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Degradation of pharmaceutical contaminants in water by an advanced plasma treatment

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ABSTRACT

Contamination of water bodies with pharmaceutical compounds and their adverse effects on human and wildlife has been a source of concern for many societies. The need for more effective water treatment processes has been felt to eliminate these contaminants from water. In this work, single electrode non-thermal plasma in a floating electrode streamer corona discharge (FESCD) system is utilized for effective degradation of antibiotic ampicillin and non-steroidal anti-inflammatory drug (NSAID) ibuprofen. It was found that, after 3 h of plasma treatment, 100% of ampicillin and 90% of ibuprofen was degraded in the solution. The energy yield (the amount of degraded contaminants by consuming 1 kWh of energy) was calculated to be 0.12–0.13 g/kWh. Total Organic Carbon (TOC) measurements showed 20% and 60% mineralization for ampicillin and ibuprofen, respectively. Hydroxyl radicals were found to play a major role in the degradation of both contaminants. Furthermore, in both cases, the formation of oxygenated by products implied a possible role of ozone molecules in the degradation mechanism. Finally, Fluorescence Excitation-Emission Matrix (FEEM) was utilized to track the degradation of the contaminants in the tap water through the change in fluorescence properties and the connections between FEEM signals and the identified degradation by products were outlined.

Keywords: Plasma; Pharmaceutical contamination; Energy yield; Mineralization; Degradation pathway; Fluorescence excitation-emission matrix

1. Introduction

The detection of pharmaceutical compounds, as subclasses of organic contaminants, in various water bodies has recently raised serious concerns due to their possible negative impacts on public health and environment [1]. Previous studies have indicated that these compounds are present in the environment at very low concentrations (in the range of ng/l to μg/l) [2,3]. However, a report published by the World Health Organization (WHO) in 2011 acknowledged that the effect of long-term exposure to these compounds, even at low concentrations, is unknown and can be catastrophic [4]. This problem becomes more acute considering the rate of the population growth, the discovery of new drugs and the realization of new applications for existing drugs [5]. The introduction of pharmaceutical contaminants can occur through various pathways including human and animal excretion,

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improper disposal of unwanted drugs from houses and hospitals, incorrect waste disposal from pharmaceutical manufacturing, etc. [6].

Antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs) are the most consumed pharmaceutical drugs around the world. Reports indicated that more than 100,000 to 200,000 metric tons of antibiotics are used annually worldwide [7]; amongst which the class of β-lactam antibiotics [8] (50–70% of all antibiotics), and more specifically penicillins [9] (up to 44% of β-lactam class), form the largest consumption group. The primary concern regarding the presence of antibiotics in water is the emergence of antibiotic-resistant bacteria that can cause life-threatening infections such as methicillin-resistant Staphylococcus aureus (MRSA) [6,10]. Other negative impacts include disruption in the metabolism of bacterial communities and interference with the photosynthesis of plants [11]. NSAIDs and in particular ibuprofen, as an analgesic drug, are one of the most used drugs around the world [12] with annual production exceeding 15,000 tons worldwide [13]. The hazardous effects of ibuprofen include interference with the growth of aquatic phototrophs, inhibition in reproduction (e.g. in snails), and lower fish survival [14].

Most of the pharmaceutical compounds can survive conventional water treatment processes, such as biological treatment, and thus find their way into various water sources [15–17]. Given that, a significant amount of research and development is currently underway to develop new methods for the effective removal of pharmaceutical compounds. Advanced Oxidation Processes (AOPs) are considered to be one of the most suitable methods for the degradation of pharmaceutical compounds in water. The working principle of all AOPs is generally based on in-situ generation of highly reactive transient oxidizing agents, such as hydroxyl radicals ($OH^{\bullet}$) in the aqueous phase [18]. These oxidizing agents can break down contaminants within the liquid and are proven to be very effective in water treatment [19,20]. Various AOPs used for degradation of pharmaceutical contaminants include ozonation [21,22], Fenton reactions [23], photocatalysis [24], etc. Recently, the application of non-thermal plasmas (NTP) for the removal of pharmaceutical compounds from water has emerged as a viable and effective oxidation technique. This method enables simultaneous production of multiple reactive chemical agents such as hydroxyl radicals, ozone, hydrogen peroxide (H_2O_2), and peroxynitrite, thereby improving the performance of the decontamination process [25–30]. Various plasma-based water treatment systems have been designed to tackle the problem of pharmaceutical contaminations in water. Magureanu et al. used a Dielectric Barrier Discharge (DBD) plasma generator with falling liquid film to remove three antibiotics from water, namely amoxicillin, ampicillin and oxacillin [31]. A similar system was used by other researchers to degrade a variety of contaminants in water such as sulfadiazine [32], pentoxifylline [33], norfloxacin [34] and enalapril [35] and many other compounds [36–39]. Another type of plasma generator that has been widely used is pulsed corona discharge type of systems. In this type of plasma generators, an asymmetric electrode configuration is used to create an intense electric field gradient. Various electrode configurations including wire-to-plate [40], wire-to-cylinder [41] and pin-to-plate [42] have been investigated. The pulsed corona discharge plasma has been already used for the degradation of pharmaceutical compounds such as ibuprofen [12] and paracetamol and β-oestradiol [15]. Despite their effectiveness, most of the plasma treatment systems based on either DBD or pulsed corona discharges suffer from at least one of the following disadvantages. First, it is necessary to use two electrodes for the generation of plasma in both systems. Previous studies have shown that the distance between the two electrodes (one high voltage and one ground electrode) significantly affects the discharge mode; transitions between the corona and the streamer mode becomes inevitable [43,44]. Moreover, submerged electrodes are susceptible to severe corrosion which is not desirable for the development of a robust system. Second, in most cases, generation of plasma is achieved using pulsed high voltages with amplitude of 10–20 kV, pulse duration of 100–300 ns and voltage rise rate of 0.5–3 kV/ns. Circuitry of such a system can be complicated and upscaling becomes a serious issue due to the high demands on the electronics of large pulse power supplies [45].

In this study, a floating electrode streamer corona discharge (FESCD) is used to degrade pharmaceutical contaminants ampicillin and ibuprofen in water [46]. The generation of plasma in the FESCD system is somewhat similar to the pulsed corona discharge setup used by Panorel et al. [15] beta-oestradiol and salicylic acid. However, in this newly designed system, plasma is generated using only one electrode. Moreover, simple alternating current (AC) waveforms can be used to create plasma between the electrode and water surface. The specific goals of this study is to (i) evaluate the feasibility of the FESCD setup for degradation of pharmaceutical compounds using standard water characterization methods such total organic carbon (TOC) analysis; (ii) identify the degradation byproducts using high-performance liquid chromatography-mass spectrometry (HPLC-MS) and; (iii) explore the application of fluorescence excitation-emission matrix (FEEM) for the characterization of water by finding the possible connections between FEEM and HPLC-MS analyses results.

2. Experimental

2.1. Materials

Ampicillin sodium salt and ibuprofen (>98%, obtained from Sigma Aldrich Ontario, Canada) were the target contaminants used throughout this study. Potassium indigotrisulfonate (Sigma Aldrich Ontario, Canada) was used for detection of ozone in water. To prepare the solutions for plasma treatment, each contaminant was dissolved separately in tap water (100 mg/l or 0.28 mM and 0.48 mM for ampicillin and ibuprofen, respectively). Tap water (initial pH and conductivity of 7.2 and 3.5 mS/cm) was used as the main water matrix due to its similarities to real life situations. The same concentration of the contaminants was also dissolved in Milli-Q water (18.2 MΩ/cm) for comparison purposes. Ambient air was used as the gas medium during the plasma generation process.

2.2. Experimental setup

Fig. 1 shows the schematic illustration of the experimental setup. Detailed description of the experimental setup can be found elsewhere [47]. Single electrode plasma in air at atmospheric pressure is created using a helical resonator. A sinusoidal wave at the resonance frequency of the resonator is fed to a power amplifier by a function generator. The input voltage and current to the helical resonator are measured to calculate the power consumption. A Pt/Ir electrode (conical shape, tip diameter of approximately 0.5 mm) is used to generate the plasma due to its stability at high temperatures. The water samples are stirred by a magnetic stirrer to assure the homogeneity of the reactions. Each solution (100 mg/l of ampicillin or ibuprofen in tap water or Milli-Q water, described in section 2.1) was treated with plasma for various periods of 0, 0.5, 1, 2 and 3 h. For each treatment time, 60±1.0 ml of the desired solution was poured into a 100 ml glass beaker. The distance between the electrode tip and water surface (air gap distance) was fixed at 2 mm.

To keep the input power to the helical resonator constant, the Root Mean Square (RMS) input voltage and current to the resonator were fixed at 71 V and 200 mA, respectively. The treatment chamber was open at the top during each experiment. A Fisher Scientific Accumet® Excel conductivity meter (XL60, Ontario, Canada) was used to measure the conductivity of the solutions. The pH of solutions was measured by a Metller Toledo FiveEasy® pH meter equipped with InLab® Expert Pro-ISM probe (Ohio, US). It is worth mentioning that the maximum water temperature increase of 15–20°C was observed after the plasma treatment process.

2.3. Characterization

To analyze the treated (0.5, 1, 2 and 3 h) and untreated solutions (0 h), three standard analysis methods were used. To evaluate the degree of mineralization in each solution (both in tap water and Milli-Q water), a Total Organic Carbon-Inorganic Carbon (TOC-IC) analyzer (TOC-L, Shimadzu, Kyoto, Japan) was used. To determine the degradation byproducts of each contaminant and propose a degradation mechanism, an HPLC-MS (Agilent, Santa Clara, CA, USA) was utilized. Finally, (fluorescence excitation-emission matrix) FEEM measurements were carried out using a Varian Cary Eclipse spectrophotometer (Agilent, USA). Moreover, to evaluate the concentration of ozone in the solutions treated with plasma, Indigo dye method was used [48].

3. Results and discussion

3.1. Removal % and energy yield

In order to evaluate the treatment process in terms of the removal percentage and energy yield, HPLC-MS chromatograms of each compound were investigated. The change in the chromatogram of ampicillin and ibuprofen as a function of the treatment time is shown in the insets of Fig. 2a and Fig. 2b, respectively. The area under the curve for these compounds was also plotted as a function of the treatment time. The insets show the extracted ion chromatograms (EIC) at retention time of 4.4 min and 5.6 min, corresponding to ampicillin (m/z of 350.11) and ibuprofen (m/z of 206.13) molecules, respectively.

As can be observed in Fig. 2, the degradation follows an exponentially decaying behavior for both parent compounds. By fitting the data shown in Fig. 2 with an exponentially decaying function ($R^2 > 0.99$), the time constant for degradation of each compound can be obtained. The results show that the time constant for the degradation of ampicillin is lower than that of ibuprofen. This possibly shows that ibuprofen molecules are more recalcitrant towards reaction

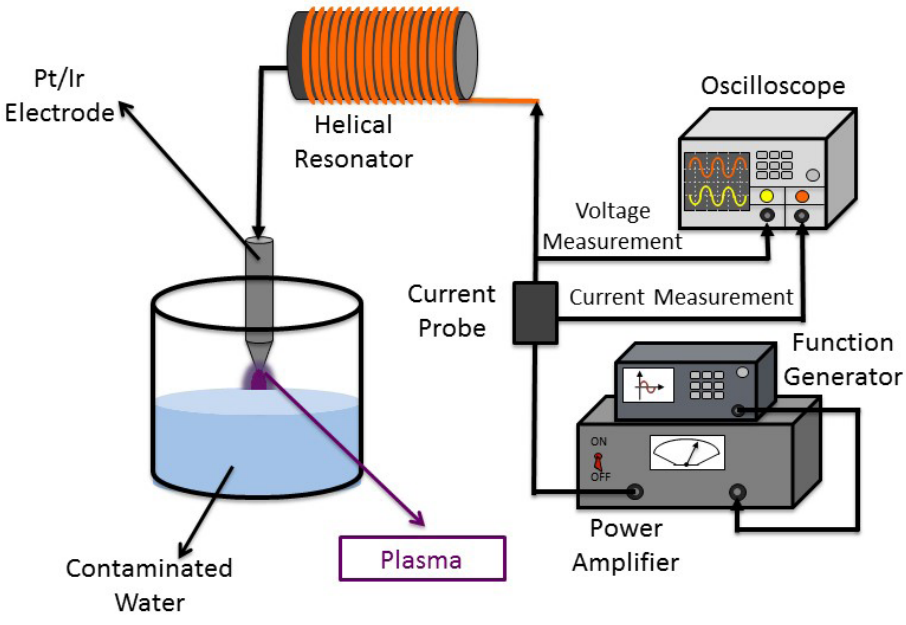

Fig. 1. The schematic representation of the experimental setup is shown.

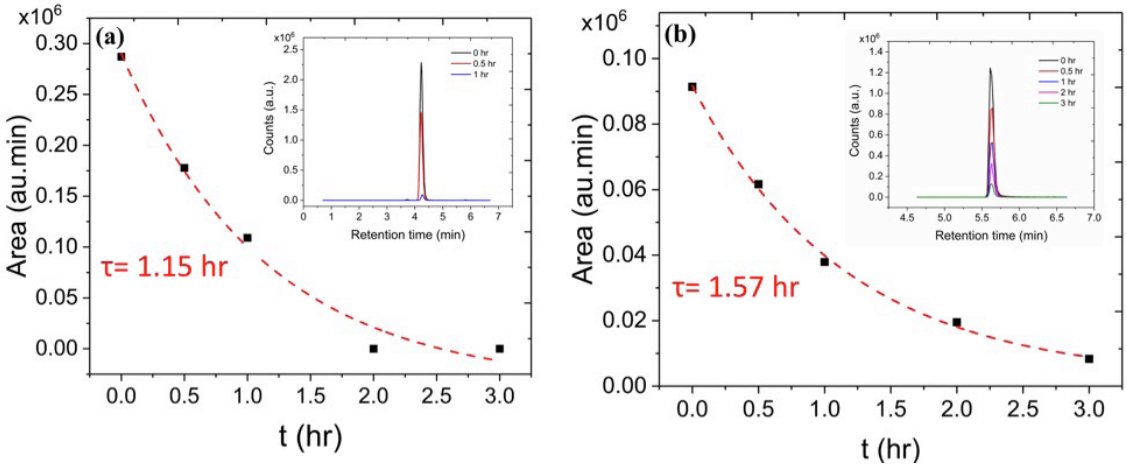

Fig. 2. The change in the area underneath the curve in the chromatogram of (a) ampicillin and (b) ibuprofen as a function of time.

with various oxidizing agents ($OH^{\bullet}$, O_3, etc.) which are created during the plasma treatment process. The removal percentage is calculated by the following equation:

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

where A and A_0 are the area under the chromatogram's peak at each treatment time and before treatment (original peak area), respectively. Hence, the removal percentage for ampicillin and ibuprofen is calculated to be approximately 100% and 90%, respectively. The lower removal percentage of ibuprofen confirms less vulnerability of these molecules towards plasma treatment process than that of ampicillin. The energy yield of the plasma treatment process is calculated as follows:

$$\text{Energy Yield} = \frac{C_0 VR}{Pt} \times 0.01 \quad (2)$$

In this equation, C_0 is the initial concentration of the compound(g/l), V is the volume of the treated sample (l), R is the final removal percentage after 3 h, P is the power input to the helical resonator (kW) and t is the duration of plasma treatment (h). Using Eq. (2), the energy yield of the process was calculated to be 0.13 g/kWh and 0.12 g/kWh for ampicillin and ibuprofen, respectively. It is worth noting that by improving the design of the treatment system, these values can be further increased to reach high values reported previously (e.g 105 g/kWh [31] oxacillin and ampicillin). For instance, the volume of the treated water can be significantly increased by using flow through systems where water is circulated between a reservoir tank and a plasma treatment tank. Moreover, each plasma electrode andits electronics can be configured in a small package. As a result, a flow through system with multiple plasma electrodes can be designed. Such improvements are the subject of our ongoing studies.

3.2. Degree of mineralization

The removal percentage only describes the degradation of the parent compounds, i.e., ampicillin and ibuprofen. However, the degradation of byproducts and their evolution during a treatment process are of great importance. TOC measurement provides a general idea about the evolution of the parent compounds and their byproducts as an ensemble. The change in the normalized TOC (TOC/TOC_0) and normalized IC (IC/IC_0) with time is shown in Figs. 3a and 3b for ampicillin in tap water and Milli-Q water, respectively. As can be seen, the degree of mineralization for ampicillin solutions in tap water is about 20%, whereas for the solutions made with Milli-Q water it is approximately 25% (TOC/TOC_0 of 0.8 vs. TOC/TOC_0 of 0.75 at 3 h). Thisindicates the potential inhibiting role of scavengers such as CO_3^{2-} that might be present in the tap water. As shown in Fig. 3a, the normalized IC of the ampicillin solutions in tap water decreased significantly over time. This behavior can be explained considering the initial IC of the tap water (about 23 mg/l-C) and the decrease in the pH of the solution after plasma treatment (data not shown). As the treatment time passes, the pH of the solution decreases possibly due to the formation of species such as NO_3^- in water [49,50]. The acidification of the solution, therefore, transforms the CO_3^{2-} and HCO_3^-, present initially in tap water, into CO_2 that eventually leaves the solution. Hence, normalized IC declines significantly. The results shown in Fig. 3b indicate that the normalized IC for the ampicillin solutions in the Milli-Q water underwent an initial increase followed by a subsequent decrease. To explain this behavior, it should be noted that the initial IC of the Milli-Q water solutions is very low (<1 mg/l-C). The initial increase in IC/IC_0 of the Milli-Q water can possibly be attributed to the formation of carbonate ions from the degradation of ampicillin and its byproducts [49].

The subsequent decline is likely due to the acidification of the solution after the plasma treatment and transformation of carbonate ions into CO_2, as described earlier. Fig. 3c and Fig. 3d shows the change in TOC/TOC_0 and IC/IC_0 of solutions containing ibuprofen in tap water and Milli-Q water, respectively. Similar to the case of ampicillin, the degree of mineralization in ibuprofen solutions is higher in the Milli-Q water compared to the tap water. The change in IC/IC_0 of solutions in tap water and Milli-Q water was also found to be the same as the ampicillin case. Taking a closer look at TOC/IC results

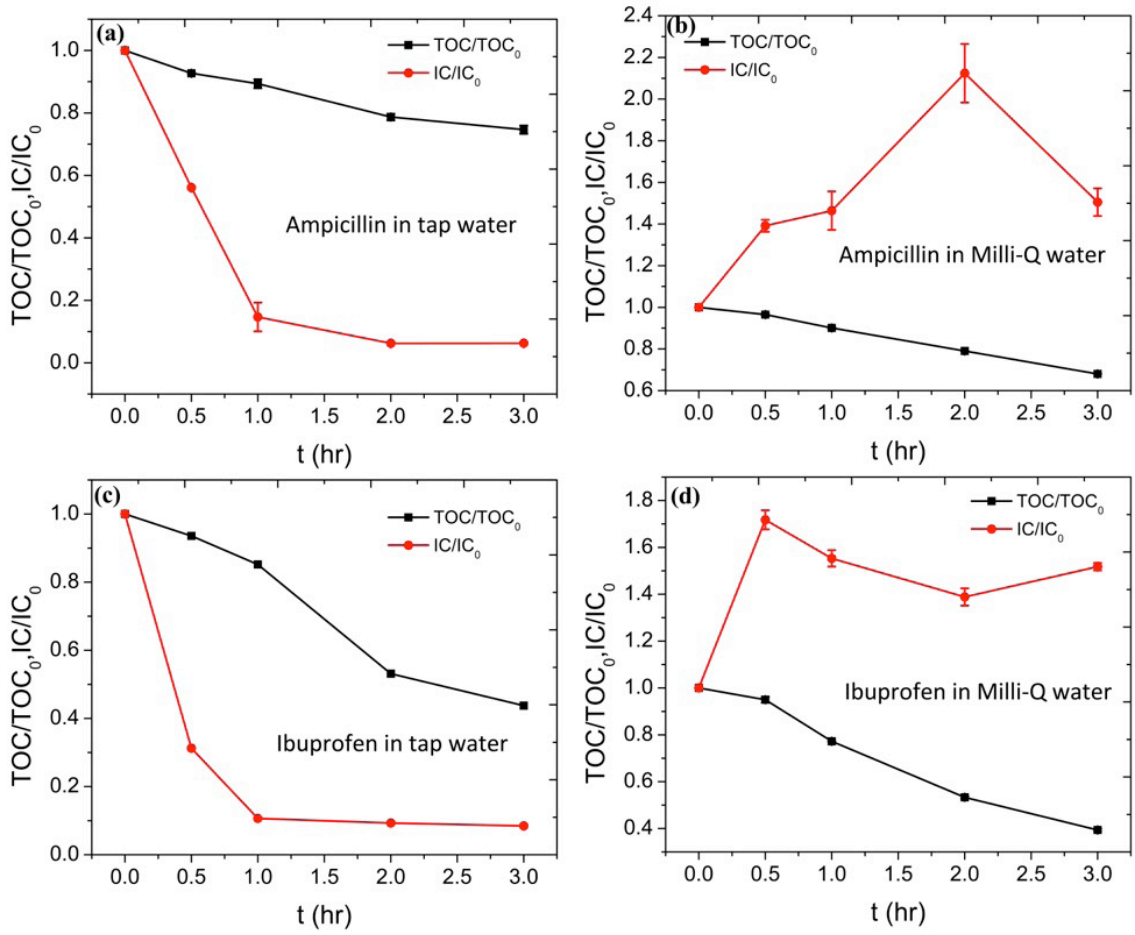

Fig. 3. The change in the relative TOC (TOC/TOC_0) and IC (IC/IC_0) of the solutions for (a) ampicillin in tap water (b) ampicillin in Milli-Q water (c) ibuprofen in tap water and (d) ibuprofen in Milli-Q water. Regardless of the nature of the pharmaceutical contamination, the inorganic content (IC/IC_0) of the tap water solutions decreased significantly after 1 h.

reveals that, regardless of the type of the water matrix, the degree of mineralization is significantly higher for ibuprofen solutions than that of ampicillin solutions (~60% vs. ~20%). This result shows that although ibuprofen itself is more recalcitrant as compared to ampicillin (see section 3.1), its degradation byproducts as a whole are more prone to degradation during the plasma treatment process.

3.3. Degradation byproducts and pathway

So far, this paper has focused on the degradation of the parent compounds and the combined evolution of the organic content in the solution. It is now necessary to identify the byproducts of the degradation process which is recognized as an important step in treating organic contaminants in water. In this study, HPLC-MS was used to analyze the solutions with Milli-Q water matrix. Table 1 shows a summary of the detected chemical species in ampicillin solutions treated for various periods. It has to be mentioned that the minimum detectable mass in this analytic method is 100 Da. It is interesting to note that HPLC-MS could not detect any compound for the treatment periods longer than 1 h. Moreover, beside ampicillin, the only detected byproduct with a known structure is ampicilloic acid. This compound was only present at the beginning of the treatment process (until 30 min treatment) and disappeared afterward.

Based on the chemical species detected by HPLC-MS for ampicillin solution, a degradation pathway was proposed, as shown in Fig. 4. Three major reaction pathways can be predicted for ampicillin solutions. The first reaction pathway is the hydrolysis of ampicillin molecules that results in the formation of ampicilloic acid. This reaction pathway is entirely independent of the plasma treatment process, and is due to the dissolution of the ampicillin sodium salt in water [9]. Based on the byproducts detected by HPLC-MS, the other two reaction pathways that happen as a direct result of plasma treatment are reaction with hydroxyl radicals and ozone molecules. Byproducts such as P1, P2, P4, and P7 were formed by the addition of one or multiple oxygen atoms to the organic molecules.

This may be explained by the action of ozone which is typically created during plasma treatment process in ambient air and dissolves in the aqueous phase [51,52]. The presence of ozone in the solution will be further explored in section 3.5. On the other hand, byproducts such as P3, P5, and P6

Table 1
Chemical species detected by HPLC-MS for ampicillin solutions

Treatment Time (hr)	Detected m/z	Identification	Ratio
0	350.11	Ampicillin	1.000
	368.12	Ampicilloic acid	0.063
0.5	350.11	Ampicillin	0.625
	368.12	Ampicilloic acid	0.016
	366.11	P1	0.013
	382.1	P2	0.011
	259.07	P3	0.008
	349.09	P4	0.017
	333.09	P5	0.004
	322.12	P6	0.004
1	350.11	Ampicillin	0.031
	366.11	P1	0.003
	382.1	P2	0.016
	349.09	P4	0.006
	398.1	P7	0.004
2	–	–	0.000
3	–	–	0.000

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

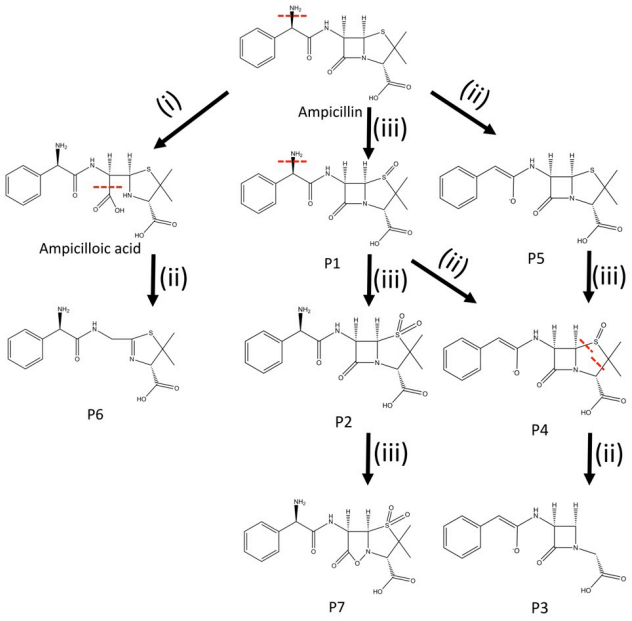

Fig. 4. A suggested degradation pathway for ampicillin in MilliQ water. Three major reactions are predicted, based on the species detected by HPLC-MS: (i) hydrolysis of the ampicillin molecules and formation of ampicilloic acid which occurs as a result of the dissolution of ampicillin sodium salt in water, (ii) reaction of organic molecules with hydroxyl radicals, and (iii) reaction of organic molecules with ozone molecules.

were formed due to the cleavage of chemical bonds (shown by a red dash line in Fig. 4). This phenomenon is likely to be related to the reaction of organic molecules with hydroxyl radicals. It is worth noting that the formation of P3 from P4 causes the detachment of one dimethyl sulfoxide (DMSO) molecule from one P4 molecule. The formation of a brownish color in the solution at initial steps of the plasma treatment is most probably due to the formation of DMSO molecules in the solution. This brownish color faded away at later stages of the plasma treatment (2 h and 3 h treatment period), indicating that DMSO molecules were degraded further and formed smaller molecules. Considering the results obtained by HPLC-MS and TOC analysis, it can be concluded that 20–25% of the organic molecules shown in the degradation pathway were completely mineralized after 3 h of plasma treatment. The rest 70–75% of the organic content remained in the solution are possibly small organic molecules that could not be detected by HPLC-MS. If the plasma treatment process takes place long enough, these small organic molecules are potentially turned into molecules with single ring structures first, then the degradation continues until all organic molecules are transformed into its smallest constituents such as SO_4^{2-} and more importantly CO_2 [49].

HPLC-MS was also used to determine the degradation byproducts of plasma treated solutions containing ibuprofen and the results are presented in Table 2.

Table 2
Information on the species detected by HPLC-MS for ibuprofen solutions

Treatment time (h)	Detected m/z	Identification	Ratio*
0	206.13	Ibuprofen	1.000
0.5	190.14	B4	0.020
	270.11	B2	0.036
	178.14	B3	0.036
	222.13	B1	0.127
	206.13	Ibuprofen	0.682
1	193.0514	B8	0.019
	150.1	B11	0.041
	226.12	B6	0.016
	190.14	B4	0.018
	256.13	B7	0.028
	175.1137	B9	0.025
	222.13	B1	0.015
	178.14	B3	0.082
	206.13	Ibuprofen	0.409
	270.11	B2	0.027
2	134.11	B5	0.127
	270.11	B2	0.064
	206.13	Ibuprofen	0.209
	226.12	B6	0.015
	193.0514	B8	0.015
3	165.0565	B12	0.017
	150.1	B11	0.032
	175.1137	B9	0.026
	206.13	Ibuprofen	0.100

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

Using the chemical species presented in Table 2, a degradation pathway was proposed for ibuprofen, as shown in Fig. 5. Two major reaction pathways can be considered for the degradation of ibuprofen and its byproducts. In the first pathway, ozone molecules can react with ibuprofen molecules. The presence of byproducts such as B2 suggests that ozone molecules possibly cleave the aromatic ring in ibuprofen molecules and create carboxylic acid functional groups [38]. A more important reaction pathway is through the reaction of hydroxyl radicals with organic molecules. Hydroxyl radicals react with organic moleculesin two ways.The first one is the hydroxylation of ibuprofen molecules and formation of B1. Since the hydroxyl functional group is an electron-donating group, it increases the electron density of the neighboring bonds through the inductive effect[53]. As a result, the bonds closerto the added hydroxyl group become stronger. That is probably why further degradation of B1 starts from the opposite side of the molecule (formation of B12), until the aliphatic chain is completely cleaved (B11). The second way in which hydroxyl radicals react with the parent compound and its byproducts is through the direct cleavage of bonds and formation of B4, B7, and B8). Results presented in Fig.5 indicate that the smallest detected byproduct in ibuprofen solutions is B5 (m/z of 134.11). However, a comparison with TOC measurements (Fig. 3d)indicates that further degradation of this compound by plasma results in approximately 60% mineralization.

3.4. Fluorescence Excitation-Emission Matrix (FEEM)

The previous section has shown that HPLC-MS analysis can be applied for identifying the degradation byproducts of ampicillin and ibuprofen. Based on these tracked byproducts, degradation pathways were proposed for each contaminant. However, identification of unknown compounds by HPLC-MS is only possible for solutions with simple water matrix, i.e. Milli-Qwater. Here in this section, the application of FEEM analysis to monitor the degradation of the contaminants in more complex water matrices such as tap water is described. In general, FEEM analysis is based on the fluorescence property of the organic molecules. The result of such a study is normally shown as contour maps with the excitation wavelength on the y-axis and the emission wavelength on the x-axis.

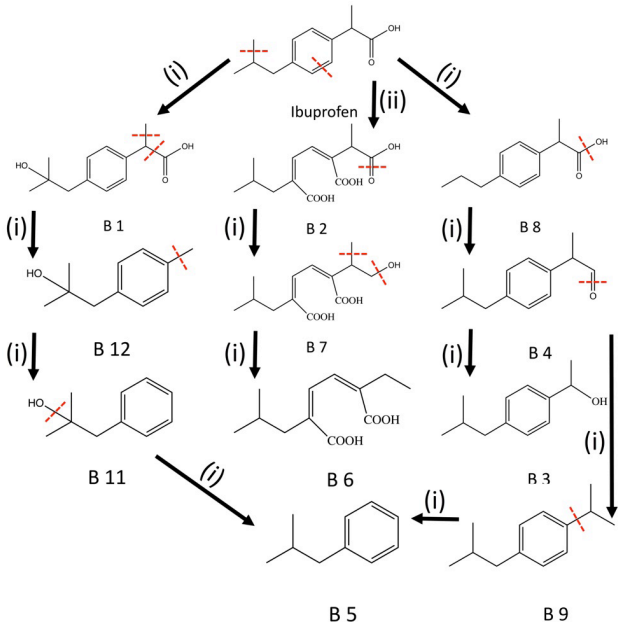

Fig. 5. A proposed degradation pathway for ibuprofen molecules. The two main reaction pathways include: the reaction with (i) hydroxyl radicals and (ii) ozone molecules.

The FEEM analysis can provide rough information about the fate of pharmaceutical contaminants in a solution. The change in the fluorescence intensity or the position of the signal in the FEEM map can be related to the possible byproducts formed during the treatment. Fig. 6 depicts the evolution of the fluorescence signal for solutions containing ampicillin as a function of the treatment time. Fig. 6a shows the FEEM signal of the blank solution (tap water without ampicillin) as the control sample. The change in the fluorescence signal of the solutions containing ampicillin and its byproducts is shown in Figs. 6b–6f, corresponding to the treatment times of 0–3 h. It is interesting to note that at the beginning of the plasma treatment process (30 min, Fig. 6c), the emission intensity of the solution increased. This was followed by a decline in the intensity at longer treatment times until the fluorescence signal almost disappeared at a treatment time of 3 h.

To interpret these changes in FEEM signals over time, a fundamental understanding of fluorescence phenomena is required. One structural feature common to all organic molecules that show significant fluorescence properties in visible and near ultra-violet (UV) wavelengths is the presence of conjugated double bond systems [54]. A possible explanation is that the non-localized π-electrons in these systems are less bound to the molecule and act in many ways similar to electrons in metals. As a result, the excitation of these electrons with visible and near UV wavelengths and their subsequent fluorescence emission is possible. The second important structural feature is related to the arrangement of these conjugated double bonds in a molecule. It is well known that the fluorescence behavior of molecules containing conjugated double bonds in a cyclic structure is different from those with conjugated double bonds in a chain structure. This is probably due to the difference in the degree of non-localization of π-electron in the two systems. In cyclic structures, electrons are completely non-localized and can circulate uniformly around the ring. On the other hand, in chain structures electrons are only free towards the center of the chain and are localized at the ends. For localized electrons, the probability of radiation less transfer from an excited state is significantly higher compared to non-localized electrons. In other words, the probability of a successful fluorescence emission is greater from an excited non-localized electron. This could be a reason why fluorescence emission is found more in molecules with cyclic structure compared to chain structures [54]. Finally, the presence of nitrogen or oxygen atoms in an organic molecule can enhance the fluorescence properties. This is likely due to the lone electron pairs in these atoms which enables them to resonance, similar to aromatic rings [55,56].

Considering the above-mentioned molecular structural features, the FEEM results obtained for ampicillin solutions

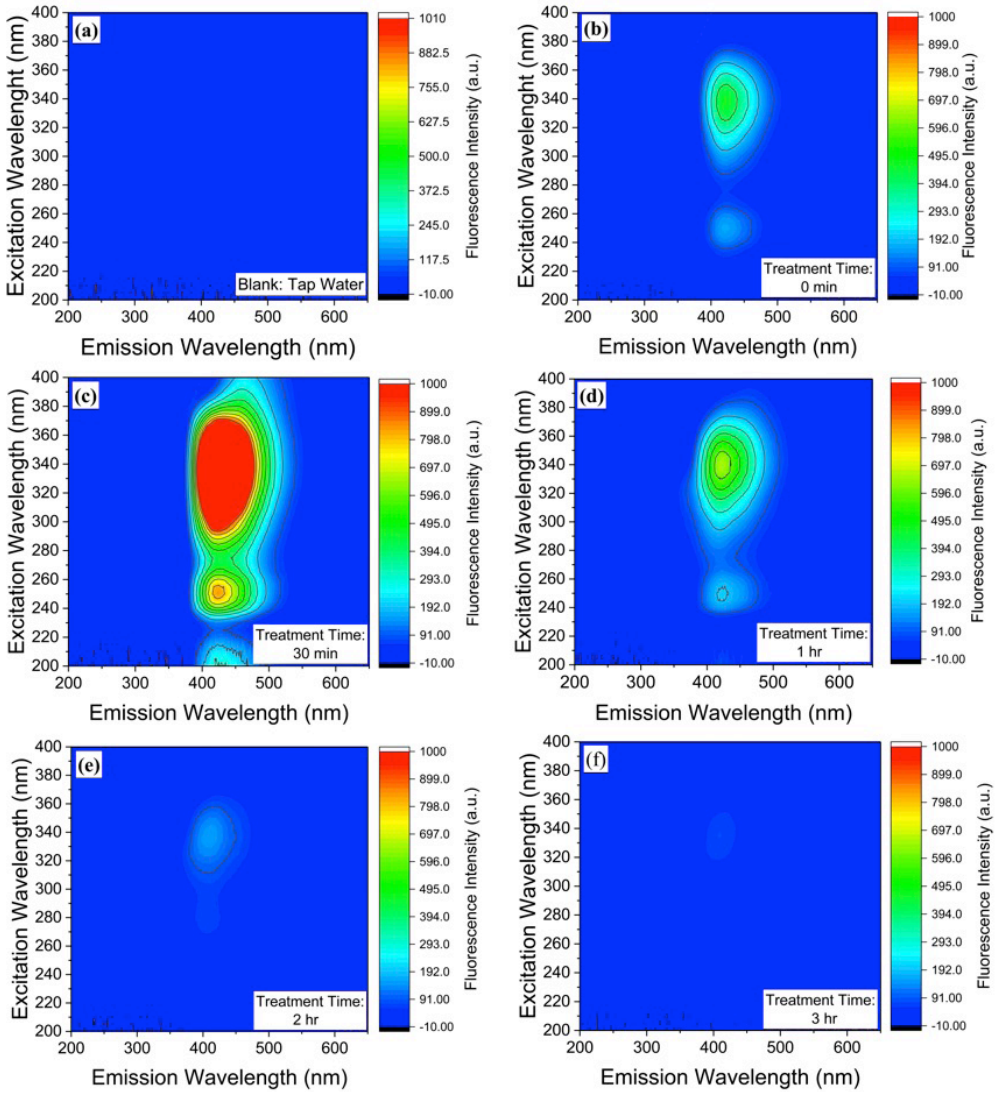

Fig. 6. FEEM results to study the degradation of ampicillin molecules and its byproducts in tap water over time.

can be explained. It should be noted that not only does the presence of oxygen or nitrogen enhance the fluorescence signal, but also their possible addition to an organic molecule can increase the fluorescence emission. As a result, the initial increase in the fluorescence emission of ampicillin containing solutions (at a treatment time of 30 min) can be attributed to the oxygenation of ampicillin or its byproducts. This hypothesis can be confirmed by HPLC-MS results that indicated the presence of oxygenated byproducts (P1, P2, P4, and P7) in the solution (Fig. 4). It has to be mentioned that oxygenated byproducts with small size (less than 100 Da) that are not detected during the HPLC-MS analysis might also contribute to this initial increase in the fluorescence properties. The subsequent decrease in the fluorescence intensity can be attributed to the breakdown of the organic molecules. After 3 h of plasma treatment, this breakdown can either cause the complete mineralization of the organic compounds (about 20–25% based on TOC results in Figs. 3a and Fig. 3b) or result in the transformation of larger molecules to much smaller molecules. These molecules were too small to be detected by HPLC-MS (Table 1, treatment time of 2 h and 3 h).

A similar analysis was performed on the FEEM results obtained for solutions of ibuprofen in tap water (Fig. 7). Contrary to the trend observed for ampicillin, the fluorescence intensity did not show any initial increase. From the fluorescence properties standpoint, either no oxygenation occurred for ibuprofen and its byproducts, or oxygenation happened at the expense of the cleavage in the cyclic structure. This result can be confirmed by means of HPLC-MS analysis. As shown by the degradation pathway in Fig. 5, although for both ibuprofen and ampicillin solutions, plasma treatment resulted in oxygenated byproducts (B2, B6, and B7), however, in the case of ibuprofen this oxygenation cleaved the aromatic ring structure. Since the probability of a successful fluorescence emission is much higher from π-electrons of a cyclic system this cleavage in the aromatic ring (i.e. interference with the cyclic conjugated double bond structure) causes the fluorescence intensity to decrease[55].

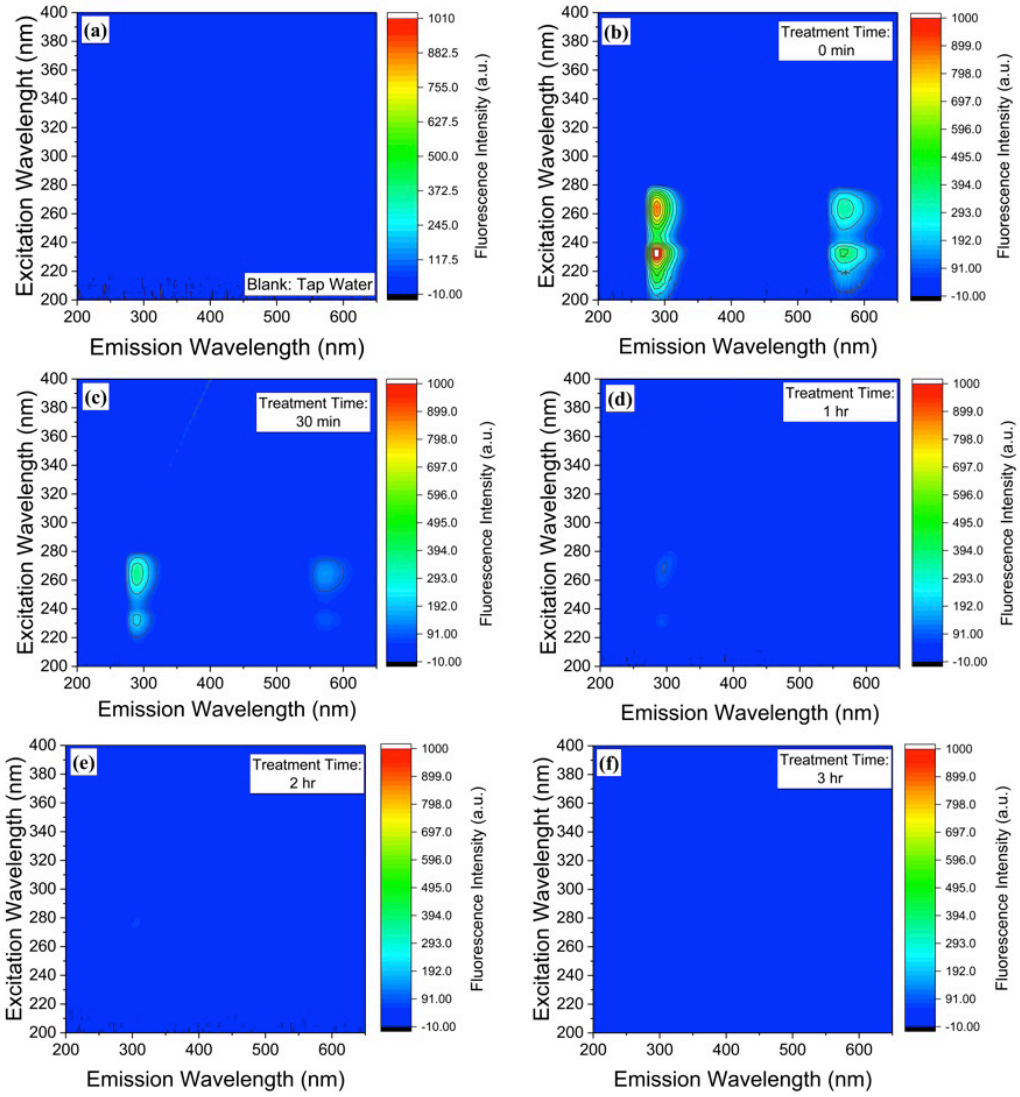

Fig. 7. FEEM results to study the degradation of ibuprofen molecules and its byproducts in tap water over time.

The continuous decline in the fluorescence intensity of ibuprofen solution over treatment time can be attributed to two reasons. The first reason is the mineralization of organic compounds (~60% based on the TOC results shown in Figs. 3) and Fig. 3d), as described for the ampicillin case. The second one is related to two notable structural changes in ibuprofen and its byproducts. The first structural change is the loss of the cyclic structures which becomes more crucial considering that this phenomenon was carried over to other ibuprofen byproducts, namely B6 and B7, as shown in Fig. 5. The other structural change that might be effective in lowering the fluorescence intensity is the loss of the oxygen atom that can be observed in transformation of B2 to B7.

3.5.Presence of ozone in the aqueous phase

As mentioned in section 3.3, one of the pathways for the degradation of ampicillin, ibuprofen and their byproducts is through the reaction with ozone. In this section, the presence of ozone in the aqueous phase is investigated employing the Indigo method. Bader et al. reported that there is only one C=C bond in the indigo molecule which is a potential reaction site with ozone (the red dash line in Fig. 8a) [48]. In an acidic environment, the amino groups in the indigo molecule are protonated; therefore, they are unreactive towards ozone. As a result, it can be expected that one molecule of indigo dye react with one molecule of ozone in the solution. The cleavage of the C=C bond by ozone molecule eliminates the absorbance of the solution at 600 nm [48]. This stoichiometric discoloration forms the basis of the quantification of ozone in the aqueous phase, using the calibration curve for potassium indigo trisulfonate (Fig. 8b).

Fig. 8c shows the change in the concentration of the detected ozone in one cycle of the plasma treatment process (15 min of the treatment stage followed by 15 min of the post treatment stage). The experiments were done in the absence and presence of ampicillin in the solution. In both cases, the concentration of ozone in the solution increased during the treatment stage. This result is reasonable as ozone is continuously created in the plasma (in the gas phase) and subse-

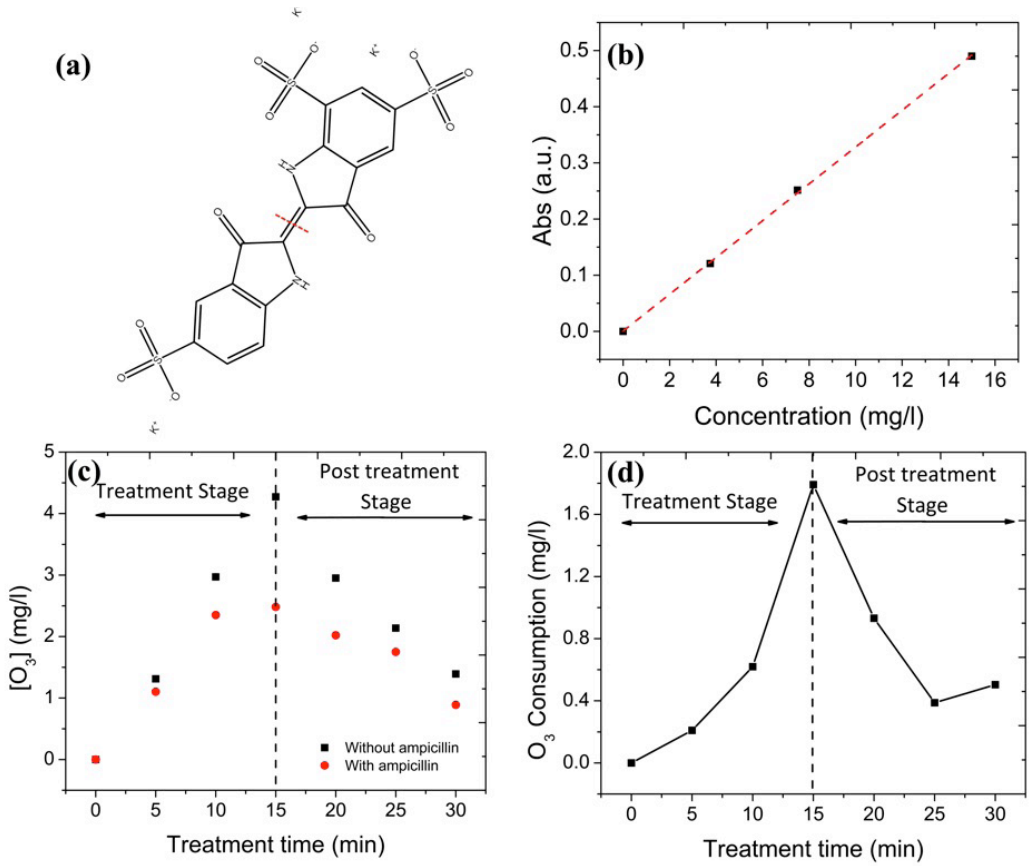

Fig. 8. Indigo method for investigating the presence of ozone in the aqueous phase [48]. (a) shows a potassium indigo trisulfonate molecule. To quantify the concentration of the ozone in the solution, a calibration curve for potassium indigo trisulfonate was required as shown in (b). The measurements were done for one cycle of the plasma treatment process, i.e. 15 min of treatment followed by 15 min of post treatment. The change in the absorbance of the indigo dye was converted into the concentration of ozone by means of the calibration curve. The concentration of ozone was measured in the presence (100 mg/l) and also absence of ampicillin in the solution (c). The difference between the concentration of ozone measured in the presence and absence of ampicillin can show the amount of ozone consumed by ampicillin molecules, as shown in (d).

quently injected into the water. In the post treatment stage, the concentration of ozone decreases possibly due to its limited lifetime in the aqueous phase and its subsequent dissociation [57,58]. When ampicillin is present in the solution, it creates a competition with indigo molecules to consume ozone. As a result, the difference between the concentration of ozone in the presence and absence of ampicillin can be used as a first approximation to calculate the ozone consumption by ampicillin [59]. Fig. 8d shows the concentration of ozone consumed by ampicillin and its byproducts during one cycle of the plasma treatment process

The ozone consumption increased during the treatment stage, possibly due to the increasing concentration of ozone created in the plasma. The decline in the ozone consumption during the post treatment stage can be attributed to the decreasing concentration of both ozone and organic molecules present in the aqueous phase

4. Conclusions

A FESCD system was used to degrade pharmaceutical drugs ampicillin and ibuprofen in tap water. After the treatment of the solutions for 3 h, 100% of ampicillin and 90% of ibuprofen were degraded. The energy yield for the degradation of ampicillin and ibuprofen was calculated to be 0.13 g/kWh and 0.12 g/kWh, respectively. TOC analysis of the solutions revealed that although removal percentage of ibuprofen was lower than ampicillin, much higher mineralization was obtained in the case of ibuprofen containing solutions (60% for ibuprofen versus 25% for ampicillin). Degradation byproducts detected by HPLC-MS indicated that for both contaminants, the major degradation pathways include reaction with hydroxyl radicals and ozone molecules. The direct effect of this oxygenation was only observed in the FEEM signals of ampicillin where the initial increase in the fluorescence intensity was attributed to the addition of oxygen atoms to organic molecules. In the case of ibuprofen, this oxygenation occurred at the expense of losing the cyclic structure. Hence, the fluorescence intensity did not increase. Further compatibility between the HPLC-MS and FEEM results was observed where the decline in the fluorescence intensity in both contaminants was attributed to the breakdown of the organic molecules. This study shows that the FEEM analysis can be used as a powerful tool for following the degradation of pharmaceutical compounds in complex water matrices.

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Supplementary Information

1. Characterization methods

1.1. Total Organic Carbon-Inorganic Carbon (TOC-IC) analyzer

To evaluate the degree of mineralization in each solution (both in tap water and Milli-Q water), a 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.

1.2. High-Performance Liquid Chromatography-Mass Spectrometry (HPLC-MS)

RP-HPLC-MS was conducted using an Agilent 1200 SL HPLC instrument. 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, fragmentor 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% to 40% mobile phase B over a period of 6 min, 40% to 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.

1.3. Fluorescence Excitation-Emission Matrix (FEEM)

FEEM measurements were carried out using a Varian Cary Eclipse spectrophotometer (Agilent, USA). The spectrophotometer showed a maximum emission intensity of 1000 arbitrary units (a.u.). Xenon excitation source was used in this study and the excitation and emission slits were set to 5 nm. To obtain FEEMs from samples, 4 ml of each sample was poured into a quartz cuvette. The excitation wavelength was incrementally increased from 200 nm to 400 nm, with steps of 5 nm. At each excitation wavelength, the emission was detected in the range of 200–650 nm, with 1 nm steps. To partially account for the Raleigh scattering, fluorescence signal of a blank sample (sample without the addition of ampicillin or ibuprofen, i.e. only tap water) was recorded and subsequently subtracted from the fluorescence spectra of the main samples. It has to be mentioned that FEEM analysis was performed at room temperature using only samples with tap water matrix. pH of all samples was adjusted to 7 beforehand using 1 M solution of NaOH (as shown in Fig. S1 in the Supplementary Information, solutions treated by plasma became acidic). FEEMs were plotted using Origin 2015 software with 10 contour lines and emission intensities in the range of –10 to 1005 a.u. Keeping the same intensity range for all the plots is very important since in this manner an apparent change in the fluorescence signal can be observed as the treatment time increases.

1.4. Measurement of ozone concentration

To measure the concentration of ozone in the aqueous phase, Indigo dye method was used[2]. The stock solution of Indigo Reagent was prepared by dissolving 1 mM of potassium indigo trisulfonate salt in 20 mM phosphoric acid solution. A calibration curve for Indigo dye (shown by Fig. S2 in the Supplementary Information) was obtained by diluting the stock solution with Milli-Q water to various ratios and measuring the absorbance of the solution at 600 nm (UV/Vis spectrophotometer Varian Carey 50, Agilent, USA). The measurements were done during one cycle of the plasma treatment process, i.e. 15 min of treatment followed by 15 min of post treatment. Furthermore, to estimate the concentration of ozone consumed by one of the model pharmaceutical compound in this study, i.e. ampicillin, experiments were carried out in the absence and presence of ampicillin (100 mg/l) in Milli-Q water. In each experiment, 60±1 ml of the solution was poured into a glass beaker. At desired time intervals (either in the treatment or post treatment stage), 0.25 ml of the Indigo dye stock solution was added to the aqueous solution and the change in the absorbance was monitored online using a fiber optic connected to the UV/Vis spectrophotometer. The difference between the ozone concentration measured in the presence and the absence of ampicillin indicated the amount of ozone consumed by ampicillin molecules.

2. Results and discussion

2.1. Change in solution pH and conductivity

The change in pH and conductivity of the solutions was monitored as a function of the treatment time, as shown

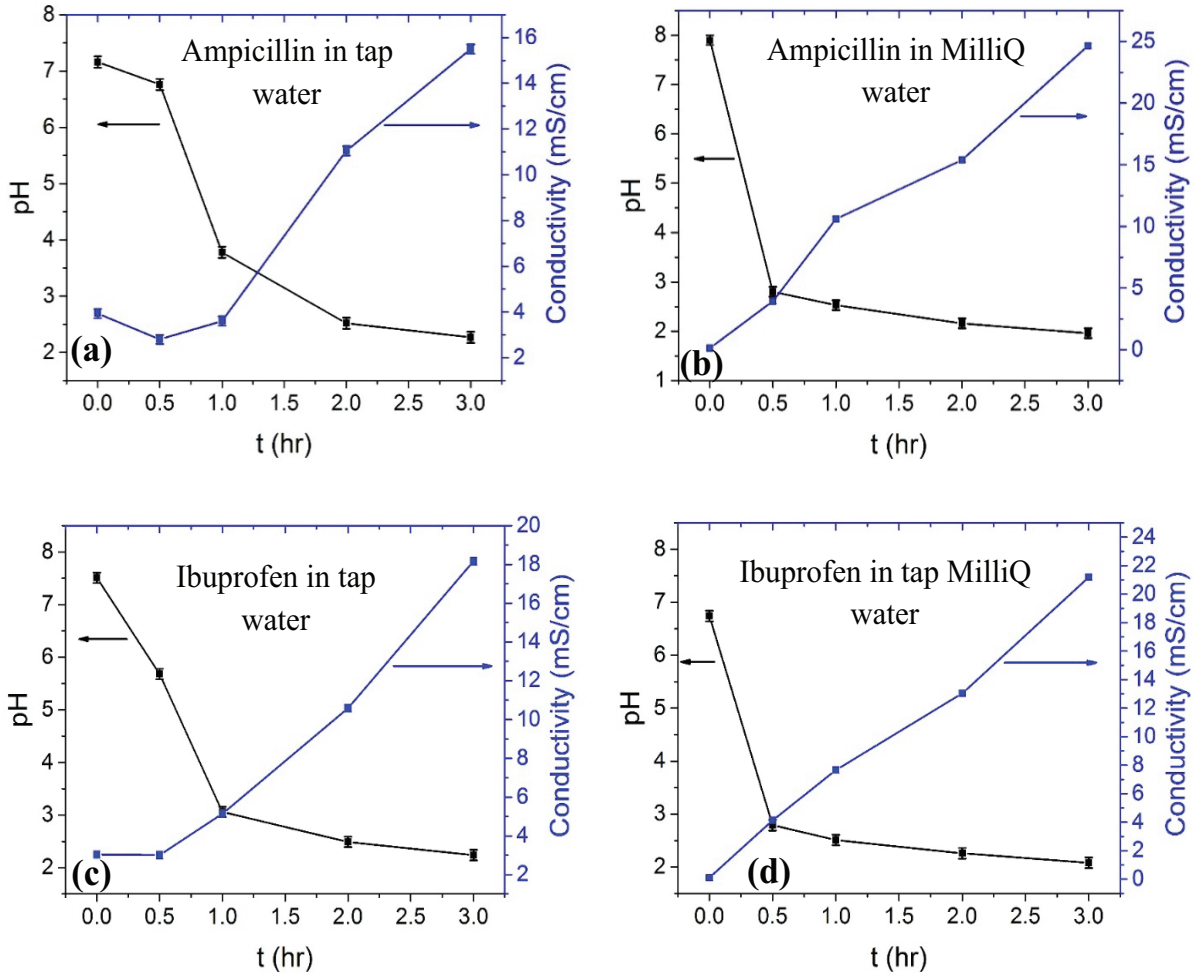


Fig. S1. The change in the pH of the solutions and their conductivity is shown as a function of the plasma treatment time. (a) and (b) represent these changes in ampicillin containing solution in tap water and MilliQ water, respectively. Similar measurements were performed for ibuprofen containing solutions in (c) tap water and (d) MilliQ water. The results indicate that regardless of the type of the contaminant or water matrix, the solutions became acidic and their conductivity increased significantly. This is due to the introduction of the nitrogen-based compounds to water ($NO_{(aq)}$ and $NO_{2(aq)}$) and subsequent formation of ionic species such as NO_2^-, NO_3^- and H^+ in the solutions[3]. Comparing the results obtained in tap water and MilliQ water shows that the change in pH and conductivity is faster in MilliQ water than tap water. This is possibly due to the presence of carbonate and bicarbonate ions in tap water (as revealed by TOC/IC analysis, Figs. 3(a) and (c)).

by Fig. S1. Regardless of the contaminant (ampicillin or ibuprofen) and the type of the water matrix (tap water or MilliQ water), the pH of the solutions decreased and the conductivity increased significantly. This is probably due to the introduction of the nitrogen-based compounds to water ($NO_{(aq)}$ and $NO_{2(aq)}$) and subsequent formation of ionic species such as NO_2^-, NO_3^- and H^+ in the solutions[3]. One interesting observation is that the above-mentioned changes occurred faster when MilliQ water is used as the water matrix. This can be attributed to the presence of various ionic species in tap water such carbonate and bicarbonate that can interact with the species created by plasma.

2.2. Indigo dye calibration curve

As discussed in the manuscript, Indigo dye method was used to measure the concentration of the ozone in the aqueous phase. Bader et al. reported that there is only one C=C bond in the indigo molecule (Inset in Fig. S2 that can be one of the sites for reaction with ozone. In acidic environment, the amino groups in the indigo molecule are protonated; therefore, they are unreactive towards ozone. As a result, it can be expected that one molecule of indigo dye reacts with one molecule of ozone in the solution[2].Since this reaction between ozone and indigo dye is stoichiometric, a calibration curve for indigo dye can be used to find the ozone concentration. Fig. S2 shows the calibration curve obtained for indigo dye by diluting the stock solution with various ratios.

2.3. MS spectra for ampicillin and its byproducts

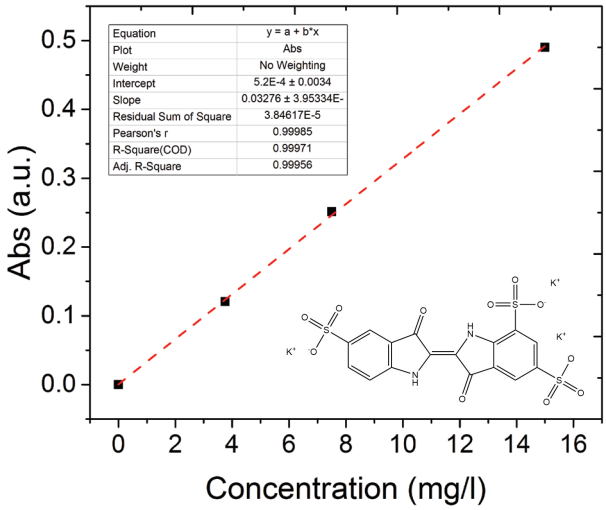
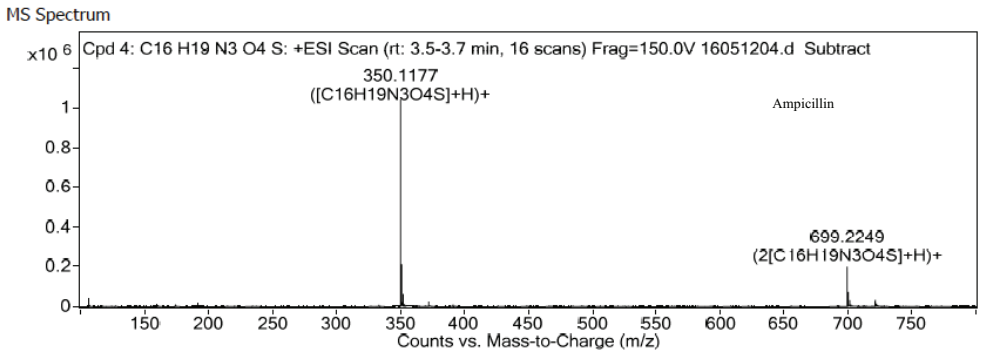
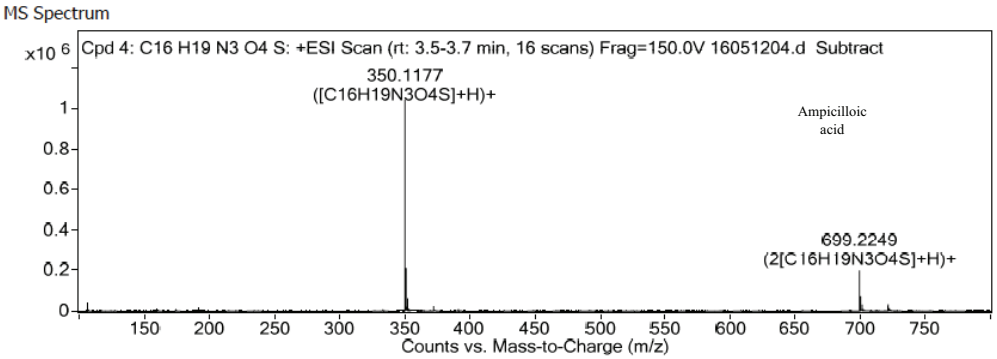
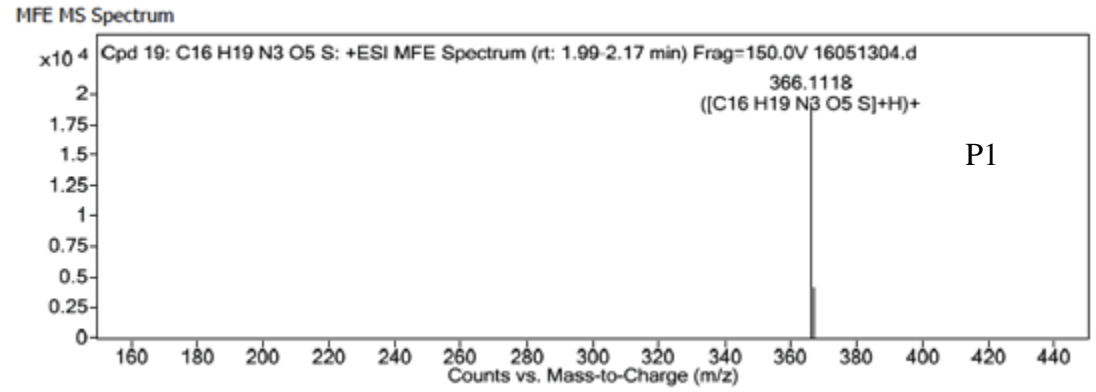
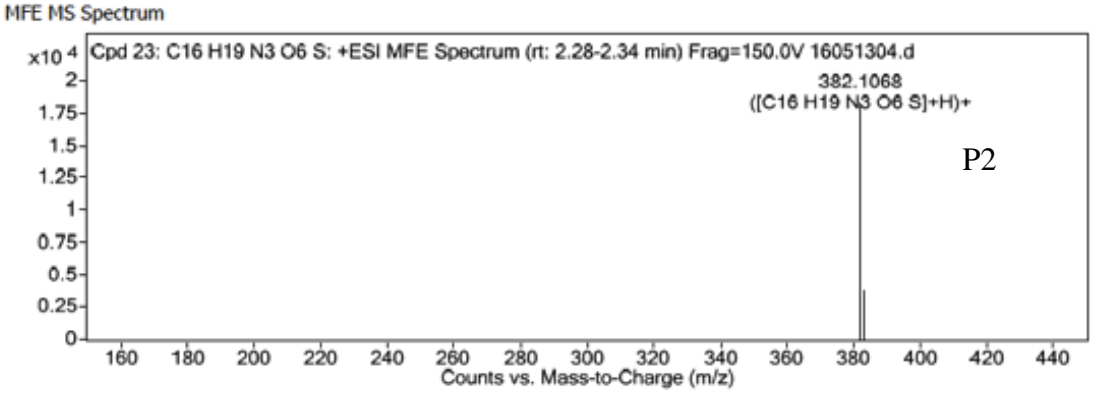


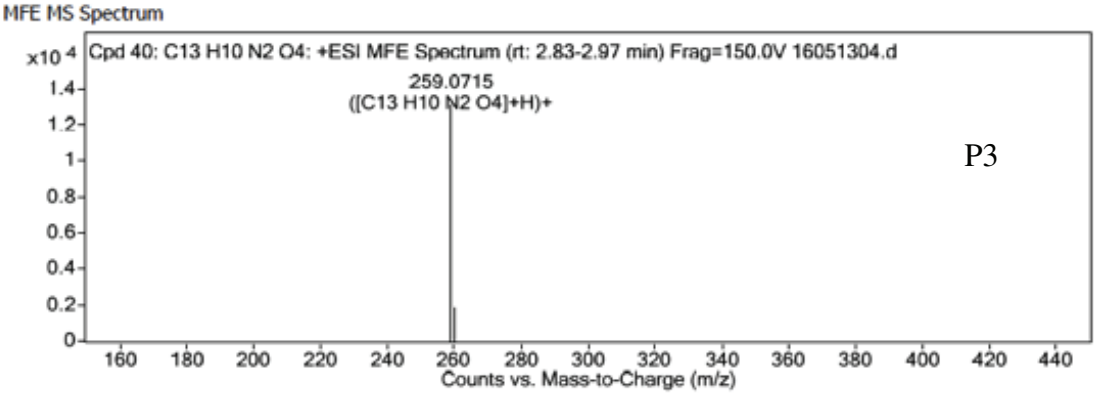
Fig. S2. A calibration curve for indigo dye was obtained to correlate the concentration of the dye in the solution to its absorbance (UV/Vis spectroscopy at 600 nm). Based on the indigo method for measurement of ozone concentration in the solution[2], at low pH values, amino groups in the indigo dye molecules are protonated and they do not participate in any oxidation process. That is why the stock solution of the indigo trisulfonate is prepared in 20 mM solution of phosphoric acid. As a result, the only C=C double bond in the center of the molecule is expected to react with an ozone molecule. Thus, it can be assumed that one molecule of indigo trisulfonate reacts with one molecule of ozone. Using the calibration curve presented here, the absorbance of the indigo solution can be converted to the concentration of the indigo dye. The change in the concentration of the indigo dye represents the concentration of ozone in the solution, as shown Fig. 8.

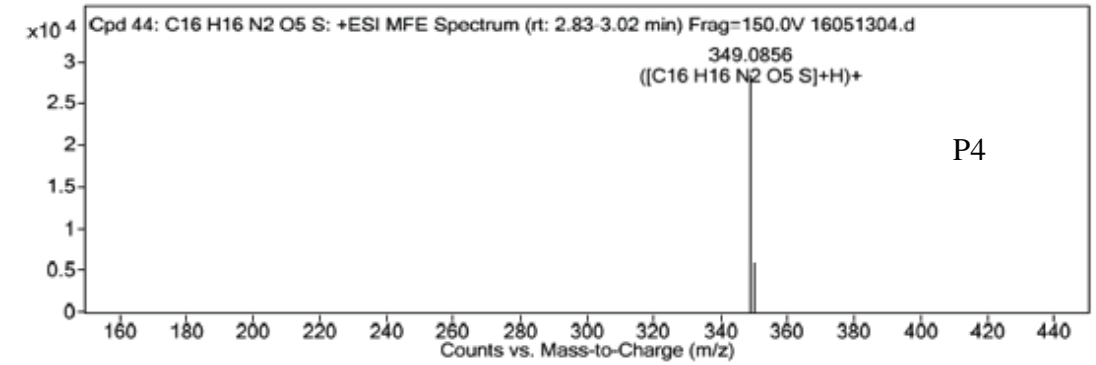


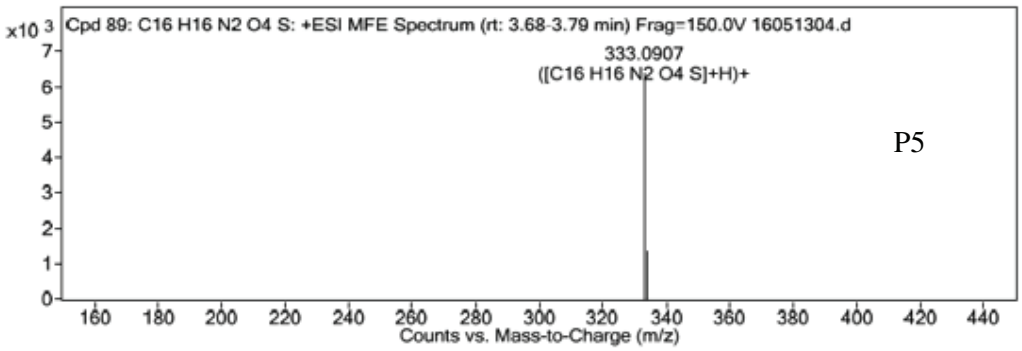


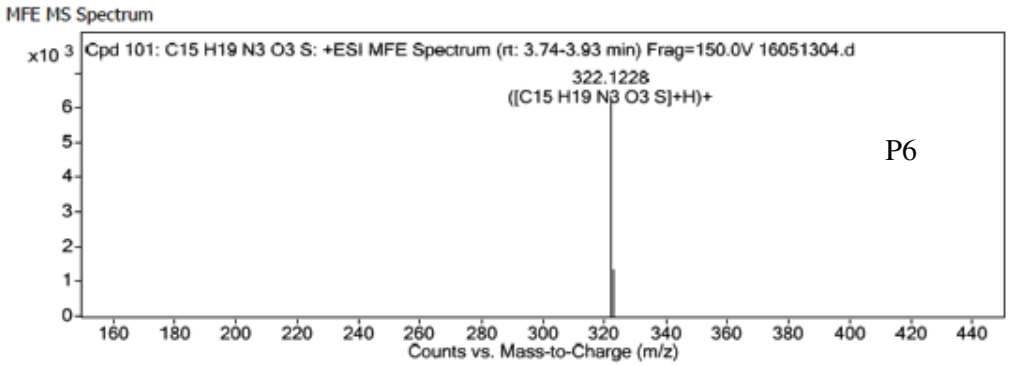

MFE MS Spectrum
Cpd 19: C16 H19 N3 O5 S: +ESI MFE Spectrum (rt: 1.99-2.17 min) Frag=150.0V 16051304.d
x10 4
366.1118
([C16 H19 N3 O5 S]+H)+
P1
Counts vs. Mass-to-Charge (m/z)

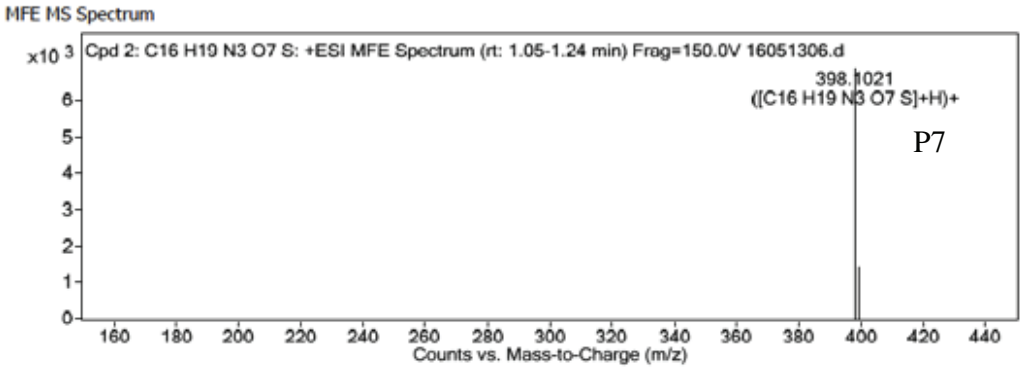

MFE MS Spectrum
Cpd 23: C16 H19 N3 O6 S: +ESI MFE Spectrum (rt: 2.28-2.34 min) Frag=150.0V 16051304.d
x10 4
382.1068
([C16 H19 N3 O6 S]+H)+
P2
Counts vs. Mass-to-Charge (m/z)


MFE MS Spectrum
Cpd 40: C13 H10 N2 O4: +ESI MFE Spectrum (rt: 2.83-2.97 min) Frag=150.0V 16051304.d
x10 4
259.0715
([C13 H10 N2 O4]+H)+
P3
Counts vs. Mass-to-Charge (m/z)

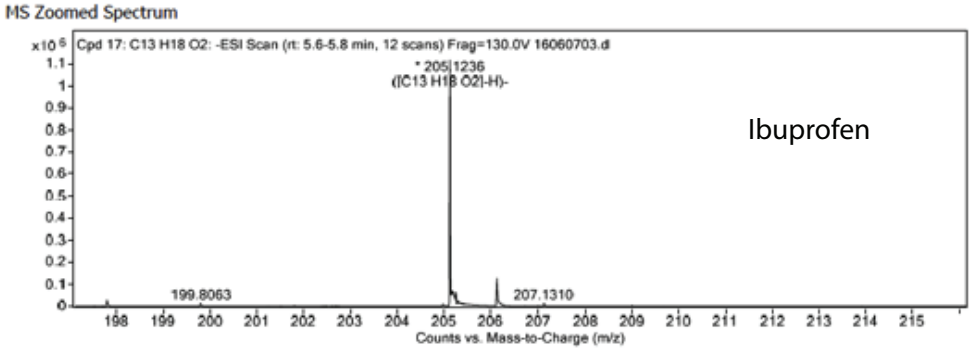

Cpd 44: C16 H16 N2 O5 S: +ESI MFE Spectrum (rt: 2.83-3.02 min) Frag=150.0V 16051304.d
x10 4
349.0856
([C16 H16 N2 O5 S]+H)+
P4
Counts vs. Mass-to-Charge (m/z)

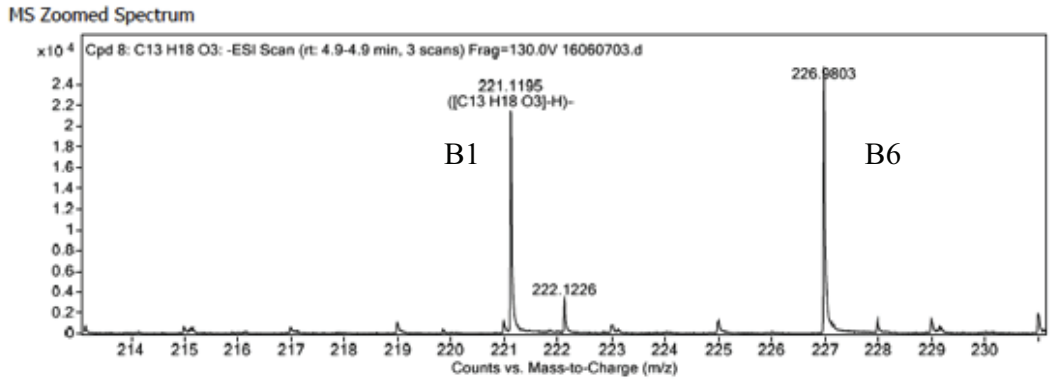


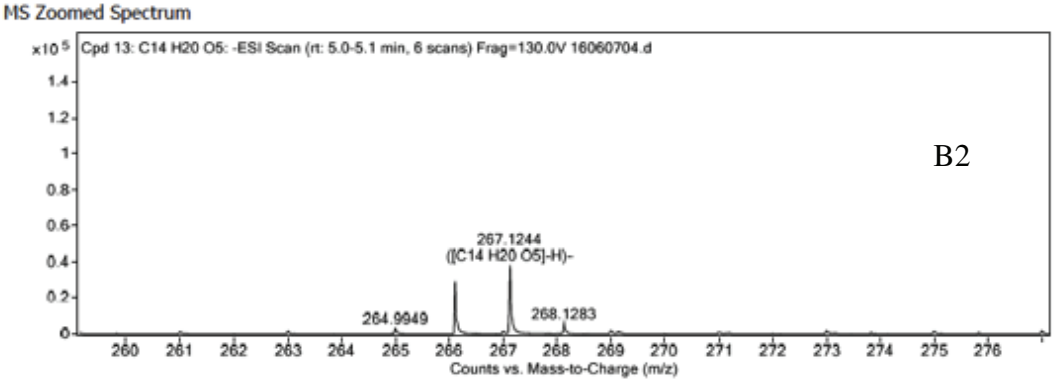


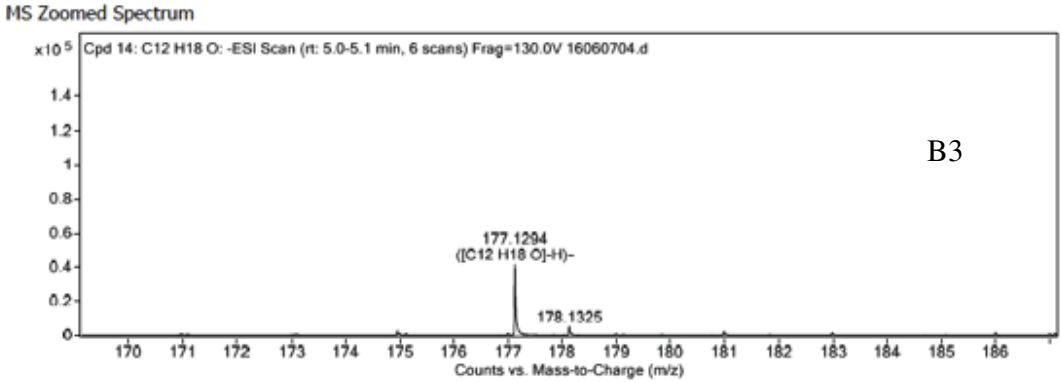


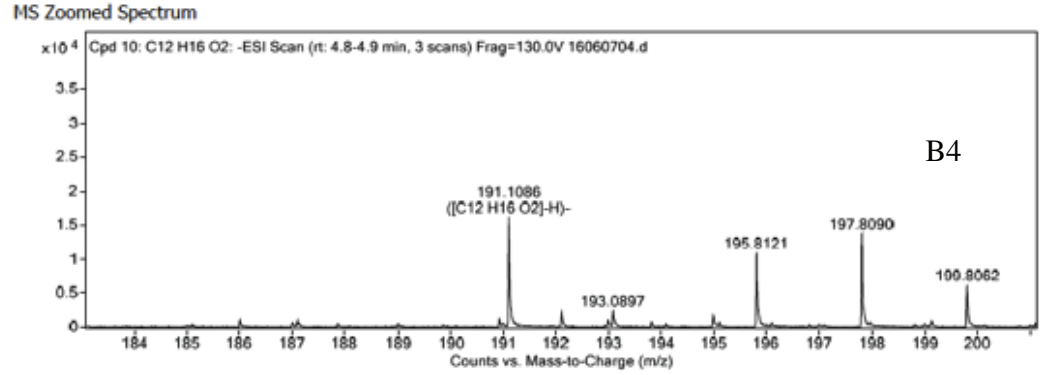
2.4. MS spectra for ibuprofen and its byproducts

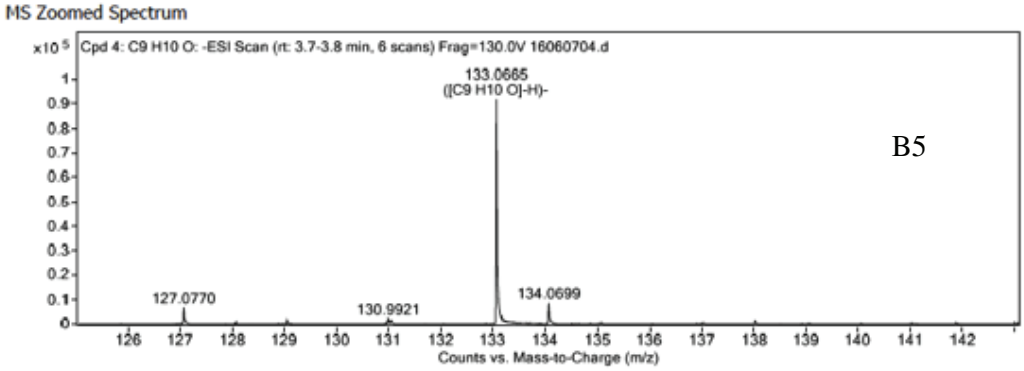


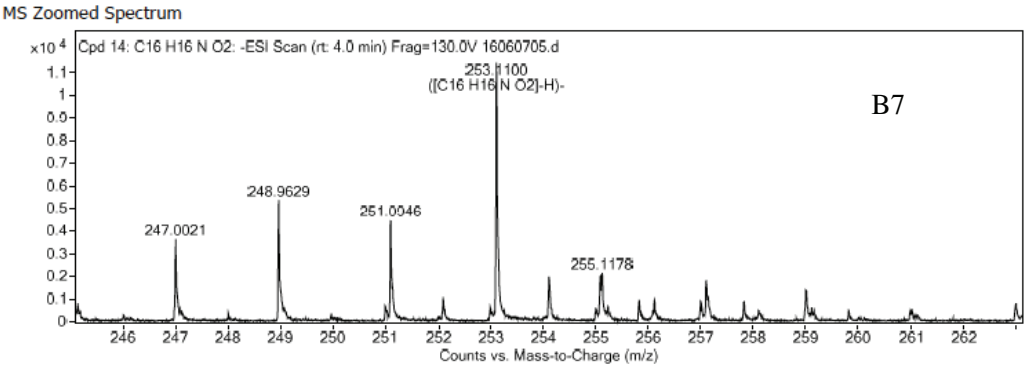

MS Zoomed Spectrum
Cpd 8: C13 H18 O3: -ESI Scan (rt: 4.9-4.9 min, 3 scans) Frag=130.0V 16060703.d
x10 4
221.1195
([C13 H18 O3]-H)-
226.9803
B1
B6
222.1226
Counts vs. Mass-to-Charge (m/z)

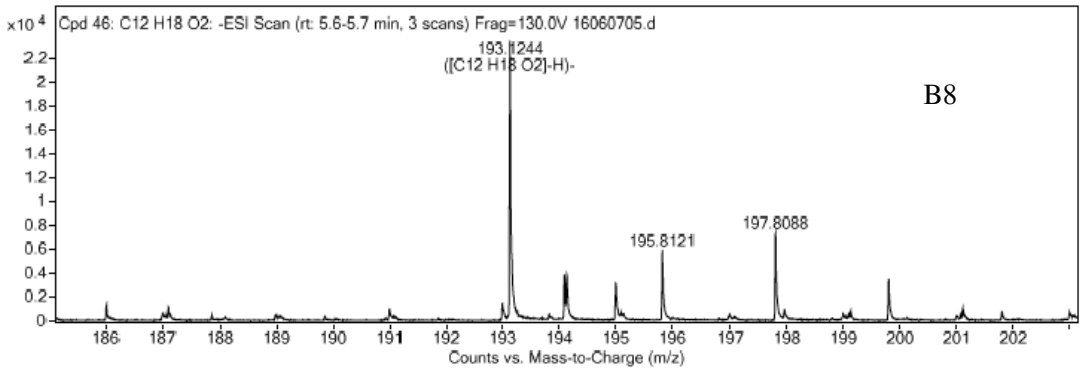

MS Zoomed Spectrum
Cpd 13: C14 H20 O5: -ESI Scan (rt: 5.0-5.1 min, 6 scans) Frag=130.0V 16060704.d
x10 5
B2
267.1244
([C14 H20 O5]-H)-
264.9949
268.1283
Counts vs. Mass-to-Charge (m/z)

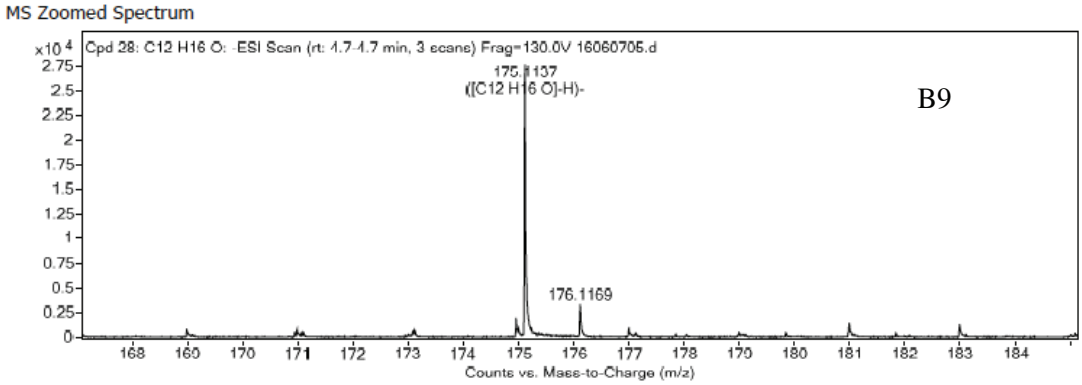

MS Zoomed Spectrum
Cpd 14: C12 H18 O: -ESI Scan (rt: 5.0-5.1 min, 6 scans) Frag=130.0V 16060704.d
x10 5
B3
177.1294
([C12 H18 O]-H)-
178.1325
Counts vs. Mass-to-Charge (m/z)

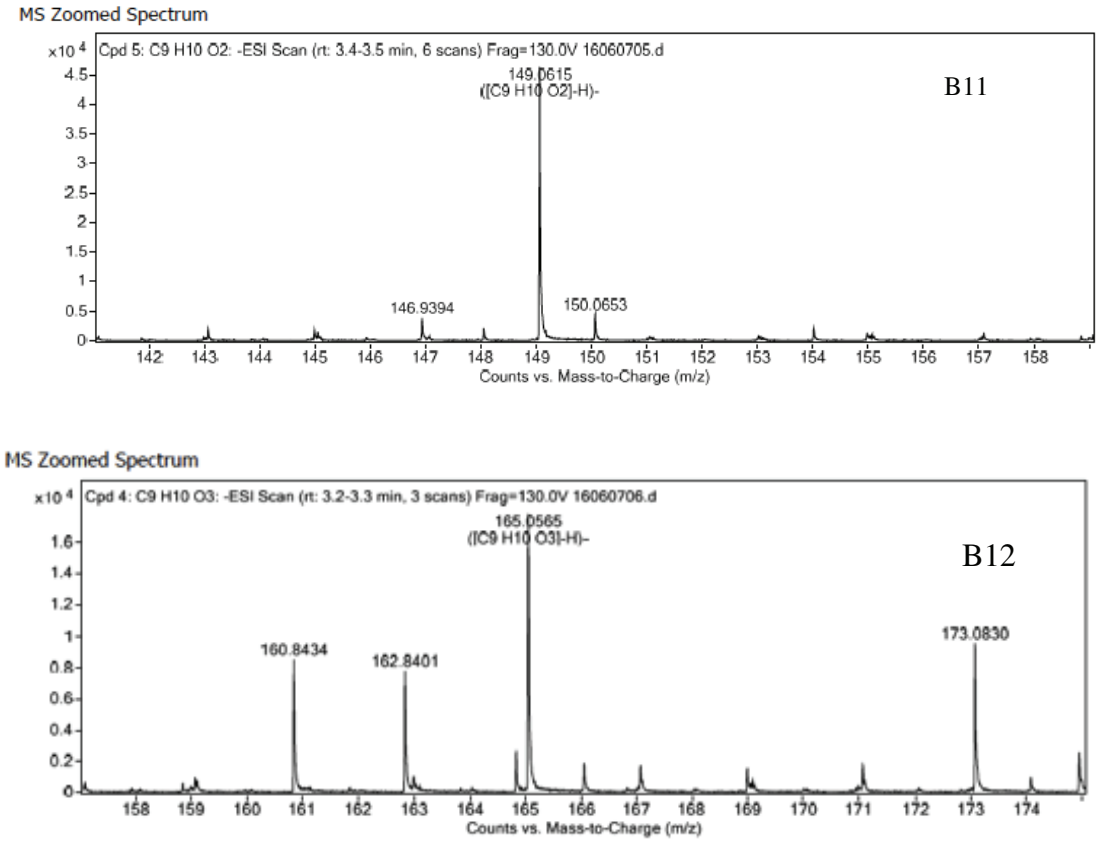

MS Zoomed Spectrum
Cpd 10: C12 H16 O2: -ESI Scan (rt: 4.8-4.9 min, 3 scans) Frag=130.0V 16060704.d
x10 4
B4
191.1086
([C12 H16 O2]-H)-
195.8121
197.8090
199.8062
193.0897
Counts vs. Mass-to-Charge (m/z)


MS Zoomed Spectrum
Cpd 4: C9 H10 O: -ESI Scan (rt: 3.7-3.8 min, 6 scans) Frag=130.0V 16060704.d
133.0665
([C9 H10 O]-H)-
127.0770
130.9921
134.0699
B5
Counts vs. Mass-to-Charge (m/z)


MS Zoomed Spectrum
Cpd 14: C16 H16 N O2: -ESI Scan (rt: 4.0 min) Frag=130.0V 16060705.d
253.1100
([C16 H16 N O2]-H)-
247.0021
248.9629
251.0046
255.1178
B7
Counts vs. Mass-to-Charge (m/z)


Cpd 46: C12 H18 O2: -ESI Scan (rt: 5.6-5.7 min, 3 scans) Frag=130.0V 16060705.d
193.1244
([C12 H18 O2]-H)-
195.8121
197.8088
B8
Counts vs. Mass-to-Charge (m/z)


MS Zoomed Spectrum
Cpd 28: C12 H16 O: -ESI Scan (rt: 4.7-4.7 min, 3 scans) Frag=130.0V 16060705.d
175.1137
([C12 H16 O]-H)-
176.1169
B9
Counts vs. Mass-to-Charge (m/z)



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[1] D.M. Jarvie, Total Organic Carbon (TOC) Analysis. 2014, No. Method C.
[2] H. Bader, J. Hoigné, Determination of ozone in water by the indigo method, Water Res., 15(4) (1981) 449–456.
[3] F. Huang, L. Chen, H. Wang, Z. Yan, Analysis of the degradation mechanism of methylene blue by atmospheric pressure dielectric barrier discharge plasma, Chem. Eng. J., 162(1) (2010) 250–256.