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REVIEW

Chiral pharmaceuticals in the environment

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Abstract Many pharmaceutical pollutants are chiral, existing in the environment as a single enantiomer or as mixtures of the two enantiomers. In spite of their similar physical and chemical properties, the different spatial configurations lead the enantiomers to have different interactions with enzymes, receptors or other chiral molecules, which can give diverse biological response. Consequently, biodegradation process and ecotoxicity tend to be enantioselective. Despite numerous ongoing research regarding analysis and monitorization of pharmaceutical ingredients in the environment, the fate and effects of single enantiomers of chiral pharmaceuticals (CP) in the environment are still largely unknown. There are only few chiral analytical methods to accurately measure the enantiomeric fraction (EF) in environmental matrices and during biodegradation processes. Furthermore, the ecotoxicity studies usually consider the enantiomeric pair as unique compound. We reviewed the current knowledge about CP in the environment, as well as the chiral analytical methods to determine the EF in environmental matrices. The degradation and removal processes of CP of important therapeutic classes, usually detected in the environment, and their toxicity to aquatic organisms were also reviewed. On the other hand, this review demonstrate that despite the great importance of the stereochemistry in pharmaceutical science, pharmacology and organic chemistry, this is normally neglected in environmental studies. Therefore, CP in the environment need much more attention from the scientific community, and more research within this subject is required.

Keywords Biodegradation · Chiral pharmaceuticals · Chiral stationary phases · Ecotoxicity · Enantiomeric fraction · Enantioselectivity

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Introduction

This manuscript is an abridged version of our chapter published in the book *Environmental Chemistry for a Sustainable World* (Ribeiro et al. 2012). Chiral compounds are substances with a similar chemical structure that, in general, confers them the same physical and chemical properties like melting point, solubility and reactivity. However, they differ in the deviation of polarized light due to the different spatial configuration, originated by planes, axis or centers of asymmetry, given two non-superposable left-handed and right-handed mirror images compounds, called enantiomers. In the case of enantiomers with asymmetric center, the most common examples are those with a carbon holding a set of four different substituents in a spatial arrangement generating a stereogenic center (Fig. 1), but other atoms such as sulfur or phosphorus can also be a stereogenic center (Fig. 2).

Despite the similar thermodynamic properties in achiral medium, enantiomers normally have a different behaviour

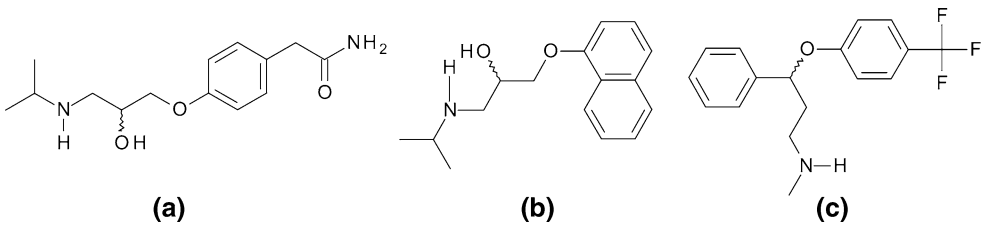

Fig. 1 Structures of three pharmaceuticals with a carbon stereogenic center: **a** atenolol; **b** propranolol; **c** fluoxetine

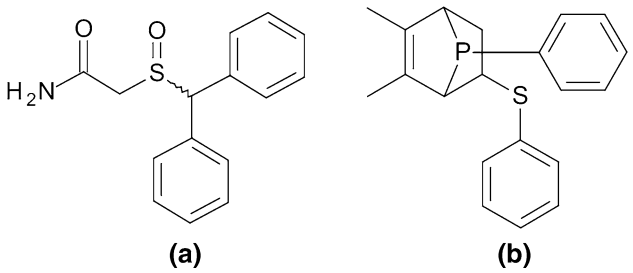

Fig. 2 **a** Structure of modafinil with a sulfur stereogenic center; **b** structure of 2,3-dimethyl-7-phenyl-5-(phenylsulfanyl)-7-(*R*/*S*)-phosphabicyclo[2.2.1]hept-2-ene with a phosphorus stereogenic center

when the environment is also chiral. Amino acids, carbohydrates, deoxyribose and ribose are chiral compounds that are the unity of important natural molecules such as proteins, glycoproteins, DNA and RNA, respectively (Müller and Kohler 2004; Hühnerfuss and Shah 2009). As such, in biological processes, enzymes, receptors and other binding-molecules have the capacity to recognize enantiomers in a different way. Therefore, enantiomers of chiral pharmaceuticals (CP) can present different pharmacokinetic and pharmacodynamic properties, different dissociation constant from the binding site and different attachment to it (Fig. 3), leading to different biological response in quality or quantity (Campo et al. 2009).

There are many CP that need to be commercialized as a single enantiomer, mostly due to the association of the enantiomers to different receptors, leading to different

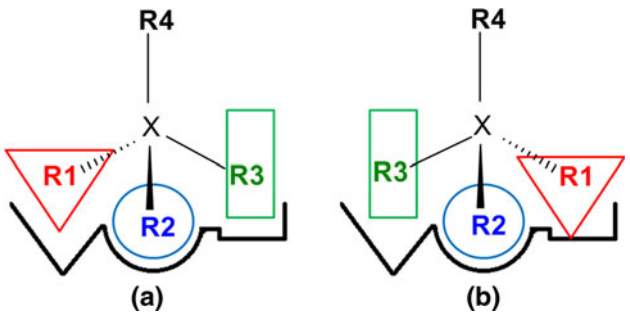

Fig. 3 Schematic process of the complementary recognition by enzymes, receptors and other binding-molecules of one enantiomer (**a**) due to its complementary configuration; rather than the other (**b**) that can be a ligand for other receptor, leading to another activity, side effects or even toxic effects

responses (Mannschreck et al. 2007). However, there are many CP that are both commercialized as racemic and enantiopure forms (Tucker 2000; Hutt and Valentová 2003; Orlando et al. 2007). Table 1 shows some CP that can be used as racemates and/or enantiopure formulations, depending on the effects of each enantiomer (Lima 1997).

The recent advances in stereoselective synthesis and chiral analysis led to an increase in the single enantiomers as drugs available in the market (Hutt 1998). The re-evaluation of the license of the enantiomeric pure drugs that were produced as a racemic mixture, called as chiral switching process, also contributed to increase the use of single enantiomers (Cordato et al. 2003; Hutt and Valentová 2003; Caner et al. 2004).

There are also some CP, such as propionic acid derivatives belonging to non-steroid anti-inflammatory drugs (NSAIDs), which suffer chiral inversion, and yet are commercialized as racemates in most countries, except naproxen (Fig. 4). Ibuprofen (IB) (Fig. 5) is a common example of NSAIDs, which is normally sold as racemate, although *S*-(+)-IB is practically responsible for the pharmacologic action. Moreover, this drug, as other profens, suffers unidirectional conversion in vivo to the pharmacologic active *S*-(+)-IB, which makes more difficult to obtain the enantiopure *S*-(+)-IB with a good percentage of conversion, justifying the use of racemates (Lima 1997; Tucker 2000; Carvalho et al. 2006).

Another therapeutic option is the use of CP with an enantiomeric ratio different from 1 to improve the benefits of each enantiomer, when applicable. Enantiomeric fraction (EF) is the proportion of the concentration of one enantiomer to the total concentration, expressing the relative concentration of an enantiomer's compound. Racemate exhibits an EF of 0.5 while an enantiomerically pure compound has a value of 0 or 1. As an example, the advantage of the administration of a mixture of *S*0.75/*R*0.25 bupivacaíne rather than the racemate was reported, with the same anesthetic properties and with less toxicity (Gonçalves et al. 2003).

This review emphasizes three pharmaceutical classes: Beta-blockers, Antidepressants and NSAIDs, due to their persistence in the environment and respective ecological effects (Ternes 1998; Trenholm et al. 2006; Vanderford and Snyder 2006; Pérez and Barceló 2008; Fernández et al. 2010; Santos et al. 2010).

Table 1 Examples of CP used as racemates or as single enantiomers

Drug	Qualitative activity		Mode of action	Description	References
	Equal	Different			
Promethazine	X		Equal pharmacologic potency; This effect is due to the equal pharmacokinetic and pharmacodynamic properties	Promethazine (anti-histaminic)	Chen et al. (1992)
Propranolol	X		Different pharmacologic potency; In this case, both enantiomers can reach the receptor, binding to it at the binding site with different dissociation constant, leading to a stronger attachment of one enantiomer, which have more biological activity	Propranolol: (−)-propranolol has a pharmacological activity 100 times superior to (+)-propranolol	Pavlinov et al. (1990)
Warfarin	X			Warfarin: anticoagulant, with greater anticoagulant potency of (*S*)-warfarin	Choonara et al. (1986)
Methadone	X			Methadone: (*R*)-methadone has higher affinity for the μ-opioid receptor and longer plasma elimination half-life	Huq (2007)
Bupivacaine	X		Both enantiomers have pharmacological activity but one of them is less toxic	Bupivacaine: (*S*)-bupivacaine has the same neural blocking characteristics, but has a higher margin of safety	Huang et al. (1998)
Fluoxetine		X	Enantiomers have different pharmacological activity	Fluoxetine: (*R*)-fluoxetine is an antidepressant and (*S*)-fluoxetine was tested for migraines prophylaxis	Steiner et al. (1998)
Propoxyphene		X		Propoxyphene: (+)-propoxyphene is analgesic and (−)-propoxyphene is antitussive	Cooper and Anders (1974)
Indacrinone		X	One enantiomer antagonizes the side effects of the other	Indacrinone: (*S*)-indacrinone is natriuretic and (*R*)-indacrinone is uricosuric	Jain et al. (1984)
Ibuprofen		X	One enantiomer is pharmacologically active and the other does not have activity	Ibuprofen: Its anti-inflammatory activity is almost due to (*S*)-ibuprofen	Mayer and Testa (1997)
Cetirizine		X		Cetirizine: Its antiallergic activity is due to (*R*)-cetirizine	Mannschreck et al. (2007)
Dopa		X	One enantiomer is pharmacologically active and the other has side effects	Dopa: L-dopa is used in Parkinson's disease and D-dopa has side effects like nausea, anorexia, involuntary movements and granulocytopenia	Hutt and Valentová (2003)
Thalidomide		X	One enantiomer is pharmacologically active and the other is toxic	Thalidomide: (*R*)-thalidomide was used for insomnia and nausea therapy; (*S*)-thalidomide is teratogenic	Smith (2009)
Picenadol		X	One enantiomer is pharmacologically active and the other is antagonist	Picenadol: (+)-picenadol is an opioid agonist and (−)-picenadol is a weak agonist/antagonist	Franz et al. (1990)

This table resumes the benefits and disadvantages, depending on the pharmacological or side effect

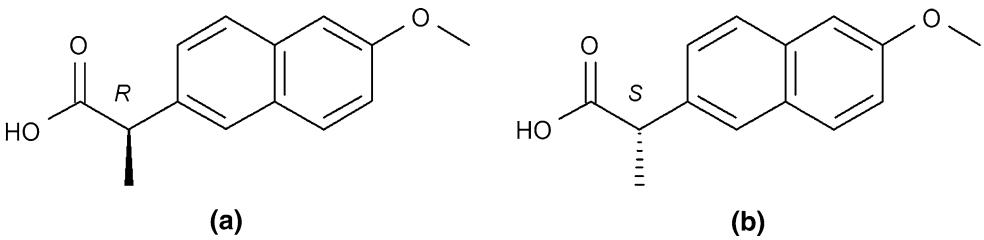

Fig. 4 Structure of (*R*)-naproxen (**a**) and (*S*)-naproxen (**b**)

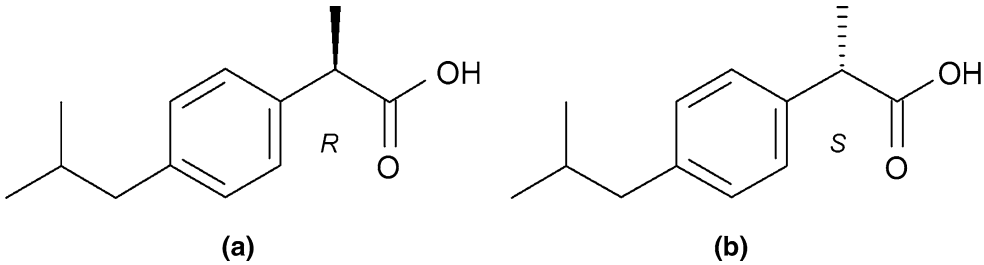

Fig. 5 Structure of (*R*)-ibuprofen (**a**) and (*S*)-ibuprofen (**b**)

Analytical methods for quantification/identification of chiral pharmaceuticals in the environment

Gas chromatography

Gas chromatography (GC) have the advantages of high efficiency, sensitivity and speed of separation, ability to separate analytes from impurities and not needing optimization of mobile phase concerning solvents, pH, modifiers and gradients (Eljarrat et al. 2008). The indirect mode resulting in diastereoisomers separation can be easily applied (Bojarski 2002; Carvalho et al. 2006; Hühnerfuss and Shah 2009) while the direct mode with a chiral stationary phase (CSP) is limited to only a few commercial CSP available. The most used columns are cyclodextrin-based and have demonstrated a great applicability in organochlorine pesticides (Wong and Garrison 2000; Eljarrat et al. 2008). Another useful CSP is based on metal complexes such as metal-β-diketonate polymers (Rykowska and Wasiak 2009).

The disadvantages of GC are the need of derivatization, in some cases, to increase the volatility, to prevent the peak tailing and thus to improve detection limits by the peak shaping (Zhang et al. 2009). The high temperature used can also lead to racemization or decomposition (Schurig 2001; Jiang and Schurig 2008). Thus, GC has several limitations to environmental analyses of CP (Huggett et al. 2003; Lamas et al. 2004; Jones et al. 2007).

High performance liquid chromatography (HPLC)–Liquid chromatography/mass spectrometry (LC–MS/MS)

High performance liquid chromatography (HPLC) has become a technique of routine analysis because of the numerous combinations of the available columns with a high diversity of mobile phases, and the detection methods that can be coupled, such as ultra-violet (UV), fluorescence (FD) and mass spectrometry (MS) (Aboul-Enein and Ali 2004; Görög 2007). Direct methods using CSP are usually the first choice for analysis of CP by HPLC. There are many different types of commercial chiral columns for HPLC: Pirkle type or donor-acceptor CSP, crown ethers CSP, ligand-exchange CSP, polysaccharide derivatives CSP, cyclodextrin CSP, protein CSP, macrocyclic glycopeptides antibiotics CSP and others such as CSP based on synthetic polymers (Pirkle and Pochapsky 1989; Haginaka 2008; Lämmerhofer 2010). The major advantage of this method is the ability of the analyte to remain unmodified. The choice of the CSP is based on the experience and the available literature, being often empirical by trial and error evaluation. However, some authors start with polysaccharides or macrocyclic antibiotics because of their broad application and the possibility to operate in normal, reverse phase, polar organic mode and polar ionic mode (Perrin et al. 2002a, b; Andersson et al. 2003; Cass et al. 2003; Sousa et al. 2004; Ates et al. 2008; Pirzada et al. 2010). The most frequent separation mode is normal phase; however, this tendency is turning to reverse phase, polar organic mode and polar ionic mode, being all applicable to the most used polysaccharides or macrocyclic antibiotics CSPs (Cass and Batigalhia 2003; Cass et al. 2003; Montanari et al. 2006; Hashem et al. 2011).

Molecularly imprinted polymers (MIP) are a synthetic alternative in which the target compound is used in the polymerization process as a template, to produce a specific receptor to one enantiomer which is known to be more retained. The removal of the template by a solvent or a chemical reaction provides a complementary site in the receptor to the target molecule, providing a MIP which can

be used as CSP and incorporated in conventional HPLC columns. These materials are easy to obtain, highly selective and stable, and the elution order is predictable. The drawback of MIP is the peak tailing produced due to the heterogeneous binding site (Wistuba and Schurig 2000; Sancho and Minguillón 2009).

The high variety of chiral commercial columns usually designed for HPLC analysis and the different elution modes makes this technique a powerful tool for chiral analysis (Perrin et al. 2002a, b; Andersson et al. 2003; Zhang et al. 2010). HPLC with different type of detection has been used for the determination of the EF of many CP in a variety of matrix, including environmental samples (Francotte 2009; Kasprzyk-Hordern et al. 2010). Few examples of analyses of environmental matrices are shown in Table 2.

Liquid chromatography/mass spectrometry (LC–MS/MS) have played a crucial role in environmental analysis (Niessen 2003; Kot-Wasik et al. 2007; Pérez and Barceló 2007; Pérez and Barceló 2008) mainly due to their versatility, sensitivity and selectivity (González et al. 2007). Recent trends in environmental mass spectrometry methods have been emerging with special focus on hybrid mass spectrometers such as quadrupole-time of flight (Qq-TOF) (Farré et al. 2008) and quadrupole-linear ion trap (Qq-LIT) (Díaz-Cruz et al. 2008). However, triple quadrupole (QqQ) mass analyzers are the most used analytical technology in environmental analyses (Gros et al. 2006; Nikolai et al. 2006; MacLeod et al. 2007; Kasprzyk-Hordern et al. 2010; MacLeod and Wong 2010; Barclay et al. 2011; Li et al. 2011). Few publications have also employed ion trap (IT) mass spectrometers for environmental determinations (Feitosa-Felizzola et al. 2007; Madureira et al. 2009; Barreiro et al. 2010, 2011).

Other techniques

Capillary electro-chromatography (CEC) is a hybrid technique of HPLC and capillary electrophoresis (CE). Likewise HPLC has high selectivity because of the wide range of mobile and stationary phases available. Likewise CE, it has high peak efficiency without the necessity of high pression (Sancho and Minguillón 2009). It is thus an easy technique with a short time of analysis and a low consumption of sample and electrolyte, providing a high potential in pharmaceutical, biomedical and environmental analysis (Li et al. 2010). The chiral selectors used in CEC include crown ethers, cyclodextrins, polysaccharides, proteins and macrocyclic glycopeptides antibiotics, the same selectors used in HPLC (Scriba 2003).

Micellar electrokinetic capillary chromatography (MEKC) is a technique that consists in the addition of a surfactant molecule (above its critical micellar

Table 2 Analytical methods of separation of several enantiomers in environmental matrices

Drug	Enantioselective method	Elution mode	Chiral stationary phase	Mobile phase	Detection limit	Matrix application	References
Fenbuconazole and metabolites	LC/MS/MS	Reverse phase	Chiralcel OD-RH	(60:40, V/V) ACN/2 mM NH_4OAc	<0.8 g kg^{-1}	Soil and water	Li et al. (2011)
Fluoxetine and norfluoxetine	LC/MS/MS	Reverse phase	Chiral α-acid glycoprotein column (chiral AGP)	(3:97, V/V) ACN/10 mM NH_4OAc (pH 4.4)	1.0–3.0 pM	Wastewater samples	Barclay et al. (2011)
Pantoprazole and lansoprazole	2DLC-IT-MS/MS	Reverse phase	RAM-BSA C_8 and amylose tris-(3,5-dimethoxyphenylcarbamate) coated onto APS-Nucleosil	ACN:H_2O	0.150–0.200 μg L^{-1}	Wastewater samples	Barreiro et al. (2011)
Omeprazole	2D-LC/UV or IT-MS/MS	Reverse phase	RAM-BSA C_8 and amylose *tris*-(3,5-dimethylphenylcarbamate) coated onto APS-Nucleosil	Phosphate buffer	5.0 μg L^{-1}; 0.025 μg L^{-1}	Waste and estuarine water samples	Barreiro et al. (2010)
Amphetamines, ephedrines and venlafaxine	LC/MS/MS	Reverse phase	Chiral-CBH column	(90:10, V/V) H_2O/2-propanol and 1 mM NH_4OAc (pH 5.0)	0.55–3.5 ng L^{-1}	Wastewater samples	Kasprzyk-Hordern et al. (2010)
Beta-blockers, selective serotonine re-uptake inhibitors and salbutamol	LC/MS/MS	Reverse phase	Chirobiotic V	(90:10, V/V) MeOH/20 mM NH_4OAc in water, 0,1% formic acid	0.2–7.5 ng L^{-1}	WWTP influents and effluents	MacLeod et al. (2007)
Beta-blockers	LC/MS/MS	Reverse phase	Chirobiotic V	MeOH/0,1% TEAA in water, acetic acid	3–17 ng L^{-1}; 17–110 ng L^{-1}	WWTP influents and effluents	Nikolai et al. (2006)

ACN acetonitrile, *MeOH* methanol, *TEEA* triethylammonium acetate, *NH_4OAc* ammonium acetate

concentration) in CE, leading to the formation of a micellar pseudo-stationary phase in solution, occurring partition mechanisms between the micellar pseudo-stationary phase and the mobile phase. Enantioresolution can be achieved using chiral surfactants or using chiral agents that are added to an achiral micellar buffer, such as combination of micelles and cyclodextrins or modified cyclodextrins, or both of them to improve the enantioresolution. A recent approach is the use of polymeric surfactants, a group of high-molecular-mass molecules that allows slower mass transfer of the analytes between the pseudo-stationary phase and the mobile phase, leading to a lower resolution compared to the conventional micelles (Hernández-Borges et al. 2005; Ha et al. 2006).

Super critical fluid chromatography (SFC) is a hybrid technique of GC and LC and has the advantages of providing higher flow rates and faster separation than LC and a lower dispersion because of the equal density, dissolving capacity, the intermediate viscosity and diffusion coefficient of its mobile phase, which is compared with those used in GC and HPLC due to the ability to carry compounds and to dissolve them, respectively (Taylor 2009). This technique is an alternative to HPLC when the enantioresolution is partial by normal phase or is not achieved by reverse phase, providing a lower consumption of solvents and the use of non-toxic and non-explosive solvents. However, there are some limitations like high cost of the equipment, complexity of the hardware and the weak experience available in this technique (Maftouh et al. 2005).

Thin layer chromatography (TLC) is preferentially used in indirect mode but it is limited because of its low resolution and weak ability to detect concentrations as low as those found in the environment. TLC can be used as complementary to HPLC since it is less expensive and allows the optimization of the separation parameters in less time and with less costs (Bhushan and Martens 1997), however, the application on environmental analysis is very limited.

Electrochemical Sensors and Biosensors provide an enantioselective analysis using an electrochemical cell coupled to a chiral receptor (potentiometric enantioselective membrane electrodes, PEME), an enzyme (chiral amperometric biosensors) or an antibody (enantioselective immunosensors), in which the sample flows without separation steps, providing direct determination in the matrix, high precision, fastness and the possibility of on-line detection with flow injection analysis and sequential injection analysis systems (Izake 2007). The principle of PEME is based on the thermodynamics of the reaction between each enantiomer and the chiral selector, with different stability in the complexes formed, leading to different reaction energies (Izake 2007).

Biotic and abiotic degradation and removal processes of chiral pharmaceuticals (CP) in the environment

Removal of pharmaceuticals in surface waters can be due to photo-transformation, biodegradation, hydrolysis and partition to sediment (Liu et al. 2009) while their removal in waste water treatment plants (WWTP) is mostly restricted to biodegradation and to abiotic processes such as oxidation and sorption. Recently, Patrick et al. (2011) reported the stereoselective microbial-assisted incorporation of organic substances into soil organo-clay complexes to form non-extractable residues. They highlighted the need to consider the formation of bound residues in environmental studies dealing with stereoselective analysis of organic pollutants in soils to study their microbial transformation (Patrick et al. 2011).

The comparison of conventional activated sludge systems and membrane bioreactors to remove CP from wastewaters was reviewed (Sipma et al. 2010). This study included racemates of CP like beta-blockers (atenolol, metoprolol, propranolol), antidepressants (fluoxetine, paroxetine) and NSAIDs (IB, indomethacin, ketoprofen, mefenamic acid, naproxen, propyphenazone).

There are many studies on microbial degradation of CP in the environment as racemates (Trautwein et al. 2008; Benotti and Brownawell 2009; Calisto and Esteves 2009; Mascolo et al. 2010; Santos et al. 2010). However, biodegradation studies of individual enantiomers are scarcer—few examples are related on Table 3 (Buser et al. 1999; Winkler et al. 2001; Fono and Sedlak 2005; Fono et al. 2006; Matamoros et al. 2009).

Biodegradation needs attention concerning the enantiomeric degradation ratio, since microorganisms can degrade selectively one enantiomer, can alter their enantioselective activity, can promote the enantiomerization and can also degrade both enantiomers at the same extent ratio, which is more unlikely to happen (Pérez and Barceló 2008).

Propranolol (PHO), a beta-blocker used for treatment of cardiovascular diseases, with annual sales of the brand Inderal® of about $30 billion (Bartholow 2010), is normally detected in surface waters and WWTP effluents (Ternes 1998; Huggett et al. 2003; Fono and Sedlak 2005). PHO is an important tool to distinguish the raw and treated sewage since PHO has an EF of 0.5 (racemic) in WWTP's influent and significantly below 0.5 in WWTP's effluent, suggesting that this CP is degraded enantioselectively through the biological treatment (Fono and Sedlak 2005). In the same study, EF decreased in microcosms inoculated with activated sludge but remain constant in not-inoculated or sterilized treatments. The same researchers found in microcosms experiments that the EF of metoprolol (MET), an analogous beta-blocker, decreased from the effluent to downstream, suggesting a enantioselective biodegradation (Fono et al. 2006).

Table 3 Biodegradation studies of individual enantiomers in the environmental

Drug	Method	Matrix	Biodegradation experiment	Observation	Sampling local	References
IB, ketoprofen and naproxen	GC/MS/MS	Synthetic wastewater	Laboratory scale membrane bioreactor (MBR)	(*S*)-IB was preferentially degraded compared to (*R*)-IB and (*R*)-ketoprofen was preferentially degraded compared to (*S*)-ketoprofen; increased concentrations of (*R*)-naproxen during MBR treatment possibly due to the enantiomeric inversion of (*S*)-naproxen	NA	Hashim et al. (2011)
Beta-blockers, salbutamol, tempazepam and citalopram	HPLC/MS/MS	Aerated lagoon and 3 tertiary WWTP	NA	EF changed over time for all drugs except to sotalol in one of the WWTP's effluent. EF differed among the 3 WWTP suggesting variations on biodegradation, except for metoprolol	Canada	MacLeod and Wong (2010)
IB and naproxen	GC/MS	WWTP influent and effluent	Microcosms experiments with synthetic and real wastewater	(*S*)-IB was degraded faster under aerobic conditions, depending on the oxidation status of WWTP. In anaerobic conditions, EF remains constant. Enantioselective degradation of naproxen is similar under aerobic and anaerobic conditions	Spain and Denmark	Matamoros et al. (2009)
Propranolol	HPLC/MS/MS	WWTP	NA	EF changed from influent to effluent for all the tested drugs, except for metoprolol, salbutamol and sotalol	Canada	MacLeod et al. (2007)
IB, metoprolol and naproxen	GC/MS/MS	Trinity River; WWTP effluent	Microcosms experiments with river water to assess phototransformation and degradation in the dark	EF decreased from the effluent to downstream, suggesting the biological-mediated degradation	Texas	Fono et al. (2006)
Propranolol	GC/MS/MS	WWTP influent and effluent	Microcosms experiments with filtered secondary effluent	EF decreased in microcosms inoculated with activated sludge but remained constant in not inoculated or sterilized treatments	USA	Fono and Sedlak (2005)
IB	GC/MS	Rivers	Incubation of a biofilm with raw river water	(*R*)-IB was degraded faster than the (*S*)-form of IB, the active one	Canada	Winkler et al. (2001)
IB	GC/MS/MS	Lakes, rivers and North Sea; WWTP influent and effluent	Incubation of fortified lake water; Incubation of WWTP' influent with activated sludge	Degradation of IB was rapid and mostly biological-mediated, with (*S*)-form being faster degraded in both experiments	Switzerland and North Sea	Buser et al. (1999)

IB Ibuprofen, *EF* Enantiomeric fraction, *WWTP* Waste water treatment plant, *NA* not applicable

Atenolol (ATE) is a beta-blocker also used for treatment of cardiovascular diseases with annual sales of the brand Tenormin® of approximately $102 million included in the Top 200 Prescription Drugs of 2009 of United States (Bartholow 2010). It was one of the 11 most frequently detected compounds in United States in drinking water, being classified as an indicator of endocrine disrupting compounds as well as an indicator of the treatment success of a WWTP (Benotti et al. 2009). In an enantioselective evaluation of effluents of three different WWTP in Canada, the EF of ATE was different for the different effluents, indicating that the different microbial communities can affect the enantioselectivity of the biodegradation (MacLeod and Wong 2010).

Fluoxetine (FX), an antidepressant of the group of Selective Serotonin Reuptake Inhibitors, is one of the most dispensed drugs in the world (Stanley et al. 2007) and one of the most prescribed drugs included in the Top 200 of the United States (Bartholow 2010). FX was found in surface waters, treated wastewater, raw influent and even in finished drinking water in United States and South Korea at ng L^{-1} levels (Trenholm et al. 2006; Vanderford and Snyder 2006). FX and also its active metabolite Nor-Fluoxetine (Nor-FX) have been detected in WWTP's effluents and in surface waters (MacLeod et al. 2007). FX was reported as a persistent pharmaceutical after chlorine treatment rather than ozone because of the more potent oxidant effect attributed to ozone (Westerhoff et al. 2005). In a dissipation study of 5 selective serotonin reuptake inhibitors in aquatic microcosms, FX was the most persistent (Johnson et al. 2005). In a study using batch incubation of seawater samples, Benotti and Brownawell (2009) included FX in the more labile group and considered that adsorption to suspended sediment was minimal.

Ibuprofen, a NSAID used for pain, fever and rheumatism, is the third most popular clinically used drug in the world and one of the 200 drugs most prescribed in the Unites States in 2009 (Bartholow 2010). Some researchers reviewed the occurrence of IB in numerous sediment and aquatic compartments (Ali et al. 2009). Buser et al. (1999) detected IB in river, lakes and influents of WWTP, with a higher concentration of the pharmacologically active (*S*)-enantiomer. In the same study, the degradation behavior was similar during experiments using WWTP influent incubated with activated sludge and lake water fortified with rac-IB, with a faster dissipation of the (*S*)-enantiomer, mostly biological-mediated. There are other studies reporting the decrease in EF of IB, the removal in the secondary biological treatment and differences in the behavior of IB EF's under anaerobic (similar degradation of both enantiomers) and aerobic conditions with (*S*)-form predominantly degraded, which are according to the biological-mediated degradation (Jones et al. 2007; Matamoros et al. 2009; Hijosa-Valsero et al. 2010). Still naproxen EF's showed a similar pattern in degradation at both aerobic and anaerobic conditions, making it a good indicator for removal efficiency in aerobic or anaerobic wastewater treatment systems (Matamoros et al. 2009). Thus, there are very few reports concerning enantioselective degradation of CP in the environment. It is important to include this issue mostly in the biodegradation studies due to the enantioselectivity of the biological processes. Assessing the more recalcitrant enantiomers is of high importance to ecotoxicity.

Toxicity of emergent chiral pharmaceuticals (CP) in aquatic organisms

There are few studies about ecotoxicity of single enantiomers of CP to aquatic organisms (Khetan and Collins 2007). On the other hand, most are performed at concentrations higher than those found in the environment (Fent et al. 2006) as shown in the Table 4.

PHO and FX were classified as compounds with a high potential of environmental risk (Christen et al. 2010). Briefly, in a recent report, the presence of three beta adrenergic receptor subtypes (β1, β2, β3) in the fathead minnow was demonstrated, with tissue localization of these receptors similar to those observed in mammals (Giltrow et al. 2011), which can be related to the potential effects that beta-blockers can cause in aquatic ecosystems.

FX in the environment has antimicrobial properties, mainly against Gram positive bacteria. This CP has a synergic activity with some antibiotics, even when there is some resistance, or can increase the activity of them, exerting toxicity by inhibiting cellular efflux pumps (Munoz-Bellido et al. 2000). The accumulation of FX in three fish species (*Lepomis macrochirus*, *Ictalurus punctatus*, and *Pomoxis nigromaculatus*) was reported in brain, liver and muscle tissues at ng g^{-1} levels (Brooks et al. 2005). Paterson and Metcalfe (2008) studied the uptake and depuration of FX in a freshwater fish species, Japanese medaka (*Oryzias latipes*), and found a half-life three times higher than in mammalian species and a lower ability to biodegrade and eliminate such drug and its metabolite Nor-FX. So, FX can indicate a recalcitrant behavior in biological tissues, suggesting the possible chronic effects (Paterson and Metcalfe 2008). FX is also related with interfering with brain expression of feeding-related peptides in female goldfish (*Carassius auratus*), decreasing food intake and reducing weight (Mennigen et al. 2009, 2010).

The studies involving the occurrence and removal of pharmaceuticals should contemplate bioassays as the reduction in the concentrations does not demonstrate the absence of toxicity (Reungoat et al. 2010). Another important features that are not considered in almost studies are the mixture effects of CP, the transformation products

Table 4 Ecotoxicological data on racemic pharmaceuticals as racemates and as enantiopure compounds, showing the effects caused in aquatic organisms by the compounds focused in this review

Drug	Test organism	Test	Effects	Observations	References
PHO	*Oncorhynchus mykiss*	10-days $NOEC^{growth}$; 10-days $LOEC^{growth}$	1.0 mg L^{-1}; 10 mg L^{-1}	Growth retarded after 10 days of an exposure of 10 mg L^{-1}, and possible adaptation after more 30 days of exposure	Owen et al. (2009)
PHO and IB	*Thaemnocephalus platyrus*	24 h LC50	10.31 mg L^{-1}; 19.59 mg L^{-1}	24 h LC50 was calculated based on the immobilization of *T. platyrus*	Kim et al. (2009)
ATE	*Thaemnocephalus platyrus*	24 h LC50	No acute toxicity		
PHO	*Oryzias latipes*	96 h LC50	11.40 mg L^{-1}	96 h LC50 was calculated based on the stereoscopic microscope observation and removal of dead larvae on the absence of heartbeat	
ATE and IB	*Oryzias latipes*	96 h LC50	No acute toxicity		
FX	*Cyprinodon variegatus* (sheepshead minnow)	96 h LOEC; 96 h NOEC	2 mg L^{-1}; 1.250 mg L^{-1} (levels above the environmental concentrations)	The effects on neurotransmitter pathways are observed at concentrations one order of magnitude higher than the reported in the environment	Winder et al. (2009)
		Sublethal effects	Effects at 0.300 and 0.030 mg L^{-1}		
FX	Sexually mature female zebrafish	Estradiol ovarian levels	Estradiol levels decreased threefold when exposed to 32 μg L^{-1} of FX	Results suggest no alteration in the ovulatory pathway, being the decrease of aromatase responsible for the decreased estradiol levels. This effect together with the reduced follicle-stimulating hormone receptor and luteinizing hormone receptor gene expression may lead to the decline in spawned eggs	Lister et al. (2009)
		Egg production	Decline in spawned eggs when exposed to 32 μg L^{-1} of FX or to 50% municipal effluent		
		Gene expression	Prostaglandins gene expression constant; Ovarian aromatase, follicle-stimulating hormone receptor and luteinizing hormone receptor gene expression was reduced		
FX	*Physa acuta*	Mortality and reproduction effects	Increased mortality and decreased reproduction (250 μg L^{-1})	The adsorption of FX to biomass and sediments must be considered to the effects on reproduction of freshwater molluscs	Sánchez-Argüello et al. (2009)
FX and ATE	*Daphnia magna*	Acute immobilization test—EC50	(*R*)- and (*S*)-FX: 8.1 and 6.9 mg L^{-1}; (*R*)- and (*S*)-ATE: 1,450 and 755 mg L^{-1}	Both enantiomers of FX were toxic to *D. magna*. ATE enantiomers showed stereoselectivity but did not show a high toxicity. (*R*)-FX is considered harmful to *P. subcapita*. (*S*)-ATE is more toxic than the (*R*)-enantiomer to the crustacean and microalga. (*S*)-FX and (*R*)-ATE are more toxic to the protozoan	De Andrés et al. (2009)
	Pseudokirchneriella subcapitata (microalga)	Growth inhibition test—EC50	(*R*)-FX: 34 mg L^{-1}; (*R*)- and (*S*)-ATE: 190 and 143 mg L^{-1}		
	Tetrahymena thermophila	Growth inhibition test—EC50	(*R*)- and (*S*)-FX: 30.5 and 3.2 mg L^{-1}; (*R*)- and (*S*)-ATE: 13.7 and 55.7 mg L^{-1}		
ATE	*Pimephales promelas*	Early life stage—NOEC/LOEC	4 days embryo: $NOEC^{hatching}$—10 mg L^{-1}; $LOEC^{hatching}$—>10 mg L^{-1}; after 28 days $NOEC^{growth}$—3.2 mg L^{-1}; $LOEC^{growth}$—10 mg L^{-1}	ATE was reported to be low toxic to fish respecting to the chronic toxicity at low concentrations and less toxic than PHO probably due to the different target receptor	Winter et al. (2008)
		Reproduction effects—NOEC/LOEC	Short-term: $NOEC^{reprodution}$—10 mg L^{-1}; $LOEC^{reproduction}$—>10 mg L^{-1}; increase in male condition index $NOEC^{CI}$—1.0 mg L^{-1}; $LOEC^{CI}$—3.2 mg L^{-1}		

Table 4 continued

Drug	Test organism	Test	Effects	Observations	References
IB	*Oncorhynchus mykiss* cell lines	Cytotoxicity and cytostatic action	IB at concentrations higher than 15 μg mL^{-1} is citotoxic to fish cells. The cytostatic effect was verified between 15 and 150 μg mL^{-1}	The cytotoxicity of IB occurred at concentrations 10,000 times greater than the higher value reported in the environment, being the bioaccumulation an important factor	Schnell et al. (2008)
FX	*Oryzias latipes*	96 h LC50	5.5 mg L^{-1}; 1.3 mg L^{-1}; 0.20 mg L^{-1}	At higher pH, there was an increased bioconcentration factor due to the higher fraction of lipophilic no ionized species, leading to more toxicity	Nakamura et al. (2008)
Nor-FX	*Dreissena polymorpha* (zebra mussels)	Effects of Nor-FX on spawning and parturition in bivalves	Spawning at concentrations 1–50 μM	Nor-FX induced spawning in zebra mussels, dark false mussels, and induced parturition in fingernail clams	Fong and Molnar (2008)
FX and Nor-FX	*Mytilopsis leucophaeata* (dark false mussels)		Nor-FX caused spawning in both sexes at concentrations 1–50 μM; FX caused spawning in males at 100 nM and in females at 500 nM	FX induces spawning in dark false mussels	
Nor-FX	*Sphaerium striatinum* (Fingernail clams)		Inducing statistically significant parturition only at 10 μM		
IB	*Oryzias latipes*	Long-term reproductive and physiological at chronic exposure	1–100 ng L^{-1}	Japanese medaka reproduced less frequently and produced a greater number of fertilized eggs when they did spawn. This effect was correlated with the concentration	Flippin et al. (2007)
FX and Nor-FX	*Spirostomum ambiguum*	Lethality tests—24 h LC50	Ca 0.55 mg L^{-1}	FX and its metabolite Nor-FX showed a high toxicity	Nalecz-Jawecki (2007)
	Thamnocephalus platyurus		Ca 0.76 mg L^{-1}		
FX	*Daphnia magna* (crustacean)	Sublethal and behavior effects—NOEC	(*R*)- and (*S*)-FX: 170 μg L^{-1} and 101 μg L^{-1}	(*S*)-FX was more toxic for *P. promelas*. The primary metabolite (*S*)-Nor-FX is more potent than the metabolite (*R*)-Nor-FX in mammals	Stanley et al. (2007)
	Pimephales promelas (fish)	Growth inhibition test—EC10	(*R*)- and (*S*)-FX revealed a EC10 of 132.9 and 14.1 μg L^{-1}, respectively		
FX	*Daphnia magna* (crustacean)	Survival	14d NOEC = 20 mg L^{-1}	Population growth rate was significantly reduced at all IB concentrations, although survival was only affected at 80 mg L^{-1}	Heckmann et al. (2007)
			14d LOEC = 80 mg L^{-1}		
		Population growth rate (PGR)	14d NOEC < 20 mg L^{-1}		
			14d LOEC = 20 mg L^{-1}		
FX	*Daphnia magna* (crustacean)	Acute and chronic effects	Chronic FX exposure increased the number of *Daphnia* offspring produced. Exposure to a pharmaceutical mixture of FX and clofibric acid, caused mortality or morphological abnormalities at 100 μg L^{-1} and 10 μg L^{-1}, respectively	Chronic FX exposure significantly increased *Daphnia* fecundity. Mixture of FX and clofibric acid at concentrations with no apparent effects when tested individually, led to acute effects	Flaherty and Dodson (2005)
Beta-blockers	*Daphnia magna*	Immobilization test—EC50	PHO 7.7 mg L^{-1}; ATE 313 mg $L^{-1;}$ MET 438 mg L^{-1}	The log P differences are responsible for the different toxicity. Higher log P, higher toxicity, with PHO being very toxic, MET being toxic and ATE seeming to be non-toxic to aquatic organisms. The toxicity is related with the bioconcentration, which depends on log P	Cleuvers (2005)
	Desmodesmus subspicatus	Growth inhibition test—EC50	PHO 0.7 mg L^{-1}; ATE 620 mg L^{-1}; MET 7.9 mg L^{-1}		
	Lemma minor	Growth inhibition test—EC50	PHO 113 mg L^{-1}; ATE and MET (no effects up to 320 mg L^{-1})		

Table 4 continued

Drug	Test organism	Test	Effects	Observations	References
Naproxen and its derivates	*Brachionus calyciflorus* (rotifer), *Ceriodaphnia dubia* and *Thamnocephalus platyurus* (crustaceans)	Acute toxicity	LC50 and EC50 values for all compounds ranged within 1–100 mg L^{-1} for all compounds, being the photoproducts more toxic. Naproxen was the compound with the lowest effect on test organisms	Chronic tests showed higher toxicity than acute tests	Isidori et al. (2005)
	Pseudokirchneriella subcapitata (alga), *Brachionus calyciflorus* (rotifer) and *Ceriodaphnia dubia* (crustacean)	Chronic toxicity	The compounds tested were bioactive at low concentrations mainly for *B. calyciflorus* and *C. dubia*		
IB and naproxen	*Desmodesmus subspicatus*	Growth inhibition test—EC50	342.2 mg L^{-1} for IB; 625.5 mg L^{-1} for naproxen	IB and naproxen were not classified as harmful to aquatic organisms since the EC50 values were superior than 100 mg L^{-1}	Cleuvers (2004)
	Daphnia magna; *Ceriodaphnia dubia*	Immobilization test—EC50	101.2 mg L^{-1} for IB; 166.3 mg L^{-1} for naproxen		
FX	*Oryzias latipes*	Evaluation of reproductive, physiological and endocrine endpoints in response to a long-term (4-week) FX exposure	0, 0.1, 0.5, 1.0 and 5.0 μg L^{-1}tested	Reproductive parameters and somatic measurements were not significantly affected. Estradiol increased in females from two lower exposure groups	Foran et al. (2004)
FX	*Pseudokirchneriella promelas*	Growth inhibition test—EC50	24–39 μg L^{-1}	The lowest effect value for acute effect is one order of magnitude higher than the highest reported environmental concentration of FX, possible occurrence of municipal effluents which do not have dilution from upstream	Brooks et al. (2003)
	Daphnia magna; *Ceriodaphnia dubia*	48 h LC50	820 μg L^{-1}; 234 μg L^{-1} respectively		
	Pimephales promelas	48 h LC50	705 μg L^{-1}		
MET; nadolol; PHO	*Hyalella azteca*	48-h LC50	MET ≥ 100; nadolol ≥ 100; PHO 29.8 ± 12.4 (mg L^{-1})	Metoprolol and nadolol represent a low hazard, based on vertebrate and invertebrate effects data	Huggett et al. (2002)
	Ceriodaphnia dubia		MET 8.8 ± 1.9; nadolol ≥ 100; PHO 0.8 ± 0.02 (mg L^{-1})		
	Daphnia magna (crustacean)		MET 63.9 ± 6.2; nadolol ≥ 100; PHO 1.6 ± 0.3 (mg L^{-1})		
	Oryzias latipes (fish)		MET ≥ 100; nadolol ≥ 100; PHO 24.3 ± 10.5 (mg L^{-1})		
FX	*Dreissena polymorpha* (zebra mussels)	Gametes spawning	5×10^{-7} to 5×10^{-4} M (males); 5×10^{-7} to 5×10^{-4} M (females)	FX was an effective spawning inducer, since it induced spawning to 100% of males of zebra mussels that were exposed to 5×10^{-6} M	Fong (1998)

PHO propranolol, *ATE* atenolol, *MET* metoprolol, *IB* ibuprofen, *FX* fluoxetine, *Nor-FX* Nor-fluoxetine, *LOEC* Lowest observed effect concentration, *NOEC* No observed effect concentration, *LC50* Lethal concentration of 50%, *EC50* Effective concentration that causes 50% of maximal response, *EC10* Effective concentration that causes 10% of maximal response

and the food quality of the organisms used in toxicological tests (Flaherty and Dodson 2005; Isidori et al. 2005; Hansen et al. 2008).

Conclusions

Methods for quantification of single enantiomers of CP in the environment were reviewed, demonstrating that they are scarce. Thus, chiral analytical methods for an accurate quantification of enantiomers in the environment are imperative for a better knowledge of the environmental fate of CP. Few studies concerning the biodegradation performance and ecotoxicity of racemic mixtures and the individual enantiomers were also related, and in many cases, enantioselectivity was observed. The biodegradation and toxicity of isolated enantiomers on non-target organisms are also fields to be investigated.

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