



Photolysis of atorvastatin in aquatic environment: Influencing factors, products, and pathways

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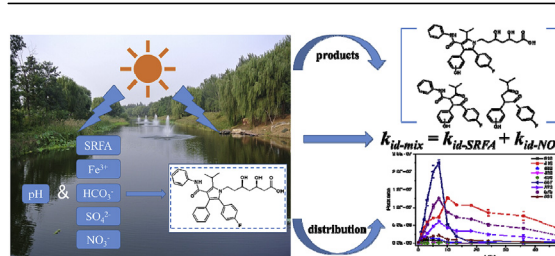
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HIGHLIGHTS

- The effect of common components in ambient water on the photolysis of ATV was evaluated.
- The concentrations of SRFA and NO₃⁻ were the major influencing factor, and their interaction was additive.
- ¹O₂ played an important role in the indirect photodegradation of ATV.
- Nine degradation intermediates were identified and degradation pathways were proposed.

GRAPHICAL ABSTRACT



Graphical abstract (5.91 cm × 14.54 cm)

ARTICLE INFO

Article history:

Received 26 June 2018

Received in revised form

15 August 2018

Accepted 17 August 2018

Available online 21 August 2018

Handling Editor: Klaus Kümmerer

Keywords:

Atorvastatin

Photodegradation

Orthogonal experiment

Degradation pathways

ABSTRACT

Atorvastatin (ATV), a second generation cholesterol-lowering drug, is detected frequently in natural water because of its extensive use and incomplete removal from wastewater. In this study, the photochemical behavior of ATV under simulated solar irradiation was systematically investigated in order to assess the potential of photolysis as its transformation pathway in aquatic environment. The quantum yield of ATV direct photolysis was determined to be 0.0041. Among various water components investigated, including pH, Suwannee River Fulvic Acid (SRFA), Fe³⁺, HCO₃⁻, SO₄²⁻ and NO₃⁻, the major factors contributing to the indirect photolysis of ATV were SRFA and NO₃⁻, and the co-existence of SRFA and NO₃⁻ showed no interaction in synthetic water containing the above water components. The results were further verified in natural water samples. Singlet oxygen (¹O₂) played dominant role in the indirect photolysis of ATV, and the contributions of ¹O₂ and ·OH to the photolysis of ATV in the solution with optimum combination of water components were calculated to be 67.14% and 0.66%, respectively. Nine phototransformation intermediates were identified by liquid chromatography - time-of-flight - mass spectrometry (LC-TOF-MS), and the degradation pathways were speculated as hydroxyl addition, pyrrole-ring open and debenzamide reactions. In addition, the evolution of products in the degradation process showed that the ring-opened product P416 and hydroxylation product P575 still remained at a certain level after two days of photodegradation, which may accumulate and cause additional ecological risks. This study provides significant information for understanding the risk and fate of ATV in aquatic environment.

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1. Introduction

The increasingly serious environmental problems, originated from continuous release of natural and anthropogenic chemicals into natural water bodies, have attracted widespread attention around the world, and especially statins (Subedi et al., 2017; Reina et al., 2018). Statins are one group of pharmaceuticals widely used in the treatment of hyperlipidemia (Machado et al., 2015; Santoko and Cooper, 2017), mainly by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase for cholesterol synthesis, among which atorvastatin (ATV) is one of the most commonly used second generation statins (Montanaro et al., 2009). ATV is either excreted (metabolized or not) by patients or dumped in drain, thus reaching municipal wastewater treatment plants (MWWTPs) (Gracia-Lor et al., 2012). Because traditional MWWTPs are not specifically designed to remove these emerging contaminants (Boleda et al., 2011; Wu et al., 2016), the residual of ATV has been discharged in wastewater effluent into aqueous environment with significant level. For example, ATV has been detected in Tennessee River water with 101.3 ng/L (Conley et al., 2008) and in drinking water with less than 0.25 ng/L (Vanderford and Snyder, 2006).

As reported, ATV has adverse effects on duckweed by inhibiting the activity of HMG-reductase with the EC_{10} value of 26.1 $\mu\text{g/L}$ (Brain et al., 2006). Exposure to different concentrations (0.05, 0.15, 0.3, 0.5 and 1 μM) of ATV for 48 h could cause bleeding in wild-type larvae of zebrafish and the amount of bleeding zebrafish increased with increasing ATV concentrations (Gjini et al., 2011). Recent studies found that the exposure of ATV acid and lactone (nominal concentrations 200 ppt and 10 ppb) for 7 days could cause up-regulated gene expression in the gill of adolescent rainbow trout (Ellesat et al., 2012). Except for ATV, its transformation products, e.g. ATV lactone and ortho-hydroxy ATV lactone, which may be formed as photodegradation intermediates of ATV, were reported to show cytotoxicity to primary rainbow trout (*O. mykiss*) hepatocytes at exposure concentrations of 0.4–400 μM , and the lactone forms of ATV were more toxic than its active acid forms (Ellesat et al., 2010). Therefore, it is of great significance to explore the transportation and transformation process of ATV in aquatic environment.

Natural and anthropogenic chemicals, including statins, undergo multiple transformation processes in natural water matrices, including biological and non-biological transformations (Wilde et al., 2016; Li et al., 2017), among which phototransformation plays an important role in the environmental fate of pharmaceutical compounds (Xia et al., 2009). It had been demonstrated that the direct photolysis of ATV could occur as it can absorb UV light at 290–320 nm, which is partially overlapped with the solar emission spectrum (Lam et al., 2004; Lam and Mabury, 2005). Various components and environmental variables can affect photodegradation of organic compounds, including pH, dissolved organic matter (DOM), cations and anions (Vebrosky et al., 2018). Behnaz et al. explored adequately the mechanism of DOM on photodegradation of ATV at the concentrations of 35.8 μM and 35.8 nM via quantifying the contribution of reactive oxygen species to degradation. The results showed that DOM has positive effect on the removal rates of ATV, and $^1\text{O}_2$ played a more important role to the degradation of 35.8 μM ATV than $\cdot\text{OH}$, while the contribution of $^1\text{O}_2$ and $\cdot\text{OH}$ to the degradation of 35.8 nM ATV were minor (Razavi et al., 2011). Some scholars found that the degradation of ATV was promoted in the co-existence of DOM, NO_3^- and HCO_3^- (Lam and Mabury, 2005). However, the interaction mechanism among DOM, NO_3^- and HCO_3^- was unclear, and the photodegradation products were rarely studied. In addition, other water constituents (i.e. Fe^{3+} and SO_4^{2-}) existed in natural water may also affect the

photodegradation of ATV in natural water environment, and their interaction with each other is not clear. For example, Fe^{3+} and DOM can undergo complexation or chelation to form iron-DOM that can produce $\cdot\text{OH}$ through the ligand-to-metal charge transfer (Voelker et al., 1997), DOM and NO_3^- can compete for light, and pH will affect the ionic morphology of DOM, HCO_3^- , and Fe^{3+} . Previous studies have focused on the influence of single-component on the photolysis of ATV, whereas the photolysis of ATV in complex water matrix and the degradation pathways and evolution of degradation products are rarely studied.

In this study, for the first time, the orthogonal array experiment was designed to explore the multi-effect of basic water components (i.e. DOM, cations, and anions) and the optimal combination of factors on the photolysis of ATV in synthetic fresh waters, which was helpful to comprehensively understand the transformation process. Similar method has been used in literature to investigate the photolysis of malachite green and crystal violet by the orthogonal experiments (Yong et al., 2015; Li et al., 2016). Moreover, the results were further verified in the real water matrices. The photodegradation products of ATV were also identified by liquid chromatography - time-of-flight - mass spectrometry (LC-TOF-MS), and the evolution and distribution of products in the degradation process were analyzed. The results provided useful information for the evaluation of the fate and ecological risk of ATV in real aquatic environment.

2. Materials and methods

2.1. Materials

Atorvastatin (3R, 5R)-7-[2-(4-fluorophenyl)-3-phenyl-4-(phenylcarbamoyl)-5-(propan-2-yl)-1H-pyrrol-1-yl]-3,5-dihydroxyheptanoic acid (ATV) was purchased from J&K Scientific Ltd. Sodium dihydrogen phosphate (NaH_2PO_4), disodium hydrogen phosphate (Na_2HPO_4), sorbic acid (SBA), sodium azide (NaN_3) and formic acid were obtained from Sigma-Aldrich Corporation. HPLC grade Methanol and isopropyl alcohol (IPA) were supplied by Merck KGaA. Suwannee River Fulvic Acid (SRFA) was provided by the International Humic Substances Society (IHSS). Other chemicals in analytical grade purity were purchased from Nanjing Chemical Reagent Co. (Nanjing, China). Deionized water (DIW) ($>18 \text{ M}\Omega \text{ cm}$) was prepared by a Millipore Milli-Q purification system. All reagents were directly dissolved in DIW and were stored in 4 °C refrigerator.

2.2. Experimental procedures

2.2.1. Irradiation equipment

Irradiation experiments were carried out in a XPA-VII photochemical reactor (Xujiang Electromechanical Plant, Nanjing, China) equipped with a 1000 W xenon lamp (Beijing Electric Light Source Institute, China) placed in a quartz cooling jacket and connected with a CHD-O515 low temperature thermostat bath to keep the temperature at 25 ± 0.5 °C (Bo Yuan Experimental Analysis Instrument Factory, Changzhou, China). In order to simulate solar irradiation, a long-pass filter was employed to cut off the incident light of $\lambda < 290 \text{ nm}$. The transmittance of the filter and the emission spectrum of the xenon lamp were shown in Fig. S1. The intensity of the light was measured to be about 1400 $\mu\text{W}/\text{cm}^2$ at 365 nm using an ultraviolet and visible light irradiation detector (Photoelectric Instrument Factory of Beijing, Normal University, China), which was close to the summer sunlight irradiation at noon in Nanjing (32°02'N). Each capped cylindrical quartz tube (50 mL with a diameter of 2 cm) containing 25 mL reaction solution were set in a merry-go-round unit at a fixed distance around the light source in

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