), which explains the non-detection of this drug in the Ipojuca River.

The concentration of DP, that ranks 4th in drug consumption in Brazil (ANVISA, 2018), ranged from non-detection to values below the quantification limit. In a study carried out in the laboratory under 13 different conditions, with pH equal to 3.5 and temperature varying between 20 and 40°C, DP was degraded in up to 20 minutes in practically all situations (Oliveira et al., 2006). Thus, few studies have published about the presence of DP in water.

However, DP metabolites are present in the environment due to the process of spontaneous hydrolysis of the main metabolite, 4-methylaminoantipyrine (4-MAA), which is subsequently metabolized into other compounds. The final metabolites, 4-formylaminoantipyrine (4-FAA) and 4-acetylaminoantipyrine (4-AAA), are often used as indicators of contamination of water bodies by sewage (Radović et al., 2015).

About 60% of the administered dose of DP excreted in the urine is represented by these four metabolites (Bueno et al., 2012), thus, studies focus almost exclusively on the presence of DP metabolites in the water, and not on the drug itself. Radović et al. (2015) encountered two DP metabolites in surface waters of the Danube River, in Serbia, in ranges from 0.009 to 0.186 μg.L^{-1} (4-FAA) and 0.031 to 0.512 μg.L^{-1} (4-AAA). Moldovan (2006) detected the presence of 4-AAA and 4-FAA metabolites in Romanian waters, in concentrations ranging from 0.312 to 1.56 μg.L^{-1} and 0.103 to 0.51 μg.L^{-1}, respectively. In the present study, DP itself was not observed in the Ipojuca River.

Drugs detected in the wastewater treatment plant and their removal

In general, NSAIDs are partially metabolized in organisms and part is excreted in urine and feces, thus reaching effluents (Kumar et al., 2023). In the studied WWTP, DC and IBU were identified and quantified in 100% of the analyzed samples, both in the raw effluent (WW-1) and in the treated effluent (WW-2), while PAR and DP were not detected or were below the limit of quantification (Table 7).

The maximum DC concentrations at points WW-1 and WW-2 were 235.5 μg.L^{-1} and 27.4 μg.L^{-1} (Table 7), respectively. These are very high concentrations when compared to what is commonly found in other studies. In a study by Patrolecco et al. (2015) in WWTPs of Rome, in Italy, DC was found in the raw effluent in a range from 0.514 to 2.230 μg.L^{-1} and in the treated effluent in the range from 0.321 to 1.424 μg.L^{-1}, with 27 to 53% efficiency in drug removal. In a WWTP in Poland, Migowska et al. (2012) found a concentration of DC in the raw effluent and in the treated effluent of 0.46 and 0.12 μg.L^{-1}, respectively, showing a removal efficiency of approximately 74%. Pereira et al. (2015) evaluated the presence of drugs in 15 WWTPs in Portugal, including the DC. The concentration of DC in the raw sewage varied from not detected to 6.36 μg.L^{-1}, while in the treated

Table 7 – Concentration of drugs in raw effluent (WW-1) and treated effluent (WW-2) from the wastewater treatment plant.

Drug (μg.L^{-1})	April			May			June		
	WW-1	WW-2	Efficiency (%)	WW-1	WW-2	Efficiency (%)	WW-1	WW-2	Efficiency (%)
DC	47.2	24.1	48.9	235.5	15.0	93.6	42.8	27.4	35.9
DP	ND	ND	-	ND	ND	-	ND	ND	-
PAR	ND	ND	-	<LQ	<LQ	-	<LQ	<LQ	-
IBU	765.2	102.9	86.6	75.7	116.4	-53.7	601.3	739.5	-23.0

DC: diclofenac; DP: dipyrone; PAR: paracetamol; IBU: ibuprofen; LQ: limit of quantification; ND: not detected.

effluent, it varied from not detected to 0.03 μg.L^{-1}, with an average DC removal efficiency of 45.6%.

DC is not completely removed by conventional sewage treatment systems and is one of the least biodegradable anti-inflammatories (Sari et al., 2014; Vieno and Sillanpää, 2014). In a study by Palli et al. (2019) in WWTPs in central Italy, DC showed recalcitrant behavior for biological treatment. DC is slightly soluble in water and has a moderately low octanol-water coefficient (log Kow) and only a minor portion of this compound is absorbed by the sludge (Vieno and Sillanpää, 2014). Américo et al. (2012) detected DC in a WWTP in Mato Grosso do Sul at a concentration of 2.471 μg.L^{-1} in raw sewage and 0.273 μg.L^{-1} in treated effluent, with a removal efficiency of 89.0% of this compound. In the present study, similar efficiencies were found, ranging from 35.9 to 93.6%.

The scenario observed in the stretch of the Ipojuca River studied herein for DC is the opposite, as the river crosses the city of Caruaru, where approximately 57% of the population is not served by the sewage collection network (SNIS, 2021). This population resorts to alternative individual solutions, such as releasing raw effluent directly into the Ipojuca River, or disposing of it on the ground through infiltration ditches and sinkholes resulting from the rains. These actions cause drugs to be released directly into the river. This may explain the higher concentrations in the Ipojuca River than in the Rendeiras WWTP effluent in Caruaru, as shown in Figure 5.

The highest IBU concentrations at WW-1 and WW-2 points were 765.2 and 739.5 μg.L^{-1}, respectively (Table 7). Ashfaq et al. (2017) investigated the occurrence of 11 drugs in different environmental matrices in Sheikhupura, Pakistan. Among them, the IBU showed the highest concentrations (703 to 1,673 μg.L^{-1}) in wastewater — values similar to those found in this study. On the other hand, the IBU concentration found by Pereira et al. (2015) in raw and treated effluent from WWTPs in Portugal varied from not detected to 1.27 μg.L^{-1} and not detected to 0.03 μg.L^{-1}, respectively.

Fluctuations in the influent drug concentrations in the WWTPs and the long HDT during the treatment cause the observed efficiencies to vary a lot for the same molecule. In the studied WWTP, the total HDT is 6.58 days, thus, in the months of May and June, the IBU presented higher concentrations in the effluent (WW-2) than in the affluent (WW-1), presenting an increase in concentration of 53.7% in May and 23.0% in June. In April, the removal was 86.6%. Several studies reported the increase in drugs during the sewage treatment process (Kasprzyk-Hordern et al., 2009; Kermia et al., 2016; Lee et al., 2019) — the same identified in this study, as shown in Figure 6.

PAR concentrations in WW-1 and WW-2 ranged from not detected to below the quantification limit. Américo et al. (2012) detected PAR only in the raw effluent of a WWTP, at a concentration of 0.13 μ.gL^{-1}. In a WWTP in Poland, Migowska et al. (2012) also determined the PAR concentration below the detection limit, in the raw effluent and in the treated effluent. The low concentrations of this drug in WWTP affluent and effluent may be associated with processes that contribute to its removal, such as adsorption, biodegradation, and photodegradation (Américo et al., 2012).

DP was also not detected at points WW-1 and WW-2 (Table 7). Although there are not many reports regarding the presence of DP in WWTPs, due to its rapid degradation (Rosal et al., 2010; Gómez-Canela et al., 2019), the presence of its metabolites has been reported in some studies (Rosal et al., 2010; Szabó et al., 2013). Radović et al. (2015) found two of the DP metabolites in surface waters of the Danube River, in Serbia, in the ranges from 9 to 186 ng.L^{-1} (4-FAA) and 31 to 512 ng.L^{-1} (4-AAA). Moldovan (2006) detected the presence of 4-AAA and 4-FAA metabolites, in concentrations ranging from 312 to 1,560 and 103 to 510 ng.L^{-1}, respectively. Thus, the possible existence of these metabolites in the treated effluent from the evaluated WWTP cannot be ruled out.

Pearson's correlation

Pearson's correlation between rainfall and NSAIDs was performed with a significance level of 5% ($p<0.05$). Among the NSAIDs investigated, only DC and IBU were detected in the analyzed sections of the Ipojuca River. Therefore, only these two NSAIDs were correlated with rainfall.

Both IBU and DC had insignificant correlation results with rainfall (-0.022 and -0.071, respectively). Thus, it was observed that, for a better understanding of the behavior of these NSAIDs in the analyzed water body, a continued study of these contaminants in the river is necessary.

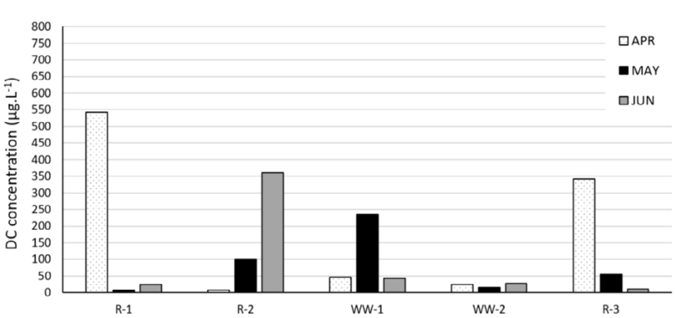

Figure 5 – Concentration of diclofenac in the river and in the effluent from Rendeiras wastewater treatment plant.

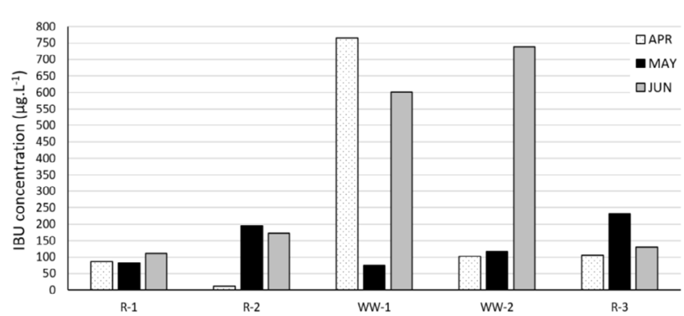

Figure 6 – Concentration of ibuprofen in the river and in the effluent from Rendeiras wastewater treatment plant.

So that the data matrix has sufficient correlations to justify the application of the factorial analysis, the KMO and Bartlett's sphericity tests were performed, related to rainfall and the NSAIDs DC and IBU, referring to the months of April, May, and June. The test results showed that the matrices were not suitable for the application of factorial analysis.

Conclusion

Among the pharmaceuticals analyzed, PAR and DP were not detected or were below the detection limit in the water from the Ipojuca River and the WWTP affluent and effluent. The non-detection of PAR is related to its high rate of biodegradation, likewise, DP is rapidly metabolized into four compounds, which makes it difficult to detect in the environment.

On the other hand, high concentrations of DC and IBU were found in the water of the Ipojuca River. This result is due to the high consumption of these pharmaceuticals worldwide, especially in Brazil, in addition to the region studied having low coverage of sewage collection, which is considered the main route of contamination of NSAIDs in aquatic matrices.

In the analyzes of the WWTP influent and effluent, DC and IBU were detected and quantified in 100% of the analyzed samples. Treatment at the WWTP was efficient in removing DC in all campaigns, reaching 93%. As for IBU, there was efficiency in removal only in a month (86.6%), while in the other months, there was an increase in concentration, which may have been influenced by the HDT of the WWTP that was not taken into consideration in the study.

Both DC and IBU had insignificant correlation results with pluviometry. Due to the limitation of the study, which evaluated the months from April to June (3 months), continuous monitoring of all drugs in the river is necessary, especially DC and IBU, for a better understanding of the behavior of these contaminants in the water body.

Thus, considering that the release of domestic effluents represents the main route of entry of contaminants into the environment and verifying the inefficiency of the complete removal of drugs by conventional treatment, it is evident the need to implement efficient technologies in the removal of drugs and expansion of the sewage collection network in the region.

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Contribution of authors:

SANTOS, R. M. S.: conceptualization, investigation, methodology, validation, writing — original draft. NASCIMENTO, R.F.: conceptualization, investigation, methodology, validation, writing — original draft. GONÇALVES, E. A. P.: investigation, methodology, validation, writing — original draft, writing — review & editing. CARVALHO FILHO, J. A. A.: conceptualization, investigation, methodology, validation, writing — original draft. BERTRAND, G. F.: validation, visualization, writing — review & editing. NAPOLEÃO, D. C.: methodology, validation, visualization, writing — review & editing. CABRAL, J. J. S. P.: conceptualization, methodology, validation, visualization, writing — review & editing. PAIVA, A. L. R.: conceptualization, funding, investigation, methodology, validation, writing — original draft, writing — review & editing.

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