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CARBON NANOTUBES: A PROMISING TOOL IN DRUG DELIVERY

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ABSTRACT

Nanomaterials are at the leading edge of the rapidly developing field of nanotechnology. Their unique size-dependent properties make these materials superior and indispensable in many areas of human activity. Carbon nanotubes (CNTs) have recently garnered interest of today's world of medicine and are being highly researched in the fields of efficient drug delivery and biosensing methods for disease treatment and health monitoring. Nanotubes are categorized as single-walled carbon nanotubes ($SWCNT_S$) and multiple walled carbon nanotubes ($MWCNT_S$). Various techniques have been developed to produce carbon nanotubes in sizeable quantities, including arc discharge, laser ablation, chemical vapor deposition, silane solution method and flame synthesis method. Research on properties and characteristics of CNTs has barely begun to tap the potential of these structures. Work till now have shown that they can pass through membranes, carrying therapeutic drugs, vaccines and nucleic acids deep into the cell to targets previously unreachable. This review attempts to understand the basics and summarize the most recent developments in the field of applied nanomaterials, in particular their application in biology and medicine, and discusses their commercialization prospects.

KEYWORDS: Carbon nanotubes, nanomaterials, biosensor, single walled carbon nanotubes, multiple walled carbon nanotubes.

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INTRODUCTION

Carbon nanotubes (also known as buckytubes) are cylindrical shaped allotropes of carbon which have been constructed with length-to-diameter ratio of up to 132,000,000:1 [1]. Nanotubes are members of the fullerene structural family, which also includes the spherical buckyballs. The diameter of a nanotube is of the order of a few nanometers (approximately 1/50,000th of the width of a human hair), while they can be up to 18 centimeters in length (as of 2010) [1]. Carbon nanotubes are categorized as single walled nanotubes (SWCNTs) and multiple walled nanotubes (MWCNTs). (Table 1) With advantage of reduced size and increased surface area, these cylindrical carbon molecules have novel properties that make them potentially useful in many applications of nanotechnology, electronics, optics and other fields of material science, as well as in architectural fields. They exhibit extraordinary strength and unique electrical properties, and are efficient thermal conductors. The nature of the bonding of a nanotube is described by applied quantum chemistry, specifically, orbital hybridization. The chemical bonding of nanotubes is composed entirely of sp^2 bonds, similar to those of graphite. This bonding structure, which is stronger than the sp^3 bonds found in diamonds, provides the molecules with their unique strength. Nanotubes naturally align themselves into "ropes" held together by Vander Walls forces. The use of CNTs in drug delivery and biosensing technology has the potential to revolutionalize medicine. Functionalization of SWCNTs has proven to enhance solubility and allow for efficient tumor targeting/drug delivery. It prevents SWCNTs from being cytotoxic and altering the function of immune cells. Various Types of nanotubes structure are described in (Figure 1).

Classification of CNTs *[2-34]*

- Carbon nanotubes are classified in following two types,
  - SWCNTs- Single walled carbon nanotubes
  - MWCNTs- Multiple walled carbon nanotubes
- Other related structures are as follows:
  - Torus
  - Nanobud
  - Cup stacked carbon nanotubes
  - Extreme carbon nanotubes

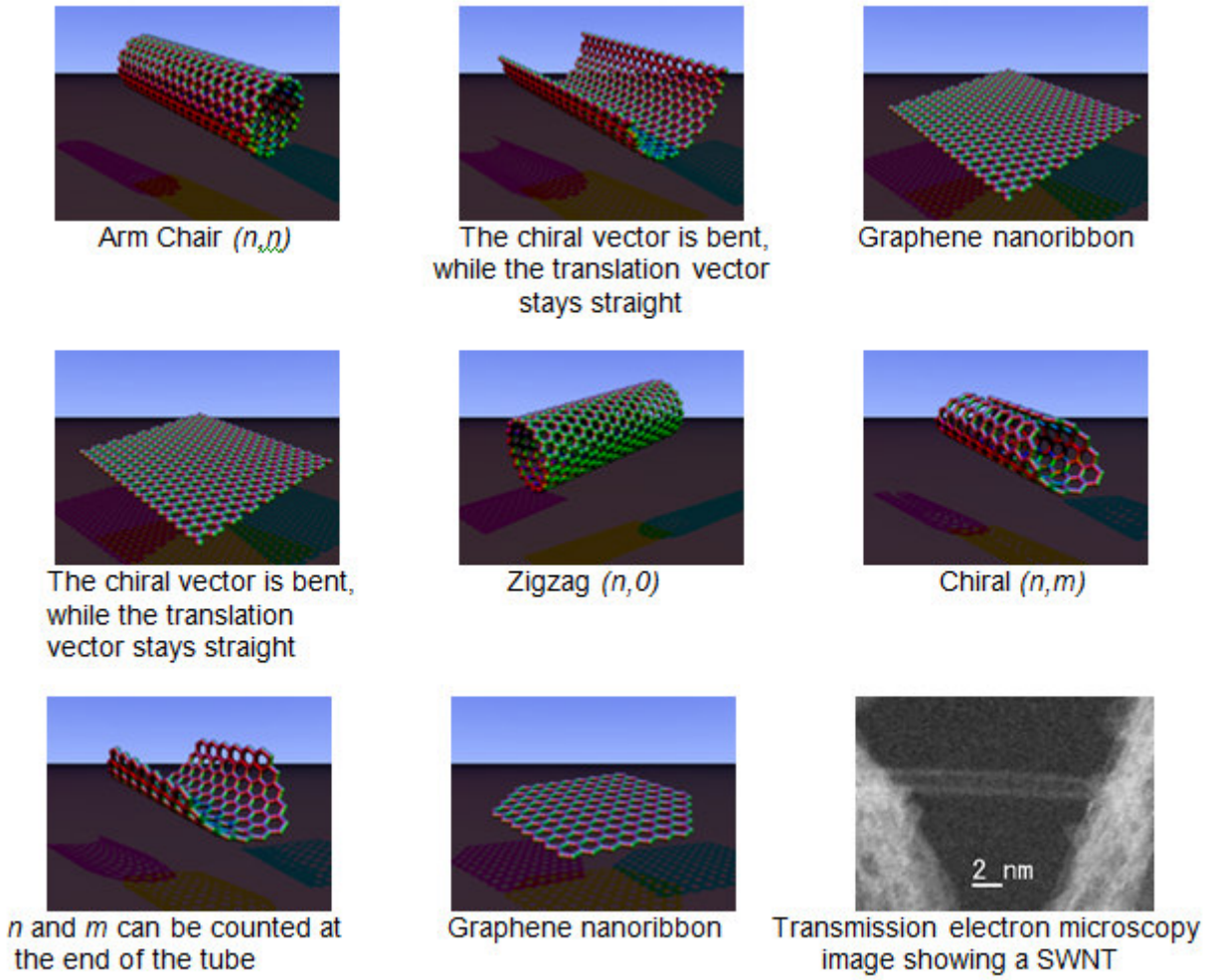

Figure 1
Types of nanotubes structure [3]

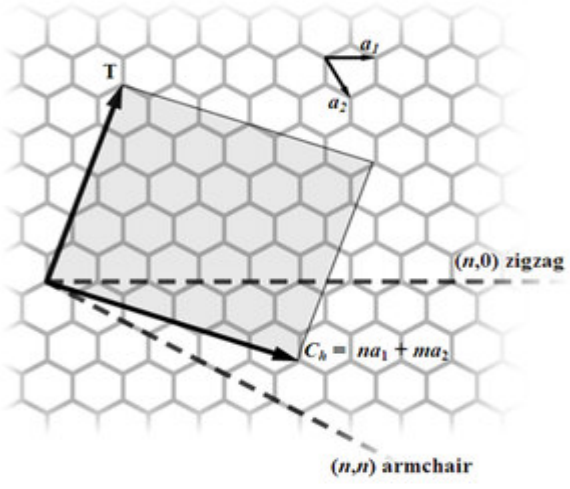

Figure 2
Various types of nanotubes [3]

The (*n*,*m*) nanotube naming scheme can be assumed as a vector (C_h) in an infinite graphene sheet that describes how to roll up the graphene sheet to make the nanotube. T denotes the tube axis, and a_1 and a_2 are the unit vectors of graphene in real space (figure 2).

Table 1
Comparison between SWCNT and MWCNT [12]

SWCNTs	MWCNTs
Single layer of grapheme	Multiple layer of grapheme
Catalyst is required for synthesis	Can be produced without catalyst
Bulk synthesis is difficult as it requires proper control over growth and atmospheric condition	Bulk synthesis is easy
Purity is poor	Purity is high
A chance of defect is more during functionalization	A chance of defect is less but once occurred it's difficult to improve
Less accumulation in body	More accumulation in body
Characterization and evaluation is easy	It has very complex structure
It can be easily twisted and are more pliable	It can not be easily twisted

1) Single-walled carbon nanotubes ($SWCNT_S$)

- Most SWCNTs have a diameter of close to 1 nanometer, while length can be many millions of times longer. The structure of a SWCNT can be conceptualized by wrapping a one-atom-thick layer of graphite called graphene into a seamless cylinder. The manner in which the graphene sheet is wrapped is represented by a pair of indices *(n,m),* called the chiral vector. The number of unit vectors along the two directions is represented by the integers *n* and *m* in the honeycomb crystal lattice of graphene. The nanotubes are called *zigzag* when *m* = 0. The nanotubes are called *arm chair* when *n* = *m*. Otherwise, they are called *chiral*. From the following equation the diameter of a nanotube can be calculated using its *(n,m)* indices where *a = 0.246 nm.*

$$d = \frac{a}{\pi}\sqrt{(n^2 + nm + m^2)}.$$

- SWCNTs have shown marked drop in price recently, from around $1500 per gram as of year 2000 to retail prices of around $50 per gram of as-produced 40–60% by weight SWCNTs as of March 2010 [13, 14].

2) Multi-walled carbon nanotubes ($MWCNT_S$)

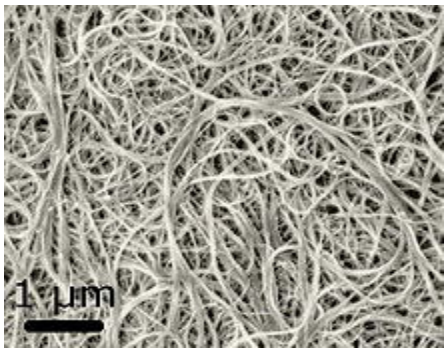

Figure 3
SEM image of bunch of multi-walled nanotubes [3]

$MWCNT_S$ consist of multiple rolled layers (concentric tubes) of graphite. The SEM image of the $MWCNT_2$ was illustrated in the (Figure 3). Two models which can be used to describe the structures are

1) Russian Doll model: Graphite sheets are arranged in concentric cylinders, e.g. a (0, 8) single-walled nanotube ($SWCNT_S$) within a larger (0, 17) single-walled nanotube.
2) Parchment model: Single graphite sheet is rolled in around itself like a scroll of parchment or a rolled newspaper. And the interlayer distance is approximately 3.4 Å.

Double-walled carbon nanotubes ($DWCNT_S$)

Properties and morphology are similar to $SWCNT_S$ but resistance to chemicals is significantly improved. This is important when functionalization is required (this means grafting of chemical functions at the surface of the nanotubes) to add new properties to the CNT. $DWCNT_S$ synthesis was proposed first in 2003 [6] by the CCVD technique on the gram-scale, by the selective reduction of oxide solutions in methane and hydrogen. In SWCNT, covalent functionalization will break some C=C double bond, leaving holes in the structure on the nanotube and thus modifying both its mechanical and electrical properties. While in case of $DWCNT_S$, only the outer wall is modified. Structure and TEM are described in figure 4 [16].

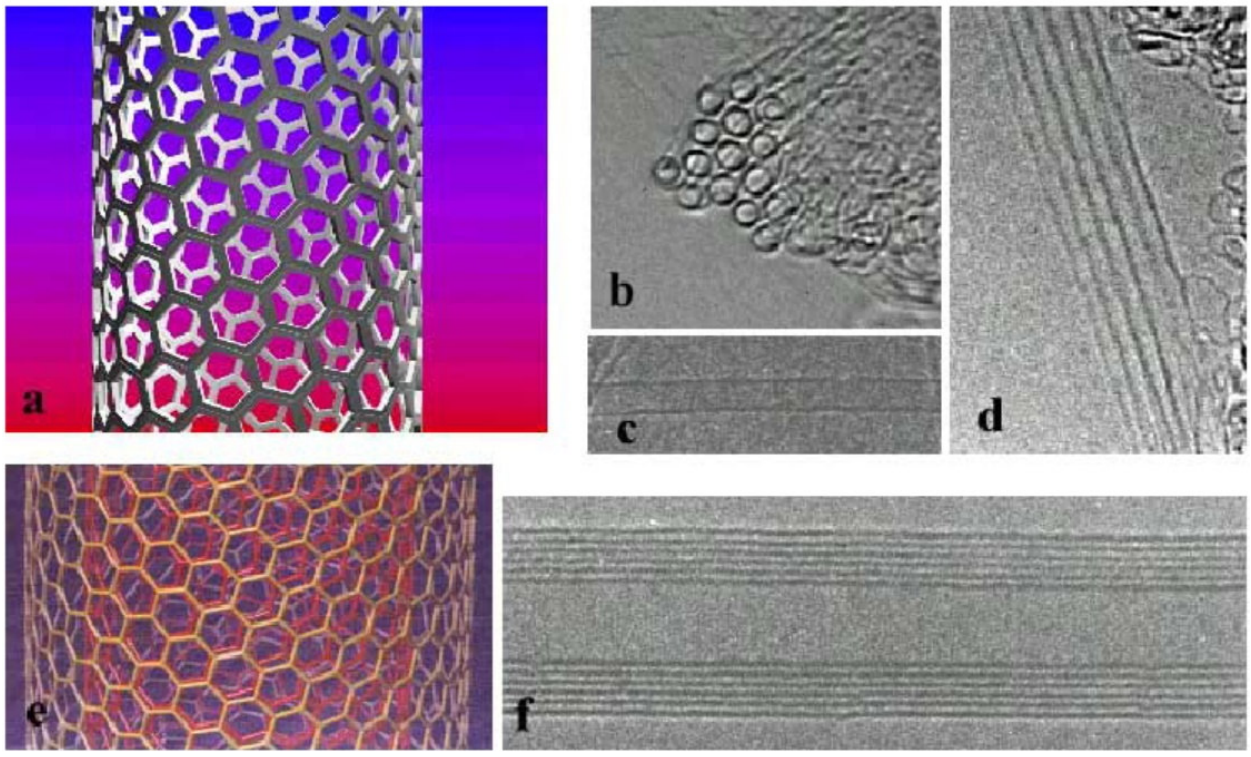

Figure 4

Structure of Single-Walled ($SWCNT_S$) (a-d) and Multi-Walled ($MWCNT_S$) carbon NanoTubes (e,f). (a) Shows a schematic of an individual helical SWMT. (b) Shows a cross-sectional view (TEM image) of a bundle of SWCNTs [transverse view shown in (d)]. Each nanotube has a diameter of 1.4 nm and the tube-tube distance in the bundles is 0.315 nm. (c) Shows the high-resolution TEM micrograph of a 1.5 nm diameter $SWCNT_S$. (e) is the schematic of a $MWCNT_S$ and (f) shows a high resolution TEM image of an individual $MWCNT_S$. The distance between horizontal fringes (layers of the tube) in (f) is 0.34 nm (close to the interlayer spacing in graphite)

3) Torus

Nanotorus is a carbon nanotube bent into a torus (doughnut) shape. Nanotori are predicted to have many unique properties, such as magnetic moments 1000 times larger than previously expected for certain specific radii [17]. Depending

on radius of the torus and radius of the nanotube the magnetic moment, thermal stability, and other properties vary widely [17,18].

4) Nanobud

Nanobuds are the newly synthesized combination of carbon nanotubes and fullerenes that posses useful properties of both (Figure 5). The fullerene-like buds are covalently bonded to the outer sidewalls of the underlying carbon nanotube. Nanobuds are exceptionally good field emitters and improves the mechanical properties of composite material (the attached fullerene molecules may function as molecular anchors preventing slipping of the nanotubes).

Figure 5
A stable nanobud structure [3]

5) Cup stacked carbon nanotubes (CSCNTs)

CSCNTs exhibit semiconducting behaviors due to the stacking microstructure of graphene layers and thus differ from other quasi-1D carbon structures that behave as a metallic conductor of electrons [19].

6) Extreme carbon nanotubes

The longest carbon nanotubes (18.5 cm long) was reported in 2009 which was grown on Si substrates using an improved chemical vapor deposition (CVD) method and represent electrically uniform arrays of single-walled carbon nanotubes [1]. The shortest carbon nanotube synthesized is that of cycloparaphenylene (Figure 6), in the early 2009 [20, 21, 22]. The thinnest carbon nanotube is armchair (2, 2) CNT with a diameter of 3 Å that was grown inside a multi-walled carbon nanotube. Characterization of carbon nanotube type was done by a combination of high-resolution transmission electron microscopy (HRTEM), Raman spectroscopy and density functional theory (DFT) calculations [23].

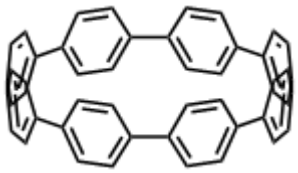

Figure 6
Cycloparaphenylene [3]

The thinnest freestanding single-walled carbon nanotube is about 4.3 Å in diameter with questionable indices, but the suggested indices can be either (5, 1) or (4, 2) SWCNT [24]. (3, 3), (4, 3) and (5, 1) carbon nanotubes (all about 4 Å in diameter) were unambiguously identified using more precise aberration-corrected HRTEM. However, they were found inside of double-walled carbon nanotubes [25] (Figure 1).

METHODS FOR PRODUCTION OF CNTS

A. Arc Discharge Method [26-29]

Arc Discharge method has been reported for producing carbon nanotubes. In this method, as

shown in figure 7 nanotubes are produced through arc vaporization of two carbon rods placed end to end with a distance of 1mm in an environment of inert gas such as helium, argon at a pressure between 50 to 700 mbar. Carbon rods are evaporated by a direct current of 50 to 100 amps driven by 20V which will create high temperature discharge between two electrodes. Due to this, anode will get evaporated and rod shaped tubes will be deposited on cathode (Figure 3). Bulk production of CNTs depends on uniformity of plasma arc and temperature of deposition.

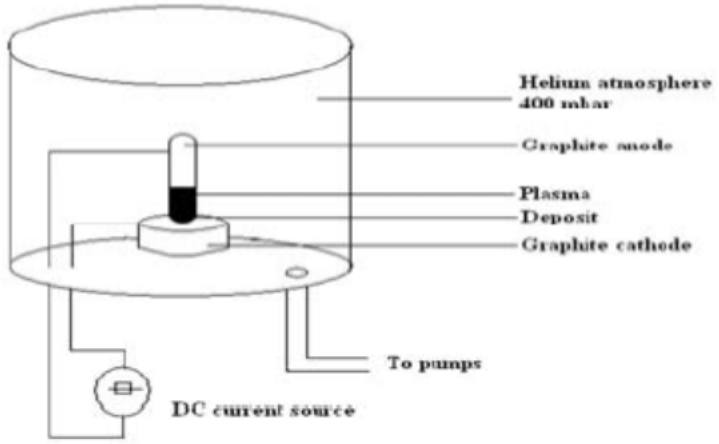

Figure 7
Arc discharge method [29]

1. Production of SWCNTs

In the production of SWCNTs anode is dipped with a metal catalyst such as Fe, Co, Ni, Y, or Mo. It produces SWCNTs with a diameter of 1.2 to 1.4nm. Efficiency of $SWCNT_S$ production by arc discharge method is improved with

a) Inert Gas

Argon with a lower diffusion coefficient and thermal conductivity has given nanotube with smaller diameter (1.2nm) and 0.2nm diameter decrease with 10% increase in argon: helium ratio, when Nickel and Yttrium is used as a catalyst (4.2:1).

b) Optical Plasma Control

As the distance between anode and cathode increases, anode vaporization increases, due to which strong visible vortices around cathode is occurred.

c) Catalyst

By changing metal catalyst, nanotubes with a diameter of 0.6 to 1.2 nm are produced. Catalysts used are Co and Mo.

d) Open Air Synthesis with Welding Arc Torch

This method is specifically used for SWCNTs with graphite rod containing metal catalyst. The arch is operated at 100 amps current and shielding Ar gas flowed through torch to enhance arc jet formation. This method is very convenient and inexpensive with Ni:Y (3.6: 0.8). Nanotubes produced by this method are of diameter of 1.32 nm.

2. Production of MWCNTs

MWCNTs are produced with the use of pure graphite arc with an inner diameter 1-3nm and outer diameter10nm (approx.). Since catalyst is not used in this process there is no need for a heavy acidic purification. So, MWCNTs can be formed with a less number of defects. Different methods used to synthesize are,

a) Synthesis in Liquid Nitrogen [27]

MWCNTs are formed by generating arc-discharge in liquid nitrogen. For which low pressure and expensive inert gas are not needed. Yield is about 70% of reaction product.

b) Magnetic Field Synthesis [28]

MWCNTs formed by this method are defect free and having high purity. In this arc- discharge is controlled by a magnetic field around the arc plasma. Extremely pure graphite rods (purity >99.999 %) are used as electrodes. Highly pure MWCNTs (purity > 95 %) are obtained without further purification, which disorders walls of MWCNTs.

c) Plasma Rotating Arc Discharge [29]

The centrifugal force caused by the rotation generates turbulence and accelerates the carbon vapor perpendicular to the anode and the rotation distributes the micro discharges uniformly and generates stable plasma. Consequently, it increases the plasma volume and raises the plasma temperature. At the rotation speed of 5000 rpm, a yield of 60 % was found at a temperature 1025 °C without the use of a catalyst. The yield can be increased up to 90% after purification if the rotation speed is increased and the temperature is enlarged.

B. Laser Ablation Method [29]

The equipment used for this method is as shown in figure 8. A pulsed or continuous laser is used which will vaporize a graphite target in an oven at 1200 °C. The oven is filled with helium or argon gas in order to keep the pressure at 500 Torr. Since the optimum background gas and catalyst mixture is the same as in the arc discharge process, this method is almost similar to arc discharge. This method is very expensive so it is mainly used for SWCNTs. Laser vaporization results in higher yield of SWCNTs with narrower size distribution than those produced in arc discharge process (Figure 7). Catalyst used for SWCNTs is Ni: Y (4.2: 1 at %).

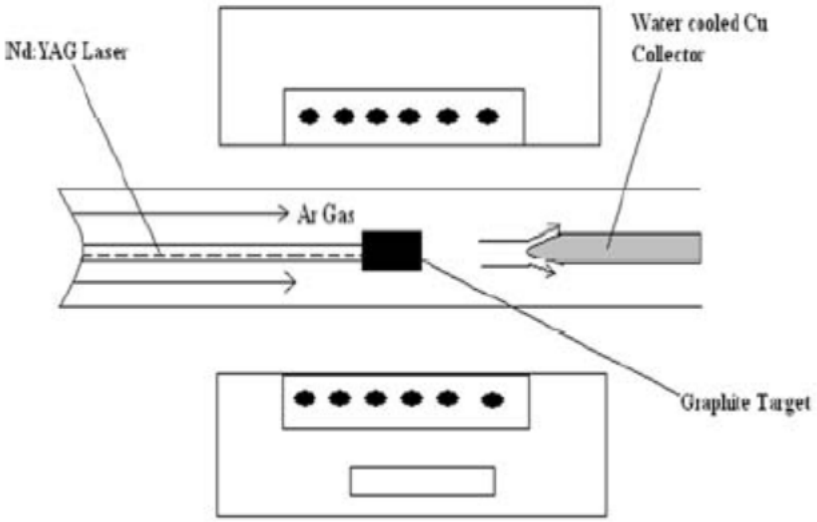

Figure 8
Laser ablation method [12]

C. Chemical Vapors Deposition Method [30, 31]

It is carried out in a two step process:-

• Catalyst is deposited on substrate and then nucleation of catalyst is carried via chemical etching or thermal annealing. Ammonia is used as an etchant. Metal catalysts used are Ni, Fe or Co.

• Carbon source is then placed in gas phase in reaction chamber. Then carbon molecule is converted to atomic level by using an energy source like plasma or heated coil. This carbon will get diffused towards substrate, which is coated with catalyst and nanotubes grow over this metal catalyst. Carbon source used is

methane, carbon monoxide or acetylene. Temperature used for synthesis of nanotube is 650 – 9000 C range. The typical yield is 30%.

D. Flame Synthesis Method

SWCNTs are formed in a controlled flame environment from hydrocarbon fuels and small aerosol metal catalyst [31, 32]. Single-walled nanotubes have been observed in the post-flame region of a premixed acetylene/oxygen/argon flame operated at 50 Torr (6.7 kPa) with iron pentacarbonyl vapor used as a source of metallic catalyst. Between 40 and 70 mm heights above burner (~30 milliseconds), nanotubes are observed to form and coalesce into clusters [33].

E. Silane Solution Method

Carbon nanotubes were produced using a silane solution method, in which a substrate such as carbon paper or stainless steel mesh was immersed in a silane solution of a metal catalyst, preferably Co:Ni in a 1:1 ratio; and a feedstock gas containing a carbon source such as ethylene was fed through the substrate and the catalyst deposited thereon while the substrate was heated by applying an electrical current thereto. Thus, a reaction occurs between the catalyst and the gas to yield CNTs supported on the conductive substrate [34].

PURIFICATION OF CNTs [35]

Nanotubes usually contain a large amount of impurities such as metal particles, amorphous carbon, and multishell. There are different steps in purification of nanotubes.

1) Air Oxidation

The carbon nanotubes are having less purity; the average purity is about 5-10%. So purification is needed before attachment of drugs onto CNTs. Air oxidation is useful in reducing the amount of amorphous carbon and metal catalyst particles (Ni, Y). Optimal oxidation condition is found to be at 673 k for 40 min.

2) Acid Refluxing

Refluxing the sample in strong acid is effective in reducing the amount of metal particles and amorphous carbon. Different acids used were hydrochloric acid (HCl), nitric acid (HNO_3) and sulphuric acid (H2SO4), but HCl was identified to be the ideal refluxing acid.

3) Surfactant aided sonication, filtration and annealing

After acid refluxing, the CNTs were purer but, tubes were entangled together, trapping most of the impurities, such as carbon particles and catalyst particles, which were difficult to remove with filtration. So, surfactant-aided sonication was carried out. Sodium dodecyl benzene sulphonate (SDBS) aided sonication with ethanol (or methanol) as organic solvent were preferred because it took the longest time for CNTs to settle down, indicating an even suspension state was achieved. The sample was then filtered with an ultra filtration unit and annealed at 1273 k in N2 for 4 h. Annealing is effective in optimizing the CNT structures. It was proved the surfactant-aided sonication is effective to untangle CNTs, thus to free the particulate impurities embedded in the entanglement. Nanotube can also be purified by multi-step purification method.

Characterization [36]

Following are the methods that are currently used for the characterization of the CNTs:

- RAMAN Spectroscopy - suitable for the quick and reliable screening of the presence of SWCNT
- Transmission electron microscopy (TEM) - assessment of detailed structures.
- Scanning electron microscopy (SEM) - provides an overview of sample structures and is less sensitive to sample preparation and homogeneity than TEM.
- Thermogravimetric analysis gives information about relative abundance of catalyst particles, nanotubes and other carbonaceous structures.
- Electron energy-loss spectroscopy.
- High-resolution transmission electron microscopy.

P. Delhaes et al. [37] have carried out the comparative study between Raman spectroscopy and surface characterization of MWCNTs which confirmed that, different

MWCNT morphologies lead to different physical and chemical characteristics.

Purification of Carbon nanotubes

Nanotubes usually contain a large amount of carbonaceous impurities which get incorporated during synthesis and for this reason purification is required to be done. The different methods for this are as follows [38]:

1) Air Oxidation

This process is useful for amorphous carbon and metal catalyst amount reduction. Optimal condition for this is 673˚K for 40 minutes.

2) Acid Refluxing

It is done with strong acid (like HCl, HNO_3 and H_2SO_4) for amorphous carbon and metal particles reduction.

3) Surfactant aided sonication

Due to the entanglement of tubes the impurities get trapped in these aggregates. For removing this surfactant aided sonication can be used (e.g. Sodium dodecyl benzene sulphonate with ethanol or methanol).

Properties

CNTs have unique chemical and physicochemical properties such as ordered structure with high aspect ratio, ultralight weight, high mechanical strength, optical, high electrical conductivity, high thermal conductivity, metallic or semi-metallic behaviour and high surface area that make them attractive for drug delivery and biosensing systems for the treatment of various diseases and the noninvasive monitoring of blood levels and other chemical properties of the human body, respectively [3, 39, 40]. Many researchers like, Shuhui Qin et L. [41], Fabian Buffa et al. [42], Daniel E. Resasco et al. [43] and Liang Zhang et al. [44] have given their contribution in understanding the properties and synthesis of CNTs.

1) Electrical and Structural

Due to the symmetry and unique electronic structure of graphene, CNTs can be metallic or semiconducting. For a given (n, m) nanotube, if n = m (armchair structure), the nanotube is metallic; if n – m is a multiple of 3, then the nanotube is semiconducting with a very small band gap, otherwise the nanotube is a moderate semiconductor [45]. Thus, some nanotubes have conductivities higher than that of copper, while others behave more like silicon.

2) Dimensional

Due to their nanoscale dimensions, electron transport in carbon nanotubes will take place through quantum effects and will only propagate along the axis of the tube. These electrical and structural properties best serve CNTs as far as biosensing is concerned because current changes in the CNTs can signify specific biological entities they are designed to detect. The fact that CNTs are small (nm scale) allows them to deliver smaller doses of drugs to specific disease cells in the body thus reducing side effects and harm to healthy cells unlike conventional drugs, whilst improving disease cell targeting efficiency [45].

3) Chemical

CNTs have been observed to have enhanced solubility and permeability through the bio-membranes when functionalized with lipids [For detailed information on functionalization] [46, 47, 48].

4) Solubility

Though SWCNTs have attracted considerable interest owing to their novel, structure-dependent mechanical and electronic properties [49], the researches and applications of SWCNTs has been hampered by difficulties associated with processing and manipulation [50]. Considerable efforts [51, 52] have thus been devoted to the modification of SWCNTs to improve their solubility in solvents and to enhance their compatibility in composite materials. Among various modification methods, sidewall functionalization of SWCNTs has been studied extensively as a route to their separation [53, 54], solubilization [55, 56, 57], and subsequent reactivity [52]. Most of these efforts have involved the use of conventional chemical techniques such as refluxing and sonication. Although some groups employed water as a clean solvent [58] and/or

directly designed non-solvent reactions [59, 60, 61], most of these functionalization processes were carried out in organic solvents over long time. Mechanochemistry, in which mechanical motions/energy control chemical reactions [62] has attracted much attention. This reaction technique has been presumed to generate local high-pressure spots and to bring the reacting species into the closest contact to cause novel chemical reactions to occur [63, 64]. Many researchers have been carried out on carbon nanotubes using such mechanochemistry method, especially the high-speed vibration mill (HSVM) technique. Konya introduced functional groups like thiol, amine, amide, carbonyl, chlorine, etc. onto carbon nanotubes by ball milling in reactive atmospheres [65]. Based on the similar ball milling technique, the functionalization of SWCNTs using alkyl-halides was reported by Barthos et al. [61]. X. Li et al. [66] have reported that SWCNTs could react with KOH through HSVM technique to prepare SWCNTs [55], which are highly soluble in water and can be readily self assembled into aligned arrays through strong surface hydrogen bond interactions. Subsequently, they also obtained C60-modified SWCNTs by this method [67]. Later they have presented the covalent functionalization of SWCNTs with alkyl and aryl groups generated from the corresponding organic chlorides using such mechanochemistry technique.

PHARMACOLOGY OF CNTs

For nanoparticles the physiochemical characteristics such as size, shape, aggregation, chemical composition, surface functionalization and solubility [67,68] are the basis for the biodistribution and pharmacokinetics .Two studies reported concerning the biodistribution of CNT were performed with water soluble CNT, which are biocompatible with the body fluids. None of the studies report toxic side effects or mortality. Wang et al. [69] reported that the CNT biodistribution was not significantly influenced by the administration route and that the ^{125}Iodine labeled multiple hydroxylated SWNT distribute quickly throughout the whole body with no tissue damage or distress. Most importantly from a safety point of view, 94% of the nanotubes were excreted into the urine and 6% in the feces as observed in this study. Another study, focusing on the intravenous route of administration and using functionalized SWCNT and MWCNT [70] reported that the biodistribution profiles were very similar for both types of functionalized [^{111}In] DTPA-SWCNT. Both types of nanotubes were found to be rapidly cleared from all tissues and a maximum blood circulation half-life of 3.5 hrs was determined. Both DTPA functionalized CNTs were found to be excreted intact through the renal route into the bladder and urine as observed by transmission electron microscopy.

TOXICITY OF CNTs

Generally, the harmful effects of nanoparticles are attributed to the combination of various factors, two of which are particularly important: (a) the high surface area and (b) the intrinsic toxicity of the surface [67]. Nanoparticles below 100 nm can potentially be more toxic to the lung (portal of entry), can redistribute from their site of deposition, can escape from the normal phagocytic defenses and can modify the structure of proteins. Therefore, can activate inflammatory and immunological responses and may affect the normal tissue function [71]. Milligram quantities of CNT possess a large number of cylindrical, fibre-like particles, with a concurrent very high total surface area. This total surface area will also depend on their degree of bundling and aggregation of nanotubes in solution [47]. Intrinsic toxicity of CNT depends on (i) degree of surface functionalization and (ii) different toxicity of functional groups. Batches of pristine CNT (non-purified and/or non-functionalized) readily after synthesis contain impurities such as amorphous carbon and metallic nanoparticles (catalysts: Co, Fe, Ni and Mo), which can also be the source of severe toxic effects [67]. The structural characteristics of nanomaterials, such as the fiber shape, the length and the aggregation status of the CNT, can also influence their local deposition in the lungs and the immunological response following exposure to CNT as shown by Donaldson et al.[72].

The toxicity of CNTs can be divided into following

1) Cytotoxicity of functionalized group

Studies have shown that functionalized carbon nanotubes are non-cytotoxic and preserve the functionality of primary immune cells [73]. This involved two types of f-CNTs (functionalized CNTs) prepared by following the 1, 3-dipolar cycloaddition reaction and the oxidation/amidation treatment.

2) In vitro cytotoxicity

In vitro toxicity of SWCNTs and MWCNTs in human astrocytoma and lung carcinoma cells was investigated using the MTT assay and calcein/propidium iodide (PI) staining [74]. The results suggested the need of a careful examination of carbon nanotubes toxic effects by means of multiple tests to circumvent the possible problem of artifactual results due to the interference of nanomaterials with the dye markers employed.

3) Cytotoxicity of SWCNTs and MWCNTs

Researchers investigated SWCNTs, MWCNTs (with diameters ranging from 10 to 20 nm, MWNT10) and fullerene (C60) on healthy alveolar macrophage cells obtained from adult guinea pigs for comparison purposes [75]. Results showed that carbon nanomaterials with different geometric structures exhibit quite different cytotoxicity and bioactivity in vitro, although they may not be accurately reflected in the comparative toxicity in vivo. S.V. Prylutska, et al. [76] studied the ways of formation of the high-stability multi-walled CNT (MWCNT) water solutions for the transport of MWCNT into the biological medium, to study the structural and spectral characteristics of the MWCNT water solutions and to estimate MWCNT cytotoxicity in vitro. N.A. Monteiro-Riviere et al. [77] studied the optimum surfactant that causes minimal toxicity to human keratinocytes, while preventing nanotube aggregation without affecting cell viability or causing inflammation as determined by IL-8 release. So far majority of the reports are concerned with the toxicology of CNT, addressing the possible negative side effects on human health and environment, and particularly from the point of view of public health and safety for CNT production plant workers. Further studies for the bioavailability of CNT in the body and IVIVC should be carried out. And the knowledge of mechanism of CNT metabolism, degradation or dissolution, clearance and bioaccumulation should be enhanced for designing effective and better therapeutic dosage form with high patient compliance. Maynard et al. [78] have studied the release of particles from unrefined SWNT material into the air and the potential routes of exposure of the workers in a small-scale production facility. They have found that handling of unrefined material produces airborne particle concentrations of 53 $\mu g/m^3$ and glove deposits of 0.2–6 mg per hand.

Applications of CNTs

1) Drug Delivery

Majorly the studies on nanoparticles aims to overcome problems like poor solubility, ability to easily cross cellular membranes, drug distribution among cells, unwanted damage to healthy tissue, toxicity, and lack of the ability to select a particular cell type for treatment [79]. Many beneficial molecules can be bonded to the walls and tips of soluble CNTs, including peptides, nucleic acids, and various drug molecules [80, 81]. One of the studies found that water soluble SWCNTs translocated easily into the cytoplasm or nucleus of a cell through its cell membrane, without producing any toxic effects. Furthermore, the researchers were able to covalently bond a peptide to the nanotube, which was also easily absorbed. This peptide triggers the G protein function, which is an important factor of signal transduction [82]. Due to the ability of the CNTs to carry molecules of interest across the cytoplasmic membrane and nuclear membrane without producing a toxic effect, are studied to design a safe and effective drug delivery method for an API/NCE [82]. Wu *et. al* [83] postulated that delivery of this antibiotic by means of CNTs would reduce the amount of antibiotic necessary resulting in improved potency reduced toxicity. CNTs have been proposed and actively explored as multipurpose innovative carriers for drug delivery and

diagnostic applications. Incorporation of CNT leads to the modulation of undesired effects and creating new conjugates with promising and improved pharmacological profiles. Their intrinsic physicochemical features enable covalent and non-covalent binding of several pharmaceutical entities and allow for rational design of novel candidate nanoscale structures for drug development. [84]

2) Targeted Drug Delivery

Targeted drug delivery has advantage of small dosage and at right place, thus fewer side-effects and good patient compliance (in terms of time, efficacy and cost). Especially if, in addition, the pharmaceutical agent were to be adapted to the cell's genome, these benefits would be categorized under the heading "personalized/ individualised medicine." However, it is important to evaluate further these claims in case of nanomedicine [85].

3) Transdermal drug delivery

Work by Strasinger et al. showed that through the use of functionalized carbon nanotube (CNT) membranes, drug delivery to the skin can be controlled by applying a small electrical bias to create a programmable drug delivery system [86]. Further using this concept, Wu et al. successfully designed the transdermal film of nicotine [87].

4) Gene Delivery by CNTs

Nanotubes can be utilized to deliver genes directly into the cell and across the nuclear membrane. Gao *et. al* reported that not only can DNA molecules be attached to the tips and walls of a CNT, it can also be encapsulated inside of the structure [88]. Currently, viral vectors for gene delivery are in use and achieve high gene expression. However, this method of delivery is far from perfect, as viral vectors can be immunogenic and can cause inflammation and oncogenic effects [89]. Functionalized CNTs can provide a safe nonviral vehicle for the delivery of DNA molecules into mammalian cells, since these DNA-CNT structures are produced under strict conditions in a cell free manner. Singh *et. al* [89] studied the functionality of a SWCNT-DNA complex as a non-viral vector to deliver plasmid DNA into an A549 cell. The research concluded that the CNT-gene structure lead to gene expression levels ten times higher than that of naked DNA alone. Gene delivery by CNT is not only complex and effective but it was reported to be of low toxicity, high aqueous solubility, stablility for long-term storage, and highly modifiable for specific on gene delivery needs.

5) Peptide Delivery by CNTs

Peptides, proteins and vaccines can be effectively delivered by using functionalized carbon nanotubes (by linking the antigen to CNT in case of vaccines). Colloborative studies to test the immunogenic response of a peptide covalently bonded to a SWCNT were first performed by the researchers from multiple universities in France and Italy. Pantarotto *et. al* [82] performed this using a peptide from the foot-and-mouth disease virus. This bonding occurred on the SWCNT wall at uniformly distributed wires containing free amino groups. They found that binding molecules to carbon nanotubes increase the efficacy of the ELISA technique, also the CNT-peptide complexes prove to be incredibly safe and effective in treating immunological diseases. This novel method of vaccine delivery has the potential to improve or even replace traditional methods.

6) Cancer treatment

Carbon nanotubes present the opportunity to work with effective structures that have high drug loading capacities, good cell penetration qualities, large aspect ratios for numerous fictionalization attachments, and the ability to be readily taken up by the cell [90].

a. Boron Neutron Capture Therapy

Researchers have recently developed a new approach to Boron Neutron Capture Therapy in the treatment of cancer using substituted Carborane-Appended Water-Soluble SWCNT. The selected tissue distribution studies showed that the boron atoms are concentrated more in tumors cells than in blood and other organs, making it an attractive nanovehicle in the treatment of cancer [91].

b. Selective cancer cell destruction

Biological systems are highly transparent to NIR light (700-1100 nm). It is found that the SWCNTs absorb strongly in this region as an intrinsic property. This property of carbon nanotubes can be used as multifunctional biological transporters and near-infrared agents for selective cancer cell destruction [92].

c. Tumor targeting

Investigations on the biodistribution of radio-labelled SWCNTs in mice by in vivo positron emission tomography (PET), ex vivo biodistribution and Raman spectroscopy showed that SWCNTs that are functionalized with phospholipids bearing polyethylene-glycol (PEG) are surprisingly stable in vivo. Studies showed that PEGylated SWCNTs exhibited relatively long blood circulation times and low uptake by the reticuloendothelial system (RES). A high tumor accumulation was observed that was attributed to the multivalent effect of the SWCNTs [93]. Another work one by Zhuang Liu *et. al* [94] showed that chemically functionalized $SWCNT_S$ have promising tumor-targeted accumulation in mice and exhibit biocompatibility with little toxicity.

7) Alternative administration of erythropoietin: CNT-based carrier system can offer a successful oral alternative administration of Erythropoietin (EPO), which has not been possible so far because of the denaturation of EPO by the gastric environment conditions and enzymes.

8) As lubricant and glidant: They can be used as lubricants or glidants in tablet manufacturing due to nanosize and sliding nature of graphite layers bound with van der waals forces.

9) As intracellular penetration enhancer: Anticancer drug Polyphosphazene platinum given with nanotubes had enhanced permeability, distribution and retention in the brain due to
controlled lipophilicity of nanotubes.

10) As a preservative: Carbon nanotubes and nanohorns are antioxidant in nature. Hence, they are used to preserve drugs formulations prone to oxidation. Their antioxidant property is used in antiaging cosmetics and with zinc oxide as sunscreen dermatological to prevent oxidation of important skin components.

11) As an artificial implants: They can be used as implants in the form of artificial joints without host rejection reaction.

12)As a catalyst: Nanohorns offer a large surface area and hence, the catalyst at molecular level can be incorporated into nanotubes in large amount and simultaneously can be released in required rate at particular time. Hence, reduction in the frequency and amount of catalyst addition can be achieved by using CNTs and CNHs.

13)Cellular imaging: CNT can be used as carrier for imaging and radio tracing. The functionalized nanotubes with phospholipids bearing PEG were found stable *in vivo* along with retention in circulation for longer time with low uptake by RES [95].

14) Platelet Activation: Study on platelet activation using SWCNT was done by Bihari P. et al. on rat with satisfactory results. CNT – induced platelet activation is associated with a marked release of platelet membrane micro particles positive for the granular secretion markers CD62P and CD63 [96].

Drug Delivery with Carbon Nanotubes for in vivo Cancer Treatment

Chemically functionalized single-walled carbon nanotubes ($SWCNT_S$) have shown promise in tumor-targeted accumulation in mice and exhibit biocompatibility, excretion, and little toxicity. It has been seen that in vivo SWCNT drug delivery for tumor suppression in mice. Paclitaxel (PTX), a widely used cancer chemotherapy drug, conjugated to branched polyethylene glycol chains on SWCNTs via a cleavable ester bond to obtain a water-soluble SWCNT-PTX conjugate. SWCNT-PTX affords higher efficacy in

suppressing tumor growth than clinical Taxol in a murine 4T1 breast cancer model, owing to prolonged blood circulation and 10-fold higher tumor PTX uptake by SWCNT delivery likely through enhanced permeability and retention. Drug molecules carried into the reticuloendothelial system are released from SWCNTs and excreted via biliary pathway without causing obvious toxic effects to normal organs. Thus, nanotube drug delivery is promising for high treatment efficacy and minimum side effects for future cancer therapy with low drug doses [94].

1) CNTs as Biosensors

Conjugated polymers are a novel class of semiconductors that have been found wide applications in many areas, such as organic light emitting diodes for flat panel displays, photovoltaic cells for solar energy conversion, thin-film transistors, and chemical sensors [97, 98]. Covalent and non-covalent modifications of the outer surface of CNTs have been proved to be successful methods to achieve soluble functional CNTs [99, 100]. Baskaran et al. [101] have successfully demonstrated MWCNTs and SWCNTs serving as an efficient electron acceptor that quenches the fluorescence of porphyrin covalently linked to CNTs. Another paper was published on surface functionalization of single-walled nanotubes by Suzuki crosscoupling reactions [102]. It would be of great interest to combine the advantages of carbon nanotubes and conjugated polymers. Guodong Xu et al. [103] reported an effective method to prepare a novel structure that have advantages of both CNTs and conjugate polymer. Perez M et al successfully investigated with the CS the effect of humidity and temperature on the electrical transport properties of SWCNTs [104]. Rajendra N et al. work paper indicated that square wave voltammetry associated with the use of SWNT/EPPGE serves as a fast and reliable tool for the analysis of salbutamol in the biological system [105].

a. Glucose detection biosensors

Carbon nanotube-plasma polymer based amperometric biosensors are been fabricated for ultrasensitive glucose detection [106].

b. DNA detection biosensors

An aligned SWCNT with integrated single-strand DNAs ultrasensitive biosensor for DNA detection was developed [107].

c. Cancer cell detection

Circulating cancer cells often express characteristic cell surface markers, which provide an opportunity for early diagnosis of progressive disease. Monoclonal antibodies specific to cell surface antigens over expressed on cancer cells can be absorbed to SWCNT devices, resulting in slight drop in conductance [108, 109, 110]. Balaji Panchapakesan et al. [111] study showed the successful application of monoclonal Antibodies - SWCNT to detect circulating diseased cell with a wide variety of markers.

d. CNT modified electrode biosensors

A microbial biosensor based on CNT modified electrodes was developed using Pseudomonas putida DSM 50026 cells as the biological component and the measurement was based on the respiratory activity of the cells estimated from electrochemical measurements. The main disadvantages faced was the high surface area of CNTs that increased the background current and the diffusion problem of electrons that occurred due to overlapping of the diffusion layers formed at closely spaced CNTs in the film. However, these problems could be overcome by optimizing the CNT and polymer amounts [112]. An example of sensing biological process between ligand and receptor using nanotubes FET (Field effect transistors) devices is as shown following figures (Figure 9), where the binding of Biotin and Streptavidin has been confirmed by the resulting change in DC [113]. Carbon nanotube transistors for biosensing applications (Figure 10)

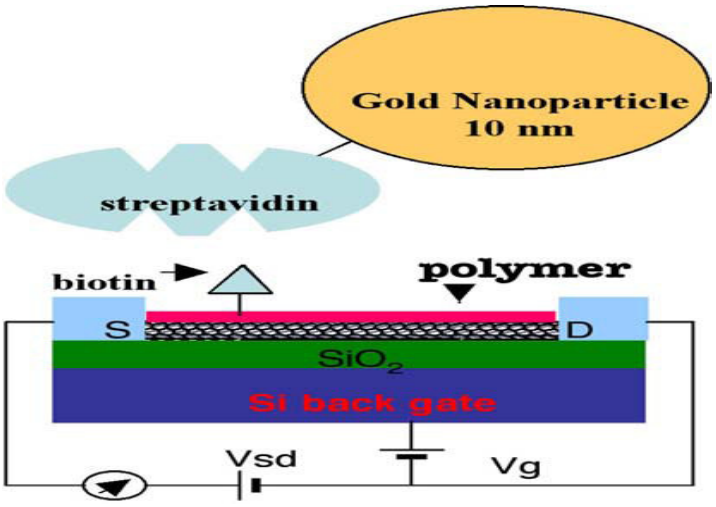

Figure 9

Detection scheme for biotin - streptavidin ligand receptor binding. The device is coated with a PEG/PEI polymer that prevents non-specific binding of streptavidin. A biotin is attached via a tether to the polymer.

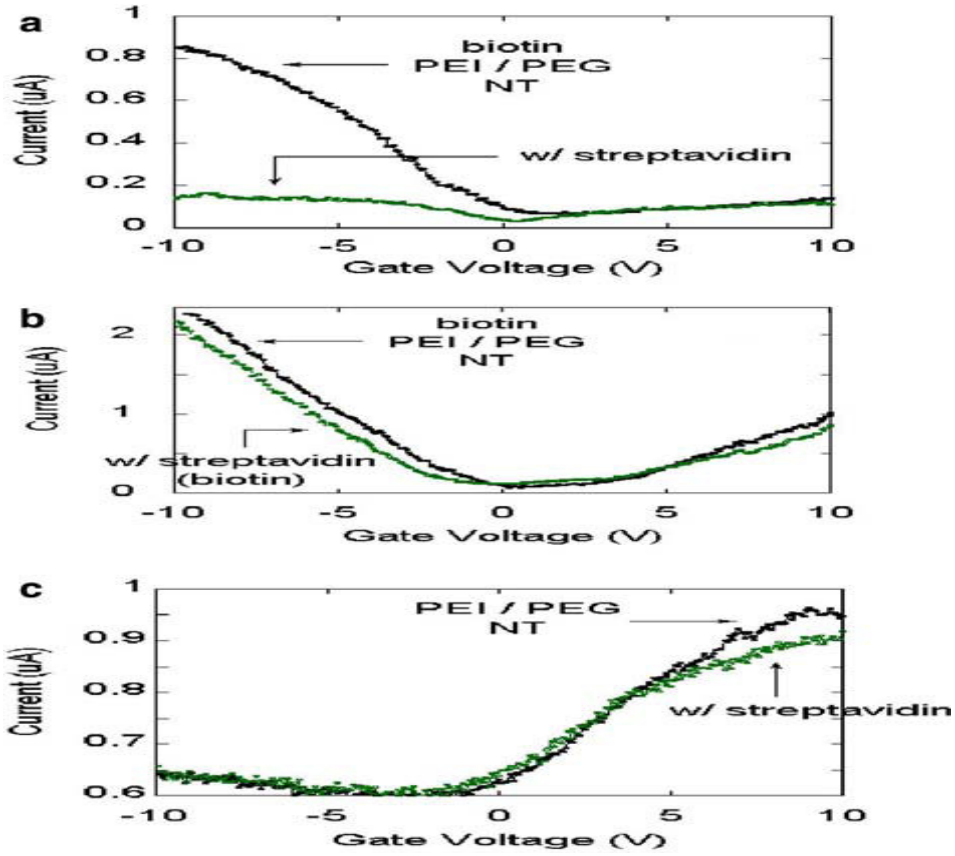

Figure 10 (a–c)

Ligand receptor binding between biotin and streptavidin. (a) Response of device shown in Figure 9. (b) Control experiment involving biotinylated streptavidin. (c) Control experiment using the device shown in Figure 9: but without biotin attachment.

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2) CNTs for Artificial implants

Majorly body shows rejection reaction for implants with the post administration pain [114]. But, miniature sized nanotubes and nanohorns get attached with other proteins and amino acids avoiding rejection. Also, they can be used as implants in the form of artificial joints without host rejection reaction. Moreover, due to their high tensile strength, carbon nanotubes filled with calcium and arranged/grouped in the structure of bone can act as bone substitute [115]. CNT make ideal artificial scaffolds for bones as the nanotubes are lightweight, very strong and the body doesn't reject them. The strength of the nanotubes will hold the bones in place whilst the tissue heals. In this way, the treatment of bone breakages and fractures will be revolutionized by an injection of carbon nanotubes into the break or fracture [116].

3) CNTs as a Preservative

Due to the antioxidant nature of carbon nanotubes and nanohorns, they are used to preserve drugs formulations prone to oxidation. Their antioxidant property is used in antiaging cosmetics and with zinc oxide as sunscreen dermatological to prevent oxidation of important skin components [117].

4) CNTs as a Diagnostic tool

Protein-encapsulated or protein/enzyme filled nanotubes, due to their fluorescence ability in presence of specific biomolecules have been tried as implantable biosensors [114]. Even, nanocapsules filled with magnetic materials, radioisotope enzymes can be used as biosensors [118]. Nanosize robots and motors with nanotubes can be used in studying cells and biological systems [119].

5) CNTs as a catalyst

Due to the large surface area of nanohorns, the catalyst at molecular level can be incorporated into nanotubes in large amount and simultaneously can be released in required rate at particular time. Hence, reduction in the frequency and amount of catalyst addition can be achieved by using CNTs and CNHs [118].

LIMITATATIONS OF CNTs [119]

- Lack of solubility in most solvents compatible with the biological milieu (aqueous based).
- Batch to batch variations: The production of structurally and chemically reproducible batches of CNTs with identical characteristics.
- High quality and minimal impurities are difficult to maintain.

EPA Regulatory issues for CNTs [120]

On September 17, 2010, the U.S. Environmental Protection Agency (EPA) issued final SNUR MWCNT (PMN P08177) and single-walled carbon nanotubes (SWCNT) (PMN P08328). EPA states that it believes the SNURs are necessary because these chemical substances may be hazardous to human health and the environment. The required notification would provide EPA with the opportunity to evaluate the intended use and, if necessary, to prohibit or limit that activity before it occurs. As per the law, Persons who intend to manufacture, import, or process either of these substances for a use that is designated as a significant new use by the final rule must notify EPA at least 90 days before commencing that activity. The final rule is effective October 18, 2010 [120].

Ethical and societal issues

A 2007 nanomedical bulletin offered the following news item: "Working with an organic semiconductor, researchers at the University of Arkansas have fabricated and tested two similar but slightly different biosensors that can measure physiological signs. Integrated into 'smart' fabrics – garments with wireless technology – the sensors will be able to monitor a patient's respiration rate and body temperature in real time" [121]. This is an example of highly interdisciplinary research that integrates functionalities of otherwise separate, nanotechnological fields and smart fabrics. Such

medical nanotechnology may enable a profound reconfiguration of the relations between doctors, patients, and hospitals. It can also further improvise the medical service to the society by bringing social behaviours (risk taking, dietary practices, stress and anger) into the realm of medical supervision. These developments are likely to be contested and call for the debate of their ethical and societal implications. Traditionally, medical ethics is patient and treatment centered rather than research and disease-centered. While medical ethics has been rather indifferent to the level of medical intervention. Nanomedical ethics should not serve to validate an uncertain future, for example, by assuming too readily an increase of diagnostic powers or an impact on life expectancy.

CONCLUSION

Nanomedicine is a growing field for the patient care (treatment and diagnosis), especially for the life threatening diseases like cancer. Theranaustic and regenerative approaches are being explored vigilantly and vigorously [122]. Properties and characteristics of CNTs are still being researched heavily and scientists have barely begun to tap the potential of these structures. However, research has proved that the CNTs are safer and more effective alternatives to previous drug delivery methods. They can pass through membranes, carrying therapeutic drugs, vaccines, and nucleic acids deep into the cell to targets previously unreachable. Hollow and porous inorganic nanomaterials can be effectively used for focusing on the drug/gene delivery in nanomedicine [123]. Also, CNTs serve as ideal non-toxic vehicles which, in some cases, increase the solubility of the drug attached, resulting in greater efficacy and safety. As such, nanomedicine can realize its promises only in the longer term due to further research required in the field. And while it makes a compelling case for big promises, it also asks for our patience. One should therefore not expect nanomedicine to revolutionize medicine. It is one promising avenue by which medicine can advance. Demonstrations of efficacy have to be considered together with physiological and environmental side-effects and general quality-of-life issues, comparing all of these to alternative treatment options. And like all disease-oriented research, it requires public deliberation on which diseases should be prioritized in the context of global health care. In brief current studies regarding CNTs have shown a very promising glimpse of what lies ahead in the future of medicines.

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