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Analytical techniques for the detection of Amphetamine-type substances in different matrices: a comprehensive review

Ana-Maria Dragan[1,#], Marc Parrilla[2,3,#], Bogdan Feier[1], Radu Oprean[1], Cecilia Cristea[1], Karolien De Wael[2,3,*]

1 'Iuliu Hatieganu' University of Medicine and Pharmacy Cluj-Napoca, Department of Analytical Chemistry and Instrumental Analysis, Pasteur 6, Cluj-Napoca, Romania

2 University of Antwerp, A-Sense Lab, Groenenborgerlaan 171, 2010 Antwerp, Belgium

3 University of Antwerp, NANOlab Center of Excellence, Groenenborgerlaan 171, 2010 Antwerp, Belgium

*Corresponding author.

Email addresses: ana.dragan@umfcluj.ro (Ana-Maria Dragan); marc.parrillapons@uantwerpen.be (Marc Parrilla Pons); feier.george@umfcluj.ro (Bogdan Feier); roprean@umfcluj.ro (Radu Oprean); ccristea@umfcluj.ro (Cecilia Cristea); karolien.dewael@uantwerpen.be (Karolien De Wael)

Highlights (max 85 characters including spaces, per bullet point)

- The analytical techniques for the detection of amphetamine-type substances (ATS) are detailed.
- The physiological effects of ATS in the human body are introduced.
- The most used bench-top analytical techniques including sample preparation are described.
- Portable methods for the detection of ATS in the field were compared.
- Key challenges and prospects for a proper identification of ATS are discussed.

Abstract

This current review focuses on contributions to amphetamine-type substances (ATS) analysis. This type of synthetic illicit drugs has been increasingly present worldwide reaching 5% of the market on illicit drugs in 2019. The increment of their production in many clandestine laboratories and easy distribution among society are two of the main concerns towards the battle against synthetic drugs. Therefore, the first part of this review details the classification and mechanism of action of ATS in the human body. Second, the pharmacological and toxicological effects of ATS on human health are described to motivate the need of early detection of ATS. Subsequently, the most used laboratory-based and portable methods are presented and critically discussed along the review. Finally, a careful

discussion on the advantages and disadvantages of portable techniques employed on the field are addressed as potential tools for on-site ATS detection by law enforcement officers.

Keywords: amphetamine-type substances; MDMA; detection methods; on-site testing; portable devices; drug seizures; forensic analysis

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1 Introduction

The drugs situation in Europe (EU) and worldwide is unprecedented, showing a tremendous increment in the types of drugs available in the market, including the new synthetic drugs [1]. The increasingly global threat of organized crime groups involved in drug production and trafficking represents a major concern to the cross-border authorities. Indeed, this fact has been dramatically translated into the increased number of seizures by law enforcements agencies (LEAs) [2]. This situation demands a considerable attention from LEAs to develop new strategies that interfere in those criminal actions involved in illicit production and trade. Besides, forensic laboratories must be committed with LEAs to develop reliable detection strategies that tackle this increment of the drug market by supporting drug-related investigations.

Synthetic drugs such as amphetamine-type substances (ATS) which include amphetamine (AMP), methamphetamine (MET) and 3,4-methylenedioxymethamphetamine (MDMA) are rapidly growing in Europe exhibiting an EU retail market of 1 billion EUR for AMP and MET, and 0.5 billion for MDMA [1,3]. These numbers from ATS represent around 5% of the total EU drug market, the latest data showing that amphetamines and MDMA account for 9% of the seizures (6% and 3%, respectively), and the consumers number in the EU being 2 million and 2.7 million, respectively [1]. This trend can be explained due to the easiness on the production nearer to consumer markets which is today concentrated in the Netherlands, and to a lesser extent in Belgium [4]. Therefore, the production of synthetic drugs is becoming more sophisticated, diverse and aggressive, particularly in the ecstasy market, as the competition among suppliers increases. For this reason, there is a huge demand of providing analytical tools for ATS determination, either in the laboratory or in the field, to assist the LEAs for a rapid and early detection of ATS.

The use of illicit drugs for its recreational purpose in society also produces collateral effects. First, the increment of violence and homicide which can be classified as: (i) psychopharmacological, committed by an individual under the influence of drugs; (ii) economic-compulsive, in which economically oriented violent crime is committed in order to support costly drug use; or (iii) systemic, aggressive patterns of interaction that occur within the system of drug markets [5,6]. Second, the contamination of the environment (e.g., wastewaters, soil) due to the disposal of clandestine laboratory wastes into sewage systems as well as the human excretion after illegal consumption of drugs [7,8]. Last but not least, the effect of the use of illicit drugs in human health (**see section 2**): (i) the illicit products can cause a wide range of harmful outcomes, such as serious, sometimes fatal, poisonings [9]; (ii) changes in how users inject themselves as they switch to new substances have also caused mass poisonings and outbreaks of infections such as HIV, hepatitis C and bacterial

illnesses [10]; and (iii), the effects on the human body is of utmost concern for the public health as chronic drug users display adverse physiological and behavioral effects such as pronounced neuropsychological impairment in the domains of executive and memory function [11,12].

Current efforts from LEAs are being made to respond to these threats in society (i.e., increment of ATS consumption). One of their tasks is to track and identify cargos and drug seizures before the illicit drugs reach the consumers. Hence, large quantities of illicit drugs are frequently seized by LEAs [2]. First, the cargo has to be analyzed on the field in order to determine whether the cargo is confiscated or not. If the cargo is positive for illicit drugs, samples are sent to forensic laboratories for further analysis. In such cases, a representative number of samples need to be quickly examined prior to destruction. It is essential to provide an accurate determination and avoid false positive or false negative results either in the field or in the laboratory. Unfortunately, no procedure has yet been set up to rapidly provide information regarding the homogeneity of the samples, the presence of controlled substances, and the degree of purity in the field, thus the current procedures are still based on laboratory facilities [13–15] (**see section 3**). However, tremendous efforts are being addressed to develop portable devices for the on-site detection of illicit drugs [16–18] (**see section 4**).

The recommended methods for the identification and analysis of ATS in seized materials according to a report published by the United Nations are classified onto qualitative or quantitative analysis [19]. Concerning the qualitative analysis, presumptive tests (i.e., provide a fast screening process of the presence or absence of the type of drug of abuse, and ideally eliminate negative samples) are based on: (i) color tests, being the simplest and quickest chemical test, although providing low accuracy with high false positive and false negative results; (ii) the anion tests determined by the presence or absence, and solubility, of a precipitate; and (iii) the microcrystal tests which involve the formation of crystals from the reaction of the target compounds with a chemical reagent [20]. Regarding the quantitative determination of ATS, several techniques can be employed: (i) thin-layer chromatography is a rapid, sensitive and inexpensive technique, although not accepted in some countries [15]; (ii) gas chromatography – flame ionization detector (GC-FID) [21,22]; (iii) gas chromatography – mass spectrometry (GS-MS) which is one of the most commonly used techniques as gold standard, providing highly specific spectral data on individual compounds in a complex mixture of compounds without prior separation [23,24]; (iv) high performance liquid chromatography (HPLC) also commonly used in laboratories, thus sharing similar technical features with GC-MS (i.e., sample preparation, time, expensive instruments) [13,15,25]; (v) Fourier transform infrared (FTIR) spectroscopy, mainly for

qualitative purpose, is usually coupled to GC [26,27] or can be used directly by employing attenuated total reflectance (ATR) FTIR [28]; (vi) Raman spectroscopy is also a promising method [29], although the presence of certain adulterants or cutting agents might exhibit high background fluorescence; (vii) immunoassays allow for high specificity, but they need expensive equipment and reagents, and trained personnel in centralized laboratories for sample preparation [30–32]; and (viii) other techniques such as capillary electrophoresis (CE) [33,34] and nuclear magnetic resonance (NMR) [35] have been also explored in the detection of ATS. In this review, the authors described the main analytical techniques employed in forensic laboratories for the detection of ATS (**see section 3**). For more details of seizure profiling, the reader is referred to the related literature [36,37].

The analysis of illicit drugs in biofluids (e.g. blood, serum, urine, oral fluid, sweat) during human consumption is of utmost importance in forensic and toxicological applications (e.g. criminal scenes, drug overdose, roadside testing) [38–41]. For this reason, huge efforts have been addressed to overcome the complexity in the analysis of biofluids and the extraction of the illicit drug from these matrices during laboratory-based analysis of ATS (**see section 3**).

The increasing need to detect illicit drugs in the field in a decentralized manner (out of the laboratory) demands the development of portable devices with the ability to perform rapid and low-cost determinations, and importantly, without the necessity of trained personnel [16,17]. Thus, any law enforcement officer could use the device when necessary and evaluate whether a drug trafficking action is present at any point of the delivery chain. Therefore, this review also tackles the current and potential portable devices for the detection of forensic drugs (i.e., portable spectroscopic methods, lateral flow immunoassays, presumptive color tests, and electrochemical devices). Besides, a critical description of the requirements of the current methods has been described for the sake of the development of an ideal portable device. The authors believe that bringing analytical techniques onto the field through portable devices is of paramount importance to assist LEAs in hindering the threat posed by drug trafficking worldwide.

The present review reports on the current methods of detection of ATS in seizures and biological samples during the last 20 years, which is a period defined by their increasing market trend. While detection methods for illicit drugs have been extensively reviewed over the last decade [42–48], this is the first time that a review entirely focuses on ATS. The first part of the review presents a classification and the mechanisms of action of ATS on the human body, allowing an easy understanding on how ATS interact with the body. Accordingly, the pharmacological and toxicological effects on the human health are described (e.g., short-term, mid-term and potentially long-term effects). Next, the current methods for detection of ATS are described and critically discussed. Finally, a deep

investigation on the portable devices that allows the on-site detection of ATS, and its current analytical features are presented. Overall, this review supplies the reader with an overview of the ATS effects, and significant insights for the selection of the suitable analytical technique for a proper determination of ATS in seizures or biological samples. Besides, this review is intended to contribute as a guideline for the use of the most suitable technique in laboratory basis as well as in the field towards an improvement of the security of society by an effective drug control strategy.

2 Pharmacology and toxicology

2.1 Classification and mechanisms of action of ATS

Amphetamines are chemically related to phenylethylamine and most of them are chiral compounds which influences the type of action they exert, and the intensity of their effects: the D-enantiomers have central nervous system (CNS)-stimulating effect, and have five times more psychostimulant activity than the L-isomers which have more of a peripheral effects [49,50]. This class can be further devised in several subclasses, according to their chemical structure, as it is shown in **Table 1**.

Amphetamines exert their effects by modulating the tree major monoaminergic systems (noradrenergic, dopaminergic and serotoninergic) due to their structural similarities with the corresponding neurotransmitters (i.e. noradrenaline, dopamine, and serotonin) [51]. ATS act on different segments of the neural pathways of these systems, including the monoamines transporters, the vesicular storage, the metabolism by enzymes, and the postsynaptic receptors [52,53].

The main targets of amphetamines are the serotonin transporter (SERT), the noradrenaline or norepinephrine transporter (NET) and, in particular, the dopamine transporter (DAT) [54]. These transporters carry the neurotransmitters from the synaptic cleft to the cytosol of the presynaptic nerve terminals, which usually stores the new synthesized monoamines [51]. From the cytosol, the monoamines are transported to the vesicular storage by the vesicular monoamine transporter 2 (VMAT2) or are degraded by monoamine oxidases type A or type B (MAO-A and MAO-B). Amphetamines act as exogenous substrates of SERT, NET and DART [53,54] and are carried into the cytosol of the presynaptic neurons instead of the neurotransmitters, blocking their physiological reuptake from the synaptic cleft. Amphetamines also bind to VMAT2 determining a reverse transport of the monoamines from vesicular storage into the cytoplasm of the presynaptic neuron, being afterwards released into the synapse cleft [51,55].

Several amphetamines (methylenedioxy derivatives for example) inhibit MAO as well, thus increasing even more the level of neurotransmitters, which are thus readily available to be

released into the synaptic cleft continuously stimulating the postsynaptic neurons of the three monoaminergic systems [56].

Table 1. Classification of amphetamines according to their chemical structure and their mechanism of action [53,57–59].

Amphetamines		Mechanism of action		
Class	**Members**	**Noradrenergic system**	**Serotoninergic system**	**Dopaminergic system**
Amphetamine* derivatives				
Monomethoxy derivatives	PMA PMMA	• Stimulation of NA release	• Stimulation of SER release • inhibition of SER reuptake	• minor influence of the dopamine system
Methylenedioxy derivatives	MDA MDEA			
Thiol derivatives	4-MTA			
		• reversible MAO-A inhibitiors		
Dimethoxy (D series) derivatives	DOB DOM DOI DOC	-	• full agonists at the 5-HT2A and 5-HT2C receptors	• agonists at the DA receptors
Trimethoxy derivatives	2,3,5-TMA 2,3,6-TMA 2,3,4-TMA 2,4,5-TMA 2,4,6-TMA 3,4,5-TMA	• stimulation of NA release • inhibition of NA reuptake	• stimulation of SER release • inhibition of SER reuptake	• Inhibition of DA reuptake
		• Reversible MAO-A inhibitors		
Halogenated derivatives	4-FA 4-ClA 4-IA	• Stimulation of NA release	• Stimulation of SER release	• Stimulation of DA release
Monomethyl derivatives	2-MET 3-MET 4-MET	• Stimulation of NA release	• Stimulation of SER release	• Stimulation of DA release
Others	Camfetamine	• Stimulation of NA release	NM	• Stimulation of DA release • inhibition of DA reuptake
	BDB	NM	NM	NM
	MBDB	NM	NM	NM
Methamphetamine* derivatives				
Methylenedioxy derivatives	MDMA** MDAI	• Agonists at the α- and β-adrenoreceptors, • Stimulation of NE release • Inhibition of NA reuptake	• Agonists at the 5-HT1 and 5-HT2 receptors • Inhibition of SER reuptake • Stimulation of SER release	• Agonists at the D1 and D2 receptors • Stimulation of DA release • Inhibition of DA reuptake
Benzofuran derivatives	5-APB 6-APB 5-MAPB 6-MAPB			
Benzodifuran derivatives	BDF	NM	NM	NM
Monomethyl derivatives	4-MMA	NM	NM	NM
Others	MPA	• Inhibition of NA reuptake	-	• inhibition of DA reuptake

*controlled substance classified in Shedule II
** controlled substance classified in Shedule I
NM=not mentioned
Abbreviations: AMP: amphetamine; APB: 5-(2-aminopropyl)benzofuran; BDB: R,S-benzo-dioxolylbutanamine; BDF: bromodragon FLY; ClA: chloroamphetamine; DOB: 4-bromo-2,5-dimethoxyamphetamine; DOC: 2,5-Dimethoxy-4-chloroamphetamine; DOI: 2,5-Dimethoxy-4-iodoamphetamine; DOM: 2,5-dimethoxy-4-methyl-amphetamine; FA: fluoroamphetamine; IA: iodoamphetamine; MAO-A: monoamine oxidase type A; MAPB: N-methyl-5-(2-aminopropyl)benzofuran; MBDB: R,S-Nmethyl-benzo-dioxolylbutanamine; MDA: R,S -3,4-methylenedioxyamphetamine, “love pills”; MDAI: 5,6-methylenedioxy-2-aminoindane; MDEA: R,S -3,4- methylenedioxyethylamphetamine, “Eve”; MDMA: R,S -3,4-methylenedioxymethamphetami ne, “Ecstasy,” “Adam,” “XTC”; MET: Methamphetamine; MMA: methyl- methamphetamine; MPA: Methiopropamine; MTA: R,S-4-methylthioamphetamine, “Flatliners”; PMA: R,S-4-para-methoxyamphetamine, ”death”; PMMA: R,S-paramethoxy methamphetamine; TMA: trimethoxyamphetamine.

2.2 Effects of ATS on health

All the processes described above produce increased levels of neurotransmitters in the synaptic cleft which determines the stimulation of the postsynaptic monoamine receptors, resulting in the effects that are desired by the users. However, the enhanced stimulation by the neurotransmitters from the consumption of ATS can generate adverse effects. All these effects are summarized in **Table 2**.

Table 2. Effects of the amphetamine-like compounds [53,55,57,58].

	Noradrenergic	Serotoninergic	Dopaminergic
Desired effects	• memory consolidation • increased level of wakefulness, alertness, vigilance • decreased fatigue • sleepiness • suppression of appetite	• hallucinogenic effects • modulation of pain perception • higher-order cognitive processing • sexual arousal	• euphoria • entactogenic effect • reward properties
Adverse effects	• tachycardia • hypertension • tachypnoea • hyperthermia • vasoconstriction • insomnia • irritability • mydriasis	• hyperthermia • prolonged vasoconstriction • convulsions • increased aggression • reduced reaction time • serotonine syndrome	• response inhibition • slower novel problem solving • affected psychomotor functions (increased motor movements, impaired coordination) • memory loss • acute psychotic symptoms • paranoia • addiction
	• Neuroroxicity • Tolerance		

The euphoric and the reinforcing effects are the main reasons for amphetamines abuse. These effects are related to amphetamines ability to release dopamine in the mesocorticolimbic “reward” system located in the limbic system that processes emotions, and promotes learning and memory [53,60]. Furthermore, ATS are known to interact with the endogenous opioid system which exerts modulatory actions on the mesolimbic dopamine system. Thus, the modulation of the two systems may be responsible for some of the rewarding properties associated with acute ATS use [55].

The toxicity of ATS can be enhanced by the consumption of other substances that have either pharmacodynamic or pharmacokinetic interferences. The pharmacodynamic interferences appear when two or more substances with the same mechanism of action or with similar effects are consumed together, leading to the amplification of ATS toxicity effects. Therefore, when ATS are consumed with selective serotonin reuptake inhibitors, tricyclic antidepressants (**Table 3**) or dextromethorphan, the chances for the manifestation of the serotonin syndrome significantly increase. In the same way, ATS consumed together with ephedrine lead to the risk of increased blood pressure and heart rate. The pharmacokinetic interferences include the inhibition of the hepatic metabolism and the inhibition of the urinary elimination of ATS. The hepatic metabolism is performed by the cytochrome P450 isoenzymes, mainly by CYP2D6 [61]. Importantly, there are several molecules that can inhibit these enzymes, therefore reducing the hepatic metabolism of ATS and prolonging their action (**Table 3**). The other route of elimination is through the urinary tract. Being weak bases, the modulation of the urinary pH can accelerate or slow the elimination of ATS in urine. For example, sodium bicarbonate increases the pH of the urine, and it slows down the elimination of ATS, prolonging their effects.

These substances can include other drugs of abuse, consumed willingly by the users as part of the polydrug consuming habit, or prescribed medicines also consumed due to different affections or patient’s conditions. Therefore, the user might not know the corresponding interaction with ATS, which can ultimately lead to severe health complications. Another category is represented by the adulterants and cutting agents of ATS sold on the illicit market, which are unconsciously consumed by the users alongside with the ATS, increasing the severity of adverse effects, including the risk of mortality. Such substances and the nature of their interaction with ATS are summarized in **Table 3**. Overall, the consumption of ATS is posing a tremendous thread to the health of drug users. For this reason, it is essential to develop analytical methods to avoid the spreading of these illicit drugs among the population, and thus avoiding health afflictions from ATS abuse.

As already mentioned, ATS spread is continuously increasing and its consumption results in toxicological, sometimes fatal outcomes. As a consequence, progress is being made by the

scientific community to meet the needs of LEAs for the detection and cessation of ATS illicit use. Thus, the following section describes and critically discusses the methods present in the literature for ATS detection.

Table 3. Substances that enhance the effects of ATS [57,61].

Class	Pharmacodynamic enhancement	Pharmacokinetic enhancement	
		Inhibition of the hepatic metabolism	Inhibition of the urinary elimination
Adultrants	Caffeine Dextromethorphan	Dextromethorphan Quinidine	$NaHCO_3$
Medicines	Theophylline Ephedrine TCA (imipramine) SSRi (fluoxetine, paroxetine) MAOi (phenelzine, moclobemide)	Ephedrine Ritonavir Thioridazine TCA (imipramine) SSRi (fluoxetine, paroxetine)	
Illicit drugs	Cocaine Ketamine LSD Psilocybin/psilocin	Cocaine Ketamine	

MAOi: monoamine oxidase inhibitors; SSRi: selective serotonin reuptake inhibitors; TCA: tricyclic antidepressants

3 Current methods of detection of ATS

Currently, many analytical techniques are available for the detection of illicit drugs. Principally, these techniques use mass spectrometry to determine the compounds of the sample. Despite of the increasing need to detect ATS, a few of them have been used for their determination. The next sections present these detection methods in a critical manner and include tables that summarize the analytical techniques found in the current state-of-the-art that have been recently used for the detection of ATS.

3.1 Electrochemical techniques

Among the current methods, electrochemistry is of great interest for the determination of forensic samples due to its simplicity in the setup and preparation of the sample, short time of analysis, affordability as well as showing excellent analytical capabilities (i.e., limit of detection –LOD–, dynamic range). Indeed, electrochemical sensors have been proven as an effective tool for the analysis in different fields such as healthcare [62] and environment [63,64]. Besides, the inclusion of screen-printing technology has also boosted the employment of electroanalysis based on screen-printed electrodes (SPEs) due to the dramatically decrease in the manufacturing cost. Moreover, electrochemical sensing has historically showed excellent performance in complex matrices (i.e., biologic fluids and

environmental samples), being unaffected by colorful mixtures or molecules that absorb in the visible or infrared spectra. Another advantage is that the electrochemical detection usually do not need long sample pretreatments and preliminary separation steps before running the tests. In contrast, the specificity of electrochemical methods is the most challenging parameter when dealing with similar compounds such as psychoactive substances. Indeed in the ATS family, MET and MDMA exhibit an oxidation peak at the same potential corresponding to the oxidation of the secondary amine of their structure [65,66]. Therefore, additional peaks are needed to distinguish among compounds such as the anodic peak of the methylenedioxybenzene group of MDMA [67]. Concerning the detection of AMP, its structure does not allow for a direct oxidation of any of its groups (e.g., primary amine) in the potential range of graphite SPEs. Therefore, new strategies for the modification of the SPEs such as the employment of nanomaterials or other type of electrodes might be used to decrease the oxidation potential of the AMP, or an *in situ* derivatization towards an electroactive group (e.g., primary to secondary amine) [68,69]. Besides, the integration of receptors (e.g. molecularly imprinted polymers - MIPs [70], antibodies [71]) might allow to increase the selectivity towards the target analyte, and permit the discrimination among other ATS. Among the electrochemical techniques, voltammetry and potentiometry are the most used. All in all, electrochemical sensors are promising tools for the determination of ATS once the scientific community tackles the aforementioned selectivity concerns.

3.1.1 Voltammetry

Voltametric methods consist of applying a desired potential and measure the corresponding current output due to the oxidation or reduction of electroactive compounds [72]. Many electroanalytical techniques such as differential pulse voltammetry (DPV) and square wave voltammetry (SWV) have been extensively used for the determination of illicit drugs because they offer excellent analytical features for rapid determination of the target molecules [73–75]. Moreover, these techniques offer a complete profile of the redox molecules and/or groups found in the compounds of interests in the sample, thus exhibiting simultaneous analyte detection. However, this complex profiling sometimes allows undesired compounds such as cutting agents to overlap the signal over the signal of the illicit drugs, therefore causing false negative situations. In this direction, careful protocol studies have been designed to overcome such issues. For example, De Wael *et al*. explored strategies based on electrode pretreatment and pH screening to overcome the suppressor effect of a common adulterant in cocaine named levamisole [76] and benzocaine [77]. Another strategy is the use of biomimetic affinity ligands [78] or biological receptors (e.g., antibodies [79–81] and aptamers [82–84]) to increase the selectivity towards the analyte of interests.

Mainly, voltametric techniques have been employed for the detection of cocaine. Nonetheless, there is an increasing trend to use voltammetry for the detection of other drugs of abuse such as the ATS (**Table 4**). Early in the 90's, Squella *et al.* reported on the electrochemical oxidation of methylenedioxyamphetamine (MDA) [85]. These substances were studied by DPV showing a single oxidation peak from the aromatic electrophore with formation of a radical cation stabilized by the dioxole ring. Besides, a pH-dependence study was performed showing the influence of pH in the peak current of the amphetamine derivative. Following the same pathway, Milhazes *et al.* characterized the electrochemical behavior of MDMA and its synthetic precursors (i.e., piperonal, 3,4-methylenedioxy-methyl-nitrostyrene and MDA) at pH 7.3 [86]. The voltammograms of MDMA showed two well-defined anodic peaks at physiological pH, the first oxidation peak, E_p = +1.05V (vs. Ag/AgCl/3 M KCl electrode), due to the removal of one electron from the aromatic nucleus; and the second wave, E_p = +1.26V, corresponding to the oxidation of the secondary amine present in the MDMA molecule. Interestingly, the electroanalysis of ecstasy in seized samples and human serum was evaluated on unmodified electrodes [67]. In this work, the oxidative behavior of MET (**Fig. 1Ai**), MDA (**Fig. 1Aii**) and MDMA (**Fig. 1Aiii**) was studied in different buffered systems by cyclic voltammetry (CV) and DPV using a glassy carbon electrode (GCE). Besides, excellent analytical parameters employing SWV allowed for the quantitative determination of MDMA (**Table 4**). Finally, the authors used the SWV approach to gather information about the content and amount of MDMA in seizure ecstasy tablets, and remarkably, validated the results with HPLC exhibiting an outstanding 99.1% recovery. Following the voltametric detection of ATS on unmodified SPEs, Cumba *et al.* proposed the simultaneous detection of MDMA and one derivative *para*-methoxyamphetamine (PMA), commonly known as 'Dr Death' due to its high mortality rate among drug addicts [87] (**Fig. 1Bi and Fig. 1Bii**). The electroanalytical sensing of MDMA/PMA was explored yielding a LOD of 1.3 µM and 0.9 µM, respectively (**Fig. 1Biii**). Importantly, the authors demonstrate that Raman spectroscopy and presumptive color tests (i.e., the Marquis, Mandelin, Simon's and Robadope tests) were not able to discriminate between PMA and MDMA present in samples.

The pretreatment of carbon-based electrodes is usually used to enrich the electrochemical profile of the redox compounds [88]. In that sense, an electrochemically pretreated pencil graphite electrode (PPGE) was used for the determination of MET [89]. The pretreatment consisted of applying anodic current (i.e., 1.7 V) for 10 min in 0.1 M Britton–Robinson buffer solution of pH 11. The pretreated electrode exhibited higher catalytic activity compared to the non-pretreated electrode. In optimal conditions, MET was analyzed by DPV showing a linear relationship of 0.074–54 µM and a LOD of 50 nM. Besides, the PPGE was employed

for the determination of MET in human serum and urine exhibiting an excellent recovery between 95.6% and 102.4%.

Other strategies are based on the use of mediators to electrochemically determine the product of the reaction between the corresponding ATS and the mediator. In this way, Barlett *et al.* proposed the detection of MET through the electrochemical reduction of an intermediate generated by the oxidized mediator (N,N′-(1,4-phenylene)-dibenzenesulfonamide) reaction with MET [90]. Galvanostatic oxidation in combination with a double square wave reduction technique resulted in detection of MET in undiluted saliva. This method could be useful for the determination of non-electrochemically active compounds such as AMP. However, the implementation of a mediator showed high variability in the response as well as undesired effects from the saliva matrix (i.e., protein composition and viscosity). Similarly, cucurbit[6]uril was used as a chemical mediator to detect MDMA employing voltammetric techniques [91]. The mediator was solved in a Nafion solution and directly cast on a GCE by drop casting or spin coating, the latter method showing improved analytical performance.

Other types of electrodes have been recently used for the detection of ATS. A boron-doped diamond electrode (BDDE) was employed for the voltametric detection of MET in the urine of drug addicted people (**Fig. 1Ci**) [65]. The MET exhibited an irreversible oxidation peak at +1.23 V (vs. Ag/AgCl/3 M KCl electrode) in pH 10 (**Fig. 1Cii**). This oxidation process was used to analytically characterize the electrode performance by DPV (**Fig. 1Ciii**). The electrode exhibited excellent accuracy ranging from 93.4% to 97.6%. However, the authors did not evaluate the selectivity towards other illicit drugs or similar compounds, which might cause false positive in the analysis. A gold electrode was used for the electrochemical oxidation of AMP and MDMA and their corresponding quantification at 0.8V [92]. However, the selectivity of this type of analysis was not appropriate for the analysis of seizures with unknown substances.

Recently, nanomaterials have been used to increase the analytical parameters of the electrodes. Rafiee *et al.* modified a SPE with gold nanoparticles (AuNPs) and multiwalled carbon nanotubes (MWCNTs) to provide an effective oxidation of MET at lower potentials than in a bare SPE (**Fig. 1Di**) [93]. Under this modification, the SPE allowed for the determination of MET using square wave stripping voltammetry (SWSV) and electrochemical impedance spectroscopy (EIS). SWVS technique showed excellent analytical parameters (linear range 3.0 – 50 µM and LOD = 6 nM) at a peak potential of 0.45 V (**Fig. 1Dii**). Unfortunately, the selectivity towards similar ATS was not assessed, therefore, hindering the identification of similar illicit drugs in seizures.

Molecular imprinted polymers (MIPs) were applied as specific recognition materials in electroanalytical applications almost two decades ago [94]. However, they have become popular for sensing application in the last decade [95,96]. MIPs bring several advantages (i.e., low-cost, specificity, durability and mass production) when compared with natural molecular recognition products (i.e., antibodies, aptamers) [94]. These materials capable of mimicking natural systems have been tuned with magnetic features [97], and coupled with nanostructured materials to enhance the analytical properties [98]. Following this trend, MIPs have been also used for the detection of illicit drugs [78,99]. Fortunately, Couto *et al.* bring the use of MIPs for the detection of MDMA in biological samples [70]. The sensor was constructed by electropolymerization using *ortho*-phenylenediamine (o-PD) as the MIP's building monomer at the surface of a SPE (**Fig. 1Ei**). The analytical behavior of the sensor was studied with SWV after an incubation period of 10 min. After a careful optimization of the analytical response (**Fig. 1Eii**), the sensor was applied to detect MDMA in human blood serum and urine samples. Another MIPs strategy employed MWCNTs to increase the charge transfer phenomenon on the electrode surface to detect MET [100]. In this case a well-defined peak was shown at about +1.0 V (vs. Ag/AgCl) using a carbon paste electrode (CPE). A quick 20 s accumulation step was only necessary for the rapid screening of MET in human urine and serum samples by SWV. Interestingly, the authors applied a fast Fourier transform technique to increase the signal intensity of the electroanalysis.

The challenge for the voltametric methods still remains in the detection of AMP, because the direct oxidation of the primary amine is not available on the range of potential offered by conventional SPE based on graphite. Recently, a derivatization approach that introduced formaldehyde to achieve the methylation, via an Eschweiler-Clarke mechanism, of illicit drugs containing primary and secondary amines was reported [68]. As a result, the electrochemical profile of AMP is unraveled, and the detectability confirmed. To illustrate the applicability, the derivatization strategy was applied to several prominent illicit drugs containing primary and secondary amines, and finally tested in seized samples. It is worth mentioning that this is the first time in which AMP is detected by a simple derivatization step on a commercial SPE.

Alternative solutions to derivatizations have been proposed by using amperometric immunosensors in which they employed antibodies selective for AMP conjugated with enzymatic reactions to indirectly determine the AMP concentration in urine [71]. Similarly, an amperometric immunosensor in the competitive format was developed for the detection of MET in urine [101]. In this case, the strategy uses an alkaline phosphatase conjugated antibody as the catalyst for the conversion of aminophenyl phosphate to electroactive p-aminophenol. Both aforementioned sensors employed several steps for the detection of the

ATS as well as the use of a redox probe, which increased the complexity of the analytical process. In order to avoid many steps for the detection of MET, Zhang *et al.* employed a label-free amperometric immunosensor based on a surface modification of a gold electrode [102]. The modification involved a functionalization with L-cysteine, the electrodeposition of a Prussian Blue (PB) layer as the electrochemical mediator, a (3-mercaptorpropyl) trimethoxysilane film, AuNPs, and finally the MET antibody. The sensing mechanism is based on shielding the active sites of PB, and thus the access of H_2O_2 from solution to the electrode after the completion of immunoassay (**Fig. 1F**). Therefore, a linear decrease in the current response is expected when MET is in the sample. Last but not least, Demir *et al.* developed an immunosensor based on a polypeptide coupled with an antibody against MET [103]. The selective binding of the analyte restricted the electron transfer on the surface of a GCE, thus a decrease in DPV signals upon increase in MET concentration was accomplished. The authors characterized the polypeptide by nuclear magnetic resonance (NMR) and IR, which they used to enhance the antibody immobilization. Besides, the sensor was validated in spiked real samples with LC-MS/MS.

Electrochemical impedance spectroscopy was also proposed for the detection of MET employing a label-free approach with aptasensors mounted on a AuNPs/gold electrode [104]. When MET was present in the sample, the gold electrode surface displayed an increase of the resistance of the interfacial electrode due to a specific folding of the aptamer and MET. The authors tested the selectivity against AMP, showing a difference on impedance between AMP and MET. However, a poor analytical characterization of the device was accomplished and further work on this direction should be performed.

Other solutions involved the electrochemiluminescent detection of AMP and MET by taking advantage of the photochemical properties of $[Ru(bpy)_3]^{2+}$ – Nafion composite film [105]. The sensor exhibited an outstanding linear range from 50 pM to 1 mM of MET and AMP. Besides, the modified films were directly formed over the surface of the electrode, thus allowing for a simple fabrication of the sensor.

Finally, Jang *et al.* proposed an organic transistor for the point-of-use detection of ATS via host-molecule-functionalized surfaces [106]. In this case, they employed cucurbit[7]uril derivatives that can selectively detect ATS on a gold electrode. This transistor was fabricated on a flexible indium tin oxide (ITO)-coated polyethylene naphthalate (PEN) substrate with the aim to become a wearable device. This type of sensors exhibited an exceptional picomolar detection limit. Despite its promising analytical features, the device needs to be tested in real samples to truly evaluate its potential.

Voltametric techniques offer rapid and affordable analysis of ATS with a broad variety of electrodes in different types of matrices (e.g. from seized materials to biofluids). However, sensors based on a voltametric approach are usually tailored towards the detection of a single analyte or few analytes, posing difficulties when dealing with samples of unknown composition. Still, a low-cost voltametric sensor able to detect a whole range of illicit drug is necessary. In the case of the analysis of seizures/cargos, voltametric sensors can offer several advantages (e.g. fast, sensitive and affordable analysis) due to the simplicity of the matrix, although several cutting agents might be present. In contrast, the analysis of illicit drugs in biological samples remains a challenge for voltametric sensors due to the biofouling process and the need to reach low cut-off values. Overall, voltametric sensors are a promising tool for the analysis of illicit drugs, although some features need to be addressed such as versatility and selectivity in order to broaden the screening capacity.

3.1.2 Potentiometry

Potentiometric techniques represent a passive electrochemical technique that does not generate a current flow through the system (or in the order of the fA). It is based on the measurement of the difference of voltage between a working and reference electrode, making it the simplest electroanalytical method. For more details, the reader is referred to the related literature [107–109].

Watanabe *et al*. early reported a method for the determination of MET in urine using a methamphetamine-sensitive membrane to build a type of ion-selective electrode (ISE) [110]. The electrode was constructed by incorporating an ion-exchanger (5 wt.% sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate), the polymer (30 wt.% poly(vinyl) chloride, PVC) and employing tricresyl phosphate as a plasticizer. This strategy exhibited an excellent LOD of 10 µM for MET with a near-Nernstian response of 56 mV decade^{-1} along the dynamic range of 0.1 mM to 10 mM. However, the selectivity towards precursors such as ephedrine and other amines was poor. Therefore, other similar ATS such as AMP might also hinder the detection of MET by the use of ion-selective electrodes.

Recently, an amphetamine-ion-selective microelectrode (**Fig. 1Gi**) was developed by employing a solid contact layer based on conductive polymer (i.e., polypyrrole) on a platinum microelectrode [111]. In this work, several ion-selective membrane compositions were tested finding that the best composition was 26 wt. % poly(vinyl chloride), 63 wt.% di-butyl phthalate as the plasticizer, 6 wt.% sodium tetraphenylborate as ion exchanger, and 5 wt.% dibenzo-18-crown 6- ether as the receptor. The sensor exhibited near-Nernstian response (53 mV decade^{-1}) within a dynamic range of 0.03 to 1 mM, and a LOD of 0.04 mM within a working pH from pH 1.5 to pH 8.5 (**Fig. 1Gii**). However, the main issue of this type of sensors is the poor selectivity against similar compounds (amines) and other cations that

might be in the sample mixture and might hamper the reliable detection of ATS. In order to improve the selectivity of this sensor, the same group employed a new ion-pair complex based on the metallocarborane, cobalt bis(dicarbollide) anion ([3,3'-Co(1,2-$C_2B_9H_{11})_2$]−) coupled to amphetamine-protonated cation which indeed improved the selectivity coefficients of similar amines [112].

Overall, potentiometric sensors might be an excellent tool for amphetamine detection in its cation form without further treatment of the sample, as it is difficult to detect the primary amine oxidation employed by other voltametric techniques. In contrast, the specific potentiometric detection of ATS might be usually of a selectivity concern. In this direction, the chemical synthesis of adequate ionophores should enhance the analytical parameters (particularly the selectivity) of these potentiometric sensors towards a trustworthy ATS sensor.

Table 4. Electroanalytical techniques for ATS detection.

Analytical technique	Type of electrode	Analyte	Sensitivity ($\mu A\ \mu M^{-1}$)	LOD (µM)	Linear range (µM)	Reproducibility (%)	Recovery (%)	Time of analysis (s)	Sample pretreatment	Observations	Ref
Amp	Ab/PtE	AMP	-	2.5	0.74 - 14.8	<15	-	720	Incubation time	Use of Ab for selective recognition	[71]
ECL	$Ru(bpy)_3]^{2+}$ – Nafion composite/ GCE	MET AMP	-	$0.05*10^{-3}$	0.005 - 1000	4.8	-	15	-	Simple modification of the electrode	[105]
CV and DPV	BDDE	MET	0.64	0.05	0.07 - 80	2.8	93.4 - 97.6 (urine)	100	Cathodic pretreatment	Unmodified electrode	[65]
SWSV and EIC	AuNPs+MWCNTs/ SPE	MET	0.12	$6*10^{-3}$	3.0 - 50	5.1	-	>200	Deposition (-0.2V, 200 s)	Low oxidation potentials	[93]
Amp	Ab/SPE	MET	-	1.3	1.3 - 10.1	-	91.5 - 104.4 (urine)	15 - 30	Incubation time	Multiple steps	[101]
Amp	L-cysteine/ PB/MPS/AuNPs/Ab /Gold E	MET	-0.5	$7.5*10^{-3}$	0.01 - 5	6.1	96.9 - 104.2 (blood)	-	35 min incubation time	Low LOD	[102]
DPV	CPE	MDAs	16.7	-	10 - 100	3.8	-	-	-	Unmodified electrode	[85]
DPV	GCE	MDMA and precursor s	-	-	-	-	-	300	-	Unmodified electrode	[86]
DPV, SWV	GCE	MDMA	$30*10^{3}$	1.2	8 - 45	1.3 – 2.1	99.1 (serum)	-	-	Validated in biofluids	[67]
DPV	SPEs	MDMA PMA	0.064 0.039	1.3 0.9	10.3 - 86.4 12 - 89.6	3.2 3.8	100 ± 2	-	-	Unmodified electrode	[87]
DPV	PPGE	MET	0.076	0.05	0.075 - 54	4.5 – 5.2	95.6 - 102.4	-	10 min anodic pretreatment	Unmodified electrode	[89]
SWV	Mediator/SPE	MET	-	2.7	2.7 - 33.5	3 – 5	-	122	-	Mediated detection	[90]
CV	Cucurbit[6]uril	MDMA	0.026	3.5	4.2 - 48	-	-	-	-	Surface	[91]

	/Nafion GCE									modification	
Amp/ transistor	Cucurbit[7]uril/ gold E	AMP	-	$1*10^{-6}$	$1*10^{-6}$ - 1	-	-	-	-	Lithographic techniques	[106]
DPV	Polypeptide / GCE	MET	$6.4*10^{-3}$	87.5	67 - 670	2.4	102.6 - 109.6 (urine, serum, saliva)	-	-	Validation in biofluids	[103]
EIC	Aptasensor / GCE	METH	-	-	-	-	-	-	-	Use of aptamers as selective element	[104]
SWV	MIPs / SPE	MDMA	0.089	0.79	Up to 200	1.8	81.0 ± 2.4 (urine) 91.4 ± 1.1 (serum)	-	10 min incubation	Use of MIPs/ low LOD	[70]
FFT-SWV	MIPs / MWCNTs / CPE	MET	9.73	$0.8*10^{-3}$	0.01 - 100	-	92.8 – 104.6	>20	20 s accumulation step	Low LOD, use of MIPs	[100]
CV SWV	Gold E	AMP MDMA	-	30.9	110.9 - 258.9 38.7- 229.2	-	97.4 – 98.5 (urine)	-	-	Validated in biofluids	[92]
EIS	Cucurbit[7]uril/AuNPSs Gold E	3-PPA	-	6.2	10 pM - 100	-	94.4 – 109.1 (serum and urine)	-	-	3D structure formation	[113]
DPV	BDDE	MDMA	0.109	0.3	1.1 - 500	1.9	99 (tablets)	-	Cathodic pretreatment	Unmodified electrode	[66]
LSW	SPE	MDMA	0.025	1.83	10 - 100	1.95	-	-	Cathodic pretreatment (-0.5 V, 20 s)	Unmodified electrode	[114]
SWV	MWCNTs/AuNPs/Fe_3O_4NPs/GCE	MET	0.33	0.016	0.05 - 50	2.54	101-111 (urine)	-	-	Nanomaterials deposition	[115]

Abbreviations: 3-PPA: 3-phenylpropylamine; Ab: Antibody; Amp: amperometry; AuNPs: gold nanoparticles; BDDE: boron-doped diamond electrode; CPE: carbon paste electrode; DPV: differential pulse voltammetry; ECL: Electrochemiluminiscence; EIC: electrochemical impedance spectroscopy; FFT: fast Fourier transform; GCE: glassy carbon electrode; LOD : Limit of detection; LSW: linear sweep voltammetry; MDA: methylenedioxyamphetamine;

MPS: 3-mercaptorpropyl) trimethoxysilane ; MWCNTs: multiwalled carbon nanotubes; PB: Prussian Blue; PMA: *para*-methoxyamphetamine; PPGE: pretreated pencil graphite electrode; PtE: platinum electrode; SPE: carbon screen-printed electrode; SWSV: square-wave stripping voltammetry.

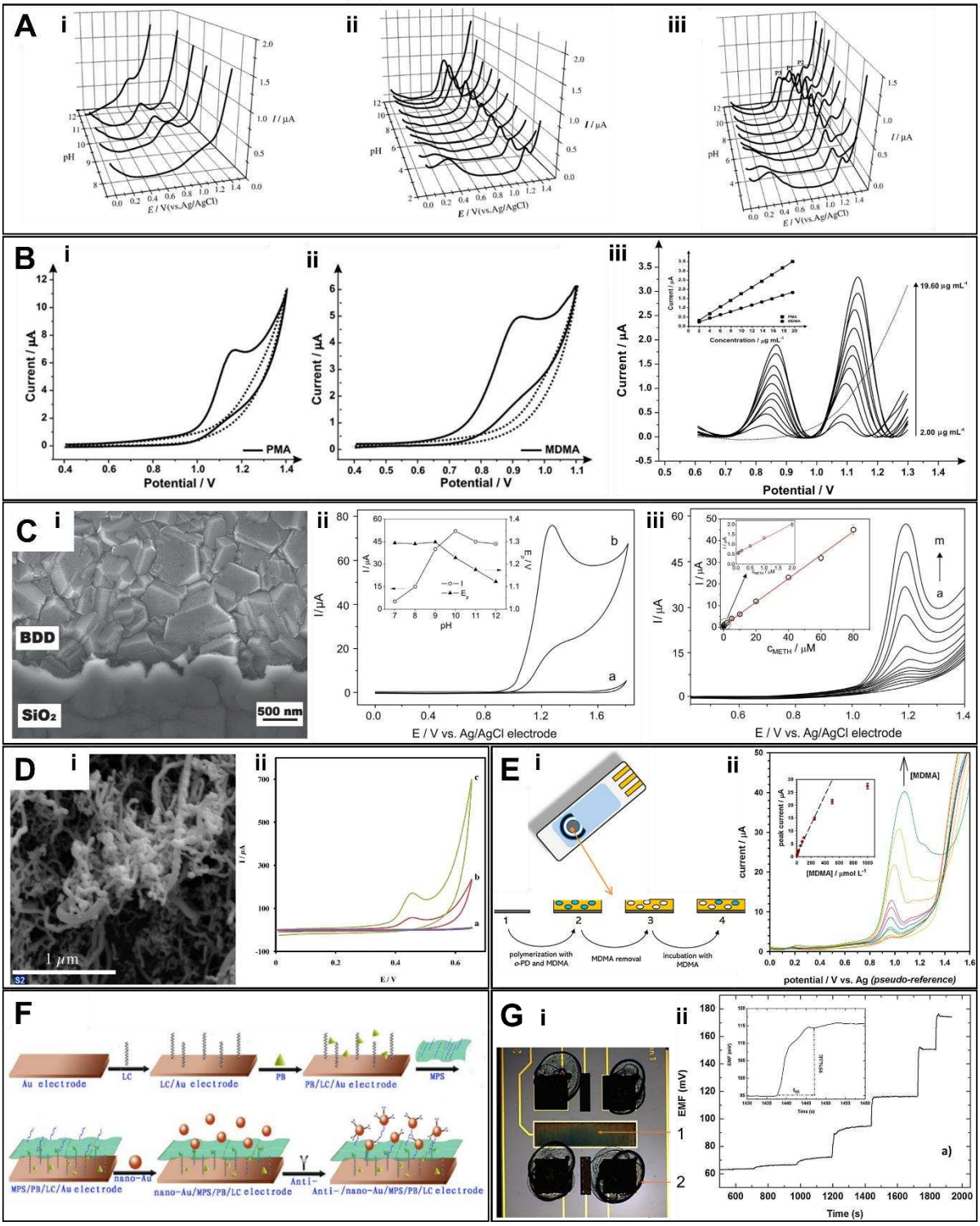

Fig. 1. Overview of the electrochemical sensors reported for the detection of ATS. Fig. 1A*: Electrochemical behavior of ATS at different pH: (**i**) DPVs of MET; (**ii**) DPVs of MDA; (**iii**) and DPVs of MDMA. Adapted from ref* [67]*, with permission from Elsevier.* ***Fig. 1B****: Electrochemical study of MDMA and PMA on SPE. CVs of SPE (**i**) in presence (500 mg/mL) and absence of PMA; (**ii**) in presence (250 mg/mL) and absence of MDMA; and (**iii**) DPVs obtained utilizing SPEs by adding aliquots of MDMA/PMA (in PBS pH 7.0) at concentrations in the range of 2.00–19.60 mg/mL (inset shows corresponding calibration curves) (Adapted from ref* [87]*, with permission from The Royal Society of Chemistry);* ***Fig. 1C****: Electrochemical study of METH on boron-doped diamond electrode (BDDE) on BR buffer pH*

*10. (**i**) SEM micrographs of the active BDD area and silicon oxide passivation interface; (**ii**) CVs (a) blank: (b) 0.1 mM METH (inset exhibits the effect of pH on the peak current and peak potential; **(iii)** DPVs of different concentrations of METH (inset shows corresponding calibration curve) (Adapted from ref* [65]*, with permission from Elsevier); **Fig. 1D**. Electrochemical determination of METH on nanomaterials-based SPE: (**i**) SEM images of the SPE surface modified with MWCNTs-Nf/GNPs. (**ii**) CVs for bare SPE (a), SPE/MWCNTs-Nf (b) and SPE/MWCNTs-Nf/GNPs (c) in 0 0.01 M MET (Adapted from ref* [93]*, with permission from Elsevier); **Fig. 1E:** Electrochemical behavior of MDMA on MIP-based SPE. (**i**) Schematic illustration of the construction of the MIP- SPCE sensor. (**ii**) SWVs of the sensor after 10 min of incubation at different concentrations of MDMA (inset shows the corresponding calibration curve) (Adapted from ref* [70]*, with permission from Elsevier); **Fig. 1F**: Label-free amperometric immunosensor for MET detection. Illustration of the preparation of the working electrode (Adapted from ref* [102]*, with permission from Elsevier); **Fig. 1G**: (**i**) Image of the microsensor with the casted membrane; (**ii**) Dynamic response of the amphetamine-selective microsensors for step changes in the concentration of amphetamine sulfate (Adapted from ref* [112]*, with permission from Elsevier).*

3.2 Techniques coupled to mass spectrometry

Mass spectrometry is a detection method that works with charged species of the parent molecule or its fragments and determines their weight by measuring the mass-to-charge ratio (m/Q or m/z) in vacuum conditions. Mass spectrometers consist of several components: the ion source that generates the charged specimens, the mass analyzer that separates the ions, and the detector. For more details, the reader is referred to the related literature [116–120].

Concerning illicit drugs screening, the MS-based methods used can be classified in targeted and untargeted screening. The later one is done by employing the full scan analysis mode, which scans the entire mass spectra of the sample (unfragmented and major fragmented ions), and the reference mass spectra libraries. This method can be used to detect any compound for which the mass spectra are available [121], but it can't be used for the detection of new compounds, with unknown structure. The targeted drug screening method uses selected monitoring mode (in case of GC) or selected reaction monitoring mode (in case of LC) to detect only pre-established specimens. This method has a better sensitivity and it is the frequently used for the screening of commonly used drugs of abuse [121].

In order to increase the sensitivity and specificity of the method, MS is coupled with chromatographic methods such as GC and LC. This way, the targets from the sample are first separated through the chromatographic method and then analyzed by MS [121]. The two chromatographic methods have in common the separation process, which is based on the partitioning of the analytes between the stationary phase and the mobile phase. The difference between the two methods consist in (i) the nature of the mobile phase: an inert gas (helium, hydrogen, or nitrogen), in case of GC, and a solvent system in case of LC; and

(ii) the nature of the molecules that can be separated: smaller, less polar and volatile molecules in case of GC and larger or more polar molecules (like ATS) in case of LC [120,122]. Besides, different techniques for the generation of the ions are employed with respect to which of the two chromatographic methods are coupled with MS. Thus, in case of GC-MS the ionization of the compounds takes place in a vacuum using one the following techniques: (i) electron ionization (EI), (ii) positive ion chemical ionization (PICI), and (iii) negative ion chemical ionization (NICI) [120,123]. When LC-MS is used for the detection, the generation of ions can be carried out by several techniques such as electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI) and atmospheric pressure photoionization (APPI). The most used method in case of ATS when dealing with polar species is ESI. In contrast, APCI is used for the analysis of less polar species. Also, APCI, APPI, and ESI take place at atmospheric pressure, which is less burdening on the vacuum systems of the mass spectrometer [120].

3.2.1 Sample preparation

The sample preparation includes several steps, especially when the matrix is of biological nature: extraction, derivatization (in case of GC-MS) and clean-up. Every additional step in the pretreatment of the sample prior to analysis contributes to the recovery of the analytes and sensitivity of the method, lowering the limits of detection and quantification, but at the same time increasing the complexity of the method and the time of analysis.

The extraction can be performed by solid-phase extraction (SPE), liquid-liquid extraction (LLE) or their variations: magnetic solid-phase extraction (MSPE), microextraction techniques (solid-phase microextraction –SPME– and liquid-phase microextraction –LPME), and matrix solid phase dispersion (MSPD) [124–126]. The extraction is usually followed by an evaporation step, frequently under a nitrogen steam, and the reconstitution with an appropriate solvent, to preconcentrate the solution [126], these two steps increasing even more the total time of analysis. The extraction methods prior to ATS analysis are discussed further, this being a largely studied aspect for ATS analysis.

SPEx has several advantages, namely high flexibility regarding the extracting schemes design and adsorbent materials selection, higher selectivity and cleaner extracts, but it needs large volumes of organic solvents and is often expensive and time-consuming. To overcome these limitations, MSPE can be used which implies small amounts of magnetic sorbents to concentrate the targets, by employing an external magnetic field for the separation of the analytes, without a centrifugation or filtration step, requiring a short equilibrium time, thus shortening the time of sample pretreatment (**Fig. 2A)** [50,125,127]. The SPME method includes two processes: the passive partitioning of the analytes between the extraction phase (a liquid polymer, a solid sorbent or a combination of both coated on a

fused silica fiber or metal wires) and the sample media, followed by the analytes desorption. This method can be performed by the direct immersion of fiber in a solution (DI-SPME, **Fig. 2Bi**) or by exposure of the fiber to the vapor phase above a solid or solution (headspace (HS)-SPME, **Fig. 2Bii**), the later one being encountered in the methods described for the detection of ATS [128].

In the liquid-based methods, the analytes undergo partition equilibrium between the acceptor phase (usually an organic solvent) and the aqueous sample solution. LLE is advantageous due to easy and fast extraction procedures, production of clean extracts and low cost, but it the downside is the impact it has on the environment and human and animal health as it uses large amounts of organic solvents [125,127–129].

With LPME, the problem of solvents amount is overcome, by the employment of small sample volumes; although, this has a negative impact on sensitivity. The LPME procedures which have been utilized for the extraction of ATS were mainly single drop microextraction (SDME) and dispersive liquid–liquid microextraction (DLLME) [125,128,130]. In case of SDME, the extraction of analytes is performed through passive diffusion in a single drop of an organic solvent suspended in an aqueous solution, which is afterwards injected into the chromatographic system. The main advantages of this method are the reduced amount of solvents, ease of operation and low cost due to the fact that the analyte isolation and purification as well as the enrichment of the sample are performed in one step. On the other hand, there is the problem of drop instability and/or dislodgement during extraction, which may reduce the precision and accuracy of the method [128,131]. DLLME (**Fig. 2C)** employs a ternary solvent system: an extraction solvent, a disperser solvent and the aqueous sample, and it is based on the formation of a cloudy solution upon the mixing of these three components. This solution is then centrifuged, and the extraction component is removed and used for analysis. The advantages of this method are the use of low amounts of organic solvent, low cost, rapidity and effectiveness of extraction, due to the high exchange surface resulted in the cloudy solution [124,128,132]. Another variation of LPME described for ATS extraction is the use of a porous membrane between the donor and acceptor phases that ensures their physical separation. Based on the nature of the acceptor phase, this method can have two components (**Fig. 2Di**), when the acceptor phase is an organic solvent and it is suitable for the GC-MS method, or three components (**Fig. 2Dii**), when the acceptor phase is an aqueous solution, which is suitable for LC or CE methods [124,128].

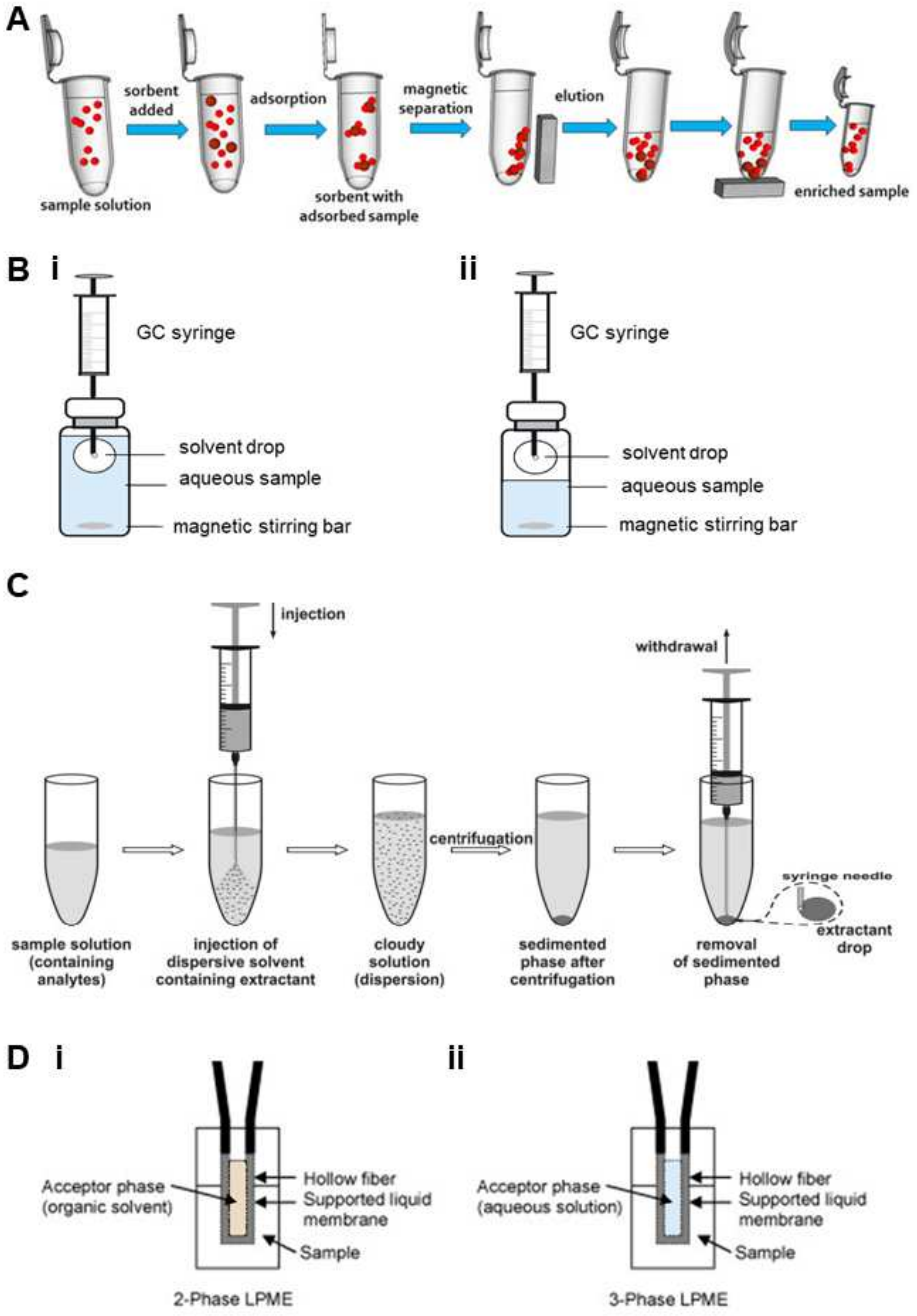

Fig. 2. *Extraction techniques used for ATS:* ***2A.*** *Magnetic solid-phase extraction (MSPE). (Reproduced from ref* [133]*, with permission from Multidisciplinary Digital Publishing Institute);* ***2B.*** *Solid-phase microextraction (SPME): (**i**) direct immersion-SPME, (**ii**) headspace-SPME (Adapted from ref* [134]*, with permission from Elsevier);* ***2C.*** *Dispersive liquid–liquid microextraction (Adapted from ref* [135]*, with permission from Elsevier);* ***2D.*** *(**i**) two-phase hollow fiber liquid phase microextraction, (**ii**) three-phase hollow fiber liquid phase microextraction. Adapted with permissions from ref* [136]***.***

3.2.2 Particularities of biological samples

In literature, the biological matrices that were tested for the presence of ATS and their metabolites include urine, blood/serum, saliva, hair, sweat and vitreous humor (**Table 5**).

Aspects regarding the advantages and challenges for the testing of these biological matrices by GC-MS or LC-MS are discussed further.

The main biological matrices used for the analysis of ATS are urine, blood and serum. Urine is the preferred biological specimen for drug screening for several reasons: is a well-known and easy to collect specimen, targets may accumulate in urine, and it exhibits a prolonged detection window [50,121]. One of the disadvantages consists in the possibility of sample adulteration (the collection of the sample might be performed without supervision). An important aspect to be considered when testing urine is that the detection can target the illicit drug or its metabolites, the latest being the most frequent case considering that metabolites are present in higher concentrations in urine compared to the parent drug. The metabolites that are eliminated in urine result after metabolic reactions that aim to reduce the toxicity and increase the hydrophilic properties of the parent molecule in order to favor its elimination.

The main reason for the analysis of blood samples for ATS testing is the correlation of the drug levels with the amount of consumed drug and with possible physiological changes. The invasive collection, small detection window (24 to 48 h) due to the metabolization and elimination of the drugs in urine, the presence of proteins in the blood and the need for anticoagulant and preservative addition which may interact with the targets are disadvantages of the whole blood as a biological matrix for the detection of ATS [137]. Moreover, a cleanup step is necessary prior to analysis which impedes the analysis in this matrix [120,137].

Alternative biological samples for the analysis of ATS include saliva, sweat and hair. The advantages of this kind of matrices include the non-invasive collection and the difficulty in adulteration (collection can be observed or performed by the examiner) [124,130]. Saliva is an aqueous suspension of enzymes, cholesterol, proteins, and electrolytes [120,130]. In this case, the parent drug is found in higher concentration than its metabolites especially in case of basic drugs, such as ATS, which are able to diffuse into saliva from the blood relatively easy. Besides the above mentioned advantages, saliva drug levels have a good correlation with concentrations of the drugs in the blood and the potential for detection of recent intake [50,130]. Disadvantages include lower concentrations of the drugs (5 to 10 times lower compared to urine) after some time of consumption which require the use of analytical procedures with increased sensitivity or enrichment of the sample using an extraction method such as SPEx [120,130]. The main advantages of the analysis of the hair samples for ATS testing are the long detection window (hair being used for overviewing of long-term exposure to drugs of abuse), and the low risk of alteration in transferring of the sample to the examiner [50,128]. Interestingly, the amount of sample used is typically less 100 mg, which facilitates the sample management. One of the disadvantages is the complex pretreatment

that includes an additional washing step for decontamination (to eliminate the hair care products and other compounds). Furthermore, the isolation of amphetamines from hair samples is usually performed by alkaline digestion, extraction with acidic solutions, organic solvents or mixtures of solvents [126], thus involving a tedious process before the analysis. Sweat can also be used as an alternative matrix because the parent drug is present in higher concentrations than its metabolites, but it is not easy to collect [50].

Another alternative matrix is vitreous humor. The advantages of this specimen include that water is the main component (around 99%), increased stability (no significant metabolic activity), low levels of endogenous interferences, easy sampling during necroscopic examinations, and good correlation with the drug levels in blood [129]. The major disadvantages are the limited volume of sample, the low levels of drugs limited by the blood-retinal barrier, and importantly, it is only limited to the analysis of death bodies [129].

The methods described in literature for the detection of ATS in biological fluids are summarized in **Table 5**. These methods used samples of 0.15-2 mL for blood, 0.2-2 mL for urine, 1 mL for saliva, 2 mL for vitreous humor and 10-30 mg of hair, for the analysis of the most common ATS being AMP, MET, MDA, MDMA and MDEA.

3.2.3 Gas chromatography

GC-MS is a robust technique and represents the gold standard method for the analysis of ATS, being used for the confirmation test of the positive results from other drug screening tests [50,121]. This method can be used for the separation, identification, and quantification of analytes from complex matrices.

Among the advantages of the GC-MS method, there are: (i) the possibility to be employed for the screening of large panels of drugs in the same run; (ii) the discrimination between similar structures and isomers; and (iii) the high resolution for the separation of the analytes due to the long GC capillaries (~30 m). Furthermore, in line with the green chemistry principles, the use of a gas mobile phase reduces the use of organic solvents [132,138]. In contrast, the main disadvantage of GC-MS method is the limited applicability for the detection of polar, nonvolatile compounds. Because the mobile phase is a gas, only the molecules characterized by low molecular weight, thermostability and are nonpolar and volatile at the used temperatures (maximum ~300°C) can be analyzed by GC-MS [121]. The compounds that do not possess these properties could be analyzed using GC-MS only after an additional derivatization step. This can be the case of ATS and of the majority of their metabolites in urine. The derivatization of ATS can be performed using different agents such as methanol, pentafluoropropionic anhydride (PFPA), trifluoroacetic anhydride (TFAA) or fluoroacyl reagent, and it can be done simultaneously or after the extraction of the analytes

from the matrix [117,121]. In the latter case, this additional step increases the time of analysis. Moreover, this method is costly, implies long time of analysis, requires qualified personnel to perform the analysis and maintain the apparatus, and is not suitable for on-site drug testing.

In case of GC-MS method, the articles found in literature, include the detection of various ATS in blood and urine mainly, but saliva, sweat and vitreous humor are also mentioned (**Table 5**). Despite the fact that the later ones have LODs and limits of quantification (LOQs) comparable with the ones obtained in blood or urine, longer analysis times are needed in the case of these alternative matrices. Furthermore, in case of quantitative determinations in saliva or vitreous humor, a correlation with blood levels needs to be investigated in order to obtain relevant information for toxicological purposes. In blood, the best performance in terms of LOD and LOQ was obtained by Zhang *et al.* using MSPE with Fe_3O_4/o-MWNT composites, reaching 0.044 ng mL^{-1} and 0.148 ng mL^{-1}, respectively for MET detection [139]. Other methods which used DLLME for the extraction step had the shortest time for the detection of ATS in this matrix, but with higher LOD values. For example, Lin *et al.* performed two steps simultaneously, with methanol as both dispersive and protein precipitation (PP) agent [127], and Mercieca *et al.* used hexyl chloroformate as the derivatization agent (besides the DLLME) with a time of reaction of only 30s [132]. All methods involving blood include a deproteinization step, the most used solvents being TFAA [124,140] and methanol [127,132], but also acetone [139]. For the detection of ATS in urine, extraction methods involved were MSPE, DLLME and SPE. MSPE exhibited the lowest LOD value (0.044 ng mL^{-1} for MET), but with single detection and a longer time of analysis when compared to the method using DLLME [132]. In terms of recoveries, for both blood and urine the best performances were obtained using DLLME: 92-115% and 92-115, respectively [132]. For the street samples Togni et al. used GC-MS for the detection of MDMA from ecstasy tablets in Brazil, with a relatively short time of analysis (20 min.). On the other hand, the values of LODs and LOQs were relatively high, but this shouldn't be a problem when analyzing tablets or powders. The method was tested in the presence of other components that are commonly encountered in Ecstasy tablets (amphetamine, methamphetamine, caffeine and others), but analogs of MDMA were not included (also these compounds were not present in the analyzed tables) [141].

Identification of NPS isomers is an essential feature in forensic analysis (e.g. fluoroampehtamine) since legal controls according to each country legislation are dependent on even minor molecular differences such as a single ring-substituent position as some might be legal and other illegal. Following this direction, Kranenburg et al. used chemometric models for discrimination between the isomers of fluoroamphetamine, methylmethcathinone

and methylethcathinone with GC-MS analysis at a low energy EI (15eV), all 3 compounds showing more information rich mass spectra. Although, regarding the separation of isomers while in case of the MMC and MEC, the use of low energy ionization gave better results, in case of FA the results at the lower energy compared to the high energy (70eV, currently used in forensic laboratories) EI were not significantly improved, the separation being observed at both levels. It is worth mentioning that, this approach could be employed only on GC-Q/TOF instrumentation and a high efficiency source for generating low energy EI would be necessary in order to use this method, as with the conventional source the sensitivity decreased to less than 10% in case of the 15 eV vs. 70 eV. Also, the authors mentioned that the chemometric models would need to be created for every analysis [142]. Interestingly, the GC coupled with vacuum ultraviolet spectroscopy (VUV) was used in addition to GC-MS for orthogonal selectivity of NPS isomers [143]. Lastly, infrared ion spectroscopy (IRIS), a mass-spectrometry-based technique exploiting resonant infrared multiple photon dissociation, was successfully applied for the identification of NPS isomers [144].

3.2.4 Liquid chromatography

LC-MS/MS has been used in place of GC-MS in drug screening and it is commonly used in ATS testing [50,121]. The ensemble contains two quadrupole detectors in tandem, the first one generating precursor (or parent) ions, which are then selectively allowed to enter the second detector, where further fragmentation occurs and product (or daughter) ions are produced [121]. The use of the tandem quadrupole detector enables this method to analyze multiple compounds simultaneously with high selectivity and sensitivity [120,125].

In comparison to GC-MS, LC-MS/MS can be used for polar, thermolabile, and nonvolatile compounds without the derivatization step, thus emerging several advantages: (i) simplicity of the preparatory procedures, which reduces the errors that appear during this phase as well as shortens the total analysis time; (ii) increased sensitivity, the target amount not being limited by the amount of the derivatized analytes; (iii) wider range of biomedical and toxicological applications, considering that most biologically active molecules, including ATS, belong to these categories [117,120,121]. On the other hand, the analytes are in solution at the end of the LC separation process. Hence, the transition of the sample into gas phase is a mandatory step for the measurement by MS. Similar to the case of GC-MS when it comes to the biological samples, LC-MS/MS needs proper sample preparation prior to analysis. It is usually the most time-consuming step in the analytical process, especially when a quantitative analysis needs to be performed because of the need to minimize the ion suppression effect, which represents a challenge due to the polar nature of the matrix. Other disadvantages include: (i) variety of method development, validation, and quality control that can appear among different laboratories; (ii) expensive equipment and its maintenance; (iii)

requirement of highly qualified staff for method development, operation of the instruments and data processing; (iv) unsuitability for on-site testing [120,125].

Similar to GC-MS, the most used matrices are blood and urine, but there are several papers that describe the detection of ATS in hair [126,145] and fingerprints [146]. The latter was used for the detection of AMP and MET in a relatively short time of analysis (20 min), using ultrasonication in methanol for the extraction of analytes [146]. The analytical performance was similar to the methods that used other matrices, but still a correlation with the blood levels needs to be performed. The analytical performance in terms of LODs for the detection of ATS in blood was similar among the methods described (**Table 5**). Interestingly, better recovery values were obtained by DLLME with chloroform as extractant solvent (74-124%) [147] or by PP with acetonitrile (72-100%) (although the LOQ was lower) [148] compared to SPEx (58-95%) [149]. From urine, AMP and MET were detected. In both cases, the best performances in terms of LODs, LOQs and recoveries were reported using MSPE with graphene oxide-Fe_3O_4 for the extraction [125], compared to SPME with a MIP sol-gel tablet [150]. However, the second method had a shorter time of analysis, and the tablet could be stored and reused for at least 20 times.

Concerning the use of hair for the analysis, time-consuming pretreatment methods were used, reaching the total analysis time of 1 hour or more. Among the described methods, SPEx showed the best performances in terms of LODs, LOQs (0.001-0.005 ng mL^{-1} and 0.01-0.02 ng mL^{-1}, respectively) [145]. Interestingly, an integrated MSPD-SP derivatization described by Argente-Garcia *et al.* showed enhanced recovery values, although with higher LODs and LOQ values [126].

In the case of street samples, LC-MS/MS was employed by Chiang et al. which quantified MDMA in a sample that also contained nitrazepam, while another sample contained MDMA and MET, both samples having instant coffee as matrix [20]. Furthermore, LC-MS/MS was used for the determination of MET enantiomers, this being another example for the necessity of distinguishing between isomers of an illicit drug since in some countries (e.g. Germany) the law attributes different limits for the enantiomers mixture vs. pure enantiomer. This can be justified from a toxicological point of view by the fact that one enantiomer (S-(+)-enantiomer) is more potent than the other. Gelmi et al. used a HPLC-MS/MS method to distinguish the two isomers of MET using A Lux 3 µm AMP column, a chiral column used for the separation of amphetamine and methamphetamine enantiomers. This method proved to be less complex in regards to the sample preparation in comparison with a GC-MS method also employed by the authors, which required more steps (dissolution of the powder obtained from the tablets in KOH, extraction with ethyl acetate, and derivatization), thus being significantly longer (approximately 2.5 hours versus 10-15 min, in the case of HPLC-

MS/MS). However, only with the GC-MS method the enantiomers were baseline separated, but both methods gave similar results in terms of concentrations of the two enantiomers in the analyzed samples [151].

Table 5. Exemples of a) GC-MS and b) LC-MS methods used for the detection of ATS.

Nr. Crt.	Matrix	Sample pretreatment	Sample amount (mL or mg*)	Analyte	LOD	LOQ	Linear range	Recovery (%)	Analysis time (min)	Observations	Ref
					(ng mL^{-1} or ng mg^{-1}*)						
a) GC-MS											
1	blood	LLE	0.2	AMP PMA MET MDA MDMA MDEA	0.22-0.81	0.65-2.4	1-500	91-104	>40	Besides the extraction on the anlytes, there is a derivatization step with TFAA. Many stepts including evaporations and reconstitutions of the samples	[140]
2	blood	HF-LPME	0.5	AMP MET MDA MDMA MDEA	3 3 3 1	4 4 5 2 2	5-500	83-110 78-81 68-78 83-87 71-81 85-92	>62	Besides the extraction of the analytes, there is a derivatization step with TFAA.	[124]
3	blood	UA-DLLME	0.2	AMP MET MDA MDMA	10	40	$40\text{-}25*10^3$	Only extraction recovery mentioned	~32	Methanol is used as both dispersive agents and PP agent, permorfing both in one step.	[127]

Table 5. Exemples of a) GC-MS and b) LC-MS methods used for the detection of ATS.

Nr. Crt.	Matrix	Sample pretreatment	Sample amount (mL or mg*)	Analyte	LOD	LOQ	Linear range	Recovery (%)	Analysis time (min)	Observations	Ref
					(ng mL^{-1} or ng mg^{-1}*)						
4	blood	DLLME	2	AMP MET MDA MDMA MDEA 4-MTA	50 5 10 50 5 2 5	50 10 10 50 10 2 10	1000	92-115	32	The method includes a PP step using methanol and a derivatization step with hexyl chloroformate haveing a short time of derivatization reaction.	[132]
5	blood urine	MSPE	1	MET	0.044	0.148	0.2-50	79.5 86.6	>45	The method includes a PP step with acetone. The magnetic properties of the sorbent enable the separation of the solid extract by means of an external magnetic feld, which shortens the time required for this step.	[139]
6	urine	DLLME	2	AMP MET MET	50 2 2	50 2 5	1000	92-115	22	Besides the extraction of the analytes, there is a PP step with methanol and a	[132]

Table 5. Exemples of a) GC-MS and b) LC-MS methods used for the detection of ATS.

Nr. Crt.	Matrix	Sample pretreatment	Sample amount (mL or mg*)	Analyte	LOD	LOQ	Linear range	Recovery (%)	Analysis time (min)	Observations	Ref
					(ng mL^{-1} or ng mg^{-1}*)						
				MDA	2	5				derivatization step with hexyl chloroformate.	
				MDMA	2	5					
				MDEA	2	5					
				4-MTA	2	10					
7	urine	SPEx	1	AMP	0.5	10	50-2000	78-83	50 min	Besides the extraction of the analytes, there is a derivatization step with PFPA (pentafluoro-propionic anhydride).	[152]
				MET	1	10		87-90			
				MDA	5	25		81-120			
				MDMA	5	50		99-106			
				MDEA	10	50		87-94			
				PMMA	0.5	10		89-95			
				PMA	1	10	100-2000	54-112			
8	saliva	LLE	1	MET	5	15	15-200	96%	57	Besides the extraction of the analytes, there is a derivatization step with HFBA (heptaflurorobutyric acid). Some interferents were tested (tramadol,	[153]

Table 5. Exemples of a) GC-MS and b) LC-MS methods used for the detection of ATS.

Nr. Crt.	Matrix	Sample pretreatment	Sample amount (mL or mg*)	Analyte	LOD	LOQ	Linear range	Recovery (%)	Analysis time (min)	Observations	Ref
					(ng mL^{-1} or ng mg^{-1}*)						
										methadone, morphine, codeine and diazepam) and no additional peak was observed.	
9	sweat	HS-SPME	-	AMP MET MDA MDEA MDMA	0.27 0.21 0.13 0.15 0.09	0.81 0.63 0.39 0.35 0.29	-	100.9 ± 6.7 95.6 ± 3.3 95.1 ± 5.0 99.7 ± 3.4 100.0 ± 1.1	>97	M.U. are ng/pad The sweat samples were colected from the forehead. The extraction procedure lasted more that 60 min, the head space being performed at high temperatures. Besides the extraction of the analytes, there is a derivatization step with acetic anhydride.	[154]
10	vitreous humor	LLE	2	MDA MDEA MDMA	2.5 1.0 1.0	10	10-400	47.2-81.5 43.6-73.4 44.4-66.4	76	Besides the extraction of the analytes, there is a derivatization step with TEA and HFBA (heptaflurorobutyric	[129]

Table 5. Exemples of a) GC-MS and b) LC-MS methods used for the detection of ATS.

Nr. Crt.	Matrix	Sample pretreatment	Sample amount (mL or mg*)	Analyte	LOD	LOQ	Linear range	Recovery (%)	Analysis time (min)	Observations	Ref
					(ng mL^{-1} or ng mg^{-1}*)						
										acid). This matrix can be used only in postmortem cases.	
11	Ecstasy tablets	ultrasonication with methanol	10*	MDMA	$1*10^3$ (1%)	$5*10^3$ (5%)	$5*10^3$-10^5	78-115	~20	The percentages correspond to the analyte amount in the tablets (w/w). The method was tested on the presence of other components that are commonly encountered in Ecstasy tablets, but not MDMA analogs.	[141]
b) LC-MS(/MS)											
12	blood	PP with acetonitrile	0.2	AMP MET MDA MDEA MDMA	0.3	0.5	1-100	72-100	~34	Although it involves only PP as pretreatment, the matrix effect was comparable with other methdos.	[148]

Table 5. Exemples of a) GC-MS and b) LC-MS methods used for the detection of ATS.

Nr. Crt.	Matrix	Sample pretreatment	Sample amount (mL or mg*)	Analyte	LOD	LOQ	Linear range	Recovery (%)	Analysis time (min)	Observations	Ref
					(ng mL^{-1} or ng mg^{-1}*)						
13	blood	DLLME	0.5	AMP MET MDA MDMA	0.5	2	2-1000	90-119 99-124 74-124 114-122	>16	Besides DLLME, which was performed with chloroform as extractant solvent and methanol as disperser solvent, there was a PP step using methanol.	[147]
14	serum, blood	SPEx	0.150	AMP MET MDA MDEA MDMA PMMA	0.8 0.2 0.8 0.2 4 0.4	5	5-250	67 75 72 61 95 62	11-15	The amphetamines were separated from samples that also contained more tham 60 NPS.	[149]
15	urine	SPME	0.2	AMP	1.0	5.0	5-5000	80%	>19	The SPME was performed using a MIP tablet which could be reused for more than 20 extraction cycles, after two washing steps using methanol and water. Interfetents test were performed for urine	[150]

Table 5. Exemples of a) GC-MS and b) LC-MS methods used for the detection of ATS.

Nr. Crt.	Matrix	Sample pretreatment	Sample amount (mL or mg*)	Analyte	LOD	LOQ	Linear range	Recovery (%)	Analysis time (min)	Observations	Ref
					(ng mL^{-1} or ng mg^{-1}*)						
										components, but not for other ATS or illicit drugs.	
16	urine	MSPE	-	AMP MET	0.02	0.05	0.05–1000	95.7-105.5 92.5-103.2	32.5	Involvs many steps and long time for the preparation of GO-Fe_3O_4, but which shortens the time of extract separation.	[125]
17	hair	SPEx	30*	AM MET 4F-MET MDA MDMA	0.005 0.005 0.002 0.005 0.001	0.02 0.02 0.01 0.02 0.02	0.02-4 0.02-4 0.01-2 0.02-4 0.02-4	75.3-89.9 70.7-72.9 68.6-82 84.6-88 82.7-92.1	>91 min	Samples were stored at room temperature until analysis.	[145]
18	hair	Ultrasound assisted alkaline digestion	10*	AMP MET MDMA	5 2.5 7.5	15 10 25	25-200 10-50 2-20	97 122 99	46 - 58	The integrated MSPD-SP method had better analytical performences in the same amount of time; however, a higher amount of hair was used when comperd to the alkaline	[126]
		MSPD-solution derivatization	25*	AMP MET MDMA	2.5 1 2.5	10 5 10	25-200 10-50 2-20	109 110 88	46 - 58		

Table 5. Exemples of a) GC-MS and b) LC-MS methods used for the detection of ATS.

Nr. Crt.	Matrix	Sample pretreatment	Sample amount (mL or mg*)	Analyte	LOD	LOQ	Linear range	Recovery (%)	Analysis time (min)	Observations	Ref
					(ng mL^{-1} or ng mg^{-1}*)						
		Integrated MSPD-SP derivatization	25*	AMP MET MDMA	0.5 0.25 0.75	1.5 1 2.5	25-200 10-50 2-20	118 109 98	46 - 58	digestion.	
19	finger-prints sweat and finger-marks	ultrasonication in methanol	-	AMP MET	1.5	5	5-500	72-94.1 60.5-82.2	20 min	The detection and quantification parameters are expressed in ug/fingerprint sweat, therefor, quantitative analysis is only valuable if a correlation with the blood concentration can be made.	[146]
20	tablets	sonication in methanol	1*	MET	1.0*	2.5*	2.5-1250	91.8-94.3	23-28	The method was used for the determination of the two isomers of MET. While the baseline separation was not achieved, the results obtaind by this method on the analyzed samples were similar to the ones obtained with a GC-MS method.	[151]

Table 5. Exemples of a) GC-MS and b) LC-MS methods used for the detection of ATS.

Nr. Crt.	Matrix	Sample pretreatment	Sample amount (mL or mg*)	Analyte	LOD	LOQ	Linear range	Recovery (%)	Analysis time (min)	Observations	Ref
					(ng mL^{-1} or ng mg^{-1}*)						
21	instant coffee	sonication in methanol	-	MDA MDMA MET	-	2* 2* 9*	-	-	~15	MDA was quantified in a sample that also conainted nitrazepam, while MDMA and MET were quantified in the same sample.	[155]

4F-MET: 4-fluoroamphetamine; AMP: amphetamine; DAM: 2,5-dimethoxy-amphetamine; DBAM: 2,5-dimethoxy-4-bromo-amphetamine; DBP: 2,5-dimethoxy-4-bromo-phenetylamine; DCAM: 2,5-dimethoxy-4-cloro-amphetamine; DIAM: 2,5-dimethoxy-4-iodo-amphetamine; DIP: 2,5-dimethoxy-4-iodo-phenetylamine; DLLME: dispersive liquid-liquid microextraction; DMAM: 2,5-dimethoxy-4-methyl-amphetamine; DMP: 2,5-dimethoxy-4-methyl-phenetylamine; DNAM: 2,5-dimethoxy-4-nitro-amphetamine; DNP: 2,5-dimethoxy-4-nitro-phenetylamine; LLE: liquid-liquid extraction; MDA: methylenedioxyamphetamine; MDEA: R,S - 3,4- methylenedioxyethylamphetamine; MDMA: 3,4-Methylenedioxymethamphetamine; MET: methapmetamine; MTA: R,S-4-methylthioamphetamine; PMA: R,S-4-para-methoxyamphetamine; PMMA: R,S-paramethoxy methamphetamine; SDME: solid phase microextraction; SPEx: solid-phase extraction;

*for hair, powders or tablets: mg instead of mL

3.2.5 Capillary electrophoresis

Capillary electrophoresis (CE) is a separation technique that uses a direct current electric field applied to capillaries with small internal diameters, filled with either a buffer alone or a chromatographic support and a buffer [156]. The separation of analytes takes place while small amounts of samples are introduced by electrokinetic (application of power for a specified time interval) or hydrodynamic techniques (application of pressure, vacuum, or gravity for a short time interval). The separation is based on their velocities, which are characterized by two phenomena that appear when the electric field is applied: electrophoresis, that influences the transport of charged particles, and electroosmosis, which represents the movement of the entire liquid inside the capillary [157]. There are different CE techniques that can be applied: capillary zone electrophoresis (CZE), nonaqueous CE (NACE), capillary isotachophoresis (ITP), capillary electrochromatography (CEC), electrokinetic capillary chromatography (EKC) (including micellar electrokinetic chromatography –MEKC–) and capillary gel electrophoresis – CGE). In terms of detection methods, CE is usually coupled with UV devices, but other detection methods such as fluorescence, laser induced fluorescence, amperometry and MS are used [156,157].

One of the biggest advantages of CE-MS detection is the small volume of sample (typically nL range after the pretreatment step) that is needed to be injected. In this way, the use of organic solvents is minimized [157,158]. On the other hand, this aspect represents a disadvantage as it leads to relatively poor LODs, but which can be addressed by employing preconcentration methods, a step that is always present in the case of biosamples [158,159]. The pretreatment methods used in CE-MS detection are the same as the ones used for the GC/LC-MS detection and were described in the previous subsection.

For the ionization process, when CE-MS are coupled, the CE instrument needs to be electrically connected to the ESI. The interfaces studied and applied until now are: sheathless, coaxial sheath-flow (this being the most frequently reported in the literature in case of ATS detection, **Table 6**), liquid-junction, and pressurized liquid-junction. In case of coaxial sheath-flow, the end of the separation capillary is inserted into a coaxial capillary tube allowing the sheath liquid to elute through the outside capillary wall. It was observed that this approach offers high spray stability, but it is characterized by turbulence that causes reduction of efficiency and resolution of the separated zones [156,160,161].

Regarding the ATS detection and analysis, when coupled to MS, the most frequently reported CE method was CZE, with ESI as the most popular approach for the ionization of analytes (**Table 6**). In CZE, which refers to separations in aqueous media, cations and/or anions migrate to different zones with a certain velocity, under the application of an electric field. Separations using CZE are carried out on open capillaries containing a selected

background electrolyte. After injection, cations and/or anions migrate under the effect of the applied current according to their own charge and mass in the cathodic or anodic compartments. Another method used for ATS analysis was NACE which refers to zone electrophoretic separations in liquid media other than water [156,157].

Most of the papers found in literature describe methods for the detection of different ATS in urine, but examples using blood, saliva or hair were also reported and are summarized in **Table 6**. Pretreatment seems to have an important influence on the results of the ATS detection in biological samples using CE-MS, this step being one of the most studied aspects regarding this method. Kim *et al.* described a method for the detection of AMP and MET in urine using in-line SMDE-CE-MS with which managed to achieve LODs lower than 1 ng mL^{-1}. The pretreatment implies the formation of a two-layer extraction drop (inner layer consisting of an acidic buffer which is also the run buffer, and the outer layer consisting of octanol) in a basic aqueous donor phase containing the analytes, after a back-pressure is applied. Using this method LODs of 0.54 and 0.299 ng mL^{-1} for AMP and MET, respectively, were obtained in a relatively short time of analysis and low quantities of solvents [159]. Interestingly, the method is mostly automated, but implies a few manually steps (the change of a reservoir with acceptor and donor solvents, and the installation and removal of a disposable plastic vial) that could affect the characteristics of the extraction drop, such as stability. When organic solvents are used as the extraction media, the analytes need to be in the lipophilic form. Because in case of ATS this would happened in a basic pH, the urine pH (physiologically acidic) needs to be properly adjusted before the addition of the extraction solvents in order to maximize the extraction rates. Kohler *et al.* described a method using DLLME for the pretreatment of the urine which exhibited low LODs (0.25 ng mL^{-1}) in a relatively short time of analysis (14 min) [160]. Another example studied the effect of the pH for the detection of several ATS in blood. In this case, it was found that a basic pH (9.5) is needed for an optimal determination [162].

In case of blood, saliva and hair, the time of analysis is usually longer, due to the fact that the pretreatment method is more time consuming. In the examples found in literature (**Table 6**), LLE was the method employed for the pretreatment of these types of matrices. Gottardo *et al.* described a method for the detection of several ATS in postmortem blood reaching LODs between 2-10 ng mL^{-1}. However, given the fact that the ESI is used as the ionization method, besides the LLE pretreatment, a preconcentration step was needed to overcome the ion suppression caused by other components in the blood, which led to a time of analysis of almost 60 min [162].

Table 6. Exemples of CE-MS methods used for the detection of ATS.

No.	Analytical technique	Matrix	Sample pretreatment	Sample volume (mL*)	Analyte	LOD	LOQ	Linear range	Time of analysis (min)**	Observations	Ref
						ng mL^{-1}*					
1.	CE-MS/MS	urine	Filtration SDME	-	AMP MET	0.54 (4nM) 0.299 (2 nM)		1.35-405.63 1.49-447.7 (10-3000 nM)	~16	Manually steps could affect the stability of the extraction drop.	[159]
2.	CE-MS	urine	centrifugation, filtration and dilution	-	AMP MET MDA MDEA MDMA MBDB	2 50 2 10 10 10	-	-	15	Sample preconcentration is performed in the separation capillary and is based on a pH-mediated stacking strategy.	[161]
3.	NACE-MS	urine	LLE	1	AMP ME MDA MDEA MDMA	60 30 70 20 20	-	-	> 32	The pretreatment includes a step where the sample is frozen before the collection of the organic layer.	[163]
4.	CE-MS	urine	LLE	2	AMP MET MDA MDMA	50-200	-	-	>18	After each run the capillary was rinsed with separation buffer.	[164]

5.	CE-MS	urine	DLLME	4	AMP MET MDA MDMA MDEA MBDB	0.25 0.25 0.5 0.25 0.25 0.25	-	-	~14	Besides DLLME, sample preparation includes other steps such as pH adjusting, centrifugation, collection of the organic layer, evaporation and reconstitution before the injection of the sample in CE-MS.	[160]
6.	CZE–MS	blood	LLE	0.5	MA MDA MDEA MDMA	10 5 2 5	30 20 10 20	30-2000 20-800 10-800 20-800	~47	The effect of the pH was tested and it was found that a basic pH (9.5) is needed for an optimal determination.	[162]
7.	CE-MS	saliva	LLE	1	4-ClA	1 ppm	-	-	>38 min	The use of auxiliary gas is not necessary; unknown matrix effects were observed.	[165]

8.	CZE-MS	hair	LLE	100*	AMP MET MDA MDMA	0.04 0.025 0.03 0.02	0.08 0.05 0.06 0.04	0.025-5	>12h	The hair was stored at room temperature until analysis. The pretreatment involved incubation overnight at 45°C in HCl 0.1M.	[166]
9.	CZE-MS	hair	LLE	100	MDA MDMA	0.01	-	-	>12h	The pretretment step was time consuming, the analysis time being ~30 min.	[167]

4-ClA: chloroamphetamine; AMP: amphetamine; CE-MS/MS: capillary electrophoresis tandem mass spectrometry; CZE-MS: capillary zone electrophoresis mass spectrometry; DLLME: dispersive liquid-liquid microextraction; LLE: liquid-liquid extraction; MBDB: R,S-N-methyl-benzo-dioxolylbutanamine; MDA: methylenedioxyamphetamine; MDEA: R,S -3,4- methylenedioxyethylamphetamine; MDMA: 3,4-Methylenedioxymethamphetamine; MET: methapmetamine; NACE-MS: non-aqueous capillary electrophoresis mass spectrometry; SDME: solid phase microextraction;
*for hair, powders or tablets: mg instead of mL; **includes pretreatment

3.3 Raman spectroscopy

Raman spectroscopy (RS) is a one of the most selective spectroscopic technique, capable to provide a structural fingerprint, allowing the reliable identification of molecules [168]. Raman spectroscopy is based on inelastic scattering of photons, known as Raman scattering. The electromagnetic radiation (usually, a laser) can be scattered in two ways: (i) elastic or Rayleigh scattering, when the scattering results in photons possessing energy equal to that of the incident radiation source; (ii) inelastic or Raman scattering, when the scattering results in photons that possess lower (Stokes) or higher (anti-Stokes) energies than the excitation source (**Fig. 3**). The Raman spectrum consists of the intensity of the scattered light plotted as a function of Raman shift, the difference in energy between the scattered radiation and the excitation source providing the vibrational signature of the sample [168]. To obtain the vibrations spectra, the sample is illuminated with a monochromatic laser beam which interacts with the molecules and originates a scattered light with a frequency different from that of incident light. The major drawback of RS is its weak signals, because relatively few photons are scattered, but the signal intensity can be typically increased 10^4–10^6 times by surface enhanced Raman spectroscopy (SERS) [168,169].

SERS involves the use of specialized plasmonic substrates (usually gold and silver nanostructures), as colloidal nanoparticles or on a solid support (**Fig. 3**). It relies on electronic and chemical interactions between the excitation laser, analyte of interest, and a SERS-active nanostructure, allowing both the significant reduction of luminescence and to boost the detection signal. The signal enhancement is influenced by the excitation laser wavelength, and the type, the size, the shape and the surface treatment of the plasmonic substrates [168,170,171]. Unfortunately, because it is difficult to create completely uniform nanoparticles, inconsistencies in SERS responses can be observed [171]. Moreover, because of the low concentrations of drugs and the presence of proteins, the application of SERS to the direct detection of drugs in body fluids has raised many problems, needing the development of SERS substrates with specific characteristic in order to solve these problems [172].

The use of RS presents many advantages: (i) RS is simple to perform, even by nontechnical personnel; (ii) it is rapid, with spectrum obtained in seconds; and (iii) it is nondestructive, the RS analysis does not require sample preparation or the use of chemical reagents. Importantly, RS analyses are not influenced by aqueous media or moisture, and they can be performed through transparent glass or plastic. Besides, portable apparatus allow on-site RS analyses of many different types of samples, in solid or liquid forms, with great selectivity, and in the case of SERS great sensitivity [168–171].

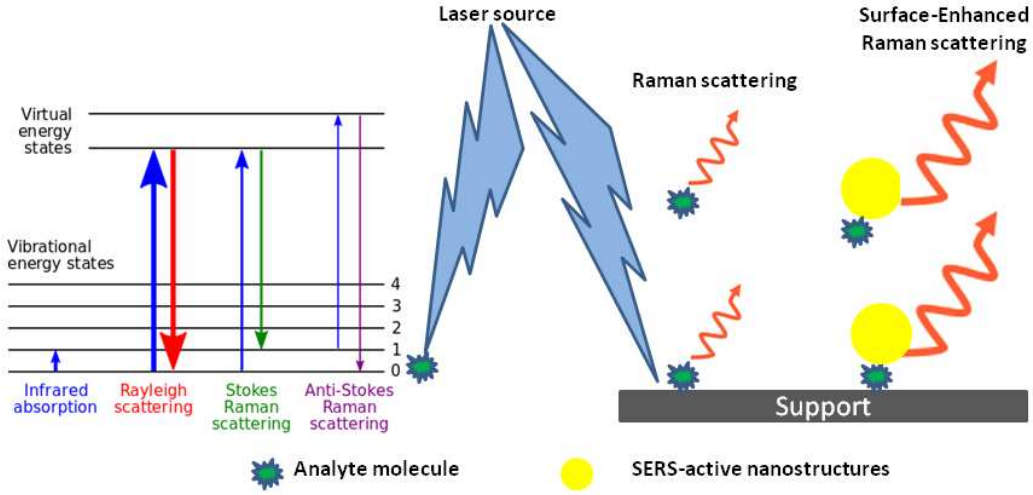

Fig. 3. *Schematic principle of Raman spectroscopy and SERS (Adapted from ref* [168,170]*, with permission from Elsevier).*

RS proved to be a useful tool for the forensic analyst, particularly in the analysis of seized drugs (**Table 7**). RS was able to detect MET from "crystal meth" (usually comprised of methyl sulfone and methamphetamine), but because MET gives a much weaker Raman signal than methyl sulfone, the detection of MET can be difficult at low concentrations [173]. MET was also detected by RS from solutions with different solvents encountered in clandestine laboratories [174]. Interestingly, RS offered useful information for the identification of drugs by summarizing the spectra of thirty drugs of abuse, degradation products, metabolites, and common cutting agent from particles collected with adhesive tapes [175]. In another work, Fourier transform RS was able to show the absence of MDMA in seized ecstasy tablets, instead caffeine, dextromethorphan, a bk-MDMA analog and clobenzorex were detected, and titanium dioxide, starch and microcrystalline cellulose as cutting agents [176]. An important drawback of RS is the limited vibrational reference libraries that hinder the detection of new drugs of abuse. RS analyses allowed only 41% of 221 seized samples suspected of containing novel psychoactive substances (NPS) to be fully identified. The percentage increased to 76% when 33 of these compounds were independently identified by NMR and mass spectrometry, and their spectra used to extend their libraries. Among the compounds identified in the samples, it can be mentioned MET, stimulant-like drugs, synthetic cannabinoids, and hallucinogens [177]. Last but not least, RS could be used for legal controls of isomers which is critical when some of the isomers might be illegal. For example, a portable Raman spectrometer was able to discriminate between all three regioisomers of fluoroamphetamine [178].

As previously mentioned, SERS has been increasingly used to enhance the sensitivity of the method towards the detection of ATS (**Table 7**). For example, the Dynamic SERS (D-SERS)

using methoxymercaptopoly(ethylene glycol) (mPEG-SH) coated gold nanorods (GNRs), with chemometric methods (used for the intelligent and automatic analysis of spectra) was used for the rapid detection of MET and MDMA from spiked urine and drug abusers' urine, with identification accuracy greater than 92% [179]. Using D-SERS, GNRs and a classification algorithm called support vector machines (SVM), the average classification accuracy of 50000, 2500, and 1000 ng mL^{-1} MET and MDMA in urine were 96.1% and 95.9%, 95.3% and 95.3%, 94.2% and 94.0%, respectively. Similarly, MET was detected from drug abusers' urine with accuracy higher than 90% [180]. Using the adsorption of MET on the surface of silver nanoparticles (AgNPs) dispersed on agarose gel, SERS was used for the detection of MET from latent fingerprints [181]. The quantitative analysis of MDMA was improved using D-SERS and ordered 3D hotspots obtained by natural evaporation of monodisperse Au-sol and 4-mercaptopyridine as internal standard, capable to reduce SERS signal variability through its ability to combine AuNPs by Au-S bonds [182]. SERS chips consisting in self-assembled, vertically-aligned silver nanorods (AgNRs) were successfully used for trace detection of MET and AMP from human urine, after the separation by acidulation of organic urea-based byproduct [183]. Interestingly, a portable kit, containing a mini-Raman device and highly reproducible 2D GNR arrays, assembled by the use of mPEG-SH capping, was used for a rapid and reliable SERS detection of MET from human urine. A 3 min pretreatment procedure proved sufficient to lower the high background signals caused by complex components in urine [184]. The SERS using AgNPs demonstrated acceptable precision (RSD of less than 15%) and a LOD of 8000 ng mL^{-1} was achieved for 5,6- methylenedioxy-2-aminoindane (MDAI) [185]. Using as SERS substrate highly uniform, pyramid-shaped, plastic-based plasmonic nano-mushrooms, it was obtained a signal enhancement of 6.85×10^{7} in dry state and 4.81×10^{8} in wet state for the detection of MET in drinking water [186]. AMP and other nine drugs were analyzed by SERS, using commercial SERS substrate Klarite®313 and Raman microscope system. During this work, the functionality of substrates and pureness of samples was assessed by vibrational peak assignments [187].

The employment of microfluidic platforms has shown promises to improve the automation and functionality of SERS devices. Combining microfluidics-based dielectrophoresis, SERS with iodide-modified AgNPs and chemometrics allowed the detection of MET from saliva in under 2 min [188]. SERS was also used to provide a sensitive and selective detection of MET within a microfluidic platform employing AuNPs of 50-60 nm, with a borate capping agent as the SERS medium [189].

Plasmonic platforms localized at the interface of two non-miscible liquids have been used for the detection of MET from complex samples as they provide enhanced and reproducible

signal, due to accumulation of the analyte at the level of the array of gold nanoparticles (GNP). In this direction, an interfacial SERS platform through the large-scale self-assembly of GNP arrays at cyclohexane (CYH)/water interface was developed for detecting MET and MDMA in human urine [190]. The molecules extracted by CYH phase from urine sample were directly localized into the self-organized plasmonic hotspots, yielding excellent Raman enhancement and making a more uniform distribution of both the analytes and GNPs in the liquid interface, with great signal reproducibility. Also, dual-analyte detection at organic and aqueous phases was possible [190]. A Raman enhancement factor larger than 10^7 was obtained using an oil-in-water emulsion method to assemble monodisperse AgNPs in CYH phase into spherical colloidal superstructures in aqueous phase, these superstructures creating 3D SERS hotspots. A fast strategy of CYH extraction for separating MET and MDMA from human urine leads to enrichment of drug molecules in the 3D hotspots with excellent stability and reproducibility, allowing quantitative detection in both aqueous and organic phases [191]. Recently, a wearable SERS sensor has been developed as a patch type to utilize as a molecular sweat sensor for the detection of 2-fluoro-methamphetamine (2-FMA) [192]. A plasmonic silver nanowire (AgNW) layer is formed to enhance the Raman signal of the molecules that penetrated through the SERS patch in a label-free method. This new type of configuration opens up innovative opportunities for the non-invasive monitoring of illicit drug consumption.

Table 7. Examples for detection of ATS using Raman spectroscopy.

No	Analyte	Matrix	Method	LOD	Observations	Ref
1	Mixtures of “crystal meth” (methyl sulfone + MET)	Aqueous solutions of “crystal meth”	Raman spectroscopy	20% MET	It can be hard to detect MET at low concentrations, because MET gives a much weaker Raman spectrum than an equal concentration of methyl sulfone	[173]
2	MET	Clandestine laboratory liquids: solutions of MET in ethanol, diethyl ether, Coleman fuel	Raman spectroscopy	0.5-10% (w/v)	A concentration-dependant Raman peak was observed at 1003 per cm in each solution in 4% w/v and greater solutions	[174]
3	MET, MDMA	Solid samples	confocal Raman spectroscopy	-	The spectra of thirty drugs of abuse particles collected with adhesive tapes, degradation products, metabolites, and common cutting agent standards were recorded	[175]

No	Analyte	Matrix	Method	LOD	Observations	Ref
4	3,4-methylene dioxy-*N*-methylcathinone (βk-MDMA)	Ecstasy tablets seized in the State of São Paulo (Brazil)	FT-Raman spectroscopy	-	No MDMA was identified. Caffeine, dextromethorphan, a bk-MDMA analogue and clobenzorex were detected instead. Cutting agents identified: titanium dioxide, starch and microcrystalline cellulose	[176]
5	MET	221 unsorted seized samples suspected of containing NPS	Raman spectroscopy	-	4 RS taken at different positions within the sample. The quality of the Raman spectra (the background fluorescence level) varied significantly between samples. Ecstasy was not found, but MET, stimulant-like drugs, synthetic cannabinoids, hallucinogens and the cutting agents were identified	[177]
6	FA regioisomers	Powder samples	A portable Raman spectrometer	-	Differentiation of *ortho*-, *meta*- and FAs	[178]
7	MET; MDMA	Spiked human urine; drug abusers' urine	Portable D-SERS with chemometric methods	drug abusers' urine: 0.4, 3, 30 ppm MET with accuracy of 94.5 %, 92.0 % , 92.5 %.	D-SERS used GNRs coated with mPEG-SH. Chemometric methods were introduced for the intelligent and automatic analysis of spectra No sample pretreatments needed The prediction accuracy of urine, urine with 50 ppm MET and urine with 50 ppm MDMA were 100%, 98.7% and 96.7% For drug abusers' urine (containing 0.4, 3, 30 ppm MET) the accuracy was 94.5%, 92.0%, 92.5% The detection from urine takes 2 min, only 2 µL sample is needed	[179]
8	MET, MDMA	Spiked human urine; drug abusers' urine	D-SERS	1 ppm	A portable Raman spectrometer was used with GNRs and a classification algorithm called support vector machines. It needs 2 µL sample and 2 min. The average classification	[180]

No	Analyte	Matrix	Method	LOD	Observations	Ref
					accuracy of 50, 2.5, and 1 ppm MET and MDMA in urine were 96.1% and 95.9%, 95.3% and 95.3%, 94.2% and 94.0%, respectively. MET was detected from urine of real drugsters with accuracy higher than 90%	
9	MET	Test solutions // Latent fingerprints	SERS	10^{-5} mol L^{-1} // 190 µg of MA	The adsorption of MA on AgNPs surface dispersed on agarose gel was used for analyses of fingerprints contaminated with MET	[181]
10	MDMA	Artificial solution	D-SERS combined with internal standard strategy	10 µM	4-mercaptopyridine was used as an internal standard, for SERS signal variability reduction. Ordered 3D hotspots were obtained by natural evaporation of monodisperse Au-sol. The intensity at strongest SERS signals of MDMA showed linear response versus the negative logarithm of concentrations	[182]
11	MET; AMP	Human urine	SERS	50 ng/mL	Nanostructure-based SERS chips: self-assembled vertically-aligned silver nanorods. By the acidulation treatments, the organic urea-based byproducts were separated. SERS spectral collections were performed on dried tiny drop	[183]
12	MET, MDMA	Human urine	SERS	0.1 ppm	The portable kit contains two sealed reagent tubes: a packet of standardized SERS substrates (2D-GNR arrays were assembled by the use of mPEG-SH capping) and a mini Raman device. 3 min pretreatment for separating amphetamines from human urine	[184]
13	MDAI	capsule of MDAI sold as 'Sparkle'	SERS	8 ppm (5.4x	Optimisation of the Ag sol and salt concentrations was undertaken to obtain the	[185]

No	Analyte	Matrix	Method	LOD	Observations	Ref
		purchased from a 'headshop'		10-5 M	AgNPs for reproducible and sensitive SERS analysis	
14	AMP	Solutions	SERS with commercial SERS surfaces	2 ppm	The drugs tested were: AMP, cocaine, methadone, diazepam, methylphenidate, oxazepam, tramadol, morphine, buprenorphine and 6-monoacetylmorphine. The SERS surface was Klarite® 313 (Renishaw Diagnostics, Ltd), equally spaced µm-sized inverted square-based pyramids etched in silicon with a 20 nm gold layer deposited onto the surface	[187]
15	MET	Drinking water	SERS and colorimetry	0.5 mg/L	Plasmonic colorimetry and SERS detection was possible using highly-sensitive, wafer-scale, high-uniform plasmonic nano-mushroom plastic-based substrate	[186]
16	MET	spiked saliva	microfluidics-based dielectrophoresis-SERS device and principal component analysis	500 nM	The iodide-modified AgNPs are trapped and released on-demand using electrodes integrated in a microfluidic channel Chemometrics were used to reliably distinguish MET positive samples from the negative control samples. The chip was reusable three times.	[188]
17	MET	Solutions	SERS within microfluidic platform	4.5 ng/ml	Ag and Au NPs were tested as metallic NPs as the SERS medium	[189]
18	MET; MDMA	Human urine	interfacial SERS platform through the large-scale self-assembly of GNP arrays at CYH/water interface	LOD for MET 0.5 ppm 5 ppm for simultaneous detec	The molecules extracted by CYH phase from urine sample were directly localized into the self-organized plasmonic hotspots, yielded excellent Raman enhancement, and realized the substrate-free interfacial SERS detection	[190]

No	Analyte	Matrix	Method	LOD	Observations	Ref
				tion		
19	MET; MDMA	Human urine	Interfacial SERS platform	1 ppb in aqueous solution // 10 ppb in urine	Monodispersed AgNPs in CYH phase into spherical colloidal superstructures in aqueous phase were assembled by oil-in-water emulsion method, creating 3D SERS hotspots, suitable for the quantitative detection in both aqueous and organic phases CYH extraction separated MET, MDMA from human urine and enriched the drugs in 3D hotspots.	[191]

AMP: amphetamine; FA: fluoroamphetamine; MDAI: 5,6- methylenedioxy-2-aminoindane; MDMA: 3,4-Methylenedioxy methamphetamine; MET: 4-methylamphetamine; NPs: nanoparticles; D-SERS: dynamic SERS; GNRs: gold nanorods

In general, the use of RS for the detection of ATS was possible for samples containing high concentrations. In contrast, using SERS with different types of nanostructures (AuNPs, AgNPs, plastic-based NPs, nanorods, pyramids) was possible to dramatically increase the sensibility and selectivity of the detection method, and thus perform the analysis in biological fluids such as urine samples (**Table 7**). However, the described methods for the detection of ATS lack a strong validation, a quantification evidence (with no calibration curves provided), and the interference studies, with only a few reproducibility and reusability studies. Hence, the SERS drawbacks (low-repeatability, non-uniformity, high-cost, complicated fabrication process) limit the use of SERS for forensic applications, hindering the replacement of conventional analytical techniques.

4 Detection on the field

4.1 Outlook of current analysis on the field

The market of drugs of abuse has been dramatically increased in the last years [1]. This fact is translated into an increment of the number of on-site analyses from LEAs in an attempt to avoid cargos to reach the end-users. Therefore, novel tools for the easy, rapid and specific detection of illegal compounds in the field are necessary to allow LEAs for a fast screening of samples. Ideally, these devices must add a robust on-site analysis of the seizures, providing detailed information from the composition of the cargo without the need of doing the analysis in a forensic laboratory (decreasing costs and time). Other uses of portable devices might be in personal anti-doping actions, fast screening of the people involved in a crime scene, driving test under the influence of drugs, among other situations where drug users are involved. Today, the on-site analysis of cargos and drug seizures is performed by portable devices based on presumptive color tests, portable spectroscopic devices which

uses FTIR and Raman spectroscopy, and last but not least electrochemical devices. Moreover, lateral flow immunoassays are widely used for the rapid analysis of illicit drugs in biofluids (e.g. oral fluid and urine) outside laboratories. For more information on portable analytical platforms for forensic chemistry, the reader is referred to the related literature [16,193,194].

4.2 Colorimetric tests

Presumptive color tests are widely used by LEAs as they provide a fast qualitative analysis of the suspicious powder by exhibiting a change of color when the illicit drug is present [195,196]. Besides, user-friendliness and affordability are key features that have allowed this type of test to be widely used [196]. However, the main disadvantage of these tests is the selectivity towards the specific drugs. Many reagents lead to false positive or true negative, therefore decreasing the accuracy of the measurements in comparison to other portable methods. For this reason, secondary confirmatory tests in forensic laboratories are still necessary to evaluate and validate the composition of the suspicious substance. Despite of this critical disadvantage, presumptive color tests is the most used test on the field due to its affordability and commercial availability.

Current commercial tests consist of mixing the suspicious powder in an ampoule where the indicator reagent is already placed. After a thoroughly mixing, the interaction between specific groups of the target compound (e.g., primary and secondary amines) and the chromogen produces a change in color allowing for a positive or negative determination. The most used reagents for ATS detection are: (i) Marquis reagent (i.e., mixture of formaldehyde and concentrated sulfuric acid), although it gives false positives for phenethylamines; (ii) Simon's reagent (i.e., a mixture of sodium nitroprusside, sodium carbonate and acetaldehyde) which allows to distinguish between primary and secondary amines; alternatively, (iii) Vitali-Morin's reagent (i.e., a mixture of fuming nitric acid, acetone and ethanolic potassium hydroxide); and (iv) Mandelin reagent (i.e., a mixture of ammonium vanadate in sulfuric acid), although different colors might appear according to the interaction of other groups such as the methoxy-groups of the compounds, therefore leading to true negative or false positive [196,197].

Recently, new strategies for the development of colorimetric sensors based on the previously described chemical reagents and new chromogens have been used to facilitate the detection of illicit drugs. Besides, the new colorimetric sensors are designed for the quantification of the drug of abuse. For example, a solid sensor was prepared by embedding 1,2-naphthoquinone-4-sulfonate (NQS) into a composite of poly-dimethylsiloxane (PDMS) with tetraethylortosilicate/silicon dioxide nanoparticles (**Fig. 4Ai**) [198]. The sensor exhibited a colored product after 10 minutes incubation time with ATS (i.e., orange for secondary

amines-related compounds and grey for primary amines compounds) (**Fig. 4Aii** and **Fig. 4Aiii**). The use of a solid-state sensor and regular buffer solutions allows for better handling of the samples. Bell *et al.,* reported a microfluidic device to perform the simultaneous detection of illicit substances based on a PDMS chip [199]. The device allowed for three color tests and one crystal test to be completed in less than 15 s using less than 1 mg sample for all four tests, overcoming the limitations of amount of sample. The authors claimed that the device used less reagents and generated less waste (up to 95% less) than traditional spot tests. The color tests used were the Marquis, Simon, and cobalt thiocyanate for the detection of MET, AMP, cocaine and oxycodone (as a substitute of heroin). The device showed promising results even with tests carried out with different operators, which is essential for on-site applications. Similarly, a sol-gel colorimetric sensor was developed for the detection of MET by entrapping Simon's reagents within a polymeric network of a sol-gel matrix [200]. A micro-PCR tube was used as a substrate to perform the colorimetric reaction upon addition of the sample. The authors evaluated the storage capacity showing 3 months as a lifetime in the freezer at -18 ◦C. It is worth to mention that long lifetime is a paramount feature when introducing products to market for on-site use. Interestingly, a rotation-driven microfluidic device coupled with a user-friendly image analysis technique for the detection of MET among other illicit drugs was presented [201]. The centrifugal microfluidic platform accommodates the suspicious powder to different reaction chambers, enabling rapid and simultaneous screening of multiple illicit drugs. Importantly, the device was validated with 30 unknown samples with a successful rate by employing a smartphone as image capture and analysis. Last but not least, a presumptive test for simultaneous detection of multiple illicit drugs (including AMP and MET) was developed using a microfluidic paper-based device [202]. The device was built on a chromatographic paper in which hydrophilic pathways were constructed by employing wax printing. Remarkably, the affordability of paper substrate and the printing capability might be advantages for the scaling of the manufacturing process. The chromogens were immobilized on the paper channels which allowed the reaction with the suspicious powder when the illicit drug was present (**Fig. 4Bi**). Thus, the sample mixed with buffer solution reached the immobilized reagents by capillarity, and a change of color was monitored by absorbance (**Fig. 4Bii** and **4Biii**). This type of devices permit the use of few amount of sample as well as an easy disposability by incineration, thus decreasing waste disposals and avoiding contamination from sample to sample.

Overall, the aim of all these sensors is to improve the selectivity of the colorimetric detection while providing easy handling and keeping affordable costs in the on-site screening. We believe that colorimetric tests, including commercial presumptive tests, are the easiest and quickest way to detect illicit drugs; and it will continue to be used in the future. However,

emerging technologies might take the chance to replace them if they improve the selectivity issues of colorimetric tests while keeping user-friendliness and affordability. The addition of new selective reagents, the multiplexed detection, and the use of green substrates (i.e., paper) might maintain colorimetric tests at the top list of most used devices for on-site detection.

4.3 Lateral flow assays

Lateral flow assays (LFAs) are paper-based platforms for the detection and quantification of analytes in complex mixtures in a short period of time, the pregnancy test being one of the most used tests worldwide. LFAs technology is based on the immunoreaction between the target analyte and an antibody labeled with nanoparticles as colorimetric proves or fluorescent proves [203]. Fortunately, LFAs have been designed for many targets and applications, for example, the detection of small molecules such as ATS. Indeed, this technology offers practical, specific, portable and rapid test for on-site screening [204], even following multiplexed configuration [205]. LFA usually provides positive/negative judgments in a short response time with excellent LOD. The typical competitive assay applied on the assays restricts the quantitation ability of LFA strips. However, different efforts have recently made to explore strategies for the quantification of the analytes such as in the detection of different drugs of abuse [206].

Regarding ATS detection employing LFAs, a rapid point-of-care (POC) test for MDMA detection in saliva was developed [207]. The authors used a commercial LFA from Cozart Bioscience Limited, UK, to study the sensitivity, specificity and accuracy for MDMA determination against MET and AMP samples. However, obtaining the results is usually subject to visual interpretation of colored areas, thus leading to human errors in the decision-making processes. Interestingly, a smartphone-based reader was designed and tested with commercial LFAs for drugs of abuse (DrugCheck SalivaScan LFAs including AMP and MET, Express Diagnostics Inc., USA) in order to increase the accuracy of the signal output [208]. Machine learning techniques were employed to perform automatic extraction of the results leading to improved decisions. Similarly, an electronic reader capable of measuring the intensities of the bands of a cassette for the specific detection of MET was developed, showing better sensitivity when the reader was used [209]. Multiplexed detection is an important feature of a device when dealing with unknown substances. In that sense, Taranova *et al.,* reported on a lateral flow microarray that combined multi-spot immunochip technology which served as a tool for the simultaneous detection of 4 drug of abuse (including MET and AMP) [206]. Besides, this technology allowed for the expansion of the linear range as each spot was loaded with different concentration of antibodies, thus providing promises for a quantification of the analyte by LFAs. Recently, new strategies for

the labeling of the antibodies that leads to improve detection have been made. For example, the technology based on up-converting phosphor particles was applied to LFA for the detection of MET in saliva showing agreement with the standard method LC-MS [210]. However, the authors did not mention the advantages of the novel particles instead of the common AuNPs. Moreover, a multiplexed immunodetection of drug of abuse (including MET) based on novel magnetic nanoparticles as a label (**Fig. 4Ci**), coupled with a multi-channel electronic reader has been presented [211]. In this case, the readout is based on magnetic signals when the conjugated particles are bonded with the antibody immobilized on the LFA (**Fig. 4Cii**). This type of readout allowed for extremely low LOD while keeping excellent reproducibility (RSD=7-11%). Last but not least, a fluorescence based LFA was able to detect drugs of abuse from sweat of a fingerprint (**Fig. 4Di**). In that sense, a cartridge was specifically developed for fingerprint sample collection of sweat for 5 s and 10 min analysis leading to a cut-off of 80 pg fingerprint^{-1} for AMP (**Fig. 4Dii**). Besides, the test was validated with LC-MS/MS showing 93% accuracy with AMP. Undoubtedly, this LFA exhibits high promises for the multiple and highly sensitive detection of illicit drugs. In contrast, an external fluorometric reader is needed for the quantification of the target, heading towards an increase in the costs.

The advances in LFA technologies for illicit drugs detection have led the production of many commercial devices, from simple strips and cassette-type test (e.g., Smarttest, Peth, Australia) to complex integrated cassettes into optical readers (Alere DDS®2 mobile test system, Abbott, USA). Mainly, the LFAs test are applied to determine small amounts of ATS (i.e., cut-off in the ng mL^{-1} range) from human fluids analysis or for field detection of ATS contamination (e.g., surface sampling in clandestine laboratories). In contrast, LFAs test are not used in cargos analysis as the sample concentration is not a limitation, and the high cost of LFAs hampers the massive screening purpose of seizures analysis. Overall, the high cost per device due to the use of biorecognition elements and nanomaterials, the stability due to a potential degradation of the bioelements, the lack of a quantification approach, and sometimes the long-time of analysis are some of the weaknesses of LFA. In contrast, the low LODs offered by LFA, and the absence of power requirements are the main strengths of these devices to be used in the field.

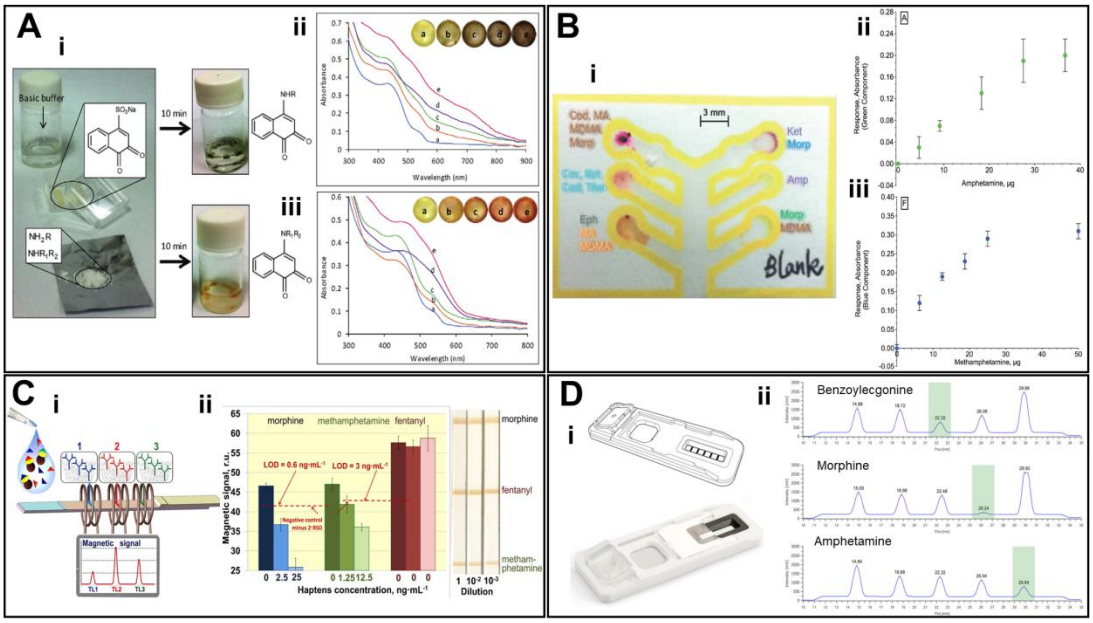

Fig. 4. Portable tests for the detection of ATS. Fig. 4A*. A solid colorimetric sensor for the analysis of amphetamine-like street samples: (**i**) Photographic image of the analysis by the colorimetric kit (composed by a vial with basic buffer, NQS-polymeric sensors and powder street samples) for AMP (up) and METH (down); absorbance spectra registered at different concentrations of (**ii**) AMP and (**iii**) METH. Inset: photographic image of sensors exposed to the assayed concentrations (Adapted from ref* [198]*, with permission from Elsevier);* ***Fig. 4B****. Paper microfluidic devices for presumptive drug detection: (**i**) A demonstration of the µPAD developed to detect seized drugs; application of ImageJ software for the detection of various drugs on the µPAD device. Pixel colors are indicated on the Y axis. Linearity ranges: (**ii**) AMP and (**iii**) METH (Adapted from ref* [202]*, with permission from The Royal Society of Chemistry);* ***Fig. 4C****. Rapid lateral flow assays based on the quantification of magnetic nanoparticle labels for multiplexed immunodetection of illicit drugs: (**i**) Scheme of multiplex registration of haptens. After migration of the sample along the membrane, the test strip was inserted into three measuring coils of the MPQ reader to readout the magnetic signals; (**ii**) MPQ signal simultaneously measured in the multiplex variant of concurrent magnetic immunoassay along with the photos of respective lateral flow strips (Adapted from ref* [211]*, with permission from Springer Nature);* ***Fig. 4D****. Drug screening using the sweat of a fingerprint: (**i**) Schematic diagram and image showing the fingerprint DrugScreening Cartridge; (**ii**) Fluorescence intensity profiles for the drug panel lateral flow assay (Adapted from ref* [212]*, with permission from Oxford University Press).*

4.4 Portable spectroscopic techniques: FTIR and Raman

Infrared (IR) spectroscopy is a highly discriminatory method based on the measurement of the amount of IR radiation which is absorbed or emitted by a sample as a function of wavelength [213]. The obtained spectrum represents the passing infrared radiation through a sample and by the end is determining the amount of the incident radiation (radiation that actually hits the molecule rather than passing through) that is absorbed at each IR frequency [214]. Hence, the IR spectra of a pure molecular compound provide a distinctive fingerprint which can be easily differentiated from the IR absorption pattern of other compounds, including isomers. The spectral domain to be explored for homeland security and law

enforcement applications remain the near IR (NIR) being between 750 and 2500 nm, where drugs of abuse have their vibrational spectra and could be used as their fingerprinting. The majority of drugs of abuse can be reliably identified when reference spectra are available or gathered in a searchable database. The technique is versatile being able to distinguish between diastereomers (such as pseudo- ephedrine and ephedrine) and free base/acid and salt forms [215]. Other advantages of this technique are related to the fact that the sample is not destroyed during analysis and the needed quantity is in milligrams range.

Portable IR and near-IR (NIR) spectrophotometers are useful for qualitative analysis and identification of a substance or substances in a mixture after a search in the internal databases [216,217]. However, in order to have accurate results, the interpretation of obtained spectra needs to be done by specialists. In an attempt to overcome this drawback, machine learning features have been integrated on the NIR readout to enhance the detection capabilities [218–220]. Regarding the use of portable IR devices for the determination of ATS, the association between a microNIR portable spectrometer and chemometrics models was reported for the analysis of complex real samples containing cocaine, AMP, MET and MDMA [221].

New approaches involving the artificial intelligence (AI) were reported by Ion *et al.* [222]. Several AI applications were designed to recognize the class of ATS and of synthetic cannabinoids based on their spectra obtained by attenuated total reflection - Fourier transform infrared spectroscopy (ATR-FTIR). Importantly, by using partial least squares regression algorithm applied to the most relevant absorptions spectra, the device was able to discriminate among ATS.

Another versatile technique which solves some limitations of other spectroscopic techniques and is suitable for forensic analysis is RS. RS could be used for qualitative analysis by measuring the frequency of scattered radiations and for quantitative analysis by measuring the intensity of scattered radiations [179]. Further information can be found in **section 3.3**. Currently, Raman spectrophotometers in the field are based in portable and hand-held devices. The differences between the two types of equipment are related to the size and the cost of the components which often accompanies a lack of capabilities in comparison to bench-top devices. For this reason, portable and hand-held RS devices usually need high concentrations of the analyte in the sample for a reliable analysis. By using hand-held equipment, *in situ* analysis is possible without any sample pretreatment which facilitate the detection of drugs of abuse in different environments (e.g. harbors or customs) where the sample amount is not a limiting factor.

The portable Raman spectrometers were reported for the identification of ATS in airports since 2008 by Hargreaves *et al.* [223]. The study demonstrated that the spectrometers are

able to collect the spectra of suspect powders, including cocaine HCl and d-amphetamine sulphate with unknown constituents rapidly and with a high degree of discrimination.
The detection of illicit drugs seized during border controls by portable Raman spectrometer was reported [224]. In a first step, the analysis methodology was optimized using reference substances such as diacetylmorphine (heroin), cocaine and amphetamine (as powder or liquid forms) to compare the spectra. Several parameters were optimized such as adequate focalization distance, times of analysis, influence of daylight and artificial light sources, and finally, the repeatability and limits of detection were computed. In a second step, the applications and limitations of the technique to detect the illicit substances in different mixtures and containers were evaluated. The authors conclude that Raman spectroscopy had several advantages over other portable techniques, such as ion mobility spectrometry, of being non-destructive technique, and remarkably, capable of rapid analysis of large quantities of substances through containers such as plastic bags and glass bottles. Other results obtained by a portable Raman spectroscopy device on over 472 alleged drugs during the first formal implementation of drug checking in Italy were reported [225]. The testing was made through a plastic bag held by the applicant and containing the alleged drug while the substance identification was done comparing the obtained spectra with a spectral library. Illicit substances were detected in over 300 samples including MDMA, ketamine, cocaine, AMP, MET, heroin and NPS. When compared to laboratory techniques (such as GC-MS), the drug checking by Raman spectroscopy proved to be effective to identify psychoactive drugs and also for tracking the drug distribution in various recreational settings.

Modern detection and identification of drugs of abuse within the forensic and homeland security contexts may require conducting the analysis in field while adapting to a non-contact type of analysis [226]. Technological achievements on both surface and resonance enhancement Raman scattering repositioned RS as one of the most adaptable spectroscopy techniques for in field and non-contact analysis of drugs of abuse even when analyzing non transparent containers or packages.

4.5 Electrochemical devices

Electrochemical devices are of excellent choice for scaling down analytical systems into portable tools, with features that include high sensitivity, inherent miniaturization, low cost, low-power requirements, and high compatibility with advanced micromachining and micro-fabrication technologies [227]. The most successful case of a portable electrochemical sensor is the disposable strips based on screen-printed technology for the measurement of glucose [228]. Currently, advances in new materials have led to the embodiment of electrochemical sensors in wearable platforms for the detection of different types of targets, including illicit drugs [18]. For example, a glove-based sensor was able to directly detect

cocaine and its cutting agents [229], or fentanyl [230] by a simple swabbing process over the suspicious powder. Overall, electrochemical sensors have proven to be an ideal platform for the miniaturization and portability of analytical systems.

Following this trend, electrochemical sensors have been used for the determination of ATS as it is described in **section 3.1** and **Table 4**. The majority of the examples described in that section could be translated into a portable device due to the potential miniaturization of the sensor and reader modules. However, some features still need to be integrated within the electrochemical sensors to truly deliver a portable device to be used in the field by LEAs. Apart from having an excellent analytical performance (i.e. sensitivity, specificity, accuracy) towards ATS determination, these features include: (i) the use of disposable and low-cost SPEs to avoid contamination during analysis of multiple samples; (ii) affordable and simple functionalization of the working electrodes allowing for scalable manufacturing; (iii) miniaturization and portability of the electrochemical reader (similar to the glucometer) [231,232]; (iv) simple analytical measurement which can be performed by an unexperienced user (e.g. add the suspicious powder onto a device or ampoule for direct measurement); (v) rapid sample treatments, if necessary (e.g. *in situ* derivatization of the ATS, short incubation time <2 min, or minimal rinsing steps); (vi) and last but not least, the electrochemical readout should be displayed in a user-friendly interface for a rapid decision-making process by the LEA officer. Moreover, the employment of data treatment [73,74] or machine learning capabilities [233] to the electrochemical output signal can enhance the specificity of the analysis, without the necessity of complex functionalization of the working electrodes. Unfortunately, none of the reported strategies until date fulfill all the aforementioned requirements, thus exhibiting room for improvement in this field. However, the approaches that uses SPEs [70,87,90,100] show promises of bringing electrochemical sensors for ATS analysis closer to on-site forensic applications.

5 Key challenges and prospects

Before the description of the key challenges of the analytical devices towards the determination of ATS, it is important to depict the process that it is currently applied on the analysis of illicit drugs at different scenarios. When dealing with detection of illicit drugs from suspicious samples either at border settings or police raids, a first screening test of a suspicious sample or cargo is carried out for a direct confiscation in the field. Subsequently, a confirmatory test in a centralized laboratory is performed as it is necessary for judgement at law court. Similarly, for the detection of drug consumption (e.g. roadside test, at workplace or during criminal scenarios), a first screening test for drugs in biofluids is needed (preferably non-invasive biofluids such as oral fluid, urine or sweat). Thereafter, the same sample or a blood sample (when possible) is obtained and sent to a forensic or toxicologic laboratory for

a confirmatory test which will be used in the law court. Taking into account these processes, it is clear that portable tools and bench-top devices are necessary for the current analysis of ATS.

Traditional analytical techniques have been used in centralized laboratories for many years and have been demonstrated their reliability in the detection of ATS. Still, advances on these techniques (e.g. GC-MS, LC-MS/MS, Raman spectroscopy) are required to constantly fulfil the new analytical demands: (i) rapid time of analysis; (ii) simple sample pretreatments, particularly when the analysis of biofluids are involved; (iii) automation, which allows for a massive analysis of samples as well as reduced human errors; (iv) greener analysis, meaning a decrease in the use of organic solvents by replacing techniques that require high amounts of solvents; and (v) easy data interpretation, which allows to a decrease of the data curing by the scientist and a rapid delivery of the analysis outcome. In general, progress is being made in laboratory analysis toward the improvement of current features as well as to facilitate the detection of isomers of drugs (e.g. fluoroamphetamine isomers being some legal and other illegal depending on the legislation of each country) and NPS.

Many analytical techniques used in laboratory-based settings are being translated into small portable devices to empower the on-site screening testing with more sensitive and accurate analysis. However, this new army of devices needs to fulfill some essential features for the successful use on the field: (i) response time of the full operation needs to be below 5 minutes period as law enforcement agents have to perform rapid tests of multiple samples; (ii) specificity, the tests must ensure that the readout is truly positive or negative for the suspicious substance to avoid wrong decision-making processes which might be turned into huge social, economic and legal impact; (iii) multidrug detection, the same device can screen multiple drugs while keeping high specificity; (iv) calibration free approaches, the device should not require a calibration to be used in the field; (v) accuracy and validation, the new portable device must be validated with standard methods and provide errors less than 10%; (vi) sampling and reproducibility, the sampling strategy should be carefully designed in order to provide reproducible results; (vii) miniaturization, particularly the reader (if needed) must be lightweight, and small to allow full portability to the point of analysis, while maintaining enough autonomy (i.e. battery) to endure a full-time workday; (viii) disposability of the sampler, the sensor or any other part of the device that is in contact with the suspicious powder or biofluid should be discarded after the analysis to avoid contamination with the following analysis, if this is not the case (e.g., spectroscopic techniques), careful cleaning of the surface must be performed following a suitable protocol; (ix) low-cost analysis, the test as an affordable module (i.e., less than 1 EUR $test^{-1}$) is essential when using a disposable approach (e.g. a SPE), in contrast, the reader module should be in the

order of 100-1000 EUR, as devices with an easy replacement should be prioritized due to highly risky activities of the LEAs; (x) use of non-invasive biofluids (e.g. saliva, sweat) for the analysis of drug of abuse in consumers (e.g. roadside test); (xi) user-friendliness, sampling of the suspicious powder or liquid should be performed in an easy way by the agent and without the necessity of training or expertise on the analytical technique; (xii) easy interpretation of the output, the results of the analysis must show a positive or negative signal for illicit drug in an intuitive interface (e.g. mobile display); and last but not least, (xiii) secure data transmission, the data from the analysis must be securely transmitted to LEA (e.g. encrypted data). **Table 8** gives an overview of the current situation for on-site screening tools and summarizes some of the features of current portable devices, such as but not limited to accuracy, LODs, sensitivity, time of analysis. However, none of them fulfill all the aforementioned features, thus, showing a room of improvement of current portable devices. Finally, wearability of the device is not an essential feature for the LEAs, although it might be useful for the operation in some cases such as road testing of drugs of abuse on users. In these cases, a wearable device on the subject at test would avoid direct contact with the LEA agent, thus preventing interaction with contaminated samples from the subject (particularly in this COVID-19 pandemic). Progress in advanced materials and sensing technologies might reshape how analytical systems are used in the field, bringing simple procedures close to the user. Overall, the integration of these features on a unique tool will pave the way towards the implementation of portable devices for on-site drug screening, increasing the safety and security of our society. Moreover, centralized laboratory analysis will keep on running as confirmatory test with a potential increase in their demand due to an increment on the on-site tests from incoming portable devices.

After reviewing the current status of the analytical techniques and the applications where these techniques are employed for the ATS detection, we foresee electrochemical sensors and portable devices based on NIR and RS in combination with data analysis and machine learning capabilities as the ideal devices for on-site screening tests of suspicious samples. Nevertheless, the type of device might be selected according to the user demands (e.g. number of tests, LEAs budget, application). Moreover, some technologies such as electrochemical sensors might be more suitable for the analysis of hidden drugs in unconventional matrices recently employed by drug traffickers (e.g. oils, alcoholic beverages, impregnated cloth, etc.). Therefore, there is not a clear technology that stands out of the other candidates, and thus further advances need to be done toward specific end-user applications. Regarding the analysis of biofluids, the current standard based on LFA might be replaced by electrochemical devices in the near future, if the latter can reach the LOD and simplicity of LFA. In centralized laboratory analysis, LC-MS/MS and GC-MS are

the norm. In this field, new advances in sample treatment and preconcentration steps are being applied, making easier the use of such devices by laboratory technicians. Hence, an improvement in the analytical parameters with shorter times of analysis is being accomplished. In general, new advances and innovations will be brought to the forensic and toxicological fields which are translated into improved trackability of illicit drugs, and consequently, a safer and more secure society.

Table 8. Comparison of portable devices for on-site illicit drug determination.

Device	Presumptive color tests	Spectroscopic techniques (Raman and FTIR)	Electrochemical devices	Lateral flow assays
Sample nature	Solid[a]/liquid	Solid	Solid[a]/liquid	Solid[a]/liquid
Accuracy	Mid	High (non-colored sample)	High	High
Specificity	Low	High	High	High
LOD	mg	mg	µM	nM
Sensitivity[b]	70%	80%	90%	95%
Multiple detection	No	Yes	Yes[c]	Yes[d]
Time of analysis	< 1 min	< 4 min	< 1 min	1 – 15 min
Output	Qualitative	Qualitative[e]	Semiquantitative and potentially quantitative[f]	Semiquantitative and potentially quantitative[g]
Sample pretreatment	Mix with buffer	-	Mix with buffer	Mix with buffer
Amount of powder	mg	mg	µg	ng
User-friendliness	High	Low[h]	Mid	High
Data treatment/ storage	No	Internal memory	Coupled to smartphone	No, unless use of external reader
Cost	Low (< 5 EUR $test^{-1}$)	High (>20 k EUR $device^{-1}$)	Mid (>1 k EUR $device^{-1}$)	Low (< 10 EUR $test^{-1}$)
Target application	Cargos/seizures	Cargos/seizures	Cargos/seizures and biological fluids (e.g. saliva or urine)	Biological fluids (e.g. saliva or urine)

FTIR: Fourier transform infra-red

[a]The sample should be mixed with a buffer solution prior analysis. [b]True positive rate (the number of true positive results divided by the number of positive samples), the results might vary depending on colored samples. [c]Depends on the electrochemical technique and the design of the sensor. [d]When multiplexing systems are applied. [e]Identification of the compound. [f]Depending on the nature of the mixture and the application of algorithms. [g]When coupled with an optical reader. [h]Bulky and heavy devices.

6 Conclusions

Since there is an increasing use of ATS among society, tackling drug trafficking and drug consumption have become one of the major priorities by LEAs to avoid drugs of abuse reaching the markets. Therefore, providing strategies, devices and tools for the accurate determination of ATS in all the situations along the delivery chain must be of critical interest

for the scientific community. Moreover, ATS has demonstrated serious toxicological effects specially in the nervous system of the human body, either after short- or long-term intake. For these reasons, research on these topics has been exemplified along this review providing much literature on ATS effects on human health and methods of detection of ATS.

All the analytical tools described in this review covers from the early detection of ATS on cargos and crime scenes (e.g., portable tests) to the validation of the composition of seizures developed in forensic laboratories (e.g., LC-MS/MS). Consequently, each analytical technique described in this review has been summarized, exemplified and critically discussed according to the target application that fits in every step of the delivery chain of ATS. For example, presumptive tests are useful for a quick screening on the field and to determine whether a cargo has to be confiscated. After this step, samples are sent to forensic laboratories where mass spectrometry verifies the illicit substance. Meanwhile, there are electrochemical techniques and spectroscopic techniques that can be almost used through the entire pathway (from suspicious powder to confirmatory tests). These last techniques include lab bench equipment with sample treatments that provide quantification and accurate measurements, as well as portable devices to be used on the field in which a compromise situation between quantification, cost and fast detection is accomplished. For this reason, this review covers in detail the most used and promising analytical techniques employed in laboratories: (i) IR spectroscopy; (ii) Raman spectroscopy; (iii) electrochemical techniques; and (iv) mass spectrometry with their corresponding separation techniques (i.e. liquid chromatography, gas chromatography and capillary electrophoresis). Moreover, a section including portable tests and devices has been critically discussed as the authors believe that on-site screening is a key operation for LEAs. For this reason, (i) colorimetric tests, (ii) lateral flow assays, (iii) portable spectroscopic methods, and (iv) electrochemical devices have been discussed.

In general, there is an increasing trend towards miniaturization of devices to become portable and even wearable while keeping excellent analytical performance. These innovative technologies will allow for a quick identification of seizures, minimizing false positives and false negatives. Importantly, versatile on-site tests are required for the detection of NPS in an increasing diversifying drug market. Moreover, there is a demand from LEAs of new tools and protocols that can facilitate the screening of samples of different nature (e.g., drugs hidden in oils, carbon, fish meat, etc.) which hinder the detection by conventional methods. Here, the challenge is to validate new portable devices by comparing with results obtained with standard methods before reaching the end-user. On the other hand, new methods for the analysis of isomeric ATS and NPS in seizures and biofluids are driving the laboratory research. Overall, ATS can be detected with a wide range of

techniques and devices, from portable systems to lab bench equipment, with the main goal of reliably identify the target ATS for a proper decision-making process. New technologies will disrupt the forensic analysis in the coming years by facilitating LEAs duties in the field such as blocking the illegal activities of crime groups, and assisting laboratory tasks with highly reliable detection methods.

Declaration of Competing Interest

The authors declare no competing financial interest.

Author Contributions

*A.D. and M.P. contributed equally to this work. All authors have given approval to the final version of the manuscript.

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