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Elimination of pharmaceutical contaminants fluoxetine and propranolol by an advanced plasma water treatment

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ABSTRACT

Human activities have contaminated water sources with pharmaceutical compounds by the improper disposal of unwanted medicine or through sewage waste. The search for the most effective water treatment processes has been ongoing for decades. In the current paper, by exposing water to non-thermal plasma in a floating electrode streamer corona discharge (FESCD) system, both the antidepressant compound fluoxetine and the antihypertensive compound propranolol are eliminated. After 3 h of plasma treatment, more than 99% of each contaminant was degraded. The energy yield, which is the amount of contaminants degraded using 1 kWh of energy, was in the range of 0.12–0.13 g/kWh. The degree of mineralization calculated from total organic carbon (TOC) measurements was 60% and 17% for fluoxetine and propranolol, respectively. Reaction with hydroxyl radicals was the only degradation pathway for fluoxetine and its byproducts. For propranolol, hydroxyl radicals primarily caused the degradation butoxidation of secondary alcohols to ketones suggested the possible role of ozone molecules.

Keywords: Plasma; Pharmaceutical contamination; Energy yield; Mineralization; Degradation pathway

1. Introduction

Advancement of analytical chemistry tools, especially mass spectrometry techniques, has enabled the detection of pharmaceutical contaminants in various bodies of water including rivers, lakes and even drinking water sources [1,2]. The introduction of these contaminants to the environment is the intentional or unintentional but direct outcome of human activities [3]. Although the concentration of various pharmaceutical contaminants in the environment remains very low (in the range of ng/l to µg/l) [4,5], in 2011 the World Health Organization (WHO) acknowledged that the effect of long-term exposure to these minute concentrations is still unknown [6]. This uncertainty, alongside population growth rate, the discovery of new drugs as well as the proven harmful effects on aquatic species [7,8], has concerned many societies worldwide [9,10].

According to a report published by the National Center for Health Statistics (NCHS) in 2011, the use of fluoxetine amongst people over the age of 12 in the United States has increased by over 400% in the period between 2005–2008 [11]. Some of the proven negative impacts of fluoxetine on wildlife [12,13] include altering the mobility of snails, changes in the reproduction behavior of fishes and disruption in the memory and cognitive function of cuttlefish. Antihypertensives, the other drugs considered in this study, are amongst the most used medication worldwide. According to the report published by WHO in 2012,

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75,000–150,000 propranolol tablets are used annually in the United States [14]. Propranolol is a beta-blocker normally prescribed to treat chest pain and heart rhythm disorder [7]. Bioaccumulation in marine organisms is a well-known detrimental impact associated with propranolol present in fresh water [15].

The prevalence of pharmaceutical contaminants such as fluoxetine and propranolol in the environment is partially due to ineffective water treatment processes for eliminating these compounds [16–18]. Consequently, significant effort has been made to develop more efficient water treatment methods that eliminate pharmaceutical contaminants; Advanced Oxidation Processes (AOPs) are one of the most studied candidates. This category of water treatment method is based on the generation of highly active transient oxidizing agents, such as hydroxyl radicals ($OH^{\bullet}$) in the aqueous phase and has proven to be very effective inthe degradation of pharmaceutical contaminants [19,20]. Amongst various AOPs, such as ozonation [21,22], photocatalysis [23,24], and Fenton reactions [25,26], treatment methods based on non-thermal plasmas (NTP) have emerged as viable candidates for the elimination of pharmaceutical contaminants. This is due to improved decontamination efficiency as a result of the simultaneous production of a wide variety of oxidizing agents, including hydroxyl radicals, ozone molecules, and hydrogen peroxide [27–29]. NTP created in pulsed corona discharge systems has been used to eliminate diclofenac [30], carbamazepine [31], and βoestradiol [18]. On the other hand, dielectric barrier discharge (DBD) configuration for the generation of NTP has been used to treat water contaminated by a variety of pharmaceutical compounds such as carbamazepine [32], amoxicillin and ampicillin [33], ibuprofen [34], and enalapril [35]. Although the effectiveness of both DBD and pulsed corona discharge configurations has been proven, they suffer from at least one of the following disadvantages. First, two electrodes are required for the creation of plasma. This makes the inter-electrode distance a crucial parameter to avoid transitions between the corona mode and the streamer mode [36,37]. Moreover, the corrosion of the immersed electrode in water becomes a serious concern. Second, generation of plasma in these configurations is mostly achieved through the application of high voltage pulses. Upscaling of the circuitry of such pulses becomes very complicated [38].

In this study, a floating electrode streamer corona discharge (FESCD) is used for degradation of fluoxetine and propranolol in water. This new system is similar to the previously used pulsed corona discharges [18,30] beta-oestradiol and salicylic acid, but with two improvements; the use of only one electrode above the surface of the water and a simple alternating current (AC) waveform for generation of NTP. The specific goals of this study are (i) to evaluate the efficiency of FESCD configuration in degradation of fluoxetine and propranolol; and (ii) to identify of the degradation byproducts and propose degradation mechanisms.

2. Materials and methods

Fluoxetine hydrochloride and propranolol hydrochloride (>98%, obtained from Sigma Aldrich Ontario, Canada) were the target contaminants used throughout this study. Plasma treatment solutions were prepared by dissolving sufficient amounts of each contaminant in tap water (main water matrix) or Milli-Q water (18.2 MΩ/cm, comparison water matrix) to achieve the initial concentration of 100 mg/l. This translates into the initial molar concentration of 0.32 mM and 0.38 mM for fluoxetine and propranolol, respectively.

To enable the creation of plasma using a single electrode and AC waveform, a helical resonator was used (Fig. 1). Detailed description of the experimental setup is provided elsewhere [39].

To study the efficiency of the treatment system over time, solutions were treated by plasma for various periods of 0, 0.5, 1, 2 and 3 h. For each treatment period, 60±1 ml of the desired solution (fluoxetine or propranolol in tap water or Milli-Q water) was used.

The input voltage and current to the resonator were fixed at 71 V and 200 mA, respectively. The pH of solutions was measured by a Mettler Toledo FiveEasy® pH meter equipped with InLab® Expert Pro-ISM probe (Ohio, USA). A Fisher Scientific Accumet® Excel conductivity meter (XL60, Ontario, Canada) was also used.

Two standard methods were used to characterize the treated (0.5, 1, 2 and 3 h) and untreated solutions (0 h). To evaluate the trend of the degree of mineralization in the aqueous phase (both for tap water and Milli-Q water samples), a Total Organic Carbon-Inorganic Carbon (TOC-IC) analyzer (TOC-L, Shimadzu, Kyoto, Japan) was used. For each sample, the TOC was calculated by subtracting the value of the IC from the value of the Total Carbon (TC). TC and IC measurements were carried out based on the infrared absorption of carbon dioxide. Measurement of IC involves the acidification of the samples (by means of 0.1 M H_3PO_4) to convert HCO_3^- and CO_3^{2-} to CO_2 and subsequent quantification of the released CO_2. TC was determined using the high-temperature combustion method [1]. For each measurement, 40 ml of the desired solution was poured into a glass vial and placed in the TOC analyzer auto sampler. To assure the accuracy of the measurements, each vial was thoroughly cleaned and preconditioned at 250°C for 2 h.

A high-performance liquid chromatography-mass spectrometry instrument (HPLC-MS, Agilent, Santa Clara, CA, USA) was utilized to identify the degradation byproducts and propose a degradation mechanism. Mass spectra were obtained in positive mode of ionization employing an Agilent 6220 Accurate-Mass TOF HPLC-MS system (Santa Clara, CA, USA). The system is equipped with a dual sprayer electrospray ionization source with the second sprayer providing a reference mass solution. Mass spectrometric conditions were: drying gas 9 l/min at 300°C, nebulizer pressure 20 psi, mass range 100–1000 Da, acquisition rate of ~1.03 spectra/s, fragment or voltage of 175 V, skimmer voltage of 65 V and capillary voltage of 3500 V. Mass correction was performed for every individual spectrum using peaks at m/z 121.0509 and 922.0098 from the reference solution. Data acquisition was performed using the Mass Hunter software package (ver. B.04.00.). Analysis of the HPLC-MS data was done using the Agilent Mass Hunter Qualitative Analysis software (ver. B.07.00). Chromatographic separation was obtained using a Kinetex

EVO C18 column with guard (Phenomenex, 2.1 mm internal diameter, 50 mm length, 1.6 µm particle size) at 40°C. The buffer gradient system composed of 0.1% formic acid in water as mobile phase A and 0.1% formic acid in acetonitrile (ACN) as mobile phase B. Samples were loaded onto the column at a flow rate of 0.5 ml/min and an initial buffer composition of 98% mobile phase A and 2% mobile phase B. After injection, the column was washed using the initial loading conditions for 1 min followed by elution of the analytes by using a linear gradient in the form of: 2–40% mobile phase B over a period of 6 min, 40–98% mobile phase B over a period of 3 min, held at 98% mobile phase B for 4 min to remove all analytes from the column and back to 2% mobile phase B over 1 min. It is worth mentioning that due to the complexity of samples containing tap water, identification of unknown byproducts in the solutions by HPLC-MS analysis was only performed only on samples with Milli-Q water matrix.

3. Results and discussion

Fig. 2 illustrates various results obtained from the characterization of the fluoxetine samples treated with plasma. Fig. 2a shows the change in the extracted ion chromatograms (EIC) of the fluoxetine solutions as a function of treatment time. The peaks at the retention time of 3.8 min belong to the parent compound, i.e., fluoxetine. As shown in Fig. 2a, the increase in the treatment time resulted in the decrease in the peak intensity, indicating the degradation of the parent compound.

To quantify this change, areas under each peak in Fig. 2a were calculated and plotted against the treatment time, the result of which is shown in Fig. 2b. The data in Fig. 2b demonstrate that the degradation of fluoxetine follows an exponentially decaying kinetics (R^2>0.99) with the time constant of 0.18 h.

To further quantify the degradation of fluoxetine by the FESCD system, Eq. (1) and Eq. (2) were used to calculate the removal percentage and the energy yield.

$$\text{Removal}\% = \left(1 - \frac{A}{A_0}\right) \times 100 \tag{1}$$

$$\text{Energy Yield} = \frac{C_0 VR}{Pt} \times 0.01 \tag{2}$$

In Eq. (1), A and A_0 denote the area under the chromatogram's peak at each treatment time and before treatment, respectively. Moreover, in Eq. (2), C_0 is the initial concentration of the contaminant (100 mg/l), V is the volume of the solution under treatment (60 ml), R is the final removal percentage, P is the power input to the resonator (kW), and t is the total treatment time. Using Eq. (1) and Eq. (2), the removal percentage and energy yield of the process for degrading fluoxetine are 99% and 0.12 g/kWh (0.38 mmol/kWh), respectively.

TOC measurements were performed to investigate the overall evolution of the organic content of the fluoxetine solutions and to obtain the degree of mineralization. Fig. 2c and Fig. 2d show the results of these measurements in tap water and Milli-Q water, respectively. As shown in these figures, the longer the solutions were treated by plasma, the more organic molecules were completely mineralized in the solution. Based on the data shown in Fig. 2c and Fig. 2d, one can obtain the final degree of mineralization of 60% and 65% for fluoxetine in tap water and Milli-Q water respectively. The lower degree of mineralization in tap water is possibly due to the inhibiting role of ionic species such as carbonate (CO_3^{2-}) ions that are present in tap water and act as scavengers for hydroxyl radicals [40]. As shown in Fig. 2c, the inorganic content (IC) of the solutions prepared by tap water declined sig-

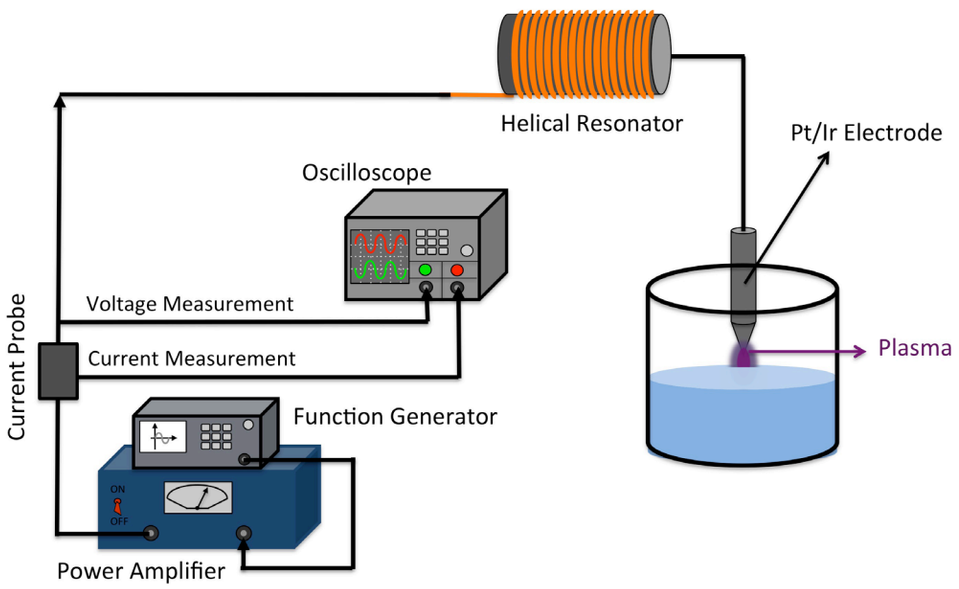

Fig. 1. Schematic of the experimental setup is shown.

nificantly as the plasma treatment process continued. To explain this trend, it is worth mentioning that, due to the presence of carbonate and bicarbonate ions in tap water, the initial IC of the solutions prepared by tap water was 23 mg/l-C. As the plasma treatment time increased, the pH of the solution decreased (data not shown).This can be attributed to the formation of ionic species such as NO_3^- in the aqueous phase due to the action of plasma [41]. This acidification in the aqueous phase transforms CO_3^{2-} and HCO_3^- ions into CO_2 molecules that eventually leave the solution. Finally, the IC of the fluoxetine solutions prepared in Milli-Q water went through an initial increase followed by a decrease as the treatment process continued, as shown by Fig. 2d. The initial IC of the solutions in Milli-Q water is very low (<1mg/l-C). The initial increase in the IC of the solutions can be attributed to the formation of carbonate ions as a result of the degradation of fluoxetine and its byproducts [42]. The further decrease in the IC is possibly due to the acidification of the aqueous phase during the plasma treatment process and the transformation of carbonate ions to CO_2 molecules, as discussed earlier.

As mentioned previously, TOC measurements can be used to evaluate the overall change in the organic content of the solutions under treatment. However, it is imperative to identify the degradation byproducts as well to understand the degradation pathway, for which we used HPLC-MS analysis. Table 1 summarizes the identified compounds at each plasma treatment period. Based on the species summarized in Table 1, a degradation pathway was proposed for fluoxetine and its byproducts, as shown in Fig. 2e. The most dominant mechanism that governed the degradation of fluoxetine and its byproducts was the reaction with hydroxyl radicals. Hydroxyl radicals are one

Table 1
Information regarding the chemical species detected in fluoxetine containing solutions by HPLC-MS

Treatment time (h)	Detected m/z	Identification	Ratio*
0	310.14	Fluoxetine	1.000
0.5	326.13	F1	0.015
	310.14	Fluoxetine	0.267
1	326.13	F1	0.004
	310.14	Fluoxetine	0.080
	249.1	F5	0.003
	255.16	F2	0.002
	220.09	F6	0.006
2	326.13	F1	0.002
	310.14	Fluoxetine	0.067
	272.16	F7	0.003
	227.12	F3	0.003
	220.09	F6	0.005
3	170.11	F10	0.010
	213.12	F4	0.005
	310.14	Fluoxetine	0.013
	272.16	F7	0.003
	147.04	F9	0.006
	177.05	F8	0.010
	227.12	F3	0.003
	220.09	F6	0.005

*The ratio is calculated by dividing the peak intensity (count) of each compound by the peak intensity of the parent compound.

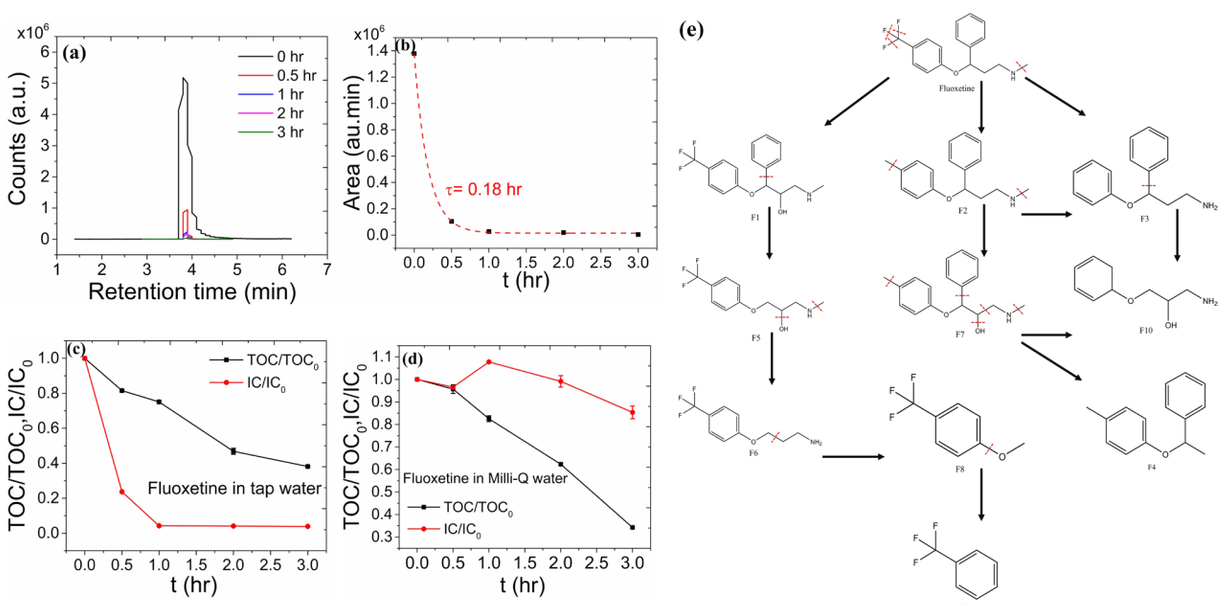

Fig. 2. Results obtained from the characterization of fluoxetine samples treated by plasma are shown. The data in (a) and (b) are obtained from the chromatograms obtained during HPLC-MS analysis. (c) and (d) depict the TOC analysis of samples in tap water and Milli-Q water, respectively. A proposed degradation mechanism is shown in (e).

of the most powerful oxidizing agents created in AOPs. In the pathway shown in Fig. 2e, hydroxyl radicals reacted with organic molecules in two ways. The first process is known as the hydroxylation of the organic molecules where a hydroxyl functional group is added to the molecule. This process is responsible for the formation of F1, F7, and F10. The second process in which hydroxyl radicals reacted with fluoxetine and its byproducts is the cleavage of the chemical bonds in the molecular structure. For instance, this process is evident in the formation of F5 from F1, F8 from F6, and F9 from F8.

Another reaction that was minimally involved in the degradation of fluoxetine is the reduction of organic molecules by hydrogen radicals (H·). One reaction for the creation of the hydrogen radicals in the aqueous phase is the dissociation of water molecules by collision with energetic electrons in the plasma [43]. The involvement of the hydrogen radicals in the degradation pathway of fluoxetine can be seen in the formation of F2 from fluoxetine. In this process, hydrogen radicals attack the trifluoromethyl group (CF_3) attached to the phenyl moiety. In this process, three fluorine radicals are released sequentially from one fluoxetine molecule, and the three carbon radicals left in the structure are terminated one by one with three hydrogen radicals to form a methyl functional group (CH_3). In other words, the trifluoromethyl group (CF_3) turns into difluoromethyl group (CHF_2) first, and this process continues until the methyl group (CH_3) is achieved.

Fig. 3 represents the results obtained from the characterization of propranolol solution treated with plasma. Fig. 3a shows the change in the chromatograms of the propranolol (retention time of 3.2 min) for various treatment periods. The decrease in the peak intensity of the chromatograms as the treatment time increased can be attributed to the degradation of the parent compound, propranolol. To investigate the degradation kinetics of propranolol, the area under the peak of each chromatogram is plotted as a function of the treatment time, as depicted in Fig. 3a. Similar to the case of fluoxetine, the degradation of propranolol followed exponentially decaying kinetics (R^2>0.99). However, in this case, the degradation time constant is 0.79 h, which is quadruple of the value obtained for fluoxetine (Fig. 2b). This shows that propranolol molecules are more recalcitrant towards degradation during the plasma treatment process as compared to fluoxetine molecules.

What's more, using Eq. (1) and Eq. (2), one can obtain the removal percentage and energy yield of 99% and 0.13 g/kWh (0.5 mmol/kWh), respectively. To evaluate the degree of mineralization of propranolol solutions and compare it to the values obtained for fluoxetine, TOC analysis was performed. Fig. 3c and Fig. 3d illustrate the TOC change for propranolol solutions as a function of the treatment time for solutions prepared in tap water and Milli-Q water, respectively. Based on the TOC results, one can obtain the degree of mineralization of 17% for propranolol solutions in tap water and 20% for solutions in Milli-Q water. The lower degree of mineralization in tap water is due to the inhibitory effect of ionic species in tap water, as discussed earlier.

Moreover, comparing the TOC results for both contaminants show that the degree of mineralization for fluoxetine solutions was much higher than this value for propranolol solutions (60% vs. 17% in tap water). This shows that not only are propranolol molecules more recalcitrant during the plasma treatment, but their byproducts are also more recalcitrant compared to fluoxetine byproducts. Finally, the IC values of the propranolol solutions in tap water and Milli-Q water showed similar trends to the case of fluoxetine. These

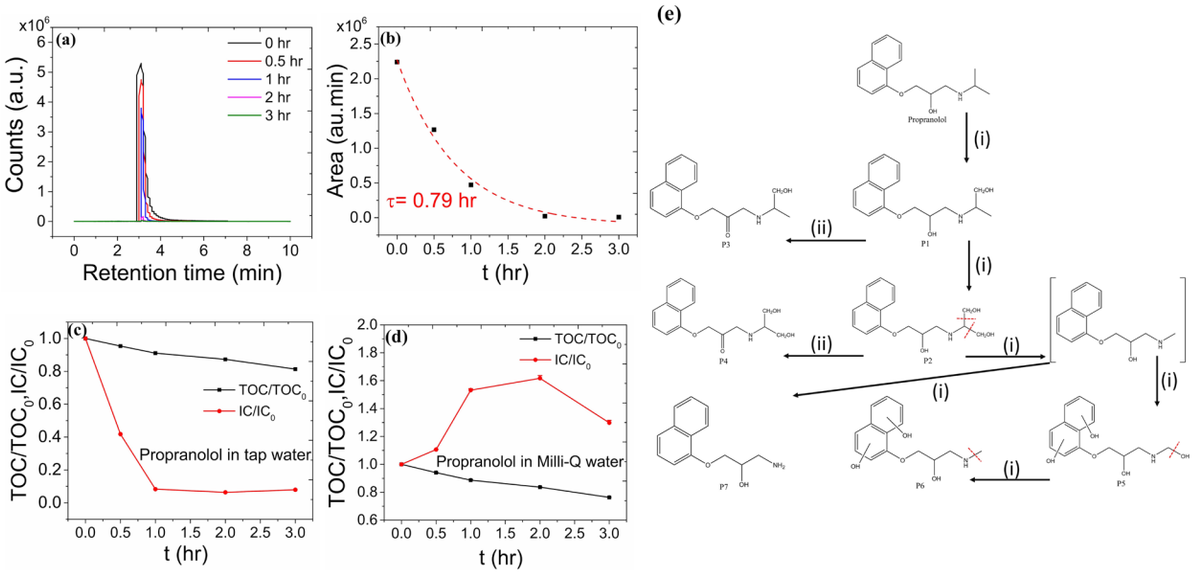

Fig. 3. Characterization results achieved from propranolol solutions treated by plasma is shown. The data in (a) and (b) are obtained from the chromatograms obtained during HPLC-MS analysis. (c) and (d) show the TOC analysis of samples in tap water and Milli-Q water, respectively. Finally, a proposed degradation mechanism is shown in (e) in which reactions with (i) hydroxyl radicals and (ii) ozone molecules are evident.

trends can be justified with explanations similar to the ones previously presented.

HPLC-MS was utilized to identify the degradation byproducts of propranolol. Table 2 lists the byproducts identified in the plasma treatment process of propranolol.

Considering the degradation byproducts in Table 2, a degradation mechanism was suggested for propranolol and its byproducts, as shown in Fig. 3e. Two main degradation pathways can be identified for propranolol and its byproducts. These are (i) reaction with hydroxyl radicals and (ii) reaction with ozone molecules. The interaction of propranolol and its byproducts with hydroxyl radicals manifests itself in two ways. The first pathway is the hydroxylation of the organic molecules. This in turn can occur in two different positions along the organic molecule's chain. The first position is the hydroxylation of the methyl functional groups (CH_3) at the end of the molecular chain. This process transforms the methyl functional groups into hydroxymethyl functional groups (CH_2OH). This can be seen in the formation of P1 from propranolol and subsequently P2 from P1, as shown in Fig. 3e. The second position for the hydroxylation of the organic molecules is in the aromatic ring. This is shown in the formation of P5 and P6. This process is one of the most well-known processes for oxidative degradation of organic molecules [44].

The second pathway for the interaction of hydroxyl radicals with propranolol and its byproducts is the cleavage of the chemical bonds in the molecular structure. This is depicted in Fig. 3e in the formation of the transient byproduct (in the bracket). Moreover, the cleavage of the bonds is evident in the formation of P6 from P5. As mentioned previously, the other primary degradation pathway for propranolol and its byproducts is through the interaction with ozone molecules. This process is known as the oxidation of the secondary alcohols to ketones [45] and can be seen in the transformation of P1 to P3 and P2 to P4. It has to be mentioned that in water treatment process that are based on the formation of plasma in air, ozone is created in the gas phase and enters the aqueous phase through the interface [46,47].

Table 2
Degradation by-products of propranolol detected by HPLC-MS

Treatment time (h)	Detected m/z	Identification	Ratio*
0	260.16	Propranolol	1.000
0.5	290.13	P4	0.073
	281.11	P5	0.027
	274.14	P3	0.043
	292.15	P2	0.050
	276.16	P1	0.233
	265.12	P6	0.070
	218.11	P7	0.027
	260.16	Propranolol	0.533
1	281.11	P5	0.053
	274.14	P3	0.023
	276.16	P1	0.030
	292.15	P2	0.040
	290.13	P4	0.058
	265.12	P6	0.040
	260.16	Propranolol	0.023
2	260.16	Propranolol	0.004
3	260.16	Propranolol	0.001

*The ratio is calculated by dividing the peak intensity (count) of each compound by the peak intensity of the parent compound.

4. Conclusion

A non-thermal plasma treatment system in the form of FESCD was used to degrade pharmaceutical contaminants fluoxetine and propranolol in tap water. The application of the FESCD system allowed the generation of plasma from only one electrode on the surface of water using a simple AC waveform. After treating the solutions for 3 h, almost 100% removal of both contaminants was achieved with the energy yield in the range of 0.12–0.13 g/kWh. TOC analysis revealed a higher degree of mineralization for solutions containing fluoxetine (60% for fluoxetine and 17% for propranolol). Based on the degradation byproducts identified by HPLC-MS, reaction with hydroxyl radicals was proposed as the primary degradation pathway for fluoxetine and its byproducts. In the case of propranolol, the oxidation of secondary alcohols to ketones suggested the possible role of ozone molecules in the degradation process alongside hydroxyl radicals.

Conflict of Interest Statement

There are no conflicts to declare.

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