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ORIGINAL RESEARCH

Sensitive determination of ketamine, methylphenidate, and tramadol in urine and wastewater samples by Porous Aromatic Framework-48 assisted electromembrane extraction coupled with ion mobility spectrometer

Fahimeh Mirzaei[1] · Ali Reza Fakhari[1] · Alireza Hashemzadeh[1] · Mostafa M. Amini[1]

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Abstract

A Porous Aromatic Framework-48 with the nitro functional groups (PAF-48-NO_2) has been introduced as a new porous structure for boosting electromembrane extraction efficiency followed by ion mobility spectrometer. We developed this method by immobilizing PAF-48-NO_2 into the microporous polypropylene hollow fibers for the extraction of three model basic drugs including Ketamine, Methylphenidate and Tramadol with different polarities (log P: 3.35, 2.25, and 2.45, respectively). The best extraction condition was obtained as following: 2-nitro phenyl octyl ether as organic solvent containing 3.0 mg mL^{-1} of PAF-48-NO_2 as sorbent, driving force of 180 V, extraction time of 20 min, pH of sample and acceptor solutions of 4.0 and 1.0, respectively, and stirring rate of 1000 rpm without any use of salt. The proposed PAF-48-NO_2-electromembrane extraction method was found to be sensitive for the extraction of the model drugs in the optimized condition with good linearties (>0.998), limit of detection (1.5–3.6 ng mL^{-1}), and high repeatability relative standard deviation 2.5–3.9%. In addition, the extraction efficiency of the proposed PAF-48-NO_2-electromembrane extraction method was higher than the classical electromembrane extraction method. Finally, the proposed method was successfully applied for the determination of Ketamine, Methylphenidate, and Tramadol in various spiked samples such as urine and wastewater samples.

Keywords Electromembrane extraction · Ion mobility spectrometry · Porous aromatic framework · Ketamine · Methylphenidate · Tramadol

Introduction

Tramadol, (TRA), Ketamine (KET), and Methylphenidate (MET) are three narcotic drugs that unfortunately, some young people abuse these drugs these days. TRA is a well-known drug analgesic; it is extensively used as a painkiller to ease moderate to moderately severe pains. KET was first used as an anesthetic in animals and later in humans and it is now used as a drug for the treatment of depression. Also, MET acts as central nervous system stimulant, which is widely prescribed to treat depression, narcolepsy, and attention deficit disorder by inhibiting norepinephrine and dopamine reuptake. The excessive use of these drugs may lead to nausea, vomiting, dizziness, and in some cases, cardiac arrest and death. Therefore, the development of an accurate and sensitive determination method for monitoring these drugs in biological fluids is very important in the clinical contexts and diagnostic research [1–5].

Recently, various methods such as chromatographic systems and UV spectrophotometry have been developed for the determination of these drugs [6–9]. Due to the trace concentration of analytes and complexity of fluids, it is necessary to apply an effective extraction method before the instrumental analysis. Many of extraction methods such as SPE [10], and liquid-liquid extraction (LLE) have been used as sample preparation techniques in this regard. However, these methods

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✉ Ali Reza Fakhari
a-zavareh@sbu.ac.ir

[1] Faculty of Chemistry, Shahid Beheshti University, G.C., P.O. Box 1983963113, Evin, Tehran, Iran

suffer from large volume of organic solvents used, time-consuming processes, large sample volumes and expensive processes for sample preparation. Therefore, to solve these problems, accelerated and miniaturized sample pretreatment methods such as electromembrane extraction (EME) have been developed. In the recent years, EME technique has been widely used due to its advantages such as rapidity, and simplicity for preparation and preconcentration of samples in the field of biological fluids, environmental and food industries [11–15]. In the last years, many efforts have been made to increase the extraction efficiency of EME technique. Among these methods, different types of sorbents have been used as modifier including di-(2-ethylhexyl) phosphate (DEHP), tri-(2-ethylhexyl) phosphate (TEHP) [16], dibenzo-18-crown-6 [17], carbon nanotubes (CNT) [18], nanosilver [19], and SBA-15 [15] immobilized into SLM.

Recently, sorbents, based on the porous organic frameworks, have been used as novel porous materials in many fields due to their excellent performance. This category of materials is introduced as porous organic frameworks (POFs) that are usually formed with linkage of organic polymerizable monomer building blocks or by post-polymerization of hyper-cross-linking [20]. In the meantime, various structures of POFs family, including porous aromatic frameworks (PAFs), have attracted considerable attention from researchers worldwide [21]. These materials have been widely applied in various fields, including gas storage [22], catalysts [23], opto-active materials, sensors [24], and molecular separation [25]. This is due to their high stability in the water, acidic and alkali tolerance, varied synthesis methods, aromatic frameworks, high surface area and uniform pore size distributions [26, 27]. PAFs, among currently available POFs with three-dimensional and porous structure polymers, are usually prepared with different polymerization procedures using polyphenylene, and triethynylbenzene [28]. These materials with unique characteristics such as programmability of porous structures, tunability of pore sizes, high surface area, regular continuous conjugated network, physicochemical stability and low skeletal density have been paid to attention universally due to large internal pore volume for their application as adsorbent materials. Moreover, PAFs have excellent potential for gas uptake, and extraction of organic molecules [27]. Also, it is well-documented that the phenyl ring could be easily functionalized with different groups through various organic reactions [29].

IMS is a powerful, fast, simple and sensitive instrumental technique for qualitative and quantitative analysis of the varied analytes [30]. In this study, the applicability of the PAF-48-NO_2 as a modifier was evaluated in the EME method for the first time. For this purpose, the PAF-48-NO_2 was added to the supported liquid membrane (SLM) and then the extraction efficiency of EME procedure for KET, MET and TRA as model basic compounds was assessed. The effect of presence of the PAF-48-NO_2 was investigated on the extraction efficiency. Finally, the performance of this method was evaluated to determine the chosen model basic drugs in urine and wastewater samples followed by IMS.

Experimental

Materials and reagents

Anhydrous aluminum chloride (99%), hydrochloric acid (37%), methanol, ethanol, acetone, trichloromethane, and tetrahydrofuran were purchased from Merck (Darmstadt, Germany). Some of the organic solvents such as 2-nitrophenyl octyl ether (NPOE), 1-octanol, nitrobenzene, n-hexadecane, n-hexane, and heptanol were obtained from Fluka (Buchs, Switzerland). All chemicals used in the analyses were of the analytical grade. KET and TRA were kindly provided from the Tofigh Daru company (Tehran, Iran) and MET was purchased from Pursina company (Tehran, Iran). Polypropylene porous hollow fibers (Membrana, Wuppertal, Germany) as membrane with an inner diameter of 0.60 mm, a wall thickness of 200 μm and a pore size of 0.20 μm were utilized in the EME process. All the hollow fibers were cut into 6.0 cm length parts and were completely immersed in acetone along with sonication for about 30 min to remove any pollution, located in the pores. Finally, the hollow fibers were dried in the air before use.

Standard solutions and real samples

The stock sample solution of each drug was prepared at the concentration of 1 mg mL^{-1} in amber glass bottles with methanol and stored at 4 °C in the refrigerator. Working solutions of drug compounds were freshly prepared by daily dilution of stock solution with deionized (DI) water. The urine samples from a volunteer and wastewater samples were collected from Besat hospital (Tehran, Iran). The spiked samples were prepared by addition of stock standard solution of the analytes into the samples.

Instrumentation

An ion mobility spectrometer (IMS) system 1000-model (Tof Tech Pars, Isfahan, Iran) was set up at the best condition as following: injector port temperature of 250 °C, cell temperature of 200 °C, corona voltage of 7000 V, drift tube length of 16 cm, drift field of 437 V cm^{-1}, nitrogen as drift gas and carrier gas at a constant flow rate of 1000 mL min^{-1} and 600 mL min^{-1}, pressure of 600 Torr and the shutter grid pulse width of 100. The peak area of samples were determined by the Vis-IMS software.

The EME equipment had a standard setup: PV-300 model (Mobtaker Aryaei J, Zanjan, Iran) with programmable voltage in the range of 0–300 V, and the current provisions were used in the range of 0–0.50 A. The platinum wires with a diameter of 0.20 mm were used as electrodes. The distance between the inner and outer electrodes was kept constant at 5.0 mm in the sample solutions, and the wall of hollow fibers, as explained in section (2.1), was used for immobilization of the SLM. In the extraction step, a heater-magnetic stirrer, Heidolph (Kelheim, Germany), was used in the stirring rate range of 100–1400 rpm.

Synthesis of sorbent

synthesis of 1,3,5-triphenylbenzene, PAF-48, PAF-48-NO_2, and PAF-48-NH_2 were described in Supplementary Materials.

Immobilization of PAF-48-NO_2 in the SLM

To prepare the immobilized hollow fibers with PAF-48-NO_2 as modifier, different amounts of PAF-48-NO_2 were completely dispersed in a tube, containing NPOE by an ultrasonic bath for about 5 min. Then, the hollow fibers were added to this tube, and the fiber pores were impregnated entirely with the mixture of PAF-48-NO_2 in the ultrasonic bath for about 30 min to make sure that all pores were successfully filled with PAF-48-NO_2 sorbent [31].

EME procedure

The EME experiments were carried out by spiking sample solutions with certain concentrations of drugs, and pH of the solutions were adjusted using HCl (1.0 M) and NaOH (1.0 M) in a 4.5 mL glass vial as a sample compartment. The SLMs were prepared with immersion of hollow fibers in the organic solvent for about 5.0 min till the pores were completely impregnated. Then, 20.0 μl of acceptor solution (100 mM HCl) using a microsyringe was inserted into the lumen of hollow fiber, and the end of the hollow fibers were thermally sealed. Afterwards, negative and positive electrodes were introduced into the acceptor and sample solutions, respectively by connecting them to the power supply. Finally, the sample glass vial was placed on a heater-stirrer at a certain stirring rate for about 30 min. At the end of the extraction procedure, the acceptor solutions were collected with a microsyringe, and 1.0 μL of these solutions were injected into the IMS for further analyses. The schematic illustration of the PAF-48-NO_2 modifier in the electromembrane extraction (PAF-48-NO_2-EME) was prsented in the Fig. 1.

Results and discussion

Characterization of synthesis sorbent

This section was completely introduced into the Supplementary Materials. The Fourier transform infrared (FTIR) spectra of PAF-48 and functionalized group were showed in the Fig. S1 and S2 (supplementary materials). In addition, the Powder X-ray diffraction (XRD) spectrum of PAF-48 was showed in the Fig. S3 (supplementary materials).

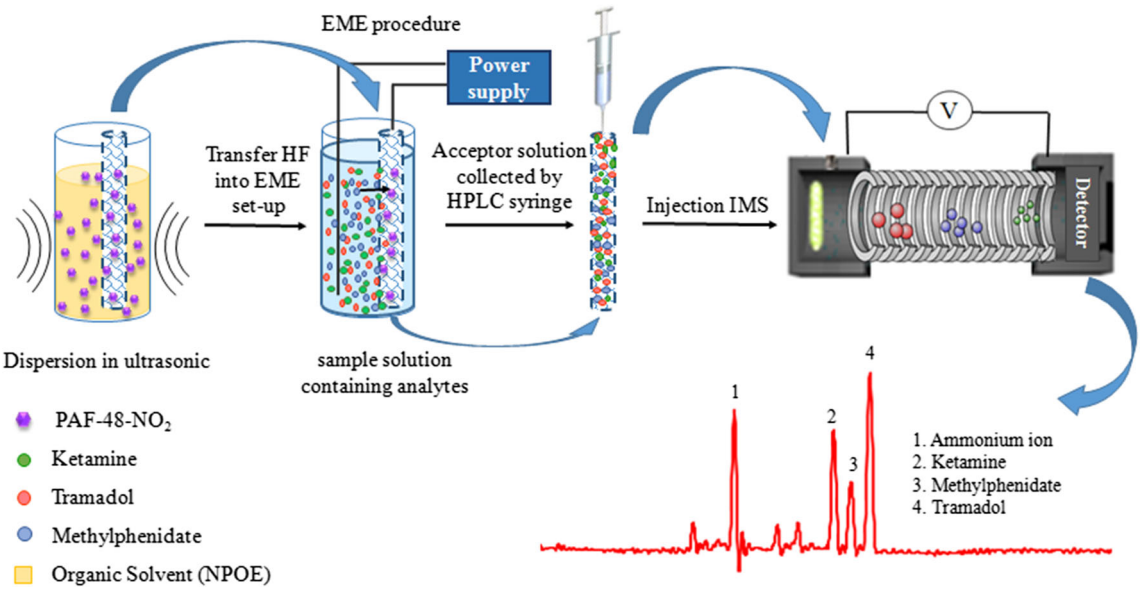

Fig. 1 Schematic illustration of the PAF-48-NO_2 modifier in the electromembrane extraction (PAF-48-NO_2-EME)

Optimization of electromembrane extraction method

Supported liquid membrane composition (organic solvent)

At first, the effect of various organic solvents used in the wall of hollow fiber as SLM was investigated. The nature of the solvents plays an important role in the diffusion coefficient of target analytes. In addition, the organic solvents must possess a certain amount of electrical conductivity to provide an electrical field between the donor and acceptor phases. It should also have a low vapor pressure to prevent solvents from losing in the extraction process. The organic solvent should be nearly hydrophobic in order not to be mixed with donor and acceptor solutions. Also, it is necessary to have an appropriate polarity with the hollow fiber so that it can be entirely immobilized into the pores [32]. Also, the SLM needs to have good stability under the electric potential [33]. To fulfill these requirements, six organic solvents including heptanol, 1-octanol, NPOE, n-hexadecane, n-hexane, and nitrobenzene were investigated as solvents in SLM. According to obtained results in Fig. 2a, NPOE was selected as optimum organic solvent for further experiments.

Effect of voltage in EME

In principles of EME, voltage, as driving force for electrokinetic migration of analytes across the SLM, is the critical parameter. Voltage causes the transportation of ionic analytes across the SLM [34]. The effect of extraction voltage was examined by applying several extraction voltages from 120 to 220 V. Figure 2b shows that as the voltage increases from 120 to 180, the extraction signal rises. However, by a further increase in voltages from 180 to 220 V, a decrease in signals was observed. This phenomenon could be explained by two different theories; firstly, when the voltage increases, water electrolysis reaction occurs in both donor and acceptor solutions via the following reactions.

$$\text{AP (negative electrode)} : 2H^+ + 2e \rightarrow H_2.$$

$$\text{DP (Positive electrode)} : H_2O \rightarrow 2H^+ + {}^1/_2\, O_2 + 2e^-$$

Thus, as voltage increases, the concentration of hydronium ions in AP decreases; consequently, pH in the AP gradually increases. Secondly, at the higher voltages, organic solvent temperature increases due to Joule heating phenomenon. It may be due to organic solvent evaporation or dissolution in

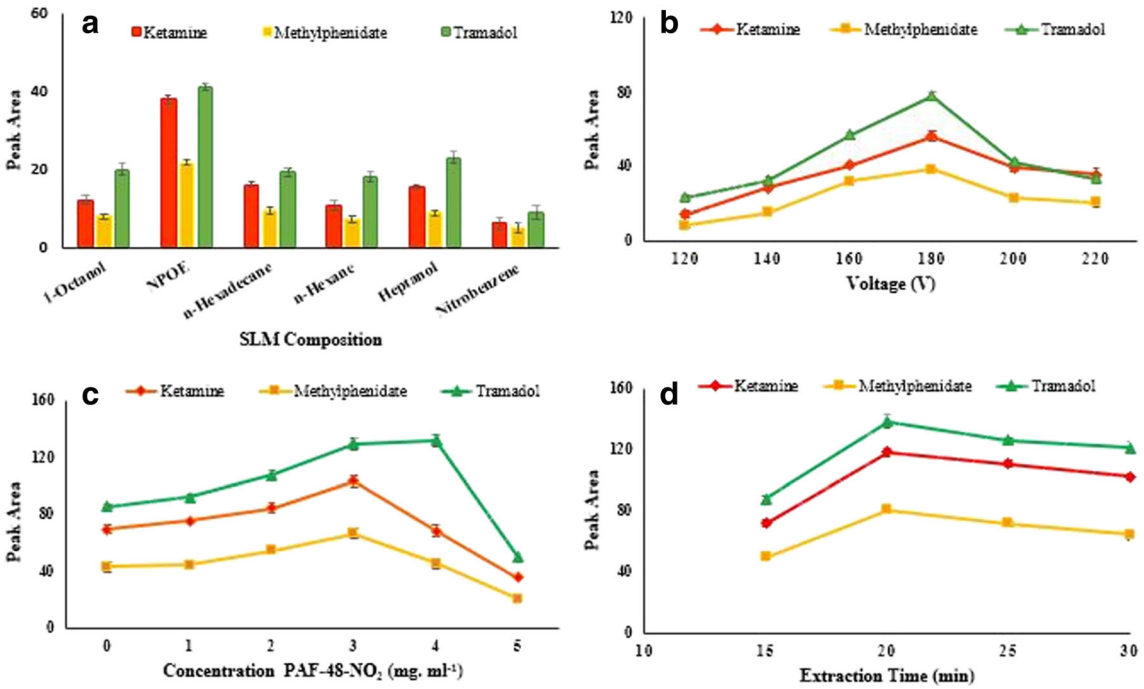

Fig. 2 **a** Effect of the SLM composition on PAF-48-NO_2-EME method; (200 ng mL^{-1} of the analytes, donor solution pH of 3.0, acceptor solution: HCl pH 1.0, voltage: 200 V, 1000 rpm as stirring rate, 30 min extraction time). **b** Effect of voltage on PAF-48-NO_2-EME method (200 ng mL^{-1} of the analytes, donor solution pH of 3.0, acceptor solution: HCl pH 1.0, 1000 rpm as stirring rate, 30 min extraction time) **c** effect of the concentration on PAF-48-NO_2 on EME extraction (200 ng mL^{-1} of the analytes, donor solution pH of 4.0, acceptor solution: HCl pH 1.0, voltage: 180 V, 1000 rpm as stirring rate, 30 min extraction time), **d** effect of extraction time on PAF-48-NO_2-EME method (200 ng mL^{-1} of the analytes, donor solution pH of 4.0, acceptor solution: HCl pH 1.0, voltage: 180 V, 1000 rpm as stirring rate, 3 mg ml^{-1} PAF-48-NO_2)

Table 1 Figures of merit of PAF-48-NO_2-EME-IMS methods for extraction Ketamine, Methylphenidate and Tramadol

Sample	Linear equation	LOD[a]	Linearity[a]	R^2	PF[b]	ER%	RSD%[c] Inrta-day	RSD%[c] Inter- day
KET	Y = 0.632x − 1.235	2.7	9–500	0.9989	196	87.1	3.5	3.9
MET	Y = 0.413x − 1.357	3.6	12–500	0.9987	195	86.6	3.4	3.8
TRA	Y = 0.696x + 0.067	1.5	5–500	0.9992	192	85.3	2.5	3.3

[a] Concentration is based on ng mL^{-1}

[b] PF and ER% were calculated at concentration of 200 ng mL^{-1} for analyte

[c] Intra-day and inter-day RSD% was calculated at concentration of 200 ng mL^{-1} of each drug

the sample solution [35]. Therefore, a voltage of 180 V was used as the optimum value in the next experiments.

Effect of pH of donor and acceptor phases

In EME method, the ratio of total ionic concentration in the sample solution to the acceptor solution, defined as ion balance, plays an essential role in the flux of target analytes. As it is known, the maximum peak area is obtained for the highest ion concentration in the acceptor solution in comparison with the sample solution [34, 36, 37]. The strong ionization of model basic drugs (KET: pKa 7.16, MET: pKa 9.09, and TRA pKa 9.23) in the sample solution is essential for providing a reliable electrokinetic migration across the SLM. Therefore, the pH of donor solution was studied in the range of 2.0–5.0 (under the lowest pKa value) to determine optimum results. As illustrated in the Fig. S4, when the pH value of donor solution increased from 2.0 (0.01 M HCl) to 4.0 (0.0001 M HCl), analytes became more ionized and this resulted in an improvement in the extraction efficiencies and peak areas of analytes. But, in the pHs lower than 4.0, ion concentration increased, and extraction efficiency decreased due to decrease in ion balance. Furthermore, at higher pH values in sample solution, the target analytes were converted into the neutral form and this could lead to a decrease in the extraction efficiencies. Thus, pH 4.0 was utilized as the pH in donor solution for the rest of this study.

In this study, the pH of acceptor solution was investigated by the same method for pH of donor solution. To achieve the highest extraction efficiency, the pH of the acceptor solution was evaluated within the range of 1.0–4.0 (HCl 100–0.1 mM) to determine the best extraction efficiency. As shown in Fig. S5, with an increase in pH of the acceptor solution, the extraction efficiencies decreased. The highest extraction efficiencies were obtained in the pH of 1.0 (100 mM HCl). Therefore, the pH value of 1.0 was selected for the acceptor solution in the subsequent experiments.

Table 2 Comparison of PAF-48-NO_2-EME-IMS method and the other methods for extraction tramadol, ketamine, and methylphenidate

Method	Analyte	LOD[a]	LDR[a]	RSD%	R[b]%	Ref.
SPE/LC-MS/MS	TRA MET	25.0 5.0	–	–	83–102 83.4–91.1	[6]
SPE/GC-MS	TRA KET	20.0 15.0	30–600	13.8	104–121 71–96	[39]
SBME[c] / HPLC–UV	MET	15.0	50–5000	3.5–3.9	86	[8]
LLE[d] / GC-MS	TRA	3.0	10–200	3.3–5.1	88–97	[40]
PSME[e] / GC-MS-MS	KET	5.0	10–250	15	63–101	[41]
EME / HPLC-UV	KET	6.7	20–1000	7.0	45.8	[42]
EM-SPME-LSV[f]	TRA	3.0	10-500	8.1	90–96	[43]
PAF-48-NO_2-EME-IMS	TRA KET MET	1.5 2.7 3.6	5–500 9–500 12–500	2.6–4.7 3.3–4.3 3.8–5.2	94–98 92–97 94–99	Present Study

[a] Concentration is based on ng mL^{-1}

[b] Recovery

[c] Solvent bar microextraction

[d] Liquid–Liquid Extraction

[e] Packed sorbent microextraction

[f] linear sweep voltammetry (LSV)

Effect of stirring rate, and salt addition

The effect of salt addition and stirring rate were illustrated in the Supplementary Materials. The obtained results showed that (Fig. S6, and S7) 1000 rpm for stirring rate and 0% of salt in the donor solution were the best values to be used in the subsequent studies.

Effect of kind and concentration of sorbents in supported liquid membrane

In the next step, effect of various functionalized PAFs was investigated, which included PAF-48, PAF-48-NO_2 and PAF-48-NH_2 mixed with the NPOE as SLM. In these series of experiments, a constant concentration of 2.0 mg mL^{-1} of each of PAFs was immobilized in the pores of hollow fibers and was used for the extraction of target analytes. The extraction efficiencies of analytes were affected by the addition of modifier to the organic solvent (Fig. S8). Among these three compounds, since the extraction processes were carried out under acidic conditions and both PAF-48-NH_2 and PAF-48 were protonated under this condition, strong interactions did not occur (hydrogen bonding). However, the PAF-48-NO_2 could improve the extraction efficiency due to the partial negative charge on its surface. Therefore, the highest extraction efficiencies were achieved through PAF-48-NO_2 as the modifier in the NPOE.

To assess the effect of the concentration of PAF-48-NO_2 as a modifier, different amounts of PAF-48-NO_2 in NPOE were evaluated in the range of 1.0–5.0 mg mL^{-1}. As illustrated in Fig. 2c, the extraction efficiency of target analytes was improved by increase in the concentration of PAF-48-NO_2 up to 3.0 mg mL^{-1}, and in the higher concentrations, the peak areas gradually decreased. The decrease in the extraction efficiency may be due to incomplete desorption of analytes from PAF-48-NO_2 into the AP. On the other hand, increase in the concentration of PAF-48-NO_2 could raise the electrical conductivity of EME, leading to an enhancement in the electrical current in the extraction procedure. This would lead to bubble formation due to the electrolysis reaction at the electrodes. In addition, it would be due to higher accumulation of nanoparticles in the pores which could block pores in the hollow fiber. As a result, analytes could not easily move into the AP. Therefore, the best concentration of the PAFs in NPOE was selected to be 3.0 mg mL^{-1} in this research. Considering these parameters, the mechanism of extraction and target analytes transfer using PAF-48-NO_2-EME procedure were a combination of liquid extraction and SPE.

Effect of extraction time

The extraction time plays an essential role in the enhancement of mass transfer to the AP and increases the efficiency of the extraction [37]. To examine the flux of analytes over time, the extraction duration was investigated in the range of 15 to 30 min. As shown in Fig. 2d, all drugs exhibited similar behaviors. The peak areas were significantly improved by an increase in the time up to 20 min and reduced at longer

Table 3 Figures of merit of proposed PAF-48-NO_2-EME-IMS for determination of Ketamine, Methylphenidate and Tramadol in urine and wastewater samples

Sample	Analyte	Added amount (ng. mL^{-1})	Founded amount (ng. mL^{-1})	RSD[b] % ($n = 3$)	RR[c] (%)
Urine 1	KET	0	_	_	_
		20	18.4	3.6	92
		50	46.5	3.1	93
	MET	0	_	_	_
		20	19.2	3.3	96
		50	47.5	2.8	95
	TRA	0	-	_	_
		20	18.6	3.7	93
		50	47	3.8	98
Urine 2	KET	0	_	_	_
		20	18.9	2.9	94.5
		50	47.5	3.6	95
	MET	0	_	_	_
		20	19	3.1	95
		50	46.5	3.3	93
	TRA	0	_	_	_
		20	46.5	3.4	93
		50	47.5	2.8	95
Urine 3	KET	0	_	_	_
		20	19.2	3.5	96
		50	49	2.5	98
	MET	0	_	_	_
		20	18.6	3.7	93
		50	47	3.3	94
	TRA	0	_	_	_
		20	19.0	2.4	95
		50	48.5	2.9	97
Waste water	KET	0	_	_	_
		20	19.2	3.2	96
		50	49	2.5	98
	MET	0	_	_	_
		20	47.5	3.1	94
		50	46.5	2.7	97
	TRA	0	_	_	_
		20	19.4	2.6	97
		50	49.5	3.2	99

[a] nd, not detected

[b] Relative standard deviations ($n = 3$)

[c] Relative Recovery

extraction time. After this time, the peak areas gradually decreased. It may be due to an increase in pH of acceptor solution and Joule heating phenomenon which can result in evaporation or dissolution of organic phase in the sample solution. These effects might be attributed to unstabilization of the transport of analytes or could result in back-extraction of target analytes to the SLM [38]. Finally, the extraction time of 20 min was selected as the optimum extraction time for the next experiments.

Method validation

To evaluate the practical applicability of the proposed EME method, the optimized extraction conditions were adopted to determine the model drugs in a drug–free human urine samples. Figures of merit of the presented method, including linearity, limits of detection (LOD), perconcentration factor (PF), extraction recovery (ER%) (Eq. 1, and 2 in the supporting information), precision and repeatability were assessed for the extraction of KET, TRA, and MET (Table 1). The proposed method presented linearities over the concentration ranges of 10–500, 15–500, and 5–500 for KET, MET, and TRA, respectively. In addition, this method provided square of regression coefficients (R^2) higher than 0.9980. The perconcentration factors were obtained within the range of 117.0–184.0 which were corresponded to extraction recoveries in the range of 77.8%–80.9% (Table 1). The LODs were estimated according to an S/N of 3 and were obtained within the range of 1.5–3.1 ng mL^{-1} for the model drugs. The repeatability (intra-day) and (inter-day) precision were obtained based on five repetitive measurements, expressed in term of RSDs%, ranging from 2.4% -3.8%, and 3.7% -4.5%, respectively.

In addition, Table 2 shows a comparison between the presented PAF-48-NO_2-EME-IMS method with other reported methods in the literature, described for the determination of target analytes. As can be seen, this proposed method provided the lower detection limits than those of conventional procedures using SPE/GC-MS [39], SBME/HPLC–UV [8], LLE/GC-MS [40], and PSM/GC-MS-MS [41]. More importantly, compared with SPE based techniques, the utilization of toxic organic solvents in EME method is negligible. Moreover, the IMS, due to swift response compared to the other methods, minimizes the analysis time.

Real sample analysis

The applicability of the PAF-48-NO_2-EME method was assessed for the determination of model drugs in four real samples (urine 1, urine 2, urine 3 and wastewater). The urine and wastewater samples were diluted at a ratio of 1:3 and 1:1 using HPLC grade water, respectively, and their pH values were adjusted to 4.0. Then, 4.5 mL of each sample solution was transferred into a sample vial and EME process was

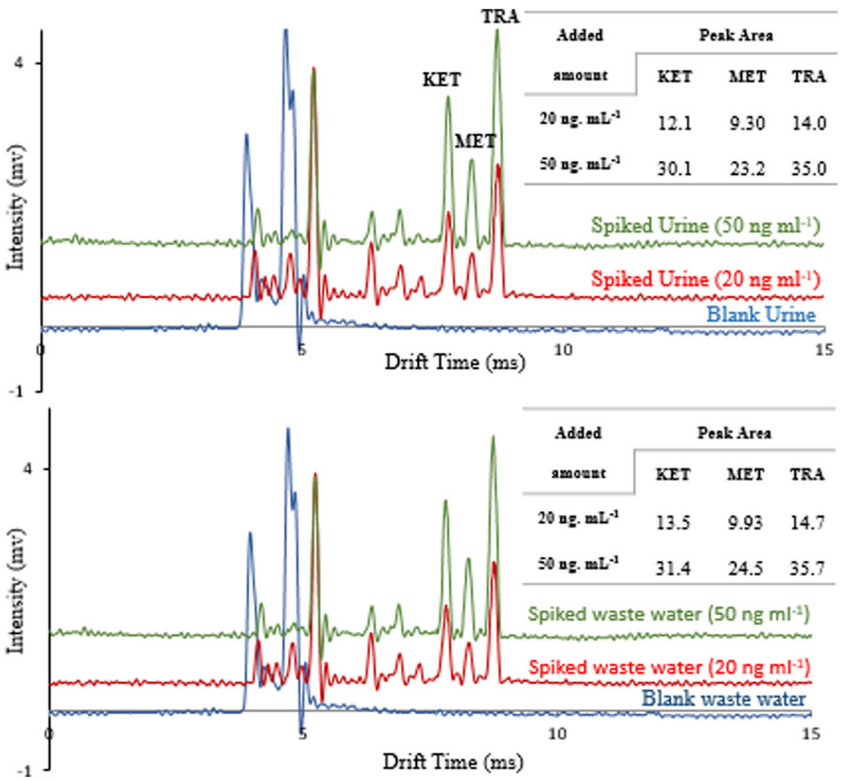

Fig. 3 Chromatograms of the nonspiked and spiked urine and wastewater samples, with 20 and 50 ng mL^{-1} of KET, MET, and TRA after PAF-48-NO_2-EME extraction under the optimum conditions

performed. To evaluate the matrix effect, the real samples were spiked with standard solutions (20 and 50 ng mL^{-1}) of KET, MET, and TRA in real samples and their relative recoveries (RR) (Eq.3 in the supporting information) were determined. The results (Table 3) illustrated that this method provided satisfactory relative recoveries in the range of 92–99%. Also, the matrix effect of modified EME method was negligible in different real samples due to high relative recoveries at the proposed method. Figure 3 shows the obtained chromatograms of the nonspiked and spiked real samples with 20 and 50 ng mL^{-1} of KET, MET, and TRA by PAF-48-NO_2-EME method under the optimum conditions.

Conclusions

In the present work, the presence of PAF-48-NO_2 as a new modifier in the SLM was assessed. The obtained results illustrated that mass transfer of charged analytes were extensively improved in the presence of PAF-48-NO_2. In fact, the combination of a solid sorbent and organic solvent in the pores of fibers is an efficient approach to increase the extraction efficiency of EME. Also, the proposed method was successfully applied to extract and determine KET, MET, and TRA in real samples. The proposed PAF-48-NO_2-EME technique in combination with IMS provided good linearties over the concentration range of 5–500 ng mL^{-1}. In addition, reasonable extraction time, satisfactory LODs and RSDs were obtained.

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Compliance with ethical standards

Conflict of interest There are no conflicts to declare.

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