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Review

Application of gas chromatography–surface ionization organic mass spectrometry to forensic toxicology

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Abstract

Surface ionization (SI), which consists in the formation of positive and negative ions along the course of thermal desorption of particles from a solid surface, was first applied as a detector for gas chromatography (GC), GC-surface ionization detection (SID); we developed many new sensitive methods for the determination of abused and other drugs by GC-SID. Recently, Fujii has devised a combination of SI and a quadrupole mass spectrometer and named this system a surface ionization organic mass spectrometer (SIOMS), which is highly selective and sensitive for organic compounds containing tertiary amino groups. We have tried to apply this mass spectrometer to forensic toxicological study; so far we have succeeded in determining important drugs-of-abuse and toxic compounds, such as phencyclidine (PCP), pethidine, pentazocine, MPTP and its derivatives from human body fluids with high sensitivity and selectivity. In this review, we describe our recent studies on the application of GC–SIOMS to forensic toxicology.

Keywords: Reviews; Forensic toxicology; Surface ionization; Phencyclidine; Pethidine; Pentazocine

Contents

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1. Introduction

Surface ionization (SI) consists in the formation of positive and negative ions along the course of thermal desorption of particles from a solid surface. In 1923, Kingdon and Langmuir first discovered SI; they observed the desorption of positive caesium ions from the surface of a heated W filament [1,2]. They also showed that SI could be interpreted by use of the Saha–Langmuir equation [3]. This equation is expressed by

$$n_+/n_o = g_+/g_o \exp\{(\phi - \mathrm{IE})/kT\}$$

where n_+/n_o is the ratio of positive ions to neutral species, ϕ is the work function of the surface where ionization occurs at temperature T, k is the Boltzmann constant, and IE is the ionization energy of the emitting chemical species; g_+/g_o represents the ratio of the statistical weights of the ions and the neutral species. Zandberg and co-workers observed the ion desorption of specific organic compounds [4] and they proved experimentally that the Saha–Langmuir equation would be applicable for the ionization of some organic compounds [5,6]. They established the general mechanism and peculiarities of SI for many organic and bioorganic molecules [7,8]. Fujii in Japan also performed studies on the SI of organic compounds [9–11]; he has discussed extensively about the principles and mechanisms of SI [12,13].

According to the Saha–Langmuir equation, the degree of ionization depends on a maximum value of work function. For the application of SI to detectors, it thus should be necessary to choose the metal surface that has the highest work function possible. Zandberg et al. made the first attempt to choose an efficient emitter suitable for organic compounds [14]. Different refractory metals like W, Mo, Ni, Re, Pt and Ir, and their oxides were studied [4,8,12,15,16]. Davis showed that oxygen in about 10^{-5} Torr increased the work function of a Re filament to about 7.2 eV [17,18]; Greaves and Stickney [19] suggested that oxidized Re would be better than oxidized W or Mo. Fujii, based on the above findings and his experiments, concluded that oxidized Re seemed the best emitter material because of its higher work function [16]. Zandberg et al. disagreed with Fujii's conclusion; they claimed that the surface of oxidized Re would be unstable and ''poisoned'' due to carbonization and/or the adsorption of organic molecules on the surface [8,14]. In the following sections, a brief discussion of the issue of which metal would be the best emitter under atmospheric condition or in a vacuum is given.

Fujii and Arimoto have developed a detector for gas chromatography (GC)-surface ionization detector (SID) [20,21] and a GC–surface ionization organic mass spectrometer (SIOMS) [9,22–24] based on this phenomenon; these instruments are very sensitive and specific for a lot of compounds containing tertiary amino groups. We have applied them for the sensitive detection and determination of drugs-of-abuse and toxic compounds containing tertiary amino groups.

In this review, we mainly describe our application of GC–SIOMS to forensic toxicology, after an overview of our previous work and other groups' studies. We also show examples of its highly sensitive detection and specific identification for medicolegally important drugs.

2. Application of gas chromatography-surface ionization detection (GC-SID) to forensic toxicology

As stated in the previous section, Fujii and Arimoto applied SI as a detector for GC, that is, GC-SID [20,21]. Fig. 1 shows the scheme of the SID system. The platinum emitter is positioned between the quartz nozzle and the collector electrode; it is heated to about 1200 °C. The ring electrode around the quartz nozzle is held at a positive potential of +200 V; the emitter and the ion collector are held at a negative potential of −200 V vs. the ring electrode.

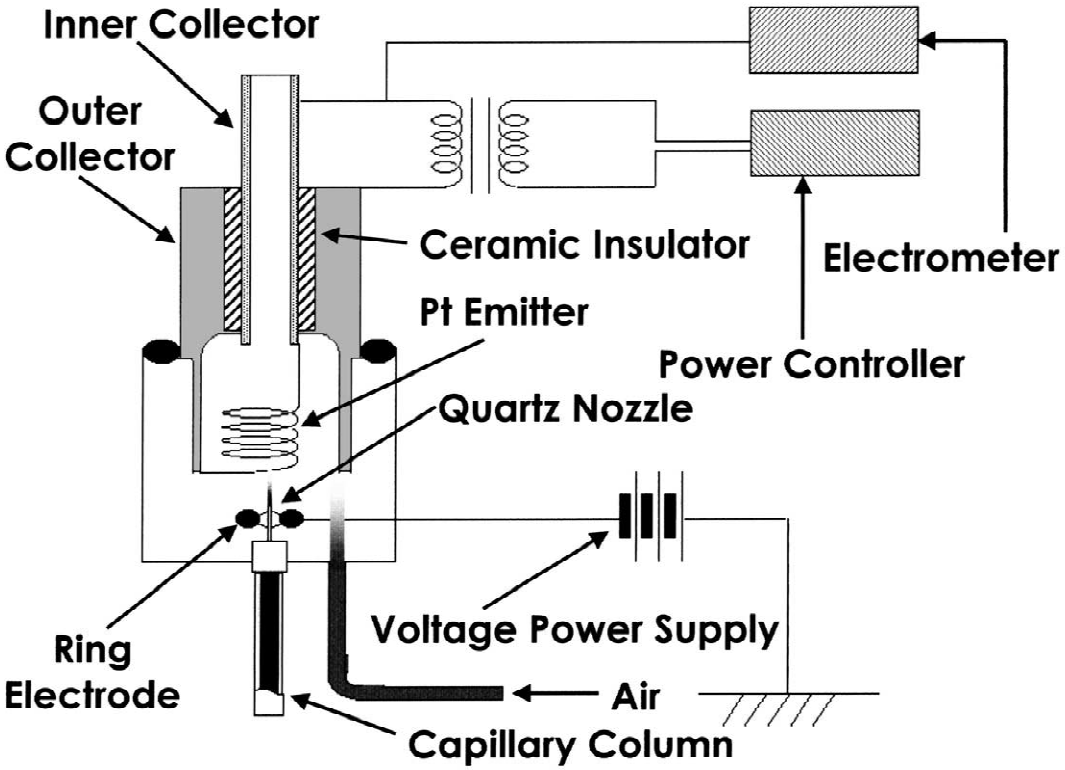

Fig. 1. Schematic representation of the GC-SID system. The figure is from Ref. [20] with slight modification. Reprinted with permission (©1985 American Chemical Society).

The emitter is 10-turn coiled platinum; platinum was chosen as an emitter material because it has a higher work function (5.65 V), and heated platinum is quite stable under atmospheric conditions [20]. In this system, tertiary amino compounds are selectively ionized on the emitter; the sensitivities for those compounds by GC-SID are about 10 to 100 times higher compared with those by the conventional GC-nitrogen-phosphorus detection (NPD).

Our group applied the GC-SID to the analyses of drugs and compounds of forensic toxicological interest. In our previous review, the applications of GC-SID to forensic toxicology were described [25]. After this review, we have succeeded in determining many drugs-of-abuse, such as cocaine [26,27], phencyclidine (PCP) [28,29], codeine [30], dimethyltryptamine [31] and trihexyphenidyl [32] in human body fluids; new methods using GC-SID for other miscellaneous drugs have also been developed [33–36].

Zandberg's group also developed a surface ionization detector for GC in the late 1970s [37,38]. Later they used monocrystalline Mo doped with Ir as the emitter that was heated indirectly [39] (Fig. 2); they proposed that this would be the best emitter under atmospheric conditions. They detected tertiary and quaternary amines such as tripropylamine, tributylamine, and tetraethylammonium chloride, with very high sensitivity. Compared with previous reports [14,37], they obtained better reproducibility using this SID detector with a monocrystalline emitter [39,40].

3. Instrumentation of our GC–surface ionization organic mass spectrometry (SIOMS) system

Fujii applied SI as an ionization method for GC–MS; he has devised a combination of SI and a quadrupole mass spectrometer, and named the sys-

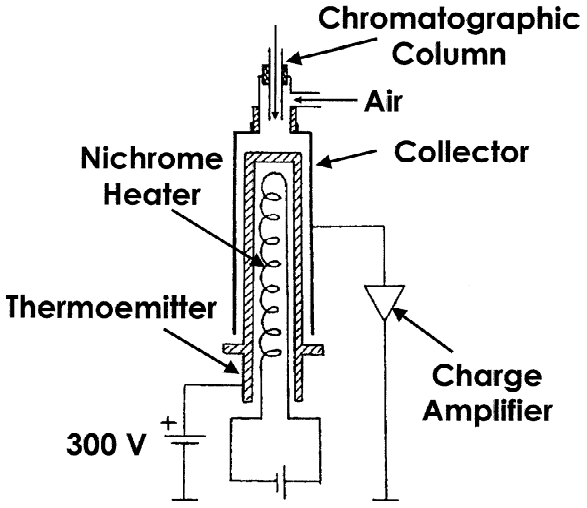

Fig. 2. Design of surface ionization detector with an indirect incandescence emitter and the connecting circuitry. The figure is from Ref. [39] with slight modification. Reprinted with permission (©Elsevier Science Ltd.).

tem SIOMS [9,22–24]. Until now, some modification or improvements of this system have been made; our group has constructed a prototype of the system, in collaboration with Shimadzu Corporation, Kyoto, Japan [24,41]. The schematic representation of SIOMS is shown in Fig. 3 [41,42]. The instrument used was a Shimadzu QP-5050A quadrupole mass spectrometer, which was modified to be usable in both electron impact (EI) and SI modes. For an SI ion source, the direct inlet probe was remodeled to a detachable SI assembly; a rhenium filament was placed on the tip of the DI probe and was inserted to the center of an EI ion source chamber. The SI assembly consisted of a ceramic insulator, two tantalum poles and a rhenium ribbon (0.8×12 mm, 0.025 mm thickness) (the lower part of Fig. 3); two tantalum poles were connected, through the ceramic insulator, to the ribbon by spot welding. The rhenium ribbon was heated by a current of about 1.6 A. The surface temperature was estimated to be about 1100

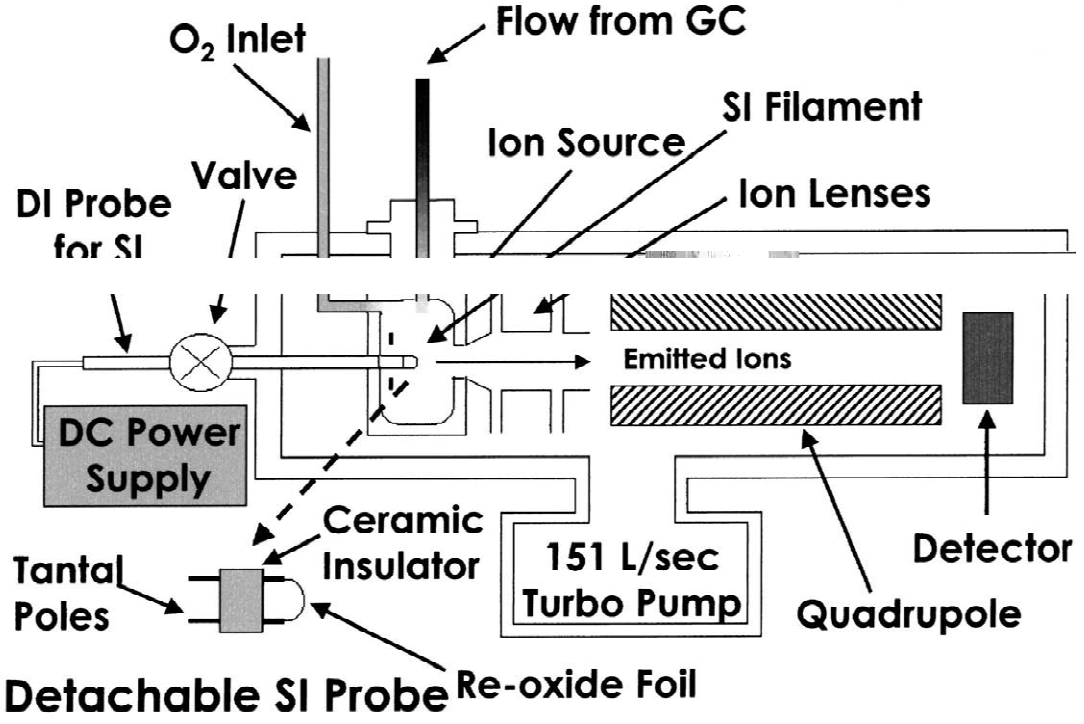

Fig. 3. Structural scheme of our GC–SIOMS system.

K [24]. Oxygen gas was supplied to the EI ion chamber to keep the oxidized rhenium surface stable. The partial pressure of oxygen was kept at $2–3\times 10^{-3}$ Pa in the ion chamber. The typical MS conditions were: interface temperature, 260–280 °C; detector voltage, 1.5 kV; ionization current and electron energy in the EI modes, 60 μA and 70 eV, respectively; and scan speed, 1000 amu/s.

Zandberg's group made an SI–MS combined with a magnetic sector MS (see their reviews [7,8]); Davis also constructed an SI–MS instrument using a magnetic sector MS [17,18]. Chatfield and Ajami [43] modified a time-of-flight (TOF) MS for the use of an SI source. The SI–MS systems using magnetic sector MS allow the analysis of metastable ions formed in the SI; high-resolution MS could be more useful for the determination of molecular structure, because it is uncommon to observe metastable ions [12]. Chatfield and Ajami claimed that the combination of a TOF-MS and SI resulted in the improvement of sensitivity without any loss in resolution [43]. Fujii pointed out the advantages of the application of a quadrupole MS for SIOMS as follows: (1) small size and weight since a large magnetic field would not be necessary, (2) rapid scanning, (3) easy to operate, (4) wide dynamic range, (5) electrical adjustment of the resolving power [13].

As ion emitters, Rasulev et al. concluded that those from W with a ''thick'' layer (up to μm) of oxides on the surface would be best rather than those made of Re oxide [40] because a thick layer of W oxide would not be ''poisoned'' easily. On the other hand, Davis [17] and Chatfield and Ajami [43] used Re as ion emitters.

4. Application of GC–SIOMS to various drugs

4.1. Phencyclidine (PCP)

Phencyclidine (PCP), a hallucinogenic compound developed in the 1950s, was first used as an anesthetic in the veterinary field, and used for humans for a short period. PCP was widely used as a hallucinogen in the early 1970s. The illicit use of PCP declined from 1979 to 1993, but the compound still remains as an important abused drug in many metropolitan areas and among certain sociodemographic groups [44,45]. It is necessary to develop a highly sensitive method for the detection of PCP because it can produce psychotic symptoms at its serum concentration of less than 0.02 μ*M* (about 5 ng/ml) [46].

As a first study of the application of GC–SIOMS, we have tried to detect and identify PCP in human body fluids [41]. The mass spectra of PCP in the EI and SI modes were taken (Fig. 4). In the SI mode, $[M-1]^+$ ion, which is characteristic for SI, appeared at m/z 242 for PCP. The base peak was m/z 156; we have proposed an aromatized structure to explain this peak (lower panel of Fig. 4). Similar phenomena were observed by other researchers [7,8,47]. We purified 12.5 ng of PCP and pethidine (internal standard, I.S.) spiked in 1 ml of human whole blood and urine samples using Bond Elut Glass columns. In the SI mode, the peaks of PCP and I.S., were clearly found in the total ion chromatogram (TIC) and mass chromatograms; the background noises were very small (Fig. 5, upper left panel). In the EI mode, a lot of big impurity peaks overlapped the peaks of the compounds in TIC; the drug peaks suffered from many noises in mass chromatograms, too (Fig. 4, right panels). In the mass chromatogram mode, the calibration curves for PCP in whole blood and urine samples showed excellent linearities in the range of 0.25 to 10 ng/ml. The detection limit was estimated to be 0.05 ng/ml (about 1 pg on-column). Using selected ion monitoring (SIM) mode, PCP was detected with much more sensitivity; the calibration curve in whole blood showed good linearity in the range of 0.025 to 1.0 ng/ml. Its detection limit was about 0.01 ng/ml. The sensitivity by SIOMS is ~25 to 1000 times higher than those by conventional EI methods in the SIM mode.

4.2. 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and its derivatives

In the early 1980s, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), an impurity of a meperidine analogue, 1-methyl-4-phenyl-4-propionoxypiperidine (MPPP), was found to be a cause of parkinsonian symptoms for MPPP abusers in the United States [48]. Since then, MPTP-induced Parkinsonism has been regarded as a good model in human and non-human primates [49].

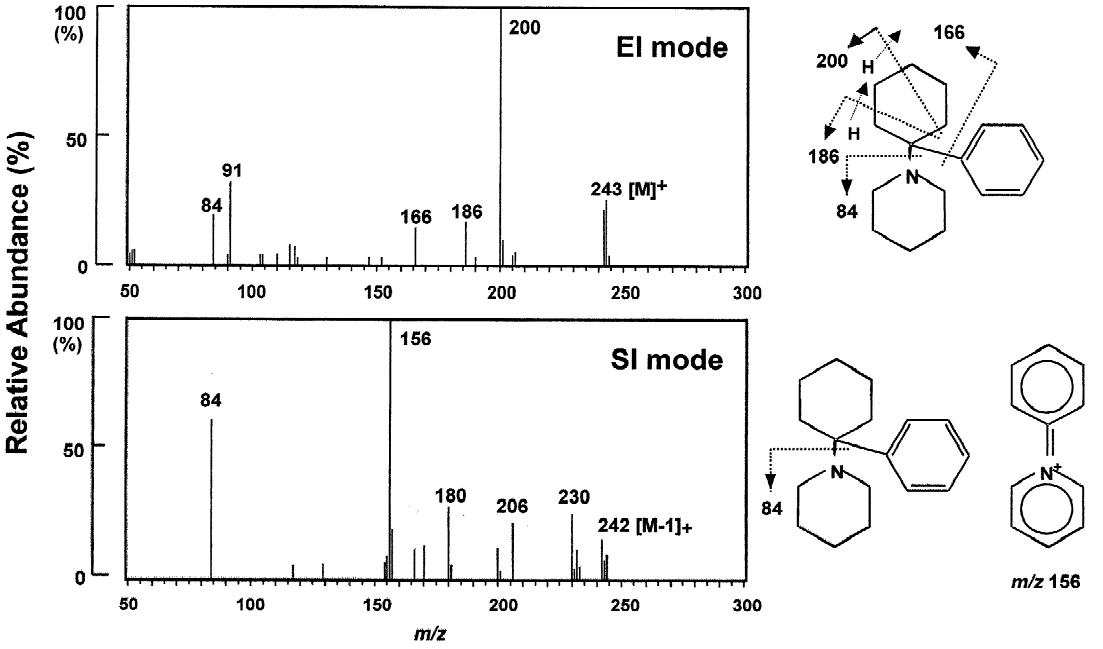

Fig. 4. Mass spectra of PCP in the EI (upper panel) and SI (lower panel) modes and its probable fragmentation pathways. Five nanograms of PCP were injected in the EI mode and 500 pg were injected in the SI mode.

We obtained positive-ion electron impact (PICI), positive-ion chemical ionization (PICI), negative-ion chemical ionization (NICI) and SI mass spectra of MPTP and its three derivatives, 1-methyl-4-(2-pyrrolylphenyl)-1,2,3,6-tetrahydropyridine (MPyPTP), 1-methyl-4-(3-methoxyphenyl)-1,2,3,6-tetrahydropyridine (3′OCH_3-MPTP), and 1-methyl-4-(2-isopropylphenyl)-1,2,3,6-tetrahydropyridine (2′-IP-MPTP) [50]. In PIEI mass spectra, molecular ions appeared for all compounds; three of them were their base peaks. The ions at m/z 94 and 96 were characteristic for these compounds, and they were formed by cleavage between the two ring structures. In PICI and NICI mass spectra, quasimolecular ions were also their base peaks. SI mode gave almost single $[M-3]^+$ peaks in all four compounds; we have proposed the aromatization of the *N*-methyltetrahydropyridine ring to explain the $[M-3]^+$ peaks such as PCP (Fig. 6). The detection limits for four compounds in the SI mode were 0.33–1.1 pmol on-column, which were about 4.2 to 8.0 times higher than those in the PIEI mode (2.1–7.9 pmol on-column).

4.3. Pentazocine

Pentazocine is a widely used narcotic analgesic drug that is often abused and controlled in many countries [51]. In our previous report, GC-SID was applied to pentazocine in whole blood and urine samples and high sensitivity was obtained [52].

We have succeeded in sensitive determination of pentazocine in human whole blood and urine, using dextromethorphan as I.S. [53]. In SI mass spectra, $[M-1]^+$ ions constituted the base peaks for both pentazocine and dextromethorphan. In this study, both compounds were measured in the SIM mode; a single ion at m/z 284 was traced for pentazocine and that at m/z 270 was traced for I.S. One millilitre of human whole blood or urine samples, spiked with 12.5 or 100 ng of pentazocine and 50 ng of I.S., were purified by solid-phase extraction using Sep-Pak C_{18} cartridges. The recoveries were above 90% for pentazocine, and 69% for I.S. The calibration curves showed good linearity in the range of 6.25 to 100

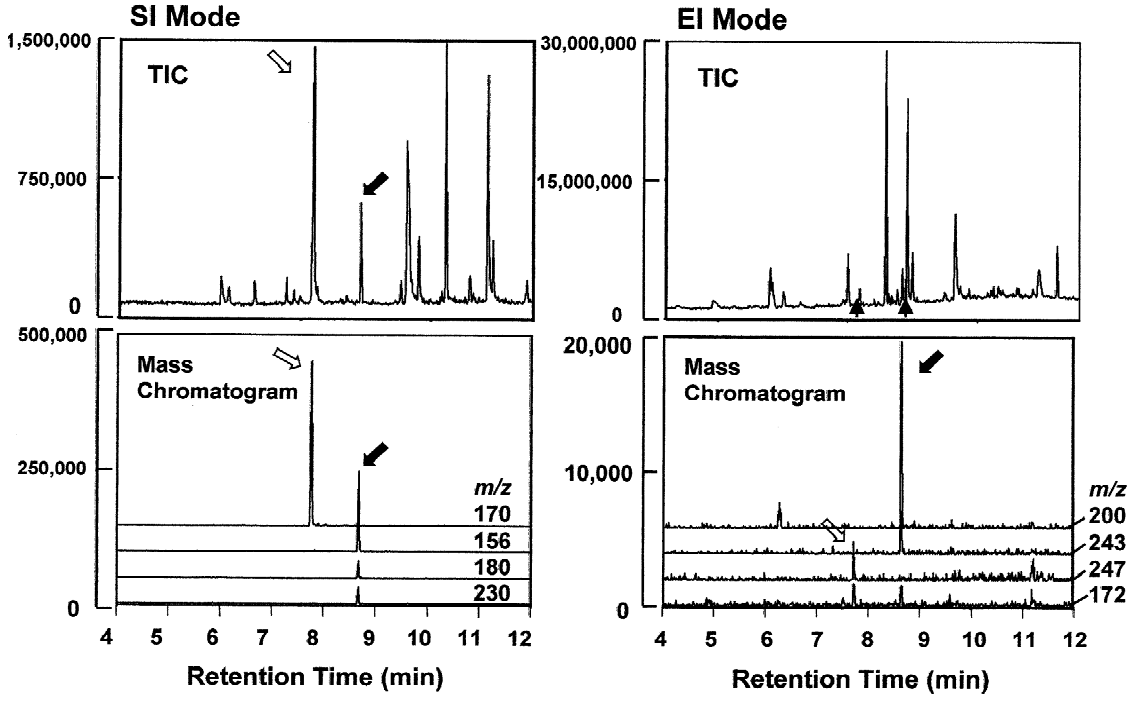

Fig. 5. Total ion chromatogram (TIC) (upper left panel) and mass chromatograms (lower left panel) of PCP and I.S. extracted from spiked human whole blood (12.5 ng/ml each) in the SI mode. Filled and open arrows show the peaks of PCP and I.S., respectively. TIC (upper right panel) and mass chromatograms (lower right panel) of the extracted compounds in the same amount, in the EI mode are also shown. In the TIC, big impurity peaks hid the peaks of both compounds; the retention times, when PCP and I.S. should appear, are shown by small peaks under the chromatogram.

ng/ml. The detection limit was 500 pg/ml for both whole blood and urine, and it was about 60 times higher than that obtained by EI-SIM. In the SI mode, the signal-to-noise ratios were much higher than those in the EI mode (Fig. 7). The reproducibility of the present method was examined. The intra-day variations were below 6.4% for whole blood and 4.2% for urine; the inter-day variations were below 9.6% for whole blood and 7.2% for urine.

4.4. Pethidine

Pethidine (meperidine) is a narcotic analgesic drug, which is widely prescribed; it was widely and most frequently abused by persons working in anaesthesia units [54]. A sensitive method using GC-SID was developed for determining pethidine in human body fluids [55].

GC–SIOMS has been applied for determining and quantitating pethidine in human body fluids [56]. Diphenylpyraline was used as I.S. in this method. In the SI mode, an intense base peak appeared at m/z 170 for pethidine; we have proposed an aromatized structure to explain the peak at m/z 170. For diphenylpyraline, the base peak was m/z 94, which seemed also aromatized; other small fragment peaks appeared at m/z 167, 114 and 70. Pethidine (12.5 or 2.5 ng) and I.S. (25 ng) were purified by solid-phase extraction using Bond Elut Certify columns; the recoveries were above 98% for pethidine and 96% for I.S. In the mass chromatogram mode, the calibration curves for whole blood and urine showed good linearities in the range of 0.625–25 ng/ml; its detection limit was estimated to be 0.2 ng/ml. In SIM mode, the detection limit was about 0.02 ng/ml (0.4 pg on-column) (Fig. 8); the sensitivity of our present method by mass chromatogram was 5–125 times higher than other methods, and that by the

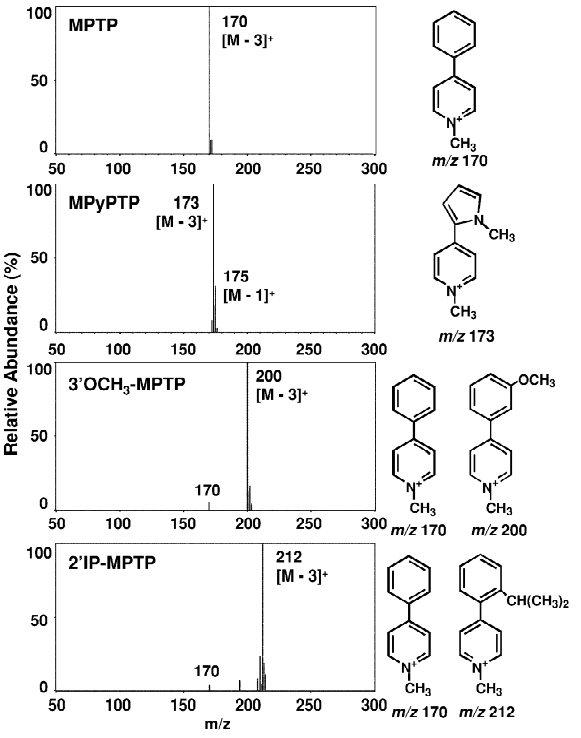

Fig. 6. SI mass spectra of MPTP, 1-methyl-4-(2-pyrrolylphenyl)-1,2,3,6-tetrahydropyridine (MPyPTP), 1-methyl-4-(3-methoxyphenyl)-1,2,3,6-tetrahydropyridine (3′-OCH3-MPTP) and 1-methyl-4-(27-isopropylphenyl)-1,2,3,6-tetrahydropyridine (2′-IP-MPTP). One nanogram of each compound was injected to GC–SIOMS.

present SIM was 8.5–1250 times higher. To validate our present method, we have quantitated pethidine in whole blood and urine of two healthy volunteers 2 and 6 h after oral administration of 10 mg pethidine; very small amounts of whole blood (0.5 ml) and urine (25 or 50 μl) were sufficient to quantitate pethidine in the body fluids (Fig. 9). A usual single dose of pethidine is 50–100 mg orally [57], and its therapeutic concentration is estimated to be 0.2–0.8 mg/ml [58]; this present method can be applicable for monitoring pethidine in clinical toxicology.

4.5. Tricyclic antidepressants

Tricyclic antidepressants, such as imipramine or desipramine are widely used for the treatment of major depression. But they are associated with a relatively high incidence of adverse-effects in normal therapeutic usage; they remain one of the commonest causes of acute self-poisoning in the world, and many of their overdose cases are fatal [59].

Fujii has taken both EI and SI mass spectra of three tricyclic antidepressants, imipramine, desipramine and clomipramine [24]. The SI spectra of these antidepressants were quite different from their EI spectra. They observed major peaks at m/z 44, 58, 70, 72 and 84; these peaks can be assigned to $[(CH_3)HNCH_2]^+$, $[(CH_3)_2NCH_2]^+$, $[(CH_3)HC{=}NCH_2]^+$, and $[(CH_3)C_2H_5NCH_2]^+$, respectively. These base peaks were m/z 58 except desipramine, of which the base peak was m/z 44; only a few small fragment ions of these compounds were found in the higher mass range. Their result is in good agreement with our results. We have obtained the SI mass spectra of imipramine, amitriptyline, trimipramine and clomipramine; they all gave very intensive fragment ions at m/z 58 as base peaks, and some few relatively characteristic peaks at m/z 230 for imipramine and trimipramine, at m/z 215 for amitriptyline, respectively (A. Ishii et al., unpublished data). Fujii calculated the ratios of the base peak intensities in the SI mass spectra to those in the EI mass spectra for these antidepressants. The values were in the range of 7.2 to 26.6; these data mean that the target molecules would be ionized with much higher efficiency in the SI mode than in the EI mode.

4.6. Neuroleptics

Phenothiazines and butyrophenones have been widely used in the treatment of psychotic disorders, chiefly schizophrenia and related disorders [60,61]. These compounds mainly block D_2-dopamine receptors and reduce dopamine neurotransmission in forebrain; extrapyramidal side effects usually occur in patients treated with such neuroleptics [61]. Thus it is important to develop sensitive methods for monitoring these neuroleptics in human body fluids.

Fujii et al. compared mass spectra of haloperidol in the EI and SI modes [47]. In the EI mode, the spectrum exhibited a detectable parent $[M]^+$ ion and many intense fragment ions; its base peak occurs at m/z 224, while a major fragment appeared at m/z 237. In the SI mode, no molecular ions were found,

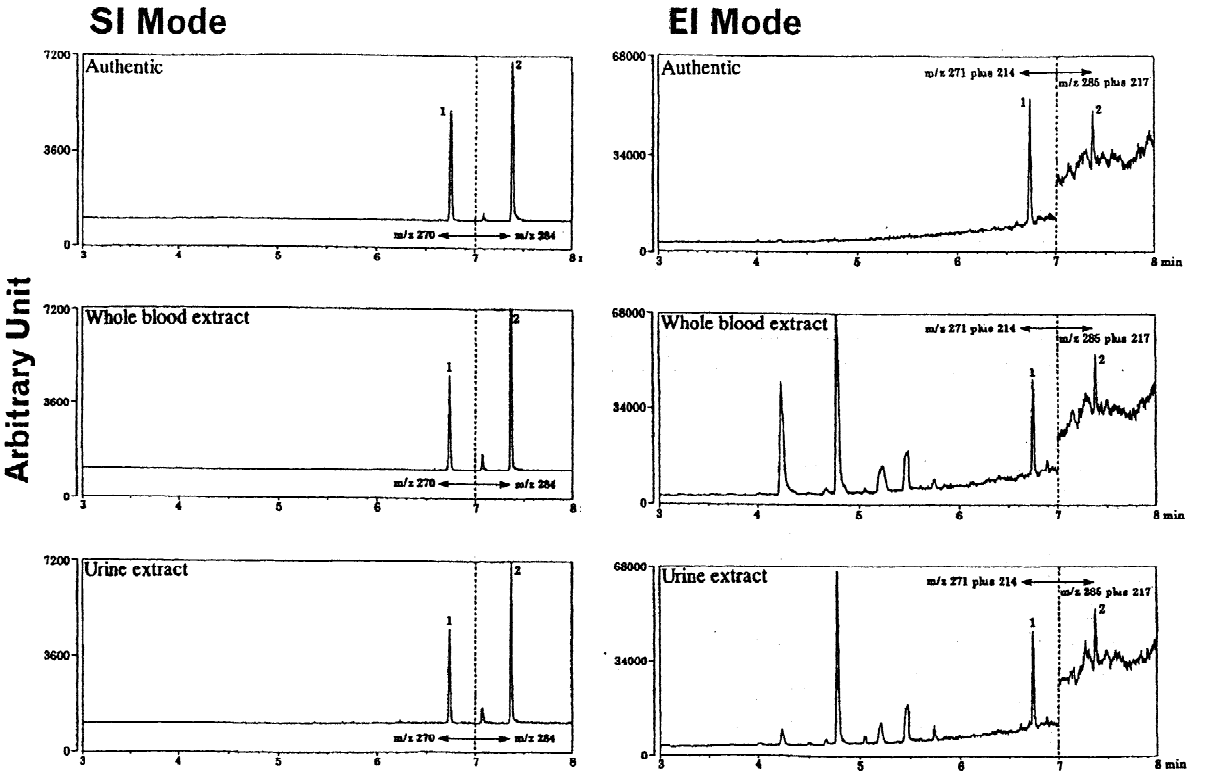

Fig. 7. SIM chromatograms obtained in the SI mode (left panels) and in the EI mode (right panels) for pentazocine (peak 2) and I.S. (peak 1). To 1 ml of whole blood or urine, 50 ng of each compound were added. In the SI mode, the ion at m/z 270 was selected for SIM from 3 to 7 min and that at m/z 285 from 7 to 8 min. In the EI mode, ions at m/z 271 plus 241 were selected from 3 to 7 min and those at m/z 285 plus 217 from 7 to 8 min.

but there were many ionic species over the entire mass region with the most intense ions at m/z 123. Quite a few abundant ions appeared at m/z 42, 56, 70 and 84; they should be tertiary alkylamino ions. Also, signals at m/z 95, 109, 123, 192 and 206 would possibly correspond to structure-specific losses of its side chains. However, some signals of higher-mass-range peaks could not be reasonably

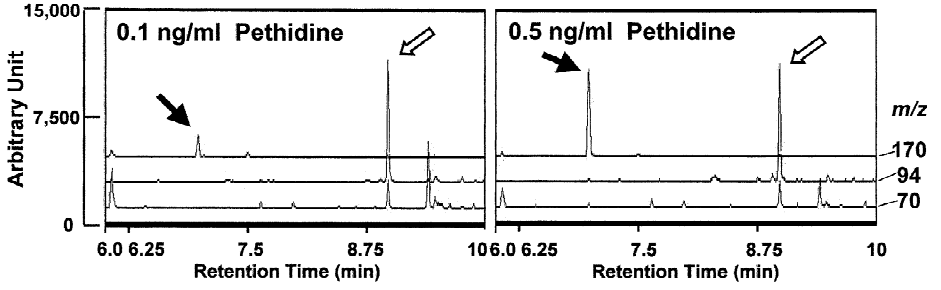

Fig. 8. SIM chromatograms for two different concentrations (left, 0.1 ng/ml and right panel, 0.5 ng/ml) of pethidine in spiked whole blood. In both panels, filled and open arrows show the peaks of pethidine and I.S., respectively.

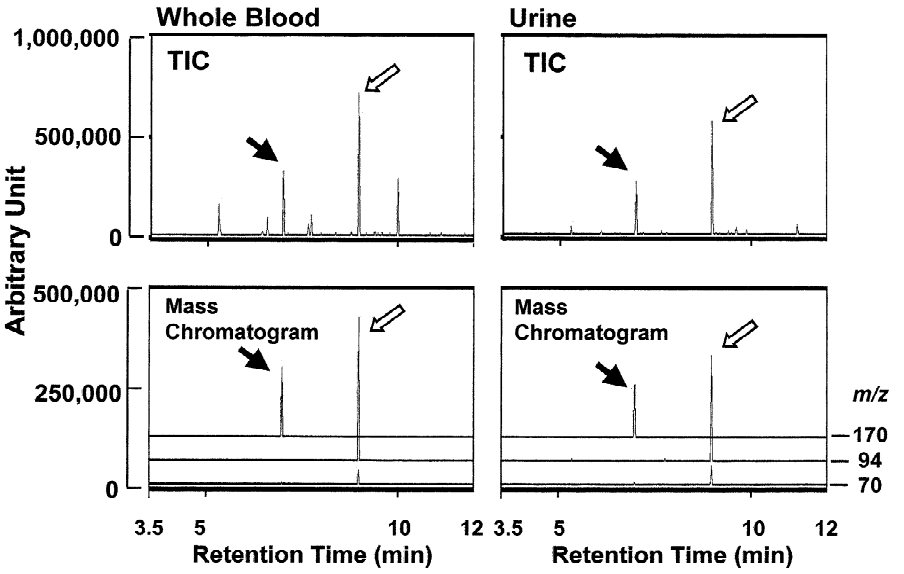

Fig. 9. The TIC and mass chromatograms for pethidine (filled arrows) and I.S. (open arrows) in whole blood (left panels) and urine (right panels) samples obtained from a healthy subject 2 h after oral administration of 10 mg pethidine.

assigned; a similar phenomenon was found in the SI mass spectra of PCP [41]. The ratio of the base peaks of the SI (m/z 123) and EI (m/z 224) modes were 9.6.

Rasulev et al. obtained the SI mass spectra of chlorpromazine, tioproperazine, periciazine [62]. Different from Fujii's results, they found some detectable quasimolecular ions $[M-1]^+$, and the $[M-1]^+$ ions were observed at lower surface temperatures; the difference may be due to the metal surface or some subtle experimental conditions. Such differences remain for further study.

4.7. Other drugs

Fujii et al. applied GC–SIOMS to lidocaine [24]; they extracted lidocaine from spiked human serum samples, and the extracts were subjected to GC–SIOMS. The TIC in the SI mode showed almost no interferance from the impurities derived from the serum. Compared to the TIC in the EI mode, GC–SIOMS did not give rise to peak-broadening, tailing and baseline drift.

We have obtained some preliminary data on several groups of compounds by GC–SIOMS. In the case of antihistaminics, most of the compounds containing aliphatic tertiary amino chain structures gave the base peaks m/z 58 due to $[CH_2N(CH_3)_2]^+$, resulting in the lack of fragment ions in the higher mass range (Watanabe-Suzuki et al., unpublished data); similar results were obtained in atypical antipsychotics (Ishii et al., unpublished data). We thus assume that only tertiary amino compounds with ring structures, such as the above mentioned compounds could be targeted for sensitive determination by GC–SIOMS [42].

Recently, SI has been applied for the ion source of ion mobility spectrometry (IMS) [63,64]; the spectra of narcotics such as heroin, morphine and codeine have been obtained, and heroin has been detected from heroin users' urine samples [65]. Also, Rasulev has developed a surface ionization drift spectrometer, a portable gas analyzer with separation of ions by their mobility; different amine compounds can be discriminated by their drift spectra [40].

5. Conclusion

In this review, we have shown highly sensitive and selective detection methods of drugs-of-abuse and toxic compounds with tertiary amino groups,

such as PCP, pethidine, pentazocine and other drugs, by GC–SIOMS. Although GC–SIOMS would be suitable for only tertiary amino compounds with ring structures, their sensitivities and signal-to-noise ratios are much higher than those in the EI mode. SI has been applied to different kinds of mass spectrometers or detectors; the applications of these new devices will be promising in the field of forensic toxicology.

Acknowledgements

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