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The Application of Nanosensors in Illicit Drugs Determination: A Review

Lawal Shuaibu[1*], AbduRahman Abdul Audu[1] and Kingsley John Igenepo[2]

[1]Department of Pure and Industrial Chemistry, Faculty of Physical Sciences, Bayero University Kano, PMB 3011, Kano, Nigeria.
[2]State Key Laboratory of Catalysis and Division of Solar Energy, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian, 116023, China.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

The utilization of nanomaterials (NMs) to produce nanosensors for detecting drugs in a wide range of materials has attracted global attention. Various categories of NMs have been synthesized and applied for the qualitative determination of some additives, contaminants, and illicit materials owing to their unique physicochemical properties at the nanoscale to impact desired effects. Rapid and facile detection techniques employed for on-site analysis of illicit drugs using NMs are reviewed. It is noted that NMs are good candidates in the fabrication of nanosensors for the sensitive detections and determinations of illicit drugs. Thus, this review is focused on the application of these sensors for illicit drug detection. Hence, the application of plasmonic/optical properties of NMs to enhance illicit drug detection in biological samples has been discussed. The fabricated sensors have been shown to possess enhanced selectivity, sensitivity, cost-effectiveness as well as improved automation. As highlighted in the in-depth review, the sensors are designed to utilize biological receptors with a transducer component to detect the analyte-biorecognition element interaction which resulted in producing an optimum signal.

**Corresponding author: E-mail: lawal.shuaibu@fubk.edu.ng;*

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1. INTRODUCTION

Nanotechnology is concerned with the design, fabrication, as well as applications of nanostructured materials (NSMs) with a typical size smaller than 100 nm. It is an integrated discipline that requires natural sciences, engineering, and medicine. Examples of nanotechnology include biomineralization, photosynthesis, strength and toughness of spider silk, adhesion mechanism in Gecko feet, peacock feather, and excellent antireflection property in moth-eye, etc [1]. Nano is a Greek name for dwarf or an unusually short person. It refers to one part of a billion units and is normally used as a prefix. As such, 1 nm is a unit part of 10^{-9} m. Broadly speaking, NMs are constituents with grain or particle sizes in the range of 1-100 nm in at least one dimension [2]. The length of 10 hydrogen or 5 silicon atoms arranged in a line is roughly 1 nm. NMs are often characterized by a dimension linked either to the dimension of the salient nanofeatures making up the materials or to their organization [3]. An idea about how much large nanomaterial (NM) is compared to their bulk counterparts can be visualized as a particle with a diameter of a little >10 µm = 10^{-5} m, which itself is extremely small to be observed by bare eyes, and compare with a particle with a diameter of 1 nm = 10^{-9} m. The ratio of the diameters of these two objects is 10^4. In other words, a nanoparticle (NP) with a size of 1 nm is smaller by 10^4 times that of an object of 10 µm in size. Also, this single micrometer-sized particle is equivalent to 10^{12} NPs by mass. This simple comparison makes it clear that NPs are really very small and also expose a huge portion of atoms on their surfaces, that is, > 90% depending upon the size, whereas bulk has an insignificant amount of surface atoms (i.e., < 1%) [1]. NMs display multifunctional characteristics that are distinctively dissimilar to bulk materials. For instance, the NM crystal has minimized lattice constants, different crystal structures, the shift of Curie temperatures, changed electrical conductivity of metals or oxides, increased oxidation and wear resistance, and higher sensitivity of sensors compared to their bulk counterparts [4]. Metals become insulators and semiconductors when the characteristic size of NPs is a few nanometers. Interestingly, Au, Pd, and PtNPs with a size below ~5 nm exhibit excellent catalytic properties at low temperatures. The decrease in Au particle size shows a blue shift (i.e., a decrease in peak absorption to a shorter wavelength). Similarly, when the size of semiconductors is reduced below their Bohr radius, a dramatic change in optical properties is encountered, for example, color changes [3].

2. NANOMATERIALS

NMs can be defined as crystalline/amorphous materials (organic or inorganic) ranging in size from 1-100 nm that differ in size from their bulk counterparts. They've been used in a variety of fields due to their peculiar optical, magnetic, catalytic, and electrical properties [5]. Since most of their constituent atoms are located at or near their surface, these materials have all important physicochemical properties that are vastly different from the same materials at the bulk scale [6].

3. TAXONOMY OF NANOMATERIALS

The taxonomy of an NM is based on its uniformity, morphology, composition, agglomeration, and dimension [7]. NMs are divided into four categories based on their dimensionality: 0-D, 1-D, 2-D, and 3-D (Fig. 1).

3. 1 0-Dimensional Nanomaterials

NMs in this category have all three dimensions within the nanometer range. They are known as artificial atoms due to their discrete energy levels [9]. Examples of these NMs are metal NPs (cobalt nanoparticles (CoNPs), nickel nanoparticles (NiNPs), copper nanoparticles (CuNPs), etc); quantum dots (QDTs), fullerenes, etc [10]. These NMs possess different shapes such as spherical, cubical, or polygonal with sizes in the range of 1-50 nm. The commonest example is fullerene (C60) which is the smallest and has the most stable structure due to the high degree of its symmetry. It consists of 60 C atoms and looks like a soccer ball. It is called a soccer ball molecule and consists of twelve pentagons and twenty hexagons whose vertexes contain C atoms. Molecules of fullerene freely rotate due to their weak intermolecular interaction. The molecules are stable, nevertheless, like in graphene (Gr); each C is surrounded by three other neighbors. There are also free valences for functionalization (i.e. surface modification) and possible attachment of metal atoms or other molecules. Owing to the 0-D structure, fullerene has the lowest surface energy. Moreover, other fullerenes are C70, C76, C78, and C84 [9].

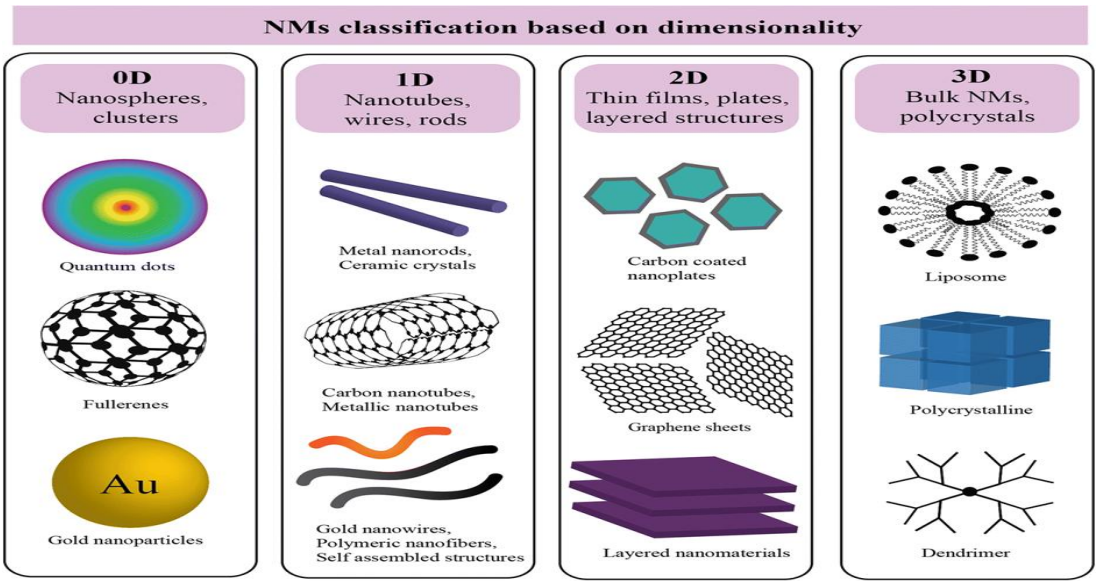

Fig. 1. Diagram illustrating various classes of NMs based on dimensionality; Reproduced with permission from [8], © 2018 Poh et al.; licensee springer nature

3.2 1-Dimensional Nanomaterials

NMs in this category have one dimension outside the nm range and two dimensions that are within the nm range. These NMs have a thickness and width of several nm (< 100 nm) and a length of a few µm [9]. Examples include metal nanorods, carbon nanotubes (CNTs), carbon nanofibers (CNFs), Au nanowires, etc [10]. The surface-area-to-volume ratio of these materials is high, useful in nanocomposite formations. A typical example is an imogolite, a naturally occurring 1-D nanosilicate with its tubes having an inside diameter of ~ 1 nm and outside diameters of ~ 2 nm. Thus, the two diameters can be adjusted by using different Si/Al ratios. The tubes are few µm in length as either natural or synthesized imogolite tubes form bundles with a diameter ranging from 5 to 30 nm. Moreover, imogolite contains Al, Si, O, and OH^- ions arranged in rings. The functionalization of other atoms/molecules by imogolite is due to the presence of OH^- ions on its surface [9].

3.3 2-Dimensional Nanomaterials

NMs in this category have two dimensions outside the nm range and one dimension in the nm scale, i.e. thickness [9]. Examples of these nanomaterials include nanoclays, nanofilms, Gr sheets, etc [10]. For instance, the thickness of nanofilms is in the range of 1-100 nm whereas the area consisting of length and width is of the order of several square cm. Montmorillonite (MMT), a nanoclay is another example that consists of octahedral alumina sheets arranged between two tetrahedral silicate sheets with ~1 nm in thickness, and the other two dimensions (length and width) are of the order of 150 nm to 2 µm [11].

3.4 3-Dimensional Nanomaterials

NMs in this category have all three dimensions outside the nm range and are regarded as equiaxed NPs [11]. 3-D NMs have nanocrystalline features at the nanoscale with multiple arrangements of nanosized crystals in a different orientation. They may contain the dispersion of NPs, nanotubes (NTs), nanowires, etc in their matrix. Hence, 3-D NMs are made up of two or more materials with very different properties that work together to produce special properties that are impossible to achieve with a single material [12]. Examples are several natural NSMs which include viruses, DNA, proteins, liposomes, and dendrimers, etc while microstructures are cells, organelles, and larger physiological structures. The human erythrocyte is ~7 µm, hair is 60 µm, and pollen is 100 µm, while lung alveoli are ~400 µm wide [12].

NMs are also classified into high-aspect-ratio and low-aspect-ratio based on morphological structures. Higher aspect ratio nanomaterials (HARN) are NMs that have lengths several times compared to their width. Examples of HARN consist of zigzagged, belted, and spiral-shaped

NTs and nanowires. Whereas lower aspect ratio nanomaterials (LARN) are NMs with relatively little length compared to their width. Examples of LARN include spherical-, helical-, pillar-, cubical- and oval-shaped NTs and nanowires. These materials occur in the form of colloids, suspensions, or powders. Furthermore, they are found as single constituent material or composite of ceramics, polymers, metals, or alloys. NMs are usually synthesized through several synthetic techniques including coprecipitation, chemical vapor deposition (CVD), chemical reduction, etc [12].

4. MAJOR APPROACHES FOR METALLIC NANOPARTICLES SYNTHESIS

There are several techniques for metal NPs synthesis, categorized into twofold: top-down and bottom-up approaches. Furthermore, these approaches are divided into different subclasses based on the process, response state, and procedures embraced. Two specific methodologies are considered to generate NPs with regulated sizes and suitable features for different uses [13].

4.1 Top-Down Approaches

Using cutting, grinding, and scratching techniques, the bulk material is broken down to nanosized dimensions in the top-down (physical) approach, i.e. NMs are made from larger/bulk material without atomic-level control. Therefore, through the mechanical disintegration of the broad metal structure, a metal bit is applied for the development of NPs by a physical process; known to be an economical, energy-intensive, and long-lasting method. Its major disadvantage is that it does not control the particle size of NPs [14]. As a result, the top-down method begins with the bulk complement, which gradually leaks out, resulting in the formation of very small NPs. For the gross synthesis of NPs, many physical approaches for instance laser ablation; thermal decomposition, lithography, etc are utilized [15].

4.2 Bottom-Up Approaches

In the bottom-up (chemical and biological) approach, the build-up of NPs is produced by atoms, molecules, or clusters. To create a wide variety of NPs, this technique involves the aggregation of atoms or molecules. It does provide full control of particle size [14]. Examples of this approach include sol-gel handling, CVD, green synthesis, chemical reduction, etc [16].

5. NANOPARTICLES SYNTHESIS METHODS

In general, NPs synthesis methods may be classified into three groups-(1) chemical, (2) physical, and (3) biological [7] (as depicted in Fig. 2).

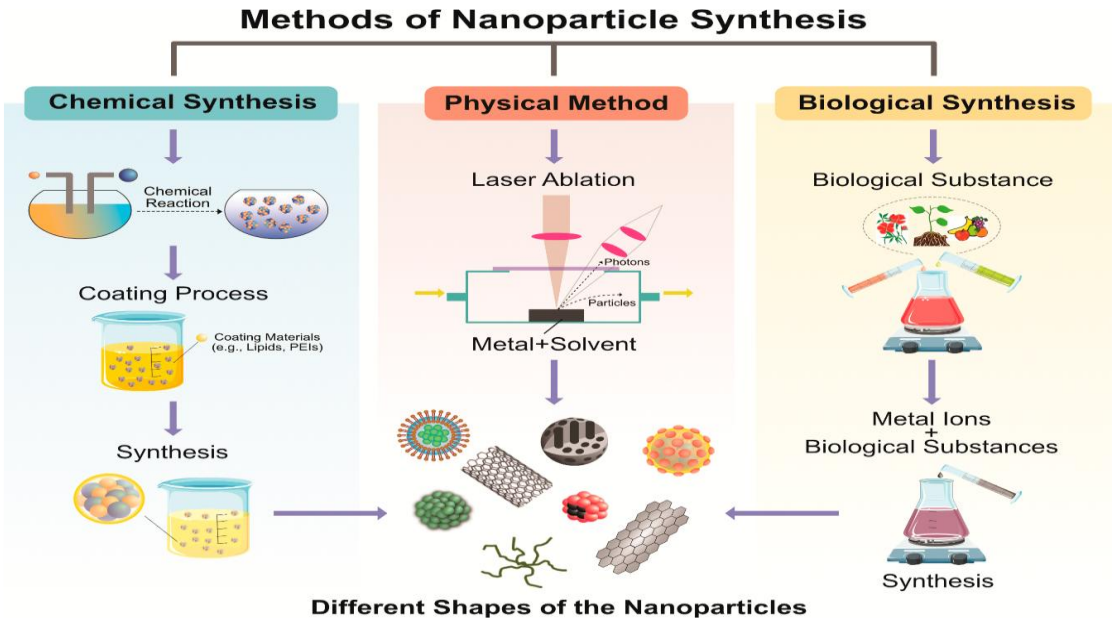

Fig. 2. Conventional methods of synthesis of NPs. Reproduced with permission from [7], © 2019 Muniyandi et al.; licensee MDPI

5.1 Chemical Synthesis of Nanoparticles

Chemical synthesis of NPs is a technique that makes use of simpler substances (e.g. atoms or smaller molecules) that are subjected to chemical reduction of the substances using an appropriate chemical reducing agent to form the NPs [17]. A typical example is the chemical synthesis of AgNPs.

This approach primarily includes the use of water-soluble positively-charged ions as precursors via a process called nucleation to cause their reduction to metal monomers. Examples of these methods comprise CVD, hydrothermal, pyrolysis, etc. The most common method for preparing metal NPs is the chemical reduction of metal ions inside reversed micelles in a nonpolar solvent. Here, chemical reduction confines a metal salt dissolved in water in reversed micelles and reduces it to metal NPs. The commonly employed reducing agents include sodium borohydride ($NaBH_4$), hydrazine hydrate ($N_2H_4.H_2O$), potassium bitartrate ($KC_4H_5O_6$), etc. The shapes and sizes of metal NPs can be manipulated by altering the reaction conditions (such as medium pH, the temperature of transformation, concentration of reducing agent, etc) [18].

5.2 Physical Synthesis of Nanoparticles

Physical synthesis of NPs is a technique that employs the use of bulk materials which are broken down into smaller units through milling or grinding or other decomposition protocols [17]. Physical synthesis of NPs follows a top-down approach and to effect particle wearing, vaporization, dissolution, or liquefaction to generate NPs, the utilization of mechanical pressure and various forms of energy are involved. The merits of the physical method include the use of nontoxic chemicals, production of highly pure materials with uniform size and shape. The demerits of this method include less productivity resulting in a high cost of production, exposure to dangerous radiation sources as well as production at high temperature and pressure resulting in a less stable compound formation at a high cost [15].

5.3 Biological Synthesis of Nanoparticles

Biological synthesis of NPs is a technique that makes use of biological materials such as microbes (e.g. bacteria, fungi, etc) or plant materials (e.g. leaves extract, bark extract, etc) containing phytochemicals used to reduce metal cations to form NPs [17]. Biological synthesis or biomolecule-assisted synthesis follows a bottom-up approach and is commonly used for the production of metal NPs for biomedical applications [7]. Examples of biomedical applications of synthesized NPs by this method include antibacterial, antifungal, antiviral, anticancer, antidiabetic, wound healing, diagnosis and imaging activity, medicinal textile and device activity, etc [18]. For instance, the production of PtNPs via this method is less effective than the chemical preparation of AgNPs, and AuNPs. However, some plants are used to synthesize PtNPs [7]. In addition, numerous studies have documented metal NPs synthesis using different microorganisms, such as bacteria, fungi, algae, yeast, etc [19]. The merits of the biological method include the production of NPs that are soluble, chemical-free, sustainable, biocompatible, cost-effective as well as environmentally friendly. This approach has some demerits such as the incapability to regulate morphology, dimensions, solidity, and accumulation of crystal, as well as a possible bacterial toxin, and time-consuming purification protocols [7].

6. PROPERTIES OF NANOMATERIALS

NMs have distinct properties due to variations in size and form caused by the materials' surface-area-to-volume ratio [20]. NMs show other phenomena including the duality of mass, the uncertainty of matter, discreteness of energy, etc. Moreover, Vander Waals forces operating among NMs are stronger compared to gravitational forces, making the materials very sticky. The properties of NMs change as a result of their size constraints. At the nanoscale, the combined electrical and magnetic force of positively charged particles is 10^{36} higher compared to gravity making the NMs decrease in size; and as the size decreases drastically, some properties become insignificant. As a result, NMs have unique physicochemical properties as highlighted below:

6.1 Electrical

Electrons are constricted at the surface of the NMs making the materials become semiconductors with small bandgap and band-edge [20] and have various applications in photocatalysis, photooptics, and electronic devices [21]. Because of their ideal bandgap and band-edge positions, semiconductor NMs can be

used in water splitting applications, inducing photoexcitation in aqueous media and H_2 evolution [22].

6.2 Optical

The interaction of NMs with light is dependent on the size of the material. This is because of the confinement of electrons at the surface that makes them respond to light uniquely. The optical properties of NMs are a result of the collective excitation of electrons at the surface in response to the light energy-this phenomenon is commonly known as surface plasmon resonance (SPR). The SPR of NMs is readily tunable with the NM size, shape, surface chemistry, and surrounding media (refractive index)-making them ideal for sensor applications. For instance, Au at the macroscale appears golden, while at the nanoscale it is reddish. Similarly, QDTs depict changes in color as their particle sizes decrease [20].

6.3 Surface-Related

Since the surface area influences the melting point, boiling point, rate of reaction, capillary behavior, and adhesion, NMs with a high surface-area-to-volume ratio exhibit dramatic differences in properties from their bulk counterparts. Au has a melting point of 1064 ℃ at the macroscale, but when the particle size is reduced from 100 to 10 nm, the melting temperature drops to 100 ℃. The melting point drops to about 50 ℃ as the particle size decreases to around 2 nm [20].

6.4 Mechanical

The mechanical properties of NMs depend on the unique parameters such as particle size, the configuration of atoms, extend of friction, etc. These parameters make NMs have special mechanical properties compared to their bulk counterparts. Nanomanufacturing and nanofabrication are improved with NMs application in material functionalization [23].

6.5 Magnetic

The magnetic properties of NMs are spin-dependent interactions. Magnetic NMs improve the capacity of storage media devices. These materials also influence the magnetic resonance imaging (MRI) of objects. For example, Fe-based metallic NPs are being utilized in cancerous cells MRI. The NPs are covered with a peptide, which is selectively bound to the tumors to improve the MRI of materials. The magnetic field directs the NPs towards the stents. This enables precise drug delivery to stents implanted in arteries [23]. Magnetic NMs can also be used in capacitors to store energy [24].

7. CHARACTERIZATION TECHNIQUES OF NANOMATERIALS

UV-Visible spectroscopy (UV-Vis), X-ray diffraction (XRD), energy-dispersive spectroscopy (EDS), Fourier transform infrared (FTIR); scanning electron microscopy (SEM), transmission electron microscopy (TEM), and other spectroscopic techniques are used to classify NMs in general. The working principles of each method, as well as their advantages in detecting NMs, are outlined below.

7.1 UV-Visible Spectroscopy

UV-Vis is used to validate the structure and strength of metal NPs/colloidal particles. The optical density of the absorption band of the analytes in the sample at a wavelength ranging from 200 to 800 nm is used in this technique. Upon exposure of metal NPs to light, the electric component of the electromagnetic wave of light causes excitation and oscillation of electrons making the electric field of the light displace the electron clouds at the surface of the NM. This phenomenon is known as SPR [25]. It is often used to determine the size of the particles for the qualitative and quantifiable determination of colloidal constituent parts where absorption spectra are used. The NPs materials are investigated using UV light absorption (200-400 nm) or Vis light absorption (400-800 nm) by an atom/molecule that results in its excitations [26].

7.2 X-Ray Diffraction

XRD is the nanocharacterization technique that measures the purity, shape, and crystalline nature of NMs. It is non-destructive, simple, sensitive, and user-friendly. Chemical compositions of metallic NMs are investigated to determine the extent of crystallinity and to reveal the atomic configuration of the NMs. Hence, the determination of the crystal structure of NMS will give detailed information regarding the position and atomic configuration, and strength of diffraction patterns of the materials. To assess the crystal structure and confirm the existence of metal NPs, this is done using the x-ray wavelength of Cu Kα (λ=1.5418Å). For example,

a beam of x-rays is normally scattered by each atom in the sample. The peaks produced reflect the nanocrystal's structural and physicochemical properties. The XRD theory opposes the law of Bragg. Diffraction patterns of NP crystals, however, are matched in the Joint Committee on Powder Diffraction Norm with the reference database (JCPDS). Thus, crystallographic analyses of formed NPs are carried out by recording their XRD profile [27].

7.3 Fourier Transform Infrared Spectroscopy

FTIR is another robust as well as sensitive nanocharacterization procedure. It is used to determine the surface chemistry, functional groups stretching frequencies, and atomic arrangement of the NMs [28]. It is also used in the analysis of biomolecules used as capping and reducing agents in nanofabrication to reveal whether they are involved in synthesis or not [29,30]. This measurement is attributed to the positions of vibrational frequencies of molecular bonds [31].

7.4 Scanning Electron Microscopy

SEM is another nanocharacterization technique that involves the use of a powerful electron microscope. It is an imaging technique that measures the surface and dimensions (i.e. length, width, and thickness) of nano and microstructures. It provides reliable data and an essential means for the elucidation of structure. It has many applications in various fields including biological and biomedical, material science, etc. It is used to characterize 3-D images of cells, organs, and tissue surfaces. SEM operates by generating magnetic electrons. The produced electrons interact with the sample, resulting in secondary and backscattered electrons that are used in the detection process. NMs structures are studied using transmitted electrons. It is non-destructive because the x-rays generated by electron interactions with the sample's electron cloud do not cause the sample's volume to be lost. It is possible to look at the same substance several times. Furthermore, SEM-EDS are commonly used to assess the percent and elemental composition of NPs in a sample [32].

7.5 Transmission Electron Microscopy

TEM is an essential nanocharacterization technique used in the determination of the size, shape, and morphology of NMs. The merits of the technique include the identification and determination of the relative amounts of NPs in cells and tissues [33]. The demerits of the technique include the inability to characterize samples with thickness > 300 nm, in which limited areas are screened. For a sample with particle dimension > 100 nm, small magnification is realized and TEM is unable to screen NPs with size < 10 nm. In conventional TEM techniques, any portion of the sample can be analyzed. Furthermore, it is a time-consuming process with tedious sample preparation protocols and destructive [7].

8. APPLICATIONS OF NANOMATERIALS

Due to their unique physicochemical properties, NMs have wider applications in the biomedical field [34]. The optical properties of NPs are utilized in making various products and sensors. For instance, AgNPs are very efficient in absorbing and scattering light compared to many dyes and pigments, exhibiting various colors that depend on the size and shape of the particles. They are widely used in appliances such as washing machines, refrigerators, and as antibiotic agents in medical devices, wound dressings, and textiles [35]. Because of their peculiar properties, NMs are widely used in bioimaging, enzyme immobilization, pollutant removal, drug delivery, and sensing, etc [36]. Hence, NMs have potential applications in various fields.

8.1 Catalysis

NMs have pioneer applications in catalysis as many elements and materials including Al, Fe, TiO_2, clays, and SiO_2 in nanoscale have been used for many years. Recently, nanocatalysis has become a known field in science as a result of its high activity, productivity, and selectivity. Metal NPs, for example, with sizes varying from 1 to 10 nm, exhibit superior catalytic activity over their metal complex counterparts. The high surface-area-to-volume ratio, surface geometric effect, electronic effect, and quantum size effect are all factors that contribute to the high reactivity of metal NPs, on the other hand, are used as heterogeneous catalysts because of their ease of product separation, recovery, and recyclability, making them environmentally friendly. The size of the nanocatalyst usually influences the catalytic performance of the particles. This effect reduces the temperature of transformation, reagent waste, and enhanced selectivity of the reaction to avoid unwanted side reactions [37].

With the utilization of nanocatalysis in various manufacturing protocols, a variety of products including fine chemicals, polymers, lubricants, paints, fuels, fibers, medicines, and other essential products are widely available. Hence, the use of nanocatalysts improves manufacturing processes making production more economical, green, and sustainable. CNT catalysts are used to make synthetic NH_3 and CH_4 from partial oxidation of fuel cells, which are widely used in photocatalytic reactions [38].

8.2 Water Treatment

NMs are widely used in water and wastewater treatment. They have strong adsorption capacities and high reactivity which are attributed to their small sizes and large specific surface areas. These unique properties make them have the capacity to remove heavy metals [39], inorganic anions [24], organic pollutants [40], and bacteria [41] in contaminated media as reported in the literature [42]. Photocatalytic degradation of TiO_2 has recently been used to successfully remove toxins from water and wastewater [43]. Because of its chemical stability, high photoactivity, commercial availability, and lack of toxicity, TiO_2 has been a promising research material [44]. In the presence of light, contaminants are readily oxidized into low molecular weight intermediate products, which are gradually converted into CO_2, H_2O, and anions such as Cl^-, NO_3^-, and PO_4^{3-}, resulting in photocatalytic degradation of TiO_2NPs [34].

8.3 Energy Storage

Pt-based NMs have potential applications in energy-related and environmental catalysis as they possess excellent electronic structure and catalytic activities that are utilized in petroleum refining, H_2 production, organic synthesis, automobile exhaust gas treatment, and fuel cell. Their huge surface areas expose active sites of contact, making PtNPs have potential use in energy-related applications [45]. Also, Li-based NMs have important energy-related applications as CNT films have recently been used to prevent dendrite growth on Li metal anodes. This aids the development of Li metal batteries that charge faster and have a higher capacity than Li-ion batteries. Due to their faster charging and holding ten times more energy than Li-ion electrodes, Li nanocomposites are incorporated into electronic devices, including cellphones and electric cars. This is achieved by coating a Li metal foil with multiwalled carbon nanotube (MWCNT) film on the Gr sheet with a high surface area and low electrical resistance [34].

8.4 Nanomedicine

Nanosilver has wide applications in customer merchandise stretching from water treatment, sterilizing home appliances and medical tools, and potential applications in nanomedicine [34]. Also, AuNPs are widely applied in nanomedicine as a result of their size-dependent unique properties, in gene therapy, photothermal therapy, photodynamic therapy, drug delivery, and biosensing, etc. They are non-cytotoxic with huge surface area, making their surfaces readily accessible to target molecules than any other NPs for several biomedical applications [46]. However, magnetite (Fe_3O_4)NPs are used in making ferrofluids, which are utilized in targeted drug delivery. Since the drugs are delivered directly to the infected cells or tissues by NMs, targeted drug delivery is very successful. This also decreases medication side effects, which is beneficial in cancer treatment since the medications are administered to the infected cells without killing healthy cells [47]. MRI also makes extensive use of ferrofluids [48]. Furthermore, in targeted drug delivery, ZnONPs [49], Fe_3O_4NPs [50], and QDTs [51] have been widely used [52].

8.5 Sensors

Nanotechnology has facilitated the use of NMs in the design of sensing devices that are used in medical diagnostics, food safety, and environmental pollution control. Various NMs, for example, have been synthesized to determine the presence of such chemicals and contaminants such as ascorbic acid (AA), bisphenol A (BPA), caffeine, sulfite (SO_3^-), nitrite (NO_2^-), etc which are commonly found in food and beverages [53]. It has also influenced the miniaturization of sensor devices and the fabrication of biosensors. Consequently, nanostructures and fluorescent NMs have been utilized to produce nanostructured biosensors for glucose sensing. A blood glucose meter has been fabricated for sensing glucose among diabetic patients [54]. Various biosensors have also been fabricated for monitoring pathogens, for example, *Escherichia coli* [55], detection of pollutants [56] as well as detection of illicit drugs/drugs of abuse, etc [57].

9. APPLICATION OF NANOTECHNOLOGY FOR ILLICIT DRUGS DETECTION

Illicit drugs are substances that either stimulate or interfere with the actions of the central nervous system (CNS) that can result in situations like hallucination, sedation, depression, etc to which their use has been prohibited globally [58]. They are sometimes also called “street drugs”. Some examples of illicit drugs include heroin, cocaine, marijuana, lysergic acid diethylamide (LSD), mescaline, phencyclidine (PCP), amphetamine (AMP), methylamphetamine (MAMP), psilocybin, and gamma-hydroxybutyrate (GHB), etc. These medications typically upset the CNS directly by altering the brain chemistry that can lead to coma, sedation, and hallucination, or a blend of these effects. They also affect the body's functions directly or incidentally and induce addiction. Permanent and damaging are the modifications to the brain caused by illegal medications. Ultimately, their addiction surpasses everything about the life of the user and becomes almost difficult to break without medical and skilled assistance [59].

The use of any banned drugs, as proscribed by the World Anti-Doping Agency (WADA), to improve athletic ability, preparation, and success, is referred to as "doping" [60]. Doping tests are usually conducted to qualitatively analyze and determine the presence of illicit materials taken by athletes [61]. Narcotics such as morphine, codeine, and tramadol, etc induce perceptible pain relief when taken by athletes and make them endure throughout the competition. Thus, narcotics and other types of illicit materials are among the four most popular banned doping products [62]. Stimulants, such as cocaine, AMPs, modafinil, and ephedrine, affect the CNS and increase the feeling of excitement while decreasing fatigue [63]. Furthermore, illicit drugs that enhanced protein synthesis in human body tissues are anabolic steroids, e.g., nandrolone, testosterone, etc [64]. Inhibiting the release of neurotransmitters, opioids such as codeine, tramadol, etc influence the actions of μ- and κ-opioid receptors to reduce pain [65]. Peptide hormones such as human growth hormone (GH), erythropoietin (EPO), insulin-like growth factors (IGF-1, etc) serve as anabolic substances that boost efficiency [66,67]. Such illicit drugs pose major global health problems, such as harm to athletes' health, and ethical problems, such as undermining the spirit of fair play at the bottom of athletic competition [57,68]. In this respect, chemical tests are needed to identify/quantify as well as classify many illicit materials being used by athletes during sporting competitions. To this end, it is a pressing concern to establish and enhance analytical identification techniques in this field. However, nanosensors developed with the integration of MNPs on transduction components of the sensors for real-time monitoring of illicit materials and doping agents, possess excellent analytical transduction signals. They are considered outstanding detection analytical tools over conventional anti-doping detection techniques such as chromatography-based approaches. Soon, the nanosensors may be commercialized and available at every international sporting competition for routine anti-doping tests [61].

NMs have been utilized in illicit drug sensing due to their unique physicochemical characteristics. Table 1 summarizes the applications of NSMs for the detection of some illicit drugs in some biological samples from past studies.

There are various advantages in the application of nanotechnology that include selectivity, sensitivity, cost-effectiveness, and automation [74]. It has been used in sensing chemical compounds, banned substances, and illicit drugs [75]. The use of nanotechnology in the

Table 1. Summary of some past studies that utilized NSMs in illicit drugs detection

NSM	Technique	Illicit drug	Real sample	LOD	REF
Citrate-stabilized AuNPs	COL	COD	Postmortem blood	0.9 μM	[69]
AuNPs	DPV	MOR	Human urine	1.33 nM	[70]
GPE	DPV	TRA	Human urine	3.8 nM	[71]
AuNPs/CNTs	DPV	TRA	Human urine	68 nM	[72]
AgNPs	SERS/MCF	MAMP	Human saliva	-	[73]

Key: NSM= Nanostructured material; AuNPs= Gold nanoparticles; CNTs= Carbon nanotubes; GPE= Graphite pencil electrode; AgNPs= Silver nanoparticles; COL= Colorimetric; DPV= Differential pulse voltammetry; SERS= Surface enhanced Raman scattering; MCF= Microfluidics; COD= Codeine; MOR= Morphine; TRA= Tramadol; MAMP= Methylamphetamine; LOD= Limit of detection; REF= References

fabrication of nanosensors for the quantification of analytes including illicit drugs provides a powerful analytical tool over conventional techniques. The limitations of traditional techniques, such as sensitivity, speed, and selectivity, have been overcome by these sensors based on this technology. Biosensors combine biomolecular recognition units with transducer quantification. Here, the biomolecular recognition unit senses a biochemical reaction and the transducer converts the concentration of the measuring analyte into a signal [76].

10. NANOSENSORS

10.1 Plasmonic Biosensors

Plasmonic biosensors are analytical detectors that employ specific biochemical reactions mediated by isolated enzyme-, aptamer-, antibody-, nucleic acid-bound NMs, etc to detect chemical compounds through instantaneous color change. A clear example is an aptamer-bound AuNPs sensing platform that has been fabricated as an imaging and recognition probe for cocaine detection and incorporated in the charge-coupled device (CCD), which is an electronic light sensor designed like a digital camera. This utilizes the SPR of AuNPs binded to latent fingerprints (LFPs) to sense the drug at the scene of the crime. The change in the plasmonic property of AuNPs caused the aptamer to detect the cocaine, producing a colorful image of LFPs [77]. Plasmonic biosensors are however utilized in doping tests to detect illegal materials consumed by athletes. These sensors are fabricated using biological recognition elements coupled with metal NPs for sensing illicit drugs. Narcotics are among the most widely used drugs among athletes for enhancing their athletic performances in sports competitions. These drugs have negative implications in committing other crimes. The most commonly abused stimulant drug by athletes is methylamphetamine (MAMP) that stimulates the CNS of the individuals and makes them feel good and energetic. Hence, its determination in checking doping by athletes. Generally, a urine sample is widely used to carry out immunoassays to qualitatively determine the presence of amphetamines (AMPs), and this determination is confirmed by GC-MS when a positive result has been indicated. Though, this technique is unsuitable for routine control [78]. However, nanotechnology has facilitated the use of new sensing platforms for rapid, routine, and on-site detection of illicit materials [78,79].

10.2 Immunosensors

Immunosensors are analytical sensing devices that use antibodies as biological recognition element and a transducer that convert the antigen-antibody complex formation phenomenon to a measurable signal. Transducers-based approaches are applied which generate a signal as a result of the formation of an antigen-antibody complex. However, illicit drugs are detected using different categories of fabricated immunosensors as highlighted below [80]:

10.2.1 Optical immunosensors

Optical immunosensors are designed to detect changes in optical signal on the transducer's surface as a result of the chemical interaction between antigen and antibody. There are two modes of measurement- direct and indirect; both depend on the optical change on the transducer. The formation of an immunocomplex generates the direct optical measurement signal. While the indirect one is due to the formation of a fluorescence-based immunocomplex that produces a better signal [81]. For instance, Gandhi et al., [66] fabricated an indirect optical fluorescence immunosensor for monitoring opiates in particular heroin and its major metabolites, morphine and monoacetylmorphine (MAM) in biological samples. To generate antibodies against the target heroin and its metabolites, an acidic derivative of MAM was synthesized and conjugated with bovine serum albumin (BSA) (as depicted in Fig. 3).

The antibody produced had a high affinity for the drug and its major metabolites. The sensor recorded excellent sensitivity in the picrogram range. Also, enzyme and fluorescence-based techniques were applied to develop a colloidal Au-based rapid immunochromatographic dipstick kit with sensitivity in the nanogram range for morphine sensing in urine samples. The established immunoassay was quick and easy to use for on-site detection, and it didn't require any complicated equipment [82]. Similarly, Yan et al., [83] developed a similar sensor for the determination of papaverine (PAP) and morphine. Though, Qi et al., [84] used an immunoaffinity column-based approach to detect PAP metabolites. The SPR immunoassays show excellent sensitivity in the monitoring of opiates [85]. Another typical example of SPR immunosensor for detecting morphine-3-glucuronide and its major metabolites was

developed by Dillon et al., [86]. Nevertheless, Dillon's group [87] has initially developed the same type of sensor in which the SPR chip was reformed with lipoate as another detection tool for morphine [88].

10.2.2 Electrochemical immunosensors

These sensors have been fabricated to detect electrochemical signals associated with antigen-antibody interaction. The signal generated is due to oxidation or reduction of analyte on the transducer (as depicted in Fig. 4).

A clear example is an electrochemiluminescence-based immunosensor that has been designed for morphine detection, which recorded good sensitivity in the nanogram range [90]. Another example is DNA-bound Au electrochemical sensor that has been fabricated for morphine detection [91].

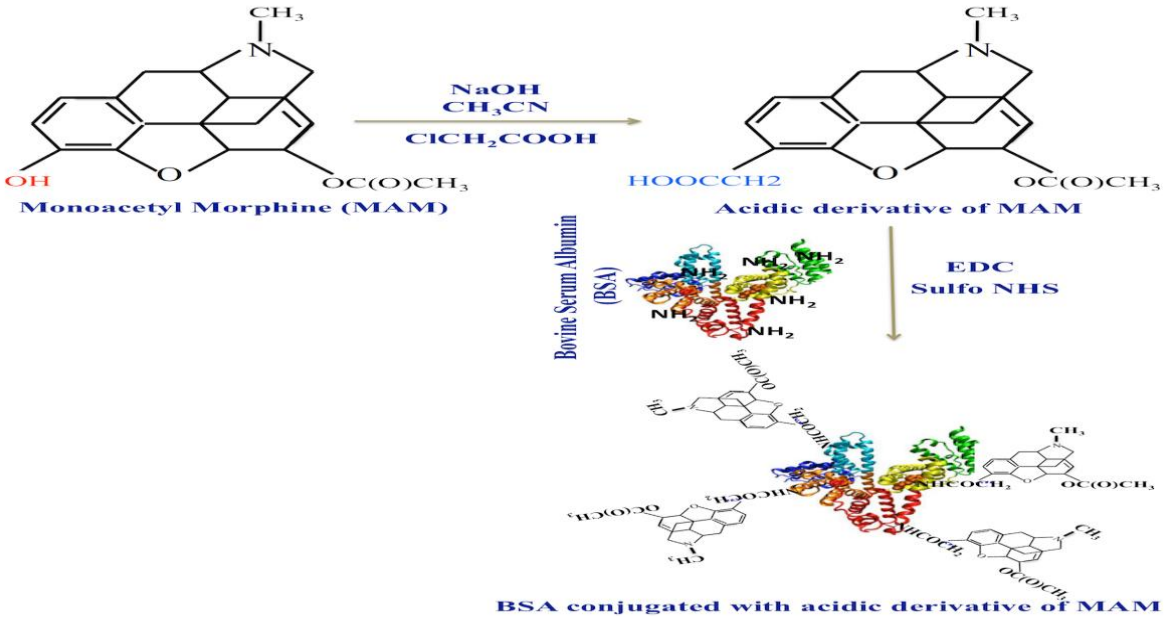

Fig. 3. Antibodies for the detection of heroin and its metabolites are produced by conjugating an acidic derivative of MAM with BSA. Reproduced with permission from [78], © 2015 Gandhi et al.; licensee TUOMS Publishing Group

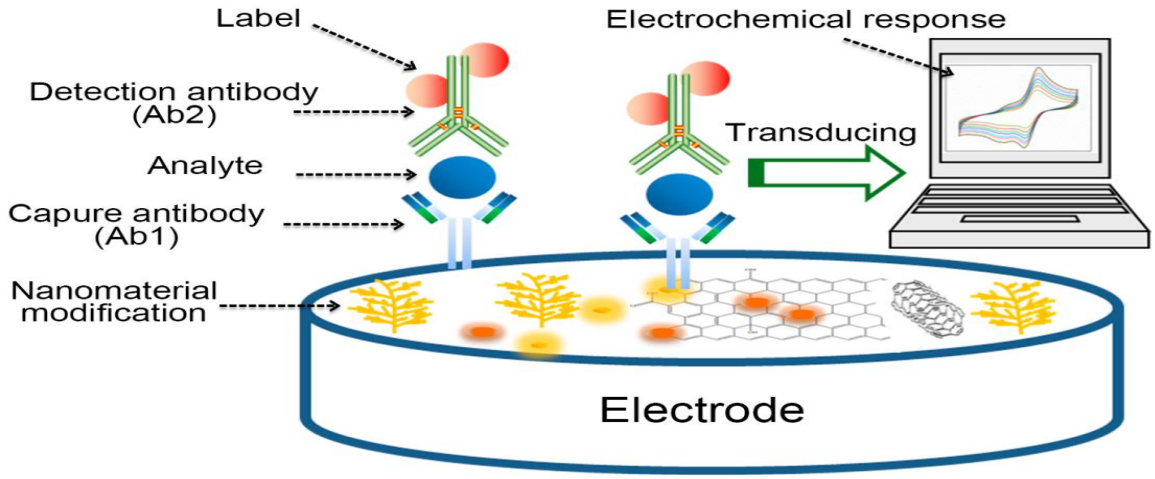

Fig. 4. A schematic representation of electrochemical immunosensor. Reproduced with permission from [89], © 2019 Zhang et al.; licensee MDPI, Basel, Switzerland

10.2.3 Carbon nanotubes based immunosensors

These sensors possess special electrical properties that enhance faster electron-transfer kinetics of analytes for better chemical functionalization [92]. Some biological recognition elements have been interfaced with CNTs for better attachment to fast-track the sensing ability of the sensors [93]. Li et al., [94] developed a CNT-based modified GCE immunosensor for the determination of morphine and noscapine with superior electrocatalytic oxidation of the analytes. Also, Tey's group [95] fabricated a similar immunosensor for rapid quantification of MAM with a detection limit of greater than the femtogram range.

10.3 SERS Sensors

SERS sensors are analytical tools that employ surface-enhanced Raman scattering of analyte molecules which are adsorbed on the NMs for their molecular detection. Illicit drugs are detected using SERS sensors based on the extent of molecular interaction with AuNPs (as depicted in Fig. 5) or AgNPs [96].

Mao et al., [98] had successfully designed a SERS sensor for qualitative and quantifiable determination of MAMP in human urine. The sensor was fabricated using 4-mercaptobenzoic acid (4-MBA) modified Au@AgNPs synthesized by the seeds growth method. The detection strategy of the drug was based on SERS upon mediation by the nanocomposite combined with MAMP aptamer, resulting in enhanced analytical performance of the sensor. 4-MBA served as a Raman reporter that produced a simple and sharp peak. The MAMP added into homogeneous nanocomposite induced the aggregation of 4-MBA modified Au@AgNPs; thereby making the signal of the reporter molecule to enhance the formation of hot spot SERS due to interaction between the drug and 4-MBA modified Au@AgNPs (as depicted in Fig. 6).

However, several binding agents were used to enhance the detection ability of the SERS sensor for sensing illicit drugs [99]. This enhancement procedure was an important step to make SERS very viable. SERS is an important analytical technique for sensing illicit drugs in biological samples. Although, water is an essential constituent of biofluids and poor Raman scatterer. Many studies have been conducted in the quest for quicker, more viable, and responsive methodologies for detecting illicit drugs in human fluids. However, biological materials are complex, and analyte signals are often obscured by the matrix's vibrational spectra, particularly when the analyte concentration is low [100]. Thus, biofluids absorb strong fluorescence light. Hence, the SERS method can be enhanced by combining many related techniques to achieve better results [101]. However, different biofluids are used in SERS detection.

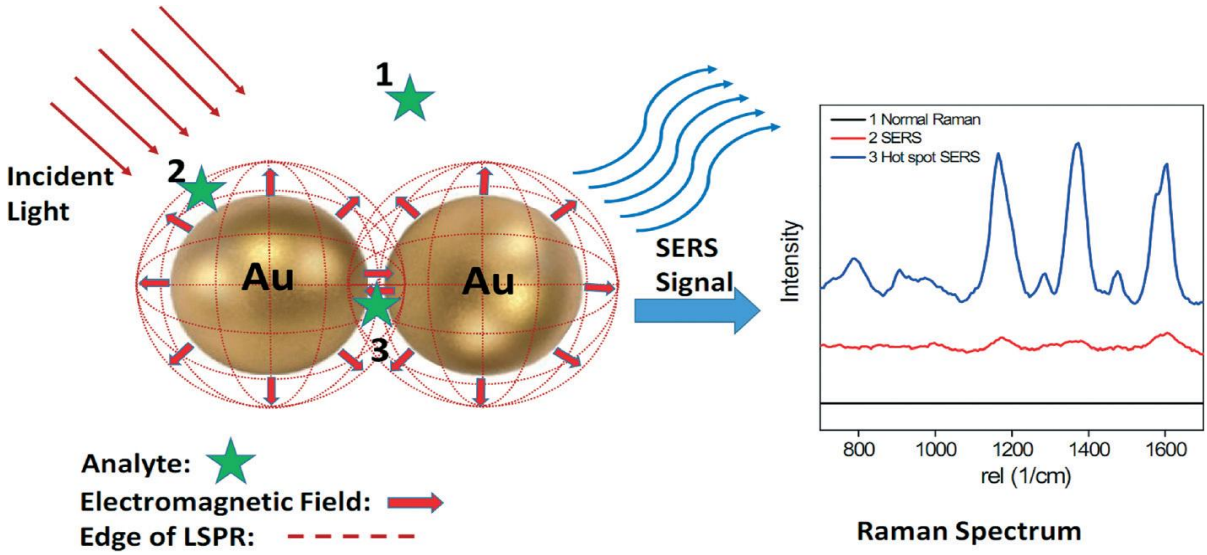

Fig. 5. A diagram depicting analytes adsorbed on AuNPs for their detection. Reproduced with permission from [97], © 2015 The Royal Society of Chemistry

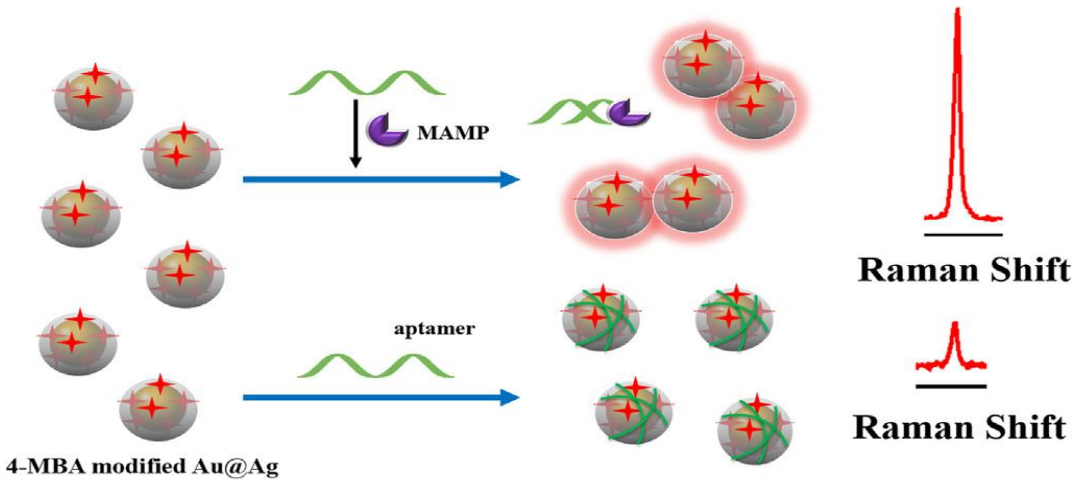

Fig. 6. A schematic representation of SERS detection of MAMP based on Au@AgNPs. Reproduced with permission from [98], © 2018 Mao et al.; licensee Elsevier

Saliva contains 99.5% water. A noninvasive sampling of saliva is required for analysis of illicit drugs as their concentrations exceed those in blood plasma [102]. Farquharson et al., [103] used SERS to determine illicit drugs and their metabolites. The group used Au colloids that were mixed with porous glass to fabricate glass capillaries for illicit drug detection. Solid-phase extraction was used to extract the drugs from the saliva matrix [104]. A software program was designed which comprise of one hundred and fifty drugs used for screening drugs. Also, a sample kit was developed to detect illicit materials in the impaired blood of a driver on a Raman spectrometer. The complete investigation took less than ten minutes [105].

Urine contains excess wastes, unmetabolized drugs, and their metabolites. It could reveal the drug consumption of four days. It is collected noninvasively and the sample can be used to monitor illicit materials [106]. Some synthetic drugs (AMP, dexamphetamine, etc) are excreted intact in urine [107]. SERS has limited application in analyzing addict samples. Urine contains some organic compounds including uric acid (UA), creatinine, albumin, and urea as major constituents and these materials affect the sensitivity of Raman techniques [108]. Alharbi et al., [109] used the SERS sensor to detect tramadol by taking advantage of salts aggregation in the urine matrix to achieve good sensitivity. The spectra were collected after the colloidal formation of silver hydroxylamine, which signals were completely lost after the precipitation of aggregates. Nuntawong et al., [110] utilized the nanostructure-based SERS chips to detect MAMP and its major metabolite AMP in the urine of MAMP abusers. The SERS substrates were decorated with Ag nanorods for signal enhancement. However, the acid treatment of the samples was carried out to remove interferences. The treatment facilitated the removal of organic urea-based by-products which lost their binding affinity to the Ag surface for clear signal enhancement.

Blood contains plasma and cells that circulate through the entire body. It is a fluid that provides vital minerals such as hormones, sugars, and O_2 in the body. It also removes waste materials from the cells in the body. Blood and its components produce very rich SERS spectra. Subaihi's group [111] used the SERS detection method through isotopic labeling to qualitatively assessed codeine in human plasma. Though, illicit drug analysis using human blood has been a very tedious and challenging task. Hence, blood has become an unsuitable medium for illicit drug detection.

10.4 Aptasensors

Aptasensors are analytical tools that utilize a biorecognition element such as DNA-, RNA-, protein-aptamer, etc to bind with target molecule for easy and fast detection of analytes. The interaction of an analyte with a detection probe (an aptamer) activates the formation of an aptamer-analyte complex, which causes the aggregation of AuNPs to detect the analyte.

Due to their exceptional properties, aptamers are used as biosensing tools in illicit drug diagnosis. They are specific and effective in sensing target molecules [80]. Various aptasensors have been

fabricated for the detection of cocaine based on chemiluminescence assay [112], induced strand displacement [113], DNA-based [114], and single QDT-based aptamer [115]. Besides drug screening, aptasensors are widely used in forensic analysis, food safety, environmental monitoring, and biomedical diagnosis [116]. New research efforts are being used to fabricate aptasensors that are affordable, facile, and portable with excellent stability for illicit drug detection [117]. Different signals result from the interaction of an aptamer with the illicit drug which includes electrochemical [118], fluorescence [119], SER scattering [98], and colorimetric [120], etc. Nevertheless, a typical colorimetric aptasensor had been developed using DNAzyme for the detection of MAMP [121]. Moreover, two prominent examples of illicit drug aptamer sensors are described as follows:

10.4.1 Optical aptasensors

A large number of detection techniques had been designed using AuNPs to identify cocaine and other illicit materials with aptamers, especially DNA. The two random coils of ssDNA had been synthesized to bind to the target molecule. AuNPs differentiated the binding of the DNA to the target drug molecule, which resulted in a change of SPR of the NMs. The change had been used to quantify cocaine in the µM range [122] (as depicted in Fig. 7).

10.4.2 Colorimetric aptasensors

Colorimetric aptasensors are widely used in illicit drug sensing due to their facile, susceptible, low-cost, and very rapid naked-eye detection ability. These sensors utilize NMs such as AuNPs on their sensing platforms. The basic amino groups of the aptamer are usually binded to negative portions of AuNPs that are stabilized under moderate salt concentration. When the sensor is dipped into a solution containing an illicit drug, an aptamer-drug complex is formed. Consequently, this causes the aggregation of the metal NPs and brings about a change in absorbance intensity of the NMs, resulting in a color change from red to blue known as the hypsochromic effect.

The degree of absorbance intensity of NMs is proportional to the concentration of the illicit drug. A typical example is a fabrication of a colorimetric aptasensor for naked-eye detection of MAMP as reported by Shi et al., [123]. To enhance the sensitivity and stability of the sensor, Ag-core shell NPs were coated on Au NMs and used for sensing MAMP [120]. The detection strategy of the sensor depends on the biorecognition element and the NMs. The synthesized Au@AgNPs were used to modify the DNA aptamer. The DNA is bound to Au@AgNPs through hybridization via noncovalent interaction [124].

However, the advantages of nanosensors over conventional analytical methods are clear contributions of modern nanotechnology toward rapid illicit drug sensing; notwithstanding, this does not automatically suggest that nanosensors are without some limitations in their inherent applications to detect illicit drugs and other materials (Table 2).

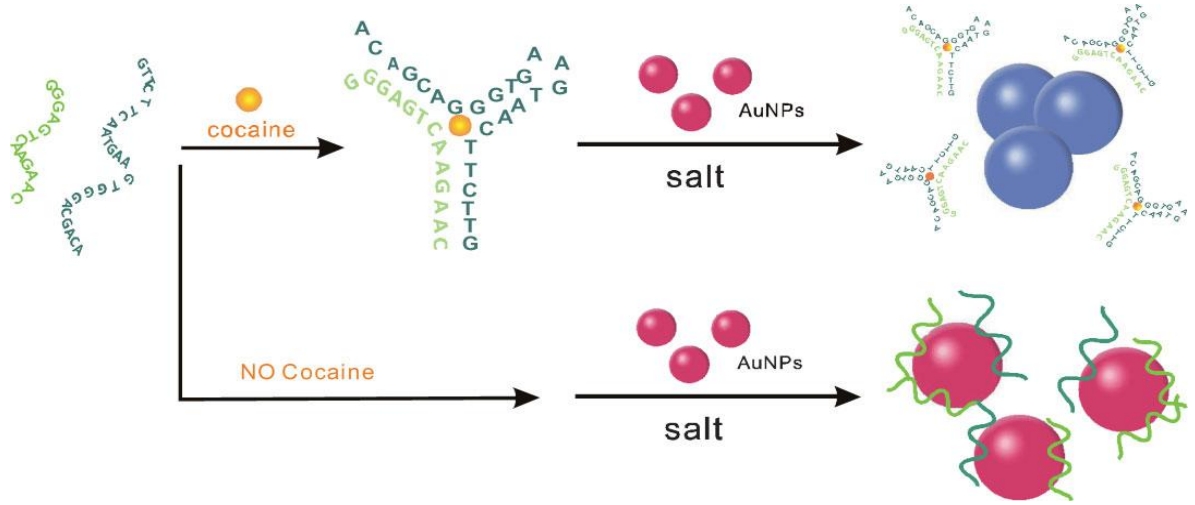

Fig. 7. Optical aptasensor based on aggregated AuNPs for cocaine detection. Reproduced with permission from [122], © 2008 Wiley-VCH GmbH

Table 2. Summary of advantages and disadvantages of some nanosensors for illicit drugs detection

Sensor type	Advantage	Disadvantage
Plasmonic biosensor	1. Label-free environment 2. Real-time, continuous measurement 3. Quick testing 4. Small sample amount/ volume 5. Highly sensitive 6. Specific to the binding event 7. Sensor chips can be regenerated 8. Measure “active” concentrations [125]	1. Immobilization effects 2. Steric hindrance effects 3. Mass transport limitation 4. Misinterpretation of data 5. Expensive sensor chips [125]
Immunosensor	1. High sensitivity 2. High selectivity 3. Suitability for miniaturization 4. Low cost [126]	1. Mass production limitation 2. Lack of speed for routine analysis 3. Beyond lab environment utilization limitation [126]
SERS sensor	1. Ultratrace detection capability 2. Wide range of target analytes 3. Smaller sample volume 4. Ability to detect analytes with low concentrations 5. Rapid analysis 6. Nondestructive [127]	1. Complicated synthetic process 2. High cost of SERS substrates 3. Low affinity of some molecules 4. Low reproducibility of SERS spectra 5. Size/ morphology dependency of the substrate [127]
Aptasensor	1. Simplicity 2. Specificity 3. Short analysis time 4. No sample preparation [128]	1. Preconcentration of the analyte 2. Steric hindrance effects[128]

11. CONCLUSION

This paper reviews the applications of some nanosensors for rapid and facile detection of illicit drugs in biofluids. The results obtained from different literature revealed the utilization of plasmonic, optical as well as SERS properties of nanomaterials to detect the drugs. Therefore, nanotechnology can help in routine assessment and control of the use of illicit materials as well as in checking doping by athletes in sports competitions. However, it is recommended that more scientific researches should be devoted towards the area of nanotechnology to come up with more noble, quick-to-use, and ready-made nanosensors for checking illegal consumption of these materials, to be utilized by the Law Enforcement Agents to track individuals associated with this illegal habit, which is a global trend, increasing at an alarming rate in our societies.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by the personal efforts of the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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