Method Article

Methods involved in the treatment of four representative pharmaceuticals in hospital wastewater using sonochemical and biological processes

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ABSTRACT

A primary pollution source by pharmaceuticals is hospital wastewater (HWW). Herein, the methods involved in the action of a biological system (BS, aerobic activated sludge) or a sonochemical treatment (US, 375 kHz and 30.8 W), for degrading four relevant pharmaceuticals (azithromycin, ciprofloxacin, paracetamol, and valsartan) in HWW, are shown. Before treatment of HWW, the correct performance of BS was assessed using glucose as a reference substance, monitoring oxygen consumption, and organic carbon removal. Meanwhile, for US, a preliminary test using ciprofloxacin in distilled water was carried out. The determination of risk quotients (RQ) and theoretical analyses about reactive moieties on these target substances are also presented. For both, the degradation of the pharmaceuticals and the calculation of RQ, analyses were performed by LC-MS/MS. The BS action decreased the concentration of paracetamol and valsartan by ~96 and 86%, respectively. However, a poor action on azithromycin (2% removal) was found, whereas ciprofloxacin concentration increased ~20%; leading to an RQ value of 1.61 (high risk) for the pharmaceuticals mixture. The analyses using a biodegradation pathway predictor (EAWAG-BDD methodology) revealed that the amide group on paracetamol and alkyl moieties on valsartan could experience aerobic biotransformations. In turn, US action decreased the concentration of the four pharmaceuticals (removals > 60% for azithromycin, ciprofloxacin, and paracetamol), diminishing the environmental risk (RQ: 0.51 for the target pharmaceuticals mixture). Atomic charge analyses (based on the electronegativity equalization method) were performed, showing that the amino-sugar on azithromycin; piperazyl ring, and double bond close to the two carbonyls on ciprofloxacin, acetamide group on paracetamol, and the alkyl moieties bonded to the amide group of valsartan are the most susceptible moieties to attacks by sonogenerated radicals. The LC-MS/MS analytical methodology, RQ calculations, and theoretical analyses allowed for determining the degrading performance of BS and US toward the target pollutants in HWW.

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- Biological and sonochemical treatments as useful methods for degrading 4 representative pharmaceuticals are presented.
- Sonochemical treatment had higher degrading action than the biological one on the target pharmaceuticals.
- Methodologies for risk environmental calculation and identification of moieties on the pharmaceuticals susceptible to radical attacks are shown.
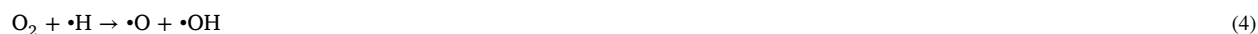
Specifications table

Subject area:	Environmental Science
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Name of your method:	*Biological and sonochemical methods to remove four representative pharmaceuticals in actual hospital wastewater*
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Introduction

After consumption, parent pharmaceuticals and their metabolites are excreted by the patients in hospitals reaching the urban sewage systems, which then are usually treated in municipal wastewater treatment plants, or directly discharged into the environment [2,3]. This last case is the most concerning one because of the potential negative effects of pharmaceuticals on ecosystems. In some developing countries, direct discharge into the environment is a very common practice [1]. Then, hospital wastewater (HWW) is known as a pollution hotspot by pharmaceuticals.

Pharmaceuticals such as azithromycin, ciprofloxacin, paracetamol, and valsartan are highly consumed and they are very common in HWW [4–8]. For instance, azithromycin, ciprofloxacin, paracetamol, and valsartan have been found in HWW from Latin American countries in the ranges of 0.40-11.63, 0.17-185.28, 0.56-667.79, and 0.04-0.79 µg L^{-1}, respectively [9]. In turn, for European HWW, azithromycin, ciprofloxacin, and paracetamol have been reported at levels of 10-10^3, 10^{-2}-10^2, and 1-10^3 µg L^{-1}, respectively [4,10]. Hence, such compounds can be used as markers of water pollution by pharmaceuticals [6–8].

To control the input of pharmaceuticals from HWW into the aquatic environment, effective treatments are required. Biological and sonochemical processes could be used. Biological systems, which comprise the action of microorganisms, are able to remove the organic matter in water susceptible to biotransformations (e.g., sugars, lipids, and proteins [11], even some pharmaceuticals). In turn, the sonochemical system is a useful process to eliminate organic pollutants recalcitrant to biological systems. Sonochemical treatment involves the action of hydroxyl radicals generated by acoustic cavitation [12]. In this process, high-frequency (200-1000 kHz) ultrasound waves)))] induce the cleavage of water vapor and oxygen molecules Eqs. 1-(4), producing hydroxyl radicals that can degrade the organic contaminants [12].

$$H_2O +))) \rightarrow \bullet H + \bullet OH \tag{1}$$

$$O_2 +))) \rightarrow 2 \bullet O \tag{2}$$

$$H_2O + \bullet O \rightarrow 2 \bullet OH \tag{3}$$

$$O_2 + \bullet H \rightarrow \bullet O + \bullet OH \tag{4}$$

Considering the issues caused by the direct discharge of HWW, biological and sonochemical systems have been tested to treat pharmaceuticals in HWW and limit their input into the environment [1]. Herein, the methods involved in the biological and sonochemical processes focused on the degradation of representative pollutions indicators (azithromycin, ciprofloxacin, paracetamol, and valsartan) in an HWW, considering the environmental risk and possible transformations, are presented. The methods and procedures are detailed below.

General procedure

Prior to the application of the treatments based on aerobic microorganisms (BS) or high-frequency ultrasound (US), the initial environmental risk associated with the target pollutants in HWW must be determined. Also, control tests using reference substances should be carried out to verify the correct performance of the experimental systems for BS and US. After verification of the proper

performance of the systems, the treatments of the HWW sample are assessed, following the evolution of pollutants by chromatographic techniques and calculation using risk quotients. Moreover, two specialized software are utilized to run theoretical analyses and obtain information about biotransformations and susceptible regions to attacks by sonogenerated radicals.

Materials, equipment, and analyses

Reagents and HWW sample

The raw HWW sample was collected from a local hospital in Tumaco-Colombia. The raw sample was directly taken from the effluent of the hospital, during one typical day of operation. This sample was preserved at 4°C until the application of the treatments. The HWW sample was used after no more than a week of the sampling. Before use, the raw sample was shaken vigorously and then submitted to settle by gravity for 1 h. This last HWW sample was used for the treatments, and it had 210 mg L^{-1} of chemical oxygen demand, 132 mg L^{-1} of total organic carbon (TOC), pH 7.3, and 1.6 mS cm^{-1} of conductivity. These quality parameters of HWW were determined according to Standard methods as reported in reference [1]. Pharmaceutical standards for the LC-MS/MS analyses were acquired from Sigma-Aldrich, LGC Promochem, Toronto Research Chemicals, Across Organics, Bayer Hispania, and Aventis Pharma. Potassium hydrogen phthalate (which was used for the TOC analyses) and glucose were obtained from Merck.

Biological system

For the biological system an aerobic mixed liquor, coming from a classical activated sludge process (CAS), was obtained from the local wastewater treatment plant in Medellín-Colombia and it was used as the source of microorganisms. Fresh mixed liquor was kept settling for 2 h; then, the supernatant liquid was utilized as the inoculum for biological treatment. At 400 mL of the HWW sample were added 25 mL of supernatant liquid of mixed liquor. The biological process was carried out on a Velp Scientifica system (F10240137, typically used for biological oxygen demand analyses) at 22°C and under constant stirring, monitoring the oxygen consumption (which was measured manometrically each 12 h) and determining the TOC removal and the concentration of the target pharmaceuticals after 36 h of treatment [1]. The experiments were performed at least by duplicate and the average values are reported, and the variation coefficients were lower than 10%.

Sonochemical system

For the sonochemical treatment, a Meinhardt Ultrasound reactor (containing 350 mL of the HWW sample to be treated) at 375 kHz of frequency and 30.8 W of acoustic power was utilized. The ultrasound reactor had an external jacket, which allows for recirculation of cold water using a Huber Minichiller, keeping the temperature of the reactor controlled at 20 ± 2°C. The acoustic power inside the ultrasound reactor was determined by the calorimetric methodology [13]. The HWW sample was treated for 1.5 h in the ultrasound reactor. The residual concentration of the target pharmaceuticals was determined using LC-MS/MS. Moreover, the TOC removal was also monitored in the ultrasound-based treatment. The experiments were performed at least by duplicate and the average values are reported and the coefficients of variation were lower than 5%.

Instrumental analyses details

The samples were kept at temperature < -18 °C until analyses. Quantification and monitoring evolution of the pharmaceuticals concentrations were performed by LC-MS/MS, injecting 100 μL of the centrifuged and 2-fold diluted HWW sample (no pre-concentration by SPE was needed) in the LC-MS/MS system (Waters Acquity UPLC interfaced to a triple quadrupole mass spectrometer Xevo TQS (Waters) equipped with an orthogonal Z-spray electrospray ionization interface (ESI) operated in positive mode). An Acquity UPLC BEH C18 column (1.7 μm, 100mm× 2.1mm) and a gradient mobile phase water/methanol (both 0.01% formic acid and 1mM ammonium acetate), at a flow rate of 0.4 mL min^{-1}, were utilized. Analyte isotope-labelled internal standards (analyte-ILIS) were added to the samples for matrix effects correction. Three MS/MS transitions were acquired for each compound, one-commonly the most abundant- for quantification (Q), and two more for confirmation (q1, q2) of the identity by evaluation of q/Q ratios and retention time (Rt) agreement in comparison with reference standards. Quality control (QCs) samples, consisting of wastewater spiked with the target pharmaceuticals at 0.1 and 1 μg L^{-1}, were analyzed together with the batch of samples for quality control of analyses [1,14].

TOC removal was measured through combustion with catalytic oxidation at 680°C (according to Standard methods 5310 B), in a Shimadzu TOC-L analyzer equipped with a non-dispersive infrared detector, using high-purity air as combustion gas and potassium hydrogen phthalate as a reference standard.

Theoretical analyses details

The microbial biotransformation routes of target pharmaceuticals were obtained through the Pathway Prediction System (PPS) from the EAWAG. The predictions are done considering biotransformation rules on the EAWAG-BBD database and the scientific literature [15]. Atomic charge analyses for the target pharmaceuticals were performed using the atomic charge calculator (ACC). ACC is a user-friendly computational tool for the determination, visualization, and analysis of atomic charges for small druglike molecules, using the electronegativity equalization method [16]. The calculations were carried out by uploading the structure of the pharmaceuticals in SDF format on the ACC website and using a B3LYP/6-31G* level of theory [17].

Table 1

Data for the risk assessment for the target pharmaceuticals in the HWW to be treated. RQ_i: risk quotient for individual pharmaceuticals in HWW, $RQ_{mix, in}$: risk quotient associated with the initial mixture of four pharmaceuticals in HWW.

Pharmaceutical	MEC* ($\mu g\ L^{-1}$)	PNEC* ($\mu g\ L^{-1}$)	RQ_i
Azithromycin	27.9	0.019	1.58
Ciprofloxacin	10.7	0.500	0.02
Paracetamol	293.8	6.920	0.05
Valsartan	17.7	0.250	0.08
$RQ_{mix, in}$			1.72

* MEC: initial concentration in the HWW sample. *PNEC values were taken from [24].

Determination of the environmental risk of the target pharmaceuticals in the HWW sample

For the determination of the environmental risk, the concentration (MEC) of target pharmaceuticals in the HWW sample is initially measured by LC-MS. After the MEC determination, the predicted environmental concentration (PEC) which is required for HWW directly discharged into the environmental water, should be calculated using the dilution factor (DF) for the specific country where the wastewater is released (Eq. 5). Then, the risk quotient (RQ_i), which is defined as the ratio between PEC and the predicted no-effect concentration (PNEC, this can be taken from literature), is estimated as shown in Eq. 6. Then, the environmental risk is categorized according to the RQ values as follows: RQ ≤ 0.1: low risk; 0.1 < RQ ≤ 1: moderate risk, and RQ > 1: high risk [9]. As we deal with a mixture of pollutants, the individual RQ is insufficient to evaluate the actual environmental risk, because the mix of pharmaceuticals may jointly affect the aquatic biota [18,19]. Hence, an equivalent risk quotient for the target substances together (RQ_{mix}) must be assessed using Eq. 7, to provide wider a panorama of the environmental hazard associated with this kind of matrix.

$$PEC = MEC/DF \tag{5}$$

$$RQ_i = PEC/PNEC \tag{6}$$

$$RQ_{mix} = \Sigma RQ_i \tag{7}$$

In the specific case of the tested HWW, paracetamol (also named acetaminophen) had the highest MEC (Table 1), which was similar to those concentrations reported for HWW from Mexico and Brazil [20–22]. Meanwhile, the concentrations of the other three pharmaceuticals were ~10-fold lower than paracetamol. More important than MEC is the environmental risk associated with pharmaceuticals, which is determined by the RQ value. Then, to obtain RQs, the PEC values were calculated using Eq. 5, with a DF of 929.87 for Colombia [23]. The corresponding RQ values for the target pharmaceuticals in the tested HWW are presented in Table 1. Also, the RQ_{mix} was determined. It can be noted that only azithromycin had a high risk (RQ_i: 1.58). Moreover, the RQ_{mix}, associated with the four target pharmaceutical together, was 1.72, indicating that this mixture has a high risk because RQ_{mix} was larger than one [18,19]. Hence, due to the environmental risk shown by the pharmaceuticals in HWW, two different processes (i.e., a biological or a sonochemical), to deal with these substances, were tested.

Treatment of the target pharmaceuticals in HWW by the biological process

Before the application of the aerobic biological method (BS) to HWW, a control test for the experimental system is performed, using glucose (at 40 mg TOC L^{-1}, glucose is a reference substance for biodegradation [25,26]) and measuring oxygen consumption. Once the proper performance of microorganisms is established, the BS is applied to the HWW sample for 36 h, also monitoring the oxygen consumption. To study the BS action, the ratio between the oxygen consumed by the microorganisms and the initial TOC of HWW is calculated, and such a ratio is compared with that for glucose control (Table 2). Besides, the removal action of BS (after 36 h) on the four target pharmaceuticals is evaluated making use of LC-MS/MS analyses as detailed above in the Materials, equipment, and analyses section. Furthermore, the theoretical analysis of microbial biotransformation on the removed pharmaceuticals is carried out using the PPS system. Then, a comparison with the literature is required to support the predicted biotransformations.

For the glucose control, it was found an oxygen consumption of 140 mg $O_2\ L^{-1}$, confirming that the aerobic microorganisms worked well. As glucose has a biodegradable nature its consumed oxygen/initial TOC ratio was 3.5 (Table 2). Interestingly, the HWW showed a ratio of 11.6, indicating that this sample contained a high amount of biodegradable organic matter (e.g., sugars, lipids, or proteins/amino acids, which are typically at higher concentrations than pharmaceuticals in wastewater [27,28]). Besides, the BS decreased the concentration of paracetamol and valsartan but it was not able to induce a significant removal of azithromycin (Table 2). Additionally, the BS action increased the ciprofloxacin concentration from 10.7 to 23.5 $\mu g\ L^{-1}$. These results observed for azithromycin

Table 2

Action of the biological process on the HWW. RQ_{BS}: risk quotient for individual pharmaceuticals after application of the biological treatment to HWW, $RQ_{mix, BS}$: risk quotient associated with the mixture of four pharmaceuticals after application of the biological treatment to HWW, and TOC: total organic carbon.

Control test of the biological system				
Sample	Consumed oxygen / initial TOC			
Glucose	3.5			
HWW	11.6			
Removal of pharmaceuticals in the HWW by the biological system (BS)				

Pharmaceutical	Residual concentration after BS action ($\mu g\ L^{-1}$)	Removal (%)	RQ_{BS}	Change in RQ (RQ_{BS} - RQ_i)*
Azithromycin	27.33	2.05	1.55	-0.03
Ciprofloxacin	23.48	-119.45	0.05	0.03
Paracetamol	11.48	96.09	0.00	-0.04
Valsartan	2.19	85.93	0.01	-0.07
$RQ_{mix, BS}$: 1.61				
TOC removal: 92.2 mg L^{-1}				

* RQ_i: initial risk quotient as defined in Table 1.
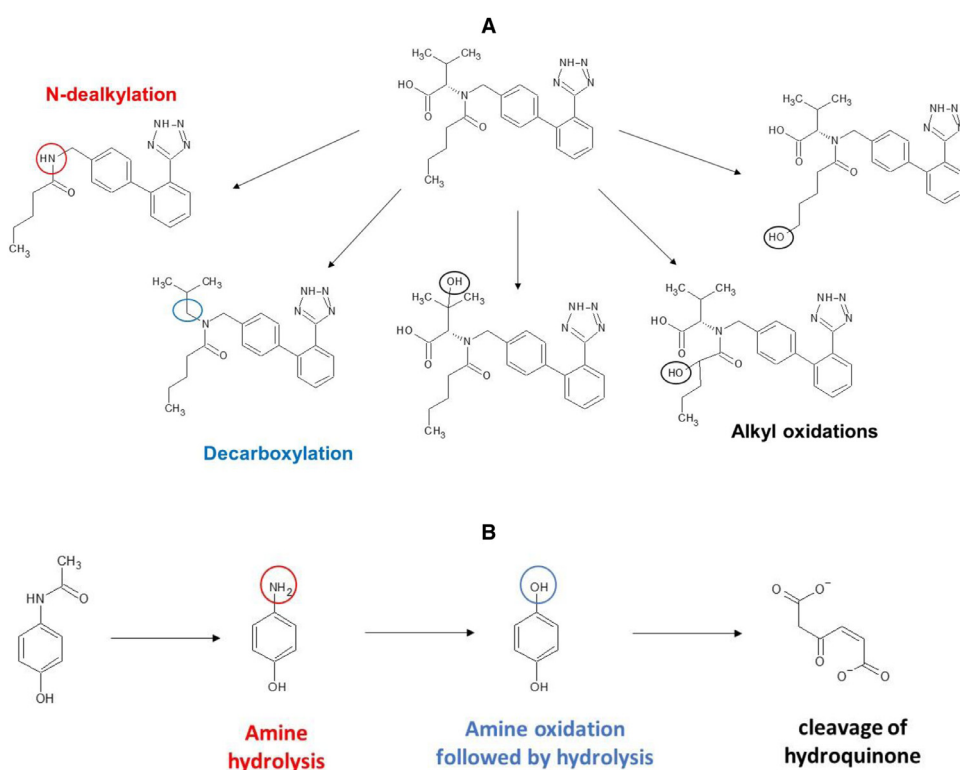
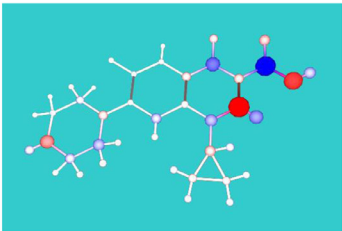Fig. 1. Predicted aerobic biotransformation pathways. **A.** Valsartan [33]. **B.** Paracetamol [31].

and ciprofloxacin can be linked to their antibiotic/bactericidal properties that could block the action of the microorganisms on such pharmaceuticals [29].

On the other hand, the increase in ciprofloxacin concentration can be related to the deconjugation of the metabolites, which may be present in the HWW [30], toward the parent antibiotic. Also, some molecules of ciprofloxacin could come from the employed aerobic mixed liquor (which is obtained from a municipal treatment plant where other sewages containing ciprofloxacin are treated). In the case of paracetamol and valsartan, the removal experienced by the biological treatment can be ascribed to their biodegradable nature (Fig. 1). This can be explained by considering the predicted biodegradation pathways (obtained with the EAWAG-BDD). Bio-transformation pathways for paracetamol showed an amide hydrolysis to produce aminophenol, which evolves toward hydroquinone
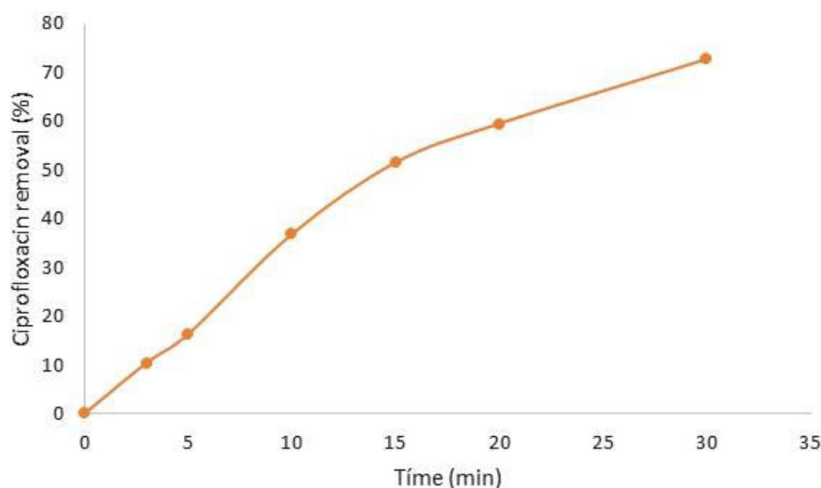
Fig. 2. Ciprofloxacin degradation in distilled water. Experimental conditions: Ciprofloxacin: 1.0 mg L^{-1}, frequency: 375 kHz, acoustic power: 30.8 W, V: 350 mL.

Table 3
Action of the sonochemical process (US) on the target compounds in HWW. RQ$_{US}$: risk quotient for individual pharmaceuticals after application of the sonochemical treatment to HWW, RQ$_{mix, US}$: risk quotient associated with the mixture of four pharmaceuticals after application of the sonochemical treatment to HWW, and TOC: total organic carbon.

Pharmaceutical	Residual concentration after US action (μg L^{-1})	Removal (%)	RQ$_{US}$	Change in RQ (RQ$_{US}$ - RQ$_i$)
Azithromycin	7.72	72.32	0.44	-1.14
Ciprofloxacin	4.03	62.36	0.01	-0.01
Paracetamol	24.30	91.73	0.00	-0.04
Valsartan	14.41	18.58	0.06	-0.01
RQ$_{mix, US}$: 0.51				
TOC removal: 27.3 mg L^{-1}				

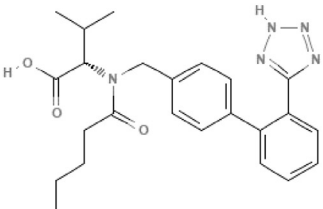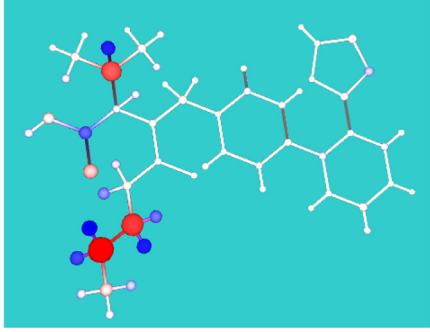*RQ$_i$: initial risk quotient as defined in Table 1.
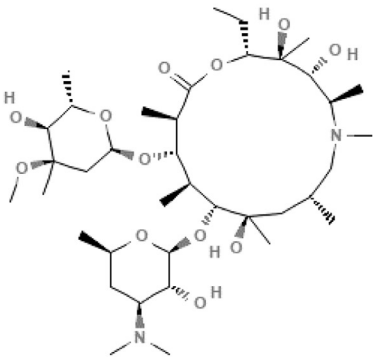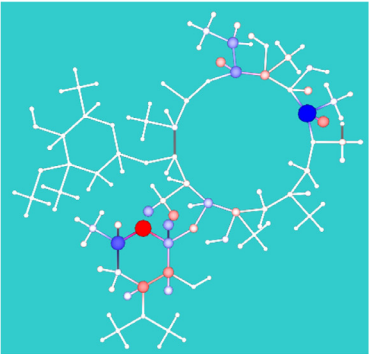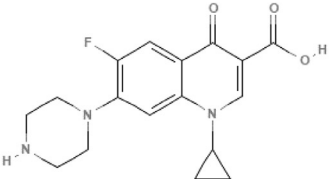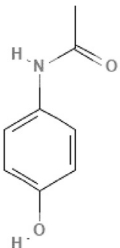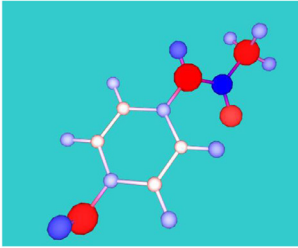
with the subsequent generation of short-chain carboxylic acids [31]. We should mention that the information provided by the pathways prediction system agreed with the experimental results for the paracetamol biodegradation reported in the literature [32]. Besides, the predicted biotransformation pathways for valsartan suggested that this pharmaceutical is susceptible to N-dealkylation, decarboxylation, and alkyl oxidation by the primary action of aerobic microorganisms [33]. Interestingly, the well-known experimental biotransformation of valsartan into valsartan acid involves N-dealkylation followed by subsequent amide hydrolysis and hydrolysis/oxidation stages [34,35], which is consistent with the pathways obtained by the predictor system used herein.

Treatment of the target pharmaceuticals in HWW by the sonochemical process

The use of the sonochemical system for degrading pharmaceuticals in complex aqueous matrices should follow this order: i) testing the system performance by the treatment of a standard solution of one of the target substances under fixed conditions of power and frequency (e.g., 30.8 W and 375 kHz) in distilled water (control experiment); ii) performing the treatment of the HWW matrix, and iii) evaluating the change in the concentration of the pharmaceuticals using LC-MS/MS, and then, calculating the mineralization degree (by measuring the TOC removal) and decreasing of the environmental risk associated to the pollutants (applying Eqs. (6) and (7)).

Herein, the control experiment considering ciprofloxacin alone (at 1mg L^{-1}) in distilled water was performed using the sonochemical process. Fig. 2 depicts the ciprofloxacin evolution. It can be noted that ~75% of the antibiotic concentration was decreased after 30 min of sonication, thus confirming the capability of the considered sonochemical process to degrade pharmaceuticals in aqueous media. Afterward, the HWW sample was submitted to the US action, determining the residual amount of the pharmaceuticals after 1.5 h of treatment (Table 3). The concentration of the four target pollutants decreased. This was associated with the attack of the sonogenerated HO•, which is a non-selective species and it can degrade the target pharmaceuticals [1], as well as other organic com-

Table 4

Atomic charge analyses for the target pharmaceuticals.

Chemical structure of pharmaceuticals	Atomic charge analyses results*
Azithromycin	
Ciprofloxacin	
Paracetamol	
Valsartan	

* Atoms having red color represent the moieties most susceptible to attacks by radicals. Meanwhile, atoms in grey and blue have low possibilities to be attacked.

ponents present in the HWW (as denoted by the TOC removal: 27.3 mg L^{-1}). Furthermore, the RQ$_{mix, US}$ value was also diminished up to 0.51; i.e., the sonochemical process was able to reduce the environmental risk associated with the target pharmaceuticals from high (see RQ$_{mix, in}$ in Table 1) to moderate (see RQ$_{mix, US}$ in Table 3). On the other hand, to better understand the degrading action of the US treatment, theoretical analyses, for identifying the moieties on the pharmaceuticals susceptible to attacks by the sonogenerated hydroxyl radical, were carried out, and the resultant information is presented in the next section.

Identification of moieties on the pharmaceutical susceptible to attacks by the sonogenerated radicals

A theoretical method, based on electronegativity equalization method (EEM) principles, is applied to identify the regions on the pharmaceuticals susceptible to attacks by electron-deficient species such as the sonogenerated hydroxyl radicals. This strategy involves the upload of the structure of the molecules in SDF format to the online "atomic charge calculator" freeware (website address detailed in the reference method [17]), obtaining the results of atomic charges on molecules (as illustrated in Table 4). It is important to remark that atomic charges describe the distribution of electron density in a molecule [16]. To support the predictive capability of the theoretical method, the results are contrasted with information in the literature about the primary transformations of the pollutants by the action of HO•.

Table 4 presents the results of atomic charges for the target pollutants. Based on the atomic charge analysis, for azithromycin, the amino-sugar group seems to be the moiety most susceptible to radical attacks, which is consistent with the transformations induced on this antibiotic by processes based on the hydroxyl radical action [36]. For ciprofloxacin, piperazyl ring and double bond close to the two carbonyl groups are the most reactive sites according to the atomic charge analysis, which agrees with previous reports about the degradation of this pharmaceutical by attacks of HO• [37],[38]. In the case of paracetamol, the acetamide group is the most susceptible moiety to the action of radical species [39]. In turn, the alkyl moieties bonded to the amide group of valsartan have the highest electron-rich regions susceptible to transformations, which fits well with the primary by-products reported for the sonodegradation of valsartan [40].

Final remarks

The LC-MS/MS methods, RQ calculations, and theoretical analyses allowed for determining the degrading performance of BS and US toward the target pollutants in the considered HWW. The initial mixture of the four target pharmaceuticals had a high environmental risk. Consequently, the HWW, containing the representative pollutants, was treated using BS or US processes individually. The biological system decreased the concentration of paracetamol, valsartan, and biodegradable organic matter, but BS had no removal of azithromycin and ciprofloxacin, thus retaining the environmental risk. The biodegradation pathways prediction revealed the moieties of paracetamol and valsartan that could experience aerobic biotransformations. In contrast to BS, the sonochemical process induced degrading effects on the four target contaminants, and then changed the environmental risks from high to moderate. Besides, atomic charge analyses allowed us to elucidate the electron-rich moieties on the target pollutants susceptible to attacks by radicals, which was consistent with transformations reported in the literature. Finally, it is important to remark that this work tested only one HWW sample, therefore providing a partial view of the action of BS and US. Considering this limitation, HWW samples collected on several days and from different hospitals should be evaluated in future works.

Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Efraím A. Serna-Galvis: Investigation, Conceptualization, Methodology, Data curation, Formal analysis, Software, Writing – original draft. **Javier Silva-Agredo:** Conceptualization, Methodology, Writing – review & editing. **Félix Hernández:** Conceptualization, Formal analysis, Methodology, Writing – review & editing. **Ana M. Botero-Coy:** Conceptualization, Formal analysis, Methodology, Writing – review & editing. **Ricardo A. Torres-Palma:** Conceptualization, Resources, Funding acquisition, Writing – review & editing.

Data Availability

Data will be made available on request.

Acknowledgments

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