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Degradation of acetaminophen and amoxicillin by ultrasound: a study of their decomposition in water.

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Abstract: Wastewater contains pesticides, aromatic hydrocarbons, chlorinated compounds, as well as metabolized and disposed pharmaceuticals. The concentration of these contaminants in waste and fresh water is projected to grow. Acetaminophen and amoxicillin are among the most abundant, with concentrations range from ng to mg per liter. Sonication coupled with other advanced oxidation processes is a way to degrade these pollutants. However, the effect of ultrasound not coupled with other processes has not been very reported. Here, we report a study of the degradation of acetaminophen and amoxicillin only by ultrasound (US). Interestingly, sonication power output, continuous vs. pulsed ultrasound and starting concentration, result in different degradation pathways, as well as the simultaneous presence of the two molecules reduces the degradation yield. Hydroquinone and hydroxyl-hydroquinone has been recognized as acetaminophen by-products, as well as 4 by-products deriving from amoxicillin. We proposed a degradation pathway mechanism based on LC-MS data and we finally regressed the amoxicillin degradation kinetics as a function of the ultrasonic power.

Introduction

EPA (Environment Protection Agency) set legal limits on 90 contaminants in drinking water [1]. Surface water and groundwater may contain pesticides [2], polycyclic aromatic hydrocarbons (PAHs), polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs), as well as uncategorized compounds coming from personal care products, and pharmaceuticals [3]. Several among them are still unknown or classified as emerging contaminants (EC) [4]. ECs are constantly growing in concentration and number [5]; sucralose, perfluorinated compounds, benzotriazoles and benzothiazoles are among the most recently detected [6] [7]. Specifically, consumption of antibiotic drugs increased by 35 % between 2000 and 2010 [8]. A further increase is likely because of the growing world population and its longer life expectation. The global pharmaceutical drugs consumption is about 1 ton/year [9]. 3000 different substances are used as pharmaceutical ingredients, and they can be found in surface, ground and wastewater [10]. An underestimated consequence of the presence of antibiotic molecules in water is the antimicrobial resistance [11], which will

make established antibiotic ineffective in the long term. Moreover, antibiotics affect the food chain in the aquatic ecosystem [12].

Acetaminophen (APAP) is an acetanilide antipyretic drug, detected in municipal wastewater treatment plants effluents [13]. The global acetaminophen market was around 800 million USD in 2014. The world production is highly concentrated in China and India; the two countries occupy about 85.6 % of the global production in 2015. The worldwide market for Acetaminophen is expected to grow at a CAGR (Compound Annual Growth Rate) of 0.9% over the next five years, will reach 780 million US$ in 2024, from 740 million US$ in 2019 [14] [15]. In 2014 the demand for acetaminophen was the highest in North America, accounting for 40 % of the market share.

Concentrations range from ng to mg per liter [16], and even trace levels present an environmental risk [17]. Moreover, APAP is a Persistent Organic Pollutant (POP), due to its decomposition resistance [18].

Amoxicillin (AMO) is a β-lactam antibiotic for the treatment of many different types of bacterial infections. As ECs, it was detected in sewage treatment plants [19], effluents [20] and surface water [21]. More than 80 % of AMO assumed as drug is released unmodified into the environment [22]. It has been demonstrated that amoxicillin also affected the microbial community and the spread mechanism of antibiotic resistance genes [23].

Advanced oxidation processes and catalytic oxidations are able to degrade acetaminophen and amoxicillin, as already reported. For example, Andreozzi et al. report APAP ozonation obtaining 40 % degradation of the pollutant in 2 hr [24]. Tao et al. degraded 96 % of APAP under UV light in 3 hr by TiO_2 nanotubes and graphene nanocomposites [25], while Ma et al. completely degraded APAP in 50 min under visible light over Ag/AgBr nanoparticles [13]. Again, Zhang et al. reported that a commercial zero valent aluminum under acidic conditions has an excellent capacity to remove aqueous organic compounds, including acetaminophen [26].

Also AMO can be degraded as a consequence of several treatments. For example, AMO ozonation converts 90 % of the substrate with a total organic carbon (TOC) removal of 18 % in 20 min [27]. Elmolla et al. reported the complete degradation of AMO (104 mg L^{-1}) by photo-Fenton process [28], while TiO_2 UV photocatalysis was able to degrade 50% of AMO in 300 min [29]. More recently, Li et al. [30] investigated the amoxicillin oxidation

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process by a UV-Fe^{3+}(EDTA)/H$_2$O$_2$ system and obtained 100% amoxicillin degradation.

Despite the hybrid advanced oxidation systems are very promising option for drugs removal, they often require addition of chemicals and thus the downstream separation of the reagents. On the contrary, ultrasonication does not require any addition of chemicals, as it is the opposite case for catalytic ozonation, Fenton reactions or photocatalytic processes.

Ultrasound (US) consists of mechanical waves of frequency higher than 20 kHz. When passing through a liquid, ultrasound creates a series of compression and expansion cycles that form cavitation bubbles [31]. The bubbles become unstable when they reach a maximum radius and they collapse generating localized hot spots with temperatures up to several thousand Kelvin, depending on operating conditions. Temperatures around 5000 K, and pressures of approximately 10 MPa produce hydroxyl radicals (●OH) due to thermal dissociation of water [32]. ●OH free radicals unselectively react with organic and inorganic molecules [33]. Many papers report US assisted degradation of either drugs or pollutants in general, or for disinfection purposes in water [34]. For example, Jawale et al. treated wastewater containing potassium ferrocyanide combining US with H$_2$O$_2$, TiO$_2$ and ozone, obtaining a strong synergistic effect and 92 % pollutant removal [35]. Sutar et al. reported the degradation of ciprofloxacin hydrochloride by laccase and US [36], showing that ultrasonication in the presence of stirring increased the degradation of ciprofloxacin hydrochloride from 8 % to 50 %. They also applied US to degrade diclofenac sodium in the presence of enzymes and degraded up to 96 % pollutant [37].

Meroni et al. sonophotocatalytically degraded over 80% diclofenac in drinking water using a micro-metric TiO$_2$ catalyst [38]. Schieppati et al. implemented a sonophotocatalytic degradation of an herbicidal pollutant and degraded 100% of it in about 3 h [39]. Khani et al. reported the sonophotocatalytic degradation of APAP and AMO over Mn-TiO$_2$ systems with tuned band-gap and reached over 25% and 50 % conversion, respectively, under UV light [40].

Only one recent paper reported the oxidation of AMO based on US and ozone [41]: the authors treated AMO by medium-high frequency US irradiation and/or ozonation; they applied ultrasonic power at 75 W, changing the frequency and obtaining a maximum AMO removal of 99 %, but with 10 % of mineralization only.

However, data about the application of US alone to degrade and mineralize aromatics in water are still very limited. Scientific literature lacks data on the effect of US as a single way to degrade pollutants.

Literature also lacks of data on the ultrasonic degradation of APAP and AMO, whether in synergy with other methods or not, despite they are the analgesic and antibiotic most assumed worldwide, respectively [42]. Additionally, literature lacks a description of degradation pathways of such contaminants in water. The degradation of a contaminant into stable intermediate compounds before mineralization is key to know the nature of these molecules to associate possible microtoxicity fallouts. Degradation molecular pathways are therefore key to identify US operating conditions to degrade and possibly mineralize pollutants in water.

Here, we report for the first time the APAP and AMO degradation by US, with power ranging from 15 W to 40 W (amplitude from 30 to 60 %). In particular, we applied US to degrade APAP and AMO respectively, in absence of other oxidation methods. Then we degraded a mixture of the two pollutants to identify a possible substrate competition in their US-induced degradation. Moreover, we proposed a degradation pathway for both, depending on the applied US power. We finally proposed a kinetic model. We also considered the energy consumption of the different approaches, in order to evaluate the energy consumption efficiency for the treatment.

Results and Discussion

Effect of the ultrasound power

We studied the effect of ultrasound (US) power in the 15-40 W range (corresponding to an amplitude from 30 to 60 %), at a constant frequency of 20 kHz for the degradation of acetaminophen (APAP) and amoxicillin (AMO) as model water pollutants (Fig. 1 and Fig. 2).
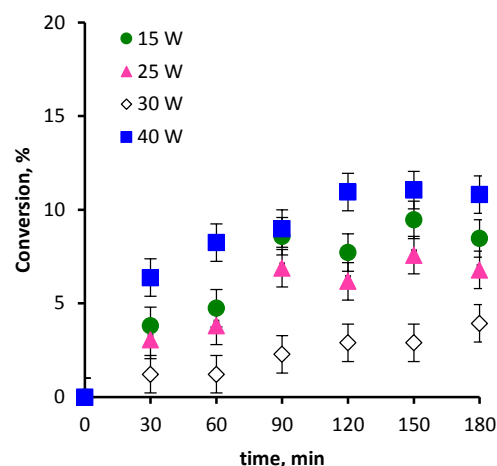
Figure 1. Acetominophen (APAP, 25 ppm starting concentration) degradation over time under US irradiation at 20 kHz and power from 15 to 40 W. A set of 3 repetitions gave a 95 % confidence interval.
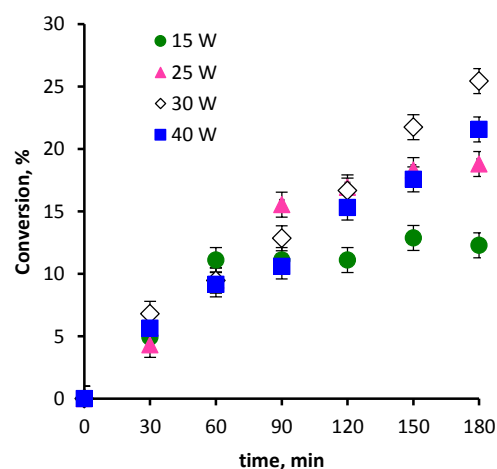
Figure 2. Amoxicillin (AMO, 100 ppm starting concentration) degradation over time under US irradiation at 20 kHz and power ranged from 15 to 40 W. A set of 3 repetitions gave a 95 % confidence interval.

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In the absence of US we observed no degradation. For acetaminophen (APAP), degradation by US reached a plateau for all the set powers and the maximum degradation was 10 (±1) % after 3 h (Fig. 1). The low degradation did not depend on the limited concentration of APAP (only 25 ppm, which is still one order of magnitude above the real concentration in the environment). Indeed, US degraded maximum 10 (±1) % after 3 h even at 100 ppm of APAP (Fig. 3). This clearly indicates that APAP is recalcitrant to ●OH radicals generated by US. The degradation did not increase proportionally with the US power. Indeed, intermediate powers (25 W and 30 W) correspond to a lower degradation rate, while 15 W and 40 W give significantly higher degradation at 8 (±1) % and 10 (±1) %, respectively. In this case, we abstain from correlating the power with the extent of the reaction, since the degradation was insufficient. Also, depending on the power, the molecular pathways involved were different, which resulted in different reaction rates, as we highlight in sections 3.4 and 3.5.

On the contrary, in case of amoxicillin (AMO), the degradation approached 25 % after 3 h at 30 W (Fig. 2). The conversion increases with the power up to 30 W, and then decreases. 30 W and 40 W degraded 25 (±1) % and 22 (±1) % of AMO, respectively. Also, the curve tended to plateau at 15 W, while the degradation is linear with time at higher powers.

The very different degradation profiles of AMO when the US intensity increased from 25 W to 30 W, pointed out a different mechanism of degradation, which occurs only over 25 W (Fig. 2). The higher degradation can be correlated to the availability of ●OH radicals in the environment, which can come also from the molecule itself. Amoxicillin contains more oxygen atoms and we can speculate that radicals are formed only beyond a certain level of US power. Moreover, a maximum in the reaction rate in function of the power, weather at intermediate or higher power is very typical [40] [43]. For most reactions an increase in power density speeds up the reaction rate. However, the reaction rate often reaches a maximum and decreases when increasing the acoustic amplitude because of the degassing of the system [44][45][46]. Indeed, the number of active cavitation bubbles generated by US increases with the increase in the irradiation power. When water is the reaction medium, as the number of active cavitation bubbles increases, the concentration of hydroxyl free radicals ●OH increases along [47]. However, also the different degradation pathways that these complex organic molecules undergo may affect the availability of ●OH radicals in the environment: cascade reactions, different products formation and their reactivity and accumulation in the reaction environment affects as well the rate of formation and the concentration of ●OH radicals. Concerning the reason why increasing the US power the reaction rate decreases for certain reactions, Vichare et al. [48] provide an interesting explanation unfolding the effects of acoustic parameters such as intensity and frequency of US from a quantitative point of view. Cavities absorb and release the energy dissipated into the system as a pressure pulse and high energy density shock waves. Increasing the amplitude of vibration may induce a coupling effect, which is a phase lag between the motion of the liquid and that of the horn. The incomplete contact between oscillating surface and liquid lowers the efficiency of US irradiation. High intensities also generate a larger number of bubbles that may escape before they collapse. These are the reasons at the

basis of the existence of an optimum US power intensity, as widely documented [49][50][51][52][53].
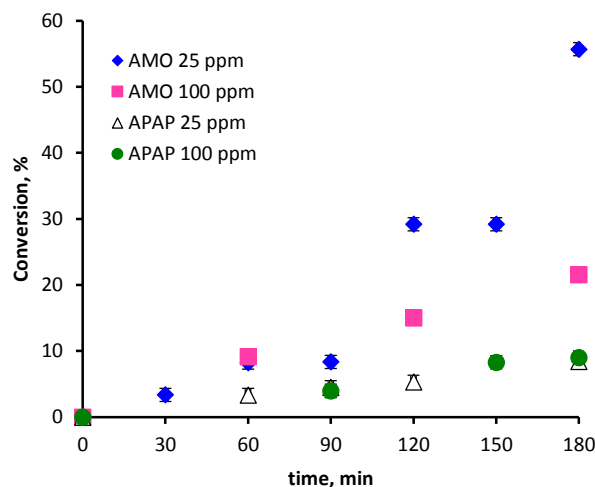
Figure 3. Acetaminophen (APAP) or Amoxicillin (AMO) degradations over time under US irradiation at 20 kHz and 40 W. Comparison between starting concentration of 25 and 100 ppm.

The ability of US to cause bonds cleavage in the reactant molecule generating radicals comes from the molecule itself. This clarifies the different degradation profiles observed comparing APAP and AMO. Oxygen is activated by cavitation, due to the electrical discharges at the collapse of cavitation bubbles [54]. While APAP contains less oxygen atoms, with only one ●OH terminal group, AMO has two terminal hydroxyl groups and other terminal atoms of oxygen. Accordingly, the higher AMO degradation by US is justified. Comparing the degradation profiles of AMO at different concentrations gave another evidence of these phenomena, because at lower concentration (25 ppm) the maximum degradation percentage increased from 20 (±1) % to more than 50 (±1) % (Fig. 3). At the same level of US power, the lower the concentration the higher the rate of formation of OH radicals, the stronger the US effect on substrate degradation. Conversely, the trend observed in the case of APAP confirmed its recalcitrant degradation if attacked by US, even due to the lower oxygen content.

Effect of the ultrasound pulses

Applying US in continuous mode degraded more organics in comparison with pulsing mode (Fig. S1 and S2 in SI). However, in case of AMO the difference between the final degradations was at most 2 (±1) % (Fig. S2). This is important for further development of US application to remove organics from water: Gielen et al. recently proved that ultrasonic energy consumption is reduced of almost 90 % at minimal pulsed setting [55]. Thus, reducing the consumption of energy and creating a more environmental benign degradation route.
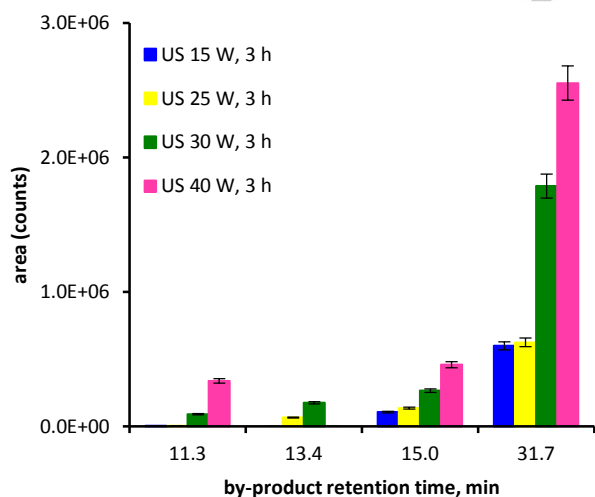
By-products

By-products formation depended on the US power applied, both for APAP and AMO. HPLC analysis detected hydroquinone (HQ) as a main by-product, followed by hydroxyhydroquinone (HHQ) (SI, Fig. S3). Higher US power generated in proportion more HQ (Fig. 4).
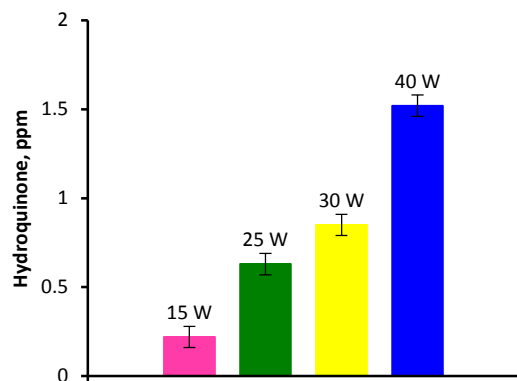
Figure 4. Hydroquinone (ppm) produced after 3 h of US irradiation in the aqueous solution of acetaminophen (APAP, starting concentration 25 ppm). Error bars: ± 0.06 ppm.

AMO degradation under US yielded four main by-products (SI, Fig. S4). Peak at 19.3 min refers to AMO. Peaks at 11.3, 13.4 and 15.0 min of retention time (Fig. S4) are unknown. We recovered the last product of the mixture (retention time 31.7) at the outlet of the HPLC column, in order to analyze it by mass spectrometry. Looking at the mass spectrum (Fig. S5), we suppose that it corresponds to the dimer of AMO. Accordingly, AMO and its dimer have an m/z of 364.1 and 729.3, respectively.

Figure 5. By-products area values over time. Error bars refer to an error of ±1 % calculated on the variation of the area of the HPLC spectrum.

The concentration of each degradation product increased over time and increasing US power (Fig. 5). Each different colored column is a different by-product, identified by HPLC with a separate peak (SI, Fig. S4). US changed the molecule structure breaking bonds, affected the reaction kinetic increasing the temperature of the solvent, enhanced the formation of hydroxyl

radicals in water and improved their reactions with organics. At this step, we supposed the possible fragmentation of the AMO according with the signal revealed by the mass spectrum. Compounds detected by HPLC gave three peaks, with m/z of 187.1, 223.1 and 338.2 respectively.
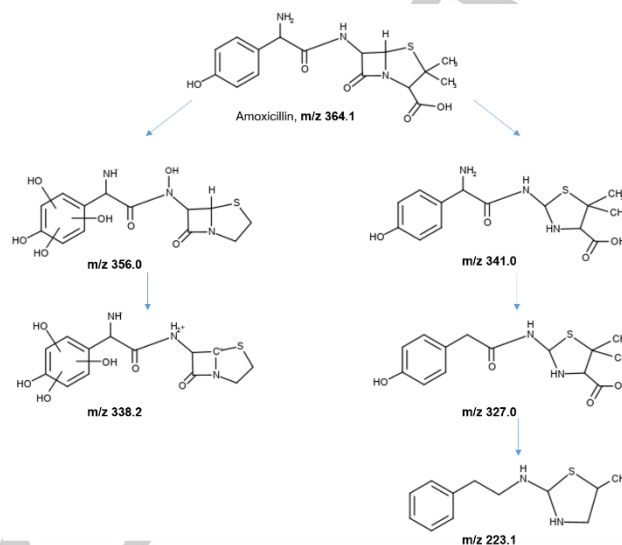
Figure 6. Proposed pathway for the formation of the m/z 338.2 first amoxicillin degradation intermediate (on the left). Amoxicillin US parallel breaking proposed by Kidak et al. [41] with further formation of m/z 223.1 by-product (right side).

During the first step, US broke the C-C bonds and separated two methyl and the carboxyl groups. OH groups from solvent sonolysis attached to the aromatic ring, and also formed N-OH bond (Fig. 6, left side). We propose that afterward, the -OH was removed as water molecule, forming the by-product at m/z 338.2. A parallel amoxicillin-breaking pathway presumes the loss of the carbonyl group following by the amine group detachment (Fig. 6, right side) [41].Differently we hypothesize the loss of the second carbonyl group, and, as occurred in the first proposed mechanism, the detachment of the two methyl groups and the carboxyl group. This molecule exactly corresponds to the mass spectrum peak at m/z 223.1 (see the HPLC spectrum in fig. S4 and the peak in the mass spectrum Fig. S5). Lastly we considered the m/z 187.1: starting from the molecule with m/z 223.1 (Fig. 6, right side) we supposed the possible detachment of the ring containing N and S, together with the attachment of 3 OH groups on the benzene ring; the formed molecule justifies the mass of 187.1, although this step requires further investigations. However, the amoxicillin degradation pathway better explains why, in case of amoxicillin and not for acetaminophen, increasing US power increases its conversion (Fig. 2 and Fig. 3). The products formed by the degradation of amoxicillin derived both from the interaction with oxidizing species (OH) and from the splitting phenomena due to sonication (Fig. 6): higher the US power, higher the breaking of

bonds. For the same reason, AMO conversion increased from 22 (±1) % to 56 (±1) %, lowering its starting concentration from 100 ppm to 25 ppm at 40 W (Fig. 3): the smaller the amount of amoxicillin, the more the physical effect of US that breaks the bonds. On the contrary, APAP conversion showed the same trends and reached plateau of 9 (±1) % both for lower or higher concentration (Fig. 3); its degradation was also most affected by the pulsing effect, which gave lower conversion (Fig. S1 and S2). AMO degradation depended on both power (W) and US frequency; APAP degradation depended mostly on frequency.

Amoxicillin's degradation kinetics

We linearly regressed the degradation of amoxicillin into its sub-products with the integral method assuming a variable-volume ($V_{(t)}$) isothermal batch reactor and measuring the variation of moles of AMO (N) over time (t). The temperature increased, reached steady state after 60 min; however, temperature variation did not deviate the initial data from the linear regression. For this reason, we neglected the effect of temperature and assumed the US emissions as the only degradation pathway for our substrate. We hypothesized a zero-order degradation kinetic because superior-order regressions gave lower R^2 correlation coefficients or presented data inconsistency (Table 1).

US power, W	Conc., ppm	k_0, mol L^{-1} min^{-1}	R^2
15	100	2.1E-07	76
25	100	3.8E-07	93
30	100	4.8E-07	99
40	100	4.0E-07	98
15	100	2.0E-07	71
15*	100	1.6E-07	94
40	100	4.2E-07	99
40*	100	4.4E-07	99
40	25	2.8E-07	79
40	100	3.8E-07	89

Table 1. Amoxicillin's degradation regressed zero order kinetic constants. * refers to pulsed mode experiments.

We interpolated the zero-order degradation kinetic ($k_{0(P)}$, mol L^{-1} min^{-1}) as function of US power (P, watt) at 100 ppm AMO concentration, with a quadratic polynomial (R^2: 96 %) and a standard error of the estimate of ±0.3 mol L^{-1} min^{-1}.

$$k0_{(P)} = -8.8 \times 10^{-10} P^2 + 5.7 \times 10^{-8} P - 4.7 \times 10^{-7}$$

The proposed model accounts for 90 % of the variance in the data (R^2) when correlating the measured versus the regressed AMO conversion (Fig. 7):
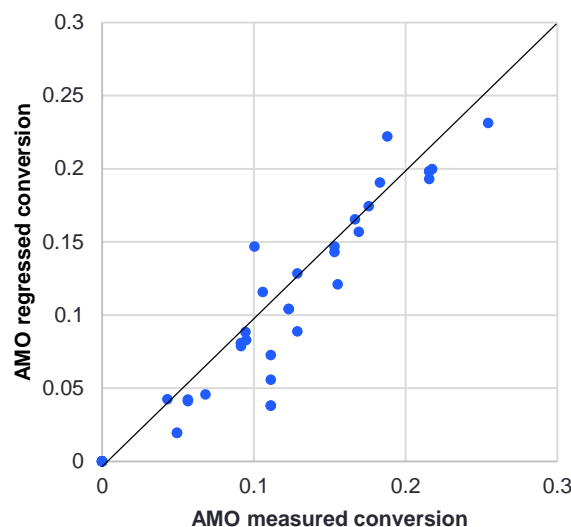
Figure 7. Experimental and regressed data validation.

Competition between acetaminophen and amoxicillin during US degradation

A solution of a mixture of APAP and AMO resulted in a different degradation kinetic, as US affected organics differently when they were presents simultaneously. We found that the presence of APAP reduced the degradation of AMO (Fig. 8). Sonication at 40 W degraded around 20 % of AMO after 3 h, starting from 100 ppm of drug (Fig. 3); for a 200 ml solution containing 50 ppm of APAP and 50 ppm of AMO, US (40 W) degraded less than 15 % of APAP, without degradation of AMO. Indeed, AMO concentration decreased from 11.4 mg to 11.3 mg per 200 ml (Fig. 8). Comparing the final degradation %, US affected APAP molecule only. We supposed that the propagation of US in the solution changed due to the presence of two cumbersome organic molecules, in a way that the molecules' geometry modified the effect of US. Considering the results obtained in the US degradation of single molecules (Fig. 2 and Fig. 3), the most plausible hypothesis is that the AMO acted as source of oxygen and •OH radicals, which reacted with both the molecules, but with greater affinity for APAP. Thus, APAP degradation is higher and the degradation amoxicillin is hampered (Fig. 8).
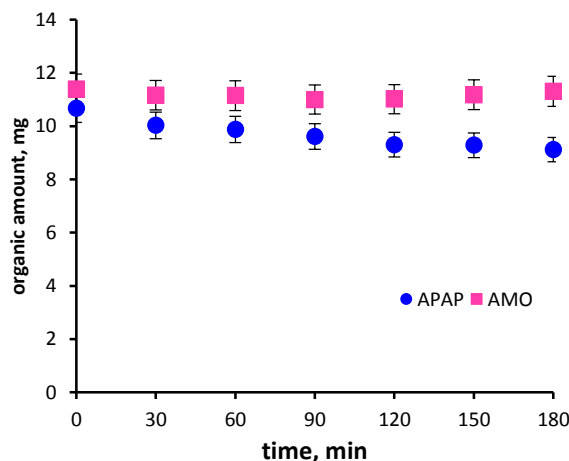
Figure 8. APAP-AMO 50 ppm (1:1) aqueous solution under US (40 W); Organic molecules (mg) over time.

US mostly affected APAP comparing with AMO. Indeed, considering their chemical structure, APAP contains 1 aromatic ring and 1 carbonyl; AMO shows a complex structure, including the aromatic ring, 2 carbon rings, the presence of S and 3 carbonyl groups. Thus, testing their simultaneous degradation by US proved that sonication affects the chemical structure according with its complexity and steric hindrance.

Conclusion

Comparing to other methods, ultrasound (US) application for water treatment does not require any additional chemicals. There are no reports about the application of US only for the degradation of pharmaceuticals in water. Here, we proposed the degradation pathway of acetaminophen (APAP) and amoxicillin (AMO) in water, by US not coupled with other methods. APAP was more resistant to continuous sonication at 40 W for 3 h, for both the starting concentrations (25 and 100 ppm). On the contrary, US was effective onto AMO, degrading 56 % of the substrate starting from a concentration of 25 ppm in 3h, because of the higher number of hydroxyl groups present in the molecule. Moreover, AMO degradation lowered by 2 % applying US in pulses, with an energy saving of more than 50 %.
Hydroquinone was identified as main APAP's byproduct; on the other hand, HPLC separated 4 byproducts for AMO including its dimer, with m/z from 338.2 to 223.1. A possible amoxicillin degradation pathway is thus proposed. Moreover, the regressed zero order kinetic constants for AMO ranged from 2.1 and 4.8 mol L^{-1} min^{-1}, depending on the US power and pulses. As last important finding, we proved that, when APAP and AMO are present in the same water matrix, they are barely decomposed by US, which highlights the importance to study molecules to degrade in a complex mixture.

Experimental Section

Materials
Acetaminophen (APAP, analytical standard, Sigma-Aldrich) and amoxicillin (AMO, Sigma-Aldrich) were the model pollutants to degrade with ultrasound (US). MeOH composing the HPLC eluent was of HPLC grade, ≥ 99.9 %, Sigma-Aldrich.

Degradation by ultrasound
A 500 W ultrasound (US) probe with a 19 mm tip diameter sonicated the aqueous solution of the drugs. The device was a VCX 500 by Sonics & Materials, Inc. (Fig. 1) and operated in continuous mode or with on/off operating cycles of 0.5/0.5 seconds. The actual power delivered by the probe (Y, watt) relates to the amplitude (X, %) according to the calibration line (Eq. 1).

$$Y = 0{,}77\ X - 6{,}7 \qquad (1)$$

In order to study the effect of US on APAP and AMO, we immerged the US tip 2 cm from the liquid surface in the center of the reactor, that was a 200 ml cylindrical beaker contained the aqueous solution of the organic molecule. The starting concentration was 25 ppm for APAP and 100 ppm

of amoxicillin, respectively. This choice has been done on the basis of reference concentrations usually reported in literature. Moreover, using such concentration of AMO it is also possible to follow its degradation, being too low concentrations hardly detectable. A magnetic stir bar kept the solution mixed and uniform, without forming vortices. A thermocouple directly connected to the US probe monitored the temperature of the solution. We checked the temperature of the water solution over time and it not exceed 30 °C.

Analytical
A Varian Prostar HPLC instrument (model 210), equipped with a Prostar 410 Auto-sampler control and a C-18 column (Microsorb MW 100-5 C18, 250x4.6, Varian, Agilent Technologies), separated and quantified the concentration of the organic molecules. The mobile phase consisted of MeOH and H_2O (HPLC grade) in a 20:80 ratio. The flow rate was 0.5 ml min^{-1}. In order to maximize the separation of compounds, wavelengths (λ) to detect APAP and AMO were 210 nm and 275 nm, consistent with their maximum absorption wavelength.
To identify the by-products we analyzed the solutions after sonication by flow injection in a 1290 UHPLC coupled to a 6460 mass spectrometer. The mobile phase was 40 % acetonitrile in water at a flow rate of 0.2 mL min^{-1} and a sampling volume of 2 µL. Both ESI positive and negative modes analyzed the samples with an Agilent Jet Stream source. The mass spectrometer operation conditions were set as follows: gas temperature of 300 °C, gas flow rate 7 L min^{-1}, nebulizer at 35 psi, sheath gas temperature at 300 °C, sheath gas flow at 12 L min^{-1}, and capillary voltage 4.0 kV and 3.5 kV for ESI positive model and for negative model, respectively. Data were collected in total ion recorded mode.

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FULL PAPER

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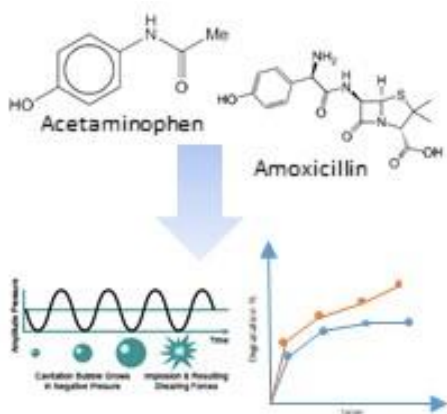
The degradation of acetaminophen and amoxicillin has been studied by ultrasound, without any other treatment. The purpose is investigating the role of US and their effect on organic matter, in different conditions. The sonication power influences the degradation, but it depends primarily on the molecular structure of the substrate. The initial concentration influences the degradation rate and also the simultaneous presence of two molecules strongly affect the effect of US.

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