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A Review On Carbon Nanotubes As Promising Drug Delivery Vehicles

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ABSTRACT

Carbon nanotubes (CNTs) are cylindrical carbon structures with diameters measured on a nanometer scale. They are derived from graphite sheets and resemble rolled-up, seamless hexagonal mesh structures where carbon atoms form at the vertices. Depending on the number of layers, CNTs can be categorized into single-walled (SWCNTs), double-walled (DWCNTs), or multi-walled (MWCNTs) nanotubes. Fabrication methods include chemical vapor deposition, electric arc method, and laser deposition. CNTs exhibit properties such as high elasticity, thermal conductivity, low density, and chemical inertness, making them pivotal in nanotechnology, electronics, optics, and materials science. Applications range from drug delivery to sensing and water treatment. Surface functionalization enhances solubility and compatibility with biological systems, facilitating targeted delivery and immune recognition in medical diagnostics and drug delivery applications.

KEYWORDS: carbon nanotubes, functionalization, arc discharge

INTRODUCTION

Carbon nanotubes are hollow, cylindrical structures, essentially a sheet of graphene rolled into a cylinder. As versatile nanomaterials, carbon nanotubes have emerged with significant potential to enhance drug delivery systems. They act as strong candidates for various biomedical applications due to their unique structural and physicochemical properties.

CNT's major contribution to drug delivery lies in their efficacy as drug carriers. They can encapsulate drugs either on their surfaces or within their hollow cores, thereby protecting them from degradation and enabling controlled release. Their extensive surface area allows therapeutic molecules to adhere, aiding targeted drug delivery to specific cells or tissues.

Additionally, functionalization of CNTs with biomolecules like peptides or antibodies improves binding affinity and specificity to targeted sites, enhancing therapeutic outcomes and creating precise drug delivery systems. CNTs' ability to penetrate cell membranes streamlines the delivery of drugs, genes, or imaging agents inside cells, offering significant advantages in treating diseases at molecular and cellular levels. Furthermore, CNTs show potential in theragnostics by combining therapeutic and diagnostic functions on a single platform, allowing for real-time monitoring of therapy efficacy [1].

Graphene

Graphene, a single layer of graphite arranged in a hexagonal lattice, is celebrated as the pioneering 2D material. Its extraordinary properties including exceptional strength, thermal and optical conductivity, transparency, and impermeability to gases and liquids have earned it the title of a "wonder material".

Graphene serves as the fundamental building block for all other carbon allotropes, encompassing carbon nanotubes, charcoal, graphite, and fullerenes.

Graphene, due to its remarkable properties and the abundance of carbon in nature, has garnered significant research attention and holds immense potential. Key characteristics of graphene include:

- High thermal and electrical conductivity
- High elasticity flexibility and hardness
- High resistance, Graphene is approximately 200 times stronger than steel, similar to diamond resistance, but much lighter.
- lonizing radiation is not affected
- Able to generate electricity by exposure to sunlight

- Transparent material
- Dense enough to block Helium atoms, yet permits water to pass through at the same rate as it would in an open container.
- Antibacterial effect.
- Low electricity consumption compared to other compounds [2].

CLASSIFICATIONS OF CARBON NANOTUBES

1. Single Walled Carbon Nanotubes (SWCNTs)

It comprises a single layer of graphene and necessitates a catalyst for its synthesis. SWCNTs exhibit low purity and lack complex structures, making them easily deformable.

2.Multi walled Carbon Nanotubes (MWCNTs)

It consists of multi-layer of graphene and doesn't require any catalyst for its synthesis.
The larger multi-walled carbon nanotubes (MWCNTs) can feature numerous concentric layers, each spaced approximately 0.34 nm apart. This is in contrast to the length of a C-C bond within a graphene sheet of a single-walled carbon nanotube (SWCNT), which measures 0.142 nm [3].

METHODS OF PREPARATION OF CARBON NANOTUBES

1. Arc Discharge Method

For achieving high-quality carbon nanotubes, method such as arc discharge can be employed. In the arc discharge method, two graphite electrodes are placed in a helium environment where a current of 50 amperes is applied.
This causes graphite vaporization, with some condensing onto the reaction vessel and some onto the cathode. Carbon nanotubes are deposited on the cathode. To produce single-walled carbon nanotubes (SWCNTs), Co or Ni metals can be introduced at the anode. The yield of SWCNTs is significantly influenced by temperature,

increasing with higher temperatures. The SWCNT bundles with 7-20 nm of diameters and the production of 45.3 g/h were prepared at the temperature of 600°C.

2. Laser method

Currently, this technique involves the use of graphite rods with a catalyst mixture of 50% cobalt (Co) and 50% nickel (Ni), heated to 1200°C in an argon atmosphere for sample preparation. In this method, metals catalyze the growth of single-walled carbon nanotubes, alongside the formation of various by-products. Nanotubes can be obtained by condensing the vaporized species after cooling them down.

3. Chemical vapor deposition

Arc discharge and laser vaporization are characterized by high temperatures (>3000K) and short reaction times (microseconds to milliseconds), while catalytic chemical vapor deposition (CVD) operates at medium temperatures and longer reaction durations (typically minutes to hours). Carbon nanotubes (CNTs) do not grow on patterned or conventional substrates. This method operates at lower temperatures and yields well-organized carbon nanotubes [4].

PURIFICATION OF CARBON NANOTUBES

Nanotubes often harbour significant impurities like metal particles, amorphous carbon, and multi shell structures, necessitating several purification steps.

1. **Air oxidation**

The typical purity of carbon nanotubes ranges from 5% to 10%. Purification of CNTs is necessary prior to drug attachment on their surfaces. Air oxidation at 400°C for 40 minutes effectively reduces impurities such as catalyst particles and amorphous carbon generated during CNT synthesis.

2. **Acid refluxing**

Refluxing the as-synthesized CNTs in strong acids effectively removes amorphous carbon, metal particles, and other impurities from the CNTs. The most commonly used acids in the purification of the CNTs are HCl, HNO_3, and H_2SO4. HCl is the most suitable refluxing acid used in the purification process of CNTs.

3. **Surfactant aided sonication, filtration and annealing**

Refluxing causes entanglement of the CNTs, trapping impurities between the nanotubes. To release these impurities, surfactant-assisted sonication is employed. Sonication of CNTs in sodium dodecyl benzene

sulfonate (SDBS) dissolved in ethanol enhances the dispersion of CNTs. After sonication, the mixture undergoes ultrafiltration and is subsequently annealed at 1000°C in a nitrogen atmosphere for 4 hours.

4. Microfiltration

Microfiltration relies on size-based separation. It captures SWNTs along with a small portion of carbon nanoparticles, while allowing catalyst metals and other fullerenes to pass through the filter. To separate SWNTs from fullerenes, one method involves initially soaking the as-produced SWNTs in a CS_2 solution. The insoluble components in CS_2 are subsequently trapped by the filter, while the CS_2-solvated fullerenes pass through.

5. Magnetic purification

In this approach, ferromagnetic (catalytic) particles are extracted mechanically from their graphitic shells. The suspension of single-walled carbon nanotubes (SWNTs) is combined with inorganic nanoparticles (primarily ZrO_2 or $CaCO_3$) in an ultrasonic bath to eliminate the ferromagnetic particles. Subsequently, these particles are captured using permanent magnetic poles. Following additional chemical processing, high-purity SWNT material is obtained [5].

PROPERTIES OF CNTS

- High surface area
- Excellent chemical stability
- Rich electronic polyaromatic structure
- Small size
- High surface to volume ratio [6].

FUNCTIONALIZATION OF CNTS

An approach to enhance the dispersion of CNTs in polymeric solvents involves functionalization to prevent agglomeration and bundling. However, the primary obstacle to utilizing CNTs in biomedical applications remains their limited solubility in aqueous environment. Functionalization addresses this challenge by introducing hydrophilic functional groups onto the side chains and caps of CNTs. This modification not only mitigates CNTs toxicity but also improves their biocompatibility, facilitating the effective delivery of drugs, proteins, and nucleic acids. Functional groups can be attached to CNTs through covalent bonding, non-covalent interactions, and electrostatic forces, thereby enhancing their aqueous solubility.

1. Covalent functionalisation

Covalent functionalization that offers a more secure connection of functional molecules is "chemical modification." In this process, chemical groups such as fluorine or carboxylic groups can be attached or coupled to the walls of the CNTs.

There are two types of covalent functionalization methods applied to carbon nanotubes (CNTs): direct and indirect. Direct functionalization occurs specifically on the side walls of the CNTs, whereas indirect functionalization involves attaching carboxylic acid groups to the surface of the CNTs.

a. Oxidation of CNTs

Oxidation, which is the predominant method for covalent functionalization of CNTs, involves treating them with strong acids.

The covalent functionalization process involves forming a covalent bond between the unsaturated carbon bond and other functional groups. Oxidizing agents like nitric acid are used to introduce carboxylic or hydrophilic groups onto the surfaces, ends, and sidewalls of the CNTs. This oxidation enhances the solubility of CNTs.

b. Cyclo-addition reaction

The cyclo-addition reaction takes place predominantly along the sidewalls rather than adjacent to the end caps. This reaction can be categorized into three types:

(1) photo-induced cyclo-addition, involving a photochemical reaction with azides;
(2) Bingel reaction, occurring in the presence of a strong base; and
(3) 1,3-dipolar cyclo-addition reaction, commonly employed for functionalizing CNTs.

c. Reaction with Acyl Peroxides or Sulfoxides

The acyl chloride reacts with the carboxylic acid to produce an amide group. Alkyl or aryl peroxides decompose via thermal methods to yield free radicals. Acyl peroxides react with CNTs, generating carboxyalkyl radicals on the CNT walls.

d. Polymer functionalised CNTs

Polymers are crucial for enhancing the dispersion of carbon nanotubes (CNTs) and for producing CNT-based complexes. The primary methods for modifying CNTs using polymers involve physical and chemical attachments. Polymer composites are created through the polymerization of functionalized carbon nanotubes, which significantly improve their chemical, physical, and electrical properties.

2. Non-covalent functionalisation

The incorporation of non-covalent surface modifications using natural and synthetic polymers addresses the solubility challenges of CNTs, while maintaining their aromatic and electronic structures intact. In this approach, long-chain polymers encapsulate the CNTs. The dispersion methods commonly employed for dispersing CNTs include ultrasonication, centrifugation, and filtration. Non-covalent functionalization utilizes surfactants and π-π stacking interactions to facilitate molecular attachment to CNTs [5].

DRUG LOADING AND RELEASE FROM CARBON NANOTUBES

Functionalized carbon nanotubes are integrated into the targeted drug delivery system to transport the medication to the affected area. Their high aspect ratio accommodates numerous therapeutic agents, while multi functionalization improves the CNT's hydrophilicity and biocompatibility. The drug loading process using ultrasonication involves dispersing functionalized CNTs in deionised water. Simultaneously, the drug is dissolved or dispersed in a solvent and added dropwise to the ultrasonicated functionalized CNTs. The mixture is then incubated for 24 hours at room temperature.

After the incubation period, the mixture is centrifuged at $1x10^4$ rpm for 15 minutes to isolate the standalone drug from the conjugate.

The drug concentration is determined, and the drug loading efficiency is calculated using the formula:

$$DLE\% = \frac{WAD - WFD\ (supernatant)}{WAD} \times 100$$

Here, DLE represents drug loading efficiency, WAD is the weight of the added drug, and WFD is the amount of free drug in the supernatant.

Understanding the mechanisms governing drug release post-loading and administration is crucial. Factors such as pH changes, drug solubility, desorption kinetics, diffusion rates, magnetic and electric fields, as well as temperature fluctuations, influence the release of the drug from carbon nanotubes (CNTs) [7].

CHARACTERIZATION OF CNTs

Thermogravimetric analysis is employed to quantitatively ascertain the levels of carbon and non-carbon constituents in bulk CNT samples, along with assessing CNT uniformity and thermal stability. This method provides a comprehensive evaluation of CNT quality as it does not selectively distinguish between CNTs and metallic impurities within the sample.

TEM

Its primary role is to analyze the morphology and assess the purity of produced CNTs. TEM offers valuable qualitative data on the dimensions, configuration, and composition of carbonaceous materials, including non-CNT impurities. However, it cannot detect metallic contaminants nor distinguish between different types of multi-walled carbon nanotubes (MWNTs). Additionally, TEM has been instrumental in imaging the cellular uptake of CNT-drug composites and investigating the post-uptake behavior of CNTs within cells.

SEM

It is employed for the initial assessment of CNT morphology. However, its conventional application is hindered by its inability to distinguish catalysts and carbonaceous impurities from CNTs. Nevertheless, SEM coupled with an energy dispersive X-ray analysis detector (SEM-EDX) is routinely utilized to estimate the metallic content of CNT samples. SEM remains the primary technique capable of providing insights into both CNT morphology and metallic impurity levels [8].

RAMAN SPECTROSCOPY

It has been employed to assess the synthesis and purification methods of SWNTs. The presence of carbonaceous impurities such as graphite, fullerenes, and amorphous carbon poses a significant challenge in interpreting Raman spectra of SWNTs, as these impurities exhibit distinctive Raman features (D- and G-bands) similar to those of SWNTs.

PROTON NMR

H-NMR spectroscopy has been employed to track the advancement of CNT functionalization. Predictions of functional group presence rely on distinctive peaks that reflect variations in the magnetic environment. The spectra of functionalized CNTs in H-NMR exhibit broad signals for proximal protons, which sharpen with increasing distance. Researchers have utilized H-NMR to oversee the synthesis and bonding of functional groups onto CNTs.

IR SPECTROSCOPY

It serves predominantly as a qualitative method for discerning functional groups and their bonding to CNT sidewalls. Various functional groups absorb distinct IR frequencies, allowing for bond identification akin to a fingerprint. This method complements NMR in verifying bonds between CNTs and attached groups [9].

CELLULAR INTERNALIZATION

It was proposed that cationic amino-functional groups facilitate the binding of nanotubes to cell membranes, enabling a spontaneous insertion mechanism through the biomembrane. This proposed 'nanoneedle' mechanism describes how single-walled carbon nanotubes (SWNTs) interact with human cervical cancer cells (HeLa), observed crossing the plasma membrane barrier via TEM. Furthermore, various types of functionalized carbon nanotubes (CNTs) were found to be taken up by diverse cell types, including those deficient in phagocytosis (fibroblasts) or incapable of endocytosis (fungi, yeast, and bacteria). Therefore, the term 'nanosyringe' was coined to depict a model wherein nanotubes interact with lipid bilayers by directly diffusing through the membrane.

Further studies showed that SWNTs functionalized with proteins and nucleic acids penetrated cell membranes by clathrin-mediated endocytosis.

Despite significant advancements in our comprehension of how nanotubes interact with cell membranes and enter cells, the processes of uptake, intracellular localization, and biodistribution seem to differ based on factors such as functionalization, length, diameter, number of walls, and concentration of CNTs.

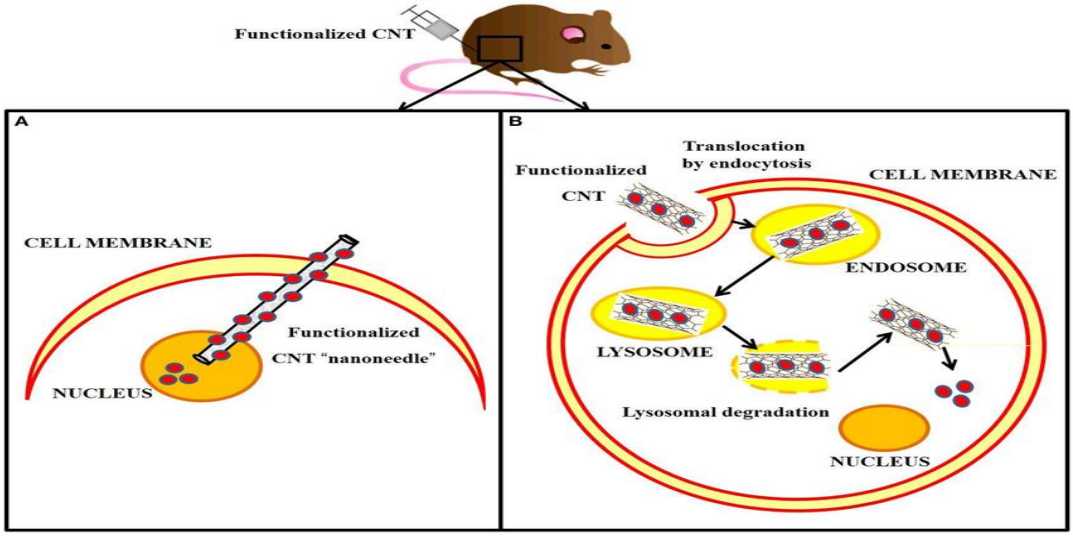

Fig no 1: **Cellular internalization of carbon nanotubes via "nanoneedle" mechanism vs. endocytotic pathway, following in vivo injection.** (A) Functionalized CNT rapidly penetrates the cell membrane directly to the nucleus, where it releases the cargo (red circles). (B) Functionalized CNT is internalized in the cell by endocytosis and delivered to the endosome, which matures to a lysosome. The accumulation into the lysosome causes swelling and rupture of the vesicle followed by the release of the functionalized CNT into the cytoplasm. The cargo is then able to diffuse through the cytoplasm [10].

APPLICATIONS OF CNTs

1. CNTs in drug delivery

Table no: 1

PATHOLOGY	DRUG	BENEFITS
Cancer	Cisplatin	Reduction in cell viability of the MDA-MB-231 [11].
	Cisplatin	Reduces the uncontrolled spread of toxic drug molecules during circulation in the blood stream and magnetically targeted site-specific release [12].
	Combretastatin	The anticancer activity of SWCNT combined with combretastatin was improved in comparison with the free drug [13].
	Curcumin (CUR)	Ease of loading of hydrophobic CUR molecules, increased biodistribution in cancer cells and good stability against A549 cells [14].
	Curcumin	The drug delivery system PVA-MWCNT promoted better release [15].

	Doxorubicin	Exceptional colloidal stability, good biocompatibility, high affinity for cancer cells, strong chemotherapeutic performance, decreased side effects and increased antitumor effect via targeted drug delivery [16].
	Paclitaxel	The dual functionalization of MWCNTs showed better aqueous dispersity and biocompatibility [17].
	Paclitaxel	Effective inhibition of cell proliferation and death of cancer cells of the A549 lineage and low toxicity [16].
Anti inflammatory	Ibuprofen	Controlled release of ibuprofen and low toxicity [18].

2. CNTs in photodynamic therapies

Table no: 2

TYPES OF CNTs	FUNCTIONALIZED	BENEFITS
SWCNT and MWCNT	Indocyanine green and hyaluronic acid	Fight against breast cancer [19].
MWCNT	Manganese dioxide and PEG	Acting as a lymphatic theragnostic agent [19].
MWCNT	PEG	Treatment of melanoma [20].

3. CNTs in tissue engineering

Table no : 3

TYPES OF CNTs	FUNCTIONALISED	BENEFITS
SWCNT and MWCNT	PSA antibody	Detection of early prostate cancer [21].
SWCNT	Thionine and gold nanotubes	Detection of cancer antigen 125 [22].
SWCNT or MWCNT	Dopamine	Detection of early breast cancer [23].

MWCNT	$PvMSP1_{19}$ protein	Diagnostic for those infected with malaria [24].
MWCNT	Polypyrolle and hydroxyapatite nanoparticles	Diagnostic for those infected with tuberculosis [25].
MWCNT	Acrylamide, N,N'-methylenebis (acrylamide) and ammonium persulfate	Diagnostic for those carriers of HIVs [26].

4. CNTs as chemical sensors

Table no :4

TYPES OF CNTs	FUNCTIONALIZED	BENEFITS
MWCNT	Poly (methylene blue)	Detection of cardiac troponin T, which is a crucial cardiac biomarker for the diagnosis of acute myocardial infarction [27].
MWCNT	Nanowires and tyrosinase	Detection of catechol [28].
SWCNT and MWCNT	Capsaicin	Detection of dopamine, epinephrine, xanthurenic acid, ascorbic acid and uric acid [29].
SWCNT and MWCNT	Cobalt phthalocyanine	Detection of artemisinin [30].
MWCNT	Hemin	Identification of nitro radical from nitrofurazone [31].

5. Artificial implants

Typically, the body exhibits a rejection response to implants, often resulting in post-administration pain. However, miniature nanotubes and nanohorns adhere to proteins and amino acids, circumventing rejection. They can thus serve as implants like artificial joints without triggering adverse host reactions. Furthermore, carbon nanotubes filled with calcium, structured to mimic bone, offer high tensile strength and can function effectively as bone substitutes.

6. Preservatives

Carbon nanotubes and nanohorns exhibit antioxidant properties, making them valuable for preserving drug formulations susceptible to oxidation. Their antioxidative characteristics are also leveraged in anti-aging cosmetics and combined with zinc oxide in dermatological sunscreens to safeguard essential skin components from oxidation.

7. Diagnostic tool

Protein-encapsulated or enzyme-filled nanotubes, which exhibit fluorescence in the presence of specific biomolecules, are being explored for use as implantable biosensors. Additionally, nanocapsules containing magnetic materials or radioisotope enzymes can serve as biosensors. Nanorobots and motors at the nanoscale, incorporating nanotubes, offer new avenues for studying cells and biological systems.

8. As catalyst

Nanohorns provide a significant surface area, enabling high incorporation of catalysts at the molecular level within nanotubes. This allows for controlled release at specific times, thereby reducing the frequency and quantity of catalyst additions [32].

9. ANTIMICROBIAL ACTIVITY AND MECHANICAL INSIGHTS OF CNTs

Table no : 5

TYPES OF CNTs	BACTERIA	CONTRIBUTING FACTOR	MECHANISM OF ACTION
SWCNT	E. coli K12	Direct contact between bacterial cell and SWCNT in solution	Membrane damage [33].
SWCNT and MWCNT	E. coli	Higher surface area of SWCNT	Membrane damage [34].

SWCNT	Soil microorganisms	Raw SWCNT enhances metal toxicity in the soil	Suppressed metabolic activity [35].
SWCNT	E. coli K12	Aggregation characteristics	Bacterial inactivation [36].
SWCNT	E. coli K12	Increasing metallic fraction	Oxidative stress [37].
SWCNT and MWCNT	Lactobacillus acidophillus, Bifidobacterium adolescentis, E. coli, Enterococcus faecalis, S. aureus	Wrapping mechanism influenced by length and piercing mechanism dependant on diameter	Membrane damage, release of DNA and RNA, potential reduction of bacterial membrane [38].

10. CNTs in gene therapy

Table no : 6

TYPES OF CNTs	FUNCTIONALIZED	BENEFITS
CNTs	Ammonia	Plasmid deoxyribonucleic acid (pDNA) delivery- low cytotoxicity and penetrate the cell easily.
SWCNTs	Hexamethylenediamine (HMDA) and poly(diallyldimethylammonium) chloride (PDDA)	Effective carrier system for intracellular delivery of SiRNA.
CNTs	Polyethyleneimine and polyamidoamine (PAMAM) dendrimer	Reduced toxicity of CNTs and enhanced efficiency of miR-503 oligonucleotide delivery to endothelial cells [39].

CONCLUSION

This review provides an in-depth exploration of carbon nanotubes, covering their structural characteristics, morphology, synthesis, purification methods, properties, benefits, and diverse applications. The unique structural attributes of carbon nanoparticles, particularly their high aspect ratio and amenability to functional modifications, make them valuable in pharmaceutical nanodelivery. Carbon nanotubes also offer significant potential as nanodevices for precise drug delivery, owing to their facile sidewall and core functionalization capabilities.

Their exceptional physical properties open up numerous application avenues, extending beyond traditional uses in carbon fibre to novel possibilities rooted in their distinctive electronic and mechanical behaviors. As gene therapy, cancer treatments, and ground breaking solutions for life-threatening diseases on the horizon, nanomedicine continues to expand rapidly, showcasing its remarkable capability to overcome barriers. Both single and multiple-walled carbon nanotubes have demonstrated their efficacy as advanced and safe alternatives in drug delivery. They efficiently traverse membranes, delivering therapeutic drugs, vaccines, and nucleic acids deep into previously inaccessible cellular targets. These nanotubes also act as non-toxic carriers that enhance drug solubility in certain cases, thereby improving overall efficacy and safety.

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