Development of surface-enhanced Raman spectroscopy application for determination of illicit drugs: Towards a practical sensor

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ABSTRACT

Surface-enhanced Raman spectroscopy (SERS) has been widely applied to identify or detect illicit drugs, because of the ability for highly specific molecular fingerprint and independence of aqueous solutions impact. We summarize the progress in determination of illicit drugs using SERS, including trace illicit drugs, suspicious objects and drugs or their metabolites in real biological system (urine, saliva and so on). Even though SERS detection of illicit drugs in real samples still remains a huge challenge because of the complex unknown environment, the efficient sample separation and the improved hand-held Raman analyzer will provide the possibility to make SERS a practically analytical technique. Moreover, we put forward a prospective overview for future perspectives of SERS as a practical sensor for illicit drugs determination. Perhaps the review is not exhaustive, we expect to help researchers to understand the evolution and challenges in this field and further interest in promoting Raman and SERS as a practical analyzer for convenient and automated illicit drugs identification.

1. Introduction

The United Nations Office on Drugs and Crime (UNODC) World Drug Report in 2017 pointed out that about quarter of a billion people, or around 5% of the global adult population, used drugs at least once in 2015. More worriedly, harm caused by drug use remains considerable. Estimated 29.5 million of those drug users, or 0.6 per cent of the global adult population, suffer from drug use disorders. In other words, their drug use is harmful to the point that they may experience drug dependence and require treatment [1]. The health consequences of illicit drug use continue to be devastating, which will lead to a variety of problems [2]. Consequently, it is a critical need to rapidly identify the illicit drugs to support the anti-drug campaign.

As one of the earliest tools, chemical color tests could provide toxicologists and criminalists with visible results for the presumptive identification of drugs and poisons [3–6]. While the fact that cannot be ignored is that these tests may be misinterpreted by subjective color perception. Gas Chromatography (GC) and high-performance liquid chromatography (HPLC) are called gold standard analytical tools for illicit drugs detection, especially when they are combined with other techniques that can capture the molecular characteristics, such as

ultraviolet-visible spectrophotometry [7], nuclear magnetic resonance [8], or mass spectrometry [9–15]. Above mentioned hyphenated techniques are good at analysis in complex environments, including simultaneous analysis of multiple components and single component analysis in bio-fluids. However, these well-established methods face some disadvantages: 1) the process of sample preparation is complicated and time-consuming; 2) such methods must be conducted by trained personnel in laboratories. So it is hard to achieve large-scale screening. In addition, electrochemical sensors have also been used to detection of illicit drugs [16–18]. But the single position of anodic/cathodic peak is easily influenced. In many instances, commercial test kits (colloidal gold) are usually used as screening tests for urines with advantages of efficiency, sensitivity and good selectivity [19,20]. While the R & D cycle is long and the commercial test kits are only for a limited number of illicit drugs at present. It is difficult to cope with the endless designer drugs and their metabolites. Moreover, the colloidal gold techniques could not be intended for quantitative determination. In terms of various kinds of controlled drugs, spectroscopy techniques (fluorescence spectroscopy [21], ultraviolet spectrum [22,23] and infrared (IR) spectroscopy [24,25],) are also applied.

Here, we introduced another important method, namely surface-

Table 1
The advantages of the SERS compared to other techniques.

Versus	Nuclear magnetic resonance (NMR)	Infrared spectroscopy (IR)	Electrochemistry (EM)	Mass spectrometry (MS)
SERS	Fast; Inexpensive; On-site detection	Without impact of water; Sensitive	Fingerprint	Fast; Convenient; large-scale screening
Analyte	Heroin	Opiates	Morphine, codeine	Cocaine, Amphetamines
Reference	[8,63]	[24,91]	[18,51,91]	[11,15,53,90]

enhanced Raman spectroscopy (SERS). SERS is a phenomenon in which the Raman signals of molecules are enormously enhanced and fluorescence is suppressed when they are very close to certain SERS-active nanostructures [26–29]. Compared to other analytical techniques, its advantages have been highlighted in Table 1. SERS is one of vibrational spectroscopic methods based Raman spectroscopy free from aqueous impact. SERS not only can provide a highly specific molecular fingerprint, but also can realize ultra-trace analysis. And it just takes only few seconds to collect one SERS spectrum. The SERS technique has potential to resolve a mixture into its individual components because of molecular specificity. Thus, it may develop to a viable method for identification of illicit drugs in complex systems.

In recent years, the demand for SERS techniques that can provide fast, reliable and even quantitative measurements of illicit drugs has increased widely. But to date, there are few reviews comprehensively about SERS application in illicit drugs detection [30–32]. For this reason, this paper mainly reviews the development of SERS as efficient sensor platform for illicit drugs detection, particularly concerning trace amount of drugs and primary form or metabolites in bio-fluid. The review is organized as follows. First, this article will be on focus of the chemical analysis of illicit drugs owing to the increasing availability of suitable nanostructures. Second, SERS applications are highlighted in the determination of illicit drugs or their metabolites in bio-fluids. Finally, the future trends of SERS technique in the field of illicit drugs analysis were mentioned.

2. Chemical analysis of illicit drugs

Many illicit drugs (opiates, cocaine, cannabis, amphetamine-type stimulants and some new psychoactive substances) are good Raman scatterers, and therefore lent to rapid analysis via Raman spectroscopy. However, Raman spectroscopy is intended for molecular structure characterization rather than detection due to its relatively low sensitivity. So SERS as a particular working mode of Raman scattering is imposed in consideration of trace amount existing (as shown in Fig. 1). SERS is a modern technique and allows one to carry out different analysis, even if the quantity of sample available is small. At present, the technique has been applied to quantitative and/or qualitative detection, which can meet the need of rapid, sensitive, and reliable analysis. In this section, the illicit drugs in simple systems mainly concern about standard samples, street drugs, drugs additives and suspicious objects.

2.1. Illicit drugs powder and suspicious objects

Raman spectroscopy is a valuable tool for detailed chemical analysis and it is often applied to identify solid powder [33]. This technique has the benefit of no sample preparation and can be performed on samples without removal from the evidence, thus there is no potential risk of contamination [34,35]. The Raman spectra of many sorts of illicit drugs' standard substances have been recorded, such as a representative range of β-ketophenethylamine, the rapidly growing family of cathinone-related "legal high" recreational drugs [36], cocaine [37] and 3,4-methylenedioxymethamphetamine (MDMA) [35]. And as the development of Raman spectrographs, small contamination of illicit drugs and suspicious objects present on fibers of clothes [38–40] and fingerprints [41,42], can also be analyzed rapidly with direct laser beams, fiber optic probes and microscopes. If trace contamination of prohibited substances were found on weighing scales or used packaging, it might be possible to link with drug related activities, in spite of no bulk powders. The technique promises to be a helpful tool for forensic science.

To promote on-site analysis, transportable Raman spectrometers were gradually applied to in situ detection of seized illicit drugs (including solid or liquid forms of heroin, cocaine and amphetamine) [43]. Moreover, the progress of the software makes it possible to get the pertinent investigative information by nontechnical personnel quickly and conveniently, thereby making field analysis simple. In the cases, such as border controls and airport environment, people usually finished the identification through an automatic identification of the spectral window after digital library was created by reference substances [34,44]. And above approaches inspire researchers to achieve field detection using more portable Raman spectrometer. It should be pointed out that, even though Raman spectroscopy has the ability to distinguish the different substances present in a sample, it is not a very sensitive technique. For this reason, SERS is an important development direction for sensitive detection.

2.2. SERS substrate development

As a kind of nano-analytical technique, the well sensitivity of SERS can be attained by improving metal-dielectric nanoparticle substrates. And various SERS substrates have been fabricated and applied in different fields. There are several review papers on SERS substrate fabrications [45–47]. The theoretical and experimental studies have shown that active substrates possessed nano-size characteristics and broad and
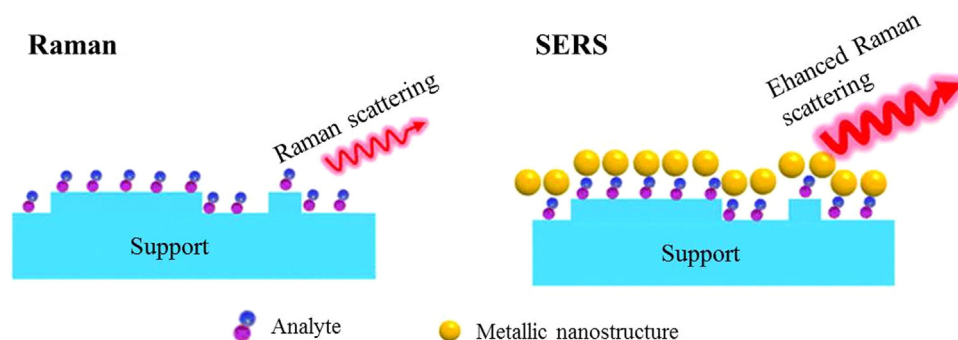

Fig. 1. Schematic of Raman spectroscopy and surface-enhanced Raman [28].

intense plasmon resonances in the visible-near infrared region [48–50]. Here we mainly discuss two types of SERS substrates: colloid-based substrate and solid surface-based substrates.

First, we discuss the colloid-based substrate. Gold or silver nanoparticles, reduced by trisodium citrate, are the most classic colloidal substrate, which had been applied to detect morphine, cocaine, methamphetamine (MAMP), mephedrone and a set of structurally similar synthetic cannabinoids [51–53]. And to the test procedures, a number of conditions were explored in relation to SERS signals optimization including pH and aggregating agents. Rana et al. studied different aggregating agents for silver sol to identify trace level of illicit drugs [54]. Aggregation of metal colloids is perhaps the simplest method to produce substrates that can exhibit field enhancements large enough for single molecule SERS detection [55,56]. According to these reports, the optimization of parameters was an important work to apply SERS to actual situations [51,52].

Our group proposed a dynamic surface-enhanced Raman spectroscopy (D-SERS) method, which can provide a three-dimensional (3D) hotspot matrix based on state translation from the wet state to the dry state. During this process, hotspots can be held between every two adjacent particles in 3D space, with minimal polydispersity of the particle size and maximal uniformity of the interparticle distance [57]. Taking advantage of the method, a series of works was explored to illicit drugs detection to improve sensitivity [58–60]. Among them, Yan et al. precisely analyzed MDMA and α-methyltryptamine hydrochloride via internal standard D-SERS strategy (in Fig. 2). As a consequence, one has reason to believe our approach is promising to challenge quantitative problems in conventional SERS analysis.

Additionally, an important criterion for SERS sensors is that 'the analyte of interest must be within a few nanometers of the nanostructured surface' [61]. Li et al. produced Au nanoparticle–Ag nanowire single hot spot platform for SERS analysis, which can provide a "nanochannel" to trap molecules with the presence of capillary imbibition (in Fig. 3A) [62]. Also with the help of capillarity induced negative pressure of water plugs in nano-channels, Yu et al. demonstrated a novel sodium chloride crystal-induced SERS platform that owns locations and trapping of illicit drugs for highly sensitive detection [63]. Moreover, three-dimensional (3D) SERS hotspots were created through 3D silver spherical colloid (in Fig. 3B). The hotspots existed not only between every two adjacent particles in 3D space, but also into the third dimension along the z-axis [64].

On the basis of colloidal substrate, surface functionalization technique was gradually used to obtain some expects. Sulk et al. proposed a selective substrate by modification with 2-mercaptonicotinic acid to detect illicit drugs of phenylalkylamines [65,66]. Alan Stewart et al. reported an example of modified silver nanoparticles with thiol monolayer to promotes adsorption and importantly achieve quantitative detection of MDMA [67]. According to Fig. 4, the analysis and quantification of the main cocaine metabolite benzoylecgonine (BCG) were achieved to monitor the vibrational changes occurring at a specific bio-interface (a monoclonal antibody, mAb) supported on silver-coated carbon nanotubes (CNT@Ag) [68]. This research provided a new idea that SERS can be used for the label-free determination and quantification of relevant small bio-metabolites that are hard to identify by conventional immunological methods, in the absence of labelling.

On the other hand, one of advances in colloid-based substrates is to fabricate SERS substrate on the novel support besides silicon wafer [69,70]. Mabbott et al. exhibited an amusing approach to improve the performance of SERS, namely deposition of silver onto British 2p coins, which had been demonstrated to be an efficient and cost effective way for the detection of illicit materials (in Fig. 5A) [71]. Lee fabricated polymer-stabilized silver nanoparticle aggregates film mounted on aluminium roll backing material and the photograph of Poly-SERS film has been shown in Fig. 5B [72]. The approach provided new investigative directions by allowing objects containing illicit drugs to be identified at scenes due to swabbing method. And Yu et al. demonstrated inkjet-printed silver nanoparticles on paper as SERS substrate (in Fig. 5C) [73,74]. The paper dipstick combined pump-free loading of liquid samples into the detection device and analyte concentration in virtue of capillary-action wicking of cellulose. They combined SERS with paper chromatography, which help to integrate sample cleanup and analyte separation without extraction.

Compared to colloid-based SERS substrates fabricated by "bottom-up" techniques as described, solid surface-based substrates were also available to illicit drugs SERS analysis. For example, large scale and reproducible vertically-aligned silver nanorods, prepared by a laboratory-made dc magnetron sputtering system with a glancing-angle deposition technique [75] and controlled fabrication of silver nanoneedles array [76]. The sample preparation was just needed to drop the analyte solution on the top of solid-based substrates and the process was simple with relatively consistent results. Although such substrates could be commercially available, the price is usually relatively expensive.

To date, more academic research focused on colloidal substrate [72,77]. And people tend to design devices for implement of SERS as effective and less expensive diagnostic tools (in Fig. 6) [78].
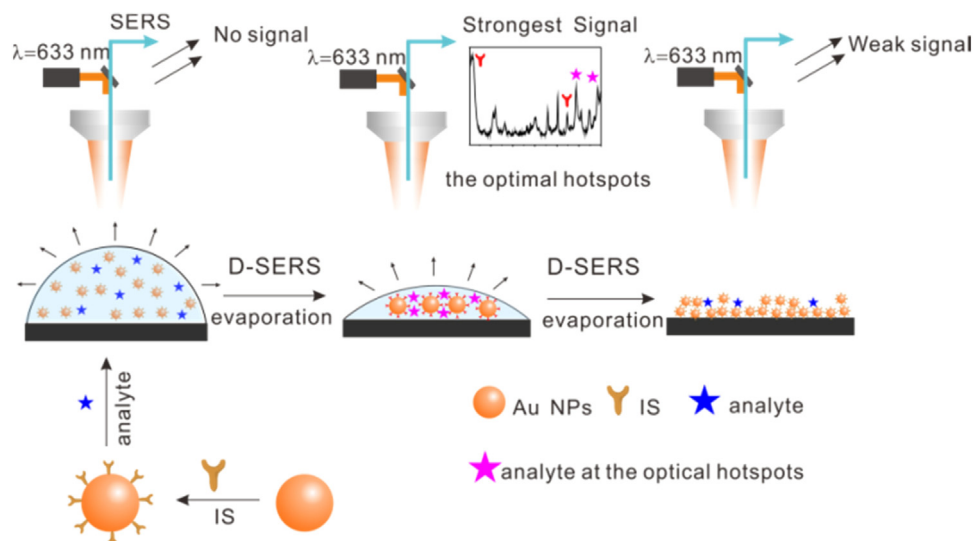

Fig. 2. Schematic diagram of the optimal hotspots created from D-SERS combined with an internal standard for quantitative detection [60].
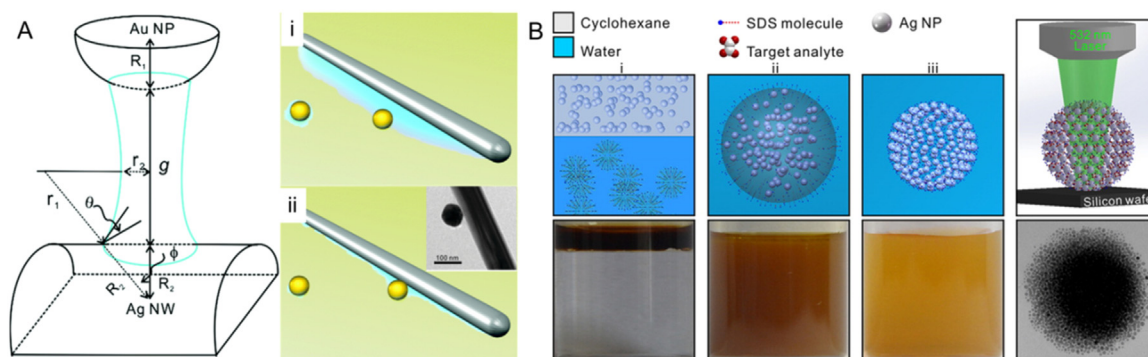
Fig. 3. (A) The illustration of the liquid-bridge between the Au nanoparticle and Ag nanowire and the schematic of the assembled single hot spot by capillary force-induced cohesion during the drying process [62]. (B) The process of the self-assembly of Ag nanoparticles into spherical Ag colloidal superstructures [64].
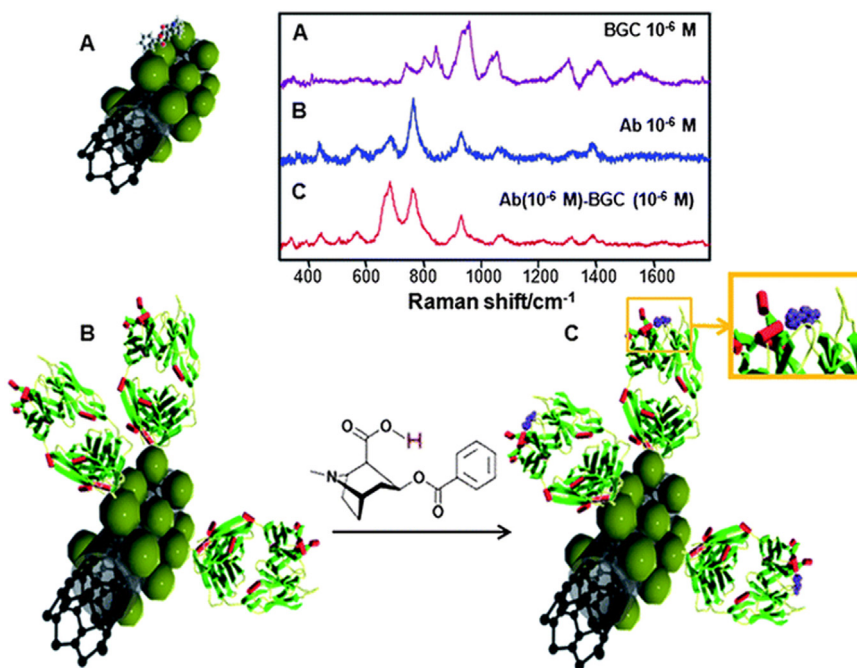

Fig. 4. Schematic representation of label-free SERS detection of BCG on silver-coated carbon with mAb and the corresponding spectra [68].
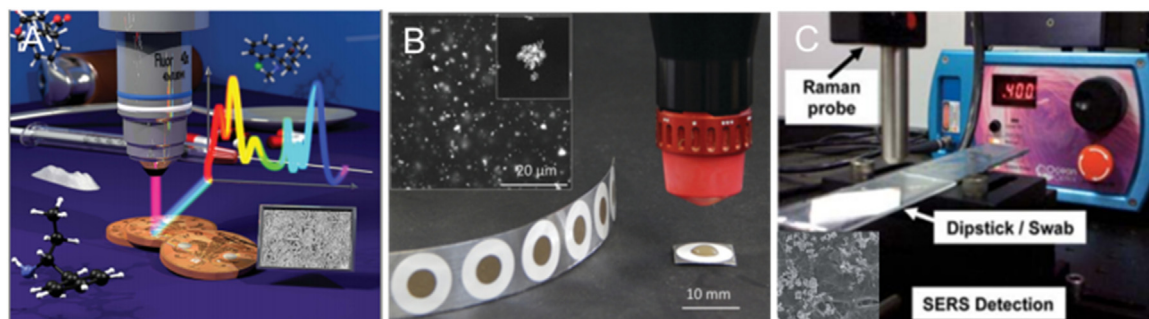

Fig. 5. (A) Schematic representation of tuppence-based SERS for the detection of illicit materials [71]. (B) Photograph showing disks of Poly-SERS film mounted on aluminium roll backing material. Inset shows SEM images of Ag nanoparticle clusters isolated within a Poly-SERS film [72]. (C) SERS detection with a portable spectrometer using inkjet-printed paper-based SERS dipsticks, inset: SEM of silver nanoparticles on paper [73].

3. Detection of illicit drugs or their metabolites in bio-fluids

SERS, a physicochemical technique, is considered to have exceptional potential for use in the analysis of bio-fluids. One of the main reasons is that water, as the major component of all bio-fluids, is a very weak Raman scatterer. There has been an increasing demand for rapid and sensitive techniques for the identification and quantification of illicit drugs and their metabolites in human bio-fluids during the past few decades. However, the applicability of SERS is limited by the fact that most biological samples are complex and the signals of analytes are often concealed by vibrational spectra from matrix, particularly when the concentration of analytes is very low. Moreover, most biological
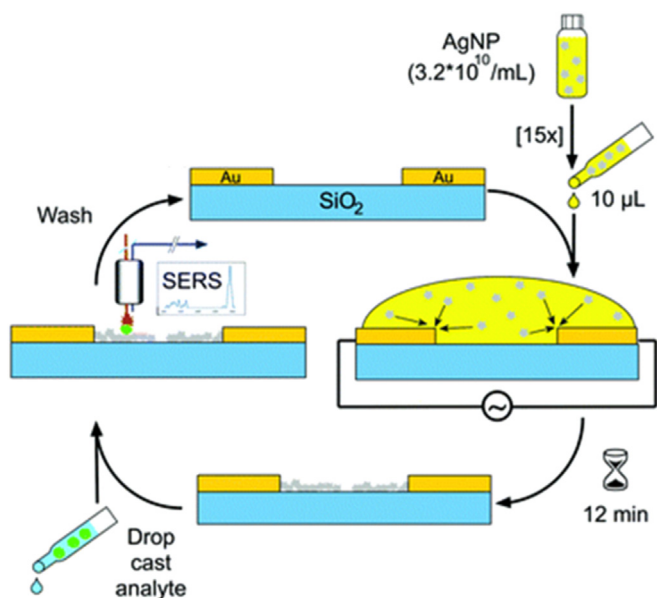
Fig. 6. Schematic representation of the SERS-active substrate preparation and detection process [78].

samples in the visible light region express strong fluorescence. Dispersive Raman systems have made great progress to improve the performance of SERS detection, which was not shown in this review. In order to enhance the detection capability of SERS, more and more techniques are combined [79,80]. Here, the related contents are now classified according to the different kinds of bio-fluids.

3.1. Urine

Urine is excess wastes extracted from the bloodstream by the kidney. And urine could reflect the drug consumption during the preceding 1–4 days. Because urine can also be collected in a noninvasive way, it is commonly used to monitor and identify drugs abuse [7,81,82]. Synthetic drugs, such as methamphetamine and amphetamine, are primarily excreted as intact drugs in urine [83]. Despite of the potential diagnostic value of urine, there are only a few groups studied urine samples from drug addicts by SERS. The main components in human urine include urea, creatinine, uric acid and albumin, which have particular sensitivity for Raman methods and they can seriously affect the determination of analytes [84,85].

Alharbi et al. took full advantage of the multiple salts in the complexity of urine to form aggregates spontaneously, which could realize the sensitivity detection of the opioid tramadol. But the spectra must be collected immediately after silver hydroxylamine colloid and the signals would be lost as aggregates precipitates [86]. Dong et al. also provided a way to directly detect illicit drugs in urine without any sample pretreatment (in Fig. 7A) [87]. He introduced D-SERS method with high sensitivity to couple with supporting vector machines (SVM) to achieve the intelligent spectral analysis. (The SVM method could help to classify different samples and deal with the SERS spectra for fast and visual identification.) Nevertheless, people are unable to perceive the difference of SERS spectra between normal urine and urine spiked with varying ppm of MAMP. Urea is the principal interference for detection in urine. Nuntawong et al. reported acidulation treatments to the specimen samples before SERS analysis to remove the interference from the urea. The organic urea-based byproducts eventually precipitate and the dissolved urine molecules would lose their affinity to bind on the silver surface. Thus the SERS signal intensity of MAMP/AM in the urine was enhanced [75]. However, the urine is of complex matrix and only removal of urea seems to be not enough for practical detection.

For the sake of more clear signature of analytes in the complex human urine, our group then developed liquid-liquid micro-extraction (LLME) techniques to pretreat urine samples for separation and purification of analytes (in Fig. 7B) [64]. Afterwards Han et al. used methoxymercaptopoly (ethylene glycol) (mPEG-SH) modified gold nanorods to act as SERS chips and proposed a portable kit for reliable SERS detection of MAMP and MDMA in human urine between 3 and 5 min (in Fig. 7C) [88]. On the basis of micro-extraction method coupled with SERS, Ma et al. further developed such technique [89]. They reported an interfacial SERS platform through the large-scale self-assembly of gold nanoparticles (Au NPs) arrays at the cyclohexane (CYH)/water interface for detecting trace drug molecules and realized the substrate-free interfacial SERS detection (in Fig. 7D). The drug molecules extracted by the CYH phase from a urine sample were directly localized into the self-organized plasmonic hotspots. Owing to the distance dependence of SERS, excellent Raman enhancement was thus yielded. Date to now, we have developed a mature technical route to achieve sensitive and simple determination of illicit drugs via LLME-SERS for drug addicts urine. Not only amphetamines, synthetic cannabinoids, cocaine and morphine could also be identified via micro-extraction coupled with SERS [53,90,91].

3.2. Saliva

Saliva (99.5% of water), the biological fluid taken by mouth, is easy to conduct chemical analysis. And sampling saliva can be implemented noninvasively and under supervision. For some synthetic drugs, the concentrations in saliva even exceed those in blood plasma [92–94]. Therefore, the exploration of illicit drugs detection in saliva is very meaningful.

The team of Stuart Farquharson has been investigating the potential of SERS to both identify and quantify drugs and their metabolites in saliva from about 2004, even though the analytes belongs to medicines of clinical trial in the beginning [95–97]. Considering illicit drugs abuse, they developed glass capillaries containing porous glass matrix with fused gold colloids to meet SERS-active need. Due to combining a solid-phase extraction (SPE) capillary to separate the drugs from saliva, many kinds of illicit drugs at low concentration could be detected [98–100]. Moreover, they built a SERS spectra library comprised of over 150 different drugs (each of which possesses a unique spectrum), and the results could be screened via a search and match software program. Furthermore, they developed a sampling kit (a saliva collector, a SPE material, and a SERS-capillary) for detection of illicit drugs in impaired driver saliva using a portable Raman spectrometer, as shown in Fig. 8 [101]. The total analysis, from sample collection to positive identification, was performed during no more than 10 min. The success of work approach was summed up in three ways: 1) the simplicity of extraction method to apply the complex matrices; 2) the high sensitivity of SERS detection; 3) the ability of Raman spectroscopy to identify molecular structures.

In order to obtain reproducible real-time SERS signals in saliva, people also try to combine microfluidic technology with SERS. Compared to traditional SERS detection in an exposed environment, microfluidic-SERS allows the direct detection of analytes with interaction between analytes and the active surface under liquid conditions [102–104]. Andreou et al. designed a microfluidics device to detect MAMP (in Fig. 9) [92]. Silver nanoparticles suspension, a saliva specimen sample, and salt solution were loaded and driven to the channel flow by a vacuum pump. Molecules to be measured in the focused stream diffused laterally into the side flows and salt ions also diffused into the colloid stream inducing nanoparticle aggregation, creating SERS-active clusters, thus provided a sensitive detection. However, there are some drawbacks in this system. For example, it may take a long time for the process of aggregation and the channel would accumulate silver nanoparticles over time because of the aggregating agent, resulting in a memory effect.
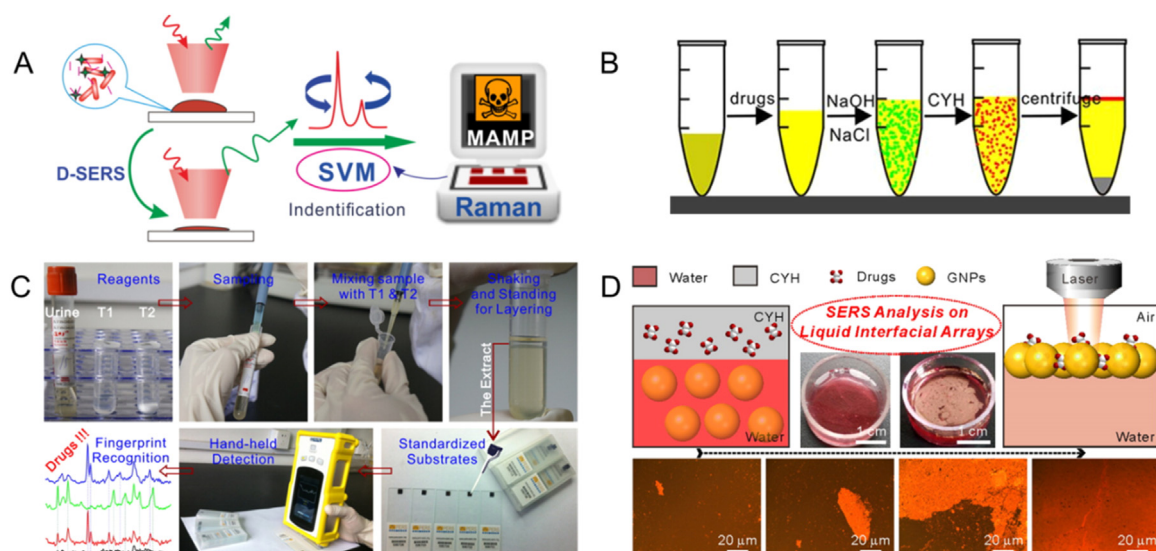
Fig. 7. (A) Schematic procedures of D-SERS coupled with SVM to direct readout of drugs in human urine [87]. (B) Schematic procedures for separation and concentration of MA or MDMA from real human urine [64]. (C) Illustration of a Portable Kit for Rapid SERS Detection of Drugs in Real Human Urine [88]. (D) Schematic illustrations and optical images of the urine extract-induced self-assembly of GNP arrays at the liquid/air interface for SERS detection [89].

3.3. Other kinds of bio-fluids

In this part, illicit drugs analysis in nasal fluid and blood is mainly presented. For nasal mucus, their main function is to capture small particles (dust, particulate pollutants, and allergens), avoiding enter the respiratory system. The parent snorted compound exists in nasal fluid, which is the natural analysis advantage. And the sampling preparation was simple, inexpensive and non-invasive [44]. For human blood, it plays a crucial role in biological activity and is commonly used to analyze illicit drugs abuse. However, according to investigation, whole human blood, blood plasma, and red blood cells would produce rich SERS spectra [105]. Chen et al. developed a microfluidic chip that consisted of front-end cell capture structures and back-end filters. And the device could be used to blood plasma separation with gradual filtration to avoid the effects of blood cells [106]. Abdu et al. successfully assess multiple human bio-fluids (urine, serum and plasma) with a range of multivariate statistical analysis techniques on the basis of full SERS spectral data [107]. And they also studied quantitative detection of codeine in human plasma using SERS via adaptation of the isotopic labelling principle and the approach was shown in Fig. 10 [108]. Unfortunately, detection of illicit drugs in human blood has to be a very challenging work.
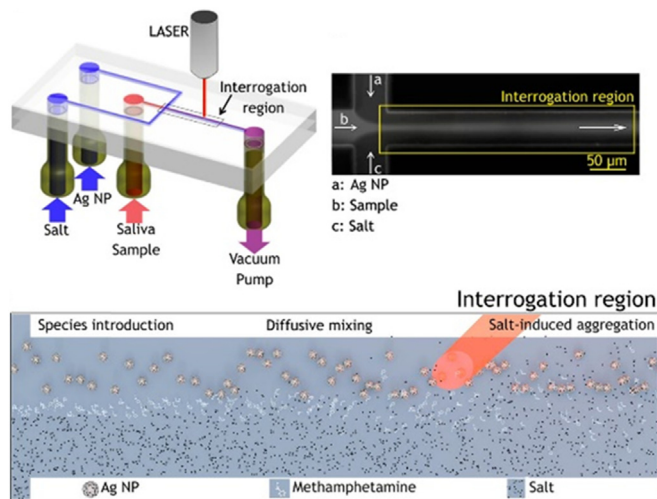

Fig. 9. Flow-focusing microfluidic device used for controlled Ag-NP aggregation [92].

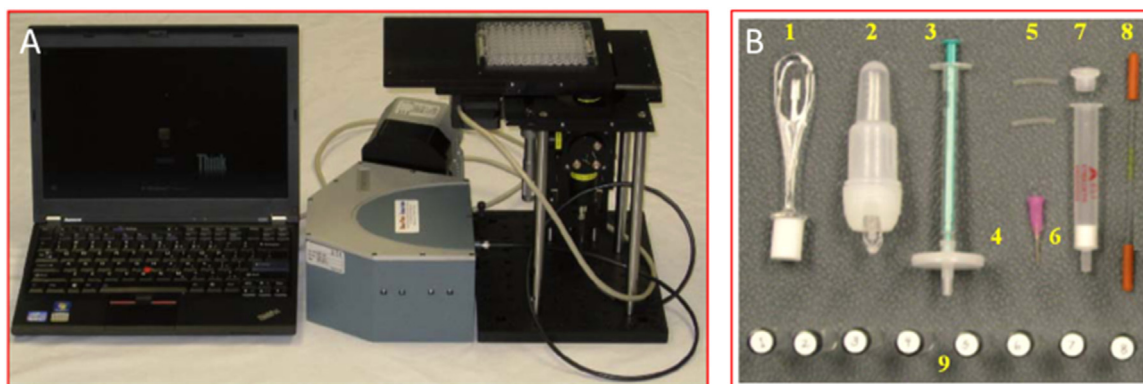
Fig. 8. (A) Photograph of dispersive Raman system used for impaired driver saliva. (B) Photograph of the components used for manual analysis of drugs in saliva. 1) Swab, 2) saliva collection tube, 3) 1 mL syringe with 4) 0.2 μm filter, 5) Tygon tubing connectors, 6) blunt needle, 7) SPE column, 8) SERS-active capillary, 9) 2 mL vials containing reagents (plus 1 for collecting waste) [101].
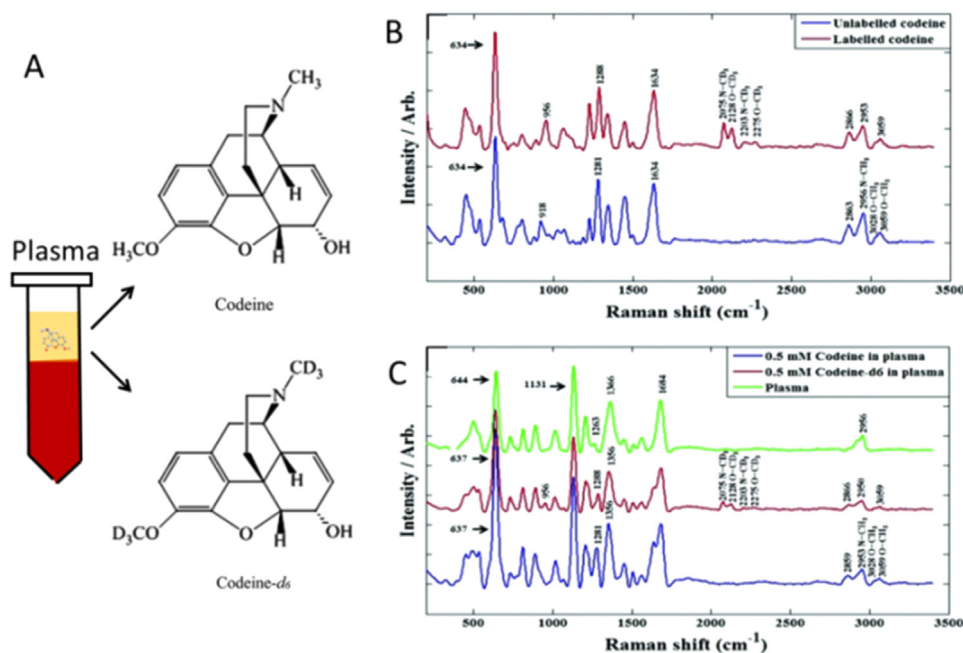
Fig. 10. The chemical structures of codeine and codeine-d$_6$ (A). Baseline-corrected SERS spectra of 100 μM codeine spiked into (B) water (C) human plasma [108].

4. Conclusions and outlooks

In this review, we have summarized the developments and applications of SERS in the field of drugs analysis in different environments. On the basis of signatures from standard illicit drugs and common additives in street samples, the real analysis in complex environments is gradually explored in order to solve practical problems. And the evaluation of newly developed method was conducted to measure the real case, not simulation samples. Even though significant progress has been made as the mentioned, there are still tricky problems considering the need for fast, reliable and even accurate quantitative measurements. And the trace levels of drugs and signal interferences may be the main difficulties for qualitative detection. The challenges must be investigated and addressed to promote the practical applications (as shown in Fig. 11).

First, surface coverage. SERS is governed by the plasmon, which is defined as: "a quantum quasi-particle representing the elementary excitations, or modes, of the charge density oscillations in a plasma" by Le Ru and Etchegoin [109,110]. Usually, the obtained weak signals by traditional Raman technique can be overcome via different morphologies of metallic nanostructures. Metallic nanomaterials however are not without problems. Among the parameters that play a major role in the appearance of the SER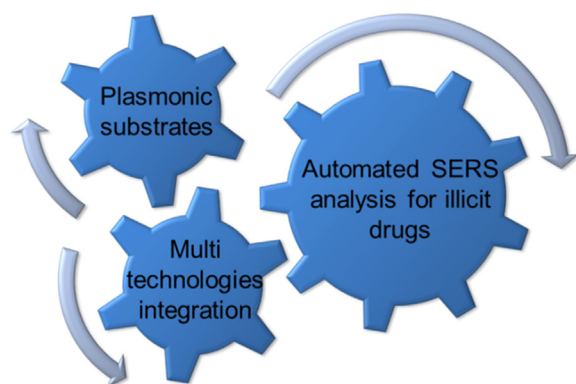S spectra, the surface coverage (molecule–metal interaction) seems to need more attention in the future. If the illicit drugs do not have strong affinity for the SERS substrate, it will be hard to obtain sensitive identification [92,111,112]. This is particularly obvious in complex fluids containing multiple species, where moieties with high affinity could bind to the exclusion of other species that may be present [65,87]. And advanced by nanotechnology and functionalization, more and more sensitive and reliable SERS substrates will be fabricated.

Second, multi technologies integration. In face of a target analyte in a simple solvent, the intensity of Raman signal can be enhanced under the help of novel substrate, thus improve the sensitivity of detection. Nevertheless, SERS is not a separation technique. When the target analyte exists in complex matrices, it is usually too difficult to obtain the signal of target directly [87,105]. In order to remove matrix interferences for the enhancement of detection capability, one way is to use capturing techniques via the selectivity for targets molecules, including antibody [113,114], aptamer [115–117] and molecular imprinting [31,118]. Another way is to couple with separation techniques (solid/liquid-phase extraction [119], thin layer chromatography (TLC) [120,121], chemical separation [65] or HPLC [122], et al.). Other techniques devices (colorimetric screening [123] and microfluidic [80,92]) can help to facilitate high-throughput detection capabilities and improve the reliability of SERS. For an extended overview of the SERS based techniques, we refer readers to the excellent review by Zhang et al. [79] Currently, SERS researches about illicit drugs detection are still in development stage. Most attention was focused on the development of various SERS substrates and the developed methods were evaluated via simple systems. Even though some studies have demonstrated the advantages of multi techniques integration to illicit drugs detection in complex environment, the vast majority of subjects are simulated samples through standard addition. And measurements will follow with interest actual samples. In addition, a more simplified pretreatment and analysis procedure are needed, which will lead to a faster and more convenient analysis in complex matrices compared with conventional chromatographic procedures.

Third, automated SERS analysis for illicit drugs. On the one hand, improve the sensitivity of detection, because the concentration of drugs to be tested is usually very low. On the other hand, get more accurate and fast test results, which is helpful for law enforcement officers to

Fig. 11. The trends of SERS development for illicit drugs analysis in the future.

popularize SERS technology for on-site drug detection. At present, a range of different statistical analysis techniques, including SVM [87], PCA [64], principal component–discriminant function analysis (PC-DFA) [104], partial least square (PLS) [124] and artificial neural networks (ANNs) [21] have been employed to investigate the test data. Even multivariate statistical analysis techniques are conducted. When the SERS spectra coupled with chemometrics, the clear differentiation of neat samples and these spiked with varying concentrations of analytes could be identified. Moreover, the relationship between SERS spectral data and the concentrations of analytes may be obtained, which could make quantification detection possible. The results of such studies demonstrate the potential of SERS application as a diagnostic screening method. The combination development of SERS and powerful machine learning technique is an important aspect to achieve on-site detection, so that nontechnical personnel can conveniently and accurately get the pertinent investigative information. Thus make it possible to realize economic and on-site SERS analysis using a portable device.

In conclusion, SERS is hopeful to be a versatile and powerful sensor platform in real-world applications for illicit drugs analysis. Of course, it ought not to be ignored that quantification is still an absolute challenge for in situ detection [60,69,70,125]. In terms of the importance to state long-term abuse of illicit drugs and drug dosing for legal therapeutics, we believe that more and more people will be inspired to use SERS for the quantitative analysis of analytes instead of lengthy and time-consuming chromatography. In the next few years, not only laboratory but also field methods are expected to flourish.

Acknowledgments

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