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Gas chromatography: A tool for drug analysis in biological samples

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A B S T R A C T

To date, diseases are very common due to environmental contamination; genetic disorders, microorganisms and drug addiction, which are cured by different drugs. Drug addiction gives rise to many dangerous diseases because it causes many abnormal behaviors in the body. The abnormal behavior depends on where the drug is accumulated in the body. It is well understood that long time consumption of any drug (especially in case of drug addiction) in any biological sample may be very harmful. Besides, it also disturbs the normal behavior of the brain because of which abnormality appears. Hence, the analysis of drugs and their metabolites in urine, plasma, serum, oral liquid, and other numerous materials have great importance in this advanced era. The analysis of drugs in numerous matters helps us in understanding the reason of abnormal behavior caused by drugs and their metabolites. In drug analysis, many chromatographic techniques have great importance. In all chromatographic techniques, gas chromatography has a unique position. The present paper reviews the role of gas chromatography for drug analysis in the different biological samples. Besides, the attempts have also been made to discuss the future challenges and perspectives of the drug analysis in the biological samples by gas chromatography.

Capsule Summary: The role of gas chromatography in the analysis of drugs in different biological samples and its advantages are discussed. Besides, future perspectives of drug analysis using GC have also been given.

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INTRODUCTION

There are many types of ailments everywhere due to various factors. Besides, there is a treatment for a specific ailment using a particular drug. All the medicines are supposed to be beneficial, but numerous have positive effects. Accumulation of the drugs may occur in numerous materials, which may cause serious side effects if a person has its addiction. Vary of the short- and long-term effects of drug abuse depends on the nature of the person. Drug abusing directly affects many people every day. The anomalous behavior that happens during obsession has been observed by many as "choices" of the dependent individual, but current imaging studies have exposed a fundamental disturbance to the different parts of the brain that are significant for the usual progressions of enthusiasm, reward, and inhibitory control in addicted persons (Volkow et al., 2003). Hence, the addiction of drugs gives rise to dysfunction of the tissue of the brain (Hassan et al., 2020; Leshner, 1997). Besides, the addiction to drugs disturbs the expression of the gene, products of protein, and circuits in the neuron (Nestler, 2001).

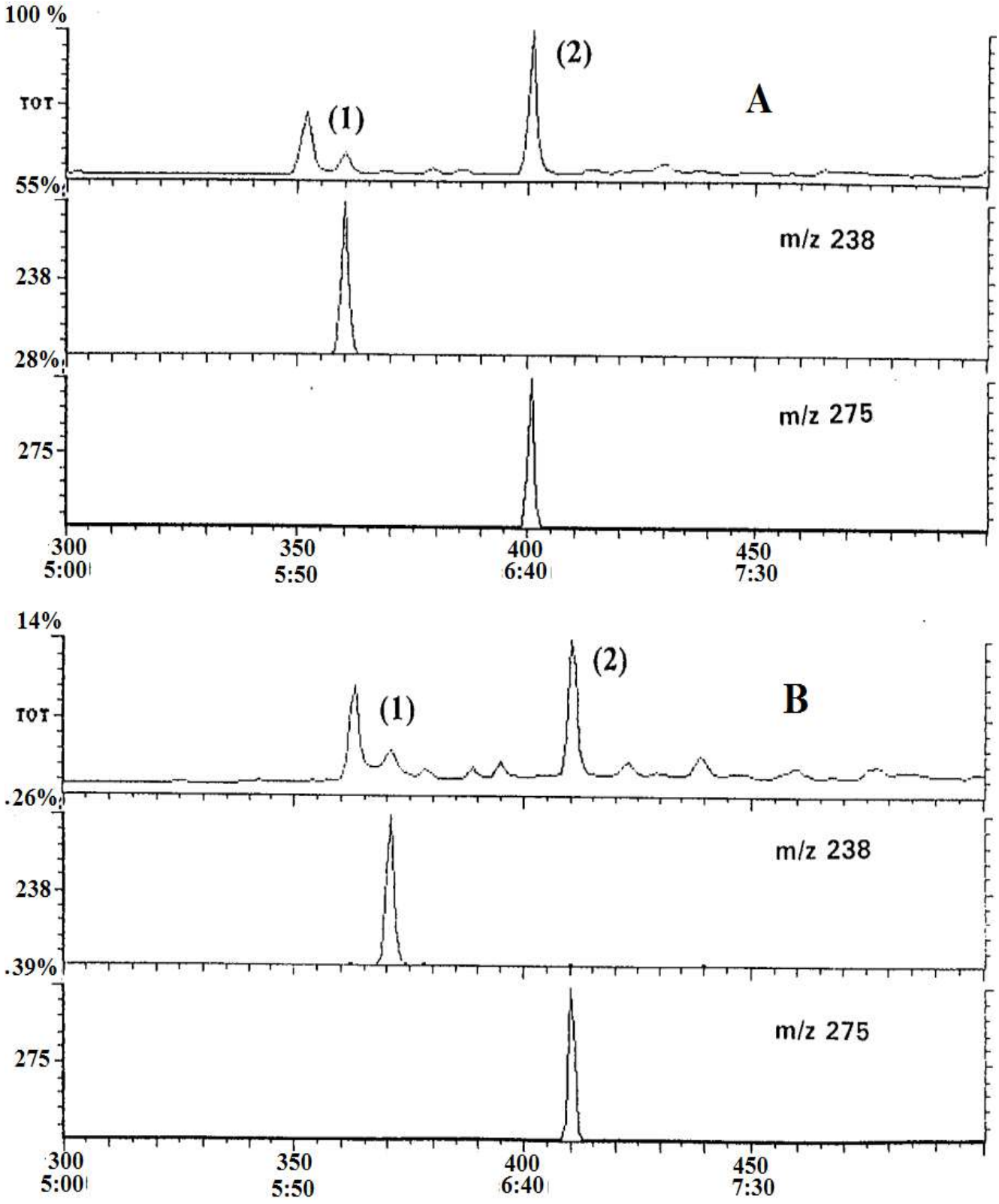

Fig. 1: Total ion current and selected ion monitoring chromatograms of a spiked plasma sample (A) and a volunteer's plasma sample (B). Peak:1 = ketamine (100 ng/ml in A); 2 = internal standard. Retention times are given in second (first line) and minutes (second line) (Feng et al., 1995).

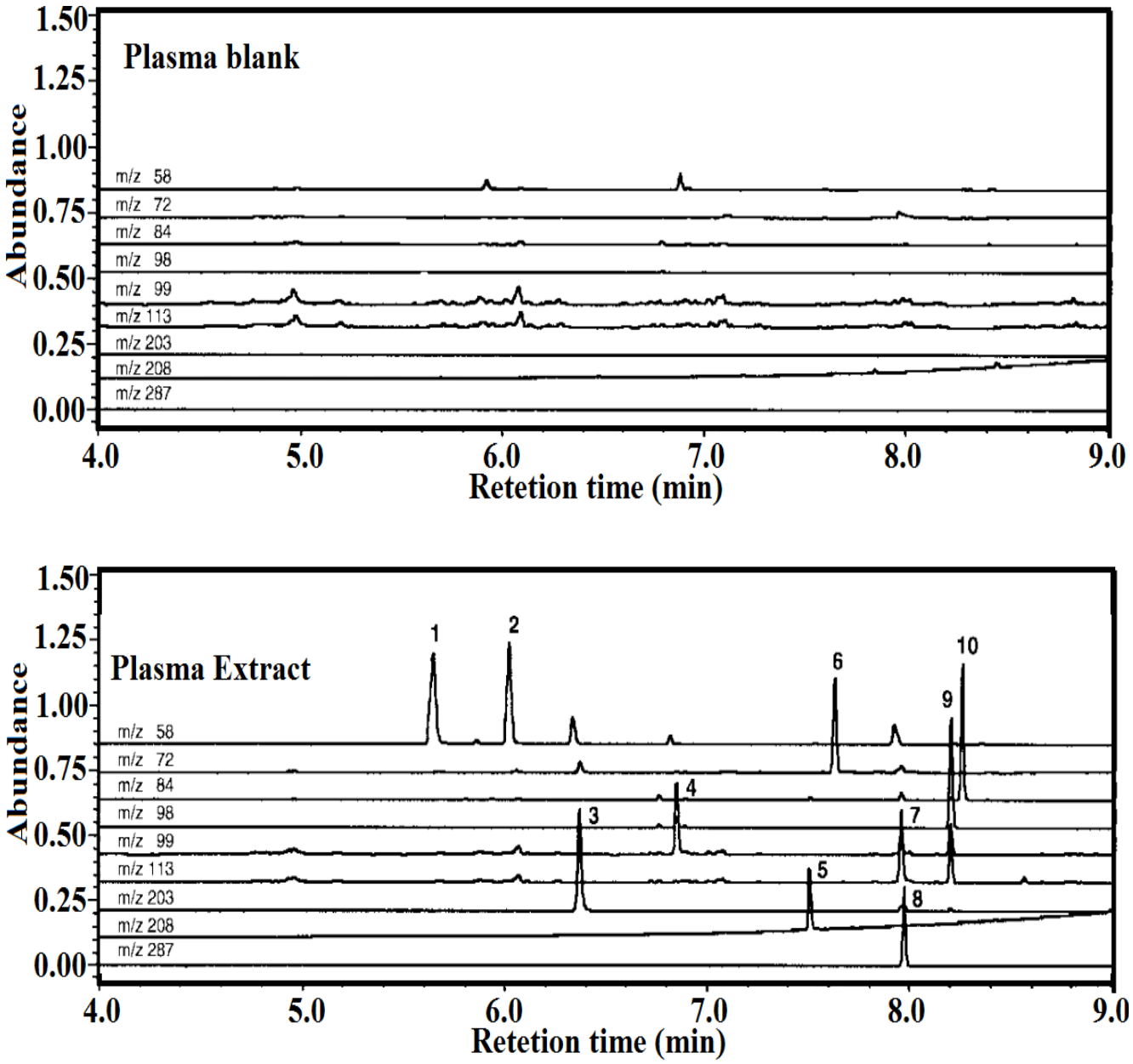

Fig. 2: SIM chromatograms for ten antihistamines from human plasma by the MonoTip C_{18} tips. The amount of each drug spiked into 0.1 mL was 20 ng. Peaks: 1 = diphenhydramine; 2 = orphenadrine; 3 = chlorpheniramine; 4 = diphenylpyraline; 5 = triprolidine; 6 = promethazine; 7 = homochlorcyclizine; 8 = cyproheptadine; 9 = cloperastine; 10 = clemastine (Hasegawa et al., 2006).

The future investigation might permit us to explain whether this is the cause that youths look to become dependent on alcohol (Slawecki and Roth, 2004) and nicotine (Chen et al., 2000). Drug addiction increases the concentration of extracellular dopamine in the regions of limbic, including the nucleus Accumbens (NAc) (Koob and Bloom, 1988) which is the reason for reward (Schultz, 2000) and salience (Lu et al., 2003; Horvitz, 2000). The drug analysis has great importance in pharmaceutical industries. For the clinical trials and other studies, we have many biological samples such as blood, plasma, serum, and urine. Accumulation of drugs for a long time may cause some side effects such as diabetes (Ram, 2008), gastrointestinal (Higuchi et al., 2009), cardiovascular (Antman et al., 2007), renal problems (Whelton, 1999) and other several effects. Besides, the existence of these drugs in the environment for a long time leads to toxicity to *flora* and *fauna*.

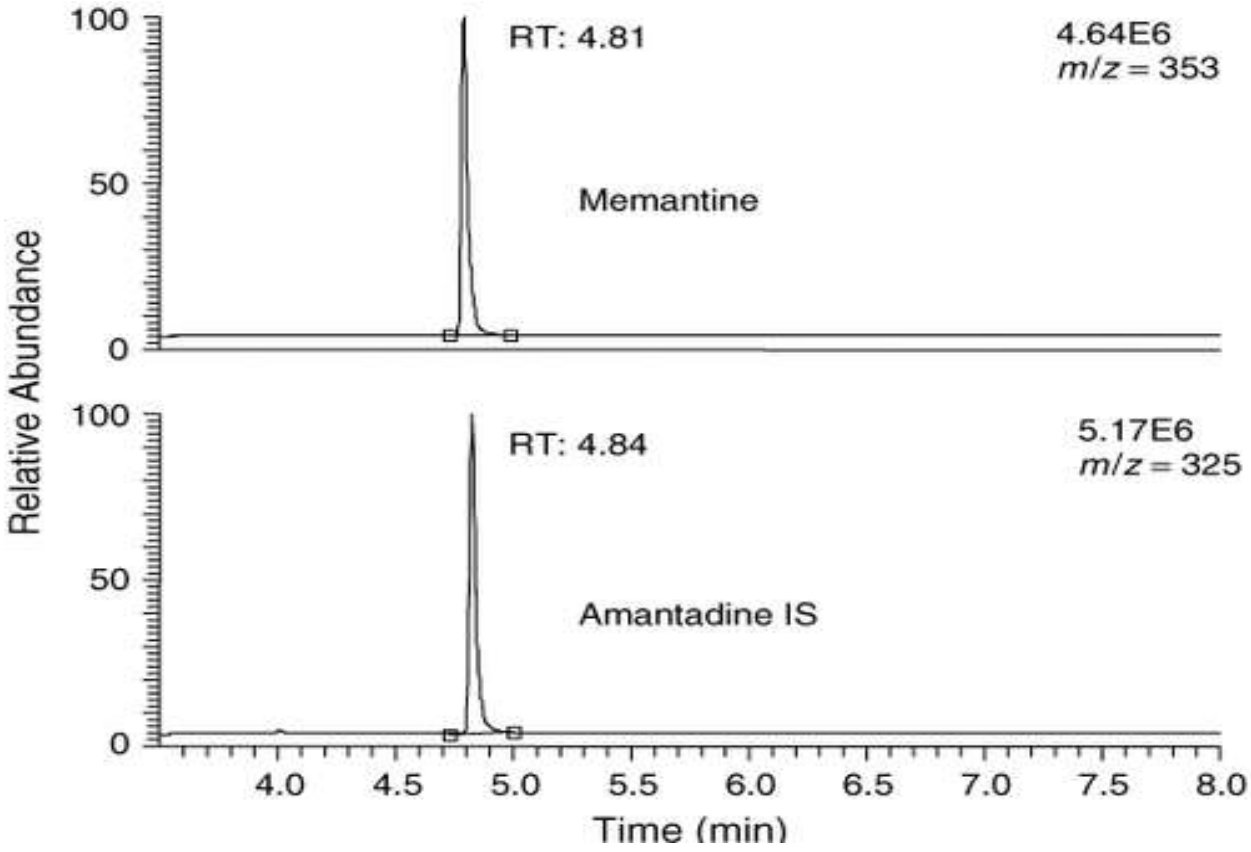

Fig. 3: Single ion recording mass chromatograms obtained after analysis of a plasma sample from a human volunteer receiving 10 mg of memantine orally (Leis et al., 2002).

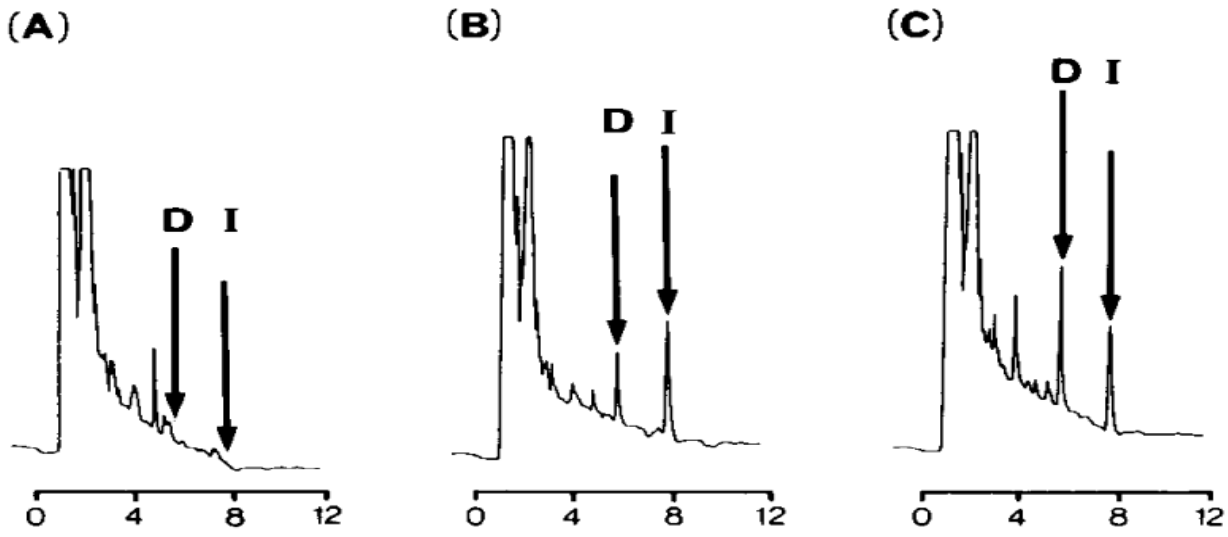

Fig. 4: Typical gas chromatograms showing (A) drug-free control plasma extract, (B) control plasma extract containing 2 ng/ml amlodipine and 2 ng/ml internal standard and (C) plasma extract of a human subject 4 h after oral administration of 20 mg amlodipine. Peaks: D = derivatised amlodipine (retention time 6 min); I = derivatised internal standard (retention time 8 min) (Beresford et al., 1987).

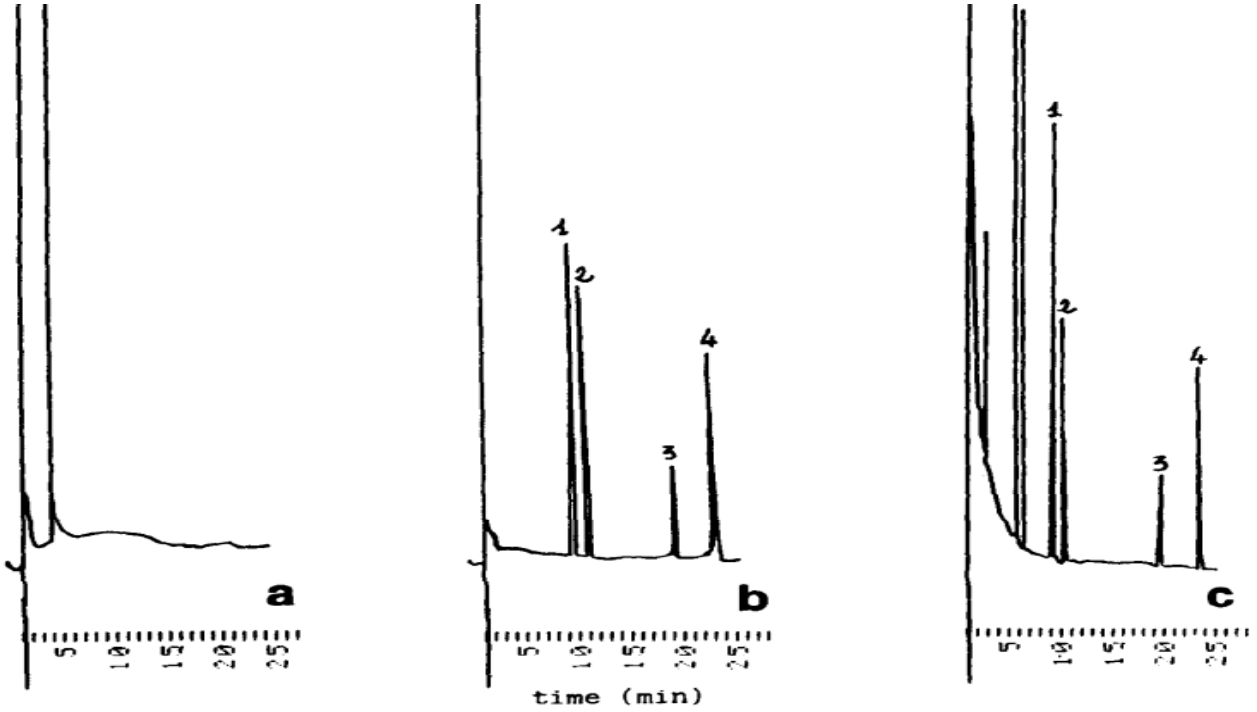

Fig. 5: Chromatograms of (a) a blank plasma, (b) an extract containing I00 ng/ml each of zolpidem and zopiclone, and (c) an extract of human plasma containing 170 ng/ml of zolpidem and I00 ng/ml of zopiclone. 1 = Zolpidem, 2 = clonazepam, 3 = zopiclone, 4 = alpidem (Stanke et al., 1996).

Additionally, their metabolites are also found in the environment, which may be toxic (Halling-Sørensen et al., 1998). Moreover, the analyses of these drugs in tissues, plasma, blood, urine, etc. are employed in clinical studies. Therefore, the drug should be analyzed in human plasma at a trace level (Li et al., 2003). Many technologies have been used for drug testing all over the world, which includes chromatography, spectroscopy, crystallization, capillary electrophoresis, membrane, biosensor, biotransformation (Settel, 1997). But an analytical technique of high reproducibility, efficiency, selectivity, rapidity is required to achieve the best results. Moreover, a low detection limit in the range of micro to nano range is required for the trace analysis from the biological matrices. Hence, gas chromatography is considered one of the best analytical techniques for trace analysis.

Gas chromatography commands a substantial role in the analysis of the pharmaceutical product (Watson, 1999). Recently, gas chromatography has been used for assay of drugs such as isotretinoin (Lima et al., 2005), cocaine (Zuo et al., 2004) and employed in the determination of residual solvents in betamethasone valerate (Somuramasami et al., 2011). Gas chromatography is also an important tool for the analysis of the impurities of pharmaceuticals. In recent years GC has been applied to estimate the process-related impurities of the pharmaceuticals (Siddiqui et al., 2017); (Hiriyanna and Basavaiah, 2008), residual solvents listed as an impurity by the International Conference of Harmonization are analyzed by the GC using a variety of detectors (Hashimoto et al., 2001; Saraji et al., 2012; Deconinck et al., 2012). Drug analysis by gas chromatography has been done in the following biological samples.

In human plasma

Researchers have developed several methods for the determination of many drugs in human plasma using gas chromatography. da Fonseca et al. (2013) described a method for the determination of seven antipsychotic drugs in human plasma using gas chromatography-tandem mass spectrometry (GC-MS). For sample preparation purposes, they used microextraction by packed sorbent (MEPS). (Pietracci et al., 2013) developed a gas chromatography-mass spectrometry (GC–MS) method to determine a new-generation antidepressants, including olanzapine (antipsychotic used in bipolar disorder), and antidepressant selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine and its metabolite (norfluoxetine, paroxetine, sertraline, venlafaxine, and mirtazapine) in plasma. The sample preparation step was done by liquid-liquid extraction.

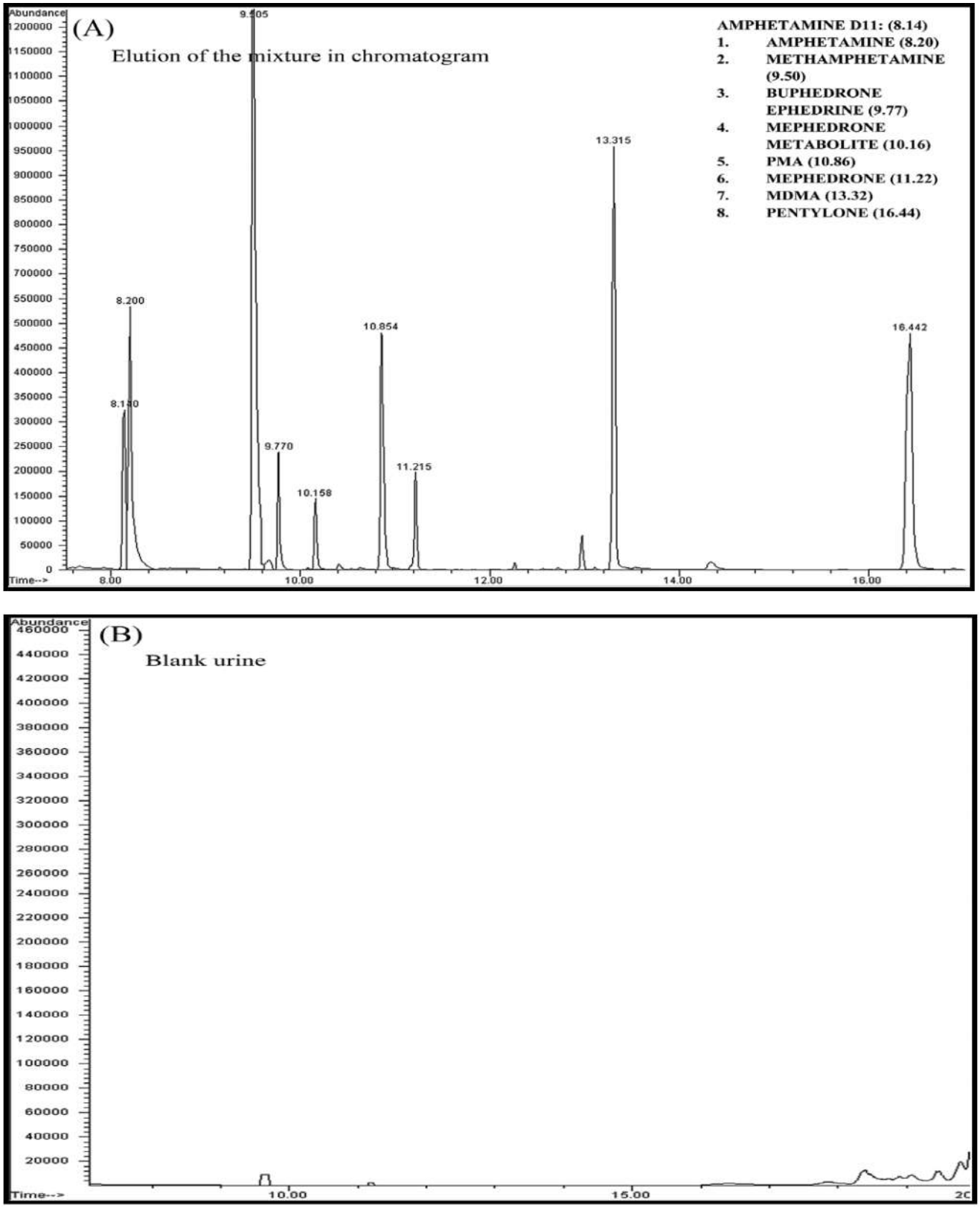

Fig. 6: (A) SIM chromatogram for the eight stimulant drugs (SPME tips and PFPA derivative; optimum conditions were applied) at a concentration of 1 µg/mL in a urine sample. (B) Chromatogram (SIM) for a blank urine sample (Alsenedi and Morrison, 2018).

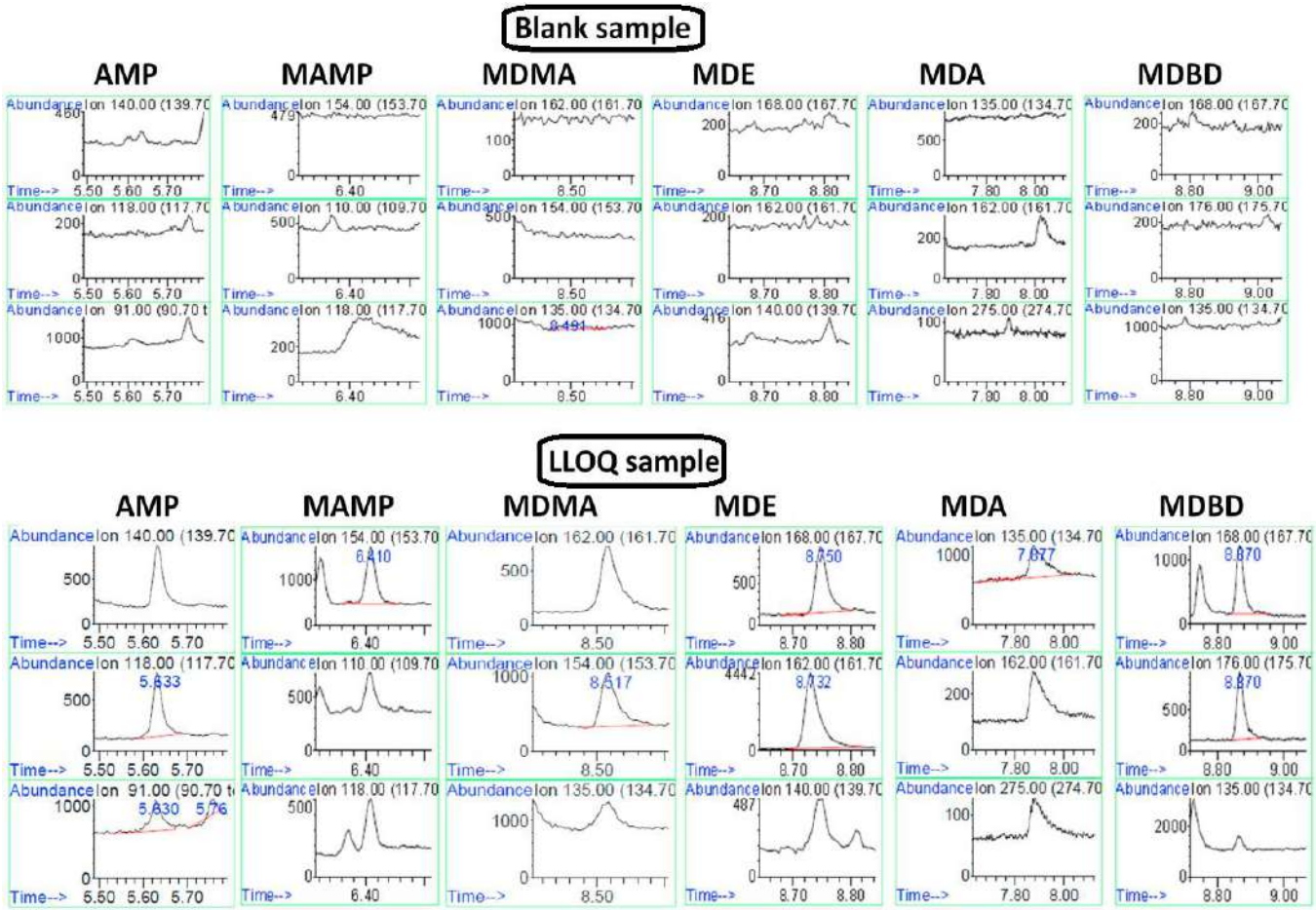

Fig. 7: Comparison of a blank urine sample with a sample spiked at the LLOQ (Malaca et al., 2019).

Feng et al. (1995) developed a sensitive and precise gas chromatography-mass spectrometry method for the determination of the phencyclidine derivative ketamine in human plasma (Fig. 1). The assay was based on an alkaline extraction from aqueous to organic solvent from plasma and on an efficient gas chromatographic separation on a DB-5 capillary column. Hasegawa et al. (2006) established the method for the determination of ten extractable antihistamine drugs, diphenhydramine, orphenadrine, chlorpheniramine, diphenylpyraline, triprolidine, promethazine, homochlorcyclizine, cyproheptadine, cloperastine and clemastine in human plasma (Fig. 2) using MonoTip C_{18} tips, inside which C_{18} bonded monolithic silica gel was fixed. Sample preparation was done with solid-phase extraction. Leis et al. (2002) determined memantine in human plasma by developing a sensitive and specific GC-MS method (Fig. 3). Memantine was extracted from plasma and derivatized to the pentafluorobenzoyl derivative in a one-step procedure avoiding any sample concentration steps. Adamantine was used as an internal standard.

Beresford et al. (1987) studied the analysis of amlodipine in human plasma using a Hewlett-Packard Model 5790 capillary gas chromatography with an electron-capture detector and Hewlett-Packard Model 3390 integrator (Fig. 4). The capillary column, 25 m×0.2 mm I.D., was a Hewlett-Packard ultra-performance column, with cross-linked 5% phenylmethylsilicone stationary phase, 0.33 µm film thickness.

Javaid et al. (1981) developed a sensitive gas chromatographic method for the determination of fluphenazine in human plasma with the use of a nitrogen detector. Fluphenazine was measured as Its Acetyl derivative. The internal standard used was perphenazine. Moreover, zolpidem and zopiclone were determined by (Stanke et al. 1996) in human plasma (Fig. 5). The extract was injected into a capillary gas chromatography after liquid-liquid extraction. OV-1 fused-silica was used as the column coupled to a nitrogen-phosphorus detector. Gas chromatography has also played an important role in chiral chromatography. It is well understood that each enantiomer of chiral compounds has its own biological activity (Ali, et al., 2016a; 2016b; 2016c; 2017a; 2017b; 2017c; 2017d; 2018a; 2018b; 2018c; 2019a; 2019b; 2020).

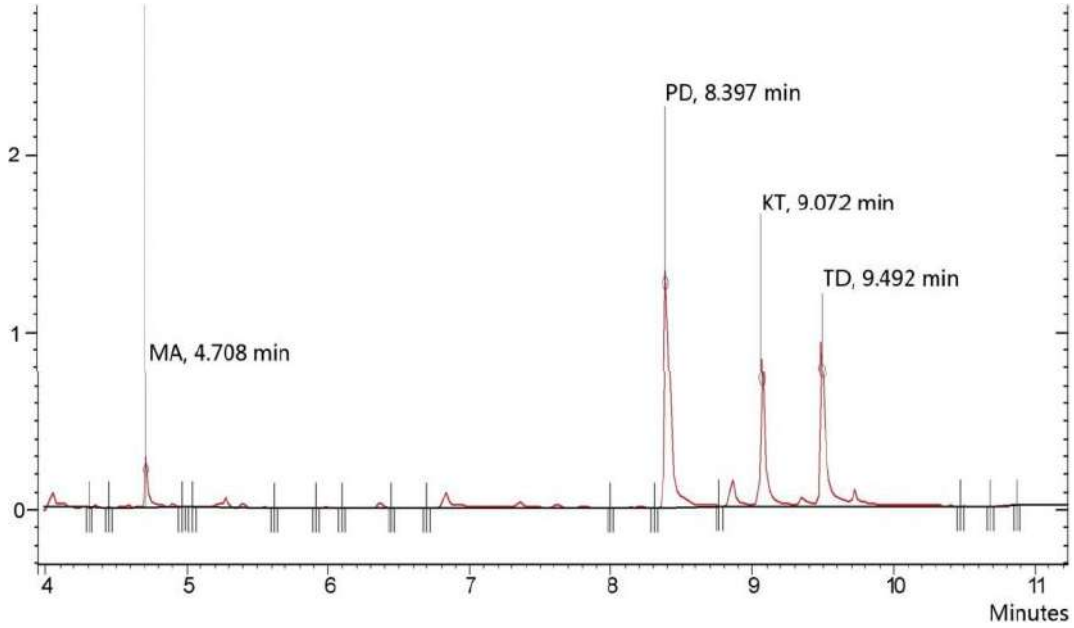

Fig. 8: Total ion chromatogram of the four drugs. Extraction conditions: sample volume, 5.00 mL; extraction solvent volume, 30.0 µL; disperser solvent volume, 0.5 mL; room temperature; concentration of each drug, 0.1 µg/mL. (Xu and Liu, 2019).

A chiral gas chromatographic method was developed by Tokuma et al. (1987) for the determination of nilvadipine (antagonist) in human plasma. An internal standard used was a deuterated analog of racemic nilvadipine. On a chiral stationary-phase column (Chiralpak OT (+) for HPLC, each enantiomer in the extract was detached and the effluents having the particular isomer were collected. After that fused-silica capillary column GC-electron capture negative ion chemical ionization MS was used for the analysis of each effluent. Moody et al. (1997) developed two methods (i) liquid chromatography-electrospray ionization-tandem mass spectrometry (LC-ESI-MS) method, and (ii) GC-PCI-MS method for buprenorphine in human plasma. The internal standard used for both methods was buprenorphine-d_4. Pentafluoropropionic anhydride was used as derivatizing agent for the GC-PCI-MS method. Borg and Garle (1972) developed a gas chromatographic method for the determination of tricyclic antidepressant drug nortriptyline and some of its desmethylated or hydroxylated metabolites in plasma. The derivatizing agent used was heptafluorobutyric anhydride. Several benzodiazepines (oxazepam, diazepam, nordiazepam, flunitrazepam, and alprazolam) in human plasma were analyzed by Reubsaet et al. (1998) using solid-phase microextraction (SPME) and gas chromatographic analysis.

In urine

Urine is also considered as a biological sample for drug analysis. Numerous works on the analysis of drugs in urine have been done. Several benzodiazepines (oxazepam, diazepam, nordiazepam, flunitrazepam, and alprazolam) in human urine were analyzed by (Reubsaet et al., 1998) using solid-phase microextraction (SPME) and gas chromatographic analysis. Borg and Garle (1972) developed a gas chromatographic method for the determination of tricyclic antidepressant drug nortriptyline and some of its desmethylated or hydroxylated metabolites in urine. McCusker et al. (1999) gave a simple method describing the direct analysis of gamma-hydroxybutyrate (GHB) from human urine. The sample preparation method, derivatizing agents and internal standard used were solid-phase extraction, silyl-derivatization, and GHB-d_6 respectively. (Springer et al., 2002) identified 4′-Methyl-α-pyrrolidinopropiophenone (MPPP) metabolites by developing a toxicological detection method in urine using solid-phase extraction, ethylation, and GC–MS. Alsenedi and Morrison (2018) developed and validated a gas chromatography-mass spectrometry (GC-MS) method for the examination of the different classes of stimulant compounds included Amphetamine-Type Stimulants (ATSs) (amphetamine, (±)-3,4-methylenedioxymethamphetamine (MDMA) methamphetamine, *para*-methoxyamphetamine (PMA), and) and synthetic cathinones (mephedrone, buphedrine (buphedrone ephedrine metabolite), 4-methylephedrine (mephedrone metabolite, and pentylone) in human urine sample using microliter amounts of organic solvent (Fig. 6). For this, a Solid Phase Micro-Extraction tip (SPME tips) was used for sample preparation.

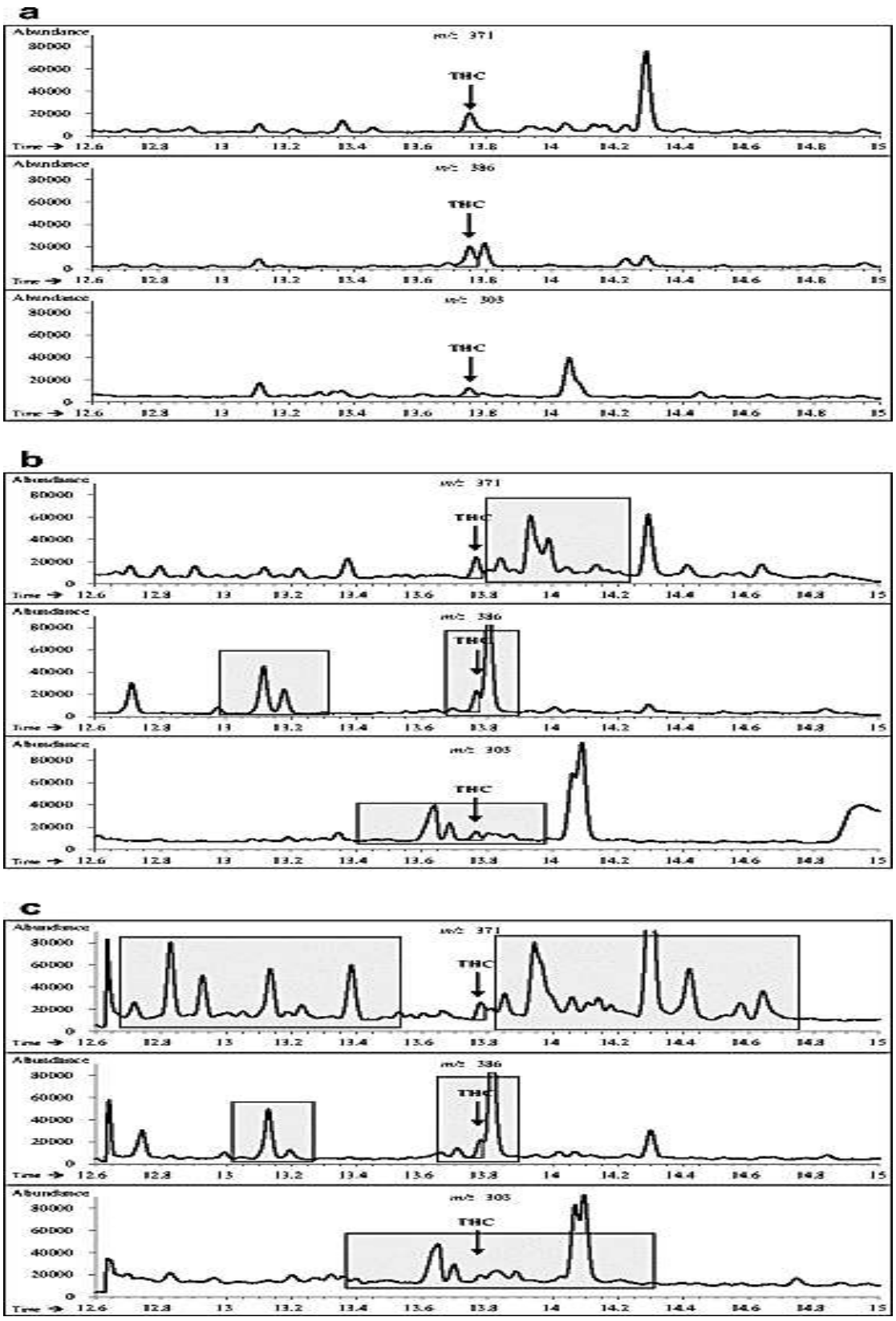

Fig. 9: GC-EI-MS single ion modus (SIM) chromatograms of blank serum spiked with 0.4 ng/mL THC and extracted with Drug II (a), C_{18} (b) and ZSTHC (c) (Gasse et al., 2016).

Table 1: The analysis of drugs in biological samples by gas chromatography (GC)

Biological Samples	Drugs	Derivatizing agents	Internal standards	Experimental conditions	References
Plasma	Chlorpromazine (CPZ), Haloperidol (HAL), Cyamemazine, quetiapine, Clozapine, Olanzapine (OLZ), and Levomepromazine	65 µL of MSTFA with 5 % TMS	Trideuterated analogue (CPZ-d_3)	Carrier: Helium, Column: A capillary with (HP-5 MS), Detector: MS, SPM: (MEPS), Temp:120°-300°C	(da Fonseca et al., 2013)
	Antidepressants and antidepressant	(HFBI)	Fluoxetine, fluoxetine-D6, paroxetine-D6, and olanzapine	Carrier: Nitrogen stream, Column: HP-5MS capillary, Detector: HP 5973 inert mass selective, SPM:LLE, Temp: 130°-290°C	(Pietracci et al., 2013)
	Phencyclidine derivative ketamine	None	Dexchlorophenaramine	Carrier: Helium, Column: fused silica capillary, Detector: ion trap, SPM: alkaline extraction, Temp:90°-260°C	(Feng et al., 1995)
	Diphenhydramine, orphenadrine, chlorpheniramine, diphenylpyraline, triprolidine, promethazine, homochlorcyclizine, cyproheptadine, cloperastine and clemastine	None	Diphenhydramine, orphenadrine, chlorpheniramine, diphenylpyraline, triprolidine, promethazine, homochlorcyclizine, cyproheptadine, cloperastine and clemastine	Carrier: Helium, Column: DB-1MS fused-silica capillary, Detector: MS, SPM: SPE, Temp:120°-300°C	(Hasegawa et al., 2006)
	Memantine	PFBzCl	Adamantine	Carrier: Helium, Column: DB-5 MS fused-silica capillary, Detector: MS, SPM: LLE, Temp: 100°-310°C	(Leis et al., 2002)
	Amlodipine	Trimethylacetyl chloride	UK-52,829 fumarate	Carrier: Nitrogen, Column: Hewlett-Packard ultra-performance, Detector: MS, SPM: LLE, Temp:250°-320°C	(Beresford et al., 1987)
	Zolpidem and zopiclone	None	Clonazepam and alpidem	Carrier: Helium, Column: OV-1 fused-silica capillary, Detector: nitrogen-phosphorus, SPM: LLE, Temp:200°-280°C	(Stanke et al., 1996)
	(+)- and (-)-Nilvadipine	None	Deuterated analogue	Carrier: Nitrogen, Column: fused-silica capillary, Detector: MS, SPM: LLE, Temp:240°-290°C	(Tokuma et al., 1987)
	Buprenorphine	PFPA	Buprenorphine-d_4	Carrier: Hydrogen, Column: DB-1 fused-silica capillary, Detector: MS, SPM: LLE, Temp:160°-310°C	(Moody et al., 1997)
	Nortriptyline and some of its metabolites	Heptafluoro butyric anhydride	Ciba 34276	Carrier: Nitrogen, Column: Silanized glass, Detector: electron capture, SPM: LLE, Temp:245°-255°C	(Borg and Garle, 1972)

Table 1: Continue...

Urine	Gamma-Hydroxybutyrate	(BSTFA) with 1% (TMCS)	GHB-d_6	Carrier: Helium, Column: methyl siloxane capillary, Detector: MS, SPM: LLE and SPE, Temp:105°-300°C	(McCusker et al., 1999)
	49-methyl-a-pyrrolidinopropiophenone	Diazoethane		Carrier: Helium, Column: HP capillary, Detector: MS, SPM: SPE, Temp:100°-310°C	(Springer et al., 2002)
	Amphetamine-type stimulants (ATSs)	50 µL PFPA and EtOAc (2 : 1)	Amphetamine-d_{11}, cathinone d_5 and pentylone-d_3	Carrier: Helium, Column: DB-5ms, Detector: MS, SPM: SPME, Temp:70°-280°C	(Alsenedi and Morrison, 2018)
	Synthetic cathinones and an amphetamine-like compound	TFAA	Amphetamine-d_6 and diphenylamine	Carrier: Helium, Column: fused-silica capillary, Detector: MS, SPM: LLE, Temp:85°-300°C	(Gerace et al., 2019)
	(AMP), (MAMP), (MDA), (MDMA), (MBDB), (MDE)	MBTFA	AMP-d_6, MAMP-d_9, MDA-d_5, MDMA-d_5 and MDE-d_5	Carrier: Helium, Column: 5% de phenylmethylsiloxane, Detector: MS, SPM: MEPS, Temp:90°-300°C	(Malaca et al., 2019)
	Methamphetamine, pethidine, ketamine and tramadol	None	Methamphetamine, pethidine, ketamine and tramadol	Carrier: Helium, Column: VF-5, Detector: MS, SPM: LLME, Temp:120°-280°C	(Xu and Liu, 2019)
	Nutmeg	Hydroxylated safrole and myristicin	MDMA-d_5	Carrier: Helium, Column: PDMS-coated, Detector: MS, SPM: LLE, Temp:130°-310°C	(Neukamm et al., 2019)
Serum	Breast cancer metabolites	50µL methoxylamine hydrochloride in 15µg/µL pyridine	Myristic-d_{27}	Carrier: Helium, Column: fused-silica capillary, Detector: MS, SPM: SPE, Temp:140°-305°C	(Hadi et al., 2017)
	THC (1 mg/mL), 11-OH-THC and THC-COOH	MSTFA	THC-d_3, 11-OH-THC-d_3 and THC-COOH-d_9	Carrier: Helium, Column: capillary column, OPTIMA® 5 MS Accent, Detector: MS, SPM: SPE, Temp:150°-300°C	(Gasse et al., 2016)
	MDPV	20mL of pyridine and 30mL of acetic anhydride	Trimipramine-D_3	Carrier: Helium, Column: Macherey–Nagel Optima 5MS Accent, Detector: MS, SPM: LLE, Temp:130°-340°C	(Grapp et al., 2017)
	2-hydroxyglutarate enantiomers	(R)-(-)-2-butano	Deuterated	Carrier: Helium, Column: chiral GC capillary, Detector: MS, SPM: LLE, Temp:80°-220°C	(Strain et al., 2020)
Meconium	Nicotine, Cocaine and Metabolites	MSTFA	Deuterated	Carrier: Helium, Column: HP-5MS, Detector: MS, SPM: DPE, Temp:130°-320°C	(Mozaner et al., 2014)

Table 1: Continue…

Multi-matrix	Higenamine	HFBA, MSTFA, and ECF	Higenamine	Carrier: Helium, Column: HP-5MS, Detector: MS, SPM: SPE, Temp:110°-280°C	(Feng et al., 2020)
Human Hair	THC, CBD, CBN	TMS	OH-THC, THC-COOH, THC-d_3, OH-THC-d_3, THC-COOH-d_3, CBD-d_3, CBN-d_3, THCA-A	Carrier: Nitrogen and Helium, Column: Zebron ZB-5MSi, Detector: MS, SPM: SPE, Temp:150°-320°C	(Kieliba et al., 2019)
Oral fluid	Methamphetamine	HFBA	Amantadine	Carrier: Helium, Column: 5-MS capillary, Detector: MS, SPM: LLE, Temp:120°-280°C	(Bahmanabadi et al., 2017)

[SPM: Sample preparation method; MEPS: Microextraction by packed sorbent; TMS: trimethylchlorosilane; MSTFA: N-Methyl-N-(trimethylsilyl) trifluoroacetamide; (HFBI):1-(heptafluorobutyryl) imidazole; HP-5MS:(crosslinked 5 % phenylmethylsiloxane; MS: Mass Spectrophotometer; PFBzCl: Pentafluorobenzoyl chloride; BSTFA: Bis(trimethyl-silyl)- trifluoroacetamide; TMCS: trimethylchlorosilane; PFPA: pentafluoropropionic acid anhydride; EtOAc: Ethyl acetate; DB-5MS: 5% phenyl/95% methylpolysiloxane; SPME: Solid Phase Micro-Extraction; TFAA, trifluoroacetic anhydride; AMP: Amphetamine; MAMP: Methamphetamine; MDA: 3,4-methylenedioxyamphetamine, MDMA: 3,4-methylenedioxyethylmethamphetamine; MBDB: 3,4-methylenedioxy-N-methyl-α-ethylfenilethylamine; MDE: 3,4- methylenedioxy-N-ethylamphetamine; MBTFA: N-methyl-bistrifluoroacetamide; MDPV: 3,4-methylenedioxypyrovalerone; DPE: Disposable Pipette Extraction; HBFA: Heptafluorobutyric acid; ECF: Ethyl chloroformate].

Waraksa et al. (2018) developed a sensitive and rapid tandem mass spectrometry-based gas chromatographic method for the determination of ibuprofen and its metabolites in human urine. Liquid-liquid extraction was used for sample preparation. Gerace et al. (2019) developed a GC/MS method for the determination of 18 synthetic cathinones and one amphetamine-like compound in human urine. Liquid-liquid extraction was used for sample preparation under alkaline. The derivatizing agent used was trifluoroacetic anhydride. Malaca et al. (2019) gave an optimized and fully validated method for the determination of amphetamine (AMP), methamphetamine (MAMP), 3,4-methylenedioxyamphetamine (MDA), 3,4-methylenedioxyethylmethamphetamine (MDMA), 3,4- and 3,4-methylenedioxy-N-ethylamphetamine (MDE) in urine samples through microextraction by packed sorbent (MEPS) attached to gas chromatography-mass spectrometry (GC–MS).

Xu and Liu (2019) developed a modest and fast dispersive gas chromatography–ion trap mass spectrometry (GC–MS) for the determination of methamphetamine (MA), pethidine (PD), ketamine (KT) and tramadol (TD) in human urine (Fig. 8). The liquid-liquid microextraction (LLME) technique was used for sample preparation. (Neukamm et al. 2019) developed an evaluated gas chromatographic-mass spectrometric (GC–MS) model for the estimation of nutmeg abuse in urine sample.

In serum

The serum is also considered as a biological sample in the medical field. Zhou et al. (2018) employed a pseudotargeted gas chromatography-mass spectrometric method for the investigation of the serum metabolic profiling of 66 significant responders and 24 nonsignificant responders at baseline and 16 weeks after gliclazide modified-release (MR) monotherapy. Hadi et al. (2017) developed a Gas chromatography-mass spectrometry (GC-MS) method for the identification of potentially significant metabolites in the serum of breast cancer patients and healthy controls. Grapp et al. (2017) reported a comprehensive collection of 3,4-methylenedioxypyrovalerone (MDPV) with a quantitative serum level using gas chromatography-mass spectrometry (GC–MS). A chiral gas chromatography-tandem mass spectrometry (GC–MS) evaluation was developed by Strain et al. (2020) for enantiomeric separation using a chiral column. The internal standard used was a stable-isotope. Serum levels of 2-hg enantiomers were studied in a trial study of 11 patients with and without IDH mutant gliomas. Gasse et al. (2016) settled a fully validated GC-MS method for the analysis of cannabinoids in serum. The sample preparation method used was solid phase extraction (Fig. 9). The internal standards used were deuterated.

In other samples

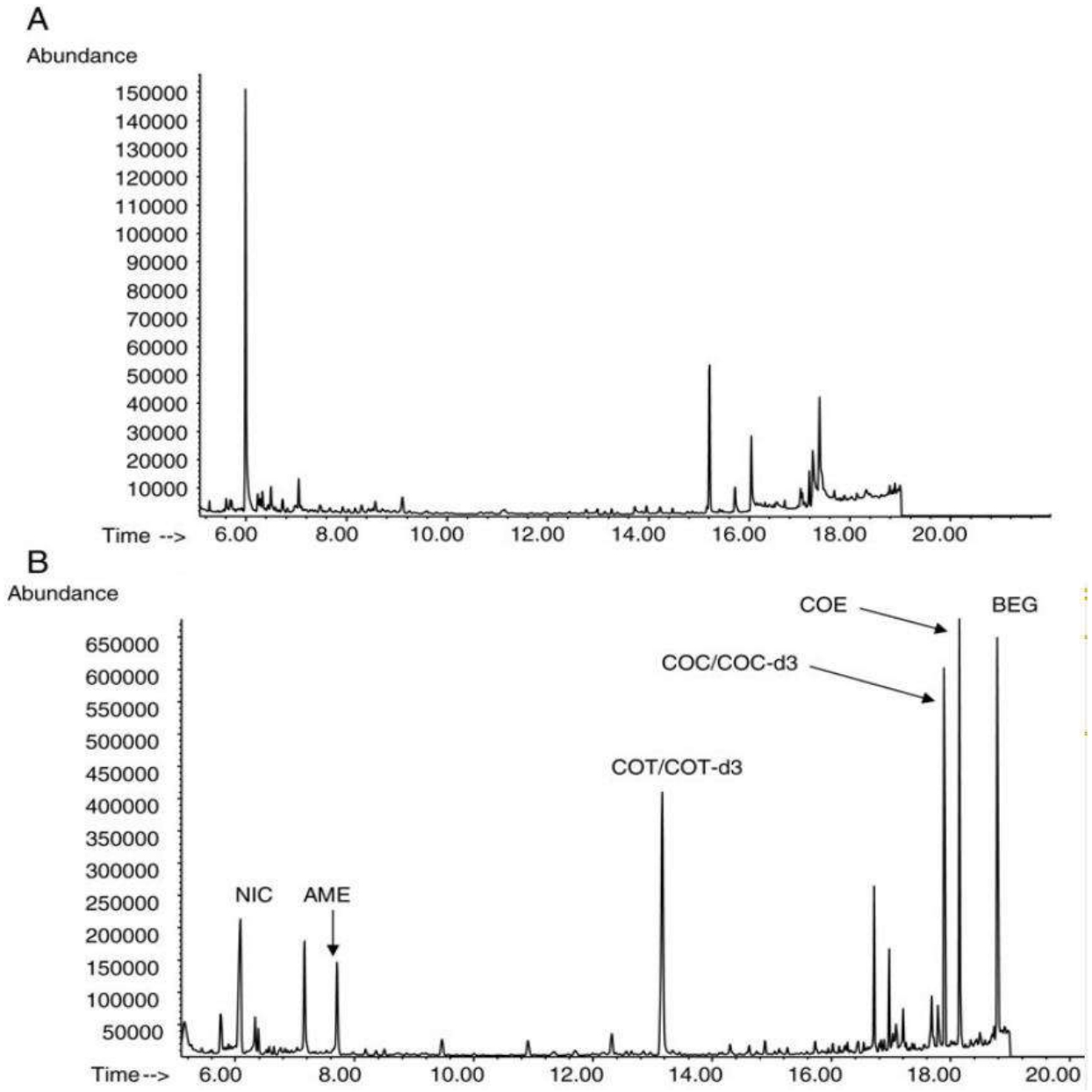

Fig. 10: Total ion current chromatograms obtained after DPX extraction of (A) drug-free meconium and (B) drug-free meconium sample spiked with all the investigated analytes (100 ng/g) (Mozaner et al., 2014).

Unlike plasma, serum, and urine, other materials are also considered as a biological sample. A gas chromatography-mass spectrometry (GC–MS) method for the determination of nicotine, cotinine, cocaine, benzoylecgonine, cocaethylene, and methyl ester anhydroecgonine was developed by Mozaner et al. (2014) in meconium using DPX. Feng et al. (2020) reported the development of a gas chromatography-mass spectrometry (GC–MS) method for the determination of Higenamine (HG) in multimatrix liquid. The derivatizing agent used was heptafluorobutyric anhydride (Fig. 11).

Kieliba et al. (2019) detected Δ^9-tetrahydrocannabinol (THC), cannabidiol (CBD) and cannabinol (CBN) in hair by developing a gas chromatography-tandem mass spectrometry (GC–MS/MS) method. At that time, testing for THC metabolites was not standard practice due to its analytical complexity. For that reason, a novel method for the detection of THC-COOH and OH-THC as well as THC, CBD, and CBN was developed using electron ionization. For sample preparation, a solid-phase extraction (SPE) was used, while silylation was used for the derivatization of all analytes.

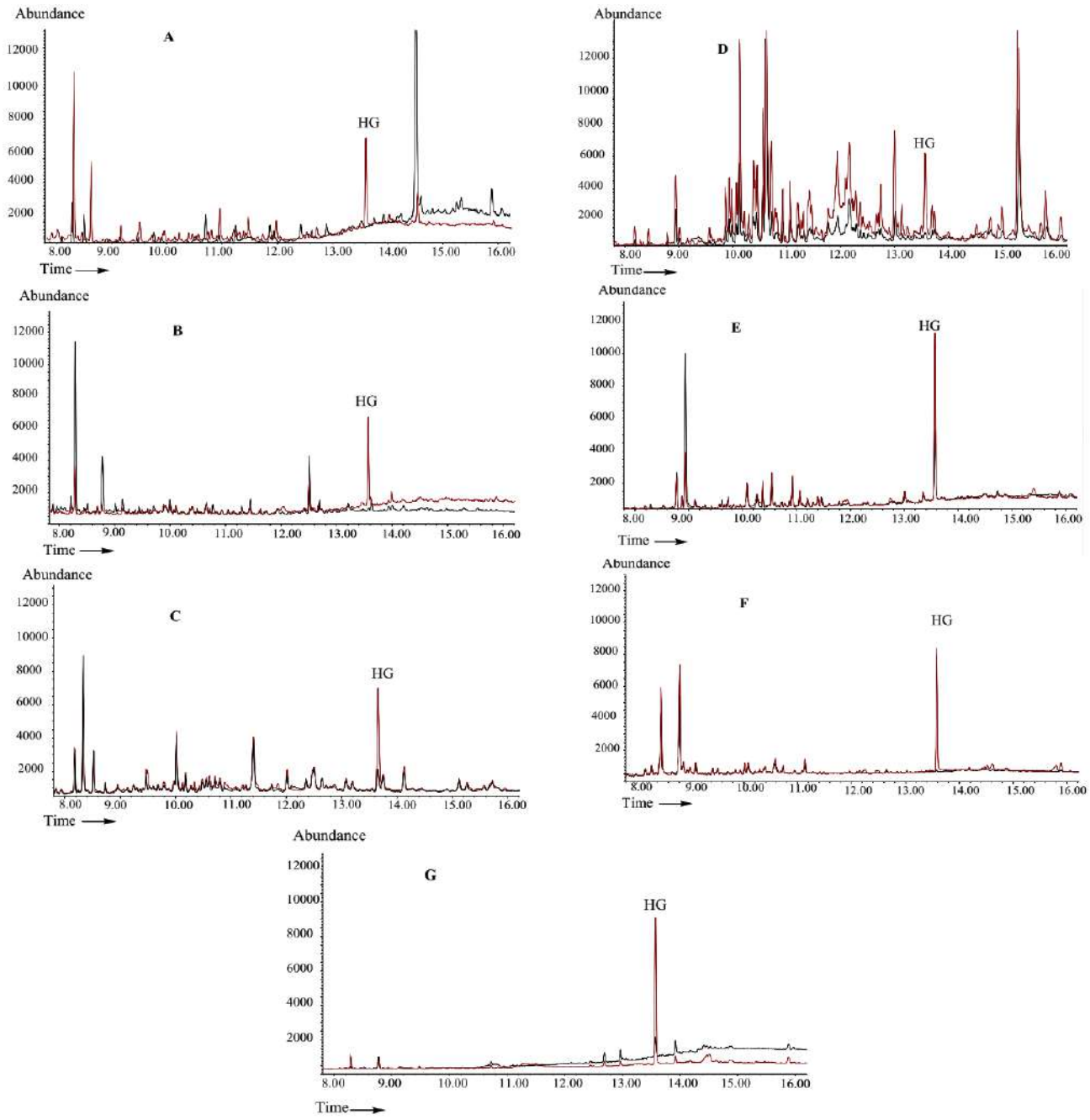

Fig. 11: Chromatograms of different blank and real samples spiked with HG at the concentration of 25 ng /mL. A: plasma sample; B: urine sample; C: oral liquid sample; D: capsule sample; E: water bolus; F: honeyed bolus; G: Chinese herbal medicine (Feng et al., 2020).

In another study, Bahmanabadi et al. (2017) established a gas chromatography/mass spectrometry (GC/MS) method for the detection of methamphetamine in oral fluid. Liquid-liquid extraction (LLE) was used for sample preparation (Fig. 12).

Future perspectives

Despite the developing technologies, the expansion of suitable gas chromatographic methods for drug analysis continues to be a challenge. Almost every type of drug was analyzed in biological samples by gas chromatography. However, only a few papers are describing the analysis of enantiomers of chiral compounds in the biological sample using GC. Of course, it is very tough to analyze the

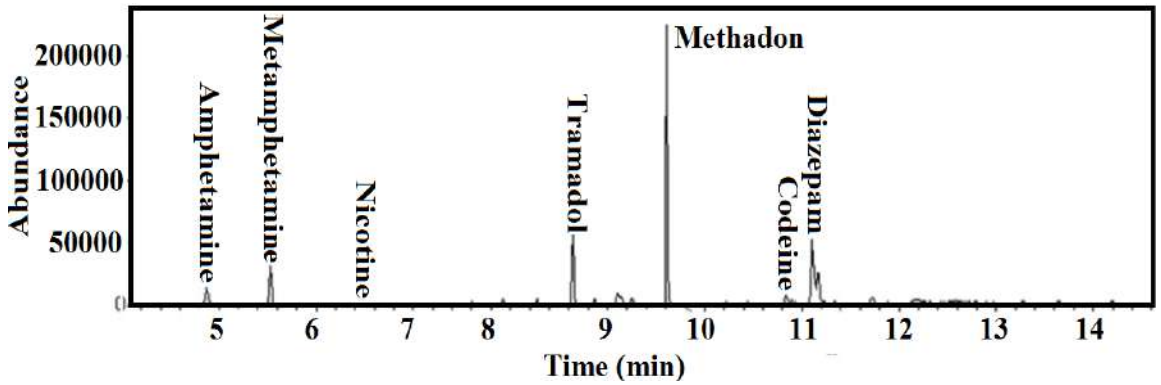

Fig. 12: Chromatogram of authentic oral fluid sample spiked with tramadol, methadone, morphine, codeine, and diazepam for selectivity assessment (Bahmanabadi et al., 2017)

enantiomeric forms of chiral compounds in the biological samples. This is due to the identical properties of the enantiomers. Moreover, the gas chromatography is not so developed that it can analyze racemates easily in the biological samples. However, other types of drugs have been analyzed easily owing to its excellent analyzing power. The advanced detector used in this chromatography is also an additional feature of GC for providing high separation power. Besides, some more advanced feature of GC makes it as a technique of choice for drug analysis in the biological sample.

CONCLUSIONS

Drug analysis in biological samples is the main area of clinical research. During the write up of this article, only some papers were found on the analysis of chiral drugs in the biological sample. The various types of drugs were analyzed in the biological samples, but the literature statement is scanty for the broad study on this important matter. There is an excessive possibility in this field using gas chromatography. This tough job may be accomplished by discovering new and different chiral capillary columns. Also, column switch and other applications may be valuable to attain the mission. Moreover, the self-disproportionation of enantiomers is a very significant feature in this filed. It is not well established. It requires more devotion of the scientist in future research.

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