https://doi.org/10.1590/S1413-415220220025

Scientific Paper

Degradation of pharmaceuticals in sanitary effluent by the combination of oxidation and photo-oxidation processes

Degradação de fármacos em efluentes sanitários pela combinação de processos de oxidação e foto-oxidação

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ABSTRACT

Most conventional sewage treatment systems are not able to fully remove micropollutants found in sewage. Thus, the simultaneous degradation of 11 pharmaceuticals identified in the effluent of a sewage treatment plant in Southern Brazil was herein investigated through advanced oxidation processes based on ozonation, ultraviolet radiation and hydrogen peroxide. For detection, samples were prepared through solid-phase extraction and pharmaceuticals were identified through ultra-high performance liquid chromatography tandem mass spectrometry. Active ingredients such as ciprofloxacin, oxytetracycline, paracetamol, sulfamethoxazole and trimethoprim had their concentrations increased for degradation analysis purposes. Trials were carried out on a bench at room temperature and neutral pH, with aliquots collected at 7.5 and 15 minutes. Two ozone doses (0.5 and 0.9 mg per mg of dissolved organic carbon), and combinations of the lowest ozone dose with photolysis (254 nm) and with 25 mg.L^{-1} of hydrogen peroxide were evaluated. Pharmaceuticals mineralization efficiency was assessed in a total organic carbon analyzer. The process combining ozone, hydrogen peroxide and ultraviolet radiation was the most efficient in the degradation of all pharmaceuticals detected in this study, since it enabled reducing oxytetracycline by 89.32%, caffeine by 96.79%, trimethoprim by 97.40%, ciprofloxacin by 97.75%, sulfamethoxazole by 99.79%, paracetamol by 99.96%, and clindamycin, ofloxacin, sulfadiazine, sulfathiazole and tylosin by 100%. This process also recorded the highest mineralization rate (60.52%), fact that confirmed the potential to decrease persistent pharmaceuticals found in conventional sewage treatment systems.

Keywords: sewage treatment; micropollutants; ozonation; hydrogen peroxide; ultraviolet radiation.

RESUMO

A maioria dos sistemas convencionais de tratamento de esgoto não é capaz de remover totalmente os micropoluentes presentes no esgoto. Assim, a degradação simultânea de 11 fármacos, detectados no efluente de uma estação de tratamento de esgoto no Sul do Brasil, foi investigada por meio de processos oxidativos avançados baseados em ozonização, radiação ultravioleta e peróxido de hidrogênio. Para detecção, as amostras foram preparadas por extração em fase sólida e os fármacos foram identificados por cromatografia líquida de ultra eficiência acoplada à espectrometria de massa em tandem. Ingredientes ativos como ciprofloxacina, oxitetraciclina, paracetamol, sulfametoxazol e trimetoprima tiveram suas concentrações aumentadas para análise de degradação. Os ensaios foram realizados em bancada a temperatura ambiente e pH neutro, com alíquotas coletadas aos 7,5 e 15 minutos. Duas doses de ozônio (0,5 e 0,9 mg por mg de carbono orgânico dissolvido) e combinações da menor dose de ozônio com fotólise (254 nm) e com 25 mg.L^{-1} de peróxido de hidrogênio foram avaliadas. A eficiência da mineralização dos fármacos foi verificada em um analisador de carbono orgânico total. O processo combinando de ozônio, peróxido de hidrogênio e radiação ultravioleta foi o mais eficiente na degradação de todos os fármacos detectados neste estudo, pois permitiu reduzir a oxitetraciclina em 89,32%, a cafeína em 96,79%, o trimetoprim em 97,40%, a ciprofloxacina em 97,75%, o sulfametoxazol em 99,79%, o paracetamol em 99,96% e a clindamicina, a ofloxacina, a sulfadiazina, o sulfatiazol e a tilosina em 100%. Esse processo também registrou a maior taxa de mineralização (60,52%), confirmando o potencial de redução de fármacos persistentes encontrados em sistemas convencionais de tratamento de esgoto.

Palavras-chave: tratamento de esgoto; micropoluentes; ozonização; peróxido de hidrogênio; radiação ultravioleta.

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Conflicts of interest: the authors declare no conflicts of interest.
Funding: none.
Received: 02/02/2022 – **Accepted:** 03/03/2023

INTRODUCTION

Thousands of tons of pharmaceuticals are annually consumed to prevent and treat human and animal diseases, mainly in Asian, American, and European countries (JIANG *et al.*, 2014; HU *et al.*, 2018; MARTINI *et al.*, 2018). However, most of these pharmaceuticals present high stability (VERLICCHI; AL AUKIDY; ZAMBELLO, 2012) and low assimilation in the body, since 50 to 90% of the administered doses are excreted as active substance in patients' urine (MARTINI *et al.*, 2018; MONDAL; SAHA; SINHA, 2018). Thus, pharmaceuticals typically soluble in water arrive at sewage treatment plants (STP), where most of their compounds are not fully removed through conventional biological processes (BALAKRISHNA *et al.*, 2017; GRAUMANS *et al.*, 2022; KRISHNAN *et al.*, 2021; LOZANO *et al.*, 2022; LUO *et al.*, 2014; KNOPP *et al.*, 2016; MARSON *et al.* 2022; VERLICCHI; AL AUKIDY; ZAMBELLO, 2012; TAOUFIK *et al.*, 2021). Consequently, recalcitrant substances such as antibiotics are released into the environment along with the final effluent (MARSON *et al.*, 2022), fact that leads to (eco)toxicological effects on several non-target organisms, mainly on the aquatic ones (LIU *et al.*, 2018; LOZANO *et al.*, 2022). In addition, these substances can be biotransformed, bioaccumulated and biomagnified at different trophic levels (MONDAL; SAHA; SINHA, 2018).

Therefore, it is necessary pursuing alternatives to enable the removal, or the maximum reduction, of several recalcitrant pharmaceuticals from municipal and industrial wastewaters. Luo *et al.* (2014) and Marson *et al.* (2022) reported the use of tertiary systems based on advanced oxidation processes (AOP), which stood out for the ease of implementation at real scale, and for the slight economic advantage, in comparison to the use of filtration membranes and activated carbon adsorption (HANSEN *et al.*, 2016). In addition, the individual application of oxidizing agents such as ozone (O_3), hydrogen peroxide (H_2O_2) and ultraviolet radiation (UV), mainly as disinfection systems to replace chlorinated agents in treatment plants, has increased (ARAÚJO *et al.*, 2016). Accordingly, there has been increase in the number of studies about the use of AOP to enable the simultaneous removal of pharmaceuticals from sanitary effluents (AFONSO-OLIVARES *et al.*, 2016; DE LA CRUZ *et al.*, 2013; HANSEN *et al.*, 2016; KNOPP *et al.*, 2016; KRISHNAN *et al.*, 2021; ZIMMERMANN *et al.*, 2011), besides the ones addressing the individual degradation of compounds (MARTINI *et al.*, 2018; MONDAL; SAHA; SINHA, 2018) or the reduced number of selected active ingredients (ALHARBI *et al.*, 2017; KATSOYIANNIS; CANONICA; VON GUNTEN, 2011).

Besides conventional processes, AOP are a promising technique that can be used to remove a wide range of organic micropollutants from wastewater (ALHARBI *et al.*, 2017; BRILLAS; MARTÍNEZ-HUITLE, 2015; TAOUFIK *et al.*, 2021) due to the formation of highly-reactive species with high oxidizing power, such as the radical known as hydroxyl ($OH^{\bullet}$) (E° = 2.80 V), which can enable the mineralization, or transformation, of several organic compounds into simpler substances (ARAÚJO *et al.*, 2016).

O_3 is an extremely strong oxidant (E° = 2.07 V) that can be widely applied to disinfect water, as well as to remove taste, odor, and color from it (KATSOYIANNIS; CANONICA; VON GUNTEN, 2011; LIM *et al.*, 2022). The transformation of organic compounds through O_3 application can happen in direct or indirect ways. The molecular ozone reacts to organic compounds in the direct mechanism via direct oxidation, whereas, in the indirect mechanism, there is the formation of $OH^{\bullet}$ radicals, which react faster to organic compounds than O_3 (HANSEN *et al.*, 2016; MAHMOUD; FREIRE, 2007; MARTINI *et al.*, 2018). Studies have described more than 70% reduction, and even the full removal, of some soluble pharmaceuticals that have reacted to ozone within the first 20 reaction min, at doses ranging from 0.5 to 0.9 mgO_3 $mgDOC^{-1}$ (dissolved organic carbon) (HANSEN *et al.*, 2016; KNOPP *et al.*, 2016; ZIMMERMANN *et al.*, 2011). However, drug removal through O_3 application can be limited by the short lifespan of the oxidizing agent and by compound adhesion to organic matter particles (KANAKARAJU; GLASS; OELGEMÖLLER, 2018). On the other hand, the combination between O_3 and UV-C radiation (200 to 360 nm) enabled O_3 photolysis and generated $OH^{\bullet}$ radicals that potentiated the degradation, and mineralization, of organic compounds. Non-reactive $OH^{\bullet}$ radicals, in their turn, recombined to each other and generated H_2O_2 (ARAÚJO *et al.*, 2016; MARTINI *et al.*, 2018).

Although H_2O_2 is a strong oxidant (E° = 1.78 V), its oxidation potential is lower than that of O_3 and $OH^{\bullet}$. Thus, reactions based on H_2O_2 are not efficient in degrading organic compounds due to their very slow decomposition in oxidizing radicals and to the strong influence of parameters such as temperature and pH (MARTINI *et al.*, 2018). Therefore, H_2O_2 is often used in combination with UV-C radiation (less than 280 nm), which breaks the O-O bond of the peroxide molecule and produces $OH^{\bullet}$ (ALHARBI *et al.*, 2017; ARAÚJO *et al.*, 2016; GRAUMANS *et al.*, 2022). It is also possible making other combinations, such as H_2O_2 and O_3, in which H_2O_2 works as homogeneous catalyst by accelerating ozone degradation to form non-selective $OH^{\bullet}$ radicals (HANSEN *et al.*, 2016; LIM *et al.*, 2022).

Photolysis based on UV-C radiation (254 nm) is widely used to disinfect drinking water, besides being increasingly applied to slightly-turbid wastewater (ALHARBI *et al.*, 2017). Although some pharmaceuticals are susceptible to degradation even at typical doses used in disinfection processes (AFONSO-OLIVARES *et al.*, 2016), degradation is achieved when there is radiation enough to break the chemical bonds of the compounds, i.e., when the photon energy exceeds the bond energy (MARTINI *et al.*, 2018). Drug degradation through UV radiation can happen both through direct and indirect ways. In the first case, molecules absorb radiation photons and break, whereas, in the second case, there is the generation of strong reactive species, such as $OH^{\bullet}$, from compounds naturally found in solution (ALHARBI *et al.*, 2017; FATTA-KASSINOS; VAZQUEZ; KÜMMERER, 2011).

Thus, it is recommended combining two, or more, AOP to form strong oxidants ($OH^{\bullet}$) (MARSON *et al.*, 2022; MARTINI *et al.*, 2018; TAOUFIK *et al.*, 2021), which can reduce the generation of toxic by-products during degradation processes (AFONSO-OLIVARES *et al.*, 2016; ALHARBI *et al.*, 2017; ARAÚJO *et al.*, 2016; GRAUMANS *et al.*, 2022). Therefore, the aim of the current study was to investigate the efficiency of simultaneous degradation, and mineralization, of pharmaceuticals in sanitary sewage post-treatment based on advanced oxidation processes comprising O_3, UV radiation and photochemical associations O_3/UV, H_2O_2/UV and O_3/H_2O_2/UV.

MATERIALS AND METHODS

Origin of the studied sanitary effluent

Post-treatment trials were performed with sanitary sewage from a sewage treatment plant (STP) located in the metropolitan region of Porto Alegre city, Rio Grande do Sul state (RS), Brazil. The mentioned system operates at mean flow

2,250 ± 250 $L \cdot s^{-1}$ and serves approximately 600 thousand people. It comprises mechanical screening, de-sanding and biological treatment units in Upflow Anaerobic Sludge Blanket (UASB) reactors, as well as activated sludge, in the process called Unitank: cyclic operations in the aeration stage, which are followed by sedimentation and disinfection with H_2O_2.

Treated effluent samples were collected in the STP emissary in April 2018, from 7 a.m. to 12 p.m.; effluent aliquots were collected every hour until reaching 40 L volume. Non-toxic high-density polyethylene (HDPE) bottles were used, previously sanitized and rinsed with the samples at collection time. A 1-L aliquot of sample was collected in amber bottle to enable determining pharmaceuticals and hormones; the bottle was stored under refrigeration (± 4°C) for further analysis.

Analytical procedures

Detection of compounds in effluent samples

Effluent samples were subjected to tests focused on detecting 44 compounds (Table 1 supplementary material), including human and veterinary prescription pharmaceuticals and hormones, at the Pesticide Residue Analysis Laboratory (LARP) of the Federal University of Santa Maria (UFSM), RS, Brazil.

Solid analyte standards with purity ranging from 95.0 to 99.6% were purchased from the German companies Dr. Ehrenstorfer and Witega. The individual standard solution of each analyte was prepared at concentration 1,000 $mg \cdot L^{-1}$ in acetonitrile. Next, a solution containing the mixture of all pharmaceuticals at concentration 10 $mg \cdot L^{-1}$ in acetonitrile was prepared. These solutions were stored in amber bottles at 5 °C.

Sample preparation

Sample preparation was based on solid phase extraction (SPE), adapted from Jank *et al.* (2014), using Strata®-X cartridges: 100 mL of sample were percolated and eluted with the acidified mixture of MeOH:MeCN (1:1, v/v) solvents. Next, samples were diluted twice in ultrapure water and analyzed through ultra-high-performance liquid chromatography coupled to tandem mass spectrometry (UHPLC-MS/MS) by Waters (USA). This process used liquid chromatograph; triple quadrupole MS detector, model Xevo TQ; electrospray ionization source; Acquity UPLC® BEH C18 analytical column (50 × 2.1 mm, 1.7 µm) by Waters (USA); and MassLynx 4.1 data acquisition system (Waters, USA). Two linear gradients were used to determine pharmaceuticals and hormones, at run time 4 and 3 minutes, respectively, flow rate 0.250 $mL \cdot min^{-1}$ and injection volume 10 µL (for both). The mobile phase adopted for pharmaceuticals, except for caffeine and paracetamol, comprised (A) water: methanol (98:2, v/v) and (B) methanol, both containing 5 $mmol \cdot L^{-1}$ ammonium formate and 0.1% formic acid (v/v); whereas the one adopted for hormones, caffeine and paracetamol comprised (A) 0.05% (v/v) aqueous ammonium hydroxide solution and (B) methanol. Analytes were quantified and identified by monitoring the selected reactions.

Sample characterization

Effluent samples were also subjected to physicochemical and microbiological characterization, before and after the post-treatment tests were applied to the most efficient process. The analyzed parameters were total organic carbon (TOC), total nitrogen (N_{Total}), alkalinity, turbidity, suspended solids (SS), temperature, pH, chemical oxygen demand (COD), biochemical oxygen demand (BOD_5), total phosphorus (P_{Total}) and thermotolerant coliforms, according to analytical methods set by the *Standard Methods for the Examination of Water and Wastewater* (APHA; AWWA; WEF, 2012).

The drug mineralization degree was determined through TOC removal in a high-sensitivity Shimadzu analyzer (model TOC-L CPH, TNM-L), based on the non-purgeable organic carbon (NPOC) fraction method. The mentioned equipment was also used to determine the dissolved organic carbon (DOC), which corresponded to the organic matter fraction permeated in a 0.45 µm filter, based on the difference between total and inorganic carbon (ZIMMERMANN *et al.*, 2011) and N_T.

Experimental procedure

After the effluent analysis, active ingredients such as ciprofloxacin, oxytetracycline, paracetamol, sulfamethoxazole and trimethoprim were added to the

Table 1 – Concentrations of pharmaceuticals found through ultra-high-performance liquid chromatography coupled to tandem mass spectrometry in the sewage sample before and after the increase of active principles for post-treatment trials.

Pharmaceuticals	LOD	LOQ	Treated sewage (TS)	TS added with pharmaceuticals
	($\mu g \cdot L^{-1}$)		($\mu g \cdot L^{-1}$)	
Caffeine	0.006	0.020	0.966	0.966
Ciprofloxacin	0.006	0.020	0.092	11.443*
Clindamycin	0.006	0.020	0.071	0.071
Ofloxacin	0.006	0.020	0.025	0.025
Oxytetracycline	0.060	0.200	1.154	7.929*
Paracetamol	0.012	0.040	1.170	151.170*
Sulfadiazine	0.006	0.020	0.078	0.078
Sulfamethoxazole	0.006	0.020	0.255	188.692*
Sulfathiazole	0.006	0.020	0.070	0.070
Tylosin	0.006	0.020	0.051	0.051
Trimethoprim	0.006	0.020	n.d.	30.647*

Note: LOD: limit of detection; LOQ: limit of quantification; n.d.: non-detected; *active principles that had their concentration increased for post-treatment trials.
Source: elaborated by the authors.

sample at concentrations higher than the ones predicted to have no effect (predicted no-effect concentrations — PNEC) on the most sensitive species, in order to enable the AOP trials. These compounds were chosen because they recorded the highest persistence and/or incidence rates in the herein investigated sample, as reported in other studies (DINH *et al.*, 2017; HU *et al.*, 2018; MARTÍN *et al.*, 2012). In this way, the objective was to find a concentration capable of enabling a better comparison between different processes.

Drug degradation trials based on O_3, UV radiation, and on combinations such as O_3/UV, H_2O_2/UV, and O_3/H_2O_2/UV, were performed at laboratory bench scale, room temperature 20.6 ± 0.3°C and pH 6.94 ± 0.02 (adjusted with 0.1 N H_2SO_4). Reaction time was set at 15 minutes, since drug degradation through AOP can happen in the early stage of the process (KNOPP *et al.*, 2016; RIVAS; BELTRÁN; ENCINAS, 2012; ZIMMERMANN *et al.*, 2011), whereas long-exposure periods would hardly be economically viable at large scale. Samples were not filtered to allow simulating real conditions.

Degradation trial based on ozonation

The dissolved organic matter (measured in DOC) is the main matrix used to determine O_3 consumption in wastewater, regardless of the drug concentration (Hansen *et al.*, 2016). Therefore, the herein adopted O_3 dose was determined based on the DOC concentration of the effluent, as explained by Zimmermann *et al.* (2011), Knopp *et al.* (2016) and Hansen *et al.* (2016), and on the production capacity of the generating plant, which was evaluated according to the indirect titration iodometric method recommended by the International Ozone Association (APHA; AWWA; WEF, 2012).

Trials were performed with two O_3 doses: the first (the lowest one) was 0.5 $mgO_3 \cdot mgDOC^{-1}$, whereas the second (the highest one) was 0.9 $mgO_3 \cdot mgDOC^{-1}$. O_3 was generated in a Purizonium compact plant with production capacity of 600 $mgO_3 \cdot h^{-1}$, based on atmospheric air suction, filtration in silica gel and electric discharge (Corona effect). The equipment outlet ducting was connected to a porous stone placed at the bottom of a 1000 mL gas scrubber-type reaction flask. The output of the flask was connected to another 500 mL gas scrubber filled with 2% potassium iodide solution in order to transform residual ozone into oxygen (APHA; AWWA; WEF, 2012). The degradation test was carried out in batch for 15 minutes; 100 mL aliquots were collected after 7.5 min, and at the end of the reaction process, for chromatographic, TOC, COD, turbidity, and pH analyses.

Degradation trial based on ultraviolet radiation

The photolysis-based degradation experiment was performed in a cylindrical photoreactor with 76 mm diameter, 480 mm length, and 2.0 L useful volume. The photoreactor was built in PVC and equipped in the center with a 15 W mercury OSRAM low UV-C pressure (λ = 253.7 nm) transparent quartz tube lamp; the effluent was placed in direct contact with the lamp, under slow agitation, to enable uniform exposure. The lamp was turned on 30 minutes before the photoreactor was powered on, in order to achieve maximum radiation. Next, the effluent was exposed to UV radiation for 15 minutes and aliquots were collected after 7.5 minutes, and at the end of the reaction process, under the same conditions adopted in the previous experiment.

Degradation trial based on ozonation and ultraviolet radiation

The ozonation experiment combined with UV radiation adopted the ozone dose 0.5 $mgO_3 \cdot mgDOC^{-1}$ in the photolysis test reactor, which was also used in the other UV experiments, under the same lamp preheating conditions. The porous stone of the O_3 generating station was placed inside the photoreactor to enable this experiment. After the system was filled with the effluent, O_3 started being injected in it in order to homogenize the solution and to enable uniform O_3/effluent/UV contact. The same residual ozone destruction procedures in 2% potassium iodide solution were adopted at the reactor outlet. This experiment followed the sample collection pattern and the time adopted in the other experiments.

Degradation trial based on hydrogen peroxide and ultraviolet radiation

This experiment comprised the addition of 25 $mgH_2O_2 \cdot L^{-1}$ (35%, Merck) effluent to the photoreactor, based on the study by Afonso-Olivares *et al.* (2016). The effluent was placed in direct contact with the lamp, under slow agitation, to enable uniform exposure. Again, the lamp was turned on 30 minutes in advance and aliquots were collected after 7.5 and 15 reaction minutes for drug degradation, TOC, COD, turbidity, and pH analyses.

Degradation trial based on ozonation, hydrogen peroxide and ultraviolet radiation

This experiment was carried out under the same conditions adopted in the previous one; however, it evaluated the influence of the combination added with O_3. The effluent containing 25 $mgH_2O_2 \cdot L^{-1}$ (35%, Merck) was added to the system, after the hose with the porous stone was inserted in the photoreactor. The experiment adopted the dose 0.5 $mgO_3 \cdot mgDOC^{-1}$, which enabled homogenization of, and uniformity in, the contact between the sample and the lamp. This system, like the others, was operated in batch; aliquots were collected halfway the reaction process, and at the end of it, to enable drug degradation, TOC, COD, turbidity, and pH analyses.

The photoreactor was washed between tests with running deionized water and homogenized with the sample to be post-treated.

The use of the lowest O_3 dosage (0.5 $mgO_3 \cdot mgDOC^{-1}$) in experiments in which there was association with other agents (O_3/UV and O_3/H_2O_2/UV) was based on preliminary results of removal of different active principles by the isolated action of photolysis (UV) and photoperoxidation (H_2O_2/UV). Associated with H_2O_2/UV, O_3 starts to act, mainly, as an aid in the degradation of compounds that present greater reactivity with molecular ozone (LIM *et al.*, 2022) in relation to OH• radicals. Still, with lower dosages of oxidizing agents, an attempt was made to minimize the possible generation of toxic intermediate metabolites, showed in the study developed by Bisognin *et al.* (2020), as well as cost minimization with a view to future application on a large scale, without compromising the reduction of target active ingredients.

Analysis of advanced oxidation processes efficiency in degrading pharmaceuticals

The efficiency in degrading pharmaceuticals is shown in Equation 1 — wherein E corresponds to efficiency (%), C_0 and C represent the initial and final concentration of interest, respectively —, which was used to evaluate drug removal/reduction efficiency, TOC, and other effluent parameters.

$$E\ (\%) = \left(\frac{C_0 - C}{C_0}\right) \times 100 \quad (1)$$

Chemical reaction kinetics principles were also taken into consideration in the herein adopted drug removal processes (ABARGUES *et al.*, 2018); linear regression was used to determine the rate constants (K), correlation coefficient (R^2) and the half-life time ($t_{1/2}$) of the pharmaceuticals in each process.

The degradation experiments were replicated in two additional times to statistically validate the processes. This validation was performed through ANOVA test based on the TOC concentration of the effluent at the beginning, and at the end, of the reaction. Results were subjected to Tukey test in order to compare the means ($p \leq 0.05$), in compliance with procedures available in the R statistical package (R CORE TEAM, 2016).

RESULTS AND DISCUSSION

Thirteen pharmaceuticals out of the 44 evaluated compounds were found in the raw effluent of the herein investigated STP, 11 of them remained in the effluent after the treatment (Table 1), thus indicating the need of developing complementary techniques to enable their full removal or reduction. Table 1 also shows the concentration of active ingredients added to the effluent due to their persistence and incidence to enable better comparing the post-treatment processes. Enrofloxacin and metronidazole, which were found in the raw effluent at concentrations 0.037 and 0.023 $\mu g \cdot L^{-1}$, respectively, were the only pharmaceuticals fully removed through the conventional system.

Degradation tests were conducted through different AOP based on the knowledge about drug concentrations, DOC (6.31 $mg \cdot L^{-1}$) and TOC (10.69 $mg \cdot L^{-1}$) in the effluent. Results are shown in Figure 1.

The herein evaluated AOP recorded different drug removal performances, except for antibiotics such as ofloxacin, sulfadiazine and sulfathiazole, which were no longer found in the early reaction minutes, regardless of the degradation process. The degradation of these antibiotics may have been favored by low ofloxacin and sulfadiazine concentrations, which ranged from 0.025 to 0.078 $\mu g \cdot L^{-1}$, respectively. However, although clindamycin was found at low concentration (0.071 $\mu g \cdot L^{-1}$) in the effluent, it was only removed through the H_2O_2/UV and O_3/H_2O_2/UV processes. This drug was more sensitive to H_2O_2 in combination with UV radiation, since O_3 and UV radiation, either in separate or in combination, did not enable eliminating the active principle due to its strongly complex molecular structure. Three other antibiotics — trimethoprim, ciprofloxacin, and sulfamethoxazole — also presented degradation rates lower than the ones recorded for other pharmaceuticals in processes evaluating the use of O_3, in separate. This outcome may have been influenced by the oxidizing agent dose, since Martini *et al.* (2018) reported that sulfamethoxazole was more easily removed through a single ozonation, after 15 reaction minutes, although with the application of 50 $mgO_3 \cdot L^{-1}$, i.e., 8.8 times the maximum application reported in the current study. The dose of 0.5 $mgO_3 \cdot mgDOC^{-1}$ did not enable full tylosin removal from the effluent, since the structural carbon, hydrogen and oxygen chain of this antibiotic is higher than that of the other herein evaluated compounds.

Sulfamethoxazole showed sensitivity to UV radiation and recorded high degradation rates in the first minutes of the process; however, the highest concentration reductions were observed in the O_3/UV and O_3/H_2O_2/UV processes — 99.57 and 99.79%, respectively (Figure 2).

On the other hand, clindamycin, oxytetracycline and trimethoprim were the antibiotics least affected by photolysis. This finding shows the limitation in the exclusive use of UV radiation in drug degradation processes, since sulfamethoxazole is co-administered with trimethoprim at ratio of 5:1 (LIN *et al.*, 2018). UV radiation, in its turn, allowed reducing ciprofloxacin concentrations by more than 50% after the evaluation period. It is worth emphasizing that the O_3/UV combination enhanced the degradation of the other pharmaceuticals in comparison to the action of O_3 and UV radiation, in separate. It happened because some active principles presented higher reactivity to molecular ozone (KNOPP *et al.*, 2016), whereas others reacted better to the oxidation triggered by $OH^{\cdot}$ radicals formed by O_3 photolysis, as reported by Rivas, Beltrán and Encinas (2012).

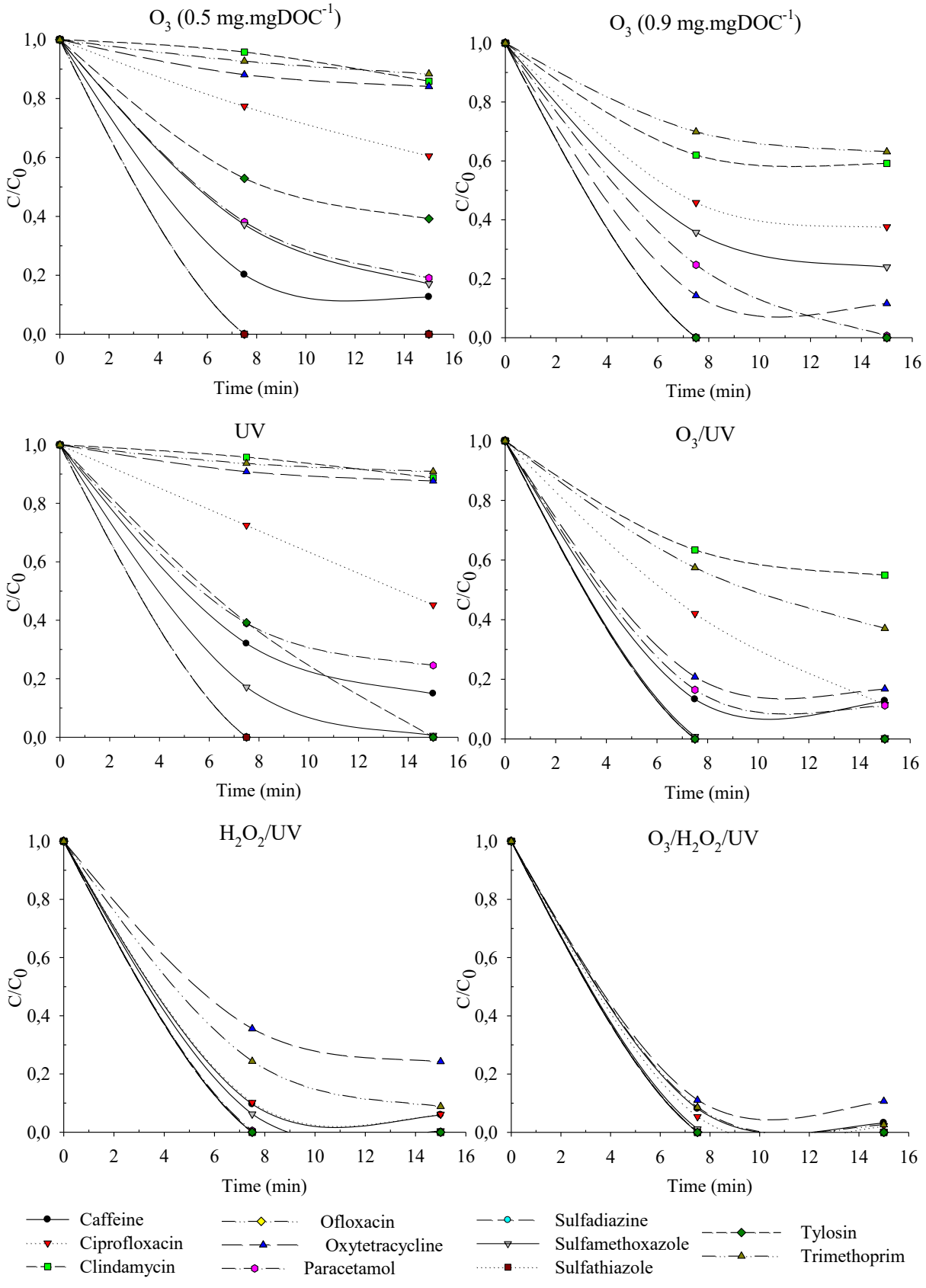
Overall, drug degradation was intensified in the H_2O_2/UV process, which enabled greater concentration reductions and celerity. Only oxytetracycline and trimethoprim were less sensitive to this combination, mainly due to the low influence of UV radiation on the mentioned antibiotics. However, the increased degradation rates in the H_2O_2/UV process can be explained by $OH^{\cdot}$ formation in the photochemical method. Such formation was triggered by the direct H_2O_2 oxidation caused by UV light, since oxidation led to molecule O-O bond breakage, which is also known as homolytic peroxide bond cleavage (ARAÚJO *et al.*, 2016; GRAUMANS *et al.*, 2022).

The action of $OH^{\cdot}$ radicals formed in the H_2O_2/UV process, in association with the direct O_3 reaction to organic molecules via electrophilic addition, and with the indirect O_3 reaction in the formation of radical species (HANSEN *et al.*, 2016; MAHMOUD; FREIRE, 2007), enabled the highest drug removal rates in the early reaction minute of the O_3/H_2O_2/UV treatment. According to Kanakaraju, Glass and Oelgemöller (2018), most hybrid and integrated techniques perform better than single treatments. However, despite the significant reduction in the concentration of all pharmaceuticals, oxytetracycline and trimethoprim showed increased resistance to degradation at the end of the reaction process.

The drug removal efficiency shown in Figure 3 clearly indicates different responses of active principles to the evaluated oxidizing agents, fact that reinforces the importance of conducting studies with real samples in order to define the process capable of presenting the best results.

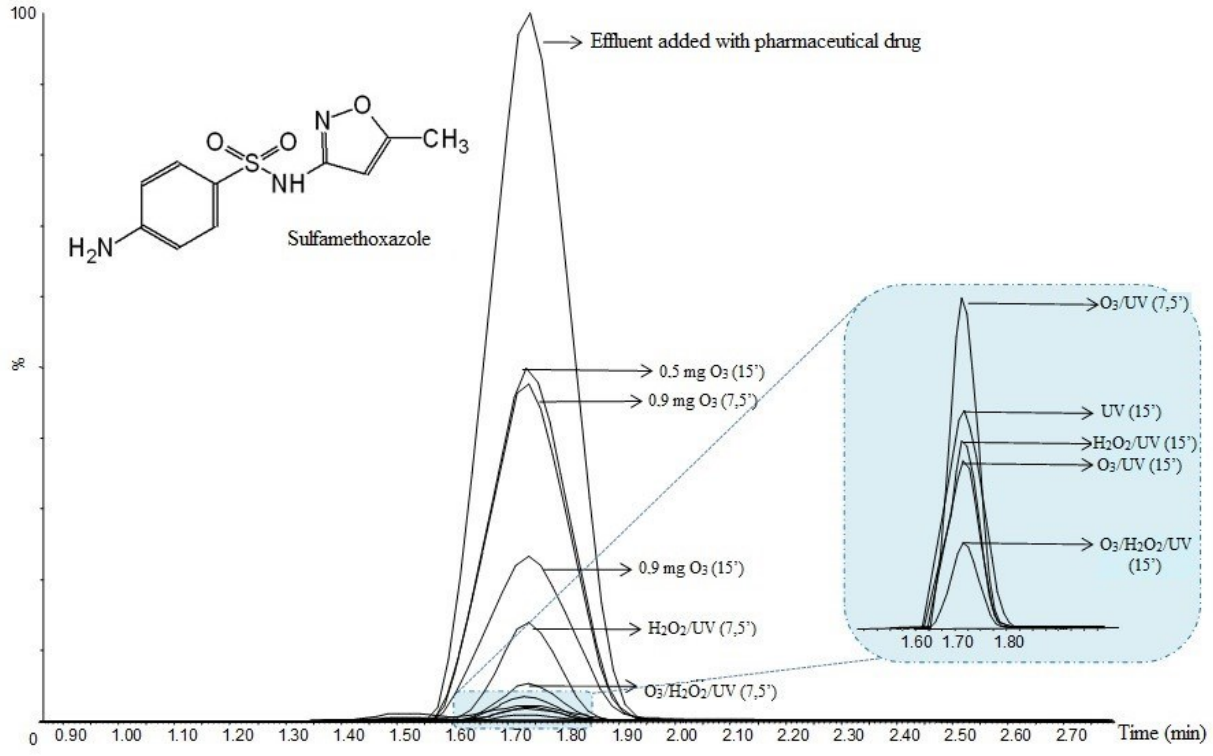
The high performance of the O_3/H_2O_2/UV process was attributed to extensive $OH^{\cdot}$ formation, due to photozonation. These radicals were amplified by H_2O_2 addition (MARTINI *et al.*, 2018). This process was mentioned by Jiang, Zhou, and Sharma (2013) as one of the main methods adopted for $OH^{\cdot}$ radical generation purposes. Antibiotics such as clindamycin, ofloxacin, sulfadiazine, sulfathiazole, and tylosin were 100% removed from the effluent; they were followed by almost full degradation of paracetamol (99.96%), sulfamethoxazole (99.79%), ciprofloxacin (97.75%), trimethoprim (97.40%) and caffeine (96.79%), whereas oxytetracycline was more persistent, although it recorded high reduction rate (89.32%). Drug removal rates higher than 90% were recorded in the early reaction minute, fact that indicated the potential of the process to degrade the target micropollutants, although studies focused on drug removal from wastewater based on the O_3/H_2O_2/UV combination are scarce in the literature (MARTINI *et al.*, 2018).

Caffeine and ciprofloxacin were more sensitive to H_2O_2/UV processes. This outcome indicated oxidation, mainly due to $OH^{\cdot}$ radicals, although caffeine was also sensitive to UV radiation. Similar to the most efficient process, caffeine, and ciprofloxacin removal higher than 90% was recorded in the early reaction minute, when there was greater $OH^{\cdot}$ availability. Results reported in the current study are similar to the ones described by Afonso-Olivares *et al.* (2016), who



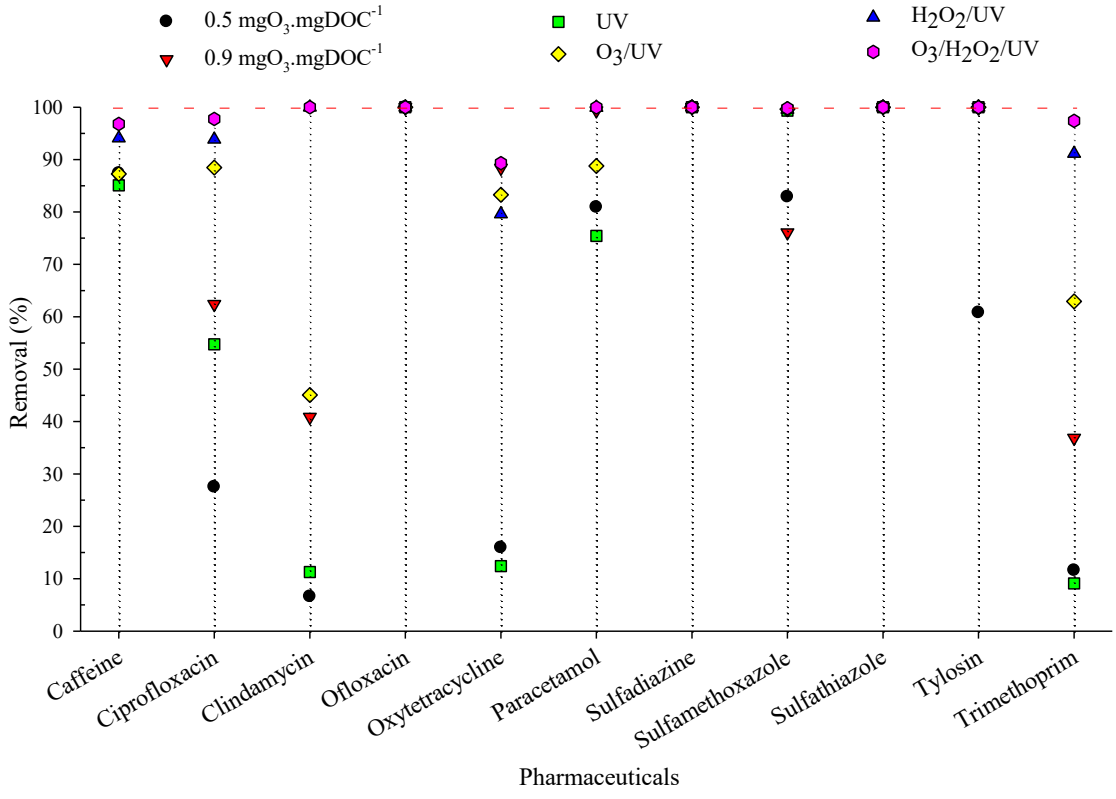
Note: relationship between the final (C) and initial (C_0) concentrations.
Source: elaborated by the authors.

Figure 1 – Drug degradation in sanitary sewage based on advanced oxidative processes: O_3 (0.5 and 0.9 $mgO_3 \cdot mgDOC^{-1}$); UV (15 W); O_3/UV (0.5 $mgO_3 \cdot mgDOC^{-1}$/UV 15 W); H_2O_2/UV (25 $mgH_2O_2 \cdot L^{-1}$/UV 15 W); O_3/H_2O_2/UV (0.5 $mgO_3 \cdot mgDOC^{-1}$/ 25 $mgH_2O_2 \cdot L^{-1}$UV 15 W).



Source: elaborated by the authors.

Figure 2 – Total ion chromatogram generated for sulfamethoxazole after effluent treatment based on different advanced oxidation processes.



Source: elaborated by the authors.

Figure 3 – Removal of the investigated pharmaceuticals through advanced oxidative processes: O_3; UV (15 W); O_3/UV (0.5 $mgO_3 \cdot mgDOC^{-1}$/UV 15 W); H_2O_2/UV (25 $mgH_2O_2 \cdot L^{-1}$/UV 15 W); O_3/H_2O_2/UV (0.5 $mgO_3 \cdot mgDOC^{-1}$/ 25 $mgH_2O_2 \cdot L^{-1}$/UV 15 W)

adopted the same H_2O_2 concentration (25 mg·L^{-1}) in association with UV. The mentioned authors recorded high caffeine (87%), ofloxacin (79%), ciprofloxacin, and sulfamethoxazole (> 99%) removal rates, whereas the current study recorded 94.10, 100, 93.86, and 99.57% removal rates for the same pharmaceuticals, respectively. Mondal, Saha, and Sinha (2018) reported full ciprofloxacin removal (C_0 = 10 mg·L^{-1}) from the effluent, after 40 minutes of UV/H_2O_2 reaction (100 mmol·L^{-1}). Graumans *et al.* (2022) also report cirpofloxacin removal (> 99%) with the H_2O_2/UV process.

On the other hand, oxytetracycline reduction was lower in the H_2O_2/UV process than in the O_3 and O_3/UV processes. This outcome indicated greater degradation of the active principle by molecular ozone action, in comparison to the increased drug removal efficiency in the O_3/H_2O_2/UV process.

Results showed that the degradation efficiency of some drugs increased as the O_3 dose increased, which was also observed in H_2O_2 concentrations (5 to 25 mg·L^{-1}) evaluated by Afonso-Olivares *et al.* (2016), and in the ones (1 to 100 mmol·L^{-1}) evaluated by Mondal, Saha, and Sinha (2018). Ciprofloxacin removal rates increased from 27.50 to 62.40% as the O_3 dose increased from 0.5 to 0.9 mgO_3·mgDOC^{-1}, whereas clindamycin removal rates increased from 6.58 to 40.85%, oxytetracycline removal rates increased from 15.94 to 88.40%, paracetamol removal rates increased from 80.91 to 99.34%, tylosin removal rates increased from 60.78 to 100%, and trimethoprim removal rates increased from 11.60 to 36.86%. Other studies also reported increased drug degradation efficiency as the O_3 dose increased (HANSEN *et al.*, 2016; KATSOYIANNIS; CANONICA; VON GUNTEN, 2011; KNOPP *et al.*, 2016; LEE *et al.*, 2013; ZIMMERMANN *et al.*, 2011).

The lowest removal efficiency rate was recorded for clindamycin at 0.5 mgO_3·mgDOC^{-1} (6.58%), due to influence of the complex molecular structure of the compound. However, UV radiation was also poorly effective in removing clindamycin from the effluent, since it reduced the initial concentration of this antibiotic by 11.27%. Similar behavior was recorded for oxytetracycline (12.40%) and trimethoprim (9.11%) reduction under UV light. Alharbi *et al.* (2017) reported trimethoprim reduction by 58.2% after 1 hour of exposure to UV radiation, which indicated low antibiotic reactivity to the process.

However, the application of UV radiation for 15 minutes enabled reducing ciprofloxacin concentrations by 54.73% in the present study; this outcome is very close to the 60% removal rate reported by Mondal, Saha, and Sinha (2018), who also applied direct photolysis to the same antibiotic, although for 120 minutes. Photolysis enabled reducing by more than 75% the concentrations of the other pharmaceuticals evaluated in the current study; this value was higher than the ones Afonso-Olivares *et al.* (2016) recorded for caffeine (10.99%) and ofloxacin (71%) after 45 reaction minutes; equal to the one recorded for sulfamethoxazole (> 99%); and lower to the ones recorded for ciprofloxacin (> 99%) and trimethoprim (18.80%). It is worth emphasizing that the mentioned authors adopted the ratio of 6.25 L sample per lamp (14 W), whereas the current study adopted the ratio of 2 L sample per lamp (15 W), although it used higher concentrations of pharmaceuticals.

The full drug degradation in wastewater is often compromised by the presence of organic matter and nitrogen, which interfere in the action of OH• radicals over target micropollutants (GRAUMANS *et al.*, 2022; KATSOYIANNIS; CANONICA; VON GUNTEN, 2011). Accordingly, the reactivity of the effluent organic matter (EfOM) composition to hydroxyl was investigated by Dong, Mezyk, and Rosario-Ortiz (2010), who recorded reduced OH• radicals as the molecular weight of the organic fraction increased. Thus, the higher the residual EfOM concentration, the greater the reduction of OH• radicals. This outcome may explain the incomplete degradation of some pharmaceuticals at the end of the process, since the herein evaluated sanitary sewage had 42.94 mg·L^{-1} of COD, 10.69 mg·L^{-1} of TOC and 27.43 mg·L^{-1} of N_{Total}. Therefore, higher O_3 and H_2O_2 concentrations, as well as extended reaction times and analyses conducted under reduced organic matter and nitrogen concentrations, should be adopted in future studies. Furthermore, in certain cases, discharged metabolites are transformed back into their pristine structure and become bioactive again (GRAUMANS *et al.*, 2022).

Kinetic analysis of the degradation

Overall, the degradation of antibiotics and other pharmaceuticals often follows first-order kinetics (KANAKARAJU; GLASS; OELGEMÖLLER, 2018). However, degradation conditions enabled by AOP can induce second-order kinetics (JIANG; ZHOU; SHARMA, 2013; KATSOYIANNIS; CANONICA; VON GUNTEN, 2011; MONDAL; SAHA; SINHA, 2018), as recorded for most pharmaceuticals exposed to O_3 (0.9 mg), UV radiation and O_3/UV combination in the current study. When these processes were analyzed in separate, only paracetamol degradation followed first-order kinetics, whereas the two processes combining the use of H_2O_2 presented similar behavior towards degradation kinetics, whose parameters are shown in Table 2.

Based on the degradation kinetics of the herein investigated pharmaceuticals, it was possible seeing that the highest rate constant (k) values were recorded for the combination O_3/H_2O_2/UV that, consequently, enabled the shortest half-life time to the active principles. This behavior reinforces the claims that drug removal happens in the early stage of the reaction, and that the process efficiency depends on operating conditions and on oxidizing agent concentrations. Other studies adopted neutral pH and recorded increased drug degradation at the beginning of reactions (HANSEN *et al.*, 2016; KNOPP *et al.*, 2016; MAHMOUD; FREIRE, 2007; RIVAS; BELTRÁN; ENCINAS, 2012; ZIMMERMANN *et al.*, 2011) triggered either by molecular ozone or by OH• radicals formed in O^3/UV, H_2O_2/UV, and O_3/H_2O_2/UV combinations. According to Jiang *et al.* (2010), Rivas, Beltrán and Encinas (2012) and Lim *et al.* (2022), O_3 and UV radiation reacted instantaneously to several pharmaceuticals and to other micropollutants through second-order kinetics, as observed in the current study. It is worth emphasizing that H_2O_2-combined processes recorded first- and second-order degradation kinetics for the same pharmaceuticals.

Overall, oxytetracycline and trimethoprim were more resistant to degradation, whereas UV radiation enabled the lowest rate constants, except for sulfamethoxazole, which was highly sensitive to the UV light. This outcome confirmed the information about photolysis-based sulfamethoxazole degradation described by Alharbi *et al.* (2017). However, the mentioned authors reported increased solution toxicity, which indicated the formation of photolytic products that were more toxic than the original ones, fact that was not reported in the H_2O_2/UV combination. Luo *et al.* (2018) described pseudo first-order kinetics under direct photolysis (254 nm) applied to sulfamethoxazole, both at pH 3 and at 7.55, unlike results observed in the current study, although degradations depend on several factors such as photoreactor and effluent characteristics. This information was corroborated by Kanakaraju, Glass and Oelgemöller (2018), who pointed out that degradation reaction orders change from study to study and that there is no clear consensus about this aspect.

Mondal, Saha, and Sinha (2018) also found second-order kinetics in ciprofloxacin degradation in UV and H_2O_2/UV processes, thus corroborating the

Table 2 – Kinetic parameters of drug degradation reactions, based on the different herein investigated advanced oxidative processes: order of reactions; kinetic constant; correlation coefficient and half-life time.

Process	Pharmaceuticals	Order of reaction	K constant (min^{-1})	Correlation coefficient (R^2)	$t_{1/2}$ (min)
O_3 (0.9 mg)	Caffeine	2	0.4478	0.9272	2.31
	Ciprofloxacin	2	0.0970	0.9436	0.90
	Clindamycin	2	0.6483	0.8323	21.73
	Oxytetracycline	2	0.0641	0.8993	1.97
	Paracetamol	1	0.3346	0.9387	2.07
	Sulfamethoxazole	2	0.0011	0.9938	4.82
	Trimethoprim	2	0.0013	0.9289	25.10
UV	Caffeine	2	0.3939	0.8718	2.63
	Ciprofloxacin	2	0.0070	0.9988	12.48
	Clindamycin	2	0.1192	0.9877	118.16
	Oxytetracycline	2	0.0012	0.9873	105.10
	Paracetamol	1	0.0936	0.9991	7.41
	Sulfamethoxazole	2	0.0529	0.9821	0.10
	Trimethoprim	2	0.0002	0.9070	163.15
O_3/UV	Caffeine	2	0.4730	0.7835	2.19
	Ciprofloxacin	1	0.1441	0.9872	4.81
	Clindamycin	2	0.7704	0.9473	18.28
	Oxytetracycline	2	0.0418	0.9138	3.02
	Paracetamol	2	0.0035	0.9742	1.89
	Sulfamethoxazole	2	0.0952	0.9967	0.06
	Trimethoprim	1	0.0662	0.9955	10.47
H_2O_2/UV	Caffeine	2	1.1006	0.9896	0.94
	Ciprofloxacin	2	0.0890	0.9923	0.98
	Oxytetracycline	2	0.0328	0.9983	3.85
	Paracetamol	1	0.4836	0.9388	1.43
	Sulfamethoxazole	1	0.3626	0.9999	1.91
	Trimethoprim	1	0.1617	0.9911	4.29
O_3/H_2O_2/UV	Caffeine	2	2.0815	0.9804	0.50
	Ciprofloxacin	2	0.2526	0.9889	0.35
	Oxytetracycline	2	0.0703	0.7778	1.79
	Paracetamol	1	0.5267	0.9119	1.32
	Sulfamethoxazole	1	0.4119	0.9367	1.68
	Trimethoprim	1	0.2432	0.9614	2.85

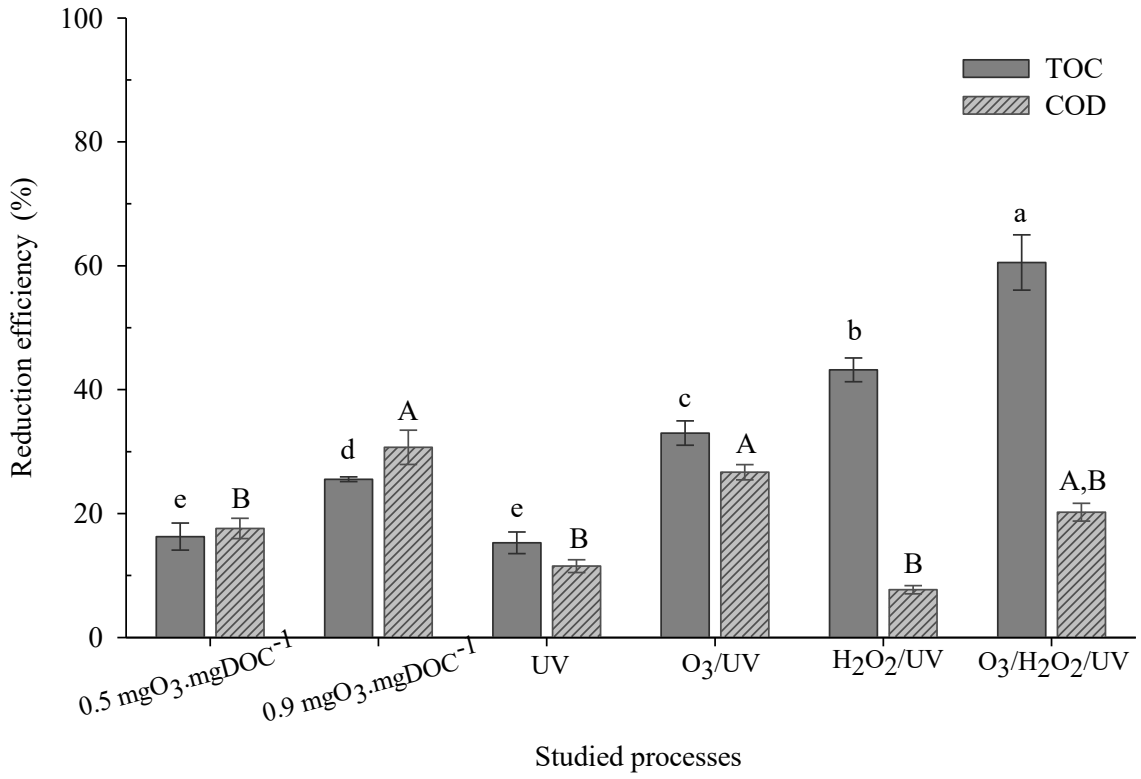
Note: parameters of ofloxacin, sulfadiazine, sulfadiazine, sulfathiazole and tylosin were not presented because these antibiotics were fully removed in the first seconds of all processes, as it happened to clindamycin subjected to H_2O_2/UV and to O_3/H_2O_2/UV; k constant: kinectic constant; $t_{1/2}$: half-life time.
Source: elaborated by the authors.

herein reported results. The mentioned authors also reported that the modified photo-Fenton was the most efficient process, since it enabled full antibiotic degradation (10 mg·L^{-1}) after 30 minutes. Zimmermamm *et al.* (2011) reported that micropollutant oxidations often follow second-order kinetics, mainly when there is O_3 action and combined conditions capable of favoring $OH^{\bullet}$ formation. This kinetics is maintained as long as the concentration of micropollutants does not significantly affect the stability of the oxidant. Therefore, kinetic results recorded in the current study suggested the joint action of direct (due to the action of O_3 and UV radiation) and indirect (due to $OH^{\bullet}$ formation) degradation.

Mineralization and chemical oxygen demand removal analysis

Drug mineralization through AOP was evaluated based on TOC reduction. COD reduction was also evaluated, as shown in Figure 4.

The highest TOC reduction in the effluent was observed in the O_3/H_2O_2/UV process, which presented mean concentration reduction of 60.52%, whereas the lowest reduction (15.28%) was found in the UV process, although it was higher than the 9.6% reduction reported by De la Cruz *et al.* (2013) in sanitary sewage photolysis based on 22 micropollutants. The O_3-based



Note: TOC: total organic carbon; COD: chemical oxygen demand. Data represent the mean and standard error (±). Lowercase letters in TOC data and uppercase letters in COD data indicate significant difference between treatments ($p \leq 0.05$).
Source: elaborated by the authors.

Figure 4 – Efficiency in reducing total organic carbon and chemical oxygen demand through advanced oxidative processes.

treatment at the lowest evaluated dose (0.5 $mgO_3 \cdot mgDOC^{-1}$) did not present TOC reduction statistically different from that of the UV treatment, because, according to Lim *et al.* (2022), complete mineralization of micropollutants is normally not achieved during ozonation. The other treatments presented statistically significant difference from one another; the best results were observed in combination processes. The limited TOC reduction may have been caused by residual organic matter found in the sewage, since it minimizes the action of $OH^{\bullet}$ radicals in the pharmaceuticals, as already reported by Dong, Mezyk, and Rosario-Ortiz (2010) and by Katsoyiannis, Canonica, and Von Gunten (2011). TOC reduction results reported in the current study were higher than that described by Mondal, Saha, and Sinha (2018) in UV-based ciprofloxacin degradation (4.04%), similar to the one obtained by the same authors in the H_2O_2/UV process (35.41%) after 40 minutes of reaction, and to the maximum rate recorded (59.99%) in the modified photo-Fenton treatment.

Márquez *et al.* (2014) also found 60% TOC reduction in a mixture of four pharmaceuticals (atenolol, hydrochlorothiazide, ofloxacin, and trimethoprim) in secondary effluent treated with solar photocatalysis and TiO_2.

There were no statistically significant differences in COD reduction among O_3 (0.9 $mg \cdot mgDOC^{-1}$), O_3/UV, and O_3/H_2O_2/UV processes. In addition, processes based on the lowest O_3 (0.5 $mg \cdot mgDOC^{-1}$), UV, and H_2O_2/UV concentrations showed statistically similar results. However, the O_3/H_2O_2/UV combination was statistically similar to both groups ("A" and "B"). This outcome can be attributed to COD increase caused by H_2O_2 addition, since H_2O_2/UV showed the lowest COD reduction rate (8.17%), whereas the maximum reduction rate (30.69%) was observed in the highest O_3 dose.

According to Quinônes *et al.* (2015), the synergy index (SI) can determine whether the combined processes are more, or less, efficient in drug mineralization than isolated processes. This index is calculated by dividing the mineralization efficiency value recorded for the combined process by the sum of the mineralization efficiency values recorded for isolated processes. SI higher than 1 means that the combined process has positive effect on efficiency, whereas SI lower than 1 indicates that the combined process is less efficient in drug mineralization. This evaluation was applied to O_3/UV processes, such as O_3/UV and O_3/H_2O_2/UV, which resulted from O_3 and H_2O_2/UV combination. Both processes recorded synergy indices higher than 1–1.05 and 1.02, respectively; this outcome indicated that these processes were more efficient in drug mineralization than the isolated methods, as already recorded in the drug removal process. However, O_3 and H_2O_2 concentrations, as well as the reaction time, may not have been enough to form the necessary $OH^{\bullet}$ radicals for drug mineralization, as also observed by Martini *et al.* (2018).

Finally, the O_3/H_2O_2/UV process enabled sanitary sewage disinfection (*Escherichia coli* elimination), mean turbidity reduction by 13.45%, BOD_5 by 15.32%, N_{Total} by 28.94% and slight pH increase from 6.94 to 7.05. There were no significant changes in SS and P_{Total}.

CONCLUSIONS

The current study investigated drug degradation in sanitary sewage based on O_3, UV, O_3/UV, H_2O_2/UV, and O_3/H_2O_2/UV processes. Results showed that antibiotics such as ofloxacin, sulfadiazine, and sulfathiazole were easily degraded through all evaluated processes, likely due to their low concentrations in the effluent. Tylosin was not fully removed by concentration 0.5 $mgO_3 \cdot mgDOC^{-1}$, only. Clindamycin was 100% removed through H_2O_2-combined processes. The O_3/H_2O_2/UV process was the most efficient one in reducing the concentration of all pharmaceuticals during the 15 minutes evaluated; oxytetracycline was the most persistent antibiotic (89.32% removal), and it was followed by caffeine (96.79%), trimethoprim (97.40%), ciprofloxacin (97.75%), sulfamethoxazole (99.79%), paracetamol (99.96%), and by the other pharmaceuticals, which recorded 100% removal. Degradations happened in the early stage of the reaction and mostly followed second-order kinetics. UV radiation enabled the lowest drug reductions when it was applied alone, except for sulfamethoxazole, which was more sensitive to the UV light (254 nm).

Despite the high drug removal efficiencies observed in the current study, the herein investigated O_3 and H_2O_2 doses, at 15-minutes reaction time, were not enough to enable drug mineralization, although the highest TOC reduction (60.52%) was found in the O_3/H_2O_2/UV process and the lowest one, in the UV radiation process (15.28%). Therefore, O_3/H_2O_2/UV combination was the most efficient process among the herein studied conditions, since it enabled substantial reduction of drug concentrations in wastewater to values far below the PNEC.

ACKNOWLEDGMENTS

Thanks to the Federal University of Santa Maria (UFSM) and to the State University of Rio Grande do Sul (UERGS) for the support and facilities.

AUTHORS' CONTRIBUTIONS

Bisognin, R.P.: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft. Wolff, D.B.: Methodology, Project administration, Supervision, Writing – review & editing. Carissimi, E.: Methodology, Project administration, Supervision, Writing – review & editing. Prestes, D.O.: Methodology, Resources, Validation, Formal analysis, Visualization. Zanella, R.: Methodology, Resources, Validation, Visualization.

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