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Elimination of cephalexin and doxycycline under low frequency ultrasound

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ABSTRACT

Cephalexin (CPX) and doxycycline (DOX) are two of the most used antibiotics to treat bacterial infections in human medicine, veterinary practices, animal husbandry, agriculture, aquaculture, among others. Nevertheless, due to their excessive consumption and incomplete absorption during their metabolization, they have been detected in different environmental matrices and the effluents of wastewater treatment plants, which reflects that conventional water treatment methods are not enough to eliminate this type of compounds. This paper presents the main results about the removal of the antibiotics CPX and DOX under low frequency (40 kHz) ultrasonic radiation (US). The effects of operational parameters such as the solution initial pH and the applied US power were assessed considering the response surface methodology and a face centered, central composite experimental design. The results indicated that evaluated operational factors significantly affect the pollutants elimination and that US technology is able to remove them completely. In addition, in terms of mineralization, experimental results showed a reduction of the organic carbon present in the solutions and a significant increase of ions (nitrates and sulfates) concentration, suggesting that part of the organic matter was transformed into CO_2, H_2O and inorganic species. Finally, results regarding the samples toxicity indicated that ultrasonic treatment could promote a significant reduction in this parameter, and the potential negative effect associated to CPX and DOX presence in water bodies.

1. Introduction

β-Lactam and tetracyclines are worldwide highly consumed antibiotics, which has led to their introduction into different bodies of water, including the influents and effluents of wastewater treatment plants, surface waters and even drinking water [1–4].

Cephalexin (CPX) belongs to the β-lactam family. This pharmaceutical compound is used widely to treat infectious diseases caused by bacteria on skin, throat, tonsils, and the urinary tract [5,6]. On the other hand, Doxycycline (DOX) is a tetracycline with potent antibacterial activity [7]. It is used to treat infections caused by bacteria, including pneumonia and other respiratory tract infections; some infections of the skin and eyes; and also infections of the lymphatic, digestive, reproductive and urinary systems [8]. CPX and DOX might be released into surface waters and ground waters due to incomplete metabolism (in animals) and discharges from drug manufacturers, a situation that could lead to the development of antibiotic-resistant microorganisms, and eventual adverse impacts on human health through potential endocrine disruption and toxic by-products generation [6,9–11].

Different techniques have been evaluated for the potential treatment of water containing antibiotics. Technologies such as chemical oxidation, ionic treatment, photodegradation, adsorption, and electrochemical process have been studied. However, in some cases these methods could present some limitations including low pollutants extent of elimination, and the potential production of more toxic intermediate substances [2,12,13].

Ultrasound (US) is a novel advanced oxidation technology (AOT) used in the treatment of water contaminated with organic products that are not treatable by conventional techniques due to its high chemical stability and low biodegradability [14]. In addition, US has unique advantages such as no addition of chemicals, and differential or selective degradation according to the pollutant nature. US mechanims of action include the production of the hydroxyl free radical (Ho•), a powerful oxidant agent (E°=2.8 V) capable of oxidizing a wide range of organic compounds [15].

Ultrasound refers to sound waves with frequencies above the

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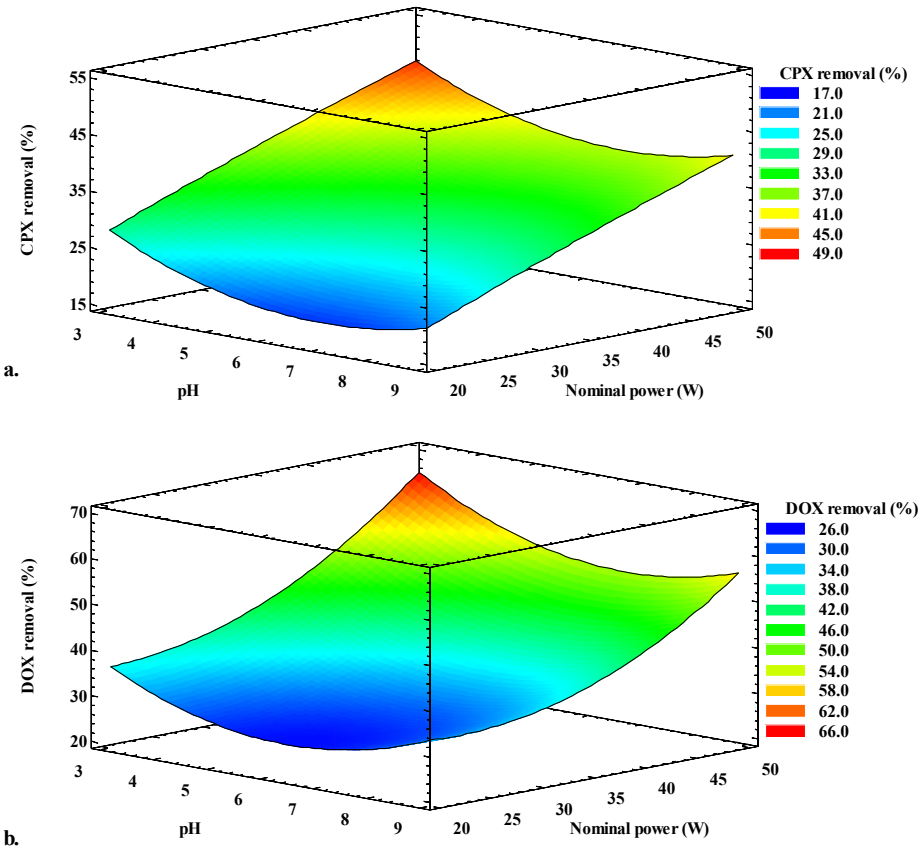


Fig. 1. Estimated response surface for a. CPX and b. DOX removal using ultrasound (pollutants initial concentration: 2.0 mg L^{-1}, temperature: 25 ± 2 °C, frequency: 40 kHz, reaction time: 30 min).

Table 1
Experimental levels evaluated in the removal of CPX and DOX using US.

Factor	Level		
	Low	Medium	High
pH	3.0	6.0	9.0
Nominal applied power (Watts)	20.0	35.0	50.0

detected by the human ear. It is ranged from 20 to 10000 kHz. Typically, ultrasound is divided into three regions according to frequency: (1) low, (2) high, and (3) very high. Low and high ultrasound frequencies are used in chemical processes, whereas very high frequency is applied in medical diagnostics. When high-intensity ultrasound waves interact with dissolved gases in liquid medium, acoustic cavitation (formation, growth, and implosive collapse of bubbles) it is promoted [15,16]. Ultrasound waves consist of compression and expansion cycles. During the expansion, waves having the sufficient intensity to exceed the molecular forces of the liquid generate bubbles. These bubbles continually absorb energy from alternating compression and expansion ultrasound cycles. Thus, bubbles grow (by diffusion of vapor or gas from the liquid medium) until they reach a critical size and then collapse. The bubble collapse acts as a localized "hot spot" with singular conditions of temperature (>5000 K) and pressure (>1000 atm), and short life [17].

In aqueous solutions, hydroxyl and hydrogen radicals are formed from the thermal dissociation of water vapor (equation (1)), and the reaction with oxygen (equations 2–5) [18,19]. Once generated, HO• radicals can migrate from the inside of the cavitation bubble to the rest of the solution and oxidize the organic matter.

$$H_2O +))) \rightarrow H\bullet + HO\bullet \quad (1)$$

$$O_2 \rightarrow 2O \quad (2)$$

$$H\bullet + O_2 \rightarrow HOO\bullet \quad (3)$$

$$O + H_2O \rightarrow 2HO\bullet \quad (4)$$

$$H\bullet + O_2 \rightarrow HO\bullet + O \quad (5)$$

Sonochemical pollutants removal could take place at three different zones: (1) in the bulk solution, (2) in the interface cavitation bubble-

Table 2
Operating conditions and mobile phases employed for the quantification of CPX and DOX using HPLC.

Analyte	Mobile phase	Flow type	Flow rate (mL min^{-1})	Column average temperature (°C)	Injection volume (mL)	Mobile phase relation	Retention time (min)
Cephalexin	A: Water (0.1% v/v formic acid) B: Acetonitrile	Gradient	0.55	35.0 ± 1.0	50.0	A:B 90:10 for 4 min, then A:B 30:70 for 1 min and finally, A:B 90:10 for 4 min.	~5.45
Doxycycline	A: Acetonitrile B: Water (0.5% v/v acetic acid) C: Methanol	Isocratic	0.80	25.0 ± 1.0	50.0	A:B:C 25:55:20 for 5 min.	~2.25

Table 3
Experimental design for CPX and DOX elimination (pollutants initial concentration: 2.0 mg L^{-1}, temperature: 25 ± 2 °C, frequency: 40 kHz, reaction time: 30 min).

Test	Solution pH	Nominal applied power (W)	CPX removal (%) experimental	CPX removal (%) calculated by model	DOX removal (%) experimental	DOX removal (%) calculated by model
1	3.0	50.0	47.0	47.4	65.8	65.8
2	9.0	20.0	21.2	20.9	32.6	32.9
3	6.0	35.0	31.3	29.5	32.4	32.5
4	3.0	20.0	29.6	28.0	34.5	36.4
5	9.0	35.0	32.7	31.4	36.4	37.5
6	3.0	35.0	37.1	38.3	45.9	44.0
7	6.0	35.0	28.7	29.5	31.8	32.5
8	6.0	20.0	17.2	19.1	28.6	26.4
9	6.0	35.0	28.3	29.5	32.5	32.5
10	9.0	50.0	39.3	40.9	57.9	56.4
11	6.0	50.0	40.8	38.8	51.4	52.8

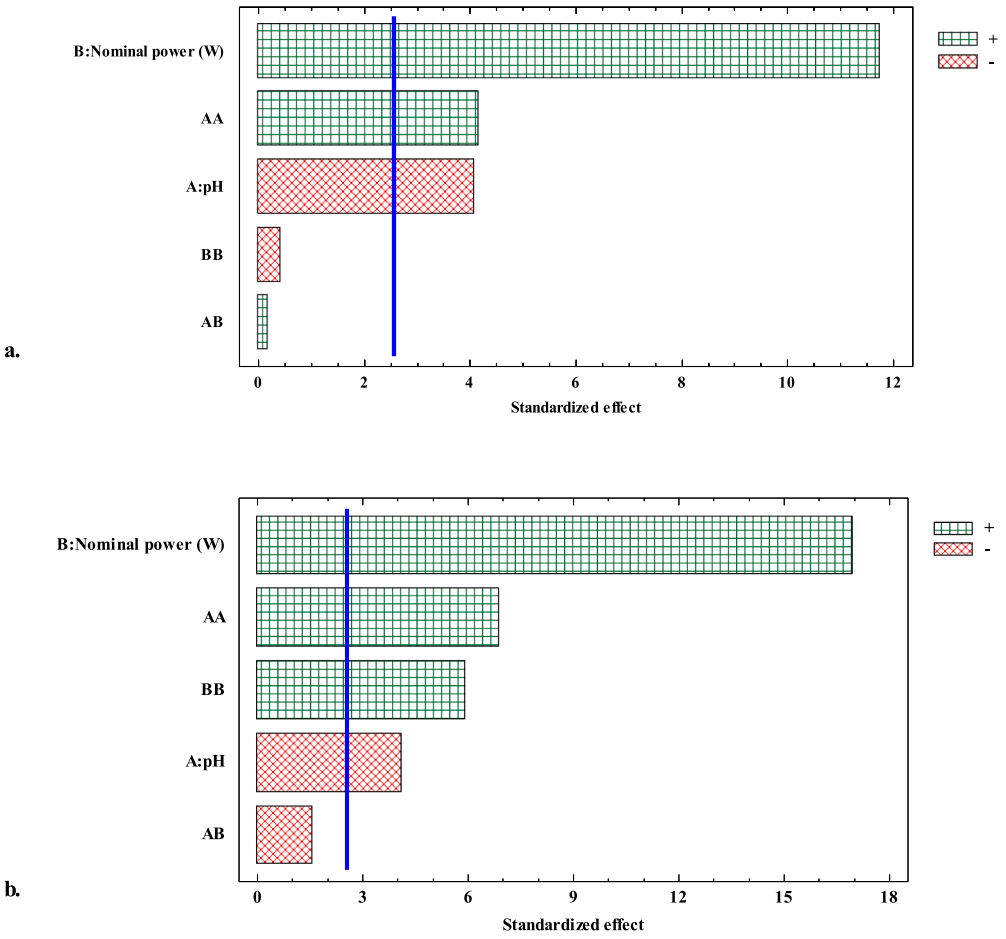


Fig. 2. Pareto charts for a. CPX and b. DOX removal using ultrasound (pollutants initial concentration: 2.0 mg L^{-1}, temperature: 25 ± 2 °C, frequency: 40 kHz, reaction time: 30 min).

solution, and (3) inside of the cavitation bubble. In this way, hydrophilic substances place in the bulk solution, hydrophobic nonvolatile compounds accumulate in the interfacial zone, while volatile substances would be inside of the cavitation bubbles. According to this, the removal of hydrophilic compounds would be promoted by hydroxyl radicals that reach the bulk solution after the bubble collapse. Hydrophobic nonvolatile compounds are eliminated in the interfacial zone by radical attacks and/or thermal reactions, and volatile pollutants are pyrolyzed inside the bubbles [17].

Having into the account the above, and the fact that there are not consolidated or deep results regarding the use of ultrasound on CPX and DOX elimination in aqueous solutions; the main aim of this study was to evaluate the potential application of low frequency US in the removal of CPX and DOX considering the effects of the solution pH, the applied US power and the pollutant initial concentration. In addition samples extent of mineralization and toxicity were evaluated.

2. Materials and methods

2.1. Chemicals

CPX ($C_{16}H_{17}N_3O_4S$) and DOX ($C_{22}H_{24}N_2O_8$) chemical standards containing>98.0% of pure compounds were purchased from AK Scientific and used as received. All the aqueous solutions were prepared using ultra-pure water (Milli-Q water, 18.2 MΩ cm). Solutions pH adjustments were done with concentrated solutions of NaOH (0.1 N) and HCl (1.0 N)

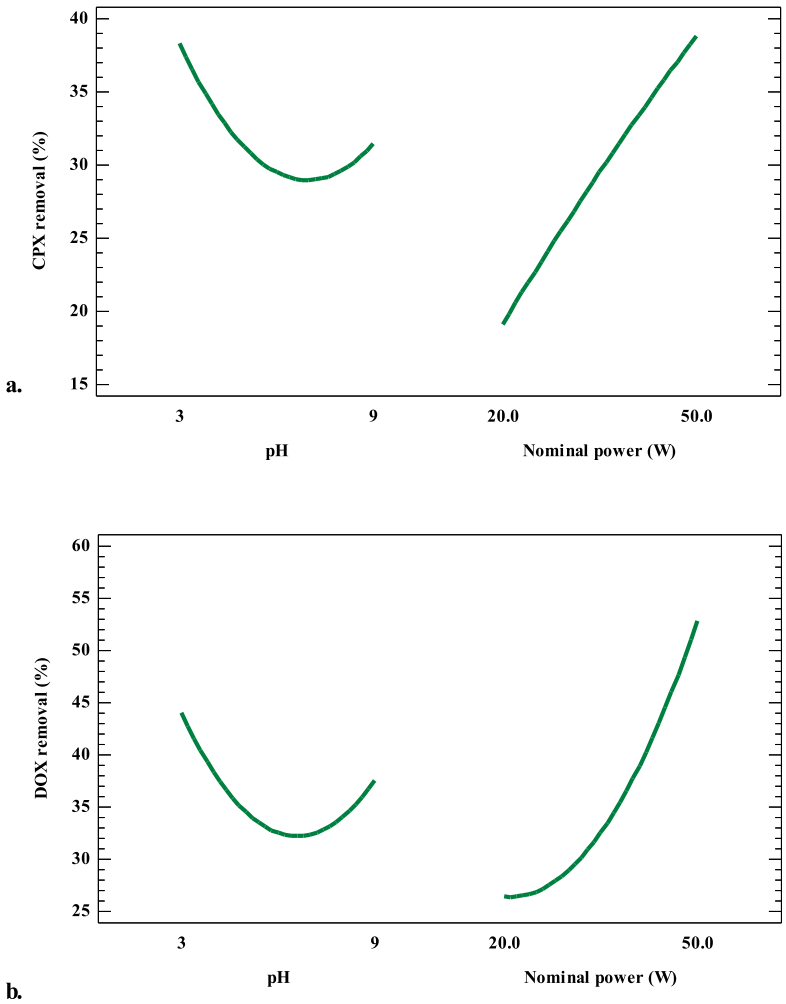


Fig. 3. Main effects plot for a. CPX and b. DOX removal (pollutants initial concentration: 2.0 mg L^{-1}, temperature: 25 ± 2 °C, frequency: 40 kHz, reaction time: 30 min).

Table 4
Physicochemical properties of CPX and DOX (NIST database, 2021).

Property	CPX	DOX
Water solubility (mg L^{-1}), 25 °C	1789.0	312.9
Henry's law constant (atm m^3 mol^{-1}), 25 °C	$2.77x10^{-17}$	4.66×10^{-24}
Octanol/water partition coefficient (Log k_{ow})	0.65	−0.02

obtained from Alfa-Aesar. The role of the HO• free radicals on pollutants removal was assessed using isopropyl alcohol (C_3H_8O, 99.8% w/w, Merck). HPLC-grade acetonitrile, methanol, acetic acid, and formic acid were used for chromatographic analysis.

2.2. Sonochemical reactor

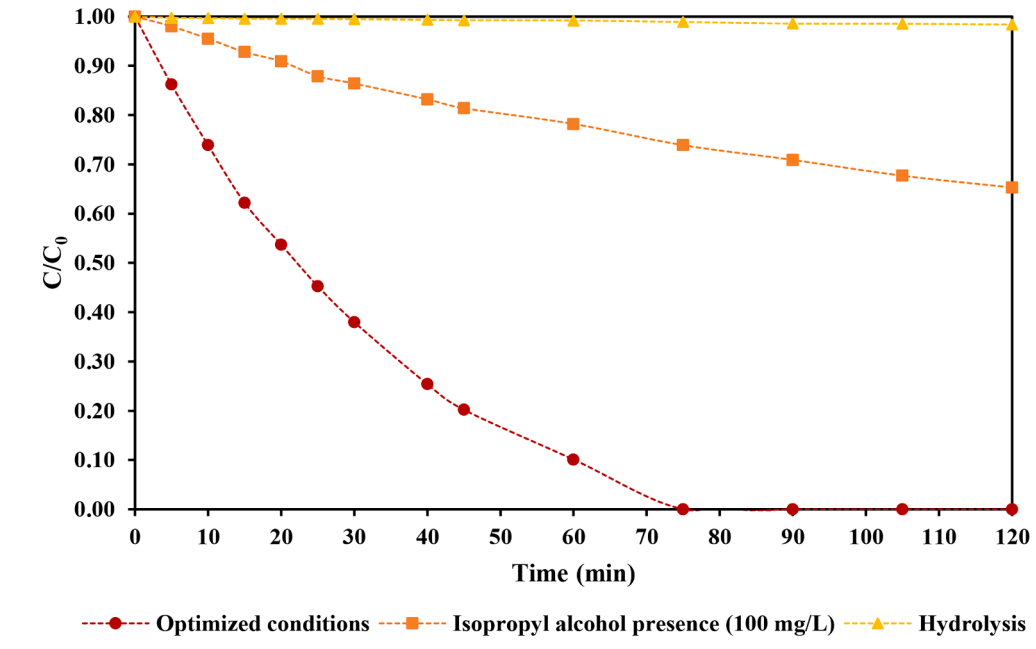
Experiments were carried out using a 40 kHz ultrasonic transducer with a variable power generator (maximal nominal power 50.0 W). The transducer was coupled to the bottom of a cylindrical glass reactor with a maximum capacity of 500 mL (Meinhardt Ultrasonics, Germany). The calorimetric method [20] was conducted to determine the real power dissipated into the solution during the ultrasonic reaction. In this way, the experimental results (Fig. 1 Supplementary material) indicated that approximately 83.33% of the power is transmitted to the solution and the rest is lost mainly in form of heat. Solution temperature was kept at 25 °C using a water-cooling bath. CPX and DOX initial concentration in most of the experiments was 2.0 mg L^{-1} (condition that allowed to satisfy the requirements of the analytical methods in terms of precision, accuracy, detection and quantification limits). A volume of 300 mL of reaction solution was used in each experiment and samples of 1.0 mL were withdrawn at different time intervals during the reaction.

2.3. Preliminary tests

Different authors have reported that the performance of the oxidation reactions in sonochemical treatments is associated with the effect of the chemically active cavitation, which is related to the effectiveness of the formation, growing and imploding of the cavitation bubbles and with the ability of the pollutant molecules to diffuse into the exterior and the interior of the bubble [21,22]. The implementation of US process should consider the control and variation of different operating parameters such as the solution pH, the applied US power and the ultrasonic frequency since they can promote the production of HO• [18,23]. In this sense, some preliminary tests were carried out to establish the experimental range of the solution initial pH and the applied US power that conduct to significant antibiotics eliminations (>50.0%). Tests were done varying the applied nominal power between 10.0 and 50.0 W under a natural solution pH (~6.0) during 30 min of reaction.

2.4. Experimental design

Table 1 shows the experimental levels that were considered to



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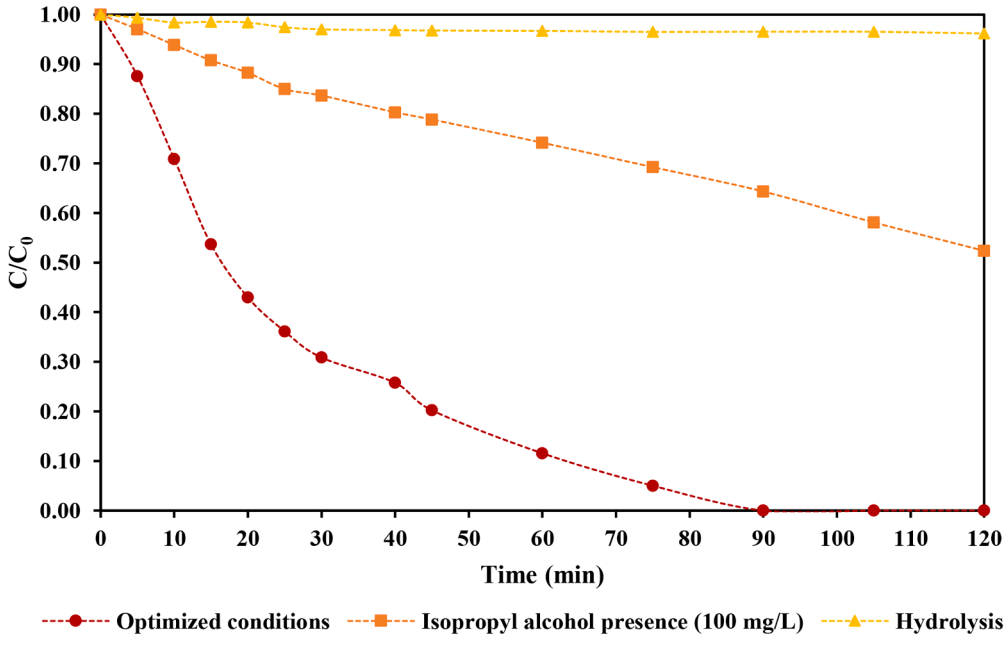


b.

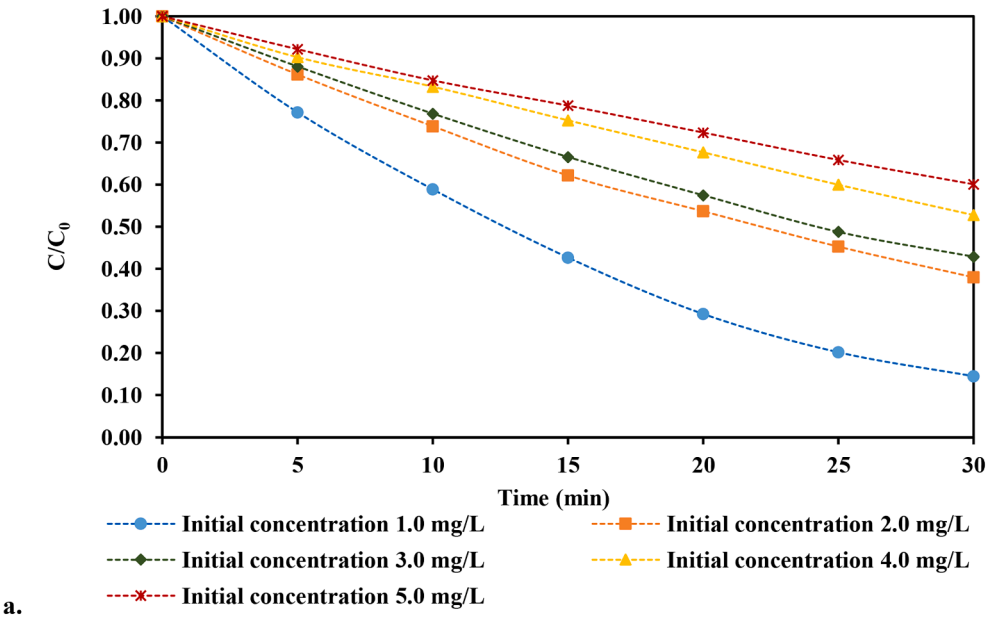
Fig. 4. Antibiotics elimination under optimized conditions a. CPX y b. DOX (pollutant initial concentration: 2.0 mg L^{-1}, pH: 3.0, US applied power: 50.0 W, frequency: 40 kHz, temperature: 25 ± 2 °C).

evaluate the effectiveness of the US technology in the removal of CPX and DOX (selected after analyzing the results of the preliminary tests). The response surface methodology based on a face-centered, central composite design was employed to determine the conditions that favor higher pollutants eliminations under the evaluated experimental conditions after 30 min of ultrasonic treatment. Statistical analysis of data was performed using the Statgraphics Centurion XVI software at a confidence level of 95%. In addition, to clarify the mechanism of reaction hydrolysis and tests under the presence of a scavenger agent were carried out. Finally, to investigate the effect of each pollutant initial concentration on reaction, experiments were conducted by varying this parameter in the range 1.0–5.0 mg L^{-1}. All tests were conducted in triplicate and coefficients of variation of the data were below 5%.

2.5. Analytical methods

2.5.1. Pollutants concentration determination

CPX and DOX concentrations in aqueous solutions were determined by reverse phase chromatography using an Agilent 1100–1200 series HPLC system. A Kinetex C18 column (silica 100 Å pore diameter, 2.5 µm, 4.6 × 150 mm), and a diode array detector (DAD) set to 261.4 nm were employed to quantify CPX. Likewise, a Phenomenex C18 column (120.0 Å pore diameter, 5.0 µm, 4.00 × 125.0 mm), and a DAD set to 325 nm were used for DOX determination. Table 2 presents the operating conditions and mobile phases employed for quantification of the studied antibiotics.



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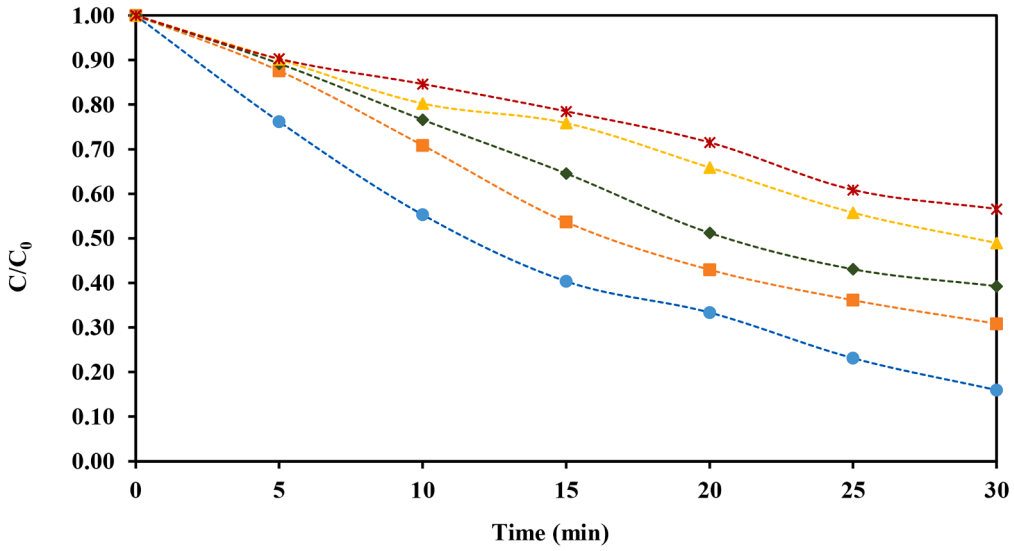


b.

Fig. 5. Effect of initial concentration: a. CPX and b. DOX removal using ultrasound (pH: 3.0, applied power 50.0 W, frequency: 40 kHz, temperature 25 ± 2 °C).

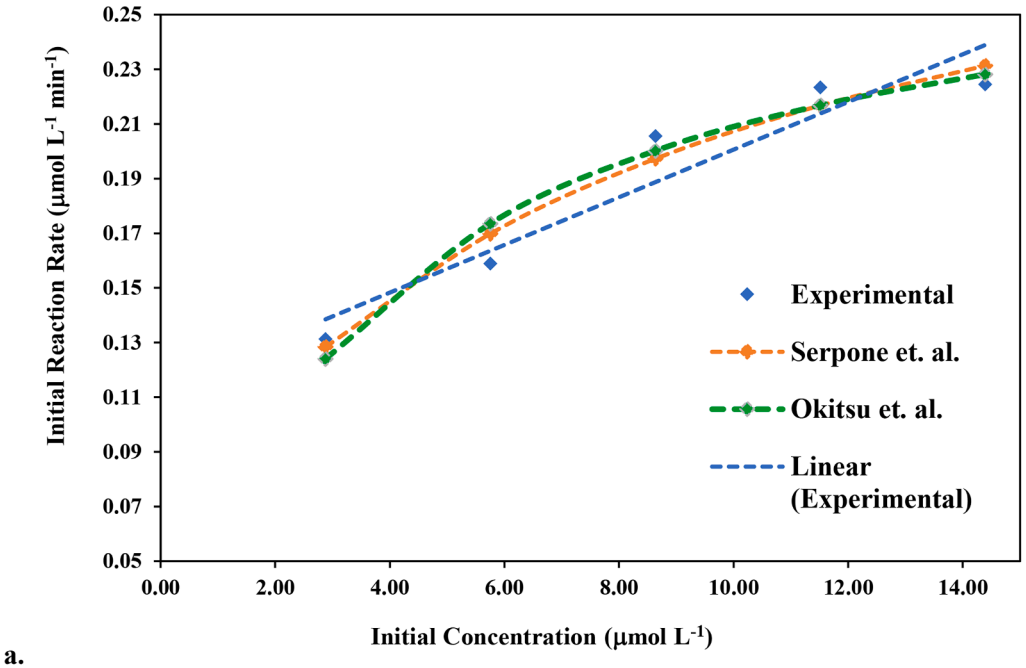
2.5.2. Total organic carbon and anions analysis

Oxidation of the organic matter was evaluated measuring the total organic carbon (TOC) content in the treated samples using an APOLLO 9000 combustion TOC analyzer (Teledyne Tekmar). The methodology of analysis was the high combustion temperature method described by the *Standard Methods for the Examination of Water and Wastewater* (2017) [47], method (5310B). In addition, the total oxidation of CPX and DOX could conduct to an increase in the nitrates and sulfates presence in the solutions. In this way, NO_3^{-1} and SO_4^{-2} were evaluated using a Dionex Integration HPLC system (Thermo Scientific). The methodology adopted was the Ion chromatography with chemical suppression of effluent conductivity, analytical method described by the *Standard Methods for the Examination of Water and Wastewater* (2017) [47], method (4110B).

2.5.3. Toxicity analysis

Samples toxicity was studied using a Microtox model 500 analyzer (Modern Water), which is an *in vitro* testing system that uses bioluminescent bacteria (*Vibrio fischeri*) to detect toxic substances. Toxicity assays measure the decrease in the natural luminescence of the bacteria. The presence of toxic substances reduces the light emission level.

Toxicity is expressed as the effective concentration EC_{50} (pollutant concentration producing a 50% reduction in the light emission).



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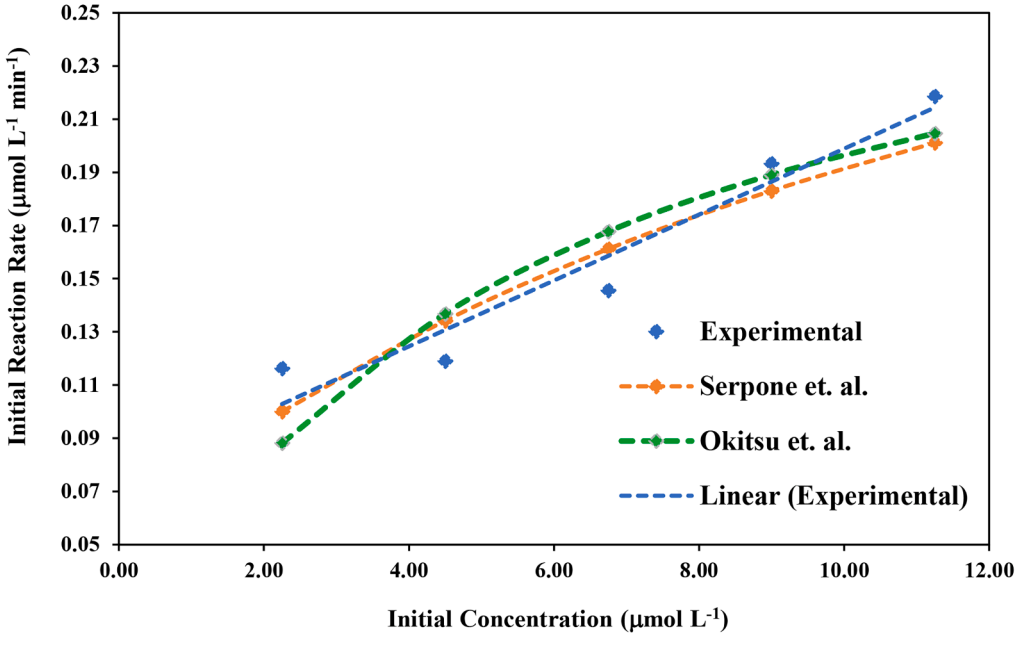


b.

Fig. 6. Initial degradation rate as function of the initial concentration: a. CPX and b. DOX and with predicted values (pH of the solution: 3.0, applied power: 50.0 W, frequency: 40 kHz, temperature: 25 ± 2 °C).

3. Results and discussion

3.1. Antibiotics removal using low frequency ultrasound

The effects of the solution initial pH and the applied power on antibiotics removal using ultrasound were evaluated according to the levels indicated by Table 1. Likewise, Table 3 shows the matrix design and the response factor, corresponding to the substrates extent of degradation after 30 min of reaction; while Fig. 1 shows the response surface obtained after carrying out the experiments. Both, Table 3 and Fig. 1, indicate that the initial pH and the applied power affect the CPX and DOX removal, and allow to infer the conditions that could promote higher degradations.

In order to optimize the reaction conditions, it was necessary to evaluate which variables and interactions between them affect significantly each substrate elimination. Fig. 2 corresponds to the Pareto charts. According to this, the variables and interactions that can be considered significantly important for CPX removal are: pH (A), the square of the pH (AA) and power (B). In addition, this figure indicates that the applied power and the square of the pH have a positive effect on pollutant elimination, while the pH has a negative effect. Likewise, the solution initial pH and the applied power, together with its square interactions (AA y BB) were the factors with significant influence on DOX removal, and it can be observed from Fig. 2b that the pH has a negative effect. In general, these results could be associated with the interactions between the evaluated factors, the radical species generation, and the

Table 5
Parameters of the models of pseudo first order, Okitsu et al. (2005) and Serpone et al. (1994) in the CPX and DOX ultrasonic treatment.

Model	Parameters	Cephalexin	Doxycycline
Pseudo first-order model	k_0 (min^{-1})	0.0087	0.0124
	R^2	0.9057	0.9339
Okitsu et al.	k_0 ($\mu mol\ L^{-1}\ min^{-1}$)	$0.28879 \pm 5.1819 \times 10^{-5}$	$0.30572 \pm 7.9139 \times 10^{-5}$
	K ($L\ \mu mol^{-1}$)	$0.26163 \pm 2.8499 \times 10^{-5}$	$0.18013 \pm 1.7899 \times 10^{-5}$
	R^2	0.9182	0.9504
Serpone et al.	k_0 ($\mu mol\ L^{-1}\ min^{-1}$)	$0.27353 \pm 8.2243 \times 10^{-6}$	$0.33542 \pm 2.6701 \times 10^{-4}$
	K ($L\ \mu mol^{-1}$)	$0.11925 \pm 6.2241 \times 10^{-5}$	$0.06837 \pm 2.4167 \times 10^{-4}$
	K_b ($\mu mol\ L^{-1}\ min^{-1}$)	$0.05849 \pm 4.3764 \times 10^{-5}$	$0.05528 \pm 3.0756 \times 10^{-5}$
	R^2	**0.9579**	**0.9841**

properties of the target contaminants.

To clarify the role of each evaluated parameter, the individual effects of the applied US power and the solution initial pH on CPX and DOX removal were analyzed. Fig. 3 corresponds to the main effects plot for pollutants removal under the selected experimental conditions. From this figure, it can be seen that higher US power levels promote a higher elimination of CPX and DOX. These results could be associated to the fact that under higher US applied powers the amount of generated HO• radicals could be higher due to an increment in the number of formed cavitation bubbles and its eventual collapse. In addition, under higher US applied power, the radicals could be distributed uniformly in the solution (more movement of the fluid) [24]. However, some authors have reported that excessive increases in the applied power could provoke a negative effect on organic compounds elimination as a result of an oversaturation of bubbles in the solution, and less implosion. Furthermore, bubbles could not be able to expand during the rarefaction stage of the acoustic cycle causing a potential decrease in the generation of the hydroxyl radicals [25–27].

On the other hand, changes in the solution pH could lead to changes in the solubility of the substrates [28]. The main effects plot (Fig. 3) shows the effect of the initial pH of the solution on the removal of CPX and DOX. From this figure, it can be seen that CPX and DOX removals in aqueous solutions are strongly dependent on pH value. Table 4 shows some of the physicochemical properties of the studied antibiotics. CPX and DOX are non-volatile compounds and the region of sono-decomposition would be at the cavitation bubble interface and/or at the bulk solution. According to the Henry's law constants, CPX and DOX have low volatility and therefore cannot be degraded by pyrolysis inside the cavitation bubbles. In contrast, these antibiotics have relatively high solubility in water and low octanol/water partition coefficients,

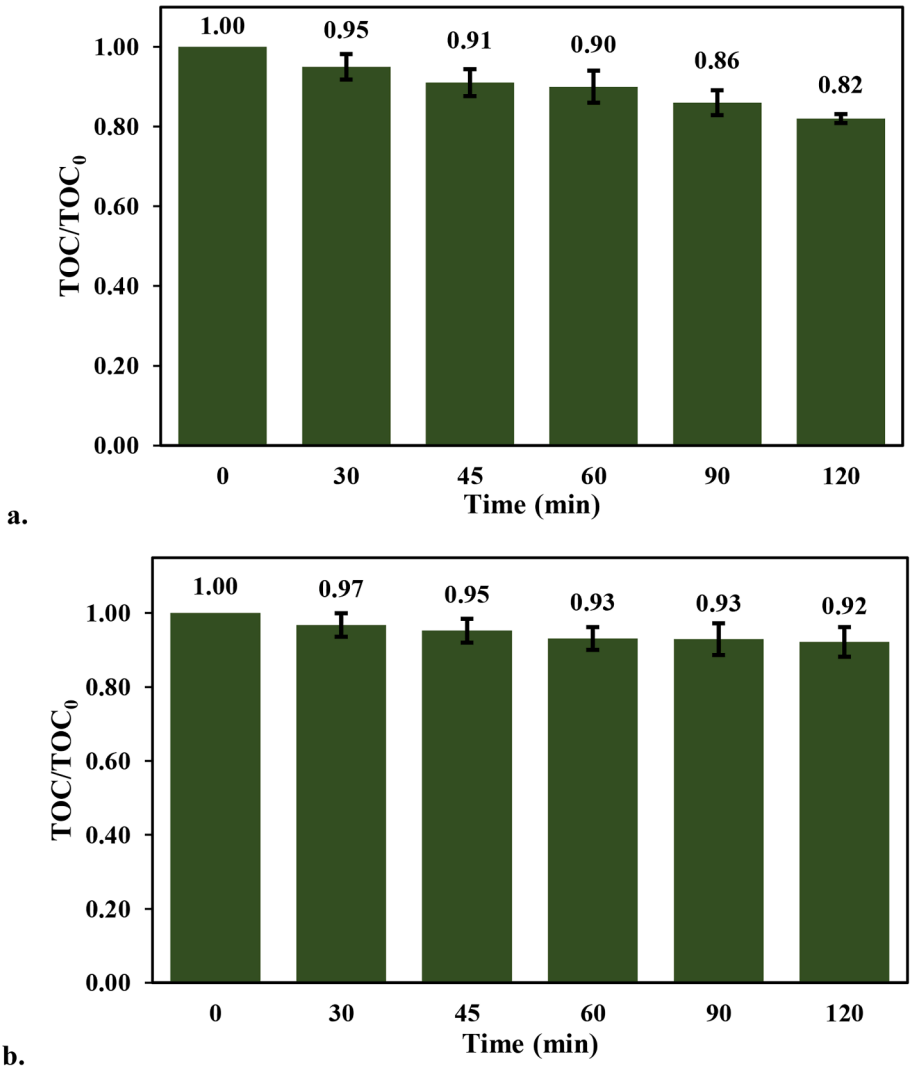


Fig. 7. Total organic carbon variation during a. CPX and b. DOX removal under optimized conditions using US (pH of the solution: 3.0, applied power: 50.0 W, frequency: 40 kHz, temperature: 25 ± 2 °C).

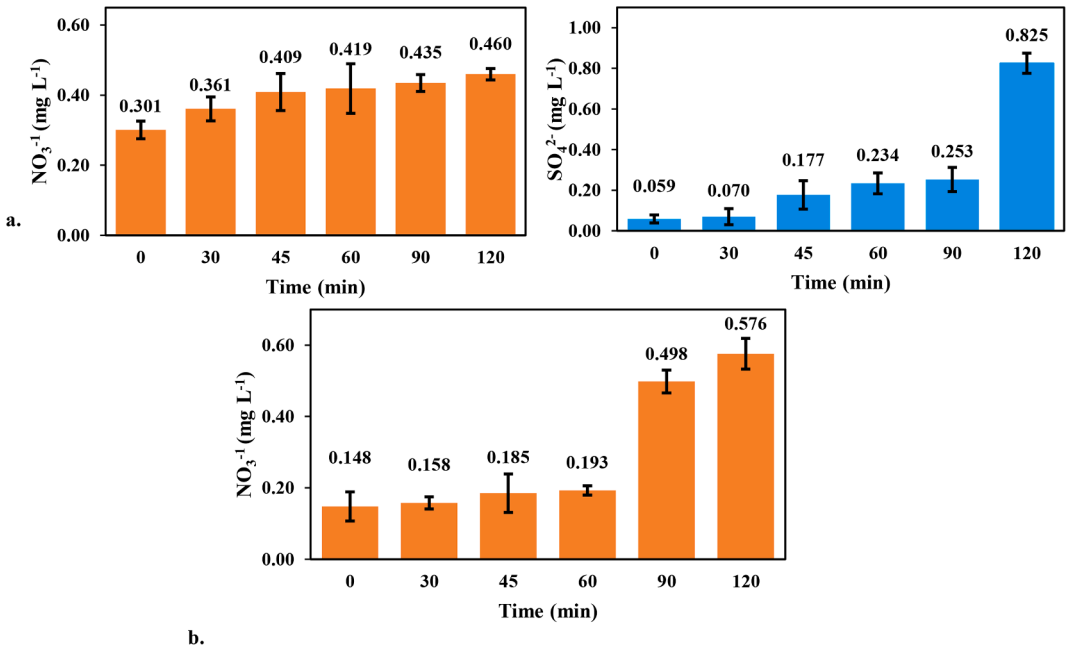


Fig. 8. a. Nitrate and sulfate ions concentration during CPX removal b. Nitrate ion concentration during DOX removal using US under optimized conditions (pH of the solution: 3.0, applied power: 50.0 W, frequency: 40 kHz, temperature: 25 ± 2 °C).

indicating that these could distribute at the interface and the bulk solution regions. In this way, the HO• radicals generated by US would be the main species responsible for the pollutant degradation, which most probably occurs not only in the bulk solution but also on the bubble–liquid interfacial region where hydroxyl free radical concentration could be higher [29–32]. In addition, DOX is less soluble than CPX, this implies that the antibiotic will be closer to the interfacial region, which favors its elimination (higher presence of radicals), and could explain the different results presented by the Fig. 3 (more DOX removal in comparison with CPX).

CPX has two pKa values (logarithm of acid dissociation constant), one at 6.88 and other at 2.56 [33], and exists in zwitterionic form in solution when the pH is between 2.56 and 6.88. In regard to the results presented by Fig. 3a, ionic forms of CPX (at pH 3.0 and 9.0), favor its removal, while a more stable nature (zwitterionic form) could imply less reactivity and an eventual lower oxidation. The primary attacks of HO• to CPX molecule could occur on three sites: 1) the β-lactam ring, which is a highly reactive site because the ring is very strained and the carbonyl-nitrogen bond is very labile (hydroxylation reaction); 2) the aromatic ring, which typically experiences electrophilic substitutions; 3) and in the secondary amide moiety, whose reactivity towards oxidants can be favored through the inductive and resonant effects generated by the substituents (oxidative reaction), besides, by the charge level in the medium [34–36].

On the other hand, DOX has three pKa values (3.50, 7.07 and 9.13) [37]. In the range of 3.50–7.07, DOX exists in zwitterionic form which could imply less reactivity. At pH 3.0 and 9.0 the cationic and anionic form of DOX could promote its removal, as it is shown by Fig. 3b, but high pH conditions may create more free radical scavengers leading to an eventual decrease of the available hydroxyl radicals, and a reduction of DOX removal at pH 9.0 in contrast with results obtained under pH 3.0 (this situation also could apply for results regarding CPX removal under alkaline pH conditions). In addition, according to some researchers, the hydroxyl radical could promote either the loss of atoms and functional groups located at the doxycycline molecule periphery or the breakdown of its aromatic rings. In this way, substitution or addition reactions in these sites, where the antibiotic is less stable could occur [7,38].

Statistical analysis of results allowed to obtain a model that relates the dependent factor with the significant factors and interactions after 30 min of sonochemical treatment. In this way, after a nonlinear regression, using the statistical software Statgraphics Centurion XVI, were obtained the reduced models represented by equations (6) and (7). The coefficients of each term in the polynomial expressions indicate the weight of the variable/interaction under the processes.

$$\text{CPX removal (\%)} = 32.69 - 8.42[\text{pH}] + 0.79[\text{power}] + 0.59[\text{pH}]^2 + 0.003[\text{pH}][\text{power}] - 0.002[\text{power}]^2 \quad (6)$$

$$\text{DOX removal (\%)} = 72.94 - 10.94[\text{pH}] - 1.14[\text{power}] + 0.91[\text{pH}]^2 - 0.03[\text{pH}][\text{power}] + 0.03[\text{power}]^2 \quad (7)$$

[pH] is the solution initial pH and [power] is the nominal applied US power.

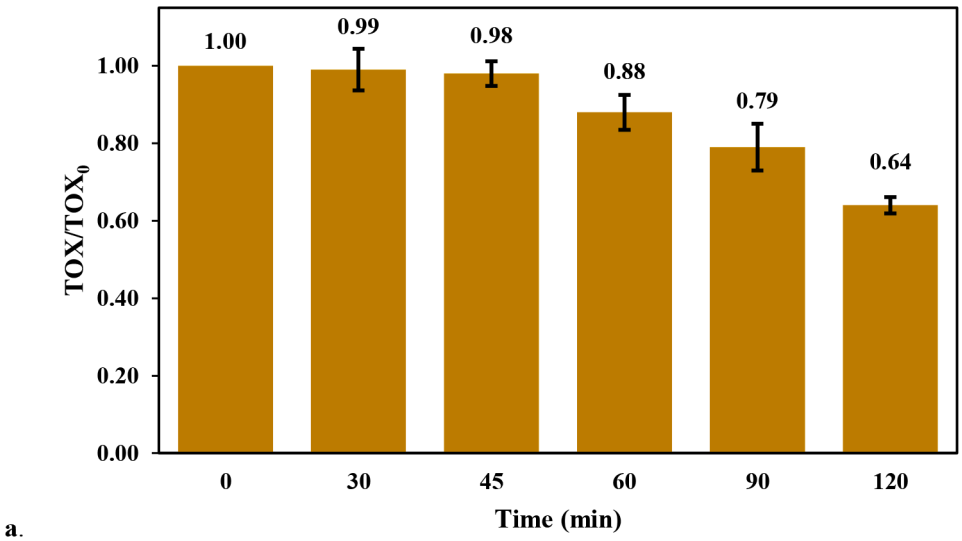
Table 3 shows the comparison between the experimental results and those predicted by the models. As it can be noted, the proposed polynomial expressions predict the experimental results adequately. Coefficients of determination (R^2) were 97.1% and 98.8% for CPX and DOX removal, respectively.

Based on the exposed results, the conditions under the evaluated experimental range that lead to higher CPX and DOX removals are 50 W nominal power and solution pH 3.0.

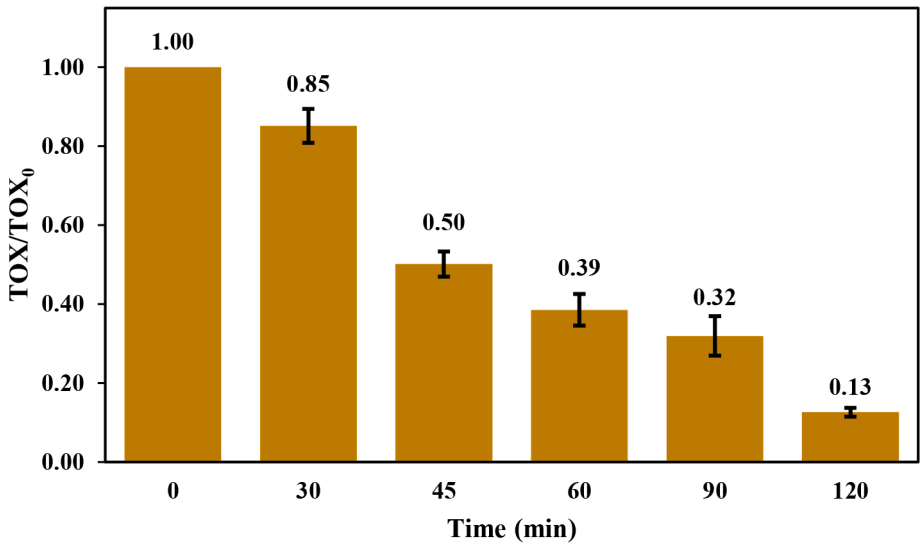
3.2. Antibiotics removal under optimized conditions

CPX and DOX ultrasonic elimination was studied considering the established optimized conditions. Experimental results are shown by Fig. 4. From this figure, it is possible to appreciate that in the case of CPX, pollutant was removed completely in 75 min of treatment, while the removal of DOX was reached after 90 min. In addition, hydrolysis experiments (at pH 3.0) indicated that after 120 min, substrates removal was just 1.6% and 3.8% for CPX and DOX respectively, which represents that antibiotics elimination is negligible in the absence of US application.

In addition, to clarify the role of HO• radicals on CPX and DOX removal, some tests were carried out under the presence of isopropanol which is known as a good HO• free radicals scavenger. Fig. 4 shows that alcohol inhibits substrates removal markedly, suggesting that HO• radicals are the main oxidizing agent of CPX and DOX under the evaluated experimental conditions.



a.



b.

Fig. 9. Toxicity variation during a. CPX and b. DOX removal under optimized conditions using US (pH of the solution: 3.0, applied power: 50.0 W, frequency: 40 kHz, temperature: 25 ± 2 °C).

3.3. Effect of antibiotics initial concentration

In order to investigate the effect of the CPX and DOX initial concentrations on each reaction, experiments were performed by varying this parameter in the range 1.0–5.0 mg L^{-1} (2.8–14.5 μmol L^{-1} for CPX and 2.2–11.2 μmol L^{-1} for DOX). The concentration variation profiles are shown by Fig. 5. From the figure, it can be appreciated that the extent of CPX and DOX elimination (C/C_0) is inversely proportional to the pollutant initial concentration. In this sense, organic pollutants removal using ultrasound irradiation can be described using a pseudo first-order reaction kinetic model (Equation (8)) [39–41]. However, as it is shown by Fig. 6, in both cases, a complete linear relationship was not observed for a first-order kinetic law and pollutants elimination could not be characterized by a single rate constant.

$$r = \frac{-dC}{dt} = k_0 C \tag{8}$$

where, r is the initial degradation rate (μmol L^{-1} min^{-1}), k_0 is the pseudo-rate constant (min^{-1}) and C is the pollutant initial concentration (μmol L^{-1}).

On the other hand, some researches have studied different kinetic models for sonochemical degradation of non-volatile compounds. These models based on a Langmuir type mechanism have suggested that substrates elimination is related to the amount of radicals and the pollutants concentration [18,42]. In this way, the sonochemical degradation of some substrates have been described using the kinetic model proposed by Okitsu et al. (2005) [43]. This model indicates that organic molecules adsorb and desorb from the liquid interface layer surrounding of the cavitation bubble, reaching a pseudo-steady state, and the degradation rate (r) can be represented by Eq. (9).

$$r = \frac{k_0 K C}{1 + KC} \tag{9}$$

where,r is the initial degradation rate (μmol L^{-1} min^{-1}), k_0 is the pseudo-rate constant (μmol L^{-1} min^{-1}), C is the pollutant initial concentration (μmol L^{-1}) and K is the equilibrium constant of the target compound at the interfacial region, i.e., between the cavitation bubbles and the solution (L μmol $^{-1}$) [43,44].

However, the most appropriate kinetic model for nonvolatile compounds was previously developed by Serpone et al. (1994) [45]. They

described two regimes; one at the lower concentration in which the reaction occurs in the bulk solution, and other regime at higher concentration in which the sonochemical reactivity occurs at the bubble–liquid interface and connects the sonochemical kinetic to a Langmuir-type mechanism. Thus, the degradation rate is the sum of the rates in the bulk and in the interface layer and can be expressed by the equation (10) [45].

$$r = k_b + \frac{k_0 KC}{1 + KC} \tag{10}$$

where, k_b is a constant representing the rate of decomposition in the bulk liquid (μmol L^{-1} min^{-1}),r is the initial degradation rate (μmol L^{-1} min^{-1}), k_0 is the pseudo-rate constant (μmol L^{-1} min^{-1}), C is the pollutant initial concentration (μmol L^{-1}) and K is the equilibrium constant (L μmol^{-1}) [45].

Having into account the above, the sonochemical degradation data of CPX and DOX were analyzed by a nonlinear regression using the Solver complement of Microsoft Excel. The results of modeling are shown in Table 5 and Fig. 6. Data indicates that the experimental results fit better (higher coefficient of determination R^2) with the model proposed by Serpone et al. (1994) in comparison with the Okitsu et al. model and the pseudo first-order kinetics model. In this way, it can be inferred that the pollutants degradation takes place at both the bubble–liquid interfacial region and in the bulk solution.

3.4. Mineralization and toxicity analysis

Figs. 7, 8 and 9 show the results regarding TOC, anions and toxicity variation after 120 min of ultrasonic irradiation under the optimized conditions. According to the results, it can be inferred that part of the CPX and DOX molecules are being mineralized (reduction on the solutions organic carbon content was around ~18.0% for CPX and ~8.0% for DOX). This, together with an increase in the presence of ions on the solution (Fig. 8) indicates that CPX and DOX are being transformed into organic compounds (byproducts) with probably low volatility and high hydrophilicity, which migrate to the bulk solution, where the concentration of radicals is much lower than in the interface (it implies that a total mineralization is not reached). A similar behavior has been found during the sonochemical degradation in water of various antibiotics [22,46].

Finally, analysis of samples toxicity (Fig. 9) shows that the reduction of this parameter was ~ 36.0% and ~ 87.0% for CPX and DOX respectively. This demonstrates that US technology is efficient not only to reduce pollutants presence but also, to inhibit samples toxicity and reduce the potential risk of hazardous effects on ecosystems and living beings.

4. Conclusions and perspectives

The removal of CPX and DOX antibiotics in aqueous samples was studied using low frequency US. Experimental results demonstrated that the solution initial pH and the applied US power have a significant effect on the antibiotics elimination. In this way, acid pH conditions and higher US power promote an increase on CPX and DOX removal, due mainly to the interaction between the ionic form of the substrates and the amount of generated HO• radicals. Kinetic equations based on a Langmuir-type mechanism and on pseudo-first order reaction kinetics were used to model the sonochemical degradation of the studied antibiotics. The expression developed by Serpone et al. showed a better fit with the experimental data in comparison with the Okitsu et al. and the pseudo-first order models, indicating that pollutants degradation takes place at both the bubble–liquid interfacial region and in the bulk solution. Finally, mineralization and toxicity analysis showed that after 120 min of treatment CPX and DOX are being transformed into organic byproducts with less toxicity.

It could be concluded that 40 kHz ultrasound is able to remove CPX and DOX from aqueous solutions.

In future works, it is important to carry out experiments under different aqueous matrices and to determine the effect of the species contained in the water on the reaction. In addition, the analysis of the effect of the ultrasound frequency and the identification of the reaction by-products also should be done.

CRediT authorship contribution statement

Rafael Santiago Cárdenas Sierra: Investigation, Writing – original draft. **Henry Zúñiga-Benítez:** Methodology, Writing – review & editing, Project administration, Supervision. **Gustavo A. Peñuela:** Writing – review & editing.

Declaration of Competing Interest

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.

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Appendix A. Supplementary data

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