Determination of Trace Amounts of Methamphetamine in Biological Samples by Hollow Fiber Liquid-phase Microextraction Followed by High Performance Liquid Chromatography

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Methamphetamineis used to treat Attention-deficit hyperactivity disorder (ADHD) or obesity as Desoxyn. In this work, for the first time a microextraction technique was introduced to detection and measurement of methamphetamine in urine and plasma samples. Hollow ûber based liquid phase microextraction (HF-LPME) followed by high performance liquid chromatography (HPLC) coupled with ultraviolet (UV) detection was used for extraction of methamphetamine. The organic solvent consists of 1-Octanol immobilized in the pores of a hollow fiber wall. A pH gradient was applied to migrate analytes from the sample solution with pH 11.6, through the organic solvent membraneinto an acidic acceptor solution with pH 2.8which was located inside the lumen of hollow fiber. Extraction recoveries upper than90% were obtainedin different biological matrices which resulted in preconcentration factors upper than 131.5 and acceptable repeatability (3.4< RSD%(n=6)<3.9). The method offers good linearity with estimation of coefficient higher than 0.9850. Finally, it was applied tothe detection and determination of methamphetamine in human plasma and urine samples.

Key words: Methamphetamine; High performance liquid chromatography; Hollow ûber based liquid phase microextraction; Microextraction.

Methamphetamineis used for treatment of Attention Deficit Hyperactivity Disorder (ADHD) and exogenous obesity[1-6].The structure and chemical properties of target compound are summarized in Table 1[7].Methamphetamine increases the amount of the neurotransmitter dopamine, leading to high levels of that chemical in the brain. Dopamine is involved in reward, motivation, the experience of pleasure, and motor function. Methamphetamine's ability to release dopamine rapidly in reward regions of the brain produces the euphoric "rush" or "flash" that many users experience[8-10].

Methamphetamine may be sold illegally. Repeated methamphetamine use can easily lead to addiction and relapsing disease[11]. Methamphetamine has short-term and long-term impact on behavior and health of consumers. Methamphetamine when taken, create a false sense of well-being and energy. In the long term, methamphetamine use can cause irreversible harms, including increasing in heart rate and blood pressure; damaged blood vessels in the brain that

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can cause strokes or an irregular heartbeat, cardiovascular collapse or death; and liver, kidney and lung damage[12-15].

Therefore, it is necessary to introduce a new method that improves detection and measurement of methamphetamine in biological fluid samples. Manymethodshave been introduced todetection and measurement of methamphetamine till now. There are several methods for measurement of methamphetamine concentration in various samples including HPLC using fluorescence detection[16-18], HPLC with chemiluminescence detection[19, 20], gas chromatography–mass spectrometry[21, 22], gas chromatography with nitrogen-phosphorus detectio[23], colourimetric detection using digital and mobile phone technology[24], andelectrochemistry techniques such as electrochemiluminescence[25, 26].

Tothe best of our knowledge,a few microextraction techniques such as solid-phase microextraction[27-31], Single drop liquid-liquid-liquid microextraction[32], and dispersive liquid-liquid microextraction[29, 33] has been reported for the detection of methamphetamine, but hollow ûber based liquid phase microextraction (HF-LPME) has not been done for detection and determination of methamphetamine in biological fluids. In this work, for the first time, three phasehollow ûber based liquid phase microextraction (HF-LPME) followed by HPLC with ultraviolet (UV) detection was optimized and validated for quantification of methamphetamine in biological samples.

HF-LPME was introduced for the first time by Pedersen-Bjergaard and Rasmussen in 1999[34].HF-LPME divided into two-phase HF-LPME and three-phase HF-LPME.In two-phase HF-LPME target analytes are extracted from an aqueous sample into the organic solvent but in three-phase HF-LPME target analytes are extracted from an aqueous sample into the organic solvent and then into the aqueous acceptor solution[35-40].

In this study, three-phase HF-LPME followed by HPLC–UV was used for the determination of methamphetamine for the ûrst time in biological fluids. All parameters were optimized to give a rapid, simple, and sensitive determination of the target analyte.

EXPERIMENTAL

Reagents and reference standards

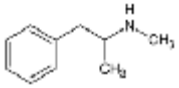
Methamphetamine standard waskindly donated byDrug and Food Administration (Tehran, Iran).1-Octanol, n-heptane, n-cyclohexanol, and n-hexane were purchased from Merck (Darmstadt, Germany). HPLC grade acetonitrile and methanol were obtained fromMerck.Sodium hydroxide and sodium chloride were obtained from Sigma–Aldrich (St. Louis, MO, USA). All of the chemicals used were of analytical-reagent grades.

Hollow-ûber PPQ3/2 Accurel KM polypropylene (600 µm inner diameter, 200 µm wall thickness and 0.2 µm average pore size) was purchased from Membrana (Wuppertal, Germany). The ultra-pure water was provided by a model Aqua Max-Ultra Youngling ultra-pure water purification system (Dongan-gu, South Korea).

HPLC conditions

Detection and separation of the target analyte were carried out by a Younglin YL9100 HPLC (Seoul, Korea) containing a Quaternary9110 HPLC pump (Korea), a 4-channel mixing valve with a 10 µL sample loop, YL9101 vacuum degasser and a YL 9120 UV-Vis detector. Chromatography data were recorded and analyzed using Young Lin Auto Chro 3000 software. The separations were performed on an ODS-3 column (150 mm × 4.6 mm, with particle size of 5 µm) from Waters (Massachusetts, USA). The mobile phase consisted of 30 mM phosphate buffer (pH=2.1) and acetonitrile (60:40), under isocratic condition. The flow rate of the mobile phase was adjusted at 1.0 mL min^{-1}. Total analysis time was 15 min. The injection volume was 10 µL for all of the samples and detection was performed at a wavelength of 205 nm.

Table 1. Chemical structures, pK_a and log*P* of methamphetamine.

Name	Chemical structure	IUPAC name	pK_a	log*P*
Methamphetamine		N-methyl-1-phenylpropan-2-amine	9.9	2.24

Extraction procedure

A 100 mg L^{-1} stock solution of methamphetamine was prepared in methanol and standard working solutions were prepared by spiking proper amount of the stock solution in pure water. Ten milliliter of sample solution was ûlled into a 15 mL vial which was placed on a magnetic stirrer plate to provide efficient stirring during the extractions. Extraction process was illustrated in fig. 1. A new 4 cm length of hollow ûber was mounted at the end of 50 mL Hamilton syringe needle that filled with acceptor phase, and subsequently dipped for a 10 s period into the organic solvent used as supporting organic membrane for impregnation. After impregnation, excess amount of organic solvent washed with distilled water, and 10 µL of the acceptor solution with pH=11.6 was injected into the hollow ûber with the Hamilton syringe, and the lower end of the hollow fiber was sealed with aluminum foil. Subsequently, the ûber was placed in the sample solution vial for extraction. During extraction, the solution was stirred at 625 rpm. After extraction, the acceptor solution was collected into a micro-vial by Hamilton syringe and ûnally, acceptor solution was injected into the HPLC instrument for analysis.

Real sample analysis

Drug-free human plasma was obtained from Iranian Blood Transfusion Organization (Tehran, Iran). Urine samples were collected from healthy young volunteer. The samples were stored at "4ÚC, thawed and shaken before extraction.

Calculation of preconcentration factor, and relative recovery

Preconcentration factors were estimated according to the following equation:

$$PF = \frac{C_{a,f}}{C_{d,i}} = \frac{n_{a,final} \times V_a}{n_{d,initial} \times V_d} = \frac{R}{100} \times \frac{V_d}{V_a} \quad ...(1)$$

where $C_{d,i}$ is the initial concentration of analyte in the donor phase and $C_{a,f}$ is the ûnal concentration in acceptor phase. $n_{d,initial}$and $n_{a,ûnal}$are the amounts of analyte present, respectively, in the donor phase and in the acceptor phase. V_d and V_a represent the donor volume and the acceptor volume, respectively. R is the recovery of the extraction given as a percentage.

Relative recovery (*RR*) was calculated by the following equation:

$$RR = \frac{C_{found} - C_{real}}{C_{added}} \times 100 \quad ...(2)$$

where C_{found}, C_{real}, and C_{added} are the concentrations (µg L^{-1}) of analyte after addition of known amounts of the standard into the real sample, the concentration of analyte in real sample, and the concentration of known amounts of the standard which was spiked into the real sample, respectively.

RESULTS AND DISCUSSION

Choice of the organic solvent

The nature of the organic membrane solvent has an important role in HF-LPME. The solvent should be strongly maintained in the pores of the ûber, thus the polarity of organic solvent should be very close to the polarity of polypropylene ûber. In addition to, organic membrane solvent nature has to be adapted to the nature of the target analyte in order to favor their transfer[41]. therefore, 1-octanol, n-heptane, n-cyclohexanol, and n-hexane were tested as organic membrane solvent. As shown in Fig. 2A,among the organic solvents tested, 1-octanol showed the maximum extraction recovery for methamphetamine. Thus, 1-octanol was used in following experiments.

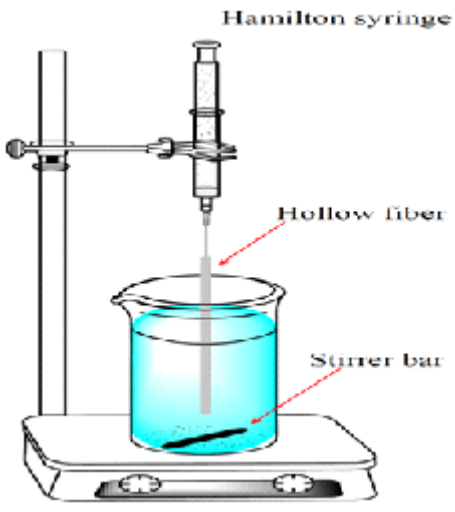


Fig. 1. Schematic diagram of proposed HF-LPME setup.

Composition of sample solution and acceptor phase

The nature of the target analyte has an important role in selection of donor and acceptor solution.The acidity constant (pKa) of methamphetamine being around 9.9. Therefore, changes in pH could change their existing form. In order to transfer target analyte to organic membrane solvent, donor solution pH should be adjusted to the pH that deionize the analyte and increase their transfer from the donor phase into the organic phase. The acceptor phase should be acidic to provide high solubility for the basic analyte and ionize them to prevent to back extracting of analyte into the organic phase. For this reason, donor and acceptor phases' pH was studied in the range of9 to 12 and 2 to 3.6, respectively. As shown in fig. 2B and 2C, the highest extraction recovery of methamphetamine was obtained using pH=11.6 and pH=2.8 for donor and acceptor phases, respectively. Therefore, this pH's was used for subsequent experiments.

Effect of stirring rate

Sample solution stirring, short extraction time by adding a convection transport to the diffusion of molecules. High stirring speed may cause the instability of organic solvent in hollow ûber pores and may generate air bubbles around the ûber. Thus, the stirring speed was set in the 100 to 1000 rpm range. Hence, according to Fig. 2D, a stirring rate of 625 rpm showed highest extraction recovery and was chosen as the optimum stirring speed for future experiments.

Table 2. Figures of merit of HF-LPME in drug-free distilled water sample.

LOD ($ngmL^{-1}$)	LOQ ($ngmL^{-1}$)	Linearity ($ngmL^{-1}$)	R^2	PF[a]	RSD% (n=6)[b]	
					Within day	Between day
10.0	30.0	30.0-1000.0	0.9850	131.5	3.4	3.9

[a] Drugs were present at 500 ng mL^{-1}.[b] Within day and between day RSDs% were obtained by six replications.

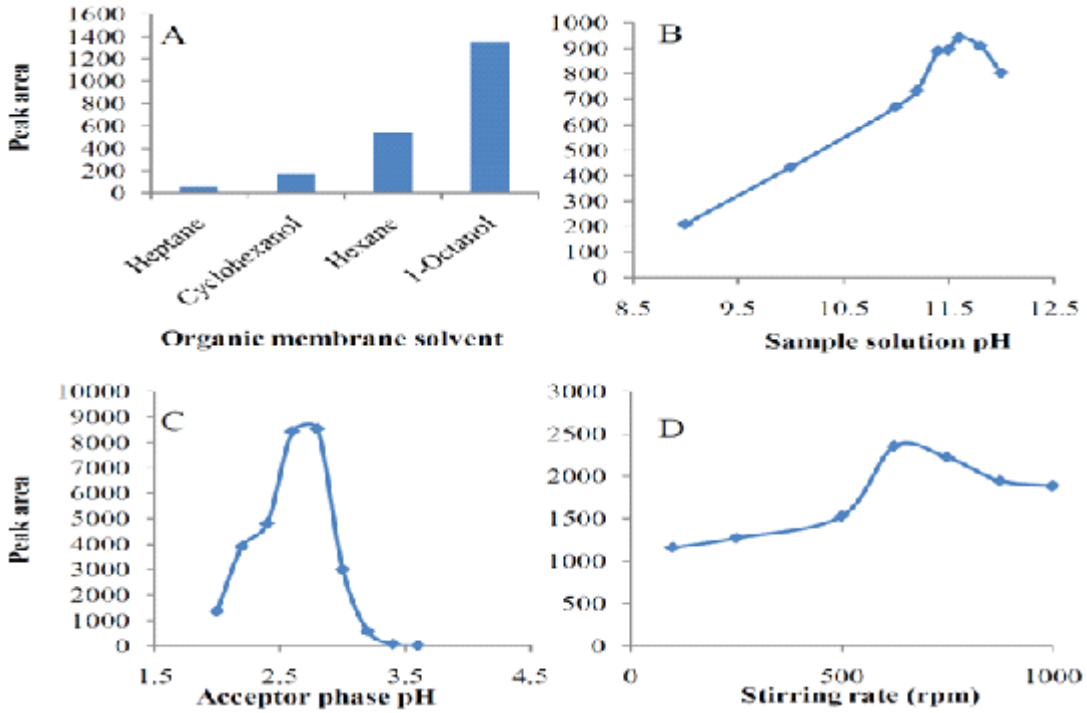


Fig. 2. Optimization of (A) organic membrane solvent, (B) sample solution pH, (C) acceptor phase pH and (D) stirring rate for extraction of methamphetamine

Effect of salt addition to the sample solution

The salting-out effect is widely used to increase the extraction recovery of uncharged polar target compounds from aqueous samples by decreasing the solubility of polar compounds in donor sample phase. In spite of these phenomena, aqueous solution viscosity would increase by the addition of salt, which lead to difficult mass transfer and decrease extraction recovery. In current work, the effect of different concentrations of NaCl in the range of 0–30% (w/v) was tested. The extraction recoverydecreased byincreasing the NaCl concentration from 0 to 30% (m/v). Considering extraction recovery of target analyte, nosalt addition was chosen as optimal condition (fig. 3A), and used in the future experiments.

Effect of extraction time

There are two liquid–liquid interfaces in three phase LPME method. Therefore, solute molecules require a long time to transfer through these interfaces. In order to study the extraction time effect on the extraction recoveries, different extraction times in the range of 20–50 min were tested. As shown in Fig. 3B ,The extraction recovery increased with the increasing of the extraction time up to 40 min. Further increasing during the extraction time over 40 minutes, lead to decrease in the extraction recovery due to organic membrane dissolution in the sample solution. Therefore, 40 min was chosen as the optimal extraction time in the next experiments.

Effect of extraction temperature

The temperature inûuence on the methamphetamine extraction recovery by HF-LLLME was investigated in the range of 4–45 °C. As shown in Fig. 3C, increasing of temperature from 4 to 25 °C increase extraction recovery, but increasing extraction temperatures higher than 25 °C decrease extraction recovery due to air bubble formation around the hollow ûber. Increasing extraction temperature affects the extraction recovery by acceleration of the mass transfer rates of analytes and increasing solubility of analytes in aqueous sample solution due to reduction partition coefficient in extraction phase. Thus, 25 ºC was selected as optimal temperature in this work.

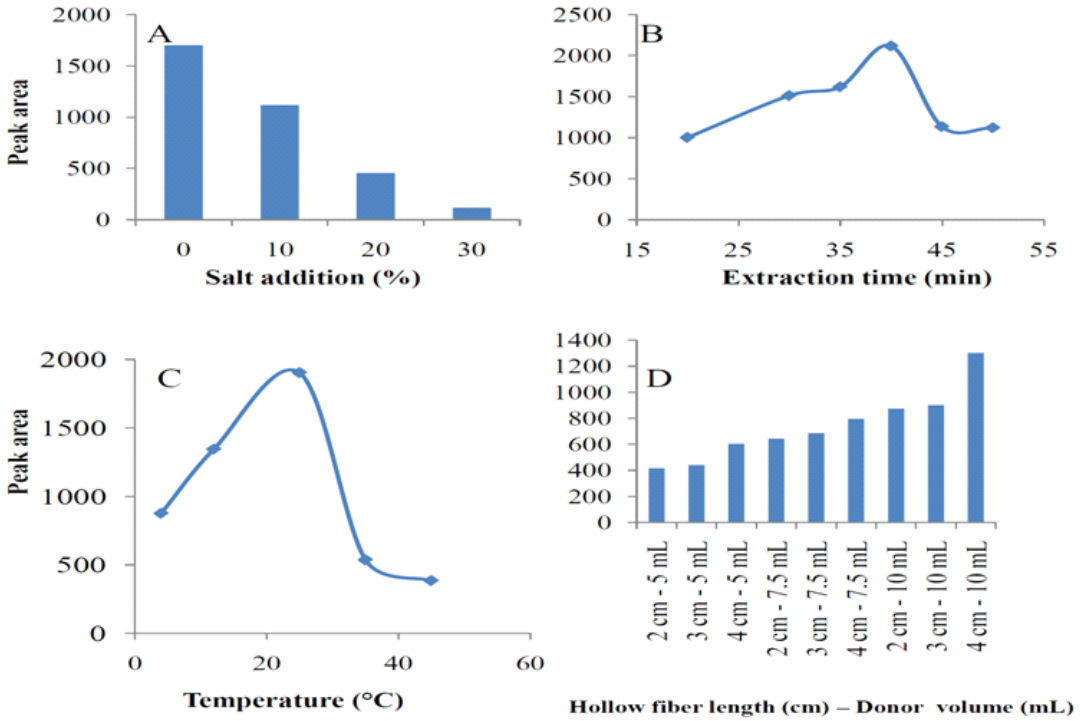


Fig. 3. Optimization of (A) salt addition effect, (B) extraction time and (C) temperature for extraction of methamphetamine.

Effect hollow fiber length (acceptor volume) and sample volume

For the study of the effect of acceptor phase and sample solution volume, different hollow fiber length and sample solution volume were tested. Acceptor phase volume is proportional to the hollow fiber length. Therefore, different hollow fiber length was used. As shown in Fig. 3D, increasing of hollow fiber length from 2 to 4 cm in constant sample volume, increase extraction recovery. Also, Increasing of sample volume from 5 to 10 mL in constant hollow fiber length, increase extraction recovery. Thus, 10 mL sample solution volume and 4 cm hollow fiber length was showed maximum extraction recoveries and selected as optimal conditions for hollow fiber length and sample volume in this work.

As a result, the optimal conditions were attained by using pH=11.6 and pH=2.8 as donor and acceptor phase composition, respectively, 10 mL sample solution volume, 4 cm hollow fiber length, and using 625 rpm as stirring rate for 40 min. In addition, the organic membrane composition was 1-Octanol. Sample temperature of 25 °C without the salt additionwas selected as optimal conditions for methamphetamine extraction.

Method evaluation

To evaluate the applicability of the proposed HF-LPME method, figures of merit were studied using standard solutions of the analyte in

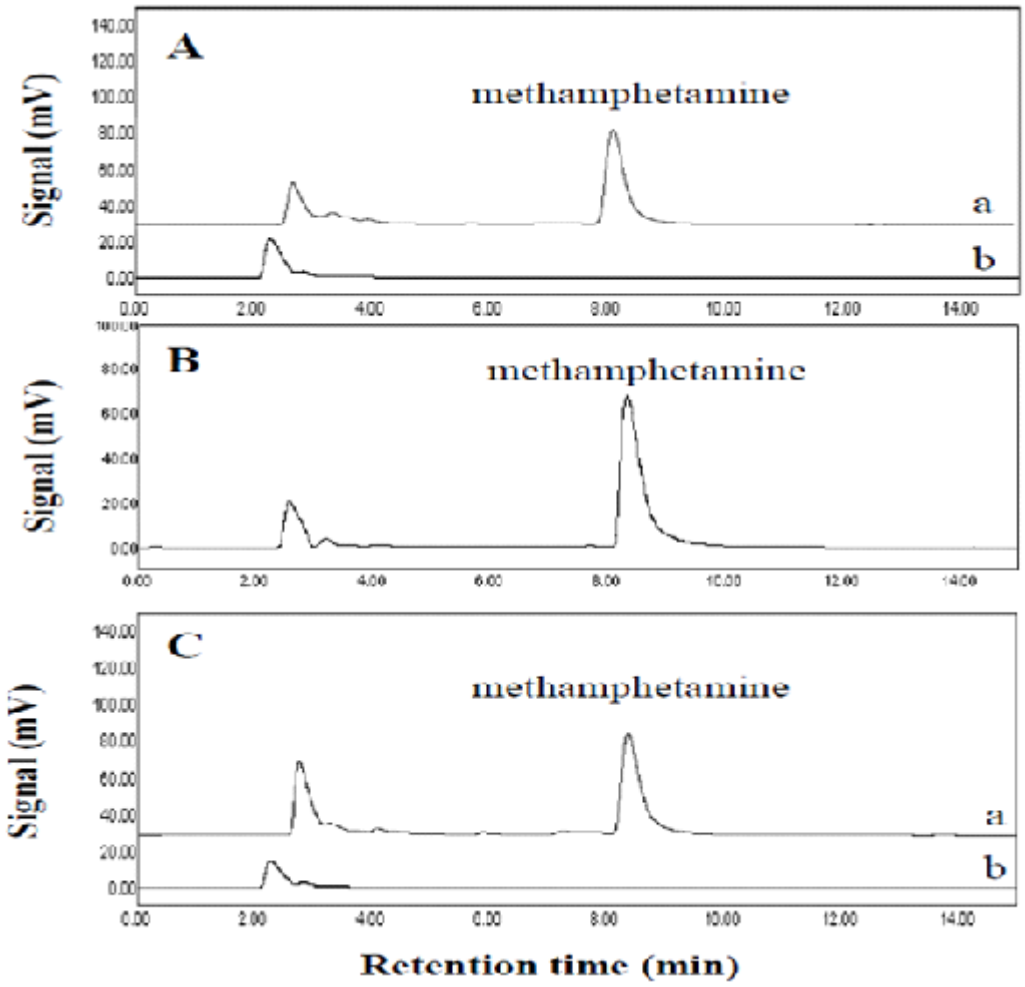


Fig. 4. Chromatograms obtained after HF-LPME extraction of (A) urine sample, (B) urine sample from a healthy volunteer who consuming methamphetamine and (C) plasma sample ((a) spiked sample and (b) non-spiked sample at a concentration level of 1.0 mg L^{-1}).

a drug-free biological samples. Optimal condition was applied to find out linearity, repeatability, and LODs of this method that summarized in Table 2. The calibration curves were linear in the range of 30.0–10000.0 ng mL^{-1} with coefûcient of determination (r^2) more than 0.9850. The relative standard deviations (RSD %,n=6) for extraction and determination of the analyte were less than 3.4% and 3.9% for intraday and interday experiment, respectively. LODs less than 10.0 ng mL^{-1} was obtained for target analyte. PF values higher than 131.5-fold was obtained for the extraction of methamphetamine.

Analysis of real sample

In order to reduce matrix effects, calibration curves were plotted in drug free urine and plasma samples.

Extraction from human urine sample

Drug-free human urine was spiked with the target drug and extraction was accomplished after dilution of urine samples (1:3) and the addition of proper amount of NaOH solution to achieve pH 11.6. The result is summarized in Table 3. A RSD %(n=6) value less than 3.4% confirm the acceptable precision of proposed HF-LPME method. Fig. 4A shows the typical chromatograms of the extracted methamphetamine from urine before and after spiking with methamphetamine.

Another urine sample was collected from a healthy volunteer who consuming methamphetamine. Fig. 4B shows the typical chromatogram of the extracted methamphetamine from this urine sample.

Extraction from human plasma sample

Frozen human plasma samples were left on the bench to thaw naturally. Small amount of perchloric acid was added to remove proteins from plasma. The sample is put into the centrifuge tube and vortexed for 1 min. The sample solution was centrifuged at 3000 rpm for 5 min. The clear upper solution was collected and diluted with water (1:3) and adjusted to pH 11.6 by addition of proper amount of NaOH solution. The result is summarized in Table 3. An RSD % (n=6)value less than 3.3%

Table 3. Determination of methamphetamine in different urine and plasma samples

Sample	C_{real} (ngmL^{-1})	C_{added} (ng mL^{-1})	C_{found}(ng mL^{-1})	RSD% (n = 6)	RR%
Plasma	nd[a]	1000.0	899.0	3.3	90
Urine	nd	1000.0	940.0	3.4	94

[a] Not detected

Table 4. Comparison of the HF-LPME with other analytical techniques for determination of methamphetamine.

Analytical method	Sample preparation method	Sample	LOD (ng mL-1)	Linearity (ng mL-1)	RSD%	Ref.
HPLC	HF-LPME	Plasma/ Urine	10.0	30.0-1000.0	3.5	This work
GC-MS	EE-SPME	Urine	25.0	70.0-1000.0	6.1	[42]
GC-FID	DLLME	Urine	18.0	30.0-1500.0	6.8	[43]
GC-MS	IL-SPME	Urine	10.0	20.0-1500.0	7.5	[28]
HPLC	Single drop LPME	Urine	30.0	50.0-1500.0	5.2	[44]
HPLC	Single drop LPME	Urine	50.0	100.0-1500.0	5.0	[45]
HPLC	Column switching	Urine	100.0	100.0-10000.0	5.1	[46]
GC	HS-SPME	Urine	60.0	200.0-500.0	5.3	[47]
IMS	HS-SPME	Serum	80.0	200.0-4000.0	7.8	[48]
GC-MS	SPME	Serum	70.0	280.0-7700.0	6.9	[49]
GC-MS	HF-LPME	Hair	20.0	50.0-2000.0	7.1	[50]
HPLC	DLLME-SPO	Urine	2.0-8.0	10.0-3000.0	6.2-7.8	[51]
GC-NPD	HS-SPME	Hair	400.0	500-50000.0	10.0	[52]

confirm the acceptable precision of proposed HF-LPME method. Fig. 4C shows the typical chromatograms of the extracted methamphetamine from plasma sample before and after spiking with methamphetamine.

Comparison of the proposed method with other methods

Comparison of the proposed method with different existing methods for extraction and determination of methamphetamine is tabulated in Table 4.

CONCLUSIONS

The proposed three-phase HF-LPME technique is arresting enough due to its simplicity, sensitivity, selectivity, analytical precision, low organic solvent consumption, and low cost. Additionally, acceptable LODs and RSDs, and good linearity ranges enable this methodfor analysis of methamphetamine in real samples.

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