



Carbon nanotube - A review on Synthesis, Properties and plethora of applications in the field of biomedical science

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ABSTRACT

Recent remarkable advances in the field of nanotechnology has been achieved in the last few years especially in the fabrication of sensors that have wide number of applications. Nanomaterials are the foundation of nanotechnology that are measured on nanoscale. Carbon nanotubes (CNTs) are tube-like materials that are made up of carbon with a diameter calculating on a nanometer scale. They are originated from graphite sheet and these graphite layers seems similar to a rolled up non-stop unbreakable hexagonal like mesh structure and the carbon molecules appears at the apexes of the hexagonal structures. Depending upon the number of carbon layers, carbon nanotubes can be single-walled carbon nanotubes (SWCNTs), double-walled carbon nanotubes (DWCNTs) and multi-walled carbon nanotubes (MWCNTs). Carbon nanotubes (CNTs) can be fabricated by three main methods i.e., chemical vapor deposition, electric arc method and laser deposition method. Carbon nanotubes exhibit various characteristic properties such as high elasticity, high thermal conductivity, low density and they are chemically more inert etc. Due to these interesting properties, carbon nanotubes have played a significant role in the field of nanotechnology, electronics, optics and other fields of materials science. Carbon nanotubes are being positively applied in drug delivery, sensing, water treatment etc. Functionalization of their surface can result in highly soluble materials, which can be further derivatized with active molecules, making them compatible with biological systems. Surface functionalization enables adsorption or attachment of various molecules or antigens, which subsequently can be targeted to the desired cell population for immune recognition or a therapeutic effect. In this review, properties of carbon nanotubes and their clinical applications such as medical diagnostics and drug delivery are being discussed. Here, antibacterial as well as antifungal activity of carbon nanotubes are also being reviewed.

1. Introduction

Nanotechnology is a wide area of research and has been a latest and advanced manufacturing technology rising worldwide. It deals with a variety of materials produced at a nanometer scale through different chemical and physical methods [1]. Of increasing interest in the field of nanotechnology are the nanostructured materials, the foundation of nanotechnology. Nanomaterials have dimensions below 100 nm. This wide group of materials enables access to various new choices of magnetic, electronic, mechanical or optical properties. Nanotubes belong to a

promising group of nanomaterials. Though many other nanotubes based on boron as well as molybdenum have been stated widely but, currently carbon nanotubes are by far the most vital group. Carbon nanotubes contain one or several concentric graphite-like layers with diameters in the range of 0.4 nm up to tens of nanometers [2]. The field of carbon nanotubes was discovered by Iijima in the year 1991 by an early experimental observation of carbon nanotubes by TEM (Transmission electron microscopy) and the succeeding reports of conditions for the synthesis of large quantities of nanotubes [3].

Carbon nanotubes can be described as graphite sheets that are rolled

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up into cylindrical shapes. The length of CNTs is in the form of micrometers with a diameter of about 100 nm [4]. Carbon nanotubes (CNTs) are considered as a derivative of both carbon fibers and fullerene with molecules composed of 60 atoms of carbons arranged in particular muffled tubes [5]. There are two types of carbon nanotubes that are classified according to the number of carbon layers present in them. Single-walled carbon nanotubes (SWCNTs) consist of single graphene layer with diameter varying between 0.4 and 2 nm and usually occurs as hexagonal-packed bundles. Multi-walled carbon nanotubes (MWCNTs) comprises of two or several cylinder, each made up of graphene sheets. The diameter varies from 1 to 3 nm [6].

CNTs can be synthesized by three different methods arc discharge method, laser ablation method and chemical vapor deposition method. Arc discharge method uses the high temperature i.e., ($>3000^{\circ}\text{C}$) necessary for evaporating carbon atoms into a plasma, forming both multi- and single-walled CNTs. The existence of a catalytic agent is not mandatory for MWNT, whereas during the preparation of individual SWNT, catalytic agent is required such as Cobalt, Yttrium, Nickel, Iron etc. Chemical vapor deposition method involves the hydrocarbon sources such as Cobalt, methane, ethylene etc. Laser ablation method involves the vaporization of graphite in an electrical furnace heated at 1200°C . The graphite purity ensures a high-level purity for the resulting products and a high converting ratio. For biomaterial purposes, the high purity level is a concern; therefore, the macroscopic processing is also employed to improve the quality of carbon nanotubes materials and to obtain specific characteristics such as length, alignment, etc. [5,6]. MWCNTs were first discovered by Iijima by Arc discharge method. This method is the most ancient method used earlier for the production of carbon fibers [7,8]. In situ emulsion polymerization was employed by Khan et al., 2016 for the successful synthesis of carbon nanotube (CNT) composites in a colloidal system with poly (styrene) or PS to form nanostructured brush.

CNTs were firstly functionalized with oleic acid following salinization with (3- aminopropyl) triethoxysilane to form cross-linking properties [9].

CNTs exhibit excellent chemical and physical properties such as high tensile strength, ultra-light weight, special electronic structures and high chemical and thermal stability. Because of these exceptional properties, scientists have developed an immense interest in these nanomaterials. Among carbon nanomaterials, carbon nanotubes are most exploited for various applications. The main applications of carbon nanotube include biomolecule, drug, and drug delivery to the targeted organs, biosensor diagnostic and analysis [10].

In this paper, an overview of different clinical applications of CNTs such as disease diagnosis and drug targeting are reviewed. It briefly describes the applications related to electrochemical sensor, DNA based sensor, piezoelectric sensor, gas sensor. Some of the antibacterial as well as antifungal activity of CNTs are also being discussed.

2. Biomedical applications of CNTs

CNTs can have many applications because of the advantageous properties that make them an appropriate material for biomedical application as they are more biocompatible as compared to others, fast electron transfer kinetics, ultra-light weight, chemical inertness, high tensile strength, wide number of antibacterial and antifungal properties, act as protein carriers, contains exposed functional groups etc. They also hold semi and metallic conductive properties that make them a suitable material for various applications such as clinical diagnostics, food safety, environmental monitoring. CNTs also play a significant role in the fabrication of sensors for detecting various pathogenic bacteria and helps in the treatment of cancer as well. CNTs even have a wide number of antimicrobial activities [11,12]. All these applications of CNTs are briefly

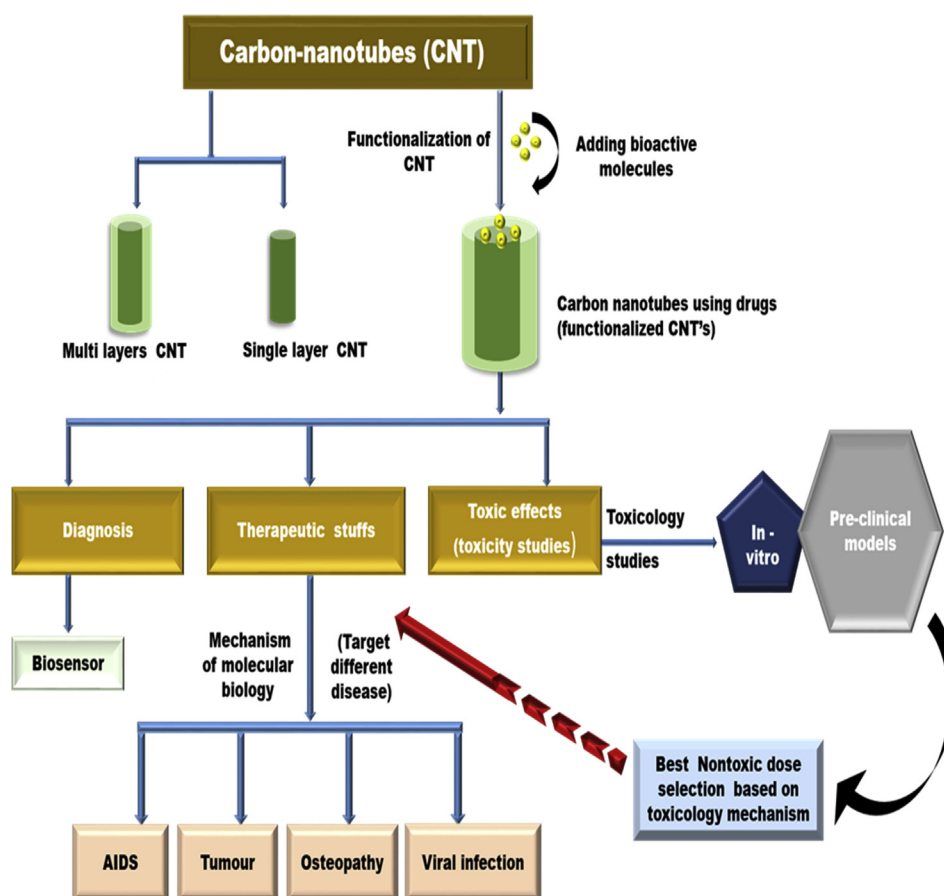


Fig. 1. Schematic representation of biomedical applications of Carbon nanotubes.

discussed below. Fig. 1 shows different biomedical application of carbon nanotubes.

2.1. Sensors based on carbon nanotubes

Exceptional properties of Carbon nanotubes such as high tensile strength, light weight, fast electron transfer kinetics, high biocompatibility, helps in protein immobilization, large surface area, chemical inertness, large number of antibacterial and antifungal properties, can be used as protein carriers, contains exposed functional groups etc. makes them tremendously attractive in various biosensor applications [7]. Multiwalled carbon nanotubes possess significant potential in biosensors due to their ease in supporting protein immobilization while maintaining protein inherent activity [13]. Fig. 2 shows the schematic representation of MWCNTs integration in biosensor assembly (see Fig. 3).

2.1.1. Electrochemical biosensor

An electrochemical biosensor is a self-contained combined device [14]. with a definite biological recognition element (bio-receptor) is combined within or closely related with an electrode (transducer) that changes the recognition event to a computable electrical signal for distinguishing the target compound (analyte) in sample [15]. Due to their specificity, speed, portability, and low cost, biosensors offer exhilarating chances for many decentralized clinical applications, extending from 'alternative-site' testing (e.g., physician's office), emergency-room screening, bedside monitoring, or home self-testing [16]. There are three types of electrochemical biosensors: amperometric, potentiometric, and conductometric [17]. Now a days, development concerns an electrochemical sensor fabricated an insulating base having an electrode

coating on its surface and a lid of deformable material which includes a concave area in the central part thereof, so that when it is coupled with the base, the lid and base form a capillary space comprising the electrode layer [18]. Carbon materials in nanoscale show various improved stuffs, representation them tremendously appropriate for the fabricating of electrochemical biosensors. Over the past two eras, advances in this field have nonstop emerged [19]. Multiwalled carbon nanotubes (MWCNTs) were used as transformers of screen-printed carbon electro transducers (SPCEs), presenting advanced properties associated to the bare SPCEs [20]. CNT with other materials such as nanoparticles and polymers are also shown exceptional features which made the material more unique and advanced.

Beden et al., 2015 developed an electrochemical sensor for sub nanomolar detection of dopamine using electroactive adducts. The sensor was modified with the MWCNTs and AuNPs for improved analytical parameters. The sensors showed better response when the electrode was modified with the nano-hybrids. The sensor showed very good and broad linear range and low detection limit [21].

Gutierrez et al. (2016) demonstrated by employing MWCNTs onto the surface of glassy carbon electrode (GCE) for qualitative and quantitative detection of albumin, glucose and amino acids. Their probe was able to detect glucose at a limit of 182 nM. The sensor was able to detect the carbohydrates, amino acids and albumin in real samples. The applicability of sensor in real samples showed its commercial potential (Gutierrez et al., 2016) Li and lee et al. (2016) improved the detection limit of sensing as well as also reduce the fabrication time by incorporating functionalized Multi-walled carbon nanotubes in sensing. They have achieved low limit of detection by using MWCNT [22,23].

Kan et al., 2016 developed a matrix based on mercapto- β -cyclodextrin self-assembled layered structured anchored onto MWCNTs. The sensor showed good analytical performance such as high selectivity and sensitivity and low detection limit. The designed sensor was employed for the detection of quercetin [24].

Palisoc et al., 2018 developed a highly sensitive nanosensor having anchored nanocomposites as an interface for the electron transfer. The nanocomposites used here are silver nanoparticles and MWCNT. Along with the nanocomposite nafion membrane was also used to develop a robust interface. The sensor was employed for the detection of heavy metals such as lead and cadmium in vegetable samples. The developed sensor has the ability to detect the trace level of heavy metals in real samples. The data presented in the paper concluded that the washed vegetables contain fewer amounts of heavy metals as compared to unwashed vegetables [25].

Revathi et al., 2018 developed an electrochemical sensor for non-enzymatic detection of hydrogen peroxide by employing amine functionalized MWCNTs. Various forms of amines were exploited for the selective determination of hydrogen peroxide. Results proved that the different forms of amine functionalization greatly affect the working of biosensor [26].

Wang et al., 2018 developed a nano sensor based on MWCNTs and Copper –nickel hybrid nanoparticles for the simultaneous detection of two nitrogenous bases i.e. Guanine and adenine. The sensor was successfully employed to detect both bases in real sample. The platform proved to be a good sensing interface for the fabrication of biosensor [27].

Ahammad et al., 2018 fabricated MWCNT based sensor on lead pencil for the simultaneous detection of hydroquinone and catechol. The sensor was employed for real sample analysis. The sensor was found to have good reproducibility and repeatability. The developed sensor replaces glassy carbon electrode (GCE) with pencil graphite which is much cheaper than GCE [28].

Wang et al., 2018 developed nickel anchored MWCNT based sensor for the determination of phenol. The Nickel was anchored on the MWCNT by electroless plating method. The sensor showed superior selectivity, sensitivity, reproducibility and stability in real sample analysis [29].

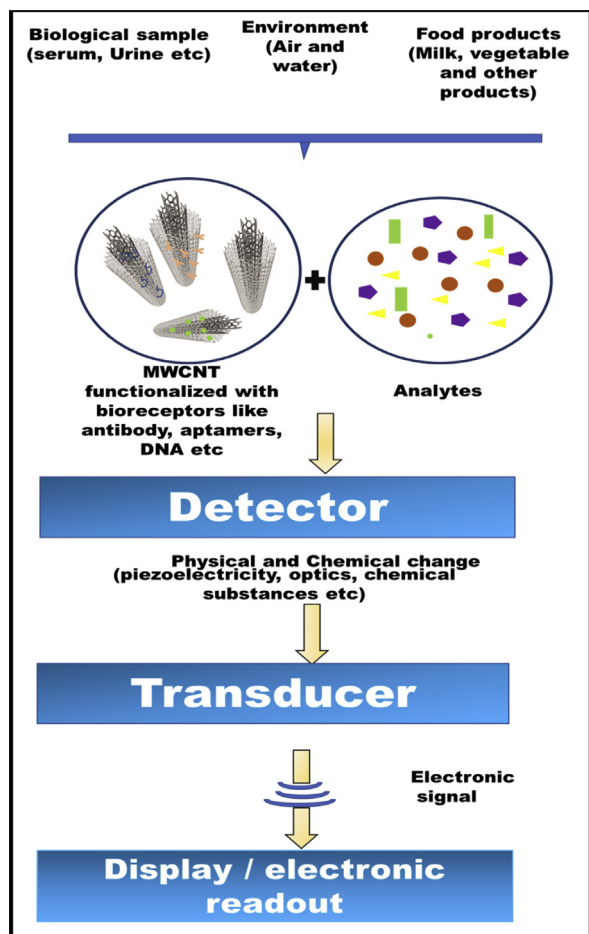


Fig. 2. Illustration of integration of MWCNTs in biosensor assembly.

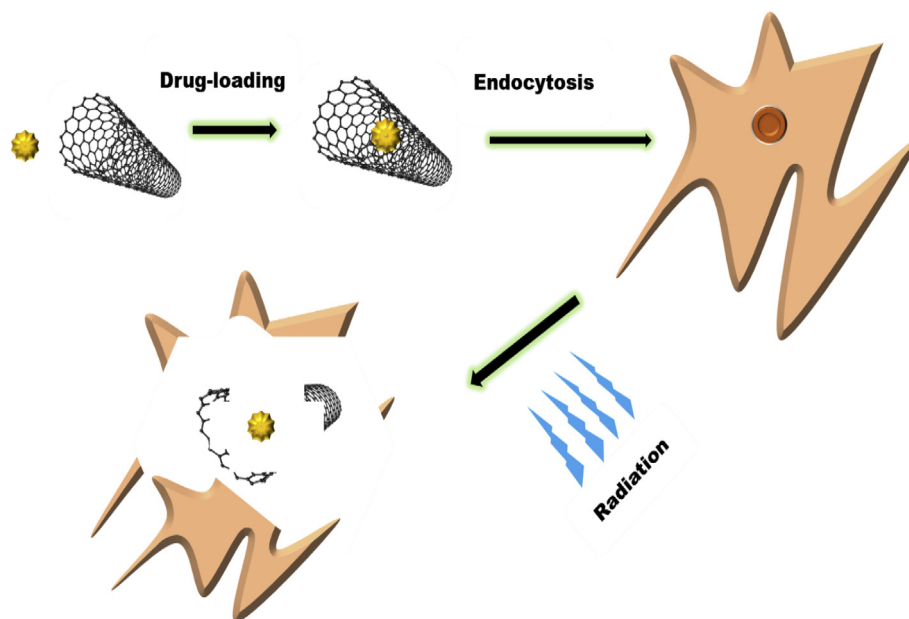


Fig. 3. Schematic representation of cancer treatment procedure employing MWCNTs.

Thangamuthu et al., 2018 developed bilirubin sensor based on MWCNT and graphene modified screen printed electrode (SPE) separately. The sensor based on graphene showed lower detection limit, wide linear range and better sensitivity as compared to MWCNT modified SPE electrode. The viability of sensor was validated by employing the designed sensor in blood samples for the detection of bilirubin. The interference was inhibited by employing nafion iconic as a membrane sheet [30].

Rahmawati et al., in year 2018 designed an electrochemical sensor by synthesizing MWCNT and Iron oxide nanoparticles from iron sand. The method used for the preparation of nanocomposite from iron sand was sonochemical method by ultrasonic horn. Various studies were done in order to detect the feasibility of nanocomposites in the designing of electrochemical biosensors. All studies reveal that the synthesized nanocomposite showed large surface area and better electron transfer kinetics. Therefore, the synthesized nanocomposite can be easily used for the designing of electrochemical biosensor [31].

Sevgi Guney et al., in 2019 described a nanosensor based on pencil graphite electrode. The electrode was modified with polymer i.e., melonium imprinted polymer and MWCNTs. The developed sensor was able to detect meldonium. They compared the analytical results of MWCNTs alone and p-MWCNTs which confirmed that employment of p-MWCNT enables high sensitivity and specificity of the developed sensor. The sensor was employed in real samples also for the trace level detection of meldonium in human urine sample. The comparison study concluded that the developed nanosensor is better in terms of fast response and ease approach among existed biosensors [32].

Lais Sales Porto et al. (2019) designed a nanosensor employing MWCNT and cobalt phthalocyanine (CoPc) onto pencil graphite electrode. The developed sensor was employed for the effective determination of pyridoxine in pharmaceutical industries. The sensor was found to achieve fast response, facile preparation, high selectivity and can be easily applied in pharmaceutical industries. The developed sensor can prove to be best alternative for detection of Vitamin B6 level [33].

Recently, Es'haghi et al. (2019) fabricated a biosensor employing MWCNT and polyurethane as nanocomposite onto the surface of PGE for the selective determination of anti-cancer drug CPT (Capecitabine) and Erlotinib HCl (ETHC). The sensor was found to have low detection limit upto molar range in case of both drugs [34].

Xinyan Liu et al. (2019) designed an electrochemical nanosensor in which aptamer was conjugated with nanocomposites for specific and

sensitive detection of β -estradiol. The employed nanocomposites were gold nanoparticles and carbon nanotubes which act as a sensing interface and immobilization matrix for the biorecognition element i.e. aptamer [35].

Basu and coworkers (2019) designed a nanosensor that is based on Poly-L-Lysine functionalized MWCNTs decked on reduced graphene nanosheets for determining cholesterol. The sensor has the capability to sense the trace levels of cholesterol in femtomolar [36].

Kim and coworkers (2019) designed a nanosensor that is based upon carbon nanotubes (CNTs) decorated onto gold electrode for the detection of humidity level. Core shell nanostructured materials were employed for humidity sensor. The resistance was also measured to determine the humidity level. The developed sensor showed high electrical efficiency without dependence on voltage and frequency [37].

Chokkareddy et al. designed an electrochemical sensor using lignin, copper oxide nanoparticles and MWCNTs as nanocomposite for the determination of chlorogenic acid in coffee. In addition, nucleophilic, redox and docking studies were also conducted. The sensor was able to detect the chlorogenic acid in coffee sample [38].

Yang et al., 2019 designed a multiplexed platform by employing nanocomposites anchored onto glassy carbon electrode for simultaneous determination of catechol, resorcinol and dihydroxy benzene isomers. The employed nanocomposites were MWCNTs and reduced graphene oxide which increased the conductivity of the developed interface. The detection limit of the three analytes comes in the range of micromolar. The developed nanosensor showed exceptional reproducibility, stability and anti-interference ability. The nano-sensor is able to detect the analytes in real samples [39].

Shetty et al., (2019) designed a biosensor for the efficient electrochemical detection of methdilazine employing carbon nanotubes-modified electrodes. The electrochemical determination of methdilazine (MDH), an antihistamine drug was carried out by the use of glassy carbon sensor modified with MWCNT in pH 9.0 phosphate buffer solution (PBS). Effect of accumulation time, pH, scan rate, excipients, metal ions, concentration on the MDH voltammetric behavior were studied by various voltammetric techniques. Very low detection limit value was found ranging from 0.1×10^{-7} M to 0.3×10^{-6} M. The designed sensor showed an outstanding response showing rapid results and was able to apply to determine the methdilazine present in urine and other samples [40].

Shetty et al. (2019) developed sensor for the detection of flufenamic acid and mefenamic acid. For this a blend of ruthenium-doped TiO₂

(RuTiO₂) nanoparticles and multiwalled carbon nanotubes (MWCNTs) were loaded onto carbon paste matrix to fabricate a novel RuTiO₂/MWCNTs-CPE sensor electrode for detecting and quantifying flufenamic acid (FFA) and mefenamic acid (MFA) drugs. Sensor assembly showed very low detection limit values of 0.68 nM for FFA and 0.45 nM for MFA [41].

Recently, Madhusudhana et al., (2020) developed an electrochemical sensor for the specific and sensitive determination of Gallic Acid at neutral pH employing Bismuth-nanoparticles decorated multi-wall-carbon-nanotubes cast-coated on carbon paste electrode. Estimation of gallic acid in clove and green tree extracts was successfully done. The developed sensor showed wide linear dynamic range with the detection limit of 1.6×10^{-7} M. The developed sensor offered many benefits such as excellent detection particularly at neutral pH, wide linear dynamic range, selectivity, stability, and reproducibility [42].

Cetirizine (CTZ) was quantified by the electrochemical technique using carbon sensor fabricated with coalesced ruthenium-doped titanium dioxide (Ru-TiO₂) nanoparticles and multi-walled carbon nanotubes (MWCNTs). Electrochemical analysis of CTZ was performed by voltammetry techniques such as cyclic voltammetry (CV), square wave voltammetry (SWV) to estimate heterogeneous rate constant, a number of proton-electron transferred in the oxidation response. The method developed showed CTZ electrooxidation with a low detection limit value of 3.10 nM and hence, the method was used to evaluate CTZ in human urine as well as from the pharmaceutical formulations [43].

2.1.2. Piezoelectric sensor

Khan and coworkers (2017) designed a stretchable sensor that is based on MWCT by exploiting its electromechanical properties. The authors found that stretchable sensor having MWCNTs on polydimethyl siloxane (PDMS) showed better linearity, sensitivity, detection limit and remarkable stability. In addition, SEM results depicted that CNTs network can be uniform and compact by spray coating technique. Compactness and uniformity play a major role in fabricating stretchable sensor [44].

Ali and coworkers developed a piezoresistive sensor based on graphene, CNT and graphene-CNTs composite. Sensitivity and percentage decrease in resistance in case of composites was found to be lower than the pure CNTs while it is higher than the pure graphene [45].

Park et al., 2019 developed same stretchable wearable sensor based on MWCNT on PDMS as substrate. They have employed this sensor in two applications namely for rehabilitation by developing robotic hand 2) strain sensing in needle for tissue characterization. They have also found that sensor is highly specific, biocompatible, ease to make, compact, flexible and economical [46].

He et al. developed stretchable sensor based on MWCNTs on thermoplastic urethane as substrate. The fibers were obtained through wet spinning process. The stretchable sensor was employed for measuring various diverse human functions as it is integrated in gloves and bandages. The results obtained are very remarkable and have potential for the next generation strain-based textile sensors [47].

Ramalingame et al. developed another stretchable sensor based on MWCNTs on PDMS substrate and showed capability to measure pressure directly without the use of deformation materials. The developed showed high flexibility and compactness which make them ideal for gait analysis in insole applications [48].

2.1.3. Gas sensor

To meet the need of gas sensors in various applications such as industrial, environmental and medical different gas sensors are designed. However, there are various conventional methods are available for gas sensing but it requires bulky instrumentation and skilled person for operation. Small scale sensor was an ideal alternative as they considerably less expensive. Nanomaterial as sensing interface offers distinct advantage in gas sensor in terms of sensitivity as well as selectivity [49].

Hieu and coworkers developed highly sensitive sensor based on

nanocomposites i.e., MWCNTs and tin oxide particle for the determination of ammonia gas. The sensor showed much enhanced response even at room temperature [50].

Abdulla et al. (2015) fabricated ammonia gas sensor and the sensor was developed by immobilizing polyaniline polymer with the functionalized MWCNTs. The developed sensor showed good analytical performance such as response time, recovery and stability as compared to unmodified electrode [51].

In 2016 Kim et al. described MWCNTs based field effective transistor type sensor for the selective determination of NO_x (Kim et al., 2016). MWCNTs were anchored onto surface of silicon wafer and deposited gold onto the developed surface. The developed sensor has intrinsic potential to detect NO_x gas at several gate source voltage. The sensor principle relies on the fact that there is decreased in resistivity upon increase in absorbed NO_x gas [52].

Cismaru and coworker developed a novel type of radio-frequency gas sensor that is based upon electro-magnetic band cap resonator with a couple like assembly covered by multiwalled carbon nanotubes transducer layer for methane gas detection. They presented result with compact dimension of the device that evidently establish the abilities of MWCNT in the application for purpose of sensing [53].

Dilonardo et al., 2017 exploited gas sensing properties of MWCNTs. Herein this work, MWCNTs were decorated onto surface of gold and palladium nanoparticles. The fabricated sensor was able to sense various pollutants. The MWCNTs decorated onto the surface of pladdium nanoparticle showed better sensing capabilities as compared to gold nanoparticles [54].

Husseini et al., 2018 designed a sensor for the selective sensing of ammonia. The sensor was employed OH-MWCNT. The sensor tests the capability of OH-MWCNT for selective sensing of ammonia gas at room temperature [55].

Mahajan et al., 2018 exploited reduced graphene oxide, MWCNT and ZnO for ammonia sensing. The sensing platform also includes polypyrrole as a functional membrane. Herein this approach ZnO acts as fillers. The developed sensor was very sensitive towards ammonia gas [56].

In 2019 Changhoon Song et al. designed a NO₂ gas sensor by patterning the MWCNTs onto NOA 63 polymer and were energized by integrated supercapacitor. The designed sensor was able to attach onto the skin defects. The deformation due to elbow movement or any other interventions does not affect the sensing property of the device due to the integrated interface. Therefore, the sensor has the potential to develop into wearable device which can sense NO₂ gas [57].

George et al., fabricated a sensor using silver ink and MWCNTs which was anchored onto substrate i.e., poly (3,4 ethylene dioxythiophene), polystyrene (PEDOT: PSS) as a sensitive material for sensing volatile organic compounds. Electrical characterizations were done in the presence of volatile organic compounds and which validates the theoretical concept and proof of concept of radiofrequency sensor [58].

Duong et al., 2019 designed a sensor based on tungsten oxide nanobricks and MWCNTs for the ammonia gas sensing. The nanocomposites were synthesized by hydrothermal route for the detection of ammonia gas. However, the gas sensing properties were observed both for CNT modified electrode and tungsten oxide (WO₃) nanobricks modified electrode. The sensor showed better response when they are used as nanocomposite (MWCNT-WO₃) for the construction of biosensor [59].

Kim et al., 2018 developed a flexible gas sensor for the simultaneous detection of harmful gases such as ammonia, Sulphur dioxide and chlorine. The sensor was fabricated by dye functionalized matrix anchored onto MWCNTs. The dye functionalized matrix was prepared by sol-gel process. The detection principle relies on the electrical and optical signals which are generated when the matrix comes in contact with the gaseous material. The developed sensor is highly flexible and can be tuned into any form maintaining the high conductance of the device [60].

In nutshell, CNTs was exploited for the fabrication of sensors along with nanoparticles such as AuNPs [24,28,44], Silver nanoparticles [29],

Copper–nickel hybrid nanoparticles [31], iron oxide nanoparticles [33, 36], cobalt phthalocyanine (CoPc) [38], copper oxide nanoparticles [47], reduced graphene oxide [48] TiO₂ nanoparticles and Ru Doped TiO₂ nanoparticles [41,43] tungsten oxide (WO₃) nanobricks [59], pladdium nanoparticle [54]. The nanoparticles along with CNT based sensor showed amplified sensing signal and more stable sensing interface as compared to nascent CNT. In addition, sensor was evaluated with nascent CNT and CNT along with NPs. The results of nanocomposites showed remarkable increase in electrical conductivity, sensitivity, specificity and selectivity as compared to nascent CNT. Polymers such as meldonium imprinted polymer [37], Poly-L-Lysine [39], polyaniline [51], Polypyrrole [56] and NOA 63 polymer [57] were also exploited for the construction of various sensors. Polymers enhanced the properties of CNT by providing more stability, biocompatibility, conductivity and anti-interference ability to the sensor. Furthermore, polymers are exploited more in the fabrication of wearable sensor as polymers provide stretch ability, insensitive to deformation and compatibility which made them more attractive. Polymers such as poly (3,4 ethylene dioxythiophene), polystyrene [58] were also used as substrate to anchor MWCNTs onto the surface. Table 1 summarizes various biosensors employing carbon nanotube for various diagnostic purposes.

3. Drug targeting

Multiwalled carbon nanotubes are used in drug targeting as well as in controlled release of drug. Targeted drug delivery can be defined as when a lively therapeutic drug agent is delivered to the precise part for extended period. Carbon nanotubes are used in drug delivery due to their hydrophobic nature that allow CNTs to stay in the circulation system for the extended period. Carbon nanotubes have utilized for target and controlled drug delivery due to variable stimuli that can be controlled through carbon nanotubes such as magnetic stimuli, electric stimuli, change in temperature and several others. Carbon nanotubes act as a carrier for the transport of various biomolecules also such as proteins, DNA, RNA, Immunoactive compounds and lectins [9,10].

Seyfoori et al., 2019 described the role of MWCNT and pH responsive gel for the delivery of duxorubicin drug. The nanohybrid system was developed by MWCNT and pH responsive gel i.e. chitosan coated magnetic nanocomposites. The developed nanohybrid system was designed to deliver the drug to U-87 Glioblastoma cell and was found that cancer proliferation was restricted when the drug was delivered through nanohybrid system [61].

Meherjuoi et al., 2017 compared the various nanotubes for the delivery of Cisplatin drug. Herein this approach molecular dynamic

phenomenon was established as they have used Ag Nanowires as a stimulator to release the drug from the interior of nanotubes. Herein this approach their nanotubes were compared i.e. Carbon nanotubes, silicon carbide nanotubes and boron nitride nanotubes. The results proved that efficiency of drug release depends on the composition and diameter of nanotubes. The results also concluded that kinetics of drugs release is fast and not related to the structural composition of nanotubes [62].

Im and coworkers (2010) developed transdermal patch using polymer-multiwalled carbon nanotubes for accessing electrical properties. The authors have utilized the good electrical properties of carbon nanotubes can speed up the issue of drugs through the effect of heating [63].

Servant et al. (2013) established an electro responsive polymer-MWCNT hybrid hydrogel for pulsatile sucrose release. They have utilized the radio labelled sucrose under the application of electric-field as hydrophilic drug model for the evaluation controlled released profile [64].

Mandal and coworkers (2016) compared the performance sustainable release of diclofenac sodium through multiwalled carbon nanotube and biodegradable, biocompatible nanocomposite hydrogel. The polymer composite of multiwalled carbon nanotubes (MWCNTs) was an improved alternate for the transdermal formulation, as it releases the diclofenac sodium in sustainable release profile [65].

4. Cancer diagnosis and treatment

Multiwalled carbon nanotubes have been utilized in cancer diagnosis as well treatment. Fig. 4 shows the cancer treatment procedure employing MWCNTs. In 2014 Wang et al. established that narrow multiwalled nanotubes (09.2 nm average diameter) had improved affinity of tissue, specifically for non-reticular endothelial tissues, as compared to broader multiwalled carbon nanotubes (39.5 nm average diameter). Authors concluded that higher aspect ratio of narrow multiwalled nanotubes might be beneficial in biological application owing to higher tissue accumulation [66].

In 2010 Samori et al. delivered anticancer drug methotrexate with help of multiwalled carbon nanotubes through release mechanism of enzymatic cleavage in invitro breast cells. Similarly, dendrimer modified multiwalled carbon nanotubes were utilized for drug doxorubicin (DOX) delivering at low pH [67].

Multiwalled carbon nanotubes are suitable carriers for peptides, proteins and genes as these macromolecules get easily degraded by enzymes present on cell surface or cell inside. In 2015 Guo et al.; developed

Table 1
Summary illustrating various biosensors employing carbon nanotubes for diagnostic purposes.

Biosensors	Principle	Target of detection	Limit of detection (LOD)	Year	Reference
Electrochemical Biosensor	Based on AuNPs/MWCNTs and Mannan-Os Adducts	Dopamine	0.17 pM	2015	[21]
	based on glassy carbon electrodes modified with multi-walled carbon nanotubes and copper microparticles dispersed in polyethylenimine	amino acids and glucose	182 nM	2016	[22]
	Based on multiwalled carbon nanotube	Clostridium tatani	1.0×10^{-16} M	2016	[23]
	Based on AgNP/MWCNT	Lead and Cadmium	0.216 ppb for Pb ²⁺ and 0.481 ppb for Cd ²⁺	2018	[25]
	Based on carbon sensor fabricated with coalesced ruthenium-doped titanium dioxide (Ru-TiO ₂) nanoparticles and multi-walled carbon nanotubes (MWCNTs).	Citrazine	3.10 nM	2019	[43]
	Based on glassy carbon sensor modified with MWCNT in pH 9.0 phosphate buffer solution (PBS)	methdilazine	0.1×10^{-7} M	2019	[40]
	Based on ruthenium-doped TiO ₂ (RuTiO ₂) nanoparticles and multiwalled carbon nanotubes (MWCNTs)	flufenamic acid (FFA) and mefenamic acid (MFA)	0.68 nM for FFA and 0.45 nM for MFA	2019	[41]
Gas sensor	based on bismuth nanoparticles decorated multi-wall-carbon-nanotubes modified carbon paste electrode (Bi-MWCNT/MCPE) at physiological pH	Gallic Acid (GA)	1.6×10^{-7} M	2020	[42]
	based on a resonant electromagnetic transducer in microstrip technology	Volatile Organic Compounds (VOCs) detection			[58]
	Based on dye functionalized matrix anchored onto MWCNTs.	ammonia, Sulphur dioxide and chlorine		2018	[60]
	Based on tungsten oxide nanobricks and MWCNTs	Ammonia gas		2019	[59]

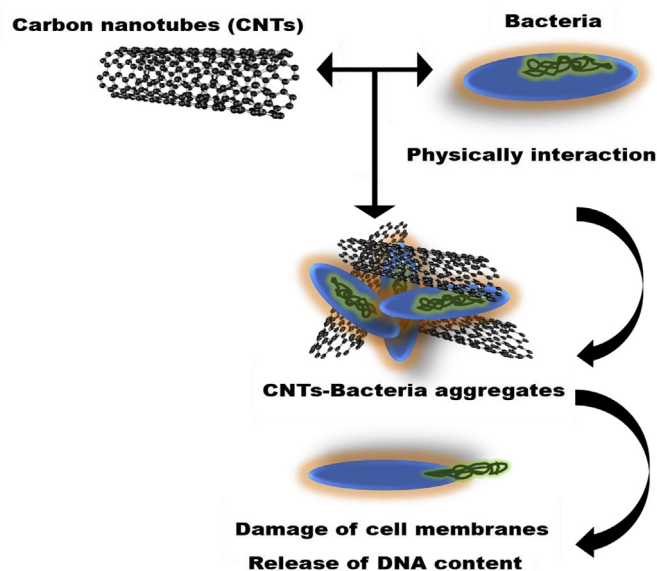


Fig. 4. Schematic representation of antibacterial activity of CNTs.

carrier cationic Multiwalled carbon nanotubes- NH_3^+ used to deliver the apoptotic siRNA against polo-like kinase (siPLK1) in calu6 tumor xenografts by direct intertumoral injections [68].

5. Antibacterial activity of CNTs

Researchers found that MWCNTs has great antibacterial potential. Anti-bacterial properties of MWCNTs depend on various factors such as surface functional molecules, density, diameter, length and purity of carbon nanotubes [69]. The aspect ratio of MWCNTs greatly influenced the antibacterial property of MWCNTs as short tube enables more interaction with the microorganisms as compared to long tube MWCNTs. As shorter tubes do more interaction with the cell membrane which changes the osmolarity of the membrane [70]. However, the same thing gets reverse in liquid medium. In liquid medium the short tube aggregates encompass a smaller number of cells as compared to long tube aggregates. Long tube aggregates can encompass a greater number of cells during aggregation process. Diameter also plays an important role as small diameter leads to more close interaction with the microbes while large sized diameter leads to less interaction with the microbes. Therefore, aspect ratio of MWCNTs played an important role in determining the anti-bacterial property of MWCNTs [71].

MWCNTs can show its antibacterial property by various ways. However, the exact mechanism behind the antibacterial property of MWCNTs is yet to be understood. There are various ways by which MWCNTs acts onto the microbial surface. First, change in the integrity of cell membrane by forming close association with the membrane surfaces [72,73]. Second, inducing ROS generation which ultimately leads to the cell death and DNA damage [74,75]. Third, impurity associated with the MWCNTs can also be an integral part of its antibacterial property. In vitro anti-bacterial activity of nanocomposites i.e. chitosan, its derivatives and derivative 4/MWCNT against both gram positive bacteria (*E. faecalis* and *S. epidermidis*) and gram-negative bacteria. Bacteria (*E. coli*) namely as gram positive bacteria was assessed by agar diffusion technique [76]. It was concluded that cationic property of nanocomposite due to amalgamation of polymer along with the MWCNT leads to the rupturing of bacterial cell membrane and leakage of all components from the cell matrix occurs. The leakage brings the change in the permeability of cell membrane and other functions of cell also get stopped. Although pH plays an important role in the mechanism as low pH facilitate more protonation of functional group associated with the polymer [77]. MWCNTs is inducing the generation of reactive oxygen species as all fullerenes compound has a closed cage like structure and

conjugation happens through π electron configuration [78]. Fig. 4 shows the antibacterial activity of carbon nanoparticles. MWCNTs enters into the bacterial nuclei and combines with the DNA which can produce the ROS which ultimately leads to the cell death. The synergistic effect of both chitosan and MWCNTs increases the antibacterial property. The orientation and aspect ratio of MWCNTs also greatly affects its antibacterial property [79].

Moreover, it has been reported that investigated derivatives have shown better activity against the Gram-positive bacteria and comparatively lower against the Gram-negative bacteria [80]. It has been reported that chitosan Derivative 4/MWCNT1 and chitosan Derivative 4/MWCNT2 have exhibited more antibacterial activity than native chitosan Derivative 4. MWCNTs have exhibited synergistic effect during bacterial inhibition by interrupting the membrane of a microorganism and thus suppress the growth of bacteria. The MWCNTs bind with bacterial cell by van der Waals forces. As a result, bacterial cell wall damaged which is followed by leakage of intracellular components from the bacterial cell. It has been reported in the literature that the nanocomposites get adsorbed at the surface of bacterial cell wall and bind with the metals of the nutrient which are essential for the bacterial cell multiplication and leads to death of bacteria [81,82].

Engel et al. (2018) have reported the antibacterial activity of single walled carbon nanotubes in combination with iron oxides against *E. coli* bacteria [83]. CNTs based filter has been fabricated for both capturing and inactivation of bacteria [84]. Membrane filters covered with carbon nanotubes were used to investigate the antibacterial activity against a number of bacteria namely *E. coli*, *Salmonella* species, *Klebsiella* and *Shigella flexneri* [85,86]. Bhaduri and his co-workers (2018) have demonstrated the antibacterial activity of single walled carbon nanotubes modified with $\text{Ag-Fe}_3\text{O}_4$ [87]. In 2013, multiwalled carbon nanotubes doped with silver were reported for antibacterial activity by Su et al. Furthermore, Rananga and Magadzu, (2014) have demonstrated that by using multiwalled carbon nanotubes doped with cyclodextrin and silver have shown enhanced antibacterial activity [88]. An investigation was carried out by Zhu et al. (2015) for the demonstration of antibacterial activity of multiwalled carbon nanotubes functionalized with carboxyl group [89]. A nanocomposite of polyaniline/graphene/carbon nanotubes have been reported for antibacterial activity against *S. aureus* and *E. coli* [90,91]. Antimicrobial activity was first reported through Carbon nanotubes by Kang et al. (2007) [92]. Functionalization of carbon nanotubes might increase the antimicrobial activity while helping to decrease the toxicity towards mammalian cells. Kang et al., 2007 demonstrated that multiwalled carbon nanotubes were more toxic when they were uncapped, debundled, and dispersed in the solution [92].

Multiwalled carbon nanotubes utilized for removal and inactivation of bacteria by Vecitis et al. (2011). The authors also described multiwalled carbon nanotube filter to treat drinking water through removal and inactivation of virus and bacteria [93].

Zardini et al., 2014 developed Multi walled carbon nanotubes functionalized with mono-, di-, and tri-ethanolamine showed better antibacterial activity than pristine Multiwalled carbon nanotubes. They demonstrated the antimicrobial activity against four-gram positive and four-gram negative strains [94].

6. Antifungal activity of CNTs

Rathore et al. (2000) have demonstrated the anti-fungal activities invitro by agar well diffusion technique. Herein this approach also derivatives of chitosan are used along with the MWCNT in order to demonstrate the antifungal activity against fungi namely *A.niger*, *C. tropicalis* and *C. neoformans* [95]. The nano-composites showed a great potential in which polymer chitosan inhibit the germination of spores, elongation of germ tube and radial growth [96]. Chitosan promotes morphogenesis of the cell wall which restricts the growth of fungi. Chitosan combines with the DNA after entering in to the cell wall as they are small in size and it was revealed by microscopic examination. After

conjugation with the DNA the transcription and translation process also get inhibited which will ultimately affects the production of enzymes and proteins which are necessary for the growth of fungal hyphae [97]. Polymer derivative with MWCNT showed unique antifungal activities than parent chitosan. MWCNTs have potential to show electrostatic interaction with the cell membrane and change its permeability. Chitosan derivatives and MWCNTs have been found more potent against *C. Tropicalis* as compared to *C. neoformans* and highest potency was observed in case of *A. niger*. Functionalized carbon nanotubes have been found effective against *Candida* strains. A study was carried out by zari et al. (2013) [98] to show the antifungal effect against various fungus viz. *A. niger*, *A. fumigatus*, *C. albicans*, *P. chrysogenum*, *S. cerevisiae*, *F. culmorum*, *M. canis*, *T. mentagrophytes*, *T. rubrum* and *P. lilacinum*. Single walled carbon nanotubes dispersed with tetra-aryl bimesityl derivative activated with by adding carboxy group were used for the demonstration of antifungal activity against *E. coli*, *S. aureus* and *C. albicans* [99].

7. Conclusion

Carbon nanotubes are rolling cylindrical structure. Multiwalled carbon nanotubes have shown improved electrical conductivity, large surface area, better chemical consistency and mechanical strength. As carbon nanotubes have shown unique advantages and therefore, acting as carrier for the effective delivery of biomolecules like antibiotics, proteins, DNA, RNA, Immunoactive compounds and lectins. Biosensors based on carbon nanotubes have shown better reproducibility, sensitivity, reliability and economic. Employment of MWCNTs in biosensing technology makes them more sensitive, specific and conducive and can be used in diagnosis of diseases and treatment for example cancer. MWCNTs based biosensors have been used to detect many analytes such as pyridoxine, dopamine ascorbic acid, uric acid and many more. Furthermore, carbon nanotubes have also exhibited antimicrobial activity. Therefore, future research should be focus on investigating more efficient CNT based devices for the betterment of human health.

8. Future perspectives

Even though CNSs emerged about three decades ago, much progress has been achieved within this small period of time. At the moment, most antibacterial carbon-nanomaterials are still under research/development. Despite the fact that several carbon-allotrope-products are commercially available now, CNSs are incapable to substitute/compete with the currently used antibacterial materials (e.g., polymers, Ag-NPs) for many reasons; for instance their toxicity profile for human cells has not been well-addressed yet, they are slow and expensive to produce, and large-scale fabrication is still very challenging. Thus, upcoming experiments should mainly concentrate on producing non-toxic CNSs in large quantities at minimal production cost. At this stage, it seems that functionalization of CNSs is a promising way to expand their performance in the biological field opening the way for wide-integration in biomaterials. Although safety issues have still to be thoroughly examined, there are potentially practical benefits in developing novel vectors for nano-medicinal applications. On the other hand, progress in carbon nanotube technology may well lead to better insights into biological and physical chemistry processes. This will make it possible to find compounds more compatible with carbon nanotube technology and to facilitate more effective use of nanotubes.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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