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Degradation of antineoplastic cytarabine in aqueous phase by advanced oxidation processes based on ultraviolet radiation

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ABSTRACT

The aim of this study was to determine the effectiveness of oxidation processes based on cytarabine degradation using UV radiation (UV, UV/H_2O_2, and UV/$K_2S_2O_8$). Results show that UV radiation alone is not effective to remove cytarabine from the aqueous medium, due to the low quantum yield of this molecule ($\Phi_\lambda = 6.88 \times 10^{-6}$ mol Einstein^{-1}). The addition of H_2O_2 or $K_2S_2O_8$ considerably increased the removal effectiveness due to the generation of HO• and $SO_4^{\bullet-}$ radicals. The reaction rate constants between cytarabine and HO• radicals and $SO_4^{\bullet-}$ radicals were $k_{HO^\bullet cyst} = 3.15 \times 10^{10}$ m^{-1} s^{-1} and $k_{SO_4^{\bullet-} cyt} = 1.61 \times 10^9$ M^{-1} s^{-1}. For both systems (UV/H_2O_2 and UV/$K_2S_2O_8$), (i) an decrease in the pH of solution reduces the cytarabine removal rate, (ii) a specific concentration of H_2O_2 and $K_2S_2O_8$ produces the highest cytarabine removal rate, (iii) the chemical composition of water considerably affects the cytarabine oxidation rate, especially in the UV/H_2O_2 system, mainly due to the lesser selectivity and greater reactivity of the HO• radical, and (iv) the total organic carbon concentration in the medium decreased with longer treatment time but the toxicity increased, especially in the case of the UV/H_2O_2 system.

1. Introduction

The presence of pharmaceutical compounds in wastewaters poses a serious environmental challenge, since most of them cannot be removed by biological degradation treatments and remain in the environment for long time periods, causing toxic effects in humans and other living organisms [1]. The pharmaceuticals most frequently detected in treatment plant effluents are antibiotics, antacids, steroids, antidepressants, analgesics, antiinflammatories, antipyretics, beta-blockers, antilipemics, tranquilizers, stimulants, and antineoplastics [2].

Antineoplastic drugs are designed to destroy cells that have excessively proliferated, such as carcinogenic cells. These agents include cytarabine (1,β,D-arabinofuranosyl-cytosine), a pyrimidine analogue used to treat certain types of leukemia (acute non-lymphocytic leukemia, acute lymphocytic leukemia, chronic myelocytic leukemia) [3]. Antineoplastic agents have mutagenic and genotoxic effects and must be removed from wastewaters to avoid damage to humans and the environment.

Several treatments have been applied to remove antineoplastics from aqueous media. Rey et al. [4] eliminated four antineoplastics (5-fluorouracil, cytarabine, azathioprine, and methotrexate) after 60 min of ozone treatment at pH = 3 and established, using the Ames test, that the degradation byproducts were not mutagenic. Castegnaro et al. [5] used sodium hypochlorite (25%), Fenton reagent, and hydrogen peroxide to degrade six anthracyclines, which was achieved in all cases after 1 h of treatment with sodium hypochlorite (25%) or Fenton reagent, and reported that the degradation byproducts were not mutagenic (Ames test).

Advanced oxidation processes (AOP) have been successfully applied in wastewater treatments [1,6]. The combination of ultraviolet radiation (UV) and hydrogen peroxide (UV/H_2O_2) is the most widely used AOP for oxidation of a large variety of organic pollutants, including: colorants [7–12], nitroaromatic compounds [13], xenobiotic compounds [14], and antiinflammatories [15,16]. This method is based on the generation of hydroxyl radicals (HO•) by photolysis of the peroxide bond –O–O–. Eqs. (1)–(6) show the most important reactions that occur during H_2O_2 photooxidation [17].

$$H_2O_2 + h\nu \rightarrow 2HO^\bullet \quad (1)$$

$$H_2O_2 + HO^\bullet \rightarrow HO_2^\bullet + H_2O \quad (2)$$

$$2HO_2^\bullet \rightarrow H_2O_2 + O_2 \quad (3)$$

$$H_2O_2 + HO_2^\bullet \rightarrow HO^\bullet + O_2 + H_2O \quad (4)$$

$$H_2O_2 + HO^\bullet \rightarrow O_2^{\bullet-} + H^+ + H_2O \quad (5)$$

$$RH + HO^\bullet \rightarrow \text{Oxidation byproducts} \quad (6)$$

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Nomenclature

$[Art]_t$	atrazine concentration at time t ($mg\,L^{-1}$)
$[Art]_0$	initial atrazine concentration ($mg\,L^{-1}$)
$[Cyt]_t$	cytarabine concentration at time t ($mg\,L^{-1}$)
$[Cyt]_0$	initial cytarabine concentration ($mg\,L^{-1}$)
$[Cyt]_{exp}$	cytarabine experimental concentration ($mg\,L^{-1}$)
$[Cyt]_{pred}$	cytarabine concentration estimated with Eq. (22) ($mg\,L^{-1}$)
E_λ	radiation energy emitted by the lamp (Einstein $s^{-1}\,m^{-2}$)
$k_{HO\cdot Cyt}$	rate constant of HO• radicals to degrade cytarabine ($M^{-1}\,s^{-1}$)
$k_{HO\cdot Atr}$	rate constant of HO• radicals to degrade atrazine ($M^{-1}\,s^{-1}$)
k_{Ap}	apparent reaction rate constant (min^{-1})
t	time (min)
ε_λ	molar absorption coefficient at the considered wavelength ($m^2\,mol^{-1}$)
Φ_λ	quantum yield (mol Einstein^{-1})

HO• radicals generated in Eq. (1) are highly oxidizing species (E_0 = 2.80 V), which can react with organic compounds (RH) or recombine with hydroxyl groups to form hydrogen peroxide or initiate a chain reaction of hydrogen peroxide. The action mechanism of HO• radicals may be hydrogen atom attraction, hydroxyl group addition, or electron transfer [18].

Peroxodisulfate ($S_2O_8^{-2}$) is a powerful oxidant (E_0 = 2.05 V) used in the petroleum industry to treat hydraulic fluids or as a reaction initiator [19]. It has also been employed to degrade some organic pollutants. Because reactions with $S_2O_8^{-2}$ are very slow at room temperature, various techniques have been proposed to activate or accelerate organic molecule decomposition [20]. The most frequent method is to generate sulfate radicals $SO_4^{\bullet -}$ (E_0 = 2.6 V) by photochemical, thermal, or chemical decomposition of $S_2O_8^{-2}$ [21–24]. Eqs. (7)–(18) show the simplified reactions in the photochemical activation of $S_2O_8^{-2}$ [20,25].

$$S_2O_8^{2-} + h\nu \rightarrow 2SO_4^{\bullet -} \quad (7)$$

$$SO_4^{\bullet -} + RH_2 \rightarrow SO_4^{-2} + H^+ + RH^\bullet \quad (8)$$

$$RH^\bullet + S_2O_8^{-2} \rightarrow R + SO_4^{-2} + H^+ + SO_4^{\bullet -} \quad (9)$$

$$SO_4^{\bullet -} + RH \rightarrow R^\bullet + SO_4^{-2} + H^+ \quad (10)$$

$$2R^\bullet \rightarrow RR\,(dimer) \quad (11)$$

$$SO_4^{\bullet -} + H_2O \rightarrow HSO_4^- + HO^\bullet \quad (12)$$

$$HSO_4^- \rightarrow H^+ + SO_4^{-2} \quad (13)$$

$$HO^\bullet + S_2O_8^{-2} \rightarrow HSO_4^- + SO_4^{\bullet -} + \frac{1}{2}O_2 \quad (14)$$

$$SO_4^{\bullet -} + HO^\bullet \rightarrow HSO_4^- + \frac{1}{2}O_2 \quad (15)$$

$$2HO^\bullet \rightarrow 2H_2O_2 \quad (16)$$

$$HO^\bullet + H_2O_2 \rightarrow H_2O + HO_2^\bullet \quad (17)$$

$$S_2O_8^{-2} + H_2O_2 \rightarrow 2H^+ + 2SO_4^{-2} + O_2 \quad (18)$$

The above reactions demonstrate that the oxidation process begins with the formation of sulfate radicals and hydroxyl radicals, which can transform organic matter (R) into more or less toxic byproducts or into CO_2 and H_2O. The sulfate ion generated as final product is virtually inert and it is not considered a pollutant, unlike H_2O_2, which must be removed after its application. For this reason, the $SO_4^{\bullet -}$ radical has been increasingly used for pollutant degradation over the past few years.

The aim of the present study was to determine the effectiveness of oxidation processes based on the use of UV radiation (UV, UV/H_2O_2, and UV/$K_2S_2O_8$) in the degradation of cytarabine in aqueous solution. This was achieved studying the effect of operational variables (initial cytarabine concentration, pH, H_2O_2 concentration, $K_2S_2O_8$ concentration, and chemical composition of water), on the time course of total organic carbon concentration, and on the toxicity of cytarabine photodegradation byproducts.

2. Materials and methods

2.1. Reagents

All reagents used in the present study (cytarabine, hydrogen peroxide, potassium peroxodisulfate, hydrochloric acid, sodium hydroxide, atrazine, phosphoric acid, acetonitrile, methanol, and ammonium acetate) were supplied by Sigma–Aldrich. Ultrapure water was obtained using Milli-Q® equipment (Millipore).

Cytarabine ($C_9H_{13}N_3O_5$) is an organic compound that can exist in protonated or deprotonated form depending on solution pH. The p*K*a of cytarabine is 4.02 [26] and its speciation diagram also shows that cytarabine is completely protonated at pH < 2 and completely deprotonated at pH > 6. The two species present in the medium are found between pH = 2 and pH = 6.

2.2. Experimental system

Cytarabine degradation experiments were conducted in a photoreactor formed of concentric tubes: a stainless steel outer tube (13 cm inner diameter and 30 cm height) and quartz inner tube (5.5 cm inner diameter and 45 cm height). The inner tube is equipped with a medium pressure mercury lamp (Heraeus Noblelight TQ718-700W) emitting in range of 238 at 334 nm. The irradiating intensity of the lamp ($I_0 = 3.75 \times 10^{-7}$ Eintein s^{-1}) was measured using atrazine as the actinometer according to the procedures published by Canonica et al. [27].

In the annular space of photoreactor was a sample holder with capacity for 6 quartz reaction tubes (1.5 cm diameter and 20 cm height). Solutions in reaction tubes were maintained at constant temperature of 25 °C using a Frigiterm ultrathermostat and were maintained in agitation by means of a magnetic agitation system.

2.3. Cytarabine degradation by UV, UV/H_2O_2, and UV/$K_2S_2O_8$ systems

Experimental cytarabine photodegradation data were obtained as follows: a concentrated (100 $mg\,L^{-1}$) cytarabine solution was prepared by adding 0.1 g of cytarabine to a 1 L volumetric flask and filling with ultrapure water. An aliquot (24–27 mL) of ultrapure water was placed in the reaction tubes and an aliquot (3–6 mL) of concentrated cytarabine solution was added to obtain a total volume of 30 mL at the desired initial concentration. Cytarabine degradation kinetics was monitored by drawing 1 mL samples at regular time intervals to measure the concentrations of cytarabine, the total organic carbon and the toxicity of photodegradation byproducts.

The pH of the solution was adjusted to the desired value by the addition of sodium hydroxide or by hydrochloric acid and then it was measured by a pH meter (CRISON microph 2002).

Reaction rate constants of cytarabine with HO• and $SO_4^{\bullet -}$ radicals ($k_{HO^\bullet}$ and $k_{SO_4^{\bullet -}}$) were determined by competitive kinetics experiments, using atrazine as reference compound ($k_{HO^\bullet atr} = 1.80 \times 10^{10}\,M^{-1}\,s^{-1}$ and $k_{SO_4^{\bullet -}atr} = 1.4 \times 10^9\,M^{-1}\,s^{-1}$) [28,29]. The experimental method was as described above except that an

aliquot of concentrated atrazine solution was added to the reaction tubes containing the aliquot of concentrated cytarabine solution.

The influence of the chemical composition of water on cytarabine photodegradation was studied using real water samples (groundwater and wastewater) from a wastewater treatment plant. Both were supplied by Aguas y Servicios de la Costa Tropical company (Motril, Spain). Water samples were filtered, characterized (pH, total organic carbon (TOC), and HCO_3^- concentration), and then cold-stored until their use. Experiments were conducted as above, replacing the ultrapure water with groundwater or wastewater.

2.4. Analytical methods

2.4.1. Cytarabine determination in aqueous solution

Cytarabine concentration in aqueous solution was determined by HPLC, using a liquid chromatograph (Thermo-Fisher) equipped with a visible UV detector and autosampler with capacity for 120 vials. The mobile phase was 97% of 0.4% phosphoric acid solution v/v and 3% methanol in isocratic mode at flow of 0.5 mL min^{-1}; detector wavelength was fixed at 271 nm; and injection volume was 20 μL.

2.4.2. Atrazine determination in aqueous solution

Atrazine concentration in aqueous solution was determined by HPLC. The mobile phase was 50% of 1 mM ammonium acetate solution and 50% acetonitrile in isocratic mode, at flow of 1 mL min^{-1}; detector wavelength was fixed at 226 nm; and injection volume was 20 μL.

2.4.3. Determination of total organic carbon

Total organic carbon (TOC) present in the system was determined with a Shimadzu V-CSH analyzer with ASI-V autosampler by the following procedure.

Total organic carbon (TOC) present in the water samples was calculated by the subtraction of the inorganic carbon (IC) value from the total carbon (TC) value. The TC value was determined by injecting the water sample (3 mL) to a chamber of reaction to 680 °C filled with oxidant catalyst, at these conditions the organic and inorganic carbon were transformed to CO_2, which was measured with a non-dispersive infrared detector.

The IC was determined by injecting the water sample (3 mL) in another chamber reaction under acid conditions. At these conditions only IC is transformed to CO_2, which was measured with infrared detector. The analysis of TC and IC was made by triplicate for sure the correct value of TOC.

2.4.4. Determination of degradation byproduct toxicity

Degradation byproduct toxicity was determined using the LUMIStox 300 system (Dr. LangeGmbH), and LUMIStherm incubator, based on the normalized biotest (UNE/EN/ISO 11348-2) [30,31] of luminescent inhibition of *Vibrio fischeri* bacteria (NRRL B-11177). Toxicity is expressed as percentage inhibition at 15 min of exposure with reference to a stock saline solution (control).

3. Results and discussion

3.1. Cytarabine degradation by UV radiation

The UV irradiation showed that after 2 h only 10% of the initial cytarabine was degraded (Exp. No. 1, Table 1). The cytarabine absorption spectrum shows a maximum absorption peak at a wavelength of 271 nm (ε = 968 m^2 mol^{-1}), and only 3% of the total energy emitted by the lamp corresponds to this wavelength; implying that the amount of radiation absorbed at 271 nm is not sufficient to degrade cytarabine.

The effectiveness of UV light in compound degradation processes is defined by the quantum yield, i.e., the number of degraded moles of the compound divided by the number of photons absorbed by the system. The quantum yield of cytarabine was assessed using Eq. (19). Experimental data were fitted to a first order kinetic model, yielding an apparent degradation rate constant value $k = 1.6 \times 10^{-4}$ min^{-1}. The quantum yield was calculated as $\Phi_\lambda = 6.88 \times 10^{-6}$ mol $Einstein^{-1}$, demonstrating the low effectiveness of direct cytarabine photodegradation. According to these results, the medium-pressure lamps, commonly used for disinfection in wastewater treatment plants, are not effective for cytarabine oxidation.

$$k_{Ap} = 2.303 \sum_{\lambda_1}^{\lambda_n} E_\lambda \varepsilon_\lambda \Phi_\lambda \quad (19)$$

3.2. Cytarabine degradation by the UV/H_2O_2 system

3.2.1. Determination of the radical reaction rate constant

Determination of the radical reaction rate constant ($k_{OH\bullet}$) is critically important for the good design of a treatment system based on the simultaneous use of UV and H_2O_2. The reaction rate constant of hydroxyl radicals for cytarabine degradation was determined by conducting competitive reaction rate kinetics experiments. The reference compound was atrazine, which has a known radical rate constant of $k_{OH\bullet atr} = 1.80 \times 10^{10}$ M^{-1} s^{-1} [28]. The initial concentration of cytarabine and atrazine was 5 mg L^{-1} and the initial H_2O_2 concentration was 5000 μM, ensuring that the contribution

Table 1
Experimental conditions and apparent reaction rate constants for cytarabine degradation by UV/H_2O_2 in Milli-Q water at T = 25 °C.

Exp. No.	[Cyt] (mg L^{-1})	[H_2O_2] (μM)	pH	$k_{AP} \times 10^3$ (min^{-1})	% degradation of Cyt at 120 min	%D
1	10	0	7	0.9 ± 0.12	10	1.45
2	10	100	7	4.2 ± 0.14	40	1.36
3	10	200	7	8.1 ± 0.72	62	6.07
4	10	300	7	11.0 ± 0.88	73	7.51
5	10	400	7	18.6 ± 0.97	90	4.14
6	10	500	7	19.3 ± 1.02	92	4.56
7	10	1000	7	33.9 ± 1.17	98	3.40
8	20	200	7	4.0 ± 0.12	38	3.25
9	5	200	7	14.1 ± 0.41	80	3.08
10	3	200	7	25.8 ± 0.78	95	3.93
11	1	200	7	45.3 ± 2.6	99	10.64
12	10	400	2	5.5 ± 0.69	48	8.03
13	10	400	4	18.3 ± 0.87	89	4.34
14	10	400	6	18.6 ± 0.61	92	7.16
15	10	400	8	21.0 ± 0.29	91	4.31

of direct photolysis was negligible in both components. The radical reaction rate constant was determined using the following equation:

$$k_{HO^{\bullet}Cyt} = k_{HO^{\bullet}atr} \times \left[\frac{Ln\left(\frac{[Cyt]_t}{[Cyt]_0}\right)}{Ln\left(\frac{[Atr]_t}{[Atr]_0}\right)} \right] \quad (20)$$

The value of the radical rate constant determined was, slightly higher than the values reported by Yuan et al. [32] for the degradation of other pharmaceutical compounds by means of HO• radicals.

3.2.2. Cytarabine degradation by the UV/H_2O_2 system. Influence of operational variables

The effectiveness of the UV/H_2O_2 system was assessed by studying the influence of the different operational variables (cytarabine concentration, pH, H_2O_2 concentration, and chemical composition of water) on cytarabine degradation kinetics. Table 1 shows the experimental conditions for each study variable. The degradation kinetics of cytarabine was interpreted by a pseudo first order kinetic model, represented by the following equation:

$$\frac{d[Cyt/Cyt_0]}{dt} = -k_{Ap}\left(\frac{Cyt}{Cyt_0}\right) \quad (21)$$

Table 1 also depicts the values of apparent reaction rate constants obtained by fitting the Eq. (21) for the experimental data. The percentage deviations were calculated with Eq. (22) and are given in Tables 1 and 2 for UV/H_2O_2 system, and Table 3 for UV/$K_2S_2O_8$ system.

$$\%D = \frac{1}{N}\sum_{i=1}^{N}\left|\frac{[Cyt_{exp}] - [Cyt_{pred}]}{[Cyt_{exp}]}\right| \times 100\% \quad (22)$$

Results show that the addition of increasing amounts of H_2O_2 (Table 1, Exp. Nos. 2–7) increased the cytarabine degradation. Thus, the addition of 300 μM of H_2O_2 increased the apparent reaction rate constant k_{Ap} around 12-fold from 0.9×10^{-3} to 11×10^{-3} min^{-1}. This is due to the generation of HO• radicals, which attack cytarabine by degrading it into byproducts of smaller molecular weight. The cytarabine removal rate also increased at higher H_2O_2 concentrations. This improves the effectiveness of the system, since UV capture by H_2O_2 is greater at higher H_2O_2 concentration, favoring the generation of HO• radicals. However, results in Table 1 show that the addition of very high concentrations of H_2O_2 does not produce an increase in cytarabine degradation rate of the same magnitude. This is because HO• radicals have low selectivity and, at high H_2O_2 concentrations, initiate secondary reactions in which the HO• radical inhibits or recombines in accordance with Eqs. (23)–(26) [17,33].

$$HO^{\bullet} + H_2O_2 \rightarrow H_2O + HO_2^{\bullet} \quad (23)$$

$$HO_2^{\bullet} + H_2O_2 \rightarrow HO^{\bullet} + H_2O + O_2 \quad (24)$$

$$2HO_2^{\bullet} \rightarrow H_2O_2 + O_2 \quad (25)$$

$$HO_2^{\bullet} + HO^{\bullet} \rightarrow H_2O + O_2 \quad (26)$$

The effect of initial cytarabine concentration was studied by performing experiments at different initial cytarabine concentrations and at the same initial H_2O_2 concentration. Table 1 depicts the results (Exp. Nos. 3, 8–11), which show that degradation kinetics accelerated with the decrease in cytarabine concentration due to an increase in the $[HO^{\bullet}]/[Cyt]_0$ ratio.

Table 1 also depicts the effect of medium pH on cytarabine degradation rate (Exp. Nos. 5, 12–15), showing a considerably reduced cytarabine degradation at pH = 2, with only 48% removal after 2 h of irradiation, compared to values >89% at pH values of 4, 6, 7, and 8. This can be attributed to the inhibiting character of chloride ions present in the system due to acidification of the medium. In accordance with Eq. (27), these ions can react with HO• radicals and reduce the concentration available for cytarabine degradation.

$$Cl^- + HO^{\bullet} \rightarrow HClO^{-\bullet} \quad k = 4.3 \times 10^9\ L\,mol^{-1}\,s^{-1} \quad (27)$$

The radical formed in Eq. (27) presents lower reactivity than the HO• radical, implying that it does not participate in cytarabine degradation, explaining the decrease in degradation rate. Moreover, the HO• radicals can recombine at acidic pH and form H_2O_2, as indicated in Eqs. (16) and (17), reducing their effectiveness in cytarabine oxidation. Furthermore, most of the oxidation reactions of organic compounds with HO• in aqueous phase are disadvantaged at acidic pH due to the generation of H^+.

In order to analyze the applicability of UV/H_2O_2 system for cytarabine degradation, experiments were conducted with ultrapure water, groundwater, and wastewater. The properties and characteristics of these types of water and the apparent reaction rate constant for the removal of cytarabine and HO• inhibition rates are listed in Table 2. It is showed that the apparent reaction rate constants (cytarabine removal) were 50% lower for groundwater and wastewater than for ultrapure water.

In order to interpret the results in Table 2, we determined the inhibition rates of HO• radicals by the species present in the medium, using Eq. (28).

$$r_{HO^{\bullet}} = k_{H^+}[H^+] + k_{TOC}[TOC] + k_{HCO_3^-}[HCO_3^-] \quad (28)$$

where $r_{HO^{\bullet}}$ is the inhibition rate of HO• radicals in $k_{H^+} = 7 \times 10^9\ M^{-1}\,s^{-1}$, $k_{TOC} = 2 \times 10^8\ M_c^{-1}\,s^{-1}$, $k_{HCO_3^-} = 8.5 \times 10^6\ M^{-1}\,s^{-1}$ [34–36]. $[H^+]$, [TOC], and $[HCO_3^-]$ are initial concentrations of each species present in the water. M_c is the molarity of natural organic matter, based on the moles of carbon, assuming 12 g mol^{-1}.

Results in Table 2 show that: (i) the wastewater had the greatest radical inhibiting capacity, reducing the concentration of HO• radicals available to react with cytarabine, and (ii) the wastewater had the lowest light transmittance, absorbing the UV radiation and considerably reducing the number of photons reaching the H_2O_2. These findings confirm that the organic matter in wastewater acts as a filter of UV light, reducing the effectiveness of the treatment to remove cytarabine from the medium. The reduced k_{Ap} value of groundwater in comparison to ultrapure water was mainly due to the greater HO• radical inhibition capacity of the species that it contains (see Table 2).

The effectiveness of a system to treat water polluted with organic compounds is dependent on: (i) the transformation of dissolved organic carbon into CO_2 (pollutant mineralization), and (ii) the low or nil toxicity of degradation byproducts. Fig. 1a shows the time course of TOC as a function of treatment time for the three types of water studied. Regardless of the chemical composition of the water, the TOC concentration in the system reduced with longer treatment time, confirming that the UV/H_2O_2 system has sufficient oxidizing power to mineralize part of the dissolved organic matter. In absolute terms, the greatest reduction in TOC concentration was observed in the wastewater, indicating that a 55% of the initial organic matter was transformed into CO_2 after 120 min of treatment.

Fig. 1b shows the inhibition percentage of *V. fischeri* bacteria as a function of UV/H_2O_2 treatment time for the three water types. Regardless of the chemical composition of the water, the percentage bacteria inhibition was greater after treatment, evidencing the formation of degradation byproducts more toxic than cytarabine. Moreover, the H_2O_2 remaining is toxic and could contribute to increase inhibition percentage of *V. fischeri* bacteria.

Table 2
Chemical characteristics of the three types of water used, apparent reaction rate constants for the removal of cytarabine, and HO• inhibition rates.

Water type	pH	TOC (mg L^{-1})	[HCO_3^-] (meq L^{-1})	T^a (%)	$k_{Ap} \times 10^3$ (min^{-1})	$r_{HO^\bullet}$ (s^{-1})	%D
Ultrapure	7.0	0.0	0.0	100	18.6 ± 0.1	7.00×10^2	4.14
Groundwater	8.1	0.0	8.9	99	9.6 ± 0.8	1.30×10^3	7.24
Wastewater	7.8	12.2	10.5	64	8.6 ± 0.6	2.05×10^5	5.96

[a] Transmittance at 271 nm.

3.3. Cytarabine degradation by the UV/$K_2S_2O_8$ system

3.3.1. Determination of the radical reaction rate constant

The reaction rate constant $k_{SO_4^{\bullet-}}$ of cytarabine degradation by the $SO_4^{\bullet-}$ radical was determined by carrying out competitive kinetics experiments. The reference compound was atrazine, which has a known radical degradation constant, $k_{SO_4^{\bullet-}atr} = 1.4 \times 10^9\ M^{-1}\ s^{-1}$ [29]. The initial concentration of cytarabine and atrazine was 5 mg L^{-1} and the initial $K_2S_2O_8$ concentration was 2000 μM. The reaction rate constant of cytarabine was determined using Eq. (20), which yielded a value of $k_{SO_4^{\bullet-}cyt} = 1.61 \times 10^9\ M^{-1}\ s^{-1}$, within the range of values reported by Manoj et al. [37] for the degradation of aromatic compounds with $SO_4^{\bullet-}$ radical.

3.3.2. Cytarabine degradation by the UV/$K_2S_2O_8$ system. Influence of operational variables

The effect of the initial $K_2S_2O_8$ concentration was assessed by performing experiments at an initial cytarabine concentration of 10 mg L^{-1} (40 μM) and $K_2S_2O_8$ concentrations of 100, 200, 300 400, 500, and 1000 μM (Table 3, Exp. Nos. 2–7). The results obtained show that the addition of a small amount of $K_2S_2O_8$ produced a major increase in the degradation rate, obtaining 95% cytarabine degradation after 2 h of treatment with 100 μM of K_2S_2O. It can also be observed that, under the same conditions, the percentage cytarabine degradation was 2.5-fold higher with this system than with UV/H_2O_2 (Table 1).

Experimental data were fitted using Eq. (21), and Table 3 lists the values of the apparent reaction rate constants obtained. Under the above experimental conditions, these rate constants were on average nine-fold higher with this system than with UV/H_2O_2 (Table 1), although the reaction rate constant of cytarabine with the sulfate radical was slightly lower than the reaction rate constant with the hydroxyl radical. These results confirm the higher concentration of radicals generated for this system due to the formation of both radicals $SO_4^{\bullet-}$ and HO• (Eqs. (7)–(18)). Méndez-Díaz et al. [38] found similar results for the degradation of the surfactant SDBS using UV/H_2O_2 and UV/$K_2S_2O_8$ ($k_{HO^\bullet}$ (SDBS) ≈ 10^{10} and $k_{SO_4^{\bullet-}}$ (SDBS) = 3.54×10^8).

The results presented in Table 3 shown that the excessive addition of $K_2S_2O_8$ does not substantially increase the cytarabine degradation rate, attributable to the excessive generation of $SO_4^{\bullet-}$ radicals at high concentrations of $K_2S_2O_8$, which can recombine according to Eqs. (29) and (30). Furthermore, as commented above, HO• radicals generated in this system are also inhibited at high concentrations of HO• (Eq. (16)).

$$SO_4^{\bullet-} + SO_4^{\bullet-} \rightarrow S_2O_8^{-2} \quad k = 4 \times 10^8\ M^{-1}\ s^{-1} \tag{29}$$

$$SO_4^{\bullet-} + S_2O_8^{-2} \rightarrow SO_4^{-2} + S_2O_8^{\bullet-} \quad k = 6.1 \times 10^9\ M^{-1}\ s^{-1} \tag{30}$$

The effect of the initial cytarabine concentration was studied by performing experiments at different initial cytarabine concentrations (1, 2, 5, 10, and 20 mg L^{-1}) with the same initial $K_2S_2O_8$ concentration (200 μM) (Table 3, Exp. Nos. 3, 8–11). The results, depicted in Fig. 2, show that the degradation kinetics became much faster with a decrease in the cytarabine concentration, as in the UV/H_2O_2 system. However, at both low and high cytarabine concentrations, the UV/$K_2S_2O_8$ system was much more effective than the UV/H_2O_2 system, as demonstrated by the k_{Ap} values in Tables 1 and 3. Anipsitakis and Dionysiou [39] studied the effect of UV radiation and/or transition metal for the activation of hydrogen peroxide, potassium peroxymonosulfate and potassium persulfate leading to the generation of $SO_4^{\bullet-}$ and HO• radicals. These radicals were used to degrade 2,4-dichlorophenol and the results showed that for the technologies UV/$K_2S_2O_8$, UV/$KHSO_5$, and UV/H_2O_2, the system UV/$K_2S_2O_8$ was more efficient following by UV/$KHSO_5$ and finally UV/H_2O_2, which was attributed at persulfate and peroxymonosulfate are more photosensitive than hydrogen peroxide. These results support the found in this work.

The effect of the solution pH on cytarabine degradation by the UV/$K_2S_2O_8$ system was studied by performing experiments at pH = 2, 4, 6, 7, and 8 at the same initial cytarabine concentration and same $K_2S_2O_8$ concentration. Fig. 3 and Table 3 depict the results obtained (Exp. Nos. 3, 12–15), showing that the cytarabine degradation was strongly affected by the pH. Thus, the lowest percentage cytarabine degradation was obtained, as with the UV/H_2O_2 system, at pH = 2, with only 50% removal after 1 h of irradiation.

Table 3
Experimental conditions and apparent reaction rate constants for cytarabine degradation by UV/$K_2S_2O_8$ at T = 25 °C.

Exp. no.	[Cyt] (mg L^{-1})	[$K_2S_2O_8$] (μM)	Water type	pH	$k_{Ap} \times 10^3$ (min^{-1})	%D
1	10	0	Milli-Q	7.0	0.9 ± 0.1	1.45
2	10	100	Milli-Q	7.0	26.0 ± 0.8	2.35
3	10	200	Milli-Q	7.0	63.8 ± 2.2	1.75
4	10	300	Milli-Q	7.0	166.5 ± 9.1	14.48
5	10	400	Milli-Q	7.0	152.6 ± 14.5	16.69
6	10	500	Milli-Q	7.0	164.0 ± 7.6	9.60
7	10	1000	Milli-Q	7.0	304.0 ± 21.8	11.35
8	20	200	Milli-Q	7.0	33.5 ± 1.4	5.86
9	5	200	Milli-Q	7.0	157.0 ± 14.3	11.15
10	2	200	Milli-Q	7.0	193.0 ± 17.1	13.62
11	1	200	Milli-Q	7.0	584.8 ± 69.9	12.38
12	10	200	Milli-Q	2.0	10.7 ± 0.7	3.67
13	10	200	Milli-Q	4.0	56.3 ± 2.9	10.72
14	10	200	Milli-Q	6.0	47.3 ± 3.2	14.94
15	10	200	Milli-Q	8.0	40.2 ± 1.9	8.34
16	10	200	Groundwater	8.1	22.9 ± 1.5	7.46
17	10	200	Wastewater	7.8	17.1 ± 0.5	2.10

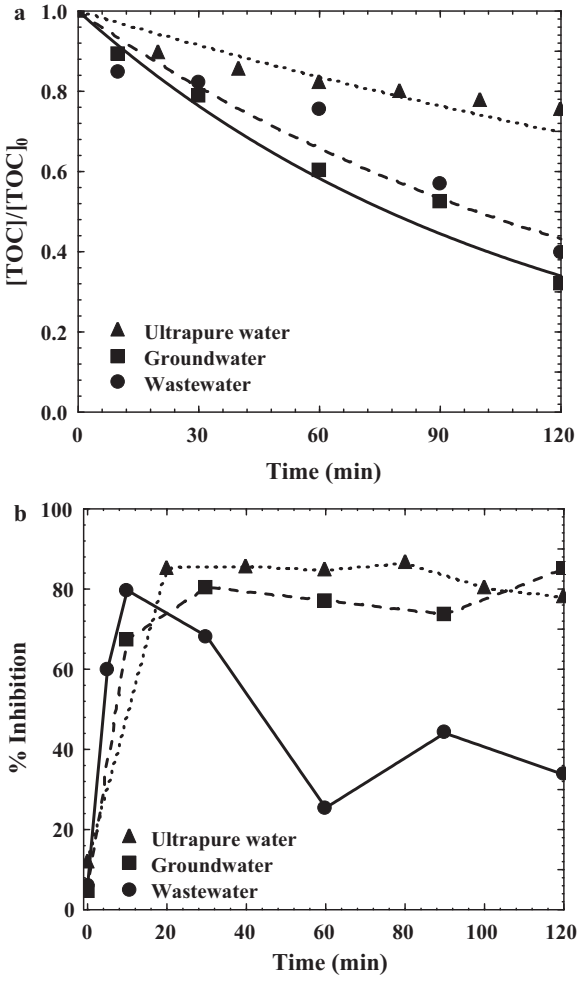

Fig. 1. (a) Effect of water type on the time course of TOC during treatment with UV/H_2O_2. [Cytarabine]$_0$ = 10 mg L^{-1}, [H_2O_2]$_0$ = 400 μM. (b) Time course of system toxicity during UV/H_2O_2 treatment of the different water types. [Cytarabine]$_0$ = 10 mg L^{-1}, [H_2O_2]$_0$ = 400 μM.

The drastic decrease in reaction rate at pH = 2 was attributable to several facts: (i) reactions (8)–(10), directly related to the attack of cytarabine with radicals, are disadvantaged as a result of protons formation; (ii) formation of additional acidic inorganic

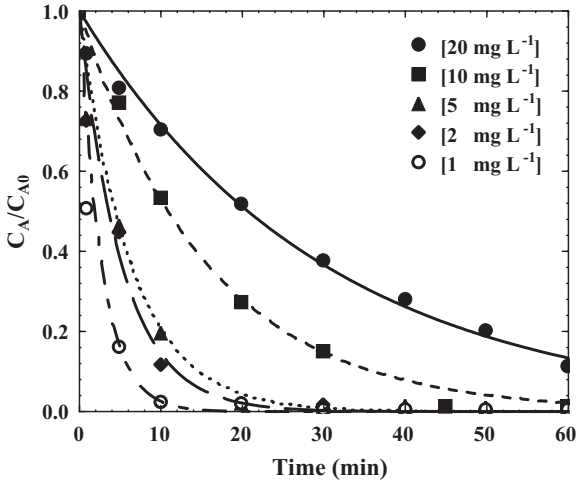

Fig. 2. Effect of initial cytarabine concentration on its degradation by UV/$K_2S_2O_8$. [$K_2S_2O_8$]$_0$ = 200 μM. Lines represent the prediction of the pseudo first order model.

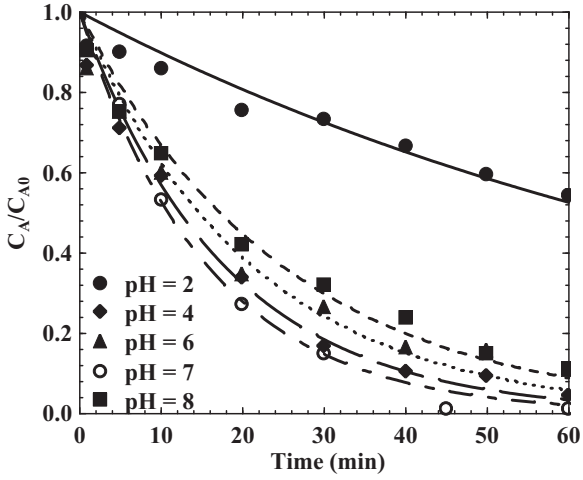

Fig. 3. Effect of solution pH on cytarabine degradation during UV/$K_2S_2O_8$ treatment. [Cytarabine]$_0$ = 10 mg L^{-1}, [$K_2S_2O_8$]$_0$ = 200 μM. Lines represent the prediction of the pseudo-first order model.

products, which are favorable at lower pH, such as H_2SO_5, H_2SO_4, $HS_2O_8^-$, HSO_4, which have a lower oxidation potential than HO• and $SO_4^{\bullet-}$ radicals [19,25]; and (iii) inhibition of HO• radicals by reactions (16) and (17), which are favored at acidic pH due to the greater stability of H_2O_2, and by reaction (27) due to the presence of Cl^-.

The percentage degradation at pH = 4, 6, 7, and 8, was 96, 94, 98, and 90%, respectively after 60 min of treatment (Fig. 3). Table 3 lists the apparent reaction rate constants as a function of solution pH, it is observed that k_{Ap} value was highest at neutral pH and decreased at basic pH because there is an excessive generation of HO• and $SO_4^{\bullet-}$ radicals, inducing their recombination (Eq. (15)). Salari et al. [19,25] obtained similar results using UV/$K_2S_2O_8$ to degrade the colorant Basic Yellow 2.

The applicability of the UV/$K_2S_2O_8$ system for cytarabine degradation was analyzed by conducting experiments with groundwater, wastewater and ultrapure water (as with the UV/H_2O_2 system). Table 2 shows the properties and characteristics of these types of water, and Table 3 (Exp. Nos. 3, 16, and 17) and Fig. 4a and b depicts the results obtained. The highest percentage degradation of cytarabine was obtained with ultrapure water (98% after 1 h), followed by groundwater (75%) and wastewater (65%) (results not shown). Table 3 also lists the apparent reaction rate constants, showing that as in the UV/H_2O_2 system the lowest degradation rate was obtained for wastewater and as commented above, this may be due to the screening effect produced by dissolved organic matter (absorbing part of the UV radiation) and to the radical scavenging capacity of some species contained in wastewater.

Fig. 4a depicts TOC values as a function of treatment time, showing a reduction in TOC concentration for all three types of water. As in the UV/H_2O_2 system, the mineralization of organic compounds was highest in wastewater, followed by groundwater and ultrapure water. These results indicate that the oxidizing power of UV/$K_2S_2O_8$ and UV/H_2O_2 systems is adequate to mineralize the dissolved organic matter.

Fig. 4b depicts the percentage inhibition of *V. fischeri* bacteria during UV/$K_2S_2O_8$ treatment of the different water types, showing that the percentage inhibition remained virtually constant with longer treatment time, regardless of the type of water studied. These results indicate that the degradation byproducts generated are not excessively toxic and sulfate ion generated as final product did not inhibited the bacteria *V. fischeri* showed that it was not toxic. We highlight the much lower percentage inhibition of bacteria in this system than in the UV/H_2O_2 system (Fig. 1b), confirming

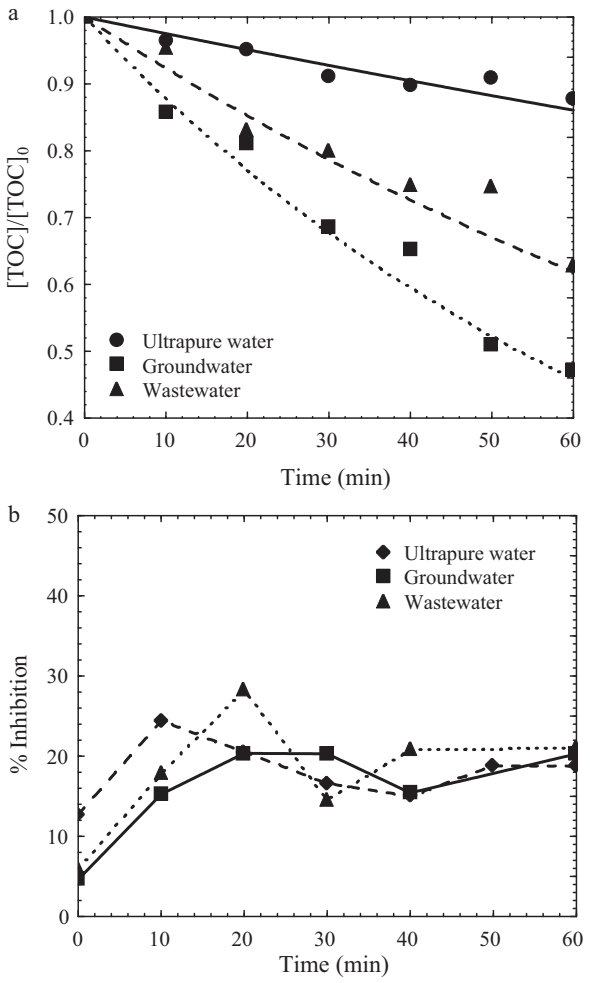

Fig. 4. a. Time course of TOC with UV/$K_2S_2O_8$ treatment of the different types of water. [Cytarabine]$_0$ = 10 mg L^{-1}, [$K_2S_2O_8$]$_0$ = 200 μM. b. Time course of medium toxicity during treatment with UV/$K_2S_2O_8$ for different types of water. [Cytarabine]$_0$ = 10 mg L^{-1}, [$K_2S_2O_8$]$_0$ = 200 μM.

its potential applicability in the removal of organic pollutants from water.

4. Conclusions

UV light proved inadequate to degrade cytarabine, and the quantum yield of this system was close to zero, demonstrating its low effectiveness.

The UV/H_2O_2 system was adequate to degrade cytarabine, yielding a reaction rate constant value of cytarabine with HO• radicals of $k_{HO•cyt} = 3.15 \times 10^{10}$ M^{-1} s^{-1}. The percentage cytarabine degradation depended on the solution pH; it was lowest at pH = 2 and varied slightly in the range HO•. The applicability of the UV/H_2O_2 system was demonstrated by the cytarabine degradation and TOC removal obtained with its use in groundwater and wastewater. However, the toxicity results indicated that the degradation byproducts of the organic matter in the medium had a higher toxicity in comparison to the original matter; therefore this treatment system should be used with caution for cytarabine degradation.

The UV/$S_2O_8^{-2}$ system was more effective than UV/H_2O_2 to degrade cytarabine, achieving higher removal percentages in shorter times due to the generation of $SO_4^{•-}$ and HO• radicals. The reaction rate constant of cytarabine with $SO_4^{•-}$ radicals was $k_{SO_4^{•-}cyt} = 1.61 \times 10^9$ M^{-1} s^{-1}. The solution pH considerably affected the cytarabine degradation, and the lowest percentage degradation was at pH = 2, due to the consumption of $SO_4^{•-}$ in the formation of anions with low oxidizing power. The maximum degradation percentage was at neutral pH. The applicability of the UV/$S_2O_8^{-2}$ system was demonstrated by the cytarabine degradation and TOC removal obtained with its use in groundwater, and wastewater. TOC results showed that UV/$S_2O_8^{-2}$ was slightly more effective than UV/H_2O_2 to mineralize the organic matter present in the different types of water. Furthermore, toxicity studies of this system found no formation of degradation byproducts with higher toxicity than cytarabine and/or the organic compounds in natural water. The UV/$S_2O_8^{-2}$ system is therefore recommended for the treatment of water polluted with cytarabine.

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