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ABSTRACT

Ozonation to achieve removal of pharmaceuticals from wastewater effluents, with pH values in the upper and lower regions of the typical range for Swedish wastewater, was investigated. The main aim was to study the effects of varying pH values (6.0 and 8.0), and if small additions of H_2O_2 prior to ozone treatment could improve the removal and lower the reaction time. The effluents studied differed in their chemical characteristics, particularly in terms of alkalinity (65.3–427 mg·ℓ^{-1} HCO_3^-), COD (18.2–41.8 mg·ℓ^{-1}), DOC (6.9–12.5 mg·ℓ^{-1}), ammonium content (0.02–3.6 mg·ℓ^{-1}) and specific UV absorbance (1.78–2.76 ℓ·mg^{-1}·m^{-1}). As expected, lower ozone decomposition rates were observed in the effluents at pH 6.0 compared to pH 8.0. When pH 8.0 effluents were ozonated, a higher degree of pharmaceutical removal occurred in the effluent with low specific UV absorbance. For pH 6.0 effluents, the removal of pharmaceuticals was most efficient in the effluent with the lowest organic content. The addition of H_2O_2 had no significant effect on the quantitative removal of pharmaceuticals but enhanced the ozone decomposition rate. Thus, H_2O_2 addition increased the reaction rate. In practice, this will mean that the reactor volume needed for the ozonation of wastewater effluents can be reduced.

Keywords: ozone; pharmaceuticals; hydrogen peroxide; wastewater effluents

INTRODUCTION

A number of pharmaceuticals of differing therapeutic class, along with their metabolites, have been detected in aquatic environments (Ternes, 1998; Kolpin et al., 2002; Fent et al., 2006; Batt et al., 2006; Snyder, 2008; Verlicchi et al., 2012). The major source of these pharmaceuticals is considered to be the discharge of effluents by wastewater treatment plants (WWTPs) that are not designed for removing trace organic pollutants, in view of the recalcitrance of such pollutants to biodegradation and their limited biological activity, especially in cold climates. Accordingly, additional treatment following biological treatment is called for.

Ozonation is one of the most promising technologies for the removal of organic micropollutants contained in wastewater. The efficiency of ozone in removing pharmaceuticals and personal care products, both from water generally and from wastewater, has been tested in both laboratory- and pilot-scale experiments (Ternes et al., 2003; Huber et al., 2005; Buffle et al., 2006a,b; Bahr et al., 2007; Benner and Ternes, 2009; Hollender et al., 2009; Hansen et al., 2010; Zimmermann et al., 2011). Ozone-based oxidation can be more energy-efficient than UV-based oxidation, especially when used for treatment of waters high in UV absorbance (Rosenfeldt et al., 2006; Hansen and Andersen, 2012).

One of the benefits of using ozonation in aqueous solutions is that the hydroxyl (OH) radicals that are produced will react non-selectively with pharmaceuticals, which could be an advantage for those pharmaceuticals that are difficult to degrade by direct reaction with ozone (Lee and Von Gunten, 2010). The OH radicals are generated through the self-decomposition of ozone in water at pH levels above 7, where the hydroxide ions are acting as initiators (Hoigne and Bader, 1983). Laboratory experiments have shown that the addition of hydrogen peroxide (H_2O_2) enhances the decomposition of ozone, promoting the production of OH radicals (Von Gunten, 2003). Furthermore, non-selective oxidation by highly reactive radicals usually enhances the reaction rates of ozone-resistant compounds, which will reduce the treatment time required (Zwiener and Frimmel, 2000; Huber et al., 2003). Balcioglu and Ötker (2003) reported that adding H_2O_2 enhances both the UV absorbance (at 254 nm) removal and the decrease of COD in wastewater. The rapid reaction of OH radicals is preferable in practice since it reduces the reactor size needed for such treatment. The efficiency of ozone treatment for the removal of pharmaceuticals can also depend upon the reactivity of the wastewater matrix in general (Nöthe et al., 2009).

The present study aimed at investigating the impact of varying pH levels, within the natural interval in Sweden (pH 6–8), on the removal of pharmaceuticals from wastewater effluents by the addition of ozone. It also determined if the reactivity of ozone can be promoted by addition of small amounts of H_2O_2 at low pH levels. Since the addition of H_2O_2 can be expected to enhance the decomposition of ozone to OH radicals, it is of interest to investigate the effect this has in the case of effluents with a pH below 7, where the reaction rate can be expected to be lower and the pharmaceutical removal rate lower due to the lack of hydroxide ions that promote the decomposition of ozone.

MATERIALS AND METHODS

Overall experimental setup

Two effluents of relatively high pH (pH 8.0) were treated with ozone, whereas two other effluents, low in pH (pH 6.0), were treated with ozone in combination with H_2O_2. Treatment was carried out at these pH levels since they correspond to the upper and lower range of pH values typically found in Swedish WWTP effluents. The effluents selected were from plants with extended nitrogen and phosphorus removal. The difference in pH is due to the origin of the potable water (ground versus surface waters). Further, the effluents also differ with respect to other chemical parameters such as alkalinity and ammonium and organic matter content. The pharmaceuticals investigated represent different therapeutic classes commonly used in Sweden, most of them having been found to be present in WWTP effluents (Falås et al., 2012).

The production of OH radicals by ozone decomposition was followed indirectly through measuring the ozone concentration. The experiments were carried out initially in effluents with a pH range between 6 and 8, with the aim to determine the minimum amount of H_2O_2 needed to increase the decomposition of ozone.

Chemicals

The H_2O_2 solution (30%) employed was purchased from Sigma-Aldrich, the NaOH and H_2SO_4 being purchased from Merck (Germany). The pharmaceutical reference standards were purchased from different suppliers as analytical grade (> 98%) solids (Appendix: Table S1). The stock solution of pharmaceuticals was prepared in methanol at a concentration of 100 mg·ℓ^{-1}. The ozone stock solution was prepared in a glass bottle containing purified water (Millipore-Billerica, MA) and provided with a diffuser to disperse the generated ozone from a 1.0 g·h^{-1} ozone generator (O3 Technology AB, Sweden) supplied with dry oxygen gas. The bottle was immersed in an ice bath to increase ozone solubility. Detailed description of the method is found in Antoniou and Andersen (2012).

WWTP effluents

The biologically-treated wastewater effluents investigated, differing in their characteristics and representing the typical variations in alkalinity, pH, and organic matter and ammonium content, were taken from 4 municipal WWTPs in Sweden: Öresundsverket (Effluent 1), Klagshamn (Effluent 2),

Uppsala (Effluent 3) and Käppala (Effluent 4). The effluent samples differed from one another in pH on the day of collection and were adjusted at the start of the experiment by use of either NaOH or H_2SO_4, so as to be exactly pH 6.0 or pH 8.0. Table 1 shows the quality parameters of the effluents.

Analysis

COD and NH_4^+-N were determined by use of the Hach Lange test kits LCK 114 and LCK 304. To measure alkalinity, a 25 mℓ sample was titrated with 0.05 M HCl to a pH of 4.5, and then the alkalinity in mg·ℓ^{-1} HCO_3^- was calculated. DOC was measured on the basis of wet chemical oxidation, using a Shimadzu TOC-Vwp analyser. The UV-absorbance at 254 nm was measured using a Varian CARY50 Bio UV-Vis spectrophotometer. The specific UV absorbance (SUVA), an indicator of the dissolved aromatic carbon that the wastewater contains, known to affect the reactivity of DOC to ozone, was determined by normalising UV absorbance at 254 nm to the DOC concentration (Weishaar et al., 2003). The O_3 doses delivered were analysed by the colorimetric method of indigo (λ = 600 nm) through preparing bottles of indigo trisulphonate solution in Milli-Q water in parallel with the treatment samples (Bader and Hoigne, 1981; Antoniou and Andersen, 2012).

For pharmaceutical analysis, 100 mℓ samples of the treated effluent were filtered through a 0.45 µm membrane filter (Millipore) and were acidified to pH 3 by use of sulphuric acid. After SPE extraction, LC/MS/MS analysis of the extracts was carried out, using a triple-stage quadrupole MS/MS TSQ Quantum Ultra EMR (Thermo Fisher Scientific, USA) coupled with an Accela LC pump (Thermo Fisher Scientific, USA) and a PAL HTC autosampler (CTC Analytics AG, Switzerland) having a Hypersil GOLD aQ™ column (50 mm x 2.1 mm ID x 5 µm particles, Thermo Fisher Scientific, USA). The method of analysing pharmaceuticals was used earlier by Hörsing et al. (2011) and Hey et al. (2012). A detailed description and a full method evaluation are presented in Grabic et al. (2012). The ionisation mode, recoveries, relative standard deviations (RSD) and limit of quantification (LOQ) of the pharmaceuticals are given in the Appendix: Table S2.

Experimental setup

For the ozone consumption experiments carried out, the biologically-treated municipal wastewater was ozonated at different pH levels and O_3 to H_2O_2 ratios. Samples were taken at different reaction times for analysis of the O_3 content. For experiments involving pharmaceutical removal, the wastewater

| TABLE 1 Quality parameters of the effluent wastewaters studied				
WWTPs	**Öresundsverket Effluent 1**	**Klagshamn Effluent 2**	**Uppsala Effluent 3**	**Käppala Effluent 4**
	High pH	**High pH**	**Low pH**	**Low pH**
COD (mg·ℓ^{-1})	41.8	32.4	18.2	35.4
DOC (mg·ℓ^{-1})	9.2	9.0	6.9	12.5
Initial alkalinity (mg·ℓ^{-1} HCO_3^-)	347.7	427	79.9	65.3
NH_4^+-N (mg·ℓ^{-1})	0.04	0.29	0.02	3.6
UV abs$_{254nm}$ (m^{-1})	16.4	24.8	16.0	29.5
pH (initial)	7.2	7.6	6.6	6.3
pH (adjusted)	8.0	8.0	6.0	6.0
SUVA (ℓ·mg^{-1}·m^{-1})	1.78	2.76	2.31	2.36
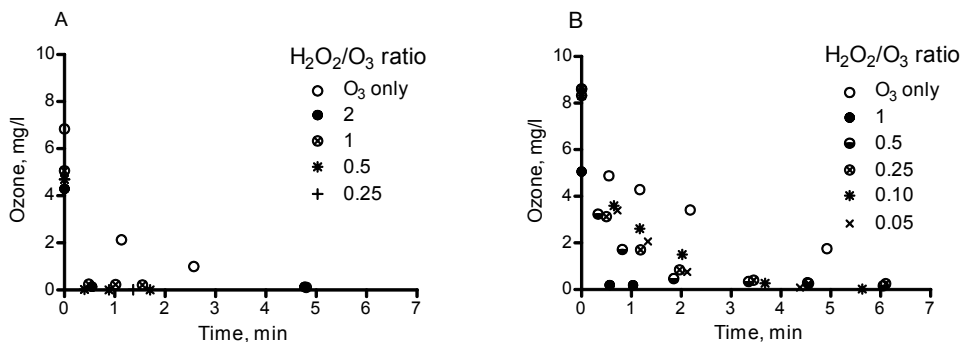
Figure 1
Ozone consumption in the WWTP effluent (Effluent 1) at pH 8 (A) and at pH 6 (B) with different doses of H_2O_2
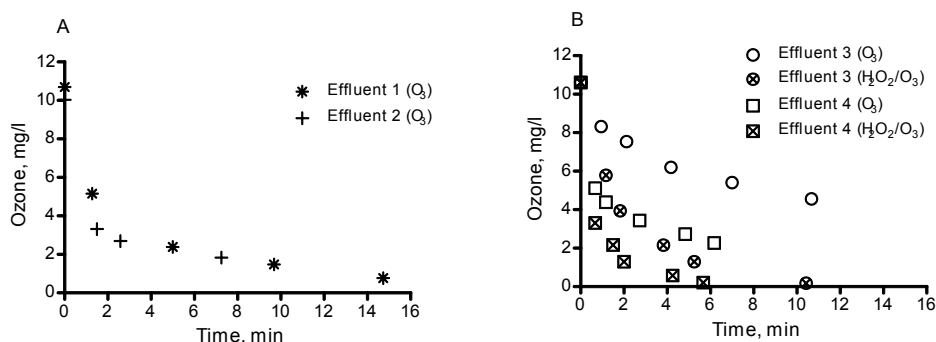

Figure 2
*Ozone consumption in WWTP effluents at pH 8.0 (A, Effluents 1 and 2) without H_2O_2 and at pH 6.0
(B, Effluents 3 and 4) both with H_2O_2 (at a H_2O_2/O_3 ratio of 0.10) and without*

effluents from 4 WWTPs were spiked with pharmaceuticals so as to provide a nominal concentration of ~1 µg·ℓ^{-1}. The spiked effluents were then transferred into borosilicate glass bottles (Schott Duran®) to which different volumes of O_3 stock solution were added to provide, in each case, a nominal concentration of between 1.4 and 10.7 mg·ℓ^{-1} O_3 for a total sample volume of 150 mℓ. The bottles were covered with aluminium foil and were placed in a 15°C water bath for 2 h. For the O_3 and H_2O_2 experiments that were conducted, the H_2O_2 was added just prior to the addition of ozone. All treatment tests conducted were run in triplicate, a relative standard deviation of up to 20% between replicates being considered for data treatment.

RESULTS AND DISCUSSION

Determination of ozone concentration profiles at different pH

As can been seen in Fig. 1, the ozone concentration in the wastewater effluents decreased rapidly after the first minute of ozone addition. Thereafter, the rate of ozone decomposition decreased gradually and stabilised. This relatively fast ozone consumption was to be expected due to the matrix components in the wastewater consuming the oxidant. In addition, the decomposition of ozone tended to proceed faster at pH 8 than at pH 6, in accordance with the results of other studies, such as Hoigne and Bader (1981), using drinking water spiked with organic compounds, and Elovitz et al. (2000) which focused on surface water and groundwater. Wert et al. (2009) also demonstrated the fast consumption of ozone in real wastewaters of varying organic carbon content.

When H_2O_2 was added to the effluents at H_2O_2/O_3 ratios ranging from 2 to 0.25 (Fig. 1), ozone was almost completely consumed during the first minute. As could be expected, the effluent of high pH (pH 8) exhibited the fastest ozone decomposition rate (< 1 min). An additional experiment was also carried out at pH 6.0, involving the use of lower doses of H_2O_2, resulting in significantly lower H_2O_2/O_3 ratios of 0.05–0.10. As can be seen (Fig. 1), the differences in ozone removal rate between the samples are most obvious in the first minute or so of treatment, where the decomposition of ozone increased with an increase in the H_2O_2/O_3 ratio for around 2 min, after which nearly all the ozone has been consumed.

O_3 concentration profiles in the WWTP effluents tested

On the basis of these findings, it is obvious that the addition of relatively small amounts of H_2O_2 is able to change the ozone concentration profile appreciably. To investigate this further, a set of experiments was carried out using 4 different effluent wastewaters (Table 1), two with relatively high pH and two with relatively low pH. The effluents, after pH adjustments to 8.0 and 6.0, respectively, were treated with ozone and the decomposition was followed (Fig. 2). In the high-pH effluents (Fig. 2A), about half of the ozone was already consumed during the first minute, especially in the case of Effluent 2. The differences observed can be attributed to the higher SUVA content in Effluent 2 than in Effluent 1 (Table 1). The relatively high content of aromatic compounds, indicated by the relatively high SUVA level, could explain the increased ozone consumption in the early stages of treatment, due to fast reactivity of aromatic compounds, as also observed by Westerhoff et al. (1999). At pH
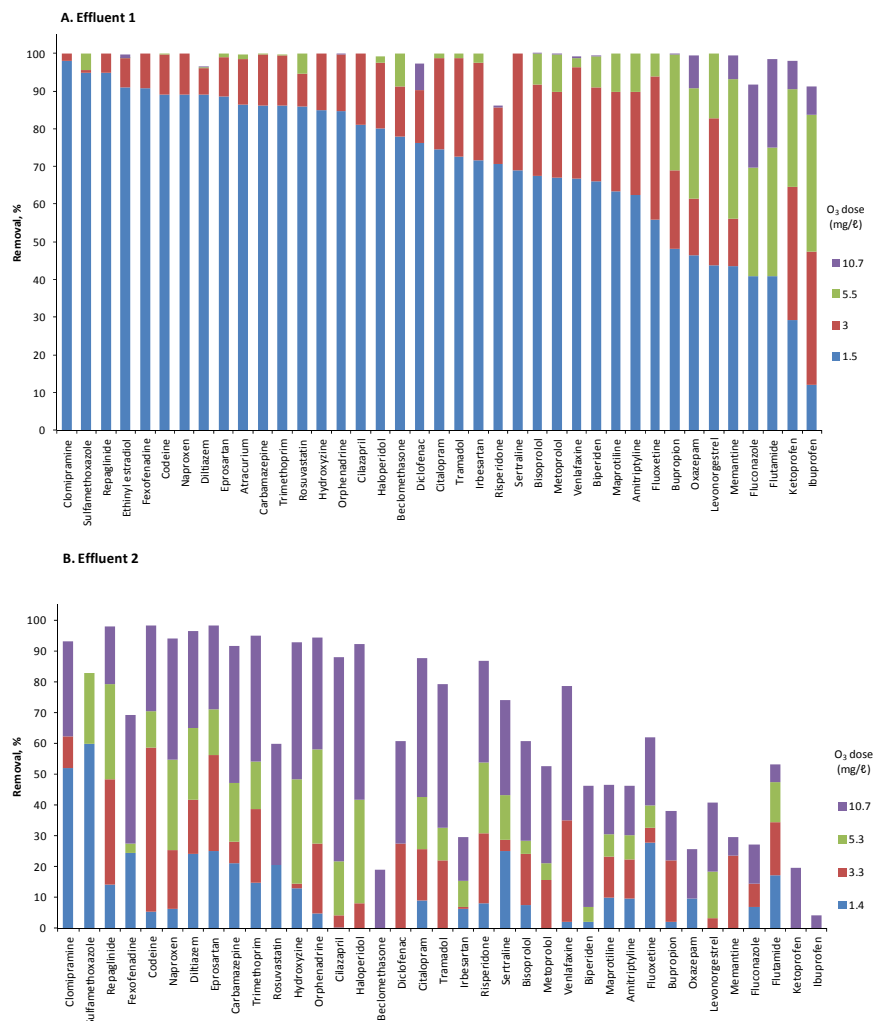
A. Effluent 1

B. Effluent 2

Figure 3

The contribution of each level of ozone dose to the removal of pharmaceuticals in Effluent 1 (A) and Effluent 2 (B) during ozonation at pH 8.0

6.0, in contrast, Effluent 3 appears to have a much lower ozone demand than Effluent 4 (Fig. 2B), this probably being due to the lower organic content of Effluent 3, which is only about half that of Effluent 4. Similar to what can be seen above (Fig. 1), the addition of H_2O_2 to the effluent led to an increased decomposition of ozone, measured as a decline in ozone concentration.

These findings show that it is important, when employing ozonation, to investigate the initial ozone demand of the wastewater due to matrix effects. The present findings also show that at low pH the combination of ozone and H_2O_2 reduces the reaction time, indicating that it is possible to reduce the size of the reaction tank employed for treatment.

Removal of pharmaceuticals by O_3 and H_2O_2

In the ozonation of pH 8.0 effluents, a significant reduction in the different pharmaceuticals was found, especially in the case of Effluent 1 (Fig. 3A), even at relatively low doses of ozone. At the lowest dose (1.5 mg·ℓ^{-1} O_3), 9 of the 40 pharmaceuticals (clomipramine, sulfamethoxazole, repaglinide, ethinyl estradiol, fexofenadine, codeine, naproxen, diltiazem and eprosartan) already showed removal rates of 90–100%; only 8 of the pharmaceuticals (bupropion, oxazepam, levonorgestrel, memantine, fluconazole, flutamide, ketoprofen and ibuprofen) exhibited < 50% removal. As the ozone dose was increased, most of the pharmaceuticals, including the less reactive ones, were degraded.

On the other hand, in Effluent 2 (Fig. 3B), the pharmaceuticals were poorly removed, even when the O_3 dose was increased. This can be attributed to the high SUVA level (2.76 as compared with 1.78) of this effluent. The high ozone reactivity of the aromatic components of the DOC may have contributed to the decrease in pharmaceutical removal from the effluent. Also, as can be observed in Fig. 3, some of the pharmaceuticals in Effluent 1 exhibited a high level of removal in response to the lowest ozone dose but did not follow the same pattern of removal in Effluent 2. For example, both clomipramine and repaglinide showed a high degree of removal at the lowest ozone dose, yet when treated with the same O_3 dose in Effluent 2 it was only clomipramine for which the degree of removal was significant (~50%). This shows clearly that both the level of removal and the reactivity of pharmaceuticals can vary depending upon the composition of the wastewater matrix.

The efficiency of ozone in removing pharmaceuticals from pH 6.0 effluents (Fig. 4A) showed that ozone alone could remove > 90% of half of the pharmaceuticals present in Effluent 3 at the lowest ozone dose (1.8 mg·ℓ^{-1}). When the dose was increased to 4.4 mg·ℓ^{-1}, all pharmaceuticals except fluconazole were degraded by over 90%. A still further increase in the ozone dose resulted in over 99% removal of all pharmaceuticals, except fluconazole (93%) and ibuprofen (96%). In contrast, the ozonation of Effluent 4 resulted in > 90% degradation of the pharmaceuticals when rather high doses of ozone (> 5 mg·ℓ^{-1}) were employed (Fig. 4B). In comparison to the pH 8.0 effluent

A. Effluent 3
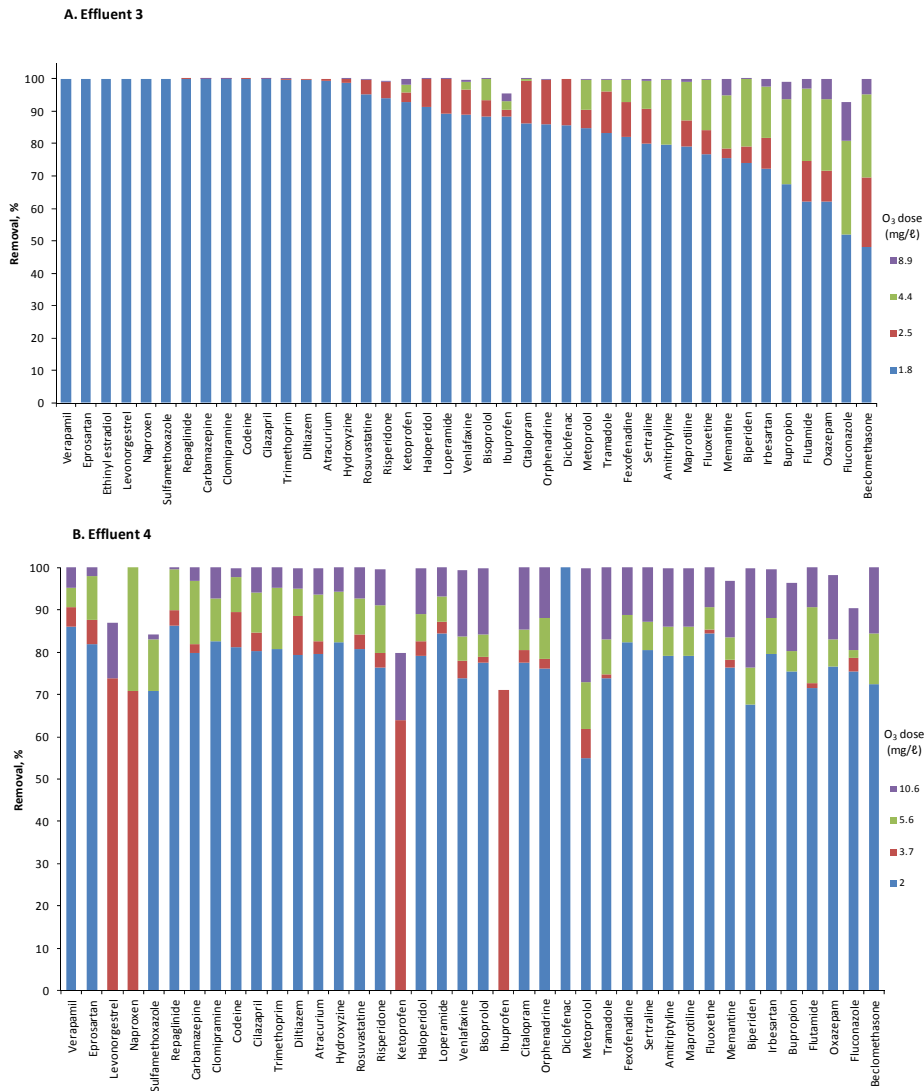
B. Effluent 4

Figure 4

The contribution of each level of ozone dose to the removal of pharmaceuticals in Effluent 3 (A) and Effluent 4 (B) during ozonation at pH 6.0

(Effluent 1), the observed high removal of pharmaceuticals in the pH 6.0 effluent (Effluent 3) is likely due to the very low organic content of this effluent (Table 1), which resulted in more ozone being available (Fig. 2B) to react with the pharmaceuticals.

Figure 5 illustrates the contribution of H_2O_2 addition to the removal of those pharmaceuticals that have been shown to have the lowest reactivity towards ozone. For fluconazole (Effluent 3), as can be seen, there was only a slight increase in removal after the addition of H_2O_2, whereas for ibuprofen no improvement in its removal occurred. Thus, the addition of H_2O_2 (at an H_2O_2/O_3 ratio of 0.08–0.13) to an initial ozone dose of 10 mg·ℓ^{-1}

Figure 5

The contribution of H_2O_2 addition to the removal of pharmaceuticals less reactive to ozone in Effluent 3 and Effluent 4

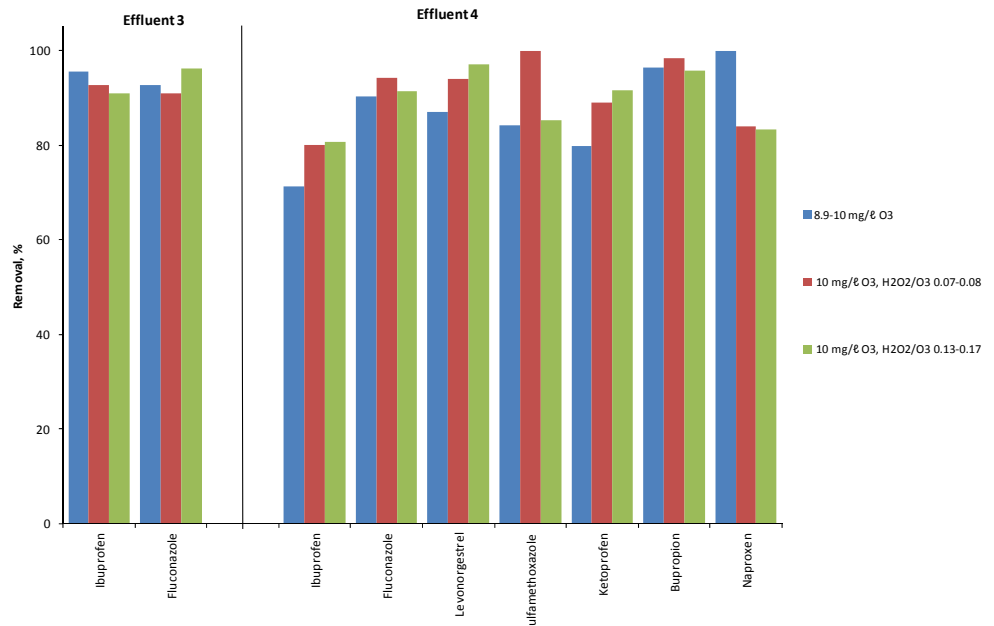| TABLE 2 Pharmaceuticals for which at least 90% removal (✓) occurs in each of the effluents when treated with ~ 5 mg·ℓ⁻¹ O₃. (NA = compound not quantified)										
Pharmaceuticals	(High pH)		(Low pH)				(High pH)		(Low pH)	
	Eff 1	Eff 2	Eff 3	Eff 4		Pharmaceuticals	Eff 1	Eff 2	Eff 3	Eff 4
Amitriptyline	✓	—	✓	✓		Hydroxyzine	✓	—	✓	✓
Atracurium	✓	NA	✓	✓		Ibuprofen	—	—	✓	
Beclomethasone	—	—	✓	—		Irbesartan	✓	—	✓	✓
Biperiden	—	—	✓	—		Ketoprofen	—	—	✓	—
Bisoprolol	—	—	✓	—		Levonorgestrel	—	—	✓	—
Bupropion	—	—	✓	—		Loperamide	NA	✓	✓	✓
Carbamazepine	✓	—	✓	✓		Maprotiline	✓	—	✓	✓
Cilazapril	✓	—	✓	✓		Memantine	—	—	✓	—
Citalopram	✓	—	✓	✓		Metoprolol	—	—	✓	—
Clomipramine	✓	—	✓	✓		Naproxen	✓	—	✓	✓
Codeine	✓	—	✓	✓		Orphenadrine	✓	—	✓	✓
Diclofenac	✓	—	✓	✓		Oxazepam	—	—	✓	—
Diltiazem	✓	—	✓	✓		Repaglinide	✓	—	✓	✓
Eprosartan	✓	—	✓	✓		Risperidone	✓	—	✓	✓
Ethinyl estradiol	✓	NA	✓	NA		Rosuvastatin	✓	—	✓	✓
Fexofenadine	✓	—	✓	✓		Sertraline	✓	—	✓	✓
Fluconazole	—	—	—	—		Sulfamethoxazole	—	—	✓	—
Fluoxetine	✓	—	✓	✓		Tramadol	—	—	✓	—
Flutamide	✓	—	✓	✓		Trimethoprim	✓	—	✓	✓
Haloperidol	✓	—	✓	✓		Venlafaxine	✓	—	✓	—

could not be expected to have any appreciable impact on the removal of pharmaceuticals in this effluent. On the other hand, for Effluent 4, the addition of H₂O₂ was found to enhance the removal of ibuprofen, fluconazole, levonorgestrel, sulfamethoxazole and ketoprofen by only 4–16% and of naproxenl by ~15%.

The overall findings of this study show that reaction time can be reduced when ozone is combined with small amounts of H₂O₂, which will be advantageous when practical implementation of the technology takes place. As for most pharmaceuticals, this addition has no impact on removal efficiency, i.e., neither increasing nor decreasing its removal.

The majority of pharmaceuticals included in this study contained acidic and/or basic groups, having different and pH-dependent charges (positive, neutral or negative) and, as a result, may also differ in their tertiary chemical structure, as a function of pH. The pharmaceuticals that are acidic can be protolysed at pH 6, with no further changes occurring then when the pH is increased to 8. In contrast, those pharmaceuticals that have basic group(s) and low pK_b values go from being unprotolysed at pH 6 to being protolysed at pH 8, the charge thus changing from positive to neutral, which can result in a change in the tertiary structure. Those pharmaceuticals having both acidic and basic groups may also undergo changes in the charge and in their tertiary structure. This can be expected to have an impact on the oxidation rate. It is not possible, however, on the basis of the experiments carried out here, to draw any final conclusions regarding this.

Table 2 provides an overview of the findings regarding removal efficiencies for the pharmaceuticals that were investigated. It can readily be seen that an ozone dose of around 5 mg·ℓ⁻¹ is sufficient to remove over half of the target pharmaceuticals, except in the case of Effluent 2, in which a much higher ozone dose may be required for removing a large fraction of the pharmaceuticals, this most likely being due to the higher SUVA level of Effluent 2. At the same time, it appears that, in the case of wastewaters such as Effluent 3 that are low in pH and organic content, a reasonable dose of ozone to remove over 90% of the pharmaceuticals is around 5 mg·ℓ⁻¹.

The oxidation of pharmaceuticals may lead to the production of by- and transformation products. Since these can be toxic to varying degrees as compared with the mother compound, toxicity evaluation of a given technology should be performed before it is considered for implementation.

CONCLUSIONS

The following conclusions can be drawn on the basis of the results of the study:

- Ozonation can be employed as an additional treatment step to enable trace pharmaceuticals to be removed effectively from wastewater effluents.
- The amount of ozone required for the removal of pharmaceuticals is dependent upon the chemical composition of the wastewater and upon the target compounds, with the content of organic matter in general and its aromaticity being of considerable importance.
- Ozone decomposition can be stimulated by adding hydrogen peroxide at low pH. The addition of hydrogen peroxide has only a limited impact on the quantitative removal of pharmaceuticals. However, it reduces the treatment time and, accordingly, the reaction volume needed, which will be advantageous in practice.

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Appendix

Supplementary information: Removal of pharmaceuticals in WWTP effluents by ozone and hydrogen peroxide

TABLE S1 List of suppliers for pharmaceuticals and the corresponding internal standards used for quantification			
Pharmaceuticals	**Supplier**	**Internal standards**	**Supplier**
Amitryptiline	Sigma-Aldrich (Steinheim, Germany)	$^2H_6$ - Amitriptyline	Cambridge Isotope Laboratories (Andover, MA, USA)
Atracurium	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^2H_3$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Beclomethasone	Sigma-Aldrich (Steinheim, Germany)	$^2H_5$ - Oxazepam	Sigma-Aldrich (Steinheim, Germany)
Biperiden	Sigma-Aldrich (Steinheim, Germany)	$^2H_6$ - Amitriptyline	Cambridge Isotope Laboratories (Andover, MA, USA)
Bisoprolol	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^2H_3$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Bupropion	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^2H_3$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Carbamazepine	Sigma-Aldrich (Steinheim, Germany)	$^2H_{10}$ - Carbamazepine	Cambridge Isotope Laboratories (Andover, MA, USA)
Cilazapril	LGC Standards (Middlesex, UK)	$^{13}C^2H_3$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Citalopram	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^2H_3$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Clomipramine	Sigma-Aldrich (Steinheim, Germany)	$^2H_6$ - Amitriptyline	Cambridge Isotope Laboratories (Andover, MA, USA)
Codeine	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^2H_3$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Diclofenac	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^2H_3$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Diltiazem	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^2H_3$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Eprosartan	CHEMOS GmbH (Regenstauf, Germany)	$^2H_{10}$ - Carbamazepine	Cambridge Isotope Laboratories (Andover, MA, USA)
Ethinyl estradiol	Sigma-Aldrich (Steinheim, Germany)	$^{13}C_2$ - Ethinyl estradiol	Cambridge Isotope Laboratories (Andover, MA, USA)
Fexofenadine	Sigma-Aldrich (Steinheim, Germany)	$^2H_6$ - Amitriptyline	Cambridge Isotope Laboratories (Andover, MA, USA)
Fluconazole	Sigma-Aldrich (Steinheim, Germany)	$^{13}C_3$ - Trimethoprim	Cambridge Isotope Laboratories (Andover, MA, USA)
Fluoxetine	Sigma-Aldrich (Steinheim, Germany)	$^2H_5$ - Fluoxetine	Cambridge Isotope Laboratories (Andover, MA, USA)
Flutamide	Sigma-Aldrich (Steinheim, Germany)	$^2H_6$ - Amitriptyline	Cambridge Isotope Laboratories (Andover, MA, USA)
Haloperidol	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^2H_3$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Hydroxyzine	Sigma-Aldrich (Steinheim, Germany)	$^2H_6$ - Amitriptyline	Cambridge Isotope Laboratories (Andover, MA, USA)
Ibuprofen	Sigma-Aldrich (Steinheim, Germany)	$^{13}C_3$ - Ibuprofen	Cambridge Isotope Laboratories (Andover, MA, USA)
Irbesartan	CHEMOS GmbH (Regenstauf, Germany)	$^2H_6$ - Amitriptyline	Cambridge Isotope Laboratories (Andover, MA, USA)
Ketoprofen	Sigma-Aldrich (Steinheim, Germany)	$^{13}C_3\,^2H_3$ - Naproxen	Cambridge Isotope Laboratories (Andover, MA, USA)
Levonorgestrel	LGC Standards (Middlesex, UK)	$^{13}C_2$ – Ethinyl estradiol	Cambridge Isotope Laboratories (Andover, MA, USA)
Loperamide	Sigma-Aldrich (Steinheim, Germany)	$^2H_6$ - Amitriptyline	Cambridge Isotope Laboratories (Andover, MA, USA)
Maprotiline	Sigma-Aldrich (Steinheim, Germany)	$^2H_6$ - Amitriptyline	Cambridge Isotope Laboratories (Andover, MA, USA)
Memantine	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^2H_3$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Metoprolol	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^2H_3$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Naproxen	Sigma-Aldrich (Steinheim, Germany)	$^{13}C_3\,^2H_3$ - Naproxen	Cambridge Isotope Laboratories (Andover, MA, USA)
Orphenadrine	LGC Standards (Middlesex, UK)	$^2H_6$ - Amitriptyline	Cambridge Isotope Laboratories (Andover, MA, USA)
Oxazepam	Sigma-Aldrich (Steinheim, Germany)	$^2H_5$ - Oxazepam	Sigma-Aldrich (Steinheim, Germany)
Repaglinide	Sigma-Aldrich (Steinheim, Germany)	$^2H_6$ - Amitriptyline	Cambridge Isotope Laboratories (Andover, MA, USA)
Risperidone	LGC Standards (Middlesex, UK)	$^2H_4$ - Risperidone	Sigma-Aldrich (Steinheim, Germany)
Rosuvastatin	CHEMOS GmbH (Regenstauf, Germany)	$^{13}C^2H_3$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Sertraline	Sigma-Aldrich (Steinheim, Germany)	$^2H_6$ - Amitriptyline	Cambridge Isotope Laboratories (Andover, MA, USA)
Sulfamethoxazole	Sigma-Aldrich (Steinheim, Germany)	$^{13}C_6$ - Sulfamethoxazole	Cambridge Isotope Laboratories (Andover, MA, USA)
Tramadol	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^2H_3$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)
Trimethoprim	Sigma-Aldrich (Steinheim, Germany)	$^{13}C_3$ - Trimethoprim	Cambridge Isotope Laboratories (Andover, MA, USA)
Venlafaxine	Sigma-Aldrich (Steinheim, Germany)	$^{13}C^2H_3$ - Tramadol	Cambridge Isotope Laboratories (Andover, MA, USA)

TABLE S2 Ionization mode, recoveries, relative standard deviation (RSD) and limit of quantification (LOQ) of the pharmaceuticals				
Pharmaceuticals	Ionization mode	Recovery (average of triplicate) %	RSD %	LOQ ng·ℓ⁻¹
Amitryptiline	HESI	83.3	7.5	5
Atracurium	HESI	85.8	7.2	0.5
Beclomethasone	HESI	25.2	12.9	10
Biperiden	HESI	106	8.4	0.1
Bisoprolol	HESI	83.1	5.1	0.1
Bupropion	HESI	96.3	4.7	0.1
Carbamazepine	HESI	101	15.1	1
Cilazapril	HESI	143	5.9	1
Citalopram	HESI	83.6	8.5	5
Clomipramine	HESI	72.7	11.4	0.5
Codeine	HESI	86.7	24.0	0.5
Diclofenac	HESI	42.1	4.4	10
Diltiazem	HESI	107	3.8	0.5
Eprosartan	HESI	62.3	4.3	5
Ethinyl estradiol	APPI	85.7	4.1	10
Fexofenadine	HESI	81.1	7.1	5
Fluconazole	HESI	89.8	12.9	0.5
Fluoxetine	HESI	97.0	11.4	5
Flutamide	HESI	91.8	3.9	5
Haloperidole	HESI	64.0	12.7	0.1
Hydroxyzine	HESI	94.5	14.2	0.5
Ibuprofen	APPI	62.4	7.4	10
Irbesartan	HESI	109	2.6	0.5
Ketoprofen	APPI	73.2	7.4	10
Levonorgestrel	APPI	99.5	3.0	10
Loperamide	HESI	61.6	15.7	0.5
Maprotiline	HESI	84.1	7.4	5
Memantine	HESI	85.7	7.7	0.5
Metoprolol	HESI	82.9	1.3	5
Naproxen	APPI	95.5	4.5	10
Orphenadrine	HESI	94.7	11.2	0.1
Oxazepam	HESI	97.4	1.1	5
Repaglinide	HESI	93.4	8.6	0.5
Risperidone	HESI	101	2.4	0.1
Rosuvastatin	HESI	147	6.4	10
Sertraline	HESI	71.2	16.5	10
Sulfamethoxazole	HESI	97.3	4.3	5
Tramadol	HESI	129	6.3	0.5
Trimethoprim	HESI	109	10.7	0.1
Venlafaxine	HESI	96.2	7.8	0.5