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Review

Chiral pharmaceuticals: A review on their environmental occurrence and fate processes

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ABSTRACT

More than 50% of pharmaceuticals in current use are chiral compounds. Enantiomers of the same pharmaceutical have identical physicochemical properties, but may exhibit differences in pharmacokinetics, pharmacodynamics and toxicity. The advancement in separation and detection methods has made it possible to analyze trace amounts of chiral compounds in environmental media. As a result, interest on chiral analysis and evaluation of stereoselectivity in environmental occurrence, phase distribution and degradation of chiral pharmaceuticals has grown substantially in recent years. Here we review recent studies on the analysis, occurrence, and fate of chiral pharmaceuticals in engineered and natural environments. Monitoring studies have shown ubiquitous presence of chiral pharmaceuticals in wastewater, surface waters, sediments, and sludge, particularly β-receptor antagonists, analgesics, antifungals, and antidepressants. Selective sorption and microbial degradation have been demonstrated to result in enrichment of one enantiomer over the other. The changes in enantiomer composition may also be caused by biologically catalyzed chiral inversion. However, accurate evaluation of chiral pharmaceuticals as trace environmental pollutants is often hampered by the lack of identification of the stereoconfiguration of enantiomers. Furthermore, a systematic approach including occurrence, fate and transport in various environmental matrices is needed to minimize uncertainties in risk assessment of chiral pharmaceuticals as emerging environmental contaminants.

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1. Introduction

Pharmaceuticals are ubiquitous in aquatic environments impacted by wastewater effluent and are often detected at concentrations ranging from ng/L to μg/L (Gómez et al., 2010; López-Serna et al., 2013; Pal et al., 2010). However, pharmaceuticals are pollutants of major concern because they are biologically active compounds that can potentially alter the physiology and behavior of a non-target organism at low doses (Arnold et al., 2013; Daughton and Ternes, 1999; Halling-Sørensen et al., 1998). For example, exposing Eastern mosquitofish to fluoxetine for 28 days at a sublethal concentrations altered their antipredator behavior (Martin et al., 2016). Furthermore, in a different study, the aggression behavior essential for survival decreased when crayfish were exposed to naproxen for 23 h (Neal and Moore, 2017). Therefore, understanding the distribution, fate, and transport of pharmaceuticals in the aquatic environment is critical for their environmental risk assessment.

At least 50% of pharmaceuticals in current use are chiral compounds often sold as racemates (Nikolai et al., 2006; Ribeiro et al., 2012a, b, c). However, enantiomers of chiral pharmaceuticals often exhibit stereoselectivity in environmental occurrence (Kasprzyk-Hordern and Baker, 2012; Ma et al., 2016; MacLeod and Wong, 2010), fate (Amorim et al., 2016; Bagnall et al., 2013; Ribeiro et al., 2013), and toxicity (Stanley et al., 2007; Sun et al., 2014). For example, a recent study on occurrence of pharmaceuticals in Dongting Lake in China showed that the concentration of (*S*)-fluoxetine was higher than that of (*R*)-fluoxetine (Ma et al., 2016). Stereoselectivity was observed in the biodegradation of amphetamine in river water and activated sludge microcosm with (*S*)-enantiomer preferentially degraded (Evans et al., 2016). Furthermore, exposing fathead minnow to fluoxetine showed that (*S*)-fluoxetine was more potent to sublethal standardized and behavioral endpoints than its antipode (Stanley et al., 2007). However, despite the growing knowledge on stereoselectivity in environmental distribution, fate and toxicity of pharmaceuticals, chirality has not been consistently incorporated in the environmental risk assessment of chiral pharmaceuticals.

Reviews on chiral pharmaceuticals in the environment show that the body of knowledge on stereoselectivity in the environment has steadily grown over the past two decades. Initial challenges in separating and detecting pharmaceuticals in complex matrices contributed to the poor understanding of the environmental behavior of chiral pharmaceuticals (Wong, 2006). However, the development of versatile chiral columns in liquid chromatography (LC) such as Chirobiotic V and application of chromatographic instruments coupled to a mass spectrometer solved much of the analytical problem (Evans and Kasprzyk-Hordern, 2014; Pérez and Barceló, 2008). Other reviews explored the application of stereoselectivity in distribution and fate as a tool for source apportionment studies (Hashim et al., 2010; Kasprzyk-Hordern, 2010; Ribeiro et al., 2012a, b, c). The purpose of this review is to summarize up-to-date progress in evaluation of chiral pharmaceuticals as environmental contaminants, and identify knowledge gaps for future research. We also consider several aspects that were inadequately addressed in the previous reviews, including enantioselectivity in adsorption, the importance of exact stereoconfiguration in environmental monitoring, and chiral inversion as a factor influencing the enantiomer composition of chiral pharmaceuticals in the environment. We further make recommendations on research opportunities, including development of multi-dimensional chromatographic methods for better enantiomer resolution, evaluation of enantioselectivity in processes such as biodegradation in soil, accumulation into plants, and metabolism in aquatic and terrestrial organisms, and better use of enantiomer profiles as predictive tools in elucidating enantioselectivity in fate and transport of pharmaceuticals as environmental contaminants.

1.1. Terminology

Chiral compounds are molecules with one or more stereogenic centers. The enantiomers of a chiral compound have identical chemical structures, but different spatial arrangements of the atoms around the stereogenic center (Ribeiro et al., 2012a, b, c). Enantiomers are non-superimposable stereoisomeric pairs of chiral compounds, while diastereomers are stereoisomers that are not mirror images (Fig. 1). The physicochemical properties of diastereomers are not identical, while those of enantiomers are similar except for their ability to rotate a polarized light. For example, *R*- and *S*-ibuprofen are enantiomers, but 17α- and 17-β estradiol are diastereomers. Enantiomers are commonly named using the *R*/*S* convention, where the Cahn–Ingold–Prelog rules are used to prioritize substituent groups around the stereogenic center (Smith, 2009). Alternatively, enantiomers are also identified