



Comparative study of the effect of pharmaceutical additives on the elimination of antibiotic activity during the treatment of oxacillin in water by the photo-Fenton, TiO₂-photocatalysis and electrochemical processes



Efraim A. Serna-Galvis^a, Javier Silva-Agredo^a, Ana L. Giraldo^b, Oscar A. Flórez-Acosta^b, Ricardo A. Torres-Palma^{a,*}

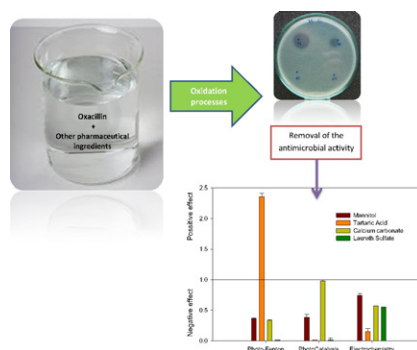
^a Grupo de Investigación en Remediación Ambiental y Biotecnología (GIRAB), Instituto de Química, Facultad de Ciencias Exactas y Naturales, Universidad de Antioquia UdeA, Calle 70 No. 52-21, Medellín, Colombia

^b Grupo de Diseño y Formulación de Medicamentos, Cosméticos y Afines (DYFOMECO), Facultad de Ciencias Farmacéuticas y Alimentarias, Universidad de Antioquia UdeA, Calle 70 No. 52-21, Medellín, Colombia

HIGHLIGHTS

- Effect of additives on oxacillin removal was evaluated by three oxidation systems.
- Tartaric acid favored the efficiency of the photo-Fenton processes.
- Calcium carbonate did not affect the TiO₂ photocatalytic system.
- In the presence of mannitol and lauryl sulfate, electrochemical process is efficient.
- TiO₂ photocatalysis removes the antibiotic activity from an urban wastewater.

GRAPHICAL ABSTRACT



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ABSTRACT

Synthetic pharmaceutical effluents loaded with the β-lactam antibiotic oxacillin were treated using advanced oxidation processes (the photo-Fenton system and TiO₂ photocatalysis) and chloride mediated electrochemical oxidation (with Ti/IrO₂ anodes). Combinations of the antibiotic with excipients (mannitol or tartaric acid), an active ingredient (calcium carbonate, i.e. bicarbonate ions due to the pH) and a cleaning agent (sodium lauryl ether sulfate) were considered. Additionally, urban wastewater that had undergone biological treatment was doped with oxacillin and treated with the tested systems. The evolution of antimicrobial activity was monitored as a parameter of processes efficiency. Although the two advanced oxidation processes (AOPs) differ only in the way they produce •OH, marked differences were observed between them. There were also differences between the AOPs and the electrochemical system. Interestingly, each additive had a different effect on each treatment. For water loaded with mannitol, electrochemical treatment was the most suitable option because the additive did not significantly affect the efficiency of the system. Due to the formation of a complex with Fe³⁺, tartaric acid accelerated the elimination of antibiotic activity during the photo-Fenton process. For TiO₂ photocatalysis, the presence of bicarbonate ions contributed to antibiotic activity elimination through the possible formation of carbonate and bicarbonate radicals. Sodium lauryl ether sulfate negatively affected all of the processes. However, due to the higher selectivity of HOCl compared with •OH, electrochemical oxidation showed the least inhibited efficiency. For the urban wastewater doped with

* Corresponding author.

E-mail address: ricardo.torres@udea.edu.co (R.A. Torres-Palma).

oxacillin, TiO₂ photocatalysis was the most efficient process. These results will help select the most suitable technology for the treatment of water polluted with β-lactam antibiotics.

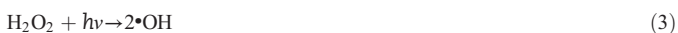
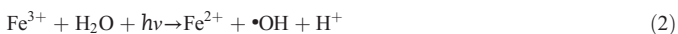
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1. Introduction

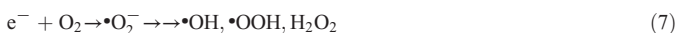
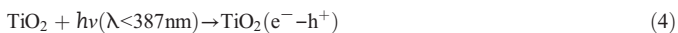
Pharmaceutical compounds are commonly used for preventing and treating human, animal and plant diseases. Therefore, every year large amounts of these substances are produced (Khetan and Collins, 2007) which end up in effluents from drug manufacturing industries. Subsequently, these effluents are discharged into wastewater treatment plants. Traditional wastewater treatment plants are unable to remove pharmaceutical compounds, and consequently, active ingredients reach natural waters (Khetan and Collins, 2007; Martinez, 2009).

Antibiotics are among the most common substances detected in the outputs of municipal wastewater treatment plants (Rivera-Utrilla et al., 2013). The β-lactam antibiotic oxacillin (OXA) has been founded in the effluents of both wastewater treatment plants and natural waters (Cha et al., 2006). Pollution in natural water by antibiotics can lead to the development of resistant bacteria (Rivera-Utrilla et al., 2013). In fact, oxacillin-resistance represents a serious problem in Latin American hospitals (Neto et al., 2012). Therefore, alternative processes for the elimination of these compounds from the effluents of both pharmaceutical companies and wastewater treatment plants are urgently needed.

In recent years, advanced oxidation processes (AOP) have been effectively applied to degrade emergent pollutants such as antibiotics (Elmolla and Chaudhuri, 2009; Homem and Santos, 2011; Pereira et al., 2013; Rivera-Utrilla et al., 2013; Sopaj et al., 2015; Villegas-Guzman et al., 2015a). AOPs are based on the production of the hydroxyl radical (•OH), which is a highly oxidant specie with a low selectivity, able to degrade a wide variety of organic pollutants. There are different ways to generate hydroxyl radicals, including the photo-Fenton process and photocatalysis using TiO₂. In the photo-Fenton system, •OH is formed through the reaction of Fe(II) with hydrogen peroxide (Eq. (1)) and the photo-reduction of Fe(III) in aqueous media (Eq. (2)) (Pignatello et al., 2006). Additionally, hydroxyl radicals can also be formed from the direct photolysis of hydrogen peroxide (Eq. (3)).

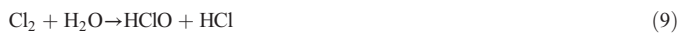


The TiO₂ photocatalytic process is initiated by the action of UV-light on TiO₂, generating electron-hole (e⁻-h⁺) pairs (Eq. (4)) that can induce redox reactions. The holes can oxidize water and hydroxide anions to produce hydroxyl radicals (Eqs. (5)–(6)). In turn, the electrons can reduce the dissolved oxygen to form superoxide anion radicals, which can evolve into hydroxyl radicals, perhydroxyl radicals or hydrogen peroxide (Eq. (7)) (Chen et al., 2005).



Another interesting alternative that has been shown to be useful for the treatment of refractory substances in water is electrochemical oxidation

using dimensionally stable anodes (DSA) (Sirés and Brillas, 2012; Sopaj et al., 2015). A well-known DSA is Ti/IrO₂. In the presence of chloride ions, this anode leads to the formation of chlorinated oxidative species (Eqs. (8)–(10)) which can degrade OXA (Eq. (11)) (Giraldo et al., 2015).



As mentioned previously, these oxidation processes are able to degrade antibiotics. However, special attention should be paid to the residual antimicrobial activity (AA) of the treated waters, because in some cases AA may remain even when the pollutant has been 100% degraded (Dimitrakopoulou et al., 2012). Therefore, during the treatment of waters loaded with antibiotics by oxidation processes, the evolution of the antimicrobial activity must be monitored.

In previous papers, oxacillin elimination by anodic oxidation in water (Giraldo et al., 2015) and TiO₂ photocatalysis (Giraldo-Aguirre et al., 2015) has been evaluated and promising results have been found. The degradation routes of oxacillin degradation by TiO₂ photocatalysis, electrochemical oxidation, ultrasound and the photo-Fenton system in distilled water have also been elucidated (Serna-Galvis et al., in press). As antibiotics in pharmaceutical wastewaters are frequently accompanied by substances such as excipients, active ingredients and surfactants used for cleaning purposes, the effects of these substances during treatment should always be assessed. Thus, for real-life applications comparative studies are needed that analyze the effect of such substances on the performance of the aforementioned treatment systems.

As a result of the above, in this work a comparative study of the removal of AA from solutions containing OXA, in presence of some of the most typical additives used in its preparation, was carried out for the three processes. In this way, the best oxidation technology for the different OXA-additive combinations was established. As the commercial formulation of OXA is an injection powder, two well-known excipients (mannitol (MAN) and tartaric acid (TA)) used in the preparation of antibiotics (Royal Pharmaceutical Society of Great Britain, 2009) were considered. Due to the fact that a pharmaceutical effluent may contain a mixture of different active ingredients, calcium carbonate (CC, as a bicarbonate ion according to the pH of the solution), a common ingredient in the preparation of antacids (Royal Pharmaceutical Society of Great Britain, 2009), was used to emulate the combination of OXA with other active pharmaceuticals. Additionally, as equipment is washed after the manufacturing process, water can be loaded with residues of antibiotics and cleaning agents. To make an initial analysis of the washing water, one of the most popular surfactants used for cleaning purposes and as ingredient of cosmetic products in the pharmaceutical industry (sodium lauryl ether sulfate (LES)) (National Library of Medicine, 2013) was also tested.

Furthermore, the application of the selected treatments on an effluent from a municipal wastewater treatment plant doped with OXA was also considered. Finally, in order to understand the effects caused by additives and matrix components on OXA and AA elimination, the progress of oxidative species such as hydrogen peroxide or HClO was

determined for the different processes and the UV spectrum of the solutions was measured.

2. Materials and methods

2.1. Chemicals

Oxacillin was provided by Sigma-Aldrich. Hydrogen peroxide, formic acid, sodium chloride and calcium carbonate were purchased from Carlo-Erba. Mannitol, tartaric acid, ferrous sulfate, sulfuric acid, methanol, acetonitrile, sodium phosphate, sodium hydroxide, sodium meta-bisulfite, ferric chloride, potassium iodide, ammonium heptamolybdate and nutrient agar were provided by Merck. Potato dextrose agar was provided by Oxoid. Commercial sodium Lauryl ether sulfate was purchased from Diver and titanium dioxide P-25 was supplied by Evonik. The sample solutions were prepared using distilled water.

The typical concentration of antibiotics in real pharmaceutical industrial wastewater may be in mg L^{-1} (Larsson et al., 2007; Sirtoria et al., 2011). Therefore, OXA was used at concentrations of $47.23 \mu\text{mol L}^{-1}$ (20 mg L^{-1}) in all of the experiments. Additionally, in commercial formulations of pharmaceutical products, additives (e.g. excipients, stabilizers, emulsifiers, etc.) are usually found at higher concentrations (ten times or more) than the active ingredient. Therefore, mannitol, tartaric acid, calcium carbonate and sodium lauryl ether sulfate were used at concentrations of $472.3 \mu\text{mol L}^{-1}$. All processes were carried out at an initial pH of 5.6 (natural pH of the OXA solution).

2.2. Reaction systems

2.2.1. Reaction systems for the photocatalysis and photo-Fenton processes

The photo-Fenton process and TiO_2 photocatalysis were performed in a homemade aluminum reflective reactor, equipped with 5 Philips lamps (TL-D Actinic BL) of 30 W. For the two processes, 150 W of light power was applied to 100 mL of OXA solution placed in beakers under constant stirring. In the photo-Fenton process, $1000 \mu\text{mol L}^{-1}$ and $90 \mu\text{mol L}^{-1}$ of H_2O_2 and Fe(II) were employed. Before the analysis, the residual H_2O_2 was eliminated using sodium meta-bisulfite. In the photocatalysis experiments, 0.50 g L^{-1} of TiO_2 was used. The lamps were turned on after 30 min, in which time the adsorption equilibrium was reached. Before analyzing the treated solutions, the catalyst was precipitated by centrifugation for 15 min at $3200 \text{ rev min}^{-1}$ in a Centaur 2 centrifuge, and filtered using a cellulose mesh of $0.45 \mu\text{m}$ (Advantech).

2.2.2. Reaction system for the electrochemical process

Electrochemical oxidations were conducted in an electrolytic cell containing 150 mL of OXA solution under constant stirring conditions. Experiments were carried out at a constant current density (5 mA cm^{-2}) under galvanostatic conditions, and using a Ti/IrO₂ anode with 4 cm^2 of working surface area. The cathode was a zirconium spiral electrode of 10 cm^2 . 0.065 mol L^{-1} NaCl was used as the supporting electrolyte.

2.3. Analytical procedures

2.3.1. Quantitative analysis of oxacillin

Quantitative analysis of OXA was carried out using a HPLC Waters (486) instrument with a C-18 column (Merck LiChrospher) and a UV detector set at 225 nm. The injection volume was $40 \mu\text{L}$. The mobile phase was a phosphate buffer (0.02 mmol L^{-1} , pH 5)/acetonitrile/methanol, 64/27/9 (% v/v), in isocratic mode (0.4 mL min^{-1}). The limit of quantification for OXA in the analytical methodology was $1.5 \mu\text{g L}^{-1}$ (or 0.0015 mg L^{-1}).

2.3.2. Determining the oxidants in the processes

Oxidants generated or consumed during the different processes (HOCl and H_2O_2) were determined by iodometry. An aliquot of $600 \mu\text{L}$ from the different reactors was added to a quartz cell containing $1350 \mu\text{L}$ of potassium iodide (0.1 mol L^{-1}) and $50 \mu\text{L}$ of ammonium heptamolybdate (0.01 mol L^{-1}). After 5 min, the absorbance at 350 nm was measured by a Jenway (6405 UV/Vis) spectrophotometer.

2.3.3. Evaluation of the antibiotic activity

The antibiotic activity (AA) was determined by analyzing the zone of inhibition in the agar diffusion test, using *Staphylococcus aureus* ATCC 6538 as the indicator microorganism because of its high sensibility to OXA. $30 \mu\text{L}$ of sample solutions was seeded on Petri dishes containing 5 mL of potato dextrose agar and 10 mL of nutrient agar inoculated with $10 \mu\text{L}$ of *S. aureus* (optical density of 0.600 at 580 nm). After 24 h at $37 \text{ }^\circ\text{C}$ in a Memmert (Schwabach) incubator, confluent bacterial growth was observed, and the diameter of the inhibitory halo was measured using a vernier.

3. Results and discussion

3.1. Evaluation of oxacillin degradation and analysis of antimicrobial activity elimination

Fig. 1 shows the relationship between antimicrobial activity removal and pollutant elimination during the degradation of OXA by the three oxidation processes. Additionally, the AA of the solution as a function of OXA concentration (with prepared standards) is shown. As seen in Fig. 1, for all treatments ~90% of antimicrobial activity remained when 50% of the antibiotic concentration was removed. Furthermore, only ~20% of AA was eliminated when the three oxidation processes degraded ~80% of the OXA. The similar trend of curves for the oxacillin standards and the treated solutions suggests that the AA is caused by the residual concentration of oxacillin in solution. On the other hand, it is interesting to observe in all curves in Fig. 1 that when the oxidation processes achieved 100% of OXA removal, the AA was completely eliminated. This suggests that all oxidation processes are able to eliminate oxacillin and transform it into substances that are biologically inactive against the probe microorganism. These results indicate that the oxidative action of the processes modifies the β -lactam nucleus (Serna-Galvis et al., 2016), which is the moiety responsible for the antimicrobial activity of oxacillin (Konaklieva, 2014).

In the next sections of this work, the potentialities of the tested processes to deal with water contaminated with OXA will focus on the capacity of the technologies to remove the AA from solutions containing

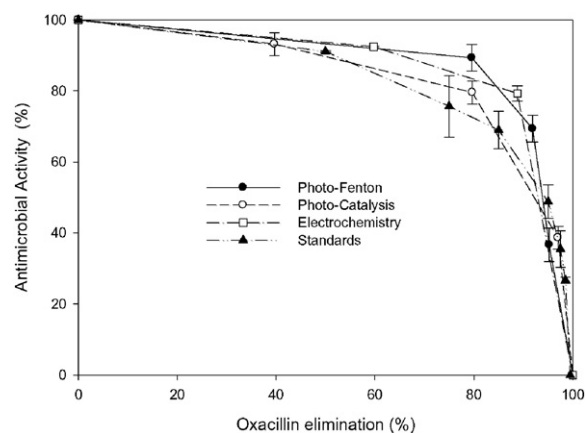


Fig. 1. Antimicrobial activity as a function of oxacillin concentration or elimination by several treatments. [OXA] = $47.23 \mu\text{mol L}^{-1}$, pH = 5.6. Photo-Fenton: [Fe(II)] = $90 \mu\text{mol L}^{-1}$, [H_2O_2] = $1000 \mu\text{mol L}^{-1}$, 150 W. TiO_2 photocatalysis: [TiO_2] = 0.5 g L^{-1} , 150 W. Electrochemistry, [NaCl] = 0.065 mol L^{-1} , Ti/IrO₂ anode, J = 5 mA cm^{-2} .

the initial pollutant and additives. AA evolution is a more suitable parameter than OXA concentration to evaluate the quality of the tested treatments. Besides its high sensibility even at low concentrations of the antibiotic (Fig. 1), the use of AA as an evaluation criterion leads to the best fit between conditions and processes, guaranteeing that treated solutions are obtained with no biological activity acting against the probe microorganism.

3.2. Effects of additives on the elimination of antimicrobial activity

It is well known that the matrix can positively or negatively affect the efficiency of antibiotic elimination when using AOP and electrochemical treatments (Neamțu et al., 2014; Pereira et al., 2014; Sirés and Brillas, 2012; Villegas-Guzman et al., 2015a). However, in the literature there is little evaluation of how the matrix affects the evolution of antimicrobial activity. Therefore, the effects of additives (mannitol, tartaric acid, calcium carbonate and sodium lauryl ether sulfate) on AA removal in the photo-Fenton, TiO_2 photocatalysis and electrochemical treatments of solutions containing oxacillin were analyzed and will be discussed in the following sections.

3.2.1. Photo-Fenton process

The action of the photo-Fenton process on antimicrobial activity removal in the presence and absence of the additives is shown in Fig. 2. The results show that only 9 min are needed to eliminate the AA of distilled water containing the antibiotic (OXA). During the process pH of the solution decreased from 5.6 to 3.7, which can avoid the formation of ferric hydroxide and limiting the participation of coagulation mechanism. In a recent paper, the positive participation of UV light in the process was verified (Serna-Galvis et al., 2016). The light used in photo-Fenton process accelerates the regeneration of Fe(II) and produces an extra hydroxyl radical (Eqs. (2) and (3)). Therefore, the photo-Fenton system degraded the antibiotic and AA faster than the Fenton process (dark conditions). In fact, with the Fenton system only 35% of the initial AA was removed after 9 min (Fig. SM 1, in the Supplementary material). This supports the use of the photo-Fenton system to remove the AA associated to the antibiotic.

Interestingly, the presence of tartaric acid (OXA + TA) accelerated the removal of antimicrobial activity by the photo-Fenton process, 4 min of treatment was enough time to eliminate it completely. In the presence of mannitol (OXA + MAN) or calcium carbonate (OXA + CC), the process was impeded, and only 20% of AA was removed after 9 min of treatment in both cases. Finally, the presence of sodium lauryl ether sulfate (OXA + LES) completely inhibited AA elimination. To understand the effects of each additive on AA removal, the rates of hydrogen peroxide consumption (r_c) were determined (Fig. SM 2 in the supplementary

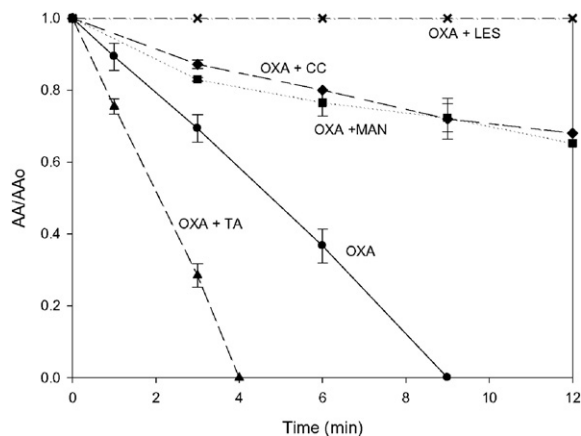
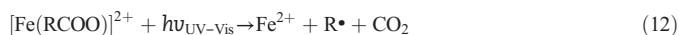


Fig. 2. Evolution of antimicrobial activity for oxacillin solutions in different matrices treated by the photo-Fenton system. [OXA] = $47.23 \mu\text{mol L}^{-1}$, [MAN] = [CC] = [TA] = [LES] = $472.3 \mu\text{mol L}^{-1}$. Other test conditions as in Fig. 1.

material). In the presence of tartaric acid, the r_c value is more than double that obtained for oxacillin alone. Tartaric acid is a carboxylic acid which can form a carboxylate complex with the Fe(III) generated during the process. As demonstrated in Fig. SM 3 (in the supplementary material), such complexes can absorb UV-Vis light, inducing additional regeneration of Fe(II) (Eq. (12)) (Moreira et al., 2015). The photo-regenerated Fe(II) can then contribute to a higher consumption of hydrogen peroxide (Eq. (2)). Consequently, more hydroxyl radicals are formed, which leads to an improvement in the removal of antimicrobial activity.



Additionally, the solubility of the ferric-tartrate complexes at the working pH can help to maintain Fe(III) in solution, which favors the photo-Fenton process.

In the presence of MAN and CC, the rates of H_2O_2 consumption were ~27% higher than when OXA was alone in the solution (Fig. SM 2). Both Mannitol and bicarbonate ions are scavengers of hydroxyl radicals (Rubio et al., 2013). As these compounds can consume hydroxyl radicals, the efficiency of AA elimination is lower in their presence.

In Fig. SM 2, the OXA + LES combination presented the lowest value of r_c , which was ~5% of that observed when OXA was alone in the solution. The chemical structure of LES has polyoxyethylene ether moieties that are able to bind Fe(II). In fact, in a control experiment the formation of such complexes between Fe(II) and LES was verified by UV-Vis spectra (Fig. SM 4, in the Supplementary material). Because of the Fe(II)-LES complex formation, a lower amount of hydrogen peroxide is consumed (Ross et al., 1992), and therefore, fewer hydroxyl radicals are produced. Additionally, the LES, which is present in a higher concentration than the antibiotic, can also react with the non-selective hydroxyl radicals generated and thus inhibit OXA degradation. Consequently, the AA remained unchanged when the photo-Fenton process was applied to OXA degradation in the presence of LES.

3.2.2. Photocatalysis using TiO_2

The TiO_2 photocatalytic process is another promising alternative for the removal of pharmaceuticals in water (Kumar and Mathur, 2006; Pereira et al., 2014; Rivera-Utrilla et al., 2013; Villegas-Guzman et al., 2015b). Fig. 3 shows the efficiency of photocatalysis combined with TiO_2 for the elimination of the AA in water solutions containing OXA. Experiments were performed in the presence and absence of the tested additives: Mannitol (OXA + MAN), tartaric acid (OXA + TA), calcium carbonate (OXA + CC) and sodium lauryl ether sulfate (OXA + LES).

Water containing the antibiotic in the absence of additives (OXA) required 45 min of photocatalytic action to remove 100% of the AA. Contrary to what was observed in the photo-Fenton process, the presence of calcium carbonate (OXA + CC), i.e. bicarbonate because of the solution pH (pH 5.6), did not affect antimicrobial activity elimination. Again, 45 min was enough time to completely remove the AA. In turn, for water containing the antibiotic and mannitol (OXA + MAN), the process reduced only 40% of the AA after 60 min of treatment. Furthermore, when oxacillin was accompanied with tartaric acid (OXA + TA), or the sodium lauryl ether sulfate cleaning product (OXA + LES), the AA did not decrease at all. In fact, with this additive, after an hour of treatment the solution conserved 100% of the initial antibiotic activity.

OXA has a carboxylic group which can interact with the surface of TiO_2 , favoring the direct oxidation of the pollutant. To analyze the differences in AA elimination exerted by the additives, their effect on the adsorption of OXA onto the catalyst surface was studied (Fig. SM 5, in the supplementary material). Surprisingly, bicarbonate ions that did not affect AA elimination caused an 83% reduction in oxacillin adsorption. In TiO_2 photocatalysis, bicarbonate ions can scavenge both holes and hydroxyl radicals. Both processes can lead to bicarbonate and carbonate radical formation (Eqs. (13)–(15)) (Kumar and Mathur, 2006; Santiago et al., 2014). These radicals are also oxidative species and have a longer lifetime than hydroxyl radicals (Mazellier et al., 2007).

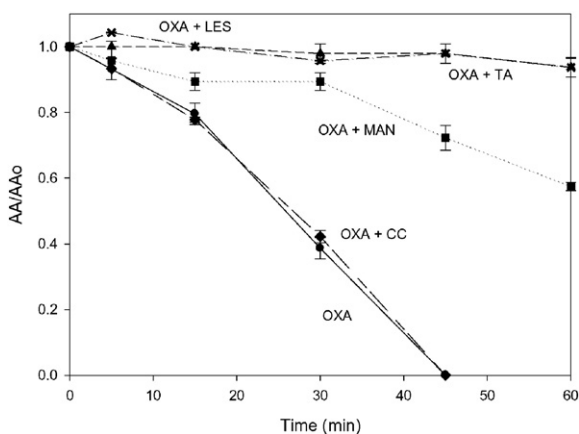


Fig. 3. Evolution of antimicrobial activity for oxacillin solutions in different matrices treated by TiO_2 photocatalysis. $[\text{OXA}] = 47.23 \mu\text{mol L}^{-1}$, $[\text{MAN}] = [\text{CC}] = [\text{TA}] = [\text{LES}] = 472.3 \mu\text{mol L}^{-1}$. Other test conditions as in Fig. 1.

Although the presence of CC diminished OXA adsorption and thereby affected the direct degradation route of the antibiotic, the bicarbonate and carbonate radicals generated reacted with oxacillin in the bulk of the solution. This supports the results obtained experimentally.



In the presence of LES, oxacillin adsorption onto the catalyst was also reduced by 83% (Fig. SM 5). However, unlike what was observed in the presence of CC, AA removal was inhibited. Under the working conditions, the LES sulfate group is negatively charged so can interact with the positively charged TiO_2 surface (Eq. (16)) (Chen et al., 2005). Therefore, LES competes with the antibiotic for the active sites on the catalyst surface, and consequently, completely inhibits AA elimination.



In contrast, the addition of mannitol reduced the adsorption of OXA onto the TiO_2 surface in 25% (Fig. SM 5). Additionally, the ability of MAN to act as a scavenger of adsorbed hydroxyl radicals (Cai et al., 2014; Pereira et al., 2013, 2014) has a negative effect on OXA adsorption and limits the degradation of the antibiotic. Therefore, antimicrobial activity in the presence of mannitol was considerably inhibited (40%).

The presence of tartaric acid caused the largest decrease in antibiotic adsorption (~91%) (Fig. SM 5). Taking into account that at the pH used in the experiment the tartaric acid had a double negative charge and the TiO_2 was positively charged (Eq. (16)), there was a strong attraction between the excipient and catalyst. Therefore, TA was able to trap the holes and scavenge the hydroxyl radical, hindering the oxacillin degradation. Consequently, in the presence of TA, the antimicrobial activity remained unchanged.

3.2.3. Electrochemical process

Due to its versatility, easy automation and environmental compatibility, the use of electrochemistry for pharmaceutical wastewater remediation is becoming increasingly important for researchers (Sirés and Brillas, 2012). Of the electrochemical technologies, electro-oxidation using DSA, which catalyzes the production of active chlorine from chloride ions (Eqs. (8)–(10)), is one of the most promising methods. The application of this process is attractive because some pharmaceutical wastewaters may contain chloride from product manufacturing (e.g. saline solution).

Fig. 4 shows the performance of electrochemical oxidation for the elimination of the antimicrobial activity of OXA solutions in the presence and absence of the tested additives. As can be seen, in the absence of any additives, only 9 min of treatment was sufficient time to completely remove the AA caused by oxacillin. Since the presence of mannitol (OXA + MAN) retards the process, 12 min of electrolysis were needed to achieve 100% antimicrobial activity elimination. In the presence of calcium carbonate (OXA + CC) or sodium lauryl ether sulfate (OXA + LES), the system was further hampered, and consequently, 15 min of electrochemical treatment were required to achieve 100% AA removal. In turn, tartaric acid (OXA + TA) strongly inhibited the process, and scarcely 10% of the initial antimicrobial activity was removed after 15 min of treatment.

In a previous study, it was stated that under electrochemical action using the $\text{Ti}/\text{IrO}_2\text{-NaCl}$ system, oxacillin was degraded through active chlorine species (i.e. HClO at pH 5.6) (Giraldo et al., 2015). Therefore, to help understand these results, HOCl accumulation was evaluated in the presence and absence of the additives (Fig. SM 6, in supplementary material). Interestingly, as seen in Fig. 4 and SM 6, the accumulation of HOCl began when at least 50% of antimicrobial activity was removed (i.e. when more than 95% of the initial pollutant was eliminated, Fig. 1). This suggests that OXA by-products are recalcitrant to the action of HOCl . As shown in Fig. SM 6, the presence of mannitol reduced HOCl accumulation. Mannitol is a sugar with primary and secondary alcohol groups which can be oxidized by active chlorine species (Deborde and von Gunten, 2008). Therefore, the mannitol competes with oxacillin for the oxidative agent, which explains the reduction in AA removal when the additive is present in the media (Fig. 4). The presence of bicarbonate also reduced the accumulation of HOCl (Fig. SM 6). Due to the basic properties of bicarbonate, it can neutralize the hypochlorous acid to produce hypochlorite ions (Eq. (17)), which are less potent oxidants than hypochlorous acid. Furthermore the process may favor the formation of chlorate from hypochlorite (Eq. (18)), which reduces the availability of active chlorine (Amstutz et al., 2012). This explains why the accumulation of HOCl and AA elimination decreases in the presence of bicarbonate ions (Figs. SM 6 and 4). The presence of LES also decreased the HOCl accumulation and retarded the removal of antimicrobial activity. This could be related with the reaction between the active chlorine species and the LES. In fact, the elimination of anionic surfactants by active chlorine species generated electrochemically has been documented previously (Lissens et al., 2003).



On the other hand, in the presence of TA, HClO did not accumulate (Fig. SM 6), which suggests that this additive has a high affinity for the

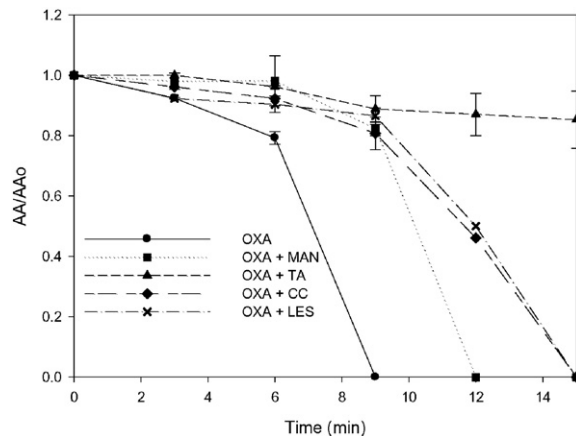


Fig. 4. Evolution of antimicrobial activity for oxacillin solutions in different matrices treated by electrochemical oxidation. $[\text{OXA}] = 47.23 \mu\text{mol L}^{-1}$, $[\text{MAN}] = [\text{CC}] = [\text{TA}] = [\text{LES}] = 472.3 \mu\text{mol L}^{-1}$. Other test conditions as in Fig. 1.

HClO species. Although the two carboxylic groups in TA have a limited reactivity towards active chlorine, the methylene group between the two carbonyl compounds has a high affinity against this oxidative species (Deborde and von Gunten, 2008). Additionally, the secondary alcohols in TA are susceptible to being oxidized by HClO. Thus, due to its strong reactivity against HClO, the TA almost completely inhibited AA elimination during electrochemical treatment (Fig. 4).

3.3. Determination of the most suitable process according to the additive

As shown in the previous sections, the evaluated additives had accelerating, inhibiting or non-interfering effects on AA removal for the different tested systems. Based on the effects of the type of additive, the most suitable treatment can be established. For comparative purposes, the ratio (Eq. (19)) between the average rates of antimicrobial activity elimination (r_e) for OXA solutions in both the presence and absence of the additives was calculated for all conditions and processes (Fig. 5). A value of $R = 1$ indicates that the additive has no effect on the process; a value of $R > 1$ indicates that it has an accelerating effect and an $R < 1$ indicates it has an inhibiting effect.

$$R = r_{e\text{OXA} + \text{ADDITIVE}} / r_{e\text{OXA}} \quad (19)$$

As shown in Fig. 5, mannitol presented values of $R < 1$ for the electrochemical treatment ($R \sim 0.75$ or 25% inhibition), TiO_2 photo-catalysis ($R \sim 0.32$ or 68% inhibition) and the photo-Fenton process ($R \sim 0.26$ or 74% inhibition). The higher inhibition observed for the two AOPs is due to the higher reactivity and lower selectivity towards the additive by hydroxyl radicals compared with HOCl. Thus, for the treatment of OXA in water containing high mannitol concentrations, the electrochemical system may be an effective alternative.

Concerning tartaric acid, varied effects were found (Fig. 5). For the photo-Fenton system, TA presented $R = 2.3$, indicating a strong accelerating effect on AA elimination. As explained in Section 3.2.1, such an effect can be associated with the formation of a complex between TA and Fe(III) which absorbs in the UV-Vis region (Fig. SM 3). In contrast, for TiO_2 photocatalysis, TA produced a very low value of R (0.05), i.e. the AA removal rate was reduced by twenty times in the presence of tartaric acid. This is because TA drastically diminishes the adsorption of the antibiotic (Section 3.2.2), and consequently limits the ability of the photocatalytic process to remove the antimicrobial activity associated to OXA. In the electro-oxidation process R is 0.09 (i.e. an AA removal rate 11 times lower than that observed for OXA alone). The effect of TA on the removal of AA by the electrochemical system mediated by chloride ions is due to the strong reactivity of this additive with HClO (Section 3.2.3). Consequently, among the tested systems and under experimental conditions, the photo-Fenton system seems to be the most adequate process to eliminate AA from water containing OXA and tartaric acid.

On the other hand, in the presence of bicarbonate ions (calcium carbonate as an additive), for TiO_2 photocatalytic treatment a value of $R \sim 1$ was found. It has been reported that when the concentration of bicarbonate ions is much higher than the target pollutant, these ions can actually improve pollutant degradation in TiO_2 photocatalysis systems (Kumar and Mathur, 2006; Santiago et al., 2014; Villegas-Guzman et al., 2015b) via the formation of bicarbonate radicals, which are able to eliminate organic pollutants. Thus, the non-interfering effect of bicarbonate ions on TiO_2 photocatalysis is probably due to fact that bicarbonate radical formation partially compensates for the radical scavenger effect of these ions. Otherwise, in the presence of bicarbonate ions, the electrochemical and photo-Fenton processes have R values of 0.60 and 0.24 respectively. This negative effect arises from the high reactivity that bicarbonate ions have with HOCl and $\bullet\text{OH}$. Again, the greater inhibiting effect observed in the photo-Fenton process comes from the higher reactivity and lower selectivity of $\bullet\text{OH}$. Due to the above, TiO_2 photocatalysis may be the best system to avoid the detrimental effect of bicarbonate ions. In fact, this process could be improved if the

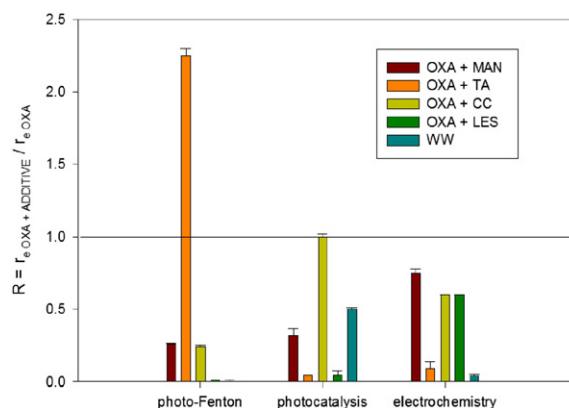


Fig. 5. Comparison of effects. The photo-Fenton ($[\text{Fe(II)}] = 90 \mu\text{mol L}^{-1}$, $[\text{H}_2\text{O}_2] = 1000 \mu\text{mol L}^{-1}$, 150 W). Electrochemical processes ($[\text{NaCl}] = 0.065 \text{ mol L}^{-1}$, Ti/IrO_2 anode, $J = 5 \text{ mA cm}^{-2}$). TiO_2 photocatalysis ($[\text{TiO}_2] = 0.5 \text{ g L}^{-1}$, 150 W). In all process $[\text{OXA}] = 47.23 \mu\text{mol L}^{-1}$, initial pH = 5.6.

concentration of bicarbonate ions were controlled at levels and conditions where the presence of carbonate and bicarbonate radicals enhanced the efficiency of the treatment.

The values of R for the photo-Fenton system, TiO_2 photocatalysis and electrochemical processes in the presence of LES were 0.01, 0.05 and 0.60, respectively. As discussed earlier (Section 3.2.1), the photo-Fenton system was strongly inhibited in the presence of LES because of the formation of a complex of Fe(II)–LES which prevented the interaction of H_2O_2 with Fe(II), thus limiting the production of $\bullet\text{OH}$. This precludes the use of the aforementioned technology when relatively high concentrations of LES are present in the water. To a lesser extent, the additive also negatively affected the TiO_2 photocatalytic process through a significant reduction in the adsorption of the antibiotic onto the catalyst surface (Section 3.2.2). According to the R values, electrochemical oxidation was the system least affected by the presence of LES. Therefore, it may be of particular use for the treatment of oxacillin solutions containing relatively high concentrations of this cleaning agent. In fact, it was recently reported that electrochemical oxidation is able to transform the antibiotic into biodegradable substrates with no antimicrobial activity (Giraldo et al., 2015).

3.4. Treatment of a municipal wastewater plant effluent loaded with oxacillin

To study the efficiency of the three oxidation processes on antimicrobial activity removal from a real matrix, an effluent from the municipal San Fernando wastewater treatment plant in Medellín, Colombia, (WW) was considered. Prior to the application of the oxidation processes, the effluent was filtered using a $0.45 \mu\text{m}$ membrane. The characterization of the filtered water sample is presented in Table 1. This water had a high conductivity, which may be associated with the presence of inorganic ions such as chloride and bicarbonate anions. In fact, the WW had 106.4 mg L^{-1} of Cl^- and a considerable alkalinity caused by the presence of bicarbonate anions. Additionally, 24.8 mg L^{-1} of dissolved organic matter were present in the WW.

The filtered effluent was then doped with $47.23 \mu\text{mol L}^{-1}$ of oxacillin, the pH was adjusted to 5.6 and the three oxidation processes were applied individually. The evolution of AA in the WW was monitored and compared with the results in distilled water (DW). The R value was also calculated and plotted in Fig. 5. For the photo-Fenton and electrochemical oxidation systems, the values of R were 0.01 and 0.04 respectively, indicating that these processes were strongly inhibited in the WW. In contrast, TiO_2 photocatalysis was considerably less affected. In fact, only 50% inhibition of AA removal ($R = 0.5$) was observed when oxacillin in the WW was treated by TiO_2 photocatalysis.

In addition to antimicrobial activity evolution, during the WW treatments the following values were measured: the rate of H_2O_2

Table 1
Characterization of urban wastewater.

Parameter	pH	Dissolved organic carbon (mg C L ⁻¹)	Conductivity (μS cm ⁻¹)	Alkalinity (as mg CaCO ₃ L ⁻¹)	Chloride anion (mg L ⁻¹)
Value	7.6	24.8	905	89.25	106.4

consumption (r_c) in the photo-Fenton process, the accumulation of HClO in electrochemical oxidation and the percentage of adsorption of OXA onto the catalyst in TiO₂ photocatalysis. In the photo-Fenton process, the r_c was 10.6 μmol L⁻¹ min⁻¹, which is ~10% of the value obtained in DW (Fig. SM 7, in supplementary material). This suggests that the matrix components of WW limit the Fenton reaction (Eq. (1)), generating a low consumption of hydrogen peroxide. In fact, it has been reported that chloride ions may inhibit the photo-Fenton system due to the formation of a less active iron complex (Pignatello et al., 2006).

Fig. SM 8 (in the Supplementary material) demonstrates the accumulation of HClO during the electrochemical oxidation of WW. In contrast to the results in DW, HClO accumulation is lower in WW, which may be related with the reaction between hypochlorous acid and species present in the wastewater matrix. Therefore, the amount of HClO available to degrade oxacillin is lower. In fact, the bicarbonate anion and organic matter may react with HOCl and strongly interfere with AA removal.

Finally, the percentage of adsorption of OXA onto TiO₂ (Fig. SM 9, in supplementary material) in the WW is ~26% lower than in the DW. Such a decrease is due to the possible interaction of species present in urban wastewater with the catalyst. Previous work (Giraldo-Aguirre et al., 2015) has shown that the photocatalytic degradation of oxacillin mainly occurs via the action of holes and adsorbed hydroxyl radicals prior to absorption of the antibiotic into the catalyst surface. Therefore, a decrease in oxacillin adsorption diminishes the pollutant degradation and AA elimination is inhibited (Fig. 5). Species such as bicarbonate and chloride ions can absorb into the catalyst surface (Chen et al., 2005). However, as already indicated, the formation of carbonate radicals and their attack on oxacillin can partially compensate for the decrease in antibiotic degradation at the catalyst surface.

4. Conclusions

This work showed that all of the tested systems (photo-Fenton, TiO₂ photocatalysis and electrochemical oxidation) are able to completely remove the antimicrobial activity of distilled water polluted with the antibiotic oxacillin. In the presence of additives considerable differences were found, which depended on the additive type and treatment system. In both photo-Fenton and TiO₂ photocatalysis processes the results were more diverse. In contrast, all of additives negatively affected antimicrobial activity removal when electrochemical action was used. However, this process turned out to be the most suitable when mannitol was present in solution. The photo-Fenton system was shown to be the most promissory when tartaric acid was used as an additive. The effect of calcium carbonate (as bicarbonate ions in solution) was negligible during AA elimination by TiO₂ photocatalysis. The presence of lauryl ether sulfate inhibited all the systems, but electrochemical oxidation mediated by chloride ions was the least affected. The matrix components in the urban wastewater drastically affected AA removal via electrochemical oxidation and the photo-Fenton process. However, the TiO₂ photocatalytic treatment was the least inhibited (~50%). The results presented here provide relevant insights into how to select the most suitable technology to treat water containing β-lactam antibiotics.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.scitotenv.2015.10.029>.

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