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OVERVIEW

Portable testing techniques for the analysis of drug materials

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Abstract

The analysis of drug material in the field is an important function of law enforcement agencies, forensic drug laboratories, and drug checking services. Portable testing techniques employed by these different groups range from inexpensive screening tools with low discriminating power, such as presumptive chemical color tests, to more sophisticated portable analytical techniques that behave as miniaturized versions of their laboratory counterparts, such as gas chromatography–mass spectrometry (GC–MS). Rapid non-destructive analysis in the field and non-laboratory environments is afforded by portable and handheld Fourier transform infrared (FTIR) spectrometers with little to no sample preparation, while handheld Raman analyzers have the added potential for drug material identification through sealed packaging using spatially offset Raman spectroscopy (SORS). Utilization of the most suitable testing technique for the given environment is demonstrated at international borders and airports wherein ion mobility spectroscopy (IMS) is frequently employed for the detection of drug (and explosive) residues owing to its ease of operation and rapid analysis. Advances in technology and materials have provided analysts with new portable testing techniques, including paper spray ionization–MS (PSI-MS), an ambient MS technique that provides sensitive, rapid, and reliable analysis without the need for sample preparation steps. A growing area of research and interest in the development of sensitive and selective optical and electrochemical portable (bio)sensors for in-field analysis of drug material indicates that new commercial sensors for drug detection will be available in the foreseeable future.

This article is categorized under:

Forensic Chemistry and Trace Evidence > Controlled and Emerging Drug Compounds

Forensic Chemistry and Trace Evidence > Emerging Technologies and Methods

Toxicology > Drug Analysis

KEYWORDS
drug analysis, field testing, handheld instruments, portable techniques, rapid identification

1 | INTRODUCTION

Drug use and abuse proliferates around the world and across most demographics as licit and illicit substances are sought-after for the psychoactive effects afforded to the user. Over the last decade, substances available on drug markets have undergone significant diversification and expansion from traditional plant-based substances such as cannabis, cocaine, and heroin, to a dynamic market for synthetic drugs (e.g., amphetamine-type substances) and non-medical use pharmaceuticals (e.g., opioids) (UNODC, 2021c). Adding to this expanding drug market are the more than 1000 new psychoactive substances (NPS) that have appeared in recent years as stimulants, cannabinoids, hallucinogens, and opioids (e.g., fentanyl analogs). These NPS are a particularly concerning group of substances owing to their unpredictable and often severe health consequences. The innovation of drug supply chains has witnessed the transition to selling and purchasing drugs via online platforms, resulting in an increase in the use of mail courier services delivering drug materials. These drug materials come in a variety of forms including powders, tablets, capsules, liquids, oils, sprays, botanical material, and impregnated blotter paper.

The analysis of drug material is performed by law enforcement agencies, customs services, drug testing services, and drug checking services. Subject to the aim and scope of testing, the analysis will include screening, identification, and/or quantification techniques, each providing an increasing level of information about the drug material to the analyst. Color tests remain the most commonly used screening technique for testing seized material in a forensic drug laboratory, while identification and confirmation of drugs is typically performed using gas chromatography–mass spectrometry (GC–MS) (UNODC, 2021a, 2021b). The highest level of selectivity is afforded by analytical techniques that can provide structural information such as infrared spectroscopy, MS, nuclear magnetic resonance (NMR) spectroscopy, Raman spectroscopy, and X-ray diffractometry. Identification can be achieved by combining these techniques with less selective methods that provide chemical and physical characteristics, such as capillary electrophoresis, gas chromatography, ion mobility spectrometry, liquid (and supercritical fluid) chromatography, microcrystalline tests, thin layer chromatography, and ultraviolet/visible spectroscopy (SWGDRUG, 2019). The least amount of selectivity is afforded by techniques that only provide general or class information such as color tests, fluorescence spectroscopy and immunoassays. The quantification of drugs in seized material is mostly performed using gas chromatography–flame ionization detection, followed by high performance liquid chromatography–diode array detection and gas chromatography or liquid chromatography coupled to single stage or tandem mass spectrometry (UNODC, 2021a, 2021b). Many of the techniques performed in a laboratory for identification and quantitative analysis are expensive to run and require trained personnel to operate the instruments and interpret the results. A growing area of interest lies in the development of portable and rapid testing techniques that can provide the same level of selectivity as their laboratory counterparts. Portable drug analysis techniques, by design, should be low cost and easy to use while still providing rapid results for law enforcement agencies and other analysts in the field. Herein, we provide an overview of the current technologies, in use and emerging, for the portable detection and analysis of drug material. These technologies include presumptive chemical color tests, field portable vibrational spectroscopic instruments, compact ambient mass spectrometers, point-of-care (bio)sensors, and other techniques that involve instrument miniaturization.

2 | CHEMICAL COLOR TESTS

Chemical color tests are presumptive screening tools typically used in the initial stages of drug analysis to determine the presence or absence of a particular drug or drug class in a sample. In these tests, chemical reagents are added to a small sample of drug material and the resulting color changes are observed with the naked eye and compared with a reference color chart. The chemistry underpinning color tests varies between color test reagents as the drug of interest reacts with the test reagent(s) to produce colored metal complexes or charged organic species (Philp & Fu, 2018). Color test reagents can be classified into three main types: general screening, drug class selective, and functional group

selective. General screening color tests react with a wide range of compounds to produce a different color for each broad class of drug compounds, while the drug class selective reagents will only show a color change with the targeted drug of interest and the functional group selective reagents indicate the presence of certain functional groups in the drug material. Commonly used color test reagents and their targeted compounds are provided in Table 1.

Chemical color test reagents are often employed in a pre-determined sequence to allow analysts to presumptively identify the drug of interest using a minimum number of tests. For example, the presence of methamphetamine in an unknown sample could be presumptively identified by a red to brown color change with the Marquis reagent, followed by a blue color change with the Simon's reagent.

Chemical color test reagents have been manufactured by several companies into portable drug of abuse test kits that are designed to be used in the field. These kits are mostly used by law enforcement agencies, however, they are also advertised on harm reduction websites for use in at home drug checking or pill testing. These simple test kits come in a variety of fabrications, including reagent bottles, ampoules, pouches, cartridges, wipes, paper strips and sprays. The lack of sample preparation required, ease of use, rapid results afforded, and low cost make commercial color test kits an ideal portable presumptive identification technique. However, false positive and false negative color test results can occur as a result of incorrect application of the color test kit, harsh environmental conditions under which the test is performed, and complex sample mixtures. The emergence of NPS, often disguised as traditional recreational drugs,

TABLE 1 Reagent chemicals and targeted compounds of commonly used color tests

Type	Name	Reagent chemicals	Targeted compounds
General screening	Marquis	Sulfuric acid, formaldehyde, and water	Alkaloids and other compounds (e.g., opiates, amphetamines, and phenethylamines)
	Liebermann's	Sulfuric acid, sodium (or potassium) nitrite, and water	Alkaloids and other compounds (e.g., amphetamines and some synthetic cathinones)
	Mandelin's	Sulfuric acid, ammonium vanadate, and water	Alkaloids and other compounds (e.g., amphetamines, some phenethylamines, and ketamine)
	Mecke	Sulfuric acid and selenous acid	Alkaloids and other compounds (e.g., opiates, some amphetamines and synthetic cathinones)
	Froehde's	Sulfuric acid and sodium molybdate	Alkaloids and other compounds (e.g., opiates and some synthetic cathinones)
Drug class selective	Duquenois–Levine	Acetaldehyde, vanillin, ethanol, hydrochloric acid, and chloroform	Δ^9-Tetrahydrocannabinol (THC) and other cannabinoids
	Scott's	Cobalt thiocyanate, water, glycerin, hydrochloric acid, and chloroform	Cocaine
	Dille–Koppanyi	Cobalt acetate, methanol, glacial acetic acid, and 2-propylamine	Barbiturates
	Chen–Kao	Acetic acid, water, copper sulfate, and sodium hydroxide	Ephedrine
	Ehrlich's	*p*-Dimethylaminobenzaldehyde, methanol (or ethanol), and hydrochloric acid (or phosphoric acid)	Ergot alkaloids, indoles, aromatic amines, and LSD
	Fast Blue B salt	Diazotized *o*-dianisidine, chloroform, sodium hydroxide, and water	Δ^9-Tetrahydrocannabinol (THC) and other cannabinoids
	Zwikker	Copper sulfate, water, pyridine, and chloroform	Barbiturates
Functional group selective	Simon's	Acetaldehyde, sodium nitroprusside, sodium carbonate, and water	Secondary amines (e.g., methamphetamine)
	Zimmermann	1,3-dinitrobenzene, methanol, potassium hydroxide, and water	Ketones (e.g., synthetic cathinones and benzodiazepines)

have led to color test validation studies to determine the effectiveness and potential cross-reactivities of current test methods (Cuypers et al., 2016), and the introduction of new chemical color test methods for NPS such as piperazine derivatives (Philp et al., 2013), synthetic cathinones (Philp et al., 2016), and *N*-methoxybenzyl-methoxyphenylethylamines (NBOMes) (Clancy et al., 2021).

Despite the relatively low selectivity of chemical color tests, their use has continued for decades owing to their simplicity, rapidity, and portability. Advances in colorimetric analysis, solid colorimetric sensors and microfluidic devices have increased the interest in chemical color tests.

2.1 | Colorimetric analysis

Qualitative chemical color test results are limited by the inherent subjective nature of the naked eye determination made by the analyst. This is compounded by the issue of uncontrolled lighting conditions under which a color test is likely to be performed, for example, a test performed under fluorescent lighting in a laboratory may appear differently to a test performed outside on an overcast day. Attempts to increase the objectivity of results have seen the application of colorimetric, spectrophotometric, and digital image-based procedures to a chemical color test. The use of portable colorimeters and spectrophotometers for the analysis of color spot test results in the field is limited, however, there is a growing area of research in the digital image-based analysis space owing to its simplicity, ease of use, and low cost.

Choodum et al. first applied digital image analysis to the products of simple presumptive color tests for amphetamine, methamphetamine (Choodum & Nic Daeid, 2011a), and opiates (Choodum & Nic Daeid, 2011b), and demonstrated its potential for semiquantitative analysis. In these early studies, a digital camera was used to collect the digital image under controlled lighting conditions, and after transferring the image to a computer, image processing software was used to obtain the Red Green Blue (RGB) color values. The relationship between the intensity of RGB values and the concentration of the illicit drug is exploited and used to produce calibration curves. Advancements made in the functionality and technology of mobiles phones provided a faster, portable, more convenient, and real-time approach to digital image analysis. The built-in camera and freely available applications on a portable smartphone (e.g., ColorAssist) are used to capture the digital image of the color test, and extract the RGB components in one step. This approach to digital-image analysis has been successfully employed in the quantitative analysis of methamphetamine using presumptive color tests (Choodum et al., 2014) and sol–gel sensors (Choodum et al., 2015). Despite digital image analysis extending the value of a simple chemical color test for illicit drugs, the inherent limitations of these presumptive tests remain.

Some smartphone applications (e.g., PhotoMetrix) further increase the portability and convenience of the system by converting RGB coordinates into histograms and employing the chemometric techniques of simple linear correlation for univariate analysis, and principal components analysis (PCA) for multivariate exploratory analysis (Böck et al., 2020). The four essential components of an analytical colorimetric system are: a sample holder, an illumination source, an image capturing device, and a computer for extraction of color histograms and construction of chemometric models (Gonçalves Dias Diniz, 2020). Quantitative analysis associated with variations in the concentration of the colored chemical species cannot be determined with the naked eye, however, studies have shown this can be achieved using digital image-based analysis (Tosato et al., 2016).

2.2 | Solid sensors

The instability of a chemical reagent will negatively affect its application in the field for presumptive drug testing, as color test kits require storage of chemicals. To overcome this, solid sensors have been developed by incorporating the chemical reagents into polymeric networks. Additional advantages include its ease of use and minimized handling of solutions. Recent developments have included the immobilization of cobalt(II) thiocyanate onto polydimethylsiloxane (PDMS) for the detection and quantification of ketamine in drug material based on the sensor color change from brown to blue-purple in the presence of a ketamine solution (Argente-García et al., 2017). Similarly, the detection of amphetamine-type substances has been realized using polydimethylsiloxane/tetraethylorthosilicate/silicon dioxide (PDMS/TEOS/SiO_2) nanoparticles doped with 1,2-naphthoquinone-4-sulfonate (NQS) reagent (Argente-García et al., 2016). Building on from this study, a colorimetric device capable of distinguishing amphetamines from

scopolamine in beverages was prepared by incorporating a second potassium permanganate sensor (Jornet-Martínez et al., 2021).

2.3 | Colorimetric microfluidic devices

Microfluidic devices are an attractive portable alternative to traditional automated and high-throughput lab-based analytical techniques due to the small volumes of sample and chemical reagents used, low cost per analysis, compact size, rapid analysis times, and the ability to perform multiplexed assays. Color test reagents have been incorporated as the detection method in microfluidic devices for the analysis of drug material, with paper being the most used substrate material in colorimetric microfluidic devices due to its low cost, availability, and being environmentally friendly. Paper-based analytical devices (μPADs) for the detection of seized drugs and cutting agents typically consist of a series of wax channels printed on chromatographic paper. The sample solution moves through the channels via capillary action toward the immobilized chemical reagent(s), wherein a chemical reaction occurs and produces a color change visible to the naked eye. The immobilization of a different chemical reagent in each channel allows for multiplexing. Several different μPAD designs have been developed for the portable analysis of drug material (Figure 1).

The limitations of this technique include the requirement for samples to be applied as solutions and the inability to impregnate the paper with concentrated acid, which is a common reagent in a number of chemical color tests (McNeill et al., 2021). In one study, Fast Blue B salt was used as an alternative chemical reagent to Mandelin's or Marquis due to the concentrated sulfuric acid reagent reacting with the paper, and ninhydrin was used as an alternative to the Simon's reagent due to the high volatility of the acetaldehyde reagent (Musile et al., 2015). Attempts to increase field usability have removed the need for samples to be in solution and instead, the drug material is applied to the μPAD directly (Lockwood et al., 2020). The use of chemoresponsive dyes in lieu of specific chemical color test reagents have also been used to create μPADS capable of discriminating eight alkaloid drugs (Dias et al., 2021). It should also be noted that in many cases, colorimetric analysis using smartphones or other digital image capturing device and software is used to analyze the color test results, and in some cases provide semi-quantitative results. Paper-based microfluidics for identification of seized drugs can employ more selective and advanced detection procedures based on recognition elements and optical or electrochemical signals (Musile et al., 2021). These techniques will be explored further in the section on (bio)sensors.

3 | VIBRATIONAL SPECTROSCOPY

Portable vibrational spectroscopy has become popular in the analysis of drug materials by law enforcement and drug checking services, as these techniques are rapid and non-destructive. There are two main vibrational spectroscopy

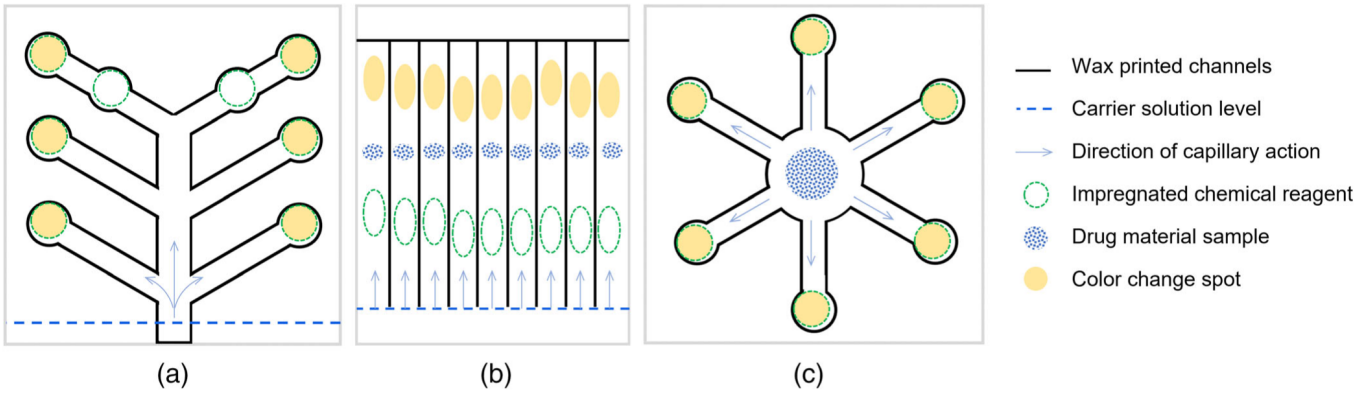

FIGURE 1 Example designs of colorimetric paper-based analytical devices using capillary action to bring drug material into contact with immobilized chemical reagents. (a) μPAD is placed in carrier solution containing the unknown drug material;(b) unknown drug material is applied to each channel and the μPAD is placed in carrier solution; (c) unknown drug material in a carrier solution is applied to the center of the μPAD

techniques which have been explored for portable analysis of drug material; Fourier transform infrared (FTIR) and Raman spectroscopy.

3.1 | Fourier transform infrared spectroscopy

Infrared activity arises from the changes in dipole moment of bonds as they absorb the energy of the incident radiation (Atkins & de Paula, 2013). The sample is irradiated with infrared radiation, the sample absorbs some of the radiation and the remainder is transmitted through the sample. This results in a unique fingerprint spectrum being obtained which is characteristic of the functional groups present within the sample. FTIR is a complementary technique often used in addition to other analytical techniques for structure elucidation and identification of unknown compounds (Shevyrin et al., 2014; Simolka et al., 2012; Zuba et al., 2013). FTIR is an ideal technique for on-site analysis as it is non-destructive, cost-effective, rapid, and requires minimal sample preparation (da Silva et al., 2018; Zuba et al., 2013).

There are four sampling techniques which can be used with FTIR: transmission, attenuated total reflectance (ATR), specular reflection, and diffuse reflectance. The most common method used for portable drug detection and identification applications is ATR. The technique of ATR–FTIR has the infrared beam directed into an optically dense crystal creating an evanescent wave which extends into the sample held in contact with the crystal (Larkin, 2011). ATR–FTIR has been shown to be useful in detecting NBOMes and lysergic acid diethylamide (LSD) on blotter papers. However, given that blotter papers are a mixture of the active ingredient and the paper matrix, the discriminating power of the technique is reduced (Coelho Neto, 2015). The use of ATR–FTIR for analysis of powders, pills and liquids in a drug checking setting revealed the presence of potentially harmful adulterants in street drugs (Tupper et al., 2018). FTIR has also been combined with chemometric techniques for the determination of purity and chemical form, and to reduce the need for specialized interpretation. ATR–FTIR combined with multivariate curve resolution (MCR) with alternating least squares discriminated between forms of cocaine rapidly and with minimal sample preparation (da Silva et al., 2018). Cocaine forms and adulterants have also been investigated by combining ATR–FTIR with hierarchical cluster analysis (HCA), principal component analysis (PCA), partial least squares-discriminant analysis (PLS-DA) and support vector machines-discriminant analysis (SVM-DA). Cocaine salt was found to possess high purity, adulterated with caffeine and lidocaine, while cocaine base was less pure and adulterated with phenacetin (Marcelo et al., 2015). ATR–FTIR with SVM classification model showed high specificity, sensitivity, and efficiency. The SVM quantification model had low error over a wide working concentration range. The use of ATR-FTIR and SVM together resulted in a straightforward, user-friendly approach (cocaine detected or cocaine not detected) for routine classification and quantification (Eliaerts et al., 2017). Trained PLS regression models used with spectral pre-processing of ATR–FTIR spectra have also been used to rapidly determine fentanyl concentrations in complex mixtures (Ramsay et al., 2021). Blotters have also been investigated through combinations of ATR–FTIR and PLS-DA. The combination of the two techniques allowed for discrimination of NBOMe and NBOH with <10% misidentification (Custódio et al., 2021). NBOMe, 2,5-dimethoxyphenethylamine (2C-H), LSD, methallylescaline on blotter papers have been classified and submodels used to discriminate three NBOMes. There were high correct classification rates for three of the four tested classes (Pereira et al., 2017). Although FTIR has been found to be useful for the detection of some drugs there are still issues with widespread use as a sole detection method. These issues include lower sensitivity for some analytes, including fentanyl (Ti et al., 2020) and LSD (Pereira et al., 2017), at low concentrations. Another issue is that the library of compounds varies with manufacturer, and therefore may require analyst expertise for interpretation, especially when mixtures are being analyzed.

3.2 | Raman spectroscopy

Raman spectroscopy was first tested and described by Raman and Krishnan (1928). Raman spectroscopy requires the incident light to be monochromatic (White, 2000). Raman spectra are produced as the absorbed energy from the incident light is emitted. Most of the emission is at the same wavelength as the incident light; this is called Rayleigh scattering (Harris, 2010). The Rayleigh scattering is removed by holographic filters on modern instruments (White, 2000). However, some of the scattered emission radiation has a slightly higher, anti-stokes, or slightly lower, stokes, frequency which is called Raman scattering (Harris, 2010). Changes in polarizability as the molecule vibrates gives rise to Raman active functional groups (Atkins & de Paula, 2013). Through this Raman spectroscopy can provide information on the

structure of a compound based on the visible vibrational bands (Atkins & de Paula, 2013). However, one major problem is that weak signals can be drowned out by fluorescence of samples. Since water has a weak Raman signal, aqueous solutions can be analyzed by Raman (Harris, 2010). Another advantage of Raman spectroscopy is the spectra are generated quickly (White, 2000). Portable Raman spectrometers are versatile as a fast and safe option as they simplify the testing process through the elimination of sample preparation and allowing for the analysis of a range of chemicals and packaging (Cooman et al., 2021).

Portable Raman spectrometers range in size from small 2.4–30 kg instruments which can include a microscope and are considered person-portable (CBRNE Tech Index, 2018; JASCO, 2017) to 0.8–3.4 kg handheld instruments to the even smaller 0.330–0.785 kg pocket-sized instruments (CBRNE Tech Index, 2018). The development of portable Raman spectrometers has allowed for the rapid on-site non-destructive identification of chemicals. Some of the portable spectrometers include barcode scanners to decrease the processing time and determine what should be inside a certain package (Agilent Technologies, 2021). Many of the handheld spectrometers allow for analysis without opening containers by using spatially offset Raman spectroscopy (SORS); which reduces the exposure risk for the analyst. The number of drug analytes in a given library database varies with manufacturer and the purpose of analysis. For example, individual databases exist for controlled and prescription drugs, inorganic materials, explosives, and hazardous analytes. According to Kelly et al., there are three main considerations which must be taken into account when choosing a portable Raman spectrometer fit for the required analysis: excitation wavelength and power, spectroscopic resolution, and numerical aperture (Kelly et al., 2012).

There are many different types of Raman spectroscopy which have been developed to overcome issues, such as fluorescence, which have arisen from conventional Raman spectroscopy. These other methods include Fourier transform Raman spectroscopy (FT-Raman), SORS, resonance Raman spectroscopy (RR), surface enhanced Raman spectroscopy (SERS) and surface enhanced resonance Raman spectroscopy (SERRS), and tip-enhanced Raman spectroscopy (TERS). Dispersive Raman spectroscopy is the conventional Raman spectroscopy method. Dispersive Raman uses an ultraviolet (UV), visible or near infrared (NIR) laser, a dispersive spectrometer and a charged coupled device (CCD) for detection (White, 2000). Raman used in an airport environment portable Raman was able to discriminate between cocaine, 3,4-methylenedioxymethamphetamine and amphetamine salts even in the presence of cutting agents (Hargreaves et al., 2008). High quality spectra were able to be acquired in less than 30 s and were identified without spectral processing (Hargreaves et al., 2008). SORS collects Raman spectra from below the surface of a sample (Matousek et al., 2005). The development of the SORS method has allowed for the development of methods which do not require packaging to be opened for analysis to occur. The advantages of the SORS is that it is non-destructive to both the sample and the packaging, it has short analysis times, and concealed substances can be identified (Olds et al., 2011). SORS combined with direct analysis in real time mass spectrometry (DART-MS) has been shown to provide a rapid and accurate method for seized drugs analysis (Cooman et al., 2021). Raman spectroscopy has the added benefit that it be conducted through packaging on both solids and liquids without compromising precision or accuracy and provide high discrimination between drug structures (Cooman et al., 2021). However, spectral deconvolution is an issue with portable and handheld spectrometers with most identifications being of the diluent of a mixture rather than the target drug (Cooman et al., 2021). This highlights the need for complementary techniques and further spectral deconvolution. SERS was discovered while studying pyridine on a silver electrode (Rodger et al., 1998). The sensitivity of the analysis is increased by six orders of magnitude (White, 2000). The effect is observed when the sample is adsorbed to a roughened metal or metal colloid surface. The metals used are gold, silver, or copper (Rana et al., 2011). The metal surface quenches the fluorescence of the adsorbed sample (White, 2000). Illicit drugs have been detected both directly and indirectly using SERS technology. SERS combined with paper spray ionization-mass spectrometry (PSI-MS) has been used for identification and quantification of fentanyl analogs within a realistic concentration range which allowed for in situ analysis at point of seizure (Fedick et al., 2020). The combination of two analysis techniques is required by many forensic regulations and the use of updatable spectral databases simplifies the adoption of these techniques in the field (Fedick et al., 2020). The combination of SERS and PSI-MS is further discussed in the section on PSI-MS.

It has been suggested by several research groups that combining Raman spectroscopy data with chemometric analysis is beneficial when differentiating samples as well as for quantification. There are two main chemometric methods used with Raman spectroscopy: PLS (Been et al., 2011; Katainen et al., 2007; Ryder et al., 1999) and PCA (de Veij et al., 2007; Noonan et al., 2009; Ryder et al., 1999; Wilson et al., 2021). Quantification by PLS and direct use of an internal standard to peak height ratio were compared by Katainen et al. (2007). Textiles impregnated with drugs have been able to be analyzed rapidly without pre-treatment or extraction when Raman was combined with automatic spectral recognition and PCA (Ali & Edwards, 2014). Novel SERS has been used with handheld Raman spectrometers to

discriminate between fentanyl analogs using PCA. Fentanyl concentration was determined with 70% accuracy and trace fentanyl was also detected in high concentrations of heroin and caffeine (Wilson et al., 2021).

4 | AMBIENT MASS SPECTROMETRY

Portable mass spectrometry (MS) has become of forensic interest, as it can alleviate pressure on forensic laboratories and provide accurate results in the field (Lawton et al., 2017; O'Leary et al., 2015). Advancements in collection and ionization methods have improved the potential for these techniques to be used easily in a forensic context with the coupling of ambient ionization methods of particular significance (Lawton et al., 2017; McCullough et al., 2020). Ambient ionization mass spectrometry is beneficial for on-site forensic analysis, as samples can be detected directly without pretreatment or extraction (Green et al., 2010). Several ambient methods have gained forensic interest, including desorption electrospray ionization (DESI) (Morelato et al., 2013), direct analysis in real-time (DART) (Lesiak & Shepard, 2014), and PSI (Domingos et al., 2017). Combining these ionization methods with portable mass spectrometers is of forensic importance to allow sensitive and reliable on-site detection of analytes of interest (Lawton et al., 2017).

The importance of sensitive techniques and their availability in field settings has increased with the rise of highly potent drugs such as synthetic opioids, which are found in trace quantities (Abonamah et al., 2019; Vandergrift et al., 2018). The development of portable mass spectrometry to detect and identify these substances has been investigated using various methods (Kang et al., 2020). A miniature MS method analyzed several matrices from beverages to surfaces such as plastic bags with limits of detection (LOD) as low as 10 ppb or 1 ng/cm^2, respectively, for fentanyl analogs (Kang et al., 2020). Portable DART-MS methods have been explored for traditional and designer drugs of abuse (Brown et al., 2016), including fentanyl analogs (Sisco et al., 2017). It has been shown to be successful in the separation and identification of drugs in mixtures (Brown et al., 2016; Sisco et al., 2017) which can assist in overdose treatment and general harm reduction services. Similarly, DESI-MS is also capable of detecting designer drugs in complex mixtures with the examination of synthetic cathinone analogs at trace levels from authentic forensic samples (Vircks & Mulligan, 2012). LOD values for these methods vary, often dependent on the substrate analyzed (Vircks & Mulligan, 2012). The miniaturization of MS instruments does have its disadvantages in comparison to benchtop laboratory instrumentation, including reduced mass accuracy, which can impact the rapid identification of compounds, even if a library is available (O'Leary et al., 2015). Despite this, the recent advancements of these methods show excellent potential for prominence in the on-site testing of illicit substances in forensic casework and harm reduction settings.

4.1 | Paper spray ionization mass spectrometry

PSI is an easy to use and well-established ambient ionization method that uses triangular paper as the substrate (Domingos et al., 2017). Analyte ions are generated through the application of a spray solvent and high voltage to the paper through a metal clip (de Paula et al., 2018; Silva et al., 2019). It is ideal for detecting small molecules such as illicit substances and shows good potential for use as a field-based forensic tool when coupled with portable MS techniques (Domingos et al., 2017). Its high sensitivity and reproducibility also make it a viable method for drug checking for harm reduction services (Borden et al., 2022). PSI can detect a wide variety of substances at low levels, from traditional illicit drugs to fentanyls, synthetic cannabinoids, and other NPS in field settings (Lawton et al., 2017; O'Leary et al., 2015). The simplicity of the method and the absence of sample preparation requirements make it a useful technique in the field (Lawton et al., 2017), and direct analysis of blotter papers has been reported (Carvalho et al., 2016; Domingos et al., 2017). A range of designer drugs were able to be detected, including LSD, NBOMes, and phenethylamines, DOC and DOB (Carvalho et al., 2016).

Combining swabbing techniques with PSI-MS has been used for drugs, explosives, and toxins in a variety of settings (Ma et al., 2015; Nguyen et al., 2021). This is important as forensically relevant surfaces could be swabbed, making the collection process non-destructive and straightforward. The use of a commercial paper strip containing a pressure-sensitive adhesive has been explored to swab surfaces such as clothing, glass and concrete before analysis is completed with a portable PSI-MS (Nguyen et al., 2021). Distribution environments could benefit considerably from this type of technology and the use in prisons, where drugs are often smuggled via absorption into paper letters, is apparent (Nguyen et al., 2021). Swabbing techniques have proven successful with trace amounts of illicit substances as described with the identification of synthetic cannabinoids from a benchtop where the LOD was estimated at 2 ng (Ma

et al., 2015). The integration of SERS technology with PSI-MS has been shown successful for on-site analysis for fentanyls (Fedick et al., 2020) and other illicit drugs (Burr et al., 2020). This combination of techniques displays great potential as a field-based approach incorporating two highly discriminating methods, which would replace the need to analyze samples in a laboratory while still maintaining required levels of analysis (Burr et al., 2020). The use of two techniques that can subsequently analyze the same substrate allows for more accurate and reliable results. The PSERS substrate can double as a collection swab and was demonstrated on various forensically relevant surfaces such as syringes (Fedick et al., 2020). The substrate can be enhanced and changed to suit these techniques as required to allow for better results. As these techniques can identify components of samples in different ways, this allows even more differentiation between analogs and even isomers, demonstrated through the separation of synthetic cannabinoid, JWH-018, isomers using these methods (Burr et al., 2020). Limitations are still common with these techniques, particularly with the ever-changing nature of NPS. While some fragmentation patterns in MS data and Raman shifts may be indicative of a compound class, it may still be necessary for library searches and matches to identify analogs of substances such as fentanyls. Samples that are complex mixtures or contain trace levels of the drug of interest may present further limitations to the analysis, including low sensitivity, ion suppression and narrow dynamic range, with these being the motivation for further optimization of paper substrates (Silva et al., 2019).

PSI-MS has been evaluated as a tool useful in harm reduction settings, with a particular focus on the opioid crisis (Vandergrift & Gill, 2019). The detection of trace amounts of highly potent fentanyl analogs and other synthetic opioids in drug samples would assist in reducing overdose and death from these substances. PSI-MS is sensitive and selective enough, with LODs for portable instruments reported in low nanogram range (Nguyen et al., 2021), making it an ideal candidate for the detection of small quantities of drugs of abuse. It also has the potential to quantify substances which enhances its use as a harm minimization tool to inform those who use drugs, pre-consumption (Borden et al., 2022).

5 | SENSORS

The identification and quantification of illicit drugs in seized material using sensing techniques is a growing area of interest and development due to the rapidity, sensitivity, and accuracy it affords as an analytical technique. In this context, a sensor is a device or instrument that can determine the presence, concentration, or quantity of an analyte. All sensors are comprised of the same basic components: a receptor, a transducer, an electronic system, and a display. The receptor is responsible for specifically recognizing the analyte of interest and therefore determines the selectivity and sensitivity of the device. Upon interaction between the receptor and target analyte a signal is generated in a process known as a recognition event. The most well-known examples of receptors are the bioreceptors such as enzymes, cells, aptamers, and antibodies that are used in biosensors, such as the enzyme-linked immunosorbent assay (ELISA) tests. Other receptors include molecularly imprinted polymers (MIP), modified nanoparticles, and modified electrodes. The second component of a sensor is the transducer, a material capable of converting one form of energy into another through a process known as signalization. The energy from the recognition event is converted to a measurable signal proportional to the number of analyte–receptor interactions. Photodiodes and various electrodes are used as transducers in optical and electrochemical sensors, respectively. The electronic system processes the transduced signal and prepares it for display to the end-user. Current and emerging trends in the use of sensing techniques for the analysis of illicit drugs has been evaluated in the literature (Ahmed et al., 2020; Dagar et al., 2022; De Rycke et al., 2020; Mao et al., 2020). Receptors and transduction events used in point-of-care optical or electrochemical sensors are shown in Table 2.

Numerous receptors have been employed in the optical detection of illicit drugs, from MIP functionalized quantum dots for the selective detection of methamphetamine (Masteri-Farahani et al., 2020) and cocaine (Chantada-Vázquez

TABLE 2 Receptors and transduction events that have been employed in the fabrication of (bio)sensors for illicit drug analysis

	Transduction event	
Receptor	**Optical**	**Electrochemical**
Antibodies	Photoluminescence	Voltammetry
Aptamers	Chemiluminescence	Amperometry
Molecularly imprinted polymers	Colorimetric	Potentiometry
Modified nanoparticles		Impedance spectroscopy
Modified electrodes		

et al., 2018), to a modified gold nanoparticle aptasensor for the rapid detection of amphetamine-type stimulants (Adegoke et al., 2020), and chromium metal–organic framework nanoparticles for the highly sensitive detection of morphine (Alhaddad & Sheta, 2020).

In recent years, electrochemical sensing has seen rapid developments and applications as a result of the numerous advantages afforded by the technique, such as high precision, high sensitivity, ease of use, and the capability for automation. Electrochemical sensors can be classified based on the type of electrochemical transducer employed. Voltammetry is the most widely used transduction event for the rapid quantitative sensing of illicit drugs with studies performed on NBOMes in blotter samples (Oiye et al., 2017), cocaine residue (Tavakkoli et al., 2019), and Δ^9-tetrahydrocannabinol in plant matter (Balbino et al., 2016). Highly sensitive amperometric detection of morphine has used a modified screen-printed electrode (Maccaferri et al., 2019), while the sensitive impedimetric detection of cocaine using molecularly imprinted polymer nanoparticle receptors showed no cross reactivity with morphine (D'Aurelio et al., 2020). A highly selective potentiometric sensor for amphetamine (Gallardo-Gonzalez et al., 2018) has also been developed. Sensing of illicit drugs using point-of-care devices is currently mostly limited to academic research, with limited translation into commercial devices. Advancements in technology and materials suggest that sensors could offer a relatively cheap, rapid, and sensitive alternative to other portable techniques in the near future.

6 | OTHER TECHNIQUES

The success of instrument miniaturization is evident with a range of different methods and instruments available for portable use. These instruments allow for fast and accurate detection of a variety of substances and mixtures, however are still expensive and not commonplace (de Araujo, 2019). Further advancement of such techniques and their commercialization would allow them to be commonly used as on-site forensic tools and reduce pressure on laboratories. Complementary methods to common vibrational spectroscopy and mass spectrometry are of recent interest for forensic applications and include ion mobility spectrometry, chromatography, electrophoresis, and X-ray diffraction (Jurásek et al., 2020; Patel & Lurie, 2021).

6.1 | Ion mobility spectrometry

Ion mobility spectrometry (IMS) is a highly sensitive analytical method that can identify analytes in a range of matrices without the need for complex sample preparation procedures (Metternich et al., 2019). It is currently used in prisons, airport security and customs as preliminary testing for illicit drugs and explosives (Armenta et al., 2015; Metternich et al., 2019). IMS utilizes the differences in drift velocity of ionic species through a gas under a weak electric field to separate analytes (Keller et al., 2006). Collection is commonly completed by swabbing a sample surface with a Teflon membrane, often with a sampling wand, and the membrane is placed onto the sample tray of the instrument (Armenta et al., 2015). Recently, other sample introduction techniques have been explored, including sonic spray for liquid samples (Pevzner et al., 2021). This method is ideal for field use as the apparatus is simple enough not to require an energy source. IMS has been shown to be a valuable tool in the detection of several classes of NPS, including cathinones (Armenta et al., 2015; Gwak & Almirall, 2015; Sysoev et al., 2014), cannabinoids (Armenta et al., 2015; Gwak & Almirall, 2015; Sysoev et al., 2014), tryptamines (Armenta et al., 2015), and phenethylamines (Armenta et al., 2015; Gwak & Almirall, 2015). It is advantageous in the identification of NPS in prison drug trafficking as IMS can detect substances such as synthetic cannabinoids in matrices that other instrumentation cannot (Metternich et al., 2019). This has been evaluated through a study of synthetic cannabinoids infused on papers seized from Scottish prisons (Norman et al., 2021). Two IMS instruments were utilized to detect a range of synthetic cannabinoids, including compounds which had not been previously detected in this setting. Due to the size and dynamic nature of NPS, it is recommended that confirmatory laboratory analysis is carried out and library databases are updated regularly to ensure identification of emerging drugs and drug threats (Norman et al., 2021). IMS is recommended for the analysis of synthetic cannabinoids due to its simplicity for sampling herbal mixtures and rapid detection in the field (Tettey et al., 2021).

There have been some reported issues regarding the portable IMS relating to its selectivity, especially between analogs with highly similar chemical structures. However, adjustments to the instrument and methods can allow for even drug mixtures to be detected at a high sensitivity (Chen et al., 2019) and this may not pose significant issues as IMS is most commonly used as a screening tool (Norman et al., 2021). Temperature and humidity can also affect the resulting

shift of analytes, and these are difficult to control in field settings, indicating a potential disadvantage for this technique (Verkouteren & Staymates, 2011). The combination of portable IMS and mass spectrometry has been reported for illicit drug and explosive detection (Du et al., 2018) to help overcome issues regarding separation ability and the high false positive and false negative rates seen with IMS.

6.2 | Portable separation techniques

Extensive reviews of the use of portable separation techniques for forensic applications (Patel & Lurie, 2021) and analysis of drugs of abuse (Fanali et al., 2022) have recently been presented and highlight the advantages of portable instrumentation for illicit drug identification.

Chromatography based methods are often advantageous due to the higher resolving power compared with techniques such as IMS and CE, although they are more difficult to make portable (Patel & Lurie, 2021). Coupling portable chromatography with miniaturized MS is commonly seen and can provide good resulting sensitivity (Patel & Lurie, 2021). Portable GC–MS has been used in drug checking to detect highly potent synthetic opioids (Gozdzialski et al., 2021), including the differentiation of fentanyl analogs which is not always possible with fentanyl test strips and other portable instrumentation, such as FTIR, in the field. Similar methodology has been used for illicit drug detection and the identification of adulterants in seized samples (Fiorentin et al., 2020). This study compared and evaluated the use of this portable method compared with conventional benchtop GC–MS instrumentation [36]. This is a common practice completed to ensure the applicability of portable counterparts (Fanali et al., 2022).

The use of capillary LC coupled with UV-absorbance detection has been assessed for a range of illicit drugs (Foster et al., 2020; May et al., 2020). The capability of this instrument, which contains an internal battery supply to be utilized remotely, has been shown for both seized drug identification and screening for illicit substances in clinical settings (Foster et al., 2020). The use of multiple detectors, emitting light at different wavelengths, may improve the identification of analytes as the ratio of the two absorptivity coefficients can provide a signature for the analyte more reliable than retention time alone.

Capillary electrophoresis (CE) is a rapid separation technique that uses electromigration of the analyte through a capillary under an electrical field (Nguyen et al., 2015). It can be applied to a wide variety of samples using small quantities of reagents, analytes, and energy, allowing easy miniaturization of many systems reagents (Moini, 2018; Patel & Lurie, 2021). CE can be coupled with detection sources such as MS and capacitively coupled contactless conductivity (C^4D), which will maintain the possibility for portability, ideal for the analysis of illicit drugs (Nguyen et al., 2015). Microchip electrophoresis methods are promising for the on-site analysis of illicit drugs, and their capability has been shown with the detection of seized synthetic cathinone samples (Lloyd et al., 2014). The portability of these methods may require further optimization, as derivatization steps may be necessary prior to analysis.

6.3 | X-ray diffraction

X-ray diffraction (XRD) uses X-ray radiation to cause incident beams from crystalline atoms to diffract, allowing the determination of the spatial structure of the molecules present in the sample (Harper et al., 2017). It is used in border control for both illicit drug and explosive screening, and the advancements in the portability of instruments are ongoing (Drakos, 2015). Recently, an investigation into the use of a portable energy-dispersive XRD to reduce the time to screen parcels has been of interest to ideally bring the parcel screening time at UK borders down from the current 30 min (Drakos et al., 2017). This method can determine the concentration of diamorphine in a range of parcels containing other materials such as sodium bicarbonate and textiles, which is advantageous for border control.

The ability of X-ray powder diffraction (XRPD) to identify NPS, including synthetic cathinones and synthetic cannabinoids, is apparent (Jurásek et al., 2019). It could be used as an ideal screening method due to its non-destructive nature, rapid analysis and simplicity, and the potential to be used in the field (Jurásek et al., 2019). XRPD can, in theory, identify any substance present in a sample, however, this would require the use of a database. Compared with IR and Raman spectroscopy, XRPD has some advantages to be used as a complementary technique (Jurásek et al., 2020). XRPD can avoid issues with fluorescence and complex mixtures that are faced by conventional vibrational spectroscopy. However, it should be noted that XRD can only analyze solid samples, meaning it will not be a suitable method for some illicit drug materials (Jurásek et al., 2020).

7 | CONCLUSION

The analysis of drug material is common practice in forensic drug laboratories, law enforcement agencies, forensic research laboratories, and drug checking services. Advancements in technology have witnessed a growing interest in bringing the performance of sophisticated benchtop instrumentation from the controlled environment of a laboratory to the field through portable techniques. Chemical color tests have been used for decades for the presumptive identification of drugs in the field owing to their simplicity and low cost per analysis. Colorimetric analysis, particularly using smartphones, has been shown to improve the objectivity of the test results while maintaining ease of use and portability. The use of colorimetric microfluidic devices allows for multiplexing and thus the ability to incorporate more than one chemical test into each device. Despite the advancements in the fabrication of chemical color test devices the selectivity of the chemical test is not enhanced, and these tests must still be used as a screening tool only. Portable ATR–FTIR and Raman spectrometers provide a rapid and non-destructive analysis of drug material, with minimal sample preparation required. The use of spectral library databases and chemometric tools allows for quantification in complex mixtures making these two spectroscopic techniques ideal for applications in the field. A particularly useful application of the SORS method in handheld Raman spectrometers allows for the analysis of drug material through packaging, while SERS methods provide increased sensitivity during field analysis. High discriminating power and sensitivity previously only attained in the laboratory can be achieved with the use of more complex portable ambient mass spectrometry techniques that can detect samples directly. PSI-MS can detect drug analytes at low levels in the field and can be combined with swabbing sample collection techniques using commercial paper strips to produce a test method highly suitable for use in the field. Another technology that is widely employed in the field for drug and explosives analysis in complex matrices is IMS. The straightforward sample collection process and instrument ease of use make this instrument highly valuable in the field. The analyte separation power of chromatography and capillary electrophoresis can be used in the field through available portable instrumentation. Coupling these separation techniques with previously discussed portable mass spectrometers affords a higher level of discriminating power for drug analysis in the field. The non-destructive nature of XRD has seen its use by customs and border control for rapid screening of packages suspected of containing drug material. Research into the growing area of sensing technologies for the detection of drug analytes in seized material has demonstrated the potential for rapid, sensitive, and selective detection of drug analytes using optical and electrochemical (bio)sensors. However, apart from immunoassays, these techniques have not yet been developed into commercial devices for use in the field.

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CONFLICT OF INTEREST

The author has declared no conflicts of interest for this article.

AUTHOR CONTRIBUTIONS

Morgan Alonzo: Conceptualization (equal); visualization (lead); writing – original draft (equal); writing – review and editing (equal). **Rhiannon Alder:** Writing – original draft (equal); writing – review and editing (equal). **Laura Clancy:** Writing – original draft (equal); writing – review and editing (equal). **Shanlin Fu:** Conceptualization (equal); writing – review and editing (equal).

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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