Science of the Total Environment 573 (2016) 518–531

Contents lists available at ScienceDirect

Science of the Total Environment

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

Tolfenamic acid degradation by direct photolysis and the UV-ABC/H_2O_2 process: factorial design, kinetics, identification of intermediates, and toxicity evaluation

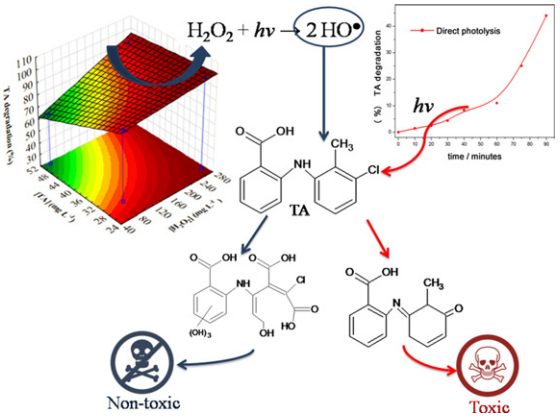
Lucas de Melo da Silva [a], Rodrigo Pereira Cavalcante [a], Rebeca Fabbro Cunha [a], Fábio Gozzi [a], Renato Falcao Dantas [b], Silvio Cesar de Oliveira [a], Amilcar Machulek Junior [a,*]

[a] Institute of Chemistry, Federal University of Mato Grosso do Sul; Av. Senador Filinto Muller, 1555; CP 549; Campo Grande, MS 79074-460, Brazil
[b] School of Technology, University of Campinas; Rua Paschoal Marmo, 1888; Limeira, SP 13484-332, Brazil

HIGHLIGHTS

- Factorial design was used as a statistical tool for the UV/H_2O_2 process.
- Determination of second-order kinetic constant of TA in alkaline medium.
- Intermediates were identified and possible degradation pathways were proposed.
- TA intermediates of direct photolysis showed acute toxicity to *Artemia salina*.
- *Artemia salina* test revealed no acute toxicity after use of UV/H_2O_2 process.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 17 May 2016
Received in revised form 3 August 2016
Accepted 19 August 2016
Available online 27 August 2016

Editor: Adrian Covaci

Keywords:
UV-ABC/H_2O_2 process
direct photolysis
tolfenamic acid
second-order kinetic constant
acute toxicity
degradation pathways

ABSTRACT

This study employed direct UV-ABC photolysis and the UV-ABC/H_2O_2 process to investigate the degradation of tolfenamic acid (TA), a common anti-inflammatory drug used in both human and veterinary medicine. A 2^3 factorial design with added center point was used to evaluate the effect of three independent variables—namely, H_2O_2 concentration ([H_2O_2]), TA concentration ([TA]), and experiment time (time)—on TA degradation and H_2O_2 photolysis during UV-ABC/H_2O_2 treatment using a high-pressure mercury vapor lamp (photon flux of 2.6307×10^4 J s^{-1}) as the UV irradiation source. The responses yielded similar values, revealing a linear behavior, with correlation coefficients $R = 0.9968$ and $R_{adj} = 0.9921$ for TA degradation and $R = 0.9828$ and $R_{adj} = 0.9570$ for H_2O_2 photolysis. The most efficient combination of variables was [H_2O_2] = 255 mg L^{-1} and [TA] = 25 mg L^{-1}, resulting in 100% TA degradation and 98.87% H_2O_2 photolysis by 90 min of treatment. Additionally, the second-order kinetic constant of the reaction between TA and HO• was determined using a competitive kinetic model, employing 2,4-dichlorophenoxyacetic acid (2,4D) as the reference compound. The kinetic constant was 1.9×10^{10} M^{-1} s^{-1} in alkaline medium. TA degradation by direct photolysis generated quinone imines as by-products, responsible for the formation of a dark red "internal filter" that increased the value of acute toxicity to *Artemia salina*. The UV-ABC/H_2O_2 process did not promote formation of quinone imines by 90 min of treatment

* Correspondence author at: Institute of Chemistry, Federal University of Mato Grosso do Sul; Av. Senador Filinto Muller, 1555, CP 549; Campo Grande, MS, 79074-460, Brazil.
E-mail address: machulekjr@gmail.com (A. Machulek).

http://dx.doi.org/10.1016/j.scitotenv.2016.08.139

and therefore did not increase acute toxicity values. Several by-products generated during TA degradation were identified and possible degradation pathways for the UV-ABC and UV-ABC/H_2O_2 processes were proposed.

1. Introduction

Population growth and urbanization are associated with increasing consumption of pharmaceuticals, leading to the generation of effluents containing these compounds (Białk-Bielińska et al., 2016; Shanmugam et al., 2014; Rivera-Utrilla et al., 2013; Santos et al., 2015). Resisting decomposition in wastewater treatment plants, many pharmaceuticals and their metabolites can reach different environmental compartments (surface water, groundwater, and sediments), affecting water quality and having harmful effects on humans and natural ecological systems (Białk-Bielińska et al., 2016; Faber et al., 2014; Rivera-Utrilla et al., 2013; Zounkova et al., 2010; Hirose et al., 2005).

Advanced oxidation processes (AOPs) have been regarded as a promising technology, because they are based on the generation *in situ* of hydroxyl radicals ($HO^{\bullet}$) capable of degrading a wide variety of organic substances, including human and veterinary drugs, that are resistant to conventional technologies (Gligorovski et al., 2015; Wols and Hofman-Caris, 2012; Gogate and Pandit, 2004; Loaiza-Ambuludia et al., 2014; Cavalcante et al., 2013).

Among AOPs, the UV/H_2O_2 process, which relies on UV-C photolysis of H_2O_2 to produce $HO^{\bullet}$, is highly effective in degrading many pharmaceutical compounds (Wols and Hofman-Caris, 2012; Batista et al., 2014; Tan et al., 2013; Vogna et al., 2004). The process generates two $HO^{\bullet}$ radicals for each H_2O_2 molecule cleaved, per quantum of radiation absorbed at 220 nm (Wols and Hofman-Caris, 2012; Kasiri and Khata, 2011; Legrini et al., 1993).

The rate of H_2O_2 photolysis in an aqueous medium can be increased under more alkaline conditions, given the higher molar absorption coefficient of the peroxide anion (240 M^{-1} cm^{-1} at 253.7 nm, beginning at pH 11.63), compared with that of undissociated hydrogen peroxide (19.6 M^{-1} cm^{-1} at 253.7 nm) (Lopez et al., 2003; Legrini et al., 1993). However, excess H_2O_2 has the ability to scavenge $HO^{\bullet}$, forming hydroperoxyl radicals ($HO_2^{\bullet}$) and subsequently O_2, which can then be reduced to $HO^{\bullet}$, inhibiting the degradation rate (Gligorovski et al., 2015; Crittenden et al., 1999; Legrini et al., 1993).

The identification of intermediates and the proposal of degradation pathways during AOPs have been subjects of growing interest. If the products and by-products are non-toxic, a high final degradation rate may not be required, thus reducing operating costs (Cavalcante et al., 2015; Calza et al., 2013; Vogna et al., 2004). Direct photolysis can also generate intermediates more toxic than the original compound—*e.g.*, highly cytotoxic compounds containing a quinone group (Passananti et al., n.d.; Liu et al., 2015; Monks et al., 1992).

Experimental design is a statistical strategy to organize and reduce the number of experiments, so that the necessary information is obtained as efficiently and precisely as possible (Glyk et al., 2015; Hibbert, 2012; Singh et al., 2004). Experimental design has been advantageously applied to AOPs, yielding more information with fewer experiments. Analytical processes can be optimized with the aid of the response surface methodology (RSM), which is based on a set of polynomial equations that provide effective parameters derived from interactions between variables (Glyk et al., 2015; Aghaeinejad-Meybodi et al., 2015; Kasiri and Khata, 2011; Bezerra et al., 2008).

Non-steroidal anti-inflammatory drugs (NSAIDs) such as diclofenac and mefenamic acid have a diphenylamine structure and are extensively used. Worldwide, diclofenac consumption currently ranges from 195 to 940 mg per person per year, depending on country (Huber et al., 2016). Mefenamic acid is one of the most consumed drugs in Switzerland, with a total of 17 tons used per year (Tauxe-Wuersch et al., 2005). Consequently, diclofenac and mefenamic acid have been found in surface water at concentrations of 1.2 and 0.065 μg L^{-1}, respectively (Diniz et al., 2015; Collard et al., 2013; Zhao et al., 2009; Pérez-Estrada et al., 2005; Cleuvers et al., 2004). Both drugs can cause acute and chronic toxicity to aquatic organisms. Damage to liver and kidney cells has been observed in fish exposed to 1 μg L^{-1} of diclofenac (Ziylan and Ince, 2011). Chronic toxicity from mefenamic acid has been detected in *Daphnia magna* exposed to concentrations of 1.0 and 0.25 mg L^{-1} (Collard et al., 2013). Tolfenamic acid (TA) (2-[(3-chloro-2-methylphenyl)amino]benzoic acid, MW = 261 g moL^{-1}), a NSAID of the fenamate family, has a diphenylamine structure typically found in emerging contaminants (Venkataraman et al., 2014). Because TA is structurally similar to diclofenac and mefenamic acid, chemical studies to identify toxic intermediates formed during TA degradation by AOPs is extremely important. To the best of our knowledge, this is the first study conducted to identify intermediates of TA degradation and investigate their toxicity.

The purpose of this investigation was to evaluate TA degradation by direct photolysis (UV-ABC) and UV-ABC/H_2O_2 using an experimental design. For the UV-ABC/H_2O_2 process, a 2^3 factorial design with added center point was employed to evaluate H_2O_2 concentration ([H_2O_2]), TA concentration ([TA]), and experiment time (time), considering two responses: percent TA degradation and percent H_2O_2 photolysis. For the UV-ABC/H_2O_2 process, the second-order kinetic constant for TA was calculated in alkaline pH under optimal conditions. Additionally, the intermediates formed during the UV-ABC and UV-ABC/H_2O_2 processes were identified and a possible degradation pathway was proposed for each process. The intermediate products were also evaluated for toxicity.

2. Materials and methods

2.1. Reagents

Tolfenamic acid (99% purity; Sigma-Aldrich), 2,4D (>97% purity; Fluka Analytical), hydrogen peroxide (30%; Vetec), and potassium hydroxide (85%; Merck) were of analytical grade. Catalase (10,000-50,000 units/mg protein; Sigma-Aldrich) was employed to quench H_2O_2. Acetonitrile, used as the mobile phase for HPLC, was purchased from Vetec Quimica Fina. Other reagents and solvents (purchased elsewhere) were used as received.

2.2. Photodegradation procedure

The experiments for TA degradation were carried out in an annular glass photochemical reactor (V = 1 L) equipped with a 125 W E27 high-pressure mercury vapor lamp (222-578 nm, with maximum absorbance at 254 nm (Zoschke et al., 2014); 0.073 W m^{-2} irradiance; Orsan) housed in a jacketed quartz tube (outlined in Fig. 1). The solution was homogenized with a magnetic stirrer throughout the experiment.

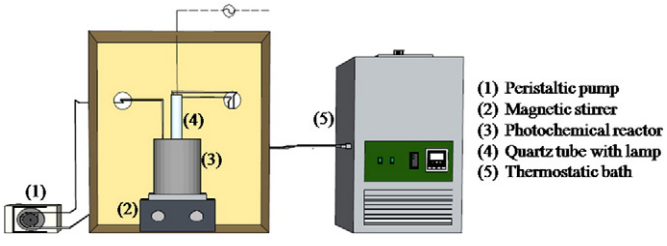


Fig. 1. Scheme of degradation system.