

# Removal of antibiotic cloxacillin by means of electrochemical oxidation, TiO<sub>2</sub> photocatalysis, and photo-Fenton processes: analysis of degradation pathways and effect of the water matrix on the elimination of antimicrobial activity

Efraim A. Serna-Galvis<sup>1</sup> · Ana L. Giraldo-Aguirre<sup>2</sup> · Javier Silva-Agredo<sup>1</sup> · Oscar A. Flórez-Acosta<sup>2</sup> · Ricardo A. Torres-Palma<sup>1</sup>

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**Abstract** This study evaluates the treatment of the antibiotic cloxacillin (CLX) in water by means of electrochemical oxidation, TiO<sub>2</sub> photocatalysis, and the photo-Fenton system. The three treatments completely removed cloxacillin and eliminated the residual antimicrobial activity from synthetic pharmaceutical wastewater containing the antibiotic, commercial excipients, and inorganic ions. However, significant differences in the degradation routes were found. In the photo-Fenton process, the hydroxyl radical was involved in the antibiotic removal, while in the TiO<sub>2</sub> photocatalysis process, the action of both the holes and the adsorbed hydroxyl radicals degraded the pollutant. In the electrochemical treatment (using a Ti/IrO<sub>2</sub> anode in sodium chloride as supporting electrolyte), oxidation via HClO played the main role in the removal of CLX. The analysis of initial by-products showed five different mechanistic pathways: oxidation of the thioether group,

opening of the central β-lactam ring, breakdown of the secondary amide, hydroxylation of the aromatic ring, and decarboxylation. All the oxidation processes exhibited the three first pathways. Moreover, the aromatic ring hydroxylation was found in both photochemical treatments, while the decarboxylation of the pollutant was only observed in the TiO<sub>2</sub> photocatalysis process. As a consequence of the degradation routes and mechanistic pathways, the elimination of organic carbon was different. After 480 and 240 min, the TiO<sub>2</sub> photocatalysis and photo-Fenton processes achieved ~45 and ~15 % of mineralization, respectively. During the electrochemical treatment, 100 % of the organic carbon remained even after the antibiotic was treated four times the time needed to degrade it. In contrast, in all processes, a natural matrix (mineral water) did not considerably inhibit pollutant elimination. However, the presence of glucose in the water significantly affected the degradation of CLX by means of TiO<sub>2</sub> photocatalysis.

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✉ Ricardo A. Torres-Palma  
ricardo.torres@udea.edu.co

<sup>1</sup> Grupo de Investigación en Remediación Ambiental y Biotransformación (GIRAB), Instituto de Química, Facultad de Ciencias Exactas y Naturales, Universidad de Antioquia UdeA, Calle 70 No. 52-21, Medellín, Colombia

<sup>2</sup> Grupo de Diseño y Formulación de Medicamentos, Cosméticos y Afines (DYFOMECO), Facultad de Química Farmacéutica, Universidad de Antioquia UdeA, Calle 70 No. 52-21, Medellín, Colombia

**Keywords** Water treatment · β-Lactam antibiotic · Advanced oxidation process · Electrochemical oxidation · Degradation pathways · Pollutant mineralization · Antimicrobial activity removal · Matrix effects

## Introduction

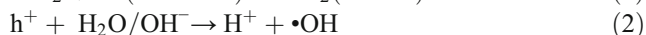
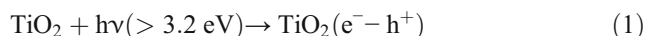
Cloxacillin (CLX) is a penicillanic antibiotic widely used to treat bacterial infections in humans and animals (Sutherland et al. 1970; Ito et al. 2001). Due to its antimicrobial properties, the biological processes applied in the conventional wastewater treatment plants usually fail to eliminate this antibiotic. Consequently, as other similar antibiotics, CLX frequently end up in natural water bodies. Penicillanic antibiotics have

been measured at concentrations of milligrams per liter in treated wastewaters (Elmolla and Chaudhuri 2009b). Particularly, CLX has been found in effluents of wastewater treatment plants (Cha et al. 2006).

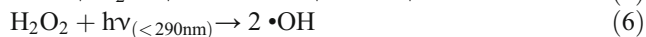
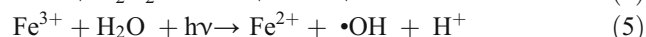
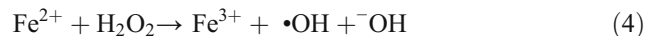
Furthermore, it is well known that antibiotics in natural environments produce several negative effects, such as the development of resistant bacteria, which can be transferred to both humans and animals (Bouki et al. 2013). Negative environmental impacts are usually observed even when the concentrations of the pharmaceuticals are low ( $\mu\text{g L}^{-1}$  or  $\text{ng L}^{-1}$ ) (Kümmerer 2009; Michael et al. 2013). Therefore, to reduce the environmental impact of antibiotics, the application of unconventional treatments to water containing these pollutants is required.

An interesting option is the use of advanced photochemical oxidation processes (AOP), such as the  $\text{TiO}_2$  photocatalysis and photo-Fenton processes, which have shown to be efficient at degrading recalcitrant pollutants in water (Elmolla and Chaudhuri 2009b; Homem and Santos 2011; Rivera-Utrilla et al. 2013; Pereira et al. 2013; Serna-Galvis et al. 2016a, b).

The elimination of pollutants by means of photocatalysis with the  $\text{TiO}_2$  semiconductor is promoted by the action of the hole or hydroxyl radical (Chen et al. 2005). When photons with energy (higher than 3.2 eV) illuminate the titanium dioxide ( $\text{TiO}_2$ ), electron excitation occurs from the valence band to the conduction band (Ohtani 2014) (Eq. 1). The generated hole can oxidize the water (or hydroxide anion) to produce the hydroxyl radical (Eq. 2). Additionally, electrons can react with the dissolved oxygen to form superoxide anion radical and it could evolve into hydroxyl radicals, perhydroxyl radicals, or hydrogen peroxide (Eq. 3) (Chen et al. 2005), which can also be used to remove pollutants.

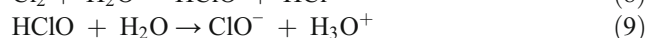
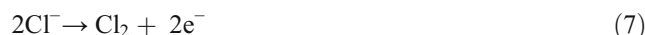


Moreover, in the photo-Fenton system, the hydroxyl radical is produced by the reaction of Fe(II) with  $\text{H}_2\text{O}_2$  (Eq. 4) and through the reduction of Fe(III) caused by the light action (Eq. 5) (Pignatello et al. 2006). When the source of light emits wavelengths lower than 290 nm, hydroxyl radicals can also be formed from the hydrogen peroxide photolysis (Eq. 6).



In addition to the previously described AOP, another interesting alternative for the treatment of pollutants in water is the electrochemical process using the  $\text{IrO}_2$  anode

in presence of NaCl as supporting electrolyte (Sirés and Brillas 2012; Guzmán-Duque et al. 2014; Giraldo et al. 2015; Sopaj et al. 2015). Pollutants can be oxidized by direct interaction with the anode surface (Panizza and Cerisola 2009; Comninelis and Chen 2010). Additionally, this system produces active chlorine species from the anodic reaction of chloride ions (Eqs. 7–9). Active chlorine species are also able to remove organic matter (Panizza and Cerisola 2009; Comninelis and Chen 2010) and the predominant species depends on the pH: when  $\text{pH} < 3$ , it is  $\text{Cl}_2$  ( $E^\circ = 1.36 \text{ V}$ ); when  $\text{pH} = 3\text{--}8$ , it is  $\text{HClO}$  ( $E^\circ = 1.49 \text{ V}$ ); and when  $\text{pH} > 8$ , it is  $\text{OCl}^-$  ( $E^\circ = 0.89 \text{ V}$ ) (Deborde and von Gunten 2008; Sirés and Brillas 2012).



In spite of the good performances reported for the aforementioned processes and the considerable risk of antibiotic presence in natural environments, the elimination of cloxacillin in water has been poorly studied. In fact, only photo-Fenton and ZnO photocatalysis (Elmolla and Chaudhuri 2009a; Elmolla and Chaudhuri 2009b; Elmolla and Chaudhuri 2010) have been successfully applied to minimize the negative environmental impact of this antibiotic. In such research works, the effect of operational parameters (e.g., light intensity, reagent concentrations, pH) was evaluated. However, the degradation routes, the organic by-products, and the residual antimicrobial activity of the treated solutions were not studied. This research work was focused on studying the application of  $\text{TiO}_2$  photocatalysis, the photo-Fenton system, and electrochemical oxidation for removing CLX from water. For each process, the main antibiotic elimination routes were determined, the initial by-products were identified, and schematic transformation pathways for each oxidation system were proposed. Furthermore, the ability of the different processes to mineralize the antibiotic was evaluated and compared. Finally, the effect of matrix components on the antibiotic removal and its associated antimicrobial activity was also assessed. For this purpose, two matrices were considered: (I) a combination of cloxacillin and glucose, and (II) natural mineral water containing a commercial formulation of the antibiotic.

## Materials and analysis

### Chemicals

Cloxacillin was provided by Syntofarma S.A. Hydrogen peroxide, formic acid, and sodium chloride were purchased from

Carlo-Erba. Mannitol, isopropanol, ferrous sulfate, sulfuric acid, methanol, acetonitrile, sodium phosphate, sodium hydroxide, sodium meta-bisulfite, potassium iodide, ammonium heptamolybdate, and ferric chloride were provided by Merck. Titanium dioxide P-25 was supplied by Evonik (Degussa). All chemicals were used as received.

## Reactors

### *Reaction system for the electrochemical process*

Electrochemical treatments were conducted in an electrolytic cell containing 150 mL of solution under constant stirring conditions. Experiments were carried out at a constant current density ( $30 \text{ mA cm}^{-2}$ ) under galvanostatic conditions, and using a Ti/IrO<sub>2</sub> anode with a working surface area of  $4 \text{ cm}^2$ . The cathode was a zirconium spiral electrode of  $10 \text{ cm}^2$ . A concentration of NaCl  $0.225 \text{ mol L}^{-1}$  was used as the supporting electrolyte.

### *Reaction system used in the photo-Fenton and TiO<sub>2</sub> photocatalysis processes*

The photo-Fenton process and photocatalysis with TiO<sub>2</sub> were carried out in a homemade aluminum reflective reactor equipped with five 30 W Philips lamps (TL-D Actinic BL). For the photo-Fenton and the TiO<sub>2</sub> photocatalysis processes, 30 and 150 W of light power were applied respectively to 100 mL of solution placed in beakers with a constant stirring. In the photo-Fenton process,  $10 \text{ mmol L}^{-1}$  and  $90 \text{ } \mu\text{mol L}^{-1}$  of H<sub>2</sub>O<sub>2</sub> and Fe (II), respectively, were used. Prior to the analysis, the residual H<sub>2</sub>O<sub>2</sub> was eliminated using sodium meta-bisulfite. For the TiO<sub>2</sub> photocatalysis,  $2.0 \text{ g L}^{-1}$  of the catalyst was used. The lamps were turned on after the adsorption equilibrium was achieved (after 30 min in the dark and under constant stirring). Before analyzing the treated solutions, the catalyst was precipitated by centrifugation for 10 min at  $3200 \text{ rev min}^{-1}$  in a centrifuge (Centaur 2) and filtered using a  $0.45\text{-}\mu\text{m}$  cellulose mesh (Advantech).

## Analysis

### *Pollutant and oxidant evolution*

CLX degradation was monitored at 225 nm using a Waters liquid chromatograph equipped with a 486 absorbance (UV–vis) detector and a Merck column LiChrospher RP-18 ( $5 \text{ } \mu\text{m}$  dp,  $250 \times 4.5 \text{ mm}$ ), at  $25 \text{ }^\circ\text{C}$  and isocratic conditions (a mixture of a phosphate buffer/acetonitrile/methanol 64:27:9 v/v), a flow rate of  $0.6 \text{ mL min}^{-1}$ , and a  $20 \text{ } \mu\text{L}$  injection volume. The oxidants produced or consumed during the different processes were determined by iodometry, as reported by Serna-Galvis et al. (2015).

### *Determination of by-products*

The organic by-products formed after 50 % of the CLX degradation in each oxidation process were extracted from the water and concentrated using Strata X cartridges loaded with 50 mL of the sample. The by-products were desorbed with 2 mL of 2 % formic acid, and then analyzed using a Thermo Scientific HPLC (Ultimate 3000)–MS (Orbitraps) instrument equipped with a Merck column LiChrospher RP-18 ( $5 \text{ } \mu\text{m}$  dp,  $250 \times 4.5 \text{ mm}$ ). The mobile phase was a mixture of acetonitrile acidified with 0.1 % of formic acid and water acidified with 0.1 % formic acid in a linear gradient from 10 to 100 % of acidified acetonitrile for 50 min and then these conditions for 5 min. The flow and injection volume were  $0.4 \text{ mL min}^{-1}$  and  $20 \text{ } \mu\text{L}$ , respectively. The mass spectrometer was operated in the electrospray positive ion mode.

### *Pollutant mineralization analysis*

The degree of pollutant mineralization during the different treatments was determined by measuring the total organic carbon (TOC). Samples were directly injected in a Shimadzu Total Organic Carbon Analyzer (TOC 5000A) previously calibrated with potassium hydrogen phthalate standards.

### *Antimicrobial activity measurement*

The residual antibiotic activity (AA) was determined using a highly sensible microorganism (*Staphylococcus aureus*, ATCC 6538, with an optical density of 0.600 at 580 nm) as probe and by measuring the bacterial growth inhibition zone. Sample solutions were diffused on Petri dishes containing agar previously inoculated with the indicator microorganism. After 24 h of incubation at  $37 \text{ }^\circ\text{C}$  in a Memmert (Schwabach) incubator, the diameter of the inhibitory halo was measured with a vernier.

## Results and discussion

### **Determination of the degradation pathways**

#### *Electrochemical treatment of cloxacillin*

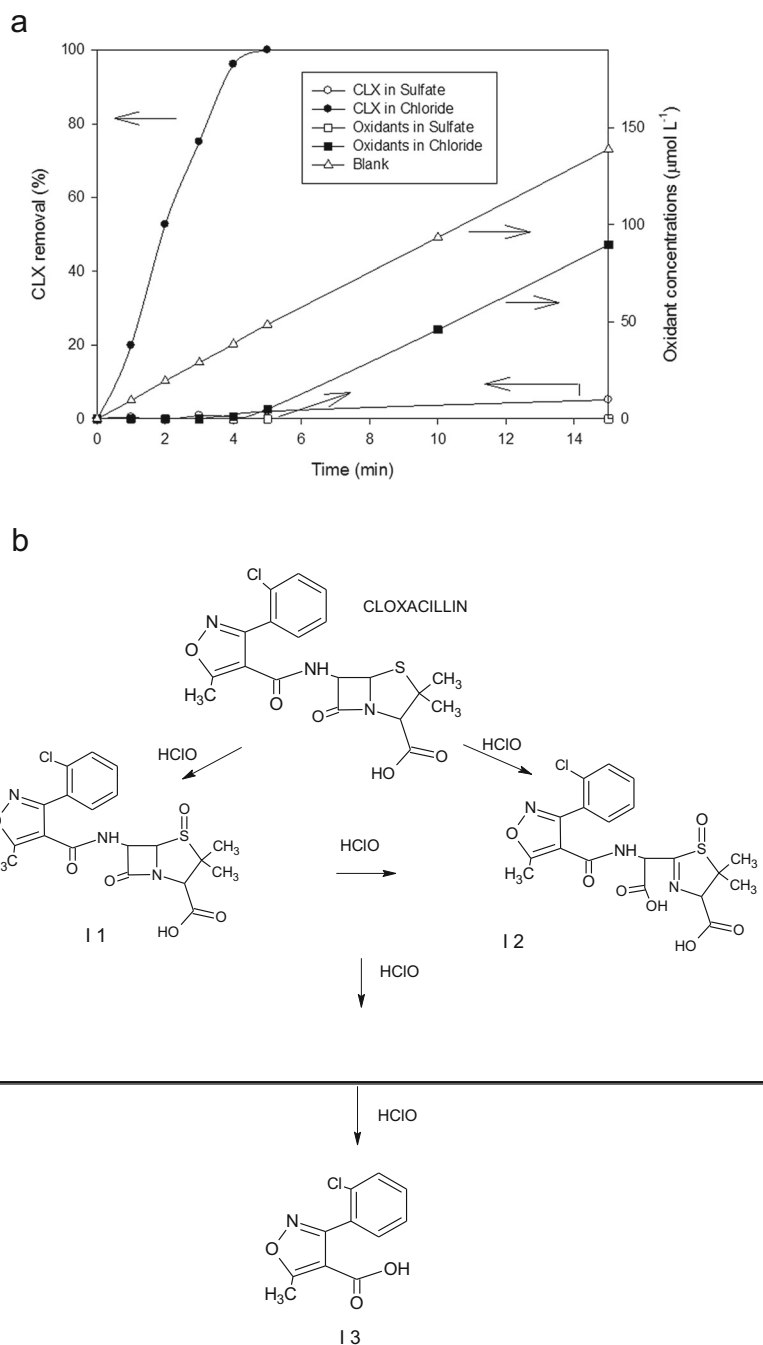
Organic pollutants treated by means of the electrochemical process using Ti/IrO<sub>2</sub> and NaCl can be degraded through direct oxidation on the anode or by reaction with the electrogenerated active chlorine species from the chloride anion (Panizza and Cerisola 2009; Sirés and Brillas 2012). Therefore, to determine the possible involvement of the mediated degradation by the active chlorine species, the electrochemical process was evaluated using NaCl as the electrolyte in both the presence and absence of the pollutant (Fig. 1a). To

analyze the contribution of the CLX oxidation onto the anode surface, experiments were also carried out using  $\text{Na}_2\text{SO}_4$  as supporting electrolyte. In the absence of the pollutant, and with sodium chloride as electrolyte, a large accumulation of hypochlorous acid (the predominant active chlorine specie at the experimental  $\text{pH}=6.0$ ) was observed. However, in the presence of CLX, the  $\text{HClO}$  accumulation only started when the pollutant was removed (Fig. 1a). In contrast, oxidant formation and cloxacillin degradation were not found after 15 min of electrolysis with  $\text{Na}_2\text{SO}_4$  as supporting electrolyte.

These results indicate that the electrochemical removal of CLX is mainly associated with the hypochlorous acid action.

Furthermore, the HPLC-MS analysis for the electrochemical process evidenced the formation of three main organic intermediaries (I1–I3). The chemical names, chemical structures, and main peaks in the mass spectrum of these compounds are summarized in Table 1. Also, based on the previously stated degradation routes and the identified by-products, a schema of electrochemical degradation for CLX is depicted in Fig. 1b. As it can be observed, I1 is probably produced by

**Fig. 1** **a** CLX degradation by means of the electrochemical process:  $\text{Ti}/\text{IrO}_2$  anode;  $[\text{NaCl}]$ ,  $0.225 \text{ mol L}^{-1}$ ;  $j$ ,  $30 \text{ mA cm}^{-2}$ ; initial  $\text{pH}$ , 6.0; and  $[\text{CLX}]$ ,  $203 \text{ } \mu\text{mol L}^{-1}$ . **b** CLX elimination schema by means of electrochemical oxidation



the attack of HClO to the thioether moiety on the CLX to generate sulfoxide. Such oxidation is reported to occur in two steps: generation of the chlorosulfonium cation ( $>S^+-Cl$ ) and its subsequent hydrolysis (Deborde and von Gunten 2008). I2 is probably generated from both thioether oxidation and the opening of  $\beta$ -lactam ring. The strain of the four-member ring and the labile nature of the carbonyl-nitrogen bond favor the ring opening (Mavronikola et al. 2009). In turn, I3 could be formed due to the breakdown of the secondary amide of the CLX, I1 and I2. In fact, it has been reported that the electrogenerated HClO produces the carboxylic group by an initial amide chlorination and subsequent hydrolysis (Thomm and Wayman 1969). As a consequence of the high reactivity of the HClO on the thioether moiety, the complete elimination of the antibiotic occurs in a relatively short period of time ( $\sim 5$  min) (Fig. 1a).

### *TiO<sub>2</sub> photocatalysis*

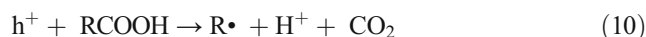
In the TiO<sub>2</sub> photocatalysis process, the organic pollutants could be degraded by UV photolysis, direct oxidation at the hole, or reaction with hydroxyl radicals (Chen et al. 2005; Villegas-Guzman et al. 2015b). To determine the participation of the first route, a CLX solution was irradiated with UV light in absence of TiO<sub>2</sub>. As Fig. 2a shows, under such conditions, CLX degradation was not observed even after 60 min of irradiation. Additionally, as Fig. SM1 (in the supplementary material) shows, the CLX absorbs wavelengths lower than 300 nm and the lamp supplied the main emission at 365 nm. Thus, the absence of CLX degradation upon the photolysis action is not unexpected. In fact, a similar result was found by Elmolla et al. (Elmolla and Chaudhuri 2010).

To study the participation of the other two routes in the degradation of CLX, a scavenger of  $\bullet OH$  radicals in the bulk of solution (2-propanol, IPA), as well as a scavenger of catalyst holes or  $\bullet OH$  radicals adsorbed (potassium iodide, KI) were tested (Chen et al. 2005; Palominos et al. 2009) (Fig. 2a). Both of them are stable to irradiation (Palominos et al. 2008) and do not react directly with the antibiotic. The results in Fig. 2a show that in the presence of 2-propanol (25 times more concentrated than CLX) a slight reduction ( $\sim 6\%$ ) in the removal of the antibiotic was produced. Additionally, the adsorption of the pollutant onto the TiO<sub>2</sub> was not affected. This fact indicates that the contribution of the hydroxyl radicals (present in the solution) to cloxacillin degradation is not significant. On the contrary, when KI was used, a strong inhibition of both adsorption onto catalysts ( $\sim 60\%$ ) and CLX degradation ( $\sim 85\%$ ) occurred (Fig. 2a). It has been reported that if adsorption of organic molecules is poor by conditions such as the coverage of TiO<sub>2</sub> by other species, the chance to be degraded by photo-generated holes and adsorbed  $\bullet OH$  (direct oxidation) is low (Chen et al. 2005). Therefore, as the CLX absorption is lowered by presence of iodide ions, which can scavenge both hole and adsorbed  $\bullet OH$ , the direct oxidation is

inhibited. Then, the aforementioned results show that the elimination of cloxacillin by heterogeneous photocatalysis with TiO<sub>2</sub> can be associated with the oxidation by the photo-generated holes and adsorbed hydroxyl radicals.

On the other hand, four primary by-products of CLX degradation upon the TiO<sub>2</sub> photocatalysis action (I2, I4, I5, and I6) were identified by means of the HPLC-MS analyses (Table 1). As a result of the identified degradation routes and the by-products, a schema of the photocatalytical degradation of CLX can be proposed as it is illustrated in Fig. 2b.

As it can be observed, the attack of the hydroxyl radicals results in hydroxylation (I5) and sulfur oxidation (I2) of the antibiotic. Similar pathways have been reported for ampicillin (another  $\beta$ -lactam antibiotic) during the application of UV/H<sub>2</sub>O<sub>2</sub> and UV/Na<sub>2</sub>S<sub>2</sub>O<sub>8</sub> (He et al. 2014). Furthermore, I5 was produced through simultaneous decarboxylation and the opening of the  $\beta$ -lactam ring of cloxacillin, which could be associated with the oxidation produced by the photogenerated holes and hydroxyl radicals, respectively. The decarboxylation by hole action (known as photo-Kolbe reaction, Eq. 10) is a typical pathway of the photocatalytic processes. In fact, this pathway was also found during the degradation of a related antibiotic (oxacillin) by means of TiO<sub>2</sub> photocatalysis (Giraldo-Aguirre et al. 2015). Additionally,  $\bullet OH$  are also able to break cloxacillin and the I2 and I5 by-products, producing I6.



On the other hand, it is well-known that the successive attack of hydroxyl radicals to aromatic moieties (as in I6 by-product) leads to ring opening and carboxylic group formation (Houas et al. 2001). These intermediaries can be mineralized via photo-Kolbe reaction. In the case of the antibiotic cloxacillin, TiO<sub>2</sub> photocatalysis presented  $\sim 20\%$  mineralization efficiency at 100 % of pollutant degradation (see “Comparative mineralization of the cloxacillin” section). Further application of the technology, longer times after CLX removal, increased the mineralization to  $\sim 45\%$  (Fig. 4). Then, the mineralization extend may be related to the ring opening of I6 and its subsequent transformations into carbon dioxide, water, and inorganic ions (Fig. 2b).

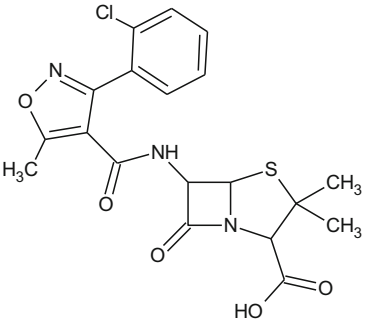
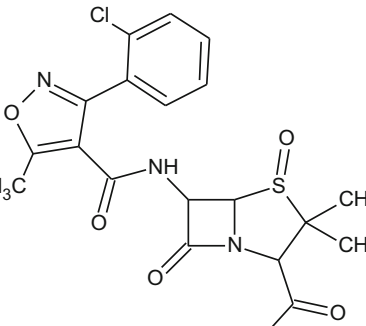
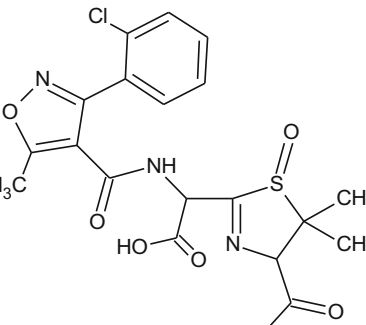
Finally, as suggested by the results, the absorption of CLX onto the catalyst surface is the key step in the process, which is limited by the mass transfer of the antibiotic to the catalyst surface. Therefore, the degradation rate is slower compared to the precedent degrading system, and 120 min is needed to completely remove CLX from the solution (data not shown).

### *Photo-Fenton process*

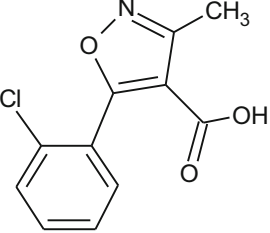
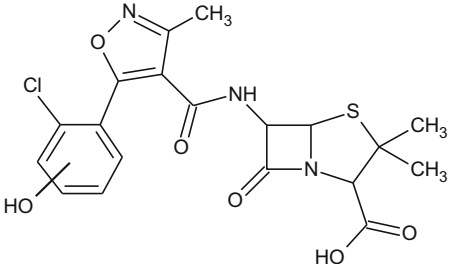
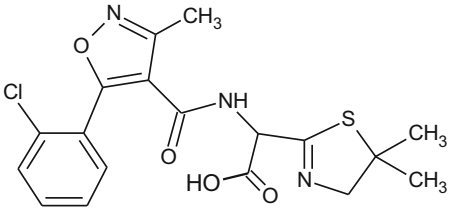
In the photo-Fenton process, the light or the hydrogen peroxide action, the Fenton process (Eq. 4), as well as the photo-



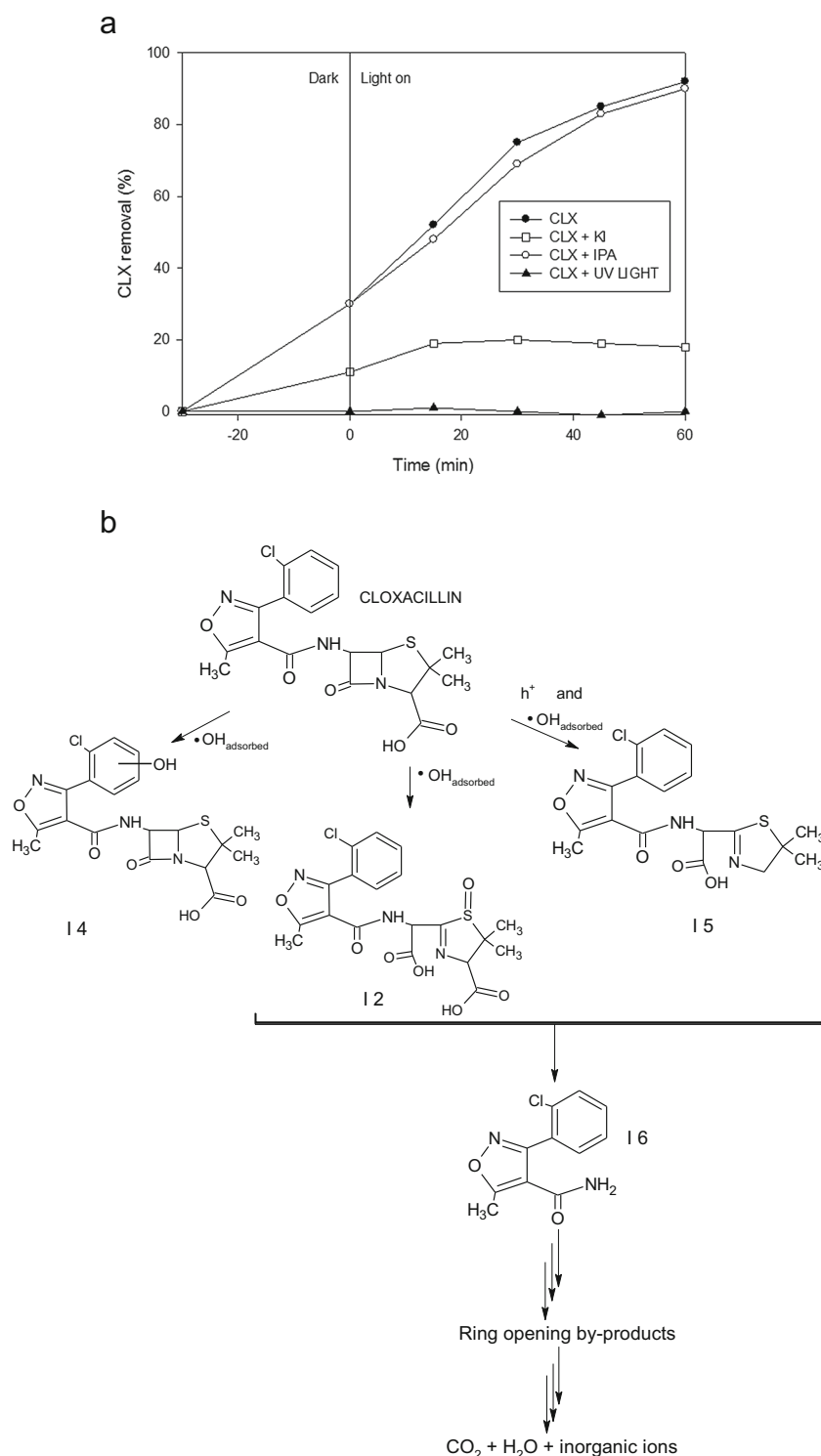
**Table 1** Characteristics of the identified organic by-products

Chemical name	Proposed structure	Main fragments	Detected in the process
<p><b>Cloxacillin</b></p> <p>[M + H] = 436</p>	 <p><b>(CLX)</b></p>	<p>277</p> <p>160</p> <p>114</p>	---
<p><b>6-({[5-(2-chlorophenyl)-3-methylisoxazol-4-yl]carbonyl}amino)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid 4-oxide</b></p> <p>[M + H] = 452</p>	 <p><b>(I1)</b></p>	<p>340</p> <p>144</p>	<p>Electrochemical oxidation</p> <p>Photo-Fenton</p>
<p><b>2-[carboxy({[5-(2-chlorophenyl)-3-methylisoxazol-4-yl]carbonyl}amino)methyl]-5,5-dimethyl-4,5-dihydro-1,3-thiazole-4-carboxylic acid 1-oxide</b></p>		<p>298</p> <p>144</p>	<p>Electrochemical oxidation</p> <p>TiO<sub>2</sub> photocatalysis</p>

**Table 1** (continued)

<p>[M + H] = 468</p>	<p><b>(12)</b></p>		
<p><b>5-(2-chlorophenyl)-3-methylisoxazole-4-carboxylic acid</b></p> <p>[M + H] = 238</p>	 <p><b>(13)</b></p>	<p>144</p> <p>105</p>	<p>Electrochemical oxidation</p>
<p><b>n-hydroxy-6-({[5-(2-chlorophenyl)-3-methylisoxazol-4-yl]carbonyl}amino)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid</b></p> <p>[M + H] = 452</p>	 <p><b>(14)</b></p>	<p>298</p> <p>259</p> <p>160</p>	<p>TiO<sub>2</sub> photocatalysis</p> <p>Photo-Fenton</p>
<p><b>([5-(2-chlorophenyl)-3-methylisoxazol-4-yl]carbonyl}amino)(5,5-dimethyl-4,5-dihydro-1,3-thiazol-2-yl)acetic acid</b></p> <p>[M + H] = 408</p>	 <p><b>(15)</b></p>	<p>298</p> <p>144</p>	<p>TiO<sub>2</sub> photocatalysis</p>

**Fig. 2 a** CLX degradation by means of  $\text{TiO}_2$  photocatalysis:  $[\text{TiO}_2]$ ,  $2.0 \text{ g L}^{-1}$ ; light power, 150 W; initial pH, 6.0; and  $[\text{CLX}]$ ,  $203 \text{ } \mu\text{mol L}^{-1}$ .  $[\text{IPA}]$  and  $[\text{KI}]$  ten times higher than  $[\text{CLX}]$ . **b** Schematic representation of photocatalytical elimination of CLX



decomposition of hydrogen peroxide (Eq. 6) could be involved in the degradation of pollutants (Pignatello et al. 2006; Neamtu et al. 2014). Therefore, the contribution of the aforementioned processes to the photo-Fenton system applied to the CLX elimination was evaluated (Fig. 3a). As it was previously demonstrated, the antibiotic was stable under the

light action. Additionally, the sole hydrogen peroxide eliminated ~24 % of the antibiotic (data not shown). However, the UV/ $\text{H}_2\text{O}_2$  system degraded ~40 % of the cloxacillin, which may be related to the formation of  $\cdot\text{OH}$  from the homolytic breakdown of  $\text{H}_2\text{O}_2$  (Eq. 6). As shown in Fig. SM2 (in the supplementary material), the lamp light can decompose the



H<sub>2</sub>O<sub>2</sub>. Moreover, the Fenton reaction represents an important contribution to the degradation of cloxacillin, as this process removed 100 % of the CLX after 120 min of treatment. Interestingly, the photo-Fenton process was able to completely degrade the antibiotic after 60 min of reaction. In Fenton, the reaction between ferrous ions and hydrogen peroxide to produce hydroxyl radical and the ferric ions (Eq. 4) has a high rate constant ( $k = 53\text{--}76 \text{ L mol}^{-1} \text{ s}^{-1}$ ), but the regeneration of Fe(II) from the Fe(III) and H<sub>2</sub>O<sub>2</sub> reaction (Eq. 10) is significantly slower ( $k = 10^{-6}\text{--}10^{-2} \text{ L mol}^{-1} \text{ s}^{-1}$ ) (Pignatello et al. 2006). In the photo-Fenton process, the light can accelerate the regeneration of Fe(II) and concomitantly increase the hydroxyl radical amount (Eq. 5). Therefore, a faster degradation of the antibiotic than in the sole Fenton reaction is obtained. These results indicate that cloxacillin degradation by means of the photo-Fenton system is mainly caused by the attack of the hydroxyl radical with a strong participation of the Fenton reaction.



By means of the HPLC-MS analysis for this process, four organic by-products (I1, I4, I6, and I7) were determined. The reaction of •OH with cloxacillin led to the hydroxylation of aromatic ring (I4) and sulfoxide formation (I1). Such β-lactam antibiotic degradation pathways have also been reported in other AOPs (Song et al. 2008; Dail and Mezyk 2010). Due to the electrophilic character of •OH and the high electron density on the aromatic ring (which can experiment electrophilic substitutions (Clayden et al. 2001; Pignatello et al. 2006)) and sulfur, the formation of I4 and I1 is plausible. In fact, I4 was also found during the application of TiO<sub>2</sub> photocatalysis (“TiO<sub>2</sub> photocatalysis” section). Besides the attack to the aromatic ring and the thioether, the hydroxyl radicals formed during the photo-Fenton process also induced the opening of β-lactam (I7) and the breakdown of the central secondary amide (I6). Considering all these results, a schematic representation of the cloxacillin elimination by means of the photo-Fenton system is shown in Fig. 3b. It is interesting to note that due to the homogeneous characteristics of the photo-Fenton system, the CLX removal is considerably faster than with the TiO<sub>2</sub> photocatalytical system. In fact, 60 and 120 min were required to completely remove cloxacillin in the photo-Fenton (Fig. 3a) and TiO<sub>2</sub> photocatalysis systems (Fig. 2a), accordingly.

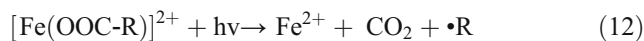
### Comparative mineralization of the cloxacillin

To evaluate the ability of the three processes to mineralize the cloxacillin, the evolution of TOC was assessed. For comparative purposes, the TOC removal at different times (*T<sub>t</sub>*) was normalized with respect to the time necessary to completely remove the antibiotic (*T<sub>CLX</sub>*) through each process. Therefore,

three different times were tested: the time of complete degradation of the antibiotic (*T<sub>t</sub>/T<sub>CLX</sub>* = 1), and two (*T<sub>t</sub>/T<sub>CLX</sub>* = 2) and four times (*T<sub>t</sub>/T<sub>CLX</sub>* = 4) the first one. As Fig. 4 shows, the degree of mineralization was according to the processes: TiO<sub>2</sub> photocatalysis > photo-Fenton system > electrochemical oxidation.

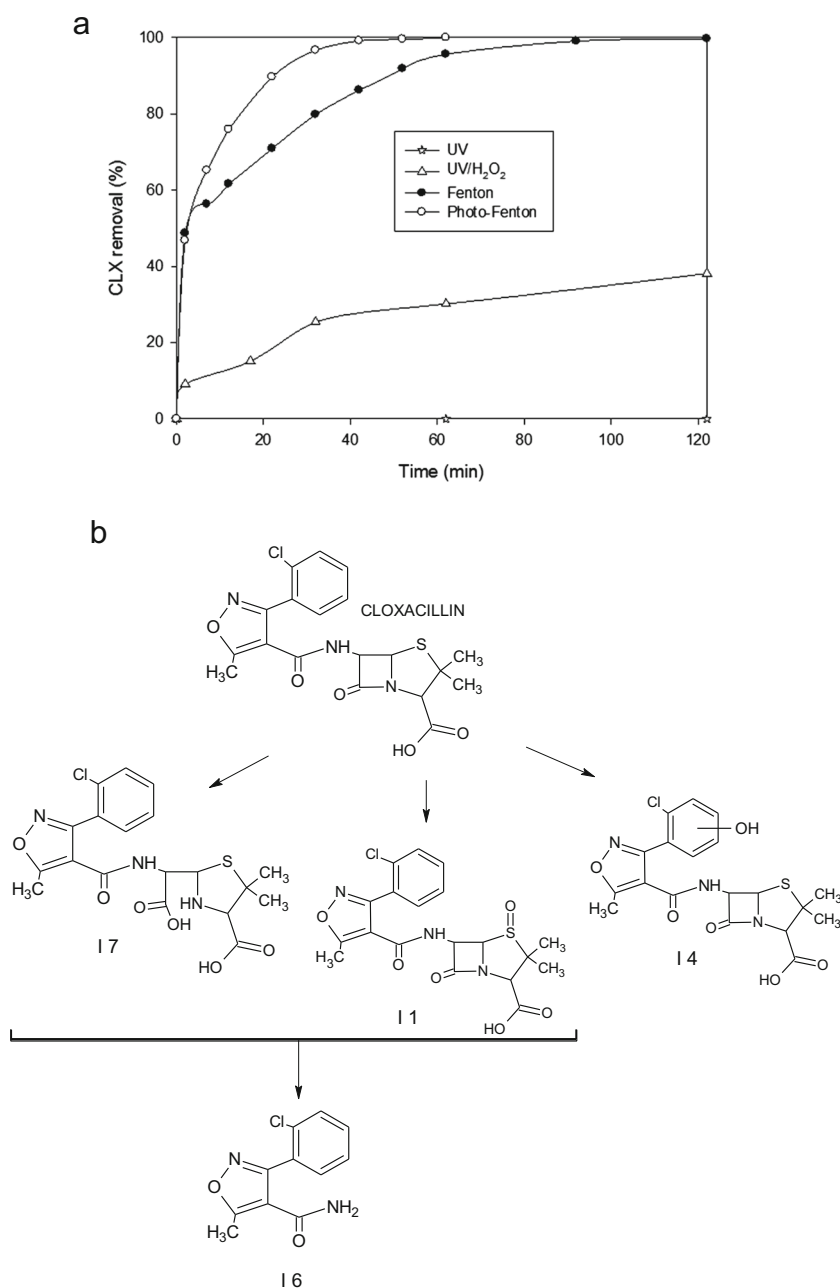
In the TiO<sub>2</sub> photocatalysis process, at 100 % of CLX degradation (*T<sub>t</sub>/T<sub>CLX</sub>* = 1), ~20 % of the initial organic carbon was removed, and at *T<sub>t</sub>/T<sub>CLX</sub>* = 4, ~43 % of TOC was eliminated. The treatment extent depends on both the degradation route and the reactivity of by-products to the oxidative species. As shown in Fig. 2b and discussed in “TiO<sub>2</sub> photocatalysis” section, one of the first steps during the TiO<sub>2</sub> photocatalysis action is the direct CLX decarboxylation, which explains the faster initial mineralization of the pollutant. Additionally, CLX is transformed into compounds containing more carboxylic acid groups, which subsequently could be easily converted into carbon dioxide (Eq. 11) (Villegas-Guzman et al. 2015b) leading to an enhanced CLX mineralization.

In contrast to the TiO<sub>2</sub> photocatalysis process, the photo-Fenton process did not remove organic carbon at *T<sub>t</sub>/T<sub>CLX</sub>* = 1 (Fig. 4). However, after *T<sub>t</sub>/T<sub>CLX</sub>* = 2, a gradual decrease of the initial TOC was observed. This process also led to the formation of carboxylic groups in the CLX (Fig. 2b). The formed carboxylic moieties could form a soluble ferric complex and their decomposition by UV–vis light could contribute to the mineralization (Eq. 12) (Pignatello et al. 2006; Neamtu et al. 2014). Furthermore, the hydroxyl radical can also release CO<sub>2</sub> by the abstraction electrons from the carboxylate groups (He et al. 2014).



Although the electrochemical process showed a fast elimination of the CLX (Fig. 1a), the amount of TOC remained unchanged even at *T<sub>t</sub>/T<sub>CLX</sub>* = 4 (Fig. 4). This fact indicates that the electrogenerated HClO was able to efficiently degrade the cloxacillin (see “Electrochemical treatment of cloxacillin” section), but it had a low reactivity to the CLX by-products. In fact, Fig. 1a shows that the HClO accumulation slope once the antibiotic was removed (8.50 μmol L<sup>-1</sup> min<sup>-1</sup>) is similar to the one observed in absence of the antibiotic (9.03 μmol L<sup>-1</sup> min<sup>-1</sup>). The hypochlorous acid has a strong reactivity to nucleophilic moieties as sulfur and nitrogen in reduced forms and activated aromatic systems (Deborde and von Gunten 2008). However, the electrochemical process by-products contain highly oxidized moieties (dimethylphenyl-isoxazole, carboxylic, and sulfoxide groups, Fig. 1b), which have a low reactivity to HClO (Dodd and Huang 2004; Deborde and von Gunten 2008). Therefore, the electrochemical process is unable to transform cloxacillin by-products into carbon dioxide, water, and inorganic ions, as it is shown in Fig. 4.

**Fig. 3** **a** CLX degradation routes in the photo-Fenton system: [Fe(II)],  $90 \mu\text{mol L}^{-1}$ ; [ $\text{H}_2\text{O}_2$ ],  $10 \text{ mmol L}^{-1}$ ; light power, 30 W; initial pH, 6.0; and [CLX],  $203 \mu\text{mol L}^{-1}$ . **b** CLX elimination schema for the photo-Fenton process

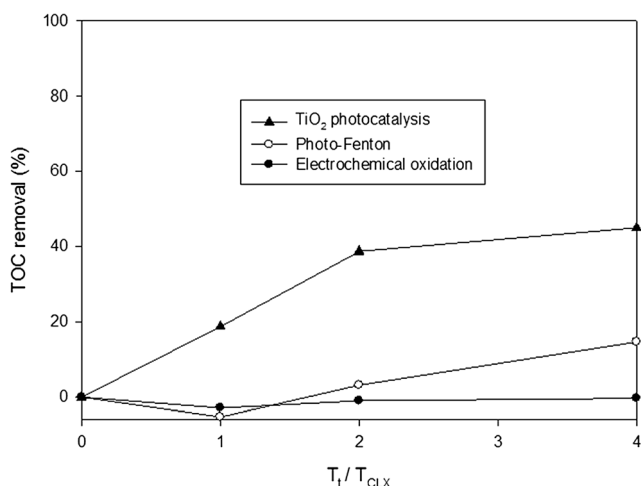


## Matrix effects

### Effect of additives on pollutant degradation

To study the performance of the oxidation processes in complex matrices, natural water containing high concentrations of inorganic matter was doped with the pollutant and tested with the tested systems in question. Therefore, natural mineral water (MW) containing  $4.93 \text{ mmol L}^{-1}$  of  $\text{HCO}_3^-$ ,  $1.16 \text{ mmol L}^{-1}$  of  $\text{Mg}^+$ ,  $0.137 \text{ mmol L}^{-1}$  of  $\text{NO}_3^-$ ,  $0.043 \text{ mmol L}^{-1}$  of  $\text{SO}_4^{2-}$ ,  $0.020 \text{ mmol L}^{-1}$  of  $\text{K}^+$ ,  $1.22 \text{ mmol L}^{-1}$  of  $\text{Ca}^{2+}$ ,  $0.252 \text{ mmol L}^{-1}$  of  $\text{Na}^+$ , and

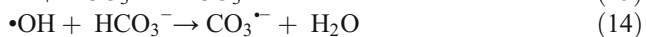
$0.068 \text{ mmol L}^{-1}$  of  $\text{Cl}^-$  was used. Additionally, to analyze the effect of organic matter on pollutant degradation, a typical excipient in pharmaceutical formulations (glucose, GLU) (Villegas-Guzman et al. 2015b; Villegas-Guzman et al. 2015a) was also considered. The pollutant removal percentages at the times required to completely eliminate the antibiotic in deionized water (5, 120, and 62 min by means of electrochemical oxidation,  $\text{TiO}_2$  photocatalysis, and photo-Fenton system, respectively) were also determined with different additives (Fig. 5). The results show that the electrochemical oxidation of cloxacillin in mineral water and in the presence of glucose is slightly affected. This indicates that the



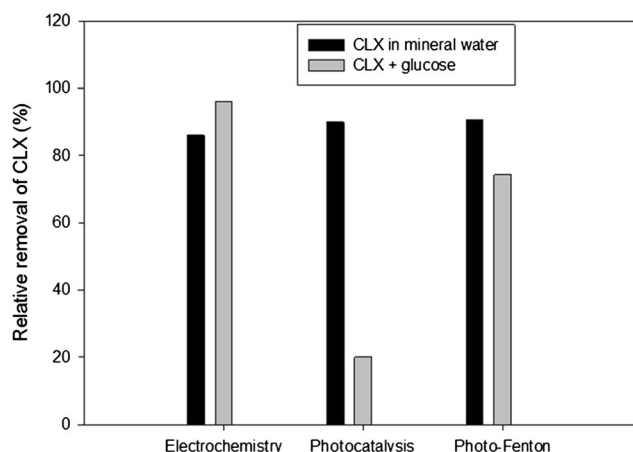
**Fig. 4** Mineralization of cloxacillin during the application of different processes. Experimental conditions as described in Figs. 1, 2, and 3

hypochlorous acid has a selective reactivity to CLX. The HClO presents high reaction rates with reduced forms of nitrogen and sulfur as the one contained in the cloxacillin molecule, while highly oxidized substances (as the inorganic ions in MW or GLU) have low interactions rates with the hypochlorous acid (Deborde and von Gunten 2008).

On the other hand, in MW and in the presence of GLU, the pollutant removal values by TiO<sub>2</sub> photocatalysis process were 90 and 20 %, respectively (Fig. 5). The inorganic anions such as bicarbonate, chloride, sulfate, and nitrate are known scavengers of hydroxyl radicals (Devi et al. 2011). Therefore, their presence may inhibit the pollutant degradation in MW. Additionally, the catalyst can adsorb bicarbonate (the most concentrated anion in MW), avoiding the pollutant-catalyst interaction and producing bicarbonate radicals (Eqs. 13–14) (Kumar and Mathur 2006; Santiago et al. 2014). These radicals are oxidative species that have a longer lifetime than hydroxyl radicals (Mazellier et al. 2007). Thus, the generated bicarbonate radicals could also degrade the antibiotic and partially compensate the scavenger effect of bicarbonate ion on holes and hydroxyl radicals (Kumar and Mathur 2006; Zhang et al. 2015). Consequently, the removal of the antibiotic is not considerably inhibited in MW (90 % of degradation, Fig. 5). In contrast, the presence of GLU induced a significant inhibition (20 % of pollutant removal). Due to the fact that glucose has a strong interaction with TiO<sub>2</sub> through the hydrogen bonds (Villegas-Guzman et al. 2015b), the availability of both hole and adsorbed hydroxyl radical is limited and, consequently, the cloxacillin degradation is significantly decreased.



In the case of the photo-Fenton process, the removal of the antibiotic from MW and in the presence of GLU was 90 and



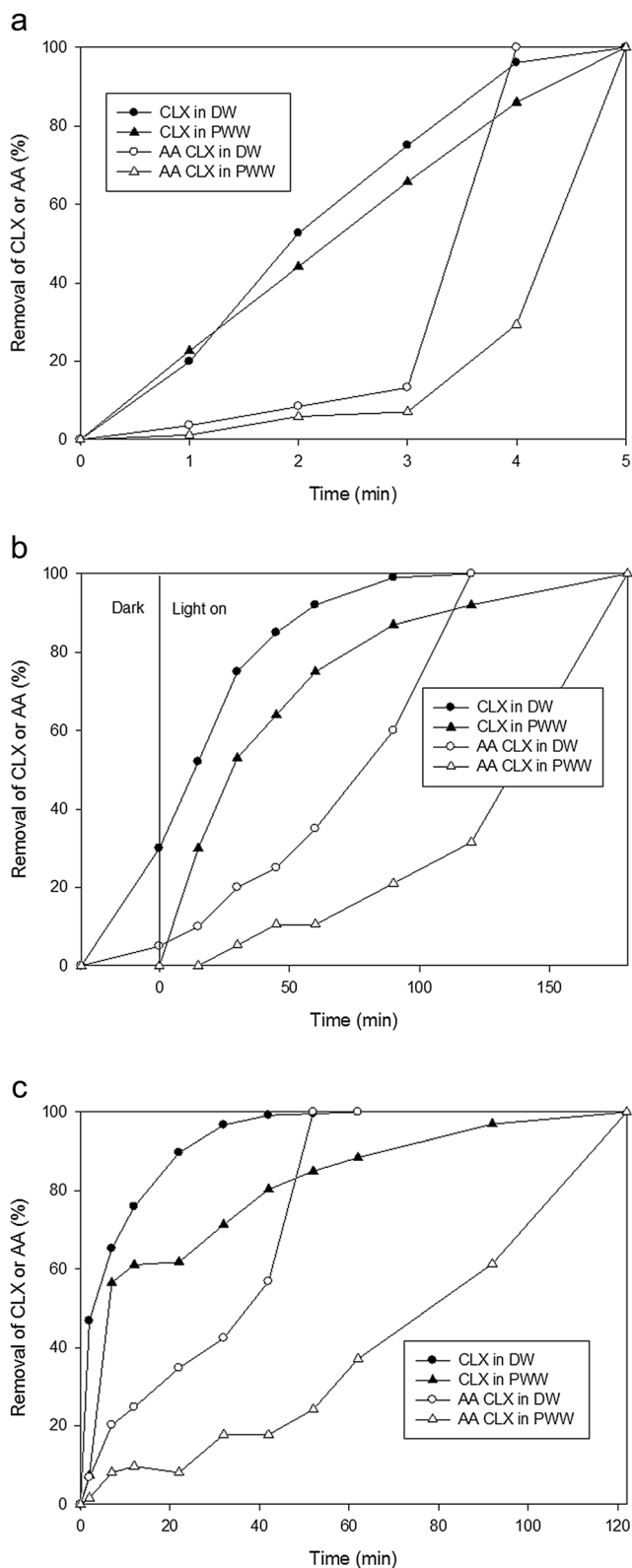
**Fig. 5** Effect of both inorganic and organic substances on cloxacillin degradation. Natural mineral water (as described in the text); GLU: glucose (5075 μmol L<sup>-1</sup>). Experimental conditions as described in Figs. 1, 2, and 3

75 %, respectively. As it has been previously mentioned, the inorganic species from the natural water are scavengers of the hydroxyl radical. Additionally, glucose is a competitive organic matter. Interestingly, these matrices showed a moderate effect on the degradation of the antibiotic (Fig. 5). These results suggest that, under the evaluated experimental conditions, the reagent concentrations and light power in the photo-Fenton system induced a high formation level of hydroxyl radicals, which is enough to efficiently remove CLX in the presence of the mentioned competitive substances.

*Effect of the water matrix on the removal of cloxacillin and the elimination of its antimicrobial activity*

The residual antimicrobial activity (AA) of treated solutions is an important aspect to take into account when water containing antibiotics is processed because AA could remain even after the antibiotic has completely degraded (Dimitrakopoulou et al. 2012). Therefore, to evaluate the residual antimicrobial activity, an indicator microorganism (*S. aureus*) was used due to its adequate response at low β-lactam antibiotic concentrations (Serna-Galvis et al. 2016b) was used. For the three oxidation processes, the evolution of cloxacillin and the AA in deionized water (DW) and a synthetic pharmaceutical wastewater (containing a commercial formulation of CLX in mineral water, PWW) were analyzed (Fig. 6).

Three interesting general features can be observed in the results: (i) all the oxidation processes were able to completely eliminate the antimicrobial activity from the tested waters; (ii) when the antibiotic concentration achieved a value of zero, the AA also disappeared; (iii) in the case of synthetic pharmaceutical wastewater, both the pollutant degradation and the elimination of antimicrobial activity required longer treatment times than in the case of distilled water. These results show that the processes are efficient for treating water containing



**Fig. 6** Effects of the water matrix on the antibiotic degradation and the elimination of residual antimicrobial activity. **a** Electrochemical treatment; **b** TiO<sub>2</sub> photocatalysis; and **c** photo-Fenton process. DW, deionized water; PWW, synthetic pharmaceutical wastewater. Experimental conditions as described in Figs. 1, 2, and 3

CLX, eliminating both the antibiotic and the associated residual AA. The simultaneous elimination of antimicrobial activity and pollutant indicates that the by-products did not have an important contribution to AA against *S. aureus*. In fact, in most of the initial by-products (Figs. 1b, 2b, and 3b) generated in all three oxidation processes, the penicillanic nucleus (moiety responsible for the AA) (Konaklieva 2014) has been modified. Furthermore, the higher time needed to remove CLX and its antimicrobial activity from PWW could be associated with the presence of both ions and excipients in the mineral water and the commercial product of cloxacillin, respectively. As it has been presented in “Effect of additives on pollutant degradation” section, anions in MW and excipients such as glucose can react with the oxidative agents generated in the different processes. Therefore, the elimination of the antibiotic is retarded and consequently the elimination of AA requires longer treatment times. However, these results highlight the ability of the tested oxidation technologies to efficiently treat problematic substances such as CLX, even in a complex matrix where excipients of commercial formulations and typical ions of wastewaters are present.

## Conclusions

The application of the electrochemical process, the photo-Fenton system, and the TiO<sub>2</sub> photocatalysis process led to the degradation of cloxacillin via HClO, hydroxyl radical, and oxidation at the catalyst surface (via adsorbed •OH and holes), respectively. Although all three oxidation processes efficiently eliminated the antibiotic, only the photocatalysis with TiO<sub>2</sub> showed a considerable degree of total organic carbon removal (~45 %). However, all the treatments generated by-products with modifications on the penicillanic nucleus (moiety responsible for the antimicrobial activity). Otherwise, the pollutant degradation in natural mineral water by the different treatments was not significantly affected. On the contrary, the presence of glucose considerably inhibited the antibiotic degradation by means of the TiO<sub>2</sub> photocatalysis process. Interestingly, for the treatment of synthetic pharmaceutical wastewater containing a commercial antibiotic formulation in mineral water, the application of the electrochemical process and the two photochemical systems efficiently degraded cloxacillin and produced solutions without any residual antimicrobial activity.

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