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Review

Fluoroquinolones metal complexation and its environmental impacts

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ABSTRACT

Fluoroquinolones (FQs), the group of broad spectrum antimicrobials, are frequently detected in different environmental compartments, mostly due to incomplete metabolism in the target organism, inefficient wastewater treatment, and disposal of expired FQs directly into the environment. Another group of the contaminants, widely present in water, air, and soils, are the metal ions (Me). In general, FQs can form stable complexes with metal ions and their co-existence with Me in the environment leads to metal complexation. The most stable complexes are formed between FQs and trivalent ions, whereas FQs and alkali-earth metal ions, i.e. Ca^{2+} and Mg^{2+}, are the least stable composites. This interaction between FQs and metal ions may alter antibiotic properties. Antibacterial activity of metal complexes is generally comparable with the parent compound; however, some FQs-metal complexes are found to exhibit higher antibacterial activity. Moreover, it was proved that FQs-Me complex can display antifungal potency toward *Candida albicans.* The mobility of FQs in soil and/or water strongly depends on pH, temperature, and type of metal ions, present in the environment. This review provides a brief description of FQs, their properties, and capacity to form complexes with metal ions. It summarizes influence of FQs-Me complexes on microorganisms and their mobility in different media. Further, the review provides a linkage between the presence of these metal ions in the environment and their effect on the chemistry and biology of fluoroquinolone antibiotics.

Contents

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1. Introduction

The discovery of antibiotics, as the large group of antimicrobials, has revolutionized pharmaceutical industry. Nevertheless, their widespread use in human and veterinary medicine has led to the fact that they are repeatedly detected in environmental compartments, mostly due to their inefficient removal during wastewater treatment [1–3]. Moreover, the deposition of antibiotics has an adverse impact on the ecosystem, due to their toxic concentration [4]. Their presence exerts a selective pressure on bacteria, leading to the occurrence, selection and dissemination of antibiotic resistant genes and antibiotic resistant bacteria, which can be detected in surface water [5–7], groundwater [5], wastewater [8] and sediments [9,10]. Moreover, it has been indicated, that antibiotics may interact with surrounding substances and their transformation products can retain their pharmacological activity, due to the preserving or gaining moiety, responsible for antimicrobial potency. For instance, a by-product of enrofloxacin is ciprofloxacin and both belong to FQ family of antibiotics having a characteristic structure of 4-pyridone-3-carboxylic acid with a ring at C-5 or C-6 position, which is essential for their antibacterial activity [11]. Thereby, antibiotics and their transformation products are a potential threat to the environment.

Fluoroquinolones (FQs) are a family of broad-spectrum synthetic antibiotics, developed in the 1970s [12–14]. They belong to quinolone antibiotics, which are based on the structure of antimalarial quinine. FQs main characteristic is a fluorine atom attached to the central ring system. Most of the FQ's name ends with the "-floxacin" suffix, i.e. ciprofloxacin (CIP) [15], ofloxacin (OFL) [16], norfloxacin (NOR) [13], levofloxacin (LEVO) [17], gatifloxacin (GTI) [18] or enrofloxacin (ENR) [19]. FQs are active against Gram positive and Gram negative strains of bacteria – their effectiveness is due to their potency to inhibit bacterial DNA gyrase and/or topoisomerase IV [20].

FQs have a higher frequency of detection in different environmental compartments. For instance, they are widely present in raw wastewater. In China, the prevailing FQs were OFL and NOR, with concentrations of 1287 ng/L and 775 ng/L, respectively [21]. In Maryland, USA, the concentration of CIP was found to be 1900 ng/L and OFL 600 ng/L in raw wastewater [22]. Moreover, the frequency of CIP detection was 100%, across all sampling sites. In Japanese wastewater influent, FQs were detected with the third and fourth highest concentration – 255 –587 ng/L for LEVO and 155–486 ng/L for NOR, following clarithromycin and azithromycin [23]. In Finland, amongst all targeted pharmaceuticals (FQs, beta-blockers, antiepileptic drug) FQs, especially CIP (200–650 ng/L), were the most prevalent compounds detected in sewage influents [24]. During wastewater treatment, FQs tend to adsorb onto sludge so that high concentration of OFL and NOR, 7.29 mg/kg and 7.01 mg/kg, respectively, was found in the sludge [21]. In the WWTPs in Michigan, USA, OFL was found in secondary effluent at a concentration of 204 ng/L and in final effluent at a concentration of 100 ng/L [25]. It was calculated that daily 4.8 g of OFL was discharged into the river due to insufficient wastewater treatment. Miao et al. (2004) investigated final effluents in WWTPs in five Canadian cities (i.e., the Greater Vancouver Regional District, British Columbia; Calgary, Alberta; Burlington, Peterborough, and Windsor in Ontario) and detected CIP, NOR and OFL with the average concentrations of 118, 50 and 94 ng/L respectively [26]. Lee et al. (2007) analyzed sewage treatment plant in Ontario, Canada, and discovered that concentration of CIP in primary and final effluent ranged between 42 and 721 ng/L [27].

Apart from wastewater samples, the other environmental compartments were also investigated. For instance, FQs were detected in Chinese reclaimed water and groundwater [28]. NOR, OFL and ENR concentration ranged between 45 and 181 ng/L in reclaimed water and followed the order [NOR] > [OFL] > [ENR]. The groundwater FQs concentration was between 36.2 and 96.8 ng/L, in the following order [NOR] > [ENR] > [OFL]. The analysis of contamination in the Seine river, France, showed that sulfamethoxazole (sulfonamide antibiotic) and NOR were the compounds with the highest concentrations of 40 ng/L and 31 ng/L, respectively [29]. According to the study of Gibs et al. (2013), in New Jersey, USA, the concentration of CIP in Hohokus Brook waters (downstream of WWTP discharge), increased from 0.03 μg/L to 0.077 μg/L in years 2001–2008 [30]. Moreover, in the same sampling site, two FQs antibiotics were detected in the sediments: OFL (21 μg/kg) and CIP (10 μg/kg), which were the second and the third highest concentrations of present antibiotics, following macrolide antibiotic, azithromycin (44 μg/kg). In Chinese rivers, FQs (CIP, NOR, OFL, LOME) exhibited the highest concentration in their sediments (ranged between 1.67 and 156 ng/g) amongst four targeted classes of antibiotics [10]. Furthermore, FQs have been also detected in soils – for instance, ENR concentration ranged between 17.36 and 26.69 μg/kg in Brazil [31] and 20–50 μg/kg in Turkey [32].

FQs frequent detection is due to their widespread usage. According to the Report of Public Health Agency of Canada, FQs were the third most-prescribed antimicrobials to Canadians between 2010 and 2013 [33]. Moreover, the overall quantity of FQs, distributed for use in animals has expanded since 2010, probably due to the approval of a new indication for use [33]. According to European Medical Agency, sales of veterinary antimicrobials decreased by 7.9% (in mg/population correction unit) in twenty-six European countries between 2011 and 2013. However, the sale of FQs, along with 3rd- and 4th-generation of cephalosporins, remained stable (or slightly increased) during this period [34].

The presence of FQs in the environment was also due to incomplete metabolism of the pharmaceutical in the target organism. In fact, from 8% (trovafloxacin) to 83% (GTI) of antibiotic may be released via urine and feces in active form into the environment [35]. For instance, unchanged CIP is excreted in 65% via urine and 25% in feces [36]. This contributes to an increasing trend of drug-resistant bacteria occurrence. In 2014–2015, in Europe, *Escherichia coli* isolates were resistant mostly to aminopenicillins (57.2% of isolates) and FQs (22.8% of isolates) [37]. Between 2012 and 2015, a significant increase of FQs-resistant *Klebsiella pneumoniae* was also noticed. Moreover, multidrug resistance, including FQs-resistance, of *E. coli* and *K. pneumoniae*, was observed as an increasing trend [37]. Thus, WHO classified FQs as critically important antibacterial agent for human medicine due to the its increased bacterial resistance [38].

Nowadays, much attention has been given to antibiotics co-contamination with metal ions. Many pharmaceuticals, including FQs, possess an ability to form metal complexes, which may modify properties of FQs, i.e. altering the antimicrobial activity of antibiotic [39–41], solubility [42] or bioavailability [43]. The extensive studies have been performed for many pharmaceuticals-metal complexes, i.e. tetracyclines, quinolones or β-lactams [41,44–47]. It