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Rapid and on-site analysis of amphetamine-type illicit drugs in whole blood and raw urine by slug-flow microextraction coupled with paper spray mass spectrometry

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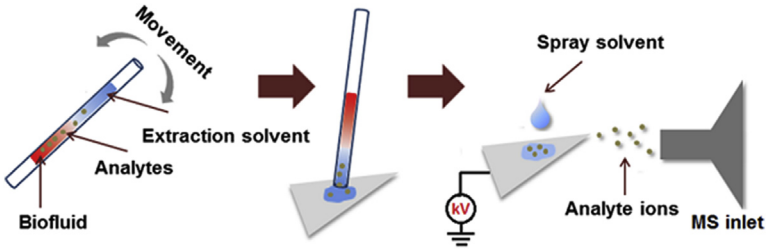
HIGHLIGHTS

- A slug-flow microextraction paper spray mass spectrometry method was developed.
- The method was applied for rapid and on-site analysis of illicit drugs.
- Trace AM, MA, and MDMA in whole blood and raw urine were successful analyzed.
- The method shows advantages of simplicity, cost-effectiveness, and sensitivity.
- We provide an useful method for clinical research and forensic science.

GRAPHICAL ABSTRACT



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ABSTRACT

In this study, a slug-flow microextraction (SFME) coupled with paper spray mass spectrometry (PS-MS) method was developed for rapid and on-site analysis of trace amphetamine-type illicit drugs including amphetamine (AM), methamphetamine (MA) and 3,4-methylenedioxy-*N*-methylamphetamine (MDMA) in complex biological samples such as whole blood and raw urine. The method involved the application of SFME for rapid extraction of trace amphetamine-type illicit drugs from whole blood and raw urine samples, followed by PS for direct MS analysis under ambient and open-air conditions. The experimental parameters including extraction solvent, extraction cycle, high voltage, and spray solvent, etc., were all investigated, and the optimized conditions showed an enhanced sensitivity of 1–2 order of magnitudes compared with PS-MS. The method showed good linearity, with correlation coefficient values (r) of no less than 0.9979 for analysis of AM, MA, and MDMA in human whole blood and raw urine without additional sample pretreatments. The limits of detection and quantification were 0.01–0.05 ng/mL and 0.05–0.2 ng/mL, respectively. Satisfactory recoveries were also obtained, with 74.2–94.9% for whole blood and 80.2–103.6% for raw urine, respectively. All of our experimental results demonstrated that

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SFME-PS-MS showed great potential for rapid, on-site, *in situ*, and high-throughput screening of amphetamine-type illicit drugs in various biological samples.

1. Introduction

Drug abuse is a serious societal and economic problem worldwide nowadays. The analysis of abused drugs and their metabolites in human blood, urine, saliva, sweat, and hair, etc., as an important step for monitoring drug abuse, has been a hot research topic in recent years. In general, the confirmation of presence of abused drugs and their metabolites in biological samples is mainly performed by using gas chromatography (GC) coupled with mass spectrometry (MS) and liquid chromatography (LC) coupled with MS methods [1–4]. Due to the high complexity of biological samples, conventional GC-MS and LC-MS methods are usually labor-intensive and time-consuming for analysis of abused drugs, requiring a series of sample pretreatment steps to eliminate matrices and enrich target compounds as well as a long chromatographic runtime for separation of analytes. In addition, GC-MS methods often demand a tedious derivatization step to achieve the effective vaporization of analytes [1]. Thus, methods for rapid, direct, on-site, *in situ*, and high-throughput analysis of abused drugs in complex biological samples are great desirable.

Ambient MS [5–8] provides the opportunity for rapid and direct analysis of complex biological samples with minimal or no sample pretreatment and without chromatographic separation. Till now, a series of ambient MS methods have been applied for drugs-of-abuse analysis. For instances, desorption electrospray ionization (DESI) [9] and wooden-tip electrospray ionization (WT-ESI) [10] have been applied for simple and rapid analysis of abused drugs in urines and oral fluids; direct analysis in real time (DART) [11–13], paper spray (PS) [14,15], extraction spray [15], and slug-flow microextraction (SFME)-nanoelectrospray ionization (nanoESI) [16,17] have been attempted to rapid and high-throughput analyze abused drugs in whole blood.

However, direct introduction of biological samples with high complexity (such as whole blood and raw urine, etc.) into mass spectrometer might lead to high matrix effect and low sensitivity for target analytes. To address this problem, coupling microextraction techniques with ambient MS has been developed. In the past two decades, strategies for coupling solid-phase microextraction (SPME) with ambient MS have been developed rapidly [18,19], and many SPME-ambient MS hyphenation techniques such as SPME-DESI [20,21], SPME-DART [22,23], surface-coated wooden-tip ESI [24,25], coated blades spray ionization (CBSI) [26], and surface-coated probe (SCP) nanoESI [27], etc., have been developed as novel strategies for rapid extraction of compounds from complicated samples and direct ionization of analytes for mass spectrometric analysis under ambient and open-air conditions.

Liquid-phase microextraction (LPME) coupled with ambient MS has also been developed rapidly, and several LPME-ambient MS hyphenation techniques including single drop microextraction (SDME)-DESI [28], LPME-PS [29], and SFME-PS [30], etc., have been successfully developed and implemented into analytical practices in recent years. Among these LPME-ambient MS hyphenation techniques, SFME-PS is a novel method developed by our group recently [30], which integrates the advantages of LPME and ambient MS, and is extremely suitable for rapid analysis of trace compounds in small-volume of complex biological samples. The method is performed by applying a disposable glass capillary for rapid extraction of a small amount (1–5 μL) of biological sample (e.g., whole blood and raw urine, etc.) using a small amount (1–5 μL) of organic solvent. During the microextraction process, the analytes in the biological sample were efficiently extracted and enriched into the organic phase with the shaking movements. After SFME, the loaded organic solvent was spotted onto the middle of a paper triangle, and a high voltage and some spray solvent were then added onto the paper triangle for mass spectrometric analysis.

In this article, we reported the application of SFME-PS-MS for rapid analysis of abused drugs in whole blood and raw urine samples. Three amphetamine-type illicit drugs controlled by the World Anti-Doping Agency (WADA) and the United Nations Office on Drugs and Crime (UNODC), i.e., amphetamine (AM), methamphetamine (MA), and 3,4-methylenedioxy-*N*-methylamphetamine (MDMA) [26], were selected as target analytes. Our developed SFME-PS-MS method enables the high-efficient extraction of amphetamine-type illicit drugs from whole blood and raw urine using a small quantity of organic solvent as well as their rapid mass spectrometric analysis under ambient and open-air conditions. In general, a whole blood/raw urine sample can be successfully analyzed within 2 min, which offers an economic, speedy, and sensitive approach for drug screening.

2. Experimental

2.1. Materials and reagents

Disposable capillaries (I.D. of 0.9 mm and length of 5 cm) were purchased from Huaxi Medical University Instrument Factory (Chengdu, China). Grade 4 chromatography paper (thickness of 0.21 mm) was supplied by Whatman International Ltd. (Maidstone, England). AM, MA, MDMA, and d_5-MA were purchased from Cerilliant (Round Rock, TX, USA). Analytical grade of acetone, chloroform, ethyl acetate, hexane, toluene, and *n*-butyl alcohol were from Guangzhou Chemical Reagent Factory (Guangzhou, China). HPLC grade of methanol and acetonitrile were supplied by Burdick & Jackson (Muskeg on, MI, USA). Pure water was purified through a Milli-Q water-purification system (Milford, MA, USA). Human whole blood and raw urine samples from healthy volunteers were donated by the First Affiliated Hospital of Southern Medical University (Guangzhou, China).

2.2. SFME-PS-MS analysis

A disposable glass capillary was used for direct SFME of whole blood and raw urine samples, by sequentially injecting 5 μL of sample and 5 μL of organic solvent into a capillary to form two adjacent liquids, and then tilting the capillary up and down for several cycles to induce slug flows of two liquids for extraction. After extraction, the sample and the organic solvent were reformed as two adjacent liquid plugs. A chromatography paper was cut into a triangle (10 mm height and 5 mm base width). The capillary was placed onto the middle of paper triangle, with the organic phase down, and the organic phase was flowed onto the paper triangle by gravity. When all of the organic phase drained, the capillary was moved away immediately. After the organic solvent volatilized and

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