Potential application of persulfate and simulated sunlight radiation on azithromycin removal

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ABSTRACT
Azithromycin (AZT) is a macrolide antibiotic whose presence in different bodies of water has been reported. This implies that conventional treatment systems are not able for AZT removal. This paper presents the main results regarding the potential use of simulated sunlight and persulfate (PS) on the removal of AZT. The effects of the solution pH and the concentration of PS were evaluated considering a face centered, central composite experimental design. Under optimized experimental conditions, it was possible to reach an AZT elimination around 70.0%, and ~30.0% reduction of the total organic matter after 120 min of reaction. Additionally, it was established that basic pH conditions favor AZT removal, and high doses of PS could have an inhibitory effect on the reaction due to a radical scavenging phenomenon. The roles of SO₄•− and OH• radicals on the reaction were evaluated by conducting tests under the presence of ethanol and tert-Butyl alcohol. In this manner, OH• radicals seem to be the main oxidizing species of AZT. Finally, the evaluation of the effect of the initial pollutant concentration allowed to establish that a pseudo first-order reaction kinetics model can be used to describe the AZT elimination under the evaluated experimental conditions.

Keywords: Advanced oxidation, Antibiotics, Azithromycin, Sulfate radicals, Sunlight, Wastewater treatment

1. Introduction
Pharmaceutical industry development has led to the introduction of different kinds of chemical compounds into bodies of water. A particular scenario is the presence of antibiotics in environmental compartments due to its incomplete absorption after being used to treat bacterial infections. In addition, in most cases, conventional wastewater treatment plants do not have the appropriate design to remove antibiotics and other types of pharmaceutical compounds promoting their discharge into aquatic environments, and representing a potential risk of bacterial resistance generation [1–3].

Azithromycin (C₃₈H₇₂N₂O₁₂, AZT) is a broad-spectrum macrolide antibiotic employed in the treatment of different types of respiratory, gastric, and sexually transmitted diseases [4]. This has promoted not only its extensive use but also that its presence in the effluents of wastewater treatment plants and different natural bodies of water has been reported [5].

Some of the alternatives that have been evaluated for the removal of antibiotics from environmental matrices are the advanced oxidation technologies (AOT). In particular, sulfate radical-based AOT represent an effective option for the elimination of organic micro-pollutants present in water. In this sense, it has been reported that sulfate radical (SO₄•−) has a strong oxidation capacity, and could react with many complex organic contaminants including polychlorinated biphenyls (PCBs), aromatic compounds and dyes [6–8].

Activation of persulfate (PS) by heat, transition metals, ultrasonic, and light radiation are some of the most common ways to generate SO₄•− and the removal of organic pollutants [10–12]. Eq. (1) shows the activation of PS by light radiation to generate SO₄•−. Besides, SO₄•− can also be transformed to OH• (a radical specie with higher oxidizing capacity) according to Eq. (2) [9].

$$S_2O_8^{2−} + hv \rightarrow 2SO_4^{•−}$$  \hspace{1cm} (1)

$$SO_4^{•−} + H_2O \rightarrow SO_3^{2−} + OH^{•}$$  \hspace{1cm} (2)
Different alternatives, such as the combination of UV light and H₂O₂, and heterogeneous photocatalysis, have been evaluated for the removal of AZT [4, 13]. However, to the authors knowledge, no previous studies have assessed the potential application of PS and sunlight in in the AZT elimination from water.

Having into account the above, this paper presents the main results regarding the evaluation of the efficacy of simulated sunlight radiation and PS in the AZT removal from aqueous solutions. In addition, effects of operational parameters such as pH, PS and pollutant initial concentrations were examined. Changes in the total organic carbon and ions presence in treated solutions were also evaluated.

2. Material and Methods

2.1. Materials

All chemicals were of at least analytical grade. AZT (98.0%) was purchased from AK Scientific. Potassium persulfate (K₂S₂O₈) supplied by Sigma-Aldrich was employed as PS source. Ethanol (EtOH) and tert-Butyl alcohol (TBA) were supplied by Mercck. Concentrated solutions of NaOH and HCl were used for modification and control of pH, and methanol and ammonium formate (NH₄HCOO) for chromatographic analysis were of LC/MS grade.

Solutions were freshly prepared using ultra-pure Millipore water (18.2 MΩ cm, 25°C) (Milli-Q Integral system, Millipore).

2.2. Photocatalytic System

SO₄• radicals were generated by activation of PS under simulated sunlight. Experiments were conducted in a sunlight simulator Suntest CPS+ (Atlas) equipped with a 1.5 KW xenon lamp and a light spectrum between 290 and 800 nm. Borosilicate glass flasks containing 50.0 mL of pollutant were used for light exposition. AZT initial concentration was 1.0 mg L⁻¹ (condition that allowed the requirements of the analytical method in terms of precision, accuracy, detection, and quantification limits). Distance from the lamp to the liquid surface was ~15.0 cm, and the liquid depth inside the flasks was ~5.0 cm.

2.3. Preliminary Experiments

Some preliminary experiments were carried out to establish the experimental range of solution initial pH and K₂S₂O₈ concentration that conducts to a significant AZT removal (> 50.0%). Tests were done varying K₂S₂O₈ dose between 5.0 and 80.0 mg L⁻¹ under natural solution pH (~5.2) and 30 min of reaction.

2.4. Experimental Design

AZT removal under preliminary test (data not shown) was between 19.7 and 64.4%. A face centered, central composite design was carried out in order to analyze the effects of pH and K₂S₂O₈ initial concentration on AZT removal after 30 min of reaction. Statistical analysis was performed using the Statgraphics Centurion 18 software. Table 1 shows the factors and levels evaluated during the experimental design.

| Factor                  | Low level | Medium level | High level |
|-------------------------|-----------|--------------|------------|
| pH                      | 3.0       | 6.0          | 9.0        |
| K₂S₂O₈ initial concentration (mg L⁻¹) | 2.5       | 5.0          | 7.5        |

2.5. Analytical Methods

AZT quantification was done using an Acquity UPLC system coupled to a triple quadrupole mass spectrometer, and an Acquity UPLC BEH C18 column (Waters Corporation). Information regarding the chromatographic method could be consulted in authors previous reports [14]. Total organic carbon (TOC) and anions (sulfate and nitrate) presence were evaluated considering the methods 526D (High temperature combustion method) and 4110B (Determination of anions by Ion chromatography) established in the Standard Methods for the Examination of Water and Wastewater (2017) [11].

3. Results and Discussion

3.1. Effect of PS Initial Concentration on AZT Removal

Fig. 1 corresponds to the main effects plot for AZT removal using PS and simulated sunlight radiation. From this figure, it can be seen that the pollutant elimination is enhanced by increasing the PS dose from 2.5 to ~5.0 mg L⁻¹, a situation that could be attributed to a higher generation of reactive species as a result of a high persulfate presence [16]. However, an excessive amount of PS (higher than 5.0 mg L⁻¹) could promote an inhibitory effect by SO₄• radical scavenging as it is indicated by Eq. (3) [17].

\[
SO₄^{••} + S_2O_8^{2−} → S_2O_6^{2−} + SO_4^{2−}
\]  

(3)

3.2. Effect of Solution pH on AZT Removal

Fig. 1 also indicates that AZT removal using PS and simulated sunlight radiation increases as the solution initial pH increased in the range 3.0-9.0. These results could be related to a higher generation of radicals, including active OH•, and probably a greater removal of AZT. According to different authors, under basic conditions organic pollutants removal using activated PS could be favored as result of SO₄• transformation to OH• radicals (Eq. (4)). In addition, basic conditions can also activate PS (Eq. (5)) leading to a higher radicals generation in comparison with acidic or neutral conditions [16, 18, 19].

\[
SO₄^{••} + OH^{−} → SO₄^{2−} + OH^{•}
\]  

(4)

\[
S_2O_8^{2−} \xrightarrow{OH^{•}} 2SO_4^{2−}
\]  

(5)

On the other hand, AZT pKa is 8.74, which implies that under acid pH conditions AZT is protonated, and at pH 9.0 pollutant is mainly in molecular form. In addition, Shokri et al. (2019) [13]
indicated that AZT tends to attract positive charges. When the solution pH becomes acidic, AZT will be transformed and removed by the absorption of positive charges.

3.3. AZT Removal under Optimized Conditions

Table 2 and Fig. 2 present the results obtained after evaluating the use of PS and simulated sunlight in the removal of AZT under a face centered, central composite experimental design. Additionally, Figure 3 corresponds to the associated Pareto chart which indicates that pH and the quadratic factor related to the initial concentration of PS are the only significant factors for AZT elimination under the evaluated experimental conditions. Pareto chart shows that the quadratic factor of PS initial concentration has a negative effect on pollutant degradation indicating that PS optimal condition is an intermediate value (very high concentrations of PS could have an inhibitory effect on AZT removal as it was discussed previously). In terms of pH, Pareto chart allows to infer that a higher pH conducts to a higher AZT extent of degradation.

According to the statistical analysis of the results, the conditions that conduct to a higher AZT removal are pH 9.0 and 5.4 mg L⁻¹ K₂S₂O₈ initial concentration.

Fig. 4 shows the results regarding the AZT removal under optimized reaction conditions. From this Figure, it can be appreciated that the combination of PS and simulated sunlight is able to remove ~70.0% of AZT after 120 min of reaction. In addition, control tests indicate that AZT does not suffer any transformation under photolysis (AZT removal using only light radiation), hydrolysis (AZT removal in dark conditions at pH 9.0) and the action of only PS (AZT removal in dark conditions under optimized concentration of PS at pH 9.0).

On the other hand, EtOH and TBA were added to the reaction to determine which radical specie (SO₄•⁻ or OH•) was primarily responsible for AZT removal. TBA reacts with OH• while EtOH could quench both OH• and SO₄•⁻ [16, 18, 20]. In this way, Fig. 4 indicates that under presence of either TBA or EtOH, AZT extent of elimination decreased. But the inhibitory effect of TBA was higher than that of EtOH. In this way, it can be inferred that both SO₄•⁻ and OH• are present in the reaction, and that the hydroxyl radical was the primary radical specie promoting the AZT removal (higher pH enhances OH• formation). One of the advantages of having OH• in the solution is that this radical is a not selective oxidizing agent that can oxidize almost all kinds of organic compounds, which could enhance not only the AZT elimination but also the generated organic byproducts mineralization.

### Table 2. Experimental Design for AZT Removal Using Simulated Sunlight Radiation and PS (pollutant initial concentration 1.0 mg L⁻¹, irradiance 500.0 W m⁻², reaction time 30 min)

| Test | K₂S₂O₈ initial concentration (mg L⁻¹) | pH | AZT removal (%) |
|------|-------------------------------------|----|-----------------|
| 1    | 2.5                                 | 6.0 | 13.0            |
| 2    | 5.0                                 | 3.0 | 17.2            |
| 3    | 7.5                                 | 3.0 | 3.9             |
| 4    | 2.5                                 | 9.0 | 15.4            |
| 5    | 5.0                                 | 6.0 | 27.4            |
| 6    | 7.5                                 | 9.0 | 27.1            |
| 7    | 5.0                                 | 6.0 | 20.1            |
| 8    | 5.0                                 | 6.0 | 27.5            |
| 9    | 7.5                                 | 6.0 | 8.0             |
| 10   | 2.5                                 | 3.0 | 9.7             |
| 11   | 5.0                                 | 9.0 | 39.4            |
3.4. Effect of AZT Initial Concentration

Fig. 5 shows the results regarding the effect of AZT initial concentration. From Fig. 5 (a) it can be noted that under a higher pollutant initial concentration extent of removal is lower, a situation that could be related to the fact that under higher concentrations of AZT, a higher amount of intermediates or by-products generation could be promoted. In this way, by-products could consume part of the photo-generated radicals representing a competitive effect, and then reducing the potential of radicals to oxidise AZT [9].

Organic pollutants removal using sulfate radical-based advanced oxidation processes can be described using a pseudo first-order reaction kinetics model (Eq. (6)) [9, 21].

\[
k_{\text{app}} = -\frac{dc}{dt} = k_{\text{app}}C
\]  

\(k_{\text{app}}\): apparent pseudo first-order kinetic constant

Fig. 5 (b) shows the relationship between AZT initial concentration and the initial degradation rate calculated as \(\Delta C/\Delta t\) over the first five minutes of reaction. From the figure, it can be noted that experimental data fit the kinetic model adequately (\(R^2 > 0.96\)) with an 0.117 min\(^{-1}\) associated apparent pseudo first-order kinetic constant.

3.5. TOC and Anions Presence Evaluation

Fig. 6 shows the variation of the TOC, \(\text{NO}_3^-\) and \(\text{SO}_4^{2-}\) content in treated samples after 120 min of reaction. According to this Figure, solution TOC was reduced in a \(~30.0\%\) which indicates that part of the organic matter is being transformed into CO2 and water. In addition, considering Eq. (7) total AZT oxidation also would conduct to HNO3 generation, therefore, an increment on \(\text{NO}_3^-\) concentration is expected as it is presented by Fig. 6.

\[
\text{C}_{38}\text{H}_{23}\text{N}_7\text{O}_{14} + \text{SO}_4^{2-}/\text{OH}^- \rightarrow \text{CO}_2 + \text{H}_2\text{O} + \text{HNO}_3 + \text{H}_2\text{SO}_4
\]

Finally, regarding the increase of sulfate, it would be associated to the \(\text{SO}_4^{2-}\) formation from \(\text{SO}_4^\bullet\) radicals as it is indicated by Eq. (2)-(4).

4. Conclusions

Combination of simulated sunlight radiation and PS is able to remove antibiotic AZT from aqueous matrices. AZT elimination was higher than \(~70.0\%\), and organic matter mineralization was \(~30.0\%\) after 120 min of reaction.
The conditions that conduct to a higher AZT removal, under the evaluated experimental conditions, are pH 9.0 and 5.4 mg L\(^{-1}\) K\(_2\)S\(_2\)O\(_8\) initial concentration. In this aspect, an excess of PS can scavenge SO\(_4\)\(^{2-}\) and reduce AZT degradation.

Presence of SO\(_4\)\(^{2-}\) and OH\(^+\) radicals on solution was evidenced, and hydroxyl radical, whose generation is favoured under basic pH conditions, seems to be the primary radical specie dominating the AZT removal.

Finally, AZT elimination, under the evaluated experimental conditions, using simulated sunlight radiation and PS can be described considering a pseudo first-order reaction kinetics model.

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**Author Contributions**

B.A.O (Undergraduate student) carried out the experiments and reported the results. H.Z. (Ph.D.) supervised the experiments execution, interpreted the results and wrote the manuscript. G.A.P. (Ph.D.) assisted in the results interpretation and the final version of the manuscript preparation.

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