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Unveiling the important roles of coexisting contaminants on photochemical transformations of pharmaceuticals: Fibrate drugs as a case study

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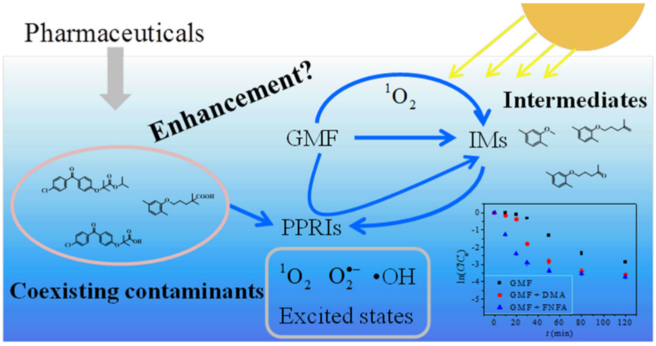
GRAPHICAL ABSTRACT



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ABSTRACT

Pharmaceuticals are a group of ubiquitous emerging pollutants, many of which have been shown to undergo efficient photolysis in the environment. Photochemically produced reactive intermediates (PPRIs) sensitized by the pharmaceuticals in sunlit natural waters may induce photodegradation of coexisting compounds. In this study, the roles of coexisting contaminants on the phototransformation of pharmaceuticals were unveiled with the fibrate drugs gemfibrozil (GMF), fenofibrate (FNF), and fenofibric acid (FNFA) as model compounds. GMF undergoes initial concentration dependent photodegradation due to the involvement of singlet oxygen ($^1O_2$) initiated self-sensitized photolysis, and undergoes pH dependent photodegradation due to dissociation and hydroxyl radical (·OH) generation. The decarboxylated intermediates of GMF and coexisting FNFA significantly accelerated the photodegradation of GMF. The promotional effects of the decarboxylated intermediates are attributed to generation of PPRIs, e.g. $^1O_2$, superoxide ($O_2{\cdot}^-$), that subsequently react with GMF. Besides, FNFA can also promote the photodegradation of GMF through the electron transfer reaction from ground state GMF to excited state FNFA, leading to the formation of decarboxylated intermediates. The formed intermediates can subsequently also facilitate GMF photodegradation. The results presented here provided valuable novel insights into the effects of coexisting contaminants on the photodegradation of pharmaceuticals in polluted waters.

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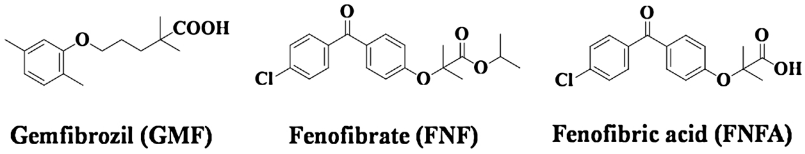

Fig. 1. Chemical structures of the target fibrates.

1. Introduction

Fibrate drugs, which are widely used as lipid regulators, have become a group of emerging contaminants due to their ubiquity in the aquatic environment and their potentially high environmental impacts that even tend to increase [1–3]. Gemfibrozil (GMF) and fenofibrate (FNF) are commonly used fibrate drugs, the structures of which are shown in Fig. 1. Due to the large consumption and continuous emission [4], GMF has been frequently detected in wastewater, surface water, and even drinking water with concentrations up to μg L^{-1} levels [3,5]. FNF was detected at much lower levels (0.04 ng L^{-1}) in wastewater and source water due to the fast hydrolysis of the ester bond to its active metabolite fenofibric acid (FNFA, Fig. 1) [3]. FNFA has been widely detected in the aquatic environment at concentrations ranging from ng L^{-1} to μg L^{-1} levels [6,7]. The fibrates were predicted to be the most hazardous compounds among the selected 2986 pharmaceutical compounds in 51 classes by Sanderson et al. due to their adverse effects on the ecosystem [8].

Fibrate drugs are recalcitrant to biodegradation [9]. Photo-induced degradation on the other hand was reported to be the main remediation method for fibrates in wastewater, using e.g. UV irradiation [10], UV/H_2O_2 [10], UV/chlorine [11], and photocatalytic [9] processes. The fibrates can be degraded in these processes by hydroxyl radicals (·OH) and by reactive chlorine species. Ma et al. found that GMF can also be oxidized by singlet oxygen ($^1O_2$), and $^1O_2$ initiated reactions account for 90.1% of GMF photodegradation [12]. These reactive species can be generated in sunlit surface waters. Thus, photochemical degradation may be the dominant elimination pathway of fibrates in natural surface waters. Cermola et al. found that fibrates can undergo direct photodegradation when irradiated with simulated sunlight [13]. However, less than 10% degradation of GMF and FNF was observed in distilled water irradiated by a 150 W Xenon lamp for 200 h.

The direct photolysis and indirect photodegradation initiated by photochemically produced reactive intermediates (PPRIs) have been well studied for many pharmaceuticals [14–16]. The PPRIs include ·OH, $^1O_2$, superoxide ($O_2\cdot^-$), hydrogen peroxide (H_2O_2) and triplet excited states. Dissolved organic matter (DOM) is ubiquitous in natural waters, and plays an important role in the generation of these PPRIs [17]. First, the excited triplet state of DOM ($^3DOM^*$) is formed by the absorption of light by the chromophoric moieties of DOM followed by the formation of excited singlet states of DOM ($^1DOM^*$). $^3DOM^*$ can induce oxidation, reduction, and energy transfer reactions of organic contaminants directly [18]. Second, $^3DOM^*$ is an important precursor of other PPRIs, e.g., $^1O_2$, $O_2\cdot^-$, and ·OH [19,20]. However, no indirect photodegradation of GMF and FNF was observed in the presence of humic acids [13], although humic acids are the components in DOM with the most reactive excited triplet states [21]. Thus, Fabbri et al. [4] considered only the inhibiting effects of DOM when predicting the environmental photodegradation half-life of GMF in surface waters.

Besides DOM, organic contaminants have also been proven to be efficient sensitizers of PPRIs in aqueous solutions [22–24]. FNF and FNFA were reported to possess high photochemical and photobiological reactivity [25,26]. First, FNF and FNFA were found to have high quantum yields for the intersystem crossing that transformed the singlet excited state into the triplet state due to the presence of a benzophenone group (Fig. 1) [27]. Secondly, the triplet excited state of FNF and FNFA is capable of generating $^1O_2$ with high quantum yields [28]. Thirdly, FNFA can be converted to a ketyl radical intermediate in the triplet excited state by the reaction with water. Meanwhile, hydrated electrons can be generated upon laser excitation of aqueous solutions of FNFA [29]. Photo-generated $^1O_2$ and other active species by FNF and FNFA can induce phototoxicity and DNA damage [28,30]. This prompted our interest to study the effect of FNF and FNFA on the photodegradation of GMF as these compounds are frequently detected in wastewater and in natural water at the same time, especially for FNFA that was detected in high concentrations [3,6]. However, the effects of coexisting pollutants on the photochemical degradation of organic contaminants are still not reported, especially for pharmaceuticals that possess high photochemical reactivity.

Thus, in this study the photochemical degradation of the fibrates GMF and FNF, and the metabolite FNFA was studied. The main objective was to investigate the effects of coexisting FNF and FNFA on GMF photodegradation. Meanwhile, the effects of degradation intermediates, which can also be considered as coexisting contaminants, on GMF photodegradation were also investigated. By density functional theory (DFT) calculations that were regarded as an efficient tool to probe reaction mechanisms [31], the mechanisms by which coexisting contaminants affect the photodegradation of GMF were explored. Finally, to better understand the photochemical transformation behavior of the fibrates in natural waters, the influence of DOM on the photochemical degradation of the target compounds was unveiled.

2. Materials and methods

2.1. Chemicals

GMF (98%), FNF (99%), FNFA (98%), 2,5-dimethylanisole (DMA, 98%), 2,5-dimethyl-1,4-benzoquinone (DBQ, 98%), sodium azide (98%), and sorbic acid (99%) were purchased from J&K Scientific Ltd. (Beijing, China). All organic solvents with chromatographical purity were purchased from TEDIA. Suwannee River Natural Organic Matter (SRNOM) was purchased from the International Humic Substances Society. Ultrapure water (18.2 MΩ) was obtained from a purification system produced by Chengdu Ultrapure Technology Co., Ltd. (China).

Freshwater (FW) samples were collected from the Songhua River (43°43′55.5″N and 126°41′30.1″E) located in Jilin, China. Seawater samples were collected from the Yellow Sea (38°50′19.2″N and 121°31′43.4″E). The samples were filtered through 0.45 μm filters and stored at −20 °C until use. SRNOM was dissolved in phosphate buffer solution, and then filtered through 0.45 mm filters to obtain a SRNOM stock solution of 250 mg L^{-1}. The total organic carbon (TOC) concentrations of the samples were determined to be 7.0 mg L^{-1}, 3.9 mg L^{-1}, and 131.6 mg L^{-1} for freshwater, seawater sample, and SRNOM, respectively.

2.2. Irradiation experiments

The irradiation experiments were performed in an XPA-7 merry-go-round photochemical reactor (Xujiang Electromechanical Plant, Nanjing, China) with quartz tubes containing the reaction solutions. A water-cooled 500 W medium-pressure mercury (Hg) lamp and a 1000 W xenon (Xe) lamp equipped with 290 nm filters were used to mimic the UV-A and UV-B portions of sunlight. The emission spectrum of the Hg and the Xe lamp is shown in Fig. S1 in the supplementary information (SI). A water bath was employed to keep the temperature fixed at 25 °C.