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Rapid screening of abused drugs by direct analysis in real time (DART) coupled to time-of-flight mass spectrometry (TOF-MS) combined with ion mobility spectrometry (IMS)

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ABSTRACT

Increasing in cases involving drugs of abuse leads to heavy burden for law enforcement agencies, exacerbating demand for rapid screening technique. In this study, atmospheric pressure ionization technologies including direct analysis in real time (DART) ion source coupled to a time-of-flight mass spectrometer (DART-TOF-MS)as well asdopant-assisted positive photoionization ion mobility spectrometry (DAPP-IMS) without radioactivity were utilized together as the powerful analytical tool for the rapid screening and identification of 53 abused drugs.The limits of detection (LOD) were 0.05–2 μg/mL when using DART-TOF-MS and 0.02–2 μg when using DAPP-IMS which could satisfy the actual requirement in forensic science laboratory. The advantages of this method included fast response, high-throughput potential, high specificity, and minimal sample preparation. A screening library of reduced mobility (K_0), accurate mass of informative precursor ion ($[M+H]^+$) and fragment ions was established respectively by employing a bench-top DAPP-IMS and TOF-MS in-source collision induced dissociation (CID) mode. Then the standardized screening procedure was developed with criteria for the confirmation of positive result. A total of 50 seized drug samples provided by local forensic laboratory we reanalyzed to testify the utility of the method. This study suggests that a method combing DART-TOF-MS and DAPP-IMS is promising for the rapid screening and identification of abused drugs with minimal sample preparation and absence of chromatography.

1. Introduction

A thorny problem has emerged over the world during the past decade in the form of the manufacture, distribution, and abuse of drugs [1–4]. These drugs consist of commonly used ones like morphine, heroin, cannabis, amphetamines [5] and new psychoactive substances [4,6–9]. High-throughput methods that can quickly achieve identification were highly required to keep in pace with the growing need to monitor the propagation of abused drugs.

There are various approaches for rapid analysis of drugs in vitro. Usually, color tests and immunoassay are applied for screening purposes. But these methods are lack of specificity and not able to detect homologous because of cross-reactivity [10]. Gas chromatography mass spectrometry (GC–MS) and liquid chromatography mass spectrometry (LC–MS) show high detection power in terms of specificity and sensitivity [2]. However, it takes long time to get the chromatographic results, which would be a big burden for crime investigation, if testing backlogs emerged. In fact, it is often urgent for forensic laboratories to be able to promptly detect and identify abused drugs with minimal sample preparation steps.

More recently, an ambient pressure desorption ionization technique-direct analysis in real time(DART)has been developed, which had been proven to be useful for rapidly detecting many

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chemical compounds [6,11]. DART [12] is a powerful ionization technique that could save time and solvent with the ability ofrequiring little or no sample preparation and eliminating the long chromatography time. The advantage of this technique is obvious that it can acquire spectrum with highly accuracy instantaneously and increase throughput greatly [12,13]. Since its first put into use, DART ion source coupled to time-of-flight mass spectrometer (DART-TOF-MS) [3,14–18] has been successfully applied in multitudinous fields, especially forensic investigation, covering the identification of synthetic cannabinoids [9,19–21], synthetic cathinones [6], 35 new psychoactive substances [22], as well as 164 pesticides on produce [23]. However, DART-TOF-MS is not always able to differentiate mixtures because of the lack of chromatographic separation, which could limit its utility.

Ion mobility spectrometry (IMS), as an analytical technique which could ionize analytes under the ambient pressure, can achieve the identification of components in a mixture [22,24–27]. Based on the size and shape of ions, IMS can finish the separation and identification within 20–40 s in total analysis time. IMS with a ^{63}Ni ionization source has been commonly used for illicit drug analysis with high sensitivity, specificity, and potential portability. Joshi et al. [24] used IMS to detect the synthetic cathinones and associated psychoactive substances. However, its application will give rise to radioactivity safety issues. In recent years, nonradioactive ionization sources were also developed to detect conventional explosives [26,27]. However, there is rare investigation of a dopant-assisted positive photoionization (DAPP) source for the detection of abused drugs.

In this study, a rapid screening method based on DAPP-IMS and DART-TOF-MS was first described for the detection of commonly used 53 drugs of abuse. A database was included in the method, which not only contained reduced mobility (K_0) obtained by DAPP-IMS, but also contained precursor ions and fragments with excellent mass accuracy obtained by utilizing the in-source collision induced dissociation (CID) mode of TOF-MS to avoid potential false positive results. Consequently, a screening procedure to process numbers of samples was provided for the first time to detect drugs of abuse rapidly and confidently.

2. Experimental

2.1. Chemicals and reagents

Drug standards were purchased from China Pharmaceutical Biological Products Analysis Institute, National narcotics laboratory and Cerilliant (Texas, USA). All compounds applied in this study are listed in Tables 1 and 2. Ultrapure water was generated with a PURELAB Ultra laboratory water purification system from ELGA (HighWycombe, UK). HPLC-grade methanol was purchased from Merck (Darmstadt, Germany). Polyethyleneglycol (PEG, average MW 600) was provided by JEOL (JEOL USA, Inc., Peabody, MA, U.S.A.).

2.2. Preparation of standard solutions

Each drug standard was dissolved in methanol at a concentration of 1 or 0.1 mg/mL.

2.3. Sample preparation

Each sample (2 mg) dissolved in 2 mL methanol as a solution was further diluted with methanol to 1 mg/mL to prevent overloading of analytes [22] in the system. The seized samples which were plant or pharmaceuticals form such as heavily coated tablets were simply fractured and dissolved in methanol.

2.4. Instrumentation

2.4.1. IMS parameters

The DAPP-IMS instrument (designed by Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian, Liaoning, PR China) was utilized for the qualitative analysis of 53 abused drugs. The factory recommended operating parameters in positive mode which were specially designed for screening drugs of abuse, were used in this study and demonstrated good performance. The inlet temperature and drift tube temperature were 231 °C and 121 °C respectively. Since the length of acquisition time for IMS spectrum was 15 ms and an output spectrum was obtained by averaging five initial IMS spectrum, 12 output spectra could be recorded within one second. Each standard (100 ng or 1 μg) was first deposited on the sampling Teflon membrane substrate, and then inserted into the thermal desorber after the evaporation of solvent. It was noteworthy that the Teflon substrates were conditioned in the thermal desorption chamber before loading each sample. In this study, the reduced mobility K_0 ($cm^2\,V^{-1}\,s^{-1}$) of analytes were used as the parameter to identify the abused drugs, and the K_0 could be calculated by Eq. (1) [27], where K_{0a} is the reduced mobility of analyte, t_{ds} and t_{da} are the drift time of the standard and the analyte, respectively. We chose cocaine with a reduced mobility K_{0s} of 1.67 $cm^2\,V^{-1}\,s^{-1}$ and a drift time t_{ds} of 8.00 ms as the quality control standard.

$$K_{0a} = K_{0s} \times (t_{ds}/t_{da}) \quad (1)$$

2.4.2. DART parameters

A DART-SVP™ ion source (Ionsense, Saugus, MA, U.S.A.) was used for ionization, coupled with an AccuTOF™ mass spectrometer (JEOL USA, Inc., Peabody, MA, U.S.A.) to acquire all mass spectra. The standard and testing sample solutions were sampled directly by Dip-it® Samplers (Ionsense, Saugus, MA, U.S.A.),which were placed in the optimal position, and then the automated rack moved perpendicular at a speed of 0.4 mm/s to the flow of ionizing gas to allow analysis of multiple samples within a single assay. The helium gas flow rate was 3.5 L/min. The temperature of the helium gas was 350 °C, and grid voltage was 200 V. In the rack, Dip-it® Samplers with samples were positioned 1.8 cm apart as reported in the literature [8], which avoided sample carryover or contamination between samples.

2.4.3. MS parameters

The AccuTOF mass spectrometer was used in positive ion mode for all measurements with a resolving power of 6000. PEG (average MW 600) diluted by methanol to 1‰ was used to make sure the exact mass determinations within the desired mass tolerance in each data acquisition.Function switching mode in orifice 1 was switched among 30, 60, 80 and 120 V to obtain four files of DART spectra, which offered multiple measurements in one sequence to obtain precursor $[M+H]^+$ ion and fragment ions of the sample at the same time. Voltages of orifice 2, ring lens, detector and RF ion guide were set at 10 V, 5 V, 2200 V, and 500 V, respectively. Mass range was set in the range of 50–600 Da. Mass Center Main together with Mass Spec Tools (MSTools) programs (ChemSW Inc., Fairfield, CA, U.S.A.) were used to process all the obtained data. Specifically, the data was averaged, background subtracted, and centroided to acquire spectra, and then the spectra were calibrated by 1‰ PEG methanol solution.

2.5. Fragmentation collection and database establishment

Each standard was analyzed individually in the function switching mode to definitively identify its precursor ($[M+H]^+$ ion) and fragment ions for establishing the screening database.