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Analysis of amantadine in biological fluids using hollow fiber-based liquid–liquid–liquid microextraction followed by corona discharge ion mobility spectrometry

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ABSTRACT

A method based on liquid–liquid–liquid microextraction combined with corona discharge ion mobility spectrometry was developed for the analysis of amantadine in human urine and plasma samples. Amantadine was extracted from alkaline aqueous sample as donor phase through a thin phase of organic solvent (*n*-dodecane) filling the pores of the hollow fiber wall and then back extracted into the organic acceptor phase (methanol) located in the lumen of the hollow fiber. All variables affecting the extraction of analyte including acceptor organic solvent type, concentration of NaOH in donor phase, ionic strength of the sample and extraction time were studied. The linear range was 20–1000 and 5–250 ng/mL for plasma and urine, respectively ($r^2 \geq 0.990$). The limits of detection were calculated to be 7.2 and 1.6 ng/mL for plasma and urine, respectively. The relative standard deviation was lower than 8.2% for both urine and plasma samples. The enrichment factors were between 45 and 54. The method was successfully applied for the analysis of amantadine in urine and plasma samples.

1. Introduction

Amantadine (1-adamantylamine) is a primary amine with aliphatic tricyclic moiety (Fig. 1) that inhibits the replication of influenza A viruses at a micromolar concentration [1–5]. Amantadine is also clinically used for the treatment of Parkinsonism [6,7], herpes zoster [8], multiple sclerosis [9,10] and hepatitis C [11,12]. The concentration of amantadine in blood plasma is individually variable, and would be influenced by renal function [5]. Amantadine is rapidly absorbed, but it is 90% excreted unchanged in the urine [13].

Due to the absence of chromophore in the amantadine molecule, it does not have distinct UV absorption or fluorescence properties [4,5]. So, many derivatization techniques coupled with GC [14–16], HPLC [4,17–22], CE [23,24] and micellar electrokinetic chromatography with laser-induced fluorescence detection [5] have been established for the analysis of amantadine in biological samples. Direct determination of amantadine by LC–MS has also been reported [3,25]. In addition, flow injection potentiometric for the analysis of amantadine has been used [2].

Before the detection of amantadine in biological matrices, different sample preparation methods such as traditional liquid–liquid extraction [16,19,26–30] and solid phase extraction [20] have been used. Conventional LLE is a time-consuming procedure and requires the use of large amounts of high-purity organic solvents, which are usually toxic. On the other hand, although SPE uses much less solvent, it still in the milliliter range.

Liquid phase microextraction (LPME) is a miniaturized solvent extraction technique [31,32] and has successfully overcome many drawbacks of conventional LLE. LPME is simple, inexpensive, and demands a few microliters of an organic solvent as it uses the minimal amount of solvent that enables extraction and enrichment of analytes in a single step. Hollow fiber-based liquid-phase microextraction (HFLPME) is one of the sampling modes of LPME [33]. Hollow fiber membrane is used to protect acceptor phase against the interference of matrices, since large molecules such as proteins, salts, acidic or basic compounds (basic compounds when extracting acidic compounds and vice versa) are prevented from entering the acceptor phase. There are two modes of HFLPME: two and three phase. In two-phase HFLPME sampling mode, the analyte is directly extracted from aqueous solution into the organic phase. In three-phase HFLPME (hollow fiber liquid–liquid–liquid microextraction; HF-LLLME), the organic phase is impregnated in the pores of the hollow fiber and sandwiched between two other phases. One aqueous phase is outside the fiber and the other phase is inside the lumen of the fiber. Since the acceptor phase is aqueous, HF-LLLME is not compatible with the detection methods such as GC and corona discharge ion mobility spectrometry (CD-IMS). Therefore, a solvent exchange step is needed. To overcome this limitation, a new concept of HF-LLLME based on using two immiscible organic solvents,

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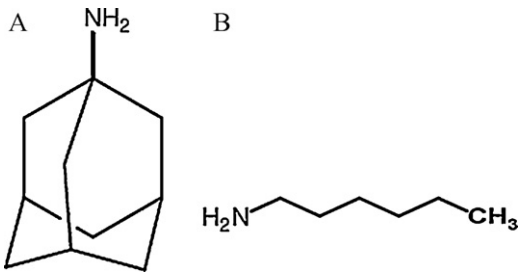

Fig. 1. Chemical structure of (A) amantadine and (B) hexylamine (internal standard).

was developed to extract analytes from aqueous samples [34]. In this method, an organic solvent is immobilized in the pores of the hollow fiber and another organic solvent present inside the lumen of the hollow fiber.

IMS is a sensitive, simple, fast and portable analytical technique for the detection of organic compounds at low concentrations. Ionization source is one of the key parts of the instrument where ^{63}Ni is a common ionization source for the IMS. Corona discharge (CD) is an alternative ionization source for IMS with several advantages relative to the ^{63}Ni. The CD is a non-radioactive source, capable of producing one order of magnitude higher current than ^{63}Ni. This results in a better sensitivity, higher signal-to-noise ratio and wider dynamic range [35].

Combination of sample preparation techniques with IMS for analysis of biological samples has not been widely investigated [36,37]. The objective of this study is the use of HF-LLLME combined with CD-IMS for the analysis of amantadine in human plasma and urine samples. In the present study, using HF-LLLME with two immiscible organic solvents, the organic acceptor phase was directly injected into the CD-IMS. Different aspects of the extraction procedure such as the kind of acceptor organic solvent, concentration of NaOH in donor phase, stirring rate, ionic strength of the sample and extraction time were investigated. Finally, the developed method was applied for the analysis of amantadine in biological samples.

2. Experimental

2.1. Chemicals and reagents

Amantadine was obtained from Amin pharmaceutical company (Isfahan, Iran). Methanol, acetonitrile (HPLC grade), hexylamine and *n*-dodecane were purchased from Merck (Darmstadt Germany). Other chemicals were of analytical reagent grade and obtained from Merck. Deionized water was prepared by OES (Overseas Equipment & Services) water purification system (OK, USA).

Q3/2 Accurel polypropylene hollow fiber membrane (with a pore size of 0.2 μm, an internal diameter of 600 μm and a wall thickness of 200 μm) was obtained from Membrana (Wuppertal, Germany).

A standard stock solution of amantadine was prepared in methanol. All working standard solutions were freshly prepared by stepwise dilution of standard stock solution with deionized water.

2.2. Instrumentation

The ion mobility spectrometer used in this work has been described previously [38]. The spectra were acquired in positive ion mode. The sample introduction system consists of a cubic shape of 60 mm × 50 mm × 25 mm dimensions. A cartridge heater, 250 W, was used for heating the port. When the sample evaporated in the injection port of the IMS, the analyte vapor was transferred into the cell using a brass tube (i.d. 3 mm and o.d. 6 mm), positioned orthogonally with respect to the corona needle. Nitrogen was used as the drift and carrier gas. In the reaction region of the IMS cell, the analyte molecules were ionized in ion-molecular exchange reactions with reactant ions. These ions were injected electronically from the ion source region into the drift region by means of an ion gate. In the drift region, ions were separated based on their mobility. The optimum experimental conditions for obtaining the ion mobility spectra of the analyte were: corona and counter electrode voltage, 10.9 and 8 kV, respectively; drift and carrier gas flow, 380 and 210 mL/min, respectively; cell and injection port temperature, 185 and 240 °C, respectively; shutter grid pulse time, 200 μs; drift filed, 533 V/cm; drift tube length, 11 cm. All IMS spectra were obtained by data acquisition software and each IMS spectrum was the average of 50 individual spectra.

2.3. HF-LLLME procedure

A 3-mL alkaline aqueous sample spiked with an appropriate amount of the analyte was introduced in a 4-mL glass vial. The porous hollow fiber was cut into 3-cm segments. The hollow fiber segments were sonicated in methanol for 5 min to remove any contaminants in the fiber, and the solvent was allowed to evaporate before use. The internal volume of the segment was 8 μL, approximately. The fiber was connected to a 25-μL HPLC syringe model 702NR (gauge 22 s and point style 3) from Hamilton (Bonaduz, Switzerland) containing organic acceptor phase (methanol). Acceptor phase also contained hexylamine (0.3 mg/L) as internal standard (Fig. 1). Hexylamine was used as internal standard to correct for variation in volume of acceptor phase. Hollow fiber was immersed into the organic solvent (*n*-dodecane) for 15 s to impregnate the pores with organic solvent. Following impregnation, the acceptor phase was introduced into the lumen of hollow fiber. To close the fiber, the other end was connected to a steel rod (0.8 mm o.d.). The excess organic solvent was removed by shaking the fiber in distilled water for 10 s. Then, the U-shaped hollow fiber (together with the syringe and the needle rod) was placed into the sample solution (donor phase). The sample solution was stirred at 1400 rpm on a magnetic stirrer (Model F60, Falc, Italy). After 20 min of extraction, the organic acceptor phase was withdrawn into the syringe, and the hollow fiber was discarded. Finally, 5 μL of the acceptor solution was injected into the CD-IMS.

Hexylamine was used as internal standard to correct for variation in volume of acceptor phase.

2.4. Real samples

2.4.1. Plasma and urine samples

Drug-free human plasma sample was obtained from the Iranian Blood Transfusion Organization (Isfahan, Iran) and kept frozen at −20 °C until analysis. Prior to use, the plasma sample was allowed to thaw at room temperature. To reduce the matrix effects, the plasma sample was diluted 4-fold before extraction.

Urine sample was collected from a healthy male adult who had not taken any medication. Urine and plasma samples were filtered through a 0.45 μm syringe filter before extraction.

2.4.2. Drug administration

The proposed method was applied to determine concentration of amantadine in plasma and urine of a 26 years old healthy male and a 28 years old healthy female volunteer, after oral administration of a 100-mg amantadine hydrochloride soft gel capsule. Blood and urine of volunteer were obtained in different times after administration. The samples were analyzed after sampling according to the procedure described above. As for the blood sample, it was centrifuged to separate plasma fraction.

Table 1
Enrichment factor, recovery factor and relative recovery in determination of amantadine in spiked plasma and urine sample.

Plasma				Urine			
Concentration (ng/mL^{-1})	Enrichment factor	Recovery factor (%)	Relative recovery (%)	Concentration (ng/mL^{-1})	Enrichment factor	Recovery factor (%)	Relative recovery (%)
20	45 (7.8)[a]	12	88.1 (7.8)	5	54 (8)	14.4	91 (8.0)
1000	53 (8.2)	14.1	83.8 (8.2)	250	46 (7.4)	11.5	93.2 (7.4)

[a] Relative standard deviation ($n = 3$).

Table 2
Concentration of amantadine found in plasma and urine samples obtained from two volunteers after oral administration of 100 mg amantadine.

	Plasma			Urine		
	Sampling time after drug-taking (h)	Concentration of amantadine (ng/mL)	RSD[a] (%)	Sampling time after drug-taking (h)	Concentration of amantadine (ng/mL)	RSD (%)
Volunteer 1 (26 years old male)	2	360	8.6	1	44	8.5
	5	253	7.8	3	114	6.8
				6	29	8.3
Volunteer 2 (28 years old female)	2	350	7.3	1	42	7.6
	5	259	5.8	3	101	9
				6	35	8.9

[a] Relative standard deviation ($n = 3$).

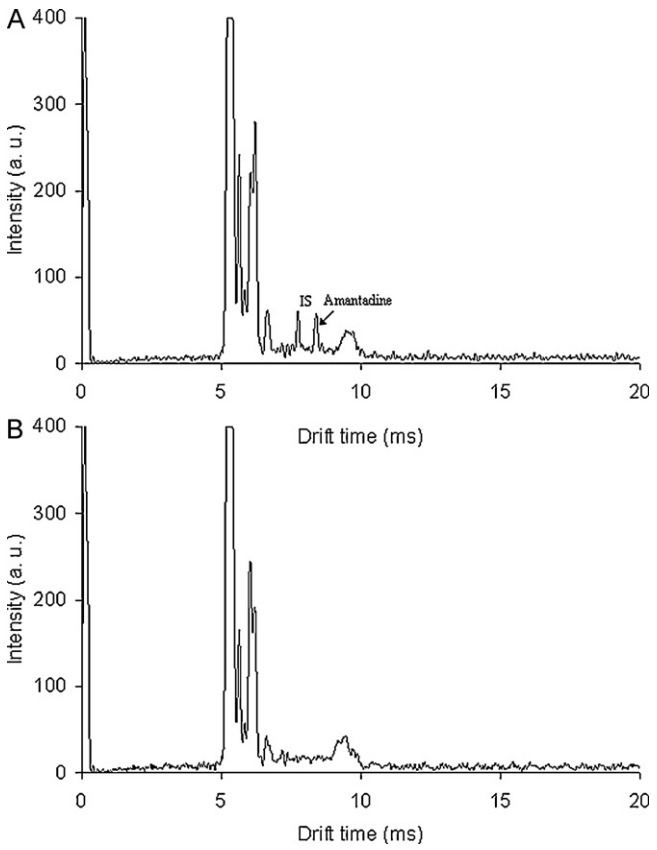

Fig. 2. (A) the ion mobility spectrum of amantadine extracted from plasma sample after 5 h from drug-taking and (B) the spectrum of extracted plasma sample before drug-taking (blank), IS (internal standard). Extraction conditions: acceptor organic solvent, methanol; donor phase, 0.05 M NaOH; stirring speed, 1400 rpm; extraction time, 20 min; salt addition, no NaCl added.

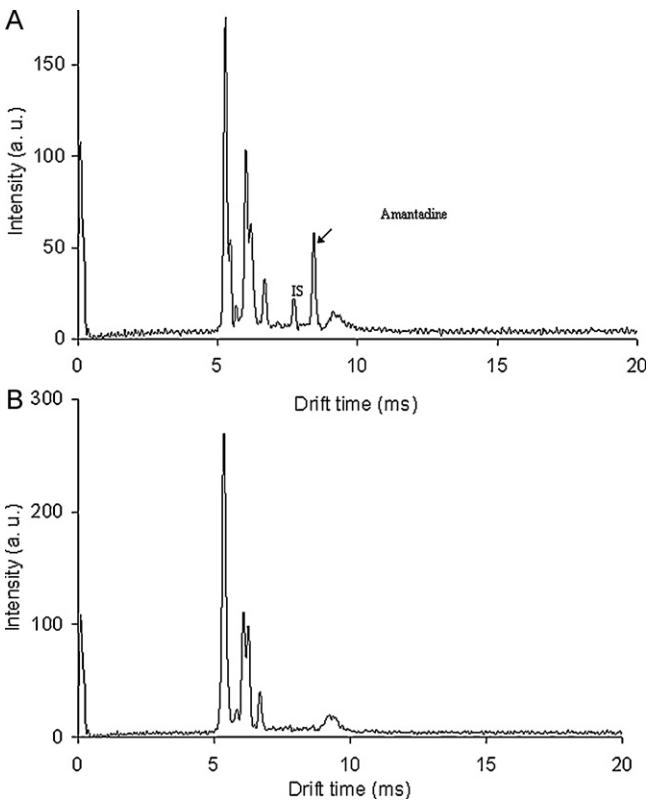

Fig. 3. (A) the ion mobility spectrum of amantadine extracted from urine sample after 3 h from drug-taking and (B) the spectrum of extracted urine sample before drug-taking (blank), IS (internal standard). Extraction conditions: acceptor organic solvent, methanol; donor phase, 0.05 M NaOH; stirring speed, 1400 rpm; extraction time, 20 min; salt addition, no NaCl added.

3. Results and discussion

3.1. HF-LLLME

In this work, amantadine was extracted from the aqueous alkaline solution (donor phase) into the organic phase which impregnated the pores of the hollow fibers and then into the acceptor organic solvent (methanol) inside the hollow fibers. After extraction, the analyte was separated and quantified by CD-IMS. Factors affecting the extraction efficiency such as choice of acceptor organic solvent, concentration of NaOH in donor phase, stirring rate, ionic strength of the sample and extraction time were studied and optimized. All experiments were performed in triplicate.

The types of two immiscible organic solvents used in HF-LLLME were important as they directly affect the extraction efficiency. Extraction solvent should be compatible with the fiber to be fixed in the pores of the fiber easily. In addition, it must be immiscible with water (donor phase) and organic acceptor phase. Therefore, selection of the extraction solvent is limited to aliphatic hydrocarbons. In this work, *n*-dodecane was used as the extraction solvent. The properties used for the selection of acceptor organic solvent are as follows. First, it must be immiscible with organic extraction solvent (*n*-dodecane). Second, it must be compatible with CD-IMS. Based on the above considerations, methanol and acetonitrile were regarded as the acceptor organic solvent. The extraction results showed that methanol could provide higher extraction efficiency (about 2.5 times more) for the target analyte than acetonitrile. Therefore, methanol was selected for further experiments.

The effect of NaCl concentration (ranging from 0% to 30%, w/v) on the extraction efficiency was investigated. Based on the experimental data, extraction efficiency of the analyte was decreased with increasing NaCl concentration. Therefore, HF-LLLME without NaCl addition was employed in further studies.

To neutralize the analyte and reduce its solubility in sample solution and increase its extractability to extraction solvent, donor phase should be alkalized. The effect of basicity of the sample on the extraction efficiency was studied by changing the sample NaOH concentration from 0.001 to 0.2 M. Maximum efficiency was obtained at 0.05 M NaOH. Higher concentrations of NaOH slightly reduced the extraction efficiency. It may be because higher concentration of NaOH increases the ionic strength of the solution.

The effect of extraction time on HF-LLLME was investigated with the time varying from 10 to 40 min. The extraction efficiency of the analyte was increased with the increasing extraction time from 10 to 30 min. However, at longer time the extraction efficiency was decreased. It may be due to solvent loss and air bubble formation. The main objective of LLLME is to achieve sufficiently high extraction efficiency for the target analytes within a relatively short time [39]. Therefore, a sample extraction time of 20 min was chosen for subsequent studies.

3.2. Validation of the method

The following conditions were selected: methanol as the acceptor organic solvent containing hexylamine (0.3 mg/L) as internal standard, porous hollow fiber (3 cm) immobilized with *n*-dodecane as the extraction solvent, 3 mL sample solution containing NaOH (0.05 M) without NaCl addition, 1400 rpm stirring rate, and 20 min extraction time.

Table 3
Comparison of analytical performance data of the present method and other techniques in the determination of amantadine in urine and plasma samples.

Extraction method	Detection system	Sample	Sample volume (mL)	Detection time (min)	Derivatization	LOD (ng/mL)	RSD (%)	Recovery (%)	Reference
LLE	GC-FID[a]	Urine	5	–	No	500	–	97	[27]
LLE	GC-ECD[b]	Plasma	2	–	Yes	10	–	–	[29]
LLE	GC-ECD	Plasma	1	15	Yes	2.3	–	90–105	[16]
LLE	LC-UV	Urine	5	–	Yes	75	6	–	[19]
SPE	LC-FL[c]	Plasma, urine	0.05	–	Yes	15		97	[20]
LLE	LC-CL[d]	Plasma	0.1	–	Yes	–		–	[30]
LLE	LC-CL	Plasma	0.05	20	Yes	–	2.9–4.8	74	[31]
LLE	CE-LIF[e]	Plasma	1	–	Yes	0.26	17	–	[41]
LLE	LC–MS	Plasma	0.2	<4	No		8.43	98.53–103.24	[3]
LLE	LC-UV	Rat plasma	0.2	<28	Yes	20	5.5	–	[4]
LLE	MEKC-LIF[f]	Plasma	0.1	6	Yes	0.5	4.8	–	[5]
HF-LLLME	CD–IMS	Plasma, urine	0.5, 0.05	1 s	No	1.4	8	87, 90.3	This method

[a] Flame ionization detection.
[b] Electron capture detection.
[c] Fluorescence.
[d] Chemiluminescence.
[e] Laser induced fluorescence.
[f] Micellar electrokinetic chromatography-laser induced fluorescence.

To determine the applicability of the proposed method in analyzing real samples and investigate the matrix effects on the determination of amantadine, the optimized HF-LLLME conditions were used for the analysis of plasma and urine samples. To study the effects of matrix components on the quantification of amantadine in plasma sample, 0.5 mL NaOH (0.3 M) was added to 2.5 mL of plasma (without protein precipitation) spiked with analyte at concentration level of 30 ng/mL. The relative recovery (RR) of the analyte was obtained from the following equation:

$$\mathrm{RR}\,(\%) = \frac{A_1 - A_2}{A_3} \times 100$$

where A_1, A_2 and A_3 are peak areas of the analyte in spiked sample extract, unspiked sample extract and spiked deionized water extract, respectively. The RR value obtained was 41% (RSD = 6.4%). In order to reduce matrix effect and increase RR, plasma sample (spiked at 30 ng/mL) was analyzed after dilution with water. The relative recoveries obtained were 79% (RSD = 5.3%) and 87% (RSD = 6.8%) for three- and four fold dilution, respectively. These data showed that extraction of diluted plasma without any sample pretreatment (e.g. protein precipitation) could lead to satisfactory results with minimum matrix interference.

Analysis of urine sample was performed without any dilution. The relative recovery obtained by the method for spiked urine sample at 30 ng/mL concentration level was 90.3% (RSD = 7.6%).

The analytical performance of the method (i.e. linearity, LOD, RSD and enrichment factor (EF)) were investigated in drug-free plasma and urine samples. The linearity of the method was determined with plasma and urine samples spiked with the analyte. The linear range were 20–1000 and 5–250 ng/mL for plasma and urine samples, respectively. The regression equations were calculated as $y = 0.097x - 0.201$ and $y = 0.101x + 0.036$ for plasma and urine, and their coefficients of determination (r^2) were above 0.990. The limits of detection (S/N = 3) were 7.2 and 1.6 for plasma and urine, respectively. The enrichment factor (EF) and recovery factor (R) were calculated using the following equations:

$$\mathrm{EF} = \frac{C_{\mathrm{AP}}}{C_{\mathrm{DP}}}$$

$$R\% = \mathrm{EF} \times \left(\frac{V_o}{V_a}\right) \times 100$$

where C_{AP} and C_{DP} are the final and initial concentrations of amantadine in the acceptor phase after HF-LLLME and donor phase, respectively. V_{o} and V_{a} are volume of organic solvent and aqueous sample, respectively. The EF and R values were calculated at the lower and upper limit of quantification (Table 1). The EF values were between 45 and 54 with the RSD lower than 8.2%.

The relative recovery obtained by the method for spiked plasma sample at 20 and 1000 ng/mL concentration level were 88.1 (RSD = 7.8%) and 83.8% (RSD = 8.2%), respectively. Spiked urine samples (at 5 and 250 ng/mL) showed RR higher than 91% (RSD < 8%).

3.3. Real sample analysis

The proposed method was applied to analyze plasma and urine samples of a 26 years old male and a 28 years old female volunteer who received oral administration of 100 mg amantadine. Plasma and urine samples were diluted 6 and 1000-fold, respectively. Quantification of amantadine in the samples was performed using single standard addition method. The concentrations of amantadine found in plasma and urine samples are presented in Table 2. The spectra obtained by CD-IMS for blood (5 h after drug-taking) and urine (3 h after drug-taking) are shown in Figs. 2 and 3, respectively. The spectra show that due to the excellent sample clean-up

capability of the method, matrix components of the samples do not interfere with the quantification process.

It is noteworthy that the reduced mobility value of amantadine ion is $1.55 \pm 0.03\ cm^2/Vs$ based on the reduced mobility of nicotinamide ($1.85\ cm^2/Vs$) [40].

4. Conclusion

The combination of HF-LLLME and CD-IMS was successfully applied to determine amantadine in human plasma and urine samples. Using an organic solvent (methanol) as acceptor phase in LLLME makes it possible to directly inject extracted solution into CD-IMS without solvent exchange. In comparison to the previously published methods for the determination of amantadine (Table 3), the proposed method shows relatively low detection limit, good precision, high recovery and efficient sample clean-up without analyte derivatization. Compared with LLE and SPE, the present method consumes less sample and organic solvent and does not need sample pretreatment steps (e.g. protein precipitation and centrifugation) for plasma analysis. In addition, the method offers a simple, fast and low cost technique for the determination of amantadine in human urine and plasma samples.

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