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Review paper on recent advances in carbon nanomaterials as electrochemical biosensors

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ABSTRACT

In the last Thirty years, a lot of scientific research has been carrying out in the field of Carbon nanomaterials over the world due to their significant useful features in electronic, optical, mechanical, chemical fields. Carbon nanomaterials based electrochemical biosensors have reported thermal properties. The zero-three dimensional Carbon nanomaterials have exhibited inseparable features that can be easily exploited in the development of advanced technology for sensing applications. The Carbon has been used for the electrochemical electrodes due to its unique electrochemical properties i.e. a large potential window, low cost, a very small background current. The biocompatibility of Carbon nanomaterials has revolutionized the field of electrochemical detection of various analytes or targets. The electrochemical analysis has been used for the qualitative and quantitative determination of amount of electro active analytes.

In this paper, a comprehensive study has been made to highlight the characteristic features of a variety of nanomaterials along with the methods employed for their synthesis. The recent developments in the field of Carbon based nanomaterials for their use as electrochemical biosensors have been thoroughly discussed along with the future prospects and possibilities in this field.

Keywords: Carbon nanotubes, Functionalization of CNTs, DNA, Biosensors.

INTRODUCTION

Carbon Based Nanomaterials

The Carbon atoms, possessing a valency of four, have the ability to form single, double and triple covalent bonds among themselves or with other elements. The ability to form long chains of atoms, thus exhibiting the phenomenon of polymerization. The Carbon atoms possess such an electronic structure and atomic size that makes them capable to exhibit different physical

structures with different physical properties in spite of the same chemical composition. The Carbon atoms can undergo sp , sp^2 , sp^3 hybridizations with a narrow band gap between their 2s and 2p electronic shells [1-3]. The diamond with sp^3 hybridization and graphite with sp^2 hybridization are the two widely known allotropic forms of Carbon. The geometrical structure of the particles in nanomaterials is the basic criterion for their classification. The particles can have shapes of tubes, horns, spheres or

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ellipsoids. The tube or horn shaped particles are called as Carbon nanotubes (CNTs) or Carbon nanohorns (CNHs) respectively; the spherical or ellipsoidal nanoparticles are present in fullerenes [4-6]. The CNMs find vast technical applications in micro and nanoelectronics, gas storage, production of conductive plastics, composites, paints, textiles, batteries with increase life times, biosensors, etc. attributed to their low toxic nature and large scale production for use [7-8]. The fullerene, Carbon nanotubes (CNTs), Graphene, Carbon Nanodiamonds (CNDs) and Carbon dots (CDs) are the most significant allotropic modifications of the nanocarbon [9]. The 0D nanodiamonds, 1D nanotubes, 2D Graphene nanosheets can act as a prototype for the nano composites.

Fullerenes

The allotropic modification of Carbon known as fullerene, was discovered in 1985 by H. W. Kroto, R. F. Curl, and R. F. Smalley [10]. It was the first nanomaterial to be successfully isolated. The characteristic feature of fullerenes is the formation of a number of atomic C_n clusters ($n > 20$) of carbon atoms on a spherical surface. The carbon atoms form covalent bonds with each other in the sp^2 hybridization in fullerenes. They are most commonly present on the surface of the sphere at the vertices of pentagons and hexagons. C_{60} is the fullerene that has been extensively studied and investigated. It has highly symmetric spherical molecules consisting of 60 carbon atoms, present at the vertices of 20 hexagons and 12 pentagons or 60 Carbon atoms comprising of 12-five member rings and 20-six member rings [11]. The diameter of fullerene is 0.7 nm [12]. Fullerenes have been used in the medical field such as in cancer therapies, MRI and gynecological malignancies [13-15].

Synthesis

Fullerenes are basically 0D form of Graphitic carbon and can be visualized as an irregular sheet of Graphene being curled up into a sphere by adding pentagons at its structure. They come in various forms and sizes ranging from 20 to 400 Carbon atoms. They can be synthesized by employing methods such as electric arc-discharge,

electron beam ablation and sputtering [16-17]. Can also be synthesized by using Graphitic electrodes [18-19]. Fullerenes were firstly synthesized by evaporating Graphite electrodes in a Helium atmosphere [20-21]. However, the practical use of fullerenes is limited due to their high synthesis cost and low yields of the methods currently available for their production.

Carbon nanotubes

One of the allotropic modifications of carbon, known as Carbon nanotubes (CNTs) were discovered in 1990 by the Japanese scientist S. Ijima [22]. In CNTs, each carbon atom with 3 electrons forms trigonally coordinated bonds to three carbon atoms by using sp^2 hybridization [23-24]. CNT is basically one layer of Graphene rolled in the form of a hollow tube seamlessly. The rolled Graphene sheets stacked in cylindrical/tubular structures with a diameter of several nanometers is the characteristic feature of carbon nanotubes. The CNTs can have variable length, diameter, the number of layers and chirality vectors. Based on their structures, CNTs can be divided into two basic groups: single walled Carbon nanotubes (SWCNTs) and multi-walled Carbon nanotubes (MWCNTs). The SWCNTs have a diameter around 1–3 nm and a length of few micrometers whereas MWCNTs have a diameter of 5–30 nm and a length around 10 μ m. However, recently the synthesis of CNTs with a length of 600 nm has been investigated and reported [27]. The CNTs have excellent physical properties like rigidity, strength and elasticity as compared to other fibrous materials. They do possess high value of aspect ratio (length to diameter ratio) than other materials. The high aspect ratios of CNTs may vary from 10^2 to 10^7 . The larger aspect ratio comes out for SWCNTs than MWCNTs as a consequence of their smaller diameter. Not only this, they do possess high thermal and electrical conductivities in comparison to other conductive materials. The strength of CNTs is 10–100 times larger than the strong steel at a fraction of steel weight [28]. The one layer of Graphene in CNTs can be rolled in different ways. Based on the rolling of Graphene sheets, the CNTs are classified as zigzag, armchair, chiral, depending on the number of unit vectors in the crystal lattice of Graphene along two directions

in honey comb structure. The chirality has a significant effect on the properties of CNTs. The electrical properties of SWCNTs are a function of their chirality or hexagon orientation with respect to the tube axis. The chirality decides whether a particular CNT is metallic or semiconducting in nature [29]. The SWCNTs can exhibit electrical conductivity or semi conductive properties that depend upon the diameter of the tubes [30-32]. The armchair SWCNTs have electrical conductivity more than that of copper whereas zigzag and chiral SWCNTs do display semi conductive properties for their use in sensor fabrication [33]. The MWCNTs are composed of multiple Carbon layers with inconsistent chirality and can display

extraordinary mechanical attributes instead of exceptional electrical characteristics. These nanomaterials do possess such characteristic feature that makes them potential candidates for use in technological fields. The CNTs have been used as an electrode in electrochemical reactions due to their significant electron transfer capabilities [34]. They can be used in electrochemical sensors as they do have the ability to make electron transfer possible in chemical reactions at the electrode interface [35]. The CNTs find immense applications in the field of nano-electro-mechanical systems [36-37]. Table I shows the values of significant physical, electronic and mechanical characteristic features of CNTs.

Table I. Significant physical, electronic and mechanical characteristic features of CNTs [38].

Specific surface area	190–950 m ² J ⁻¹
Specific gravity	0.7–2.5 g ⁻¹ cm ⁻²
Electrical conductivity	2 × 10 ⁻² –0.3Scm ⁻¹
Thermal conductivity	7000 Wm ⁻¹ K ⁻¹
Elastic Modulus	>1 TPA
Tensile strength	>100 GPa

Synthesis

The CNTs have been synthesized by using Carbon arc discharge, Chemical Vapour Deposition (CVD) and laser ablation methods [39-40]. The Carbon arc discharge with a suitable catalyst was firstly used to synthesize SWCNTs or MWCNTs with a high yield and better control over the size of the synthesized nanotubes [41]. The Laser ablation method gives a lower yield and much smaller diameter but much finer quality [42]. The metallic and semi conductive CNTs can be synthesized through selective functionalization [43]. Selective destruction by electrical heating or separation by density gradient ultra centrifugation [44]. The CVD has been used to produce high quality SWCNTs and MWCNTs in vertically aligned array by using transition metal nanoparticle catalysts [45]. They have been synthesized on a very large scale by using arc

discharge and CVD methods. The CVD method needs simple equipment and mild temperature and pressure conditions and is more suitable for the large scale production of CNTs than the other two methods [46]. The metallic and quasi crystalline substrates have been used to synthesize vertically aligned arrays of CNTs [47]. The transition metals present in Graphite electrodes have produced CNTs with more product output and reproducibility [48]. The transition metal catalysts along with CVD method have been researched to get good quality CNTs in vertically aligned arrays [49]. The CVD synthesis employs the use of catalysts in substrates on which nanotubes grow. The metallic nanoparticles are employed as catalysts and their size depends on the diameter of the nanotubes to be synthesized (0.3–5 nm for SWCNTs, 8 to 10 nm for MWCNTs). The nanoparticles Ni, Co, Fe have been used as nano

catalysts for the synthesis of CNTs. The CVD reactors use inert gas methane for SWCNT production and ethylene for MWCNTs. In case of SWCNTs, the substrate is heated up to 750 °C–1000 °C and 450 °C–800 °C for MWCNTs synthesis. The thermal decomposition of hydrocarbons produces Carbon which is dissolved in the metal nano catalyst. The research is going on for the last step so that high quality of the synthesized material may be obtained [50]. After the production of CNTs there is a need to purify the material to remove the amorphous carbon materials. Although, arc discharge and laser ablation methods produce SWCNTs in a high quantity but they suffer from drawbacks also as there is a need to evaporate C-atom from solid state source at a very high temperature (>3000 °C) and the nanotubes bundle together during the formation which limits their applications [51]. The length of CNT depends on the time taken for their growth. The diameter of synthesized SWCNTs varies from 0.6 to 3 nm [52]. And 10 to 250 nm for MWCNTs [53]. The different types of drugs can be effectively loaded on the internal and external surfaces of CNTs due to their large surface area [54].

Graphene

It is a 2D allotropic form of Carbon comprising of a single layer of Carbon atoms. The Carbon

atoms exhibit a hexagonal crystal lattice joined to each other by and bonds in sp^2 hybridization with an interatomic distance of 0.140 nm of Carbon hexagons. The Graphene was first explored, searched by a Canadian theoretical physicist, P. R. Wallace in 1947 whereas the samples were later investigated by a Dutch-British physicist A. Geim and a Russian-British physicist K. Novoselov [55]. Although, the theoretical investigations on the Graphene have been conducted extensively, the real material has been synthesized only recently. The research on the characteristic features of Graphene is still going on. It do possess extremely high mechanical rigidity and a high thermal stability. The electrical properties of this carbon allotrope basically distinguish from the properties of 3D materials. Graphene is a building block of other allotropes of carbon as it can be wrapped up, rolled up cylindrically or stacked up to get 0D fullerenes, 1D carbon nanotubes and 3D Graphite respectively[56]. Thus it depicts the structural element of some other Carbon allotropes such as fullerenes, CNTs and Graphite. The Graphene rolled into 0D buckyballs, 1D nanotube and stacked up into 3D graphite is shown in the Fig.1. [56]

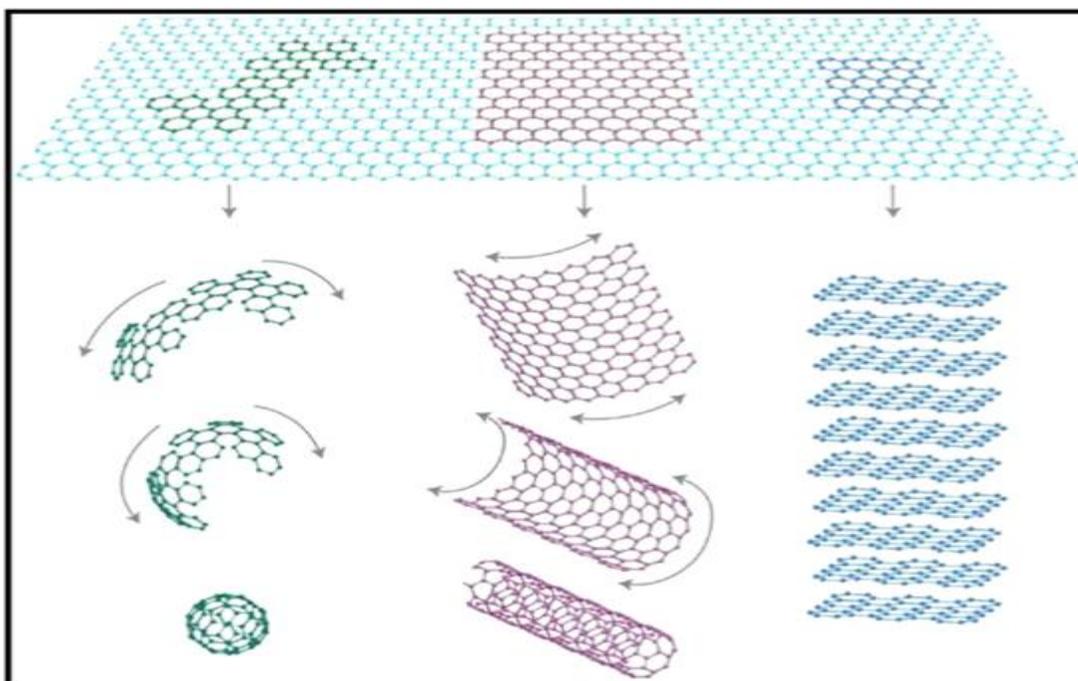


Figure 1. Graphene rolled into 0D buckyballs, 1D nanotube and stacked up into 3D Graphite

Graphene is a semiconductor material with zero band gaps, am bipolar electric field with charge carrier mobility more than 15500 to $20000 \text{ cm}^2 \text{ Vs}^{-1}$ at room temperature. It possesses excellent mechanical, physical, chemical and thermal properties and is transparent to light up to 98% . That's why it is a potential candidate for the application in highly sensitive electrochemical

sensors [57-58]. The mobility of electrons in the layers of Graphene is one hundred times more than that in Silicon [60]. Graphene finds immense application in sensors due to its large specific surface area and high charge carrier mobility [61-62]. Table II shows the values of significant physical, electronic and mechanical characteristic features of Graphene.

Table II. Significant physical, electronic and mechanical characteristic features of Graphene.

In plane modulus	1 TPa	58
Strength	120 GPa	58
Specific surface area	$2600 \text{ m}^2 \text{ g}^{-1}$	62
Thermal conductivity	5500 W mK^{-1}	62
Electron mobility at room temperature	$100 \text{ cm}^2 \text{ Vs}^{-1}$	62

Synthesis

The CVD technique has been applied for the synthesis of Graphene modified electrodes and devices to be used in electrochemical sensors. The Graphene has also been fabricated by the use of transition metal substrates like Ni, Po, Pt, Cu on a

very large scale. As a consequence of a very low stability of Carbon in Copper, the CVD growth of Graphene over Copper results in a highly crystalline Graphene layers [63]. The Epitaxial Graphene can be synthesized by graphitization of doped SiC single crystal wafers at high

temperature as well as of undoped crystals of SiC[64-65]. Graphene Oxide (GO) has been produced by the chemical oxidation of Graphite at a very low production cost. The Hummers method has been employed for the growth of GO as it takes very small time for the growth and does not dissolve harmful chemicals. The synthesis of Graphene oxide (GO) has also been reported by making use of potassium permanganate and concentrated Sulphuric acid as oxidation agent and for peeling off Graphite. The acidic treatment accounts for the hydrophilic character of GO. The GO sheets can be dispersed well in water. The GO can be reduced back to Graphene by using chemical reduction methods such as by the direct addition of reducing agents like hydrazine or by thermal reduction at high temperatures[66]. The solution growth of Graphene has been reported to produce GO in which Graphite is oxidized due to which an aqueous colloidal form of GO flakes is produced. As a result, the basal plane of the Graphene is functionalized with hydrophilic functional groups [67-68]. GO has a high density of oxygen functional groups (carboxyl, hydroxyl, carbonyl, and epoxy) at its basal plane and its edges due to which it forms a colloidal solution in water and polar solvents and is a novel Graphene material.

Reduced graphene oxide (rGO)

The electrochemical reduction method has also been applied to obtain reduced Graphene oxide (rGO)[69]. Various reduction methods have been employed to reduce Go partially to form reduced Graphene oxide (rGO) by using laser radiation, annealing, and chemical methods [70]. However, the harsh use of chemicals for oxidation degrades the properties of Graphene by

damaging the basal plane of the Graphene. That's why peeling off of Graphene from Graphite is done under suitable solvents and surfactants. The Graphene has a tendency to aggregate into Graphite in some solvents. Thus it is difficult and challenging to prepare pure and uniformly dispersed single layer Graphene in the solvents. The mechanical peeling of the Graphite is done to obtain pure 2D Graphene by making use of the adhesive tapes 4 that has lesser density of defects. Reduced graphene oxide (RGO) is the form of GO that is processed by chemical, thermal and other methods in order to reduce the oxygen content, while graphite oxide is a material produced by oxidation of graphite which leads to increased interlayer spacing and functionalization of the basal planes of graphite.

1. Treating GO with hydrazine hydrate and maintaining the solution at 100 for 24 hours.
2. Exposing GO to hydrogen plasma for a few seconds.
3. Exposing GO to another form of strong pulse light, such as those produced by xenon flashtubes.

Graphene oxide, which has C/O ratio of 2/1, is non conductive. It usually has a conductivity of less than a micro S/m. reducing graphene oxide to C/O ratio above 6 is required to make graphene oxide conductive by partially restoring the aromatic graphene structure.

Graphene Oxide films can be deposited on essentially any substrate, and later converted into a conductor. This is why GO is especially fit for use in the production of transparent conductive films, like the ones used for flexible electronics, solar cells, chemical sensors and more. The structures of Graphene based nanomaterials are shown in the Fig.2 [69].

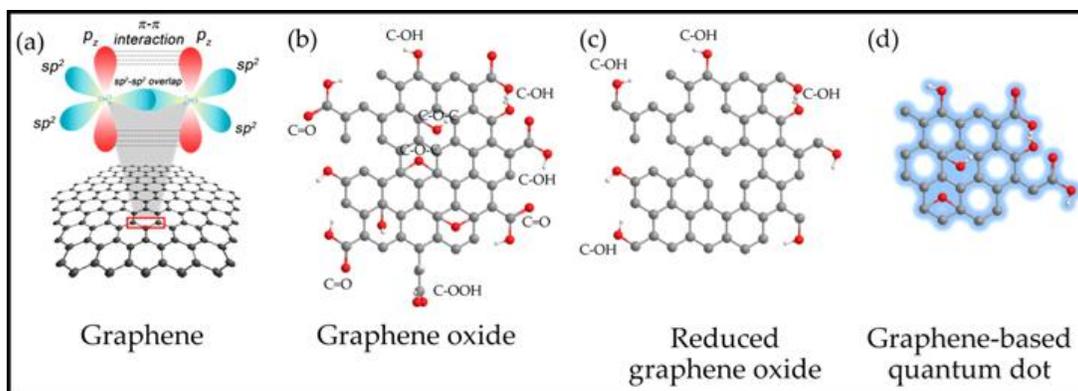


Figure 2. Structures of Graphene based nanomaterials (a) Carbon atoms in pure Graphene with sp^2 hybridization (b) Graphene Oxide (GO) (c) Reduced Graphene Oxide (rGO) (d) Graphene Carbon Quantum Dot (GCQD).

Carbon Nanodiamonds

Another allotrope of carbon, Carbon Nanodiamonds (CNDs) is the nanoparticles with the crystal structure of Diamond, and exhibit excellent properties of diamond [70-71]. The CNDs consist of a crystalline Diamond core which is surrounded by an anion like amorphous Graphite shell [72]. They do possess very small size, large surface area and large adsorption capacity for the attachment of chemical to biological molecules [73-74]. They exhibit exceptional hardness, thermal conductivity, refractive index, coefficient of friction, insulation characteristics and have very low toxicity [75]. The CNDs display fluorescence due to the presence of a complex defect N-V, containing nitrogen (N) and a vacancy (V). Since CNDs are chemically stable, their photo luminescent behavior can be used for the several in-vivo and in-vitro applications [76]. The CNDs are the potential fluorescent probes for use as biomarkers and in bio labeling studies [77]. Nanodiamond is a 0D carbon nanomaterial. There have been many reports on ultrananocrystalline diamond films with special properties. To utilize this nanodiamond, in many instances, functionalization and solubilization becomes necessary.

Synthesis

The CNDs are synthesized artificially by the detonation of explosive to produce these nanoparticles [78]. As diamond exhibits fluorescence due to the presence of a complex

defect (N-V), containing nitrogen (N) and a vacancy (V), the fluorescent CNDs can be synthesized by doping of N vacancies by means of electron irradiation and annealing in the free space [79]. The scientific investigations have reported the fluorescent CNDs consisting of roughly 350 Carbon atoms and Silicon vacancies that have the potential for use in sensing applications [80]. The CNDs can be functionalized by the covalent or non-covalent method to provide extra stability to them [81]. The covalent modifications of CNDs have produced stable complexes of drugs, whereas with non-covalent methods, the drugs can be easily attached to the CNDs but with decreased stabilities. The colloidal behavior of the nanodiamonds can be enhanced by transforming the surface of CNDs [82]. A number of functional bio molecules and drugs have been attached on the surface of CNDs by non-covalent methods [83]. The surface modified CND films were used to absorb small molecules like alkyl alcohol, Sulphonic acids and complex structures like DNA and enzymes [84-86]. Using alkyl chains, fluorine and Si, the covalent attachment on the surface of CNDs is feasible [87-88]. A functionalized CND particle with alkyl group can be distributed in the organic solvents uniformly whereas the non-modified CNDs can be dispersed in water but not in organic solvents. A functionalized CND particle with a Silane coupling reagent can transform a glass substrate [89]. The functionalization of CNDs results in the fluorescent behavior without N-V defects. The protein and biotin- supported

CNDs were investigated in order to increase their affinity towards the biological molecules. These modified CNDs have the potential to be used for drug delivery systems [90]. The fluorescent CNDs can be used for designing nanosensors due to the presence of N-V centers [91]. The CNDs can be very easily functionalized with biomolecules after undergoing purification by the ozone gas [92-93].

Carbon nanohorns

Carbon Nanohorns (CNHs) are one of the allotrope of Carbon consisting of closed cages of Carbon atoms with a diameter of 2–5 nm and length 40–50 nm [94]. They are more beneficial to use than CNTs as they can be synthesized at a larger scale at room temperature without any use of metal catalysts. They can be synthesized by using arc discharge of Carbon rods [95]. Laser ablation of pure Graphite, and Joule heating. The CNHs do possess high surface area and good porosity which can be exploited for their potential application in the field of bio sensing [96]. Carbon nanohorn (CNHs) are the conical shaped carbon nano structures sometimes also called as carbon nanocone are in the group of one dimensional carbon nanostructures with a very exceptional property compared to other carbon nanostructures. Carbon nanohorns are first explored by Harris *et al.* from the waste product of shoot formed during production of fullerene via arc discharge process. After heating to 2500–3500 K with positive-hearth electron gun for ~4 h, it is converted into two types of nanohorn, single walled (SWCNHs) and multi walled (MWCNHs). “Dahlia” of nanohorn was first synthesized via laser ablation process of graphite in an Ar atmosphere by Kasuya *et al.* Large scale industrial synthesis of nanohorn is well adapted due to high yield, no need of purification and cheap production procedure.

Carbon dots

The Carbon Dots (CDs) are zero-dimensional CNMs consisting of Carbon atoms with a size below 10nm. These materials do possess significant electronic and optical properties as exhibited by Quantum Dots [97]. They do possess low toxicity, stability and biocompatibility for their application as electrochemical Biosensors

[98-99]. The CDs have been synthesized by using laser ablation method applied to the Carbon atoms [100]. The various processes like pyrolysis, hydrothermal synthesis, electrochemical methods and microwave synthesis [101], have been used to synthesize CDs. They can also be prepared by using the soot of the candle flame [102]. CDs can be classified into Carbon Quantum Dots (CQDs) and Graphene Quantum Dots (GQDs). The CQDs and GQDs have a diameter range from 1 to 10 nm. The GQDs consist of Graphene layers of size less than 10 nm. They can be synthesized by using thermal plasma jet technique with low fabrication cost. They can be an alternative to the Nanodiamonds [103-104]. The fundamental mechanisms responsible of the fluorescence capability of CQDs are much debated. Some authors have provided evidence of size-dependent fluorescence properties, suggesting that the emission arises from electronic transitions with the core of the dots, influenced by quantum confinement effects. Whereas other works have rather attributed the fluorescence to recombination of surface-trapped charges, Or proposed a form of coupling between core and surface electronic states. The excitation-dependent fluorescence of CQDs, leading to their characteristic emission tunability, has been mostly linked to the inhomogeneous distribution of their emission characteristics. Due to polydispersity, although some works have explained it as a violation of Kasha's rule arising from an unusually slow solvent relaxation. The fundamental mechanisms responsible of the fluorescence capability of CQDs are very debated. Some authors have provided evidence of size-dependent fluorescence properties, suggesting that the emission arises from electronic transitions with the core of the dots, influenced by quantum confinement effects, whereas other works have rather attributed the fluorescence to recombination of surface-trapped charges, or proposed a form of coupling between core and surface electronic states. The excitation-dependent fluorescence of CQDs, leading to their characteristic emission tunability, has been mostly linked to the inhomogeneous distribution of their emission characteristics. due to polydispersity, although some works have explained it as a violation of Kasha's rule arising

from an unusually slow solvent relaxation Carbon Nanofibres (CNFs) are cylindrical wire shaped nanostructures in which graphene sheets are piled in different arrangements such as ribbon-like, platelet or herringbone. The length of CNFs varies in order of micrometers and can be up to 10 μm whereas their diameters vary from 10 to 500 nm. Their mechanical strength and electric properties are just like that of CNTs [105]. As a consequence of stacking of graphene sheets with different shapes in different arrangements, CNFs have more edge sites on their outer walls in comparison to CNTs. The presence of edge sites makes it feasible to transfer electrons with electro active species in solution and the detector substrate [106-107]. The CNFs do possess attributes like good electrical conductivity, large surface area, biocompatibility and easy fabrication process that are vital for electrochemical sensing applications. Moreover, CNFs can be easily functionalized to suit a particular detection mechanism.

Synthesis

The CNFs can be prepared by employing arc discharge, and laser ablation methods. The thermal chemical vapour deposition (CVD), Plasma enhanced chemical vapour deposition (PECVD) and electro spinning have also been employed for the preparation of CNFs [108]. During thermal CVD method, a compound containing hydrogen

and carbon is thermally decomposed by employing a metal catalyst at a constant temperature [109]. This method is further divided into three types based on the way in which the catalyst is employed i.e. Substrate method, Spray method and Gas phase flow catalytic method. During PECVD method, the high energy electrons present in the plasma collide with the gas molecules. As a result, they transfer their kinetic energy to them, thereby, causing excitation, ionization and decomposition which results in production of CNFs [110]. During electro spinning process, the polymers like silk, DNA, collagen and polyester have been used to obtain CNFs. The polymeric solution is firstly subjected to a potential of very high volts for getting charged, then to a spinning port where it is moved at a very fast rate. As a result, the nanofibres get deposited at the collecting plate in the form of a mat. The fiber mat undergoes oxidation and is carbonized in nitrogen atmosphere to produce CNFs [111]. The CVD produces CNFs with impurities which require a further complicated purification process whereas electro spinning produces CNFs through a very easy process with high purity [112-113]. The Fig. 3 shows the SEM images of alignment of CNFs grown on a Silicon substrate in plasma growth process in the presence of electric field (a) & (b) and CNFs exposed density (c). [114].

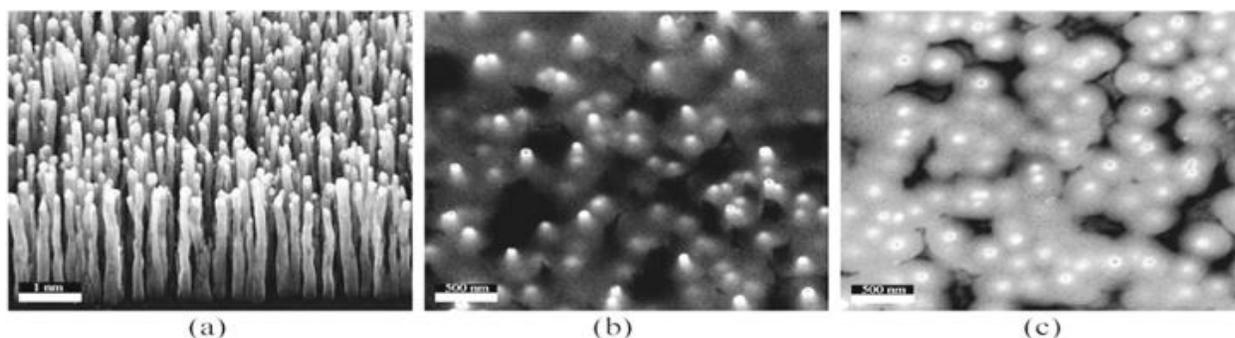


Figure 3. SEM images of CNF array. (a) & (b) Alignment of CNFs grown on a Silicon substrate in plasma growth process (c) CNFs exposed density.

Carbon black

The Carbon black (CB) is a nanomaterial prepared from the combustion of petroleum products. They are the nanoparticles spherical in

shape and are strongly bonded to each other to form aggregates. The size of Carbon black particles varies from 3.0 to 100nm. The significant physical, electronic and mechanical characteristic

features of Carbon black are given in Table III. The conductivity of Carbon black can be enhanced by heating up to 7000 °C because more number of electrons in sp^2 hybridization state with delocalized pi-bonds is available for the conduction of current [115]. Due to their large surface area; a large number of oxygenated groups are formed at the edges of the Carbon black nanoparticles. It is the presence of sp^2 hybridized Carbon atom edge planes and oxygenated groups over the Carbon black nanomaterials that make

them capable to attach biomolecules on their surface to act as electrochemical biosensors. They can be used for the detection of analytes for the biosensing applications. Carbon black (subtypes are acetylene black, channel black, furnace black, lamp black and thermal black) is a material produced by the incomplete combustion of heavy petroleum products such as FCC tar, coal tar, or ethylene cracking tar. The details of Carbon black was tabled in Table III.

Table III. Significant physical, electronic and mechanical characteristic features of Carbon black.

Surface area	10–1000 m^2g^{-1}	[116]
Electrical conductivity	$1.0-2 \times 10^3 Sm^{-1}$	[117]
Thermal conductivity	$0.1-0.4 Wm^{-1}K^{-1}$	[118]
Young's Modulus	$1-60 MNm^{-2}$	[119]
Tensile strength	20–60 MPa	[120]

Synthesis

The Carbon black nanoparticles can be prepared by employing furnace, channel and acetylene processes [121]. The preparation process is very easy and has low cost. The properties of Carbon black can be easily tailored by introducing other materials such as polymers or metallic nanoparticles into them for better electrochemical sensing applications [122].

Biosensors

Biosensors have been extensively used for the detection of biological molecules. An electrochemical biosensor is attached with sensitive biological molecules on the surface of solid electrodes by the target molecules on the surface of electrode. As a result of this process, a reaction signal is converted into an electrical signal like voltage, current, impedance etc. which can be easily detected. Most of the biosensors that have been developed are electrochemical in nature. The electrochemical biosensors are potentiometric, amperometric or conductometric depending upon the signal generated from the electrochemical

process which can be a resistance, current or voltage signal respectively. The electrochemical biosensors are highly sensitive to ensure detection, highly selective to avoid the interference of other species, small in size, easy to use and cost effective [123]. Biosensors are devices comprising a biological element and a physiochemical detector that are used to detect analytes. These instruments have a wide range of applications ranging from clinical through to environmental and agricultural. The devices are also used in the food industry.

The term “biosensor” is short for “biological sensor.” The device is made up of a transducer and a biological element that may be an enzyme, an antibody or a nucleic acid. The bio element interacts with the analyte being tested and the biological response is converted into an electrical signal by the transducer. Biosensors provide positive impact in diagnosing, monitoring and maintaining health. Biosensors also play an important role in driving healthy behaviors such as preventive health, “wellness”, and/or sports programs where tracking and trending of physiologic functions is of paramount importance.

The CNMs have been extensively used for the electrochemical biosensors due to their large surface area due to which many detection events can occur simultaneously on their surface and also, the attachment of the biomolecules is possible very easily. These materials have such electronic, optical, physical and mechanical properties which make them potential candidates for use in biosensors. Their charge storage and electron transfer properties can be engineered for the electrochemical applications. These materials have low cost, wide potential range over which the CNMs electrode can operate, high electro catalytic activities for a large number of redox-active chemical and biological systems. The electrochemical performance of the biosensors can be optimized by modifying the structure of these molecules to engineer their electronic, chemical and crystalline properties for a particular application. The CNT sensors do possess the ability to transport electrons faster, highly sensitive and are capable of detection even at very low limits. The Graphene has also been effectively used for the electrochemical sensing due to their significant electron transport features as described in the Table no I and II. The CNT or Graphene based electrochemical sensors have higher sensitivity, higher selectivity, fast electron transfer the doping can significantly influence the electronic,

mechanical and conducting properties of CNTs. The density of states for CNMs varies with their structure and can be adjusted by making changes in their atomic bonding structures. It also depends upon the tube diameter in case of CNTs. The density of states can be increased by peeling off CNTs in a controlled manner[124]. The CNMs do possess a high surface to volume ratio, electrical conductivity and mechanical strength that makes them potential for use in electrochemical biosensors[125-126]. The large surface area electrical, thermal conductivity and strength of CNTs make them suitable for use in electrochemical biosensors. The photo thermal technique has been used to reduce/eliminate the size of tumors [127].

Carbon Nanotubes as Electrochemical Biosensors

The CNTs have been widely explored for their use in the electrochemical sensing of biomolecules for various biomedical applications as shown in the Fig. 4. [128-129]. The characteristics of CNTs as biosensors can also be tailored by the peptides and nucleic acids as they do have the inherent capability to be acquainted with bio-elements or biomolecules. The method of analysis i.e. In vivo or in vitro determines the design of a biosensor.

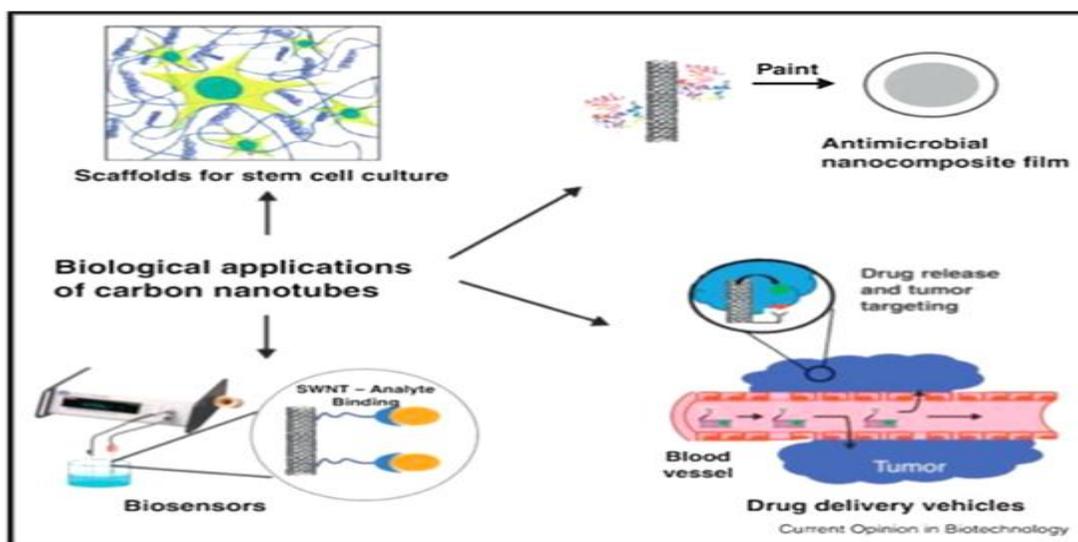


Figure 4. CNTS as biosensors for different applications, Reprinted with permission.

Covalent or non-covalent functionalization of CNTs

The physical and chemical properties of nanoparticles can be engineered by subjecting them to functionalization, by attaching some molecules on their surface [130]. The CNTs are not soluble in aqueous solutions but when they undergo oxidation in a mixture of acids, the carboxylic groups attach to the surface and side walls of the nanotubes making them soluble in aqueous solutions. Thus, functionalization has proved to be a boon to the CNTs for modifying their physical and chemical properties. [131]. The vertically aligned SWCNTs are attached on a GCE with a covalent bonding or on a gold surface by diazonium have been studied and investigated. The SWCNTs modified with diazonium have displayed the highest electron transfer in cellobiose hydrogenase from phanerochaete Sordida with small values of lactose oxidation potential [132]. However, the covalent functionalization of CNTs has an influence on its intrinsic properties as the change in CNT surface by covalent attachment can cause hybridization to change from sp^2 to sp^3 . As a consequence of it, the mechanical strength and electrical properties could be hampered due to the decrease in conjugation abilities of the CNTs [133]. The non-covalent functionalized CNTs by aromatic compounds have been used for the bioelectrocatalysis of oxygen, glucose biosensors, H_2O_2 detection, ethanol biosensor and trichloroacetic acid biosensor [134]. The polymers have been employed for the non-covalent functionalization of CNTs for use in biosensors. The polymers like polypyrroles, glycolipids, polyethyleneimine have been used for the non-covalent functionalization of CNTs. The commonly used tailoring techniques for CNTs have been functionalization with conducting polymers, mixing with surfactants or polyelectrolyte, using metal oxides or nanoparticles, adding enzymes and doping with heteroatom [135].

Detection of blood cholesterol level

The amount of blood cholesterol level has been detected by the amperometric electrochemical biosensors [136-138]. An amperometric cholesterol

biosensor has been fabricated through layer by layer deposition of (poly (diallyl dimethyl ammonium) chloride) and cholesterol oxidase enzyme on a MWCNT electrode modified by the gold nanoparticles. A protective coating of non conducting (poly (o-phenylenediamine) film has been produced over it by means of the electrochemical methods. A limit of detection of 0.2 mM to the detection of cholesterol has been reported by the fabricated biosensor. The amperometric biosensors employing sol gel chitosin/silica and MWCNTs organic-inorganic nanohybrid composite material has been reported for the detection of cholesterol in the blood.

Detection of cancer cells

The biosensors have been reported to detect O_2 released which have been fabricated from the hollow Carbon cubic (HCC) and porous Carbon cubic (PCC) nanomaterials. The HCC and PCC are attached on the surface of Screen printed Carbon electrode (SPCE). The HCC based sensor have exhibited a limit of detection 200 nM whereas the PCC electrode have reported a limit of detection 130 nM to detect the O_2 released. The selectivity of the biosensors has been examined by studying the amperometric response in the presence of interfering agents like 4-acetamidophenol, uric acid, ascorbic acid, D-glucose. The biosensors displayed very small current response to them, thereby, exhibiting excellent selectivity [139]. A final diagnosis of cancer is based on an examination of tissue or cells under a microscope by a pathologist. Biopsies can be taken using a fine needle, large. Imaging tests used in diagnosing cancer may include a computerized tomography (CT) scan, bone scan, magnetic resonance imaging (MRI), positron emission tomography (PET) scan, ultrasound and X-ray, among others. Biopsy. During a biopsy, your doctor collects a sample of cells for testing in the laboratory. CT angiography (CTA) is a diagnostic tool used to locate tumors in the body, determine whether cancer has spread, and detect abnormal blood vessels that may indicate a health risk. CTA produces multiple X-rays of cross sections of the body, which are reconstructed through a computer to form a 3-D image. Examples of blood tests used to diagnose cancer include: Complete blood count

(CBC). This common blood test measures the amount of various types of blood cells in a sample of your blood. Blood cancers may be detected using this test if too many or too few of a type of blood cell or abnormal cells are found. The technology that is used in airport security scanners has the potential to be a skin cancer diagnostic tool, a scientist is claiming. The scanners use so-called terahertz radiation ("t-rays"), which has the ability to look through human skin and tissue. T-rays are

considered non-ionizing, similar to visible light. Because sound waves echo differently from fluid-filled cysts and solid masses, an ultrasound can reveal tumors that may be cancerous. However, further testing will be necessary before a cancer diagnosis can be confirmed. The synthesis of Hollow Carbon Cubic (HCC) and Porous Carbon Cubic (PCC) nanomaterial and various steps involved in the detection of superoxide anions in HeLa cell are shown in Fig.5 [139].

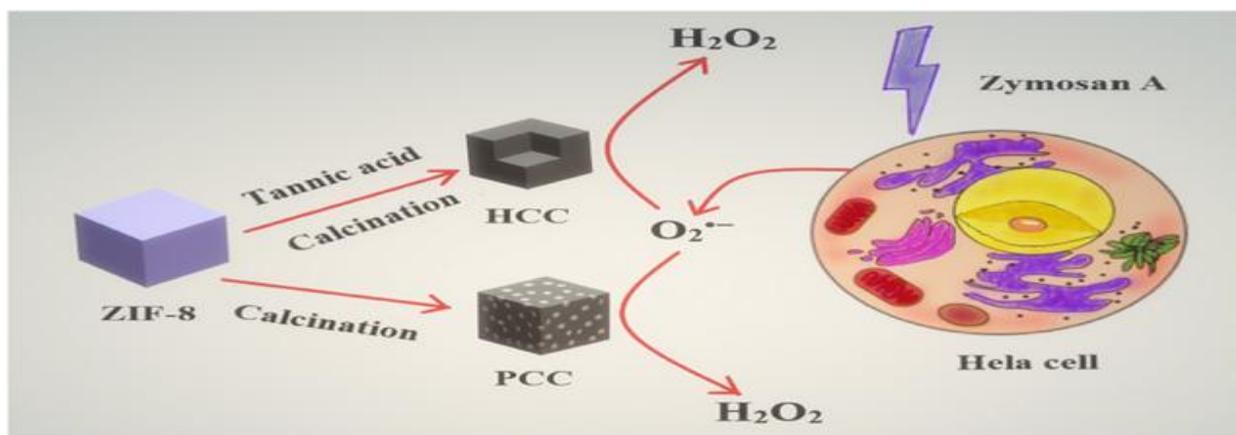


Figure 5. Synthesis of Hollow Carbon Cubic (HCC) and Porous Carbon Cubic (PCC) nanomaterial and various steps involved in the detection of superoxide anions in HeLa cell.

The surface ITO electrode coated with an assembly of CNT multilayer and antibodies to the epithelial cell adhesion molecules have been used to detect the cancer cells of liver[140].The Au-Ag alloy coated MWCNTs have been used for the detection of volatile biomarkers of the gastric cancer cells .The femtomolar level gastric cancer biomarker miRNA-106a has also been detected and reported[141].The carcinoembryonic antigen has been detected by the CNT based electrochemical immunosensor employing gold nanoparticles. The electron transfer is facilitated by the encapsulation of gold nanoparticles in the interior structure of the device. The immunosensor has exhibited a wide concentration range from 10 pgmL^{-1} to 50 ngmL^{-1} and the limit of detection has been reported to be lower as compared to the ELISA test [142].

Graphene Based Electrochemical Biosensors

The application of Graphene based nanomaterials for the electrochemical biosensing have been widely reported. The GO can be a potential candidate for use in sensors [143]. Therefore; Graphene and GO nano-sheets have been engineered for the detection of biomolecules and as efficient nano carriers for the drug delivery systems [144-145]. The multilayer Graphene nanoflake films have been grown on the Silicon substrates without any use of catalysts. These films contained Graphene sheets stacked with each other to a thickness of several tens of nanometers. The performance of Graphene based electrochemical sensors has been enhanced by using oxygen plasma treatment that results in the generation of oxygenated functionalities, edge plane sites and defects. It has been reported that the metallic impurities present in the CNTs it is more suitable for use in bio-sensing applications [146]. The

Graphene is synthesized from graphite which is not very costly whereas the CNTs are synthesized from Carbon containing gas in which nanoparticles are used as templates. The Graphene do posses a large surface area for the attachment of biomolecules and more uniform distribution of active electron sites than those in CNTs. The electrochemical sensing features like sensitivity and selectivity can be enhanced by customizing the properties of Graphene by various methods such as Oxygen plasma treatment, formation of Graphene-inorganic oxide hybrids, doping of Graphene with heteroatom, covalent bonding with dienophiles, and non-covalent bonding.

Detection of glucose

The first Graphene based electrochemical biosensor for the detection of glucose. The device displayed a limit of detection in the range of 2–14 nM and has highly stable output. Another biosensor employing the attachment of Glucose Oxidase in a Graphene-chitosan nanocomposite has been reported which has detected glucose in a range from 0.08 mM to 12 mM with greater sensitivity. A porous Graphene biosensor has been fabricated by the attachment of catalase enzyme [147]. The in detection of the glucose and urea within the same sample has been made possible. The pH of the sample gets increased by the oxidation of urea by urease and suppressing the electron transfer of $\text{Fe}(\text{CN})_6^{3-}$. A glucose oxidase enzyme based biosensor using spatially separated electrochemically reduced Graphene oxide (ERGO) by MWCNTs functionalized with 4-(pyrrole-1-yl) benzoic acid has been reported for the detection of glucose in real food samples. Through CV experiments, it was reported that the presence of ERGO in the conductive material increase the rate of electron transfer between the enzyme redox centre and the electrode surface.

Detection of DNA

The detection of DNA plays a pivotal role in the diagnosis of various genetic medical ailments in the body. The electrochemical biosensor employed for detection of DNA has attracted the attention of researchers due to its low cost, high sensitivity and high selectivity for the detection of DNA sequences or mutated genes responsible for

the various human diseases. The electrochemical DNA sensor working on the principle of direct oxidation of DNA is the simplest one. The Graphene has been used for the direct oxidation of DNA. The Graphene electrode has displayed the well resolved oxidation current signals of the free bases. Thus the Graphene electrode has displayed a higher electro catalytic activity to the oxidation of DNA. The electrochemical signals for the oxidized single stranded and double stranded DNA at the Graphene electrode have been well resolved [148]. The rGO nanowalls deposited on a Graphite rod by electrophoretic deposition method has also been employed for the detection of four bases of DNA which displayed the highly resolved oxidation signals for the four bases of DNA [149]. The anodized epitaxial Graphene with a large number of Oxygen related defects has been reported which has detected all the DNA bases that are well resolved on the DPV. The single nucleotide mismatch of DNA by the hybridization can be detected by the anodized epitaxial Graphene on the DPV. The Graphene based sensors have been employed to detect a wide range of DNA molecules [149]. The fluorescence resonance energy transfer based process has been used in GO based sensor for the detection of DNA. The detection is highly selective to even a single mismatch in DNA and the limit of detection has been reported to be 40 pM. The additional surface area provided by the presence of nanoparticles, enhanced electro affinity for the analyte or improved redox properties has been provided by the Graphene in the presence of substances like gold nanoparticles, Fe_3O_4 , nickel hydroxide, and cobalt. A specific sequence can be detected in total cell DNA by hybridization with a radiolabeled DNA probe. The DNA is denatured by heating to 95°C , yielding single-stranded molecules. The DNA to be analyzed is digested with a restriction endonuclease, and the digested DNA fragments are separated by gel electrophoresis. There are two differences that distinguish DNA from RNA: (a) RNA contains the sugar ribose, while DNA contains the slightly different sugar deoxyribose (a type of ribose that lacks one oxygen atom), and (b) RNA has the nucleobase uracil while DNA contains thymine. Nearly every

cell in a person's body has the same DNA. Most DNA is located in the cell nucleus (where it is called nuclear DNA), but a small amount of DNA can also be found in the mitochondria (where it is called mitochondrial DNA or mt DNA).

Detection of other biomolecules

The advanced electrochemical Graphene based sensors has been investigated extensively and reported. The $\text{Fe}_3\text{O}_4\text{-NH}_2$ in Graphene has been used to detect ascorbic acid and uric acid which have exhibited enhanced electrochemical oxidation of these acids as compared to the Graphene electrodes [150]. The Graphene has been used to detect the uric acid, ascorbic acid. The Graphene nanosheets have been used as immunodetectors for the detection of carcinoembryonic antigen and alpha-fetoprotein in the biological fluids. The

simultaneous monitoring of both the antigens has been reported with the wide working ranges from $0.02\text{--}250 \text{ ngmL}^{-1}$ and $0.01\text{--}90 \text{ ngmL}^{-1}$ for the carcinoembryonic antigen and alpha-fetoprotein respectively with a limit of detection 1 pgmL^{-1} . In another research, the Micro-cystine LR-aptamers are attached onto the Graphene surface to fabricate an aptasensor system. The sensor exhibited a wide linear range of $1\text{--}100 \text{ pM}$ and a low limit of detection of 0.8 pM to detect the aptamer [151]. An electrochemical aptasensor employing rGO has been fabricated for the evaluation of dynamic cell surface of N-glycan in which the concanavalin A has been attached on the surface of dendrimer conjugated rGO modified GCE which causes multivalent bonding between Con A and N-glycan on the surface of cell as shown in the Fig. 6. As a result of which the efficiency of aptasensor for the cell capture has been enhanced [152].

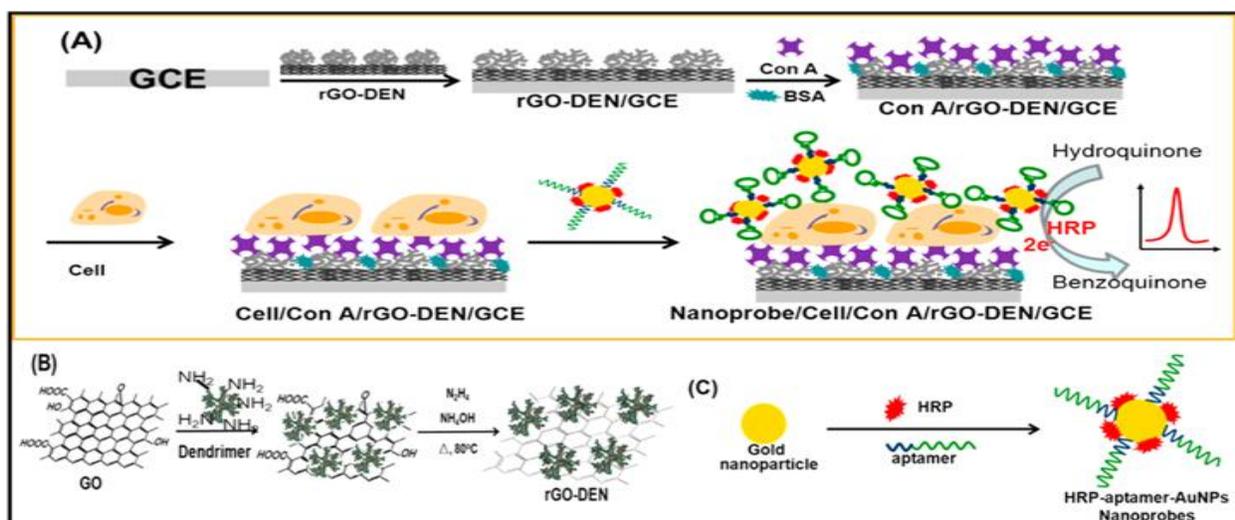


Figure 6. Synthesis of an electrochemical aptasensor employing r GO for the evaluation of dynamic cell surface of N-glycan.

Carbon Nanohorn Based Electrochemical Biosensor

The single walled carbon nanohorn (SWCNH) based biosensors employing attachment of enzymes or proteins have been vastly investigated and reported. The sensor has exhibited a lower limit of detection, high sensitivity and high selectivity to the detection of glucose. An electrochemical biosensor has been reported by

attaching protein on the surface of SWCNHs which has been functionalized by the non-covalent bonding. The biosensor exhibited good electro catalysis to the reduction of H_2O_2 [153]. The surface area of CNHs has been used to restrict the recognition components. The biosensor has reported a good response for the MC-LR with a limit of detection $0.3 \mu\text{g}^{-1}$ which is less than the safe limit of $1 \mu\text{g}^{-1}$ as per the recommendations of WHO in the drinking water [154]. The two

bioenzymes which are horseradish peroxidase and glucose oxidase has been used to fabricate the biosensor. A limit of detection of 0.33 pg ml^{-1} has been reported for the detection of alpha-fetoprotein by employing this CNH based immunosensor with high selectivity [155]. The Au nanoparticles grown on the carboxylated CNHs which are further functionalized with streptavidin. The sensor exhibited a limit of detection 0.024 pg ml^{-1} . The carcinoembryonic antigen has also been detected by employing this CNH immunosensor for which limit of detection 0.032 pg ml^{-1} has been reported [156]. The CNH has the ability to quench the fluorescence of an analyte [157]. They have been used as an optical biosensor for the detection of DNA. The sequence related to the human immunodeficiency virus (HIV) has been detected by making use of the capability of CNHs to quench the fluorescence. The CNHs has different binding affinity for DNA. The HIV virus has a strong affinity for binding on the surface of CNH through. As a consequence of it, the quenching of fluorescence occurs. The binding affinity is eliminated if a double strand is obtained in the presence of the target sequence [158]. The functionalization of CNHs with a fluorescein labeled protein by non-covalent bonding has been employed to detect the presence of thrombin. The sensor displayed a limit of detection of 100 pM to the detection of thrombin. The high selectivity of

the biosensor has been demonstrated by employing 100 nM human IgG and 100 nM .

Carbon Dots Based Electrochemical Biosensors

The CDs exhibit a biocompatibility that can be engineered for the development of in vivo biosensors. The CD based biosensors present a favorable environment for the detection of ions which are biologically very significant. The CD based nano sensor functionalized with zinc responsive quinoline derivatives has been reported for the detection of quinoline. As a consequence of binding of Zn^{2+} ions on the nano surface of CDs, there is a shift in the fluorescence from weak blue to the strong green color. The CD based biosensor displayed a limit of detection of 6.4 nM to the detection of quinoline molecules which is much lower than the detection limit of 270 nM . The CDs have been employed to detect a vast number of biomolecules like DNA, cholesterol, glucose, ascorbic acid, histene, human carcino embryonic antigen [159]. The biosensors employing GQDs and CQDs to detect biomolecules have been reviewed and reported [160]. The various steps involved in the detection of CTnI involving the use of an Au/GQD/PAMAM nano hybrid electrode are shown in the Fig. 7. [161].

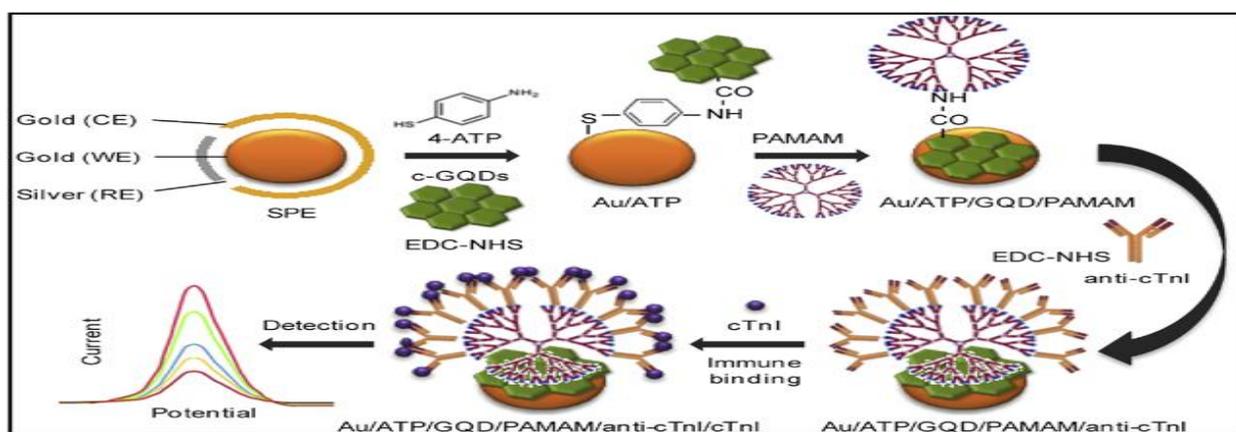


Figure 7. Various steps involved in the detection of CTnI involving the use of an Au/GQD/PAMAM nano hybrid electrode.

Carbon Nanofibres Based Electrochemical Biosensors

The CNFs can be used as a substrate for the attachment of biomolecules for electrochemical detection purposes. The surface functional groups can be introduced into CNFs by the chemical treatment that not only enhances their solubility but also increases their selective interaction with biomolecules. The oxygen containing surface functional groups can be increased in them by their oxidation with conc. Acids [162]. With the formation of functional groups on the surface of CNFs, it becomes easier for the attachment of selective biomolecules such as proteins, enzymes and DNA on their surface. The CNFs do possess more functionalized surface area for attachment of biomolecules in comparison to CNTs [163].

Detection of glucose

A critical review of CNFs based biosensors has been reported [164]. The Ni nanoparticles loaded CNFs prepared by electro spinning have been used to detect the presence of glucose. The fabricated biosensor exhibited a limit of detection $1 \mu\text{M}$ with a linear range of $2\text{--}2800 \mu\text{M}$ [165]. In another study, the bimetallic CuCo nanoparticles embedded in CNFs by employing electro spinning has been used to detect the presence of glucose in human urine. The presence of glucose has also been detected by Copper oxide nanoneedles with reduced graphene oxide with CNFs. The fabricated composite has exhibited a limit of detection $0.1 \mu\text{M}$ in the linear range of $1\text{--}5.3 \text{ mM}$ [166]. Another research has reported a limit of detection 0.03 mM in the linear range of $0.06\text{--}6 \text{ mM}$ to the detection of glucose for a palladium nanoparticles decorated helical CNF hybrid [167]. Principle: Glucose oxidase is an enzyme extracted from the growth medium of *Aspergillus niger*. Glucose oxidase catalyse the oxidation of Beta D- glucose present in the plasma to D glucono -1,5 - lactone with the formation of hydrogen peroxide; the lactone is then slowly hydrolysed to D-gluconic acid.

Sources of glucose

1. Carbohydrate: Includes bread, rice, pasta, potatoes, vegetables, fruit, sugar, yogurt, and milk. Our bodies change

100 percent of the carbohydrate we eat into glucose.

2. Protein: Includes fish, meat, cheese, and peanut butter.
3. Fat: Includes butter, salad dressing, avocado, olive oil.

As glucose is a simple sugar, one of the most specific methods for the quantitative estimation of glucose is the use of glucose oxidase, which catalyzes the oxidation of α -d-glucose to d-glucono-1,5 lactone (gluconic acid) with the formation of hydrogen peroxide.

The A1C test is a blood test that provides information about your average levels of blood glucose, also called blood sugar, over the past 3 months. The A1C test is sometimes called the hemoglobin A1C, HbA1c, glycated hemoglobin, or glycohemoglobin test.

The normal blood glucose level for non-diabetics should be between 3.9 and 7.1 mmol/L (70 to 130 mg/dL). The global mean fasting plasma blood glucose level in humans is about 5.5 mmol/L (100 mg/dL); however, this level fluctuates throughout the day.

Detection of other biomolecules

The fabricated biosensor has reported a limit of detection of $0.2 \mu\text{M}$, $0.7 \mu\text{M}$ and $15 \mu\text{M}$ in the linear range of $0.5\text{--}160 \mu\text{M}$, $2\text{--}200 \text{ mM}$ and 4 mM . In another study, the GCE modified with CNFs loaded with Ag-Pt alloy nanoparticles. The magnetic composite of polydopamine, laccase and Ni nanoparticles decorated CNFs prepared by electro spinning and high temperature carbonization method have exhibited a limit of detection of $0.69 \mu\text{M}$ for catechol in the real water samples in a linear range from 1 to 9.1 mM along with good selectivity [168]. The vertically aligned CNFs i.e. CNFs grown perpendicular to the substrate is also the potential candidate for use in electrochemical biosensing applications. A nanoelectrode array based on vertically aligned CNFs have been reported for the detection of C-reactive protein with a limit of detection of 90 pM [169].

Detection of DNA hybridization/proteins

The Vertically aligned CNF arrays grown on silicon wafers has been reported to detect the DNA

hybridization by employing AC Voltammetry. The study of scans of sequential AC Voltammetry detects the presence of hybridized DNA with a high sensitivity of approx. 1000 PCR amplicon molecules with excellent selectivity. Another electrochemical biosensor have been prepared. By using cyclic voltammetry, the hybridization is detected by the change in oxidation peak current of ferrocene carboxylic acid at the sensor interface. The sensor exhibited a limit of detection of 88pM in the dynamic range of 0.50 and 40nM with an excellent selectivity by exhibiting insignificant current change for non-complementary DNA targets [170]. The CNFs modified onto carbon paste electrode has been used for the detection of amino acids with a limit of detection 0.1 μ M, For the early diagnosis of myocardial infection, a CNF based nanoelectrode have been reported which exhibited a limit of detection 0.2 ng ml⁻¹

Carbon Black Based Electrochemical Biosensors:

Detection of glucose

The application of Carbon black (CB) based nanomaterials for the electrochemical biosensing have been widely reported. The Carbon black has been used for the electrochemical sensing of biomolecules. The Carbon black based sensors has been used for the detection of glucose. A biosensor employing poly attached on the CB surface has been reported that can be used for the detection of glucose [171]. The glucose oxidase biosensors based on CB nanoparticles in electrode have exhibited a better electron transfer between the glucose oxidase enzyme and the CB electrode in comparison to other electrodes made up of SWCNTs, MWCNTs, C60, GO, rGO and SWCNHs. They have exhibited comparable limit of detection, linear range and better sensitivity [172]. Principle: Glucose oxidase is an enzyme extracted from the growth medium of *Aspergillus niger*. Glucose oxidase catalyse the oxidation of Beta D- glucose present in the plasma to D glucono -1,5 - lactone with the formation of hydrogen peroxide, the lactone is then slowly hydrolysed to D-gluconic acid.

Sources of glucose

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As glucose is a simple sugar, one of the most specific methods for the quantitative estimation of glucose is the use of glucose oxidase, which catalyzes the oxidation of α -d-glucose to d-glucono-1,5 lactone (gluconic acid) with the formation of hydrogen peroxide. The A1C test is a blood test that provides information about your average levels of blood glucose, also called blood sugar, over the past 3 months. The A1C test is sometimes called the hemoglobin A1C, HbA1c, glycated hemoglobin, or glycohemoglobin test. The normal blood glucose level (tested while fasting) for non-diabetics, should be between 3.9 and 7.1 mmol/L (70 to 130 mg/dL). The global mean fasting plasma blood glucose level in humans is about 5.5 mmol/L (100 mg/dL); however, this level fluctuates throughout the day.

A non-enzymatic biosensor has been reported employing carbon nanoparticles functionalized carbon black composite modified GCE fabricated by microwave method to detect the presence of glucose in biological fluids and human serum samples.

Detection of DNA hybridization

The CB has also been used for the biosensing of DNA molecules. A Tungsten disulphide – acetylene black composite formed by using hydrothermal process has been reported for the DNA biosensing applications fabricated by using composite formed by CuS nanosheets and acetylene black(AB) by employing solvothermal process with the help of ethylene glycol. The surface of GCE was modified with CuS-AB film, later gold nanoparticles are deposited on it by the electro deposition method. The detector exhibited a decrease in current for the [Fe (CN)₆]³⁻ redox couple every time when there is a hybridization between the attached ss DNA probe and target ssDNA. In another significant research, an electrochemical biosensor employing pencil graphite electrodes modified with CB has reported.

Detection of proteins

The presence of oxygenated functional groups and active sites on the CB particle surface facilitates the biosensing process. A biosensor employing GCE substrate has been modified with a mixture of hemoglobin-Carbon black (Hb-CB) which is anchored by using Nafion film. By using cyclic voltametry, it has been confirmed that there is a direct electron transfer from the Hb protein to the CB modified electrode which is attributed to the presence of oxygenated functional groups and active sites on the CB particle surface [173]. The direct electron transfer of different Fe attached on the electrodes modified with CB and didodecyldimethyl ammonium bromide have been thoroughly investigated and reported [174]. The direct electron transfer of Cytochrome C and Hb biosensor based on CB nanoparticles have also been reported [175-176]. Western blotting is a widely used method for protein detection, using antibody-based probes to obtain specific information about target proteins from complex samples. It is a routine method in molecular biology, biochemistry, and cell biology fields with a multitude of applications. Direct protein determination is when protein content is calculated based on the analysis of amino acid residues. Indirect protein determination can for instance be inferred following the determination of the nitrogen content, or after chemical reactions with functional groups within the protein. Antibody dependent methods: Enzyme-linked immunosorbent assay (ELISA): Specifically can detect protein down to pg/mL. Western blot: couples gel electrophoresis and incubation with antibodies to detect specific proteins in a sample of tissue homogenate or extract. Because proteins are made up of chains of amino acids joined by peptide bonds, they can be hydrolysed to their component amino acids, which can then be measured by ion-exchange, gas-liquid or high-performance liquid chromatography. The sum of the amino acids then represents the protein content (by weight) of the food.

Enzymatic biosensors

The Carbon black has the potential to substitute graphite powder for the fabrication of enzyme

linked biosensors. The enzymatic biosensor constructed by combining carbon black paste with tyrosinase enzyme have demonstrated highest sensitivity of $625 \text{ nA} \mu\text{M}$ with a limit of detection of $0.008 \mu\text{M}$ to the detection of catechol, thereby, showing electrochemical features even better than graphite and carbon nanotube tyrosinase paste electrode [177]. The Bisphenol A has been used in the coating of metallic cans for storage of tomato juice samples. Its detection is very important as it can cause serious health implications. The fabricated biosensor has demonstrated a sensitivity of approx. $5.0 \text{ nA} \mu\text{m}^{-1}$ and limit of detection $0.2 \mu\text{M}$ [178]. Another biosensor capable of detecting H_2O_2 in the samples of oxygenated water and milk has been reported in which Zein, a protein in corn seed is combined with carbon black to attach the haemoglobin. The fabricated biosensor has demonstrated a limit of detection $4 \times 10^{-6} \text{ molL}^{-1}$ using differential pulse voltammetry [179]. The presence of urea was detected by the amperometric sensing of carbamic acid which is produced during the enzymatic conversion of urea. The biosensor exhibited a linear response in the range $2.0 \times 10^{-4} \text{ molL}^{-1}$ to $4.0 \times 10^{-3} \text{ molL}^{-1}$ [180]. The fabricated biosensor has exhibited a limit of detection of $8.0 \times 10^{-9} \text{ molL}^{-1}$ and $8.7 \times 10^{-7} \text{ molL}^{-1}$ in the linear range from $4.5 \times 10^{-7} \text{ molL}^{-1}$ to $2.4 \times 10^{-5} \text{ molL}^{-1}$ and $3.7 \times 10^{-7} \text{ molL}^{-1}$ to $5.0 \times 10^{-5} \text{ molL}^{-1}$ for hydroquinone and catechol respectively.

CONCLUSIONS

The excellent electrochemical properties of CNMs have paved the way for their use in a wide range of electrochemical biosensors for the detection of biomolecules and for various biomedical applications. The electrochemical sensing performance (sensitivity and selectivity) of the CNTs can be modified by the covalent or non-covalent functionalization of CNTS. In order to enhance their sensitivity and selectivity. The CNT modified electrodes can act as linking agents to the biomolecules. They do have large surface area that makes them suitable for the attachment of substrate on their surface. The CNTs with non-covalent functionalization has been effective for the

attachment of biomolecules with more biocompatibility. The electrochemical characterization of the nanomaterials can be done by employing various electrochemical techniques. The amperometric bio-sensing of the substrates has been feasible due to the electro catalytic activity of CNT based electrodes. The CNTs have been used for the detection of biomolecules with immense applications in the biomedical field. Graphene and GO nano-sheets have been engineered for the detection of biomolecules and as efficient nano carriers for the drug delivery systems without any use of catalysts. The electrochemical biosensing features like sensitivity and selectivity can be enhanced by customizing the properties of Graphene by various methods. The CDs, CQDs and GQDs have exhibited better efficiency and selectivity for the attachment of proteins, enzymes and antibodies by adsorption, covalent deposition

or chemical reactions. These materials have exhibited chemical stability, solubility in water and organic solvents. They have displayed excellent electro catalytic display towards the detection of H₂O₂ and O₂. In Carbon Black, the presence of sp² hybridized carbon atom edge planes and oxygenated groups over the nanomaterials make them capable to attach biomolecules on their surface to act as electrochemical biosensors. The Carbon Nano Fibres do possess attributes like good electrical conductivity, large surface area, biocompatibility and easy fabrication process that are vital for electrochemical sensing applications. Since the CNMs based biosensors are unable to differentiate between the responses of compounds with same functional group in their structures, their accurate quantification becomes difficult. The addition of some other materials such as metals, metal oxides, organometallic.

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