



Multi-residue enantioselective analysis of chiral drugs in freshwater sediments

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Abstract

Pharmaceutical and illicit drugs are emerging contaminants found in the environment globally. Many are chiral and stereochemistry plays an important role on their environmental fate and effects. However, investigations at the enantiomeric level are limited, particularly for complex particulate matrices such as sediments. This is due to further sample processing requirements and a lack of suitable analytical methods. Therefore, here a new enantioselective methodology is proposed for 15 drugs in sediment. Sample treatment by accelerated solvent extraction and solid phase extraction was critical for subsequent enantioselective separations. Using liquid chromatography–tandem mass spectrometry, a Chiral-V enantioselective column enabled multi-residue separations of anti-depressants, beta-blockers, beta-agonist, anti-histamine and stimulants. Method trueness for all enantiomers was 86–121% and method quantitation limits were below 3 ng g⁻¹ dry weight. Application of the method revealed the enantiomeric composition of fluoxetine, amphetamine, propranolol, venlafaxine and citalopram in sediment for the first time. All drugs except venlafaxine were present in non-racemic form, i.e. unequal enantiomer concentrations. This is significant considering drug toxicity towards benthic organisms could be enantiospecific.

Keywords Vancomycin · Metabolite · Septic tank · Sewage · Wastewater · River

Introduction

Pharmaceutical and illicit drugs are emerging contaminants as their fate and effects in the environment are not fully understood (Cizmas et al. 2015; Wilkinson et al. 2017). The main source of drugs in the environment is the discharge of effluent from centralised wastewater treatment plants. However, septic tanks can play a significant role with 20% of United States households served by a septic tank or similar system (Schneider et al. 2017). In Scotland, 7% of the population is estimated to use a septic tank (Ramage et al. 2019). Nevertheless, little attention has been given to the impact of septic tanks to surrounding aquatic systems with respect to drugs.

Drug stereochemistry plays an essential role in the environmental behaviour of a drug. Approximately, 50% of drugs are chiral and exist as two or more enantiomers (Kasprzyk-Hordern 2010). Most drugs are dispensed in racemic form, i.e. equal concentration of all enantiomers, despite most of the pharmacological activity normally residing with one enantiomer. However, chiral drugs can be subject to enantiospecific metabolism in the human body and during wastewater treatment (Ribeiro et al. 2012). Therefore in the environment it is common to find chiral drugs enriched with one enantiomer. This is significant as enantiospecific toxicity can occur in the environment (Stanley et al. 2007). For example, *S*(+)-fluoxetine is ~ 10 times more toxic towards the protozoa *Tetrahymena thermophila* than *R*(-)-fluoxetine (De Andrés et al. 2009). Despite this knowledge there is still a lack of studies undertaken in the environment at the enantiomeric level, particularly for particulate matrices such as sediments. A contributing factor is the lack of good analytical methodologies available for these complex matrices.

Multi-residue enantioselective methods exist for biosolids applied to farmland as fertiliser (Evans et al. 2015) and soils (Petrie et al. 2018). However, no such methods exist for river sediments. Previously developed methods for sediments are

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limited to a single therapeutic drug group. For example, methods exist for the anti-inflammatories ibuprofen, ketoprofen and flurbiprofen (Yuan et al. 2018), the antibiotic flumequine and its metabolite 7-hydroxyflumequine (Xue et al. 2018) and the antifungals econazole, ketoconazole and miconazole (Huang et al. 2013). However, numerous other chiral drugs have been reported in sediments, (Vazquez-Roig et al. 2010; Silva et al. 2011; Bagnis et al. 2018) with no information on their enantiomeric composition. Therefore, the objectives of the study were (i) to establish a new methodology for multi-residue enantioselective profiling of chiral drugs in sediments, and (ii) to determine the enantiomeric composition of chiral drugs present in sediments impacted by wastewater treatment plants and septic tanks.

Experimental

Materials

Analytical reference and deuterated surrogate standards were purchased from Sigma Aldrich (Gillingham, UK) and Toronto Research Chemicals (North York, Canada). The standards were *R/S*(±)-amphetamine, *R/S*(±)-methamphetamine, *R/S*(±)-atenolol, *R/S*(±)-chlorpheniramine, *R/S*(±)-citalopram, *R/S*(±)-desmethylcitalopram, *R/S*(±)-fluoxetine, *R/S*(±)-propranolol, *R/S*(±)-salbutamol, *R/S*(±)-venlafaxine, *R/S*(±)-desmethylvenlafaxine, *R/S*(±)-bisoprolol, *R/S*(±)-acebutolol, *R/S*(±)-metoprolol and *R/S*(±)-sotalol (Table S1). The deuterated surrogates were *R/S*(±)-amphetamine- d_{11} , *R/S*(±)-methamphetamine- d_{11} , *R/S*(±)-atenolol- d_7 , *R/S*(±)-chlorpheniramine- d_6 , *R/S*(±)-citalopram- d_6 , *R/S*(±)-fluoxetine- d_6 , *R/S*(±)-propranolol- d_7 , *R/S*(±)-salbutamol- d_3 , *R/S*(±)-venlafaxine- d_6 , *R/S*(±)-bisoprolol- d_5 , *R/S*(±)-acebutolol- d_5 , *R/S*(±)-metoprolol- d_7 and *R/S*(±)-sotalol- d_6 . Mixed calibration standards were prepared in methanol at 0.01–250 ng mL⁻¹ (including 200 ng mL⁻¹ of each deuterated surrogate). These were stored at -20 °C and prepared weekly. HPLC grade methanol, acetic acid and ammonium acetate were purchased from Fisher Scientific (Loughborough, UK). Ultrapure water was 18.2 MΩ cm⁻¹ quality. Sediment (~500 g) from the top 5 cm surface layer was collected for method development from the River Don, Aberdeenshire. This was frozen at -20 °C until further processing.

Sample extraction

Sediments were freeze dried and sieved (2 mm). Two grams of samples was spiked with a methanolic mixture of all deuterated surrogates at 50 ng g⁻¹ and left for 1 h. Samples were mixed with 1 g diatomaceous earth and packed into 10 mL accelerated solvent extraction cells (Fisher Scientific). The

remaining cell volume was filled with Ottawa sand and two 2–4 μm Dionex glass fibre filters (Fisher Scientific) fitted at each end. Sample extraction was performed using a Dionex ASE 350 (California, USA) system. The final method utilised an extraction solvent of 50:50 water:methanol at 100 °C. Two extraction cycles were undertaken per cell with the following settings: 5 min pre-heat, 5 min heat, 5 min static extraction time, 60% solvent flush volume, 150 s nitrogen purge and 1500 psi pressure. During development the influence of sample mass, extraction temperature and solvent composition to enantiomer recovery were investigated. Collected extracts (~22 mL) were diluted to 250 mL using water (<10% methanol content). Samples were loaded (5 mL min⁻¹) onto Oasis HLB solid phase extraction cartridges (3 mL, 60 mg, Waters, Manchester, UK) preconditioned with 2 mL methanol and 2 mL water at 1 mL min⁻¹. Enantiomer elution was in 4 mL methanol at 1 mL min⁻¹. Extracts were dried at 40 °C under nitrogen and reconstituted in 0.5 mL mobile phase.

Enantioselective liquid chromatography–tandem mass spectrometry

Chromatographic analysis was undertaken using an Agilent 1200 series liquid chromatography system (Cheshire, UK) using an InfinityLab Poroshell 120 Chiral-V column (150×2.1 mm; 2.7 μm particle size) fitted with a 0.2 μm pre-filter. A polar ionic mobile phase consisting of 2 mM ammonium acetate in methanol containing 0.01% acetic acid at a flow rate of 0.15 mL min⁻¹ was used (McKenzie et al. 2020). The column temperature was 15 °C whilst the injection volume was 10 μL. The detector was an Agilent 6420 triple quadrupole in positive electrospray ionisation mode. The capillary voltage was 4,000 V with a desolvation temperature of 350 °C and nitrogen gas flow of 12 L min⁻¹. The nebulising pressure was 50 psi. Nebulising, desolvation and collision gases were nitrogen. Multiple reaction monitoring transitions and instrument performance data are compiled in Table S2 and Table S3.

Study site

A sub-catchment of the River Don, Aberdeenshire known to be impacted by septic tank discharge and not any centralised wastewater treatment plants was focused upon (Ramage et al. 2019). Five sampling locations were selected and ~100 g of sediment from the top 5 cm surface layer was collected. Samples were transported to the laboratory on ice and frozen at -20 °C in aluminium foil until further processing (as described in Sect. 2.2). Sediment was also collected from the River Don itself, approximately 7 km downstream of the nearest centralised wastewater treatment plant. Samples

were collected during October 2019 and all analysis was in triplicate.

Results and discussion

Method development

Vancomycin chiral selectors are popular due to their multi-residue separation capabilities (Ribeiro et al. 2013; Evans et al. 2015; Petrie et al. 2018). A Poroshell 120 Chiral-V column was used due to the comparatively short run time (30 min) achievable for multi-residue analysis over other commercially available vancomycin columns (McKenzie et al. 2020). Operation in polar ionic mode using a mobile phase of 2 mM ammonium acetate in methanol containing 0.01% acetic acid facilitated simultaneous

enantioseparations (Fig. 1). In total, 12 of 15 drugs achieved the minimum enantiomer resolution (R_S) threshold of 1 for quantitative purposes (Evans et al. 2015). The remaining drugs had enantiomer R_S of 0.5–0.8 and the valley drop method was used for integration (Camacho-Muñoz and Kasprzyk-Hordern 2017). The inclusion of $R/S(\pm)$ -desmethylcitalopram required a run time of 40 min (Fig. 1). Nevertheless, this remains shorter than previous enantioselective methods for $R/S(\pm)$ -desmethylcitalopram which require ≥ 80 min (Evans et al. 2015).

Accelerated solvent extraction was used due to its previous success for extraction of drugs from soil followed by enantioselective analysis (Petrie et al. 2018). However, it was not possible to directly apply this extraction method to sediments. Extraction of 5 g (freeze dried) organic rich sediment resulted in loss of chiral recognition for most drugs in subsequent enantioselective analysis. Therefore, a new

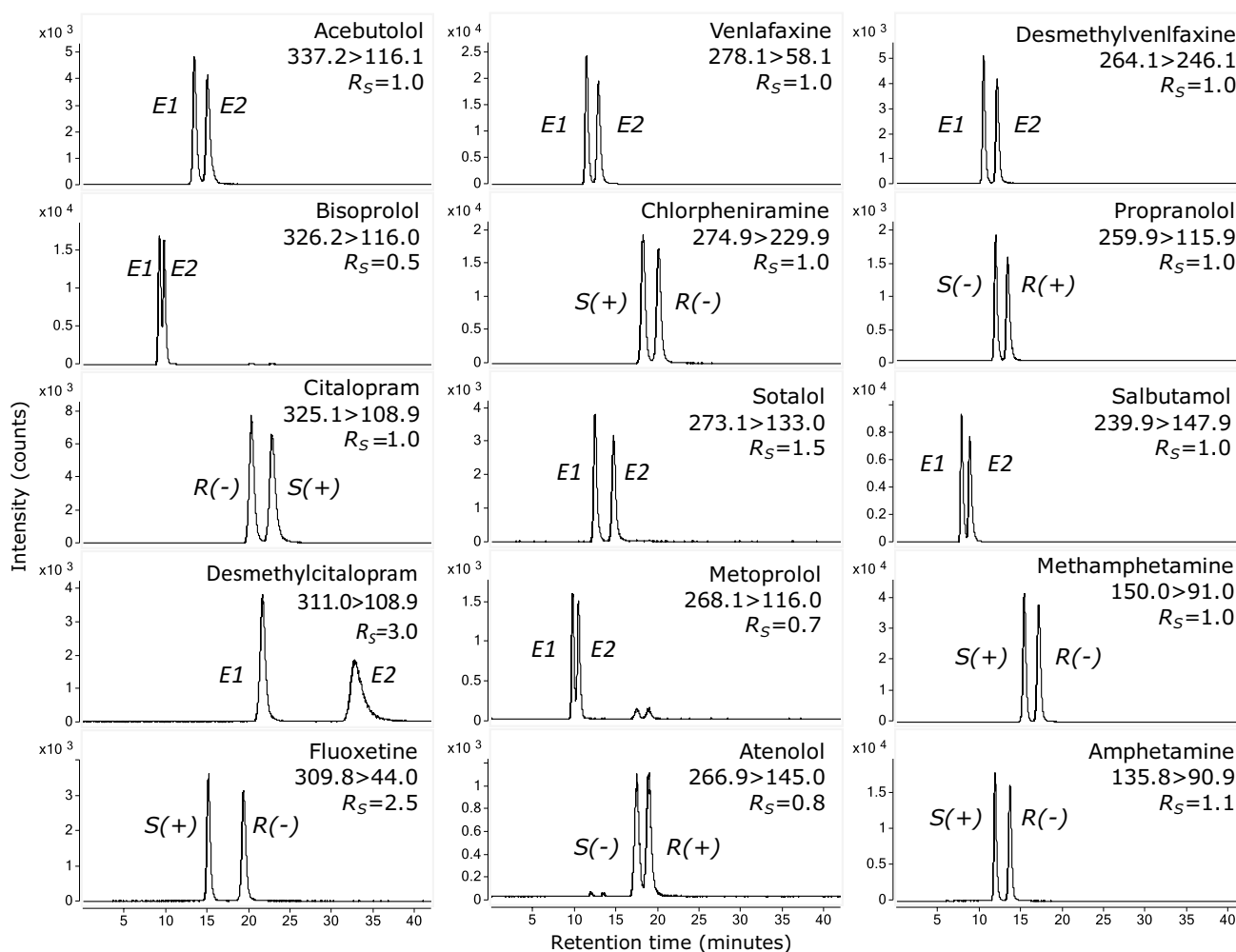


Fig. 1 Enantioselective liquid chromatography–tandem mass spectrometry chromatograms of studied drugs at 100 ng mL^{-1} . Each chromatogram shows the monitored MS/MS transition and enantiomer resolution. Key: $E1$, enantiomer 1; $E2$, enantiomer 2 (where order

of enantiomer elution is not known). $S(-)$, $S(-)$ -enantiomer; $R(+)$, $R(+)$ -enantiomer; $S(+)$, $S(+)$ -enantiomer; $R(-)$, $R(-)$ -enantiomer (where order of enantiomer elution is known)

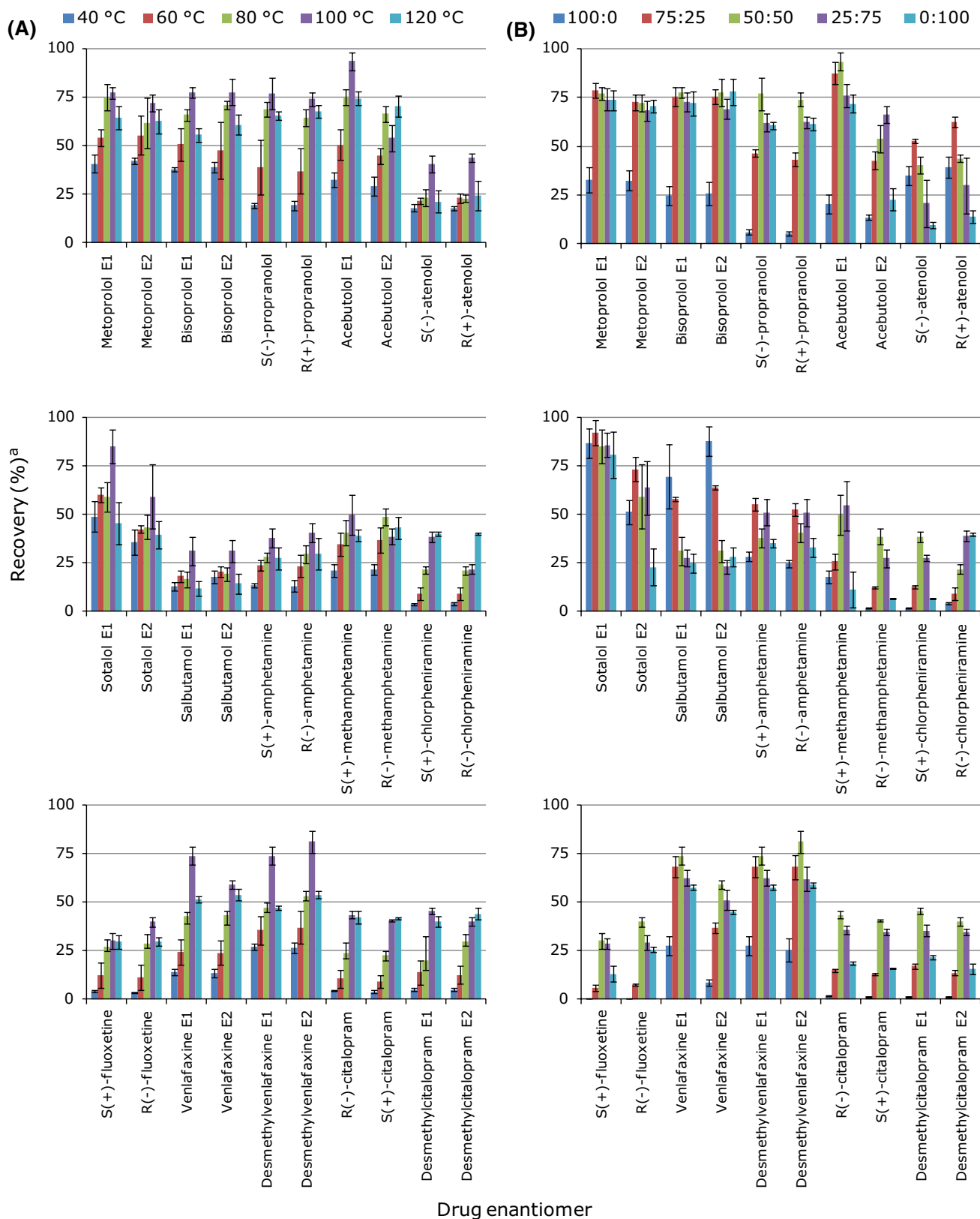


Fig. 2 Influence of extraction temperature (a) and water:methanol extraction solvent composition (b) on enantiomer recovery. Note: at varying extraction temperature the solvent composition was 50:50 water:methanol (a), and under varying water:methanol extraction solvent compositions the temperature was 100 °C (b). The spiking concentration was 50 ng g⁻¹ and all analysis was performed in triplicate. Key: $\text{Recovery}(\%) = \frac{(PA_S - PA_U)}{PA_{STD}}$, where PA_S is peak area of the extracted spiked sample, PA_U is the peak area of the unspiked sample and PA_{STD} is the peak area of a corresponding standard solution assuming 100% recovery through the extraction process

extraction protocol was needed. The maximum sample mass extractable which ensured no loss of chiral recognition was 2 g. Due to the low ng g⁻¹ drug concentrations in sediments (Vazquez-Roig et al. 2010; Silva et al. 2011), further development work was undertaken to ensure maximum recoveries were achieved. Both solvent extraction temperature and solvent composition were studied as they have considerable influence on drug recovery (Petrie et al. 2018).

Enantiomer recovery was investigated at extraction temperatures of 40, 60, 80, 100 and 120 °C. Findings showed ≥ 80 °C was required to achieve the greatest recovery of the more hydrophobic drugs fluoxetine, venlafaxine, chlorpheniramine and citalopram ($\log K_{OW} > 3$ Table S1). Recovery of 40% (12/30) of the studied enantiomers was significantly greater at 100 °C than any other temperature (Fig. 2). However, significantly higher recovery was achieved for some enantiomers at a different temperature (e.g. *R*(-)-chlorpheniramine at 120 °C). Nevertheless, the best overall recovery for the suite of drugs investigated was at 100 °C. Analyte losses can be from the extraction processes but also by signal suppression during electro-spray ionisation (Petrie et al. 2018). Therefore, improved extraction at higher temperature can be compensated by increased signal suppression. This could be the case at 120 °C as sample extracts were visibly ‘dirtier’ than other extraction temperatures.

The different water:methanol extraction solvent compositions investigated were 100:0, 75:25, 50:50, 25:75 and 0:100. Methanol was selected as the organic solvent due to the greater performance over other solvents such as acetonitrile (Nieto et al. 2010). Greatest simultaneous recoveries were achieved using 50:50 water:methanol (Fig. 2). Under such extraction conditions (2 g sediment extracted at 100 °C using 50:50 water:methanol) enantiomer recoveries ranged from 22 ± 3% for *R*(-)-chlorpheniramine to 93 ± 5% for acebutolol-*E1*. This range of recoveries is comparable to multi-residue achiral methods for sediments (Vazquez-Roig et al. 2010).

Method performance

Performance of the methodology was assessed in terms of trueness, signal suppression and sensitivity. Method

trueness (accounting for deuterated surrogate response) was determined at enantiomer concentrations of 10, 50 and 100 ng g⁻¹. All drug enantiomers displayed method trueness in the range 86–121% (Table 1). Both desmethylvenlafaxine and desmethylcitalopram had greatest deviation from 100% as they did not have their own deuterated surrogate. Instead they were quantified using the corresponding enantiomer of venlafaxine-*d*₆ or citalopram-*d*₆, respectively, and can only be considered semi-quantitative. Method precision was ≤ 20% for all enantiomers (Table 1).

Signal suppression during electrospray ionisation (i.e. loss of response due to co-extracted matrix quenching analyte signal) ranged from -28% (i.e. signal enhancement) for salbutamol-*E2* to 42% for *R*(-)-citalopram (Table 1). Such losses are low considering it is not uncommon to encounter > 50% suppression (Vazquez-Roig et al. 2010; Petrie et al. 2018). However, several drugs including citalopram, salbutamol, acebutolol, metoprolol, atenolol and atenolol demonstrated enantiospecific suppression (e.g. > 10% between enantiomers). To demonstrate, signal suppression of acebutolol-*E1* and acebutolol-*E2* were -4% and 34%, respectively (Table 1). Such observations demonstrate the necessity of using deuterated surrogates for enantioselective analysis of sediments.

Method sensitivity was assessed by determining the method detection and quantitation limits. Method quantitation limits were ≤ 3 ng g⁻¹ for all enantiomers with the majority being < 1 ng g⁻¹ (Table 1). Such limits enable the determination of drugs at the enantiomeric level considering the concentrations previously reported in sediments (Vazquez-Roig et al. 2010; Silva et al. 2011). Furthermore, the method detection and quantitation limits are similar to previously published achiral methodologies for sediments (Vazquez-Roig et al. 2010; Al-Khazrajy and Boxall 2017).

Enantiomeric profiling of chiral drugs in sediments

The new methodology was applied to freshwater sediments collected in North-East Scotland (Fig. 3). Sampling focused on a small stream impacted by septic tank discharge (Ramage et al. 2019). The receiving river impacted by both wastewater treatment plant effluent and septic tanks was also sampled. Within the small stream, sediment was collected from a control site with no upstream households. Here, the surrounding land use was arable crop with no biosolids or animal slurry applications within the last two years. No drug enantiomers were detected at this location (Fig. 3).

Samples 1–3 were collected downstream of a suspected septic tank effluent discharge point (without dissipation though a soak away) (Ramage et al. 2019). Both fluoxetine and amphetamine were present. Concentrations of *S*(+)-fluoxetine ranged from 1.6 to 5.0 ng g⁻¹ and

Table 1 Performance data of the accelerated solvent extraction-solid phase extraction-enantioselective liquid chromatography–tandem mass spectrometry methodology

Drug group	Enantiomer	Method trueness (% ± SD) ^a			Signal suppression (%) ^b	MDL (ng g ⁻¹) ^c	MQL (ng g ⁻¹) ^d
		10 ng g ⁻¹	50 ng g ⁻¹	100 ng g ⁻¹			
Beta-blocker	Metoprolol- <i>E1</i>	96 ± 12	99 ± 4	87 ± 3	3	0.26	0.81
	Metoprolol- <i>E2</i>	96 ± 15	100 ± 5	95 ± 4	13	0.28	0.87
	Bisoprolol- <i>E1</i>	104 ± 11	101 ± 5	90 ± 2	14	0.03	0.13
	Bisoprolol- <i>E2</i>	106 ± 12	97 ± 4	99 ± 3	21	0.03	0.13
	<i>S</i> (-)-propranolol	101 ± 15	102 ± 4	95 ± 1	17	0.10	0.32
	<i>R</i> (+)-propranolol	94 ± 2	100 ± 4	102 ± 3	18	0.10	0.34
	Acebutolol- <i>E1</i>	102 ± 8	95 ± 5	91 ± 4	-4	0.03	0.11
	Acebutolol- <i>E2</i>	104 ± 18	99 ± 2	101 ± 3	34	0.05	0.19
	<i>S</i> (-)-atenolol	107 ± 9	102 ± 1	95 ± 4	19	0.91	3.05
	<i>R</i> (+)-atenolol	100 ± 7	102 ± 1	101 ± 3	2	0.85	2.84
	Sotalol- <i>E1</i>	96 ± 5	102 ± 3	90 ± 2	2	0.38	1.24
	Sotalol- <i>E2</i>	95 ± 9	98 ± 4	96 ± 6	29	0.55	1.78
Beta-agonist	Salbutamol- <i>E1</i>	106 ± 1	103 ± 3	92 ± 2	-15	0.08	0.24
	Salbutamol- <i>E2</i>	102 ± 3	98 ± 2	101 ± 3	-28	0.08	0.24
Stimulant	<i>S</i> (+)-amphetamine	104 ± 13	98 ± 2	88 ± 4	17	0.07	0.26
	<i>R</i> (-)-amphetamine	103 ± 1	101 ± 2	98 ± 3	11	0.06	0.24
	<i>S</i> (+)-methamphetamine	104 ± 16	100 ± 3	93 ± 3	26	0.05	0.15
	<i>R</i> (-)-methamphetamine	99 ± 17	95 ± 3	99 ± 6	28	0.07	0.20
Anti-histamine	<i>S</i> (+)-chlorpheniramine	103 ± 7	86 ± 4	95 ± 13	21	0.19	0.64
	<i>R</i> (-)-chlorpheniramine	103 ± 12	91 ± 6	96 ± 9	22	0.34	1.14
Anti-depressant	<i>S</i> (+)-fluoxetine	102 ± 11	98 ± 6	93 ± 4	27	0.42	1.33
	<i>R</i> (-)-fluoxetine	99 ± 7	94 ± 5	99 ± 6	20	0.31	1.00
	Venlafaxine- <i>E1</i>	90 ± 17	99 ± 4	94 ± 7	11	0.03	0.14
	Venlafaxine- <i>E2</i>	100 ± 20	103 ± 3	101 ± 5	13	0.04	0.17
	Desmethylvenlafaxine- <i>E1</i>	113 ± 13	109 ± 7	109 ± 11	24	0.14	0.47
	Desmethylvenlafaxine- <i>E2</i>	112 ± 17	121 ± 5	115 ± 14	22	0.12	0.43
	<i>R</i> (-)-citalopram	103 ± 16	102 ± 7	103 ± 11	42	0.29	0.99
	<i>S</i> (+)-citalopram	104 ± 11	102 ± 10	105 ± 8	30	0.30	1.04
	Desmethylcitalopram- <i>E1</i>	120 ± 13	112 ± 11	105 ± 3	32	0.28	0.94
	Desmethylcitalopram- <i>E2</i>	112 ± 8	104 ± 16	108 ± 17	37	0.31	1.06

SD, standard deviation; MDL, method detection limit; MQL, method quantitation limit

^aTrueness(%) = $\frac{(\text{Conc}_S - \text{Conc}_U)}{\text{Spike}} \times 100$ where Conc_S is the determined concentration of the spiked sample, Conc_U is the concentration of the unspiked sample and Spike is the spiked concentration.

^bSignal suppression(%) = $100 - \left(\frac{\text{Slope}_{MM}}{\text{Slope}_S} \times 100 \right)$ where Slope_{MM} is the slope of the external calibration prepared in matrix and Slope_S is the slope of the external calibration prepared in methanol.

^cMDL (ng g⁻¹) = $\frac{(S \cdot IDL \times 100)}{(\text{Rec} \times CF)}$

^dMQL (ng g⁻¹) = $\frac{(S \cdot IQL \times 100)}{(\text{Rec} \times CF)}$ where S is the volume of sample used for extraction divided by the mass of sample extracted (mL g⁻¹), IDL and IQL

are the instrument detection and quantitation limits, respectively (ng mL⁻¹), Rec is the absolute recovery (%), not accounting for the deuterated surrogate response) and CF is the concentration factor.

R(-)-fluoxetine from 1.0 to 3.4 ng g⁻¹ (Fig. 3). Chiral drug composition was described using enantiomeric fraction:

$$\text{Enantiomeric fraction} = \frac{(+)}{[(+) + (-)]} \quad (1)$$

Here (+) is the concentration of the (+)-enantiomer and (-) is the concentration of the (-)-enantiomer. In each sediment an enrichment of *S*(+)-fluoxetine resulted in enantiomeric fractions of 0.59–0.61. The enantiomeric composition of

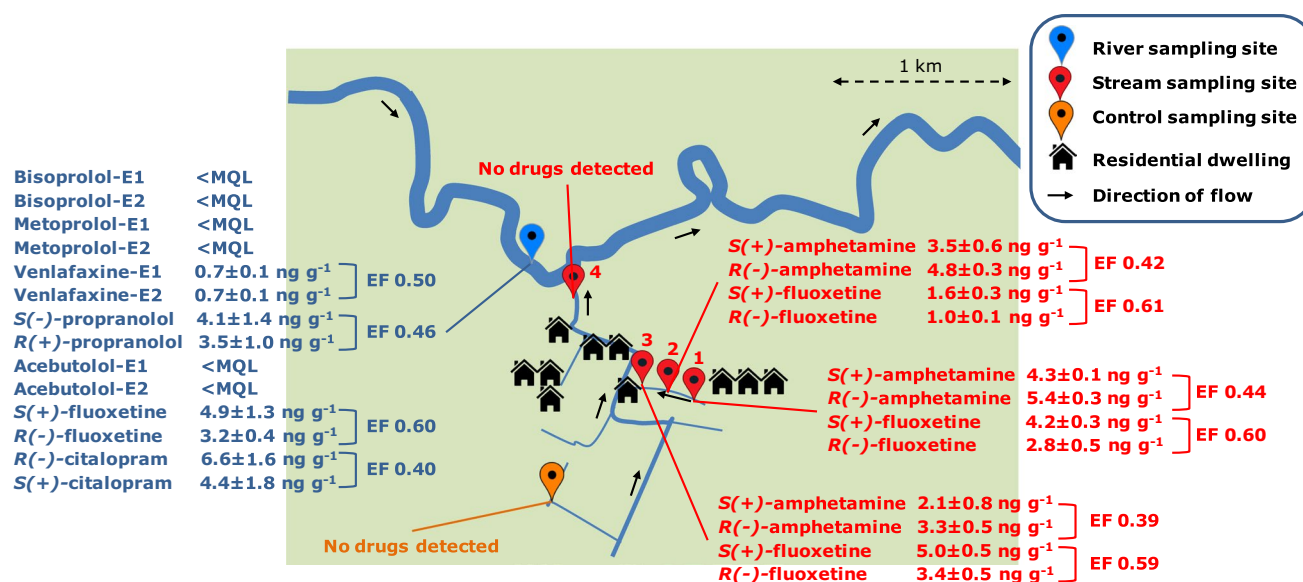


Fig. 3 Enantiomer concentrations and enantiomeric fractions of those drugs detected in sediments collected from a small stream (<0.1 m³ s⁻¹) impacted by septic tank discharge and a receiving river (9.5

m³ s⁻¹) impacted by wastewater treatment plants and septic tanks. Key: EF, enantiomeric fraction, <MQL, below method quantitation limit

fluoxetine in sediments agrees with other environmental matrices such as wastewater effluent (Evans et al. 2015). All amphetamine enantiomers were present at concentrations in the range 2.1–5.4 ng g⁻¹ (Fig. 3). An enrichment of *R*(-)-amphetamine resulted in enantiomeric fractions of 0.39–0.44. This corresponds with previous research whereby amphetamine in this stream water was 470 ng L⁻¹ with an enantiomeric fraction of 0.43 (Ramage et al. 2019). Interestingly, < 1 km downstream (prior to the stream discharge into the receiving river), no drug enantiomers were found. This indicates a localised impact of septic tanks to sediments. However, differences in the composition of sediments could play a role (Al-Khazrajy and Boxall 2016), and requires further investigation for this catchment.

In the sediment sample collected from the receiving river, enantiomers of seven drugs were present. Enantiomer concentrations of the beta-blockers acebutolol, bisoprolol and metoprolol were below quantitation limits (Fig. 3). *S*(-)-propranolol and *R*(+)-propranolol were present at 4.1 ± 1.4 ng g⁻¹ and 3.5 ± 1.0 ng g⁻¹, respectively. This is in agreement with other environmental studies whereby enrichment of *S*(-)-propranolol is typically observed (Fono and Sedlak 2005). Enantiomers of the antidepressants venlafaxine, fluoxetine and citalopram were at low ng g⁻¹ concentrations and enantiomeric fractions of 0.50, 0.60 and 0.40, respectively (Fig. 3). The study showed that the most drugs in freshwater sediments

were non-racemic (enantiomeric fraction ≠ 0.50). Therefore, further investigation is needed on the enantiospecific fate and effects of chiral drugs in freshwater sediments.

Conclusion

Reported here is the first analytical method for the multi-residue enantioselective profiling of chiral drugs in river sediment. Application of the methodology revealed the enantiomeric composition of several drug in sediment for the first time including fluoxetine, amphetamine, propranolol, venlafaxine and citalopram. Most of the drugs were present in non-racemic form demonstrating further enantiospecific investigations are needed in sediments. Such studies can be facilitated using this new multi-residue methodology.

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