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Persistent phototransformation products of vardenafil (Levitra®) and sildenafil (Viagra®)

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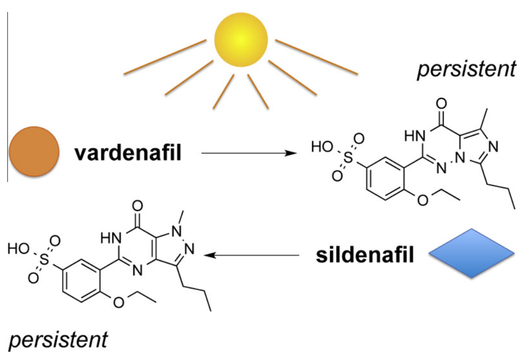
HIGHLIGHTS

- We identify the solar phototransformation products of vardenafil and sildenafil.
- We investigate the effect of humic/fulvic acid on the formation of these products.
- Two products were persistent and of potential higher environmental impact.

GRAPHICAL ABSTRACT



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ABSTRACT

As pharmaceutically active compounds (PhACs) are increasingly detected in the aquatic environment, the importance of investigating their transformation products–products of naturally occurring hydrolysis, biodegradation, and solar-mediated photochemical reactions – for persistence and ecotoxicity remains an important part of assessing the pharmaceutical's environmental impact and fate. In this study, the solar phototransformation of vardenafil (active ingredient in Levitra®) and sildenafil (Viagra®), two structurally similar compounds used to treat erectile dysfunction, was studied, with special attention to potentially persistent phototransformation (PT) products. PT products for vardenafil are identified here for the first time. Dilute solutions were prepared in buffered (pH = 7.4) aqueous solutions, both with and without Suwanee River humic acid (SRHA) and fulvic acid (SRFA), and exposed to simulated sunlight. The PT products were identified via Liquid Chromatography–Electrospray Ionization–Mass Spectrometry (LC–ESI–MS) and confirmed by MS/MS. Both SRHA and SRFA were observed to lead to more extensive degradation of VRD while having minimal effect on SLD. At least two PT products, SLD-392 and VRD-392, were observed to be notably persistent, indicating their potential impact in the aquatic environment and highlighting the need for investigations of transformation products in natural water samples.

1. Introduction

Since landmark publications in the 1990's (Halling-Sorensen et al., 1998; Daughton and Ternes, 1999), concern over the effects of pharmaceutically active compounds (PhACs) in the aquatic environment has continued to grow. These early reports as well as more recently published critical reviews (Escher and Fenner, 2011; Fatta-Kassinos et al., 2011; Boxall et al., 2012) agree that one of the "big questions" related to the impact of PhACs on the aquatic environment is that of the risk associated with their transformation products. Once PhACs enter the environment, processes

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including hydrolysis, biodegradation, and photodegradation can lead to transformation into new, structurally-related compounds. The processes of hydrolysis and biodegradation often result in transformation products that are more hydrophilic than the parent PhAC and therefore more susceptible to further breakdown into even smaller molecules. Only the PhACs dissolved in surface waters are susceptible to solar phototransformation but this process is an important one, as photochemical reactions can lead to the formation of radicals and result in compounds that have the potential to be more persistent and/or more ecotoxic than the original PhAC.

PhACs that can absorb sunlight are susceptible to direct photodegradation. The presence of dissolved organic matter (DOM) in these solutions opens the possible photochemical pathways to those that involve the indirect transfer of energy from excited-state DOM (DOM*) to the PhAC via (1) the formation of reactive oxygen species (ROS) including singlet oxygen, hydroxyl radicals, and superoxide ions and/or (2) the transfer of energy via triplet–triplet excited states. In these cases, DOM acts as a photosensitizer by absorbing then imparting the energy to the compound of interest. In other cases, DOM has been observed to act as a sunlight filter, reducing the rate of photodegradation for the PhAC.

Vardenafil (VRD) and sildenafil (SLD) are phosphodiesterase-5 (PDE5) inhibitors available by prescription in the U.S. for the treatment of erectile dysfunction. The two compounds are structurally very similar, with differences only in the position of a nitrogen in the fused heterocyclic rings and the alkyl group (ethyl for VRD, methyl for SLD) attached to the piperazine ring (Fig. 1). Both PhACs are widely used in the US and around the world; the National Institutes of Health estimates that erectile dysfunction affects thirty million men in the United States (2009). Sales for Viagra exceeded $2 billion in 2012 while sales for Levitra that same year were $422 million (Phillips, 2013). These so-called "lifestyle drugs" have been detected in effluents from wastewater treatment plants at low ng L^{-1} concentrations (Nieto et al., 2010; Schroder et al., 2010).

Previous photodegradation studies of erectile dysfunction drugs include those of sildenafil and its major metabolite (Eichhorn et al., 2012) and tadalafil (Temussi et al., 2010). Compounds with structural similarities to VRD and SLD include the fluoroquinolone class of antibiotics, which also contain a piperazine ring – a moiety that has been observed to be susceptible to phototransformation (Sturini et al., 2012; Babic et al., 2013; Wammer et al., 2013).

In this study, the phototransformation of vardenafil and sildenafil were studied. Aqueous solutions in dilute buffer at an environmentally-relevant pH of 7.4 were prepared in order to mimic natural water samples. Suwanee River humic acid (SRHA) and fulvic acid (SRFA) were chosen as forms of dissolved organic matter for investigating the possibility of indirect photodegradation on both VRD and SLD and the effect it has on the amounts of PT products formed. These solutions were exposed to simulated natural sunlight for two, three, and four day timepoints, then analyzed by LC–ESI–MS and MS/MS. The phototransformation (PT) products were identified and relative amounts in different solutions were compared. These PT products were monitored over time to study the potential for their persistence in aquatic samples. The effects of SRHA and SRFA on the structures and amounts of the PT products for both VRD and SLD are reported here. The potential for persistence of the observed PT products is discussed; those observed to be notably persistent at relatively high concentration are identified.

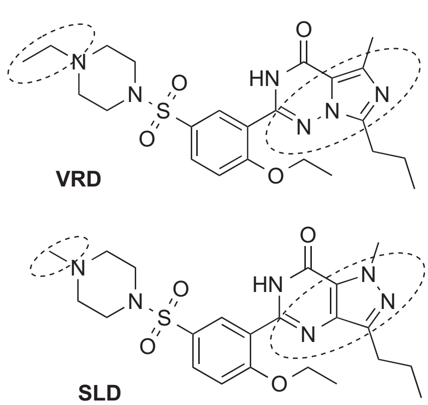

Fig. 1. Structures for vardenafil (VRD) and sildenafil (SLD). Important differences are circled with dashed lines.

2. Materials

Vardenafil hydrochloride (VRD), >99%, was obtained from AK Scientific Inc (Union City CA). Sildenafil citrate (SLD), >99%, was obtained from Pfizer Global R&D (Groton CT). Suwanee River humic acid (SRHA) and fulvic acid (SRFA) were obtained from the International Humic Substances Society (St. Paul MN). LC–MS grade 0.1% formic acid in acetonitrile, LC–MS grade 0.1% aqueous formic acid, and Optima grade methanol were purchased from Thermo Fisher Scientific (Waltham MA). Phosphate buffer (1.0 M, pH = 7.4) was obtained from Sigma–Aldrich (St. Louis MO). Distilled water was produced in house. All other reagents were J.T. Baker brand (Avantor Performance Materials, Center Valley PA).

2.1. Solution preparation

VRD and SLD solutions were prepared at 10 ppm in 5 mM phosphate buffer (pH = 7.4) diluted with distilled water. SRHA and SRFA were added to separate aliquots of these solutions at 20 ppm such that all solutions contained identical concentrations of the pharmaceutical.

2.2. N-oxide preparation

Sildenafil N-oxide was prepared using a variation of the procedure described in the sildenafil citrate USP monograph (2012) with 2.8 mg of sildenafil citrate dissolved in a combination of 260 μL 30% hydrogen peroxide and 130 μL anhydrous formic acid, vortex-mixed, and allowed to sit uncapped for 48 h. Vardenafil N-oxide was prepared in the same way, starting with 2.2 mg vardenafil hydrochloride.

2.3. Phototransformation of VRD and SLD

The 10 ppm solutions (3.5 mL) of VRD and SLD, with and without SRFA and SRHA, were placed in 3.5 mL quartz vials capped with PTFE-lined septa (NSG Precision Cells, Farmingdale NY) and exposed in a SolSim Solar Simulating Photoreactor (Luzchem, Ottowa Ontario) at 40 000 Lux with 0.5 mL aliquots removed after 48, 72, and 96 h and transferred to amber glass HPLC vials for LC–ESI–MS analysis.

2.4. UV Spectra of VRD and SLD

UV spectra were obtained for the 10 ppm solutions of vardenafil and sildenafil, buffered at pH = 7.4, using an Ocean Optics USB4000 with a 1-cm quartz cuvette.

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