



Nitrofurantoin hydrolytic degradation in the environment



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HIGHLIGHTS

- Hydrolysis of NFT was investigated at three different pH-values and temperatures.
- Half-lives ranged from 0.5 days at pH 9 and 60 °C to 3.9 years at pH 4 and 20 °C.
- Temperature dependence of the hydrolysis rate constant was determined by Arrhenius equation.
- Three hydrolysis degradation pathways were suggested.

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ABSTRACT

Occurrence of pharmaceuticals, especially antibiotics in the environment increased attention to their environmental fate. Hydrolysis is one of two abiotic processes by which compounds are degraded in the environment. According to authors knowledge this is the first study investigating hydrolytic degradation of nitrofurantoin at pH-values normally found in the environment. Nitrofurantoin hydrolytic degradation appeared to be much slower at acidic (pH 4) solution compared to neutral (pH 7) and alkaline (pH 9) solutions at all three investigated temperatures (20 °C, 40 °C and 60 °C). In all cases nitrofurantoin hydrolysis followed the first-order kinetics with half-lives ranged from 0.5 days at pH 9 and 60 °C to 3.9 years at pH 4 and 20 °C. Temperature dependence of the hydrolysis rate constant was quantified by Arrhenius equation; obtained E_a values were as follows: 100.7 kJ mol⁻¹ at pH 4, 111.2 kJ mol⁻¹ at pH 7 and 102.3 kJ mol⁻¹ at pH 9. Increase in hydrolysis rate constants for each 10 °C increase in temperature were 3.4, 3.9 and 3.5 at pH 4, pH 7 and pH 9, respectively. The structures of hydrolytic degradation products were determined and degradation pathways were suggested. Three main processes occurred depending on pH-values: protonation of the nitrofurantoin followed by cleavage of the NN– single bond, heterocyclic non-aromatic ring cleavage, and reduction of the non-aromatic heterocyclic ring.

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1. Introduction

One of the most important group of the emerging pollutants are pharmaceuticals which are used in human and veterinary medicine. They are discharged in the environment by many routes (Andreau et al., 2007), but it has been confirmed that they are mainly introduced in the environment by wastewater treatment plants which are not designed to remove these types of pollutants (Gracia-Lor et al., 2012).

Among the different groups of pharmaceuticals, antibiotics are of most concern since they can cause the development of bacteria with antibiotic resistant genes, which could lead to their

inefficiency in the treatment of various diseases (Bryce et al., 2016; Ho et al., 2016; Martinez, 2009; Schwartz et al., 2003).

Nitrofurantoin (NFT), 1-[(5-nitrofururylidene) amino] hydantoin belongs to the group of nitrofurans, class of synthetic antibiotics containing a furan ring with a nitro group (Vass et al., 2008). Since nitrofurans have a broad spectrum of antibacterial and anti-parasitic properties they are used in human and veterinary medicines (Pietruszka et al., 2007) as well as feed and food additives (Busker and Henegouwen, 1987). NFT is used in the treatment and prophylaxis of urinary tract infections caused by a wide spectrum of Gram-positive and Gram-negative bacteria such as *Escherichia coli*, *Enterococcus faecalis* and *Staphylococcus aureus* (Ensom and Decarie, 2006; Race et al., 2005; Guay, 2001; Chen et al., 1976). Its use in treatment of urinary tract infections increased with the development of bacteria resistance to commonly used

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antimicrobials such as trimethoprim-sulfamethoxazole, fluoroquinolones (McKinnell et al., 2011), β -lactams, macrolides, aminoglycosides and glycopeptides (Butt et al., 2004). However, nitrofurans usage in food-producing animals was prohibited 1995 in the European Union due to doubts regarding their safety concerns, particularly their carcinogenic properties (Commission Regulation, 1995). Regardless of mentioned facts nitrofurans are still used in some developing countries due to cheapness and effectiveness. Therefore, papers dealing with their determination in different animal tissues can be found (Zhang et al., 2016; Xia et al., 2008; Mottier et al., 2005; Leitner et al., 2001; McCracken and Kennedy, 1997; Horne et al., 1996), while papers dealing with their determination in environmental samples are very scarce (Yu et al., 2013; Pietruszka et al., 2007). The lack of environmental monitoring data for the vast majority of pharmaceuticals, and the overwrought focus on a selected few, had already been recognized. Several papers are dealing with this important issue (called The Matthew Effect, the “bandwagon effect” or “iceberg effect”) which can bias the exposure assessment (Daughton, 2014; Hughes et al., 2013; Howard and Muir, 2011). In the study of Daughton (2014), among 73 pharmaceuticals identified as highly prescribed pharmaceuticals lacking of environmental monitoring data, nitrofurantoin is included in the group of 20 pharmaceuticals with minimal published data (maximum of 1–2 published reports).

After release in the environment pharmaceuticals may be exposed to a variety of processes such as sorption to soil and sediment, abiotic (hydrolysis and photolysis) or biotic (biodegradation by bacteria and fungi) processes (Biosoć et al., 2017; Babić et al., 2013; Periša et al., 2013; Kümmerer, 2009).

Although hydrolysis is important degradation process of pharmaceuticals in the water environment, literature data about their hydrolytic stability/instability are very scarce. Hydrolysis proved to be very significant process in the degradation of β -lactam antibiotics (Mitchell et al., 2014). Investigating influence of pH-value and temperature on hydrolytic degradation of other classes of antibiotics (tetracycline, lincosamide, sulfonamide, macrolide) it was found out that they are stable under studied conditions except in the case of tetracycline antibiotics (Xuan et al., 2010; Loftin et al., 2008). Stability of two amphenicol and two macrolides in aquatic systems under ambient temperature and pH-values typical for natural waters was also found (Mitchell et al., 2015). However, according to recommendations of the European Medicines Agency (EMA) and the Food and Drug Administration (FDA), research of pharmaceuticals hydrolysis rate in water as a function of pH-values important for the environment (pH 4–9) should be implemented in accordance with OECD 111 procedure (EPA, 2008; OECD, 2004). To the best of our knowledge, there are only two papers investigating hydrolytic degradation of pharmaceuticals based on the OECD 111 procedure; in the case of twelve sulfonamides (Bialk-Bielinska et al., 2012) and three β -blockers (Maszkowska et al., 2014).

Currently, to the best of author's knowledge, there is no information about fate and effects of NFT in the aquatic environment. Therefore, the aim of this study was to investigate hydrolytic degradation of NFT which can contribute to the assessment of its environmental fate. Besides investigating degradation kinetics, the second aspect of this study was to determine the structure of the degradation products and suggest the degradation pathways of investigated NFT.

2. Materials and methods

2.1. Materials and chemicals

High purity (> 98%) analytical standard of NFT (CAS number: 67-

20-9) was supplied by Acros Organics. Physico-chemical properties (pK_a and $\log K_{ow}$) of NFT can be obtained elsewhere (Guay, 2001; PubChem, 2016). Acetonitrile, formic acid, citric acid and inorganic salts were of analytical grade and supplied by Kemika (Zagreb, Croatia). Ultrapure water was prepared by a Millipore Simplicity UV system (Millipore Corporation, Billerica, MA, USA).

2.2. The hydrolytic stability of nitrofurantoin

The hydrolytic stability of NFT was determined based on OECD 111 procedure (EPA, 2008; OECD, 2004). The experiments were conducted in capped glass vials under dark conditions. In order to determine hydrolysis rate of NFT and to identify its degradation products samples (before and after hydrolysis experiments) were analyzed using HPLC-MS/MS method. All experiments were done in three (Tier 1)/two (Tier 2) replicates.

2.2.1. Test conditions

Hydrolysis experiments at three different pH-values, 4, 7 and 9 were performed. Buffer solution pH 4 was prepared by mixing aqueous solutions of 0.2 M K_2HPO_4 and 0.1 M citric acid in the ratio 38.55/61.45 (v/v). pH 7 buffer was consisted of 0.1 M NaOH, 0.1 M KH_2PO_4 and water in the ratio 29.63/50.00/20.37 (v/v/v), and pH 9 of 0.1 M NaOH, 0.1 M H_3BO_3 in 0.1 M KCl and water in the ratio 21.30/50.00/28.70 (v/v/v). The pH of each buffer solution was checked with pH-meter S20 SevenEasy (Mettler Toledo, Greifensee, Switzerland).

Stock solution of NFT was prepared in acetonitrile. Initial concentration of 10 mg L^{-1} of NFT used in the experiments was prepared by dilution of stock solutions with appropriate buffer solutions. Since solvent content in the final solutions used for hydrolysis was negligible (1%), solvent effect was not considered during experiment. NFT solutions were bubbled by nitrogen to get rid of the oxygen.

Higher concentrations of NFT were used in the experiments since its lower initial concentrations can lead to formation of degradation products (DPs) which could be difficult to detect. Therefore, in order to produce DPs in a sufficient amount to permit their elucidation, follow their formation/degradation and to define the degradation pathways tested NFT concentrations were higher than those found in the environment.

2.2.2. Performance of the test

2.2.2.1. Tier 1. The preliminary test of NFT hydrolytic stability was performed for 5 days at 50 °C (Incubator shakers KS 3000 i control, IKA, Staufen, Germany) at three mentioned pH-values.

2.2.2.2. Tier 2. The higher test was performed for 30 days at three different temperatures (20 °C, 40 °C and 60 °C) and at the pH-values at which compound was found unstable. Kinetic behavior of NFT was described as first-order reaction. First-order hydrolysis rate constant, k_h (day^{-1}) and half-life ($t_{1/2}$) of the NFT were calculated by plotting the natural logarithm of the concentrations as a function of time.

After the determination of rate constant (k_h), the first-order (i.e., un-catalysed) rate constant (k_N) and second-order acid- and base-catalysed rate constants (k_A and k_B) were calculated using Eq. (1):

$$k_h = k_A [H_3O^+] + k_N + k_B [OH^-] \quad (1)$$

where k_h is cumulative rate constant.

Considering obtained rate constant the activation energy of the hydrolysis reaction was determined using Arrhenius Eq. (2):

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