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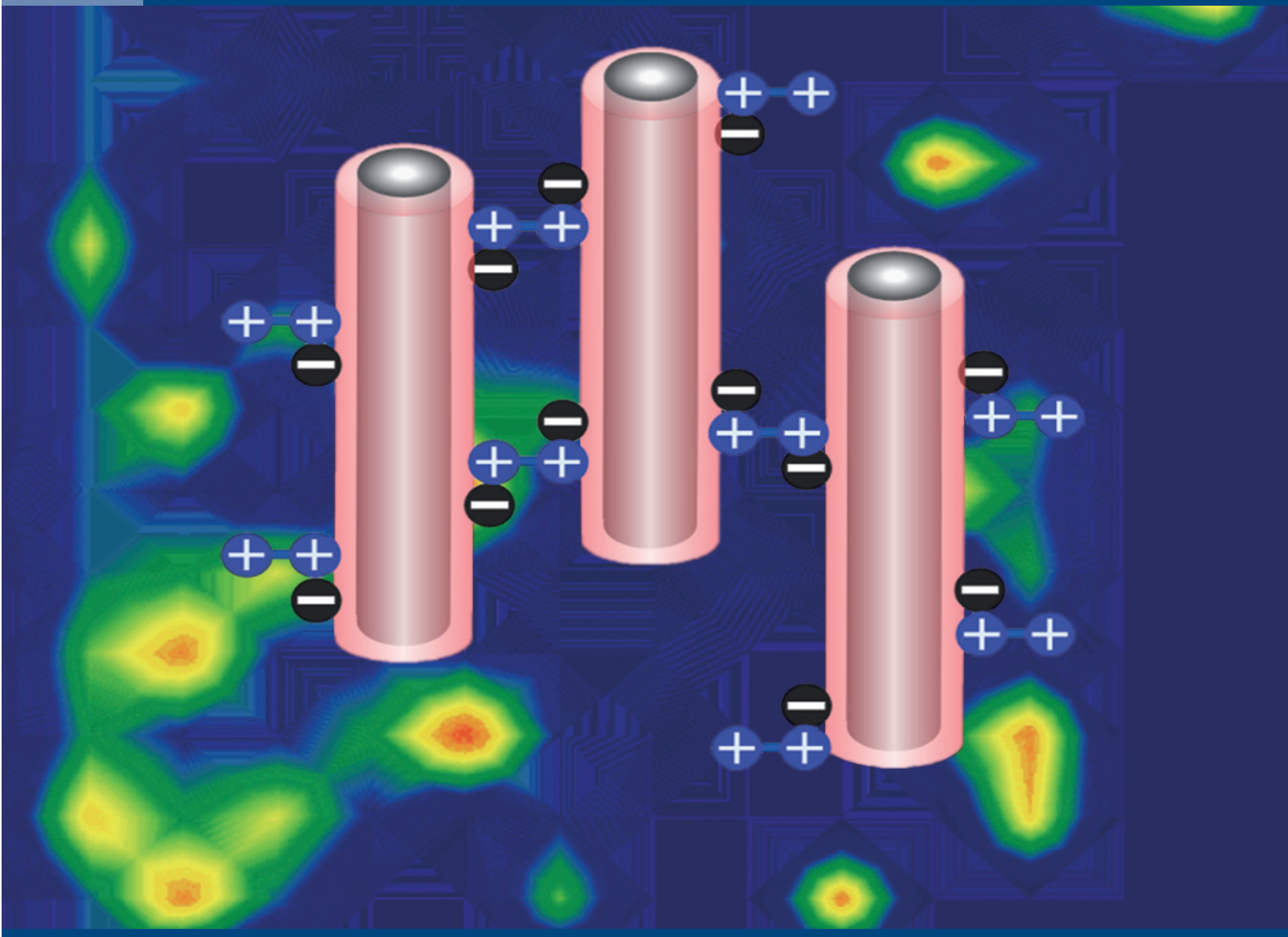

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RESEARCH ARTICLE

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Ion-pair switchable-hydrophilicity solvent-based homogeneous liquid–liquid microextraction for the determination of paraquat in environmental and biological samples before high-performance liquid chromatography

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Written informed consent was obtained from all volunteers who donated urine samples.

An approach involving ion-pair switchable-hydrophilicity solvent-based homogeneous liquid–liquid microextraction coupled to high-performance liquid chromatography has been applied for the preconcentration and separation of paraquat in a real sample. A mixture of triethylamine and water was used as the switchable-hydrophilicity solvent. The pH was regulated using carbon dioxide; hence the ratio of the ionized and non-ionized form of triethylamine could control the optimum conditions. Sodium dodecyl sulfate was utilized as an ion-pairing agent. The ion-associate complex formed between the cationic paraquat and sodium dodecyl sulfate was extracted into triethylamine. The separation of the two phases was carried out by the addition of sodium hydroxide, which changed the ionization state of triethylamine. The effects of some important parameters on the extraction recovery were investigated. Under the optimum conditions (500 μL of the extraction solvent, 1 mg sodium dodecyl sulfate, 2.0 mL of 10 mol/L sodium hydroxide, and pH 4), the limit of detection and the limit of quantification were 0.2 and 0.5 μg/L, respectively, with preconcentration factor of 74. The precision (RSD, $n = 10$) was <5%. The recovery of the analyte in environmental and biological samples was in the range of 90.0–92.3%.

KEYWORDS
environmental and biological samples, homogeneous liquid–liquid microextraction, ion pairs, paraquat, switchable-hydrophilicity solvent

1 | INTRODUCTION

Paraquat (PQ) is a quaternary ammonium herbicide with wide applications in agriculture due to its physical and chemical properties [1]. However, it shows toxicity to humans and animals [2]. PQ can be absorbed through the skin or orally ingested [3] and mainly accumulates in the lung [4]. It is known that the toxicity of PQ is based on redox reaction and intracellular oxidative stress generation leading to pulmonary edema and fibrosis [5,6]. Therefore, a number of detection methods such as GC–MS [7,8], HPLC [9], LC–MS [10], and derivative spectroscopy [11] have been used to monitor PQ in biological samples. However, it is necessary to select a sample preparation method before chromatographic analysis due to the low concentration of PQ in complex biological matrices. To decrease of these limitations, different preconcentration

Abbreviations: IP-SHS-HLLME, ion-pair switchable-hydrophilicity solvent-based homogeneous liquid–liquid microextraction; PF, preconcentration factor; PQ, paraquat; SHS, switchable-hydrophilicity solvent; TEA, triethylamine

Conflict of interest: The authors declare that there are no conflict of interest.

methods have been studied, including headspace SPME [12], SFE [13], and SPE [3,8,14,15]. Nevertheless, some of these methods have some limitations like time-consuming, requirement to large volumes of extraction solvents that can generate secondary toxic wastes, and lead to environmental problems. Recently, the microextraction methods are performed toward green solvents to reduce waste produced and also eliminate toxic solvents using analytical procedures [16–21]. An alternative for hazardous solvents called a switchable hydrophilicity solvent (SHS) has received great attention as a new green solvent in microextraction methods [22–24]. A switchable solvent can be switched in two states either as a miscible liquid or biphasic mixture with water [23]. Amidines and tertiary amines have been identified as switchable solvents [25] that can be affected by the changes of pH and show two different states, ionic and nonionic form by adding or removing of CO_2 [26]. Therefore, the back extraction can be possible under flow of an inert gas such as N_2 or with addition of sodium hydroxide (aqueous) solution [26]. It means that SHSs have a tunable hydrophilicity. The switching process is performed in response to CO_2 as the trigger due to low cost, nontoxicity and easy removal [27–31]. A chemical reaction between the CO_2 and water changes the miscibility of the amine and generates water-soluble protonated amine as carbonate salt [32]. The most important advantage of SHSs is the extraction of the analytes in a homogeneous phase without dispersive solvent. Therefore, these solvents have been successfully considered for green chemistry [26]. The major problem of PQ along with its preconcentration and determination is its low solubility in organic solvents, as it is difficult to monitor its extraction by conventional techniques [33]. The introduction of an ion pair agent would offer benefit of extraction of PQ from different mixture samples [33]. In our work, PQ was extracted from the environmental and biological samples using an ion-pair switchable-hydrophilicity solvent-based homogeneous liquid–liquid microextraction and analyzed with HPLC–UV. SDS was added as an ion pair agent to form an ion-associated complex between the cationic herbicide and the anionic surfactant. As a result, PQ was easily extracted into the extraction solvent. Thus, the application of SDS as the ion pair would present some advantages for the extraction of PQ from the real sample.

2 | MATERIALS AND METHODS

2.1 | Reagents and solutions

PQ dichloride was supplied by Sigma Chemical (St. Louis, MO). A stock standard solution of PQ (1000 mg/L) was prepared by dissolving proper amount of concentrated solution in methanol and stored at 4°C in a fridge. CO_2 (dry ice) was purchased from Zarin Chemical Company (Tehran, Iran). Triethylamine (TEA), HCl, NaCl, and NaOH were obtained from Merck (Darmstadt, Germany).

2.2 | Instrumentation

The separation of PQ was performed by Waters 600 HPLC instrument equipped with a Waters 600 pump, Waters 486 UV-Vis detector, as well as a 50 μL sample loop. The Autochrom 2000 program for LC was performed to process data. The separation of PQ was performed on a capital HPLC column (Scotland, UK) ODS-H C_{18} (250×4.6 mm^2, id = 3.5 μm). An isocratic elution was applied using a mobile phase consisting of a mixture of sodium chloride (0.01 M, pH = 3.0) and methanol (10:90, v/v) at a flow rate of 1 mL/min. The analyte was detected at 258 nm. A Universal 320R centrifuge equipped with a swing out rotor (6-place, 5000 rpm, Cat. No. 1628A) was obtained from Hettich (Kirchlengern, Germany). The pH values were determined using a pH meter (model 692, Herisau, Switzerland) along with a glass combined electrode.

2.3 | Synthesis of switchable solvent

The switchable solvent was prepared by adding 100 mL of TEA and 100 mL of Milli-Q water into a 1000 mL flask. After stirring the mixture and forming a two-phase system, 15 g of dry ice was added. To obtain a single protonated triethylamine carbonate phase, the dry ice was added ten times. The preparation of 200 mL of the 1:1 (v/v) water/TEA solution allows more than 400 extractions since each one extraction requires only 500 μL of the mixture[22].

2.4 | Sample preparation

A urine sample was provided from a healthy volunteer and collected into a 15 mL vial. The sample was placed at −4°C in a refrigerator before analysis. The supernatant of the sample was filtered through a 0.45 μm pore size filter after centrifuging at 4000 rpm for 5 min. The filtrate was diluted with ultrapure water to decrease the matrix effects.

The plasma samples (obtained from the Iranian Blood Transfusion Organization [Tehran, Iran]) were kept in glass tubes at 4°C in the fridge. To precipitate the proteins of the plasma samples, 1 mL of human plasma, 0.5 mL of zinc sulfate solution (0.7 mol/L) and 0.1 mL of 1 mol/L sodium hydroxide solution were added. The mixed solution was centrifuged for 10 min at 2000 rpm. The supernatants were transferred into another vial and diluted to 10 mL with ultrapure water.

River water sample (Kan River, Tehran, Iran) and fruit juice sample (purchased from a local supermarket) were filtered through 0.45 μm membrane filters to remove any suspended particulate matter before performing the extraction procedure.

2.5 | IP-SHS-HLLME procedure

Ten milliliters of the sample solution containing 100 μg/L PQ was placed into a centrifuge tube and the pH was adjusted to 4. Then 1 mg SDS and 500 μL of the extraction solvent were added into the centrifuge tube and the mixture was sonicated in an ultrasonic bath for 1 min. Subsequently, 2.0 mL of NaOH (10 mol/L) solution was injected and well mixed under sonication condition. At this stage, the solution became turbid, and protonated triethylamine carbonate was converted to triethylamine and hence, SDS-PQ complex was extracted into the fine droplets of triethylamine. The mixture was centrifuged at 4000 rpm for 3 min to accelerate the separation of the two phases. The floated triethylamine phase was collected on the surface of the sample solution. Finally, 30 μL of the solvent was directly injected into the HPLC–UV for analysis.

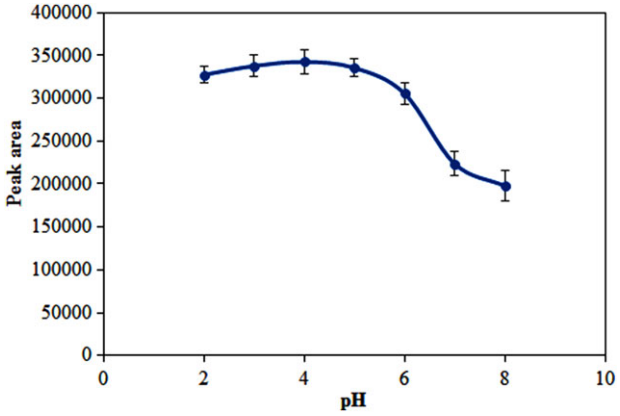

FIGURE 1 Effect of pH on the extraction of PQ; Conditions: sample volume (10 mL; 100 μg/L of PQ), extractant volume (500 μL), NaOH volume (2.0 mL (10 mol/L))

3 | RESULTS AND DISCUSSION

An amine is considered as a SHS when the logarithm of the octanol/water partition coefficient (log K_{ow}) is between 1.2 and 2.5 and the strength of their conjugate acids (pK_{aH}) is above 9.5 [27]. TEA with log K_{ow} = 1.647 and pK_a = 10.75 is considered as a nonpolar solvent. TEA is a suitable SHS in extraction processes with considering a 1:1 volume ratio of water to TEA. The mixture of water and TEA shows a biphasic state when their ratio is 1:1. Increasing the amount of water causes to dissolve more amount of P-TEA-C in aqueous phase and hence provide a monophasic mixture. Furthermore, in presence of CO_2, the system tends to form a monophasic system that is stable when CO_2 is removed by addition of NaOH. Therefore, the ratio between two components should be optimized to form a SHS system [27].

3.1 | Effect of pH

The pH of the sample solution should be adjusted due to the formation of an analyte with sufficient hydrophobicity. Therefore, pH is responsible for the distribution of species in sample solution. The effect of the pH of sample solution on the peak area in the presence of SDS was investigated in the range of 2–8. According to the obtained results in Fig. 1, with the increase of pH from 4 to 8, the peak area of the analyte reduced. This probably occurred because PQ is stable in acidic or neutral media without any changes in the structure of the PQ. In alkaline condition, the analyte is unstable and easy to break down. Thus, pH 4 was selected for analysis of PQ.

3.2 | Effect of extractant volume

The dry ice was used as the trigger to convert TEA form to P-TEA-C form while NaOH was used to convert protonated

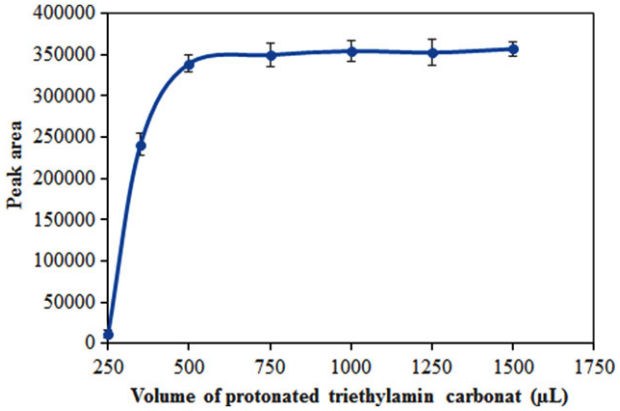

FIGURE 2 Effect of the extractant volume (protonated triethylamine carbonate) on the extraction of PQ; Conditions: sample volume (10 mL; 100 μg/L of PQ), NaOH volume (2.0 mL (10 mol/L))

triethylamine carbonate (P-TEA-C) form to TEA form. Thus, TEA and P-TEA-C were considered as a solvent pair. The effect of the volume of P-TEA-C on the peak area of PQ was studied in the volume range of 250–1500 μL by using 2 mL of 10 mol/L NaOH as is seen in Fig. 2, the peak area was increased up to 500 μL of the volume of P-TEA-C. After that, the peak area was constant. By increasing the volume of P-TEA-C, the volume of the floated phase increased and preconcentration factor (PF) decreased. To obtain complete extraction of the analyte, high extraction recovery, and high PF, 500 μL of P-TEA-C was used.

3.3 | Effect of NaOH volume

To convert the ionization state of the amine to hydrophobic form, CO_2 should be removed from the solution. NaOH (10 mol/L) was used as a transition mediator. The effects of different volumes of 10 mol/L NaOH were investigated in the range of 0.5–3 mL. The maximum peak area was observed

using 2.0 mL of 10 mol/L NaOH solution. There was no improvement in the peak area when more sodium hydroxide was used. This indicates that 2 mL NaOH solution is sufficient to convert the P-TEA-C to TEA and more amount of NaOH may cause a change in pH of sample solution and the cloudy state may not well formed. Thus, the extraction recovery of PQ decreases. Thus, 2 mL of 10 mol/L NaOH was used in all subsequent experiments.

3.4 | Effect of ion-pairing agent concentration

The SDS with the negative charge on hydrophilic head group was paired with cationic PQ. Thus, SDS acted as an ion pair agent to convert cationic PQ to hydrophobic form. Therefore, effect of SDS as ion pair agent was studied in the range of 0–3 mg in the presence of 100 µg/L PQ. In the absence of the anionic surfactant, the peak area was low, because the PQ has high solubility in water (620 g/L) [14]. With the addition of SDS, an extractable form is obtained through the association of cationic PQ with SDS. Therefore, the ion associate has lower solubility in sample solution due to its neutral charge, and a higher affinity for the hydrophobic SHS solvent. As a result, the analytical peak area of the analyte increased by increasing the concentration of SDS up to 1 mg, and then remained constant. Therefore, 1 mg was used for the best recovery.

3.5 | Analytical performance

Some individual analytical characteristics were proposed to evaluate the performance of proposed method. The LOD, LOQ, PF, linearity along with correlation coefficient (r^2), and the RSD% was calculated based on the optimized conditions. The calibration curve linearity was over the range of 0.5–500 µg/L with a correlation coefficient of 0.9967. LOD and LOQ in terms of three and ten times the SD of the blank signal were determined to be 0.2 and 0.5 µg/L, respectively. The RSD for ten replicate measurements of 100 µg/L PQ was < 5%. The PF and extraction recovery percentage (ER%) were used as the parameters to evaluate the extraction method. PF was calculated by Eq. (1).

$$\mathrm{PF} = \frac{C_{\mathrm{rec}}}{C_{\mathrm{i}}}, \tag{1}$$

where C_{rec} is the concentration of the analyte in the triethylamine phase and C_{i} is the initial concentration of the analyte in the sample solution.

ER was calculated by Eq. (2):

$$\mathrm{ER} = \mathrm{PF} \times \frac{V_{\mathrm{org}}}{V_{\mathrm{aq}}} \times 100, \tag{2}$$

TABLE 1 Comparison of the proposed method with other reported procedures

Methods	LOD (µg/L)	RSD (%)	Total extraction time (min)	Ref.
SPE-HPLC-MS	0.94	<3.2	>10	[3]
SPE-GC-MS	50	<10	10	[8]
Headspace SPME-GC-MS[a]	0.1	1.103	>20	[34]
IP-SHS-HLLME-HPLC-UV	0.2	<5	3	This work

[a]Headspace solid-phase microextraction–gas chromatography–mass spectrometry.

where V_{org} and V_{aq} are the organic extractant volume and the sample solution volume, respectively. Based on cited equations, PF and ER for PQ were found to be 74 and 91.0%, respectively.

Some characteristic data of the current method was compared with other methods. Based on Table 1, the comparable analytical performance as well as sensitive properties for determination of PQ was achieved in less time (3 min) and these characteristics are comparable or even better than most of the other methods. Also this method was compared with the results of other methods with reference to extraction time and the type of solvent. This method was performed without dispersive solvent and toxic solvent with short extraction time [35–37].

3.6 | Analysis real sample

The method was evaluated with respect to different validation parameters such as precision and accuracy. The data are presented in Table 2. The accuracy was tested by a series of recovery experiments of the spiked samples at different amounts of PQ. The relative recovery percentage (RR%) was checked by Eq. (3).

$$\mathrm{RR}\% = \frac{C_{\mathrm{found}} - C_{\mathrm{real}}}{C_{\mathrm{added}}} \times 100, \tag{3}$$

where C_{found} is the concentration of the analyte after the addition of a known amount of standard to the real sample, C_{real} is the concentration of the analyte in the sample before spiking, and C_{added} is a known concentration of standard solution spiked in the real sample. According to the obtained results, the relative recoveries for the spiked samples were in the range of 90.0 and 92.3.1%.

Also, the precision of the method was studied by checking intraday precision (1 day) ($n = 5$) and interday precision (three different days) ($n = 5$) in the urine sample at different concentration levels of PQ (Table 3). The results for intra- and

TABLE 2 Analytical results for determination of paraquat in environmental and biological samples

Compound	Spiked (μg/L)	Found (μg/L)	Recovery (%)	RSD[a] (%)
River water	0	ND	-	-
	0.5	0.5	90.3	4.1
	1.0	0.9	91.7	3.5
	10.0	9.1	91.1	2.7
	100.0	91.6	91.6	2.9
Apple juice	0	ND	-	-
	0.5	0.5	90.6	4.6
	1.0	0.9	91.0	3.5
	10.0	9.2	92.2	2.4
	100.0	9.2	92.1	3.4
Urine-1	0	ND	-	-
	0.5	0.5	90.1	4.1
	1.0	0.9	90.9	4.3
	10.0	9.2	92.3	3.9
	100.0	91.8	91.8	4.4
Urine-2	0	ND	-	-
	0.5	0.5	90.4	4.9
	1.0	0.9	90.9	2.3
	10.0	9.2	91.8	1.8
	100.0	91.2	91.2	3.7
Plasma-1	0	ND	-	-
	0.5	0.5	90.0	3.5
	1.0	0.9	91.2	3.8
	10.0	9.1	91.4	2.9
	100.0	91.1	91.1	4.6
Plasma-2	0	ND	-	-
	0.5	0.5	90.4	4.9
	1.0	0.9	91.4	3.2
	10.0	9.2	92.3	4.6
	100.0	91.6	91.6	3.8

[a]Relative SD($n = 3$).
ND, not detected.

interday precision were in the acceptable range of 3.24–4.67 and 3.80–4.82% for urine samples at different concentrations, respectively. This indicates the good evaluation for the proposed method.

Figure 3 shows typical obtained chromatograms of a standard solution (7 mg/L) of PQ, as well as the spiked urine sample at 100 μg/L along with nonspiked urine sample after extraction. The retention time of the herbicide in the chromatogram of the urine sample was the same as the chromatogram of the standard. Also any interfering peak at the retention time of the herbicide was not obtained in the chromatogram of nonspiked urine sample. Thus, the determination of PQ can efficiently be performed without any interference in samples.

4 | CONCLUSION

The nature of quaternary ammonium group in PQ does not permit to extract from the aqueous media to the organic solvent due to its high polarity. In this study, a simple method, ion-pair switchable-hydrophilicity solvent-based homogeneous liquid–liquid microextraction has been developed for preconcentration of PQ in the real sample. The switchable solvent allows the extraction of the analyte in a homogeneous phase without dispersive solvent and easy operation without additional steps. In this method, SHS was switched between the two forms, hydrophobic and hydrophilic, using CO_2 and NaOH. The miscibility was changed by the reaction of hydrated CO_2 and the SHS. The extraction recovery of PQ was dependent on the concentration of the surfactant added to the medium. SDS was recognized as the best surfactant and amount of SDS was optimized for the high recovery. Therefore, SDS as an ion pair was used to convert cationic form of PQ to hydrophobic form. The simplicity and high stability in the synthesis of switchable solvent was observed. The proposed method was the simple with fast operation. The extraction of the analyte was carried out in a homogeneous phase without dispersive solvent and with relatively cheap reagents. The current method could be considered for the

TABLE 3 Method inter- and intraday reproducibility ($n = 5$) as SDs for spiked urine samples

Compound	Spiked concentration (μg/L)	Intraday measured value		Interday measured value	
		Relative recovery (%)	Precision (%)	Relative recovery (%)	Precision (%)
	0.5	90.7	3.95	91.5	3.99
	1.0	91.2	4.31	90.6	4.82
	5.0	91.4	4.67	90.8	3.98
Paraquat	10	92.3	3.34	90.4	3.80
	50	91.6	3.24	92.3	4.15
	100	91.5	4.59	91.1	4.03

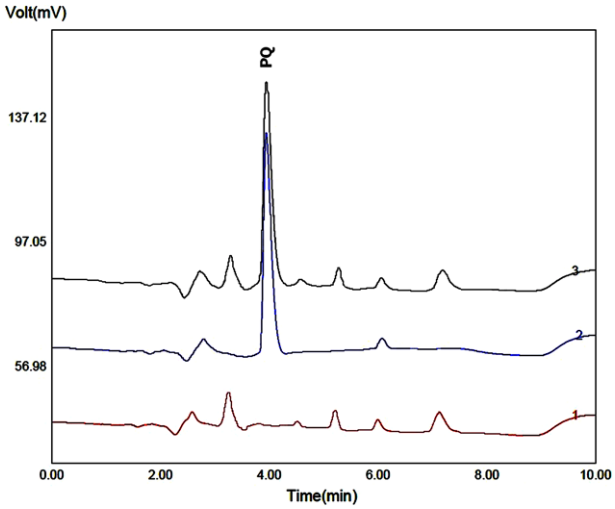

FIGURE 3 HPLC–UV chromatograms of (1) urine blank sample after microextraction (Red) (2) standard solution of PQ (7 mg/L) (Blue), and (3) spiked urine sample by 100 µg/L of PQ after microextraction (Black)

extraction of other analytes that contain a quaternary ammonium moiety.

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