ORIGINAL ARTICLE

Degradation of Carbamazepine in Aqueous Solution Using Ozanation Process Removal of Carbamazepine

Khadijeh Darabi[1], MA;
Abooalfazl Azhdarpoor[2], PhD;
Mansooreh Dehghani[3], PhD

Abstract

Background: Carbamazepine is a pharmaceutical compound used as an anticonvulsant for epilepsy and can enter the environment by inappropriate treatment of hospital wastewater. Therefore, the present study aimed to investigate the removal of carbamazepine from the aquatic environment, using the ozonation process.

Methods: This is an experimental study in which certain concentrations of carbamazepine were removed, using the ozonation process. The effect of such factors as pH (3-11), carbamazepine concentration (5-15 ppm), ozone dose (200-400 mg/hr), and reaction time (15-180 seconds) on the removal efficiency was studied. Data analysis was performed to measure carbamazepine, using the High-Performance Liquid Chromatography (HPLC).

Results: The results showed that the carbamazepine removal efficacy at pHs of 5, 7, and 11 was 81%, 66%, and 21%, respectively at 15 ppm, the reaction time of 30 seconds, and the ozone dose of 200 mg/hr, respectively. Also, at the dose of 200 and 400 mg/hr injectable ozone at pHs of 5 and 7, removal efficiency was 81%, 66%, 97%, and 78%, respectively.

Conclusion: According to the results, at pH=5, reaction time of 30 seconds, the carbamazepine concentration of 15 ppm, injectable ozone dose of 200 mg/h, a removal efficiency of 81% was obtained. The ozonation process can react directly or indirectly with the drug contaminant in very low concentrations in aqueous solutions due to its high oxidation power, leading to its destruction or elimination, which may indicate that the ozonation method may be used as an effective method to remove carbamazepine and other similar contaminants.

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[1]MA student of Environmental Health, School of Health, Shiraz University of Medical Sciences, Iran
[2]Associate Professor of Environmental Health, School of Health, Shiraz University of Medical Sciences, Iran
[3]Professor of Environmental Health, School of Health, Shiraz University of Medical Sciences, Iran

Correspondence:
Abooalfazl Azhdarpoor, PhD;
Associate Professor of Environmental Health, School of Health, Shiraz University of Medical Sciences, Iran
Tel: +98 71 37251001
Email: azhdarpoor@sums.ac.ir
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Introduction

A large group of industries are the pharmaceutical and chemical ones that produce wastewater with a wide variety of chemicals and properties.[1] Drugs come into water in various ways. While solid and liquid waste from pharmaceutical plants, hospitals and health centers are the most important sources of drug entry into the environment, other important and common ways of presenting drugs in the environment are disposal of unused or semi-consumed drugs in dishwashers; toilets and trash cans; disposal of non-absorbable drugs through urine and stool to sewage network; drainage of unabsorbed livestock drugs through the urine and stool of animals in the farms and pastures; and finally unauthorized disposal of out-of-date medicines (expired).[2] Carbamazepine is a very polar medicinal compound that is commonly used as an anti-seizure and behavioral stabilizing drug for a variety of epilepsy diseases.[3] Carbamazepine is one of the most durable pharmaceutical compounds in the aquatic

environment due to its resistance to biodegradation and photodecomposition.[4] The commercial carbamazepine, known as Tegretol, is a triple-drug for the treatment of psychiatric disorders, epilepsy, depression and neuralgia, with an estimated worldwide consumption of more than 1,000 tons per year.[5] Absorption of Carbamazepine (*CBZ*) in the body is slow and its velocity is unpredictable, with approximately 1 to 2% being excreted in the urine and approximately 22% returning to the environment through feces.[6] Carbamazepine is one of the most durable drugs in the environment and in different waters, with a concentration of 0.01 to 2 mg/l. Carbamazepine can remain healthy beneath the surface of the earth without being destroyed or devastated after)8-10(years. Carbamazepine concentrations are often reported in the range of 1 to 3600 ng/l in surface water, hospitals, treatment plant's wastewater, and from 10 to 443 mg/l in the pharmaceutical industry wastewater.[7] One of the most commonly used methods for degradation of pollutants in the world is the use of compounds that have a high oxidation potential. Ozone (O_3) is a highly oxidizing gas. Ozone is usually unstable and acts as chlorine in many reactions. Its boiling point is -111°C, its melting point is -251°C, and its density is 1.5 times that of oxygen under standard conditions.[8] The ozonation process due to the high oxidizing power of the ozone molecule is a promising technology in removing pollutants that cannot be eliminated by conventional methods.[9] In previous studies, Yazdanbakhsh et al. studied "Efficacy of the ozonation process to remove ibuprofen from aqueous solutions" in 2016 and their results showed that pH and hydraulic retention time were the most important variables affecting ibuprofen removal.[10] Azuma et al. in 2019 studied the "drug removal in water using ozonatedmicrobubbles" and reported that O_3-MB combined treatment with UV or H_2O_2 could minimize the environmental pollution burden of discharged drugs into rivers and eliminate most medications.[11] Andersen et al. in 2019 studied the elimination of drugs, toxicity and natural fluorescence by biologically ozonation of treated hospital wastewater, and concluded that the toxicity of hospital wastes decreased during the moving bed biofilm reactor (*MBBR*) treatment by Vibrio Fischeri (a reduction from 80% to 50%) and with ozonation, this inhibition was reduced to 20%.[12] Considering the high consumption of carbamazepine and its disposal to the environment, it is necessary to provide a solution that can remove this drug from the aqueous solutions at a high rate and efficiency. Therefore, the aim of this study was to investigate the removal of carbamazepine from aqueous environments by ozonation process and to achieve optimal utilization parameters.

Materials and Methods

This study is an experimental study with an applied approach in which certain concentrations of carbamazepine were removed using the laboratory-scale ozonation process.

Materials and Supplies

In this study, pure carbamazepine powder was purchased from Sigma-Aldrich Corporation (Germany), and other materials including methanol, acetonitrile, and HPLC water were purchased from the Merck Corporation (Darmstadt, Germany). In this study, PH meter (made by Metrohmcompany,Switzerland), ozone generator 400 mg/hour ozone (made by *ShokufanToseeh,Arda* company,Iran), and HPLC device (manufactured by Knauer company, Germany) were used.

Ozonation and Operation Parameters

A specific volume of the drug wastewater sample was introduced into the pilot cylinder and ozone gas was injected into the sample at a specified concentration. In all experiments, the volume of the solution used in 250-ml Erlenmeyer flask was 100 ml. After the contact times (15-180S), to measure Carbamazepine from each container, 1-ml samples were taken by pipette. To determine the optimum ozone dose, ozonation was performed at 2 concentrations (200 and 400 mg/hr). The removal percentage was obtained from the following relationship.

$$\textit{Removal efficiency}\ (\%)=\frac{(Co-Ce)}{Co}\times 100$$

C_0: Initial concentration of carbamazepine in mg/l

C_e: Residual concentration of carbamazepine in mg/l

Samples containing carbamazepine were dissolved in 3 concentrations of 15, 10, 5 mg/l. The pH of the samples was adjusted to 11, 9, 7, 5, and 3, using 0.1M HCl and NaOH. To investigate the effects of different parameters on the efficiency, at each stage, one of the parameters was changed and the others were kept constant.

Preparation of Carbamazepine Stock Solution and Its Analysis

A dose of 0.1g carbamazepine was diluted to a purity of 99% in 100 ml of methanol; then, it was brought to a volume of 1 liter until the stock solution was 100 mg/l and stored in 4°C. In addition, *KNAUER* model HPLC was used to measure *input/output*carbamazepine concentrations. The concentration of carbamazepine was read by a high-performance liquid chromatography (HPLC) equipped with UV/VIS detector at 235 nm. The column used is 5 µm in diameter, 250×4.6 mm and 18 c. The combined mobile phase is a *volume* percentage of 35 to 65 of acetonitrile, water at a flow rate of 2 ml per minute, and an injection volume of 40 µl. The lowest concentration of the detectable (LOD) by the proposed method was 0.05mg/l, while the minimum quantifiable concentration (LOQ) of the carbamazepine was 0.15mg/l.

Results and Discussion

Effect of pH on Carbamazepine Removal

In this part of the study, the effect of pH in the range of 3 to 11 was investigated and the results are summarized in Figure 1. At a carbamazepine concentration of 15 ppm and the ozone dose of 200 mg/h, after 30 seconds of ozonation, at pH=5, a maximum removal efficiency of 81% was observed. Ozone reacts with organic matter in two direct and indirect ways (mainly hydroxyl radicals). In the indirect method, ozone is converted to secondary oxidizers (mainly hydroxyl radicals) by chain reactions, which have much higher oxidizing potential (E^0=2.8 V) than the ozone molecule (E^0=2.0 V).[13] At a pH below 5, the ozone molecule cannot react directly with carbamazepine, but the reaction rate of ozone with carbamazepine also increases with decreasing pH. Also, in acidic environments, the high H^+ concentration leads to the formation of H^0 radicals, which are combined with the oxygen present in the solution to form HO_2^0 radicals, which eventually become OH^0 radicals.[14] Organic matter is dissolved by the ionic dissociation coefficient in either molecular or ionic forms in water and when the pH of the aqueous solution is higher than the ionic dissociation coefficient, the organic matter is dissolved in an aqueous solution. Carbamazepine, on the other hand, is a drug with ionic dissociation coefficient of 2.3 and an octanol coefficient to water of 2.45. This drug is ionically dissolved in aqueous media with acidic pH in the water, and the carbamazepine ionic form, compared with its molecular form, tends to react with the hydroxyl radical, and the highest ionic form of carbamazepine occurs at pH=5. After this pH, the carbamazepine ionic form is stable in aqueous solution.[15] Results from previous research indicate that the ozonation process at acidic pH has a good performance. In a study by Rosal et al. (2008) on the catalytic ozonation of naproxen and carbamazepine on titanium oxide, they concluded that the highest removal efficiency of carbamazepine at pH=5 was 73% and the catalyst at acidic pH increased ozone degradation, while at neutral pH, the catalyst acts as an inhibitor.[16]

Effect of Ozone Dose on Carbamazepine Removal

As can be seen in Figure 2, the effects of carbamazepine at 15 ppm, reaction time of 30 seconds, the effect of dosing at 200 and 400 mg/h were evaluated. At an ozone dose of 400 mg/h and pH=5, the removal efficiency of the ozonation process was 97%. Ozone is capable of converting the low-molecular-weight compounds in the wastewater over a period of time and then eliminating them. At low pH (especially pH=5), a significant portion of ozone is degraded by the direct slow oxidation method and

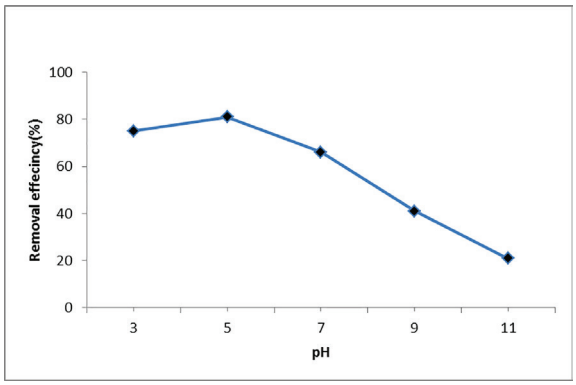

Figure 1: Influence of pH on carbamazepine ozonation process efficiency (15 ppm carbamazepine concentration, 200 mg ozone injection dose and 30 seconds reaction time)

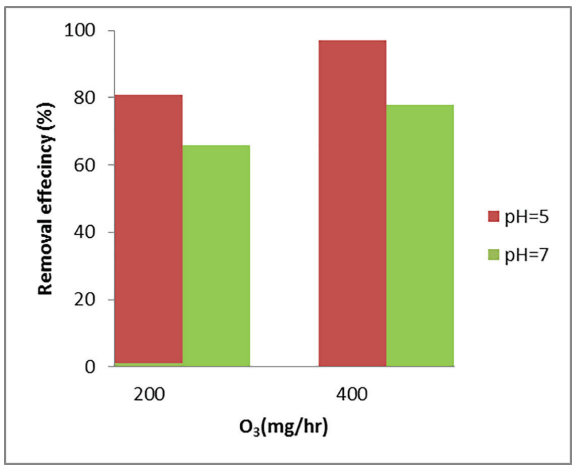

Figure 2: Effect of ozone dose on carbamazepine ozonation process efficiency (carbamazepine concentration 15 ppm, pH=5, 7 and 30s reaction time).

selectively breaks down the carbamazepine molecule. The present study showed that an ozone dose of 200 mg/h is sufficient to eliminate 81% of carbamazepine, considering the economical savings in resources and energy consumption. According to the results of the study of the freezing the drug compounds, conducted by Naddeo et al. in 2015, after 40 minutes of ozonation at a dose of 10 mg/L, removal of 59% of carbamazepine was achievable due to the high reactivity between ozone and unsaturated aromatic compounds, the removal efficiency increases.[17] In another study, Garoma et al. (2010) investigated the removal of sulfadiazine and sulfamethizole from ozone by aqueous solution. They showed that with increasing the ozone concentration, the degradation efficiency increased as well, so that at 3.2 mg/l, 90% of the sulfadiazine and 95% of the sulfamethizole were degraded; in addition, as the reactivity rate of the drugs ($2*10^4 M^1 s^1$) increased with ozone, they resulted in increased degradation in a shorter time.[18] Hansen et al. (2016) in their study of ozonation of hospital wastewater showed a 90% removal of wastewater and concluded that by increasing the dose of ozone, the removal of compounds also increased, but due to the different drug structure, the ozone dose requirements

were different because ozone tended to react with compounds with higher electron density.[19]

Effect of Carbamazepine Concentration

At this stage of the study, different concentrations of carbamazepine (5, 10, and 15 ppm) were introduced into the medium and the process efficiency was evaluated. As shown in Figure 3, at pH=5, reaction time of 30 seconds, and injectable ozone dosage rate of 200 mg/h, carbamazepine removal percentage at the concentration of 5 ppm was 94%. Ozone degradation by carbamazepine occurs through a ring-opening mechanism due to the *attack* of *ozone* on the *non-aromatic carbon-carbon double bond* of carbamazepine and forms the epoxy-carbamazepine metabolite. Mehralipour et al. (2014) in their studies on the removal of ciprofloxacin with ozone/persulfate process reported that at concentrations of 10 and 100 mg/l, the removal efficiency was 96.3 and 38.7%, respectively, and decreased with increasing ciprofloxacin concentration due to increased consumption of oxidizing agents (hydroxyl radical, hydroxyl radical and ozone molecule) under constant ozone conditions. As a result, the high-concentration pollutant decomposition process is not fully implemented due to the presence of more pollutants in the environment, reducing the efficiency and production of intermediate products.[20]

Effect of Reaction Time on Carbamazepine Removal

In this phase of the study, the effect of reaction time in the time range of 30 to 180 seconds was investigated. The results shown in Figure 4 show that at a concentration of 15 ppm carbamazepine, an ozone dose of 200 mg/h and a pH=7, with an increase in reaction time from 15 s to 180 s, the carbamazepine removal reached from 5 to 100%. The removal efficiency in the first few minutes of the ozonation was done with a high gradient and then continued with a slight gradient until the end of the reaction. Research shows that in the process of ozonation, the highest amount of ozone and pollutant degradation occurs in the first few minutes of the reaction, as the rate of consumption is less than the stoichiometric level, and as the reaction progresses, the amount of ozone consumed exceeds its stoichiometric level.[21] To investigate how this parameter affects the rate of degradation and elimination of pollutants, Aghaeinejad-Meybodi et al. (2015) conducted studies on fluoxetine antidepressant. They stated that increasing the contact time would increase the concentration of ozone molecules in the solution and the aqueous solution would be almost saturated with ozone. Therefore, more hydroxyl radicals are formed.[22] Moreover, Gadberry et al. (2018) performed carbamazepine removal in low concentrations from drinking water and found that in 7 minutes of ozonation and 0.015 ppm carbamazepine

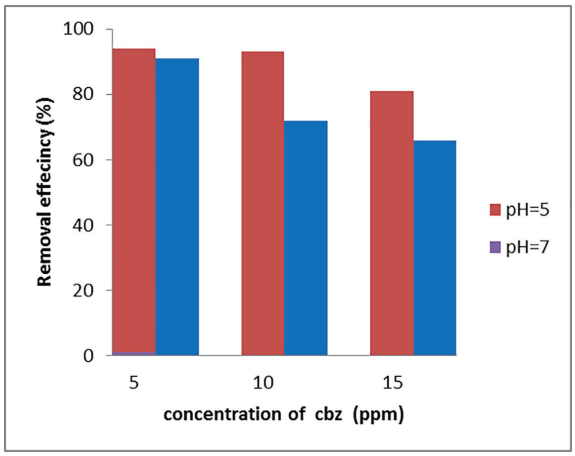

Figure 3: Effect of Carbamazepine concentration on Carbamazepine removal Efficacy (Ozone Injection Dose 200 mg/h, pH=5, 7 and 30 s reaction time).

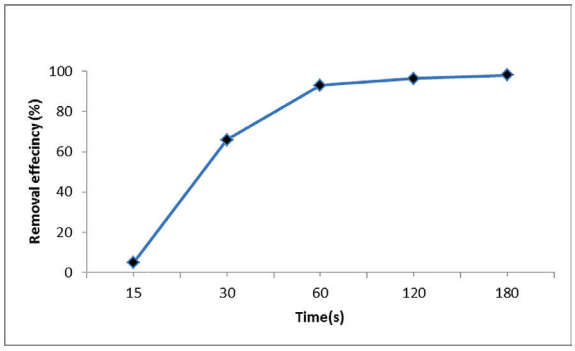

Figure 4: Influence of reaction time on the efficiency of carbamazepine removal (concentration of 15 ppm carbamazepine, pH=7 and ozone injection dose 200 mg/h).

concentration, removal was 98.5%; that is, the molar ratio of carbamazepine to ozone is approximately 2: 1 and will result in the degradation of carbamazepine as ozone solubility increases with increasing pressure.[23]

Conclusion

In this study, the ozonation process was investigated to remove carbamazepine from the aqueous solution. The results showed that at pH=5, reaction time of 30 seconds, the carbamazepine concentration of 15 ppm, and injectable ozone dosagerate of 200 mg/h, carbamazepine removal efficiency was 81% and by increasing the time to a minute in acidic conditions, the percentage of removal of this drug reached 100%. The ozonation process due to its high oxidation power can produce hydroxyl radicals in acidic conditions and react with the drug contaminant, resulting in its destruction or elimination. The ozonation process due to its high oxidation power can produce hydroxyl radicals in acidic conditions, react with the drug contaminant, and result in its destruction or removal; however, the removal and destruction efficiency depends on various parameters such as solution pH, injectable ozone dose, contaminant concentration, and contact time. According to the results of this method, ozonation can be used as an effective method of removing carbamazepine and other similar pollutants.

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Conflict of Interest: None declared.

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