HHS Public Access

Author manuscript

Talanta. Author manuscript; available in PMC 2016 September 01.

Published in final edited form as:

Talanta. 2015 September 1; 142: 190–196. doi:10.1016/j.talanta.2015.04.044.

Rapid Analysis of Synthetic Cannabinoids Using a Miniature Mass Spectrometer with Ambient Ionization Capability

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Abstract

Synthetic cannabinoids are an emerging class of drugs of abuse and are of a great concern for transport control and usage regulation. In this study, we have developed rapid analytical methods using a miniature mass spectrometer for the identification of synthetic cannabinoids, as the traces of bulk powders on surfaces or substances in blood and urine. Significantly simplified work flows were developed by employing two ambient ionization methods, the paper spray and extraction spray ionization. Using five synthetic cannabinoids as examples, a limit of detection of 2 ng was estimated for the detection of trace powders on a bench surface and limits of quantitation as good as10 ng/mL were obtained for the analysis of blood and urine samples.

Graphical Abstract

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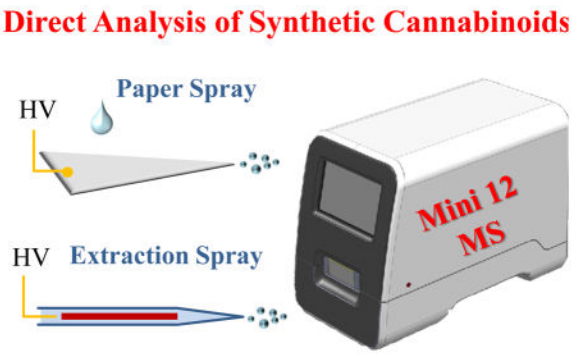

Keywords

ambient ionization; biofluids; tandem mass spectrometry; drug of abuse; paper spray; extraction spray

Introduction

Synthetic cannabinoids were initially developed in pharmacological research for the study of the endocannabinoid system [1]; however, recently they have emerged as a class of designer drugs. Synthetic cannabinoids for illicit use are distributed mainly in the forms of dried herbs or powdery products [2] and are deceptively marketed as herbal blends, room deodorizers, air fresheners, or incense products [3]. Although the chemical structures of the synthetic cannabinoids can differ substantially from that of delta-9-tetrahydrocannabinol (Δ^9-THC), they have a similar psychoactive effect of the primary natural cannabinoids [4]. They have a high binding affinity to the cannabinoid receptor CB_1, found primarily in the brain and central nervous system, or to CB_2 found in the peripheral nervous system, especially in cells associated with the immune system [5, 6]. Easy access of the synthetic cannabinoids at low costs [7] and the lack of effective means for routine screening have contributed to the fast growth in their use [8], especially by the young and first-time drug users [9, 10]. Emerging evidence has shown that the administration of synthetic cannabinoids may cause various adverse psychological and physiological effects on human health, with symptoms including anxiety, agitation, panic, paranoia, intoxication, psychosis, and seizures [11, 12]. The social and medical issues associated with the use of synthetic cannabinoids have drawn a significant attention from the international community and legal actions are being undertaken to control their use [8, 13]. Enforcement of the restrictions on the use of synthetic cannabinoids overall is a complicated process; however, the lack of governmental regulations in many countries on use of these compounds certainly is resulting in uncontrolled prevalence of the drug use. There are no established cutoff levels yet for regulatory detection of synthetic cannabinoids, because information about their dose-dependent effects is very limited [1].

Legal surveillance of the distribution and use of synthetic cannabinoids calls for the development of effective analytical methods for detecting and quantifying the synthetic cannabinoids from samples in a variety of forms, including the herbal blends [14–17], bulk powders [18, 19], urine [20–22], whole blood [23, 24], serum [25–27], hair [28–30], and

saliva samples [31–33]. The analytical techniques that have been demonstrated for analyzing synthetic cannabinoids mainly include micellar electrokinetic chromatography [14, 16], immunoassay [19, 20], nano-liquid chromatography [17], gas chromatography-mass spectrometry [15, 18], and high-performance (HP) or ultra-performance (UP) liquid chromatography (LC) coupled with mass spectrometry (MS) [21–32]. These methods are typically implemented in analytical laboratories using the bench-top equipment and often require laborious sample preparation procedures. The development of rapid and on-site analytical methods for fast identification of synthetic cannabinoids is highly desirable for a variety of applications, such as the forensic investigation, roadside inspection, workplace drug testing, and the screening at check points.

As already demonstrated in conjunction with HPLC, mass spectrometry can provide high sensitivity and high selectivity for both qualitative and quantitative analysis of the synthetic cannabinoids. Conventional laboratory-scale mass spectrometers are large and heavy, which limits their usage for in-filed applications. Miniature mass spectrometers have been developed to enable the on-site chemical analysis [34]. As opposed to the traditional chemical analysis work flow, where samples are brought to the laboratory for analysis, the miniaturized instruments can now be brought to the samples [34, 35]. However, sample preparation would also need to be done quickly in the field. Ambient ionization, in which the analytes in untreated samples are directly sampled and ionized for MS analysis, represents a promising solution for simplification of the sample preparation during on-site analysis.

Direct chemical analysis using MS with ambient ionization methods has advanced significantly in the past decade [36]. Since desorption electrospray ionization (DESI) [37] and direct analysis in real time (DART) [38] were reported in 2004 and 2005, respectively, more than 40 ambient ionization methods have been developed [36, 39–41]. Sample pretreatment and chromatographic separation, traditionally required for MS-based analysis, can now be bypassed. Analysis of synthetic cannabinoids using DART with a time-of-flight instrument has been previously demonstrated.[42, 43] Notably, miniature mass spectrometry systems with ambient ionization capability, e.g., paper spray [41, 44], extraction spray [45], or low temperature plasma [46], have been shown to be promising for on-site applications in food safety [47, 48], pharmaceutical drug development [49], environment monitoring [50–52], and homeland security [53, 54], as well as for biomedical diagnosis [55].

In this study, direct identification of synthetic cannabinoids in bulk powder or biofluid samples has been developed using a miniature ion trap mass spectrometry system with two ambient ionization methods, the paper spray and extraction spray ionization (Fig. 1). Five synthetic cannabinoids, exemplary of a class of drugs of a significant concern for regulatory control, were selected for method development and validation.

Experimental

Chemicals and reagents

Naphthalen-1-yl-(1-pentylindol-3-yl) methanone (JWH-018), naphthalen-1-yl-(1-pentylindol-3-yl)-1,1,2,2,3,3,4,4,5,5,5-d_{11}-methanone (JWH-018-d_{11}), 4-

methoxynaphthalen-1-yl-(1-pentylindol-3-yl) methanone (JWH-081), 1-[(5-fluoropentyl)-1H-indol-3-yl]-(naphthalen-1-yl) methanone (AM-2201), 2-(4-methoxyphenyl)-1-(1-pentyl-indol-3-yl) methanone (RCS-4), and [1-(5-fluoropentyl)-1H-indol-3-yl](2,2,3,3-tetramethylcyclopropyl) methanone (XLR-11) (structures shown in Fig. 2), each dissolved in methanol at concentrations of 1 mg/mL, were purchased from Lipomed AG (Arlesheim, Switzerland). All synthetic cannabinoids reference standards had purities greater than 99%. Whatman Grade 1 cellulose chromatography paper was purchased from Whatman (Piscataway, NJ, USA) and used to prepare sample substrates for paper spray and extraction spray ionization. Bovine whole blood stabilized with $EDTAK_2$ was purchased from Innovative Research (Novi, MI, USA). Synthetic urine was purchased from CST Technologies (Great Neck, NY, USA). Methanol of HPLC grade was purchased from Mallinckrodt (Hazelwood, MO, USA). Other chemicals used in the experiment were purchased from Sigma-Aldrich (Milwaukee, WI, USA). Stock solutions of the analytes were prepared by dilution with the methanol and were subsequently spiked into the raw samples for analysis.

Instrumentation

A desktop miniature mass spectrometry system, Mini 12 [56], was utilized to perform the analysis. The integrated Mini 12 system weighed 25 kg, had outside dimensions of 19.6×22.1×16.5 in., and consumed a power less than 100 W. The pumping system was composed of a HiPace 10 turbomolecular pump (Pfeiffer Vacuum, Nashua, NH, USA) and a two-stage diaphragm pump (MPU 1091-N84.0-8.99, KNF Neuberger, Trenton, NJ, USA). A discontinuous atmospheric pressure interface (DAPI) [57, 58] was used to enable efficient transfer of ions from the ambient ionization sources to a rectilinear ion trap (RIT) [59] located within the vacuum manifold in a pulsed fashion. For each scan, the DAPI was opened briefly for about 15 ms for ion introduction and closed during the rest of the time in each scan cycle. The ions trapped in the RIT were then mass analyzed using an rf (1 MHz) amplitude scan. Resonance ejection was performed using an AC excitation (350 kHz) with its amplitude ramped with the rf scan. A scan speed of 10,000 m/z per second was used. The user interface for instrument control and data acquisition was developed in-house.

MS/MS Analysis of Synthetic Cannabinoids Using Mini 12

The MS/MS capability of the Mini 12 miniature mass spectrometer plays an essential role in the direct, in situ MS analysis of complex samples without any traditional sample pretreatment or chromatographic separation. The sensitivity can be significantly improved by the elimination of chemical noise through the MS/MS process [60]. Characteristic fragmentation patterns corresponding to the structural features of the analytes are useful, together with information of the molecular mass, for confirmation of chemical identities so that high specificity in analysis can be retained in miniature mass spectrometers without ultra-high mass accuracy or high mass resolution [60]. The fragmentation of the molecular ions generated by nanoESI was first studied for each synthetic cannabinoid using in-trap collision induced dissociation (CID) with the Mini 12. Due to the special mode of ion introduction using the DAPI, residual air was used as the collision gas instead of helium that is the gas of choice for lab-scale ion trap instruments. It has been previously demonstrated

that helium can be used with DAPI-MS but longer scan time was required and the improvement to performance was not significant.[61] Notched SWIFT (stored wavelength inverse Fourier transform) waveforms were used for ion isolation. An AC excitation signal was applied for subsequent CID of the isolated precursor ions.

In the positive ionization mode, the protonated molecular ions of the synthetic cannabinoids were produced and isolated for the CID. The instrumental parameters of the Mini 12 for MS/MS analysis of synthetic cannabinoids were optimized, including the high voltage for the spray, the amplitude of the SWIFT signal, the frequency and the amplitude as well as the duration of the AC excitation, to obtain a maximum signal intensity for the fragment ions. Product spectra recorded under the optimized conditions (Table S1) are shown in Fig. 3 and S1–3, representative of in-trap fragmentations with air at 1 mtorr as the collision gas. For example, the MS/MS spectrum of protonated JWH-018 m/z 342 (Fig. 3a) indicates cleavages at both sides of the carbonyl group. The base peak at m/z 155 results from cleavage between the carbonyl group and the indole part. Another peak at m/z 214 originates from cleavage between the carbonyl group and the naphthalene ring. Similar fragmentation was observed for XLR-11 (Fig. 3b), JWH-081, AM-2201, and RCS-4 (Fig. S1–3). The fragment ion m/z 214 contains the indole unit and was subjected to further fragmentation which occurred with successive losses of the alkyl side chain C_5H_{10} and CO to yield fragment ions at m/z 144 and 116, respectively. Similar fragmentation patterns were also observed for the synthetic cannabinoid AM-2201 (Fig. S2). These identified MS/MS transitions can be used for analysis of the corresponding synthetic cannabinoids in complex mixtures. Note that the optimized conditions and the relative intensities are specific for in-trap CIDs performed by RIT with air as the collision gas. For future applications, a data base can be constructed with MS/MS spectra obtained for each synthetic cannabinoid at set conditions for chemical identification and confirmation.

Surface Analysis using Paper Spray

Rapid detection of drugs of abuse at check points is essential for the control of illegal drug transport. Bulk powders are often found but their chemical identity cannot be immediately determined. Sampling methods using cotton swabs have been previously used to collect the samples from a surface for subsequent analysis using ambient ionization.[62] As a part of this study, we demonstrate a protocol of detecting synthetic cannabinoids from surfaces using Swiffer-type sample collection followed by MS analysis using the miniature mass spectrometer and paper spray ionization. As shown in Fig. 4a, a piece of Whatman Grade 1 cellulose chromatography paper (Whatman, Piscataway, NJ, USA) cut into a square of 1x1 cm^2, wetted with 10 μL methanol, was used to wipe a surface (Fig. 4a). To analyze the samples collected on the paper through wiping, the paper square was then cut into a triangle with a sharp tip; a copper clipper was used to hold the paper triangle in front of the DAPI inlet of the Mini 12; 20 μL solvent was dropped onto the paper to elute the compounds in the collected sample; a high voltage of 4.0 kV was applied to induce the spray from the tip of the paper triangle for MS analysis (Fig. 4a).

As demonstrated in previous studies [63, 64], paper spray is a process integrating analyte extraction, analyte transfer on paper, and spray ionization. The properties of the solvent

chosen for paper spray can have a significant impact on the overall analytical performance, which is also highly dependent on the chemical properties of the target analyte. Using open source software (Estimation Program Interface (EPI) Suite version 4.0), the partition coefficients of the synthetic cannabinoids used in this study were calculated to be between 5.80 and 6.98, which indicate their relatively low polarities hence low solubility in aqueous solvents. In an attempt to optimize the overall elution-ionization efficiency, several pure organic solvents, including methanol, ethanol, acetonitrile and isopropanol were tested as the spray agents. The highest signal intensity was observed with methanol. Addition of 0.1% formic acid to the methanol was found to further improve the signal intensity for the synthetic cannabinoids in the positive mode of paper spray.

This protocol was optimized for direct analysis of powders of the synthetic cannabinoids from a bench surface. A methanol solution (5 μL) containing the five synthetic cannabinoids of interest, each of 20 ng (4 ng/μL), was dropped on to the bench surface, spreading to an area of about 1.0 cm^2. After it had completely dried, the benchtop surface was wiped by the square paper substrate to collect the samples, and the paper was subsequently cut into a triangle for paper spray. Signal-to-noise (S/N, calculated by peak heights) ratios better than 30 were obtained for both MS (Fig. 4b) and MS/MS analyses (Fig. 4c–e). The limit of detection (LOD) was estimated to be better than 2 ng (absolute amount) for an analysis of these synthetic cannabinoids using this protocol.

Quantitation of Synthetic Cannabinoids in Biofluids

Analysis of illicit drugs and their metabolites in urine and blood samples has been applied for conviction of drug abuse, development of therapeutic drugs, monitoring of therapy compliance, etc. [65–67] Use of integrated MS analytical systems with simple procedures would potentially allow testing to be done directly by nurses, physicians and police officers. Mandatory requirements for sensitivity and quantitative precision need to be met for these applications. In this study, we applied extraction spray ionization using the Mini 12 to measure quantitative performance for direct analysis of synthetic cannabinoids in urine and blood samples. Extraction spray ionization has been shown to provide good sensitivity and very stable spray signals [45], which is important for achieving high precision in quantitation for DAPI-MS systems when internal standards are used [56]. The proteins and salt in blood or urine samples also bind well with cellulose in the paper substrate, which helps avoid clogging at the spray tip.

A paper strip, 8 mm long, 0.6 mm wide and 0.8 mm thick, was cut from Whatman Grade 1 cellulose chromatography paper. The urine or blood samples, each of 5 μL, were first loaded onto a glass slide and then taken up by capillary action into this paper strip. After being allowed to dry in open air for 10 min, the paper strip was inserted into a borosilicate glass capillary (1.5 mm o.d., 0.86 mm i.d., 5 cm length) with a pulled tip for nanoESI [45]. A methanol solution of 10 μL containing 0.1% formic acid was then added into the capillary for extraction and spray ionization. The nanoESI capillary was placed in front of the DAPI inlet of Mini 12, with a high voltage of 2.5 kV applied via a metal wire.

The five synthetic cannabinoids were spiked into synthetic urine samples and bovine whole blood samples at concentrations over a wide range for testing. Representative MS/MS spectra recorded at a concentration of 50 ng/mL are shown in Fig. 5 for JWH-018 in blood (Fig. 5a), JWH-081 in urine (Fig. 5b), AM-2201 in blood (Fig. 5c), and RCS-4 in urine (Fig. 5d). The S/N ratios obtained for the direct analysis of the raw samples using the extraction spray and Mini 12 are comparable with those obtained for samples diluted in methanol solutions (see Fig. 5e for 50 ng/mL XLR-11 in methanol as an example). The SWIFT notches used for precursor isolations were wider than a mass unit, so some other ions survived and contributed to the peaks around the precursors as shown in Figure 5a–d. Since a single frequency AC excitation was used for CID, these ions did not contribute much to the fragment peaks in the MS/MS spectra.

A series of blood samples was prepared with JWH-018 spiked at different concentrations from 5 to 1000 ng/mL and with JWH-018-d_{11} added as the internal standard (IS) at a same concentration of 200 ng/mL. These samples were analyzed using extraction spray and the Mini 12. The MS/MS transitions m/z 342→155 and m/z 353→155 were used for JWH-018 and JWH-018-d_{11}, respectively. The ratio of the fragment ions m/z 155 from the analyte and the internal standard was calculated for each sample and plotted in the calibration curve as shown in Figure 5f. Relative standard deviations (RSD) better than 10% were achieved over the entire concentration range and good linearity ($R^2 > 0.99$) was also obtained. The limit of quantitation (LOQ), determined as the concentration with a S/N of 10 obtained for the MS/MS fragment peak m/z 155, was 20 ng/mL for JWH-018 in both blood and urine. Similar procedures were applied for JWH-081, AM-2201, RCS-4, and XLR-11, and the LOQs for these synthetic cannabinoids in blood and urine were determined to be between 10 and 20 ng/mL.

Conclusions

The simple analytical protocol for detection and quantitation of the synthetic cannabinoids are based on the use of miniature mass spectrometer and ambient ionization. The MS/MS capability enabled by the ion trap mass analyser is important for retaining adequate sensitivity and quantitation precision for direct sampling ionization. The analytical performance demonstrated with the five representative synthetic cannabinoids validates the capability of an integrated, miniature ion trap mass spectrometry system with the paper spray or the extraction spray for potential on-site chemical analysis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by the Youth Talent Program of Chinese Academy of Inspection and Quarantine, the Science Research Program of Chinese Academy of Inspection and Quarantine (2014JK016), the National Key Technology Research and Development Program of China (2013BAK04B03), the National Natural Science Foundation of China (21307123), the National Institute of General Medical Sciences (1R01GM106016) from the US National Institutes of Health. The authors thank Linfan Li, Yue Ren, Xiao Wang, and Chien-Hsun Chen for helpful discussions.

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Highlights

- Direct analysis of synthetic cannabinoids using miniature mass spectrometry system
- MS/MS patterns of 5 representative synthetic cannabinoids were obtained
- Traces of synthetic cannabinoids on surfaces detected by Swiffer-type sample collection
- Direct quantitation of synthetic cannabinoids in blood and urine samples

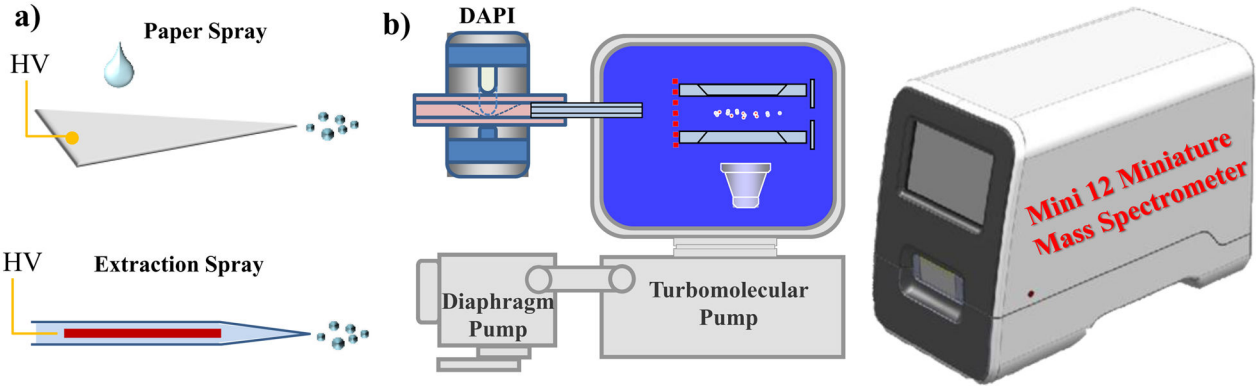

Fig. 1.

a) Paper spray ionization, extraction spray ionization, and b) Mini 12 desktop ion trap mass spectrometer for the identification of synthetic cannabinoids

Compound	Chemical Structure				CAS	Formula	MW
	Core	Link	Ring	Tail			
JWH-018	indole	methanone	naphthyl	pentyl	209414-07-3	$C_{24}H_{23}NO$	341.5
JWH-081	indole	methanone	4-methoxynaphthyl	pentyl	210179-46-7	$C_{25}H_{25}NO_2$	371.5
AM-2201	indole	methanone	naphthyl	5-fluoropentyl	335161-24-5	$C_{24}H_{22}FNO$	359.4
RCS-4	indole	methanone	4-methoxyphenyl	pentyl	1345966-78-0	$C_{21}H_{23}NO_2$	321.4
XLR-11	indole	methanone	2,2,3,3-tetramethylcyclopropyl	5-fluoropentyl	1364933-54-5	$C_{21}H_{28}FNO$	329.5

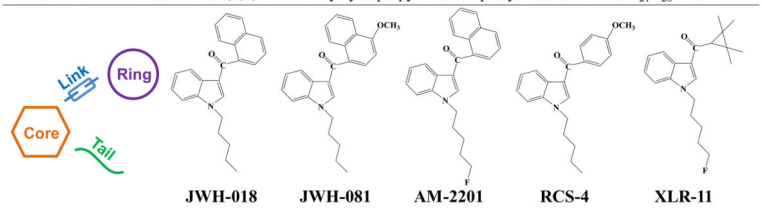

Fig. 2.

Chemical structures of the studied synthetic cannabinoids, which can be broken down into four main parts: the core and substituents, the link section, the ring and substituents, and the tail section

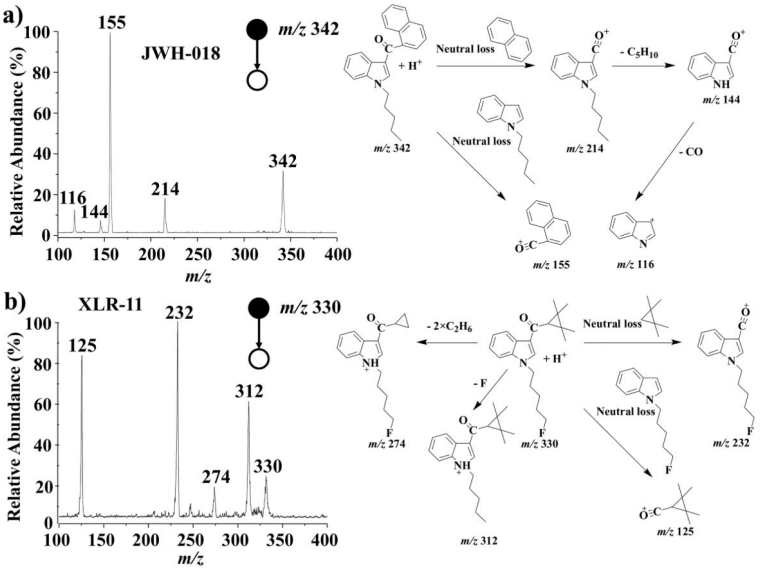

Fig. 3.

MS/MS spectra and proposed fragmentation pathways for a) JWH-018 and b) XLR-11

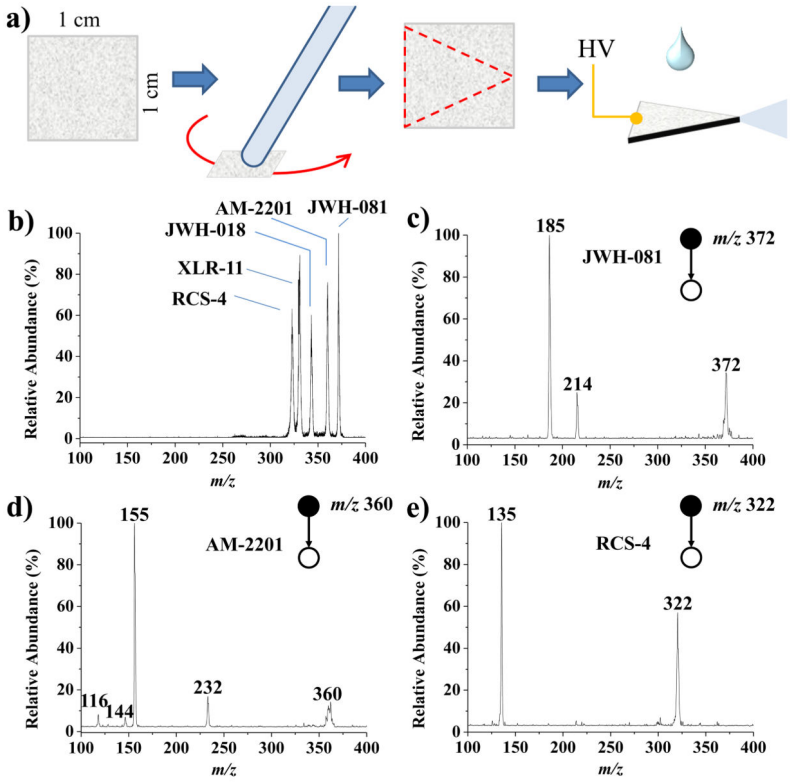

Fig. 4.

a) Procedure for Swift-type sample collection from surfaces followed by paper spray ionization for MS analysis. b) MS spectrum for analysis of synthetic cannabinoids spread on a bench surface at a density of 20 ng/cm^2. Corresponding MS/MS spectra for c) JWH-081 d) AM-2201 and e) RCS-4

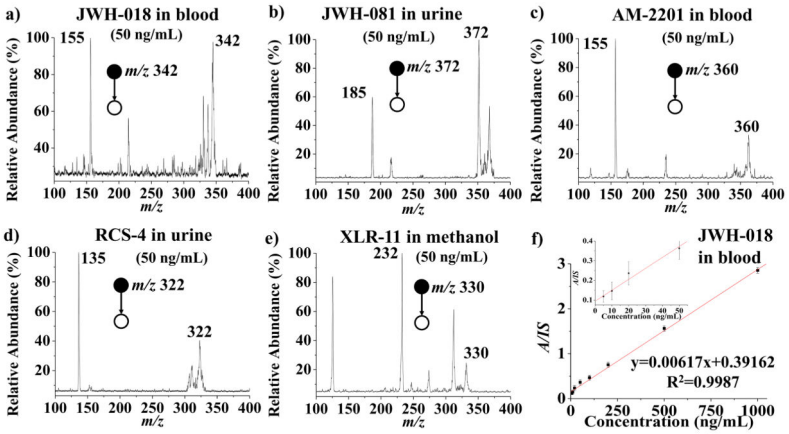

Fig. 5.

MS/MS spectra for analysis of (a) JWH-018 in whole bovine blood, (b) JWH-081 in urine, (c) AM-2201 in blood, (d) RCS-4 in urine, (e) XLR-11 in methanol, each at 50 ng/mL, with extraction spray ionization and Mini 12. (f) Calibration curve for the analysis of JWH-018 in bovine blood samples, MS/MS transition m/z 342 to 155 for JWH-018, and m/z 353 to 155 for internal standard JWH-018-d_{11}