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Is the phototransformation of pharmaceuticals a natural purification process that decreases ecological and human health risks?

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ABSTRACT

Sunlight photodegradation has long been considered a significant process in lowering the concentrations of pharmaceuticals in surface waters and thus decreasing the ecological risk. For the first time, this study identified the significance of investigating the environmental photodegradation of a pharmaceutical residue mixture (rather than a single compound) and the associated toxicity of transformation byproducts in environmental waters, including rivers, hospital wastewaters, and effluents from wastewater treatment plants and pharmaceutical production facilities. Pharmaceuticals undergo phototransformation rather than mineralization (11–23% in 34 h). Pharmaceutical mixtures could possibly act as dissolved organic matter for each individual compound and subsequently affect the photolysis rates. The increased toxicity of irradiated pharmaceutical mixtures challenges the validity of the current understanding of sunlight photolysis. The implications of this work suggest that current knowledge concerning the occurrence, natural attenuation, ecotoxicity, and human health risks of pharmaceuticals is far from complete; photolysis is not necessarily a purification process.

1. Introduction

Over the last decade, the presence of pharmaceuticals in wastewater and aquatic environments has become a major concern in terms of both human health and the environment. A wide variety of pharmaceuticals, with concentrations on the order of ng/L to μ/L, have been detected in the effluents of wastewater treatment plants (WWTPs), hospitals, pharmaceutical production facilities, and dairy facilities as well as in environmental water (Brown et al., 2006; Lin et al., 2008; Verlicchi et al., 2012). Furthermore, numerous studies have been conducted on the removal of pharmaceuticals from wastewater, and the results indicate that dozens of these pharmaceuticals have low removal efficiencies (<50%) in WWTPs and may not even be removed during treatment (Baker and Kasprzyk-Hordern, 2013; Kasprzyk-Hordern et al., 2009; Roberts and Thomas, 2006; Tauxe-Wuersch et al., 2005). This recurring observation has raised concerns regarding the safety of aquatic ecosystems. Occurrences of pharmaceuticals in aquatic ecosystems were reported as early as two decades ago; however, the environmental fate of these compounds has only recently been investigated.

When pharmaceuticals enter the aquatic environment via the receiving waters of wastewater treatment facilities, they undergo natural attenuation to determine their environmental fate. Natural attenuation is a combination of naturally occurring processes, including physical phenomena (e.g., dispersion, dilution, volatilization, and sorption), biological processes (e.g., biodegradation and biotransformation), and chemical reactions (e.g., hydrolysis, photolysis, sorption, and oxidation) (Gurr and Reinhard, 2006). These substances may be more interesting in terms of solar photodegradation after being discharged to natural surface water environments because they are not thoroughly removed by biodegradation, hydrolysis, oxidation, or sorption in WWTPs. Numerous pharmaceuticals are simultaneously present in the environment; thus, discussing the effects of solar phototransformation on pharmaceutical mixtures rather than (or in addition to) examining a single compound, as has been considered in previous studies, is important.

In recent years, studies have been published on the solar photodegradation potential of various pharmaceuticals, such as antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), β-blockers, and chemotherapeutic drugs, and on the ability of solar photodegradation to reduce the concentration of pharmaceutical residues, thereby mitigating the ecological risk they pose in aquatic environments (Andreozzi et al., 2003; Boreen et al., 2003, 2004; Chen et al., 2008; Lin and Reinhard, 2005; Lin et al., 2013c; Wang and Lin, 2012). Photodegradation has been demonstrated to be the most important degradation pathway in determining the natural fate of various drugs. For example, Liu et al. (2009a) found that

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propranolol does not undergo hydrolysis and biodegradation in environmental water and that metoprolol and atenolol undergo slight hydrolysis and biodegradation. These drugs all undergo significant solar photolysis. The same conclusions were found for fluoroquinolone antibiotics (Ge et al., 2010; Wammer et al., 2013), cephalosporin antibiotics (Wang and Lin, 2012), nonsteroidal anti-inflammatory drugs (NSAIDs) (Packer et al., 2003), histamine H_2-receptor antagonists (Latch et al., 2003), and 5-fluorouracil (Lin et al., 2013c) occurring in surface waters. Two classes of photochemical mechanisms—direct and indirect photodegradation—occur in natural waters. Direct photolysis occurs when a photon is absorbed by a compound, which leads to bond cleavage to form a new, stable product. The rates of direct photolysis in dilute solutions are fitted as in pseudo-first-order reactions. Pharmaceuticals such as ketoprofen, tetracycline, metronidazole, and fluoroquinolone antibiotics have rapid reaction rates (with half-lives of a few minutes) (Lin and Reinhard, 2005; Tong et al., 2011; Wammer et al., 2013, 2011). Furthermore, although many pharmaceuticals do not undergo (or only slightly undergo) direct photolysis, they are degraded through indirect photolysis (Andreozzi et al., 2006; Latch et al., 2003; Piram et al., 2008; Ryan et al., 2011). Previous research has identified dissolved organic matters (DOMs), NO_3^-/NO_2^-, and HCO_3^-/CO_3^{2-} in natural water as significant photosensitizers of indirect photolysis (Mill, 1999). These substrates produce transient excited species under sunlight, such as triplet-state DOMs, singlet oxygen, hydroxyl radicals, carbonate radicals, and other radical species ($ROO^{\bullet}$, e_{aq}^-) (Haag and Hoigne, 1986; Huang and Mabury, 2000; Larson and Zepp, 1988; Mill et al., 1980; Russi et al., 1982; Zepp et al., 1985), which can react with target pollutants in surface water.

Previous studies have demonstrated that numerous pharmaceuticals largely undergo phototransformation (with only limited mineralization), resulting in various photo byproducts (Chowdhury et al., 2011; Jiao et al., 2008b; Li et al., 2011; Lin et al., 2013c; Trovó et al., 2009; Wang and Lin, 2012). Thus, understanding the environmental toxicity of phototransformation products is critical. Microtox is widely used as a screening toxicity test of organic and inorganic pollutants due to its sensitivity, reproducibility, rapid screening, low cost, and easy application. Furthermore, Microtox tests have shown a significant correlation between the *Vibrio fischeri* bioluminescence assay (EC_{50}) and the LC_{50} values of several hundred chemicals for many aquatic organisms (such as fish, shrimp, alga, and daphnia) (Dewhurst et al., 2002; Kaiser, 1998; Ribo and Kaiser, 1983). Researchers have also reported the high sensitivity of *Vibrio fischeri* bioluminescence using other standard toxicity assays (Dalzell et al., 2002; De Zwart and Slooff, 1983; Rojíčková-Padrtová et al., 1998). Therefore, the Microtox test may be a sensitive indicator of toxicity for ecotoxicological assessments in aqueous ecosystems.

There are limited studies on the toxicity of hospital and WWTP effluents (Emmanuel et al., 2004; Tsakona et al., 2007; Villegas-Navarro et al., 1999). For instance, Emmanuel et al. (2005) used three bioassay tests, which resulted in more than two toxicity units ($TU = 100/EC_{50}$) on *Vibrio fischeri* and *Daphnia magna* and 9–56 TU on algae in a hospital effluent in France. These observations illustrate that heavy metals, detergents, disinfectants, ammonia nitrogen, and pharmaceuticals may be the source of toxicity; however, the specific cause of toxicity has not yet been identified. Numerous pharmaceuticals have frequently been detected in the effluents of WWTPs and hospitals, and an environmental risk assessment has been performed; the results from several studies indicated that at the observed concentrations, less than 12% of these pharmaceuticals had a hazard quotient (HQ) or risk quotient (RQ) greater than one (in aquatic species including bacteria, algae, daphnia, invertebrates, and fishes) (Han et al., 2006; Sanderson et al., 2003; Verlicchi et al., 2012). Thus, these researchers concluded that no significant environmental risk of pharmaceuticals was observed in the effluents of WWTPs and hospitals. However, after the effluents of wastewaters discharged into the aquatic ecosystem are irradiated by sunlight, these pharmaceuticals could phototransform into byproducts that may exhibit ecological effects different from those of the parent pharmaceuticals.

This is the first work to comprehensively investigate the sunlight photolysis of pharmaceutical mixtures in environmental waters. The objectives of this study were to (1) investigate the photodegradation mechanism in an environmentally occurring concentration level for pharmaceutical mixtures and compare this mechanism with that of a single compound; (2) investigate the Microtox acute toxicity of pharmaceutical mixtures and the phototransformation byproducts of these mixtures in wastewaters and natural water; and (3) reevaluate and revisit the concept and risk of phototransformation—a process that has long been considered a natural purification process in fate and risk assessment calculations and models.

2. Materials and methods

2.1. Chemical and pharmaceutical preparation

LC-grade methanol was purchased from Mallinckrodt Baker (Phillipsburg, PA, USA). ACS-grade formic acid was obtained from Riedel-deHaën (Seelze, Germany). Twenty-seven of the selected pharmaceuticals (all ≥98% purity), ACS-grade ammonium acetate, sodium hydroxide, hydrochloric acid, and potassium hydrogen phthalate were purchased from Sigma–Aldrich (St. Louis, MO, USA) and Fluka (Buchs, Switzerland). The concentrations of the stock solutions of individual pharmaceuticals ranged from 700 to 9000 μM in ultrapure water (MilliQ), and some of these pharmaceutical solutions were prepared with HCl or NaOH due to their low solubility in MilliQ and were subsequently stored in amber glass bottles at 4 °C for a maximum of 30 days.

2.2. Sample collection and preparation

Wastewater effluent grab samples were collected from the four major medical center hospitals (H1 to H4) in the Taipei region, from the first large WWTP (W1) in northern Taiwan, and from the top two pharmaceutical production facilities (P1 and P2) in Taiwan, which are considered to be sources of typical wastewaters. Detailed information about these hospitals, pharmaceutical industries, and WWTP are provided in the Supplementary Data, Table S-1. According to the Environmental Protection Administration of Taiwan, these wastewaters are only treated to meet the minimum effluent standards (BOD: 30 mg/L, COD: 100 mg/L, suspended solids: 30 mg/L, true color: 550 color units, and *Escherichia coli*: 200,000 CFU/100 mL) before being discharged into the receiving rivers.

The Jingmei River (JMR) is located in southern Taipei and has a drainage area of 114 km^2 and a length of 28 km. The daily discharge of the Jingmei River was 100–300 $cm^3\ s^{-1}$ in 2007–2009. The 99%-probability water level of the sampling site for each year was 0.1 m (WRA, 2013). The stream drainage range of the upstream Jingmei River includes wastewater from 10 animal husbandry operations, approximately 150 hospitals and clinics, a Taipei zoo, and a tea tree farm.

Sample collection was performed while avoiding days in which heavy rainfall occurred to minimize losses due to overflow. Wastewater effluent was collected at the final discharge point prior to release into receiving river waters. Grab samples (2 L) were collected from the wastewaters and from the JMR in amber glass bottles in May 2013, filtered through 0.22-μm cellulose acetate membrane filters (Advantec, Toyo Roshi Kaisha, Japan), and then stored at 4 °C. The grab samples were analyzed for several parameters, including pH, DOC, NO_3^-, and alkalinity (Table S-1). The photodegradation experiments were performed on the same day that the waters were sampled.

2.3. Photolysis experiments

Photochemical experiments were conducted in a solar simulator (Suntest CPS; Atlas, Chicago, IL, USA); detailed operating conditions for these experiments have been previously reported (Lin and Reinhard, 2005). The irradiation intensity was set at 700 W/m^2 for all photolysis experiments. The temperature in the water bath was maintained at 20 °C using a cooling thermostat. Standards of 27 pharmaceuticals (each with a concentration of 4 μM) were spiked as a mixture in MilliQ (G1G2mixture_MilliQ) and in nine different environmental waters, including the JMR, WWTP effluents, pharmaceutical industry effluents, and hospital effluents (G1G2mixture_environment). Tests were also performed with lower initial target concentrations of the pharmaceuticals (0.1–2 μM each) spiked as a mixture in MilliQ. The samples were then placed in capped quartz glass reaction tubes (3.5 cm i.d. × 16 cm depth, volume 110 mL) and irradiated with a sunlight simulator. Dark