




Propranolol degradation through processes based on the generation of hydroxyl free radical

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ABSTRACT

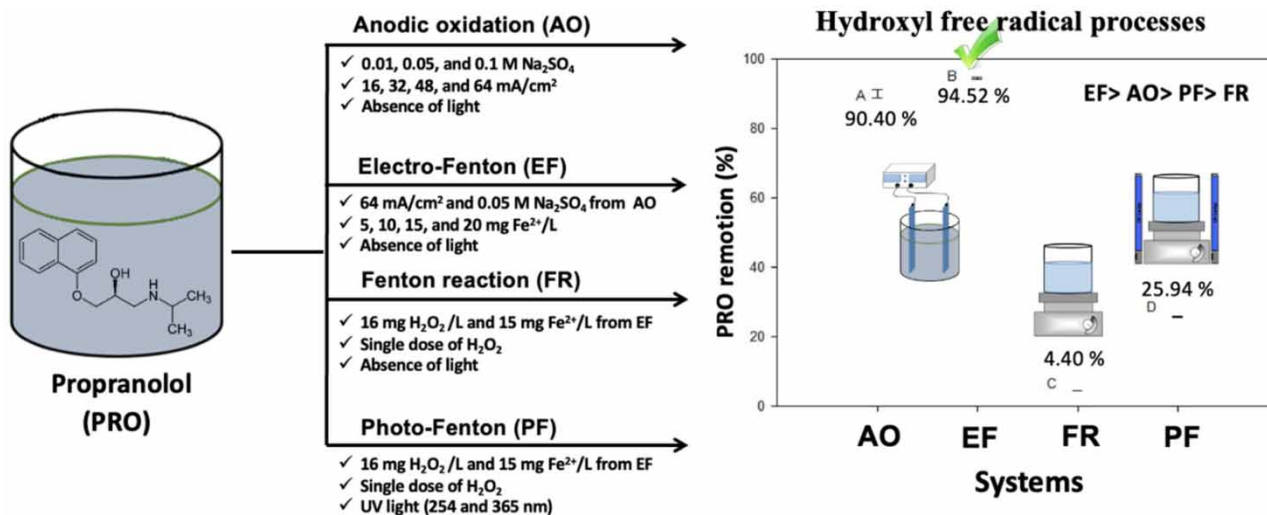
Pharmaceutical substances such as propranolol (PRO) are an emerging class of aquatic contaminants that have increasingly been detected in ground and surface water. For this reason, the aim of this study was to evaluate the efficiency of advanced oxidation systems for the PRO degradation. The tests started with anodic oxidation (AO), using 0.01, 0.05, and 0.1 M Na₂SO₄ as the supporting electrolyte and 16, 32, 48, and 64 mA cm⁻² as current density. Under the best conditions obtained in AO, the electro-Fenton (EF) process was reviewed, where the effect of Fe²⁺ was analyzed with 5, 10, 15, and 20 mg Fe²⁺ L⁻¹. The Fenton reaction (FR) was studied using the Fe²⁺ concentration that promoted the highest percentage of PRO removal and initial concentration of 16 mg L⁻¹ of H₂O₂, in addition to these conditions, in the photo-Fenton (PF) system, the effect of UV light with wavelengths 254 and 365 nm were evaluated. The results obtained showed that the degradation efficiency of the EF > AO > PF > FR system along with a percent removal of 94.52, 90.4, 25.97, and 4.4%, respectively. The results showed that PRO can be removed through the studied systems, with the EF system being the most efficient.

Key words: advanced oxidation processes, emerging pollutants, mineralization, propranolol degradation, wastewater treatment

HIGHLIGHTS

- Propranolol degradation was evaluated through various advanced oxidation processes.
- The advanced oxidation process with the highest degradation efficiency of propranolol was determined.
- Under the evaluated conditions, the electro-Fenton (EF) system was the best advanced oxidation process for propranolol degradation.

GRAPHICAL ABSTRACT



INTRODUCTION

The study of emerging pollutants, including pharmaceutical compounds, has become one of the biggest environmental concerns today (Patel *et al.* 2020) due to these products that are used greatly in quantity, variety and on many occasions without a medical prescription. So, as for various compounds associated with pharmaceuticals that have been detected in the freshwater and wastewater worldwide, it usually ranges within ng L⁻¹ to µg L⁻¹ (Vulliet & Cren-Olivé 2011; Mutiyar & Mittal 2014; Aus der Beek *et al.* 2016).

The problem with these compounds is due to that it enters the environment polluting the surface and ground waters, causing negative impacts upon living organisms. These aquatic organisms are exposed continuously to low concentrations of compounds during their life cycle, presenting associated adverse effects that include birth defects, morphological alterations, as well as in growth and reproduction, genotoxicity, among others (Marcoux *et al.* 2013).

Currently, the pharmaceuticals emerging pollutants are more detected in the freshwater and wastewater worldwide that are known as Nonsteroidal anti-inflammatory drugs, lipid regulator, anticonvulsants, antibiotics, and β-blockers (Luo *et al.* 2014; Patel *et al.* 2020; Singh & Suthar 2021). Propranolol (PRO) is one of the most widely used β-blockers, it is prescribed as a treatment for multiple cardiovascular disorders, such as hypertension, angina pectoris, pheochromocytoma, cardiac arrhythmias, hypertrophic cardiomyopathy, and myocardial infarction (Al-Majed *et al.* 2017; Hosseini *et al.* 2021). Numerous studies have generated sufficient evidence to show that the presence of PRO in a wide concentration range, from 0.5 to over 200 mg L⁻¹, may be capable of triggering adverse effects on different aquatic organisms (Pino *et al.* 2016; Menz *et al.* 2017; Sumpter *et al.* 2021). On that subject, and based on various studies carried out in recent years, the harmful effects of β-blockers, such as PRO, range from affectations to the endocrine system of fish, to exerting immobilization, toxic effects and mortality on fish, algae and crustacea (Bittner *et al.* 2018; Godoy *et al.* 2019; Fonseca *et al.* 2021).

Its presence in aquatic ecosystems has been associated with higher mortality rates and reduced heart rates in zebrafish and medaka embryos (Finn *et al.* 2012), a decrease in length of sea urchin larvae (Ribeiro *et al.* 2015), a decrease in mussels' feeding rates, gill activity (Solé *et al.* 2010) and loss of orientation, reduced appetite, decreased hatching capacity and significant bioaccumulation of PRO in plasma of fathead minnows (*Pimephales promelas*). Overall, β-blockers are commonly found in the environment showing a potential risk for aquatic and terrestrial organisms at very low concentrations (Kwon & Lee 2019; Marothu *et al.* 2019). These types of compounds are not easy to be degraded by conventional biological treatments and are soluble in water and hence are found in the environment (wastewater and freshwaters) for a long time (Michael *et al.* 2013; Patel *et al.* 2020; Verma & Haritash 2020). Therefore, in recent years, advanced oxidation processes (AOP) have emerged as methods capable of potentially transforming these compounds into innocuous substances that have been tested in the elimination of β-blockers in water, as such is the case of processes by photocatalysis (Marothu *et al.* 2019; Giordani *et al.* 2021), electro-Fenton (EF) and photoelectro-Fenton (PEF) (Isarain-Chávez *et al.* 2011; Nsubuga *et al.* 2019), UV/hydrogen peroxide

(UV/H₂O₂) and UV/persulfate (UV/PDS) (Yang *et al.* 2019). Their oxidation mechanisms are based on the generation of highly reactive free radicals, such as the hydroxyl radical (\bullet OH) (Stefan 2017).

Hydroxyl radical is a neutral free radical that is one of the most powerful oxidizing radical species and non-selective oxidizing agent ($E^\circ = 2.80$ V), which reacts with most organic compounds to produce dehydrogenated or hydroxylated derivatives, until achieving its complete mineralization, that is, its conversion to CO₂, water, and inorganic ions (Barrera-Díaz *et al.* 2014; Stefan 2017). When these radicals are generated, they react quickly, and generally indiscriminately, with most organic compounds (McKenzie *et al.* 2018), either by addition to a double bond or by the abstraction of a hydrogen atom from aliphatic organic molecules. Although the degradation of PRO has been studied with various AOP, our overall research did not find a study that evaluates the degradation efficiency of this compound under comparable conditions among the different AOP. For this reason, this study evaluated the degradation of the β -blocker PRO by anodic oxidation (AO), EF, Fenton reaction (FR), and photo-Fenton (PF) processes, under conditions that allow comparing their efficiency, measured as a percent of PRO removal, where the AO and EF processes were evaluated first, and the best of them was compared with the FR and PF systems.

METHODS

Chemical substances

Anhydrous sodium sulfate (CAS No.7757-82-6), sodium hydroxide (CAS No.1310-73-2), hydrogen peroxide (CAS No. 7722-84-1), and titanium dioxide (CAS No.13463-67-7) were purchased from Meyer[®]; sulfuric acid (CAS No. 7664-93-9) and ferrous sulfate (CAS No.7782-63-0) from Faga Lab[®]; absolute ethanol (CAS No. 64-17-5) from Hycel[®]. All the substances were purchased in an analytical reagent grade. The PRO with which the treatability tests were carried out were purchased in a pharmaceutical grade from the local market and used with prior purification.

Propranolol purification

For PRO extraction, approximately 9.00 g of the pharmaceutical product was macerated, which represented approximately 3.6 g of active ingredient (AI). The mass obtained was dissolved in 200 mL of absolute ethanol and maintained with constant agitation for 5 min. Subsequently, it filtered using Whatman[®] filters with a <0.2 μ m pore size. The recovered extract was evaporated at 83 °C on a rotary evaporator (Hahn Shin Scientific Co, model HS-2000 NS) until a dense paste was obtained. Finally, the residual moisture was removed using a desiccator for approximately 12 h. PRO was identified by determining the melting point, its absorption spectrum, and by gas chromatography coupled to a mass spectrum. The melting point was determined in the Fisher-Johns team (Scorpion Scientific[®]). The absorption spectrum was obtained by scanning it in the 200–400 nm range, using a UV/Vis spectrophotometer (Optima SP-3000 nano), while the mass spectrum was obtained using a VARIAN Saturn 2200 system. The mass spectra of the compounds of interest were compared with those in the NIST02 library.

General considerations

All treatability tests were performed in a reaction volume of 50 mL ($\varnothing = 43$ mm, $h = 54$ mm), with an initial PRO concentration of 100 mg L⁻¹. The pH of the reaction medium was adjusted up to 3 using a 10% H₂SO₄ and 15% NaOH solution, this pH value was used since it is the optimal value of the Fenton process reported by others (Brillas *et al.* 2009; Vazquez-Medrano *et al.* 2018; Jiang *et al.* 2021). During the entire reaction time (30 min), the system was maintained with a stirring and constant temperature (850 rpm and 25 ± 2 °C, respectively); in all cases, the reaction medium was kept in complete darkness, with the only exception being the PF system tests, where radiated light was controlled (254 and 365 nm). During the reaction, the residual PRO concentration was monitored every 5 min, taking a sample of the reaction medium which was analyzed by gas chromatography coupled to a mass spectrometer (GC-MS).

Electrochemical oxidation tests were carried out in an undivided electrolytic cell, using a Na₂SO₄ solution as the supporting electrolyte. Boron-doped diamond (BDD) electrodes were used as the anode and cathode, both with an effective surface of 6.25 cm² (2.5 \times 2.5 cm), arranged in parallel with 2 cm of separation. The current supplied to the system was induced by a NISA EJ15-5A2D30-3AD power source operated at open voltage.

Experimental tests

The AO tests were developed following the structure of a two-factor design, where the first factor, current density, was evaluated under four different levels (16, 32, 48, and 64 mA cm⁻²), and the second factor, support electrolyte concentration, was evaluated under three different levels (0.01, 0.05 and 0.10 M). All tests were carried out in the complete absence of light.

The EF tests were designed to assess the effect of Fe²⁺ concentrations (5, 10, 15, and 20 mg L⁻¹) on PRO removal. These tests were carried out under the best operating conditions that were obtained in the AO (Na₂SO₄ concentration and electric current density). During the 15 min prior to the oxidative process, the accumulation of H₂O₂ in the reaction medium was allowed, which started with the addition of PRO and Fe²⁺.

The FR tests were operated with 16 mg L⁻¹ of H₂O₂ along with the Fe²⁺ concentration that reported the highest removal efficiency of PRO in the EF system. Finally, in the PF system, two UV light intensities (254 and 365 nm) were evaluated, under the same FR operating conditions. The PF system was irradiated with a UV lamp (UVP, Model UVGL-25, Upland, CA, USA) of 4 W power. The lamp was placed 2 cm above the reaction medium surface and it was irradiated for 30 min.

Chromatographic method

A 1 mL sample was taken from the reaction medium and diluted with 2 mL of distilled and deionized water. The PRO was extracted from the diluted sample using a 100 μm polydimethylsiloxane/divinylbenzene (PDMS/DVB) coated fiber, following the methodology used by [Gutiérrez *et al.* \(2007\)](#). The PRO was quantified using the VARIAN Saturn 2200 system, which was arranged with a 30 m × 0.25 (0.25) Factor Four VF-5 ms column (Agilent Technologies). Helium with a constant flow of 1 mL min⁻¹ was used as the carrier gas. The column was kept at 50 °C for 10 min, and a temperature increase of 15 °C min⁻¹ was programmed until reaching 280 °C, maintaining this temperature for 10 min. The injector's temperature was maintained at 250 °C. The mass spectra were acquired in electronic impact mode at a voltage of 70 eV and compared with those of the NIST02 library.

Total organic carbon

The total organic carbon (TOC) was quantified using a TOC analyzer Model TOC-V_{CPH/CSH} (Shimadzu Co., Tokyo, Japan). For this determination, a sample of 1 mL was taken of the reaction medium and diluted in 19 mL of deionized water. For 10 min, the sample was homogenized using a vortex mixer and finally was quantified using the TOC analyzer.

Analysis of experimental data

The data obtained from the treatability tests with the different systems were analyzed using a one-way analysis of variance. In each case, the analysis was performed after checking the assumptions of normality, independence, and homoscedasticity. When the analysis showed the existence of a significant difference between the treatments, a mean separation test (Tukey's test) was performed. All tests were executed with a significance level $\alpha = 0.05$.

RESULTS AND DISCUSSION

Identification of the AI

The PRO purification process had a recovery efficiency of 94.4%. The recovered crystals showed a white color and a melting point of 163 °C, this concurs with the data reported by [Al-Majed *et al.* \(2017\)](#), who determined the melting point of the PRO in a 162–165 °C range. On the other hand, the absorption spectrum of the crystals recovered ([Figure 1\(a\)](#)) was like the results reported by [Al-Majed *et al.* \(2017\)](#) ([Figure 1\(b\)](#)). Both spectra were generated with a solution of 10 mg L⁻¹ PRO and the absorption scan was performed at 200–400 nm. Finally, the analysis of the crystals was performed by GC-MS. The mass spectrum obtained from the crystals ([Figure 2](#)) was compared with the NIST02 database. These results confirmed the presence of the purified AI. Therefore, the treatability tests were carried out using the crystals recovered from PRO.

Preliminary tests and determination of reaction time

In [Figure 3](#), the results obtained in the preliminary tests, carried out to establish the reaction time that was used in all the treatability tests, are shown. As can be seen, PRO concentration decreases over time, reaching 10 mg L⁻¹ after 30 min and an undetectable level at 40 min. Based on these results, the reaction time was established at 30 min. The PRO residual concentration profile ([Figure 3](#)) was generated in these tests without current application and without adding Fe²⁺, which means that the free radical was not present, and it shows that PRO concentration remains at 99.65 ± 0.16 mg L⁻¹. This value indicates that the removal of propranolol caused by other factors that are not attributed to the studied systems could be ignored.

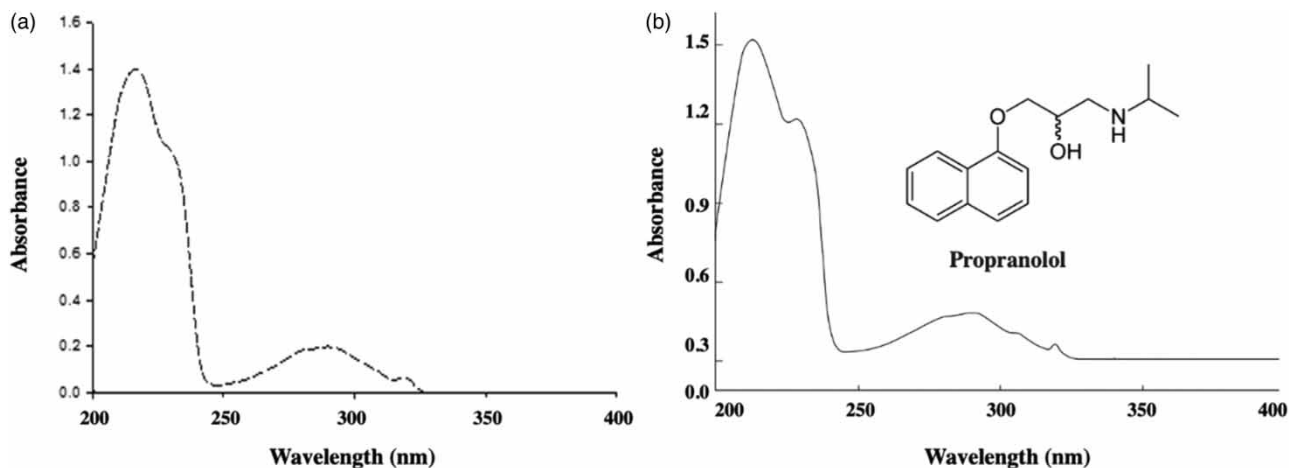


Figure 1 | Absorption spectrum (a) crystals recovered and (b) reported by Al-Majed *et al.* (2017).

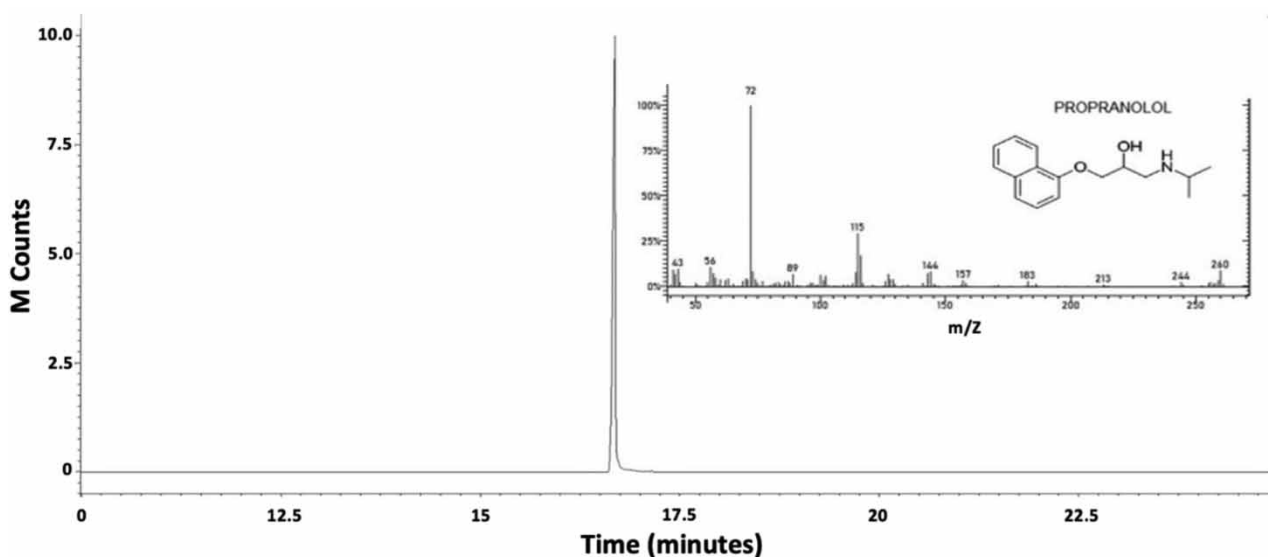


Figure 2 | Chromatogram and mass spectrum of the crystals recovered from the PRO extraction process.

Anodic oxidation

The first set of tests was designed with the objective of evaluating the efficiency of AO to degrade PRO. The results obtained were studied using a two-way analysis of variance with a significance level of $\alpha = 0.05$. Prior to the analysis, the assumptions of normality, homoscedasticity and independence were verified. The ANOVA result verified the existence of the interaction between the evaluated factors ($df = 6$, $F = 5.781$, $p < 0.001$); therefore, it can be established that, under this study conditions, the oxidative process was controlled by both the current density and the concentration of the supporting electrolyte. In [Figure 4](#), a positive correlation can be observed between the current density and the removal percent, i.e., at more current density, greater PRO removal percentage. A similar direct relationship was reported by [Ganiyu *et al.* \(2017\)](#) in the β -blockers degrading. Under study conditions, the maximum PRO removal and mineralization achieved by AO were 90.4% and 12.9%, respectively; these were achieved in 30 min, when the system was operated at a 64 mA cm^{-2} current density and a 0.05M support electrolyte concentration. These efficiencies achieved were higher than that reported by [Ganiyu *et al.* \(2017\)](#) who used the same time and a 30 mg L^{-1} PRO solution. They achieved 66% maximum PRO removal and 10% of the mineralization.

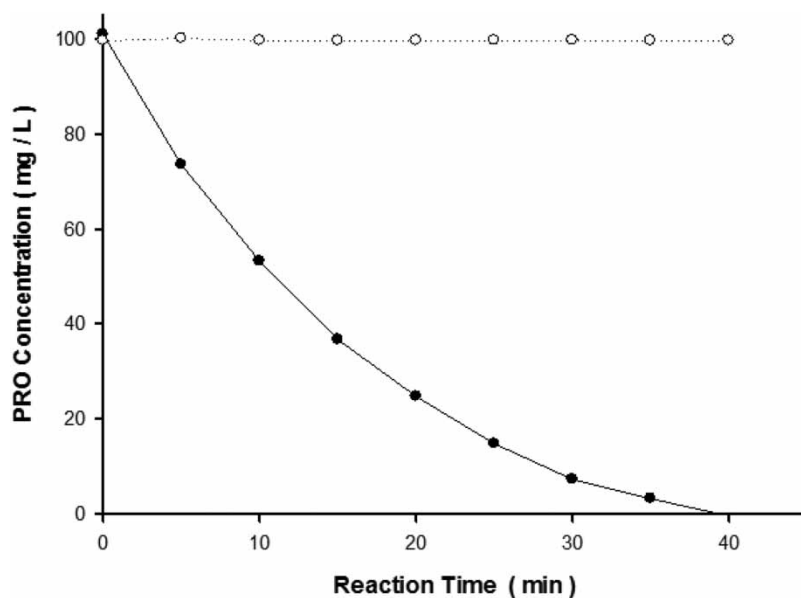


Figure 3 | PRO residual concentration profile at preliminary tests under next condition: 100 mg L⁻¹ PRO of initial concentration, 0.05 M Na₂SO₄, pH 3, $j = 32 \text{ mA cm}^{-2}$. (○) Control test, (●) Determination of reaction time.

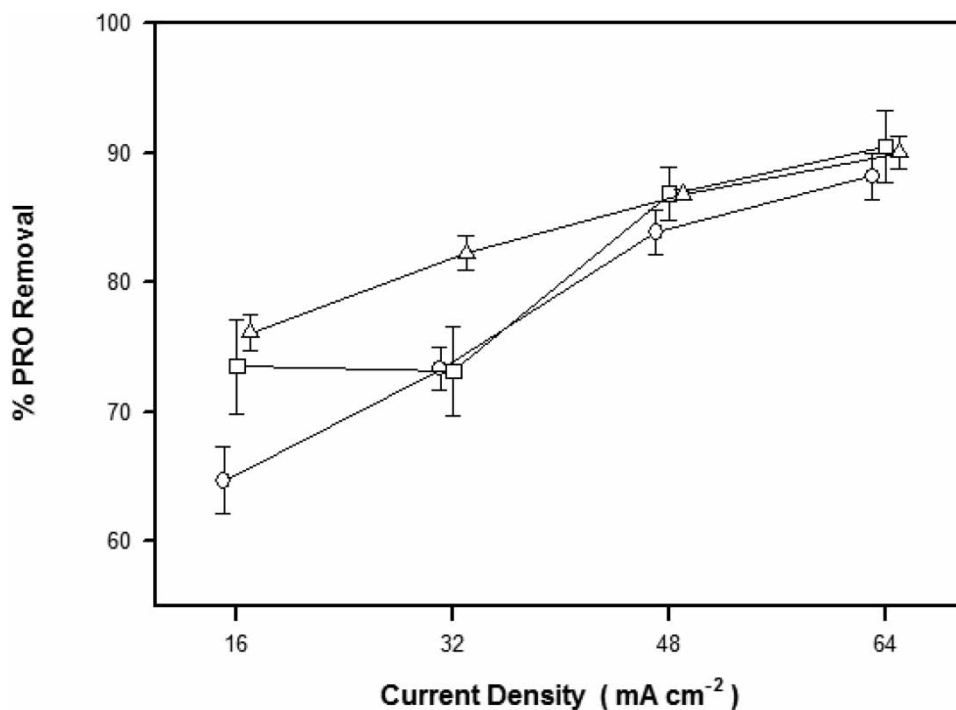


Figure 4 | Removal percentage achieved during PRO anodic oxidation. (○) 0.01 M, (□) 0.05 M, (Δ) 0.1 M Na₂SO₄.

Electro-Fenton

In order to be able to compare the efficiency of the EF system against AO on the removal of PRO, the oxidation tests with the EF system were carried out using the best conditions observed in AO ($j = 64 \text{ mA cm}^{-2}$ in 0.05M of Na₂SO₄). During these tests, the effect of the Fe²⁺ concentration as a facilitator in the formation of •OH was evaluated, using the electrogenerated

H₂O₂ as a precursor, according to Equations (1) and (2).



The results obtained in this set of tests are shown in Figure 5. Statistical analysis of these results revealed the existence of a significant difference among the four treatments ($df = 3$, $\alpha = 0.05$, $F = 38.422$, $p < 0.001$). The maximum PRO removal was reached when the system was operated with a concentration of 15 mg L⁻¹ of Fe²⁺. Under these conditions, 94.52% PRO removal was achieved, which was slightly higher than that achieved with AO, this can be attributed to the simultaneous generation of •OH promoted both the Fenton system's characteristic equation (Equation (2)) and the AO's characteristic equation (Equation (3)). On the other hand, excessive production of •OH generates collateral reactions to the main oxidation reaction, within these reactions may be the recombination reaction, which results in a decrease in the degradation efficiency. This explains the decrease in PRO removal efficiency when the EF system is studied with the maximum concentration of Fe²⁺ (Figure 5), as well as a small increase in PRO degradation as compared to AO.



where M is the cathode, M(•OH) is the free •OH radical adsorbed on the surface of the cathode.

FR and photo-Fenton system

The degradation tests by FR were carried out with an initial H₂O₂ concentration of 16 mg L⁻¹ and with a Fe²⁺ concentration of 15 mg L⁻¹. The 16 mg L⁻¹ H₂O₂ concentration was used since this was the maximum concentration reached in the EF system before starting the oxidative process. Under these conditions, the maximum removal achieved was 4.4% of the initial PRO concentration; this can be attributed to the low initial concentration of H₂O₂, which was consumed according to the conventional FR equation (Equation (4)). Comparing the percentage of degradation achieved by FR with that percentage of degradation achieved by the EF system (94.52%), it can be observed that maintaining the constant electro-generation of H₂O₂ during the

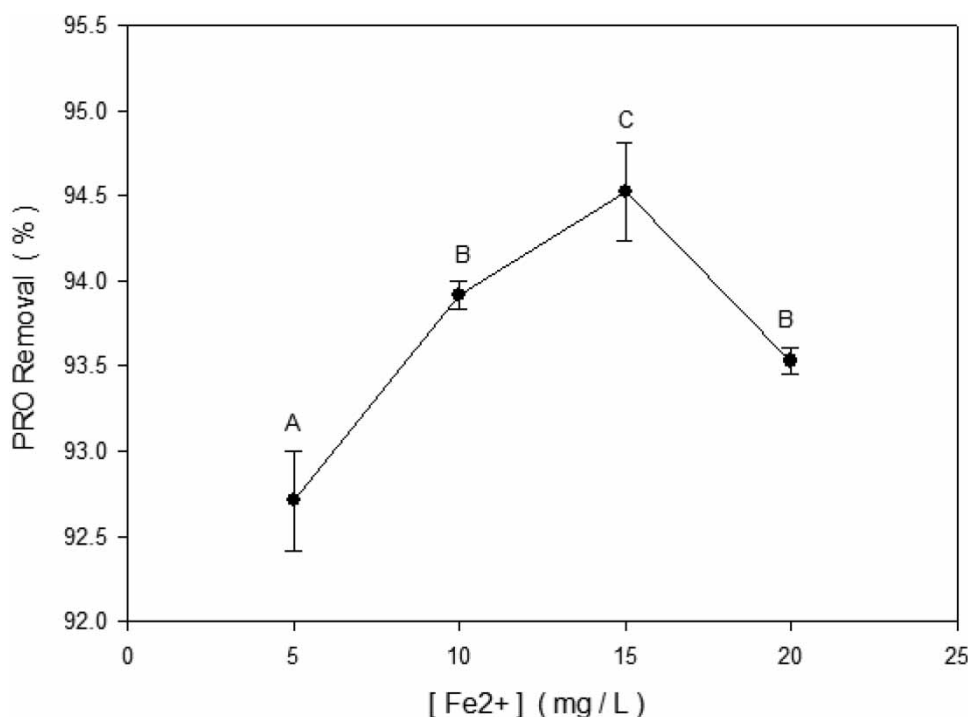


Figure 5 | Removal percentage of PRO under the different Fe²⁺ concentrations evaluated. Capital letters represent results according to Tukey's tests.

whole oxidative process, as is achieved with the EF system (Equation (1)), allows a significant increase in the removal percentage concerning the RF. For this reason, the EF system turned out to be significantly more efficient than the FR.



Alternatively, the PF system was evaluated under the same conditions as FR but irradiating the system with UV light of two different wavelengths (254 and 365 nm). Although the removal percentages were similar in both photo-assisted processes (Table 1), the analysis of variance showed the existence of a significant difference between the treatments ($df = 1$, $\alpha = 0.05$, $F = 9,428.637$, $p < 0.001$). The maximum removal achieved in this set of tests was 25.79% of the initial PRO concentration, which was attained when the system was irradiated with the highest energy light (light of 254 nm). This removal percentage was higher than achieved by FR and can be attributed to the additional amount of the main oxidizing species in these systems, $\bullet\text{OH}$, provided both to the reduction reaction described by Equation (5), as well as the H_2O_2 photolysis described by Equation (6).



The analysis of variance of the data obtained in the PRO degradation tests, under the best conditions of each evaluated system, shows the existence of significant differences between each treatment ($df = 3$, $\alpha = 0.05$, $F = 14,785.67$, $p < 0.001$). These results are presented in Figure 6, and they show that the electrochemical systems reached PRO removal percentages

Table 1 | Mean (M) and standard deviation (SD) of PRO degradation percentage under PF systems condition

Wavelength (nm)	M	SD
254	25.79	0.076
365	20.39	0.058

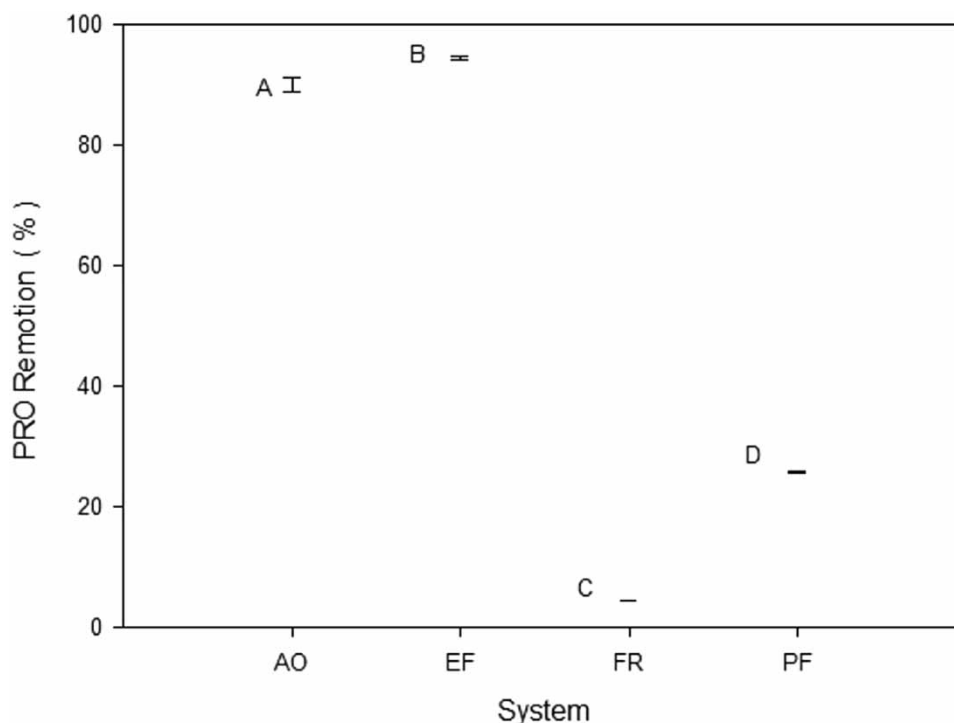


Figure 6 | Comparison between the treatments evaluated under the best conditions. Capital letters represent the results of the mean separation test.

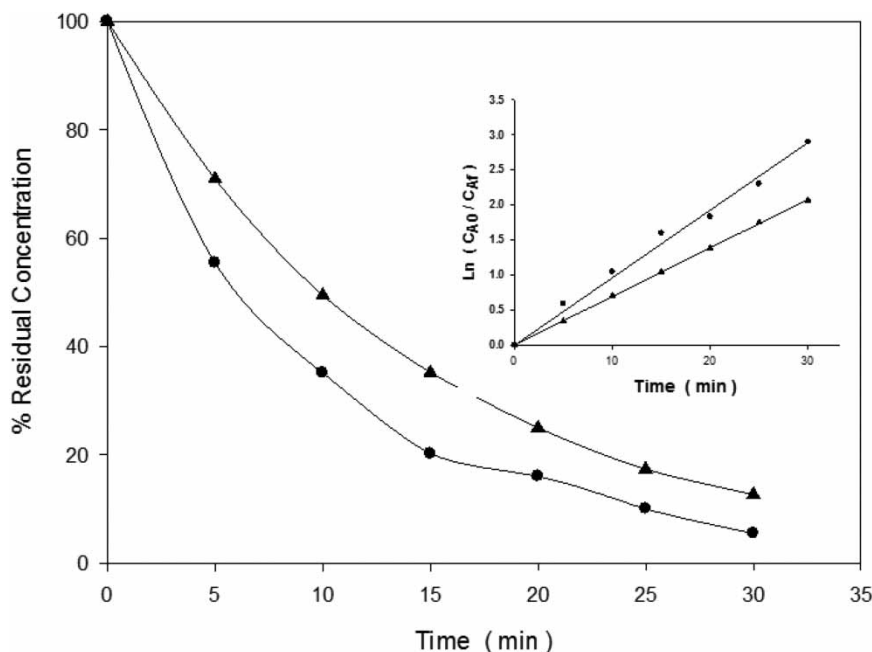


Figure 7 | Profile of the residual concentration of PRO under the best conditions in the AO (▲), and in the EF system (●). The graph at the top right checks the behavior of pseudo first-order kinetics.

Table 2 | Kinetic constant of the studied electrochemical processes and their adjustment coefficient to a straight line

System	K ($L\ mg^{-1}\ min^{-1}$)	R^2
AO	0.0695	0.9998
EF	0.0961	0.9895

significantly higher than those from chemical systems. This can be attributed to the continuous generation of the main oxidizing species, free $\bullet OH$ radical. However, even though both the AO and the EF system have PRO removal percentages greater than 90% of the initial concentration, the Tukey Test demonstrates the existence of a considerable difference between these two treatments ($df = 3$, $\alpha = 0.05$, $F = 14,786$, $p < 0.001$). Figure 6 indicates that the treatment with the highest PRO removal is the EF system.

Degradation kinetics

The residual concentration profile in both the AO and the EF system is depicted in Figure 7, where it is possible to observe that in both systems the residual concentration followed the behavior of pseudo first-order kinetics, which is consistent with what was reported by Ganiyu *et al.* (2017). The pseudo first-order kinetics are characterized by the high concentration of one of the reactants, in our case the $\bullet OH$ electrogenerated in electrochemical systems, which promotes the reaction rate dependence of only one of the reacting species, the PRO, in our case. Table 2 shows the values of the kinetic constants of each electrochemical system evaluated, as well as the fit of the data to a straight line (R^2). Also, allows us to see that the EF system not only achieves a greater removal of the initial concentration of PRO but also accomplishes it more quickly ($K_{EF} = 0.0961\ L\ mg^{-1}\ min^{-1} > K_{AO} = 0.0695\ L\ mg^{-1}\ min^{-1}$).

CONCLUSION

The tests that were carried out with comparable conditions confirmed that it was possible to degrade PRO through the processes based on the generation of free radicals $\bullet OH$ under studied conditions. Although PRO was degraded by the four systems analyzed, a significant difference in degradation efficiency was observed between electrochemical processes and

chemical processes, the former being the most efficient (EF > AO > PF > FR). The maximum removal of PRO (94.52%) was achieved with the EF system, being also the fastest ($K = 0.0961 \text{ L mg}^{-1} \text{ min}^{-1}$).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

All relevant data are included in the paper or its Supplementary Information.

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