Rapid qualitative and quantitative analysis of novel drug analogues via Desorption Electrospray Ionisation - Mass Spectrometry (DESI-MS)

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“Learn from yesterday, live for today, hope for tomorrow. The important thing is not to stop questioning.” - Albert Einstein.

“To be yourself in a world that is constantly trying to make you something else is the greatest accomplishment.” - Ralph Waldo Emerson.

Certificate of authorship and originality

I certify that the work in this thesis has not previously been submitted for a degree nor has it been submitted as part of the requirements for a degree except as fully acknowledged within the text.

I also certify that the thesis has been written by me. Any help that I have received in my research work and the preparation of the thesis itself has been acknowledged. In addition, I certify that all the information sources and literature used are indicated in the thesis.

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DATE:

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Abbreviations

1B3P – 1-Benzyl-3-pyrrolidinol

2C-I – 4-Iodo-2,5-dimethoxyphenethylamine

4-DEAB – 4-(Diethylamino)benzaldehyde

4-F-AP – 4-Fluoroamphetamine

4-MMC – 4-Methylmethcathinone

4-MTA – 4-Methylthioamphetamine

4-OH-AP – 4-Hydroxyamphetamine

5-HT – Serotonin

ABDF – Bromobenzodifuranylisopropylamine

AccuTOF – Accurate time-of-flight

AF – Ammonium formate

AFP – Australian Federal Police

AGAL – Australian Government Analytical Laboratories

AIDIP – Australian Illicit Drug Intelligence Program

AP – Amphetamine

API – Atmospheric pressure ionisation

APPI – Atmospheric pressure photoionisation

AP-MALDI – Atmospheric pressure – matrix assisted laser desorption ionisation

ASAP – Atmospheric-pressure solids analysis probe

ATR – Attenuated total reflection

ATS – Amphetamine-type substances

BE – Benzoylecgonine

BZP – *N*-Benzylpiperazine or 1-benzylpiperazine

CC – Cinnamoyl cocaine

CCD – Central composite design

cps – Counts per second

C_{the} – Theoretical concentration

DAPPI – Desorption atmospheric pressure photoionisation

DART – Direct analysis in real time

DBZP – 1,4-Dibenzylpiperazine

DESI – Desorption electrospray ionisation

DMA – *N,N*-Dimethylamphetamine

DMAA – Dimethylamylamine

DMMP – Dimethyl methylphosphonate

DMS – Dimethyl sulfone

EBCP – Ethyl 1-benzyl-4-carboxypiperazine

EC – Ethyl centralite

EI – Electron ionisation

EIC – Extracted ion chromatogram

ELDI – Electrospray-assisted laser desorption ionisation

EME – Ecgonine methyl ester

EP – Ephedrine

ESI – Electrospray ionisation

FA – Formic acid

FFD – Full factorial design

FI – Flow injection

FTIR – Fourier transform infrared

GC-FID – Gas chromatography - flame ionisation detector

GC-MS – Gas chromatography - mass spectrometry

GSR – Gun-shot residue

H_2O – Water

HCl – Hydrochloride

HPLC – High performance-liquid chromatography

HS-GC – Head space - gas chromatography

IRMS – Isotope ratio - mass spectrometry

IS – Internal standard

IT – Ion trap

KBr – Potassium bromide

K-*t*BuO – Potassium tert-butoxide

LC – Liquid chromatography

LC-MS – Liquid chromatography-mass spectrometry

LOD – Limit of detection

LOL – Limit of linearity

LOQ – Limit of quantitation

LSD – Lysergic acid diethylamide

M – Mean of the experimentally determined concentrations

MA – Methylamphetamine

MALDESI – Matrix-assisted laser desorption electrospray ionisation

MBCP – Methyl 1-benzyl-4-carboxypiperazine

MC – Methyl centralite

mCPP – 3-Chlorophenylpiperazine

MDA – 3,4-Methylenedioxyamphetamine

MDDMA – 3,4-Methylenedioxydimethylamphetamine

MDEA – 3,4-Methylenedioxyethylamphetamine

MDHOET – 3,4-Methylenedioxy-*N*-(2-hydroxyethyl)amphetamine

MDMA – Methylenedioxymethylamphetamine ('Ecstasy')

MDP-2-P – 3,4-Methylenedioxyphenyl-2-propanone

MDP-2-POH – 3,4-Methylenedioxyphenyl-2-propanonol

MeOH – Methanol

MeOPP – 4-Methoxyphenylpiperazine

MS – Mass spectrometry/Mass spectrometer

MS/MS – Tandem mass spectrometry

MUX – Multiplexed

NHSP – National Heroin Signature Program

NMI – National Measurement Institute

NMR – Nuclear magnetic resonance

OFAT – One-factor-at-a-time

OMPP – 2-Methoxyphenylpiperazine

P2P – Phenyl-2-propanone

PCDL – Personal Compound Database and Library

pEP – Pseudoephedrine

PMA – 4-Methoxyamphetamine

PMMA – 4-Methoxymethylamphetamine

pMMA – Polymethyl methacrylate

PMP-2-P – 4-Methoxyphenyl-2-propanone

PN – Piperonyl nitrile

PTFE – Polytetra fluoroethylene (Teflon)

PVC – Polyvinyl chloride

QC – Quality check samples

QTOF – Quadrupole time-of-flight

IR – Infrared

RDX – Trinitrohexahydro-1,3,5-triazine

RE – Relative error

RSD – Relative standard deviation

SEM-EDX - Scanning electron microscopy – energy dispersive X-ray

SD – Standard Deviation

SNR – Signal-to-noise ratio

TFMPP – 3-Trifluoromethylphenylpiperazine

THC – Δ^9-Tetrahydrocannabinol

TLC – Thin-layer chromatography

TOF – Time-of-flight

UNODC – United Nations Office on Drugs and Crime

US – United States

UV – Ultraviolet

UV-DAD – Ultraviolet diode array detector

Abstract

Desorption electrospray ionisation - mass spectrometry (DESI-MS) is an ambient ionisation technique that can be applied to the analysis of illicit drugs and novel drug analogues in seized drug material. Currently used preliminary identification techniques lack sensitivity and selectivity and are prone to false positive and false negative results. Therefore, it was important to investigate the use of DESI-MS as a novel preliminary identification technique in the analysis of a range of compounds with the potential for future automated library matching aiding in the rapid identification of unknowns.

In this research, 4-methylmethcathinone (mephedrone or 4-MMC), cocaine, 1-benzylpiperazine (BZP), 3-trifuoromethylphenylpiperazine (TFMPP), 3-chlorophenylpiperazine (mCPP), 4-methoxyphenylpiperazine (MeOPP) and other amphetamine-type substances (ATS) such as amphetamine (AP), methylamphetamine (MA), 3,4-methylenedioxymethylamphetamine (MDMA), *N,N*-dimethylamphetamine (DMA), 4-methoxyamphetamine (PMA), and 4-methoxymethylamphetamine (PMMA) were the drugs of interest since they are increasingly prevalent drugs of abuse globally.

The optimisation of the technique and the application of DESI-MS to the analysis of these compounds were demonstrated. A particularly suitable surface, semi-porous polytetra fluoroethylene (PTFE, Teflon) was utilised, as it gave superior signal stability and reproducibility as compared to other surfaces (polymethyl methacrylate (pMMA) and polyvinyl chloride (PVC)).

The limits of detection (LOD) of 4-MMC and the piperazine analogues were determined to range between 0.0023 - 2.30 μg/mm^2. The LOD of the ATS was determined to be in the range 0.02 - 2.80 μg/mm^2. DESI-MS was also utilised in the preliminary analysis of illicit cocaine samples. The LOD of cocaine was determined to be 3.47 μg/mm^2. The chemical profiles obtained using DESI-MS were also compared to two current confirmatory analysis techniques, gas chromatography – mass spectrometry (GC-MS) and liquid chromatography – mass spectrometry (LC-MS). The by-products and impurities detected were used to link samples to their synthetic route of manufacture and to the precursors used. The detection of truxillines in the seized cocaine samples aided in determining their geographical origin.

Selectivity and matrix effects were evaluated for the compounds of interest in each study. The effect of adulterants including caffeine, procaine, levamisole, lignocaine, paracetamol, and atropine on the detectability of cocaine were investigated. The detectability of ATS were evaluated by adding caffeine, paracetamol, magnesium stearate, and dimethyl sulfone. Piperazine compounds were adulterated using caffeine and a mixture of piperazines (TFMPP and BZP) was also evaluated since these are commonly found in combination. 4-MMC was adulterated with caffeine, paracetamol, MA, phentermine, AP, MDMA, 4-hydroxyamphetamine, 4-fluoroamphetamine, nordiazepam, diazepam, oxazepam, cocaine, heroin, methadone, cathine, cathinone, 4-diethylaminobenzaldehyde, 1-benzyl-3-pyrrolidinol, and methylone. In most cases, despite the presence of ion enhancement or suppression due to the addition of adulterant, the analytes remained detectable.

Quantitative experiments for 2 µL spotted solutions of 4-MMC, using codeine-D_6 as an internal standard, introduced in the desorption spray solvent, showed a linear correlation (R^2 > 0.9840) over the range 50 – 800 µg/mL. The precision for triplicates analysed on five different days (n = 15) was <38 % RSD. The accuracy, expressed as relative error, was <13 %. Identification based on accurate mass and MS/MS spectra aided in discriminating compounds with the same molecular formula. The results obtained using DESI-MS demonstrate its applicability in the rapid qualitative analysis (and preliminary quantitative analysis of 4-MMC) of cocaine, 4-MMC, BZP, TFMPP, mCPP, MeOPP and ATS.