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ORIGINAL PAPER

Stereoisomeric profiling of pharmaceuticals ibuprofen and iopromide in wastewater and river water, China

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Abstract Stereoisomeric compositions can provide insights into sources, fate, and ecological risks of contaminants in the environment. In this study, stereoisomeric profiles of ibuprofen and iopromide were investigated in wastewater and receiving surface water of the Pearl River Delta, south China. The enantiomeric fraction (EF) of ibuprofen was 0.108–0.188 and 0.480, whereas the isomer ratio (IR) of iopromide was 1.426–1.673 and 1.737–1.898 in the influent and final effluent, respectively, suggesting stereoselective degradation occurred for both pharmaceuticals during wastewater treatment. Ibuprofen showed enantioselective degradation in the anaerobic, anoxic, and aerobic conditions, whereas iopromide displayed isomer-selective degradation only under the aerobic condition. In the river waters, the EF of ibuprofen was 0.130–0.327 and the IR of iopromide was 1.500–2.531. The results suggested that pharmaceuticals in the mainstream Pearl River were mainly from discharge of treated wastewater, whereas in the tributary rivers and urban canals, direct discharge of untreated wastewater represented a significant contribution. The IR of iopromide can be an applicable and efficient tracer for wastewater discharge in the environment.

Keywords Pharmaceuticals · Stereoselective degradation · Enantiomeric fraction · Isomer ratio · Wastewater · The Pearl River

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Introduction

Pharmaceuticals have been detected in the environment worldwide, which has become an increasing concern in recent decades due to their designed bioactivity and thus potential adverse ecological impacts (Daughton and Ternes 1999; Halling-Sørensen et al. 1998; Kolpin et al. 2002; Stamm et al. 2008). Many pharmaceuticals are chiral compounds with one or more chiral centers. In spite of identical chemical–physical properties, enantiomers of pharmaceuticals usually differ in their biological properties, leading to differences in their biological effects, such as toxicity and biotransformation (Lees et al. 2003; Knoche and Blaschke 1994; Qian et al. 2009). Thus, chiral pharmaceuticals in the environment may experience stereoisomer-specific behavior (Buser et al. 1999; Fono and Sedlak 2005; MacLeod and Wong 2010; Nikolai et al. 2006; Wong 2006) and exhibit stereoisomer-specific ecotoxicity (Stanley et al. 2009).

Besides, chirality of some pharmaceuticals has been successfully used to identify sewage discharges and apportion contribution of wastewater in surface waters (Buser et al. 1999; Fono and Sedlak 2005; MacLeod and Wong 2010; Nikolai et al. 2006). Therefore, it is crucial to study the stereoisomeric compositions of chiral pharmaceuticals in the environment in order to gain a better understanding of the release, fate, and reliable assessment of their environmental risks (Wong 2006).

Ibuprofen is a widely used non-steroid anti-inflammatory drug and is among the most popular drug in the world (Buser et al. 1999). Iopromide is an X-ray contrast agent. Both pharmaceuticals have been widely detected in the environment (Huang et al. 2011; Krause et al. 2009; Peng et al. 2008; Putschew et al. 2000; Steger-Hartmann et al. 2002; Tixier et al. 2003; Yu et al. 2011; Zuccato et al. 2000). Ibuprofen has an asymmetrically substituted carbon atom and therefore has two enantiomers. It is administered in racemic form with desired pharmacological effects almost exclusively in the *S*(+)-enantiomer. The inactive *R*(−)-ibuprofen undergoes extensive chiral inversion to the active *S*(+)-enantiomer in humans and other mammals (Bonato et al. 2003), causing higher concentrations of *S*(+)-ibuprofen in raw wastewater (Buser et al. 1999; Matamoros et al. 2009). However, a lower excess of *S*(+)-enantiomer was observed in the treated wastewater and surface water, which meant that *S*(+)-ibuprofen was degraded faster during treatment in sewage treatment plant (STP) (Buser et al. 1999). Similar result was observed in the wastewater of Spain (Matamoros et al. 2009). Iopromide has two atropisomers known as (Z)- and (E)-isomers due to steric hindrance of free rotation of the dihydroxypropyl-N-methlamino group by the 3 bulky iodine atoms on the phenyl ring. Both E and Z isomers are chiral. As a result, iopromide consists of a mixture of 4 isomers, namely E1, E2, Z1, and Z2, belonging to two pairs of enantiomers (Fontanive 2011). According to the United States Pharmacopoeia (2009), a medical product of iopromide must contain 8.0–12.0, 9.0–14.0, 32.0–40.0, and 38.0–46.0 % of E1, E2, Z1, and Z2 isomers, respectively. However, stereoisomeric composition of iopromide in the environment was scarcely elucidated.

Distribution patterns of ibuprofen and iopromide in the wastewater and river waters in the Pearl River Delta, South China, have been investigated previously (Peng et al. 2008; Huang et al. 2011; Yu et al. 2011). This work aimed to delineate stereoisomeric compositions of ibuprofen and iopromide in the wastewater and the receiving river water. Stereoselective behaviors of the pharmaceuticals throughout the wastewater treatment were illustrated by sampling influent and effluents at outlets of major treatment units in a large scale STP.

Materials and methods

Standards and reagents

Iopromide was bought from the United States Pharmacopeia (Rockville, MD, USA). Racemic ibuprofen and *S*(+)-ibuprofen were purchased from Sigma-Aldrich (St. Louis, MO, USA). Iopromide-d_3 and racemic ibuprofen-d_3 were bought form C/D/N isotopes Inc. (Pointe-Claire, Quebec, Canada). The standards were obtained as solid form and were of at least 97 % purity.

HPLC grade methanol, acetonitrile, formic acid, and ammonium acetate were purchased from Merck (Darmstadt, Germany). Ultrapure water was generated by a Milli-Q ultrapure water system (Millipore, Billerica, MA, USA). Analytical grade sodium chloride (NaCl) and sodium azide (NaN_3) were obtained from Bodi Chemical (Tianjin, China) and were washed with methanol prior to use. Hydrochloric acid (HCl) was also from Bodi Chemical and was used as received.

Study area and sample collection

Located in the South China, the Pearl River Delta is one of the most urbanized and densely populated areas in China. The annual municipal wastewater production in this area has been about 5 billion tons in recent year, in which approximately 70 % is treated before discharge (Guangdong Statistics 2012). Both the treated wastewater and the rest of untreated wastewater are discharged into the Pearl River and the tributaries (Fig. 1).

The investigated STP is located in Guangzhou, the biggest city of the Pearl River Delta. A detailed description of the STP has been provided previously (Yu et al. 2011). In brief, the STP has three parallel treatment systems with a total capacity of 550,000 $m^3\ d^{-1}$ and serves about a population of 1,500,000.

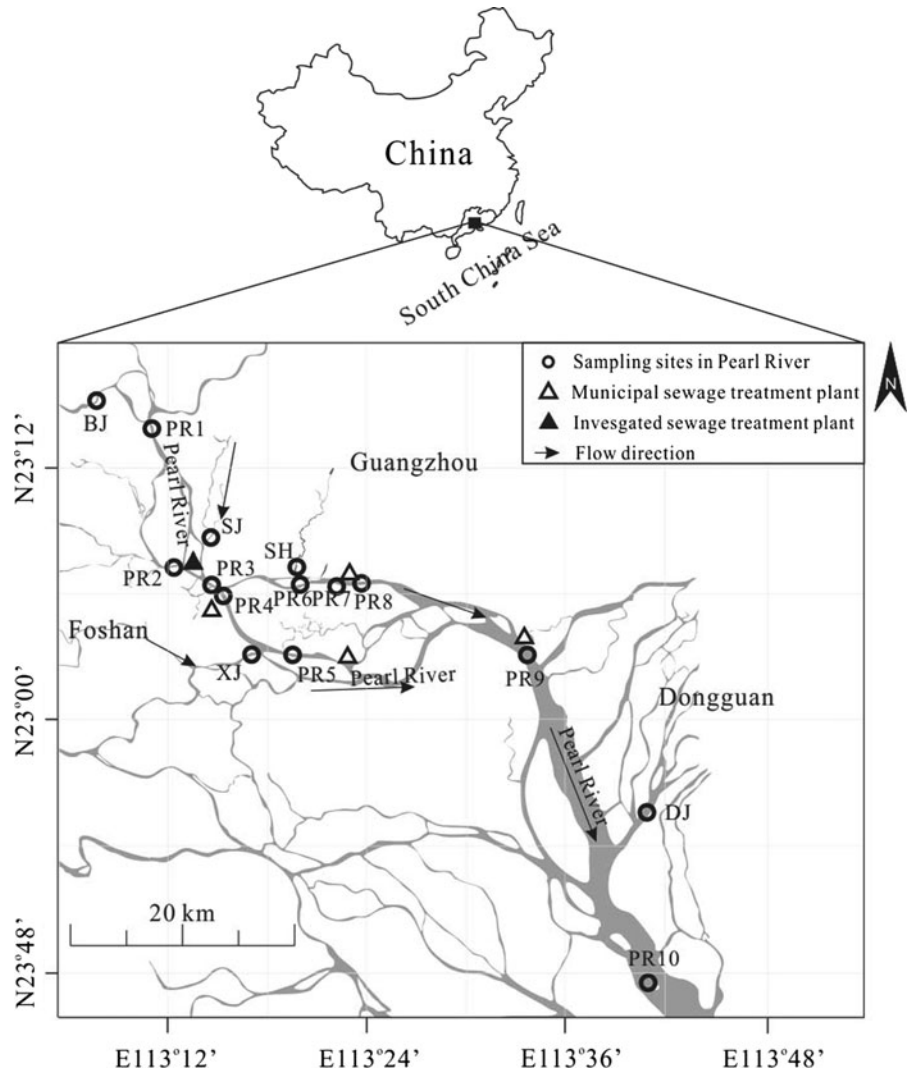


Fig. 1 Sketch map of the study area and sampling sites

The first and second treatment systems treat predominant domestic wastewater (~90 %) and use identical treatment techniques composed of a grit chamber, a bioreactor consisting successively of anaerobic, anoxic, and oxic processes and a secondary clarifier. The third system has a bioreactor that is composed successively of anoxic, anaerobic, and oxic processes and treats also a certain amount of industrial wastewater and municipal landfill leachate. The hydraulic retention time is 11.5 h in all treatment lines. Chlorination is employed before the final discharge of the treated effluent.

The influent and final effluent of the first and third treatment lines were sampled from February 15 to 21 in 2011 to see daily variations of the stereoisomeric compositions of the pharmaceuticals in the wastewater over a period of 1 week. The influent and effluents from outlets of major treatment units were collected along the first treatment line were sampled step-by-step on March 10, 2008 and February 21, 2011 to study the stereoisomeric fate of the pharmaceuticals. Wastewaters were collected hourly from 8:00 to 12:00 am to build a composite sample (10 L for the influents and 40 L for the effluents) into amber glass bottles without headspace.

River water was sampled in December 2010 in the mainstream Pearl River, three tributary rivers (Beijiang River, Xijiang River, and Dongjiang River) and two urban canals (Shijin River and Shahe Stream).

The canals are designed to collect surface runoff and probably also receive random discharge of wastewater. Ten sites were set along the mainstream Pearl River (sites PR1 to PR10) and each one in the tributaries (sites BJ, XJ, and DJ) and the urban canals (sites SJ and SH) near their confluences with the mainstream Pearl River. Grab samples (10 L/each) were always collected during ebb period to prevent dilution by intruding seawater.

NaN_3 was added to every sample (0.5 g L^{-1}) immediately after sampling to suppress potential biological activities. Samples were kept on icepacks during transportation to the laboratory where they were stored in dark at 4 °C until treatment within 48 h.

Sample preparation and analysis

Details about the sample treatment have been provided previously (Huang et al. 2011; Yu et al. 2011). Briefly, water samples were filtered with 0.7-μm glass fiber filters (Whatman, Maidstone, UK). Two aliquots of the filtrate (each of 100 mL for influent and anaerobic effluent and 250 mL for the other effluents and river water) were spiked with ibuprofen-d_3 and iopromide-d_3 separately and enriched by solid phase extraction on HLB cartridges (Waters, Milliford, MA, USA) under pH 4 and 7, respectively. The analyte was eluted by 5 mL of methanol after the cartridge was washed by 5 mL of 5 % methanol solution for iopromide or 5 mL of 10 % methanol solution for ibuprofen. The extracts were evaporated to just dryness under a gentle flow of high purity nitrogen and reconstituted in 160 and 400 μL of ultrapure water prior to instrumental analysis for ibuprofen and iopromide, respectively.

An Agilent 1200 liquid chromatography system coupled to an Agilent 6410 triple quadrupole mass with electrospray ionization in positive mode (Agilent, Palo Alto, CA, USA) was used. Separation of ibuprofen enantiomers was achieved on a 4 mm × 100 mm (5.0 μm particle size) α1-acid glycoprotein column coupled with a 2 mm × 10 mm guard column with the same sorbent (ChromTech, UK) at 25 °C. The mobile phase was 2 % acetonitrile in 10 mM L^{-1} ammonium acetate solution (pH 7.0) under isocratic condition with a flow rate of 0.2 mL min^{-1}. The two enantiomers were eluted within 15 min. An Agilent ZORBAX Exlipse XDB C18 column was used to separate iopromide stereoisomers at 25 °C. Two peaks were eluted by an isocratic mobile phase consisting of ultrapure water with 0.2 % of formic acid and acetonitrile (95:5, v/v) at 0.3 mL min^{-1} within 4 min.

Data acquisition was performed in multiple reactions monitoring (MRM) mode. Internal standard method was adopted for quantification (Table 1). The MS parameters and ion transitions for the two pharmaceuticals have been provided previously (Huang et al. 2011; Yu et al. 2011).

Stereoisomeric composition

Chirality of ibuprofen was expressed as enantiomeric fraction (EF) and was calculated using the following equation:

$$\mathrm{EF} = \frac{[R(-)]}{[R(-)] + [S(+)]} \quad (1)$$

where $[R(-)]$ and $[S(+)]$ are calculated concentrations of $R(-)$- and $S(+)$-ibuprofen, respectively. EF of 1 or 0 indicates a single enantiomer, and EF of 0.5 denotes the racemate.

For iopromide, only two peaks were separated albeit it has four stereoisomers. Stereoisomeric composition of iopromide was thus expressed as isomer ratio (IR) because the isomers could not be identified due to lack of individual isomer standards.

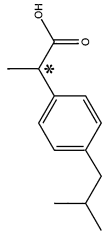
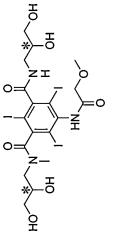
$$\mathrm{IR} = \frac{C1}{C2} \quad (2)$$

where $C1$ and $C2$ are measured concentration of the first and secondly eluted isomers.

Chromatogram simulation and statistics

Deconvolution and chromatogram process were performed using a four-parameter exponentially modified Gaussian function of PeakFit software (Version 4.12, SeaSolve Software Inc., San Jose, USA) that is currently the most widely used chromatographic model capable of modeling tailing to generate accurate peak areas and chromatographic performance measures from asymmetric peaks (SeaSolve Software Inc. 2003). Data were processed with Origin 8.0 (OriginLab, Northampton, MA, USA). Differences were assessed by one-way ANOVA. Data were considered to be significantly different when the probability (p) was less than 0.05 unless otherwise specified.

Table 1 Structure, limit of detection/quantitation (LOD/LOQ, ng L^{-1}), and resolution factor (*R*) of the chiral pharmaceuticals

Compound	Chemical structures[a]	Isomer	Internal standard	Linearity[b]	R ($n = 9$)	EF/IR ($n = 9$)	LOD/LOQ	
							Wastewater	River water
Ibuprofen		*R*-(−)	*R*-(−)-ibuprofen-d_3	1.000	1.07 ± 0.04	0.506 ± 0.007	8/24	3/8
		S-(+)	*S*-(+)-ibuprofen-d_3	0.999			9/27	3/8
Iopromide		I_1	I_1-iopromide-d_3	0.999	1.19 ± 0.04	1.011 ± 0.056	18/55	6/18
		I_2	I_2-iopromide-d_3	0.998			16/50	5/16

EF enantiomeric fraction, *IR* isomer ratio

[a] http://www.syrres.com/esc/physdemo.htm

[b] Linear range from 25 to 250 ppb for enantiomers of ibuprofen and from 10 to 500 ppb for stereoisomers of iopromide

* Chiral center

Results and discussion

Method performance

Satisfactory separation and resolution were achieved for ibuprofen enantiomers and iopromide stereoisomers with a resolution factor of 1.07 ± 0.04 and 1.19 ± 0.04, respectively (Fig. 2; Table 1). Recoveries of ibuprofen and iopromide were 66 ± 6 and 85 ± 12 %, and 40 ± 8 and 61 ± 6 % from the wastewater and river water, respectively (Huang et al. 2011; Yu et al. 2011). The limits of quantification ranged from 8 to 55 ng L^{-1} for the individual stereoisomers of ibuprofen and iopromide in the wastewater and river water (Table 1). The accuracy and precision of instrumental analysis over the experimental period were monitored by replicate injections of standard solutions, with relative standard deviations (RSDs) from 0.1 to 6.6 % ($n = 24$) for the analytes. The RSD of duplicated analysis of wastewater samples ranged from 0.1 to 12.2 % and from 2.1 to 8.6 % for quantification of the individual iopromide and ibuprofen stereoisomers, respectively (Fig. 3, 4).

EFs of ibuprofen were calculated to be 0.506 ± 0.007 and 0.515 for standard and medicine (Sino-US SmithKline Pharmaceutical Co., Ltd, Tianjin, China) marketed in China, respectively. IR of iopromide standard and marketed medicine (Bayer Schering Pharma AG, Berlin, Germany) were 1.011 ± 0.056 and 1.460 (Table 1).

Enantiomeric composition of ibuprofen in wastewater

Figure 3 showed the enantiomeric composition along with the concentration of ibuprofen in the wastewater. The EF of ibuprofen in the influent was 0.170–0.174 and 0.108–0.188 in the first and third treatment line of the STP, respectively, much lower than that of the marketed medicine, indicating that ibuprofen in the wastewater was metabolized and excreted by humans after use. The EF increased gradually to 0.480 in the final effluent after treatment in the STP (Fig. 3a), demonstrating faster degradation of *S*(+)-ibuprofen. This result was in good agreement with previous research (Buser et al. 1999; Winkler et al. 2001; Matamoros et al. 2009). Obvious increase in EF occurred during anaerobic, anoxic, and aerobic bioprocesses, accompanied by significant decrease in the

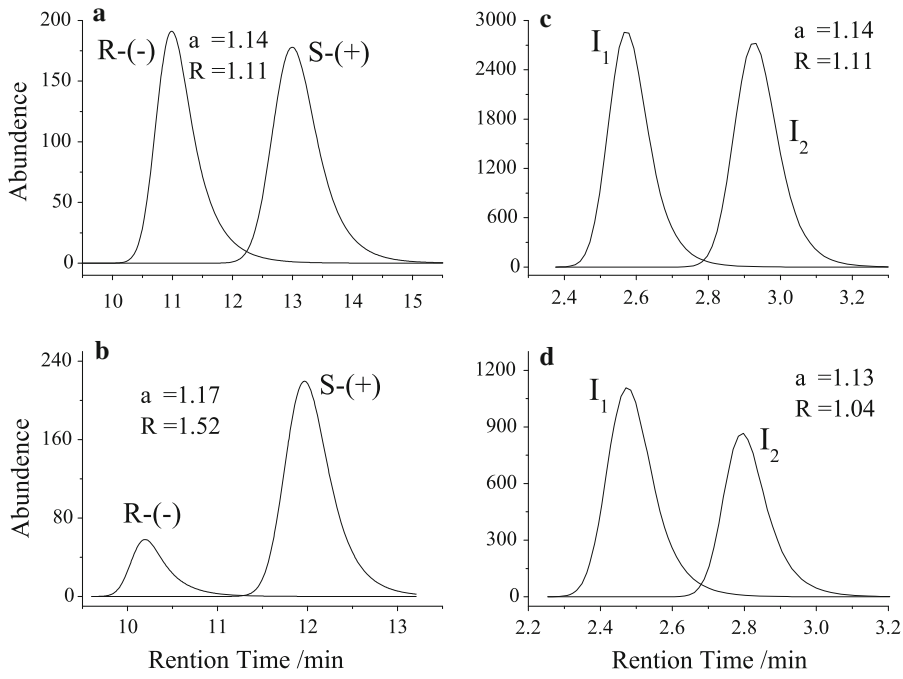


Fig. 2 Simulated chromatograms by PeakFit of **a** ibuprofen standard, **b** ibuprofen in an influent sample, **c** iopromide standard, **d** iopromide in an influent sample. α = Separation factor. R = Resolution factor

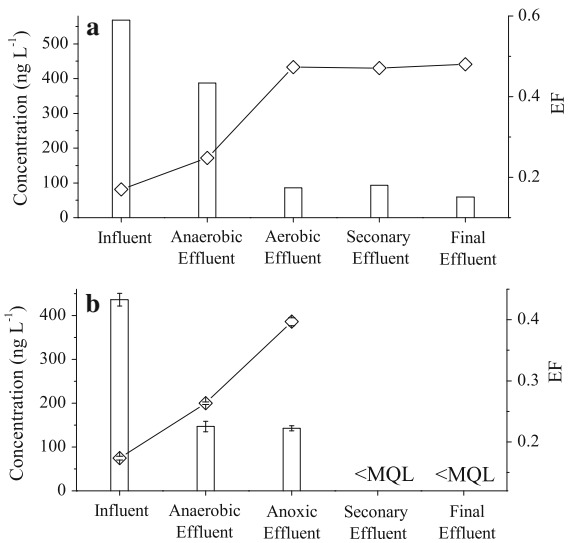


Fig. 3 Concentration (*bars*) and enantiomeric fraction (*symbols*) of ibuprofen in the wastewater during treatment in the STP. **a** Sampling campaign in March 2008, **b** sampling campaign in Feb 2011. *Error bars* represent absolute deviations of duplicate analysis

concentration (Fig. 3a, b). Matamoros et al. (2009), however, observed no enantioselective degradation of ibuprofen under anaerobic condition. On the other hand, the EF did not vary obviously after chlorination even if the concentration reduced, demonstrating that enantioselective degradation happened only during bioprocesses. Daily variation of the enantiomeric composition of ibuprofen could not be elucidated because the EF could only be calculated for limited wastewater samples.

Stereoisomeric composition of iopromide in wastewater

The two peaks of iopromide were detected in all the wastewater samples. IR of iopromide was calculated to be in the range of 1.426–1.673 in the influent, slightly higher than that of the medicine currently marketed in China which is 1.460. The IR increased to 1.737–1.898 in the final effluent after treatment in the STP. No significant daily variation was observed for the IR in both the influent and the effluent over a period of a week despite the big fluctuations of the concentration (Fig. 4a, b). However, statistically significant difference in the iopromide's IR was observed between the influent and the final effluent ($p < 0.01$), indicating occurrence of isomer-selective degradation in the wastewater during treatment in the STP. Obvious increase in the IR was observed only after aerobic bioprocess, and the same case was for the concentration (Fig. 4c), illustrating stereoselective degradation only under aerobic condition.

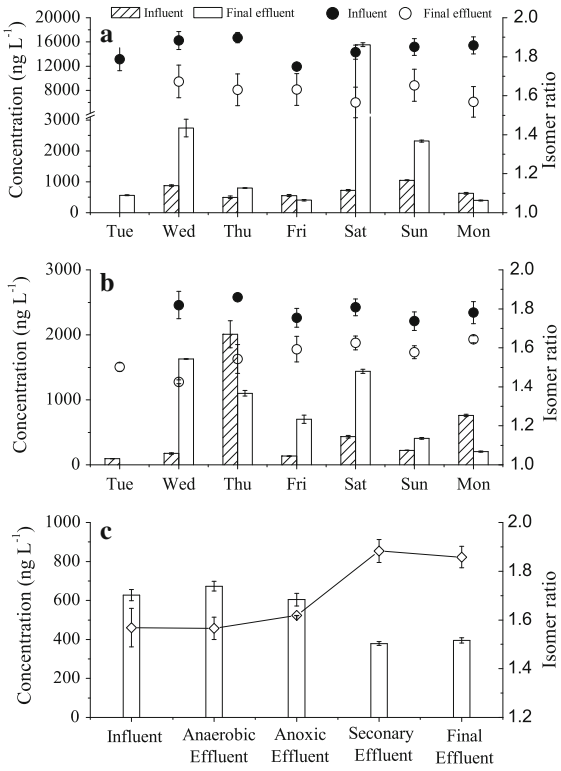


Fig. 4 Stereoisomeric fate of iopromide in the wastewater of the investigated STP. **a** Daily variation of concentration (*bars*) and isomer ratio (*symbols*) in the first treatment line over a period of 1 week, **b** daily variation of concentration (*bars*) and isomer ratio (*symbols*) in the third treatment line, **c** variation of concentration (*bars*) and isomer ratio (*symbols*) during wastewater treatment. *Error bars* represent absolute deviations of duplicate analysis

Stereoisomeric compositions of the pharmaceuticals in the surface water

Enantiomers of ibuprofen were detected above the limit of quantification in only a few river water samples. The EF of ibuprofen ranged from 0.130 to 0.158 in the urban canals (sites SH and SJ). In the mainstream Pearl River, the EF of ibuprofen could only be calculated at sites near outlets of urban canals (PR6 and PR7) and STPs (PR3 and PR8), ranging from 0.187 to 0.327 (Fig. 5a).

On the other hand, isomers of iopromide were quantified ubiquitously. The IR was in a narrow range of 1.712–2.531 throughout the mainstream Pearl River although the concentration fluctuated from 43 to 828 ng L^{-1}, while in the tributary rivers, the IR of iopromide was in the range of 1.500–1.733 (Fig. 5b).

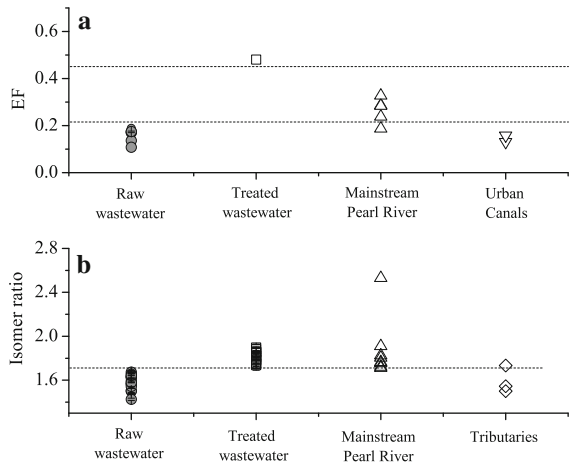


Fig. 5 Stereoisomeric composition of ibuprofen (**a**) and iopromide (**b**) in the river water of the Pearl River Delta catchment. Stereoisomeric composition of iopromide was not analyzed in the urban canals. *Error bars* represent absolute deviations of duplicate analysis

The consistency of enantiomeric composition of ibuprofen in the influent made it a good tracer of municipal wastewater discharge in the environment. The close approximity of ibuprofen's EF in the urban canals to that of the influent suggested a predominant contribution of untreated wastewater in the canals. This is reasonable because the canals receive random discharge of domestic wastewater. Enantiomers of ibuprofen were only occasionally quantified in the river waters, which might be ascribed to its extensive transformation in STPs as shown in this work (Fig. 3) and reported in literature (Clara et al. 2005; Huang et al. 2011; Joss et al. 2005; Nakada et al. 2006). The EF along the mainstream Pearl River was between those of the influent and the final effluent (Fig. 5a). Besides, ibuprofen was readily biotransformed (Fig. 3), suggesting that ibuprofen in the mainstream Pearl River was significantly sourced from leakages of untreated wastewater and might experience enantioselective biodegradation once it was discharged into the river. However, the application of ibuprofen's chirality as a reliable tracer for wastewater discharge might be limited due to the occasional detection. On the contrary, isomers of iopromide were widely quantified. The IR also varied in a very narrow range in the influent but was significantly different from that in the final effluent as shown above (Figs. 4, 5b). In addition, iopromide has been reported to be quite persistent (Batt et al. 2006; Díaz-Cruz and Barceló 2008; Ternes and Hirsch 2000;

Yu et al. 2011). Therefore, the stereoisomeric composition of iopromide may not change significantly after discharge into the environment considering the hydraulic retention time during which extensive biodegradation could not be expected. Thus, the IR of iopromide could be a very applicable and efficient tracer for wastewater contribution in the environment. The IR of iopromide in the mainstream of Pearl River was found to be significantly different ($\rho = 0.003$) from that of the influent but quite similar to that of the final effluent ($\rho = 0.343$, Fig. 5b), suggesting that iopromide in the mainstream Pearl River stems predominantly from discharge of treated wastewater. However, in the three tributaries, discharge of untreated wastewater might exist indicated by the iopromide IR values (Fig. 5b).

Conclusions

Stereoisomeric compositions and behavior of ibuprofen and iopromide were investigated in wastewater and receiving river water of South China. Enantiomeric composition of ibuprofen was quite consistent in the influent with EF of 0.159 ± 0.030. Enantioselective degradation was observed for ibuprofen under anaerobic, anoxic conditions, and in the wastewater. Isomer ratio of iopromide in the influent varied in a narrow range (1.426–1.673), independent of the concentration. Stereoselective biodegradation was observed for iopromide only under aerobic conditions. Stereoisomeric composition of both pharmaceuticals could be used to trace wastewater discharge in the environment. However, the enantiomers of ibuprofen could only be occasionally quantified in the river water, thus limiting the application of the EF as an effective tracer of wastewater contribution. On the other hand, the isomers of iopromide were detected widely, making the isomer ratio a reliable and applicable tracer for identification of wastewater discharge in the environment.

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Conflict of interest The authors declare that they have no conflict of interest.

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