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Degradation kinetics and pathways of three calcium channel blockers under UV irradiation

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ABSTRACT

Calcium channel blockers (CCBs) are a group of pharmaceuticals widely prescribed to lower blood pressure and treat heart diseases. They have been frequently detected in wastewater treatment plant (WWTP) effluents and downstream river waters, thus inducing a potential risk to aquatic ecosystems. However, little is known about the behavior and fate of CCBs under UV irradiation, which has been adopted as a primary disinfection method for WWTP effluents. This study investigated the degradation kinetics and pathways of three commonly-used CCBs, including amlodipine (AML), diltiazem (DIL), and verapamil (VER), under UV (254 nm) irradiation. The chemical structures of transformation byproducts (TBPs) were first identified to assess the potential ecological hazards. On that basis, a generic solid-phase extraction method, which simultaneously used four different cartridges, was adopted to extract and enrich the TBPs. Thereafter, the photo-degradation of target CCBs was performed under UV fluences typical for WWTP effluent disinfection. The degradation of all three CCBs conformed to the pseudo-first-order kinetics, with rate constants of 0.031, 0.044 and 0.011 min^{-1} for AML, DIL and VER, respectively. By comparing the MS^2 fragments and the evolution (i.e., formation or decay) trends of identified TBPs, the degradation pathways were proposed. In the WWTP effluent, although the target CCBs could be degraded, several TBPs still contained the functional pharmacophores and reached peak concentrations under UV fluences of 40–100 mJ cm^{-2}.

1. Introduction

In the last few decades, the occurrence of pharmaceuticals and personal care products (PPCPs) in the environment has received increasing attention and induces great challenge to the safety of aquatic ecosystems (Schwarzenbach et al., 2006). These PPCPs are mainly discharged from private households, hospitals and pharmaceutical industries, and eventually reach wastewater treatment plants (WWTPs). However, most of these compounds are only partly removed during wastewater treatment and thus appear in receiving waters and bio-solids (Batt et al., 2008; Chari and Halden, 2012).

Calcium channel blockers (CCBs), such as amlodipine (AML), diltiazem (DIL), and verapamil (VER), are a group of pharmaceuticals that can selectively block the influx of calcium ions through a calcium channel. They are widely prescribed to lower the blood pressure and to treat arrythmias, angina and other heart diseases (Elliott and Ram, 2011). The occurrence of these CCBs in the WWTP effluents and downstream river waters have been frequently reported in recent years, with a concentration range of 3.0–510.0 ng L^{-1} (Hummel et al., 2006; Batt et al., 2008; Spongberg and Witter, 2008). Although no direct harmful effects to human have been reported, it is proved that an exposure to a certain concentration of CCBs in the WWTP effluent can induce ecological hazards to fish (Du et al., 2014). Wang and Gardinali (2013) also reported that DIL in reclaimed water can be ingested by fish and accumulate in fish body with a bio-concentration factor larger than 16 and an *in-vivo* half-life larger than 117 h, indicating a potential ecological risk.

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Because of its distinct advantages such as high inactivation efficiency, easy operation, and small space-occupancy, ultraviolet (UV) technologies have been increasingly applied for drinking water and wastewater disinfection (Parkinson et al., 2001; Li and Blatchley, 2009). Recently, UV photolysis of water-borne PPCPs during the WWTP effluent disinfection process has been more frequently reported (Sun et al., 2014; Wang et al., 2014); however, few studies have focused on the degradation kinetics and mechanism of CCBs under UV irradiation. As revealed by previous researches, most CCBs (e.g., ALP, DIL) are unstable against UVA (320–400 nm), UVB (290–320 nm), or solar irradiation (Fasani et al., 2008; Kawabe et al., 2008), which indicates that the photo-degradation of CCBs under 254 nm UV is possible.

Moreover, co-existing matrix materials, such as dissolved organic matter (DOM) and NO_3^-, may also affect the degradation kinetics of micro-pollutants under UV irradiation by altering UV light penetration and producing/scavenging hydroxyl radicals (•OH). Mack and Bolton (1999) suggested that in the presence of NO_2^- and NO_3^- in aqueous solution, UV irradiation could yield •OH with a quantum yield ($\phi_{\bullet OH}$) of up to 9%. Wols and Hofman-Caris (2012) reported that DOM could not only act as important scavengers of •OH with rate constants of about $(2–8) \times 10^8$ M^{-1} s^{-1} in surface water and wastewater, but also produce other radicals to indirectly degrade organic compounds. They also summarized the photochemical constants of over 100 organic compounds; however, none of the selected CCBs was included.

In the present study, three CCBs, including AML, DIL and VER, were selected on behalf of the 1,4-dihydropyridine, 1,5-benzothiazepine and phenylalkylamine classes, respectively. The degradation kinetics was investigated and the transformation byproducts (TBPs) were identified after exposing a relatively high concentration level of studied CCBs (i.e., 1.0 mg L^{-1} each) to UV irradiation in Milli-Q water (MQ water). Then, the existence of functional pharmacophores in the TBP structures was examined and the degradation pathways were proposed accordingly. On that basis, a generic solid-phase extraction (SPE) method, which simultaneously used four different cartridges with different extraction modes, was adopted to extract and enrich TBPs formed in the photolytic experiments of target CCBs at a relatively low concentration level (i.e., 100 ng L^{-1} each) under UV fluences typical for WWTP effluent disinfection. Moreover, the effects of co-existing matrix materials, including humic acid (HA), NO_3^- and Cl^-, on the photo-degradation of AML were particularly clarified.

2. Materials and methods

2.1. Chemicals

The studied CCBs (>99% purity) including (+/−) verapamil hydrochloride (CAS No. 152-11-4), amlodipine besylate (CAS No. 111470-99-6) and (+)-*cis*-diltiazem hydrochloride (CAS No. 33286-22-5) were purchased from Sigma Aldrich (Schnelldorf, Germany), whose major physicochemical properties are shown in Table 1. Internal standards (amlodipine-d_4 maleic acid and verapamil-d_6 hydrochloride salt) were purchased from Toronto Research Chemicals (Ontario, Canada). Methanol and acetonitrile (ACN) were purchased from Fisher Scientific (Geel, Belgium), and ethyl acetate from Merck (Darmstadt, Germany). Formic acid (98%–100%, ACS grade) and HA sodium salt (CAS No. 68131-04-4, technical grade) were obtained from Sigma Aldrich, and KNO_3 and NaCl were from Panreac (Barcelona, Spain).

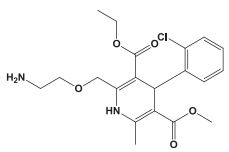
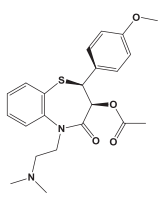
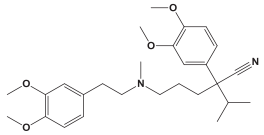
2.2. UV reaction system

Photo-degradation experiments were conducted in batch mode with a 2.0 L cylindrical glass reactor. The reaction solution was magnetically stirred and maintained at a constant temperature of 25 °C using a water bath (Fig. S1). A low-pressure mercury lamp (4 W, 30% UVC efficiency, Philips TUV G4T5) was used as the light source, which was initially warmed up for about 10 min to ensure a relatively stable output prior to each experiment. Atrazine actinometry was applied to measure the average UV fluence rate in the reactor (Canonica et al., 2008), which was equal to 0.77 mW cm^{-2} for MQ water and 0.52 mW cm^{-2} for the WWTP effluent (Text S1).

2.3. Experimental procedures and sample pretreatment

Photolytic experiments were conducted at two concentration levels of the target CCBs. Each experiment was run in triplicate and all glass containers were covered with aluminum foils to avoid

Table 1
Major physicochemical properties of target CCBs.

Compound	Structure	Chemical formula	Molecular weight (g mol^{-1})	Water solubility[a] (mg L^{-1})	pK_a[a]	Log K_{ow}[a]
Amlodipine (AML)		$C_{20}H_{25}O_5N_2Cl$	408.1452	7.4	9.45	2.22
Diltiazem (DIL)		$C_{22}H_{26}O_4N_2S$	414.5178	16.8	8.18, 12.86	3.09
Verapamil (VER)		$C_{27}H_{38}O_4N_2$	454.6016	3.94	9.68	3.79

[a] Calculated by the ALOGPS 2.1 software (http://www.vcclab.org).

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