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Original Article

# Sonochemical degradation of azithromycin in aqueous solution

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**Abstract**

**Background:** The presence of pharmaceutical substances and their residual in water resources is an important environmental concern. Azithromycin, an antibiotic that is used for the treatment of infectious diseases, is a pollutant agent in the wastewater. The aim of this study was to investigate azithromycin degradation in aqueous solution through ultrasonic process in the presence of zinc oxide nanoparticles as catalysts.

**Methods:** Sonocatalytic experiments were performed at variable conditions including pH (3-8), temperature (20-60°C), time (3-21 minutes), catalyst dosage (0.25-2 g/L), hydrogen peroxide concentration (15-100 mg/L) and initial azithromycin concentration (10-100 mg/L).

**Results:** The optimum values for pH (3), temperature (40°C), time (15 minutes), catalyst dosage (1 g/L), $H_2O_2$ concentration (50 mg/L) and initial azithromycin concentration (20 mg/L) were determined. The highest degradation efficiency of 98.4% was achieved after 15 minutes of ultrasonic irradiation under optimum condition.

**Conclusion:** According to the results, ultrasonic irradiation is able to degrade azithromycin. In addition, ZnO and hydroxyl radical can successfully accelerate the reaction process in the shortest possible time.

**Keywords:** Azithromycin, Catalysis, Wastewater, Ultrasonics

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## Introduction

One of the important pollutants in the environment is drug substance. More than 90% of the drugs are disposed and discharged into urban wastewater, and since the conventional treatment system is not efficient to remove these materials, hence, they enter the environment as water resources (1-3). Moreover, pharmacies and unprocessed drugs are also the main sources of drug entry into the environment. Antibiotics account for about 15% of total drug usage and are considered as one of the major pollutants of aquatic systems such as wastewater treatment plants besides surface, drinking and ground waters (4,5). The presence of antibiotics and pharmaceuticals in water has become a significant concern in recent years.

azithromycin as one of the most important macrolide antibiotics in medicine, is used to treat infection in humans and animals (6). Usually, these substances are not removed in the usual primary and secondary purification processes of a refinery, therefore, they can enter into the water supplies (7,8). The presence of these compounds in the aquatic environment can lead to toxicity, development of antibiotic-resistant strains, and subsequently, treat the human health and ecosystem function. Therefore, an efficient purification system is necessary to remove these compounds (9). In recent years, the chemical oxidation processes such as ozonation, oxidation, and photolysis have been introduced to remove such contaminants. Baran et al studied the removal of four antibiotics (sulfadiazine, sulfamethoxazole, sulfathiazole and sulfacetamide) by photocatalytic method and reported that the produced intermediates had less toxicity than the primary compounds (10). Uslu and Balcioglu reported almost total removal of antibiotics i.e. oxytetracycline and sulfamethazine, but the main concern with the ozonation process is the possibility of converting toxic compounds into undegradable compounds (11). The ultrasonic method is a sample of advanced oxidation processes (AOPs) that decomposes and degrades organic pollutants. The ultrasonic method has some unique benefits such as non-use of chemicals, ease of use and high efficiency compared to other technologies (12). Recently, the use of ultrasonic method alone or combined with other materials or processes has been considered as the most efficient method. Using the ultrasonic process alone will require a long time and high energy consumption to remove pollutants. Therefore, in order to reduce the time

and energy consumption, semiconductor nanoparticles such as titanium dioxide (TiO2), zinc oxide (ZnO) and copper oxide (Cu2O) are used (13-15). The ultrasonic process using catalysts, is a relatively new process in water treatment compared to the other AOPs that can make antibiotics less toxic or less toxic byproducts, therefore, it is used as an effective method for the decomposition of pollutants with low biodegradability, such as antibiotics (16). Villaroel et al examined ultrasonic degradation of acetaminophen, and reported that ultrasound has shown remarkable ability to degrade acetaminophen, and in comparison to other AOPs (Fenton, photo-Fenton, UV/$H_2O_2$), it showed no harmful effects (17). Ultrasonic method can improve the catalytic oxidation process by activating the catalyst surface. The combination of a catalyst with ultrasound has a synergistic effect on the pollutant degradation. In addition, the ultrasonic process consumes considerable energy and time, which makes it a costly affair. To solve this problem, catalysts are added to the ultrasonic reaction system to reduce the activation energy and accelerate the response (18). Hartmann et al showed that the degradation of diclofenac in water by ultrasonic process in the presence of a catalyst is a useful method for the degradation of pharmaceutical compounds in water. Using this combined method in the presence of titanium dioxide ($TiO_2$), 84% of diclofenac was removed from water in 30 minutes (19). Zinc oxide nanoparticles are cheap and its catalytic properties will be appeared if the input energy be more than the energy required for its stimulation (20). Accordingly, the ultrasonic process with ZnO as a catalyst, can be used in the process of sonocatalysis (ultrasonically assisted catalysis) to purify water resources. This catalyst is a non-toxic, corrosion resistant and strong oxidizer (21). The purpose of this study was to investigate the azithromycin degradation through ultrasonic process in water using a ZnO catalyst considering the effect of different parameters such as pH, azithromycin concentration, catalyst concentration, time and temperature in order to find the optimal values.

## Materials and Methods

### Materials

Azithromycin powder was prepared by Sigma (St. Louis, MO, USA), ZnO nanoparticles as a catalyst, with size ranging from 20 to 60 nm and purity of 99.5%, was taken from Rouinsazan company, Iran. The SEM of ZnO nanoparticles is shown in Figure 1. Methanol and $H_2O_2$ were purchased from Merck (Darmstadt, Germany). In addition, pH meter (Istek, 915PDC), ultrasonic device (PARSONIC 7500 S, 220 VAC, Iran), UV-Vis spectrophotometer (Shimadzu Corporation, Japan), were also used.

### Preparation of azithromycin solution

Azithromycin is an erythromycin derivative that its chemical formula is $C_{38}H_{72}N_2O_{12}$. Its solvent is generally methanol. Figure 2 shows its molecular structure. The concentrations of azithromycin solution were determined by dissolving different amounts of azithromycin powder in 100 mL of methanol (20, 40, 70, and 100 mg/L). The solution was adjusted at various pHs (3, 4, 5, 6, 7 and 8) using HCl and 0.01 M NaOH. At each stage, different parameters such as ultrasonic time (3, 6, 12, 15, 18 and 21 minutes), temperature (20, 30, 40, 50 and 60°C), catalyst concentration (0, 0.25, 0.5, 0.75, 1, and 2 g/L) and $H_2O_2$ at different concentration (15, 20, 40, 50, 75, and 100 mg/L) were tested using an ultrasonic device at a frequency of 35 kHz. Samples were taken at selected times, filtered through Whatman no. 0.45 filter paper and prepared for reading.

### Analysis

To determine the concentration of azithromycin, UV analysis was performed by UV-Vis spectrophotometer at a wavelength of 547 nm, and the optimal value of each parameter and removal rate were determined.

## Results

### Effect of pH solution on azithromycin degradation

Several studies have shown that pH of the solution plays an important role in the ultrasonic removal of organic pollutants. This can be due to its effects on the distribution of electric charge on the catalyst surface and oxidation potential. Studies have also shown that pH has a significant effect on the degradation and removal of antibiotics. In
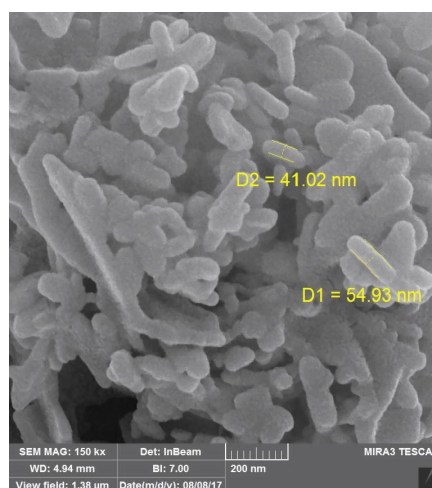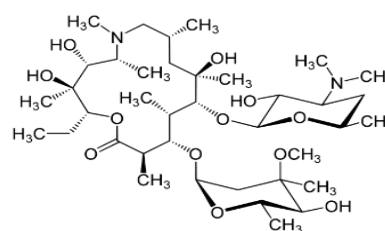


**Figure 1.** SEM of ZnO nanoparticles.



**Figure 2.** Molecular structure of azithromycin.

this study, the pH values from 3 to 8 were tested under test conditions (concentration of azithromycin = 40 mg/L, catalyst concentration = 1 g/L and temperature = 30°C) for 15 minutes in the presence of ZnO catalyst (Figure 3).

### Effect of reaction temperature on azithromycin degradation

To determine the effect of temperature on azithromycin degradation, experiments were performed at 5 different temperatures ranging from 20 to 60°C and constant values of other parameters (contaminant concentration = 40 mg/L, ZnO catalyst concentration = 1 g/L and time = 15 minutes) and optimized pH value. As shown in Figure 4, the removal rate has increased with increasing temperature, especially from 20 to 40°C. But at temperatures from 40 to 60°C, there was a steady decrease in the removal rate.

### Effect of reaction time on azithromycin degradation level

To investigate the effect of reaction time on the azithromycin degradation, under optimized conditions (pH = 3 and temperature = 40°C) and constant parameters (azithromycin concentration = 40 mg/L, and catalyst concentration = 1 g/L), sampling was carried out at intervals of 3 to 21 minutes after experiment using low-frequency ultrasound (35 kHz). Figure 5 shows the removal rate of azithromycin over time. The results demonstrated that there was a significant increase in the
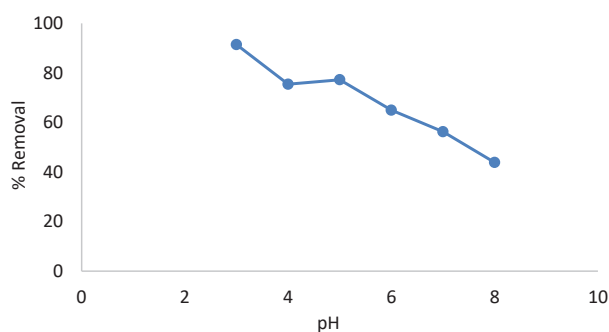
percentage of removal in the first 15 minutes, then, no significant change was observed.

### Effect of zinc oxide catalyst concentration on azithromycin degradation

Degradation of azithromycin in water was performed in the presence of ZnO catalyst. The presence of catalysts accelerates the degradation of pollutants in the reaction. In a solution of 40 mg/L azithromycin at pH = 3 and 40°C, the optimum catalyst level was obtained by ultrasonication of 1 g/L ZnO catalyst after 15 min of degradation. According to Figure 6, the increase in catalyst content in the solution from 0.25 to 2 g/L leads to an increase in the removal efficiency of azithromycin.

### Effect of $H_2O_2$ on azithromycin degradation rate

According to researchers, the addition of an oxidizing agent, such as $H_2O_2$, as a hydroxyl radical producer, significantly increases the efficiency of organic pollutant degradation in AOPs. To maximize efficiency, $H_2O_2$ concentration should be selected according to the type and concentration of pollutants. To investigate the effect

**Figure 5.** Effect of time on azithromycin degradation level at pH=3, temperature=40°C, azithromycin concentration=40 mg/L, and catalyst concentration=1 g/L.

**Figure 3.** Effect of pH on azithromycin degradation at azithromycin concentration=40 mg/L, catalyst concentration=1 g/L, temperature=30°C, and time=15 min.

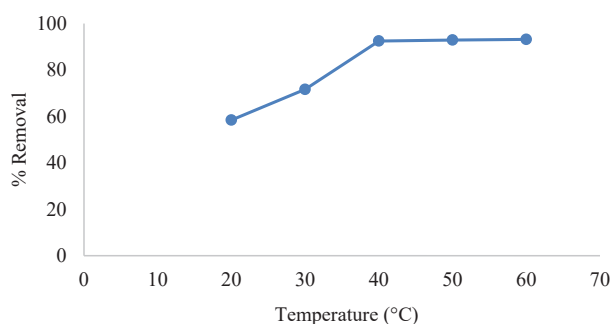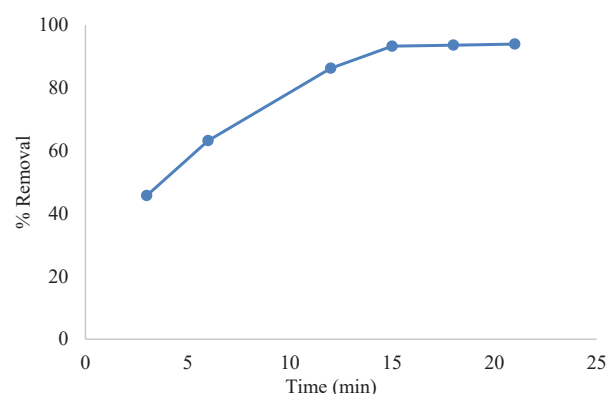**Figure 4.** Effect of temperature on azithromycin degradation at contaminant concentration=40 mg/L, catalyst concentration=1 g/L, time=15 min, and pH= 3.
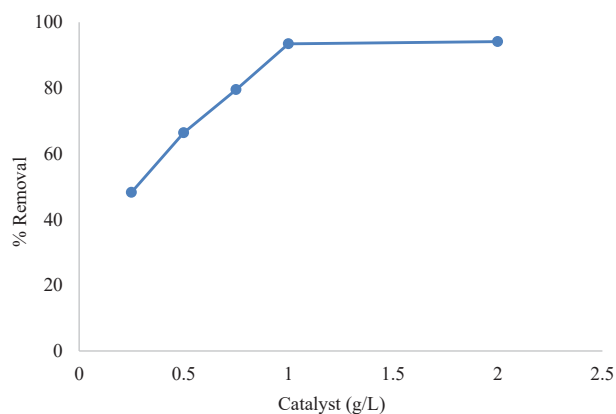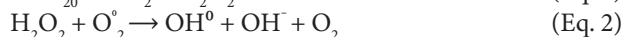
**Figure 6.** Effect of catalyst concentration on azithromycin degradation at pH=3, temperature=40°C, azithromycin concentrations=40 mg/L, and time=15 min.

of $H_2O_2$ at different concentrations (15, 20, 40, 50, 75, and 100 mg/L), azithromycin concentration = 40 mg/L, ZnO catalyst concentration = 1g/L, temperature = 40°C, pH = 3 in 15 minutes are essential. The percentage of azithromycin removal at different concentrations of $H_2O_2$ is shown in Figure 7. The results reveal that the use of $H_2O_2$ with a catalyst has a direct effect on the azithromycin removal rate. So that the sonocatalysts solely increased from 81.78% to 98.4% at 40 mg/L azithromycin in a 15-minute period using 50 mg/L $H_2O_2$ (optimal amount).

### Effect of azithromycin concentration on degradation rate

By optimizing the effective parameters of degradation efficiency, the azithromycin concentration that had the highest degradation efficiency in optimal conditions, was selected. For this purpose, different concentrations (10, 20, 40, 70, and 100 mg/L) of azithromycin solution were prepared under optimal conditions (pH = 3, temperature = 40°C, catalyst concentration = 1 g/L and $H_2O_2$ concentration = 50 mg/L) was sonolyzed for 15 minutes. Figure 8 shows the azithromycin degradation percentage at 5 different concentrations. Based on the results, the decrease in azithromycin concentration increased the removal efficiency. Decreasing contaminant concentration had the same effect as increasing the catalyst concentration. By decreasing azithromycin concentration from 100 mg/L to 10 mg/L, the degradation rate increased from 30% to 99.8% after 15 minutes.

### Discussion

According to the results obtained in Figure 2, with increasing pH, the degradation process of azithromycin decreased and acidic conditions helped degrade azithromycin. As pH decreased due to the reduction of hydroxyl radicals, the efficiency of the process also decreased. The effect of acidic environment to increase the efficiency can be shown as follows:

$2HO_{20} \longrightarrow O^{\cdot}_2 + H_2O_2$ (Eq. 1)

$H_2O_2 + O^{\cdot}_2 \longrightarrow OH^0 + OH^- + O_2$ (Eq. 2)

$e^- + O_2 \longrightarrow O^{\cdot-}_2$ (Eq. 3)

$O^{\cdot-}_2 + H^+ \longrightarrow 2HO^{\cdot}_2$ (Eq. 4)

The basis of AOPs is hydroxyl radical production. But at higher pHs, $H_2O_2$ decomposes quickly and reduces radical formation [7,22]. The effect of pH on azithromycin degradation depends on the structure and properties of the agent and also on its PKa value. The pKa value of azithromycin is 8.74. Accordingly, in acidic solutions, it will usually be molecular. The molecular forms mainly directed to the liquid bubble transfer region, where there is a high OH concentration. According to the studies, the accumulation of catalyst particles in the acidic solution decreases, resulting in an increase in the effective surface of the catalyst, which leads to an increase in the sonocatalytic degradation in acidic conditions [15,23-25]. Villaroel et al reported that in the degradation of acetaminophen by ultrasonic method, acidic medium (pH = 3-5.6) is more
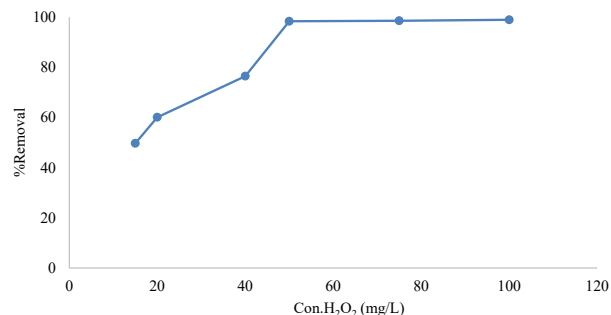


**Figure 7.** Effect of $H_2O_2$ on azithromycin removal percentage at azithromycin concentration=40 mg/L, ZnO catalyst=1 g/L, temperature=40°C, pH=3, and time=15 min.



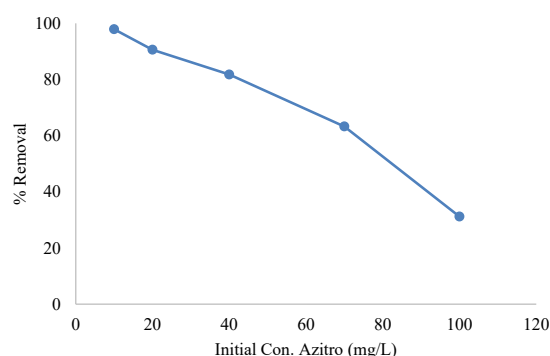**Figure 8.** Effect of initial azithromycin concentration on removal percentage at pH=3, temperature=40°C, catalyst concentration=1 g/L, H2O2 concentration=50 mg/L, and time=15 min.

suitable, thus acetaminophen (PKa 9.5) in acidic solutions in molecular form could has a higher degradation [17]. Im et al also performed experiments at three different pHs (3,7 and 10) to investigate acetaminophen and naproxen degradation by oxidation processes (Sonocatalytic and Fenton). The results showed that when pH of the solution is low, the decomposition of compounds increases that in turn, increases the hydrophobic property of the acidic medium [25].

Ultrasonic tests are usually performed in the temperature control system to ensure that the isothermal conditions are maintained [26]. The increase in temperature significantly increases the cavitation intensity and leads to azithromycin reduction. As the temperature increases, the vapor pressure increases and leads to the generation of more cavitation bubbles. Decomposition at a lower temperature reduces the concentration of radical hydroxyl, and subsequently decreases the degradation of contaminant [27-29]. Braeutigam et al have shown that the rate constant depends on the reaction temperature, and the increase of the temperature has a positive effect on the reaction process. Reactions at temperatures below 25°C lead to the lower cavitation bubbles formation and concentration, and for substances with low solubility, the reaction is improved at higher temperatures [30]. The removal rate of organic compounds is directly proportional

to the temperature, because organic molecules migrate from the solution to the region where the hydroxyl radical concentration is high (31). Su et al investigated the sonocatalytic degradation of amoxicillin using sulfate radicals to determine the effect of temperature. They performed the experiments at a temperature ranging from 24 to 70°C and reported that the temperature increase, particularly from 24 to 40°C, increased the degradation efficiency (32).

The reaction time is one of the variables that influences the performance of oxidation process. Optimizing time in the removal reactions will save the cost of utilization and energy consumption (33). Increased reaction time results in the production of hydroxyl radicals, further contact of these radicals with antibiotics, and ultimately, further degradation of azithromycin. Over time, active sites will change for antibiotic absorption and the number of products produced by the catalyst reaction increases in the aqueous medium, and subsequently the degradation efficiency increases (34,35). The continuation of reaction for a long time leads to high energy consumption. Hence, achieving 93% removal in 15 minutes will save energy (36).

The direct effect of increasing the catalyst on degradation efficiency is due to an increase in the level of access or active catalyst positions. As the amount of catalyst increases, the amount of hydroxyl radical produced also increases. In other words, the presence of catalysts in the sonocatalyst process leads to the production of additional nuclei, which increases the number of active bubbles and radicals (37,38). In an ultrasonic process, the water is pyrolyzed in a portion of hydrogen radical, hydroxyl radical and oxygen radical, and then reacts with the pollutant. The reactions that occur are as follows (39,40):

$$H_2O \longrightarrow OH^0 + H^0 \qquad \text{(Eq. 5)}$$
$$OH^0 + OH^0 \longrightarrow H_2O_2 \qquad \text{(Eq. 6)}$$
$$2\ OH^0 \longrightarrow H_2O + O^0 \qquad \text{(Eq. 7)}$$
$$ZnO + H^0 \longrightarrow Zn^{2+} + H_2O \qquad \text{(Eq. 8)}$$
$$Zn^{2+} + 2\ OH \longrightarrow ZnO + H_2O \qquad \text{(Eq. 9)}$$
$$Zn^+ + 2\ OH^0 \longrightarrow Zn(OH)_2 \qquad \text{(Eq. 10)}$$
$$Zn(OH)_2 \longrightarrow ZnO + H_2O \qquad \text{(Eq. 11)}$$
$$Zn^{2+} + 2O_2^0 \longrightarrow ZnO + 3/2\ O_2 \qquad \text{(Eq. 12)}$$

According to Figure 5, azithromycin removal efficiency increased with increase of catalyst concentration up to 1 g/L and then remained almost constant. The addition of more amounts of catalyst to the reaction system results in the interactions between catalyst particles, thus, ultrasonic energy cannot reach the catalyst surface, resulting in the less active production of active radicals. This can be explained by the fact that when all of the antibiotic molecules settle on the nanoparticles, adding more amounts of catalyst does not affect the efficiency due to the absence of antibiotic molecules (41,42). Actually, ultrasonic device is used as an energy source to activate catalyst nanoparticles. Due to the high energy levels, nanoparticles tend to accumulate, but ultrasonic waves

lead to their dispersion and non-accumulation. When the concentration of the catalyst nanoparticles exceeds a certain limit, ultrasonic energy will not be enough to disperse them, therefore, the removal efficiency remains constant despite the addition of more catalysts (43). These results were consistent with the results of other studies that investigated the effects of various concentrations of ZnO nanoparticles on the organic pollutants decomposition in AOPs (44). Excessive catalyticity in the sonolysis due to the turbulence occurring in the process, leads to increased darkness in the solution, and consequently its incremental effect will not continue (45).

The formation of hydroxyl radicals may be due to the breakdown of O-O bond in $H_2O_2$ by ultrasonic waves (14,46,47). The effect of $H_2O_2$ (the production of most hydroxyl radicals) is defined in the following formulas:

$$H_2O + US \longrightarrow \bullet H + HO\bullet \qquad \text{(Eq. 13)}$$
$$H_2O_2 + \bullet H \longrightarrow H_2O + HO\bullet \qquad \text{(Eq. 14)}$$
$$H_2O_2 + \bullet O \longrightarrow HO_2 + HO\bullet \qquad \text{(Eq. 15)}$$
$$H_2O + \bullet O \longrightarrow 2HO\bullet \qquad \text{(Eq. 16)}$$
$$H_2O_2 + US \longrightarrow 2HO\bullet \qquad \text{(Eq. 17)}$$

The hydrogen formed in reaction 13 reacts with $H_2O_2$ to produce hydroxyl radicals (Eq. 14). On the other hand, the oxygen atoms produced by the dissolution of molecular oxygen in the reaction with $H_2O_2$ (Eq. 15) and water (Eq. 16), generate more radicals. In addition, the sonolysis can directly act as a source of hydroxyl radical production in response to $H_2O_2$ (Eq17) (48). $H_2O_2$ is broken down by ultrasound (sonolysis) into OH, in two following ways (49,50):

$$\bullet H + H_2O_2 \longrightarrow \bullet OH + H_2O \qquad \text{(Eq. 18)}$$
$$H_2O_2 \longrightarrow 2\ \bullet OH \qquad \text{(Eq. 19)}$$

In the study on sonochemical degradation of ofloxacin in the presence of 100 mM $H_2O_2$ by Hapeshi et al, degradation efficiency increased from 28% to 50% (51). The reason for increase in the degradation efficiency along with the reduction of the initial concentration can be explained by the fact that, under the same conditions, other parameters (catalyst concentration, contact time and pH) increased the density of OH-radicals in the lower concentrations, which increased the decomposition of azithromycin released by radicals (51). On the other hand, at higher initial concentration of azithromycin, due to the limited amount of adsorption at the catalyst level, the removal percentage decreases. By increasing the concentration of azithromycin, the probability of a reaction between the pollutant and the reactive species is decreased. In addition, intermediates may be formed during side reactions (32,52,53). Serna-Galvis et al examined the sonochemical degradation of fluoxetine (FLX) with various parameters, including the initial concentration of the pollutant. The results showed that high concentration of FLX leads to an increase in degradation rates, and stated that the amount of $H_2O_2$ accumulation decreased with increasing the concentrations of pollutants. On the other hand, at higher concentration of the pollutant, the FLX molecules

**Table 1.** The degradation of pharmaceutical compounds by ultrasonic methods using various catalysts

| Pollutant | Catalyst | | Time (min) | Removal (%) | Reference |
| | Type | Concentration | | | |
|---|---|---|---|---|---|
| Amoxicillin | $Co^{2+}$ | 0.045 mmol/L | 60 | 98.7 | 32 |
| Levofloxacin | $CCl_4$ | 0.02 mL | 35 | 80 | 37 |
| Tetracycline | $Fe_3O_4$ | 1 g/L | 90 | 89 | 52 |
| Acetaminophen, Naproxen | $TiO_2$ | - | 30 | AAP 60.1, NPX 72.4 | 25 |
| Fluoxetine | - | - | 60 | 80 | 54 |
| Sulfamethoxazole | Carbon nanotubes | 10 g/L | 60 | 88 | 55 |
| Ibuprofen | Carbon nanotubes | 10 g/L | 60 | 94 | 55 |
| Ibuprofen | - | - | 30 | 98 | 56 |
| Azithromycin | ZnO | 1 g/L | 15 | 98.4 | Present study |

are closer to the cavitation bubbles, therefore, the reaction with $OH^0$ is performed (54).

Table 1 shows the degradation of pharmaceutical compounds by ultrasonic methods in the optimum conditions. As shown in Table 1, various catalysts increased the degradation efficiency. However, the use of ZnO as a catalyst has some advantages including high efficiency, short reaction time, and easy workup.

## Conclusion

In this study, degradation of azithromycin from aqueous sources was investigated by ultrasonic method using ZnO catalyst. Studies have shown that parameters such as pH, temperature, initial concentration of pollutant, catalyst, and time, affect the degradation process. According to the results, a high percentage of azithromycin removal was obtained in optimal conditions at pH = 3, temperature = 40⁰C, initial concentration of azithromycin = 20 mg/L and ZnO dosage = 1 g/L after 15 min. In these conditions, the azithromycin removal was 90.59%. Addition of $H_2O_2$ as an oxidizing agent, significantly increased the removal percentage (98.4%). Recently, researchers have explored the effective and cost-effective methods for wastewater treatment. Therefore, based on the previous studies and the results of the present study, it is concluded that the AOPs are suitable methods for the treatment of wastewaters containing pharmaceuticals.

## Acknowledgments

## Ethical issues

There were no ethical issues in the performance of this study.

## Competing interests

The authors declared no competing interests.

## Authors' contributions

All authors were participated in all stages of this article, like data collection, analysis and interpretation and the manuscript approval.

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