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A Review on CNTs for Targeted Drug Delivery

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Abstract

The development of innovative and effective drug delivery methods is critical for improving the pharmacological profiles of many medicinal compounds. Currently, several types of drug delivery systems are available, and while they have been beneficial in certain circumstances, there are significant downsides, including harm to healthy tissue and unpleasant means of producing the medication. Nanotechnology uses current advances in chemistry, physics, materials science, and biology to generate innovative materials with unique characteristics due to their nanometer-scale structures. Carbon Nanotubes have been considered as the prototypical nano-materials, with one of the most active sectors of nano-science and nanotechnology. Carbon nanotubes, which operate as scaffolds, offer potential therapeutic uses in drug delivery, diagnostics, biosensing, and tissue engineering. Carbon nanotubes that have been functionalized can also be used as vaccine delivery methods. They can penetrate across membranes, delivering medicinal medicines, vaccines, and nucleic acids to areas previously inaccessible by traditional drug delivery methods.

Keywords: *Nanotechnology, Drug delivery, Carbon nanotubes, Biomaterials*

INTRODUCTION

The discovery of innovative and effective drug delivery methods is critical for improving the pharmacological profiles of many kinds of medicinal compounds, as well as their limitless potential to enhance human health. Nanotechnology, on the other hand, is concerned with the creation

of functioning systems at the molecular level. Nanoscale biomaterials can be employed as controlled release reservoirs for medication delivery.

Controlled composition, shape, size, and morphology can be used to create drug delivery systems. To fit the needs of the target region of administration, their surface qualities can be modified to improve solubility, immunological compatibility, and cellular absorption. Current medication delivery methods include drawbacks such as inadequate bioavailability, limited effective targeting, and possible cytotoxicity. [1] Carbon Nanotubes (CNTs) are promising nanomaterials that can be exploited for material translocation and transport [2]. CNTs' unique inherent physical and chemical characteristics have been studied in recent years. Carbon nanotubes provide significant prospects for the development of fundamentally new material systems, ranging from unique electrical capabilities and thermal conductivity higher than diamond to mechanical qualities with stiffness, strength, and resilience that transcend any contemporary material. [3] After functionalization, CNTs demonstrate reduced toxicity and are not immunogenic, paving the way for enormous applications in the fields of Nano-biotechnology and Biomedicine.

Structure of CNTs

Carbon nanotubes have a bonding structure between carbon atoms that is comparable to graphite. CNTs are hollow nanostructured materials made up of carbon atoms that are connected with three neighboring atoms via sp2 bonds that are stronger than the sp3 bonds found in diamond, giving the structure its particular strength. CNTs are graphene sheets that have been coiled up. Carbon exists in a variety of forms, and the qualities of the substance are mostly determined by the structure and arrangement of the atoms. The unique mechanical and chemical capabilities of CNTs are due to the structural arrangement of the carbon tubes.

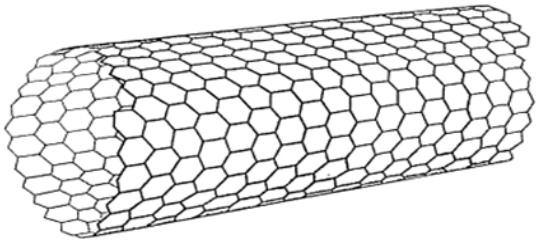


Figure 1: A part of a zigzag single wall carbon nanotube (SWNT) [4]

CNTs are classified into two types: single wall carbon nanotubes (SWCNT) and multi wall carbon nanotubes (MWCN) (MWCNT). A SWCNT is formed by rolling up one graphene sheet, whereas a MWCNT is formed by rolling up several concentric graphene sheets. MWCNTs have more strength than SWCNTs however SWCNTs can be readily twisted and are more liable than MWCNTs.

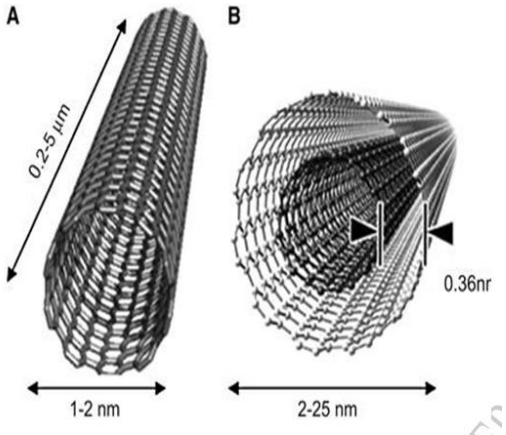


Figure 2: Conceptual representation of Single wall Carbon Nanotubes (SWCNT) (A) and Multi Wall Carbon Nanotubes (MWCNT) (B). [5-6]

Fabrication of carbon nanotubes

ARC discharge

The carbon arc-discharge technique is a high-temperature procedure that may be utilised to create nanotubes. The Kratschmer-Huffman process was used to mass produce fullerenes for the first time [7]. The generated product and yields are mostly determined by the environment and catalysts used. This is most likely one of the easiest approaches for producing nanotubes on a wide scale. An arc is ignited between two graphite electrodes in a gaseous backdrop (often argon/hydrogen) in the carbon arc-discharge technique. [8] Synthesis of single-walled carbon nanotubes: a direct comparison of laser ablation and carbon arc methods [9-10]

While the carbon evaporates, it cools and condenses, and some of the product develops as filamentous carbon on the cathode. The optimization of metals used in the anode resulted in the formation of single-walled carbon nanotubes [12-13].

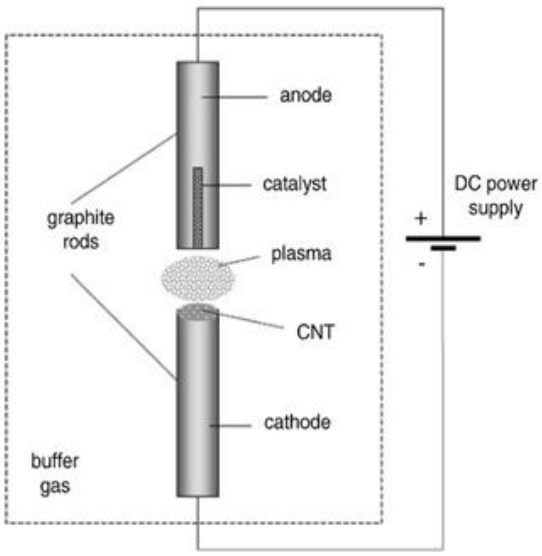
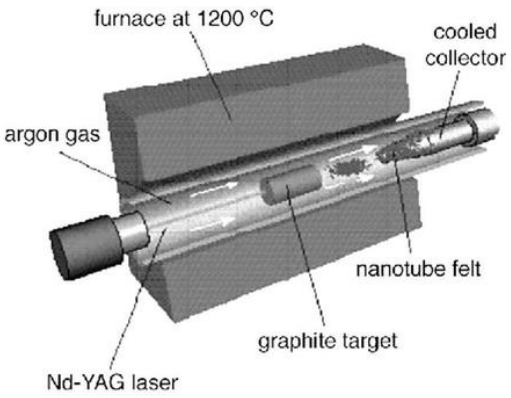


Figure 3: A Schematic representation of ARC Discharge Process [11]

Laser ablation



In the laser ablation process, a pulsed laser is used to evaporate a graphite target in a high temperature reactor in the presence of an inert gas such as helium. [14] As the evaporated carbon condenses, nanotubes form on the reactor's colder surfaces. The most viable techniques for collecting nanotubes also require a water-cooled surface [15]. The laser ablation process generates mostly single-walled carbon nanotubes with a controlled diameter dictated by the reaction temperature and yields approximately 70%. It is, however, more costly than arc discharge or chemical vapour.

Chemical Vapor Deposition

Although catalytic chemical vapour deposition of carbon was first described in 1959[17], it was not until 1993 that carbon nanotubes were produced in this manner [18]. A substrate coated with metal catalysts such as nickel, cobalt, iron, or a mixture is heated to around 700°C during CVD. The development process begins when two gases pass through the chamber: a carrier gas such as nitrogen, hydrogen, or argon, and a hydrocarbon gas such as acetylene (C2H2) or methane (CH4). The synthesis production yield, which represents the percentage of carbon nanotubes in the transformed carbon, exceeds 90% [19]. CVD is extensively employed in industry since the process has been well researched and produces acceptable results on a large scale.

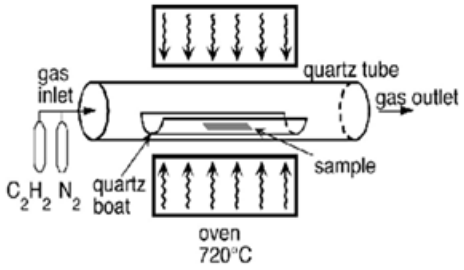


Figure 5: Schematics of a CVD Deposition Oven [20]

Flame synthesis method

Hydrocarbon fires with metal aerosol catalysts offer a unique mix of chemical and catalytic variables that promote carbon nanotube initiation and development [21]. Gases present in the post-flame environment (CO, CH4, C2H2, C2H4, and C2H6) provide a diversified supply of gaseous carbon [22].

Catalysts in the proper form (substrate or aerosol) offer the reaction sites for solid carbon deposition. The shape and qualities of the catalysts have a significant impact on the structural properties of carbon nanotubes. In the post-flame zone of a premixed acetylene/oxygen/argon flame operated at 50 Torr with Iron Pentacarbonyl vapour as the catalyst, single-walled nanotubes were found. The fuel gas is heated to 800oC in a controlled atmosphere to allow the synthesis of CNTs on the tiny metal particles. The fuel gas composition, catalyst, catalyst carrier surface, and temperature may all be changed as optimization factors. [23]

Silane Solution Method

Carbon nanotubes were created 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 was deposited thereon while the substrate was heated by applying an electrical current [24]. As a result of the interaction between the catalyst and the Gas, CNTs supported on the conductive substrate are formed.

Purification of CNTs

Impurities like as metal particles, amorphous carbon, and multishell are common in nanotubes. There are many phases in the purification of nanotubes.

Oxidative treatment

The oxidative treatment of SWNTs is an effective method for removing carbonaceous contaminants or clearing the metal surface [25].

The primary drawbacks of oxidation are that it oxidises not just the contaminants but also the SWNTs. Fortunately, the damage to SWNTs is less severe than the damage to impurities [26].

These impurities have a higher number of flaws or a more open structure. Another reason why impurity oxidation is favoured is because these impurities are frequently linked to the metal catalyst, which also functions as an oxidising catalyst. Overall, the procedure's efficiency and yield are highly dependent on a variety of elements, including metal content, oxidation period, atmosphere, oxidising agent, and temperature. Because metal functions as an oxidising catalyst, the metal content should be included when calculating the oxidising time. SWNTs, for example, will oxidise even in the absence of a catalyst

when the temperature is elevated over 600 °C60. The same is true for thermal54, fixed air, and pure oxygen oxidations. Because they can readily oxidise all of the components, temperature and time should be carefully monitored [25].

Acid Treatment

In most cases, the acid treatment will dissolve the metal catalyst. First, the metal's surface must be exposed by oxidation or sonication. The metal catalyst is subsequently dissolved in acid. The SWNTs are still suspended. When HNO3 is used for treatment, the acid has no impact on the metal catalyst. It has no impact on carbon particles or SWNTs [27]. If HCl is utilised to treat the SWNTs and other carbon particles, the acid has a significant influence on them. As a result, HCl is regarded as the optimal refluxing acid [28-29].

Magnetic Purification

This approach mechanically separates ferromagnetic (catalytic) particles from their graphitic shells [30]. To eliminate the ferromagnetic particles, the SWNT suspension is combined with inorganic nanoparticles (mostly ZrO2) in an ultrasonic bath. The particles are then trapped by permanent magnetic poles. A high purity SWNT material will be created after a further chemical treatment. This procedure requires no significant equipment and allows for the fabrication of laboratory-sized quantities of SWNTs with no magnetic contaminants.

Ultrasonication

Particles are separated using ultrasonic vibrations in this process. Agglomerates of various nanoparticles will be driven to vibrate and disperse [27]. The particle separation is heavily influenced by the surfactant, solvent, and reagent utilised [31]. The solvent has an effect on the stability of the system's distributed tubes. SWNTs are more stable in weak solvents if they are still linked to the metal. Mono dispersed particles, on the other hand, are highly stable in certain solvents, such as alcohols [32].

The purity of the SWNTs relies on the exposure period when an acid is applied. When the tubes are exposed to the acid for a short period of time, just the metal dissolves, but after a longer period of time, the tubes are chemically sliced [33].

Functionalization

As-produced CNTs tend to bundle and are insoluble in most solvents, making them challenging to utilise in biological applications. Furthermore, certain CNTs

with no functionalization have been proven to be poisonous. CNTs must thus be functionalized before they may be integrated into biological systems. Functionalization can make carbon nanotubes soluble and increase their biocompatibility [34]. Surface functionalization of carbon nanotubes is done in two ways: covalent and non-covalent. [35]

Covalent Functionalization

In the process of covalent fictionalization, chemical processes are carried out to establish bonds with the sidewalls of nanotubes. Oxidation and carboxyl-based couplings are used in this functionalization approach. The tube cap apertures and perforations in the side walls are generated by an oxidation process using strong acids in this procedure.

The oxidation induced to the caps and side walls with carboxylic groups increases the solubility of CNTs in aqueous solutions in addition to opening tube caps and producing side wall holes. Through amide and ester bonds, the carboxylic groups allow for covalent interactions with other molecules. [36]

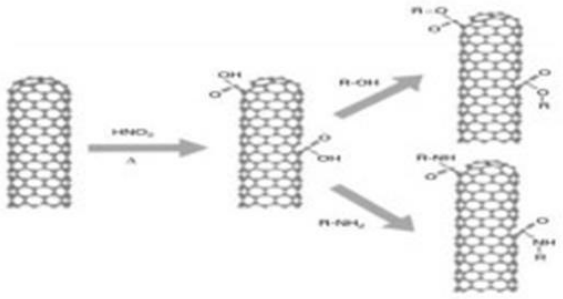


Figure 6: Functionalization of CNTs through oxidation followed by carboxyl-based couplings. The tubes are oxidized by a strong acid followed by the reaction of the carboxyl groups [37]

CNTs can be conjugated with a variety of functional groups using this approach. Importantly, CNTs can become soluble in aqueous or organic liquids by connecting with appropriate groups. The presence of carboxylic groups on the sidewalls of carbon nanotubes lowers Van der Waals interactions between the tubes, allowing nano-tube bundles to be divided into individual, isolated tubes.

Non-covalent functionalization of carbon nanotubes

Non-covalent functionalization has the benefit of not destroying the conjugated system of the CNTs sidewalls, and hence does not impact the final structural Characteristics of the material [38]. Non-covalent functionalization is an alternate approach for adjusting nano-tube interfacial characteristics. CNTs are

functionalized non-covalently by aromatic chemicals, surfactants, and polymers, mostly by - stacking or hydrophobic interactions. Non-covalent alterations of CNTs can accomplish a lot to retain their desirable characteristics while enhancing their solubilities dramatically in these procedures. Surfactants and polymers can be used to do functionalization. A surfactant's characteristic structural feature stems from its duality, namely the hydrophilic section of the molecule or the polar head group and the hydrophobic area or the tail group, which often consists of one or more hydrocarbon chains [39]. Adsorption of amphiphilic molecules at the interface of immiscible bulk phases, such as oil and water, air and water, or particles and solution, reduces surface tension [40]. Adsorption at the interface and self-accumulation into supramolecular structures are two significant characteristics of surfactants that are advantageously exploited in the manufacturing of stable colloidal dispersions. CNTs are frequently dissolved in amphiphilic polymers or soluble polymers. The primary advantage of utilising polymers rather than tiny molecule surfactants is that polymers lower the entropic cost of micelle production. Furthermore, certain conjugated polymers have a substantially greater energy of interaction with nanotubes than tiny molecules do. The fundamental issue for polymers is that interactions with mechanically hard SWNTs might cause them to adopt an energetically unfavourable conformation. Some polymers have been proposed to wrap around nanotubes in a helical pattern to decrease strain in various conformations [41].

Properties of Carbon Nanotubes

When compared to convectional materials, the electric and thermal characteristics are significantly improved. The enhanced capabilities of CNTs are attributable to the network's creation, which takes advantage of the tube's high aspect ratio between length and diameter. The development of networks also increases the mechanical characteristics of the matrices; for example, the basic material has tensile strength 20 times that of steel.

Another important attribute of CNTs is their ability to easily perforate cell membranes and enter into cellular components without causing visible cellular damage. Because of their long and thin form, Carbon Nanotubes resemble microscopic needles and can operate as needles at the cellular level. Medical researchers use this ability of CNTs by

attaching chemicals drawn by cancer cells to the nanotubes and delivering medications directly to the afflicted cells [42].

Carbon Nanotubes in Drug Delivery

A drug delivery system is intended to improve a drug molecule's pharmacological and therapeutic properties [43]. Carbon nanotubes are highly explored in the realms of effective medication delivery and tissue engineering approaches in today's world of medical research. Pure carbon nanotubes are insoluble. Techniques for functionalizing molecules with organic molecules and making them soluble cleared the path for medicinal uses. Because of their large surface area, they can absorb or conjugate with a wide range of medicinal compounds. CNTs can thus be surface engineered (i.e., functionalized) to improve their aqueous phase dispersibility or to offer the proper functional groups that can bind to the required therapeutic material or target tissue to trigger a therapeutic effect [44-47].

The functionalization also protects CNTs from being poisonous and from altering the function of immune cells. CNTs may aid in the penetration of the attached medicinal chemical into the target cell to treat illness. The vast interior capacity of tubes enables for the encapsulation of pharmaceuticals with both low and high molecular weight [48]. By filling the tubes with more than one medicament, CNTs can also be employed for multi-drug treatment. Furthermore, CNTs can function as a controlled release mechanism, releasing medications over time.

Use of Carbon Nanotubes Cancer therapy

Cancer is a category of disorders characterised by abnormal cell growth and division. It is one of the main illnesses being studied in terms of how it reacts to CNT medication delivery. Traditional cancer therapies include radiation, chemotherapy, and surgery. These treatments are beneficial in many situations, but they are unpleasant, destroy many healthy cells, and have negative side effects such as toxicity in the patient's body. Metastasis, or the spread of cancer from one organ or portion to another that is not nearby, is the leading cause of cancer mortality [49]. CNTs are regarded anticancer agents, and when combined with conventional medications, they can greatly boost their chemotherapeutic impact thanks to carbon nanotubes' superior drug delivery mechanism. Carbon

nanotubes and nano-horns have been explored in vitro for medication delivery. SWNTs that have been functionalized and solubilize may transport peptides, proteins, genes, and DNA across cell membranes with negligible cytotoxicity [50- 54].

However, it is crucial to assess the in vivo efficacy of CNTs loaded with anti-cancer medicines. Several prior investigations in animal models revealed in-vivo targeting of tumours using carbon nanotubes, but no medicines were delivered to the target location [57-58]. Lack of solubility, clumping, and half-life are further issues with carbon nanotube drug delivery systems [59]. CNT structure is being improved in order to alleviate these drawbacks. Carbon nanotubes may be made with or without end caps due to their tube structure. The medication stored inside CNTs without end caps would be more accessible. Additionally, drug encapsulation has been demonstrated to improve water dispersibility, Bio availability, and toxicity in Single Walled Carbon Nanotubes. Encapsulation of molecules also serves as a material storage application, as well as protection and controlled release of loaded molecules throughout time.

Targeted cancer cell destruction

Biological systems are very permeable to near-infrared (NIR) light ranging from 700 to 1,100 nm [60]. The significant absorbance of SWCNTs in this specific spectral window [61], which is an inherent feature of SWCNTs, can be exploited for optical stimulation of nanotubes inside live cells, allowing for multifunctional nanotube biological transporters. When oligonucleotides are carried within cells through nanotubes, NIR laser pulses cause endosome rupture, allowing the oligonucleotides to enter the cell nucleus. Continuous NIR radiation, on the other hand, can cause cell death in vitro due to excessive local heating of SWNTs. Selective cell destruction may be accomplished by the functionalization of SWNTs with a folate moiety, selective internalisation of SWNTs into cells tagged with folate receptor (FR) tumour markers, and NIR-triggered cell death, all while causing no harm to receptor-free normal cells [62]. The intrinsic physical features of SWNTs can thus be used to create new types of biological transporters with important functions for developing new drug delivery and cancer therapy approaches.

One of the major drawbacks of employing Carbon Nanotubes for medication delivery in the human body is the difficulty in

managing nanotube breakdown, which can result in unintended toxicity and tissue damage. CNTs can be physiologically broken down into harmless components, according to recent research.

Carbon nanotubes were originally thought to be bio persistent, meaning they did not degrade in biological tissue or in nature. According to studies, laboratory animals exposed to carbon nanotubes by inhalation or injection into the abdominal cavity experience significant inflammation. This, together with the tissue alterations (fibrosis) caused by exposure, results in reduced lung function and, perhaps, cancer. Other scientists' alarming studies claimed that carbon nanotubes are extremely comparable to asbestos fibres, which are highly persistent and may cause lung cancer (meso-thelioma) in people for a long period after exposure.

CONCLUSION

Carbon nanotubes outperform expectations, and their simple mechanism with extended life makes them more dependable to employ. Carbon Nanotubes in cancer therapy may promise up to 85% cure rate, which other therapies cannot offer, and having 100% site target with its body friendly nature adds to its benefit. CNTs' diverse qualities are the benefits that allow them to be used in a variety of applications. Organic functionalization has expanded our understanding of CNT biological characteristics. Carbon cylinders' biocompatibility has been determined. Because pure CNT are very poisonous and insoluble, the primary goal was to test CNT solubility in physiological fluids. Functionalized CNTs have a greater proclivity to traverse cell membranes, which is enabled by the needle-like shape of CNTs. CNTs can be loaded with physiologically active moieties, which are subsequently transferred to the nucleus of the cell. The chemistry of CNT allows for the simultaneous employment of many functions on the same tube, such as targeting molecules, contrast agents, medicines, or reporting molecules. The main issue with using CNTs for medication administration is the lack of control over the degradation. However, new study has discovered that MPO (Myeloperoxidase), a specific enzyme produced in certain types of white blood cells (neutrophils), may degrade Carbon Nanotubes into water and carbon dioxide, making them body friendly.

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