Removal and transformation products of ibuprofen obtained during ozone- and ultrasound-based oxidative treatment

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Abstract

The oxidation of ibuprofen (IBP) in water was evaluated using oxidative treatments: ozonation, sonication, hydrogen peroxide addition and combinations of these processes. After 20 minutes of treatment, ozone coupled with hydrogen peroxide at pH 7, 15ºC, an ozone dose of 16 mg/L and a hydrogen peroxide concentration of 7.1 mg/L was found to have the highest IBP (95%) and COD (41%) removals. A synergistic effect was observed for the combined ozonation/sonication process, which might be explained by an improved mass transfer of ozone in the solution due to the presence of ultrasonic pressure waves. Transformation products were detected in the treated solutions. The nature of 5 of these products was confirmed by LC-MS, including 4-isobutylacetophenone (4-IBAP), oxo-ibuprofen, 4-acetylbenzoic acid, 4-ethybenzaldehyde and oxalic acid. In addition, COD analyses for each experiment showed that the ratio of %COD removal to %IBP removal was highest with sonication; suggesting that this oxidative process offers other mechanisms of removal which may lead to further degradation of products formed. This study presents the first data on removal of IBP by sonication coupled to ozonation and provides some insight into the potential of this combined treatment approach for the removal of contaminants of emerging concern.

Keywords: ibuprofen, hydrogen peroxide, ozonation, sonication, transformation products

1 Introduction

The presence of pharmaceuticals in water has concerned the scientific community for a few decades and pharmaceutical consumption has been increasing across all OECD countries in terms of volume and quantity (OECD 2011). The human body metabolises only a portion of these pharmaceuticals, which are then excreted either unchanged or transformed into metabolites with very similar structures to their parent compound. These drugs thus make their way into the sewage treatment systems and then into the aquatic environment if not efficiently removed during wastewater treatment.

Ibuprofen (IBP), a widely used non-steroidal anti-inflammatory drug (NSAID), is a good example of this type of pharmaceutical. Its consumption is very high in many countries (Hudec et al. 2008) and is one the most commonly used analgesics for pain in children (Smith and Goldman 2012), resulting in significant amounts being released into the sewage treatment systems every year. Due to its low removal during conventional wastewater treatment (Gagnon and Lajeunesse 2008), IBP is continuously discharged into receiving water bodies along with treated wastewater. For example, IBP was detected at a concentration of 7.86 ng/L in the primary effluent from a wastewater treatment plant in Montreal, Quebec, Canada (Gagnon and Lajeunesse 2008). This is of concern as ibuprofen has been shown to have pharmacological effects on aquatic fauna (Brown et al. 2007; Boxall et al. 2014).

Previous research on removal of IBP has shown that oxidative processes such as ozonation and sonication can only partially degrade IBP. Only low removals of IBP and chemical oxygen demand (COD) were obtained; 12% IBP removal with ozonation (Zwiener and Frimmel 2000) and 8% COD removal with sonication (Méndez-Arriaga et al. 2008). During degradation of IBP, transformation products are formed and one product previously identified, 4-IBAP, was found toxic (Miranda et al. 1991). Caviglioli et al. (2002) reported oxidation products of IBP and products such as 4-IBAP have been detected at a concentration of 540 ± 40 mg/L at the influent of a sewage treatment plant in Sweden (Zorita et al. 2009).

Studies conducted on the removal of contaminants using sonication coupled with ozonation have been performed on reactive dyes (Ince and Tezcanlí 2001; He et al. 2007; Song et al. 2007), p-nitrotoluene (Ince and Tezcanlí 2001; He et al. 2007; Song et al. 2007) and tetracycline (Wang et al. 2012) but no work has been done on the removal of IBP using sonication coupled to ozonation. Studies on reactive dye showed a better efficiency when combining ozone with sonication than using ozonation or sonication alone (Ince and Tezcanlí 2001; He et al. 2007; Song et al. 2007). Further, the removal efficiency of both p-nitrotoluene and total organic compound (TOC) was significantly higher with simultaneous treatments compared to separate treatment (Song et al. 2007). The potential benefit of combining these processes relates to the pressure waves induced by sonication, which, in addition to forming hydroxyl (OH) radicals, might increase the rate of ozone transfer into the water (Destaillats et al. 2000; Weavers et al. 2000) and improved mass-transfer rate of ozone (Wang et al. 2012). An increased power applied to the system might also increase the removal of the compound of interest through the formation of hydrogen peroxide, as observed by Méndez-Arriaga et al. (2008). The nature of the transformation products of IBP that might be formed using this combined-process approach has yet to be determined.

This study presents a comparison of different oxidative processes, sonication, ozonation and reaction with hydrogen peroxide, used separately or in combination, to remove ibuprofen and

minimize the formation of potentially toxic transformation products. Considering that previous studies (He et al. 2007; Song et al. 2007; Méndez-Arriaga et al. 2008; Wang et al. 2012) have reported that operating parameters such as pH, temperature, ultrasonic power and the addition of hydrogen peroxide can influence the removal of aqueous contaminants during these oxidative treatments, the impact of these parameters, over a range of conditions encountered in wastewater treatment and in literature, was studied. The nature of the transformation products formed was also investigated.

2 Materials and Methods

2.1 Chemicals

Ibuprofen (IBP) sodium hydroxide, sodium sulfite, hydrogen peroxide, 4-acetylbenzoic acid, 4-ethybenzaldehyde and oxalic acid were obtained from Sigma-Aldrich Canada. Oxo-ibuprofen was obtained from Santa Cruz Biotechnology Inc. 4-isobutylacetophenone (4-IBAP) was obtained from TCI America. Stock solutions of 100 mg IBP/L (0.5 mM) were prepared in reverse osmosis water. For each experiment, the stock solution was diluted in reverse osmosis water to a concentration of 5 mg/L. This concentration was selected for ease of analysis and is considered representative of the IBP concentrations observed in the first-wash water of vessels used in the manufacturing of IBP-containing tablets, where such oxidative treatments might be applied.

2.2 Experimental plan

Different oxidative treatments, listed in Table 1 with their range of operating parameters, were studied. The five oxidative treatments considered include, ozonation (O_3), sonication (US) and the addition of hydrogen peroxide to ozone or ultrasound (O_3/H_2O_2, US/H_2O_2), and the combination of ozonation and sonication (US/O_3). The ranges of the operating parameters, summarized in Table 1, were based on values commonly found in literature. In addition, knowing that ozone solubility increase at low temperatures, impact of the solubility of ozone on the removal was evaluated using a low temperature of 5°C. The treatment performance criteria were based on the percentage of removal of IBP and COD determined for each set of conditions studied tested using triplicates.

Table 1: Parameters studied for each oxidative treatment

Oxidative treatment	Ozone dose (mg/L)	pH	Temperature (ºC)	Power to ultrasonic reactor (W)	Addition of Hydrogen peroxide
O_3	8, 12, 16	5, 7, 9	5, 15, 25	*NA*	2, 4.5 and 8 mg/L (1.2 mL/min added at different molarity to obtain 25, 35, 45 wt%, $H_2O_2/0_3$)
US	*NA*	4, 7	5, 15, 25	5.0	3.5, 8, 16, 24, 50 mg/L
US/O_3	8, 16	4, 7	5, 15, 25	5.0	*NA*

2.3 Reactor setup

A semi-continuous 900-mL jacketed glass reactor was designed and built in order to perform ozonation and sonication experiments under controlled conditions (resonance frequency of 241

kHz, power 0 to 5 watts, ozone dose 8, 12 and 16 mg/L, temperature 5, 15 and 25°C). The piezoelectric disk (piezotransducer BM400, Sensortech inc.) was connected to an electrical system composed of a transformer, an amplifier (Amplifier Research #75A250) and a function generator (RACAL-DANA model F64). The design allowed the operation using oxidative modes separately or simultaneously (sonication/ozonation), with an ozone injection done through a porous stainless steel ring (Mott Corporation, 2µm) placed at the bottom of the reactor around the piezotransducer disk. The reactor was covered with a loosely fitted lid to avoid pressure build-up in the reactor. An OZO-4VTT generator (Ozomax, Granby, Qc, Canada) was used to generate the ozone containing gas. Figure 1 illustrates the setup used for this project.

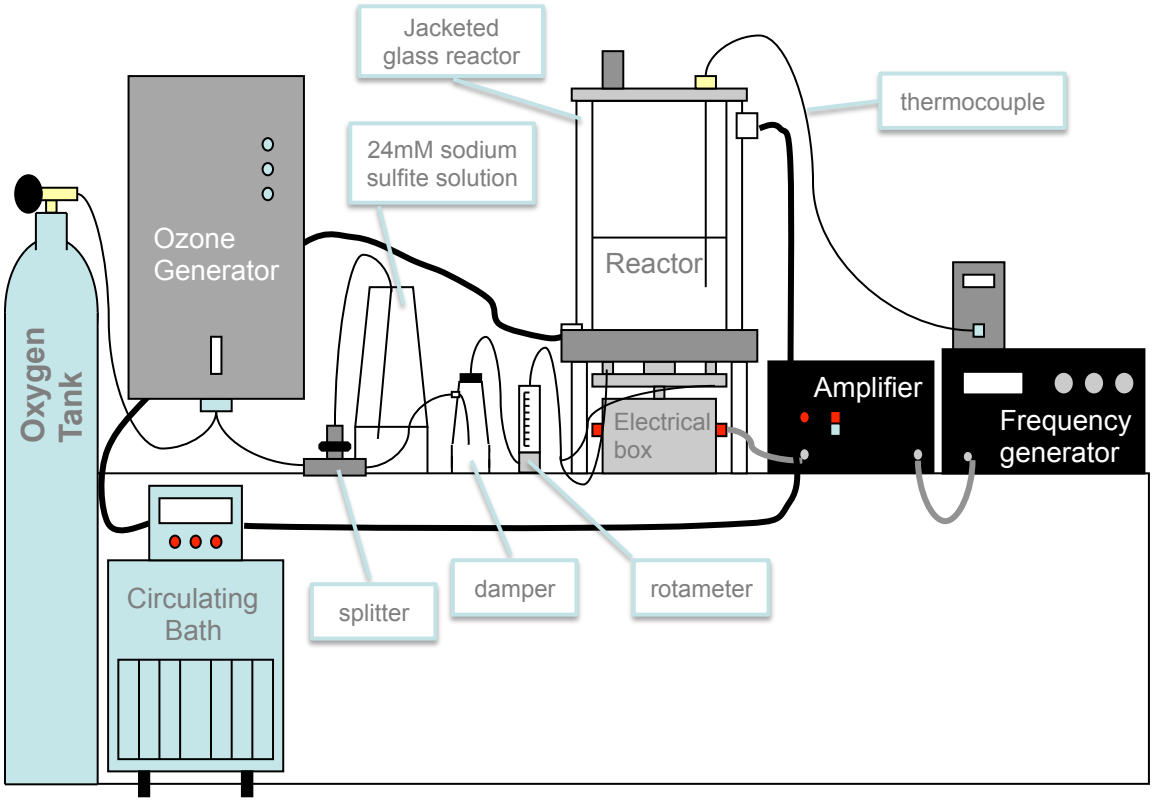

Figure 1: Schematic of the setup used.

2.4 Ozonation and Ozonation with hydrogen peroxide procedure

Ozone experiments were performed using 300 mL of 5 ppm IBP solution. A 5-mL sample was taken after transfer of the solution into the reactor (considered as time 0) and subsequently after 10 and 20 minutes of ozonation, which corresponds to ozone doses of 8 and 16 mg/L, respectively. An oxydo-reduction titration based on sodium thiosulfate and potassium iodide (KI) (*standard method #22350E*) was performed to calculate the ozone flowing in and out of the reactor. The difference in these ozone values represented the corresponding ozone doses transferred. For experiments in presence of hydrogen peroxide, a peristaltic pump (Cole Palmer, Model: Masterflex L/S) was used to continuously feed the hydrogen peroxide solution at a rate of 1.2 mL/min to the reactor. In order to maintain the total volume constant in all experiments, the different doses of H_2O_2 were obtained by adding solutions of different molarities (0.016 to 0.029 v%). The three levels

tested corresponded to H_2O_2:O_3 ratios of 25wt%, 35wt% or 45wt% (2, 4.5 and 8 mg/L, respectively). A propeller-mixer was also used to ensure good dispersion of the hydrogen peroxide.

2.5 Sonication and Sonication with hydrogen peroxide procedure

Sonication experiments were performed using 300 mL of 5 ppm IBP solution. A 5-mL sample was taken initially and after 10 and 20 minutes of sonication. The frequency was set to 241.4 kHz and was readjusted right after the sampling at 10 minutes to 243.6 kHz. This readjustment was necessary in order to maintain a good match with the resonance frequency of the system, which varied slightly due to the decreased volume of liquid in the reactor following sampling. Experiments done to determine the effect of hydrogen peroxide with sonication were performed using the same method as the one described above for ozonation. The power transmitted to the water was calculated using a calorimetric method (Mason et al. 1992). The power obtained was 5W, which was close to the power applied to the system because of the good impedance match. For a volume of solution of 300 mL contained in the reactor, the resistance of the system was measured to be 80+6j ohm using an Agilent Vector Network Analysis.

2.6 Ozonation coupled to sonication procedure

This series of experiments was also performed with 300-mL of 5 ppm IBP solution. The procedures described in the previous two sections were used in combination for these experiments.

2.7 Analytical techniques

Samples collected were filtered using 0.22 µm syringe filters prior to analysis. The COD was measured using a HACH Digital Reactor Block (DRB 200) and a HACH spectrophotometer DR/2500 as an indication of the degree of organic content removal. The concentration of IBP was monitored by HPLC (Agilent 1200) equipped with a variable wavelength detector and a Zorbax Eclipse XDB-C18 (4.6mm X 250mm, 5µM) column. Eluents consisted of methanol, water and 20mM ammonium acetate buffer adjusted to pH 3 with formic acid. IBP and its degradation products were monitored 220 and 254 nm, respectively. Solutions of 15µL were injected into the column. The flow rate was set to 0.7 mL/min and run time was 30 min. Initial eluent ratio was 60% methanol, 3% buffer solution and 37% water. Each 2 min, ratio of methanol was increased by 7% at the expense of water up to 10 min where a concentration of 95% methanol was reached. This ratio was kept for the last 20 minutes. Column temperature was maintained at 40°C. The transformation products detected were collected based on their retention time using a fraction collector coupled to the HPLC-UV mentioned above. Identification of the transformation products was performed by liquid chromatography (LC) coupled to mass spectrometry (MS) using a QTRAP 5500 from AB Sciex Instruments. Fractions collected were analyzed in both negative and positive modes and the nature of the transformation products detected was confirmed by comparison with the spectra of standards of compounds previously reported in literature as potential transformation products of IBP (Caviglioli et al. 2002).

3 Results and discussion

3.1 Effect of pH on IBP removal

IBP removal values were obtained at different pH levels (adjusted using NaOH) for different treatment types and operating conditions in order to determine an optimal initial pH. Figure 2 summarizes the results obtained. For ozonation, the increasing removal obtained with increasing pH is in agreement with results reported by Oh et al. (2007). They reported removals of IBP of 95% IBP at pH 7 and 10% IBP at pH 5 with an ozone dose of 0.4 mg/L, a temperature of 12ºC and an initial IBP concentration of 10µM (2 mg/L). The lower initial concentration might explain the higher level of removal obtained in Oh et al. (2007) study. For sonication, an opposite trend was observed resulting in lower removal levels at higher pH. This can be explained considering the pK_A value of IBP of 4.9. When the pH of 4.0 is used, the pH is lower than the pK_A, making IBP more hydrophobic. It is hypothesized that the removal is increased because at low pH IBP tends to accumulate near to the cavitation bubbles, where the OH radical concentration is highest as demonstrated by Méndez-Arriaga et al. (2008). For the combined treatment sonication/ozonation, the effect of pH followed the trend observed during ozonation; that is increased removal at higher pH. Considering the limited benefit in using alkaline pH for the combined treatment and the fact that wastewater is often at neutral pH, it was decided to compare the efficiency of the various treatments at neutral pH.

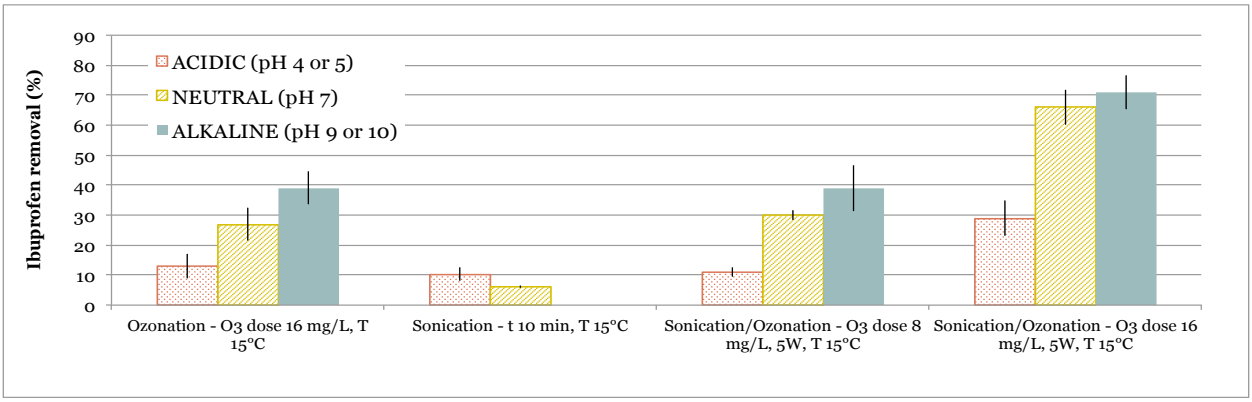

Figure 2: Removal of IBP obtained at varied pH for the studied oxidative treatments. Error bars represent one standard deviation of n=3.

3.2 Effect of temperature on IBP removal

IBP removal values were obtained at different temperatures (adjusted by circulating a fluid in the jacket of the reactor) for different treatment types and operating conditions in order to determine the effect of temperature on the efficiency of treatment. Figure 3 summarizes the results obtained. In all conditions tested, higher temperature had a positive effect on removal. These results indicate that the kinetics of the reaction plays a major role during treatment and has more impact than the solubility of ozone, which increases at lower temperature and might have enhanced the removal at lower temperatures (tested at T=5˚C). For ozonation, the activation energy was determined, based on a second-order rate constant model, to be 79 kJ/mol with an Arrhenius constant of $4x10^{13}s^{-1}$. The activation energy obtained by Huber et al. (2003) for the degradation of IBP by ozonation was slightly lower, 57 ± 8 kJ/mol. For ozonation coupled to sonication, an activation energy of 82 kJ/mol and an Arrhenius constant of $2.7x10^{12}s^{-1}$ was calculated. These values are similar to the

values calculated for ozone alone, suggesting that the combined system is not affected differently by changes in temperature in the range of temperature studied. It was thus decided to compare the efficiency of the various treatments at a temperature of 15˚C, the average temperature of the typical water to be treated.

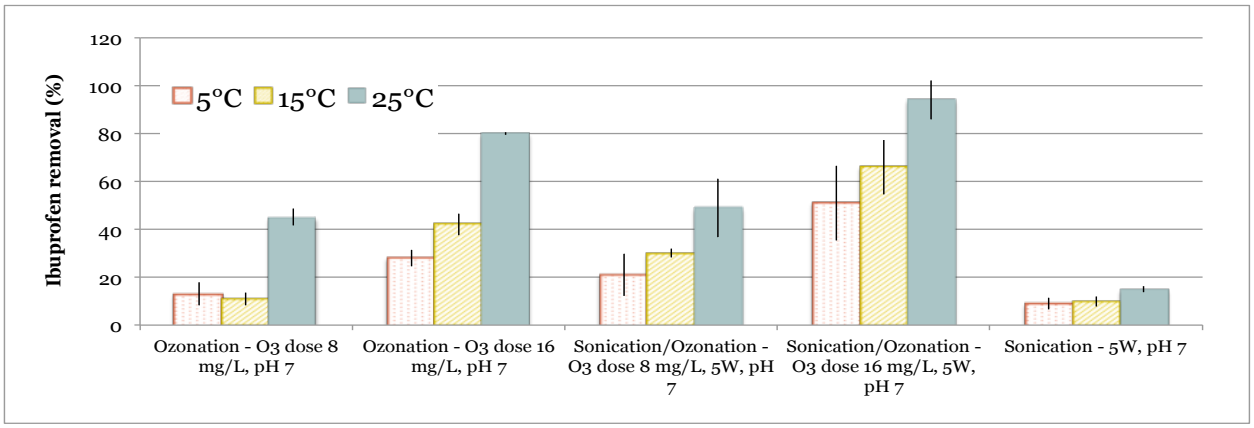

Figure 3: Removal of IBP obtained at varied temperature for the studied oxidative treatments. Error bars represent one standard deviation of n=3.

3.3 Effect of H_2O_2 dose on IBP removal

IBP removal values were obtained at different doses of hydrogen peroxide for different treatment types and operating conditions in order to determine its effect on the efficiency of treatment. Figure 4 summarizes the results obtained. Knowing that IBP is more reactive towards hydroxyl radicals (Wert et al. 2009), different hydrogen peroxide concentrations were used to treat the 5-ppm IBP solution at pH 7, 15˚C and exposed to sonication (5W) for 20 minutes. Results presented in Figure 4 indicate that the presence of hydrogen peroxide did not have a significant effect on IBP removal during sonication even when the hydrogen peroxide concentration was increased up to 50 mg/L. This is alignment with trends reported by (Patil et al. 2014) for the degradation of imidacloprid during sonochemical degradation in presence of varying hydrogen peroxide.

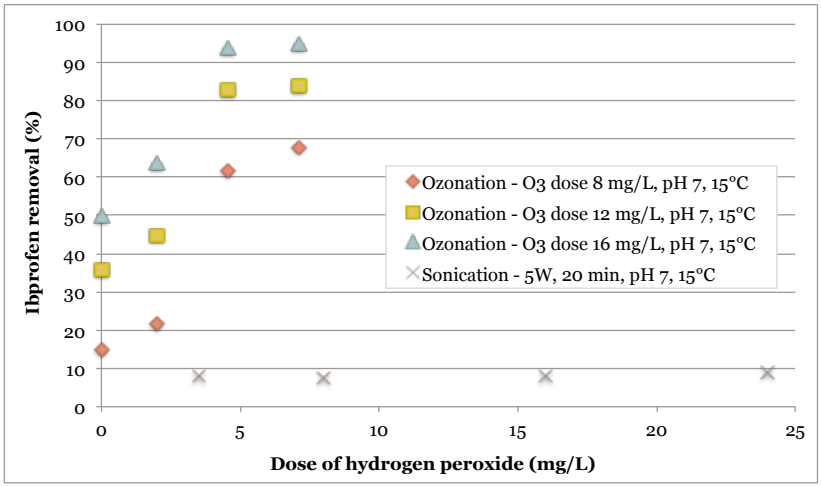

Figure 4: Removal of IBP obtained at varied doses of H_2O_2 for the studied oxidative treatments.

These results suggest that no significant increase in hydroxyl radical formation was obtained or that hydrogen peroxide acted as a radical scavenger, as previous observed in other studies (Behnajady et al. 2008). On the contrary, ozonation experiments conducted with the addition of hydrogen peroxide showed a significant increase in ibuprofen removal for all the mass ratios of the flow rates of H_2O_2 to O_3 tested. For ozonation, an optimal dose of 4.5 mg/L (ratio of about 35wt% H_2O_2/O_3) was observed considering that further increases in the dose to 45% had limited impact on removal of IBP. These results are similar to the data obtained by Huber et al. (2003) when pharmaceuticals were added to a glass bottle containing hydrogen peroxide. At a concentration of hydrogen peroxide corresponding to 35% of the ozone concentration (ozone dose of 2 mg/L, 10ºC and a pH of 8), they observed an increase in ibuprofen removal from 40% to 80%, while we observed increase in removal from 36% to 83% using a the rate ratio of hydrogen peroxide flow rate to ozone flow.

3.4 Comparison of the oxidative treatments

The optimal operating parameters for better IBP removal were sometimes different for the various oxidative treatments studied. This indicates that various removal mechanisms were in action and suggests that different transformation products were possibly formed. In order to compare the efficiencies of the treatments, experiments were conducted using the operating parameters selected based on the results presented in the previous sections, which are: 20 minutes of sonication, 16 mg O_3/L and 7.1 mg H_2O_2/L and treatment conditions most representative of those encountered in wastewater treatment, ie. neutral pH and 15°C. The COD and IBP removals obtained for each of these treatments are presented in Figure 5.

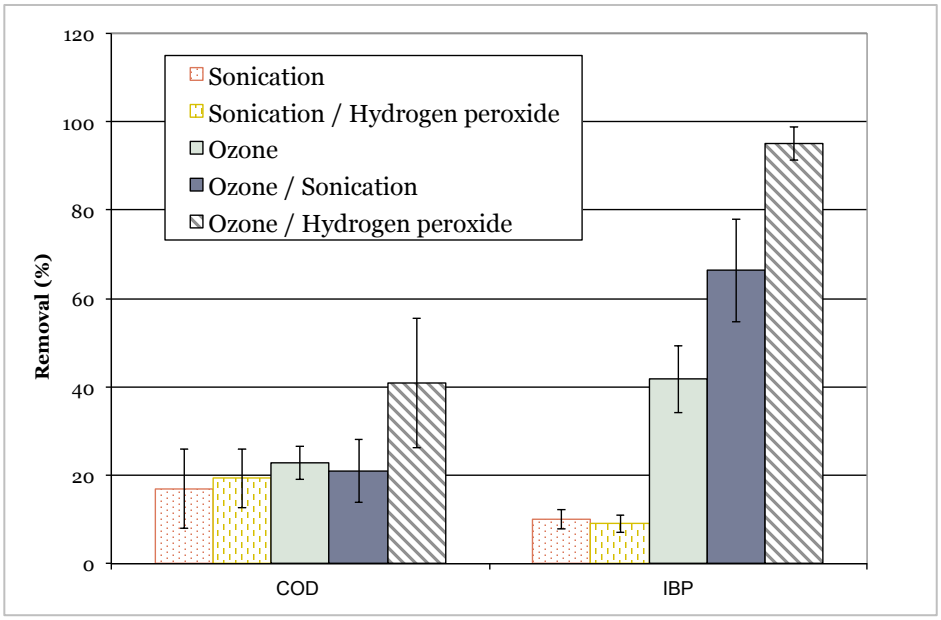

Figure 5: Comparison of COD and IBP removals obtained after 20 minutes of treatment performed at neutral pH, 15°C and when relevant, 16 mg O_3/L and 7.1 mg H_2O_2/L. Error bars represent one standard deviation of n=3.

Interestingly, similar COD removals were obtained for all oxidative treatments tested, expect when hydrogen peroxide was coupled with ozonation. This approach led to an almost doubled COD

removal and the highest removal of IBP. A possible explanation might be due to the effects of a higher amount of OH radicals, which are less selective, and are known to be formed under these conditions (Huber et al. 2003). The formation of these hydroxyl radicals can contribute to the removal of transformation products that might be less reactive towards ozone.

The ozonation and ozonation/sonication experiments had similar COD removals while ozonation/sonication had higher IBP removals. It is possible that the amount of OH radicals was higher with ozonation/sonication, but not enough to degrade the transformation products formed. It was also interesting to note that the IBP removal obtained during the combined treatment (ozonation/sonication) experiments (66%) was significantly higher than the sum of the removals obtained by ozonation (41%) and sonication (10%) performed separately. This observation suggests a synergistic effect between the two oxidative approaches. In literature, n o synergy was observed for the treatment of compounds highly reactive towards ozone (Weavers et al. 2010) but in other cases, synergistic effects were reported (Destaillats et al. 2000, Wang et al. 2012). It is hypothesize that sonication coupled to ozonation improves mass transfer and enhances contact between the oxidative species formed during treatment and IBP present in solution might, explaining this synergetic phenomenon. The higher IBP removal obtained with the combined treatment might be due to a higher ozone gas diffusion coefficient and/or possible hydrogen peroxide formation, known to be formed during sonication at a certain power level (Méndez-Arriaga et al. 2008). A test based on molybdate salt as a H_2O_2 indicator and absorbance at 350nm in a UV-spectrometer (Chai et al. 2004) was used to determine if a significant amount of hydrogen peroxide was formed at the power level used. Under the conditions tested here, no H_2O_2 was observed suggesting that the increase in the ozone diffusion coefficient contributed the most to the higher IBP removal using the combined treatment approach. Also, previous results indicated that ozonation alone is more efficient when IBP is in its anionic state (IBP^-) (Huber et al. 2003) while sonication allows a better removal when IBP is not in its anionic state. The experiments presented in Figure 5 were performed at a pH level of 7 so it is probable that there was a certain amount of IBP^- and IBP in the solution because of the proximity to its pKa value (4.9). This might have also contributed to the synergistic effect observed for the process combining ozonation and sonication.

3.5 Comparison of the degradation products formed during the different treatments

During HPLC analysis, several transformation products were observed as new peaks on the chromatogram of the samples collected after treatment using the oxidative methods and operating conditions described in section 3.4. Figure 6 shows superposed chromatograms, one for each oxidative method tested. Some similarities were noted between the retention times of new peaks observed, suggesting that some common products were formed. Products were then labelled I to VIII, as presented of Figure 6 and according to their retention times. The products were detected at a wavelength of 254 nm with the exception of product VI and I, which were detected at 220 nm.

The most abundant product formed (based on the peak area) was Product VI, and was common to all oxidative treatments, except sonication used alone. However differences were observed between treatments in terms of the abundance (based on peak area) and nature (based on retention time) of the transformation products formed. Some transformation products such as products I, III, IV were more abundant (observed by higher peak areas) for ozonation-based than for the sonication-based treatments. This suggests that the use of ultrasounds either prevents the formation of these products or enhance their further degradation into other products.

The nature of transformation products of IBP formed during ozonation and sonication has not been reported before. However, some transformation products of IBP were reported in literature for other oxidative treatments such as treatment using heat, hydrogen peroxide, $KMnO_4$ and $K_2Cr_2O_7$ (Caviglioli et al. 2002; Skoumal et al. 2009). These previously reported oxidative transformation products were considered as potential products formed and standards of these compounds were used for comparison in HPLC-MS analysis and confirmation of the nature of products detected by comparison of the MS spectra. Transformation products I, II, III, IV, VI, VII and VIII, shown on Figure 6, were produced in amounts large enough to be collected in vials using a fraction collector installed on the HPLC for further analysis by HPLC-MS.

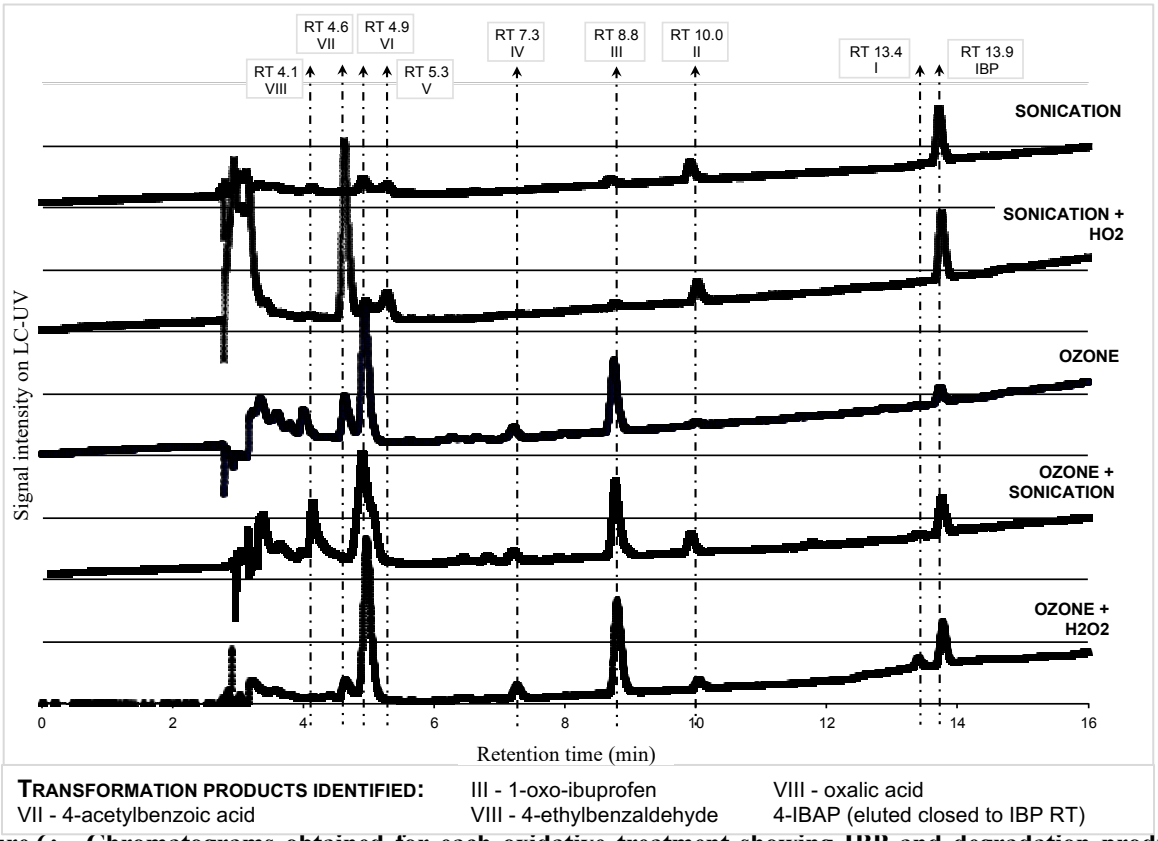

Figure 6: Chromatograms obtained for each oxidative treatment showing IBP and degradation products detected at 254 nm and 220 nm (products I and VI).

Product III collected at a retention time of 8.8 was shown to have the same retention time and a similar MS spectral to that of oxo-ibuprofen (O-IBP, 2-(4-isobutyrylphenyl)propionic acid). Product VII collected at a retention time of 4.6 had a similar MS spectral to that of 4-acetylbenzoic acid, Product VIII collected at a retention time of 4.1 min is suspected to contain two products that eluted at the same time, namely 4-ethylbenzaldehyde and oxalic acid. Products III, VII and VIII: 4-ethylbenzaldehyde were also reported to be formed during thermal or oxidative treatment ($KMnO_4$, H_2O_2 or $K_2Cr_2O_7$) of IBP (Caviglioli et al. 2002). Some of these, products, 4-ethylbenzaldehyde and oxalic acid (product VIII) were also reported to be formed during electrochemical advanced oxidation processes (Skoumal et al. 2009). The other peaks (I, II, IV, VI) did not correspond to previously reported transformation products of IBP and their identification requires tandem mass spectrometry and the use of label surrogates treated the same way in order to elucidate their respective structures. Due to the toxic nature of the product 4-IBAP,

a transformation product of IBP previously reported in literature for oxidation of IBP by NaOH (Caviglioli et al. 2002), the treated solutions were analyzed for this product. Analysis of a standard of 4-IBAP indicated that for the chromatography method used, the retention of this compound was very similar to that of IBP. An additional fraction was then collected at that retention time and analyzed by mass spectrometry. The results revealed a MS spectrum comparable to the one of 4-IBAP, confirming the formation of this transformation product during all the oxidative treatments studied. The transformation products that were successfully identified are listed on Figure 6. These results suggest the potential formation of toxic products. Considering that Wang et al. (2012) reported that the acute toxicity of a tetracylcine solution treated by ozonation combined with ultrasound reached a maximum after 10 min treatment and then gradually decreased with the prolonging reaction time, further investigation of these products as a function of treatment time is recommended.

Conclusions

This study is the first one presenting results on the removal of IBP using ozonation coupled with sonication. All parameters studied, ozone dose, pH, temperature, power to ultrasonic device and addition of hydrogen peroxide, influenced the potential of the oxidation processes studied to remove IBP. Performances obtained for ozonation, ozonation/H_2O_2 and ozonation/sonication were higher at increased pH, temperature and ozone dose while sonication performance was increased at lower pH. At the ultrasonic power studied, no measurable amount of hydrogen peroxide was formed during sonication. Further, the primary mechanism of action leading to an increased performance and synergistic effect using the combined process (ozonation/sonication) was hypothesized to be due to improved mass transfer of ozone in the solution. However, for the compound selected, the optimal performance was obtained using ozonation/hydrogen peroxide. This trend might however not apply to all contaminants and further testing using a suite of indicator compounds would be required. Five of the transformation products formed during removal of IBP by ozonation, ozonation/H_2O_2, sonication and ozonation/sonication were identified as 1-oxo-ibuprofen, oxalic acid, 4-acetylbenzoic acid, 4-ethylbenzaldehyde and 4-IBAP. This confirms the potential formation of toxic products such as 4-IBAP and potentially others considering that the nature of many of the transformation products detected could not be elucidated. Further analysis is thus required to fully assess the performance of these treatments for the removal of a wider range of contaminants, and considering changes in residual toxicity as a selection criterion in addition to percentage of removal of the contaminants.

Acknowledgements

We gratefully acknowledge funding from the Natural Sciences and Engineering Council (NSERC) of Canada through a Discovery Grant to V. Yargeau. We also thank Eugenie Ulmer Lamothe Fund for the scholarship awarded to F. Danylo.

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