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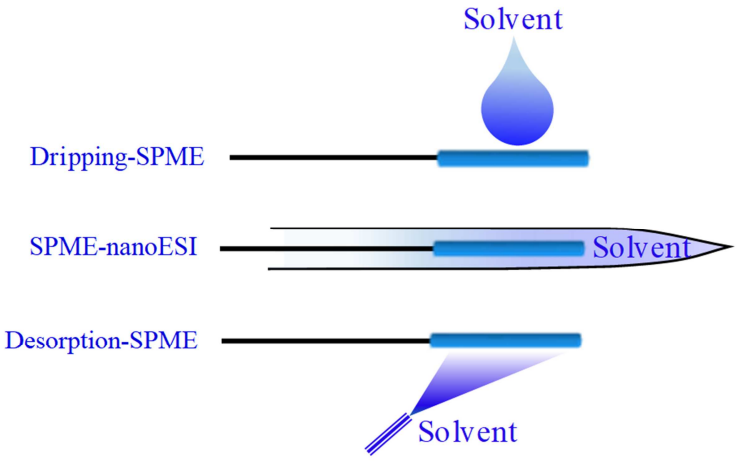
Graphic abstract



Direct Coupling of Solid Phase Microextraction with Electrospray Ionization Mass Spectrometry: A Case Study for Detection of Ketamine in Urine

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Abstract

Electrospray ionization mass spectrometry (ESI-MS) is a commonly used technique for analysis of various samples. Solid phase microextraction (SPME) is a simple and efficient technique that combines both sampling and sample preparation into one consolidated step, preconcentrating extracted analytes for ultra-sensitive analysis. Historically, SPME has been coupled with chromatography-based techniques for sample separation prior to analysis, however more recently, the chromatographic step has been omitted, with the SPME device directly coupled with the mass spectrometer. In this study, direct coupling of SPME with ESI-MS was developed, and extensively validated to quantitate ketamine from human urine, employing a practical experimental workflow and no extensive hardware modification to the equipment. Among the different fibers evaluated, SPME device coated with C_{18}/benzenesulfonic acid particles was selected for the analysis due to its good selectivity and signal response. Different approaches, including desorption spray, dripping, desorption ESI and nano-ESI were attempted for elution and ionization of the analytes extracted using the SPME fibers. The results showed that the desorption spray and nano-ESI methods offered better signal response and signal duration than the others that were evaluated. The analytical performance of the SPME-nano-ESI-MS setup was excellent, including limit of detection (LOD) of 0.0465827 ng/mL, limit of quantitation (LOQ) of 0.1 ng/mL, linear range of 0.1-500.0 ng/mL (R^2=0.9995) and recoveries of 90.8-109.4% with RSD 3.4-10.6% for three validation points at 4.0,40 and 400.0 ng/mL, far better than the performance of conventional methods. The results herein presented, demonstrated that the direct coupling of SPME fibers with ESI-MS-based systems allowed for the simple and ultra-sensitive determination of analytes from raw samples such as human urine.

1. Introduction

Mass spectrometry (MS) is a powerful tool for analytical and research purposes, and electrospray ionization (ESI) is one of the most commonly used ionization techniques in MS [1]. Conventional ESI uses a capillary for sample delivery and ionization. Development of nano-ESI– facilitates consumption of smaller volume of samples and tolerance of more complex matrices [2]. In recent years, use of solid substrates for sample delivery and ambient ionization has attracted a lot of attention [3-14]. Solid-substrate ESI-MS allows convenient sample loading and direct analysis of various forms of samples [8, 9, 12, 15-24], including viscous liquids [25], powders [26, 27], and bulky solids [28], as well as quantitative analysis [29]. Moreover, *in vivo* and real-time detection [5, 30, 31] using solid-substrate ESI-MS has been reported to provide transient and dynamic information about the metabolic processes, with minimal or negligible sample preparation. Unlike other ambient ionization techniques that typically require additional settings such as solvent spray, plasma or a laser, the assembly and operation of solid-substrate ESI-MS devices is practical and straightforward. Therefore, due to the minimal modification required to commercial mass spectrometers systems, these techniques have encouraged experts in the booming fields of proteomics, metabolomics, and molecular diagnostics to consider its applications [32].

Although solid-substrate ESI-MS allows direct analysis of samples in their original state, given that the entire raw sample is directly loaded on the substrate, severe suppression/enhancement of the signals of the target compounds can occur. Therefore, solid substrates that allow selective extraction/enrichment and ionization are ideal for improving analysis of complex matrices [7, 33, 34]. Recently, surface-modified blades [33] and wooden tips [7, 35, 36] were developed for selective and sensitive detection of analytes from mixtures using solid-substrate ESI-MS. In these studies, blades and wooden tips were modified with

specific functional groups on the surfaces and were used as solid phase microextraction (SPME) probes for sampling. SPME is a commonly used technique for sampling/sample pretreatment [37], and SPME fibers with various coating materials and various configurations have been developed and commercially available [17, 38-40]. SPME is typically coupled to MS with gas chromatography (GC-MS) [41] or liquid chromatography (LC-MS) [37, 41, 42] for detection of the extracted and enriched analytes. Detection of analytes extracted on SPME fibers directly by mass spectrometry has been also explored [43, 44], and ionization techniques such as matrix-assisted laser desorption ionization (MALDI) [45, 46], direct analysis in real-time (DART) [47-49], desorption electrospray ionization (DESI) [50], and nano-ESI [51] have been attempted. Likewise, SPME fibers have also been coupled with direct electrospray probe (DEP) that was made of copper coil [52], thermal desorption technique [48], direct infusion chamber [53], open port probe (OPP) [54], microfluidic open interface (MOI) [55] and the capillary gap sampler [56] . Unsurprisingly, the development of simple and efficient techniques for coupling of SPME fibers and ESI-MS is still an on-going field of research [17].

Conventionally, detection and quantitation of drugs-of-abuse in body fluids requires intensive sample pretreatment workflows and time-consuming chromatographic separation prior to MS analysis [57-59]. Due to the high analytical demand, development of rapid and reliable methods for analysis of drugs-of-abuse is highly desirable. Recently, we developed a wooden-tip ESI-MS (WT-ESI-MS) method [20] for direct analysis of drugs-of-abuse in urine and oral fluids [29, 60]. Our results demonstrated that WT-ESI-MS was an efficient method for rapid detection and quantitation of ketamine and its metabolite norketamine in urine and oral fluid. However, the performance of WT-ESI-MS for analysis of the drug in body fluids was not as effective as those offered—by conventional methods, mainly due to the

interferences and signal suppression during the ionization process. Therefore, by replacing the wooden tip with a SPME fiber that is capable of selectively extracting and enriching analytes, ionization and quantitation of ketamine and its metabolite are expected to be significantly improved.

In this study, we explored the direct coupling of SPME fibers with multiple ESI-MS formats (termed SPME-ESI-MS), ultimately applying this approach for the analysis of ketamine in urine, in order to validate the method and to detect ketamine excreted in urine following the intake of ketamine [61]. The SPME fibers were directly mounted onto a standard nano-ESI ion source without any hardware modification and desorption and elution solvent was introduced by a spray emitter for SPME-ESI-MS analysis, or the desorption step was preformed directly inside the nano-ESI emitter, a method similar to some of the previous studies [22-24]. Employing a C_{18}/benzenesulfonic acid (mixed-mode) coated SPME fiber, SPME-ESI-MS demonstrated better analytical performance than that of conventional methods. Furthermore, it was elucidated in this study that desorbing the fibers directly into the nano-ESI emitter prior to the ionization event resulted in the lowest LOQs and the best figures of merit out of the four formats that were evaluated. Succinctly, this study demonstrates that SPME fibers could be conveniently coupled with ESI-MS for rapid and sensitive detection of ketamine in urine samples.

2. Experimental

2.2 Reagents and materials

Ketamine and internal standard ketamine-d_4 were purchased from Alfasan (Woerden, Holland). Methanol and acetonitrile were the products of Tedia (Fairfield, OH, USA). Other chemicals were purchased from Sigma-Aldrich (St. Louis, MO, USA). For the SPME-ESI-

MS experiments, formic acid (FA) and ammonium acetate (AA) were purchased from Sigma-Aldrich (Saint Louis, MO, USA), and LC-MS grade methanol (MeOH), acetonitrile (ACN), isopropanol (IPA) and water were purchased from Fisher Scientific (Bartlesville, OK, USA). Individual working stock standard solutions were prepared in MeOH at a concentration of 100 μg/mL and stored at -80°C. SPME fibers tested in this study were kindly provided by Supelco (Bellefonte, PA, USA), with fused silica fibers coated with PDMS (polydimethylsiloxane, 100 μm), PDMS/DVB (polydimethylsiloxane/ divinylbenzene, 60 μm), and PA (polyacrylate, 85 μm) as well as Bio-SPME fibers (200 μm nitinol wire) coated with C_{18} (octadecyl, 50 μm) and mixed-mode (C_{18}/benzenesulfonic acid, coating thickness: 40 μm, coating length: 10 mm) [37, 40, 62] as the coating, respectively. The specifications of the nano-ESI emitters were as follows: coated Glasstip (1.0/0.78, o.d./i.d., mm; 4 μm tip) were obtained from New Objective Inc. (Woburn, MA, USA). Urine samples were collected from healthy volunteers. A urine sample spiked with 1.0 μg/mL ketamine was used to optimize the analytical procedures. Pure water used in this study was produced by the Milli-Q water-purification system (Milford, MA, USA).

2.2 Mass spectrometry

The qualitative analysis of ketamine was carried on a Q-TOF2 mass spectrometer (Waters, Milford, MA, USA), while the quantitative data were acquired with multiple reaction monitoring (MRM) mode on a triple quadrupole mass spectrometer (MS) (Waters Quattro Ultima, Milford, MA, USA). A 3.5 kV high voltage was applied onto the SPME fibers to initiate the ESI event; Cone voltage was 30 V; Source temperature was set to 80 °C. For the MRM experiments, ion pairs *m/z* 238 > 125 and *m/z* 242 > 129, for ketamine and d_4-ketamine (internal standard), respectively, were chosen and the peak heights were used for the quantitation, similar to those in the previous study [29]. The collision energy was 25 eV, and

the dwell time was set at 0.2 second. For the SPME-nano-ESI experiments, the quantitative data was acquired in the MRM mode on a Thermo Scientific TSQ Vantage triple quadrupole MS (San Jose, CA, USA). A 1.3 kV voltage was applied to initiate ionization, and was maintained for 10s. The same ion pairs stated above were used, and the MS dwell time was fixed at 0.1s. Data processing on the TSQ Vantage was done using Thermo Scientific Trace Finder v4.1 (San Jose, CA, USA).

2.3 SPME-ESI-MS

The whole analytical procedure of SPME-ESI-MS analysis can be divided in 4 basic steps, including cleaning/conditioning (Figure 1a), sampling/extraction (Figure 1b), washing (Figure 1c), and elution/ionization (Figure 2). Briefly speaking, the SPME fibers were immersed into 1 mL solvent (water/methanol, 1/1, v/v) for 5 min with vortex to remove background compounds and condition the solid phase coating. Then, the SPME fiber (with the whole 10 mm coating part) was immersed into 300 μL of urine sample (1.0 ml of Eppendorf tube) and vortex for 10 minutes (speed: ~1500 rpm). Subsequently, the fiber was rinsed by pure water for 50 seconds before the SPME fiber was mounted onto the nano-ESI ion source for detection (Figure 2).

As shown in Figure 2, the setup of SPME-ESI-MS was simple and convenient, without any hardware modification. SPME fibers were mounted onto a commercial nano-ESI ion source (Waters, Milford, MA, USA) by an inner screw and with the aid of a conductive elastomer, similar to the setup of nano-ESI needles for nano-ESI analysis. SPME fiber's direction and distance from the MS inlet could be readily adjusted by using the settings of the nano-ESI ion source. Four different approaches: desorption spray, dripping, desorption electrospray ionization (DESI), and direct insertion of the SPME fiber into the nano-ESI emitter filled

with desorption solvent were attempted for desorption and ionization of the extracted analytes in this study. As shown in Figure 2a, in the desorption spray approach, a high voltage was applied directly onto the SPME fiber, and desorption solvent (water/methanol/formic acid, 1/1/0.001, v/v/v) was sprayed onto the SPME fiber. As shown in Figure 2, the vertical distance (d1) and horizontal distance (d2) between the SPME fiber and MS inlet was 6 mm, respectively; the spray emitter was placed on the side of the SPME fiber with an optimized distance (d3) and angle of 3 mm and 45°, respectively. The flow rate of desorption solvent was 5 μL/min and the nitrogen gas pressure rate was 10 psi. In the dripping approach (see Figure 2b), desorption solvent was directly dripped onto the SPME fiber by a pipette. In the DESI approach (see Figure 2c), all the settings were identical with those of the desorption spray approach, except that the high voltage was applied onto the spray emitter instead of the SPME fiber. In the SPME-ESI-MS, the mass spectra were obtained by averaging the data acquired in 2 minutes in desorption spray and DESI mode, while the duration in dropping mode is ~10 seconds. In the nano-ESI approach (Figure 2d), the fiber was placed directly inside the nano-ESI emitter that was pre-filled with 4 μL of 95:5 MeOH: H_2O (0.1 % formic acid, 12 mM ammonium acetate). The nano-ESI emitter was placed 3 mm back from the center of the MS inlet, and the desorption was performed for 3 minutes. Following the desorption, a 1.3 kV high voltage was applied to the nano-ESI emitter, initiating a spray event with a flow rate of *ca.* 0.2 μL/min. In this study, a 10 sec of duration time was recorded for rapid detection of the analyte.

3. Results and Discussion

3.1 Optimization of SPME-ESI-MS

Figure 3a is a typical ESI-MS spectrum of ketamine obtained by SPME-ESI-MS analysis of 1 μg/mL ketamine aqueous solution with the dripping method. Ketamine was observed as the

protonated molecule at *m/z* 238 in the spectrum. In this study, a urine sample spiked with 1 μg/mL ketamine was used to optimize the conditions and establish the analytical protocol. Different types of SPME fibers and various experimental settings were attempted and their influences to the ketamine signals were investigated and evaluated.

As shown in Figure 3b, GC-based fibers (PDMS, PDMS/DVB and PA) provided low signal intensities for ketamine in urine, which was believed to be mainly caused by the nonpolar properties of the coating materials that might not effectively extract ketamine from the urine samples. It was found that electrospray plume was difficult to generate from these tips even if a higher voltage (e.g., 4.5 kV) was applied. LC-based SPME fibers (C18 and mixed-mode) used an electrically conductive material as a support (i.e., nickel-titanium metal alloy), facilitating generation of electrospray and thus good detection of ketamine signals from the fibers. Higher ketamine signals were obtained using the mixed-mode fiber in comparison to the C18 one, due to higher extraction efficiency of this coating. Indeed, the mixed-mode fiber contained C18 and benzenesulfonic acid on the fiber surface and could have both hydrophobic and ion-dipole interactions with ketamine that contains phenyl and amide groups (inset of Figure 3a). Consequently, further experiments were performed using the mix-mode fiber in this study.

Four approaches, i.e., desorption spray, dripping, DESI, and nano-ESI, as described in the Experimental Section, were attempted for desorption and ionization of the analytes extracted on the SPME fibers. For the dripping approach that could be conveniently used, the solvent was added manually using a pipette and typically only a limited volume (typically 1.0 μL) of solvent could be held by the fiber for analyte elution and ionization, leading to poorer signal intensities and duration. For the DESI approach, charged droplets were generated and sprayed

onto the surface of the SPME fiber for the elution and ionization of the retained analytes; the results revealed that the desorption and ionization efficiency was quite low with this approach [63]. In the desorption spray approach, the solvent was sprayed onto the SPME fiber surface in a continuous and uniform manner, which provided sufficient solvent volume and duration for analyte elution, and the high voltage was directly applied onto the fiber to more efficiently induce spray ionization, leading to good signal response and signal duration. Finally, in the nano-ESI approach, the fiber was desorbed into an small volume of solvent (~4 μL), resulting in extremely high sensitivity and low background noise, as listed in Table S1. Coupled with the spray stability, nano-ESI was deemed to be the best approach and was thus employed for subsequent quantitative analysis.

Extraction time, washing time as well as elution and ionization solvent were also optimized for SPME-ESI-MS analysis of ketamine in urine using the mixed-mode fiber. As shown in Figures 4 a and b, the extraction was found to reach equilibrium at 10 minutes, and the optimal washing time was determined as 50 seconds with water as the washing solvent for removing polar interference compounds (Figure S1). Various solvents were attempted to elute and ionize the ketamine analyte retained on the SPME fiber, and water/methanol/formic acid (1/1/0.001, v/v/v) was found to be the most efficient one as indicated by the ketamine signals detected using the desorption spray mode. In the nano-ESI experiments, prior experiments and publications have deemed that 95:5 MeOH: H_2O + 0.1% FA & 12 mM AA was the optimal spray solvent for quantitative analysis of small molecule pharmaceuticals [51]. For this reason, this solvent composition was chosen for the respective analysis.

3.2 Performance for analysis of ketamine in urine using SPME-ESI-MS

Figure 5a is a spectrum obtained by analyzing a urine sample spiked with 100 ng/mL ketamine with SPME-ESI-MS using the optimized conditions as shown above. Protonated molecule of ketamine (*m/z* 238), confirmed by MS/MS spectrum (Figure 5b),[10] was predominately observed in the spectrum with very few interference signals such as the peak at *m/z* 114 ([Creatinine+H]$^+$). In our experiments, the target analyte was selectively enriched by the SPME fiber, and loosely attached matrix components were removed during the washing process. Furthermore, the use of nanoESI allowed reduced ion signal suppression. The above results indicated that the SPME-ESI-MS protocol could efficiently enrich ketamine in urine, significantly reduce matrix effect, and enhance the signal of ketamine.

The limit of detection (LOD) and limit of quantitation (LOQ) of the SPME-nano-ESI format for analysis of ketamine in urine were measured. The signal/noise ratio (S/N) was obtained by comparing the intensity of the "spiked" sample to that of the "blank" one (Figure S3), i.e., $(I_{analyte}/I_{IS})_{spiked}/(I_{analyte}/I_{IS})_{blank}$, where $I_{analyte}$ and I_{IS} were the MRM chromatogram intensities (peak areas) of analyte and internal standard (i.e., d_4-ketamine), respectively, and the subscripts "blank" and "spiked" represented the samples spiked with the internal standard only and spiked with both analyte and internal standard, respectively. As shown in Table 1, the LOD (S/N$\geqslant$3) and LOQ (S/N$\geqslant$10) of the present method for detection of ketamine in urine were ~0.027 ng/mL and 0.1 ng/mL, respectively. Since the lowest calibration point (0.1 ng/mL) generated a S/N of ~10.8, the LOD was approximated. No tailing was observed for the technique since no signals were detected when the high voltage was not being applied. As shown in Figure S2, the signals was observed only between 0.1 and 0.3 min with the application of the high voltage. These results determined that the LOD and LOQ of SPME-nano-ESI-MS for detection of ketamine in urine could be at least 2000 folds better than those obtained with WT-ESI-MS (LOD of 20 ng/mL and LOQ of 50 ng/mL) [29] and far better

than those obtained with most conventional methods (LOD of 0.5-25 ng/mL and LOQ of 1.5-50 ng/mL for using GC-MS [64, 65], and LOD of 0.03-5 ng/mL and LOQ of 0.1-3.17 ng/mL for using LC-MS [66-68]).

The calibration curve for quantitation was constructed with ten sets of experimental data. Each set of data was obtained by detecting triplicate samples containing different levels of the analyte (0.1, 0.5, 1.0, 2.5, 5.0, 25.0, 50.0, 100.0, 250.0 and 500.0 ng/mL) and a fixed amount of internal standard (20.0 ng/mL). As shown in Figure 6, excellent linearity (R^2=0.9995) was obtained over the concentration range from 0.1 to 500.0 ng/mL. The implementation of the internal standard effectively compensated the deviations during the extraction/desorption/ionization processes and enabled such an excellent linearity. Such low concentration could not be achieved for quantitation with other SPME-ESI-MS, WT-ESI-MS or conventional methods [64-68].

The precision and accuracy of the SPME-ESI-MS approach were evaluated by quantitation of ketamine in urine samples spiked with ketamine of low, middle and high concentrations. Each sample was analyzed three times and the data were averaged for comparison. Recoveries of SPME process was determined by spiking samples of different concentrations (i.e., 4, 40, and 400 ng/mL), i.e., $(I_{analyte}/I_{IS})_{spiked}/(I_{analyte}/I_{IS})_{calculation}$, where $I_{analyte}$ and I_{IS} were the MRM chromatogram intensities of ketamine and d_4-ketamine, respectively; and the subscripts “spiked” and “calculation” represented the experimental value of the spiked samples (i.e., 4, 40, and 400 ng/mL) and back-calculation using the line of best fit from the calibration curve in Figure 5. For 4.0, 40 and 400.0 ng/mL spiked samples, the recoveries were in the range of 90.8-109.4 % with RSD 3.4-10.6 % (n=3) (Table 2). The figures of merit for the accuracy and precision using the nano-ESI technique revealed that the accuracy and

precision obtained were acceptable for bioanalytical sample analysis. This technique is applicable for analysis of different urine samples containing different levels of matrix, since the selective extraction of the SPME fibre allows effective removal of matrix and the use of an internal standard can correct the deviations from the samples and the analysis.

The entire extraction and desorption procedure for SPME-nano-ESI-MS took approximately 13 minutes to analyze one fiber, and this could be greatly reduced using high-throughput extraction protocols or a more comprehensive automated nano-ESI interface [69]. This analysis time is much shorter than the analysis time of several hours per sample required with the conventional methods. Another notable feature of SPME fibers is their re-usability. Our experimental results showed that a SPME fiber could be reused over 200 times with no obvious degradation of performance. This allows much reduced costs and good reproducibility of results since the same fiber can be used for the experiments.

4. Conclusions

Direct coupling of SPME with ESI-MS has been developed in this study. The setup of SPME-ESI-MS was optimized, and SPME fibers placed directly inside the nano-ESI emitter was employed to provide stable and sensitive analytical signal of attained analytes. Such direct coupling avoids chromatographic separation, makes use of the rapid and selective extraction capability of SPME, and integrates with nanoESI-MS that has good ionization efficiency and tolerance to ion suppression. We demonstrated that SPME-nano-ESI-MS could provide analytical performance much better than most conventional methods, with minimal compromise in terms of total analysis time. These results indicated that SPME-ESI-MS could be a simple and efficient method for rapid, sensitive and selective detection of analytes in mixture samples. Given the popularity of both SPME and ESI-MS, as well as the

easy setup of the coupling technique, SPME-ESI-MS is expected to have great potentials for sample analysis in various areas.

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Table 1. Response of ketamine at low concentrations in urine as detected by SPME-ESI-MS

Spiked ketamine (ng/mL)	Signal-to-noise
0.1	10.8
0.5	52.4
1.0	87.7
2.5	216.7
5.0	420.6

Table 2. Precision and accuracy for detection of ketamine in urine by SPME-ESI-MS

Spiked ketamine (ng/mL)	Accuracy (n=3), %	Precision (n=3), %
4.0	90.8	8.1
40.0	109.4	3.4
400.0	104.8	10.6

Figure captions

Figure 1. Procedures for SPME sampling: (a) cleaning/conditioning, (b) sampling/extraction, (c) washing.

Figure 2. Schematic diagram of SPME-ESI-MS with different settings for applying elution and ionization solvent: (a) desorption spray (with a top view photo), (b) dripping, (c) DESI, (d) nanoESI.

Figure 3. (a) Mass spectra obtained by analysis of 1 μg/mL ketamine aqueous solution with SPME-ESI-MS; (b) Effects of different SPME fibers for detection of ketamine.

Figure 4. Effects of various factors on SPME-ESI-MS signal of ketamine: (a) extraction time, (b) washing time. Each data point was the average of three individual measurements, where the error bar represented the standard deviation.

Figure 5. (a) Mass spectra obtained by analysis of a urine sample spiked with 100 ng/mL ketamine using SPME-ESI-MS under optimized conditions, (b) MS/MS spectrum of ion at *m/z* 238.

Figure 6. Quantitative analysis of ketamine in human urine. Blue markers represent calibration points, and orange markers represent validation points. The following extraction parameters were used: 10 min extraction time, 1500 rpm orbital agitation, and room temperature. Each data point was the average of three individual measurements (n=3), where the error bar depicts the standard deviation.

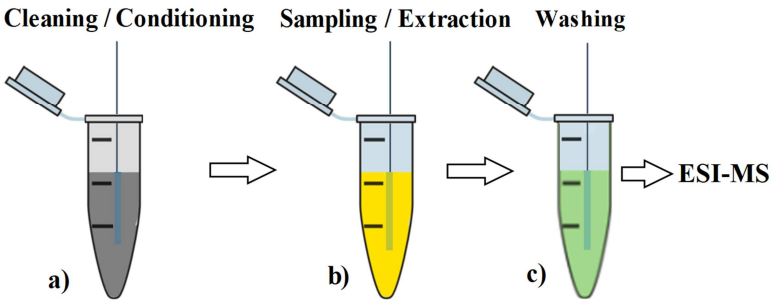


Figure 1

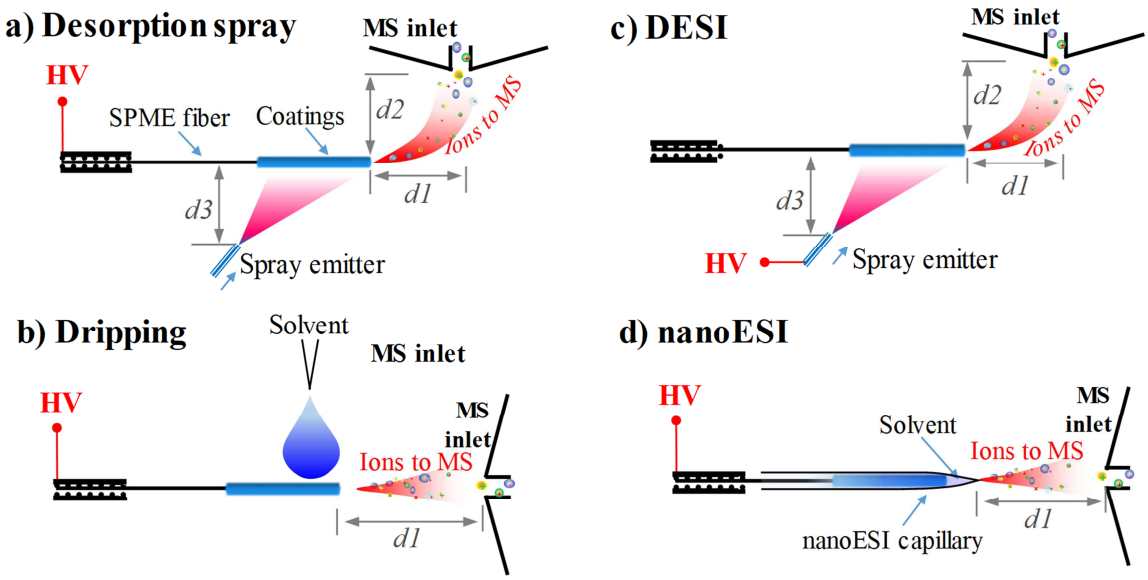


Figure 2

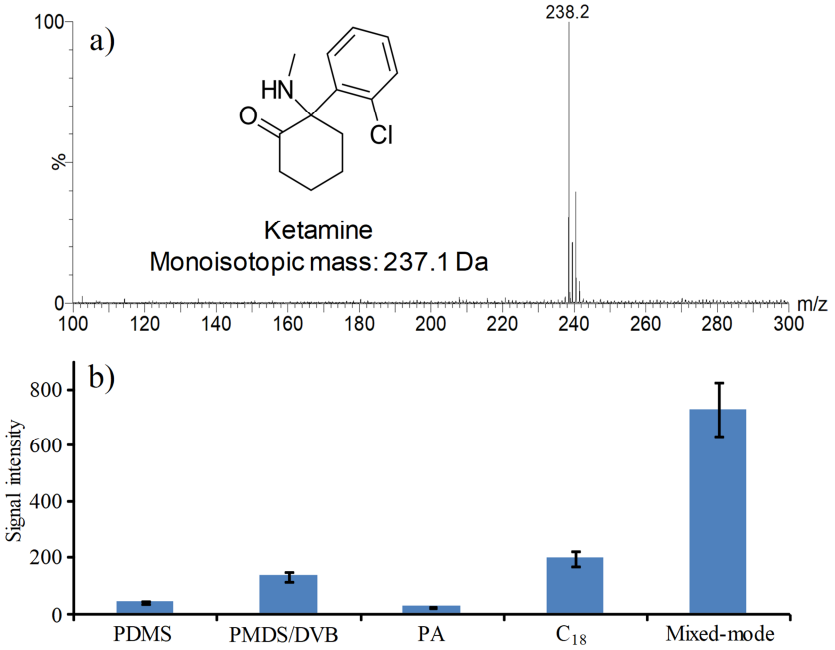


Figure 3

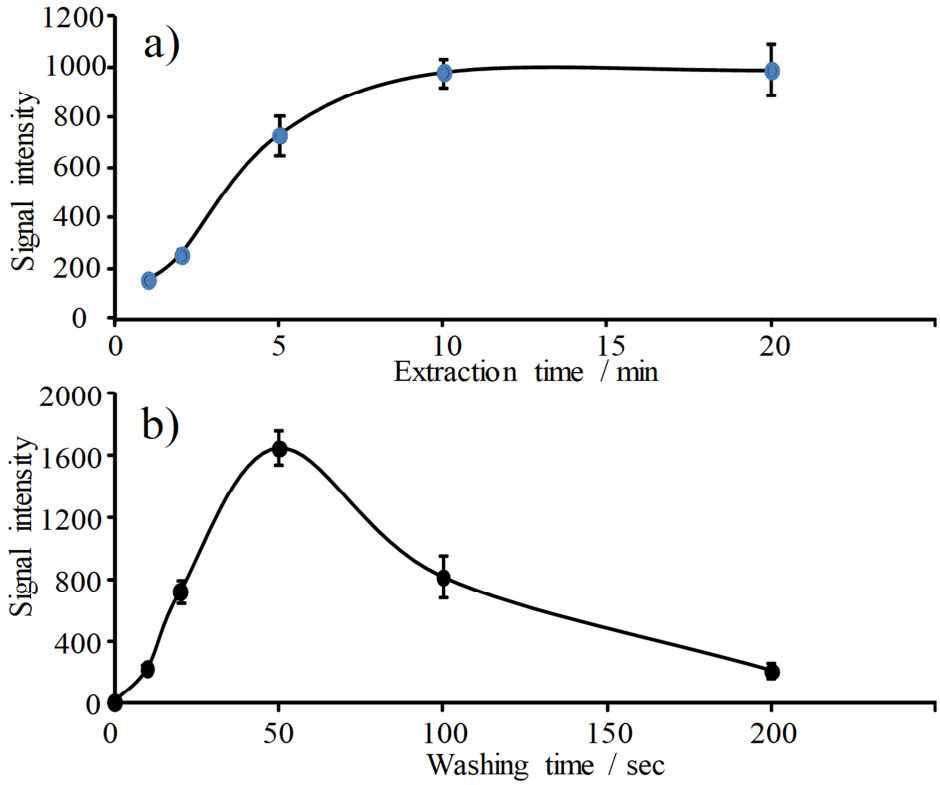


Figure 4

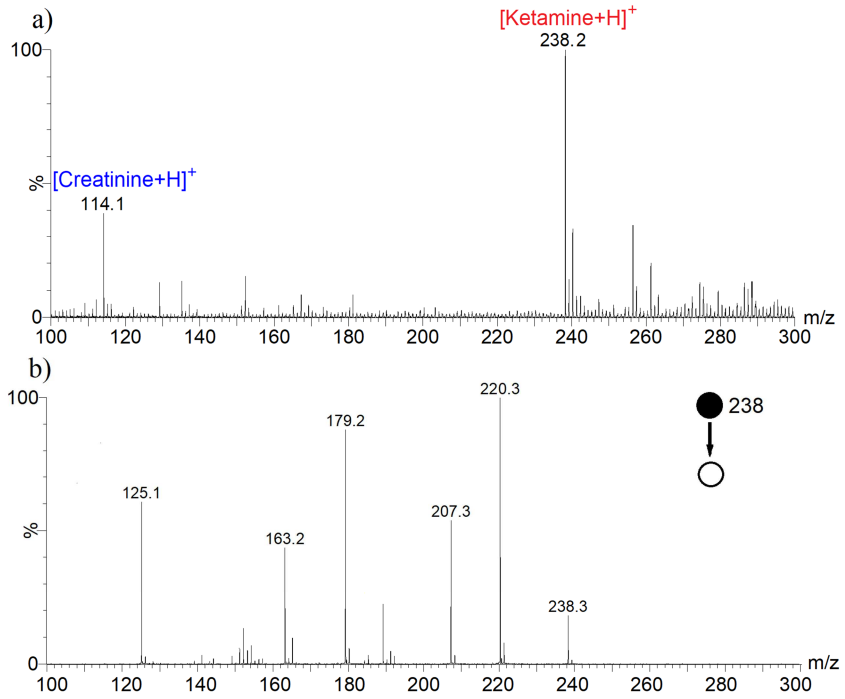


Figure 5

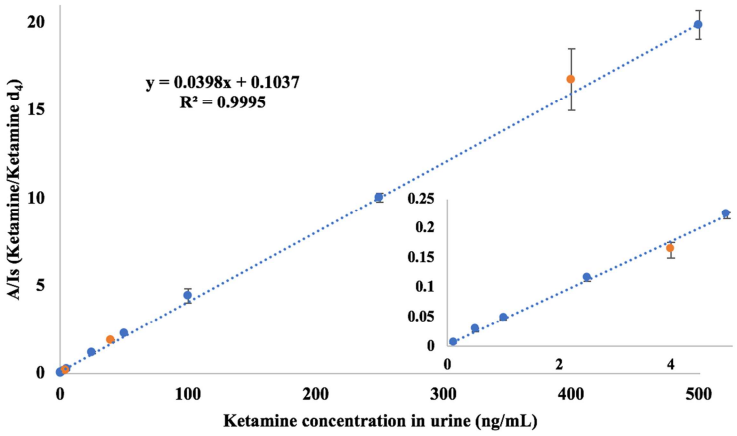
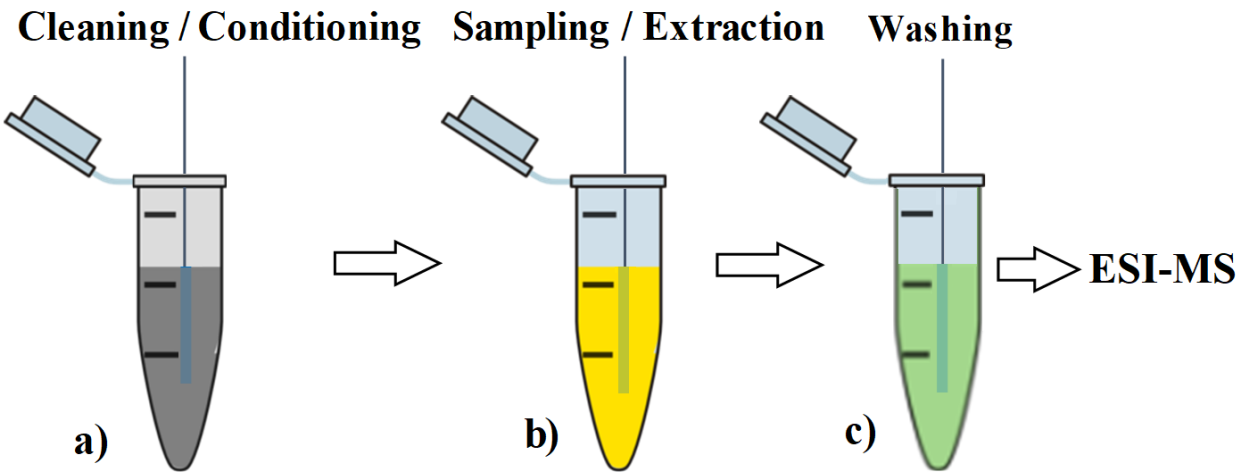
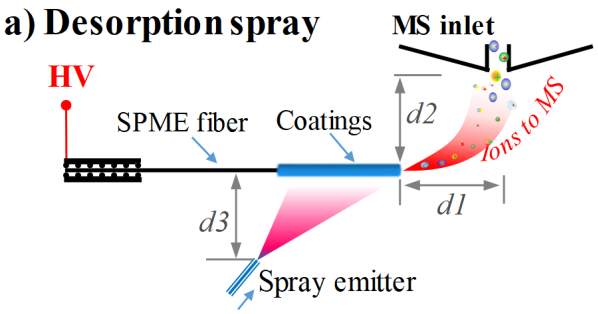
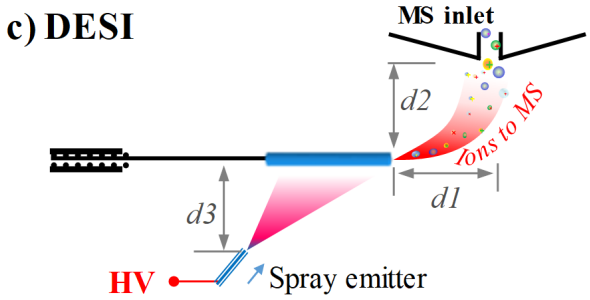
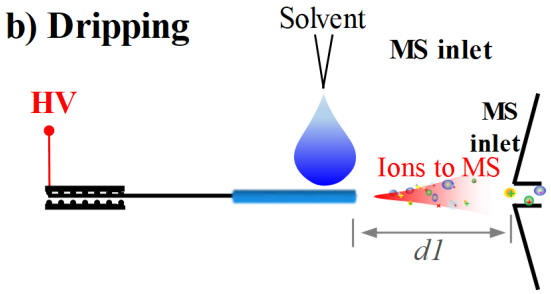


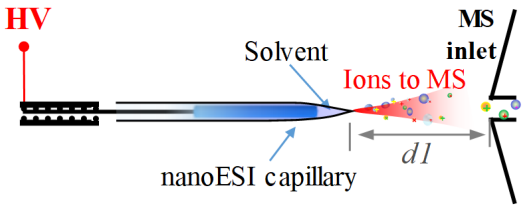
Figure 6

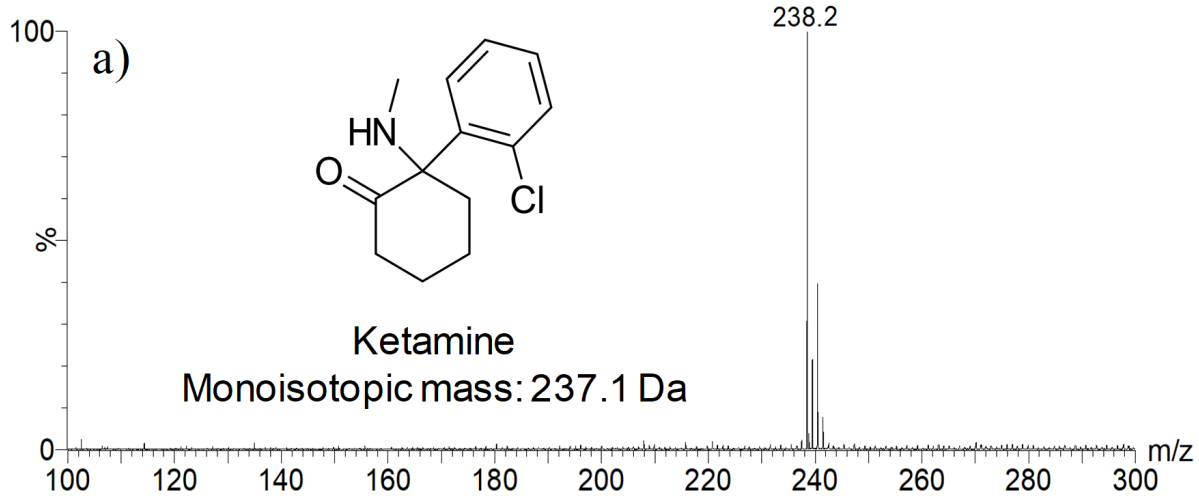


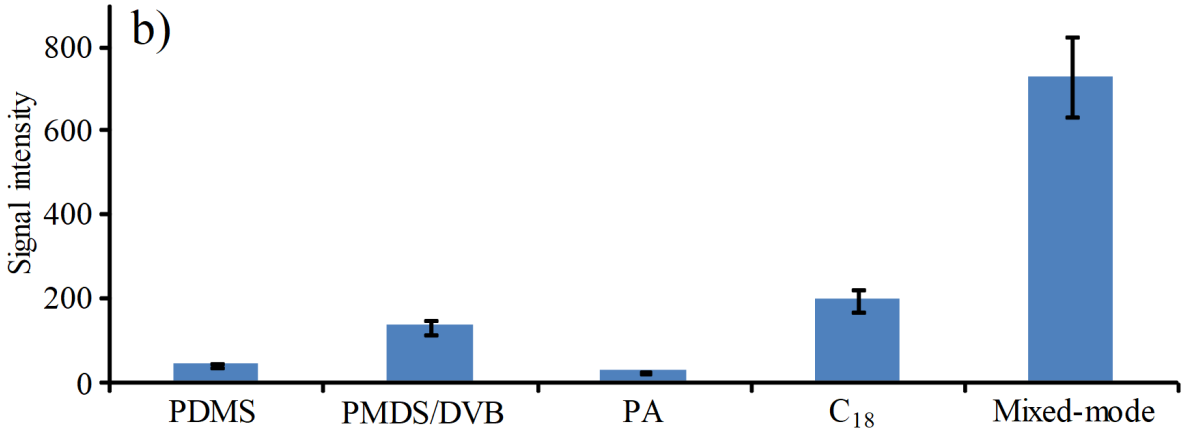


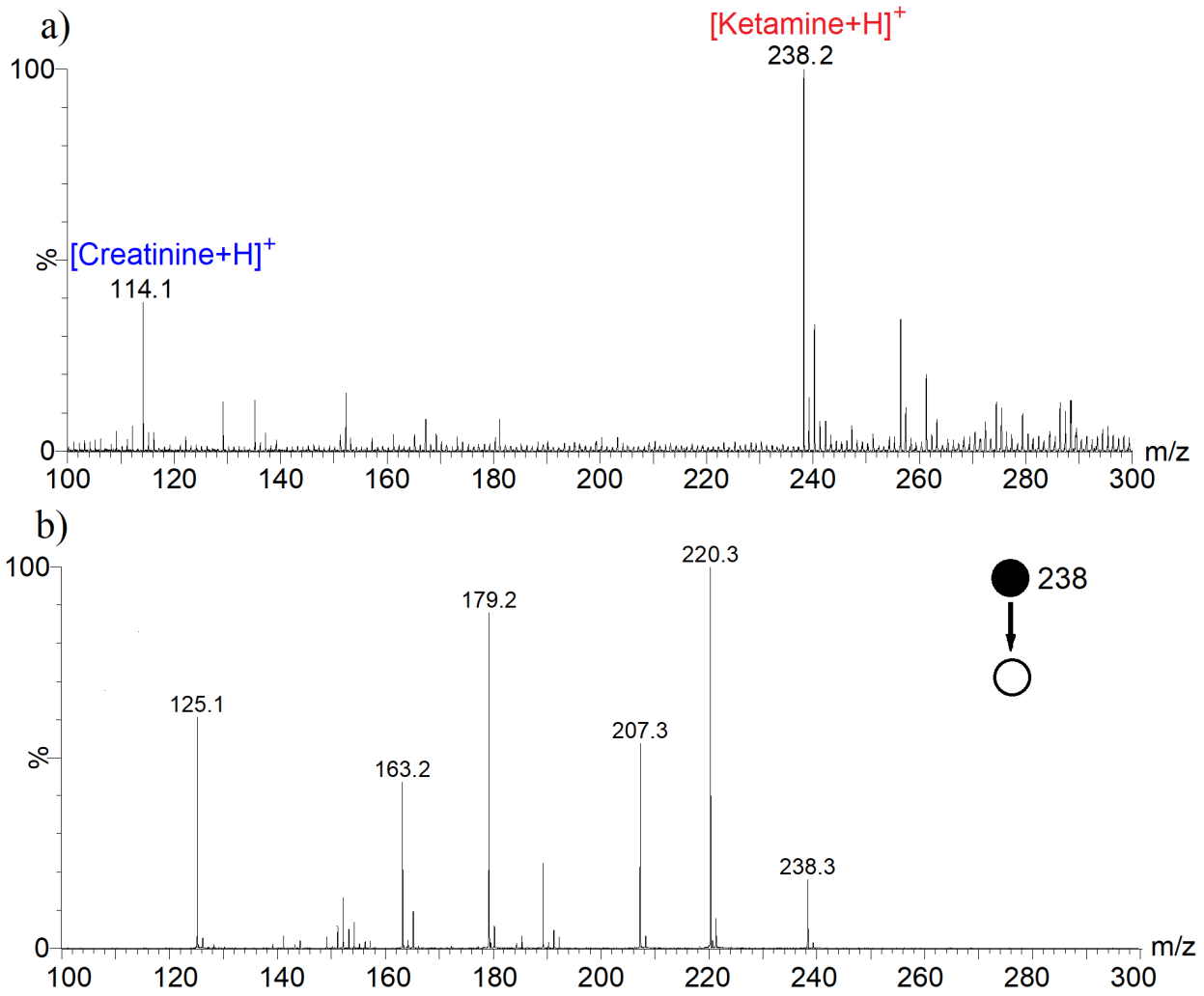







a)
100
%
0
238.2
HN
O
Cl
Ketamine
Monoisotopic mass: 237.1 Da
100
120
140
160
180
200
220
240
260
280
300
m/z


b)
Signal intensity
800
600
400
200
0
PDMS
PMDS/DVB
PA
C18
Mixed-mode


a)
[Ketamine+H]+
238.2
100
%
[Creatinine+H]+
114.1
0
m/z
100
120
140
160
180
200
220
240
260
280
300
b)
100
220.3
238
179.2
125.1
207.3
163.2
%
238.3
0
m/z
100
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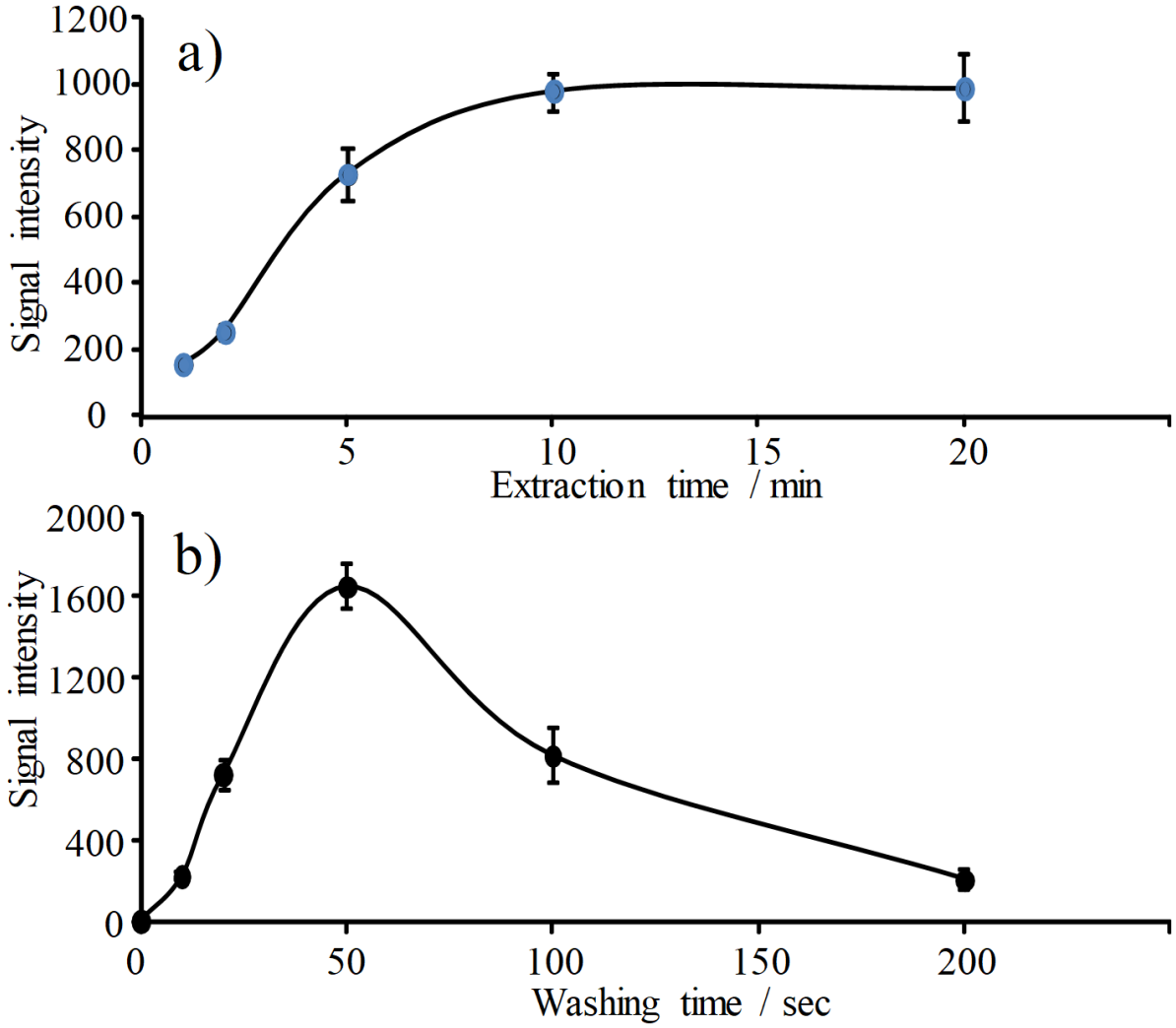
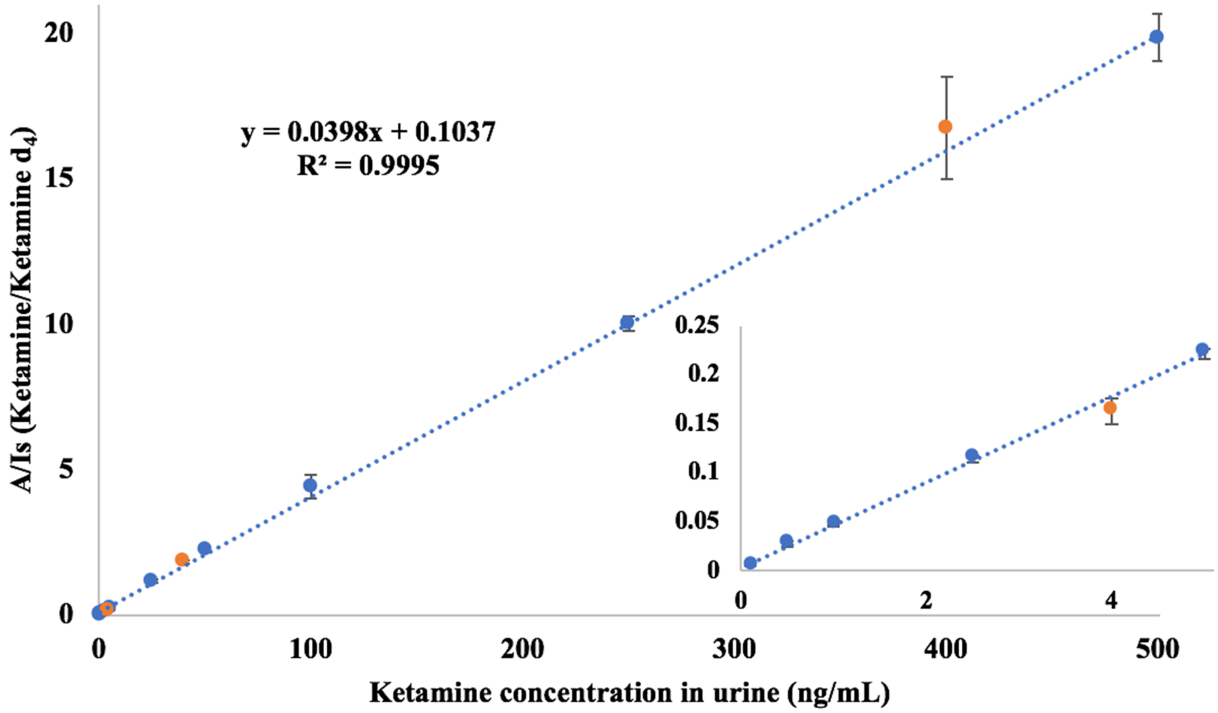

a)
Signal intensity
1200
1000
800
600
400
200
0
0
5
10
15
20
Extraction time / min
b)
Signal intensity
2000
1600
1200
800
400
0
0
50
100
150
200
Washing time / sec



Highlights

- Direct coupling of SPME with ESI-MS
- Rapid detection of ketamine in urine
- Comparison of different methods, i.e., desorption spray, dripping, DESI and nano-ESI, for the coupling
- Much improved analytical performances obtained by SPME-nano-ESI-MS