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Tailored Therapeutics: Functionalized Carbon Nanotubes as the Future of Targeted Drug Delivery

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A B S T R A C T

Carbon nanotubes (CNTs) have emerged as a promising class of material in nanomedicine, particularly in drug delivery systems, due to their unique structural, chemical, and physical properties. The discovery and structural morphology of CNTs are introduced at the beginning of this paper, which offers a thorough overview of the material. Detailed structural properties of single-walled and multi-walled carbon nanotubes (CNTs) are discussed, along with how their superior mechanical strength, electrical conductivity, and surface area make them the ideal candidates for the delivery of drugs. The synthesis techniques, such as chemical vapour deposition (CVD) and arc discharge, are discussed, emphasizing the benefits and drawbacks of each process. To improve the solubility and biocompatibility of CNTs, both covalent and non-covalent functionalization techniques and purification procedures are explored. The review examines into the toxicity and kinetics of CNTs.The applications of carbon nanotubes (CNTs) in drug delivery systems are explained, highlighting their versatility in enabling controlled release, improving drug solubility, and targeting certain cells and tissues. The collection of patents regarding carbon nanotubes (CNTs) in drug delivery is also discussed, Limitations and obstacles, including possible cytotoxicity, scale up production, and targeting efficiency, are thoroughly examined. In order to fully understand the potential of carbon nanotubes in drug delivery and overcome present challenges future directions are finally suggested, highlighting the necessity for further research.

Keywords: Functionalization, carbon nanotubes, toxicity of carbon nanotubes, chemical vapour deposition, arc discharge, laser ablation, purification, cancer drug delivery.

1. INTRODUCTION

Carbon nanotubes (CNTs) were discovered in 1991 by Iijima and coworkers. Since then, they have become the strongest candidates in the field of biomedical engineering, biotechnology, and pharmaceutical nanotechnology. CNTs appear to be more dynamic in their biologic application due to their unique properties. CNTs are hollow, ordered, carbon graphitic nanomaterials with a range of properties such as high surface area, high aspect ratio, and ultralight weight.[1,2]

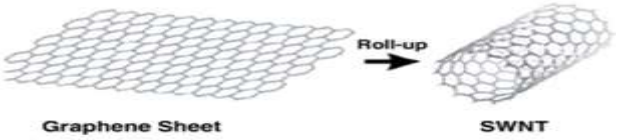


Fig.1: A graphene sheet rolled up to obtain a single-walled CNT [http://dx.doi.org/10.1016/B978-0-12-819712-7.00016-4]

1.1 Structure of carbon nanotubes [15]

The graphene sheet is rolled up cylindrically in which atoms of carbon bonded as sp2 hybridization has been acknowledged as some tube-like hollow fullerenes. CNTs are made up of rolled graphite sheets, which, in addition to graphite, can also form fullerenes and other carbon allotropes. [3,4,5] Carbon nanotubes, also known as buckytubes, are used in many different sectors due to their unique properties and cylindrical shape.[6,7]

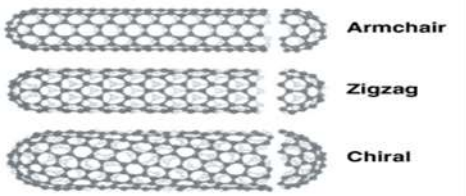


Fig. 2: Geometry of carbon nanotubes

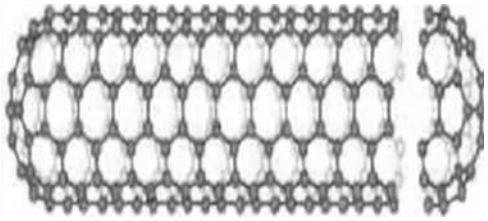


Fig. 3: Structure of carbon nanotubes[8]

[http://dx.doi.org/10.1016/B978-0-12-819712-7.00016-4]

1.2 Classification of carbon nanotubes [6]

Depending upon the number of sheets rolled into concentric cylinders, these are broadly categorized into 4 types such as of CNTs, namely, singlewalled (SWCNTs), double-walled (DWCNTs), triple-walled (TWCNTs), and multi-walled (MWCNTs).

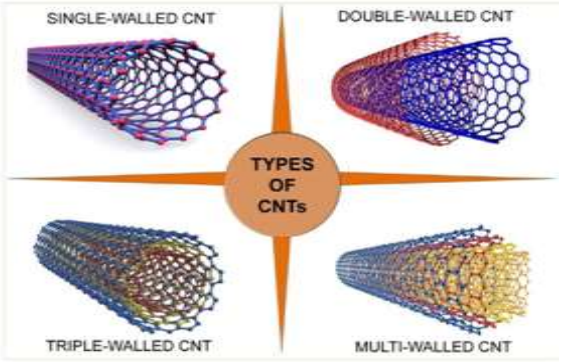


Fig.4: Types of CNTs[6]

1.3 Comparison between SWCNTS & MWCNTS [8]

Table.1: Comparison between SWNT and MWNT

SWNT	**MWNT**
Single layer of graphene.	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.

2. PROPERTIES [9,1]

2.1 Electronic [1]

- The hexagonal lattice arrangement of carbon atoms in carbon nanotubes (CNTs) results in covalent bonds between three neighbouring carbon atoms through the use of sp2 molecular orbitals.[10]
- Because of this, each unit's fourth valence electron is still free. These free electrons are distributed throughout all atoms and add to the electrical properties of CNTs. SWCNTs are metals with resistivities ranging from 1.0 10-4 U cm to 0.34 10-4 U cm. [11]

- Thus, based on the type of chirality, CNTs can be either conducting or semiconducting.[10]

2.2 Mechanical

- The Young's modulus of MWCNTs is 1.7-2.4 TPa, while that of SWCNTs can reach 2.8-3.6 TPa.[12]
- Especially when it comes to the axial direction, CNTs are incredibly robust materials. [13]
- According to Ref. 14, a MWCNT exhibited a tensile strength of 63 GPa, which is equivalent to 1.2 GPa for high carbon steel. [14]
- CNTs possess extremely high elastic moduli, approximately 1 TPa (compared to w70 Gpa for aluminium). [15]
- When compared to high carbon steel, which has a specific strength of 154 kN m/kg, carbon nanotubes (CNTs) have the best-known specific strength of 48,462 kN m/kg due to their low solid density of 1.3–1.4 gm/cm^3. [16]
- Vander Waal's forces can bend two adjacent nanotubes, as demonstrated by the first observation of radial elasticity made with a Transmission Electron Microscope (TEM). [17]
- TEM investigation into CNTs has demonstrated the materials' flexibility and resistance to breaking when bending.[18]

2.3 Thermal

- At room temperature, the thermal conductivity of individual MWCNTs is found to be 3000 W/K, which is higher than that of graphite. For SWCNTs, the result is larger than 200 W/m K.[19]
- The thermal conductivity and specific heat at low temperatures provide concrete proof of the one-dimensional quantization of the phonon band structure in carbon nanotubes.[20]

In the medical field, three main attributes of CNTs have been exploited:

- Their small size.
- Their high surface area to volume ratio.
- Their ability to contain chemicals.

3. SYNTHESIS OF CNTS [21]

3.1 Arc Discharge

The easiest and most popular method of making CNTs is arc discharge, which was first used to make C60 fullerenes. By arc-vaporizing two carbon rods positioned end to end and spaced apart by roughly 1 mm inside a container that is often filled with inert gas at low pressure, this technique produces carbon nanotubes (CNTs). A high temperature discharge between the two electrodes is produced by a direct current of 50 to 100 A0, driven by a potential difference of around 20 V. One of the carbon electrodes' surfaces is vaporised by the discharge, and the other electrode accumulates a tiny, rod-shaped deposit. Nanotubes with a diameter of 0.6 to 1.2 nm are created by altering the metal catalyst. Molybdeum and cobalt are employed as catalysts.

3.2 Laser ablation

To vaporise the target more evenly in laser ablation, a second pulse was used after the first one during laser vaporisation. The quantity of carbon deposited as soot is reduced when two consecutive laser pulses are used. The larger particles ablated by the first laser pulse are broken up and fed into the structure of the developing nanotubes by the second pulse. The material obtained from this process resembles a mat of ropes with diameters ranging from 10 to 20 nm and lengths up to 100 μm or more.

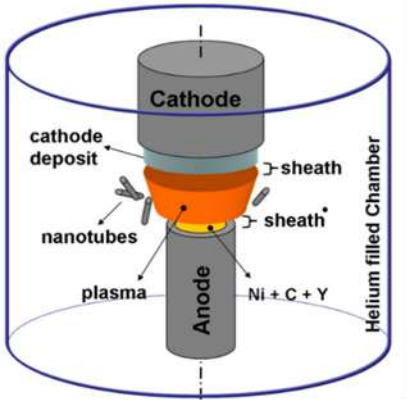


Fig.5: Arc Discharge Method

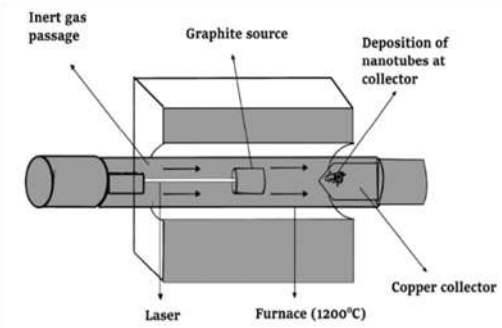


Fig.6: Laser Ablation Method[3]

[DOI:10.1088/0022-3727/45/31/315305]

3.3 Chemical Vapor Deposition

Carbon materials such as carbon filaments and fibres have been produced by Chemical Vapour deposition of hydrocarbons on a metal catalyst. Acetylene can be catalytically CVD over iron and cobalt catalysts supported on silica or zeolite to generate large amounts of CNTs. Catalytic breakdown of an H_2-CH_4 combination over well-dispersed metal particles, including cobalt, nickel, and iron, over magnesium oxide at 10,000C has generated high yields of single walled nanotubes. The newly produced nanoparticles are prevented from growing further by the breakdown of CH4, which leads to a very high proportion of SWNTs and few MWNTs.

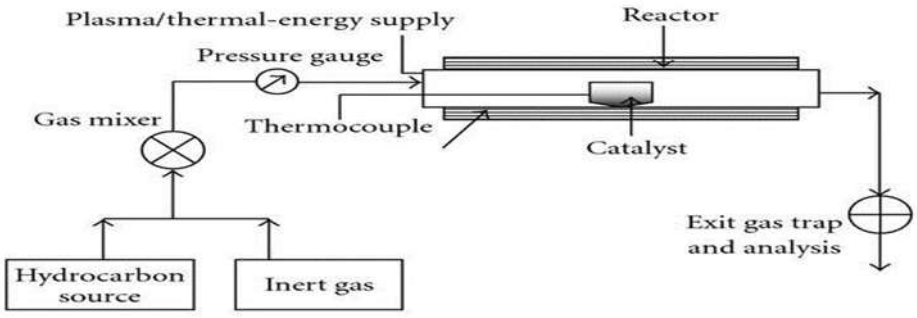


Fig.7: Chemical Vapor Deposition [DOI:10.1155/2010/395191]

4. PURIFICATION [8]

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

4.1 Air Oxidation

The average purity of carbon nanotubes is approximately 5–10%, having less purity. Purification is therefore required prior to drug attachment to CNTs. The amount of amorphous carbon and metal catalyst particles (Ni, Y) can be decreased by air oxidation. It seems that 673 k for 40 minutes is the ideal oxidation condition.

4.2 Acid Refluxing

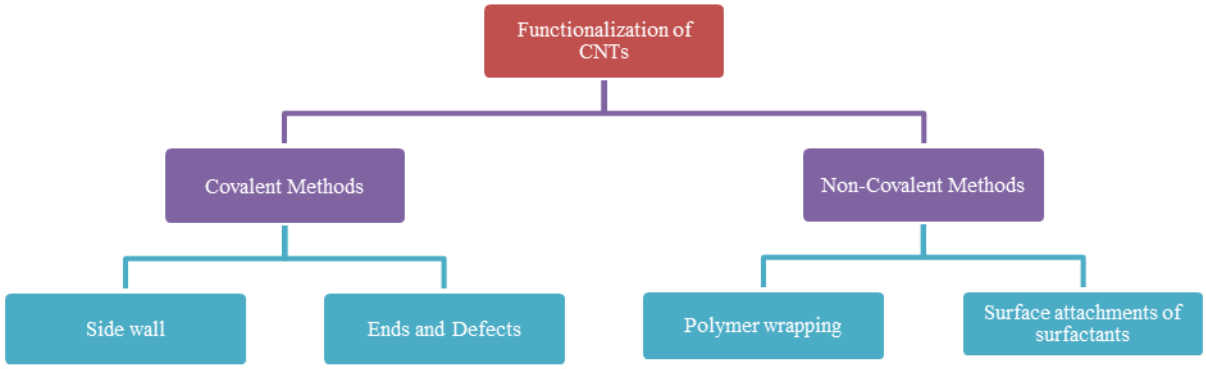
Refluxing the sample in strong acid effectively reduces the amount of amorphous carbon and metal particles. Hydrochloric acid (HCl), nitric acid (HNO_3), and sulfuric acid (H_2SO_4) were the different acids that were used; despite all, it turns out that HCl was the best refluxing acid.

4.3 Surfactant aided sonication, filtration and annealing

The carbon nanotubes were purer after acid refluxing, but most of the impurities including carbon and catalyst particles, were trapped in the entangled tubes and were challenging to filter out. Thus, surfactant-assisted sonication was used. The most desired organic solvent for sonication with ethanol (or

methanol) was sodium dodecyl benzene sulphonate (SDBS), as this combination allowed the CNTs to settle down slowly, indicating that an even suspension condition had been achieved. After that, the sample underwent ultra filtration and was annealed for four hours at 1273 k in N_2. The CNT structures can be effectively optimised through annealing. It has been demonstrated that surfactant-assisted sonication works well to untangle CNTs and release any particle contaminants that are entangled.

5. FUNCTIONALIZATION:



5.1 Covalent functionalization of carbon nanotubes [22,23]

A different method of making carbon nanotubes soluble in a variety of solvents is to modify their sidewalls and tips through organic functionalization, which can be ensured, for instance, by covalently attaching hydrophilic moieties. Functional groupings are now attached to CNT using two primary techniques.

5.1.1 Oxidative treatment using strong acid solutions

Carboxylic functions at the tips and defect spots of the carbon nanotubes are covered by variations in the type of acid, its concentration, and the reaction conditions (temperature, sonication). The CNT solubility was subsequently increased by incorporating various additional groups using the carboxylates. Thionyl chloride or carbodiimide was used to activate COOH during the introduction process. Similarly, direct heating in the presence of amino polymer was able to solubilize oxidised carbon nanotubes.

5.1.2 Addition reactions to CNT

Utilising the chemistry of fullerenes, CNT have been effectively produced by 1,3-dipolar cyclo addition of azomethineylides, aryl diazonium salt addition, or reductive alkylation employing lithium and alkyl halides. The incorporation of several functional groups on the nanotube, which may then be further derivatized, was made possible by this direct sidewall modification of CNT. Compared to a noncovalent dispersion, a covalent link has the benefit of being more resilient to manipulation and processing. However, CNT functionalization—both covalent and noncovalent—has been used to apply these materials in the realm of drug delivery.

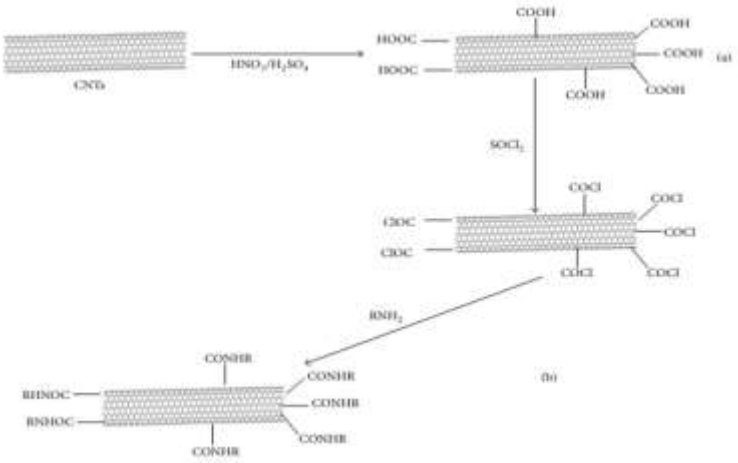


Fig.8: Covalent functionalization of CNTs by (a) oxidation reaction by strong acid and (b) further attaching hydrophilic molecules by amidation reactions.[27]

5.2 Noncovalent functionalization of carbon nanotubes[24]

As the name implies, non-covalent functionalization involves the adsorption and wrapping of biomolecules, surfactants, polymers, and other chemicals to form non-covalent binding (adsorption forces) like electrostatic force, hydrogen bonds, van der Waals force, and π-stacking interactions.[25] Compared to chemical functionalization (covalent functionalization), non-covalent functionalization has the benefit of being able to be used under relatively mild reaction conditions and preserving the sidewalls and structural characteristics of CNTs in order to preserve their flawless graphitic structure.[26]

CNTs can be made noncovalently functionalized by covering them with amphiphilic molecules of surfactant or polymers (polyethyleneglycol). Carbon nanotubes are excellent partners for noncovalent interactions with appropriate complementary molecules and macrobiomolecules (DNA) due to their enormous hydrophobic surface that is aromatic (π- electrons). Both the inside and outside of CNTs may be the site of these interactions. Nevertheless, macromolecules are not able to be connected inside. Following functionalization, carbon nanotubes (CNTs) acquire hydrophilicity and can be coupled with medications or biomolecules (proteins, enzymes, DNA, genes, biosensors, etc.) to facilitate their transport into the intended target cells or organs.[27,28,29,30]

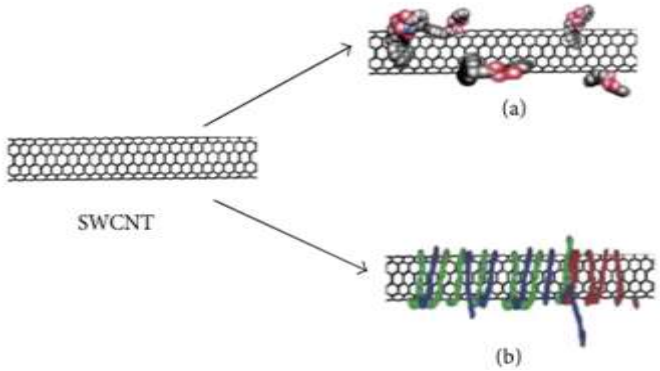


Fig.9: Noncovalent functionalization of CNTs with (a) surfactants such as protein adsorption and (b) polymers such as DNA wrapping.[27]

6. ATTACHMENT OF DRUG TO CNT AND ITS RELEASE[31]

Drugs are typically attached to their external surfaces by amide, ester, or disulphide bonds between molecules. This is to use a bond that, by biological cleavage, releases the payload either inside the cell or, more beneficially, close to the cell. It was discovered in a recent study that the amide bond that connects the anti-cancer medication methotrexate to the f-CNT was the reason for a lack of improved efficacy between the drug's distribution and the nonconjugated drug. The bond was found to be too stable and not biologically cleaved. A biologically stable link that can be broken within the cell by an enzyme can lead to better delivery since it won't break down before it reaches the location of interest (Prato et al., 2008)[32]. Since living things are typically transparent to NIR, using NIR to release drugs enclosed in carbon nanotubes is another intriguing release method. This is especially applicable for polar drugs that have difficulty passing through the lipid bilayer. The near IR can be utilised to speed up the diffusion of the substances inside the tube to the cell by heating the CNT. Molecules with high polarity are trapped by extremely low diffusion coefficients. The release of polar drugs is facilitated by a heated diffusion coefficient that can rise up to seven times (Chaban et al., 2010).[33]

6.1 Kinetics of CNTs:

To achieve the intended therapeutic benefits, CNTs' administration, absorption, and transportation as drug carriers must be taken into account. Oral and injectable methods of CNT delivery, including as subcutaneous, abdominal, and intravenous injections, have been investigated. When CNTs are administered through various routes, there are several methods of absorption and transportation. Blood or lymphatic circulation carries the absorbed CNTs from the administration sites to the effect-relevant areas. The first crucial stage for drug carriers to finish their drug-delivering mission is absorption, which comes after administration. Research indicates that carbon nanotubes (CNTs) have the ability to be absorbed. Additionally, it has been demonstrated by transmission electron microscopy that physically shorter CNTs can be absorbed through the intestinal mucous membrane's columnar cells (Liu et al., 2011).[34] The distribution of carbon nanotubes (CNTs) as drug carriers is crucial for understanding the sites and locations where the CNTs can be absorbed.

There have always been concerns about the nonbiodegradability and noneliminability of these substances in the body, which raise questions on their potential for effective usage in clinical practice. It appears that the animal body can metabolise functionalized SWCNTs. over instance, SWCNTs with carboxylated surfaces have shown a remarkable capacity to degrade in a phagolysosomal simulant over ninety days, resulting in a reduction in length and a build-up of ultrafine solid carbonaceous debris. Similar circumstances cause no degradation of arylsulfonated SWCNTs that have not been modified or ozonolyzed. The distinct chemistry of acid carboxylation, which not only introduces the reactive, modifiable COOH groups onto CNT surfaces but also causes collateral damage to the tubular graphenic backbone in the form of adjacent active sites that serve as points of attack for additional oxidative degradation, may be responsible for the observed metabolism phenomenon (Raffa et al., 2010).[35]

7. TOXICOLOGY/BIOSAFETY PROFILE OF CNTS [36]

Although carbon nanotubes (CNTs) possess a number of desirable properties, their inherent lipophilicity, related impurities, asbestos-like similarity, high aspect ratio and surface area, surface flaws, functionalizations, etc. Have raised concerns about their toxicity. There have been reports of CNTs causing DNA damage, increased oxidative stress, accumulation in tissues, and mitochondrial stress.[37-39] Since CNTs are comparable in size to microorganisms, they trigger the foreign body reaction, which impedes phagocytosis. Consequently, a large oxidative burst is produced by activating the myeloperoxidase pathway, which in turn increases ROS levels and activates NF-kB signalling, thereby contributing to oxidative stress [40-42] Oxidative stress is also induced by residual catalysts including iron (Fe), nickel (Ni), and cobalt (Co), which can be contained inside the CNT structure or localised on its surface.[43-45] Annealing, refluxing, or steam purification using acidic treatments are methods to reduce these contaminants. It was discovered that oxidative stress, decreased clearance, and cellular accumulation were caused by the intrinsic lipophilicity of pure CNTs. According to a report, longer carbon nanotubes may have greater potential for toxicity than shorter ones. Evidence suggests that longer CNTs exhibit greater toxicity compared to their shorter counterparts, owing to their reduced ability to evade immune recognition, thus perpetuating frustrated phagocytosis[43,50,51]. Acute inflammation, fibrosis, necrosis, and granuloma formation have been associated with single-walled carbon nanotubes (SWCNTs), while multi-walled carbon nanotubes (MWCNTs) have been reported to induce cell hyperplasia, damage to Kupffer cells, and eye irritation[52,53]. Importantly, an optimal degree of functionalization is critical for ensuring proper tissue distribution and excretion of CNTs [54-56]. In biological systems, the degree of CNT suspension determines the fate and bioavailability of the particles. CNTs suspended in suspension have better dispersion, increased mobility, and more effective clearing. On the other hand, CNT aggregation might adversely impact these properties[57,58]. Surface imperfections on carbon nanotubes can lead to incomplete bonding, non-carbon element doping, and the addition of various functionalities[59,60]. Shortening of CNTs through concentrated acid-ultrasonication has been reported to induce surface defects, thereby amplifying oxidative stress and inflammation[59-61]. Current strategies to circumvent these limitations include functionalization of CNTs with amphiphilic molecules, reducing their lengths, judiciously selecting the appropriate CNT type, optimizing the degree of functionalization, and maintaining an appropriate particle size and suspension state[62,63,64].

8. ANALYTICAL TECHNIQUES FOR CARBON NANOTUBES [22]

8.1 TEM

It is employed to ascertain the morphology and provide qualitative information on the purity of CNTs that are created. The size, shape, and structure of carbonaceous materials as well as non-CNT structured contaminants in a sample may all be qualitatively determined using TEM, which is unique in this regard. On the other hand, it does not distinguish itself from MWNTs and cannot detect metallic contaminants. The utilisation of TEM has also been applied to observe the cellular uptake of CNT-drug composites and identify the subsequent fate of the CNT component following cellular uptake.

8.2 SEM

It is applied to the initial assessment of CNT morphology. In its traditional setting the technique is limited by its inability to differentiate catalyst and carbonaceous impurities from CNTs. However, SEM combined with an energy dispersive x-ray analysis detector is a common method used to determine the metallic content of CNT samples (SEM-EDX). In any case, SEM is most likely the only method that can provide details on the metallic impurity content as well as the shape of the CNTs.

8.3 Raman Spectroscopy

It has been applied to assess the processes involved in the synthesis and purification of SWNTs. Because carbonaceous impurities have Raman features (D- and G-bands) that are identical to those of SWNTs, they pose a significant challenge to the interpretation of SWNT Raman spectra. Examples of these impurities include graphite, fullerenes, and amorphous carbon, etc.

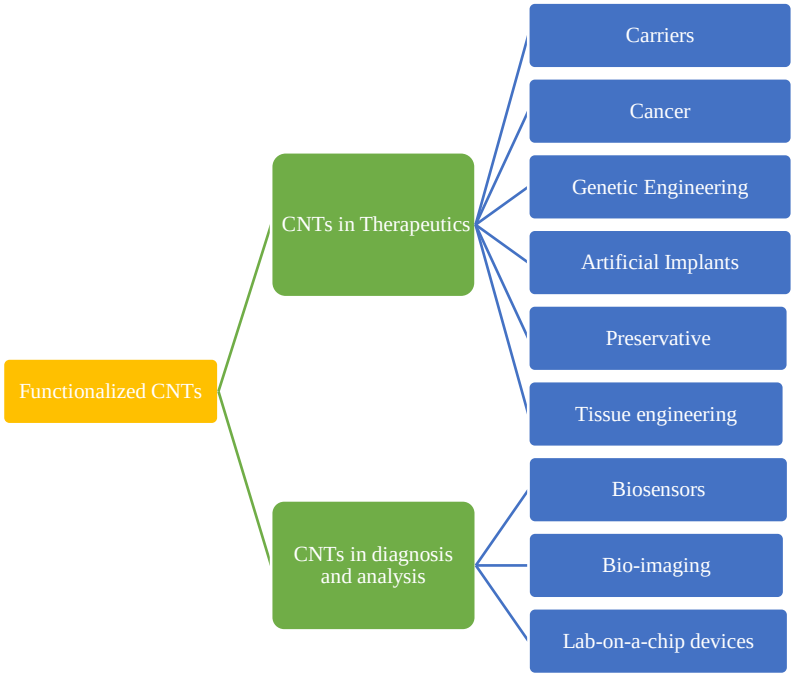
8.4 Proton NMR

It's been applied to track the development of CNT functionalization. The characteristic peaks resulting from the variation in the magnetic environment can be used to forecast the presence of functional groups. Protons next to the functionalized carbon nanotube (CNT) exhibit broad bands in their H-NMR spectrum, which narrow with increasing distance. The production and attachment of functional groups to carbon nanotubes (CNTs) have been observed using H-NMR.

8.5 IR Spectroscopy

Its main application is as a qualitative tool to detect functional groups according to the type of attachment they have to CNT sidewalls. Different functional groups absorb distinct infrared radiation frequencies, resulting in fingerprint identification of bonds. It is a complementary technique to NMR for verifying the existence of bonds and associated moieties in CNTs.

9. Applications



9.1 Delivery of various anticancer agents using CNTs [36]

By using CNTs, many anticancer treatment drugs have been successfully administered to tumour tissues as shown in (fig.10). When taken in high doses, platinum-based drugs for cancer such as carboplatin, cisplatin, and others have been demonstrated to cause severe side effects such myelosuppression, neurotoxicity, and nephrotoxicity. Because of this, therapeutic usage of sub-toxic doses of platinum drugs clinically has increased tumour resistance and treatment failure[80]. Numerous studies have delivered platinum-based cancer treatments to tumours using f-CNTs, either with or without homing devices. Early research by Lippard and colleagues showed that phospholipid-polyethylene glycol (PL-PEG) surface-modified SWCNT (SWCNT-PL-PEG) could successfully transport Pt(IV), a platinum prodrug and that uptake of SWCNT-PL-PEG was mediated by endocytosis[81]. Additionally, they developed SWCNTs of -Pt (IV) functionalized with folic acid (FA) (SWCNT-Pt (IV)-FA) to deliver Pt(IV) selectively to human nasopharyngeal carcinoma (KB) and folate receptor-positive (FRÍ) human choriocarcinoma (JAR). When compared to SWCNT-Pt(IV) and naïve drug, SWCNT-Pt(IV)-FA exhibits greater tumour selectivity, better cellular uptake, and enhanced cytotoxicity[81,82].

To target EGF receptors overexpressed in head and neck carcinoma (HNCC), Bhirde and colleagues produced Cisplatin (CP) conjugated SWCNTs surface modified with endothelial growth factor (EGF) (SWCNT-CP-EGF). In mice, HNCC was markedly decreased by SWCNT-CP-EGF as opposed to naive CP[83]. Hampel and colleagues are the first introduce endohedral filling, or interior filling, of the anticancer medication carboplatin (CA) into CNTs. They used a wet chemical method to construct the MWCNT-CA complex. In addition to demonstrating a regulated release of CA from MWCNT, they also showed that MWCNT-CA had higher anticancer effectiveness against bladder cancer cells, EJ28. It has been reported that MWCNTs and SWCNTs have immediate and sustained release characteristics, respectively[84,85,86,87]. For example, L. L. Wu and colleagues developed MWCNT-PEG-OX, which is PEGylated MWCNT endohedrally loaded with oxaliplatin. Based on testing on HT-29 cells, the study's findings show that MWCNT-PEG-OX demonstrated both superior anticancer effects and sustained releasing capabilities[85]. Using different f-CNTs, doxorubicin (DOX), an anthracycline anticancer drug, was administered to tumour cells. Liu and colleagues found that DOX-loaded PEGylated SWCNTs (PEG-SWCNT) had better drug retention in the tumour tissues and less off-target adverse effects, which increased DOX's anticancer efficacy. When tested on MCF-7 breast cancer cells, noncovalently functionalized DOX loaded MWCNTs exhibited an increase in cytotoxicity, according to a different study by Ali-boucetta and colleagues[88]. In addition, a number of research teams developed different CNT-based formulations of Paclitaxel (PTX) and Gemcitabine (GEM) in an effort to enhance their cytotoxicity and site-specific delivery[90-94]. Liu and colleagues work showed that PEG-SWCNTs loaded with PTX had better cytotoxic potency than the naïve drug[95]. In an additional investigation, it was found that a MWCNT-GEM construct functionalized with FA and PEG, as opposed to naïve GEM, improved cytotoxicity and decreased pancreatic cancer metastasis rates[93].

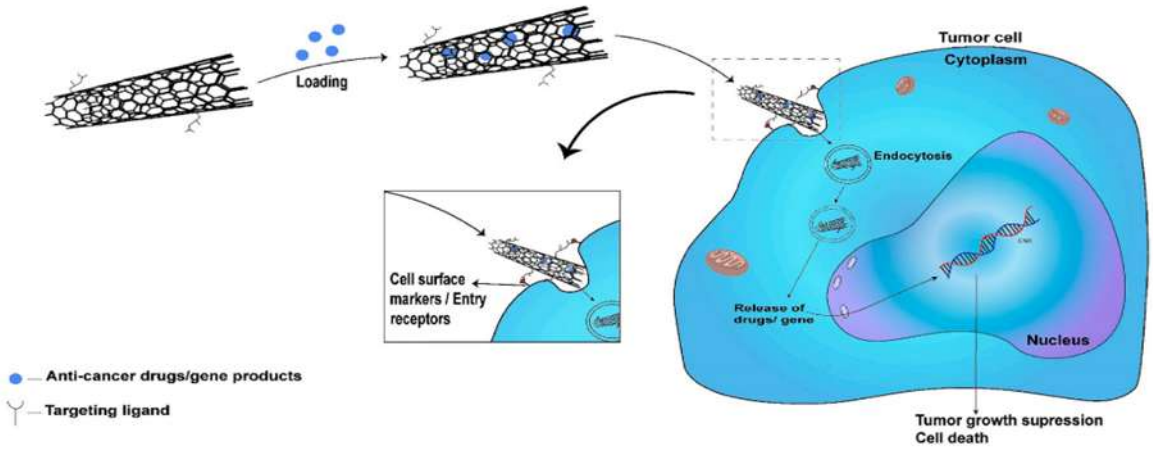


Fig.10: Mechanisms of cellular entry of SWCNT: The functionalized CNTs laded with drugs or gene products, enters the cell either through endocytosis or cellular pores, releasing the drugs or gene products into the cytoplasm.[36]

In one study, magnetic nanoparticles loaded with epirubicin (EPI) (mMWCNTs-EPI) showed prolonged retention and sustained release, resulting in higher cytotoxicity compared to free EPI[96].The elevated activity in bladder cancer both in vitro and in vivo may have been caused by the sustained release of drug-loaded MWCNT, which may have been caused by an initial burst release from peripheral sites followed by sustained release from the core region[89,84,85,96]. It was clear from the previously mentioned research that carbon nanotubes have a greater potential for delivering anticancer drugs specifically to tumour regions.

9.2 Carrier for drug delivery [97]

Research studies have proved CNTs and CNHs as a potential carrier for drug delivery system.

1. It has been shown that functionalized carbon nanotubes can target cells with amphotericin B.
2. Oxidised SWNHs containing cisplatin have demonstrated a delayed release of the drug in an aqueous medium. While the SWNHs by themselves did not exhibit anticancer activity, the released Cisplatin was successful in stopping the proliferation of human lung cancer cells.
3. Because of the nanotubes controlled lipophilicity improved the anticancer drug Polyphosphazene platinum's permeability, distribution, and retention in the brain.
4. Doxorubicin, an antibiotic, has been reported to have improved intracellular penetration when administered with nanotubes.
5. The hydro-gel gelatin CNT combination has been investigated as a potential carrier system for biomedicals.
6. Erythropoietin (EPO) denaturation by the stomach environment and enzymes has prevented EPO from being successfully administered orally until now. However, a CNT-based carrier system may be able to provide an effective oral alternative.
7. Because of the sliding nature and nanosize of graphite layers bonded by van der Waals forces, they can be employed as lubricants or glidants in tablet manufacture.

9.3 Genetic Engineering [97]

CNTs and CNHs are utilised in genetic engineering to modify atoms and genomes for the purposes of tissue engineering, proteomics, and bioimaging. Their tubular structure has demonstrated their utility as a gene therapy vector. By joining its unique nucleosides, the unravelled DNA encircles the SWNT and modifies its electrostatic characteristics. This gives it the potential to be used in both therapy and diagnostics (polymerase chain reactions).

9.4 Tissue engineering [27]

The steady advancement of CNT-based tissue engineering and regenerative medicine has been facilitated by recent discoveries in the fields of cell and organ transplantation as well as CNT chemistry. Out of all the materials that can be used to create tissue scaffolds for tissue engineering, such as natural and synthetic polymers, carbon nanotubes may be the best option because they are biocompatible, resistant to biodegradation, and can be functionalized with biomolecules to improve organ regeneration. By integrating with the host's body, CNTs can be utilised as additives in this field to strengthen the mechanical strength of tissue scaffolding and conductivity. In fact, a composite nanomaterial employed as a scaffold in tissue regeneration was effectively created by MacDonald et al. by combining carboxylated SWCNTs with a polymer or collagen (poly-l-lactide or poly-D,L-lactide-co-glycolide). Recent research has also looked into other tissue engineering uses of CNTs, including cell tracking and labelling, monitoring cellular behaviour, and improving tissue matrices.

9.5 Artificial Implants [97]

Implant rejection is typically manifested by post-administration pain. However, in order to prevent rejection, tiny nanotubes attach themselves to other proteins and amino acids. Additionally, they can be utilised as implants in the form of prosthetic joints without causing host rejection. Furthermore, calcium-filled carbon nanotubes clustered and organised in the structure of bone can serve as a substitute for real bone because of their high tensile strength.

9.6 Preservative [97

In nature, carbon nanotubes are antioxidants. They are thus employed in preserving drug formulations that are vulnerable to oxidation. Their anti-oxidant qualities are utilised in anti-aging cosmetics and in dermatological sunscreen formulations with zincoxide that prevent the oxidation of vital skin constituents.

9.7 Diagnostic Tool [97]

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

9.8 Lab-on-a-chip devices[104]

Lab-on-a-chip (LOC) devices are miniature systems in which tiny volumes of fluids flowing in various channels that are designed for purposes such as drug screening, cell growth, and disease models. In LOC devices, CNTs have been employed as channel walls, sensors, and membrane channels.

9.9 Biosensors

Because of their unique optical, mechanical, and electrical characteristics, carbon nanotubes (CNTs) are a desirable candidate material for the production of optical and electrochemical biosensors. [105] A biosensor is an analytical tool that combines a physicochemical detector and a biological component to detect analytes. Recent advancements in biosensing nanotechnology have made the application of CNTs to therapeutic monitoring and in vitro and in vivo diagnostics quite fascinating. For instance, numerous researchers have combined carbon nanotubes (CNTs) with glucose-oxidase biosensors to control blood sugar in diabetic patients more accurately and easily than with biosensors alone[98,107,108]. Additional CNT-based enzyme biosensors, like those for dehydrogenase, peroxidase, and catalase, have also been developed for various therapeutic monitoring and diagnostic applications[108,109]. Alkaline phosphatase (ALP) linked to carbon nanotubes (CNTs) increased the assay sensitivity for electrical DNA detection over that of ALP alone. In comparison to conventional fluorescence and hybridization assays, the sensitivity of the experiment employing the SWCNT-DNA sensor which was produced by integrating SWCNTs with single-strand DNAs (ssDNA) was significantly greater. By utilising specific antibody-antigen recognition, this CNT-biosensor-linked assay can be modified for antigen detection.[102,108]

9.10 Bio-imaging

CNTs have many favourable features that make them ideal for optical detection. The near-infrared (NIR) portion of the electromagnetic spectrum is where CNT transitions take place, and thus results in very little signal interference. The optical window ranging from 900 to 1300 nm in the infrared spectrum is highly significant for biomedical applications because of its modest auto-fuorescent background and decreased photo-absorption. Because of the reduced absorption in the chosen spectral band, optical signals can penetrate deeper. Furthermore, CNTs have excellent photostability[110]. Techniques for tracking the movement of carbon nanotubes (CNTs) throughout the body over an extended period of time include fluorescence spectroscopy and Raman scattering. Because of their hydrophobicity, the CNTs are able to remain inside the cells during multiple cell divisions, indicating that they could be utilised to create probes to examine stem-cell differentiation and proliferation. CNTs have the potential to be used as image contrast agents in Raman scattering, nuclear imaging, photoacoustic, optical detection, magnetic resonance, photoacoustic, and fluorescent video imaging techniques.[111]

Table.2: Application of CNTs in bioimaging

Type of CNT	Functionalization	Applications	References
SWCNTs	Poly(2-methacryloyloxyethyl phosphorylcholineco–n-butyl methacrylate; PMB)	Imaging of brown fat	112
SWCNTs	Cyclic Arg-GlyAsp (RGD) peptides	Tumor detection	113

MWCNTs	-	Ultrasound scan of liver and heart	114
SWCNTs	Graphene quantum dots	Imaging of human osteosarcoma	115
SWCNTs & MWCNTs	-	Raman Bio-imaging for live cell imaging	106

10. Limitations of CNTs

- Lack of solubility in most solvents compatible with the biological milieu (aqueous based).
- The production of structurally and chemically reproducible batches of CNTs with identical characteristics.
- Difficulty in maintaining high quality and minimal impurities.

11. Challenges

- **Scale-up Production:** Nowadays, generating high-quality CNTs requires time-consuming, costly, and non-scalable processes. The commercialization of CNT-based drug delivery devices depends on the development of large-scale, cost-effective production techniques.
- **Long-term Toxicity Studies:** Long-term, thorough in vivo toxicity studies are required, even if preliminary research indicates that some CNTs are biocompatible. For ethical clinical use, it is essential to comprehend the potential for immunological reactions, long-term biodegradation, and chronic inflammation.
- **Targeting Efficiency:** Even though functionalization makes it possible to attach targeting moieties to carbon nanotubes (CNTs), it is still difficult to precisely and effectively deliver materials to particular cell types. It is crucial to optimise targeted tactics and understand the complicated in vivo environment.
- **Control Release Mechanisms:** The goal of developing CNT-based systems with customisable and predictable drug release characteristics is still being pursued. Approaches that use biocompatible polymers as gatekeepers or stimuli-responsive release (such as pH, light, or temperature) are currently being investigated.

12. Future Directions

- **Next Generation Synthesis:** Research on new synthesis techniques that are more scalable, controlled, and environmentally friendly has great potential. This involves researching methods with precise control over the characteristics of CNTs, such as chemical vapour deposition (CVD).
- **Computational Modelling:** Targeted and biocompatible drug delivery systems can be designed with the help of computational modelling, which helps learn how CNTs interact with biological systems.
- **Smart CNTs:** A promising path for the future is the development of "smart" CNTs with integrated functions like self-assembly, biodegradability, and triggered drug release. These innovative characteristics may provide better safety profiles and increased therapeutic efficacy.
- **Integration with Microfluidics:** Combining Microfluidics and CNT-based drug delivery systems together present intriguing opportunities for on-demand therapy and controlled drug release. Accurate dosing and real-time drug delivery monitoring may be possible with microfluidic devices.

13. Conclusion

In conclusion, carbon nanotubes have significant potential for application in drug delivery systems because of their special structural and functional characteristics, which serves a wide range of biological applications. Chemical vapour deposition(CVD) is the most extensively utilised technology because of its efficiency and scalability; this paper has provided about their synthesis processes. Since functionalization greatly increases the solubility and decreases the toxicity of CNTs, its significance in functionalization with biocompatible chemicals has been addressed. The development of CNTs for industrial applications has helped greatly from this functionalization. In an attempt to lower production costs and increase purity, researchers are constantly developing novel techniques. Even with the promising applications particularly in cancer treatment and targeted drug delivery, there are still several challenges to overcome. Because of the widespread toxicity and limited effectiveness of the current cancer therapy approaches, carbon nanotubes(CNTs)

are seen as a promise yet unsatisfactory treatment. Therefore, to fully understand the toxicity of carbon nanotubes to humans and the environment, considerably more research is required. Overcoming these toxicity problems will be critical to the success of CNT uses in medicine.

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