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RESEARCH ARTICLE

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Spray-assisted drop formation liquid-phase microextraction for the determination of sertraline in environmental water samples with matrix-matching calibration in GC–MS

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Abstract

Sertraline is used as an antidepressant drug for the treatment of psychiatric disorders, including anxiety and depression. In the current study, a simple and effective method was developed for the sensitive monitoring of sertraline in water samples using a GC–MS system. The spray-assisted droplet formation liquid-phase microextraction (SADF-LPME) method was used as a sample preparation method for the enrichment of analytes. Accordingly, dichloromethane was used as an extraction solvent and easily dispersed into a sample/standard solution using a lab-made modified spray device without using a dispersing solvent. The significant factors affecting the SADF-LPME efficiency, including sample pH, mixing conditions, extraction solvent type, and spray cycle, were univariately optimized to ascertain the extraction performance and applicability of the system. Under the optimized conditions, the plotted calibration curve of the method was linear in the range of 100.2–2011.7 µg/kg (mass-based standard preparation) with a good correlation coefficient (R^2) of 0.9997. The detection and quantification limits of method were found to be 37.5 and 125 µg/kg, respectively. Validation of the method was successfully carried out using different tap water samples and applying a matrix-matching calibration strategy. The acceptable percent recoveries were recorded between 77.3 and 133.7%, with high repeatability. The recommended method is an alternative and fast extraction method with several advantages, including a simple experimental process, good dispersibility, and fast and superior extraction performance. It can be readily applicable to the monitoring and quantification of sertraline in tap water samples with good precision and accuracy.

Keywords Sertraline, Gas chromatography, Tap water, Matrix-matching calibration, Microextraction

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Introduction

Antidepressant drugs are the most prescribed drugs for treating psychiatric disorders and depression, which directly affect the concentration of neurotransmitters in the central nervous system including serotonin, dopamine, and norepinephrine (Truta et al. 2016; Wang et al. 2023). Selective serotonin reuptake inhibitors (SSRIs) have a range of therapeutic benefits in humans and block presynaptic serotonin reuptake transporters (Brooks 2014). Sertraline hydrochloride, one of the SSRIs, is commonly used as an antidepressant drug with better efficiency and acceptability than other antidepressants (Atty et al. 2020; Khosrokhavar et al. 2020; Shoja et al. 2016). Sertraline has a high specific affinity for the central serotonin uptake sites, which has an effective therapeutic range with minimal and tolerable side effects (Khraiwesh et al. 2011). Additionally, sertraline is employed for the treatment of different kinds of psychiatric diseases, such as major depression, post-traumatic stress, anxiety, panic or social phobia, and obsessive–compulsive disorders (Huddart et al. 2020; Khraiwesh et al. 2011; Shoja et al. 2016). Sertraline has been widely prescribed for children and adults; hence, it has been reported to be one of the most detected pharmaceutical substances in wastewater treatment plant effluents and surface water (Mohamed et al. 2023). Most pharmaceutical drugs, especially antidepressants, cannot be completely metabolized, and the unchanged parent compounds or their active metabolites are afterward disposed into the sewage system. Antidepressant-contaminated wastewater is continuously released into the environment because of the insufficient treatment of these drugs by wastewater treatment plants (Zhang et al. 2023). Accordingly, they can rapidly penetrate human bodies through seafood consumption or drinking water and lead to health issues (Khan et al. 2023). Even though these drugs are eliminated during the treatment process in wastewater and surface water, some drugs can still exist in wastewater at ng/L or µg/L levels. This can alter the biological processes of various species, especially fish, affecting gene transcription and compromising anti-predator behavior at low levels. For example, tissue-specific bioaccumulation of sertraline, citalopram, and venlafaxine in *Oncorhynchus mykiss* (rainbow trout) has been observed in the brains and livers of most fish (Melchor-Martínez et al. 2021). According to the report published by the World Health Organization in 2012, pharmaceutical concentrations are reported as less than 0.1 µg/L in groundwater, surface water, and poorly treated water, while generally below 0.05 µg/L in treated water (Fallah et al. 2021). Therefore, rapid and sensitive analytical methods are required for monitoring the quantification and presence of antidepressants to evaluate their potential effects on the environment.

Analytical methods are important to provide rapid and accurate analytical information in preclinical and clinical pharmacokinetic studies, as well as environmental research (Bozyiğit et al. 2023; Jain et al. 2005). The most commonly used chromatographic techniques involving gas chromatography-mass spectrometry (GC–MS) (Boumba et al. 2016; Koçoğlu et al. 2017; Ntoupa et al. 2020; Rosado et al. 2017; Papoutsis et al. 2012)), and high performance liquid chromatography (HPLC) (Ferrarini et al. 2010), liquid chromatography–tandem mass spectrometry (LC–MS/MS) (Patel et al. 2009; Zhang et al. 2011) have been reported for the determination of sertraline in various matrices. In addition, sample preparation methods are generally needed to enrich analytes, make them suitable for the analysis system, eliminate matrix interferences, and obtain the appropriate analyte form for the detection/extraction (Farajzadeh et al. 2017). Different sample preparation methods, such as solid phase extraction (SPE) (Arghavani-Beydokhti et al. 2023), solid phase microextraction (SPME) (Mohammadi et al. 2020), liquid-phase microextraction (Hansen et al. 2020), and dispersive liquid–liquid microextraction (DLLME) (Akramipour et al. 2016), can be applied for the detection of trace levels of pharmaceuticals as they overcome the limits caused by the matrix effects and the low amount of analytes before the chromatographic analysis. DLLME has gained great popularity due to its simplicity and the ability to be performed for different analytes in a various matrices (Ahmad et al. 2015). This method can be easily modified to achieve a superior enrichment factor, reduce the amount of organic solvent and cost, and provide better selectivity and reproducibility with minimal experimental steps using the previously reported simple spray apparatus (Erulaş et al. 2020).

The objective of the presented work was to establish the determination of sertraline in environmental water samples. SADF-LPME as sample preparation was performed using a commercial spray apparatus that led to the formation of the droplets. This system was coupled with a GC–MS system for the quantitative detection of the studied analyte. The main factors affecting the preconcentration system were evaluated using a comprehensive optimization approach. Additionally, this system was used for the first time for the sertraline determination of in tap water matrix.

Experimental

Instrumental and chromatographic conditions

GC–MS analysis was conducted by an Agilent 6890 GC system coupled with an Agilent 5973 mass spectrometry detector. The studied analyte was separated by using an HP-5MS (Agilent, USA) capillary column (30 m × 0.32 mm i.d., 0.25 µm film thickness). The helium

(purity 99.995%) as carrier gas has flowed with a constant flow rate of 2.5 mL/min, and sample/standard volume was injected as 1.0 µL in the splitless mode at an inlet temperature of 280 °C. The ion source and quadrupole temperature of the mass spectrometer were kept at 230 °C and 150 °C during analyses in the ionization energy mode (70 eV), respectively. The temperature program of the GC oven was initially set to 70 °C, then increased to 280 °C at 50 °C/min, and finally 280 °C to 300 °C at 60 °C/min. The major quantitative/qualitative ions of sertraline HCl were selected as 276/274 due to their high selectivity and good sensitivity. Chromatographic analyses were accomplished by both techniques, including the total ion chromatogram (TIC) and scanning ion mode (SIM). Data acquisition and instrument control were processed with ChemStation® software.

The efficient and uniform dispersion of the extraction solvents was carried out into sample/standard solutions using a basic and commercially available spray apparatus. The features of the designed system were detailed in our previous study (Erulaş et al. 2020). Briefly, the system consisted of the following parts: a transfer tube, an extraction solvent container (20-mL internal volume), a centrifuge tube cap, and a spray head. The extraction solvent was easily dispersed without the use of a dispersive solvent to minimize the experimental step and organic solvent consumption. The spray apparatus is illustrated in Fig. 1.

Chemicals and solutions

The standard of sertraline HCl with a high purity (≈100%) was provided by Biofarma pharmaceutical company (İstanbul, Türkiye). HPLC-grade ethanol was supplied from Isolab (Germany) to prepare a standard stock solution with a concentration of 1267.9 mg/kg (mass-based). Extraction solvents, including dichloromethane 1,2 dichloroethane and chloroform, were of analytical reagent grade and taken from Merck (Darmstadt, Germany). The standard solutions were prepared by gravimetric and, all dilutions were done with deionized water having the conductivity of 18.2 MΩ/cm (ELGA PureFlex III). The buffer solution (pH 6.0) was prepared by using potassium hydrogen phthalate and HCl solution (37%) in the studied concentrations, both purchased from Merck (Darmstadt, Germany). The working/calibration standard solutions were prepared freshly and daily before everyday usage and stored in a refrigerator (− 20 °C) protected from light.

Extraction and preconcentration procedure

The 8.0 mL of working/sample solutions were placed in a 15-mL centrifuge tube and a 0.50 mL of pH 6.0 buffer solution was added into the solution. Dichloromethane as an extraction solvent was sprayed at two cycles. As depicted in Fig. 1, the centrifuge tube was coupled to the spray apparatus, and the spraying process was carried out by turning the system upside down. After the spraying, the cloudy solution was formed, and the samples were vortexed at 60 s, ensuring a homogenous dispersion process and increasing mass transfer. The formed phase was then centrifuged for 2.0 min at 3000 rpm to accelerate phase separation. The organic phase (dichloromethane) was collected in an insert vial, and the extracted sample was injected into the GC–MS system for analysis.

Sample preparation

Tap water samples were employed to verify the practicality and accuracy of the SADF-LPME method. The

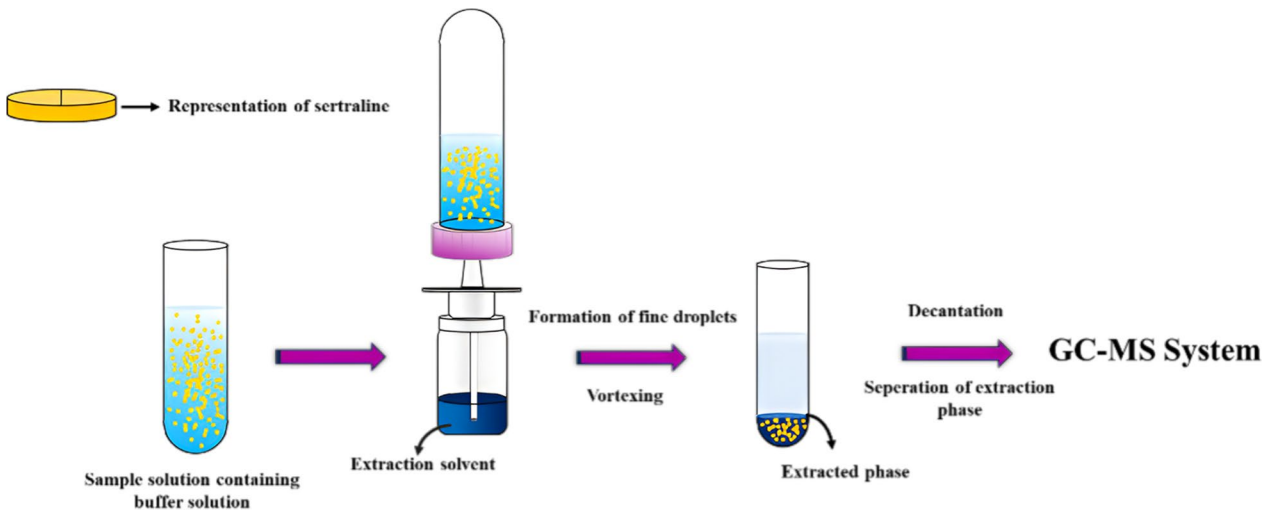

Fig. 1 Illustration of SADF-LPME method for sertraline

samples, namely TW1 and TW2, were taken from two different locations in İstanbul, Türkiye. Accordingly, TW1 was directly sampled from a laboratory outlet (Esenler, İstanbul), and TW2 was sampled from a household tap (Büyükçekmece, İstanbul). The PET (polyethylene terephthalate) bottles were used in the sampling process and rinsed thoroughly with tap water before the collection of samples. The matrix-matched samples were prepared to eliminate matrix interferences and directly used for the extraction of sertraline without any filtration. Samples were collected freshly to minimize the possibility of contamination or degradation and stored in a wooden cabinet under ambient conditions.

Results and discussion

Optimization of effective factors in SADF-LPME

The experimental parameters including pH of sample solution, extraction solvent type, spray repetition, mixing type, and mixing period were systematically studied for the quantitative determination of sertraline to obtain the highest extraction efficiency in terms of low limit of detection (LOD) and limits of quantification (LOQ). The optimization studies of the above-mentioned parameters were carried out using one variable at a time method with three parallel groups. The optimal conditions were selected according to the comparison of average peak area and relative standard deviation (%RSD). Precision was expressed as %RSD, which indicated the repeatability of the signals. The spray apparatus mentioned in Sect. "Instrumental and chromatographic conditions" was used for the distribution of the extraction solvent and single-step extraction of the studied analyte from aqueous samples. The sample/standard solution volume was fixed at 8.0 mL, considering the efficient distribution of extraction solvent and the applicable volume of the spray system.

Optimization of the pH

The pH has a significant impact on the water solubility and extractability of analytes, which depend on the chemical structure and pK_a value of the analyte(s). The ionic forms of analytes assist in the transition from the organic solvent to the aqueous phase; while, the molecular forms of the analytes tend to be transferred to the organic solvent (Caldas et al. 2010) (Ghane et al. 2022). Accordingly, the weak acids exist in ionic form in the sample medium when their pH values are greater than their pK_a values. This not only increases their water solubility but also reduces their retention in the extraction device (Ghani et al. 2021). In this study, the effect of pH on the extractability of sertraline was evaluated in the range of pH 4.0–8.0 by adding 1.0 mL of buffer solution. The findings are demonstrated in Fig. 2A. Although the highest peak area was achieved at pH 4.0, the repeatability of signals notably decreased. The satisfactory results were achieved using a phthalate buffer solution prepared with potassium hydrogen phthalate and HCl at pH 6.0. Hence, the buffered samples at pH 6.0 were selected as the ideal sample medium due to their good signal repeatability and satisfactory extraction outputs.

The volume of the buffer solution was then adjusted between 0.50 and 1.5 mL to ensure a good buffer capacity and proper extraction performance. The final volume of test solutions was fixed using deionized water to compare different buffer solution volumes at the same concentration without dilution of analytes. As shown in Fig. 2B, the peak areas and repeatability of signals were decreased by increasing the buffer volume up to 1.5 mL. The highest responses with the lowest %RSD were recorded at 0.50 mL of the buffered solution. The 0.50 mL of pH 6.0 buffer solution was selected as an optimal condition for its excellent buffering capacity and extraction of sertraline without further diluting it.

Selection of the extraction solvent type

In LPE-based extraction methods, a suitable extraction solvent is required for the complete extraction of analytes (Azadkish et al. 2023). The extraction solvent should exhibit features, e.g., higher density than water, low water solubility, non-volatility during the extraction process, and compatibility with the analytical techniques used. Halogenated solvents are widely employed as extraction solvents in DLLME-based methods, involving tetrachloroethylene, chloroform, methylene chloride, and carbon tetrachloride (Lobo and Magalhães 2020). In this regard, three water-immiscible halogenated solvents, including chloroform (CHL), dichloromethane (DCM), and 1,2-dichloroethane (DCE), were compared to assess their effects on extraction performance with two spray cycles. The results demonstrated that signals significantly decreased with CHL and DCE solutions, according to Fig. 2C. DCM proved to have superior extraction capability due to its greater solubility for sertraline, enabling better extraction from the aqueous sample. Hence, DCM was selected as an optimal extractant in the following experiments.

Optimization of extraction solvent volume

Accordingly, the effect of the DCM volume was examined to ensure optimal detection sensitivity and good extraction efficiency for the studied analyte. An excessive volume of extractant can lead to analyte dilution; while, a low volume may not be sufficient for the complete extraction of the analyte. In this context, the number of spray cycles was optimized by testing 2, 3, and 4 cycles. As expected, the results indicated an incremental decrease

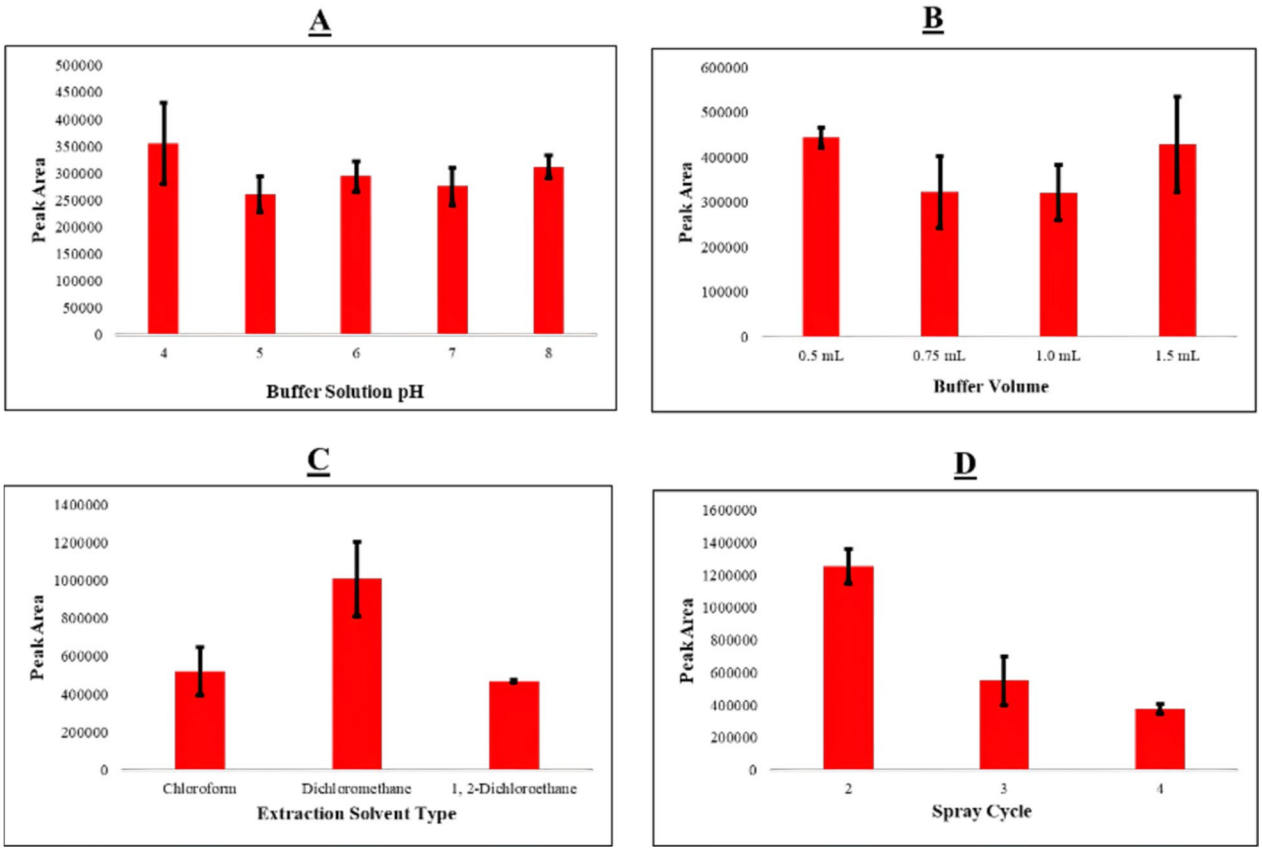

Fig. 2 Effect of **A** buffer solution pH, **B** buffer solution volume, **C** extraction solvent type, and (**D**) spray cycle on the extraction performance of sertraline (Error bars represent SD, $n = 3$)

in peak areas with increasing spray cycles (Fig. 2D). The spray cycle is related to the volume of extractant and leads to dilution of the analyte in increasing cycles. Additionally, one spray cycle was not tested due to the challenges of phase separation and the collection of the dispersed extractant. Consequently, the dispersion of extractant for extracting sertraline from environmental water samples was conducted using a designed apparatus at two spray cycles. Additionally, the DCM solution was dispersed using an analytical balance into clean centrifuge tubes with six replicate cycles, and the average extraction solvent volume consumed in one spray cycle was recorded as 0.07953 g with a 0.0041 SD.

Optimization of mixing conditions

The effect of the mixing type on the extraction performance was studied using vortex, ultrasonication, and mechanical mixing for a constant period of 15 s. Additionally, the extraction process was repeated without any mixing conditions to assess the mixing effect on extraction outputs. Based on experiment results, ultrasonication proved to have the best extraction capability, but the %RSD value was quite high compared to other mixing processes. This can be explained by the fact that mass transfer and equilibrium cannot be established effectively. The vortex was therefore used for optimum mixing due to better extraction outputs. The effect of vortex period on extraction efficiency was assessed from 20 to 100 s in 20 s intervals at ambient temperature. The average peak areas showed a decrease at 40 s, then the extraction efficiency increased linearly between 40 and 80 s. This is most likely the result of an insufficient and unstable equilibrium process. The highest responses were obtained with 60 s. Hence, 60 s was selected as the suitable vortex period for the next experiments.

Analytical performance of the SADF-LPME method

The performance of SADF-LPME combined with the GC–MS system for the determination of sertraline was investigated under optimized extraction conditions (Table 1).

Under optimal extraction and chromatographic conditions, the method was verified using analytical performance parameters, including the LOD, LOQ, linear dynamic range (LDR), linear coefficients (R^2), and repeatability. The lowest concentration that can be determined

Table 1 Optimal extraction conditions of the presented SADF-LMPE method for sertraline

Parameter	Conditions
Initial sample volume	8.0 mL
Buffer solution/volume	pH 6.0/0.50 mL
Spray repetition	2 times
Extraction solvent	Dichloromethane
Mixing type/period	Vortex/60 s

with statistical significance using a particular analytical technique is known as the limit of detection, or LOD. The lowest analyte concentration that can be quantitatively identified with a certain level of accuracy and precision is known as the limit of quantification (LOQ). The range of concentrations where the signals are exactly proportionate to the analyte concentration in the sample is known as the linear dynamic range. A detectable signal is given down below in Fig. 3. The calibration plots and curves were constructed by plotting peak areas versus the concentrations. The LOD and LOQ values were calculated using the following expressions: $3*\sigma/m$ and $10*\sigma/m$, respectively. m represents the slope of the regression equation of the calibration plot and σ represents the standard deviation of the lowest concentration ($n=6$). LOD and LOQ values of the recommended method were recorded at 37.5 µg/kg and 125.0 µg/kg, respectively. Linearity was obtained in the range of 100.2–2011.7 µg/kg with $R^2>0.9997$. All results are summarized in Table 2. As seen in the Table 2, the conventional chromatographic methods can be used in the determination of sertraline in various real sample matrices. Additionally, any sample preparation method applied prior to instrumental measurements of these samples may enhance the accuracy and the sensitivity of the analytical method. Similarly, the detection power of the GC–MS system in the determination of sertraline in the study was enhanced by developing a simple and rapid microextraction technique. Furthermore, the results show that the SADF-LPME-GC–MS method can be used for the quantitative determination and monitoring of sertraline at trace amounts in environmental analysis with respect to comparable detection limits with the methods used in the literature for the aim of sertraline determination.

Application for tap water samples

The tap water samples were used to ascertain the reliability and feasibility of the proposed method in practical applications. Accordingly, the analysis of procedural blank samples was accomplished under optimal

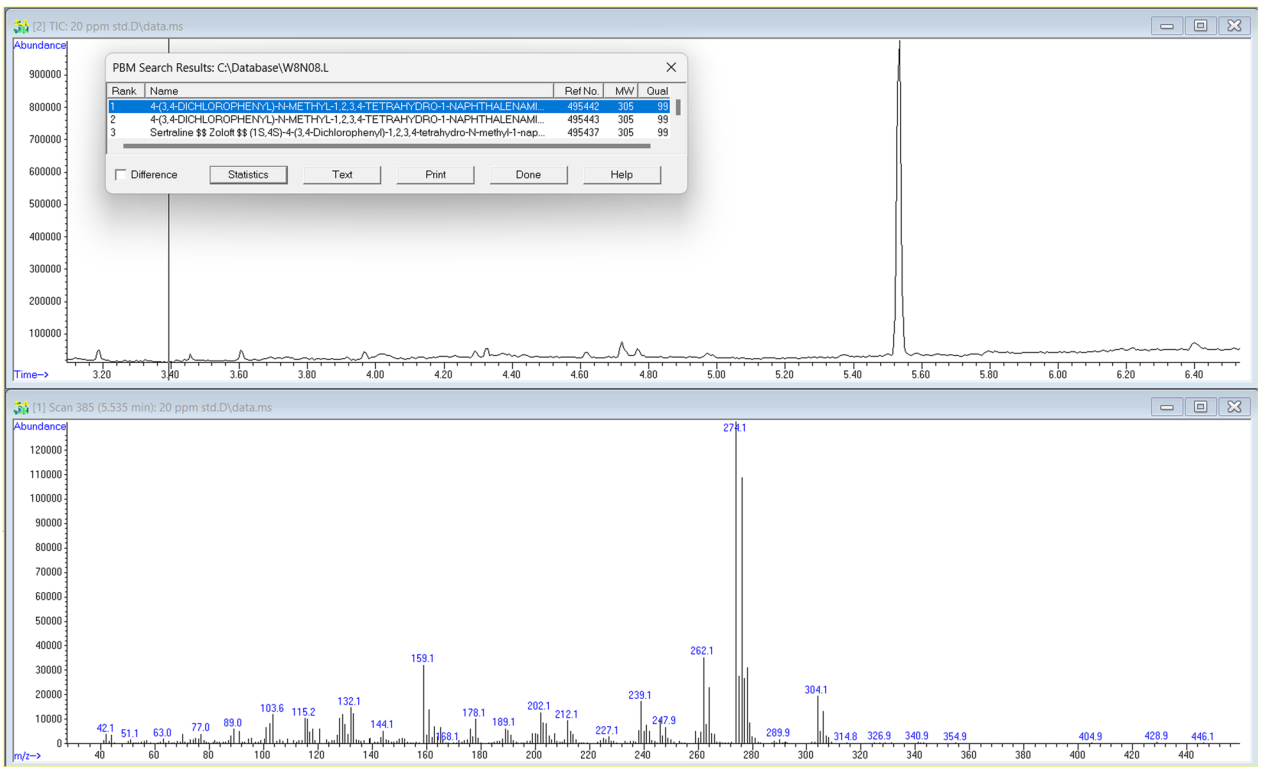

Fig. 3 Total ion chromatogram signal of Sertraline-HCL corrected by NIST MS Library Software

Table 2 Analytical performance parameters for sertraline in the presented methods and comparison with previously published methods

Method	LOD	LOQ	Dynamic range	Calibration equation	R^2	Real samples	References
GC-MS[a]	1.1 mg/kg	3.8 mg/kg	2.49–88.83 mg/kg	$y = 15{,}229.5x + 138{,}412.6$	0.9930	–	This study
SADF-LPME-GC-MS[b]	37.5 µg/kg	125.0 µg/kg	100.2–2011.7 µg/kg	$y = 1661.6x + 52{,}120.5$	0.9997	Tap water	
Supportive liquid–liquid extraction-GC–MS	0.43 ng/mL	1.43 ng/mL	1.0–1000 ng/mL	$y = 0.0114x - 0.0928$	0.999	Tap Water and wastewater	Koçoğlu et al. (2017)
HPLC[c]	0.029 µg/mL	0.097 µg/mL	1.0–120 µg/mL	$y = 32439x - 42{,}461$	0.9999	Bulk drug, tablets, and capsules	Chen et al. (2004)
SLE-HPLC–MS/MS[d]	0.09 ng/mL	0.30 ng/mL	1.0–100 ng/mL	$y = 1.0785x + 1.3579$	0.9967	Human plasma	Zheng et al. (2021)
RP-UHPLC[e]	0.2085 µg/L	0.6321 µg/L	10–50 µg/mL	$y = 85.27x + 69.94$	0.9999	Bulk drug and dosage form	Chaudhari et al. (2022)
UA-DLLME-SFOD[f]	0.4 ng/mL	1.2 ng/mL	1.2–40.0 ng/mL	$y = 17{,}057\ C_{SER} + 866.89$	0.9985	Human serum and urine	Farsimadan et al. (2016)

[a] Gas chromatography-mass spectrometry

[b] Spray assisted drop formation-based liquid-phase microextraction–gas chromatography–mass spectrometry

[c] High-performance liquid chromatography tandem mass spectrometry

[d] Solid-phase supported liquid–liquid extraction-high-performance liquid chromatography tandem mass spectrometry

[e] Reversed phase ultra-high-performance liquid chromatography

[f] Ultrasound-assisted dispersive liquid–liquid microextraction based on solidification of floating organic droplets—high performance liquid chromatography

Table 3 Percentage recoveries for the determination of analyte obtained from tap water samples

Sample	Spiked concentration, µg/kg	% Recovery	± Standard Deviation ($n = 3$)
TW1	205.4	105.2	17.5
	354.2	91.5	10.7
	807.9	85.9	15.8
	1532.7	77.3	6.9
TW2	200.2	115.9	1.6
	351.8	125.1	7.8
	805.3	103.7	6.1
	2029.1	133.7	4.4

extraction conditions. The detectable signals were recorded to be notably greater than the blank signals of the deionized water at the retention time of the studied analyte. A blank correction procedure was used for the quantification of sertraline in matrix-matching calibration strategy. Subsequently, the spiking procedure at different concentrations was applied for TW1 and TW2, and the %recoveries were calculated by applying a matrix-matched calibration strategy. Equation from spiked TW1 was used to calculate the %recoveries of spiked TW2, and the equation from spiked TW2 was used for recoveries of spiked TW1. The results are summarized in Table 3, and acceptable percent recoveries were found to be in the range of 77.3–133.7%.

Conclusion

In the current work, a simple and effective microextraction method was developed for the preconcentration of the most frequently prescribed antidepressant drug, sertraline, in tap water samples prior to the GC–MS system. The presented extraction strategy can easily overcome the limitations of the conventional DLLME method due to several advantages, such as single-step and fast extraction, easy handling, and an affordable process. The modified spray apparatus was employed for the efficient distribution of the extraction solvent without the need to use a dispersion solvent. Accordingly, the mass transfer between the organic and aqueous phases was successfully established with the help of a spraying device. Under the optimal conditions, LOD and LOQ were recorded as 37.5 µg/kg and 125 µg/kg, respectively, with good linearity in the range of 100.2–2011.7 µg/kg. The method was verified using tap water samples to examine the system's feasibility and effectiveness. The acceptable percent recoveries were found to be in the range of 77.3–133.7% with high precision using matrix-matched samples. The method demonstrated good extraction capability, sufficient sensitivity, and precision, indicating its possibility for widespread application. In addition, AGREE (Analytical GREEnness Metric Approach and Software) score of the presented method was calculated as 0.62. Hence, the presented method can be used for antidepressant drugs, especially sertraline, to determine concentration during therapeutic monitoring, clinical research, and environmental assessments at the µg/kg level.

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Author contributions
Nagehan Kübra Zeytinci contributed to data curation, formal analysis, investigation, methodology, validation, visualization, and writing—original draft. Hilal Akbıyık contributed to data curation, formal analysis, validation, visualization, and writing—original draft. Buse Tuğba Zaman contributed to data curation, formal analysis, validation, visualization, and writing—original draft. Emine Tezgin contributed to formal analysis, validation, visualization, and writing—original draft. Gamze Dalgıç Bozyiğit contributed to formal analysis, validation, visualization, and writing—original draft. Meltem Şaylan contributed to formal analysis, validation, visualization, and writing—original draft. Sezgin Bakırdere contributed to conceptualization, investigation, methodology, supervision, validation, writing—review and editing.

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Availability of data and material
Data will be available upon reasonable request.

Declarations

Competing interests
The authors declare that they have no competing interests.

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