Comprehensive Evaluation of Non-Catalytic Wet Air Oxidation as a Pretreatment to Remove Pharmaceuticals from Hospital Effluents

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ABSTRACT

Removal of pharmaceuticals from wastewater using chemical processes is a promising solution to mitigate pollution in drinking and surface waters. Non-catalytic wet air oxidation (WAO) is a highly efficient advanced oxidation process that uses air and water at high temperatures and pressures to remove high concentrations of organic compounds from various wastes without use of catalysts. However, the elimination of pharmaceuticals in hospital wastewater with a low organic content by WAO has not yet been sufficiently studied. The objective of the present study was to evaluate both the efficiency and costs of WAO treatment to remove pharmaceuticals present in hospital effluents. First, a laboratory-scale WAO batch unit was used to optimize oxidation temperatures and residence times to achieve high elimination of ten pharmaceuticals of interest in spiked deionized water. Then, optimal conditions were applied to treat hospital wastewater effluents. Results showed that even at low chemical oxygen demand values (< 600 mg $O_2 L^{-1}$), WAO at 290 °C with 15 min residence time removed between 95.0 % and 99.1 % of the target compounds spiked at 10 μ g L⁻¹ in hospital wastewater. Acute toxicity bioassays using the crustacean Daphnia magna and the bacterium Aliivibrio fischeri showed that the toxicity of hospital wastewater increased after WAO treatment due to the generation of transformation products. However, since the intended use of WAO is as pretreatment for hospital effluents before municipal water treatment, it is not yet clear if WAO treated effluents could affect bacteria in activated sludge. The study included a techno-economic analysis to evaluate capital expenditures (CAPEX) and operational expenditures (OPEX) of an industrial-scale WAO unit to remove pharmaceuticals from the wastewater effluent of a local hospital. This analysis demonstrated that CAPEX for an 86 L min⁻¹ WAO industrial-scale unit was \$ 2.35 M (in Canadian dollars), while OPEX was \$ 1.09 M, which corresponds to a relative price of \$ 27 per m³. Initial investment for the WAO unit might be reduced by up to 44 % by employing a preconcentration unit to increase the effluents' chemical oxygen demand in smaller volumes which could also make the process autothermal while reducing WAO's operating expenses by more than 20%.

1. Introduction

Over the past few decades, the occurrence of pharmaceuticals in the aquatic environment has been an increasing cause for concern. A growing number of studies have shown that these micropollutants may have adverse effects on aquatic biota¹⁻⁵, microbiota⁶ and possibly on human health ^{4, 7 8}. Another reason to be concerned by pharmaceuticals is that the presence of antibiotics in water bodies, even at low concentrations, could contribute to the dissemination of antibiotic resistance in the environment ^{6, 9-11}.

Pharmaceutical consumption has increased in the last decades because of diverse factors such as aging and increase of the population, changes in clinical practices, discovery of new pharmaceuticals, etc. ¹². For example, between 2000 and 2015, the Organisation for Economic Cooperation and Development (OECD) countries almost quadrupled their consumption of cholesterol-lowering drugs and nearly doubled their consumption of antihypertensives, antidiabetic, and antidepressant drugs ¹³. Thus, several drugs that may present adverse effects for the environment are used more and more frequently. For those reasons, the European Union, the United States, the United Kingdom, and Canada have applied environmental risk assessments to human pharmaceuticals or issued recommendations in order to protect the environment from the potential deleterious effects of these compounds ^{14, 15}.

Pharmaceuticals enter the aquatic environment principally via municipal wastewater as they are primarily excreted via urine and feces, either unchanged or as metabolites ¹⁶. Hospitals are considered a major contributor to this problem and indeed, Oliveira, et al. ¹⁷ reported that their contribution to the content in pharmaceuticals and personal care products of municipal wastewater can be as high as 59 %. In many cases, hospital effluents have higher concentrations of pharmaceuticals than municipal wastewater ¹⁸, and they are also known to be an important source of antibiotics and antibiotic resistance genes in the environment ^{19, 20}. Therefore, hospital effluents can contribute significantly to the occurrence of pharmaceuticals in sewage. For instance, a study in Italy showed that, in average, between 11 % to 67 % of the concentrations of 16 pharmaceuticals found in a municipal influent of a city with a population of 120000 came from the effluents of one hospital with 900 beds²¹. Depending on the size of the hospital and the composition of its effluents, treating hospital wastewater before they reach wastewater treatment plants seems a viable option to reduce inputs of pharmaceuticals in the aquatic environment²¹. Also, adding an on-site hospital wastewater treatment could be beneficial in slowing down the development of antibiotic resistance in microorganisms. Such treatment could be beneficial for both the environment and society where, in OECD countries, an additional US\$10000 to 40000 is spent by hospitals to treat a patient infected by antibiotic-resistant microorganisms¹³.

To enhance the removal of pharmaceuticals during wastewater treatment, several tertiary treatments have been proposed, such as advanced oxidation processes (AOP)²². Unlike secondary treatment processes, AOP remove organic contaminants by oxidation through the generation of hydroxyl radicals (°OH), which are strong oxidants known to be effective against a wide range of organic pollutants ²². Among the diverse AOP used for removing pharmaceuticals from wastewater, wet air oxidation (WAO) remains one of the least studied up to date.

WAO uses water near but below the critical point of water (374 °C and 218 atm) combined with an oxidant, usually air, to oxidize organic compounds. In these conditions, organic compounds are

broken down into smaller structures by a series of oxidation reactions set out by the presence of dissolved oxygen ²³. WAO is effective to degrade organic compounds and removal rates often above 99 % have been reported for diverse contaminants such as benzene and xylene ²³, polycyclic aromatic hydrocarbons, chlorinated solvents, chlorophenols, and malathion ²⁴. WAO is also considered a green process because there are no emissions of NO_x, SO₂, HCl, dioxins or furans ²³, ²⁵ and unlike other AOP it does not require addition of hazardous and costly reagents such as peroxide or ozone ²⁵.

Mineralization of organic compounds is not practically achievable by WAO as the main oxidation product formed, acetic acid, is refractory to further oxidation ^{25, 26}. This water treatment process is suitable for effluents heavily loaded with organic matter, more precisely for effluents that are too diluted to be incinerated but too concentrated and toxic for biological treatment ^{25, 27}. For those reasons, WAO is used as a pretreament to improve biodegradability of toxic effluents ²⁵. Moreover, WAO tends to become autothermal as this highly exothermic process requires little external energy input for chemical oxygen demand (COD) values above 20000 mg O₂ L^{-1 28}. In that regard, WAO is an interesting alternative to incineration which might require a high energy-consuming dehydration stage.

In the past years, a considerable amount of research has focused on catalytic wet air oxidation (CWAO) to reduce energy demands in the WAO process ²⁹. However, some catalysts used in CWAO can be costly, e.g., noble metals such as iridium, platinum and ruthenium. Additionally, these catalysts are also easily poisoned by matrix components which makes them inadequate for industrial-scale applications ²⁹. Non-noble catalysts have been developed for CWAO (e.g., oxides of copper, cesium, manganese and titanium) but they often suffer from instability issues and leach from reactors ²⁵. More studies on non-catalytic WAO for the removal of pharmaceuticals are needed since its performance as pretreatment for wastewater effluents with low COD, such as hospital waters, remains yet unknown. Previous studies have analyzed the performance of WAO or CWAO for the treatment of pharmaceutical industry wastewater ^{23, 30, 31} but the removal of pharmaceutical compounds in hospital wastewater by WAO has not yet been studied. Moreover, comprehensive evaluations of pharmaceutical removal from wastewaters taking into account performance and costs ^{32, 33} as well as toxicity ³⁴, for others AOP has been published in the last years but none has been reported for WAO.

For those reasons, the objective of the present work was to determine if non-catalytic WAO could be applied efficiently and economically as a pretreatment to eliminate pharmaceuticals from hospital effluents before being sent to the municipal sewer system. To accomplish these aims, a series of tests with a batch WAO reactor without adding catalysts was conducted to find the optimal oxidation temperature and residence time for a quasi-total elimination of 10 target pharmaceutical compounds in both spike deionized water and hospital wastewater. These experimental results allowed then the calibration of the CAPEX-OPEX estimation model for a proposed industrialscale unit under optimal reaction conditions. Additionally, bioassays were performed to consider potential changes in toxicity of hospital wastewaters. This study thus represents a complete evaluation of WAO for hospital wastewater treatment.

2. Materials and methods

2.1 Chemicals and reagents

All pharmaceuticals (acetaminophen, gabapentin, quetiapine, pregabalin, carbamazepine, diclofenac, sulfamethoxazole, trimethoprim, cetirizine and baclofen) were purchased from Sigma-Aldrich Canada (Oakville, ON). Methanol (MeOH), acetonitrile (ACN), water and formic acid were Optima LC/MS grade and were obtained from Fisher Canada (Ottawa, ON).

Stock solutions of each pharmaceutical were prepared in MeOH or water at 1000 mg L⁻¹. Stock solutions prepared in water or MeOH were stored, respectively, at 4 °C and -20 °C. The solutions were renewed at least every six months.

2.2 Selection of target pharmaceuticals

The hospital selected for this study is located in the province of Québec, Canada. It has 166 beds and serves a population of about 51000. To identify which pharmaceuticals should be targeted for WAO removal studies, a risk quotient was calculated for the most consumed compounds according to the hospital's inventory. Since the risk of a compound is determined by both exposure and hazard, the risk coefficient used here includes ecotoxicological and hospital pharmaceutical consumption data.

To evaluate potential exposure, the mass of pharmaceuticals (in kg) rejected in wastewater was calculated using pharmaceutical consumption data for a 9-month period (March 5 to December 9, 2017) obtained from the hospital. The information received contained the number of units and mass of the active ingredients for each pharmaceutical in the hospital's inventory. Percentages of pharmaceuticals excreted unchanged, found in DrugBank ³⁵ or product monographs, were used to estimate the mass of each pharmaceutical discharged in the hospital effluents. Finally, concentrations of pharmaceuticals in the hospital effluents were calculated using an average daily water consumption per bed (420.8 L) in Québec ³⁶.

To determine hazard for each compound, median lethal concentration (LC₅₀) data (in mg L⁻¹) for *Daphnia magna* after 48 h of exposure were obtained using the Ecological Structure Activity Relationships (ECOSAR) Predictive Model, a free software maintained and developed by the United States Environmental Protection Agency ³⁷. In a recent benchmarking study of five predictive models used for estimating aquatic toxicity of organic chemicals, ECOSAR ranked second, with an accuracy of 61%. Its main advantages over the top ranked model were ease of use, free access and speed ³⁸.

Equation 1 below describes how the risk quotient was calculated:

$$Risk \ quotient = \frac{Estimated \ concentration \ of \ pharmaceutical \ in \ hospital \ effluent}{LC_{50} \ Daphnia \ magna \ 48h} (Eq.1)$$

2.3 Sampling and preparation of hospital wastewater for quantification of target pharmaceuticals

Samples of hospital effluents were collected at a discharge point from the hospital to municipal sewers on three different dates (February 8, June 26, and June 27, 2019). First, suspended particles in wastewater samples were removed using 1.2 µm pore size hydrophilic glass fibre filters and then 0.45 µm pore size hydrophilic mixed cellulose ester membrane filters both made by MilliporeSigma (Burlington, MA). Then, the pH of samples was adjusted to 6.5 with NaOH 0.1 N or HCl 0.1 N and disodium ethylenediaminetetraacetate dihydrate (200 mg L⁻¹) was added to improve extraction recoveries. Samples were divided in 6 subsamples of 200 mL each and the target analytes were spiked into the subsamples at different concentrations (0, 25, 50 and 75 μ g L⁻ ¹) according to the standard additions method. Next, the subsamples were extracted by solid-phase extraction. The cartridges used were Strata-X-CW polymeric weak cation exchangers (Phenomenex) with a particle size of 33 µm, a sorbent mass of 200 mg and a cartridge volume of 6 mL. Before extraction, cartridges were conditioned by adding successively 5 mL of ACN-MeOH (1:1 v/v) and then 5 mL of water at pH 6.5. After loading the subsamples, cartridges were washed with 2×5 mL of water at pH 6.5. If analysis could not be done the same day, cartridges were dried, wrapped in aluminum foil and stored at -20 °C until analysis. Elution was performed with 2×2.5 mL 5% NH₄OH in ACN-MeOH (1:1, v/v). Eluates were evaporated under a gentle nitrogen flow and then reconstituted to 400 µL with H₂O-MeOH (92:8 v/v) prior to analysis by liquid chromatography-triple quadrupole mass spectrometry (LC-QqQMS).

2.4 WAO tests with spiked deionized water samples

WAO experiments with spiked deionized water samples were performed in a batch reactor model Cellule 2646 1000 made by TOP Industrie (Vaux-le-Pénil, France). The reactor has a volume of 150 mL and can withstand pressures and temperatures of up to 300 bar and 350°C, respectively. For each test, a fixed volume of spiked water is added to the reactor, then air is purged with nitrogen to create an inert atmosphere. The heating system is then set at the desired temperature and once this value is reached, a fixed amount of air (compressed to 140 bar) is injected to initiate the oxidation process. A diagram of the reactor is shown in Figure 1.



Figure 1. Diagram of the WAO setup used in this study.

This study performed nine different tests to optimize WAO operating conditions, first, a temperature range test where samples were taken at eight different temperatures between 100 °C and 300 °C and then, three tests at 200 °C, 250 °C and 300 °C where samples were taken at eight different times between 5 min and 60 min of residence time. Finally, three tests at 27°C 5, 290°C, and 300 °C with 20 min residence time and two tests at 260 °C and 275 °C with 30 min residence time were performed. For these optimization tests, initial concentration of each target pharmaceutical was 1500 μ g L⁻¹. After completing the tests, samples were refrigerated at 4 °C until analysis by LC-QqQMS to measure the percentage removal of target pharmaceuticals.

2.5 WAO tests with spiked hospital wastewater samples

WAO tests with samples collected on January 27, 2020, were performed with a HA1001 model batch reactor manufactured by TOP Industrie, a slightly different reactor that the one described in the previous section. This reactor has a volume of 530 mL and can withstand higher pressures and temperatures (450 bar and 5000°C, respectively) than the previous reactor. Also, it is more suited for complex matrices such as wastewater since it has a titanium coating which is much more robust and tolerant to corrosion.

For each test, a sample volume of 150 mL was spiked with a concentrated pharmaceutical mixture to have the desired concentration $(1500 \ \mu g \ L^{-1} \ or \ 10 \ \mu g \ L^{-1})$ and then introduced in the reactor; air is purged with nitrogen to create an inert atmosphere. A heating ramp (3 °C min⁻¹ beginning at 60 °C) was then applied until reaching the target temperature and right after this, air (compressed to 140 bar) was injected in the reactor to start oxidation. WAO tests were performed at fixed values of temperature and residence times and at the end of the test, samples were collected and then frozen to -20 °C until analysis. Treated samples did not require further preparation and were injected directly into the LC-QqQMS instrument after thawing.

2.6 Analysis by liquid chromatography-triple quadrupole mass spectrometry

Quantification of the target pharmaceuticals was performed by LC-QqQMS. Two instruments were used and most of the samples were quantified using a LC-QqQMS instrument consisting of a Quattro Premier mass spectrometer coupled to an Acquity ultra-performance liquid chromatograph, both manufactured by Waters (Milford, MA). The other LC-QqQMS instrument used was a Xevo TQ-S micro, also manufactured by Waters.

For both LC-QqQMS systems, chromatographic conditions were identical. The column was an Acquity UPLC HSS T3 (2.1×50 mm, 1.8μ m) from Waters. The mobile phase was constituted of 0.1% formic acid in H₂O as solvent A and 0.1% formic acid in MeOH as solvent B and its flow rate was 0.5 mL min⁻¹. Wash solvents for the needle and the injection port are 900 µL of eluent A and 300 µL of eluent B. The elution gradient was: at initial time, 3% of solvent B; at 1 min, 3% B; at 13 min, 65% B, at 15 min, 67% B, at 16 min, 100% B; at 20 min, 100% B; at 21 min, 5% B; at 25 min, 5% B. The injection volume was 20 µL in full loop mode.

For both systems LC-QqQMS, mass spectrometry conditions were identical except for multiple reaction monitoring (MRM) transitions (Tables SI-1 and SI-2, Supplementary Information). Ionization was done by electrospray in the positive mode (ESI+). ESI source parameters were: source gas N_2 , flow rate 0.5 mL min⁻¹; capillary voltage 1 kV; source temperature 150°C; desolvation temperature 500 °C; cone gas flow 50 L h⁻¹. Analysis was done in the MRM mode. Masslynx software was used for data acquisition and QuanLynx software was used for all the data processing. The mean smoothing method was used for integration of MRM peaks. Method performance and quality control information are found in the Supplementary Information (Tables SI-3, SI-4, and SI-5 as well as Section SI-1.2)

2.7 Toxicity bioassays

Two bioassays, the first based on immobilization of the crustacean *Daphnia magna* after 48 h of exposure and the second on the inhibition of bioluminescence of the bacterium *Aliivibrio fischeri* after 5 min of exposure were carried out to measure changes in sample toxicity before and after various levels of WAO treatment.

The acute immobilization bioassay using *D. magna* was based on the OECD Guideline 202³⁹ and it was carried employing the Daphtoxkit F magna microbiotest from EBPI (Burlington, ON). In this microbiotest, neonates are obtained from ephippia instead of stock cultures. Median effective concentrations (EC₅₀) are determined by fitting the percentage of immobilized daphnids after 48 h as a function of the volume percentage of the test sample with a dose-response model. Additional details on the protocol are found in the Supplementary Information (Section SI-1.3)

The *A. fischeri* acute bioluminescence inhibition bioassay was performed using the ISO 11348-1:2007 method as a basis and following the testing procedures provided with the testing kit. Briefly, acute toxicity was measured with a testing kit purchased from EBPI containing all necessary solutions and reagents to perform the assay. Toxicity was determined by the decrease in bioluminescence from *A. fischeri* and was measured by the Microtox M500 analyzer (Strategic Diagnostics Inc.) in light intensity. The light intensity values used to determine 20% effective concentrations (EC₂₀) were measured after 5 minutes of incubation time. Toxicity results are presented as volume percentage of the sample required to cause an effect in 20% of the luminescent bacteria. Additional details on the protocol are found in the Supplementary Information (Section SI-1.4).

2.8 Techno-economic analysis

The techno-economic analysis was based on an industrial WAO system for the treatment of hospital waters by using a semi-theoretical methodology developed by the Centre de transfert technologique en écologie industrielle (CTTÉI)⁴⁰. This methodology uses experimental results of COD and elimination of pharmaceuticals in a batch reactor to estimate a plausible reaction performance at industrial scale in continuous mode. Then, a process flow diagram is generated

with Prosim version 3.6, a process simulation software developed by ProSim Inc. (Labège, France). The related process simulation is calibrated with the estimated performance. Then, the mass and energy balances calculated with the simulation results feed the capital expenditures (CAPEX) and operational expenditures (OPEX) models allowing a first economic assessment of the process. It is worth noting that this is an early-study assessment with a great price deviation that can only be narrowed with further detailed engineering studies. Figure 2 shows the process flow diagram of the proposed WAO process for pharmaceutical degradation in Prosim.



Figure 2. Process flow diagram for removal of pharmaceuticals in hospital wastewater using a continuous WAO reactor.

First, a liquid pump increases the pressure of the hospital water stream to approximately 90 bar, avoiding excessive vaporization inside the reactor. Then, HE-1, a tube and shell exchanger that uses the heat released by the exothermic reaction, increases the temperature of the liquid stream to 265 °C. HE-2, an exchanger that uses either electrical power or natural gas, provides the additional heating requirement to obtain a stream at 290°C and 90 bar, which are the optimal temperature and pressure settings for this specific WAO process. Simultaneously, a compressor allows the injection of air at the bottom of the bubble column reactor while ensuring a bubble regime flow with a uniform distribution of oxygen through the liquid phase ³¹. The process simulation model considers a moderate factor of 1.1 for the excess of air, an assumption to be validated through pilot testing in a further project stage. Next, the treated water stream flows from the top of the column to HE-1 to heat the inlet liquid stream. After then, HE-3, an exchanger such as a vapour-compression refrigeration device, decreases the temperature of the treated water stream below 50°C followed by a pressure regulator that allows to stock the treated water and air mixture inside an atmospheric separator. Finally, the offgas is released to the atmosphere while the treated water stream is sent to the municipal wastewater station for further treatment.

The experimental plan included eight preliminary kinetic tests with several residence times at a temperature of 290 °C according to optimization results. The assumptions for the process simulation and the CAPEX-OPEX model are presented in Table 1 and 2. These assumptions were based on local data and the optimization of the WAO process using the lab-scale batch units described previously. Costs of materials and labour were estimated with Prosim's Economic Evaluation Tool which includes theoretical equations for the price of equipment. In addition, the parameters of that module were adjusted according to data from WAO equipment manufacturers.

Parameters	Assumption	Comments	
Flow rate	86 L min ⁻¹	In the province of Quebec, the water consumption per hospital is estimated between 420.8 and 4665.8 L day ⁻¹ per bed ³⁶ . The value used in the model corresponds to the lower range of expected flow rate for a local hospital with 166 beds.	
Total COD in hospital waters	1400 mg O ₂ L ⁻¹	-1 Maximum COD value for typical hospita effluents according to literature ^{41,42}	
Total pharmaceutical concentration	150 μg L ⁻¹	Assuming a conservative value of about 15 μ g L ⁻¹ for each of the ten target pharmaceuticals. Such value is conservative considering that concentrations higher than 50 μ g L ⁻¹ have been detected in hospital effluents for single pharmaceutical ¹⁷ .	
Excess air factor	1.10	Presumption of satisfactory performance of an industrial bubble column with this excess factor; to be validated with pilot testing.	
Reaction conditions (Temperature and residence time)	290 °C and 15 min	Optimal conditions for temperature and residence time obtained from the results of WAO experiments described in the present study.	
Operating pressure	87 bar	Pressure capable of limiting the vapour fraction in the column to 5 %.	
Organic load reduction	80% - 100%	According to COD reduction and removal of pharmaceuticals observed in the present study.	
Model molecules	Glucose and acetaminophen	Glucose was chosen to model the organic load and acetaminophen for the pharmaceutical content given their availability in the software's thermodynamic database.	
Thermodynamic model	Non-random two- liquid (NRTL)	Accurate model for non-ideal liquid mixtures	

Table 1. Process simulation assumptions for the estimation of the CAPEX-OPEX for the removal of pharmaceuticals in hospital wastewater by WAO.

Table 2. CAPEX-OPEX assumptions for the removal of pharmaceuticals in hospital wastewater by WAO. Currency is in Canadian dollars (CA\$).

Parameters	Assumption	Comments		
Methodology	Functional modules +/- 50 %	Preliminary price estimates (order magnitude) from early studies and witho engineering drawings.		
Operating time	7920 h per year	24 h per day - 330 days per year - 35 days for maintenance.		
Project life	15 years	To estimate the depreciation cost.		
Exchange rate	1.5 CA\$ per EUR	Currency conversion needed as available price models are in euros.		
Power fees	CAD 0.05 per kWh	Local power utility fee for industries.		
Natural gas fees	CAD 0.25 per m ³	Average market price of natural gas in Québe taken from a 2019 market survey.		
Labour	Technician: CA\$ 40 per h Engineer: CA\$ 70 per h	Labour fees taken from a 2019 market survey from CTTÉI. This study considers three technicians at 1/3 of the time and one engineer at ¹ / ₄ of the time.		
Materials	Conventional steel (low pressure and clean fluids). Stainless steel (high pressure and dirty fluids). No corrosion resistance required due to low chloride content in tested samples.			
Other data	Duty free: no importation costs included. Estimates for a temporary (early) civil construction.			

3. Results and discussion

3.1 Selection of compounds

The consumption list of pharmaceuticals from the selected local hospital initially contained 70 different compounds for a total of 170.71 kg consumed between March 5 to December 9, 2017 (Table SI-6, Supplementary Information). From this list, metabolization percentages were used to estimate the amount of each pharmaceutical present in the hospital effluents. After that, only the top 25 compounds were considered, since the other compounds represented less than 1 % of the total mass discharged by the hospital. Estimated concentrations of excreted pharmaceuticals in the effluents (Table SI-7 Supplementary Information) were then divided by the median lethal concentrations (LC₅₀) for *Daphnia magna* to determine risk quotients with Eq. 1 (Table 3). Unfortunately, some compounds were eliminated from the risk coefficient list due to technical reasons. For example, phenytoin and metformin, which were ranked among the top 25 compounds with high-risk quotients, were rejected due to inadequate LC-QqQMS method validation for these compounds. Some compounds were also removed for lack of metabolism or ecotoxicological data, e.g., docusate. Finally, four compounds (carbamazepine, diclofenac, sulfamethoxazole and trimethoprim) were added to the list in order to compare the results with previous studies on elimination of pharmaceuticals by other AOP. The ten compounds selected are presented in Table 3.

Pharmaceutical	Туре	Consumed mass (kg)	Excreted mass (kg)	LC ₅₀ ^a (mg L ⁻¹)	Risk Quotient (×10 ⁻⁶)
Acetaminophen	Analgesic	105.22	3.16	63.3	2600
Baclofen	Muscle relaxant	0.045	0.04	5070	0.39
Carbamazepine	Anticonvulsant	N.A.	N.A.	14.1	N.A.
Cetirizine	Antihistaminic	0.039	0.02	3410	0.36
Diclofenac	Anti-inflammatory	N.A.	N.A.	25.8	N.A.
Gabapentin	Antiepileptic	1.84	1.84	4340	22
Pregabalin	Analgesic	1.48	1.45	7200	11
Quetiapine	Antipsychotic	1.70	0.08	9.49	470
Sulfamethoxazole	Antibiotic	N.A.	N.A.	6.43	N.A.
Trimethoprim	Antibiotic	N.A.	N.A.	6.38	N.A.

Table 3. Target pharmaceuticals selected according to their risk quotient. Carbamazepine, diclofenac, sulfamethoxazole and trimethoprim were added for comparison purposes.

^a Values predicted by ECOSAR software. N.A.: Not available.

3.2 Quantification of target pharmaceuticals in hospital wastewater

Results of the quantification of target pharmaceuticals in hospital effluents are shown in Figure 2. Only five out of the ten selected compounds were present at least one of the three collected samples. Baclofen, carbamazepine, gabapentin and pregabalin were not quantified in any samples, even if their limits of quantification (LOQ) were relatively low, 5.4 ng L⁻¹, 1.7 ng L⁻¹, 6.4 ng L⁻¹, and 26 ng L⁻¹, respectively (Table SI-4). Unfortunately, acetaminophen could not be quantified in the samples using the standard additions method. The concentration of the target pharmaceuticals varied substantially between both compounds and sampling times. For example, quetiapine and sulfamethoxazole were only observed in the sample collected on February 8th. On the other hand, diclofenac was not observed in that sample but was observed on those collected on June 26th and June 27th with a difference of ≈ 48 ng L^{-1} between these two days. As for trimethoprim, it was detected on both February 8th and June 27th samples, but with a difference of ≈ 80 ng L⁻¹. Such high variability in concentration data is in agreement with a previous study on pharmaceuticals in hospital effluents in Italy, showing differences of more than 50 % between summer and winter values for some compounds and less than 5 % for others ²⁵. Results obtained were also compared to a study of several hospital effluents in the United Kingdom ¹⁷ and another study that took place in Italy²¹. In those studies, concentration ranges for diclofenac (3 to 530 ng L⁻¹), trimethoprim (68 to 1800 ng L^{-1}) and quetiapine (10 to 60 ng L^{-1}) were of same order of magnitude as the values reported in Figure 3. However, sulfamethoxazole was about 30 to 300 times more concentrated in United Kingdom study (900 to 6500 ng L⁻¹) compared to the present study. Also gabapentin was detected at concentrations of up to 90780 ng L⁻¹. Such disparities may be explained by pharmaceutical consumption differences, e.g., sulfamethoxazole was not part the hospital's inventory. Water consumption in Québec, the United Kingdom and Italy could also explain the results: Québec water consumption is between 420.8 L day⁻¹ and 4665.8 L day⁻¹ per bed ³⁶ while in the United Kingdom it is between 530 L day⁻¹ and 1138 L day⁻¹ and in Europe between 500 L day⁻¹ and 1000 L day^{-1 44}. Finally, its also possible that the sampling point chosen was not representative of the hospital total pharmaceutical use.



Figure 3. Quantification of the target pharmaceuticals in hospital wastewater in three grab samples collected in three different days in 2019 (n=1). Length of error bars represents the uncertainty of the concentration determined with the standard additions method ⁴⁵.

3.3. Optimization of WAO

3.3.1. WAO tests with spiked deionized water

Residence time and oxidation temperature were optimized to achieve maximum percentage removal of the ten target pharmaceuticals by WAO treatment. At first, an exploratory test was conducted to identify an effective oxidation temperature range in a single run (Figure 4). For this test, each compound was spiked at 1500 μ g L⁻¹ in deionized water. Addition of oxidant (air) was carried out at room temperature and samples were taken at selected temperatures during the heating process. Figure 4 shows that significant removals (> 90%) were observed around 200 °C for acetaminophen, baclofen, diclofenac, gabapentin, and pregabalin. However, removals were < 70 % for carbamazepine, sulfamethoxazole, quetiapine, cetirizine, and trimethoprim. At 300 °C, elimination of at least 90% was achieved for all compounds.



Figure 4. Removal by WAO of the target pharmaceuticals during the exploratory temperature range test (n=1). Compounds were spiked at 1500 µg L⁻¹ in deionized water.

Three other trials were performed to evaluate the effect of the residence time (maximum 60 min) on the removal percentage at temperatures between 200 °C and 300 °C. Results are shown in Figure 5. The removal observed at 0 min is not caused by oxidation, since the oxidant (air) is yet to be added, but by thermal decomposition ⁴⁶ or hydrolysis ²⁸ that could take place during the heating period.

Results in Figure 5 show that carbamazepine, sulfamethoxazole and trimethoprim are more resistant than gabapentin and diclofenac to WAO treatment. At both 200 °C and 250 °C, degradation of carbamazepine, sulfamethoxazole and trimethoprim is < 75%, even after 60 min, while removal of gabapentin and diclofenac is > 80% before addition of oxidant. At 300 °C, almost complete removal (concentrations were < LOQ) for all compounds were observed after only 20 min.



Figure 5. Removal by WAO of target pharmaceuticals spiked at 1500 μ g L⁻¹ each in deionized water at A: 200°C; B: 250°C and C: 300°C. For each temperature *n*=1.

In an attempt to decrease WAO operating conditions of temperature and residence time, five conditions (275 °C, 290 °C, 300 °C with 20 min residence time; 260 °C, 275 °C with 30 min residence time) were selected. Results in Figure 6A show that removal at 275 °C was relatively low for carbamazepine (76 %) and trimethoprim (68 %); however, results for those two compounds at 290 °C (\geq 93%) were comparable to those obtained at 300 °C (\geq 97%). Figure 6B shows that a longer residence time at 275 °C improved slightly both carbamazepine (86%) and trimethoprim (77%) removal percentages. Therefore, an oxidation temperature of 290 °C and a residence time of 20 min were selected as optimal WAO conditions. It is worth noting that most compounds were degraded with subcritical water (> 260 °C) without oxidant. Nonetheless, WAO seems necessary to ensure the degradation of both resistant compounds (carbamazepine and trimethoprim).

Additionally, we hypothesize that most transformation products may only be removed completely after addition of oxidant. Experiments are under way to test this hypothesis.

Comparison between results of the present study and removal percentages obtained with other AOP demonstrated that WAO gives equivalent or better removals for some of the tested pharmaceuticals ⁴⁷. For example, ozonation can remove completely carbamazepine, diclofenac, sulfamethoxazole and trimethoprim from Milli-Q water using ozone doses lower or equal to 4.5 mg L^{-1 48}. Treatment with UV radiation (540 mJ cm⁻²) and H₂O₂ (6 mg L⁻¹) of ultrapure water spiked with sulfamethoxazole, trimethoprim and diclofenac removed 91 %, 68 % and 99 % of those compounds, respectively ⁴⁹. Ozonation combined with sonolysis (20 kHz) was able to remove spiked diclofenac (94 %), sulfamethoxazole (61 %) and carbamazepine (56 %), from distilled water. However removal efficiencies decreased in mixed solutions containing the three pharmaceuticals ⁵⁰. Nevertheless, it is difficult to evaluate the suitability of these AOP methods to

remove pharmaceuticals since information on performance and costs at industrial scales is not often reported.



Figure 6. Optimization of WAO temperature at A: 20 min and B: 30 min residence times using a mixture of target pharmaceuticals spiked in deionized water at 1500 μ g L⁻¹ each. Data for pregabalin at 275 °C did not pass quality control tests and were rejected. For each temperature, n=1.

3.3.2. WAO treatment of spiked hospital effluents

To validate the optimized conditions performance experiments were conducted on real hospital wastewater samples. Based on quantification results of target pharmaceuticals in the hospital effluent (Figure 4), it was decided to spike each compound at 1500 μ g L⁻¹ (same concentration used for optimization trials) in the sampled wastewater. Tests at 290 °C were carried out with residence times of 20 min (*n*=2) and 15 min (*n*=1), respectively. Table 4 shows that removal percentages obtained with a residence time of 15 min were comparable to those generated with 20 min. Thus, according to those results, the final optimal WAO conditions for target pharmaceuticals removal were a temperature of 290 °C and a residence time of 15 min. The two tests at 20 min also demonstrated that WAO removal reproducibility was high. For all compounds, except trimethoprim, removal differences were less than 3 percentage points.

Table 4. Removal of pharmaceuticals in hospital wastewater by WAO at 290 °C with different conditions in duplicate experiments. Pharmaceuticals were spiked at $1500 \,\mu g \, L^{-1}$ in all cases except indicated otherwise.

Pharmaceutical	15 min ^a (%)	20 min ^a (%)	High COD ^b (%)	High COD, spiked at 10 μg L ^{-1 b} (%)
Acetaminophen	98.6	98.5; >99.4	99.4; >99.4	95.3; 99.0
Baclofen	99.1	98.8; 99.9	99.5; 99.7	95.2; 99.0
Carbamazepine	92.7	96.9; 99.8	99.6; 99.7	95.0; 99.0
Cetirizine	99.3	99.5; 99.9	99.5; 99.6	95.2; 99.1
Diclofenac	98.8	98.6; 99.9	99.5; 99.8	95.2; 98.9
Gabapentin	98.9	98.8; 99.8	99.5; 99.7	95.2; 99.0
Pregabalin	99.5	99.3; 99.9	99.5; 99.8	95.0; 99.0
Quetiapine	96.0	95.8; 99.4	99.2; 99.6	99.1; 95.2
Sulfamethoxazole	98.8	98.5; 99.9	99.6; 99.6	95.1; 99.0
Trimethoprim	85.9	86.3; 99.9	99.6; 99.6	95.0; 98.9

^a COD = 573 mg $O_2 L^{-1}$, ^b COD = 1400 mg $O_2 L^{-1}$, residence time = 15 min. Note: The 15 min experiment was performed only once.

3.2.3. Effect of initial chemical oxygen demand on removal

According to Boillot, *et al.* ⁵¹ COD of a hospital effluent can vary up to about 800% within the same day. Then, to study the possible interference of other organic compounds in pharmaceutical removal in hospital waters by WAO, the test samples were spiked with each compound at 10 μ g L⁻¹ or 1500 μ g L⁻¹ and glucose was added to raise the initial COD value to 1400 mg O₂ L⁻¹, a realistic high limit found in hospital effluents ^{41,42}.

The results in Table 4 show that, except for carbamazepine and trimethoprim, all the pharmaceutical compounds are effectively removed from the hospital wastewater samples regardless the initial COD; in fact, elimination rates lie above 95 % at all conditions of residence time and initial organic and pharmaceutical concentration. However, when analyzing

carbamazepine and trimethoprim results, the results show a slight tendance towards better removal rates at higher initial COD that need to be confirmed by further experimental studies.

3.2.4. Effect of initial pharmaceutical concentration on removal

Pharmaceutical concentrations in hospital wastewater are much lower than 1500 μ g L⁻¹. For that reason, hospital wastewater samples were spiked with each compound at a lower concentration of 10 μ g L⁻¹, closer to reported values in other hospital effluents ^{18, 21, 52}. Glucose was also added to raise the initial COD value to 1400 mg L⁻¹. Results of WAO with optimized conditions (Table 4) showed a slight performance decrease in average of 3 percentage points with a lower initial pharmaceutical concentration. Since such difference is close to the observed WAO removal reproducibility, it is possible that the high variability of pharmaceutical concentrations found in hospitals effluents does not influence the WAO treatment performance under similar COD conditions.

3.4. Toxicity bioassays

Toxicity bioassays provide an overview of possible changes in the overall toxicity of hospital wastewater samples due to treatment. In AOP, multiple oxidation products of pharmaceuticals are usually formed ^{47, 53} and they can be, in some cases, more toxic than the parent compound. For example, ozonation of bezafibrate, diclofenac and fenoprofen generated unknown transformation products that increased the toxicity of the samples towards bioluminescent bacteria⁵⁴. The same effect was observed by Klamerth, et al. 55 when removing atrazine, diclofenac, carbamazepine and ketorolac from effluent wastewater by photo-Fenton process; toxicity towards bioluminescent bacteria increased after about 20 min of treatment time. Few studies have successfully identified the transformation products responsible for such increase in toxicity since many compounds are generated simultaneously and synergistic effects could be observed. A study by Dirany, et al. ⁵⁶ found that 3-amino-5-methylisoxazole, p-benzoquinone and possibly short-chain carboxylic acids explained a fraction of the toxicity observed when treating sulfamethoxazole spiked water by electro-Fenton. A paper by Le, et al. 57 also identified 2-hydroxy-4-(N-acetyl) aminophenol, 1,4benzoquinone, benzaldehyde and benzoic acid as toxic oxidation products generated by electro-Fenton treatment of acetaminophen solution. In WAO, if residence times are long enough, small carboxylic acids are usually observed ²³. However no studies have investigated the effect of WAO treatment on the toxicity of deionized water spiked with pharmaceuticals or hospital wastewater samples.

3.4.1 D. magna toxicity bioassays

Results of *D. magna* toxicity bioassays (Figure 7, red bars) show, as expected, that untreated samples have low toxicity or no measurable toxicity since target pharmaceuticals predicted acute toxicity at relatively high concentrations (14 to 7200 mg L⁻¹, Table 3). For hospital wastewater, an EC₅₀ equal to (72 ± 28) % v/v was measured. This value indicates that 72 % v/v of that sample

caused the immobilization of half of daphnids exposed to the sample for 48 h. However, after WAO treatment, an increase in toxicity was observed in both types of samples.

For the spiked deionized water samples, after 10 min of WAO treatment, an EC₅₀ equal to $(18 \pm 3) \% v/v$ was measured, and a slightly higher toxicity was observed at 25 min of WAO treatment [EC₅₀=(13.0 ± 0.8) % v/v]. Such changes in toxicity could be explained by the formation of oxidation products more toxic to *D. magna* than the parent compounds during the WAO treatment. The same effect has already been observed in other types of AOP treatment, as mentioned earlier.

For the hospital wastewater samples, EC_{50} at 48h of exposure increased from $(72 \pm 28) \% v/v$ to $(39\pm 12) \% v/v$ after 10 min residence time and did not change significantly up to 25 min of residence time [$EC_{50}=(31 \pm 11) \% v/v$]. Interestingly, toxicity of treated hospital wastewater was always lower than the toxicity of the spiked deionized water. This suggests that the presence of relatively high concentrations of target pharmaceuticals in the spiked deionized water allowed the generation of high enough concentrations of oxidation products to produce a toxic effect. Hospital wastewater should contain numerous pharmaceuticals but as shown in Figure 3, their concentrations should not be particularly high. Also, other types of organic compounds found in these effluents (e.g., primary metabolites) could be readily oxidable thus forming lesser amounts of toxic oxidation products. Future studies will focus on the nature and origin of these transformation products and their link with the observed toxicity.



Figure 7. Effect of residence time of spiked deionized water and hospital wastewater on the *D.* magna EC_{50} and the *A. fischeri* EC_{20} measured at 48 h and 5 min, respectively. For both sets of data, length of error bars represents the 95 % confidence interval. For only one sample (hospital wastewater treated for 15 min) the fitting failed and no EC_{50} could be calculated for *D. magna*.

3.4.2 A. fischeri toxicity bioassays

To complement the *D. magna* toxicity bioassay, acute toxicity tests were conducted using the bioluminescent bacterium *A. fischeri*. Results of the acute toxicity bioassay (Figure 7, blue bars) showed that both the untreated wastewater and spiked deionized water had no measurable toxicity. The volume percentage value reported for the other samples, represents the percent of the sample required to inhibit the bioluminescence of 20% of the bacteria (EC₂₀). The trends of the measured EC₂₀ are similar to the EC₅₀ reported for *D. magna*, and further support the formation of toxic transformation products during WAO treatment. For both types of water, the treated samples were more toxic than the untreated ones, but the toxicity does not appear to change significantly with the residence time. A few differences were also observed between the results of both bioassays. The most important was that, unlike the *D. magna* bioassay, the *A. fischeri* bioassay could not generate EC₅₀ values. Such outcome can be explained by the sensitivity of both bioassays. It has been reported that the acute bioassay based on *D. magna* is more sensitive than the one based on *A. fischeri* towards organic compounds ^{58, 59}. In one study it was reported that differences of sensitivity between these two methods can be of a factor of up to 3000 ⁵⁸.

Nevertheless, while WAO generated toxic oxidation products towards *D. magna* and *A. fischeri*, the intended use of WAO is as a pretreatment for hospital wastewaters, not as a final treatment prior to discharge into the aquatic environment. Considering that the WAO effluent would be sent to a municipal wastewater treatment plants for further treatment, the toxicity towards daphnids is less relevant in that context. It is, however, unknown if the toxicity of the WAO treated waters observed on *A. fischeri*, might suggest possible effect on the bacteria in the activated sludge treatment step. To our knowledge, WAO succeeds in transforming non-biodegradable compounds into compounds more biodegradable by conventional wastewater treatment methods ⁶⁰. Therefore, by using WAO as pretreatment for hospital wastewater, the transformation products generated by WAO could be removed by secondary treatment in municipal wastewater plants.

3.5. Techno-economic analysis

3.5.1. Process Simulation

Table 5 summarizes the mass and energy balances for the selected WAO unit based on the assumptions listed in Table 4 and a flow rate of 86 L min⁻¹. A more detailed version of this table is available in the Supplementary Information (Table SI-8).

3.5.2. CAPEX – OPEX

CAPEX-OPEX estimations for an 86 L min⁻¹ WAO unit are shown in Table 6. The total CAPEX of the project is CA\$ 2.35×10^6 which includes equipment procurement and installation. The annual OPEX is CA\$ 1.09×10^6 that corresponds to a relative price of CA\$ 27 per m³. The equipment costs account for almost 46 % of the total initial investment while labour expenses account for 41% of the total operation costs; hence, equipment costs and labour expenses are plausible targets for cost optimization.

Regarding labour, project managers can explore human resources strategies such as personnel reassignment or outsourcing; this lies out of the scope of this work though. On the other hand, equipment costs usually decrease with lower inlet feeds as do OPEX. However, to decrease the inlet flow rate of hospital wastewater, the process setup must include an additional unit that concentrates the total chemical oxygen demand (COD) from the hospital effluent before sending it to the WAO unit such as reverse osmosis or ultrafiltration ⁶¹. Thus, a sensitivity analysis to estimate CAPEX and OPEX for the WAO unit (excluding the required concentration stage) as a function of the inlet flow rate was performed. The definition of a suitable concentration unit and its subsequent pricing remain the subject of further studies.

Table 5. Mass and energy balance for a WAO unit of 86 L min ⁻¹	

Mass balance				
	Effluent	Treated effluent		
Total flow (kg h ⁻¹)	5188	5195		
Total flow (L min ⁻¹)	86	87		
$COD (mg L^{-1})$	1400	280		
Acetaminophen concentration (µg L ⁻¹)	150	pprox 0		
Energy balance				
Total electricity consumption (MWh year-	1049			
Heat consumption (GJ year ⁻¹)	1484			
Energy balance (GJ year ⁻¹)	2533			
Proportion electricity/heat (%)	41% / 59%			

Table 6. CAPEX-OPEX for a WAO unit of 86 L min⁻¹

Capital Expenditures (CAPEX)			
Item	Cost (CA\$)		
Studies and project management	250 000		
Process equipment	1 075 000		
Setup and Installation	775 000		
Temporary civil works	250 000		
Total	2 350 000		
Operating Expenditures (OPEX)			
Item	Cost (CA\$)		
Electricity	52 500		
Natural gas	35 000		
Maintenance	72 500		
Labour	450 000		
Plant overhead	320 000		
Depreciation	160 000		
Total expenses	1 090 000		
Annual treated volume (m ³)	41 000		
OPEX per m ³	27		

The results of the sensitivity analysis are illustrated in Figure 7 based on the parameters of the concentration unit indicated in Table SI-9 (Supplementary Information). These results show that CAPEX is about twice as sensitive to inlet flow rates as OPEX for this case of study; for instance, when comparing cases of 86 L min⁻¹ and 5 L min⁻¹, CAPEX decreases by 44 % while OPEX decreases only by 20 %. This is explained by the fact that air plays a crucial role in OPEX estimations as the total COD remains unchanged regardless of the concentration factor; therefore, air compression expenses remain the same for all scenarios considered. This sensitivity analysis excluded the CAPEX and OPEX related to the preconcentration unit as those estimations should follow a selection between alternatives such as reverse osmosis or ultrafiltration. However, when considering a moderate concentration factor of 3.5 and thus a flow rate of 25 L min⁻¹, a realistic cost optimization would provide a CAPEX of CA\$ 1.77×10^6 and an OPEX of CA\$ 9.60×10^5 for the WAO unit, which corresponds to a relative OPEX of CA\$ 8 per m³ (including CAPEX depreciation). This latter value is closer to the OPEX per cubic metre of other AOP treatments that have been proposed previously for similar applications as in the present study such as a membrane biological reactor followed by UV/H₂O₂ treatment (US\$ 2.94 per m³, equivalent to about CA\$ 3.61 per m³)³³. However, the estimation of CA\$ 8 per m³ for WAO must be validated by future studies on the preconcentration of hospital effluents.



Figure 7. Sensibility analysis of CAPEX – OPEX to the inlet flow rate for the WAO process.

4. Conclusion

Results showed potential for the application of WAO to eliminate pharmaceuticals from hospital wastewater and thus prevent their release into municipal wastewater and minimize their presence

in surface waters. Reduction of environmental loads of these substances is essential to avoid longterm deleterious effects on public health, aquatic ecosystems and water quality. As shown by the techno-economic analysis, WAO demands a high energy consumption leading to high operating expenses; however, this project's sensitivity analysis demonstrated that the CAPEX and OPEX would decrease by using a preconcentration unit since it will reduce the volumetric capacity of the unit as well as decreasing the need for an external energy flow. Moreover, the excess heat that might be released under this alternative approach could contribute to the profitability of operations.

The performed bioassays showed that the toxicity of samples treated by WAO increased with treatment time, suggesting that toxic transformation products were formed. However, in the context of using WAO as a pretreatment to municipal wastewater treatment, this residual toxicity might be removed during treatment at the wastewater treatment plant. The WAO process to remove recalcitrant compounds thus remains a promising approach for pretreatment of hospital wastewater. Future research should focus on coupling a preconcentration unit to WAO to reduce costs, the reduction of toxicity of treated effluents and the identification and quantification of transformation products generated by WAO.

Conflicts of interest

There are no conflicts to declare.

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