Removal of pyrazinamide and its by-products from water: Treatment by electro-Fenton process and feasibility of a biological post-treatment

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Abstract: This paper reports a study on oxidative degradation and mineralization of pyrazinamide in an aqueous medium at pH = 3 and room temperature ($\approx$ 19 °C) by the electro-Fenton process, using carbon felt as a cathode and platinum as an anode. The degradation/mineralization is assessed by the chemical oxygen demand by analyzing applied current intensity and concentration of Fe^{2+} catalyst. Thus, the main objective is to determine the optimal values of these parameters. Some stable intermediate products have been identified using high-performance liquid chromatography and liquid chromatography tandem mass spectrometry, which show the successive formation of the aromatic/cyclic organics and aliphatic intermediates. The second part of this work corresponds to the study of the biodegradability giving by the ratio: BOD_5/COD during the mineralization of pyrazinamide by EF in order to examine the possibility of combining electro-Fenton with a biological post-treatment.

Keywords: Water treatment; pyrazinamide antibiotic; electro-Fenton process; oxidative degradation; mineralization; biodegradation.

Introduction

The treatment/removal of active pharmaceuticals and its degradation products from the environment have received great interest, given their negative impact on human health, on fauna and flora, So, they are important pollutants in surface waters [1]. In recent years due particularly to the advanced oxidation processes (AOPs) as alternative or complementary methods to conventional wastewater treatment techniques. Indeed, it is important to know that the by-products are generally more toxic than the starting molecules, thus causing a real danger on the environment. Also, among the (AOPs), processes related to chemical oxidation in homogeneous phase processes [2,3], ozonation [4], photochemical reactions [5-8], photocatalysis [9,10], direct and indirect electrochemical processes [11-15], hybrid technique [16] etc, are worth considering. AOPs, in fact, relies on an in situ a generation of hydroxyl radicals •OH which shows higher oxidizing power than the conventional oxidants H_2O_2, Cl_2, ClO_2^-or O_3. These radicals can mineralize the organic and organometallic compounds either partially or entirely.

Some studies have shown that pyrazinamide antibiotic has a phototoxic potential to participate in several kinds of photochemical reactions [8]. In another study on the degradation of isoniazid and pyrazinamide antibiotics under UV radiation, TiO_2 showed better photocatalytic activity than ZnO [17], undertook research to determine the forced degradation of pyrazinamide by various conditions such as acid, alkali, oxidation, thermal and photolytic [18]. Also, forced degradation study for assay method of rifampicin, isoniazid and pyrazinamide in combined pharmaceutical dosage form has recently been reported in the literature [19].

In the domain of electro-chemistry, the effectiveness of "Electro-Fenton" (EF) process in the degradation of persistent and/or toxic organic pollutants including pharmaceuticals in aqueous medium was also demonstrated [20-23].

This process (electro-Fenton) is based on the in situ production of hydroxyl radicals (according to reaction (1)) in acidic medium [24-26].

$$H_2O_2 + Fe^{2+} + H^+ \rightarrow {}^\bullet OH + Fe^{3+} + H_2O \qquad (1)$$
$$O_2 + 2\,H^+ + 2\,e^- \rightarrow H_2O_2 \qquad (2)$$
$$Fe^{3+} + 1\,e^- \rightarrow Fe^{2+} \qquad (3)$$
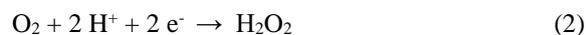
The regeneration of Fe^{2+} (reaction (3)) from electro-reduction of Fe^{3+} produced by reaction (1) and the regeneration of H_2O_2 (reaction 2) also ensures the continuous formation of ${}^\bullet OH$.

In an acidic medium (pH about 3), the oxidizing power of the hydroxyl radical is very high (E° (${}^\bullet OH$ /H_2O) = 2.8 V/SHE, and its reactivity is optimal. Under this condition, these hydroxyl radicals can attack any organic molecule present in the solution and the oxidative degradation leads to finally mineralization to CO_2.

Generally, during degradation/oxidation by AOPs, the biorefractory molecules degrade into small biodegradable molecules. This shows the possibility of combining the advanced oxidation process (Fenton or Photo-Fenton or Electro-Fenton) with the biological process to treat efficiently and economically aqueous solutions contaminated with persistent organic pollutants, as shown in the literature [27-32].

The present study shows the possibility of coupling electro-Fenton and a biological process for the effective removal of pyrazinamide from the water. The electrochemical reactor used in this study involves a carbon-felt cathode and a platinum anode. Several electrolysis experiments were carried out on aqueous solutions of pyrazinamide at a constant current intensity at pH = 3 and in the presence of Fe^{2+} catalyst. We study in this way, the effect of the applied current intensity and the concentration of Fe^{2+} (catalyst) on the kinetics of degradation and mineralization of pyrazinamide. The degradation was followed by changes in the concentration of pyrazinamide and mineralization of the treated solutions by monitoring the chemical oxygen demand (COD).

Methods of chromatographic analysis using high-performance liquid chromatography (HPLC) and liquid chromatography-mass spectrometry (LC/MS-MS) have been used to identify the intermediate products. The biodegradability of pyrazinamide has assessed at various times during the electro-Fenton process in order to estimate the optimal time to introduce the biological process. The biodegradation tests were conducted using domestic wastewater, and the biodegradability is expressed by the BOD_5/COD ratio [33]. This value gives information about the portion of organic materials present that can be aerobically degraded during five days.

Experimental

Chemicals

Pyrazinamide (PZA, Table 1) was obtained from Pharma 5. Ferrous sulfate, sodium sulfate, potassium chloride and sulfuric acid were obtained from Shangai Chemical Reagents Co. (Shangai, China). Acetonitrile (HPLC grade) was obtained from Carlo ERPA. The aqueous solutions used in all experiments were prepared with ultra-pure water obtained from a Millipore Milli−Q system.

Table 1. Proprieties of pyrazinamide molecule.

Compound	Structure	Molecular Weight	wavelength of absorption	Water Solubility
Pyrazinamide		123.115 g/mol	Range: 200-400 nm	15000 mg/L (at 25 °C) *MERCK INDEX (1996)*
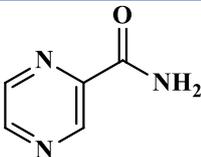
The electrolytic system

In order to carry out the electro-Fenton (EF) treatments, we employed Voltalab Potentiostat/Galvanostat instrument, type PGZ 100. Electrochemical tests were performed in an open cell of 250 mL capacity. A surface of platinum (2.5 cm × 2 cm) was used as an anode, and three-dimensional surface of carbon felt (6 cm x 5 cm x 0.5 cm, Carbone-Lorraine) as a cathode. The anode was placed in the center of the electrolyte just in front of the cathode.

The concentrations of the components of aqueous solutions for the electrolysis were: 0.3 mM pyrazinamide, 0.5 mM Fe^{2+} and 0.05 M Na_2SO_4 at pH = 3 (each one in distilled water with a volume of 200 ml, constituting thus, the solution to be treated)). The temperature was kept at (temperature ≈ 19 °C). The applied current intensity was in the range of 60 mA to 400 mA. The solutions were subjected to constant agitation to ensure mass transport to the electrodes.

Analytical procedures

Chemical oxygen demand (COD) is as method to monitor the degradation of pyrazinamide in treated solutions. The evaluation of COD was carried out by using spectrophotometer DR/125 (Hach Company USA) by the dichromate method. An appropriate amount of sample was introduced into a solution containing potassium dichromate, sulfuric acid and mercuric sulfate, was used a range of 0 to 150 mg O_2 L^{-1} of a digestion solution. The mixture solution was then incubated for 120 minutes at 150 °C in Lovibond® COD VARIO photometers. Variation in time of concentration of pyrazinamide was followed by reverse-phase high-performance liquid chromatography (HPLC) using a Waters 2695 coupled photodiode-array detector (PDA) 2998, selecting at optimum wavelengths of 270 nm. Data acquisition was performed through the Empower 2 Software data registration, and fitting with a Thermohypersil C 18, 5 μm, 25 cm, 4.6 mm (i.d.), column at 40°C. The analyses on 100μL sample volume were performed isocratically using a phosphate buffer (pH2.2)/acetonitrile 46:54 (v/v) mixture as a mobile phase at a flow rate of 1.5 mL min^{-1}.

The stable intermediate products formed during electro-Fenton treatment of pyrazinamide were identified under the same operating conditions using liquid chromatography-mass spectrometry LC/MS-MS (AB Sciex - API 3200 QTRAP®, instrument triple quadrupole) by operating in the negative ion mode. Data acquisition was performed with analysis software ® Version 1.5. Reaction aliquots were infused directly into the ion source at a speed of20μL/min using a micro-syringe (Hamilton Company, Reno, NV, USA). Typical conditions of ESI are: heated capillary temperature, 300°C; sheath gas (N_2) at a flow velocity of 20 mL/min; spray voltage -4.5 kV; gas flow and the nebulizing gas curtain of the apparatus were adjusted at 30 and 10 ml/min, respectively.

The BOD was measured by an OxiDirect, by using respirometric evaluation method in 5 days (BOD_5) at a temperature of 20°C in dark conditions. pH was adjusted between 6.5 and 7.5, and N-allylthiourea was used as a nitrification inhibitor. KOH pellets were added to the bottles to trap CO_2.

In order to degrade the PZA molecule biologically, we have used domestic wastewater obtained from the National Office of Electricity and Drinking Water, Rabat, Morocco.

Results and discussion

Influence of applied current on the oxidative degradation kinetics of pyrazinamide aqueous solution.

The important influencing factors on the electro-Fenton process are the intensity of applied current, catalyst concentration, solution pH and background electrolyte. In many studies, it has been clearly shown that the optimal pH value is about 3 [34-36] and sodium sulfate acts as the best-supporting electrolyte [21].

The effect of applied current value on the oxidative degradation of pyrazinamide by hydroxyl radicals •OH was studied for 200 mL of 0.34 mM pyrazinamide solution with 0.1 mM Fe^{2+} at pH = 3, during EF process (Fig. 1).

The use of these data above has allowed us to determine the optimum value of the applied current for which the oxidation of pyrazinamide considered would be kinetically favored.

Thus, the evolution of the concentration of pyrazinamide as a function of the electrolysis time is followed by high-performance liquid chromatography (HPLC).

Increasing the applied current intensity from 60 to 400 mA leads to accelerated degradation kinetics of pyrazinamide. This demeanor can be explained by the acceleration of the rate of electrochemical reactions (2) and (3) leading to the generation of more •OH radicals (Fenton reaction at pH = 3 (1)).

The complete disappearance of pyrazinamide was checked at 60, 40, 20 and 25 min for 60, 100, 300 and 400 mA current values, respectively. These results show that the degradation rate of pyrazinamide was not significantly changed after 300 mA current. Therefore, the optimal current value is 300 mA. Additional increase in current intensity led to decreasing oxidative efficiency of pyrazinamide while making long treatment time for the complete disappearance of pyrazinamide. This behavior is confirmed in (the inset of Figure 1) which demonstrates that the apparent rate constants (Kapp) for the oxidation of pyrazinamide by •OH follows pseudo-first-order reaction kinetics. Indeed, we may find similar results in the literature, where there are deductions and ascertainments, which tend to us [21].
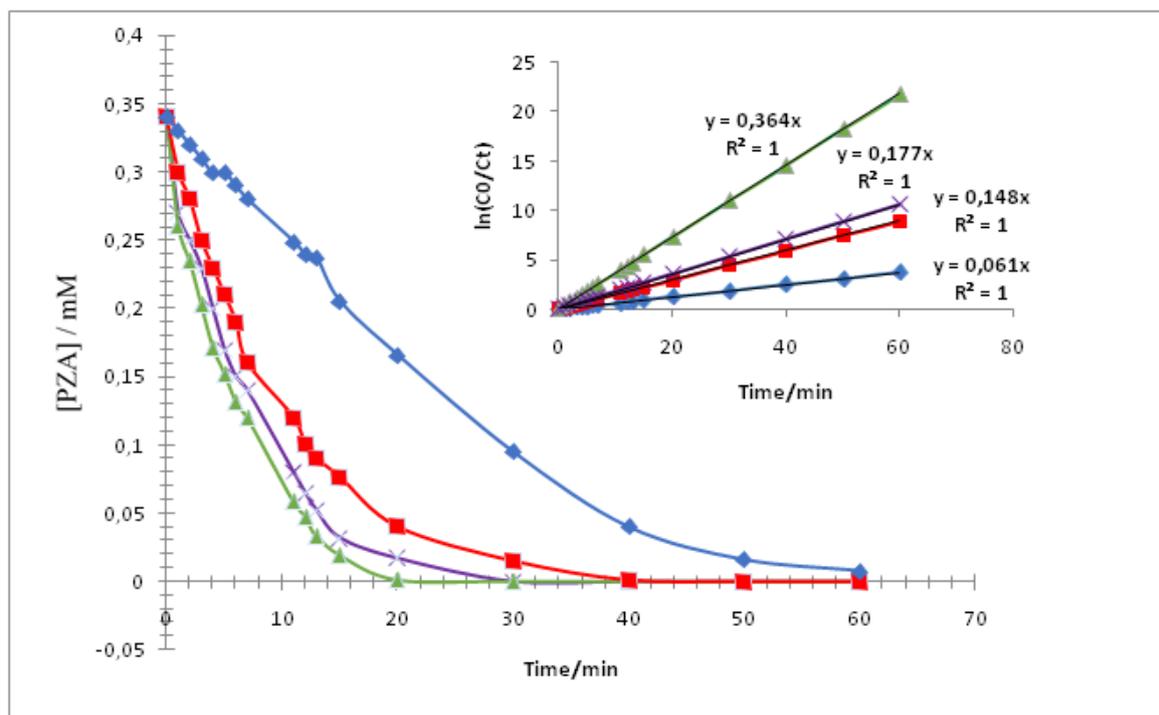
Figure 1. Effect of applied current on degradation of pyrazinamide during EF treatment at pH3, $[PZA]_0 = 0.34$ mM, with $[Fe^{2+}] = 0.1$ mM, I (mA) = 60 (-♦-), 100 (-■-), 300 (-▲-) and 400 (-×-)

The apparent rate constant values (Kapp) for the oxidation of pyrazinamide correspond to the slopes of the linear, $\ln(C/C_0)$, were plotted as a function versus time (Table 2).

Table 2. Apparent rate constants Kapp obtained during the EF treatment at various applied current intensity for pyrazinamide.

Initial PZA concentration	Fe^{2+} concentration	Applied current intensity	Apparent rate constant Kapp
(mM)	(mM)	(mA)	(min^{-1})
0.34	0.10	60	0.0618
0.34	0.10	100	0.1486
0.34	0.10	300	0.3645
0.34	0.10	400	0.1776

The Kapp value at 400 mA is lower as compared to at 300 mA. Higher applied current intensity could be responsible for the acceleration of wasting reactions such as 4 e⁻ a reduction of O_2 leading to H_2O (reaction (4)) instead of H_2O_2, the evolution of H_2 (reaction (5)) and the oxidation of H_2O_2 (reaction (6)).

$$O_2 + 4\,e^- + 4\,H^+ \rightarrow 2\,H_2O \qquad (4)$$
$$2\,H_2O + 2\,e^- \rightarrow H_2 + 2\,OH^- \qquad (5)$$
$$H_2O_2 \rightarrow O_2 + 2H^+ + 2\,e^- \qquad (6)$$
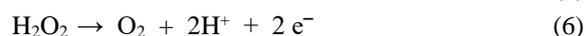
The increase in the Kapp values from 0.061 to 0.364 min^{-1} agrees with the expected enhancement of the production of ˙OH radicals during Fenton reaction (3).

Influence of experimental parameters on the mineralization kinetics of pyrazinamide aqueous solution

Several experiments were performed with different applied current values in the presence of 0.1 mM Fe^{2+} to study the mineralization kinetics of aqueous pyrazinamide through electro-Fenton process (Fig. 2(a)).

We noticed that during electrolysis the COD decreases in a continuous way indicating the degradation of pyrazinamide (initially put in solution) as well as its degradation products. At high electrolysis times, COD reaches values very weak, showing the complete mineralization of the organic solution studied. For example, for the case of the intensity of applied current equal to 300 mA, the COD decreases and reaches a corresponding value at an 81.63% mineralization rate after 6 hours of electrolysis.
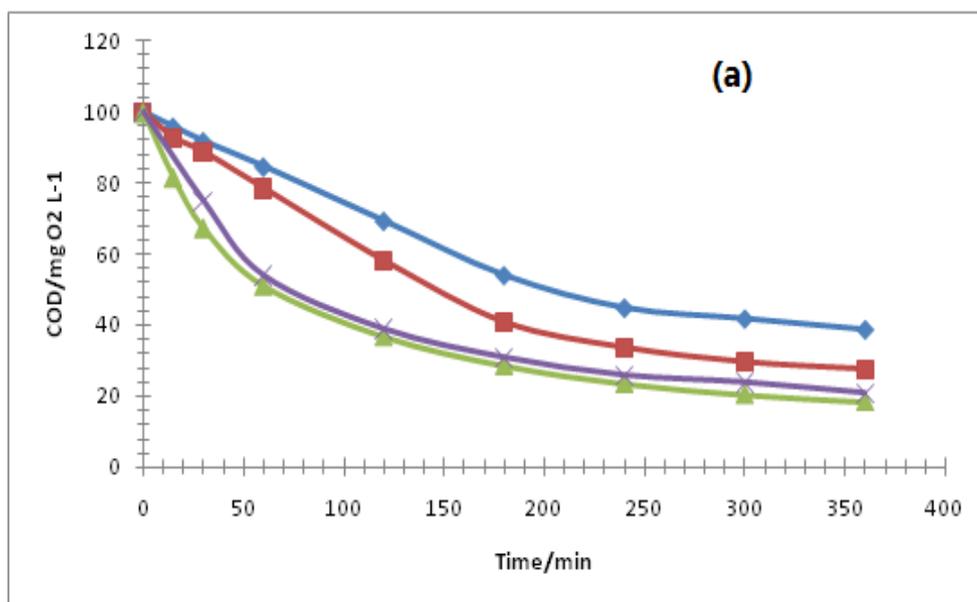
Figure 2 (a). Effect of applied current on pyrazinamide (0.34 mM) mineralization during electro-Fenton treatment at pH 3, 0.05 M Na₂SO₄ at room temperature in 0.05 M Na₂SO₄ solution. $[Fe^{2+}]$ (mM) = 0.1. I (mA) = 60 (-♦-), 100 (-■-), 300 (-▲-) and 400 (-×-).
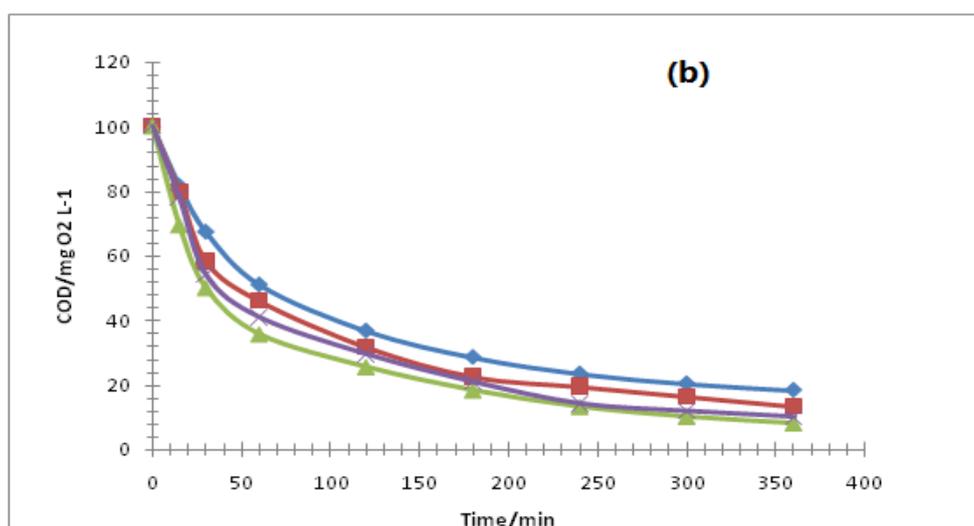

Figure 2 (b). Effect of catalyst concentration on pyrazinamide (0.34 mM) mineralization during electro-Fenton treatment at pH 3, 0.05 M Na₂SO₄ at room temperature in 0.05 M Na₂SO₄ solution. I (mA) = 300. $[Fe^{2+}]$ (mM) = 0.1 (-♦-), 0.2 (-■-), 0.5 (-▲-) and 0.8 (-×-).

Figure 2 (a) shows that the COD decay rate increases by increasing the applied current intensity from 60 to 400 mA. After 300mA value, an increase in the applied current intensity did not give any positive effect on COD abatement rate and therefore led to a weak COD removal kinetics due to the enhancement of wasting reactions (4) that may damage a generation of Fenton's reagent.

Therefore, the applied current intensity of 300 mA can be considered as the optimal applied current intensity for a maximum mineralization rate for pyrazinamide. Whereas, the mineralization degrees of pyrazinamide solution after 6 hours of electro-Fenton treatment was 61.22%, 72.45%, 81.63% and 79% for 60, 100, 300 mA and 400 mA, respectively.

Several experiments have been carried out by changing the catalyst concentrations in the range of 0.1–0.8mM at 300 mA during the treatment with EF (results in Fig. 2(b)).

COD decay rate increases by increasing the amount of Fe^{2+} catalyst concentration from 0.1 to 0.5mM. After a certain value, as 0.8 mM, the removal rate of pyrazinamide solution decreases, which can be explained by the parasitic reaction between Fe^{2+} and hydroxyl radicals' reaction (7) [37]. We can find similar results in the literature, where there are deductions and ascertainments who approach us [20]. It can be the said based on the results that the concentration of the catalyst (Fe^{2+}) is very significant in the electro-Fenton process.

$$Fe^{2+} + {}^{\bullet}OH \rightarrow Fe^{3+} + OH^{-} \qquad (7)$$

To further clarify the effect of applied current on the mineralization of the treated solution by the EF process, we calculated the efficiency of the mineralization current (instantaneous current efficiency (ICE)), at different electrolysis times.

As shown in (Fgure3), ICE can be calculated by the values of COD using the relation (8), as expressed below [22]:

$$ICE = \frac{(COD_0 - COD_t)FV}{8It} \qquad (8)$$

Where, COD_0 refers to the starting COD value, COD_t refers to the final COD value, I is the applied current (A), F is the Faraday constant (96.487 C mole^{-1}), t is the treatment time (s), and V is the volume of the solution (L).
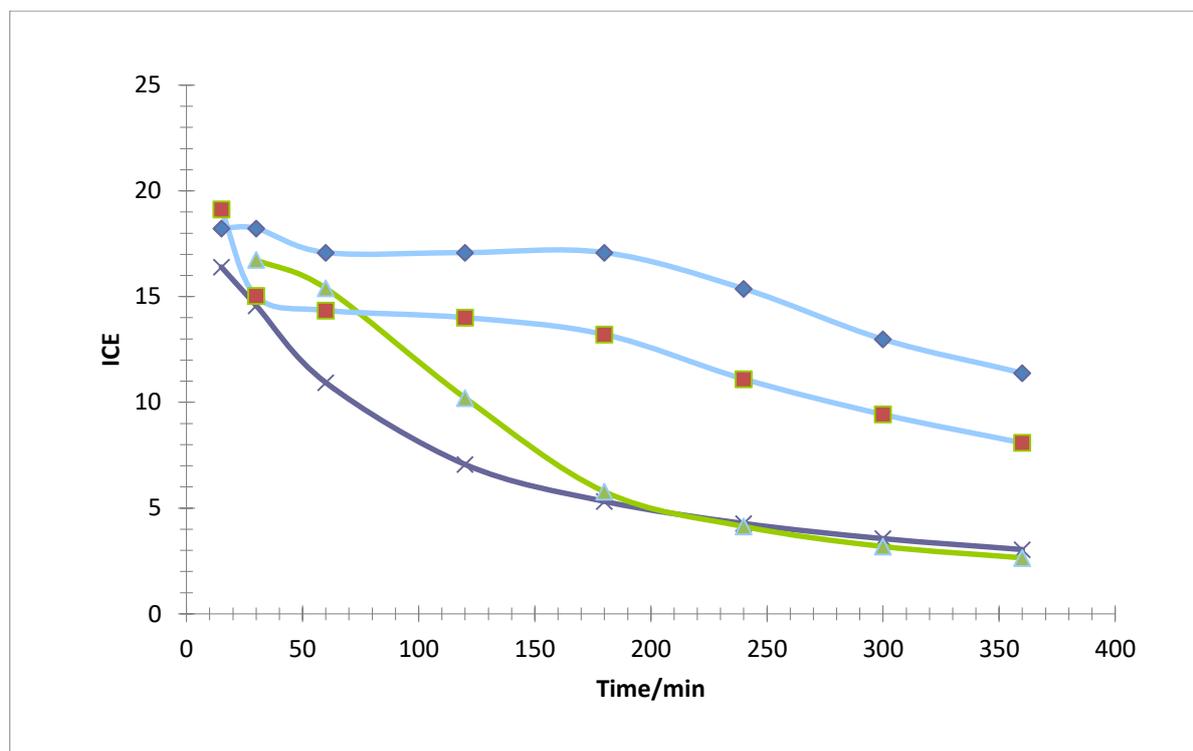

Figure 3. Instantaneous current efficiency change during the electro-Fenton process, $[Fe^{3+}] = 0.1$ mM, $[Na_2SO_4]$ = 0.05 M, V = 200 ml, I (mA) = 60 (-♦-), 100 (-■-), 300 (-▲-) and 400 (-×-).

Better ICE% values were obtained for 60 mA followed by 100 mA, reaching 17.08 and 14.35 %, respectively. ICE increases with the decrease in applied current that can be related to a decrease in the concentration of aromatic/cyclic organic products in aqueous solution and the formation of short-chain carboxylic acids. It is noteworthy that the acids resist the mineralization and enhance the parasitic reactions (4) and (7) which, under the mentioned conditions, become dominant [22], which might harm the generation of Fenton's reagent.

Influence of pyrazinamide concentration on the mineralization rate in aqueous solution

The mineralization removal values were investigated by using different pyrazinamide concentrations under the optimal conditions, as shown in Fig. 4.

The oxidation efficiency of the EF process was evaluated using different pyrazinamide concentrations under the optimal conditions in this work. Fig. 4 shows the effect of different initial pyrazinamide concentrations of 0.22, 0.30 and 0.41 mM. In all the cases, the pyrazinamide decreased as a function of time. The COD removals were 94%, 87% and 86% respectively for the previous concentrations of the antibiotic solutions. It can be explained that in this case, the further increase in pyrazinamide concentration causes an increment in the number of collisions between the pyrazinamide molecules with themselves: nevertheless, the probability of collisions between pyrazinamide with ${}^{\bullet}OH$ decreases.
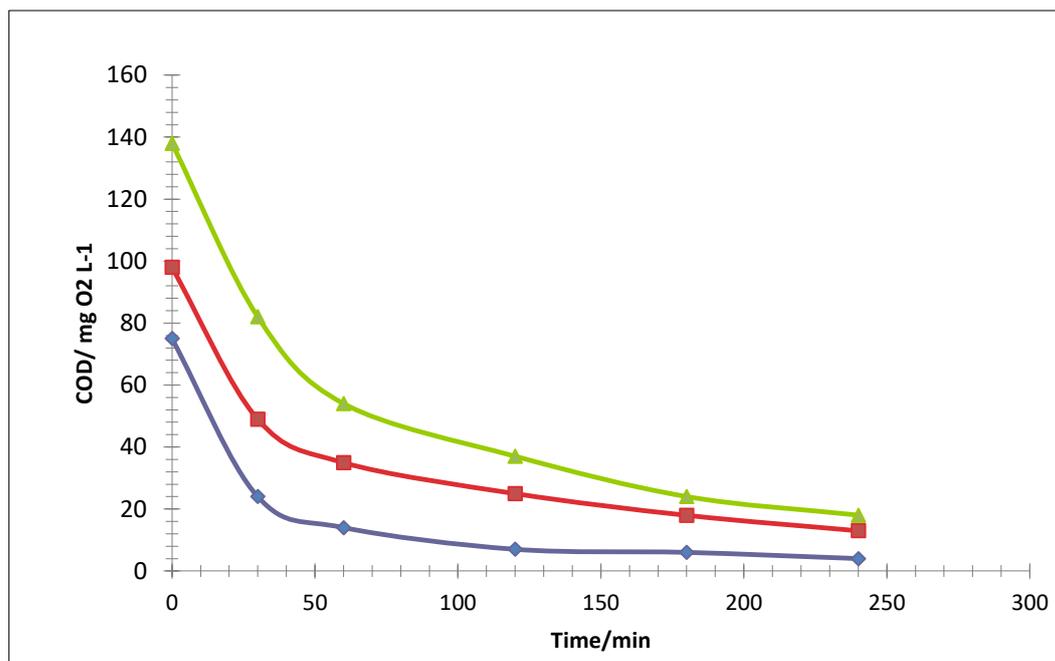
Figure 4. Effect of different pyrazinamide concentrations, for 0.22 (-♦-), 0.3(-■-) and 0.41 .mM (-▲-) solutions, on PZA mineralization during electro-Fenton under the conditions: $[Fe^{3+}] = 0.5$ mM $[Na_2SO_4] = 0.05$ M, 300 mA and V = 200 ml.

Identification of the reaction intermediates

We identified the stable intermediate products formed during treatment using HPLC and LC/MS-MS analyses. The obtained results are taken in the first 1 h (4 min, 8 min, 15 min and 1 h) of electrolysis during electro-Fenton process showed an increasing disappearance of pyrazinamide and formation of some aromatic and aliphatic intermediate products. The concentration of these intermediate products goes to maxima and then decrease until full disappearance.

Table 3 represents the identified intermediates products, while HPLC chromatograms and mass spectra of these intermediate products are given in Figures 5 and 6, respectively.
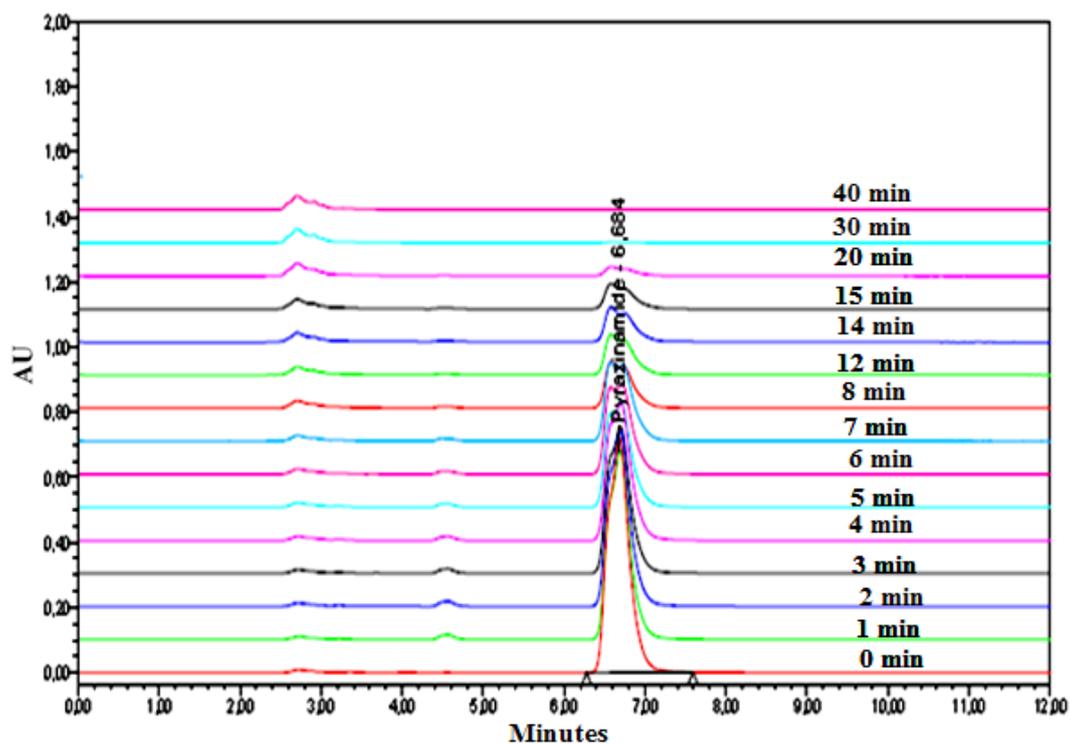

Figure 5. Chromatograms showing the decrease of the existence of pyrazinamide in the solution during the first 40 min of treatment by electro-Fenton process. $[Fe^{2+}]=0.5$ mM, I = 300 mA, $[Na_2SO_4] = 0.05$ M, V = 200 ml.
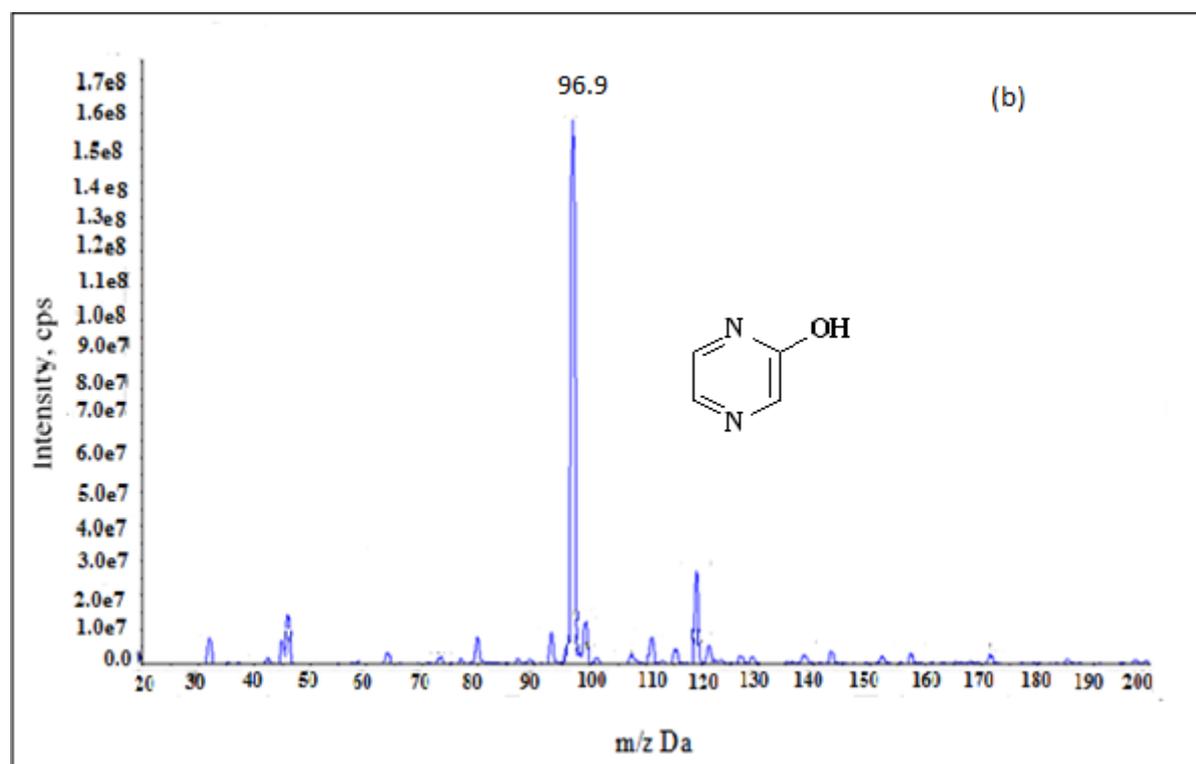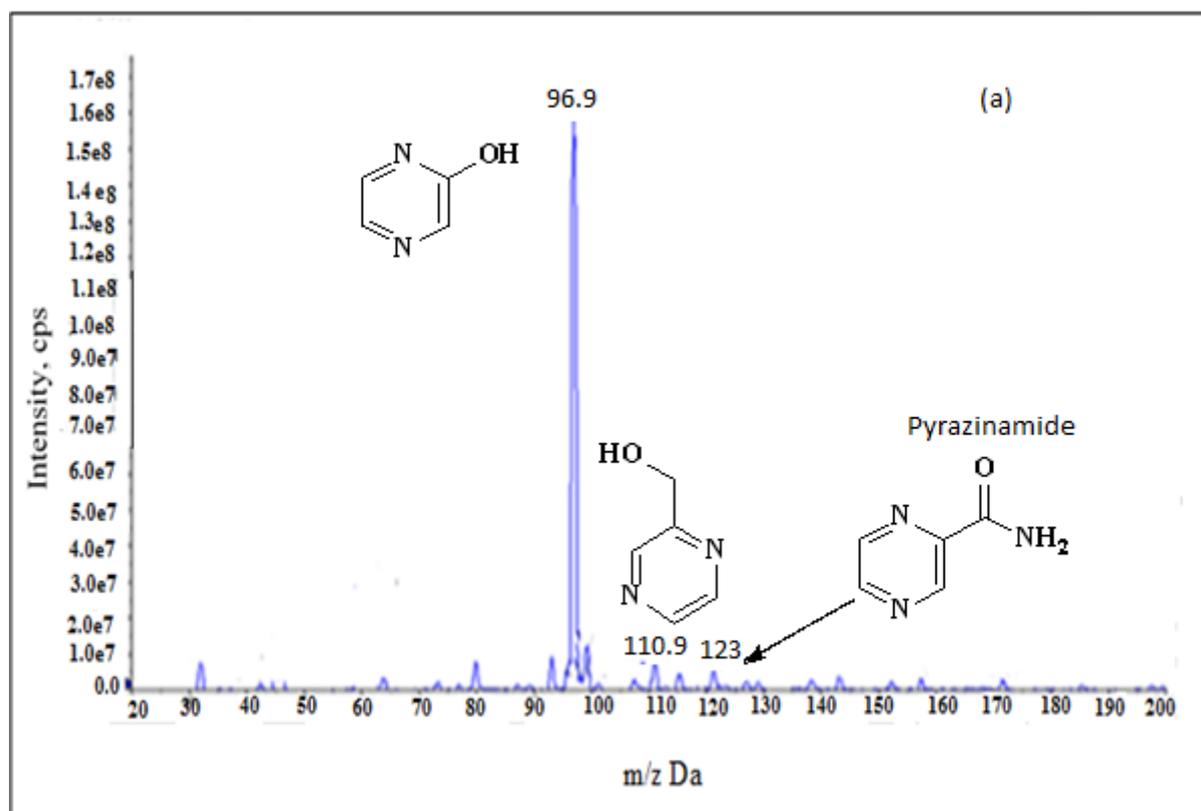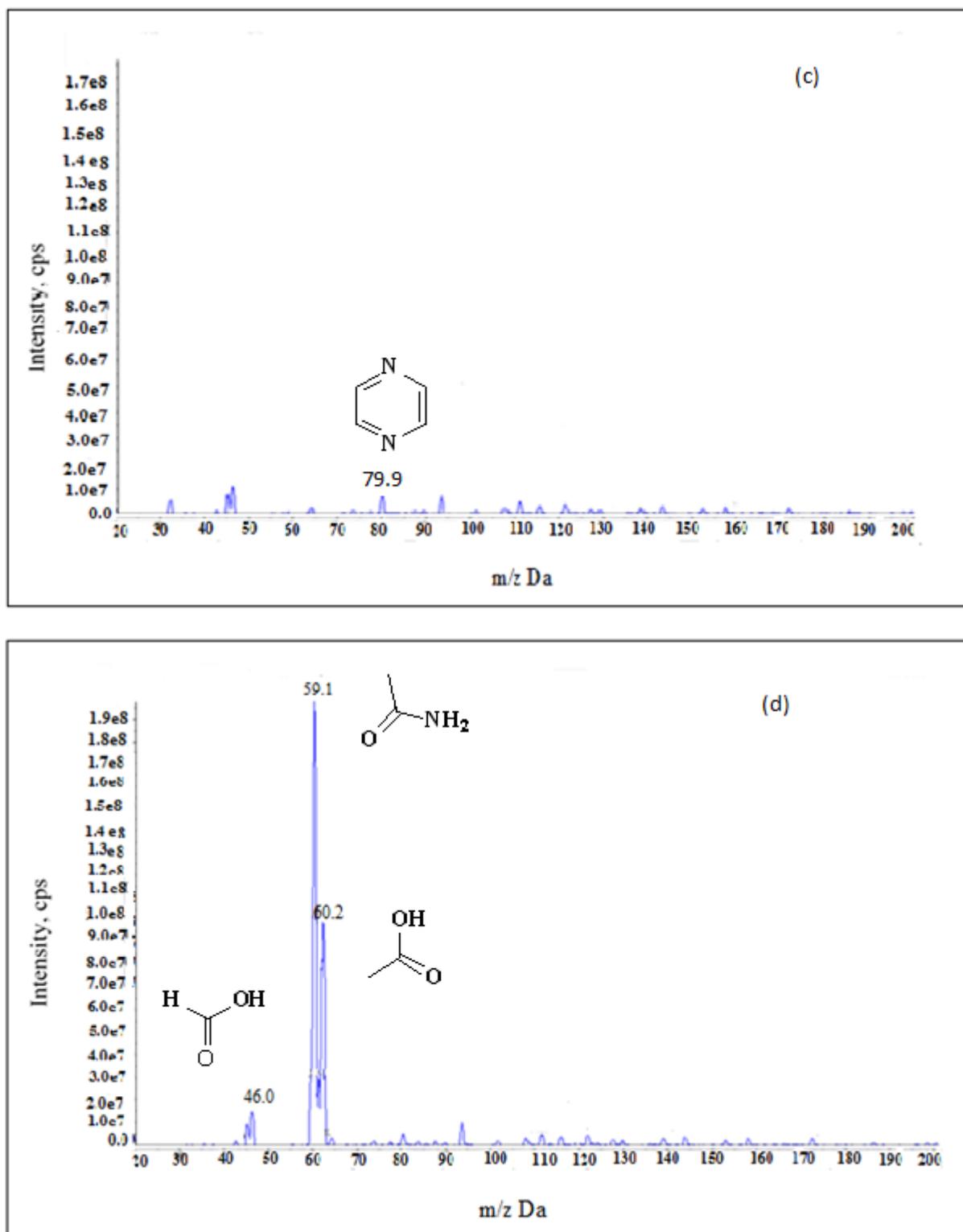
Figures 6. (a, b, c, d) Mass spectra of intermediate products present in the solution during 1 h of mineralization by electro-Fenton process of pyrazinamide. $[Fe^{2+}] = 0.5$ mM, $I = 300$ mA, $[Na_2SO_4] = 0.05$ M, pH 3.

Table 3. The intermediates identified by LC/MS-MS during the degradation of pyrazinamide by electro-Fenton treatment.

Intermediates	Chemical formula	Molecule name	m/z	References
(1)	HO─[pyrazine ring structure]	pyrazin-2-ylmethanol	110.1	8, 17
(2)	[pyrazine ring with OH]	pyrazin-2-ol	96.9	17
(3)	[pyrazine ring]	pyrazine	79.9	8, 17
(4)	[structure with NH₂ and O]	Acetamide	59.9	17
(5)	[structure H, OH, O]	Formic acid	45.9	17
(6)	[structure OH, O]	Acetic acid	61.0	17
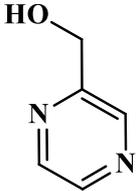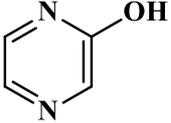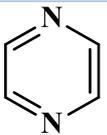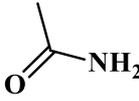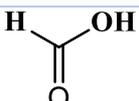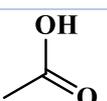
Biodegradability study

Investigation of biodegradation and mineralization rates during EF treatments of the samples are described in Fig. 7 at constant current intensity of 300 mA and a catalyst (Fe^{2+}) concentration of 0.5 mM.
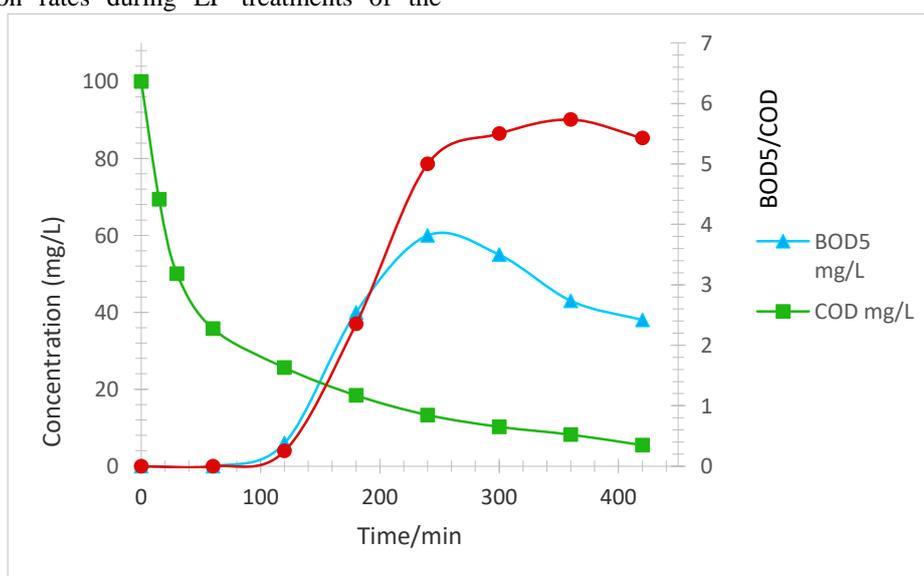

Figure 7. Biodegradability evolution (BOD_5/COD ratio) and mineralization evolution during the treatment by EF at I = 300 mA and with a concentration of Fe^{2+} of 0.5 mM.

These results show that untreated pyrazinamide is non-biodegradable with BOD_5/COD ratio is equal to zero. Likewise, this ratio remains zero during 100 minutes of treatment, indicating that the primary pyrazinamide degradation products are also non-biodegradable. After this time, the biodegradability

increases gradually, and at t = 180 minutes (3 hours) of electrolysis, the BOD5/COD ratio reaches the value 2.4 which indicates that the solution becomes biodegradable as is known in the literature [38]. Finally, during the times from 180 to 420 min, the reaction intermediates keep reacting with the ˙OH radicals, in fact significantly enhancing the biodegradability to 5.43.

Feasibility of the coupling of the advanced oxidation process (EF) with the biological post treatment

The results of the degradation/mineralization and biodegradability studies show that the pyrazinamide is non-biodegradable, but it is quickly oxidized by ˙OH and is completely degraded after 20 minutes of EF treatment (Fig. 1) and gives rise to the formation aromatic by-products ((1), (2) and (3), Table 3). These aromatic products are also non-biodegradable, quickly oxidized by ˙OH and are completely degraded into short-chain aliphatic by-products ((4), (5), (6), Table 3). These aliphatics resist at the mineralization because they are difficult to oxidize by ˙OH, but perfectly biodegradable by the microorganisms of wastewater as is known in the literature [37].

Moreover, it is interesting to note that globally there are two different stages during EF treatment: the first step of 0 to 3 hours and the second of 3 to 7 hours of electrolysis. During the first 3-hour stage, a significant rate (82%) of COD abatement is reached, while the remaining 18% require a much longer period (4 hours) to be mineralized in $CO_2 + H_2O$ during this period. This is explained by the fact that the first treatment step corresponds to the degradation of the aromatic products (pyrazinamide and its by-products (1), (2) and (3)) by ˙OH which is done with a fast kinetics and the second stage corresponds to the degradation of the aliphatic by-products that are difficult to mineralize in CO_2 by ˙OH.

During this second stage of the EF treatment, much more energy was consumed unnecessarily because of the parasitic reactions (4) and (7) which consume the ˙OH reagent as was demonstrated previously in the study of the applied current effect on the mineralization of the solution treated by the EF process.

These two steps can be illustrated by Figure 8 giving the global diagram of degradation/mineralization of pyrazinamide in an aqueous medium and the successive formation of recalcitrant and biodegradable organic reaction intermediates using EF process as treatment under optimal conditions (300 mA and [Fe^{2+}] = 0.5 mM). Indeed, the intermediates are in agreement with the fragments found in mass spectrometry.

Based on these results, it seems feasible to switch the EF process to a biological process after 3 h of electrolysis. Indeed, on the one hand, after 7 h of electrolysis we obtained a 97% abatement rate, and on the other hand, we found a rate of 82% after 3 hours of EF treatment. Thus, by adopting the biological method after 3 h of treatment by the EF method, we will economize relative energy to 4 h of electrolysis, this means more than half of the total treatment time (7 h) required for complete mineralization. in ($CO_2 + H_2O$) by the electro-Fenton process.

Biorecalcitrant aromatics   Biorecalcitrant aromatics   Biodegradable aliphatics   Mineralisation
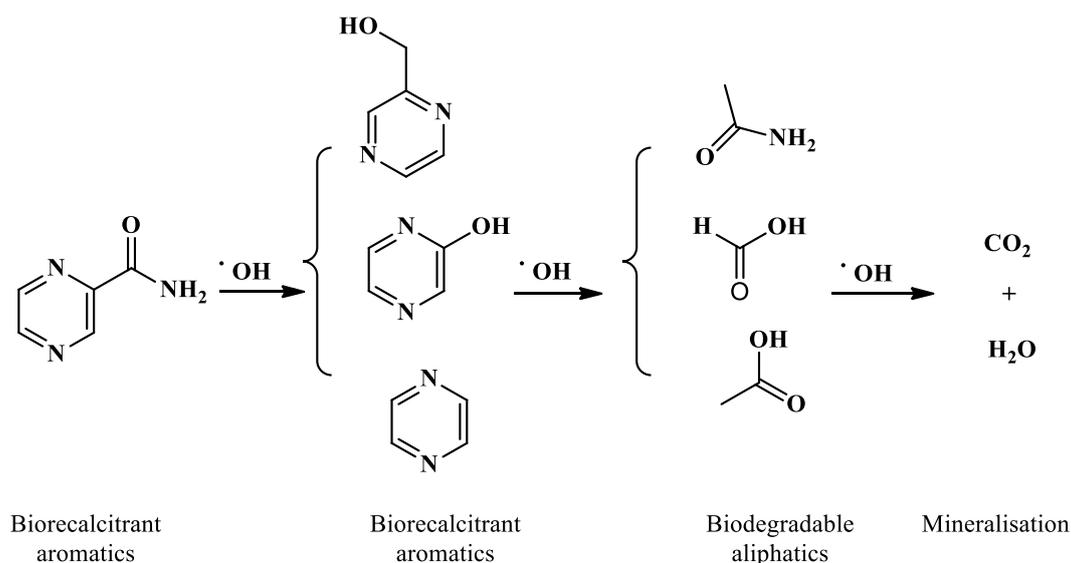
Figure 8. Global diagram of degradation/mineralization of pyrazinamide in an aqueous medium using the EF process as treatment under optimal conditions (300 mA and [Fe^{2+}] = 0.5 mM)

Conclusion

It has been found that for a 0.34 mM pyrazinamide concentration, the optimal parameters are I = 300 mA and [Fe^{2+}] = 0.5 mM. Under these experimental conditions, pyrazinamide degrades completely after 20 min of EF treatment, and the COD

reduction rate reaches 97% after 7 hours indicating the total mineralization of the solution.

The stable reaction intermediates identified by HPLC and LC/MS-MS are of two types: cyclic aromatic products and short-chain aliphatic products. Aromatic products are the dominant species of the solution during the first 2 hours of EF treatment. They gradually degrade afterwards to give rise to the formation of aliphatic products, which are finally mineralized with $CO_2 + H_2O$.

The biodegradability study showed that during the first 2 hours of EF treatment, the value of the BOD_5/COD ratio is almost equal to zero indicating that the treated solution is non-biodegradable, thus showing that pyrazinamide and its sub - Aromatic products are bio-refractory and do not lend themselves to biological treatment. The BOD_5/COD ratio reaches a value of 2.4 after 3 hours of treatment indicating that the solution, which contains mainly the short-chain aliphatic products, becomes biodegradable. These results show that electro-Fenton pretreatments can improve biodegradability by forming more biodegradable intermediates that could be easily degraded by a biological process.

Thus, a combination between electro-Fenton with a biological post-treatment could be considered as a perspective for predicting suitable electrolysis time in order to achieve good biodegradability and to pass to the biological treatment in order to minimize the cost of the global treatment.

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