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Enantioselective Determination of Amphetamine-Type Stimulants in Environmental Waters Using SPE and CE–MS/MS

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ABSTRACT

The growing concern over drug abuse, particularly involving amphetamine-type substances (ATS), has led to their monitoring in environmental waters. These chiral compounds, commonly found in river water and wastewater treatment plant (WWTP) effluents, require analytical methods capable of enantiomeric discrimination, as their enantiomers can exhibit different pharmacological and environmental behaviours. A method based on capillary electrophoresis (CE) coupled with tandem mass spectrometry (MS/MS) was developed using a dual cyclodextrin (CD) system consisting of 0.1% 2-hydroxypropyl-β-CD and 0.1% γ-CD in the background electrolyte (BGE), which enabled baseline resolution of the target enantiomers of the ATS under study. Samples were pretreated with solid-phase extraction using a mixed-mode cation exchange sorbent, ExtraBond SCX. Samples of 100 mL for WWTP influent and 250 mL for river water and WWTP effluent were extracted and then eluted with 5 mL of 5% NH_4OH in methanol. Recoveries ranged between 40% and 67% for all amphetamines studied, with detection limits between 0.1 and 0.8 µg/L. Analysis of environmental samples from the Ebre River and WWTPs in Reus and Tarragona (Catalonia, Spain) confirmed the presence of some of the target compounds. Both enantiomers of 3,4-methylenedioxymethamphetamine (MDMA) were determined in WWTP influents and effluents, whereas *R*-amphetamine was quantified in an influent sample. No target compounds were detected in the analysed river water samples. These findings demonstrate the potential of the developed chiral CE–MS/MS method for robust enantiomeric profiling in environmental waters, attributed to efficient separation based on differences in effective mobility (μ_{eff}), electroosmotic flow (μ_{eo}) and selective interactions with CD chiral selectors. The method showed moderate adherence to green analytical principles, achieving an AGREE score of 0.47. Its environmental advantages include the use of CE, minimal solvent consumption and non-toxic chiral selectors, offering a more suitable alternative to more traditional LC-based methods.

1 | Introduction

In recent years, drug abuse has become one of the most significant global public health concerns. Amphetamine-type stimulants (ATS) are among the most widely consumed recreational drugs worldwide, with reports estimating that approximately 36 million people consumed ATS in 2021 alone [1–3].

ATS are a group of synthetic compounds controlled under the Convention on Psychotropic Substances of 1971, which includes well-known substances, such as methamphetamine (MAMP), amphetamine (AMP) and 3,4-methylenedioxymethamphetamine (MDMA) [4]. These compounds are generally associated with recreational use, especially in nightlife entertainment, and are often referred to by

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street names, such as 'speed' (AMP), 'crystal meth' (MAMP) and 'ecstasy' (MDMA) [3].

A key feature of ATS is their chirality. They exist as two enantiomers (*R* and *S* forms) with different pharmacological, pharmacokinetic and toxicological properties [5]. For example, although *S*-AMP is prescribed to treat attention deficit hyperactivity disorder in adults, *R*-AMP is typically associated with recreational and illicit use [6, 7]. Given these differences, it is essential to develop analytical methods that can distinguish between enantiomers, particularly for pharmaceutical quality control and environmental monitoring applications.

The rising consumption of ATS poses not only a public health risk but also an environmental threat. These compounds can reach environmental waters through various pathways, including human excretion via urine that ends up in wastewater treatment plants (WWTPs). Even after treatment, trace amounts may still be discharged into rivers and other surface waters [8–10]. Previous studies have confirmed the presence of ATS in various environmental waters at concentrations typically ranging from ng/L to µg/L. For example, nearly half of the European cities that monitor wastewater reported an increase in MDMA residues between 2021 and 2025 [3, 11].

It is a challenge to analytically determine ATS in environmental waters because it is necessary to use sensitive methods capable of enantioselective discrimination. Various separation techniques have been used for this purpose, including capillary electrophoresis (CE) and chiral liquid chromatography (chiral LC) [12–20]. Among these, CE offers several advantages, such as high separation efficiency, lower analysis times and low consumption of reagents and samples. In addition, enantioseparation in CE is straightforward, as it simply requires a chiral selector to be added to the background electrolyte (BGE) [12, 14, 17–25]. In contrast, LC methods often rely on the use of expensive chiral columns and a more complex method development, which can bake less flexible than CE for enantiomeric analysis. Furthermore, CE is considered a greener technique than LC, as it requires lower sample and solvent volumes, so it generally has a lower environmental impact.

A wide variety of compounds can act as chiral selectors in CE, including cyclodextrins (CDs) and their derivatives, which are the most commonly employed, followed by macrocyclic antibiotics, chiral surfactants and crown ethers [13, 18–22]. For ATS analysis, sulphated-CDs, such as sulphated γ-cyclodextrin (γ-CDS), sulphated β-cyclodextrin (β-CDS) and sulphated α-cyclodextrin (α-CDS), have been demonstrated to be effective for enantioseparation [13, 19, 20, 26–29].

Prior to CE analysis, sample pretreatment is required due to the complexity of environmental water matrices and the typically low concentrations of ATS, which are usually found in the ng/L to µg/L range. Solid-phase extraction (SPE) is the most widely applied technique for this purpose [13, 15, 16, 30–36], due to its effectiveness, ease of use and high selectivity [37]. SPE offers a wide range of available sorbents, and different types of interactions can be established between analytes and sorbent materials. According to the structure and the physicochemical properties of ATS, the most suitable sorbents are those based on reversed-phase interactions and/or ionic interactions [37, 38].

Several studies have investigated the use of various sorbents for extracting ATS from environmental waters. Wang et al. [16] and Berset et al. [35] successfully used Oasis HLB (a polymeric reverse-phase sorbent) to extract ATS from wastewater samples (influent and effluent) using LC–MS/MS. These approaches obtained detection limits in the ng/L levels and recoveries exceeding 60%. However, the non-selective nature of these sorbents may also lead to the concentration of other hydrophobic matrix compounds, thereby interfering with the analysis by causing ion suppression or enhancement with ESI-MS. To mitigate this, the deuterated internal standards are used.

An alternative approach to enhance selectivity and reduce matrix effects involves using more selective sorbents, such as mixed-mode sorbents, which combine ionic and reverse-phase interactions. These sorbents can improve selectivity and allow an additional clean-up step to remove unwanted matrix components [37].

Given that ATS have p*K*a values above 9, they are usually present in their cationic form under acidic conditions. Mixed-mode cationic exchange sorbents are therefore suitable for extracting them. Several studies have successfully used this type of sorbent to extract ATS from various environmental waters with recovery values above 70% using the sorbent Oasis MCX [15, 30, 32, 34].

Despite these advances, no studies have focused on the combination of chiral CE coupled with tandem mass spectrometry (CE–MS/MS) with SPE for the enantioselective determination of ATS in different environmental waters. Therefore, the main aim of the present study is to develop and validate a green, enantioselective analytical method for determining selected ATS substances (AMP, MAMP and MDMA) in three types of environmental waters, including river water and WWTP influents and effluents. This method combines SPE with CE–MS/MS. Additionally, to determine their extraction efficiency, we evaluated and compared the performance of different types of SPE sorbents for extracting ATS. Finally, the environmental sustainability of the method is evaluated using the AGREE—analytical greenness metric approach, which provides a quantitative evaluation of the method's greenness on a scale from 0 to 1 [39–42].

2 | Materials and Methods

2.1 | Chemicals and Reagents

Standards of AMP, *S*-AMP, *R*-AMP, MAMP, *S*-MAMP, *R*-MAMP and MDMA (Figure 1) were purchased from Sigma-Aldrich (St. Louis, MO, USA). Individual stock standard solutions were prepared in methanol (MeOH) at a concentration of 100 mg/L and stored in the freezer at −20°C. The working solutions were prepared by diluting at different concentrations a mixture solution containing the compounds at a concentration of 1 mg/L in MeOH:H_2O (5/95, v/v). These solutions were stored at −20°C. The chiral selectors γ-CDS sodium salt (degree of substitution (DS) ~ 14), β-CDS sodium salt (DS ~ 9) and 2-hydroxipropyl-β-CD (2-HP-β-CD) (DS ~ 0.7) were obtained from Cyclolab (Budapest,

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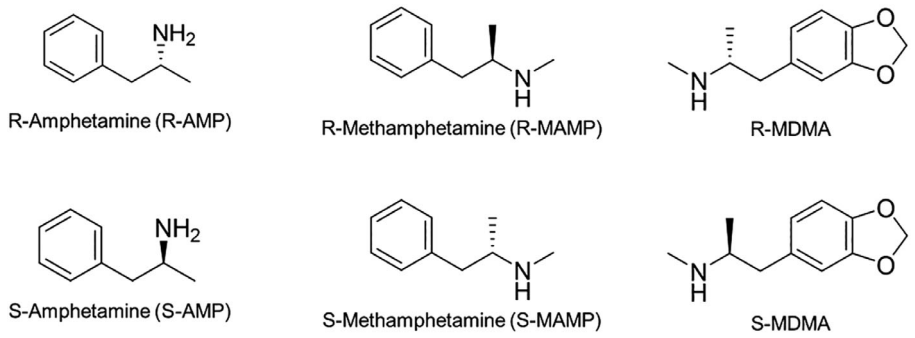


FIGURE 1 | Chemical structure of the enantiomers of the amphetamines studied. MDMA, methylenedioxymethamphetamine.

Hungary). MeOH was supplied from Carlo Erba Reagents (Milano, Italy). Formic acid (HCOOH) (purity ≥ 98%) and ammonium acetate (purity 28%–30%) were supplied by Sigma-Aldrich. Ultrapure water was produced using an Integral Water Purification System (Merck Millipore, Burlington, MA, USA).

Oasis MCX (500 mg) SPE cartridges were purchased from Waters Corporation (Milford, MA, USA) and ExtraBond SCX (500 mg) cartridges from Scharlab (Barcelona, Spain).

Bare fused silica capillaries were purchased from Polymicro Technologies (Phoenix, AZ, USA).

2.2 | Capillary Electrophoresis Coupled With Tandem Mass Spectrometry

2.2.1 | Instrumentation

The CE instrument was an Agilent model 7100 series system, coupled to an Agilent 6460 series triple quadrupole mass spectrometer with an electrospray ionization (ESI) interface from Agilent Technologies (Waldbronn, Germany). The MassHunter Workstation Software (version B.09.00) was used for data analysis and instrumental control. The pH was measured with a GLP 21 pH-meter from Crison (Barcelona, Spain). A miVac Duo sample concentrator from Genevac (Ipswich, UK) was used to evaporate the solutions.

2.2.2 | CE–MS/MS Conditions

CE separations were performed using a bare fused silica capillary of 50 μm inner diameter with a total length of 80 cm, maintained at 25°C throughout the analysis. The BGE consisted of a mixture of 1 M ammonium formate:1 M formic acid (0.1:4.9 v/v) with 0.1% 2-HP-CD and 0.1% γ-CDS as chiral selectors. The sheath liquid was a mixture of 10 mM ammonium acetate and MeOH (50:50, v/v).

The conditioning of new capillaries (outside the MS system) consisted of sequentially flushing (930 mbar) 1 M NaOH for 40 min, followed by 0.1 M NaOH for 10 min, ultrapure water for 10 min, and finally the BGE for 10 min. At the beginning of each day, conditioning was performed with 0.1 M NH_4OH, followed by ultrapure water and finally with BGE, each for 10 min. Samples were hydrodynamically injected at 50 mbar for 10 s, and the separation was performed by applying a voltage of 30 kV.

In the CE–ESI–QqQ system, the optimized parameters were as follows: the ESI operating in positive ionization mode to enhance ionization of the basic ATS compounds, source gas temperature of 200°C, nitrogen flow rate of 2 mL/min, nebulizer pressure of 7 psi, capillary voltage of 4000 V, cone voltage of 100 V and collision energy between 4 and 15 eV. Table 1 shows the selected reaction monitoring (SRM) transitions, and the collision energy applied in each transition for each analyte. Figure 2 shows the electropherogram obtained with the optimized conditions.

2.3 | Solid-Phase Extraction

SPE was performed using ExtraBond SCX sorbent (500 mg). The extraction began with a conditioning step using 12 mL of MeOH and 12 mL of ultrapure water adjusted to pH 3 with formic acid. Water samples were adjusted to pH 3 before loading in the sorbent. Sample volumes were 250 mL for river and WWTP effluent waters and 100 mL for WWTP influent water. After sample loading, a washing step with 5 mL of MeOH was performed, and finally, the compounds were eluted from the sorbent using 5 mL of 5% NH_4OH in MeOH. Extracts were then evaporated to dryness using a miVac Duo sample concentrator and finally reconstituted in 0.5 mL of 5% MeOH in water. Finally, samples were filtered through a 0.45 μm polytetrafluoroethylene (PTFE) syringe filter prior to CE–MS/MS analysis. Figure 3 shows the recovery values obtained for each compound in the different types of waters.

2.4 | Method Validation

The method was validated according to the international guidelines for analysing drugs [43–45]. The parameters evaluated included instrumental detection and quantification limits (LOD, LOQ), linearity, method detection and quantification limits (MDL and MQL), precision as repeatability (intra-day) and reproducibility (inter-day), accuracy expressed as absolute recovery (R%) and matrix effects (%ME). Migration times (m_t) were accepted within ±2.5% tolerance and ion ratios within ±20% [46].

Instrumental linearity was evaluated over a concentration range of 90–600 μg/L with determination coefficients (r^2) considered

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TABLE 1 | Optimized conditions of the capillary electrophoresis coupled with tandem mass spectrometry (CE–MS/MS) acquisition method.

Compound	m_t (min)	Precursor ion (m/z)	Cone voltage (V)	Product ion 1 (m/z) (Q)	Collision energy 1 (eV)	Product ion 2 (m/z) (q)	Collision energy 2 (eV)	Ratio (q/Q)×100
R-AMP	12.39	136.1	100	119	4	91	10	57.7
S-AMP	13.52							70.8
R-MAMP	12.76	150.1	100	119	8	91	10	137.1
S-MAMP	13.34							189.3
*E*1-MDMA	14.93	194.1	125	163	10	133	15	25.6
*E*2-MDMA	15.92							28.2

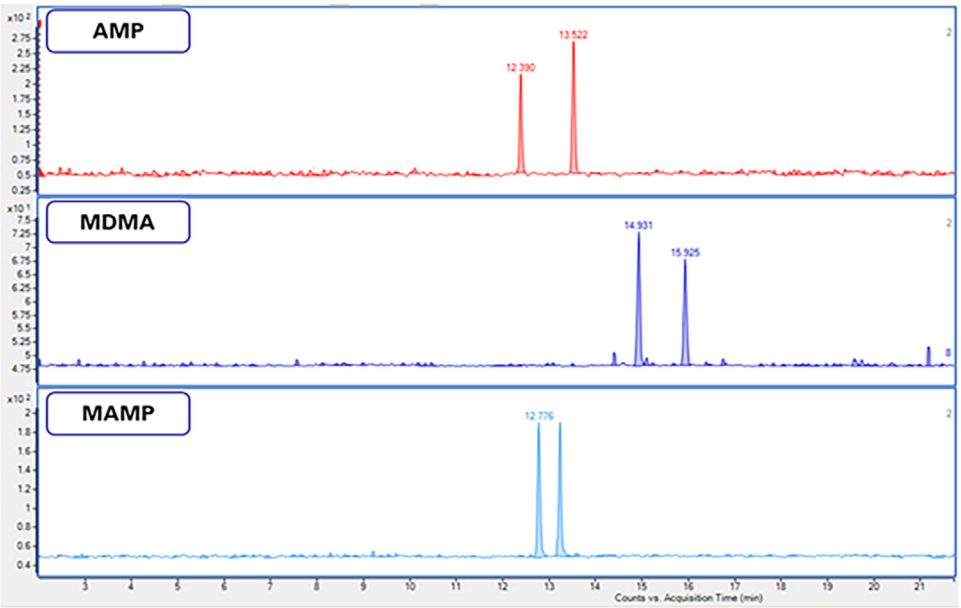


FIGURE 2 | Electropherogram of a standard sample of 200 μg/L analysed using 0.1% γ-CDS and 0.1% 2-HP-β-CD as chiral selectors and the optimized CE–MS/MS conditions (Section 2.2). AMP, amphetamine; MAMP, methamphetamine; MDMA, 3,4-methylenedioxymethamphetamine.

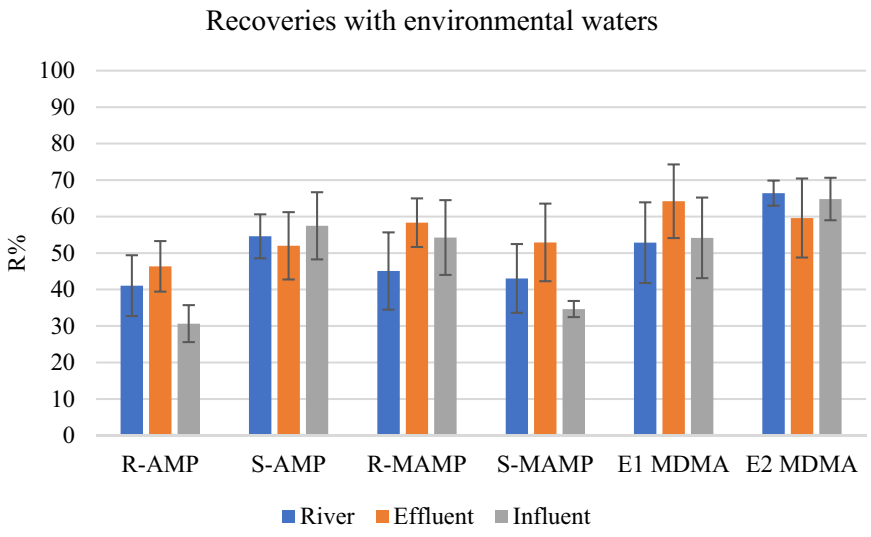


FIGURE 3 | SPE recoveries of the compounds using ExtraBond SCX sorbent and the optimized conditions (Section 2.3) with river water (250 mL), WWTP effluent (250 mL) and WWTP influent (100 mL). AMP, amphetamine; MAMP, methamphetamine; MDMA, 3,4-methylenedioxymethamphetamine; WWTP, wastewater treatment plant.

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satisfactory above 0.99. LOD was determined on the basis of a signal-to-noise (S/N) ratio greater than or equal to 3, whereas for LOQ, the S/N ratio required was greater or equal to 10.

MDL and MQL were calculated on the basis of the instrumental limits of the target compounds, taking into account the recoveries and the concentration factor. Precision was evaluated in terms of repeatability (intra-day) and within-laboratory reproducibility and expressed as relative standard deviation (%RSD), using five replicates ($n = 5$) of each water type at three concentration levels. For effluent wastewater and river water: 0.3 µg/L (low), 0.6 µg/L (medium) and 1.2 µg/L (high); and for influent wastewater: 0.75 µg/L (low), 1.5 µg/L (medium) and 3 µg/L (high).

Accuracy values, as absolute recovery % (R%), were calculated as the ratio between the experimental concentration obtained after SPE and the theoretical concentration of the standard solutions prepared in ultrapure water.

Matrix effects (%ME) were calculated using the following formula: $\%ME = ((C_{exp}/C_{the}) \times 100) - 100$, where C_{exp} is the concentration obtained by spiking a non-spiked sample after SPE, and C_{the} is the theoretical spiked concentration.

2.5 | Analysis of Real Samples

To demonstrate the applicability of the method, three different samples of each type of water were analysed. River water was collected from Ebre River in 2024. The WWTP effluents and influents were provided by facilities from Reus and Tarragona (Catalonia, Spain), and they were collected on different days in 2024.

All samples were collected in 1000 mL polypropylene bottles and stored at −20°C. Before analysis, all samples were filtered through a nylon filter of 0.45 µm.

Although the samples were not collected on the same day, the extraction and analysis have done in triplicate.

3 | Results

3.1 | CE–MS/MS Optimization

MS/MS parameters were optimized by direct infusion of individual standard solutions of each compound at a concentration of 1 mg/L prepared in a MeOH:H_2O (50:50, v/v) solution. On the basis of the physicochemical properties of ATS, we selected ESI in positive mode as it provided better ionization efficiency and higher S/N ratios for all the analytes under study.

The precursor and product ions selected for each compound are summarized in Table 1. $[M + H]^+$ ions were chosen as precursor ions based on a previous published study of our research group focused on determining ATS in urine samples [13]. Various collision energies (ranging from 0 to 25 eV) were evaluated, and optimal values are also reported in Table 1, along with the quantification ion ratios for each enantiomer.

For CE–MS/MS separation, the BGE and the sheath liquid composition (10 mM ammonium acetate:MeOH (50:50)) were adapted from a previous study conducted by our research group [13]. However, additional optimization was performed in the present study to the enantioresolution and reduces analysis time. The optimization process involved adjusting the separation voltage and the chiral selector composition. Three separation voltages were evaluated (20, 30 and 40 kV), with 30 kV providing the best results, reducing the analysis time by 3 min in comparison with the method developed by Pascual-Caro et al. [13]. Moreover, the enantioresolution improved between 30% and 76%.

3.1.1 | Chiral Selector Optimization

To achieve the enantiomeric separation of the ATS analysed in this study, a chiral selector must be added to the BGE. However, this presents a significant analytical challenge due to the limited MS compatibility of most chiral selectors. These compounds are typically non-volatile compounds, and their presence in the BGE can lead to signal suppression and contamination of the MS detector [29]. To address this, several strategies, such as the countercurrent migration technique (CMT) or the partial filling technique, have been developed [14]. In this study, the CMT approach was applied using charged CDs (CD sulphated sodium salts). With these conditions, the electrophoretic mobility of the chiral selector exceeded the electroosmotic flow (cationic) in the opposite direction, resulting in its migration toward the inlet while the analytes were transported toward the ESI+. This prevents the entrance of CD into the detector, avoiding contamination and preserving signal intensity [14, 29].

Previous research carried out by Pascual-Caro et al. [13] demonstrated the viability of CDs as chiral selectors for ATS separation. In that study, 0.2% γ-CDS was established as optimal, obtaining resolution values above 1.3. In the present study, with the aim of improving this separation and reducing analysis time, some other CDs, such as β-CDS and γ-CDS and combinations between them, were evaluated.

β-CDS and γ-CDS were tested at different concentrations ranging from 0.1% to 0.4%. In the case of β-CDS, no satisfactory separations could be achieved at any concentration. In contrast, 0.2% γ-CDS yielded a good separation for most ATS enantiomeric pairs, except for AMP, which remained unresolved. Increasing the γ-CDS percentage to 0.4% led to higher background noise without any improvement in resolution.

Preliminary studies carried out in our group using CE-UV revealed that 2% 2-HP-β-CD provided a good separation of ATS enantiomers. However, due to its neutral charge and high concentration, this CD is not suitable for MS applications, as it can contaminate the MS system and cause ion suppression. To overcome these limitations while maintaining MS compatibility, we explored a dual CD system, reducing the percentage of this charged CD and combining it with γ-CDS. A mixture of 0.1% γ-CDS and 0.1% 2-HP-β-CD provided baseline separation of all ATS enantiomers, and the peaks exhibited high efficiency, as shown in Figure 2. Importantly, the low percentage of 2-HP-β-CD did not adversely affect the MS system, and no ion suppression was observed. Moreover, good resolution values were achieved: 4.3 for

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AMP enantiomers, 2.3 for MAMP enantiomers and 3.9 for MDMA enantiomers.

These values represent a clear improvement over those reported by Pascual-Caro et al. [13]. Thus, our results demonstrated enhanced enantioselective performance, proving that the separation was improved using an optimized BGE composed of a mixture of 1 M ammonium formate:1 M formic acid (0.1:4.9 v/v) with 0.1% 2-HP-CD and 0.1% of γ-CDS.

3.2 | SPE Optimization

In this study, two mixed-mode cation exchange sorbents were evaluated to determine the most suitable material for the ATS extraction: Oasis MCX and ExtraBond SCX (both 500 mg cartridges). These sorbents were selected according to the physicochemical properties of the target compounds, which have p*K*a values above 9 (AMP: 10.1; MAMP: 10.1 and MDMA: 9.0) (Figure 1). Therefore, at pH values below 9, these compounds exist predominantly in their cationic form, facilitating their retention through cationic electrostatic interactions with the sulphonic acid groups of these sorbents [37].

Oasis MCX and ExtraBond SCX are mixed-mode strong cation exchange sorbents that contain sulfonic acid groups ($-SO_3^-$) in their structure, offering a dual retention mechanism via cationic exchange interactions (with the sulfonic groups) and reverse-phase interactions (with the base structure). The main difference between the two sorbents is in the base material: Oasis MCX is a polymeric-based sorbent, whereas ExtraBond SCX is silica-based. The latter exhibits higher selectivity in general, particularly for basic compounds [37].

The optimization process was focused on obtaining maximum recovery values by evaluating different key parameters, including sample loading conditions (pH and volume), clean-up conditions (solvent type and volume) and elution conditions (solvent and volume).

For the loading step, the sample pH was adjusted to 3 using formic acid to enhance cationic interactions between the negatively charged sulphonic groups of sorbents and the protonated ATS. Although previous studies in the literature have used pH 2 when working with Oasis MCX and have obtained satisfactory results [15, 30–32], we avoided this pH value with ExtraBond SCX to prevent potential degradation of the silica support under highly acidic conditions [37]. Therefore, pH 3 was used uniformly for both sorbents to enable a fair comparison.

The elution volume was the first parameter optimized. We used a sample volume of 100 mL of ultrapure water (adjusted at pH 3) spiked with the analytes at a concentration of 0.3 µg/L. The elution was performed using 10 mL (divided into two 5 mL aliquots) of 5% NH_4OH in MeOH [37], followed by evaporation to dryness using a miVac Duo Concentrator and the final reconstitution with 0.5 mL of 5% MeOH in H_2O. The results indicated that a volume of 5 mL was sufficient to quantitatively elute all analytes from both sorbents, achieving recoveries higher than 70%. Thus, to reduce the evaporation time and therefore the analysis time and the energy consumption while enhancing the method's greenness, 5 mL was selected as the optimal elution volume.

To improve selectivity and reduce matrix effects, a washing step was included to eliminate weakly retained and hydrophobic interferences without disrupting the ionic retention of cationic analytes. MeOH was selected as the washing solvent due to its ability to break the hydrophobic interactions without disrupting the cationic interactions [37]. The volume of MeOH was evaluated using two aliquots of 2.5 mL (total of 5 mL).

After the washing step, some analyte losses were observed with Oasis MCX, and consequently, the final recoveries dropped below 30%. In contrast, with ExtraBond SCX, recoveries remained above 60% for all enantiomers; thus, a washing step using MeOH could be applied with this sorbent. The different volumes studied (2.5 and 5 mL) did not negatively affect the retention of the target compounds; therefore, 5 mL was selected as the optimal washing volume to enhance the removal of matrix interferences.

Another critical parameter is the sample volume, as it directly influences the concentration factor and the extraction efficiency and, consequently, the sensitivity of the method. Using ultrapure water, it was shown that volumes up to 500 mL could be processed through the sorbent without exceeding the sorbent breakthrough volume. However, due to the varying complexity of the environmental matrices analysed in this study, additional optimization was performed for each environmental water type.

River water and effluent wastewater are relatively low-complexity matrices. Therefore, sample volumes of 500 and 250 mL were tested. When 500 mL was used, the recoveries decreased by approximately 50% for all enantiomers compared to those obtained with 250 mL, establishing the latter as the optimal volume. At this volume, recoveries ranged from 41% to 67%.

In contrast, for influent wastewater, which is more complex, a lower sample volume was required. In this case, 100 mL loading was determined to be the most effective, achieving recoveries between 26% and 65%. Processing larger volumes (250 mL) led to significant decreases in the recoveries (more than 20% for all enantiomers), attributed to both breakthrough effects, partial sorbent saturation or blockage and clogging of the sorbent [47].

These results demonstrate that ExtraBond SCX enables efficient selective extraction of ATS from different types of environmental water matrices, regardless of their complexity. Figure 3 shows the obtained recovery values for all enantiomers for the different water matrices using ExtraBond SCX.

Overall, ExtraBond SCX emerged as the most effective sorbent, combining strong analyte retention, low matrix interference and high selectivity. In addition, the method enabled the processing of large sample volumes, resulting in high concentration factors and improved sensitivity, with detection limits in the range of µg/L.

Comparing with other previous studies, the results achieved using ExtraBond SCX are satisfactory. For instance, Kasprzyk-Hordern et al. [32] used Oasis MCX to extract a group of ATS and other basic drugs from wastewater at pH 2, reporting slightly higher recoveries (approximately 80%) in posterior determination by chiral-LC detector. However, their approach involved smaller sample volumes, resulting in lower concentration factor.

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Coelho et al. [15] determined some enantiomers of ATS in river water using Oasis MCX for the extraction, and they obtained recoveries comparable to those obtained in the present study (around 50%). However, their procedure involved a clean-up step with 4 mL of ethanol and elution carried out in two different steps (4 mL each), which increased the volume of solvents used and the extraction time.

Although the recoveries obtained in the present study are not significantly higher than those reported in other studies, we could conclude that this method has several advantages in terms of selectivity, simplicity and greenness in comparison with previous studies. Moreover, the good results obtained with ExtraBond SCX prove their applicability and add this sorbent to the list of sorbents that can be applied for extracting ATS.

3.3 | Validation of the SPE–CE–MS/MS Method

The performance of the optimized SPE–CE–MS/MS method was evaluated according to internationally accepted guidelines for analysing drugs [43–45]. The studied parameters included instrumental linearity, instrumental LOD, instrumental LOQ, precision in terms of repeatability and within-laboratory reproducibility, matrix effect, MDL and MQL.

The instrumental parameters of CE–MS/MS were validated using ultrapure water. The instrumental linearity of the method ranged from 90 to 600 μg/L for all ATS enantiomers with the lowest concentration point corresponding to the LOQ. The calibration curves exhibited excellent linearity, with determination coefficients (r^2) higher than 0.99. Instrumental LODs ranged from 50 to 70 μg/L. The precision of the method was evaluated through repeatability (intra-day) and reproducibility (inter-day) studies at three levels of concentration (low, medium and high), with five replicates ($n = 5$) for each. The intra-day precision was determined by analysing the same samples five times in a single day, while inter-day was assessed by analysing the samples across five consecutive days. The precision results were expressed as %RSD and remained below 10% for all enantiomers, for both repeatability and reproducibility, demonstrating good precision.

Method validation was performed using real environmental water samples from the three different water matrices being studied: river water, WWTP influent and WWTP effluent.

The results of MDL, MQL, *R*% and ME% are summarized in Table 2.

The MDLs and MQLs were calculated on the basis of the instrumental limits, taking into account the recoveries and the concentration factor obtained after SPE for each water matrix; the values are summarized in Table 2. The MDLs were below 0.80 μg/L in all matrices, with the lowest values obtained for river water (ranging from 0.16 to 0.31 μg/L). The MQLs ranged between 0.30 and 1.15 μg/L, and the lowest values were for AMP in river water. These values confirm the method applicability for trace-level monitoring of ATS enantiomers in environmental waters, enabling the detection of concentrations in the low range of μg/L.

ME% values ranged from 1% to −17% in river water, from 15% to −20% in effluent wastewater and from 2% to −20% in influent wastewater. As expected, the ME values were slightly higher for effluent wastewater in comparison to river water due to the increased complexity of the matrix. However, the relatively moderate ME values in influent wastewater, despite its inherent complexity, can be attributed to the reduced sample volume used for the extraction step (100 mL). Overall, the method exhibited low to moderate ME for all water types, highlighting the efficiency of the optimized extraction procedure. In particular, the inclusion of a washing step greatly contributes to eliminating interferences that could affect the ionization processes in MS detection.

In all cases, the method exhibited good repeatability (inter-day), in the range of 8%–15%, and within-laboratory reproducibility, with values between 10% and 24%, expressed as RSD% ($n = 5$). The values were below 25% in all cases, showing the good precision of the method developed.

3.3.1 | Greenness Assessment

The greenness of the developed method was evaluated using the AGREE, which assesses analytical procedures based on the 12 principles of green analytical chemistry. The method is scored from 0 (nongreen) to 1 (fully green). The optimized SPE–CE–MS/MS method achieved an AGREE score of 0.47, indicating a moderate alignment with green chemistry principles. As it could be observed in Figure 4, several factors contribute positively to this result. These include the use of CE, which is inherently considered a green technique due to its low reagent and solvent consumption and the absence of hazardous derivatization steps. Additionally, non-toxic chiral selectors compatible with MS detection are used. These are not classified as harmful to health or the environment.

However, there are certain aspects of the method that could be improved to further enhance the method's sustainability. The SPE step involves manual sample handling, processing of relatively high volumes of sample, considerable energy demand (especially during evaporation) and generation of waste. Although solvent usage is reduced in CE-based methods compared to LC methods, sample preparation still contributes significantly to the overall environmental footprint. Furthermore, the sourcing of reagents, particularly non-local or specialized materials, may contribute to a higher carbon footprint due to transportation and production processes.

Overall, the method balances analytical performance and environmental sustainability. The AGREE score indicates that the method, while not fully green, offers a considerably more suitable alternative to traditional chiral LC-MS/MS methods, particularly for environmental monitoring applications.

3.4 | Real Samples

The practical applicability of the developed SPE–CE–MS/MS method was demonstrated through the analysis of environmental waters collected from the Ebre River, as well as from influent and effluent wastewaters provided by facilities of Reus and

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TABLE 2 | Validation results of SPE–CE–MS/MS method for different environmental water samples.

	250 mL river						250 mL effluent WWTP						100 mL influent WWTP					
			R%						*R*%						*R*%			
Compounds	**MDL (μg/L)**	**MQL (μg/L)**	**Low[a]**	**Medium[b]**	**High[c]**	**ME%[b]**	**MDL (μg/L)**	**MQL (μg/L)**	**Low[a]**	**Medium[b]**	**High[c]**	**ME%[b]**	**MDL (μg/L)**	**MQL (μg/L)**	**Low[d]**	**Medium[e]**	**High[f]**	**ME%[e]**
R-AMP	0.16	0.30	49	41	43	−14	0.19	0.33	58	46	49	−11	0.31	0.55	26	31	26	−20
S-AMP	0.18	0.32	45	55	52	1	0.23	0.42	54	52	48	15	0.54	0.98	62	57	54	2
R-MAMP	0.31	0.44	50	45	40	−17	0.29	0.42	49	58	54	−19	0.80	1.15	43	54	49	−2
S-MAMP	0.17	0.34	49	43	54	−10	0.21	0.42	46	53	52	−20	0.35	0.69	35	35	34	−15
*E*1-MDMA	0.30	0.42	46	53	50	−14	0.36	0.51	61	64	58	−8	0.76	1.08	57	54	56	−2
*E*2-MDMA	0.27	0.53	58	66	59	−3	0.24	0.48	67	60	63	−4	0.65	1.30	60	65	65	−3

Abbreviations: MDL, method detection limits; ME, matrix effects; MQL, method quantification limits; WWTP, wastewater treatment plant.

[a]Low concentration: 0.3 μg/L.

[b]Medium concentration: 0.6 μg/L.

[c]High concentration: 1.2 μg/L.

[d]Low concentration: 0.75 μg/L.

[e]Medium concentration: 1.5 μg/L.

[f]High concentration: 3.0 μg/L.

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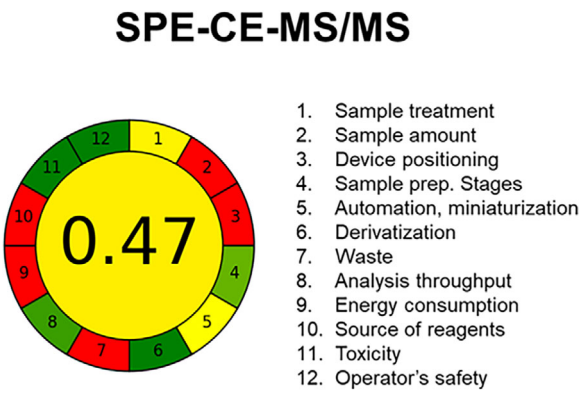


FIGURE 4 | Method evaluation according to the AGREE–analytical greenness metric approach.

Tarragona (Catalonia, Spain). The WWTP samples were collected on different days, so the results are not directly comparable. The quantification was performed using external calibration, taking into account the recoveries and the concentration factor obtained after SPE. Each sample was extracted by triplicate to ensure the reliability of the results obtained. Table 3 summarizes the concentrations of the ATS enantiomers found in these analysed samples.

In the river water samples, as can be seen in Table 3, none of the ATS enantiomers targeted in this study could be detected. This finding aligns with previously published studies that report trace or non-detectable levels of ATS in surface waters, likely due to dilution and degradation processes in the aquatic environment. For example, Racamonde et al. [48], using SPME–GC–MS for determining ATS in river water in a northwest region of Spain, could not detect MAMP or MDMA in most of the river water samples analysed. MDMA was only quantified in one sample at a concentration of 12.2 ng/L. Similarly, Berset et al. [35] were unable to detect AMP and MAMP in 22 river water samples from Switzerland and detected MDMA in only 25% of the samples analysed at concentrations below 1.4 ng/L. In another study, Verovšek et al. [49] quantified MDMA in just one sample from the Sava River (Slovenia) at a concentration of 0.262 ng/L.

In the analysed effluent wastewater samples, MDMA was the only ATS detected. MDMA had poor removal rates in wastewater treatments; for these reasons, it could be detected in effluent waters [7]. It was quantified in one sample with an enantiomer-specific concentration of 2.60 μg/L for *E*1-MDMA and 0.77 μg/L for *E*2-MDMA. The enantiomeric ratio indicates a higher consumption of *E*1-MDMA.

This finding aligns with the literature. For example, Kasprzyk-Hordern et al. [32] also reported *E*1-MDMA in concentrations lower than 10 ng/L and *E*2-MDMA below 4 ng/L in effluent samples. In both studies, MDMA was the only ATS detected. In addition, these authors found higher concentrations of both enantiomers in comparison with the concentrations found in the present study, possibly reflecting regional consumption differences or temporal variability.

As expected, influent wastewater samples contained higher concentrations and a broader range of ATS enantiomers, as these waters reflect direct human excretion prior to treatment. In one of the samples, no ATS were detected. In another sample, only *E*1-MDMA was quantified.

In a third sample, both MDMA enantiomers and *R*-AMP were found. *R*-AMP was found at 1.21 μg/L, which is consistent with its known association with nightlife and recreational uses [6]. *E*1-MDMA and *E*2-MDMA were quantified at 1.60 and 0.85 μg/L respectively.

A similar pattern was also reported in the study carried out by Kasprzyk-Hordern et al. [32], in which the authors detected AMP and both enantiomers of MDMA in influent wastewater samples from northwestern Spain. Both in the present study and that carried out by Kasprzyk-Hordern et al. [32], *R*-AMP was the most detected enantiomer of AMP. This enantiomer is associated with recreational and illicit uses related to nightlife. Therefore, it is consumed extensively, and it is usually more prevalent than *S*-AMP, which is prescribed for medical treatment to treat hyperactivity. For MDMA, in both studies the concentration of *E*1-MDMA was significantly higher (above 50%) than for *E*2-MDMA.

The results obtained also reflect regional consumption trends reported by the European Union Drugs Agency (EUDA) [3], which highlighted stable levels of AMP and MDMA consumption in the Tarragona region (Catalonia, Spain) during the monitoring period. The absence of MAMP in all samples is also in line

TABLE 3 | Concentrations found in real environmental water samples (μg/L).

	River			Effluent WWTP			Influent WWTP		
	1	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**
R-AMP	nd	nd	nd	nd	nd	nd	nd	nd	1.21 ± 0.3
S-AMP	nd	nd	nd	nd	nd	nd	nd	nd	nd
R-MAMP	nd	nd	nd	nd	nd	nd	nd	nd	nd
S-MAMP	nd	nd	nd	nd	nd	nd	nd	nd	nd
*E*1-MDMA	nd	nd	nd	nd	nd	2.60 ± 0.6	nd	<MQL	1.60 ± 0.3
*E*2-MDMA	nd	nd	nd	nd	nd	0.77 ± 0.08	nd	nd	0.85 ± 0.2

Abbreviations: AMP, amphetamine; MQL, method quantification limit; MAMP, methamphetamine; MDMA, 3,4-methylenedioxymethamphetamine; WWTP, wastewater treatment plant.

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with the EUDA data [3], indicating that this compound is not commonly consumed in the studied area.

4 | Conclusions

A novel, selective, versatile and green method based on SPE followed by CE–MS/MS was successfully developed and validated for the enantioselective determination of a group of ATS compounds in environmental waters. Chiral separation was achieved using a dual-CD system composed of 0.1% 2-HP-β-CD and 0.1% γ-CDS, enabling an efficient separation, with high resolution in a reduced analysis time (30 min).

The optimization of the pre-treatment step, based on the SPE technique, involves comparing two different sorbents. Among them, ExtraBond SCX demonstrated a superior performance in terms of recovery, selectivity and concentration factor. The inclusion of a clean-up step did not considerably affect the recoveries, which remained around 50% for most enantiomers in all the different waters under study. The method was successfully validated in terms of linearity, precision, recovery and matrix effect. Low MDLs between 0.16 and 0.80 µg/L, and low MQLs from 0.30 to 1.15 µg/L were achieved. The method was suitable for determining and quantifying these enantiomers at low concentration levels in real water samples.

The method was successfully applied to analyse water samples from the Ebre River and from WWTPs of the Tarragona region. Although ATS compounds were not detected in river water, enantiomers of MDMA and *R*-AMP were successfully detected and quantified in WWTP waters reflecting patterns of recreational drug use consistent with regional monitoring data. The AGREE yielded a score of 0.47, highlighting the method's moderate environmental compatibility and demonstrating that the method is a considerably greener and more suitable alternative to traditional chiral LC-MS/MS methods, particularly for environmental monitoring applications.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

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