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Photodegradation study of three dipyrone metabolites in various water systems: Identification and toxicity of their photodegradation products

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ABSTRACT

The photochemical behaviour of three relevant metabolites of the analgesic and antipyretic drug dipyrone, 4-methylaminoantipyrine (4-MAA), 4-formylaminoantipyrine (4-FAA) and 4-acetylaminoantipyrine (4-AAA), was evaluated under simulated solar irradiation (Suntest system). For 4-MAA, different aqueous solutions (synthetic seawater, freshwater and Milli-Q water) as well as different operational conditions were compared. According to the experimental results, 4-MAA resulted as being an easily degraded molecule by direct photolysis, with half-life times ($t_{1/2}$) ranging from 0.12 to 0.58 h, depending on the irradiation conditions. Faster degradation was observed in synthetic waters, suggesting that the photolysis was influenced by the salt composition of the waters. However, no effect on the degradation rate was observed by the presence of natural photosensitizers (dissolved organic matter, nitrate ions). 4-FAA and 4-AAA showed slower photodegradation kinetics, with $t_{1/2}$ of 24 and 28 h, respectively.

A study of photoproduct identification was carried out by gas chromatography–mass spectrometry (GC–MS) and liquid chromatography-time-of-flight mass spectrometry (LC-TOF-MS) (ESI positive mode), which allowed us to propose a tentative photodegradation pathway for 4-MAA and the identification of persistent by-products in all the cases. Finally, the application of an acute toxicity test (*Daphnia magna*) showed an increase in toxicity during the photolytic process, a consequence of the formation of toxic photoproducts.

1. Introduction

Nowadays, the occurrence of pharmaceuticals and related compounds in the aquatic environment has been recognized as an emerging worldwide problem. In fact, many studies in different countries relate the occurrence of pharmaceuticals in surface waters at concentrations that can even reach the $\mu g L^{-1}$ range (Halling-Sørensen et al., 1998; Heberer, 2002; Jones et al., 2002; Bound and Voulvoulis, 2006).

The principal introduction route of these drugs and their metabolites in the environment is the conventional sewage treatment plants (STPs) (Zwiener and Frimmel, 2000; Hernando et al., 2006; Gómez et al., 2007). In many cases, the concentration levels of pharmaceuticals are reduced during the treatment process through microbial degradation or

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adsorption into activated sludge, but they are not completely eliminated (Wiegel et al., 2004). The continuous discharge of pharmaceuticals into the environment results in a chronic exposure of aquatic organisms to these compounds and/or their bioactive metabolites (De Lange et al., 2006): because their transformation/removal rates are compensated by the continuous input into the environment. Since photochemical degradation is likely to be the most important loss mechanism for many pharmaceuticals in surface water, knowledge of it is essential in understanding the persistence of these compounds (Andreozzi et al., 2003), and thus predicting their environmental fate and risk of long-term exposure, which can generate chronic toxicity within animal and vegetable populations.

Among the most common pharmaceuticals detected in the environment are the analgesics. According to Sanderson et al. (2004) more than 500 tonne were consumed in Germany in 1997. Dipyrone (also known as metamizole) is a commonly used analgesic and antipyretic drug (Fabre et al., 1982). Although its use has been banned in some countries (USA, UK), because of its association with diseases like agranulocytosis (Banchero and Giachetto, 2002), in Germany, Italy and Spain, it is still one of the most consumed pharmaceuticals. A recent paper (Feldmann et al., 2007) shows the predicted and measured loads of dipyrone metabolites in different sewage effluents and sewage-prone surface waters, evidencing the high consumption of this drug, especially in clinical use. With respect to its action mechanism, dipyrone is considered as a prodrug. After oral intake, it is rapidly hydrolysed to 4-methylaminoantipyrine (4-MAA), which is absorbed and bio-transformed by enzymatic reactions (Ergün et al., 2004). In the liver, 4-MAA is metabolized to 4-aminoantipyrine (4-AA) via demethylation and further acetylated to acetylaminoantipyrine (4-AAA) by polymorphic *N*-acetyltransferase. Another important metabolite, 4-formylaminoantipyrine (4-FAA), is generated by an, as yet, uncharacterized oxidation of the *n*-methyl group (Geisslinger et al., 1996). The metabolic route is shown in Fig. 1. These compounds are not completely eliminated by biological treatment and thus their presence has been referenced in STP effluents (Gómez et al., 2007; Martinez Bueno et al., 2007; Feldmann et al., 2007) and surface water (Wiegel et al., 2004; Zuehlke et al., 2004; Moldovan, 2006) at high concentrations. A summary of levels found is included in Table 1, highlighting the need to study in depth the fate and toxic effects of this group of pollutants in the environment.

With this context in mind, the aim of the study was (i) to investigate the photolytic behaviour of 4-MAA and two of the main metabolites 4-AAA and 4-FAA in different aqueous media (reconstituted seawater, freshwater and Milli-Q water), (ii) to identify the degradation products generated during the direct photolysis process and (iii) to determine the toxicity of these compounds and their photoproducts.

2. Materials and methods

2.1. Chemicals

Standards of 4-MAA, 4-FAA and 4-AAA (purity >98%) were provided by Sigma-Aldrich (Steinhem, Germany). HPLC-grade

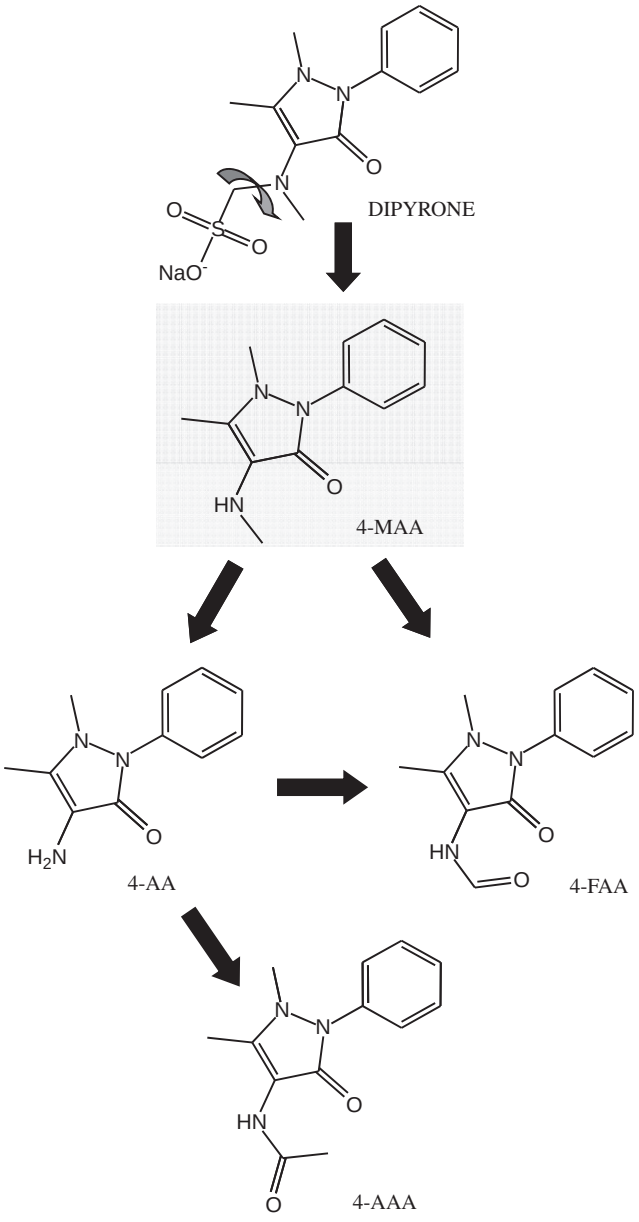

Fig. 1 – Metabolic pathway of the drug dipyrone in humans.

methanol and acetonitrile were supplied from Merck (Darmstadt, Germany). A Milli-Q-Plus ultra-pure water system from Millipore (Milford, MA, USA) was used throughout the study to obtain the HPLC-grade water used during the analyses. Formic acid (purity 98%) was obtained from Fluka (Buchs, Germany).

2.2. Irradiation system

Photolysis experiments were carried out in a solar UV simulator Suntest CPS+ (Heraeus, Germany), equipped with a 1100 W xenon arc lamp as the radiation source and special filters restricting transmission of wavelength below 290 nm. Irradiation intensity could be continuously adjusted within a range from 250 to 765 W m^{-2} approximately. These values are related to light doses per hour of irradiation adjusted to 900