Review Article

A Review on Carbon Nanotube and Its Applications

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ABSTRACT

Nanomaterial offers interesting physicochemical and biological properties for biomedical applications due to their small size, large surface area and ability to interact with cells. Within the family of nanomaterial, CNT is derived from rolled graphene which is a sheet of 2D single or multilayer sp2 hybridized carbon atoms with exceptional electrical, chemical, thermal properties. It emerged a new alternative and effective tool for transporting and translating therapeutic molecules. CNT categorized as single-walled nanotubes (SWNT) and multi-walled nanotubes (MWNT). The techniques developed for the synthesis of CNT include the arc discharge method, laser ablation method, chemical vapour deposition method, silane solution method, and flame synthesis method. Because of unique physicochemical properties, low toxicity and non-immunogenic nature CNT holds great potential in nanobiotechnology and nanomedicine. This review leads to deliver useful knowledge related to a general overview, types, preparation method, purification method, properties, mechanism and application of CNT in the field of drug delivery.

Keywords: Carbon nanotubes, nanomedicine, drug delivery.

INTRODUCTION

Carbon-based materials like graphite, diamond, fullerenes, nanotubes, nanowires, and Nano-ribbons have been used for various applications in electronics, optics, optoelectronics, biomedical engineering, tissue engineering, medical implants, medical devices, and sensors. Graphene is an important part of carbon family in these each graphene attached to another carbon atom in the same plane with strong carbon-carbon bonding cause production of weak Vander- Waals forces make it soft material. Similarly, carbon nanotubes are forms of carbon, which have tubular arrangement responsible for their specific properties. The strong carbon-carbon bonding in the plane, aromatic structure, presence of π electron and reactive site of surface reaction make graphene a unique material with exceptional electrical, chemical, thermal[1-5]. Carbon nanotubes are formed by rolled-up graphene sheet, with a diameter range in between >1 nm up to 50 nm.[6-7] Carbon nanotubes having Young's modulus in the range between 100-1000 GPa and strength between 2.5-3.5 GPa.[8-9] Their densities can be as low as ~1.3g/cm^3. CNTs have received much attention from scientific communities because of their properties such as having a wide gap, high melting point, high tensile strength, high thermal conductivity.[10]

Advantages of Carbon nanotubes:[7, 12-13]

- Biocompatible, non-biodegradable, and non-immunogenic in nature.
- Highly elastic in nature and have the possibility of intracellular delivery.
- Having low toxicity.
- Excreted by urine 90% and remaining 4% by feces.
- It has an open end on both sides, which makes inner surface usable and incorporation of substance within nanotube easy.
- CNT was able to enter cells by spontaneous mechanism due to tubular and nanoneedle shape.
- It has a distinct inner and outer surface, which can be differentially modified for chemical biochemical functionalization.

Types of Carbon nanotubes:

Carbon nanotubes are of two types[4-8, 12-13]

Table 1: Types of carbon nanotubes

Single-walled nanotubes (SWNTs)	Multi-walled nanotubes (MWNTs)
A single layer of graphene	Multilayer of graphene
Catalyst require for synthesis	Can be Produced without catalyst
Bulk synthesis is difficult because requires control over growth and atmospheric conditions	Bulk synthesis easy
Purity is poor	Purity is high
Less accumulation in body	More accumulation in body
Characterizations and evaluation easy	Characterizations and evaluation difficult due to structure complexity
A chance of defect is more during functionalization	A chance of defect is less during functionalization but once occurred difficult to improve.

Preparation of Carbon nanotubes:[4-8, 14-16]

1. Arc discharge method

The arc discharge method produces the best quality nanotubes. This method used for producing C60 fullerene, is the most common and easiest method for carbon nanotubes. It involves passing a current of about 50 amps between two graphite electrode in presence of inert gas shows an increase in temperature which causes the graphite to vaporize, some of them condensed on walls of the reaction vessel and some on the cathode. It deposits on cathode forms carbon nanotubes. Single-walled nanotubes (SWNTs) produced when Co, Fe, and Ni or any other catalyst added to two graphite electrode. The catalyst can be introduced by packing the metal powder into a hole in the anode, during this metal was consumed along with graphite and created catalyst particles with small diameter SWCNTs[17]. Multi-walled nanotubes (MWNTs) are formed when there is no catalyst between two graphite electrode. In the case of MWNTs purity and yield depend sensitively on gas pressure in the reaction vessel. Also, different atmosphere affects the morphology of CNTs.

2. Laser abrasion method

This method is used for large scale production of SWCNTs a pulsed or continuous laser is used to vaporize 1.2% Co or Ni with 98.2% of graphite that is placed in a 1200°C quartz tube furnace with inert gas. In principle Arc discharge and Laser ablation method are similar, as both use metal impregnated graphite to produce SWCNTs and MWCNTs[18]. However, the MWCNT produce by this method has a shorter size than that produced by the arc discharge method. Therefore this method not used for the synthesis of MWCNTs.

3. Chemical Vapour Deposition method (CVD)

The carbon source is placed in the gas phase in the reaction chamber. Then carbon molecule is converted to atomic carbon by using energy source like plasma or heated coil. This carbon will get diffused towards the substrate, which is coated with catalyst and nanotubes grow over this catalyst. The carbon source used is methane, acetylene, carbon monoxide; ethane ethylene and catalyst are Fe, Ni or Co, etc.[4, 6] Temperature used for the synthesis of nanotubes is 650-9000°C range.

4. Silane Synthesis method[19]

In this method, 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 were fed through the substrate and catalyst deposited. When the substrate was heated by applying an electric current. Thus, a reaction occurs between the catalyst and gas to yield CNTs.

5. Flame Synthesis method[20]

SWNTs formed in control flame environment from hydrocarbon fuel and small metal catalyst[21, 22]. SWNTs observed in the post-flame region of premixed acetylene / argon / oxygen flame operated at 50 Torr with iron pentacarbonyl vapors used as a source of metallic catalyst. Between 40 and 70 mm, height above burner nanotubes is formed to form coalesce into clusters[23].

Purification of CNTs:[4, 6, 15]

Nanotubes usually contains a large number of impurities such as metal particles, amorphous carbon, and multi-shell. There following steps involve in the purification of CNTs.[24]

1. Air Oxidation

CNTs having less purity, the average purity is 5-10%. So purification is needed before attachment of drugs on CNTs. Purification of SWCNTs based on the selective oxidation of carbonaceous impurities by heating at constantly increasing the temperature in air. It is useful in reducing the amount of amorphous carbon and metal catalyst particles. The optimal oxidation condition is found to be at 673k for 40 min. This process allows the efficient removal of carbonaceous impurities without significant loss of nanotubes[25,26].

2. Acid refluxing

Refluxing of a sample in strong acid is effective in reducing the amount of an amorphous carbon and metal catalyst particles. Different acid was used hydrochloric acid (HCl), nitric acid (HNO_3) and Sulphuric acid (H_2SO_4) but HCl found as ideal acid for purification[27].

3. Surfactant added sonication, filtration, and annealing

After acid refluxing CNTs are purer but tubes get entangled, trap most of the impurities, such as carbon and metal catalyst particles. This is difficult to remove with filtration. So surfactant aided sonication was carried out. Sodium dodecyl benzene sulphonate (SDBS) aided sonication with methanol/ ethanol was carried out because it took the longest time for CNTs to settle down, indicating an even suspension state was achieved. The sample filtered with the ultra-filtration unit and annealed at 1273 k in N_2 for 4 hrs. Annealing is effective in optimizing of CNT structure. Nanotubes are also purified by a multi-step purification method.

Properties of CNTs:

1. Mechanical properties

CNTs are the strongest and stiffest material due to its strength and elastic modulus. The strength results due to covalent sp^2 bonds formed between individual carbon atoms. Carbon nanotubes having Young's modulus in a range between 100-1000 GPa and strength between 2.5-3.5 GPa which is higher than steel. Their densities can be

as low as ~1.3g/cm^3. Due to these property CNTs are used in several areas of technology[28].

2. Electrical Properties

CNTs are not only strong but they have interesting electrical properties. A single graphite sheet is a semimetal, which means that it has properties intermediate between semiconductors and metals. When graphite rolled up in between nanotubes not only do carbon atoms have to line up around the circumference of the tube, quantum mechanical wave functions of electrons must also match up. Due to quantum mechanics, the CNTs carry an electrical current density of 4×109A/cm^2 which is more than 1000 times greater than metals such as copper[28].

2. Thermal Properties

All nanotubes are expected to be very good conductors, they exhibiting a property known as ballistic conduction. The temperature stability of carbon nanotubes is estimated to be up to 2800°C in vacuum and 750°C in the air[29, 30].

3. Chemical Properties

The chemical reactivity of CNTs is, compared with the graphene sheet shows enhanced as a direct result of the curvature of the CNT surface. This curvature causes the mixing of π and σ orbitals, which cause hybridization between the orbitals. As the degree of hybridization becomes larger as the diameter of SWNT gets smaller. This shows an increase in the reactivity of CNTs. Covalent chemical modification of sidewalls shown to be possible. Therefore, CNTs considered as usually chemically inert[31].

4. Optical Properties

The optical properties of CNTs are related to their one-dimensional nature. Theoretical information explains that Optical activity of CNTs disappear if nanotubes become large therefore it is expected that other physical properties are influenced by these parameters. Use of optical activity results in Optical devices in which CNTs play an important role.

Characterization of CNTs[32]

- RAMAN spectroscopy used for quick and reliable screening of SWCNTs.
- Transmission Electron microscopy (TEM) used to study assesses detailes structure.
- Scanning Electron Microscopy (SEM) provides overview of sample.
- Thermogravimetric analysis gives information about the relative abundance of catalyst particles, nanotubes.

Functionalization of CNTs[6]

Carbon nanotubes have a highly hydrophobic surface, and are not suitable for aqueous solutions. For biomedical application, functionalization is required to solubilize CNTs improve biocompatibility and low toxicity. Covalent and non-covalent are two types of surface functionalization of CNTs[33].

1. Covalent Functionalization of CNTs

Functionalization of CNTs done by various covalent reactions and oxidation is one of the most common. CNTs oxidization carried out using an oxidizing agent such as nitric acid results in a reduction in length while generating a carbonyl group which increases dispensability in aqueous solution[34, 35].

During this process, carbonyl group formed the end of tubes as well as a side wall. The sp^3 carbon atoms on SWCNTs after oxidation and covalent conjugation with amino acids[36]. Modification carried out by attaching hydrophilic polymer such as polyethylene glycol (PEG) to oxidized CNTs, Which produce CNT-polymer conjugates stable in a biological environment. These CNTs synthesized for both In-vitro and In-vivo study. Also functional groups amino-terminated PEG introduced via a modified α-amino acid is used for further conjugation of biological molecules[37].

2. Noncovalent Functionalization of CNTs

Noncovalent Functionalization of CNTs can be carried out by coating CNTs with amphiphilic surfactant. Since the chemical structure of π-network of Carbon nanotubes not disrupted, except for shortening of length due to sonication employed in the functionalization process, the physical properties of CNTs are essentially preserved by noncovalent approach.

Solubility under physiological conditions is a prerequisite to make CNT biocompatible. In addition, F-CNTs can be linked to a wide variety of active molecules, includes peptides, proteins, nucleic acids, and other therapeutic agents[38].

Pharmacology of CNTs

The cellular uptake of CNTs has been confirmed in a study but the mechanism is not clear. Because of their needle-like shape, CNTs able to perforate cellular membrane and pass into a cell without any cellular damage. An in-vitro CNTs nanoinjector system has been designed using an atomic force microscope. (AFM) tip and functionalized MWCNTs attach to a model carbon compound via disulfide linker. The MWCNTs nanoinjector when transported into a cell the disulfide bond gets break, result in the release of carbon compound into the cytoplasm[39, 40]. Functionalized CNTs having a high capacity to cross cell membranes[41, 42]. These CNTs labeled with a fluorescent agent were easily internalized and could track into cytoplasm using confocal microscopy. The cellular uptake of *f*-CNTs has been appearing as passive and endocytosis-independent. CNTs can also be visualized by using Transmission Electron Microscopy (TEM)[43].

Applications of Carbon nanotubes

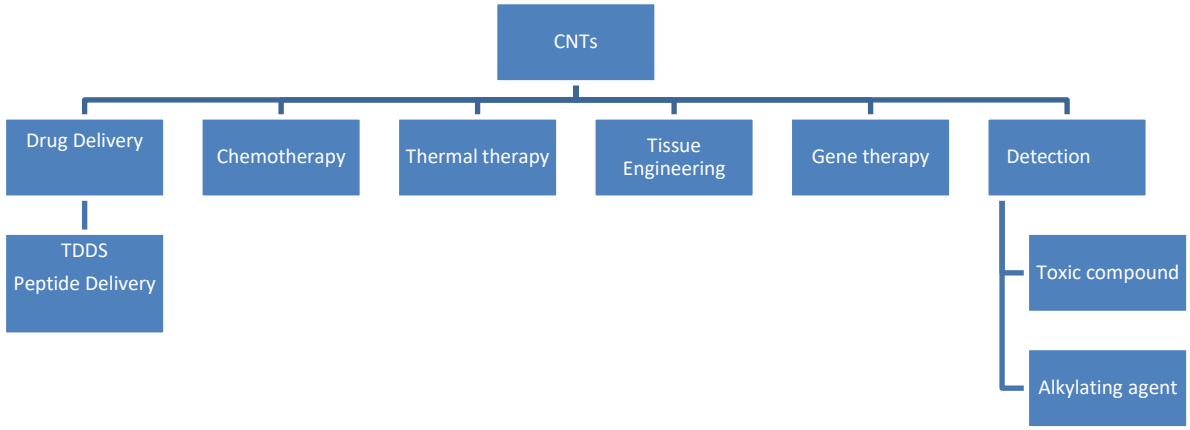

Figure 1: Application of Carbon Nano-tubes

1. Genetic Engineering

CNTs are used to manipulate genes and atoms in development of bioimaging genomes, proteomics, and tissue engineering. The unwound DNA winds around SWNT by connecting its specific nucleotides and causes a change in its electrostatic property. Wrapping of carbon nanotubes by single-stranded DNA was found to be sequence-dependent; hence it can be used in DNA analysis. Nanotubes due to their unique cylindrical structure and properties are used as the carrier for genes to treat cancer and genetic disorders. Nanotubes complexes with DNA were found to release DNA before it was destroyed by cells defense system, boosting transfection significantly[44, 45].

3. Carbon Nanotubes in Diagnosis[10]

Screening of tumor at an early stage is a way to cure the disease and detection is important. Also conventional clinical cancer imaging techniques like X-ray, CT, and MRI, not possess sufficient resolution for early detection of the disease. Various morphologic changes are also absent in most early neoplastic disorders, they can easily avoid being detected by these imaging techniques. Positron emission tomography (PET) is a highly sensitive and accurate imaging technology that relies on changes in tissue biochemistry and metabolism. It is the most important to identify early-stage alterations in molecular biology, often before there is any morphologic change[46-48]. That's why developed new tools for early cancer diagnosis molecular imaging with single-walled carbon nanotubes. When Gd3+-functionalized SWCNTs were applied to MRI, high resolution and good tissue penetration were achieved. But the level of sensitivity still remained low[49]. Since CNTs exhibit unique electronic, mechanical and thermal properties, they have been proposed as a promising tool for detecting the expression of indicative biological molecules at the early stage of cancer[50].

3.Carbon Nanotubes in cancer therapy

Among all cancer treatment options, such as surgery, chemotherapy, radiotherapy, thermotherapy, and immunotherapy, etc. surgery continues to play a major role in early-stage cancer survival by removing a detectable tumor. Although these modalities are successful in some cases, systemic toxicity may develop at the same time due to a lack of selectivity for these treatments. The transporting capabilities of carbon nanotubes combined with appropriate surface modifications and their unique physicochemical properties can lead to a new kind of nanomaterials for cancer therapy[51].

4. As Catalyst

Nanotubes having large surface area hence, the catalyst at a molecular level can be incorporated into nanotubes in large amount and simultaneously can be released in the required rate at a particular time. Hence, a reduction in the frequency and amount of catalyst addition can be achieved by using CNTs[51].

5. Preservative

Carbon nanotubes are antioxidant in nature. Hence, they are used to preserve drug formulations prone to oxidation. Their antioxidant property is used in anti-aging cosmetics and with zinc oxide as sunscreen dermatological prevents the oxidation of important skin components.[52]

6. Carbon Nanotube Membranes for Transdermal Drug Delivery

The CNT is used in the development of a transdermal drug delivery system that can usefully treat a variety of syndromes and given an individual patient's needs in a manner that will both improve therapeutic administration and efficacy[53].

7. Carbon nanotubes Peptide delivery

Application of CNT as a template for presenting bioactive peptides to the immune system. B-cell epitope of the foot-and-mouth disease virus (FMDV) was covalently attached to the amine groups present on CNT, using a functional linker. The peptides around the CNT form the appropriate secondary structure for recognition by specific monoclonal and polyclonal antibodies. The immunogenic features of peptide–CNT conjugates were subsequently assessed in vivo[54].

8. Nucleic acid delivery by carbon nanotubes

Ammonium-functionalized CNT shows its ability to form supramolecular complexes with nucleic acids via electrostatic interactions. Many cationic systems are being investigated for the delivery of nucleic acids to cells[55, 56, 57]. Their common goal is to enhance gene transfer and expression, because plasmid DNA alone penetrates into cells and reaches their nucleus with considerable difficulty. Similar to other families of non-viral vectors the macromolecular cationic nature of the f-CNT has been exploited to condense plasmid DNA[58]. To explore the potential of CNT as gene transfer vectors, plasmid DNA pCMV-Bgal expressing b-galactosidase was adsorbed on f-CNT carrying ammonium groups. Both single- and multi-walled cationic CNT are able to form stable complexes, characterized by electron microscopy.

9. Artificial implants

Normally the body shows rejection reaction for implants with the post-administration pain. But, miniature sized nanotubes 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 reactions. Moreover, due to their high tensile strength, carbon nanotubes filled with calcium and arranged/grouped in the structure of bone can act as a bone substitute[59].

Drug delivery with carbon nanotubes

The new and effective drug delivery systems is a fundamental issue of interest. A drug delivery system is designed to improve the pharmacological and therapeutic effect of a drug molecule[60]. The ability of f-CNT to penetrate into cells offers the potential of using f-CNT as vehicles for the delivery of small drug molecules[61]. The development of delivery systems able to carry one or more therapeutic agents with recognition capacity, optical signals for imaging and specific targeting is of fundamental advantage, for example in the treatment of cancer and different types of infectious diseases. For this purpose, we have developed a new strategy for the multiple functionalization of CNT with different types of molecules. The antibiotic linked to the nanotubes was easily internalized into mammalian cells without toxic effects in comparison with the antibiotic incubated alone In an alternative approach by a different group, SWNT have been functionalized with substituted carbon cages to develop a new delivery system for an efficient neutron capture therapy[62].

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