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RESEARCH ARTICLE

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Accurate and simple determination of oxcarbazepine in human plasma and urine samples using switchable-hydrophilicity solvent in GC–MS

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Abstract

This work presents a sensitive and rapid analytical method for the determination of oxcarbazepine in human plasma and urine samples. A vortex-assisted switchable hydrophilicity solvent-based liquid phase microextraction (VA–SHS–LPME) was used to preconcentrate oxcarbazepine from the samples before the determination by gas chromatography mass spectrometry. The switchable hydrophilicity solvent was synthesized by protonating *N*,*N*-dimethylbenzylamine with carbon dioxide to make it totally miscible with an equivalent volume of water. Parameters of the VA–SHS–LPME method including volume of switchable hydrophilicity solvent, concentration/volume of sodium hydroxide and vortex period were systematically optimized. Under the optimum conditions, good linearity ranging from 27.03 to 353.47 μg/kg was obtained for the analyte. Limit of detection and quantitation values were found to be 6.2 and 21 μg/kg (mass base), respectively. The relative standard deviation was calculated as 6.9% for six replicate measurements of the lowest concentration of the calibration plot. Satisfactory recovery results were calculated in the range of 97–100% for human plasma and urine samples spiked at five different concentrations.

KEYWORDS

gas chromatography–mass spectrometry, human plasma, oxcarbazepine, switchable hydrophilicity solvent, urine

1 | INTRODUCTION

Epilepsy is a common neurological disorder affecting ~0.7% of the population, which equals over 50 million patients worldwide. Antiepileptic drugs are used to alleviate epileptic seizures as well as for the treatment of psychological diseases (LaPenna & Tormoehlen, 2017). Oxcarbazepine (10,11-dihydro-10-oxo-5H-dibenz[b,f]azepine5-carboxamide) is the active substance of the drug oxcarbazepine (OXC), which is used to treat partial or tonic–clonic seizures in epileptic patients (Flesch, Czendlik, Renard, & Lloyd, 2011; Wellington & Goa, 2001). OXC is also a carbamazepine analog and has been used since the turn of the twenty-first century (Schmidt & Elger, 2004). This chemical is metabolized into its pharmacologically active form, licarbazepine (10,11-dihydro-10-hydroxycarbamazepine) (Gérard Flesch, 2004). There are several studies on OXC in the literature, but there are some contradictions regarding the efficiency and safety of this drug and the active compound (Geng & Wang, 2017). Nausea, vomiting, cutaneous rashes, diarrhea and headache are common side-effects for OXC (Beydoun, 2000). It was also reported that antiepileptic drugs may be toxic or cause unwanted metabolic reactions because of their narrow range of recommended concentrations in plasma (Behbahani et al., 2013; Kuhn & Knabbe, 2013; Paglia, D'Apolito, Garofalo, Scarano, & Corso, 2007). Furthermore, OXC is excreted in urine or feces, leading to its

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occurrence at trace levels in urban wastewater cycles (Brezina, Prasse, Meyer, Mückter, & Ternes, 2017). It is therefore crucial to develop analytical methods for the accurate and precise determination of OXC in plasma and urine samples.

Analytical methods for OXC determination are mostly based on liquid chromatography coupled with different detectors (Serralheiro, Alves, Fortuna, Rocha, & Falcão, 2013; Yin et al., 2016). Some gas chromatographic techniques have been reported in the literature for OXC (Bülau, Paar, & von Unruh, 1988; Levine, Green-Johnson, Moore, & Fowler, 2004). Gas chromatography (GC) is the most preferred chromatographic technique for volatile and semi-volatile compounds. Detectors for GC systems are designed to improve the application range, sensitivity, selectivity and specificity for analytes (Christian, Dasgupta, & Schug, 2014; McNair, Miller, & Snow, 2019). Mass spectrometry is the most commonly used detector in GC systems, and ionized analytes in this system are distinguished based on different mass to charge ratios via electric and magnetic fields in mass analyzers (Santos & Schug, 2017). In the analysis of volatile drug compounds by GC systems, more efficient elution is achieved with respect to LC systems that require different combinations of mobile phases. This offers high resolution and sensitivity, and mitigation of matrix effects (Heath et al., 2010).

Sample preparation is a crucial step for the determination of any analyte in complex matrices like urine, plasma and environmental samples. Preconcentration of analytes and elimination of interferences from sample matrices are the two basic goals of sample preparation procedures (Rani, Malik, & Singh, 2012). Liquid–liquid and solid-phase extraction are used to extract OXC from the biological samples (Bugamelli et al., 2002; de Sousa Maia et al., 2007; Pienimäki, Fuchs, Isojärvi, & Vähäkangas, 1995). In addition to these conventional methods, microextraction by packed syringes is frequently employed for OXC isolation from bulk samples (Rani et al., 2012). Small chemical volume usage, small sample volume and high extraction yield are considered very important factors in the design of analytical procedures. Solid- and liquid-phase microextraction are the two main groups of modern preconcentration methods, but the former has some disadvantages such as high cost and fragile nature of the sorbents used for extraction (Krogh, Johansen, Tønnesen, & Rasmussen, 1995; Mashayekhi, Abroomand-Azar, Saber-Tehrani, & Husain, 2010; Pedersen-Bjergaard & Rasmussen, 2008). Efforts have been made to increase the greenness of analytical methods using ecofriendly solvents. In 2005, Jessop and his coworkers synthesized switchable hydrophilicity solvents (SHS), with miscibility properties that can be switched by the addition of chemicals (Jessop, Heldebrant, Li, Eckert, & Liotta, 2005; Yilmaz & Soylak, 2015). The SHSs are immiscible liquids in aqueous solutions, but carbon dioxide addition results in miscibility with the help of SHS protonation reactions. Carbon dioxide is employed as a trigger for the protonation reaction, and is ideal owing to its low-cost, non-toxicity and ease of separation from reaction media (Ezoddin, Abdi, & Lamei, 2016; Vanderveen, Durelle, & Jessop, 2014). The protonated form of SHSs can be changed into its original form via addition of sodium hydroxide and inert gases like nitrogen and argon. Owing to their polar nature, SHSs do not require disperser solvents in order to achieve efficient extraction of analytes (Yilmaz & Soylak, 2015). Some studies regarding SHS-based liquid phase microextraction methods have been published in the literature. Some example are the extraction of the ammonium herbicide paraquat from plasma and urine samples (Lamei, Ezoddin, Kakavandi, Abdi, & Ghazi-khansari, 2018), nitrazepam from urine samples (Shahraki, Ahmar, & Nejati-Yazdinejad, 2018) and amino acids from human plasma samples (Zare, Ghaedi, Jannesar, & Tayebi, 2018).

In this study, a rapid, green and sensitive analytical method for trace determination of OXC in biological samples was developed. A vortex-assisted switchable-hydrophilicity solvent-based liquid phase microextraction (VA–SHS–LPME) method was used to preconcentrate OXC from human plasma and urine samples. Parameters affecting the microextraction method were investigated in order to lower the detection limit of the analyte in GC–MS systems. Bisphenol A (BPA-*d16*) was used as internal standard. The accuracy and applicability of the developed method were validated by spiking experiments at ppb levels for human plasma and urine samples.

2 | MATERIALS AND METHODS

2.1 | Chemicals and reagents

The OXC standard (98.7%, purity) was obtained from Ali Raif Pharmaceutical Company (Istanbul, Turkey). Isotopically labelled bisphenol A standard (98.0%, purity) was obtained from Dr. Ehrenstorfer (Augsburg, Germany). BPA-*d16* (100 mg/kg) and OXC (200 mg/kg) stock solutions were prepared in ethanol. *N*,*N*-Dimethylbenzylamine (≥98.0%, purity), sodium hydroxide (≥97.0%, purity) and ethanol (96%, purity) were purchased from Merck (Darmstadt, Germany). Dry ice (solid carbon dioxide) was purchased from a local pastry shop (Istanbul, Turkey). Ultrapure water from a water purification system was used for sample/standard preparation and cleaning purposes. All samples and standard solutions were prepared gravimetrically using an analytical balance (four digits) throughout the study.

2.2 | GC–MS conditions

An Agilent HP6890 series gas chromatograph, equipped with an HP G1512A autosampler unit, an HP5973 series mass spectrometer detector and an HP5MS capillary column (30 m × 250 μm inner diameter × 0.25 μm film thickness) was used for the elution and quantification of OXC. Electron impact ionization mode at 70 eV was used in the mass spectrometer. Helium was used as the carrier gas at a constant flow rate of 2.5 ml/min and the injection port temperature was set at 250°C. The initial oven temperature was 70°C, which was increased at 50°C/min to 280°C (1.0 min hold time) and a final ramp of 60°C/min to 300°C (1.47 min hold time). Temperatures of the GC–MS transfer line and the ion source were set at 280 and 230°C, respectively. The retention times, qualifier ions and quantifier ion (underlined value) for the analyte and internal standard are given in Table 1.

2.3 | Sample preparation

Human plasma and urine samples were collected from healthy volunteers in our research group. Ethanol (2.0 g) was added to 1.0 g of human plasma to precipitate the protein molecules. After centrifuging the plasma sample, 0.33 g of the supernatant phase was transferred into a clean centrifuge tube and spiked to the desired OXC concentrations. The spiked plasma was diluted to 17 g after the addition of BPA-*d16* stock solution (0.08 g) as an internal standard. For the urine sample, 0.90 g was spiked at different OXC concentration and diluted to 18 g with deionized water. BPA-*d16* stock solution (0.09 g) was also used as an internal standard for the urine sample. The spiked samples with internal standard were extracted under the optimum conditions of the developed method. Dilution factors for plasma and urine samples were calculated from the total amount of the sample solution divided by initial sample amount. Hence, sample dilution factors were found to be 150- and 20-fold for plasma and urine samples, respectively.

2.4 | VA–SHS–LPME procedure

The SHS was synthesized by mixing *N*,*N*-dimethylbenzylamine and distilled water (1:1, v/v) with continuous addition of dry ice. The mixture produced two separate phases with the amine layer on the top of the deionized water. Small pieces of dry ice were added periodically to the flask, stirred constantly on a magnetic stirrer at a rate of 500 rpm. The addition of dry ice was stopped when a clear and homogeneous single phase was obtained.

In the VA–SHS–LPME procedure, 0.75 ml of the synthesized SHS was pipetted into 8.0 ml of aqueous sample/standard solution. After the extraction of analyte, 1.0 ml of 1.0 M sodium hydroxide was subsequently added to the aqueous solution to convert the water-miscible SHS into its immiscible form. The solution was mixed with vortexing for 15 s and the deprotonated solution was centrifuged for 2.0 min at 3461***g*** for phase separation. Finally, the upper phase (~50 µl) was taken into an insert vial and introduced into the GC–MS system. The extraction protocol is represented in Figure 1.

3 | RESULTS AND DISCUSSION

In all optimization steps, Tukey's method based on the *post hoc* test was used to evaluate the significant difference between experimental variable means. Lower-case letters were used to depict the difference in variable means and the highest variable mean was selected as the optimum value for each optimization step.

TABLE 1 Retention times and mass to charge ratios for the analyte and internal standard

Compound	Retention time (min)	Fragment ions
OXC	4.74	180, 209, 152, 252
BPA-*d16*	4.68	224, 242, 125, 97

3.1 | Optimization of SHS volume

SHS was utilized as an extraction solvent to isolate and preconcentrate OXC. The preconcentration factor is inversely proportional to the volume of extraction solvent used, based on the principle of dilution. Therefore, 0.75, 1.0, 1.5 and 2.0 ml volumes of SHS were tested to obtain a high preconcentration factor for the analyte. While there was no big difference between 0.75 and 1.00 ml, the peak area value of 0.75 ml was 1.8 times greater than the 1.5 and 2.0 ml volumes of SHS (Figure S1). Thus, 0.75 ml of SHS was employed for the subsequent studies. When SHS volumes <0.75 ml were tested, there was no separate amine phase observed above the aqueous solution. Optimum SHS volume was therefore selected as 0.75 ml.

3.2 | Optimization of sodium hydroxide concentration

Sodium hydroxide was utilized as a deprotonation agent to cause separation of aqueous and organic phases, via conversion of protonated amine back into its nonpolar form. Sodium hydroxide concentration is an important parameter for an efficient phase separation. Therefore, the concentration of sodium hydroxide was investigated at 1.0 and 2.0 M to obtain a high signal-to-noise ratio for the analyte. Sodium hydroxide concentrations lower than 1.0 M were tested but phase separation was not observed owing to the insufficient deprotonation. The peak areas for the tested concentrations were similar to each other, and there was no significant difference between the mean peak area values with respect to statistical analysis (Figure S2). Therefore, 1.0 M sodium hydroxide was selected as the optimum value to avoid the consumption of large quantities of chemicals.

3.3 | Optimization of sodium hydroxide volume

In VA–SHS–LPME methods, sodium hydroxide volume is another important parameter that facilitates phase separation. The final volume of separated amine phase is directly proportional to the volume of sodium hydroxide added for deprotonation. For this reason, sodium hydroxide volumes in the range of 0.50–2.0 ml (0.50 ml increment) were added to equivalent standard solutions for deprotonation. The highest peak area value was obtained for 1.0 ml sodium hydroxide volume as shown in Figure 2. The relatively low peak area value obtained for 0.50 ml signified insufficient volume for deprotonation, and the low values obtained for the higher volumes of sodium hydroxide can be attributed to dilution. The 1.5 ml volume showed minimal difference from the other volumes, probably owing to its high standard deviation value as depicted by the error bars in Figure S3.

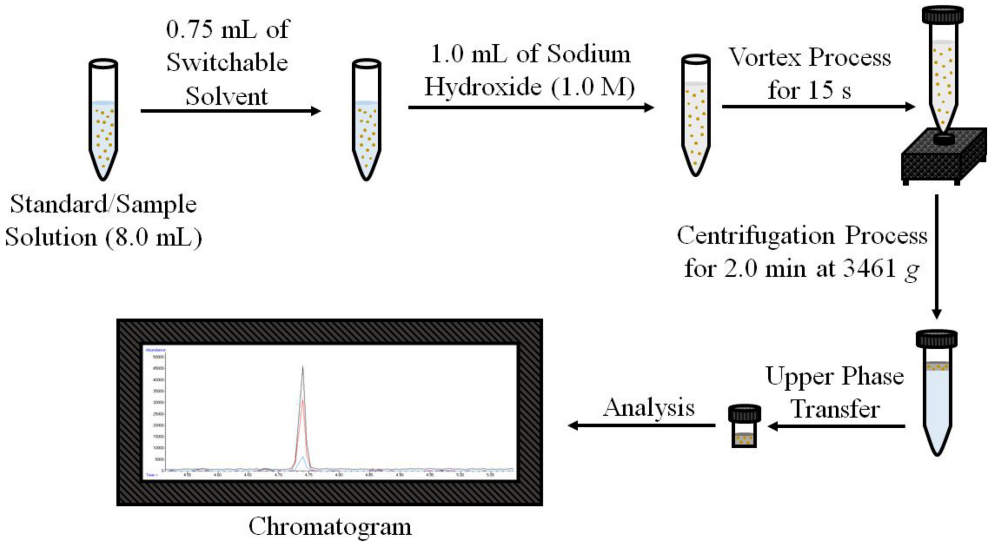


FIGURE 1 Extraction protocol

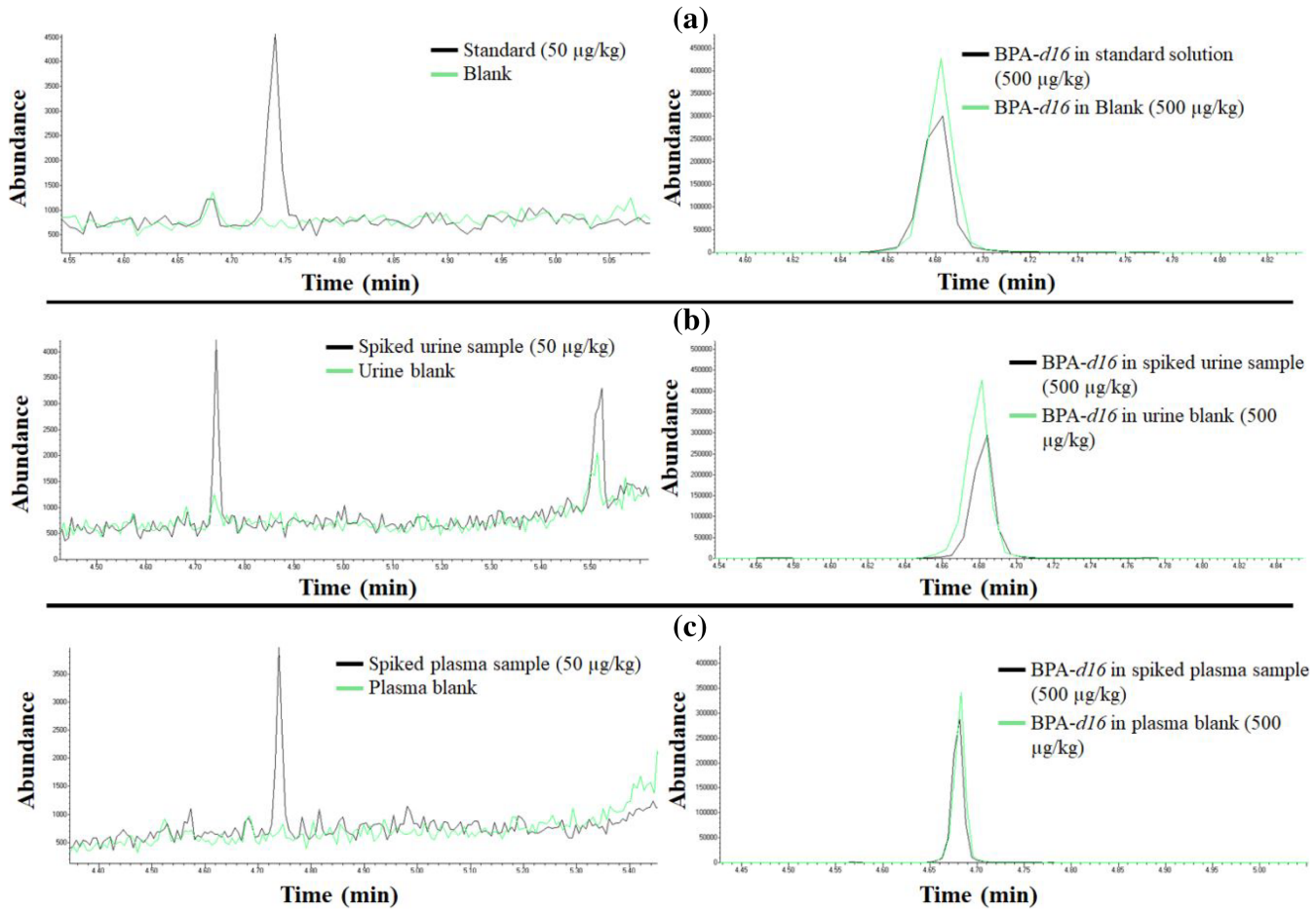


FIGURE 2 Chromatograms for standard solution and its blank (a), spiked urine sample and its blank (b) and spiked plasma sample and its blank (c)

3.4 | Vortex period

The deprotonation process was observed by the rapid formation of a cloudy solution upon addition of sodium hydroxide, but the cloudiness did not reach the bottom of the tube and therefore required mixing to provide homogenous deprotonation. Vortexing, a very practical sample agitation tool, was optimized for different periods to maximize the efficiency of deprotonation. During the deprotonation process, the

amine phase including analytes in the low-volume upper phase were separated from the aqueous solution. Thus, mixing enhanced mass transfer of analytes into the extraction solvent. Vortex periods of between 15 and 60 s were tested and the results obtained were compared with deprotonation performed without mixing. A significant decreasing trend was observed for increased vortex period (Figure S4), and the extraction performed without mixing was marginally lower than the 15 s vortex period. The 15 s vortex period was selected as the final optimum value for the study.

3.5 | Analytical figures of merit

Under the optimum chromatographic conditions, nine calibration standard solutions (50% ethanol–deionized water, w/w) prepared in the range of 0.18–99.21 mg/kg were directly sent to the GC–MS for the evaluation of the analytical performance of the system. Limit of detection (LOD) and limit of quantification (LOQ) values were determined as 0.17 and 0.55 mg/kg, respectively. Other parameters such as dynamic range, relative standard deviation (RSD) and coefficient of determination (R^2) for the GC–MS system are summarized in Table 2.

Seven different concentrations of aqueous oxcarbazepine standard solutions (1.5% ethanol) prepared in the range 27–1,764 μg/kg were spiked with 500 μg/kg BPA-*d*16 as an internal standard and extracted under the optimum extraction and chromatographic conditions of the developed method. The extracts of each calibration concentration were sent to the GC–MS system for six replicate measurements. The LOD and LOQ values for the VA–SHS–LPME-GC–MS method were determined as 6.2 and 21 μg/kg, respectively. By comparing the LOQ values of both systems, an enhancement in quantitation limit value of 19-fold was obtained. The other system analytical performance values are summarized in Table 2. The LOD and LOQ values were calculated for the VA–SHS–LPME-GC–MS system using the following equations:

$$\mathrm{LOD} = 3 \cdot \frac{s_{\mathrm{LC}}}{m} \quad (1)$$

$$\mathrm{LOD} = 10 \cdot \frac{s_{\mathrm{LC}}}{m} \quad (2)$$

where s_{LC} is the standard deviation of the lowest concentration in the linear dynamic range and m is the slope of the linear plot.

When the developed method was compared with other studies in literature such as microextraction by packed sorbent high-performance liquid chromatography diode array detection (Saracino et al., 2010), liquid chromatography–electrospray ionization–mass spectrometry (Breton et al., 2005) and molecularly imprinted solid phase extraction high performance liquid chromatography-diode array detection (Beltran et al., 2009), the VA–SHS–LPME-GC–MS was superior with regard to LOD, LOQ and dynamic range. In addition, this is the first study using VA–SHS–LPME-GC–MS method for the determination of OXC in plasma and urine samples. It offers a green and fast analytical protocol with high sensitivity. Moreover, the developed extraction protocol is compatible with GC–MS instruments but liquid chromatography systems may require an extra laboratory step like SHS evaporation (Wang et al., 2018).

3.6 | Recovery studies

The combination of VA–SHS–LPME with the GC–MS system for the determination of OXC was applied to human plasma and urine samples to verify accuracy and applicability to real samples. Firstly, all samples were extracted with the VA–SHS–LPME method after the sample pretreatment processes given in Section 2.3. The extracts were sent to the GC–MS system to determine the OXC content but there was no detectable oxcarbazepine in these samples, according to the method's LOD. Therefore, five different concentrations (between ~50.0 and 300.0 μg/kg) were spiked into the human plasma and urine

TABLE 2 System analytical performance values for GC–MS and SHS–LPME–GC–MS systems

System	Limit of detection	Limit of quantitation	Dynamic range	RSD (%)[a]	R^2	Reference
GC–MS[b]	0.12 mg/kg	0.40 mg/kg	0.39–10.42 mg/kg	8.3	0.9999	Present study
VA–SHS–LPME–GC–MS[c]	6.2 μg/kg	21 μg/kg	27.03–353.47 μg/kg	6.9	0.9997	Present study
MEPS–HPLC–DAD[d]	0.015 μg/ml	0.050 μg/ml	0.100–5.00 μg/ml	-	0.9992	Saracino, Tallarico, & Raggi, (2010)
LC–ESI–MS[e]	—	0.4 mg/L	0.4–20 mg/L	18.0	0.999	Breton et al. (2005)
MISPE–HPLC–DAD[f]	—	40 μg/L	0.04–1 mg/L	4.7	0.999	Beltran, Marcé, Cormack, & Borrull (2009)

[a]RSD, Percentage relative standard deviation.
[b]GC–MS: Gas chromatography–mass spectrometry.
[c]VA–SHS–LPME–GC–MS, Vortex-assisted switchable hydrophilicity solvent-based liquid-phase microextraction gas chromatography–mass spectrometry.
[d]MEPS–HPLC–DAD, Microextraction by packed-sorbent high-performance liquid chromatography diode array detection.
[e]LC–ESI–MS, Liquid chromatography–electrospray ionization–mass spectrometry.
[f]MISPE–HPLC–DAD, Molecularly imprinted solid phase extraction high-performance liquid chromatography–diode array detection.

TABLE 3 Recovery results for spiked plasma and urine samples

Sample	Spiked concentration (μg/kg)	Recovery (%)	±SD
Plasma	50.2	97.7	3.7
	73.7	98.4	12.9
	101.1	98.9	2.1
	150.5	99.2	6.9
	299.1	99.6	1.7
Urine	51.3	97.69	0.90
	76.3	98.18	3.16
	98.3	98.74	1.79
	148.4	99.28	1.13
	276.5	99.56	3.31

samples, and BPA-*d*16 was added to all samples as the internal standard (~500 μg/kg). The spiked samples were sent to the GC–MS system after applying the optimized VA–SHS–LPME method. Relative recovery results calculated for human plasma and urine samples as presented in Table 3 were in the range 97–100%. Chromatograms belonging to standard and sample solutions are shown in Figure 2.

4 | CONCLUSION

In this work, a switchable hydrophilicity solvent was produced and used to preconcentrate oxcarbazepine from biological samples for its determination at trace levels by gas chromatography mass spectrometry. To the best our knowledge, this is the first study to employ the VA–SHS–LPME method to preconcentrate oxcarbazepine. The VA–SHS–LPME method is rapid, easy to perform and green, and it produced satisfactory enhancement relative to the conventional extraction methods. Under the optimum microextraction conditions, the developed method enhanced the quantitation limit by about 19-fold. Percentage recovery results calculated between 97 and 100% established the method's quantification accuracy and applicability to human plasma and urine samples.

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DECLARATION OF INTEREST

None.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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