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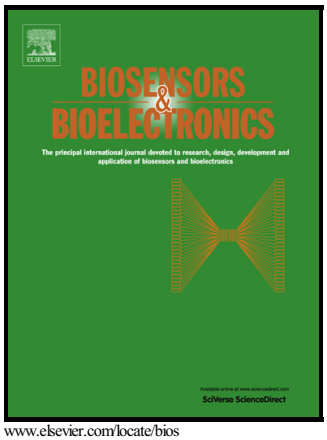

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Graphene, Carbon Nanotubes, Zinc oxide and Gold as Elite Nanomaterials for Fabrication of Biosensors for Healthcare

Sandeep Kumar[1]*, Wandit Ahlawat[1], Rajesh Kumar[2] and Neeraj Dilbaghi[1]

[1]Department of Bio and Nano Technology, Guru Jambheshwar University of Science and Technology, Hisar- Haryana, 125001, India.

[2]Department of Mechanical Engineering, University Institute of Engineering and Technology, Panjab University, Chandigarh. 160014. India.

*Corresponding authors: Dr. Sandeep Kumar: ksandeep36@yahoo.com

Abstract

Technological advancements worldwide at rapid pace in the area of materials science and nanotechnology have made it possible to synthesize nanoparticles with desirable properties not exhibited by the bulk material. Among variety of available nanomaterials, graphene, carbon nanotubes, zinc oxide and gold nanopartilces proved to be elite and offered amazing electrochemical biosensing. This encourages us to write a review which highlights the recent achievements in the construction of genosensor, immunosensor and enzymatic biosensor based on the above nanomaterials. Carbon based nanomaterials offers a direct electron transfer between the functionalized nanomaterials and active site of bioreceptor without involvement of any mediator which not only amplifies the signal but also provide label free sensing. Gold shows affinity towards immunological molecules and is most routinely used for immunological sensing. Zinc oxide can easily immobilise proteins and hence offers a large group of enzyme based biosensor. Modification of the working electrode by introduction of these nanomaterials or combination of two/three of above nanomaterials together and forming a nanocomposite reflected the best results with excellent stability,

reproducibility and enhanced sensitivity. Highly attractive electrochemical properties and electrocatalytic activity of these elite nanomaterials have facilitated achievement of enhanced signal amplification needed for the construction of ultrasensitive electrochemical affinity biosensors for detection of glucose, cholesterol, E.coli, influenza virus, cancer, human papillomavirus, dopamine, glutamic acid, IgG, IgE, uric acid, ascorbic acid, acetlycholine, cortisol, cytosome, sequence specific DNA and amino acids. Recent researches for bedside biosensors are also discussed.

Keywords: Graphene, Carbon nanotubes, Zinc oxide, Gold, Nanomaterial, Electrochemical Biosensors.

1. Introduction

Recent advancements in the field of nanotechnology have opened the gates for the tremendous achievements in biosensing. Emergence of new materials and their hybrids have raised hopes for development of new biosensors capable of delivering on site results of variety of analytes (at smaller level) simultaneously without requiring skilled personnel or sophisticated machinery. A biosensor is a device consisting of a biological sensing component i.e the bioreceptor, which is connected to a detector or transducer, the bioreceptor detect the analyte and transducer convert the recognizable response into a measurable signal. Depending upon the types of bioreceptors, biosensors can be categorized as immunobiosensors, enzymatic biosensors, genobiosensors and based upon the transduction process, biosensors can further be classified as optical, piezoelectric, electrochemical, and thermometric biosensors. The electrochemical biosensors are successfully commercialized, more prevalent and are numerous (Dzyadevych et al., 2008). These are further subdivided into amperometeric, potentiometric and impedimetric biosensors. The history of biosensors began with the fabrication of enzyme electrodes by Leland C. Clark in 1962. After that researchers from numerous fields of science have come together to develop more sophisticated, reliable biosensors which detect small molecules exactly, effectively, and expeditiously which is paramount for clinical screening, diagnoses, drug discovery, and for developing various research assays.

Viewing the last decade of biosensor growth, one can clearly make out the rapid technological developments in the field of nanotechnology. This emerging technology brings new possibilities for construction and development of novel biosensors (Turner, 2013). See

supplementary file, section 1 for figure 1 depicting the growth of biosensors. At nanoscale, materials show unique properties that help to fabricate sensors with high sensitivity and rapid analyte detection. Nanomaterials have been used for direct wiring of biological element to electrode surface to enhance the electrochemical reaction and for amplification of signal. Nanomaterials based biosensors use an entrapped bioreceptor probe that is specific for the specific analyte molecules. Graphene, carbon nanotubes, nanowires, dendrimers, quantum dots and various nanocomposites are used for inventing new novel sensors. Nanomaterials are revolutionizing the areas of biological and chemical analysis, to enable fast detection of multiple analytes in vivo by developing nanosensors, nanoprobes and other nanosystems. Few existing examples of sensors are mentioned here such as Ag Plus diagnostics have patented an immunoassay for troponin, thyroid stimulating hormone and estradiol tests in their detection system utilizing silver nanoparticles; Nova biomedical has developed hand held point of care biosensors named Stat strip Gluc, Stat strip Lac, Stat sensor Creat for glucose, lactate and creatinine respectively; Abbot Point of Care has developed i-STAT, bedside blood testing biosensor which gives results within minutes; Medtronic diabetes have developed Guardian real time system which sense glucose every 5mins and Palm Sens have fabricated screen printed electrodes (SPE) named AC1.AChE, AC1.GOx, AC1,W1.R1 etc for detection of acetylcholinesterase, glucose and dopamine which are used in heatlhcare and onsite detection of important chemicals which are useful in forensic, national security and diagnostics. For fabrication of desired sensor, there are few important parameters that should be taken into account such as type of sensing materials, type of transducer, design of sensor, ease of operation, less energy consumption, packaging, electronic circuit and automation of sample acquisition (Kaushik et al., 2014).

In this paper, we review recent developments done for utilization of biosensors in various fields as well as their future applications. In particular, we have reviewed the use of nanomaterials of elite group such as graphene, carbon nanotubes, zinc oxide and gold in modifying the electrode surface and hence increasing the sensitivity for the analyte. We have discussed immunosensors, genosensors and enzymatic sensors for detection of various biological molecules such as glucose, cholesterol, uric acid, antibodies etc. Providing a cost effective biosensor to a common man with limited budgets for meeting the everyday requirements is a challenge which can be met by innovative technologies. Researchers are tremendously engaged in raising the standards of biosensors.

2. Nanomaterials Used in Biosensor

2.1. Carbon based Nanomaterials

2.1.1. Graphene

Graphene, a two dimensional nanomaterial, consisting of closely packed carbon atoms arranged in a hexagonal manner forming a monolayer, has received considerable attention in the field of sensing due to its unique physicochemical properties such as large surface area to volume ratio, strong mechanical strength, acceptable biocompatibility, excellent thermal & electrical conductivity, low cost, safety and ease of production in comparison to other carbon based nanomaterials (Shao et al., 2010). It also exhibits a broad electrochemical potential and low charge-transfer resistance compared to that of graphite and glassy carbon (GC) (Zhou et al., 2009). Electron transfer is favoured by both the surface physicochemistry and electronic structure of graphene (Tang et al., 2009). Graphene offers high enzyme loading capacity that sharply increases the sensitivity. Graphene also offers a direct electron transfer between the functionalized graphene and active site of bioreceptor without involvement of any mediator and all these features make graphene a suitable material for electrochemical sensors. Graphene (sheet like) proved themselves a better performer than single and multi walled carbon nanotubes (SWCNT and MWCNT) due to large availability of active sites. Graphene based biosensors are available for sensing enzymes, hydrogen peroxides, dopamine, and reduced b-nicotinamide adenine dinucleotide (NADH) molecules (Shan et al., 2009; Wang et al., 2009a; Alwarappan et al., 2009). Enzymatic biosensors face a serious problem of enzyme inactivation and enzyme loss which affects the biosensor performance. Fan et al has developed a novel H_20_2 biosensor using biomimetic graphene capsules which initially encapsulated horseradish peroxidise (HRP) with the help of porous CaCO3 as sacrificial templates which mimic the real enzymes. Further indium tin oxide was taken as substrate and a multilayered biosensor was constructed by assembling the capsules and graphene-poly (sodium 4-styrenesulfonate) alternatively. The sensor presented an excellent stability, dynamic range of 0.01-12 mmol/L & a lower detection limit of 3.3 mmol/L (Fan et al., 2015). Such feasible enzyme sensors must be considered as a bud to come out with different fruitful results as on the same principle and availability of numerous enzyme, researchers could construct various biosensors without losing the activity of enzyme and saving the money invested for the purchase of enzyme every time.

Numerous materials such as conducting polymers, proteins, noble metals, cyclodextrin, quantum dots etc have been investigated to enhance the electrochemical properties of graphene and its derivatives by hybridization (Pavlidis et al., 2014). Graphene nanohybrids were precisely designed to achieve ultra high sensitivity. First time in 2009, graphene was utilized to construct a glucose biosensor. A modified electrode consisting of nanocomposites of graphene and polyethylenimine (PEI) functionalized ionic liquid was used that exhibited broader linear glucose response, good reproducibility and high stability (Shan et al., 2009). PEI (conducting polymer) improved the sensitivity of graphene electrode. A very simple, sensitive, label free, low cost, quick, easy to operate, point of care biosensor for detection of platelet derived microparticles was designed with graphene oxide (Kailashiya et al., 2015). Platelet derived microparticles are risk factor circulating in the blood of patients suffering from cardiovascular diseases like mycocardial infarction and strokes. Although there are many detection techniques that require huge money, time, big instruments, facilities and expert technicians but developing a biosensor with such an ease, accuracy, speed and sensitivity by using commonly available reagents and methods is a milestone in the history of biosensors. A low cost graphene based biosensor for E.coli detection with 60 % sensitivity was developed on a flexible acetate sheet for 4.5×10^7 cfu/mL concentration of E.coli (Basu et al., 2014). Another genosensor for E.coli detection was recently reported which utilized graphene oxide modified iron oxide-chitosan film deposited on indium tin oxide (ITO) coated glass substrate. The sensor exhibited wide detection range of 10^{-6}-10^{-14} M and retains 90% of initial activity after six cycles of use (Tiwari et al., 2015). Recently, graphene with gold nanorod and polythionine were used to modify glassy carbon electrode on which capture probe was immobilized to connect the target DNA strand and the DNA nanostructure specific for the human papillomavirus DNA (Huang et al., 2015). The method exhibits excellent results in human serum samples and presented a great potential in clinical and diagnostic analysis without labelling and use of enzyme. From literature, one can easily conclude that graphene with gold nanoparticles is majorly used in fabrication of immunosensor and genosensors because gold helps in immobilization of immunological entities and graphene itself provides large network of active sites. Detection of the disease causing pathogens and fabrication of DNA sensors for specific sequence detection could provide platform to cure disease and fight with the diseases on right time. Thus, attempts should be made to construct novel sensors for severe diseases and pathogens. See supplementary file for more health care and explosives detection sensors, Section 2.1.1. and table 1 for more literature. Figure 1 represents the generalized approach for construction of biosensor based on graphene.

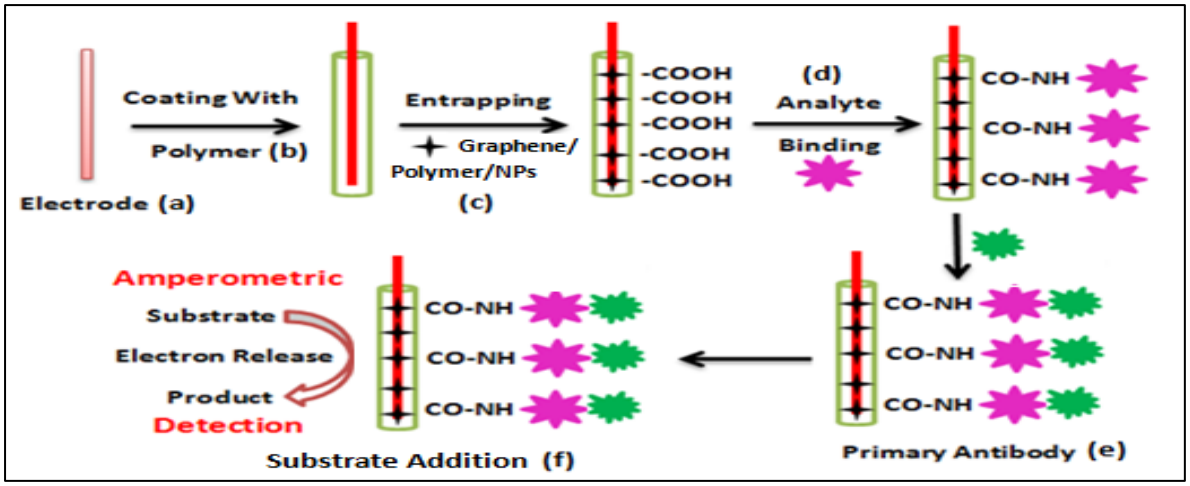

Figure 1. Basic representation of biosensor fabricated using graphene nanocomposite: (a) Any conducting electrode (Gold,Platinum etc) with immobilized graphene layer (b)Modified electrode coated with conducting polymer (c) Modified electrode with nanocomposite (graphene+polymer+nanoparticles) (d) Analyte binding with nanoparticles (e) Primary antibody interaction with analyte (f) Addition of substrate results in electron release and amperometric detection.

2.1.2. Carbon Nanotubes (CNTs)

CNTs are sp^2 hybridized carbon atom rolled graphene sheets which are hollow from inside with diameter in nanosize and can have length from nanometers to microns. Due to their remarkable structural, electronic and mechanical properties, CNTs have gained enormous interest since their discovery. These exhibit variable conductivity and have small size which make them a good choice to be used in the field of molecular electronics as molecular wires. Functionalization of CNT can be done by both covalent and non-covalent binding with different chemical groups which makes CNTs biocompatible for conjugation with biomolecules and hence making them a suitable candidate for biosensing. The functional groups such as amine and carboxyl, increase the rate of electron transfer. In practical, both the water-soluble polymers based functionalization of CNTs or surface functionalization with ionic or hydrophilic groups of CNTs helps to achieve CNT solubilization in aqueous media and is a significant parameter for CNTs to work as a supporting matrix or scaffold for the entrapment of proteins/DNA/Antibody/enzymes. Functionalization of CNTs also improves the direct electron transfer between the biological element active sites and the electrode. Because of the above reason, conductivity of CNTs (mainly MWCNTs) is commonly improved by functionalizing them with redox polymers, hapten molecules, thiol derivatives and N-ethyl-N-(3-dimethylaminopropyl carbodiimide-N-hydroxy succinimide (EDS-NHS). An amperometric

acrylamide biosensor was fabricated by immobilization of Hb onto nanocomposite of cMWCNT and Fe_2O_4 nanoparticles (NPs) electrodeposited onto gold electrode through a polymer chitosan film (Batra et al., 2013). A remarkable increased sensitivity and selectivity was obtained for acrylamide. The sensor presented a quick response, wider linear range, lower limit of detection (0.02 nM), good reproducibility, and long stability. Recently, an immunosensor was reported for cancer detection utilizing poly (diallyldimethylammonium chloride) (PDDA)-functionalized CNTs for assembly of HRP and concanavalin A (ConA) on the gold electrode. Utilizing the biospecific interaction between HRP and ConA, PDDA modified CNTs form a complex of CNTs/PDDA/HRP/ConA which later on combined with Ab labelled HRP and form a sandwich. The immunosensor exhibits a good linear range from 0.05-5 ng/mL to 5-200 ng/mL and a detection limit of 0.018 ng/mL (Yang et al., 2014). A fresh glucose biosensor was fabricated using free CNTs and enzymatic electrode immobilizing glucose oxidase (GOx), GOx coating and GOx precipitate coating. This sensor reflected fabulous improvement in sensing, stability and electron transfer (Kim et al 2015). See supplementary file, section 2.1.2. and table 2 for more literature. Figure 2 depicts the schematic representation for construction of biosensor based on CNTs.

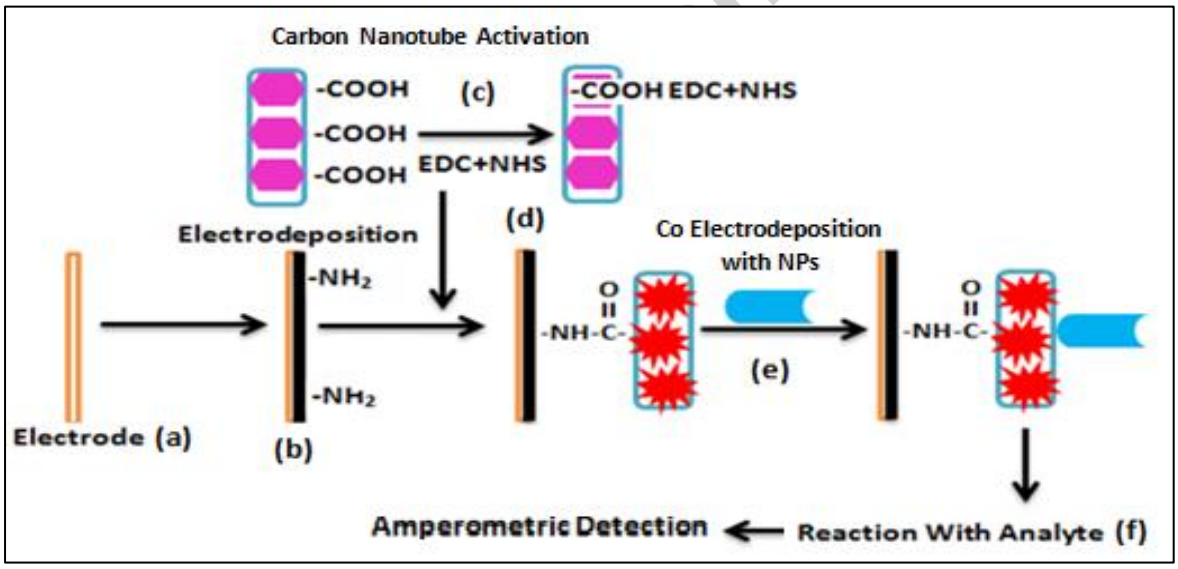

Figure 2. Basic representation of biosensor fabricated using carbon nanotube: (a) Working electrode (Gold, Platinum etc) (b) Modified electrode (c) Carboxylated carbon nanotubes activated by EDC-NHS (d) Co-Electrodeposition of activated carbon nanotubes and nanoparticles (ZnO,TiO_2, Fe_3O_4 etc) on electrode (e) Binding of analyte to electrode (f) Reaction of analyte resulting in amperometric detection.

2.2. Metal and metal oxide nanoparticles.

2.2.1. Zinc oxide (ZnO)

ZnO has a wide band gap of 3.37 eV which makes it an attractive nanomaterial in comparsion to others. ZnO is a semiconducting material that exhibits high surface area to volume ratio, high biocompatibility, highly stability, biomimetic, less toxicity and have a good electron transferring feature. ZnO nanoparticles (NPs) are good source for immobilization of proteins due to high isoelectric point. Numerous biosensors with ZnO have been reported for biomolecules including cholesterol, glucose, urea, cortisol, H_2O_2, glutamate etc. Different shapes of ZnO were exploited to fabricate biosensors. For example, spherical and flower shaped ZnO NPs were immobilized on Au electrode to fabricate two cholesterol biosensors (Umar et al., 2009; Umar et al., 2009a). A layer of nafion was also applied to flower shaped ZnO. The sensor with nafion offered more sensitivity and reproducibility, low Km value, lower detection limit and quick response which were due to the network formed by nafion which prevents enzyme leaking. Different structure of ZnO such as ZnO nanorod and nanocomb were also executed to construct glucose biosensor by modifying electrode (Wei et al., 2006; Wang et al.,2006). GOx was immobilized to both ZnO structure and nafion was used to cover nanocombs. Presence of nafion increases the enzyme-electrode interaction and thus enhanced performance of biosensor. Two label free, low cost immunosensors for detection of cortisol were developed utilizing one dimensional ZnO nanorods (ZnO-NRs) and two dimensional ZnO nanoflakes (ZnO-NFs) (Vabbina et al., 2015). Both the nanostructures provide large surface area, stability, biocompatibility and enhances the sensing ability of sensor. The immunosensors exhibit selective electrochemical cortisol detection at 1 pM 100 times better than enzyme linked immunosorbent assay (ELISA). 7.74 μA/M and 11.86μA/M values were the sensitivity measured for ZnO-NFs and ZnO-NRs respectively. Lately, Kumar et al. reported a chemical biosensor for hydrazine which is ultra-highly sensitive and is based on ZnO nanocones. The sensor offered a high sensitive of 50 x 10^4 μA/μM/cm^2 and low detection limit of 0.01 μM (Kumar et al., 2015).

ZnO often formed nanocomposite with polymers, AuNPs, graphene, MWCNTs etc and these hybrids are well known for immobilization of enzymes that helps in direct electron transfer between the electrode and active site which results in superior properties for amperometric sensing. An amperometric glucose biosensor with good selectivity, stability, reproducibility and repeatability was fabricated using the ZnO and MWCNTs on glassy carbon electrode (Palanisamy et al., 2012). The sensor exhibited a linear range of 0.2 - 27.2 mM, 20 μM as limit of detection and a sensitivity of 4.18 μA/ mM. A ZnO/graphene and S6 aptamers based

biosensor for detection of SK-BR-3 breast cancer cells was constructed on ITO electrode (Liu et al., 2014). A low detection limit of 58 cells mL^{-1} and a dynamic linear range of 1x 10^2- 1x10^6cells mL^{-1} was observed. Lately, ultra sensitive uric acid biosensor was developed using ZnO nanosheets grown on electrode with high sensitivity, stability, reproducibility and selectivity (Ahmad et al., 2015). ZnO nanosheets provide more surface to interact and result in higher electron transfer between active sites of electrode and enzyme. Extent of communication between enzyme and electrode plays a key role in defining the level of sensitivity, i.e., more the interaction, higher the electron transfer and hence enhanced sensitivity. See supplementary file, section 2.2.1. for more literature. Schematic representation for fabrication of ZnO and gold based biosensor is presented below in figure 3.

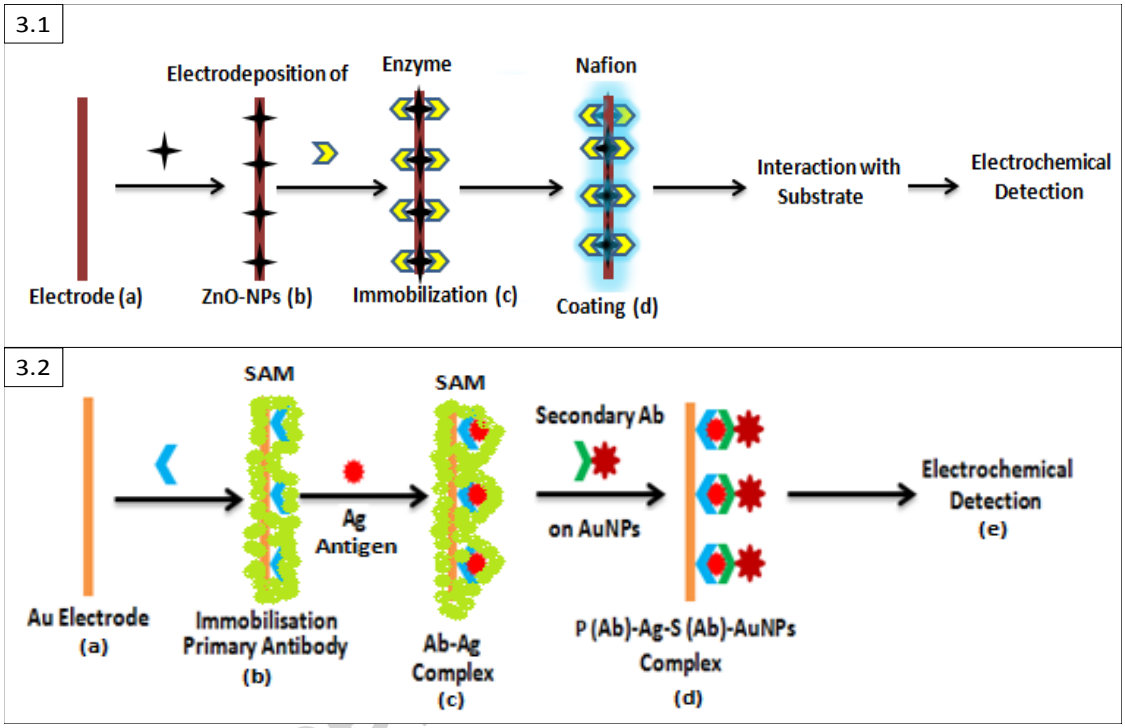

Figure 3.1. Basic representation of biosensor fabricated using ZnO modified electrode: (a) Conducting electrode (Gold, Platinum etc) (b) Electrodeposition of ZnO NPs on electrode (c) Immobilization of enzyme on modified electrode (d) Modified electrode coated with nafion membrane to form matrix. Interaction of enzyme with substrate resulted in electrochemical detection and 3.2. Represents an immunosensor fabricated using gold: (a) Gold electrode (b) Primary antibody immobilized to electrode with help of self assembled monolayer (c) Specific Antigen from serum would bind to forms Ab-Ag complex (d) AuNPs carrying secondary Ab binds to specific antigen resulting in electrochemical detection.

2.2.2. Gold

Gold is an inert metal. Gold nanoparticles (GNPs) show totally different properties from its bulk size. GNPs are biocompatible and extensively employed as stable immobilizer for biomolecules like antibodies, antigen, enzymes etc without distorting their bioactivity. GNPs have high specific surface area, high surface energy, high conductivity and offer numerous adsorption sites to antibodies, enzymes and proteins which make them an ideal choice for biosensors. Gold is a common metal used to modify the electrodes to improve the conductivity and hence the sensitivity. Numerous research has been focused on the use of GNPs coating on electrode to improve the interaction of biomolecule with the electrode surface. An acetylcholinesterase biosensor was fabricated by electrodeposition of GNPs on the electrode surface (Shulga et al., 2007). The sensor delivered good performance on modification with GNPs due to better electron transfer. Modification of gold electrode with ferrocene, casein, CNTs, aptamers and gold nanoparticles have been done for achieving enhanced sensitivity (Mars et al., 2013; Espinoza-Castaneda et al., 2013; Zheng et al., 2013). An universal immunosensor for detection of influenza A virus was fabricated on Au electrode which was a big achievement in the field of sensing. The sensor utilized electrochemical impedance spectroscopy. High sensitivity, small size, low cost, exchangeable elements, universal nature, rapid response are the best features offered by the sensor (Nidzworski et al 2014). Ravalli et al reviewed many GNP based biosensors for detection of numerous biomolecules including carbohydrate antigen 125, prostrate specific antigen, carcino embryonic antigen, mucinI, Human epidermal growth factor receptor 2 & 3, platelet derived growth factor, abnormal prothrombin, alpha fetoprotein, interleukin 6 and concavalin A (Ravalli et al 2015).

Gold Screen printed electrodes (Au-SPE) are most commonly used electrodes for exploring different kind of biosensors. Au-SPE helps to cast antibody in close vicinity with SPE transducer and GNP helps to cast antibody in close vicinity with the antigen and hence results in the increase of sensitivity to pico/femto level. A low cost biosensor for label free detection of cardic troponin I was fabricated using GNP onto SPE. The detection limit obtained was 4.3ng mL^{-1} and linear range was 0.2ng mL^{-1} (Bhalla et al., 2012). See supplementary file, section 2.2.2. for more literature. Streptavidin labelled gold nanoprobe and specific nucleic acid aptamers was used for detection of TNT (Priyanka et al., 2014). More examples of GNP biosensor are provided in supplementary file, section 2.2.2. Thus, it can be concluded that gold is an excellent choice for the development of new biosensors for health care.

Conclusion

Nanomaterials have paved the way to build highly sensitive sensors showing incredible sensing properties and their sensitivity have brought solutions to the unanswered questions. In our review, we have presented that nanomaterial such as graphene, CNT, ZnO and gold are the most sought after and are used to improve the sensitivity for detection of analyte, quicker response time, good reproducibility, longer stability, dynamic linear range, a low detection limit and brought exciting possibilities for development of hybrid devices for health care. Utilization of above nanomaterial in biosensors has resulted in increased detection capabilities with enhanced specificity and lesser analyte requirement. Biosensors are exploited from a simple blood test to high level disease treatment such as cancer. Best feature of biosensor is their low range of detection, that is, can sense analytes in pico/femto levels, small size, cheap, time saving and bedside testing of patient. Though significant advancements have been realized in this emerging field, still there is a big challenge to fabricate more point of concern and point of care precise biosensors for several lethal and unlethal diseases.

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HIGHLIGHTS

- Graphene, CNTs, ZnO and Gold belong to Elite Group of Nanomaterials.
- Fabrication of modified electrodes for electrochemical sensing of variety of analytes based on these elite nanomaterials.
- Biosesnors for healthcare applications.
- Promising Biosensors for on site detection of exploives and useful in Forensic, National Security and diagnostics.