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A Novel Liquid–Liquid Extraction for the Determination of Sertraline in Tap Water and Waste Water at Trace Levels by GC–MS

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Abstract A simple, green and fast analytical method was developed for the determination of sertraline in tap and waste water samples at trace levels by using supportive liquid–liquid extraction with gas chromatography–mass spectrometry. Different parameters affecting extraction efficiency such as types and volumes of extraction and supporter solvents, extraction period, salt type and amount were optimized to get lower detection limits. Ethyl acetate was selected as optimum extraction solvent. In order to improve the precision, anthracene-D10 was used as an internal standard. The calibration plot of sertraline was linear from 1.0 to 1000 ng/mL with a correlation coefficient of 0.999. The limit of detection value under the optimum conditions was found to be 0.43 ng/mL. In real sample measurements, spiking experiments were performed to check the reliability of the method for these matrices. The spiking experiments yielded satisfactory recoveries of 91.19 ± 2.48%, 90.48 ± 5.19% and 95.46 ± 6.56% for 100, 250 and 500 ng/mL sertraline for tap water, and 85.80 ± 2.15% and 92.43 ± 4.02% for 250 and 500 ng/mL sertraline for waste water.

Keywords Sertraline · Supportive liquid–liquid extraction · GC–MS · Internal standard

Pharmaceuticals include many compounds belonging to different chemical families. These compounds are disposed into the environment after medical and veterinary usage, and are therefore referred to as environmental pollutants (Puckowski et al. 2016; Nikolaou et al. 2007; Boxall et al. 2012; Kümmerer 2009). These bioactive compounds are found in the environment at trace levels but they may cause adverse effects on the ecosystem and human health because of their continuous entry into the environment and their bioaccumulative characteristic (Yuan et al. 2013; Daughton and Ternes 1999; Shao et al. 2009; Calisto and Esteves 2009). Psychiatric drugs have an important impact on this issue as much as antibiotics and other drugs (Yuan et al. 2013; Krasner et al. 2009; Jelic et al. 2011). The presence of psychiatric pharmaceuticals and their significant biological toxicity in different environmental samples have been reported in literature (Yuan et al. 2013; Till 2005; Bound et al. 2006). Selective serotonin reuptake inhibitors (SSRIs) are among these psychiatric pharmaceuticals and sertraline is a member of the SSRIs widely used for the treatment of depression (Asgharinezhad et al. 2015; DeVane 1999; Lamichhane et al. 2014; Minagh et al. 2009; Schultz et al. 2010). In comparison to other SSRIs, sertraline is known to pose minimal toxic effects to the environment and aquatic organisms (Huang et al. 2012; Edwards and Anderson1999). However, it should be noted that when the concentration of sertraline exceeds a certain limit, intoxication may occur (Lamichhane et al. 2014; Huang et al. 2012; Sasajima et al. 2010). Hence, sensitive and accurate determination of this analyte is very important to monitor the contamination level in environmental and biological samples (Izadyar et al. 2016). Gas chromatography–mass spectrometry (GC–MS) (Huang et al. 2012; Khraiwesh et al. 2011; Lamas et al. 2004; Kocoglu et al. 2016; Bakariki et al. 2016), high performance liquid chromatography

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(HPLC) equipped with ultraviolet (UV) absorption (Huang et al. 2012; Melo et al. 2009; Chaves et al. 2010; Serbest et al. 2016), fluorescence (Huang et al. 2012; Bahrami et al. 2009; Khalil et al. 2010), and MS detection (Yuan et al. 2013; Huang et al. 2012; Zheng et al. 2010; Conley et al. 2008; Frahnert et al. 2003; Jones et al. 2009) are some of the instruments reported for the detection of this analyte. In addition, specific sensor has been designed for a rapid and linear response for sertraline (Khater et al. 2015). Differential pulse voltammetry is another sensitive method for the selective determination of sertraline in different matrices (Cheng et al. 2012). On the other hand, there are many difficulties in establishing an analytical method with high accuracy and precision for the analysis of samples due to their complexities and low analyte concentrations. Hence, a series sample pretreatment steps are necessary before instrumental analysis (Huang et al. 2012). By applying different extraction methods, not only interference free measurements are obtained, but also lower detection limits could be achieved. Liquid–liquid extraction (LLE) (Asgharinezhad et al. 2015; Lacassie et al. 2000), solid phase extraction (SPE) (De Castro et al. 2008; Wille et al. 2005; Gonzalez Alonso et al. 2010), solid phase microextraction (SPME) (Lamas et al. 2004), and stir bar sorptive extraction (SBSE) (Unceta et al. 2010) are some of the extraction/preconcentration methods used in literature for pharmaceuticals. In liquid–liquid extraction, the organic solvent and the aqueous phase should be immiscible with each other and the organic solvent should has a good extraction capacity for the analyte of interest (Dobrowska et al. 2016). A high surface tension exists between the aqueous and organic phase layers. A supportive solvent could be added to decrease the tension and thus enhance extraction output. An ideal supportive solvent should be miscible with both aqueous and organic phases in order to increase their interaction (Dobrowska et al. 2016; Al-Saidi and Emara 2014). With the addition of salt to an aqueous solution, the ionic strength is changed, and this situation directly affects the extraction efficiency. The solubility of analytes in the water phase decreases with the addition of salt. Thus, salt enhances analyte partitioning into the organic medium (Dobrowska et al. 2016; Li et al. 2015).

The main purpose of this study was to develop a sensitive and accurate analytical method for the determination of sertraline at trace levels. Supportive liquid–liquid extraction was used for extraction/preconcentration of sertraline and GC–MS determination was done after adding anthracene-D10 as internal standard to all samples/standards.

Materials and Methods

A Hewlett Packard 6890 Gas Chromatograph equipped with a mass selective detector (Hewlett Packard 5973) and an autosampler (Hewlett Packard G1512A) was used for the qualitative and quantitative determination of sertraline. An HP-5MS 5% phenyl methyl siloxane column (Agilent, 30 m x 250 µm; 0.25 µm) was used for the separation of sertraline from other matrix components. Helium was used as carrier gas at a flow rate of 1.8 mL/min. Injector and interface temperatures were set to 290 and 280°C, respectively. All sample/standard (1.0 µL) injections were done in the splitless mode.

A ramp temperature program consisting of an initial 80°C (held for 1.0 min) was increased to 130°C (50°C/min) and then to 300 (50°C/min) and held for 4.0 min. Analytical peaks from the total ion chromatogram (TIC) were integrated according to the prominent ion fragment of analyte (m/z 274) and internal standard (m/z 188).

Sertraline hydrochloride was obtained from Sanovel Company. Ethyl acetate, sodium chloride, and anthracene-D10 were purchased from Merck. All chemicals used throughout the experiments were of high-purity. Ultrapure water produced from a Milli-Q® instrument was used in all sample and standard preparations. All experimental apparatus were washed with soap, rinsed with tap water and deionized water before usage in the experiments. When not in use, all beakers, flasks, and sample containers were kept and stored for at least 1 day in 1.0 M HNO_3 to eliminate any possible contaminants.

Tap water sample was taken from the analytical chemistry laboratory of Yıldız Technical University to perform the spiking experiments for sertraline. Simulated municipal synthetic waste water sample was taken from the Environmental Engineering Department, Yıldız Technical University. Under the optimum conditions, sertraline was extracted from the tap/waste water samples by using supportive liquid–liquid extraction and determined by GC–MS.

Parameters affecting the recovery of the analyte were optimized to get lower detection limit. Selection of a proper extraction solvent is one of the most crucial parameters for supportive liquid–liquid extraction in order to obtain high extraction output.

Aqueous sertraline standard solutions were prepared in the range 1.0–1000 ng/mL and sent to the GC–MS system to determine the linear calibration region. The calibration plot was developed based on integrated peak areas. In the calculation of limit of detection (LOD), and limit of quantitation (LOQ), the standard deviation from replicate measurements of the lowest concentration in the linear calibration plot and slope were utilized as in the formula given below;

$$LOD = 3 \times Standard\,Deviation/Slope$$

$$LOQ = 10 \times Standard\,Deviation/Slope$$

Results and Discussions

Optimization of all system parameters were carried out to increase the extraction output of sertraline. Optimization was performed by varying one parameter at a time while keeping all other parameters constant. Reproducibility of optimization steps were determined by calculating the percent relative standard deviation of triplicate extractions.

Three organic solvents namely 1,2-dichloromethane, ethyl acetate and chloroform were tested to find the highest extraction output for sertraline. 1.0 mL of each organic solvent was separately added to sertraline standard solutions (10 mL of 0.10 mg/L sertraline) and they were mixed for 30 min on a mechanical shaker and then the organic phase was taken for analysis. No extraction of analyte was achieved by 1,2-dichloromethane. Ethyl acetate gave the sharpest peak with the biggest peak area which was at least 40% higher than chloroform was therefore chosen as optimum extraction solvent.

Though immiscible, the organic solvent should interact well enough with the aqueous solution to ensure mass transfer of analyte into the organic phase. Thus, mixing efficiency directly affects the extraction output. In this study, a mechanical shaker was used to mix up the aqueous solution and extractor solvent, and the mixing period was optimized by testing 5.0, 15, 30, 60 and 90 min. According to the results obtained, increasing the mixing period did not have any significant effect on the extraction output of analyte. But, 60 min mixing period was chosen as optimum one for further studies to make sure that the analyte would be extracted into the organic phase.

The extraction process was carried out with the addition of four supportive solvents which could be used to improve the mixing ratio of the extractor solvent and sample solution leading the higher extraction efficiency, and ethanol gave the best extraction efficiency (at least 10% higher than the closest one). After the selection of ethanol, its volume was optimized by testing 0.02, 0.05, 0.10, 0.20, 0.30, 0.50 and 1.0 mL. No significant difference was observed in the results, hence, 0.02 mL ethanol was selected and used in further optimization studies.

The effect of three different salts on the extraction of sertraline was studied to find the optimum one. 0.50 g each of Na_2SO_4, NaCl and KNO_3 were weighed and used in the extraction process. The highest extraction output was obtained for NaCl and its optimum amount was also optimized. Peak areas of sertraline were obtained as 18,618, 74,014, 131,979, 172,101, 201,253 for 0.10, 0.20, 0.50, 1.0 and 2.0 g NaCl, respectively. As seen, the extraction output increased with increasing NaCl amount up to 2.0 g (16.9% higher than the usage of 1.0 g NaCl), which was chosen as the optimum value.

Under the optimum conditions, extraction/preconcentration procedure was applied to standards, tap water and waste water samples under the optimum conditions given in Table 1. 10 mL of sample solution was put into a 15 mL centrifuge tube, then 2.0 g NaCI was added and then 0.02 mL ethanol as supportive solvent and 1.0 mL ethyl acetate as extractor solvent were added to solution. Mixture was shaken for 60 min by mechanical shaker and then the organic phase was taken with a pipette and it is transferred into vials for GC–MS measurements.

The analytical performance of the GC–MS system for sertraline was determined under the optimum conditions summarized in Table 1 and the results are presented in Table 2. Anthracene D10 was added as internal standard to all calibration standards to improve the accuracy and precision of the quantitative determinations. It was used as internal standard because there was no chance of finding this rare isotope in the sample matrix. The concentration of anthracene D10 used was 1.0 and 20 µL of it was added to 100 µL of samples/standards after extraction. The calibration plot was developed by plotting concentration against the peak area ratio of standard to internal standard. Linear calibration plot for sertraline was obtained in the range of 1.0–1000 ng/mL with a typical equation of $y = 0.0114x - 0.0928$ (based on peak area measurements). The R^2 value of the linear calibration plot was found to be better 0.999. Overlay chromatograms of the calibration standards after extraction are represented in Fig. 1. The LOD and LOQ values for sertraline using the optimum parameters and internal standard were found to be 0.43 and 1.43 ng/mL, respectively.

This analytical method was developed for its applicability to real samples. However, the complicated matrix of samples could affect extraction efficiency. Therefore, it is very important to perform recovery experiments to determine the effectiveness of the method for real sample matrix. The recovery of sertraline from tap and waste water matrices was done by first running blank extractions

Table 1 Optimized parameters for sertraline extraction by SLLE–GC–MS system

Parameter	Optimized value
Extraction solvent (amount)	Ethyl acetate (1.0 mL)
Mode of mixing	Mechanical shaking
Mixing period	60 min
Supportive solvent (amount)	Ethanol (0.02 mL)
Electrolyte (amount)	NaCl (2.0 g)

Table 2 Validation results of developed method for sertraline using the optimum parameters given in Table 1

Parameter	Calibration plot for sertraline
Regression equation	$y = 0.0114x - 0.0552$
R^2	0.999
LOD (ng/mL)	0.43
LOQ (ng/mL)	1.43

to ensure that sertraline was not present in the samples (no sertraline was detected), after which spike samples were extracted and then analyzed. Spiking concentrations of the samples were 100, 250 and 500 ng/mL for tap water, and 250 and 500 ng/mL for waste water. The percent recoveries were found to be 91.19 ± 2.48%, 90.48 ± 5.19% and 95.46 ± 6.56% for 100, 250 and 500 ng/mL, respectively, in tap water, and 85.80 ± 2.15% and 92.43 ± 4.02% for 250 and 500 ng/mL, respectively, in waste water. Overlay chromatograms obtained from the spiked tap water sample at two concentrations can be seen in Fig. 2.

Sertraline occurs at trace levels and is not directly determined by conventional analytical methods without interference effects. Hence, with the motivation to improve upon the sensitivity of GC–MS instrument, in the present study, a supportive liquid–liquid extraction method was developed not only for the separation of sertraline from sample matrix, but also its preconcentration into measureable quantities. All the system parameters that affect extraction output such as extractor solvent type and amount, supporter solvent amount and salt effect were optimized to obtain lower detection limit and high recovery from the real matrices. A simple, efficient and rapid extraction protocol was developed for the extraction/preconcentration of sertraline without any decomposition. Calibration plot of the analyte showed good linearity and low percent relative standard deviations. Recovery studies were performed for tap and waste water samples at different concentrations, and the percent recoveries recorded were between 90.48%–95.46% for tap water and 85.80%–92.43% for waste water. The %RSDs obtained were lower than 13% even for even very low concentrations. Results of the study confirms that the method can be applied for sertraline determination in tap and waste water sample with high precision. As a conclusion, it should be underlined that developed analytical method is efficient, simple, inexpensive, green, and it is applicable for the determination of sertraline in tap and waste water matrices at proper recoveries.

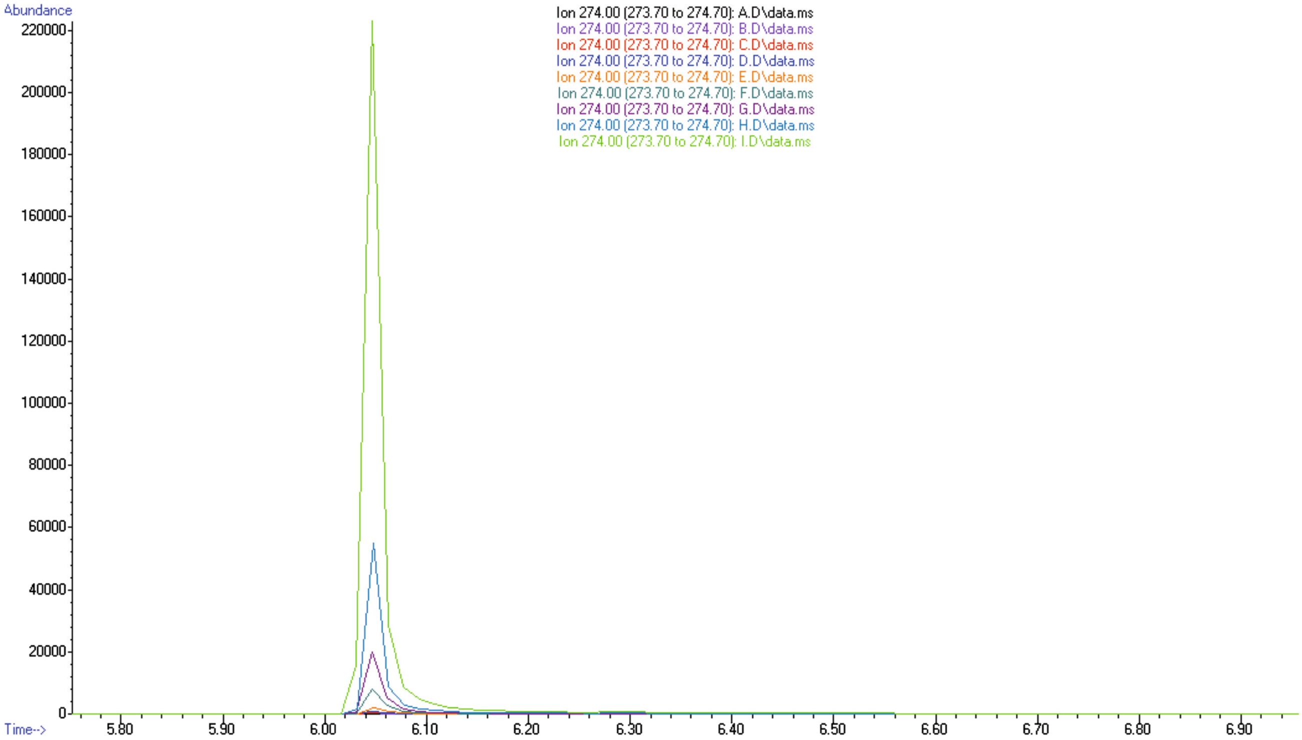

Fig. 1 Overlay chromatogram (m/z 274) of calibration standards after extraction: **a** 1.0 ng/mL **b** 2.0 ng/mL **c** 5.0 ng/mL **d** 10 ng/mL, **e** 20 ng/mL, **f** 50 ng/mL, **g** 100 ng/mL, **h** 250 ng/mL and **i** 1000 ng/mL under the optimum conditions given in Table 1

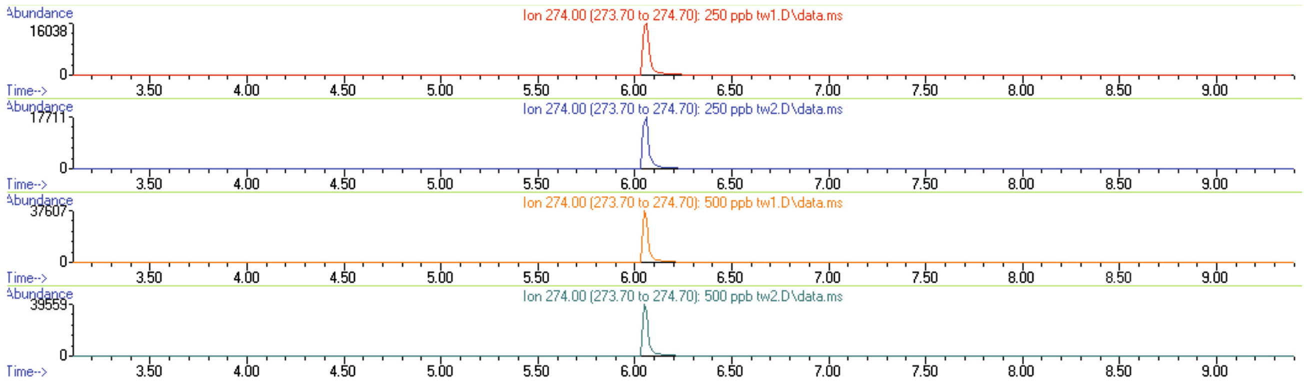

Fig. 2 Overlay chromatogram (m/z 274) of tap water samples under the optimum conditions given in Table 1

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