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Original article:

AMPHETAMINES ANALYSIS IN WASTEWATERS - METHOD PERFORMANCE OF SOLID PHASE EXTRACTION - HIGHER PERFORMANCE LIQUID CHROMATOGRAPHY MASS SPECTROMETRY TECHNIQUES (SPE-HPLC MS/MS)

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ABSTRACT

Recently, many articles have reported different levels and distribution of amphetamine hitherto detected in biological fluids now appreciably found in aquatic environment at ng/L levels. Identification and measurement of amphetamine and its metabolites in surface and sewage waters using higher performance liquid chromatographic methodologies in the literatures now on current trend have provided information that are of scientific interest and effectively replaced immunological methods which only suggest the presence of these substances. Active research on both distribution and impacts of this important drug of abuse and related metabolites in the wastewaters are on-going.

Keywords: amphetamine, solid phase extraction, wastewaters, higher performance chromatography, drug metabolites

INTRODUCTION

The survey of reported liquid chromatography tandem mass spectrometry (HPLC-MS/MS) methods from literatures for the determination of amphetamine and human metabolites in waters (van Nuijs et al. 2009a; Zuccato et al., 2005, 2008; Castiglioni et al., 2006; Hearn et al., 1991; Bones et al., 2007) is discussed in this paper. The higher performance liquid chromatography-mass spectrometry (HPLC-MS) or with tandem mass spectrometry (HPLC-MS/MS) were becoming popular in their separation and detection capabilities, as they appear very rapid, sensitive and selective method at ng/mL concentration levels. The concentrations of amphetamine and its metabolites in aqueous media using HPLC-MS or HPLC-MS/MS appeared to have largely replaced GC-MS in the analysis of illicit substances particularly in aqueous media. The extraction volumes, mobile phases, detectors (interfaces) and acquisition modes used by different scientists to provide sensitivity and selectivity are shown. The separation procedures rely on the principles of reversed-phase columns with different solvent gradients depending on applications. Tabulated are limits of quantifications depending on matrices for quantification and confirmation of drugs. Recently, variations over convectional HPLC-MS method have appeared in the literature with the name: Ultra-performance liquid chromatography (UPLC-MS/MS) is unique for its short columns packed with small particles sizes and stability at pH range (Bijlsma et al., 2009; Wood et al., 2005; Huerta-Fontela et al., 2008a; Boleda et al., 2007; Kasprzyk-Hordern et al., 2007, 2008). With the development of this rela-

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tively new technology, a shorter analysis times as well as gain in separation, efficiency, resolution and sensitivity have been reported. To minimize the effects of ion suppression on the analytical signal, a relatively new HILIC (Hydrophilic interaction chromatography) technique was also carried out in some experiments. Since analytes were better retained on HILIC column, unaffected by ion suppression and a reduction in analytical signal was minimised, the possibilities of using HILIC approach in the quantitative determination of polar compounds such as amphetamine and its metabolites was apparently justified (van Nuijs et al., 2009b; Gheorghe et al., 2008). The use of MS/MS with triple quadrupole (QqQ) analyzers with electrospray ionization (ESI^+) were mostly used in selected reaction monitoring mode (SRM) to minimize the matrix interferences. The choices of ionization in ESI positive-ion mode were to have achieved ionizations and simultaneous determinations of analytes.

To assess inherent selectivity and peculiar reservations of each method based on the compound and its metabolites wide range of polarities and extraction challenges from different aquatic (wastewater, sediment, sludge) matrices, this paper therefore hopes to review the high quality work published in the literature on amphetamine and its metabolites using HPLC methods to maximise future application needs.

AMPHETAMINE AND METABOLITES

Among the drugs classified as amphetamines are amphetamines (AM), methamphetamines (MA, "speed") and methylenedioxymethamphetamine (MDMA, "ecstasy or Adam"). They are usually taken orally but can be snorted, smoked or injected. They are addictive stimulant drugs that affect the central nervous system among other risks of dependence and abuse. Other designer drugs are methylenedioxyamphetamine (MDE, "eve") and 3,4-methylenedioxyamphetamine (MDA, "love pills") (EMCDDA, 2007).

The major metabolic pathway involves deamination of cytochrome P450 to para-hydroxyl amphetamine and phenylacetone, this later compound is oxidised to benzoic acid and excreted as glucuronide or glycine (hippuric acid) conjugates. Smaller amounts of amphetamine are also converted to norepheridine by oxidation. Although most enzymes involved in amphetamine metabolism have not been clearly defined, CYP2D6 is known to be involved with the formation of 4-hydroxylamphetamine.

Since CYP2D6 is genetically polymorphic, population variation in amphetamine metabolism are a possibility (Ensslin et al., 1996). Figure 1 shows that MDMA generates free and conjugated MDA, which is a common metabolite of MDE and MDMA. Other metabolites from MDMA are 4-hydroxy-3-methoxymethamphetamine, HMMA and 4-hydroxy-3-methoxyamphetamine, HMA (Kloss et al., 1984). With normal urine pHs, approximately half of an administered dose of amphetamine is excreted as derivatives of alpha-hydroxylamphetamine and another approximately 30-40 % of the dose can be excreted as parent amphetamine, this is because the urinary recovery of amphetamine is depending on pH and urine flow rate (Dollery, 1991).

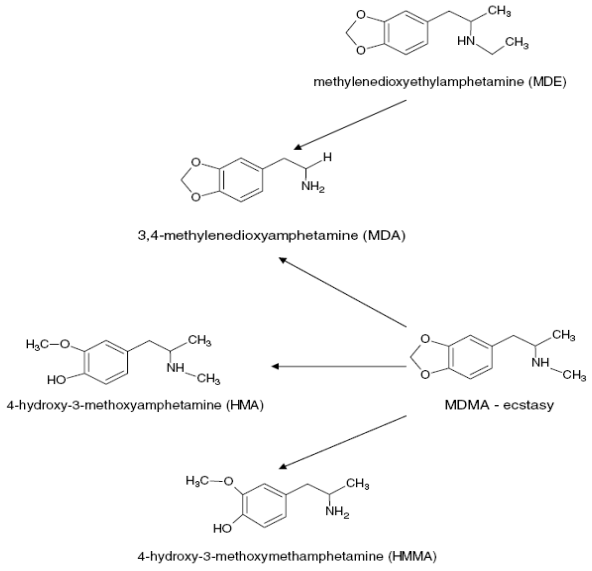

Figure 1: Main metabolites of 3,4-methylenedioxymethamphetamine (MDMA) in urine (Kloss et al., 11984)

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HPLC-MS/MS METHODOLOGIES

Emerging contaminants of various biological active compounds, pharmaceuticals, personal care products, herbicides and antibiotics are present in complex and varying compositions in wastewaters and sewages. The procedures employed by different authors and published in the literatures in the past decade which include sample preconcentration as an important step to the determination of amphetamine and related metabolites, followed by higher performance liquid chromatographic-tandem mass spectrometry separation and detection have been reviewed and summarised in Table 1 (at the end of this paper).

Sample pre-concentration

Improved sample clean-ups, pre-treatment, chromatographic separation, centrifugation, filtration, alternative ionization and the use of deuterated compounds as surrogate standards have been employed by authors (Kloss et al., 1984; van Viet et al., 1990; Ellenhorn and Barceloux 1988; Kolbrich et al., 2006; Cone, 1995; Hilton and Thomas, 2003; Marais and Laurens, 2009) to reduce the signal effects thereby correcting the matrix influences. To avoid sample degradation, dark-glass bottles with samples stored at -20 ^{o}C at a pH of 6 have been recommended (Hearn et al., 1991; Bones et al., 2007; Bijlsma et al., 2009; Wood et al., 2005). Solid phase extraction using different extraction protocols achieving different extraction method recoveries of 50-105 %, (Kloss et al., 1984); 50-65 % (Ellenhorn and Barceloux, 1988); 73-96 % (Hummel et al., 2006); 90 % (Hilton and Thomas, 2003), and 65-106 % (Drummer et al., 2007) respectively. When using HPLC-MS/MS with electro spray ionization detector (ESI) as interface, the matrix effect is one of the major factors affecting the isolation and analysis of drugs in complex matrices like wastewaters and sewages (Hummel et al., 2006). Co-elution of matrix substituents causes suppression or enhancement of signal which ultimately affects the accuracy and reliability of results.

Amphetamine in the aqueous environment

The major metabolites that have been so found and quantified are summarised in Table 2. However, the presence of some human amphetamine metabolites identified in biological fluids (Kloss et al., 1984; Cone, 1995; Ambre, 1985; Chen et al., 2008; Zhang and Zhou, 2007; Quintana et al. 2005; Wylie et al., 2005; Yu et al., 2009) are yet to reported in the aquatic environment.

Table 2: Amphetamine and metabolites

Human metabolites identified in biological fluids	Human metabolites identified in the aquatic environment
Chen et al., 2008; Zhang and Zhou, 2007; Quintana et al., 2005; Wylie et al., 2005; Yu et al., 2009	*Kloss et al., 1984; Ellenhorn and Barceloux, 1988; Cone, 1995; Ambre, 1985*
Amphetamine	detected
Metamphetamine	detected
p-OHMA	not detected
p-OHMA-Glu	not detected
p-OHMA-Sul	not detected
MDA	detected
MDMA	detected
MDEA	detected
MBDB	detected

In many parts of Europe, amphetamine and its metabolites have been reported in many wastewaters, surface waters and sewage at nanogram and microgram concentration levels with influent samples containing more of amphetamine and metabolites than effluents collected from sewage treatment plants, STPs (Table 3).

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Table 3: Amphetamine and metabolites concentration in wastewaters worldwide

Analytes	Matrix	Influent (ng L^{-1})	Effluent (ng L^{-1})	SW (ng L^{-1})	Volume	References
Amphetamines	3 Rivers, Italy	-	-	< 0,65	N/A	Zuccato et al., 2008
	Eastern Spain	1400	110-210	-	N/A	Bijlsma et al., 2009
	2 STPs, Italy	5.4-14.7 ± 10.6	2.8	-	1-2 L	Castiglioni et al., 2006
	42 STPs, NE Spain	03-6880	04-2100	-	N/A	Huerta-Fontela et al., 2008
	Barcelona, Spain	20.8-41.1 ± 9.1	0.45-2.2 ± 0.1	2.84	1 L	Postigo et al., 2008
	5 STPs, Spain	15	< 1.0	< 0.8	1.5 L	Huerta-Fontela et al., 2008
Metamphet-amine	5 STPs, Nebraska, USA	1.3 ± 0.1-1.4	3501 ± 78.3	-	2.5 L	Bartelt-Hunt et al., 2009
	Eastern Spain	-	< 100-540	-	N/A	Bijlsma et al., 2009
	2 STPs, Italy	< 500	< 1.11-3.5 ± 2	-	1-2 L	Castiglioni et al., 2006
	42 STPs, NE Spain	3-277	3-90	-	N/A	Huerta-Fontela et al., 2008
	3 STPs, USA	15 ± 2-66 ± 14	0.8-1.3	-	N/A	Jones-Lepp et al., 2004
	Barcelona, Spain	4.8-18.2 ± 5.8	2.1-6.3 ± 0.6	2.87	1 L	Postigo et al., 2008
	Murray, USA	6.0-34	03-7	-	2 L	Hearn et al., 1991
MDA	42 STPs, NE Spain	03-266	01-200	-	N/A	Huerta-Fontela et al., 2008
	3 Rivers, Italy	-	-	3 ± 0.3-4	N/A	Zuccato et al., 2005
	Eastern Spain	500-1400	410-680	-	N/A	Bijlsma et al., 2009
	2 STPs, Italy	4.6 ± 7.3-8.7	0.9 ± 1.9-1.1 ± 1.5	-	1-2 L	Castiglioni et al. 2006
	5 STPs, Spain	03-266	1-200	-	1.5 L	Huerta-Fontela et al., 2008
MDMA	3 Rivers, Italy	-	-	1.1-4.0	N/A	Zuccato et al., 2008
	Eastern Spain	326-2700.5	100-2100.2	-	N/A	Bijlsma et al., 2009
	2 STPs, Italy	13.6 ± 12.6-14.2 ± 14.5	4.4 ± 3.7-5.1 ± 3	-	N/A	Castiglioni et al., 2006
	5 STPs, Spain	91	67	3.5	1.5 L	Huerta-Fontela et al., 2008
	STP, Italy	2-598	2-267	-	1 L	Huerta-Fontela et al., 2008
	Barcelona, Spain	133-135.13 ± 29.8	82.1-148.2 ± 22.2	129	1 L	Postigo et al., 2008
	Murray, USA	< 1.0-10.0	-	-	2 L	Hearn et al., 1991
	42 STPs, NE Spain	2-598	2-267	-	N/A	Huerta-Fontela et al., 2008
MDEA	5 STPs, Spain	27	< 2.1	-	1.5 L	Huerta-Fontela et al., 2008
	2 STPs, Italy	4.19-1.5 ± 3.8	< 1.64	-	N/A	Castiglioni et al., 2006
	STP, Italy	6-114	12	-	1 L	Bijlsma et al., 2009
	STP, Spain	< 500	< 100	-	N/A	Huerta-Fontela et al., 2008

HPLC method performances

The survey of reported HPLC-MS/MS methods for the determination of amphetamine and human metabolites in water with the extraction volumes, mobile phases, detectors (interfaces) and acquisition modes used by different scientists to provide sensitivity and selectivity is shown in Table 1.

The application of LC-MS^2 to the simultaneous analysis of a wide variety of illicit drugs in waste water was first reported by Castiglioni et al. (2006). The HPLC column (XTerra MS C18, 100 x 2.1 mm, 3.5 µm) with four separate total gradient elution times of 28, 32, 36 and 26 min for amphetamines, cocainics, opiods and cannabinoids were reported respectively. Wastewater samples (50 mL) were spiked with 20 ng of internal standards (cocaine-d_3, benzoylecgonine-d_3, norcocaine-d_3, cocaethethylene-d_8, amphetamine-d_6, methamphetamine-d_9, MDA-d_5. MDMA-d_5, MDEA-d_5, morphine-d_3, morphine-3β-D-glucuronide-d_3, 6-acetylmorphine-d_6, methadone-d_3, EDDP-d_3 and 11-nor9-carboxy-Δ-THC-d_3) and extracted using a standard Oasis MCX SPE procedure. Quantitation was based on the MH^+ peak areas of the analyte relative to the MH^+ peak areas of the corresponding internal standards. The

mobile phase solvent A: acetic acid 0.05 % in water and solvent B: acetonitrile. But solvent A for cannabinoids was triethylamine 0.05 % in water. ESI gave abundant protonated molecule ions (MH^+) for each of the analytes and internal standards. Measured quantitation ranges were: 0.2-1 µg/L for cocaine and its metabolites, 80-200 ng/L for morphine, 10 ng/L for 6-acetylmorphine, 60-90 ng/L for methadone and its metabolite 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine and lower than 20 ng/L for amphetamines. The overall method variability was ≤ 10 % for the influents, ≤ 5 % for effluents and recoveries in wastewater were ≥ 80 %.

The use of Polar Organic Chemical Integrative Samplers (POCIS) methodology for sampling was introduced by Bartelt-Hunt et al. (2009), the samplers were installed in rivers upstream and downsteam of treated WWTP at five different sites. The HPLC separation was performed isocratically on a Betabasic-18 column (250 x 2.1 mm, 5 µm, and 50 ^oC) with a mobile phase of methanol with 0.1 % formic acid in water. The electrospray ionization in positive mode (ESI^+) by multiple reaction monitoring gave the mass spectrum of the analytes. Each of the POCIS devices was removed from its deployment canister, and the contents were transferred with 20 mL high-purity methanol into silane-treated vials, stored at -20 ^oC and compounds were eluted with 50 mL of high-purity methanol through silane-treated gas gravity flow chromatography columns into 120 mL evaporation tubes. After addition of the internal standards (metamphetamine-d_9, $^{13}C_3$-caffeine, and $^{13}C_8$-sulfamethazine), the eluates were evaporated to approximately 1 mL under nitrogen and quantitatively transferred to autosampler for analysis. The estimated detection limits for most compounds were less than 1 pg/µL while the averaged recovery was 123 ± 30 %; however, the determination of the uptake rates for the compounds of interest for quantitative analysis is the limitation of POCIS.

Ultra-performance liquid chromatography (UPLC-ESI-MS/MS) is a variation over convectional HPLC-MS method. The ultra-fast LC-MS^2 is unique for its short columns packed with small particles sizes and stability at pH range; with the development of this relatively new technology, a shorter analysis times as well as gain in separation, efficiency, resolution and sensitivity are introduced (Huerta-Fontela et al., 2008).

The occurrence of psychoactive drugs in wastewaters using the new UPLC-ESI-MS^2 technique (Huerta-Fontela et al., 2008; Wood et al., 2005) on an Acquity BEH C_{18} UPLC column, (100mm x 2.imm i.d., 1.7 µm particle size) after enrichment by solid phase extraction (SPE). The optimized separation conditions were for solvent A: acetonitrile with 0.1 % formic acid; solvent B: 30 mM formic acid/ammonium formate (pH 3.5) at a flow rate of 0.5 mL/min. The ESI working in positive mode with acquisition in selected reaction mode (SRM) gave abundant protonated molecular ion of each compound as the precursor ion: nicotine (163>130; 163>117), cotinine (177>80; 177>98), caffeine (195>138; 195>110), paraxantine (181>124; >181>96), amphetamine (136>119; 136>91), MDA (180>163; 180>105), metamphetamine (150>91; 150>119), MDMA (194>163; 194>105), MDEA (208>163; 208>133), ketamine (238>125; 238>220), cocaine (304>182; 304>105), benzoylecgonine (290>169; 290>150), LSD (324>223; 324>208), PCP (244>85; 244>159) and fentanyl (337>188; 337>105). The LODs were lower than 1.5 ng/L and 300 ng/L where LOQs were lower than 5 ng/L and 850 ng/L, respectively, with the recoveries ranged from 70 to 101 %.

At the University of Glamorgan, Sustainable Environmental Research Centre, UK, Kasprzyk-Hordern et al. (2007) made use of the new, fast and sensitive method for the broad range of pharmaceuticals, illicit drugs which include amphetamines with triple quadrupole tandem mass spectrometry with positive-ion mode (ESI^+) was used for separation of up to 30 compounds on Acquity UPLC BEH C_{18} column (1.7 µm; 1 mm x 100mm) with mobile phase A: (pH,

2.8) of 94.5 % of H_2O, 5 % MeOH, 0.5 % CH_3COOH and mobile phase B: (pH, 3.2) of 99.5 % MeOH and 0.5 % CH_3COOH after Oasis MCX, sorbent extraction. The methods limits were of quantification ranged from 0.3 to 50 ng/L with the instrumental limit of quantification from 0.2 to 10 µg/L.

Bijlsma et al. (2009) recently reported use of UPLC-MS/MS method came from for the simultaneous determination of amphetamines, cocaines, cannabis and their metabolites in surface and waste water. After SPE enrichment, the selected drugs were separated on Acquity BEH C_{18} UPLC column, (50 mm x 2.1 mm i.d., 1.7 µm particle size) with methanol (solvent A) and 5 mM ammonium acetate/0.1 % formic acid (solvent B). The use of MS/MS with triple quadrupole (QqQ) analyzers with electrospray ionization (ESI^+) was used in selected reaction monitoring mode (SRM) to minimize the matrix interferences. The choice of ionization in ESI positive-ion mode was deliberate to have abundant ionization of THC-COOH as well as simultaneous determinations for all the analytes. The recoveries of 70-120 % were reported with precision of ≤ 20 % for all compounds.

CONCLUSIONS

HPLC-MS has been widely used as a good technique for highly polar, highly molecular weight and thermolabile compounds for the determination of amphetamine and its active metabolites in waters. No hydrolysis, no derivatization, one-step extraction especially with the introduction of API and ESI interfaces, the technique has been popular.

The Oasis MCX was also a good choice because its mixed mode materials during loading, washing and elution steps allows improved selectivity towards basic analytes due to pH and polarity changes. The internal standard was found as valuable tool for standardization and quantification and has almost identical physicochemical properties like the normal drugs and their metabolites analogues. Like cocaine analysis and similar drugs, the Oasis HLB cartridge built of a hydrophilic and a lipophilic monomer and Oasis MCX cartridge - a mixed reversed-phase/cation-exchange - were common cartridges for drug extraction with good recoveries. However, insufficient reference standards in contrast to GC-MS technique (which has large data bases of mass spectral) has made HPLC less attractive in studies where structural confirmation is needed.

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Table 1: Survey of reported HPLC-MS/MS methods for the determination of amphetamine and human metabolites in water (2000-2010)

Analytes	Matrix	Sample preparation			LC		MS		Method LOQ (ng/L)	Reference
		Volume (mL)	Extraction	Method Recovery (%)	Chromatographic column	Mobile phase	Detector (interface)	Acq. mode		
1 ALC	WW	500 mL	SPE (Strata-XC, 200 mg)	50-65 %	HPLC: Phenomenex Onyx C_{18} (200 x 3.0 mm i.d.)	NR	NR	NR	36-120	Bones et al., 2007
5 ALCs	WW	50 mL	SPE (Oasis, MCX, 60 mg)	50-105 %	HPLC: XterraMS C_{18} (100 mm x 2.1 mm, 3.5 µm)	250 µL/min A: CH_3COOH/ H_2O B_1: AcN A_2 0.05 % TEA/H_2O	QqQ (EST^+)	MRM	300 pg/L ^{wwinf} 1 ng/L ^{wweff}	Castiglioni et al., 2006
1 ALC	WW	250 mL	SPE (Oasis, HLB, 200 mg)	36-49 %	HPLC: Varian Pursuit XRs C_{18} (100 mm x 2.0 mm, 3 µm)	A: de-ionized water/ 0.5 % HCOOH B: 82 % CH_3OH/ 18 %/AcN/ 0.5 % HCOOH		Scan (CID)	0.25-5.0	Hearn et al., 1991
5 ALCs	WW	100 mL	SPE (Oasis, HLB, 200 mg)	70-110 %	UPLC: Acquity BEH C_{18} (100 mm x 2.1 mm, 1.7 µm)	A: AcN/0.1 % HCOOH B: 30 mM $HCOOH/NH_4HCO_2$ (pH 3.5)		QqQ (EST^+)	5 and 850	Huerta-Fontela et al., 2008
1 ALC	SW	100 mL	SPE (Oasis, MCX, 60 mg)	65-106 %	UPLC: Acquity BEH C_{18} (1.7 µm, 1 mm x 100 mm)	A: 94.5 % H_2O 5 % MeOH, 5 % CH_3COOH (pH 2.8) B: 99.5 % MeOH + 0.5 % CH_3COOH (pH 3.2)	QqQ (EST^+)	MRM	0.3-50	Kasprzyk-Hordern et al. 2007

Acq. mode - Acquisition mode- SRM, Selected reaction monitoring; CID, Collision-induced dissociation. Detector and interface used – QqQ, Triple quadrupole; ITMS, Ion Trap mass spectrometry, ESI, Electrospray ionization. MeOH – Methanol; TEA, Triethylamine; NH_4HCO_2, Ammonium acetate; AcN, Acetonitrile, H_2O, Water. WW, Wastewater; SW, Surface water; WW^{inff}, Waste water influent; WW^{eff}, Waste water effluent. RPLC, Reversed-phase liquid chromatography; UPLC, Ultra-performance liquid chromatography; HILIC, Hydrophilic interaction chromatography. ALCs: amphetamine-like compounds