Separation and Purification Technology 136 (2014) 137–143

Contents lists available at ScienceDirect

Separation and Purification Technology

journal homepage: www.elsevier.com/locate/seppur

Kinetics of paracetamol oxidation by ozone and hydroxyl radicals, formation of transformation products and toxicity

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ARTICLE INFO

Article history:
Received 10 December 2013
Received in revised form 4 September 2014
Accepted 5 September 2014
Available online 16 September 2014

Keywords:
Paracetamol
Ozonation
Hydroxyl radicals
Rate constants
By-products
Toxicity

ABSTRACT

Paracetamol oxidation by ozonation and H_2O_2/UV processes was investigated. The second-order rate constant for the reaction of paracetamol with ozone was determined at pH 7.2 ($k_{O_3/PRC} = 2.57 \times 10^6\ M^{-1}\ s^{-1}$). The rate constant of the elementary reaction of ozone with the ionized form of PRC was then calculated and the pH dependence of the ozonation reaction of PRC was estimated. The second-order rate constant of the reaction of paracetamol with HO· radicals was also determined at pH 5 through the H_2O_2/UV oxidation system ($k_{HO^{\cdot}/PRC} = 4.94 \times 10^9\ M^{-1}\ s^{-1}$). In the light of the high rate constants obtained, two conclusions on the kinetics of paracetamol ozonation in real water were drawn: (i) hydroxyl radicals do not have any impact on the removal of paracetamol during ozonation of real waters; (ii) a half-life of 0.03 s can be estimated for paracetamol, for a residual ozone concentration of 0.4 mg L^{-1}. Hydroquinone and two other ozonation transformation products were identified by LC/UV, LC/MS and MS/MS analyses. In parallel, for the first time, toxicity was measured in ozonated paracetamol solutions with the luminescent bacteria *Vibrio fisheri* test. The results showed an increase in toxicity as paracetamol degraded. This toxicity could not be assigned to hydroquinone formation only. One or several other transformation products more toxic than paracetamol might be formed.

1. Introduction

Pharmaceuticals have been identified as major emerging contaminants due to their presence in natural waters in recent years. This environmental pollution is related to the use of both human and veterinary drugs. Many pharmaceuticals are highly polar, hydrophilic and have been detected in sewage treatment plant effluents, surface and ground waters, and even in drinking waters in several countries [1–5]. Moreover, recent studies showed that some of them can bioaccumulate in aquatic organisms [6–10].

Paracetamol (PRC), also known as acetaminophen ($pK_{a\ PRC}$ = 9.38 [11]), is widely used as an analgesic and antipyretic drug. PRC is metabolized (up to 90%) in the organism by hepatic biotransformation into glucuronic acids and sulfonate conjugates, which are renally eliminated. Only 3–5% of PRC are excreted unmetabolized by the kidneys [12–15]. Despite its high metabolization and considering its high prescription frequency, between 292 and 585 t of PRC is assumed to reach sewage treatment plants every year [16]. In a recent study conducted by Kim et al. [17], the PRC concentration in wastewaters was shown to be less than 10 ng L^{-1} after biological treatment. Otherwise, this pharmaceutical was detected in sewage treatment plant effluents at concentrations up to 6 μg L^{-1} in another study [1]. Many authors also investigated the occurrence of PRC in the aquatic environment [18–21]. In surface waters, low concentrations ranging from 4 to 73 ng L^{-1} were documented [20]. Although concentrations are usually low, the presence of this biologically active molecule in the aquatic environment may still affect aquatic organisms (especially upon long-term exposure) [22]. Effects on fish cell line BF-2 and *Daphnia*, with EC_{50} (half maximal effective concentration) values ranging from 19 to 50 mg L^{-1}, were reported for PRC [23]. Lower toxicities were observed on luminescent bacteria *Vibrio fisheri*, algae, ciliates or fish embryos with an EC_{50} ranging from 112 to 920 mg L^{-1} [23].

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http://dx.doi.org/10.1016/j.seppur.2014.09.004
1383-5866/

Measures aimed at reducing the environmental exposure of pharmaceuticals have to be studied in order to avoid potential adverse effects. Ozonation is a current well known advanced water treatment strategy and its potential for pharmaceutical removal is thus of interest. Ozone is a strong oxidant used in drinking water and wastewater treatment plants to remove microorganisms, inorganic ions and organic pollutants [24,25]. During ozonation, like other advanced oxidation processes (such as H_2O_2/UV), HO· radicals that are known to be highly reactive oxidants can be generated.

In recent years, several investigations have focused on the removal of pharmaceuticals at laboratory and pilot scales. The efficacy of oxidative treatment against pharmaceuticals in drinking water has been demonstrated [26–28]. In the case of levofloxacin, a study investigated the oxidation by ozone and hydroxyl radicals generated by H_2O_2/UV system. From this work, a 1.38 s half-life can be expected during ozonation of water for a residual ozone concentration of 0.4 mg/L [29]. Similarly, the oxidation of PRC in aqueous solution by ozonation and H_2O_2 photolysis was studied [30,31]. According to Andreozzi et al. [30], PRC could be completely removed by the two systems, with mineralization rates of up to 30% for ozonation and 40% for H_2O_2 photolysis. Some transformation products were identified. In a secondary effluent, according to Kim et al. [31], the removal efficiency of PRC by direct photolysis was shown to be 1%, while the H_2O_2/UV process would enable 90% PRC removal. In the present work, the kinetic of PRC oxidation by ozonation and H_2O_2/UV processes were studied. Ozone rate constants ($k_{O_3/PRC}$) were determined using the competitive kinetic method with phenol (PHN) as competitor. The H_2O_2/UV oxidation system was chosen to determine the rate constant of hydroxyl radicals on PRC ($k_{HO\cdot/PRC}$). A model of PRC degradation during ozonation in real waters was developed on the basis of these results. The identification of ozonation transformation products was investigated. Finally, the toxicity on *V. fisheri* was monitored for the first time. Transformation product formation and toxicity variations were also compared.

2. Materials and methods

2.1. Chemicals and stock solutions

All chemicals were used without further purification. PRC, PHN and hydroquinone (HDQ) (over 98% purity) were purchased from Sigma Aldrich. Tert-butanol (99.5%) was obtained from Acros Organics. Phosphate buffers, colorimetric agents and reductants were supplied by Fisher Scientific and Prolabo. Solutions were prepared with MilliQ purified water (18.2 MΩ cm; Millipore). Stock solutions of PRC, PHN and HDQ were prepared daily at appropriate concentrations. A Trailigaz generator (100 W) was used to produce ozone from oxygen. Ozone stock solutions (11–21 mg O_3 L^{-1}) were prepared by bubbling ozone in a semi-continuous reactor (800 mL) containing MilliQ water. A commercial solution of hydrogen peroxide (30%) delivered by Fluka was used for the experiments with the H_2O_2/UV system.

2.2. Experimental setup for ozonation experiments

2.2.1. Kinetic study

The rate constant of the reaction of ozone with PRC was determined using the competitive kinetic method. PHN was chosen as competitor because similar rate constants were expected ($k_{O_3/PHN} = 2.79 \times 10^6\ M^{-1}\ s^{-1}$ at pH 7.2 [32]). The experiments were carried out in a series of batch reactors containing 100 mL solution adjusted to pH 7.2 with phosphate salts and equimolar (1 μM) target compound (PRC) and reference compound (PHN). For each experiment, tert-butanol (3.16 mM) was introduced as HO· radical scavenger. Different ozone doses ranging from 0 to 6.8 μM were added to all reactors. After complete ozone consumption (i.e. 24 h), residual concentrations of PRC and PHN were determined by liquid chromatography (LC).

Under these conditions, since PRC and the reference compound PHN were simultaneously present in the reaction system, and based on second-order rate laws, the kinetic expressions for the ozone reaction can be integrated as follows:

$$\ln\frac{[PRC]_{T,n}}{[PRC]_{T,0}} = \frac{k_{O_3/PRC}}{k_{O_3/PHN}} \ln\frac{[PHN]_{T,n}}{[PHN]_{T,0}} \quad (1)$$

where $k_{O_3/PRC}$ and $k_{O_3/PHN}$ are the second-order rate constants for the reaction of ozone with PRC and the reference compound PHN, respectively. The ozone doses are represented by n.

The ratio of ($k_{O_3/PRC}/k_{O_3/PHN}$) was determined from the slope of the representation of $\ln([PRC]_{T,n}/[PRC]_{T,0})$ versus $\ln([PHN]_{T,n}/[PHN]_{T,0})$ for each experiment. The rate constant $k_{O_3/PRC}$ was calculated from the previously reported $k_{O_3/PHN}$ value [32].

2.2.2. Identification of transformation products and toxicity

Toxicity was monitored and transformation products were identified during ozonation experiments conducted in a 200 mL semi-batch reactor containing PRC solution (1 g L^{-1}). This initial concentration was chosen on the basis of the EC_{50} and EC_{20} values of PRC towards *V. fisheri* determined in a preliminary toxicity test (EC_{50} = 0.56 and EC_{20} = 0.21 g L^{-1}), in order to better assess the toxicity changes. Ozone was introduced continuously into the reactor during the experiment (flow rate: 6 mg min^{-1}). The pH to 7.2 was adjusted with phosphate buffer (ionic strength = 0.2 M). 2 mL of solution were withdrawn and analysed by liquid chromatography (LC) at different time intervals to monitor transformation product formation. 0.5 mL of samples was also withdrawn for toxicity measurement in Lumistox 300.

2.3. Experimental setup for the H_2O_2/UV system

The rate constant of PRC with HO· radicals was determined in order to evaluate the contribution of the HO· radicals during ozonation. The photolysis of H_2O_2 was used to produce hydroxyl radicals, as indicated in Eq. (2):

$$H_2O_2 + 2h\nu \rightarrow 2HO\cdot \quad (2)$$

Experiments were performed at 20 °C in a cylindrical batch reactor (volume: V = 5 L; annular path length: l = 6.3 cm) equipped with a low pressure mercury vapour lamp (HANAU NN 40/20, monochromatic emission at 254 nm) enclosed in a quartz sleeve in axial position. The incident UV light intensity measured by chemical actinometry [33] using hydrogen peroxide (0.05 M) as actinometer was equal to 10.1×10^{-6} E s^{-1}. Due to the negligible pH effect on the kinetics of PRC removal in the H_2O_2/UV system for pH < 7.5, the experiments were conducted in unbuffered solutions (pH = 5). At regular irradiation time intervals, samples were withdrawn for analyses of PRC and H_2O_2. To determine the rate constant of HO· with PRC, high concentrations of H_2O_2 relative to PRC were introduced so that the UV radiation would mainly be absorbed by H_2O_2. Eq. (3) was validated.

$$R = \frac{\varepsilon_{H_2O_2}[H_2O_2]_0}{\varepsilon_{H_2O_2}[H_2O_2]_0 + \varepsilon_{PRC}[PRC]_{T,0}} > 0.95 \quad (3)$$

where $[H_2O_2]_0$ = 50 mM, $[PRC]_{T,0}$ = 5 μM, ε_{PRC} = 7891 M^{-1} cm^{-1} at 254 nm and pH 5 (determined in this work) and $\varepsilon_{H_2O_2}$ = 18.6 M^{-1} cm^{-1} at 254 nm and pH < 9.