Anal. Bioanal. Electrochem., Vol. 14, No. 6, 2022, 557-581

Analytical &
Bioanalytical
Electrochemistry

2022 by CEE
www.abechem.com

Review

Recent Advances on Smart Nanomaterials for Sensing Pharmaceuticals in Various Matrices: A Mini-review

Sefiu Olaitan Amusat,[1,*] Kabir Opeyemi Otun,[2] Azeez Olayiwola Idris,[3] Temesgen Girma Kebede,[1] Edward Ndumiso Nxumalo,[3] Simiso Dube,[1] and Mathew Muzi Nindi,[3,*]

[1]Department of Chemistry, College of Science, Engineering and Technology, University of South Africa, Florida Campus, Christian de Wet & Pioneer Avenue, Florida, 1709, South Africa
[2]Department of Chemical, Geological and Physical Sciences, College of Pure and Applied Sciences, Kwara State University, Malete, PMB. 1530, Ilorin, Nigeria
[3]Institute for Nanotechnology and Water sustainability (iNanoWS), College of Science, Engineering and Technology, University of South Africa, Florida Campus, 28 Pioneer Avenue, South Africa

*Corresponding Author, Tel.: +277625798781

E-Mails: amusatolaitan@gmail.com ; nindimm@unisa.ac.za

Received: 31 March 2022 / Received in revised form: 10 June 2022 /
Accepted: 16 June 2022 / Published online: 30 June 2022

Abstract- The invaluable advantages of smart nanomaterials are being explored in several fields nowadays which have made the nanomaterials applicable in sensing pharmaceuticals products at different concentrations in various media including nanomedicine, drug innovation, and delivery, and water treatment plants. Pharmaceutical detection in the food sector, biomedical diagnostics, and water monitoring are very cogent owing to the risks associated with the composition of these drugs when existing above permissible limits in a matrix. Therefore, this review summarizes the recent research activities on the use of smart nanomaterials for sensing pharmaceuticals in various mediums. Classifications and synthesis of various nanomaterials are also discussed. Lastly, the application of smart nanomaterials in sensing pharmaceuticals in various matrices was also reviewed. It is expected that this review will guide towards tailoring nanomaterials for sensing pharmaceuticals in different matrices and for possible improvement on their applicability.

Keywords- Sensing; Smart nanomaterials; Pharmaceuticals; Water pollutant detector; Biomedical diagnosis

---

1. INTRODUCTION

Nanotechnology is currently receiving huge attention and becoming a trending research area across all the disciplines of science owing to the enormous applications of nanomaterials in various fields. The unique properties of nanomaterials such as electrical, optical, and mechanical behaviors have made them extensively applicable in different sectors, such as aerospace, medicine, fuel cells, energy storage, sensory devices, sound absorption material, wound dressing, tissue engineering, drug delivery systems, and water treatment, among others [1–5]. The International Union of Pure and Applied Chemistry (IUPAC) defines a biosensor or biological as an analytical tool that uses numerous biochemical reactions moderated by independent enzymes, immune systems, tissues, or entire cells to identify chemical substances usually employing electrical, thermal, or optical signals, or an analytical tool used to interpret biological information into the readable response [6]. There are two distinctive parts of biosensors: the biological sensing part, (usually, antibody, cell, tissues, and enzyme) bridged directly with a transducer which is an electrical output signal [7].

One of the leading factors on the list of environmental challenges facing human and aquatic organisms globally now is the potential toxic effect of the organic pollutant discharge into the environment, especially the water bodies, which necessitates the innovation of analytical devices that can accurately quantify these pharmaceutical drugs in soil and water samples [3]. Recently, the increase in numbers of surface water contaminants e.g. surfactants has sparked the attention of researchers toward the development of highly sensitive and highly selective sensors for monitoring water quality. Tetracycline, one of the groups of antibiotics majorly utilized by humans and in agricultural practices, there has been increasing concern over their potential biological toxicity because of high usage which has led to their concentration in the ecosystem, surface, and groundwater [8]. This has necessitated the quest for an alternative to the conventional methods such as liquid chromatography-mass spectrometric (LCMS) [9], high-performance liquid chromatography (HPLC) [10], and thin-layer chromatography (TLC) which are popular convectional analytical methods employed for the detection of pharmaceutical compounds in water.

The conventional methods are not only slow but are also very costly to practice and some involved the use of toxic chemicals[11]. Therefore, sensor development has become a hotspot as it has been extensively explored as a promising alternative to the conventional methods for the detection of pharmaceutical drugs such as antibiotics. This is because they are highly sensitive, and have good selectivity, fast detection time, and ease of operation [12,13]. Shan et al developed an electrode via modified carbon nanotube for sensing tetracycline in fishpond water. The study exhibited good accuracy in a very short time with a low detection limit for tetracycline in the fishpond water [14]. Benvidi et al also reported the fabrication of sensors from a glassy carbon electrode which was modified with GO nanosheets for tetracycline detection, with a low limit of detection and it was successfully used to detect tetracycline [15].

In the area of the biomedical, a biosensor is an indispensable tool in the design of biomarkers and instruments for medical diagnostics that are more flexible, accurate, and very cheap to assemble, for instance, a novel magnetic/bead gold biosensor which is user friendly, more rapid and highly sensitive biosensors, was developed to analyze parasite in blood samples present at very low concentration level [16]. Similarly, a novel biosensor for accurate determination of α2,6-sialylated glycan from gold nanorod was also developed by Li et al in 2019, with excellent results in the detection of the potential tumor builder [17]. Also, a highly sensitive and user-friendly biosensor with good stability that can easily reproduce was assembled from silver nanowires, to monitor lactate in the human sweat [18]. A sensitive protein biosensor was also made from porous silicon, the biosensor was reported to show a low limit of detection for the HSP70 as low as a range of 3000 – 500000 ng mL^{-1} [19].

2. SMART NANOMATERIALS

Smart nanomaterials are often regarded as ‘’brilliant’’ or ‘’ intelligent’’ nanomaterials’’ that possess fascinating tunable properties in different media to perform their specific functions promptly in the most optimum condition concerning the changes in their environment [20]. Nanomaterials that exhibit these unique properties such as high selectivity, timely response, self-actuation, flexibility, and directness are referred to as smart nanomaterials. These excellent characteristics have recently attracted researchers' attention towards utilizing them as promising candidates in the development of sensing devices for biosensors and sensing applications [21].

Numerous smart nanomaterials have been studied for the design of sensors used in pharmaceutical and medical applications to be promising for the advancement of sensing devices [22]. The examples include carbon nanomaterials [23–29], Gold nanoparticles [30-41], Quantum dots [42–51], Silver nanoparticles [52–56], Palladium-based nanomaterials [57–61], Iron oxides [62,63], Titanium dioxide nanomaterials [64,65]. Currently, nanotechnology has made it easy to visualize drugs in their raw forms or their various metabolites forms, for this regard, much special regard has been given to nanotechnology for making this possible in very little time [66–70].

2.1. Classifications of nanomaterials

Although, different classifications of nanomaterials exist, generally, there are different ways of classifying nanomaterials, but three major classifications are generally accepted. They can be classified based on their origin [71], dimension [72], and Chemical composition [73], as shown in Figure 1.

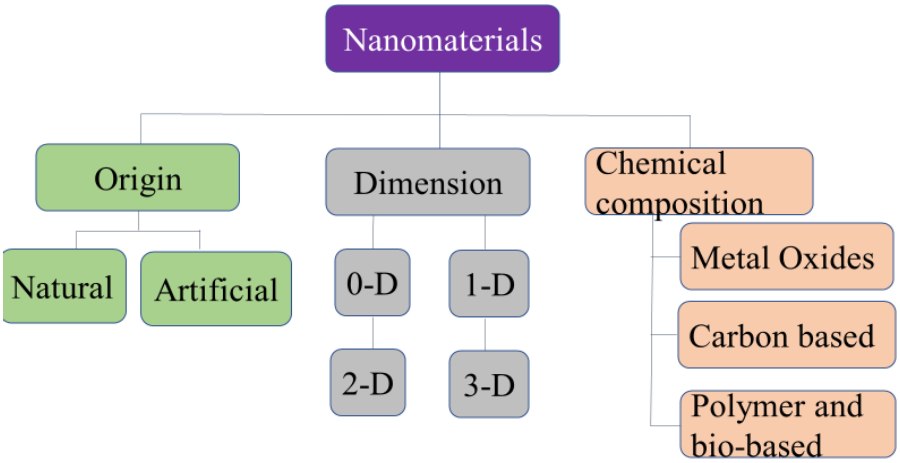

Figure 1. The major classification of nanomaterials by origin, dimension, and chemical composition

2.2. Based on Origin

Nanomaterials can be classified based on their origin into natural or anthropogenic activities emanated from intentional making composites or incidentally formed. Although some nanomaterials have their origin from natural and incidental processes, such nanomaterials are referred to as ultrafine particles. The natural occurrence that can lead to the formation of these natural or incidental nanomaterials from inorganic includes natural disasters such as volcanic eruptions, earthquakes, breaking sea waves, sand storms, and forest fire as well as suspended generated nanoparticles dust on the road [74]. Routine human activities could also unintentionally results in the formation of inorganic nanomaterials such as fumes generated from metals, various polymers, power plants, during various processing stages, and dust from other manufacturing companies [75].

2.3. Based on Dimensionality

The structural dimension of nanomaterials can be used in the classification of nanomaterials. Nanomaterials were first classified by H. Gleiter in the year 1995, who classified nanostructured materials based on their respective shape and their chemical composition [73]. Gleiter classification was criticized because some sp^2 carbon compounds such as fullerene, nano flower, and carbon nanotube which are zero-dimensional (0-D) and one-dimensional (1-D) in nature could not be classified based on his classification method, therefore abnormality in Gleiter classification was amended by Pokropivny and Skorokhod scheme, which accounted for other classes of carbon compounds into consideration [72], therefore, nanostructural materials could be classified into 0-D, 1-D, 2-D, and 3-D [76]. The classification based on a structural dimension with their examples of the nanomaterials that fall into respective classes is shown in Figure 2.

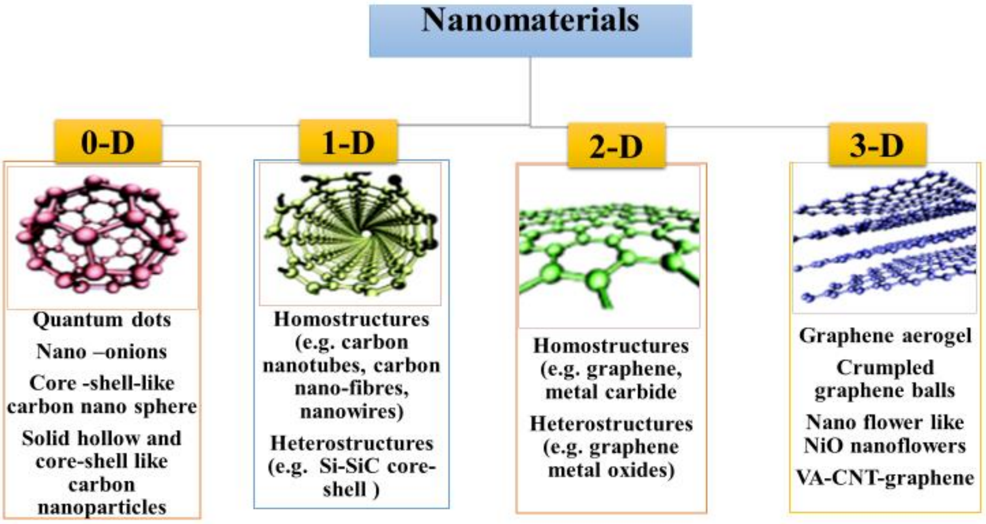

Figure 2. Schematic diagram of the various dimensional structure of nanomaterial; zero dimension (0-D), one dimension (1-D), two dimensions (2-D), and three dimensions (3-D)

Zero-dimensional nanomaterials are referred to as nanomaterials having all their dimensions in the nanoscale range i.e. all their external dimension is <100nm, examples of zero-dimensional nanomaterials include metallic nanoparticles e.g. gold and silver nanoparticles, which can be crystalline or amorphous. They also have different shapes and they can exist alone or can be engineered to form a matrix [77], quantum dots with regular arrangement patterns that are being used for electrical applications [78]. The SEM images of gold nanoparticle, a classical example of a 0-D structure is shown in Figure 3(a).

One-dimensional nanomaterials (1-DNMs) are various kind of materials that have two dimensions in which one of the dimensions fall within the nanoscale range while the second dimensions are beyond the nanoscale range. They do not have equal length and width. 1-DNMs can be metallic or ceramic, amorphous, or crystalline, and can also be single or polycrystalline. Examples of 1-DNMs include nanotubes, nanowires, nanorods which are majorly used in making circuits for computers, and coatings of eyeglasses [79]. SEM image of a carbon nanotube, a classical example of a 1-D structure is shown in Figure 3.

Two-dimensional nanomaterials (2-DNMs) are materials with one of their dimensions falling in the nanoscale range, while the other dimension is not within the nanoscale. Examples include nanoribbons, nanofilms, and graphene nanosheets [80]. 2-DNMs can be amorphous or crystalline and consist of metallic or ceramic or polymeric materials. They possess high mechanical properties owing to the thickness and they are transparent and this has made them used in the development of sensitive biosensors, and electronic devices as well as for other environmental applications [81] SEM image of graphene nanosheet, a classical example of 2-D structure is shown in Figure 3.

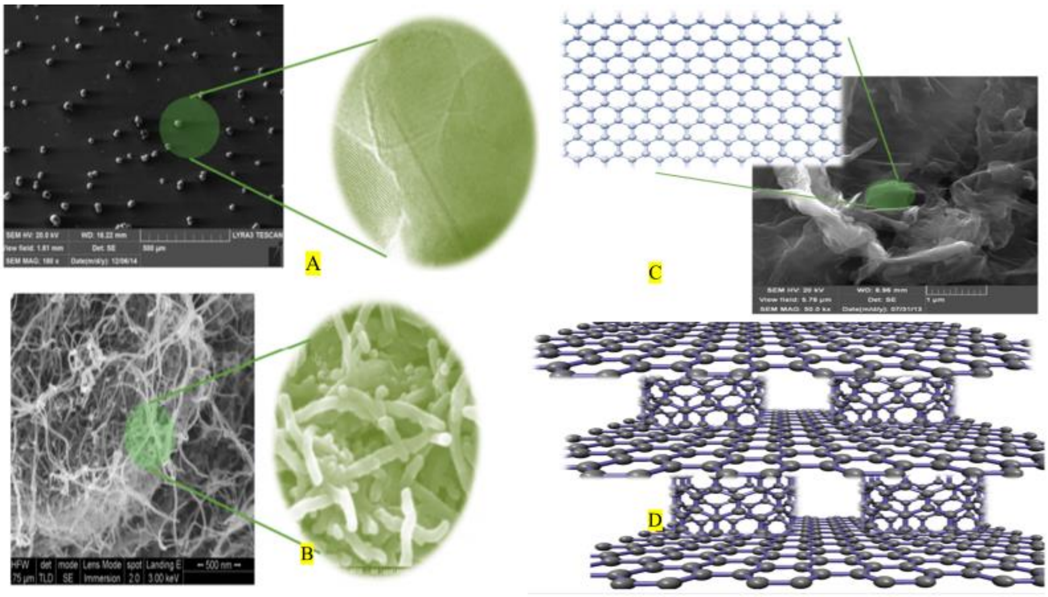

Figure 3. SEM images of 0-D NM (a) gold nanoparticle, 1-D NM (b) carbon nanotube, 2-D NM (c) graphene nanosheet, and (d) CNT-graphene structure of 3-D NM. Reproduced with the permission form [82] Elsevier 2016.

Three-dimensional nanomaterials (3-DNMs) are materials with none of their dimensional structures falling within the range of nanoscale i.e. their dimensions are > 100 nm. In 3-DNMs, there is a free movement electron among the 3 dimensions. They are composed of majorly dispersed nanoparticles or powder fibers, composites of layers, nanowires, and nanotubes [72]. CNT-graphene structure is shown in Figure 4 as an example of 3-D nanostructured materials.

2.4. Based on Chemical Composition

Nanomaterials can also be classified based on their respective chemical compositions, as shown in Figure 4. This includes metal oxide nanomaterials, carbon-based nanomaterials, and polymer-based and bio-nano materials [83]

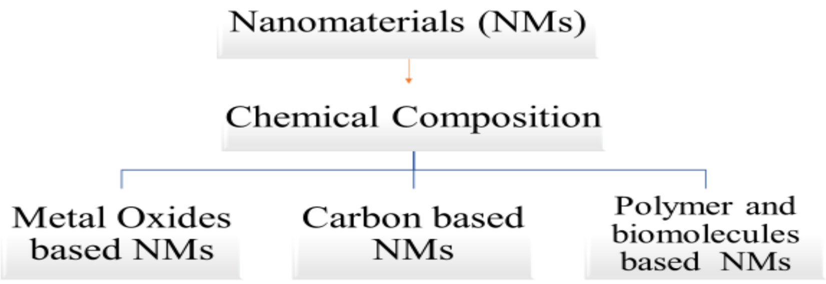

Figure 4. Classification of nanomaterials based on their chemical composition into metal oxide nanomaterials, carbon-based nanomaterials, and polymer and biomolecule-based nanomaterials

Metal oxide nanomaterials: Examples of metal-based nanomaterials are gold, copper, silver, iron, and aluminum. Most metal oxide-based nanomaterials are characterized by good stability and coupled with high electrochemical properties owing to the presence of metals in their compositions such as gold, silver, and copper nanoparticles. The opportunity offered by their great properties was utilized for the development of sensors for various applications [84].

Carbon-based nanomaterials contain carbon with various structures such as graphene, nanotube, nanosphere, and fullerenes, they possess intriguing properties such as; high stability, very conductive, ease of intriguing and low cost, therefore, they have been extensively functionalized with nanomaterials e.g. graphene, carbon nanotube(CNTs) and effectively used in various electrochemical, sensor and environmental applications [85].

Polymer and bio-nano materials. A combination of the catalytic characteristic of polymer and biomolecule with excellent properties in nanoscale materials have resulted in the development of sensor and biosensing devices in biomedical diagnostics, food sensitivity, and as well as environmental applications [86] [87]. The sensitive biosensor was established in 2016 by Betty and co-workers, the sensor was developed by incorporating extracts from chili fruits with nano biocomposites polymer from the ammonia-lysed enzyme of L-phenylalanine [88].

3. CARBON-BASED NANOMATERIALS

Carbon-based nanomaterials are mainly made up of carbon, which constitutes the highest percentage in the composition of carbon-based nanomaterials. Carbon nanotubes and fullerenes are among the prominent families of carbon-based nanomaterials. Some unique properties of carbon-based nanomaterials such as high heat and electrical conductivity, their stability, compatibility, and high mechanical properties have rendered them useful for numerous sensing applications. Other properties, such as the electrocatalytic activity of carbon-based nanomaterials, are a function of the choice of the synthesis method used to produce them, and therefore various classes of carbon-based nanomaterials have been successively used in the production and construction of major components of the biosensor [89]. Researchers have worked extensively on the improvement of synthesis, functionalization, and application of CNTs and other carbon-based smart nanomaterials in various areas since the discovery of carbon nanotubes by a great scientist, Sumio Iijima in 1991 [90].

3.1. Graphene-based nanomaterials

In recent times, researchers have focused much attention on graphene and its nano-based materials for diverse applications. Their smart chemical, optical, electronic, and mechanical properties accorded them these great opportunities [91,92]. Graphene is a member of two-dimensional (2D) carbon-based materials with a unique arrangement of the lattice structure that exhibits exceptional properties such as outstanding electrocatalytic activity, good stability, chemical inertness, higher sensitivity, and good selectivity which have offered them great opportunity to be used in the production of electrochemical biosensors in various matrices [93]. These unusual characteristics of graphene such as excellent physicochemical, electrical, large surface area, and biocompatibility have been evident over the past decade, resulting in the recent use of graphene nanomaterial in various applications [94]. Therefore, graphene and its derivatives graphene oxide (GO), reduced graphene oxide (rGO), and other modified graphene composites exhibit promising potential applications in the development of stable, sensitive, and highly selective electrochemical biosensors [95]. Qian et al reported the highly sensitive graphene oxide (GO-based) electrochemical sensor with a sensitivity of 0.60 μA $mM^{-1}cm^{-2}$ within the concentration range of 10 μM–1 mM towards the detection of naproxen using an actual pharmaceutical matrix [96]. Similarly, a highly sensitive anti-cancer drug (raloxifene) biosensor was also fabricated from graphene oxide entrapped with neodymium sesquioxide nanoparticles, it has been stated that the established electrochemical sensor displayed a limit of detection (LOD) of 18.43 nM in the of 0.03 and 472 μM as shown in Figure 5. Furthermore, the fabricated Nd_20_5NPs GO sensor has been successfully tested for the detection of raloxifene drugs in human blood and urine [97].

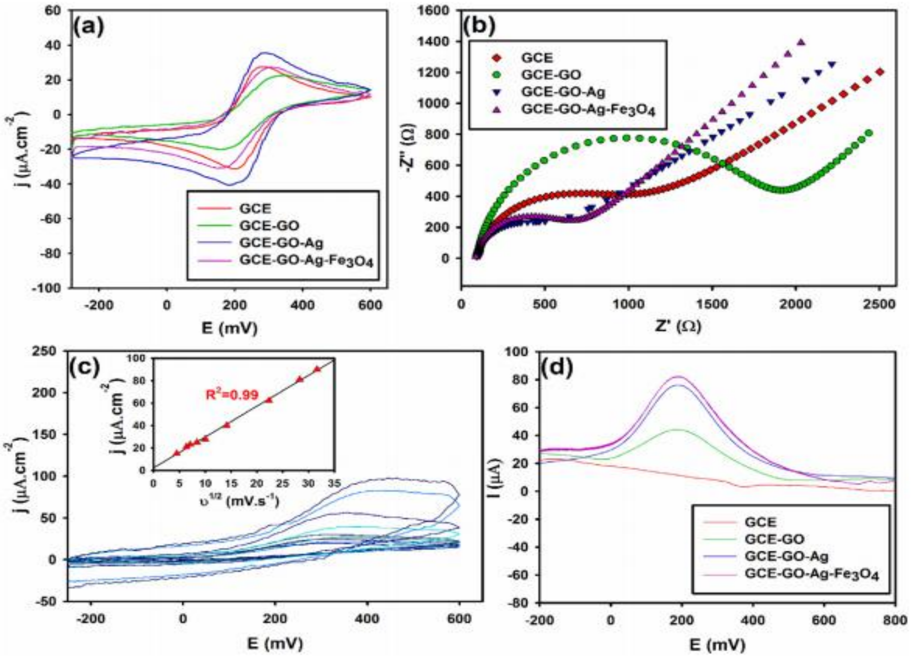

Figure 5. (a) Cyclic voltammetry and (b) Nyquist plots of GCE, GCE-GO, GCE-GO-Ag, and GCE-GO-Ag-Fe_3O_4 electrodes in 0.1 M KCl (c) obtained CV at various scan rates in 0.1 M PBS at pH 7.0 on GCE-GO-Ag-Fe_3O_4 electrode, and (d) showed DPV obtained with pH 7.0 in the absence of any external redox probe on the GCE, GCE-GO, GCE-GO-Ag and GCE-GO-Ag-Fe3O4 electrodes [98]. Reproduced with permission from [98] Elsevier 2020.

Furthermore, Hashemi et al recently developed a stable and highly selective biosensor from graphene oxide decorated with silver and magnetite nanoparticles for the rapid and qualitative detection of ascorbic acid in human blood fluid, this modified graphene nanomaterial-based electrochemical biosensor exhibited a LOD of 74 nM and sensitivity of 1146.8 µA mM^{-1} cm^{-2}, in the concentration range of 0.2 – 10 µM [98].

In summary, it is clear here that nanomaterials can detect pharmaceuticals in different media efficiently with good detection limits and high sensitivity. More so, the functionalization of nanomaterials can help improve their properties and sensing performance.

3.2. Metal nanoparticles

Fascinating physicochemical and electronics properties of metal combined with the smart properties of materials in the nano range have made them a great choice for making essential components such as the transducer of an electrochemical biosensor. Hence, much attention has been shifted towards the utilization of metal nanoparticles as a good candidate to detect the concentration of enzymes, protein, pharmaceuticals compounds, and protein in various matrices [99]. For example, gold nanoparticles have been reported to exhibit an excellent detection limit when used as a sensor in various applications. It also has very high sensitivity characteristics of gold nanoparticles that have been utilized to develop a sensitive and selective electrochemical biosensor for various matrices by combining them with bio-recognition elements, for instance, Chandra reported the construction of aptamer by AuNPs immobilization on the surface of conducting polymer for sensitive and selective sensing of daunomycin in human urine [100].

3.3. Magnetic nanomaterials

Magnetic nanomaterials are types of nanomaterials that possess excellent magnetic properties (e.g. excellent physicochemical, unique nanoscale size, high surface area ease synthesis method) which have offered them to be widely considered as a promising candidate in various applications such as analytical applications, biosensor development, and numerous medical applications [101]. For instance, copper nanoparticles have been found useful in the medical diagnosis of various ailments [102], as well as Palladium-based nanomaterials are found used in drug delivery and anticancer [103]. Subsequently, owing to the promising potentials of magnetic nanomaterials, great efforts were devoted to the design of electrochemical biosensors from MNs for the detection of major groups of the pharmaceutical drug (antibiotics) in many matrices such as in environment, human and body fluids, and food processing industries [104].

3.4. Quantum Dots

Quantum dots are carbon-based carbonaceous materials in the nanoscale size range usually between 2 to 10 nm in diameters. They also possess other properties such as unique optical properties, good biocompatibility, and rapid electrochemical response which have made them extensively utilized materials in the development of selective and sensitive sensors or biosensors of pharmaceutical products in various matrices in recent years [105]. Despite the numerous advantages offered by their properties, the utilization of QDs in making sensitive biosensors is restricted due to the toxicity of some heavy metal-based. Additionally, the synthesis of quantum dots is time-consuming and cumbersome, while reproducibility and potential agglomeration of the QDs nanomaterials are also challenging [106]. Although, much effort has been dedicated to developing new approaches for the synthesis of QDs with the pursuit of rapid and vast methods and simplicity in synthesis [107].

4. SYNTHESIS OF SMART NANOMATERIALS

Obtaining materials in the nanoscale range (1-100 nm) is one of the major considerations when synthesizing nanomaterials. Generally, the top-down approach and the bottom-top approach are the two prominent approaches that are often employed in the production of nanomaterials. Although, both approaches can be combined as reported in a study where advantages of both approaches were utilized for the successful fabrication of carbon nanotubes with the uniform surface of different sizes [108]. Figure 6 shows the main methods of synthesizing nanomaterials.

Top-down approach: The top-down approach involves the fabrication of materials on the nanoscale by breaking down (destruction) the bulk materials into smaller pieces using mechanical forces e.g. ball milling, chemical forces, or other forms of energy [82]. The top-down method is saddled with inherent setbacks such as the inability to produce materials with uniform structure, high energy inputs, demands in scale-up production, and environmental factors which are major considerations in the sustainable synthesis of nanomaterials [109].

Bottom-top approach: The bottom-top approach can be referred to as the self-assembly approach that involves the fabrication (construction) of nanomaterials from their respective smallest particle sizes/atomic units or molecular species by the use of chemical reaction which allow the agglomeration of building up of the reacting particles into a desired arranged structure. The bottom-top approach has some advantages over the latter approach, such as low cost of production, being can be scaled up easily, and also results in the production of nanomaterials with uniform sizes [82]. Examples are the chemical synthesis of nanoparticles and the production of powder by the sol-gel approach.

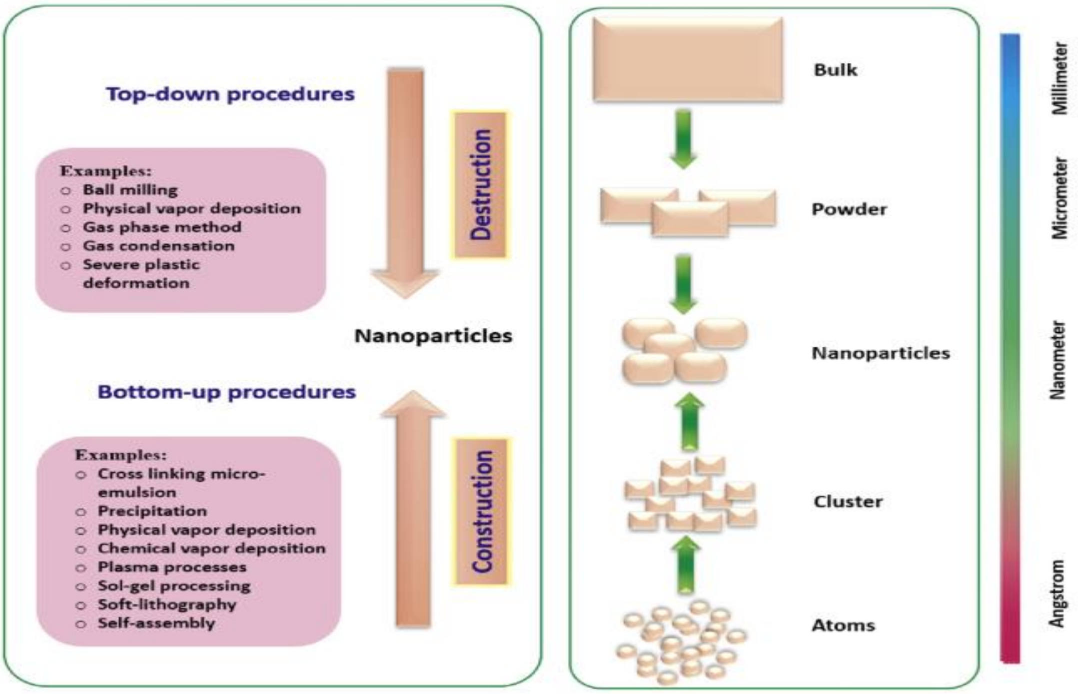

Figure 6. Various methods of synthesizing nanomaterials. Reprint with the permission form [82] Elsevier 2016

Some methods that have been used in the fabrication of different nanomaterials will be briefly described in this study, details and other methods can be found elsewhere, these methods include but are not limited to the sol-gel method, microwave method, direct dispersion method, ball milling process, and hydrothermal process.

4.1. Sol-gel method

The sol-gel method has been well established as one of the chemical processes in industries for obtaining colloidal nanoparticles using liquid-phase techniques. Over the year, the method has witnessed significant improvement in the production of various cutting-edge nanomaterials for numerous applications and coating [110]. The main process stages in sol-gel methods are shown in Figure 7. The sol-gel method has been successfully used in the synthesis of nanomaterial for the electrochemical-based sensor of hydrazine with high selectivity and good reproducibility [111], CO_2 sensor[112], and caffeine sensor [113].

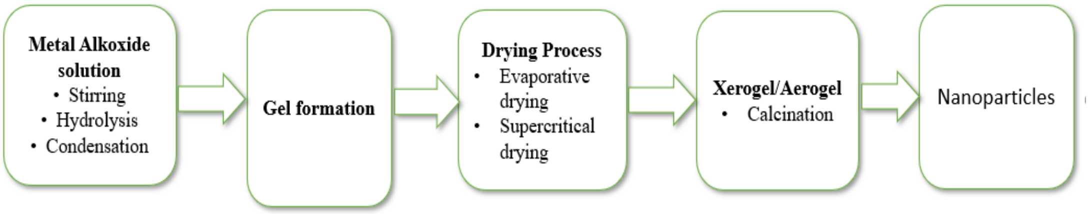

Figure 7. Main process stages in the sol-gel method of synthesis of nanomaterials [114]

4.2. Microwave synthesis method

The microwave synthesis route involves subjecting the starting materials to radiation from microwaves to obtain the desired products (nanomaterials). Microwave synthesis is a rapid method, low cost, and does not produce any waste products. This synthesis method has been employed in various chemical industries such as pharmaceutical companies, food processing, and different higher education sectors for synthesis. Applications of this technique for the synthesis of functional nanomaterials have been reported [115].

4.3. Direct dispersion method

The direct dispersion method is employed in producing polymer nanocomposites. This can be achieved by functionalizing nanoparticles by the use of chemicals after synthesis to enhance their homogeneous mixing with polymer for the formation of uniform polymer-based nanocomposites. This method offers complete homogeneity without exerting unnecessary forms that can deform the nanocomposites.

4.4. Ball milling process

Mechanochemical fabrication of nanomaterials and nanocomposites by ball milling methods has become a prominent process in the synthesis of novel nanomaterials owing to the low cost, green synthesis approach and it is regarded as an efficient method suitable for the environmentally sustainable fabrication of nanomaterials for various applications [116]. Although ball milling has been long in use in many industries for reducing the size of materials. The process utilized the collision of the moving ball with the inner lining disc combined with the exerting of centrifugal force to reduce the size of the bulk materials [117].

4.5. Hydrothermal process

Hydrothermal synthesis of nanomaterials involves the use of hydrothermal autoclaves to produce nanomaterials at higher vapor pressure and temperature. It is a solution based on a solution reaction-based approach in which the reactant may not completely dissolve but offer the advantages of synthesis of nanomaterials with high vapor pressure with little waste of materials. Hydrothermal techniques have been used for the production of graphene nanosheets, nanotubes, nanoparticles, and hollow nanospheres [118].

5. SMART NANOMATERIAL FOR SENSING PHARMACEUTICALS

Despite their tremendous potential in sensing applications, NMs are primarily used to build clinical and field-deployable analytical instruments for different monitoring applications (e. g., health, environment, biological method, and food safety) so with their huge benefits (e.g. cost-effectiveness, high sensitivity, selectivity, rapid response, and portability) [119]. To explore pragmatic applications, a broad range of electrochemical sensors with various sensing principles e.g., differential pulse voltammetry (DPV), cyclic voltammetry (CV), square wave anodic stripping voltammetry, electrochemical impedance spectroscopy (EIS) was briefly reviewed in the next section.

5.1. Application of nanomaterials for sensing pharmaceuticals in water

Contamination of the ecosystem with pharmaceuticals and other chemical substances which are being utilized by a human, livestock farming, and other agricultural practices is now a major challenge. Pharmaceutical compounds include analgesics, antimicrobials, antipyretics, anti-inflammatories, hormones, and antibiotics. When these chemical substances are metabolized, their accumulation in the body and their toxicity become a great concern in the environment even at a low level [120]. The breakthrough recorded in antibacterial drug (sulfamethazine) in the sewage of animal urine using optical immunosensors as reported by Akkoyun et al 2000 [121], which also further confirmed that the waste sewage of livestock animals could also be a potential source of pharmaceuticals contaminants into the wastewater, while the immunosensor could be employed to monitor the release and inflow distribution of pharmaceuticals compounds in the water cycle. Therefore, the development of biosensors that can detect pharmaceutical drugs in an aqueous matrix from nanomaterials has received huge attention in the last decades [122]. Thereafter, tremendous efforts have been made towards the development of highly sensitive biosensors with smart nanomaterials because of their smart properties as well as their electronics, optical, and unique magnetic properties. Furthermore, they can successfully alter the two main parts of various sensors by increasing the surface area of the transuaders, subsequently, bringing about a significant increase in the catalytic characteristics of the sensor. Hence smart materials have been found very invaluable in the development of a sensor that can detect various pharmaceutical pollutants in water and wastewater [123].

Smart magnetic properties of functionalized gold nanomaterial, most especially gold nanoparticles and gold nanorods, coupled with their rapid detection and effective determination of chemical contaminants from the pharmaceutical origin, nanorods have made them be used in the development of nanomaterials based biosensors that could detect various pollutants in water matrices [124].

A combination of one or more nanomaterials or with other enzymes can also enhance their utilization in the development of rapid biosensors. For instance, Lacasse contained biosensor can be used in the determination of indirect drugs that undergoes parallel reactions. Novel Lacasse biosensor for detection of dopamine drug was also developed from carbon nanotube-based biopolymer of botryosphaeria using square-wave voltammetry technique, the biosensor can successfully detect dopamine drugs in the concentration range of 2.99–38.5 μmol L^{-1} as shown in Figure 8 which has a limit of detection (LOD) of 0.127 μmol L^{-1} [125].

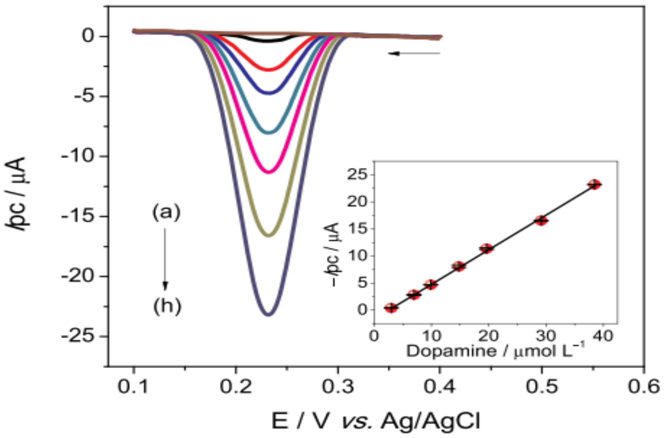

Figure 8. Square-wave voltammograms (SWV) attained at pH (6.0) using laccase-EPS-MWCNT/GCE biosensor at 2.99–38.5 μmol L^{-1} dopamine concentrations

Also, different kinds of biosensors based on nanomaterials were built for the identification of medicinal substances in water and wastewater for the detection of chloramphenicol, Munawar et al fabricated a sensor from 3DCNT@Cu nanocomposite, the sensor produced was extremely reactive and selective against chloramphenicol even though interference occurs even in the presence of interference. The sensor response under the various concentration of chloramphenicol in Figure 9(A) and the cyclic voltammetry curve shows the response of the sensor towards the detection of chloramphenicol in the presence of various interfering agents in Figure 9(B) [126].

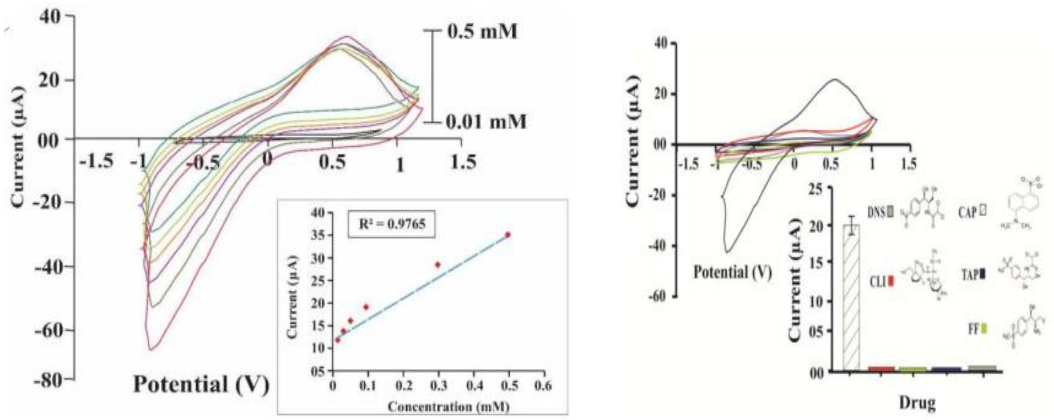

Figure 9. The sensor response under the various concentration of chloramphenicol and B, the cyclic voltammetry curve shows the response of the sensor towards the detection of chloramphenicol in the presence of various interfering agents [126]

Some recently developed nano-based biosensors that have been applied in the detection of pharmaceutical contaminants are summarized in Table 1.

Table 1. Some nanomaterial-based electrochemical biosensors for the detection of pharmaceutical contaminants in water

Nanomaterials-based biosensor	Technique	Target drug	Limit of detection (mol L^{-1})	Linear concentration range (mol L^{-1})	Ref.
CNTs	SWV	Dopamine	0.127 μmol L^{-1}	2.99 – 38.5 μmol L^{-1}	[125]
MWCNT-Sb NPs	DPV	Sulphamethoxazole	24 nmol L^{-1}	25.0 – 100.0 mol L^{-1}	[127]
MWCNT-Sb NPs	DPV	Trimethoprim	31 nmol L^{-1}	25.0 – 100.0 mol L^{-1}	[127]
Tyr-AuNPs	EIS	Sulphamethoxazole	22.6 ± 2.1 mM		[128]
P – RGO	CV	Acetaminophen	0.36 nM	1.5 – 120 μM	[129]
Fe_3O_4 - RGO	SWV	Capecitabine	0.324 nM	22.6 ± 2.1 μM	[130]
GC/carbon nanoballs	DPV	Paracetamol	8.0×10^{-9}	8.0×10^{-8}– 2.3×10^{-4} mol L^{-1}	[131]
AgNPs/graphene	LSV	Metronidazole	2.8 nM	0.05 10 μM	[132]
CP/AuNPs	Impedimetric	Kanamycin	9.4 nM	0.05–9.0 μM	[133]
RuSiNPs/Nafion	CV	Tetracycline	0.23 μmolL^{-1}	0.05 –9.0 μM	[134]

5.2. Application of nanomaterials for sensing pharmaceuticals in biomedical and diagnostics

The development of nanomaterials is currently solving the long-aged inherent setback including but not limited to low precision, poor solubility, very fast drug clearance, anaerobic decomposition, and limitation of targeting that obstruct the distribution of medications into the targeted parts in human organs, such as cells and tissue. In the light of the aforementioned challenges, the noteworthy properties of nanomaterials are emerging as a promising candidate to curtail these problems by utilizing the advantages of the nanoscale size of nanomaterials to allow the transport of drugs to the targeted cell even through the smallest capillary, enhance the capacity of drug loading capacity ease of usage which could get into the vessel, and the fast drug clearance could be avoided by administration of drugs through eyes [135].

Biosensors have become a very effective diagnostic tool and are commonly used in clinical research, identification of biowarfare agents, and pharmaceutical analysis [136]. The quest for the quantitative determination of glucose in human fluid because of the cogent roles it plays in the regulation and combating of diabetes, has made researchers explore nanomaterials to develop highly sensitive and rapid biosensors. There is also a need for improved biocompatible sensing systems and more efficient glucose sensors. Due to their electrocatalytic reactions to glucose oxidation, such sensing systems have continually evolved with the input of smart nanomaterials such as copper, metal alloys/adatoms, titanium, graphene, composites, and glucose-specific organic matter [137].

An extremely flexible and stable glucose biosensor was built on the silica nanoparticles and platinum nanomaterials by immobilization of glucose oxidase. The developed nanomaterial-based biosensor (GOx-MS and PtNP) could be used in the human serum sample for quantitative detection of glucose without interruption in a broad linear range of $1 -10^{-6}$ to $2.6 -10^{-2}$ mol L^{-1} with 0.8 mmol L^{-1} detection limit. Similarly engineered glucose biosensors may deliver many advantages over the existing analog, usually as well as high sensitivity, reproducibility, and durability, as well as the potential to react in a short time. The nanomaterial-based biosensor has proved its capability through pharmaceutical research, such that glucose can be ascertained quantitatively in actual human serum [138]. Furthermore, Rahstbari and co-workers developed a glucose biosensor from manganese-calcium oxide nanoparticles which was characterized by TEM, FTIR, SEM, and XRD. It was found that the sensor exhibits a 6.12×10^{-6} nmol L^{-1} detection limit. The potentials of this nanomaterial-based biosensor for the detection of glucose and H_2O_2 were tested and it was reported to act as a non-enzyme method for fast detection of glucose via spectrophotometry method and as well with the naked eye [139].

Various sensors based on nanomaterials have been investigated to detect pharmaceutical drugs and steroidal hormones in human fluids, for instance, CDs-GO nanocomposites were used to fabricate aptamer for biosensing of P4 progesterone hormone. Schematic preparation of aptamer-Au-CuO-Cu_2O bioconjugate and assembly of cathodic PEC sensor for P4 determination is shown in Figure 10. It was reported that CDs-GO enhanced stability and reproducibility of the fabricated PEG biosensor and also showed high selectivity at a low detection limit of 0.17 nM in the concentration range between 0.5 Nm to 180 Nm, it was established that the sensor can be used for P4 detection in human fluids [140].

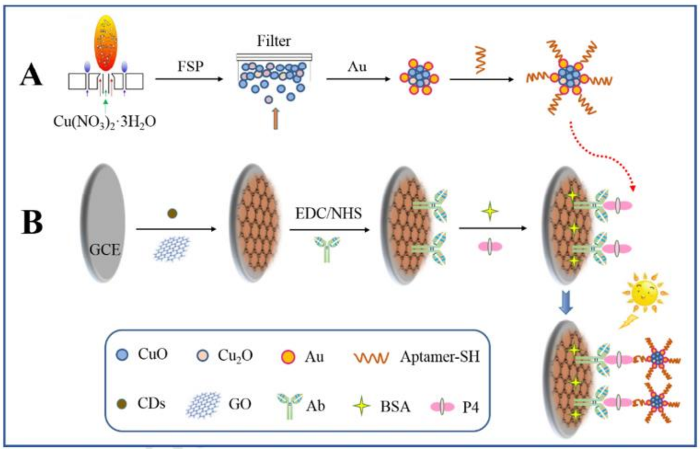

Figure 10. Schematic diagram of (A) aptamer-Au-CuO-Cu2O bioconjugate preparation and (B) cathodic PEC monitor for P4 determination [140]

A comparative study between CNTs and GO for glucose biosensors in conjunction with gold nanowire (AuNWAs), and a gravity-driven microfluidic injection was examined and reported by Liu and Lin [141], the findings showed that the carbon material-based glucose biosensors / AuNWAs exhibited high efficiency at the relatively low working potential of – 0.2 V versus Ag / AgCl (3 mol / L KCl). Also, the biosensor was characterized by high sensitivity, good anti-interference capability, and high performance (45 h^{-1}), with a linear range of 100 – 3,000 μmol/L with a sensitivity of 4.12 $\mu A/cm^2$ mmol/L. Whereas, 50–4,000 μmol / L and 8,59 μA/ (cm2 mmol / L), linear range and sensitivity respectively were recorded for GOx – rGO – AuNWAs-based glucose biosensor which was higher than those of the GOx–CNT – AuNWAs-based glucose biosensor, indicating that rGO nanosheets in combination with AuNWAs are a good medium for developing glucose biosensors. In another study, in a bit to overcome the inherent setback of low sensitivity facing flexible and wearable glucose biosensors, a stable electrochemical glucose biosensor was produced by encasing an enzyme on a polymer matrix electrode modified with GOx/Au/MoS_2/nanofilm, the study showed an increase on the sensitivity of the biosensor more that the convectional flexible glucose biosensor. The modified glucose biosensor shows a detection limit of 10 nM, the increase in sensitivity could be attributed to the facilitation of electron transfer by MoS_2. Therefore, Because of its high sensitivity, high versatility and easy manufacturing procedure, the flexible glucose biosensor composed of the enzyme/gold / MoS_2 / gold nanofilm on the polymer electrode may be used as a versatile sensing framework for developing wearable biosensing systems [142].

Similarly, the unique properties of ZnO such as high sensitivity towards glucose, Efficient electron transfer, a high volume-to-volume ratio, and stability were combined with exemptional conductivity and chemical stability of graphene to fabricate a stable and highly sensitive nanomaterial-based glucose biosensor. The glucose biosensor exhibit three excellent features of the sensor which are a response time of 5 s, detection limit of 0.003–30000 mg / dL, and long-term electrical stability [143].

5.3. Application of nanomaterials for sensing pharmaceuticals in food safety

High demand for food has led to significant growth of modern agriculture and industrial revolution in the food industry to meet up with the ever-increasing demand. Currently, different varieties of pesticides and antibiotics being utilized for food production have increased dramatically, and this has made food safety become a great concern globally as a result of the potential toxicity of accumulation of these chemicals and antibiotics drug residues used in livestock farming [144–146]. The aggregation may contribute to foodborne diseases, which would adversely impact human safety and the profitability of the food industry. The increasing interest in quantitative identification contributed to the production of super-accurate electrochemical biosensors for the determination of compounds in foods [147]. The development of nanostructured electrochemical platforms consisting of carbonaceous nanoparticles, metal nanoparticles, magnetic nanoparticles, metal-organic platforms, and quantum dots has been suggested to identify antibiotic residues in an attempt to fix this issue. Despite considerable success, more efforts are also required to improve multifunctional nanomaterials and ensure effective portability for communication devices within electrochemical sensors [104]. Consequently, various developed smart nanomaterial-based electrochemical biosensors for sensing pharmaceutical residues in the food industry are summarized in Table 2.

Table 2. Some nanomaterial-based electrochemical biosensors for the detection of pharmaceutical residues in the food industry

Nanomaterials-based Sensor	Technique	Target drug	Matrices	Detection Limit (nM)	Linear range (M)	Ref.
MWCNT CTAB-PDPA	DPV	Chloramphenicol	Honey and milk	2	$1×10^{-8}$ - $1×10^{-5}$	[148]
GR)2/MWCNTs -CS	DPV	Tetracycline	Spiked milk	0.005	$1×10^{-10}$ - $1×10^{-3}$	[149]
HNP-Pt-Cu/GR TH/GCE	DPV	Kanamycin	Chicken and pork meat	0.0008	$1×10^{-12}$ - $1×10^{-7}$	[150]
Au/C3N4/GN	SWV	Ciprofloxacin	Milk samples	420	$0.6×10^{-6}$ - $120×10^{-6}$	[151]
Au/C3N4/GN	SWV	Chloramphenicol	Milk samples	27	$0.7×10^{-6}$ -$120×10^{-6}$	[151]
MIP/NPAMR	CV	Metronidazole	Fish and drug	0.00002	$8.0×10^{-14}$ - $1.0×10^{-6}$	[152]
Po-AP/GQD	DPV	Levofloxacin	Milk	10	$0.05×10^{-6}$ - $100×10^{-6}$	[104]
Magnetic aptamer-QDs	SWV	Chloramphenicol	Fish	1.0 x 10^{-3}	$3.0×10^{-12}$ -$3.0×10^{-7}$	[104]
CS-MnO_2	DPV	Chlortetracycline	Fish, milk, and shrimp	260	$0.5×10^{-6}$ - $300×10^{-6}$	[153]

6. CONCLUSIONS AND OUTLOOK

In this review, the classification, synthesis, and application of various Smart nanomaterial-based electrochemical sensors employed in the detection of pharmaceutical compounds in water, medical diagnostic, and food safety were summarized. Since the discovery of the unique properties of smart nanomaterials has been recognized as a significant area of research, the high selectivity, durability, and versatility of nanomaterial-based biosensors are seen to be positioning them as capable candidates to produce quantitative sensors for pharmaceuticals drugs in the food processing industry, drug development and delivery research, water and wastewater treatment, and biomedical diagnostics applications. It is likely that, in the future, the face of current biomedical detection techniques will be radically transformed. Very soon, flexible, and cheap smart nanomaterials biosensors will flood the market to improve their applicability. There are, however, certain obstacles regarding their negative impacts on human health and environmental safety which calls for serious concern and perhaps, an extended research investigation. Nevertheless, smart nanomaterials are expected to play a major role in the development of biosensing devices for the detection of pharmaceuticals in the food industry, drug discovery and development, biomedical diagnostics, and water and wastewater treatment in the nearest future.

Acknowledgments

This review article was compiled based on the full support received from NRF-TWAS African Renaissance Ph.D. Fellowship Program with grant numbers 116111 and 139178. The University of South Africa (UNISA) is also acknowledged.

REFERENCES

[1] M. Holzinger, and A. Le Goff, S. Cosnier, Front. Chem. 2 (2014) 63.
[2] S. Chen, Q. Zhang, Y. Hou, J. Zhang, and X. J. Liang, Eur. J. Nanomedicine 5 (2013) 61.
[3] S. Akhtar, K. Shahzad, S. Mushtaq, F. Safi, I. Ali, and K. A. Bhatti, Mater. Res. Express. 6 (2019) 075068.
[4] E. de S. Gil, and G.R. de Melo, Brazilian J. Pharm. Sci. 46 (2010) 3.
[5] L. Rotariu, F. Lagarde, N. Jaffrezic-Renault, and C. Bala, TrAC - Trends Anal. Chem. 79 (2016) 80.
[6] D. R. Thévenot, K. Toth, R. A. Durst, and G. S. Wilson, Biosens. Bioelectron. 16 (2001) 121.
[7] J. M. Kauffmann, Fabad J. Pharm. Sci. 28 (2004) 107.
[8] M. C. Danner, A. Robertson, V. Behrends, and J. Reiss, Sci. Total Environ. 664 (2019) 793.
[9] Q. Zhou, Y. Zhang, N. Wang, L. Zhu, and H. Tang, Food Control. 46 (2014) 324.
[10] S. A. Kraemer, A. Ramachandran, and G. G. Perron, Microorganisms. 7 (2019) 180.
[11] D. Madunić-Čačić, and M. Sak-Bosnar, Int. J. Electrochem. Sci. 6 (2011) 1630.
[12] V. Gaudin, Biosens. Bioelectron. 90 (2017) 363.
[13] Y. Zhou, L. Tang, G. Zeng, C. Zhang, X. Xie, Y. Liu, J. Wang, J. Tang, Y. Zhang, and Y. Deng, Talanta 146 (2016) 641.
[14] X. Shan, Y. Pan, F. Dai, X. Chen, W. Wang, and Z. Chen, Microchem. J. 155 (2020) 104708.
[15] A. Benvidi, M.D. Tezerjani, S.M. Moshtaghiun, and M. Mazloum-Ardakani, Microchim. Acta 183 (2016) 1797.

[16] A. De La Escosura-Muñiz, L. Baptista-Pires, L. Serrano, L. Altet, O. Francino, A. Sánchez, and A. Merkoçi, Small 12 (2016) 205.

[17] J. Li, J. He, C. Zhang, J. Chen, W. Mao, and C. Yu, Biosens. Bioelectron. 130 (2019) 166.

[18] Q. Zhang, D. Jiang, C. Xu, Y. Ge, X. Liu, Q. Wei, L. Huang, X. Ren, C. Wang, and Y. Wang, Sens. Actuators B 320 (2020) 128.

[19] N. H. Maniya, and D. N. Srivastava, Materials Science in Semiconductor Processing 115 (2020) 105126.

[20] T. Takagi, J. Intell. Mater. Syst. Struct. 1 (1990) 149.

[21] S. Thangudu, Appl. Nanomater. Hum. Heal, Springer (2020) pp. 287.

[22] A. Chen, and S. Chatterjee, Chem. Soc. Rev. 42 (2013) 5425.

[23] S. Kurbanoglu, and S. A. Ozkan, J. Pharm. Biomed. Anal. 147 (2018) 439.

[24] F. Arduini, S. Cinti, V. Mazzaracchio, V. Scognamiglio, A. Amine, and D. Moscone, Biosens. Bioelectron. 156 (2020) 112033.

[25] A. Fiorani, J. P. Merino, A. Zanut, A. Criado, G. Valenti, M. Prato, and F. Paolucci, Curr. Opin. Electrochem. 16 (2019) 66.

[26] H. Gergeroglu, S. Yildirim, and M. F. Ebeoglugil, SN Appl. Sci. 2 (2020) 1.

[27] R. Leary, and A. Westwood, Carbon 9 (2011) 741.

[28] Z. Zhu, Nano-Micro Lett. 9 (2017) 1.

[29] W. Yang, K. R. Ratinac, S. R. Ringer, P. Thordarson, J. J. Gooding, and F. Braet, Angew. Chemie-Int. Ed. 49.12 (2010) 2114.

[30] Y. Li, H. J. Schluesener, and S. Xu, Gold Bull. 43 (2010) 29.

[31] J. M. Pingarrón, and P. Yáñez-Sedeño, Electrochim. Acta 19 (2008) 5848.

[32] D. Quesada-González, and A. Merkoçi, Biosens. Bioelectron. 73 (2015) 47.

[33] H. Aldewachi, T. Chalati, M. N. Woodroofe, N. Bricklebank, B. Sharrack, and P. Gardiner, Nanoscale 10 (2018) 18.

[34] Z. Zhu, New Dev. Gold Nanomater. Res. 3 (2016) 2308.

[35] E. Hutter, and D. Maysinger, Trends Pharmacol. Sci. 34 (2013) 497.

[36] P. Yáñez-Sedeño, and J. M. Pingarrón, Anal. Bioanal. Chem. 382 (2005) 884.

[37] M. Lin, H. Pei, F. Yang, C. Fan, and X. Zuo, Adv. Mater. (2013) 3490.

[38] J. Cao, T. Sun, and K. T. V. Grattan, Sens. Actuators B 195 (2014) 332.

[39] J. J. Storhoff, S. S. Marla, P. Bao, S. Hagenow, H. Mehta, A. Lucas, V. Garimella, T. Patno, W. Buckingham, W. Cork, U. R. Müller, Biosens. Bioelectron. 19 (2004) 875.

[40] M. Vidotti, R. F. Carvalhal, R. K. Mendes, D. C. M. Ferreira, L. T. Kubota, J. Braz. Chem. Soc. 22 (2011) 3.

[41] J. H. Lee, H. Y. Cho, H. K. Choi, J. Y. Lee, and J. W. Choi, Int. J. Mol. Sci. 19.7 (2018) 2021.

[42] M. Li, T. Chen, J.J. Gooding, and J. Liu, ACS Sensors 4 (2019) 1732.

[43] H. Sun, L. Wu, W. Wei, and X. Qu, Mater. Today 16 (2013) 433.

[44] M. Stanisavljevic, S. Krizkova, M. Vaculovicova, R. Kizek, and V. Adam, Biosens. Bioelectron. 74 (2015) 562.

[45] X. Zhang, Q. Guo, and D. Cui, Sensors 9 (2009) 1033.

[46] Y. Zhang, and A. Clapp, Sensors 11 (2011) 11036.

[47] M. F. Frasco, N. Chaniotakis, Sensors 9 (2009) 7266.

[48] S. Zhu, Q. Meng, L. Wang, J. Zhang, Y. Song, H. Jin, K. Zhang, H. Sun, H. Wang, and B. Yang, Angew. Chemie-Int. Ed. 125 (2013) 4045.

[49] L. Shi, V. De Paoli, N. Rosenzweig, and Z. Rosenzweig, J. Am. Chem. Soc. 128 (2006) 10378.

[50] P. Jorge, M. A. Martins, T. Trindade, J. L. Santos, F. Farahi, Sensors 7 (2007) 3489.

[51] L. Shao, Y. Gao, and F. Yan, Sensors 11 (2011) 11736.

[52] A. Loiseau, V. Asila, G. Boitel-Aullen, M. Lam, M. Salmain, and S. Boujday, Biosensors 9 (2019) 78.

[53] C. Wang, M. Luconi, A. Masi, L. Fernandez, Silver Nanoparticles, Vol. 12 (2010).

[54] A. D. McFarland, and R.P. Van Duyne, Nano Lett. 3 (2003) 1057.

[55] C. Liu, X. Yang, H. Yuan, Z. Zhou, and D. Xiao, Sensors 7 (2007) 708.

[56] T. V. Duncan, Colloid Interface Sci. 363 (2011) 1.

[57] D. Song, Y. Li, X. Lu, M. Sun, H. Liu, G. Yu, F. Gao, Anal. Chim. Acta. 982 (2017): 168

[58] L. M. Lu, H. B. Li, F. Qu, X. B. Zhang, G. L. Shen, R. Q. Yu, Biosens. Bioelectron. 26 (2011) 3500.

[59] T. D. Thanh, J. Balamurugan, S. H. Lee, N. H. Kim, J. H. Lee, Biosens. Bioelectron. 85 (2016) 669.

[60] Z. Li, X. Wang, G. Wen, S. Shuang, C. Dong, M.C. Paau, M. M. F. Choi, Biosens. Bioelectron. 26 (2011) 4619.

[61] K. V. Ragavan, P. Egan, S. Neethirajan, Sens. Actuators B Chem. 273 (2018) 1385.

[62] C. Feng, X. Yue, F. Li, and C. Wei, Biosens. Bioelectron. 39 (2013) 51.

[63] H. Bagheri, E. Ranjbari, M. Amiri-Aref, A. Hajian, Y. H. Ardakani, and S. Amidi, Biosens. Bioelectron. 85 (2016) 814.

[64] D. Ziental, B. Czarczynska-Goslinska, D. T. Mlynarczyk, A. Glowacka-Sobotta, B. Stanisz, T. Goslinski, and L. Sobotta, Nanomaterials10 (2020) 387.

[65] M. Maniruzzaman, S. D. Jang, and J. Kim, Mater. Sci. Eng. B 177 (2012) 844.

[66] A. A. Petrie, A. M. van der Ven, and J. F. Honek, Future Medicine (2013) 68.

[67] G. M. Whitesides, Small. 1 (2005) 172.

[68] W. A. Goddard, D. Brenner, S. E. Lyshevski, G. J. Iafrate, CRC press (2007).

[69] N.R. Scott, Vet. Res. Commun. 31 (2007) 139.

[70] V. Thomas, D. R. Dean, Y. K. Vohra, Curr. Nanosci. 2 (2006) 155.

[71] P. I. Dolez, Nanoengineering: Global Approaches to Health Safty Issues, Elsevier, USA (2015).
[72] V. V. Pokropivny, V. V. Skorokhod, Mater. Sci. Eng. C 27 (2007) 990.
[73] H. Gleiter, Acta Mater. 48 (2000) 1.
[74] Y. Yang, M. Vance, F. Tou, A. Tiwari, M. Liu, and M. F. Hochella, Environ. Sci. Nano 3.3 (2016) 534.
[75] G. Oberdörster, E. Oberdörster, and J. Oberdörster, Environ. Health Perspect. 16 (2008) 927.
[76] Z. Yu, L. Tetard, L. Zhai, and J. Thomas, Energy Environ. Sci. 8 (2015) 702.
[77] K. An, N. Lee, J. Park, S. C. Kim, Y. Hwang, J. G. Park, J. Y. Kim, J. H. Park, M. J. Han, J. Yu, and T. Hyeon. Am. Chem. Soc. 128 (2006) 9753.
[78] A.M. Smith, and S. Nie, Acc. Chem. Res. 108 (2004) 5905.
[79] P. N. Sudha, K. Sangeetha, K. Vijayalakshmi, and A. Barhoum, Emerg. Appl. Nanoparticles Archit. Nanostructures Curr. Prospect. Futur. Trends (2018) 341.
[80] A. Yamano, K. Takata, and H. Kozuka, J. Appl. Phys. 111 (2012) 054109.
[81] J. Y. Lee, J. H. Shin, G. H. Lee, C. H. Lee, Nanomaterials 6 (2016) 193.
[82] T. S. Abdo, V. G. Kumar, Nanomaterial and Polymer Membranes (2016) 83.
[83] T. A. Saleh, V.K. Gupta, Nanomater. Polym. Membr. Eds. 7 (2018) 490.
[84] X.Y. Yu, Z. G. Liu, X. J. Huang, Trends Environ. Anal. Chem. 3 (2014) 28.
[85] P. Ramnani, N. M. Saucedo, A. Mulchandani, Chemosphere 143 (2016) 85.
[86] F. Liu, G. Xiang, X. Chen, F. Luo, D. Jiang, S. Huang, Y. Li, and X. Pu, RSC Adv. 4 (2014) 13934.
[87] A. M. Wen, and N. F. Steinmetz, Chem. Soc. Rev. 45 (2016) 4074.
[88] M. I. Sabela, T. Mpanza, S. Kanchi, D. Sharma, and K. Bisetty, Biosens. Bioelectron. 83 (2016) 45.
[89] H. Cerjak, Mater. Technol. (2009) 74.
[90] S. Iijima, Nature. 354 (1991) 56.
[91] M. Pumera, Chem. Soc. Rev. 39 (2010) 4146.
[92] Z. Yang, J. Ren, Z. Zhang, X. Chen, G. Guan, L. Qiu, Y. Zhang, and H. Peng, Chem. Rev. 115 (2015) 5159.
[93] X. Yu, W. Zhang, P. Zhang, and Z. Su, Biosens. Bioelectron. 89 (2017) 72.
[94] P. Orsu, and A. Koyyada, Mater. Today Commun. 22 (2020) 100823.
[95] Y. Alhamoud, D. Yang, S. S. Fiati Kenston, G. Liu, L. Liu, H. Zhou, F. Ahmed, and J. Zhao, Biosens. Bioelectron. 95 (2019) 103208.
[96] L. Qian, A. R. Thiruppathi, R. Elmahdy, J. van der Zalm, and A. Chen, Sensors 20 (2020) 1252.
[97] T. W. Chen, J. Princy Merlin, S. M. Chen, S. Anandaraj, M. S. Elshikh, T. W. Tseng, K. Wang, D. Qi, and J. Jiang, Ultrason. Sonochem. 64 (2020) 104717.

[98] S. A. Hashemi, S. M. Mousavi, S. Bahrani, S. Ramakrishna, A. Babapoor, and W. H. Chiang, Anal. Chim. Acta 1107 (2020) 183.

[99] C. Zhu, G. Yang, H. Li, D. Du, and Y. Lin, Anal. Chem. 6 (2015) 230.

[100] P. Chandra, H. B. Noh, M. S. Won, and Y. B. Shim, Biosens. Bioelectron. 26 (2011) 4442.

[101] J. Kudr, Y. Haddad, L. Richtera, Z. Heger, M. Cernak, V. Adam, and O. Zitka, Nanomaterials 7 (2017) 243.

[102] O. Rubilar, M. Rai, G. Tortella, M. C. Diez, A. B. Seabra, and N. Durán, Lett. 35 (2013) 1365.

[103] A. C. Niehoff, A. Moosmann, J. Söbbing, A. Wiehe, D. Mulac, C. A. Wehe, O. Reifschneider, F. Blaske, S. Wagner, M. Sperling, H. Von Briesen, K. Langer, and U. Karst, Metallomics. 6 (2014) 77.

[104] L. Lan, Y. Yao, J. Ping, and Y. Ying, Biosens. Bioelectron. 91 (2017) 504.

[105] N. K. Bakirhan, and S. A. Ozkan, Handbook of Nanomaterials for Industrial Applications, Chapter 28, Elsevier (2018) pp. 520-529.

[106] M. Pedrero, S. Campuzano, and J. M. Pingarrón, J. AOAC Int. 100 (2017) 950.

[107] M. S. Islam, Y. Deng, L. Tong, A. K. Roy, S. N. Faisal, M. Hassan, A. I. Minett, V.G. Gomes, Mater. Today Commun. 10 (2017) 112.

[108] Y. Wang, D. Lu, F. Wang, D. Zhang, J. Zhong, B. Liang, X. Gui, L. Sun, Carbon 161 (2020) 563.

[109] N. Malanowski, T. Heimer, W. Luther, and M. Werner, John Wiley & Sons (2008).

[110] J. A. Calabria, W. L. Vasconcelos, D. J. Daniel, R. Chater, D. McPhail, and A. R. Boccaccini, Constr. Build. Mater. 24 (2010) 384.

[111] T. Beduk, E. Bihar, S.G. Surya, A.N. Castillo, S. Inal, and K. N. Salama, Sens. Actuators B Chem. 306 (2020) 127539.

[112] A. B. Abou Hammad, A. M. Elnahrawy, A. M. Youssef, and A. M. Youssef, Int. J. Biol. Macromol. 125 (2019) 503.

[113] W. D. J. R. Santos, M. Santhiago, I. V. P. Yoshida, L. T. Kubota, Sens. Actuators B Chem. 166 (2012) 739.

[114] S. P. Sajjadi, J. Polym. Eng. Technol. 13 (2005) 38.

[115] L.Y. Meng, B. Wang, M. G. Ma, and K. L. Lin, Mater. Today Chem. 1-2 (2016) 63.

[116] M. Kumar, X. Xiong, Z. Wan, Y. Sun, D. C. W. Tsang, J. Gupta, B. Gao, X. Cao, J. Tang, and Y. S. Ok, Bioresour. Technol. 312 (2020): 123613

[117] S. O. Amusat, T. G. Kebede, S. Dube, and M. M. Nindi, J. Water Process Eng. 41 (2021) 101993.

[118] Y. X. Gan, A. H. Jayatissa, Z. Yu, X. Chen, and M. Li, J. Nanomater. 27 (2020) 1699.

[119] G. Maduraiveeran, W. Jin, Trends Environ. Anal. Chem. 13 (2017) 10.

[120] B. Feier, A. Florea, C. Cristea, and R. Săndulescu, Curr. Opin. Electrochem. 11 (2018) 1.

[121] A. Akkoyun, V. F. Kohen, U. Bilitewski, Sens. Actuators B Chem. 70 (2000) 12.

[122] B. Prieto-Simón, N. M. Bandaru, C. Saint, and N. H. Voelcker, Biosens. Bioelectron. 67 (2015) 642.

[123] S. Kurbanoglu, S. A. Ozkan, and A. Merkoçi, Biosens. Bioelectron. 89 (2017) 886.

[124] C. Wang, and C. Yu, Rev. Anal. Chem. 32 (2013) 1.

[125] J. H. Coelho, A. P. P. Eisele, C. F. Valezi, G. J. Mattos, J. G. Schirmann, R. F. H. Dekker, A. M. Barbosa-Dekker, and E. R. Sartori, Talanta 204 (2019) 475.

[126] A. Munawar, M. A. Tahir, A. Shaheen, P. A. Lieberzeit, W. S. Khan, and S. Z. Bajwa, J. Hazard. Mater. 342 (2018) 96.

[127] I. Cesarino, V. Cesarino, and M. R. V. Lanza, Sens. Actuators B Chem. 487 (2014) 82.

[128] L. Del Torno-De Román, M. Asunción Alonso-Lomillo, O. Domínguez-Renedo, and M. Julia Arcos-Martínez. Sens. Actuators B Chem. 220 (2015) 340.

[129] X. Zhang, K. P. Wang, L. N. Zhang, Y. C. Zhang, and L. Shen, Anal. Chim. Acta. 1036 (2018) 26.

[130] M. Afzali, A. Mostafavi, and T. Shamsipur, Arab. J. Chem. 13 (2020) 6626.

[131] P. A. Raymundo-Pereira, A. M. Campos, C. D. Mendonça, M. L. Calegaro, S. A. S. Machado, and O. N. Oliveira, Sens. Actuators, B Chem. 252 (2017) 165.

[132] C. Li, B. Zheng, T. Zhang, J. Zhao, Y. Gu, X. Yan, Y. Li, W. Liu, G. Feng, and Z. Zhang, RSC Adv. 6 (2016) 45202.

[133] Y. Zhu, P. Chandra, K. M. Song, C. Ban, and Y. B. Shim, Biosens. Bioelectron. 36 (2012) 29.

[134] X. Chen, L. Zhao, X. Tian, S. Lian, Z. Huang, and X. Chen, Talanta 129 (2014) 26.

[135] S. Tran, P. J. DeGiovanni, B. Piel, and P. Rai, Clin. Transl. Med. 6 (2017) 1.

[136] Y. Zhang, R. Zhang, X. Yang, H. Qi, and C. Zhang, J. Pharm. Anal. 9 (2019) 9.

[137] E. Sehit, and Z. Altintas, Biosens. Bioelectron. 159 (2020) 112165.

[138] H. Li, J. He, Y. Zhao, D. Wu, Y. Cai, Q. Wei, and M. Yang, Electrochim. Acta 56 (2011) 2960

[139] S. Rashtbari, G. Dehghan, and M. Amini, Anal. Chim. Acta 1109 (2020) 148.

[140] Y. Zhu, Z. Xu, J. Gao, W. Ji, and J. Zhang, Biosens. Bioelectron. 160 (2020) 112210.

[141] G. Liu, and Y. Lin, Electrochem. Commun. 8 (2006) 251.

[142] J. Yoon, S. N. Lee, M. K. Shin, H. W. Kim, H. K. Choi, T. Lee, and J. W. Choi, Biosens. Bioelectron. 140 (2019) 111343.

[143] Z. Rafiee, A. Mosahebfard, and M. H. Sheikhi, Mater. Sci. Semicond. Process. 115 (2020) 105116.

[144] R. H. Farahi, A. Passian, L. Tetard, and T. Thundat, ACS Nano 45 (2012) 125101.

[145] D. Du, W. Chen, W. Zhang, D. Liu, H. Li, and Y. Lin, Biosens. Bioelectron. 56 (2014) 38.

[146] D. Wu, D. Du, and Y. Lin, TrAC-Trends Anal. Chem. 83 (2016) 95.

[147] Y. Zeng, Z. Zhu, D. Du, and Y. Lin, J. Electroanal. Chem. 781 (2016) 147.

[148] K. Kor, and K. Zarei, J. Electroanal. Chem. 733 (2014) 39.

[149] Y. Guo, G. Shen, X. Sun, and X. Wang, IEEE Sens. J. 15 (2014) 1951.

[150] X. Qin, Y. Yin, H. Yu, W. Guo, and M. Pei, Biosens. Bioelectron. 27 (2017) 713.

[151] Y. Yuan, F. Zhang, H. Wang, L. Gao, and Z. Wang, ECS J. Solid State Sci. Technol. 7.12 (2018) 201.

[152] H. Song, L. Zhang, F. Yu, B.C. Ye, and Y. Li, Electrochim. Acta 208 (2016) 10.

[153] T. Gan, Z. Lv, N. Liu, Z. Shi, J. Sun, and Y. Liu, J. Electrochem. Soc. 162 (2015) 200.