Analytica Chimica Acta 946 (2016) 1–8

Contents lists available at ScienceDirect

Analytica Chimica Acta

journal homepage: www.elsevier.com/locate/aca

Modifier-assisted differential mobility–tandem mass spectrometry method for detection and quantification of amphetamine-type stimulants in urine

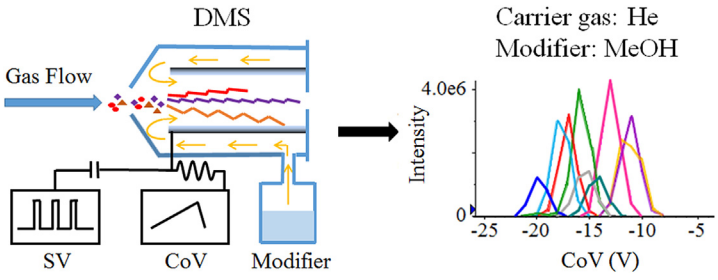
Pai-Shan Chen [a, b, *], Shu-Hua Chen [c], Jung-Hsuan Chen [a, b], Wan-Yun Haung [a, b], Hsin-Tung Liu [d], Po-Hsin Kong [a], Olivia Hsu-Yuan Yang [e]

[a] Department and Graduate Institute of Forensic Medicine, College of Medicine, National Taiwan University, Taiwan
[b] Forensic and Clinical Toxicology Center, National Taiwan University College of Medicine and National Taiwan University Hospital, Taiwan
[c] Department of Chemistry, Texas A&M University, College Station, TX, USA
[d] Graduate Institute of Toxicology, College of Medicine, National Taiwan University, Taiwan
[e] SCIEX, Taiwan

HIGHLIGHTS

- Directly analyze structurally similar amphetamine-type stimulants in gas phase.
- Methanol in He was first time used to improve the sensitivity and selectivity.
- Results from DMS-MS/MS showed reasonable agreement with those from LC-MS/MS.
- The whole analysis has been shortened significantly.
- The high throughput can be achieved.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 14 June 2016
Received in revised form
23 September 2016
Accepted 24 September 2016
Available online 30 September 2016

Keywords:
Amphetamine-type stimulants
Differential mobility spectrometry
Drug of abuse
Liquid chromatography
Mass spectrometry
Urine

ABSTRACT

An advantage of differential mobility spectrometry (DMS) is it provides an orthogonal mechanism to mass spectrometry (MS). The DMS-MS/MS detects analytes in the gas phase on the basis of differences in ion mobility in low and high electric fields, which makes DMS-MS/MS an alternative to chromatographic separation-MS. One drawback of DMS is its limited resolution and sensitivity, especially for detecting small molecules when using a nonpolar inert gas as the carrier gas. The present work has evaluated the effects on peak capacity of adding chemical modifiers to inert carrier gases (nitrogen, helium, argon and carbon dioxide). Use of a methanol-helium mixture gave improvements in both separation and sensitivity. Nine structurally similar amphetamine-type stimulants were determined in urine without pretreatment of the samples before analysis. After optimization of carrier gas, nature and concentration of chemical modifier, and DMS temperature, limits of detection ranging from 1.1 to 2.7 ng mL^{-1}, with a linear range of three orders of magnitude (5–5000 ng mL^{-1}) were achieved. Precision was <15% and the accuracy of the quality control samples was 87.6–113.7%. For the quantitation of urine samples from drug abusers, data obtained using DMS-MS/MS showed reasonable agreement (within ±19.5%) with that obtained using LC-MS/MS. The analysis time for DMS-MS/MS was only 1.1 min and a paired sample *t*-test

* Corresponding author. Department and Graduate Institute of Forensic Medicine, College of Medicine, National Taiwan University, Taiwan.
E-mail address: paishanchen@ntu.edu.tw (P.-S. Chen).

http://dx.doi.org/10.1016/j.aca.2016.09.027
0003-2670/

between the two methods gave a *p*-value of 0.0894, which indicates that DMS-MS/MS is a reliable method, with comparable precision and sensitivity to LC-MS/MS.

1. Introduction

Rapid on-site testing for both legal and illegal drugs has been achieved using devices based on enzyme-linked immunosorbent assays and enzyme multiplied immunoassay techniques [1–3]. Although immunoassays are rapid and high throughput, they do not allow accurate quantitation of drugs and false positive results can lead to serious medical or social consequences [4]. Confirmation of the results is thus needed and this is typically carried out by chromatographic separation, using either gas chromatography (GC) or liquid chromatography (LC), coupled with mass spectrometry (MS). A major disadvantage of these chromatography-based methods is the requirement for time consuming and labor intensive sample preparation, usually by solid phase extraction [5–7] or liquid-liquid extraction [8–11], prior to analysis.

An alternative to chromatography is ion mobility spectrometry (IMS), which provides an orthogonal mechanism for resolving analytes with similar structures, particularly small molecules [12–17], lipids [18] and proteins [16,19–24]. IMS can be combined with tandem mass spectrometry (IMS-MS/MS) to provide a powerful analytical technique. Differential mobility mass spectrometry (DMS), also known as high-field asymmetric ion mobility spectrometry (FAIMS) is a rapidly developing IMS technique. In the DMS cell, an asymmetric oscillatory field is created between two electrodes, which causes the ions to oscillate toward one electrode or the other depending on differences in the ion's mobility during the high- and low-field portions of the waveform. To ensure that ions are transmitted to the mass spectrometer, a compensation voltage (CoV) is ramped until ions are deflected away from collisions with the electrodes and toward the MS detector. The characteristic CoV value for ions to be directed to the MS detector is compound-dependent, which means that different analyte ions migrate towards the walls of the DMS cell at different rates and separation is achieved. A chromatography-like CoV spectrum obtained from the analytes of interest, provides information about the species present in the sample. The CoV value is controlled by the mass-to-charge ratio, molecular shape and interaction with the carrier gas [25]. This means that the resolving power and peak capacity can be improved by optimizing the composition of the carrier gas.

The use of different carrier gases alters interactions between ions and neutral species and can be used to achieve ion separation. Nitrogen and air are the most commonly used carrier gases for DMS [12], whereas helium is the most commonly used gas in studies comparing theoretical gas phase ion conformations with experimental data [20,21]. The use of carbon dioxide as the carrier gas has been reported to improve resolution at higher temperatures [26,27]. Argon [12], sulfur hexafluoride [28], and ammonia [29] have been used as novel drift gases and recent evidence suggests that using a two- or three-component mixture as the drift gas can improve ion separation. Low-mass nonpolar drift gases, such as mixtures of helium and nitrogen, generally provide better peak resolution and separation. For example, Shvartsburg et al. [30] achieved 100% separation capability using a mixture of helium and nitrogen (75:25) as the carrier gas for peptide and protein digests and McCooeye et al. [31] showed that a mixture of helium and nitrogen (6:4) significantly improved the analysis of morphine and codeine in human urine. The use of helium/nitrogen (80:20) as the drift gas also led to an overall improvement in resolution and sensitivity balance when analyzing peptides on IMS microchips [32]. The benefits of helium-rich gases arise because of helium's small size and low polarizability, which provide closer repulsive walls and shallower potentials and lead to higher mobilities for these ions [30,32]. Although a mixture of hydrogen and nitrogen, with up to 90% hydrogen provides better resolution than helium/nitrogen mixtures because hydrogen is more resistant to breakdown than helium, the use of hydrogen is limited by its flammability, which requires special safety precautions [15,33]. The addition of small amounts of carbon dioxide improves sensitivity and Barnett et al. noted that using a mixture of carbon dioxide and nitrogen (5:95) as carrier gas in FAIMS enhanced the sensitivity for three isomers of phthalic acid 2–7-fold. The main reason for the improvement in intensity is that weak ion-carbon dioxide clusters are formed during low electric fields and dissociate during the high-voltage portion that occurs in each cycle, giving a significant change in mobility. The presence of carbon dioxide also protects fragile ions, which dramatically reduces both adduct peaks and parent ion fragmentation in FAIMS [34,35]. Cui et al. have described the use of a three-gas system containing helium, carbon dioxide and nitrogen, as the drift gas for analysis of platinum species. The signal intensity increased 10-fold when the carbon dioxide concentration was increased to 8% [36], although the CoV span was reduced. Using the inert gases described above improves resolution by reducing peak width, but has little effect on peak capacity or selectivity. Separation and selectivity are mainly a result of geometric cross-sections and chemical interactions play a much smaller role [37].

Schneider et al. [37] and Varesiothe et al. [38] recently reported that addition of a polar chemical modifier to the drift gas has an important chemical effect that improves ion separation and sensitivity. Since the addition of modifiers enhances the formation of clusters, especially in the low field, the mobility difference between high and low fields is amplified and peak capacity and separation power are markedly increased. Chemical modifiers, such as water vapor, alcohols and ketones have been widely tested in proteomics [19], the analysis of drugs of abuse [13,38,39] and peptides [29,40,41]. These studies show that different modifiers provide distinctive selectivity enhancements as a result of their different chemical structures. Suitable modifiers reduce chemical noise and remove interferences in atmospheric pressure ionization mass spectrometry, thus significantly improving the selectivity and sensitivity of the DMS device [25,40,42]. Chemical modifier-assisted DMS clearly has improved mass spectral signal/noise ratios and offers an ion separation system that is orthogonal/complementary to MS.

It has been clearly demonstrated that DMS resolution can be improved by either changing the carrier gas or using chemical modifiers. Different drift gases or inert gas mixtures have been shown to provide better resolution in IMS but, despite reports of improved separation following addition of chemical modifiers to nitrogen, there is little information about using chemical modifiers in carrier gases other than nitrogen. When using nitrogen mixed with large amounts of helium and other low molecular weight carrier gases, access to high-voltage conditions decreases the