REVIEW ARTICLE

Carbon Nanotubes as Emerging Nanocarriers in Drug Delivery: An Overview

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ABSTRACT

Carbon nanotubes (CNTs) have been frequently acquired as one of the fascinating and advanced nanocarriers for drug delivery and many potential applications due to its unique physicochemical properties. During recent years CNTs have been attracted by many researchers as a drug delivery carrier. CNTs are the third allotropic form of carbon-fullerenes rolled into cylindrical tubes. To be integrated into the biological systems, CNTs can be chemically modified or functionalized with therapeutically active molecules by forming stable covalent bonds or supramolecular assemblies based on noncovalent interactions. Owing to their high carrying capacity, biocompatibility, and specificity to cells, various cancer cells have been explored with CNTs for evaluation of pharmacokinetic parameters, cell viability, cytotoxicity, and drug delivery in tumor cells.

Keywords: Carbon nanotubes, Drug delivery, Graphene, Tumor.

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INTRODUCTION

Carbon nanotubes (CNTs), allotropes of carbon with high aspect ratio were first described by the Japanese physicist, Sumio Iijima in 1991.[1] Tremendous interest in the study of CNTs has been generated ever since, with potential applications ranging from electronics, material engineering, as well as biomedical applications, especially in cancer cell imaging and drug delivery. CNTs are allotropes of carbon in a honeycomb-like lattice, and they are essentially 'rolled up' sheets of graphene with internal diameters of 1 nm.

Basically, CNTs are hollow cylinders of sp^2 hybridized carbon atoms that are basically rolled tubes of graphite terminated by two end caps. Its unique intrinsic physicochemical properties make them potential and most versatile candidates for biomedical applications. High mechanical strength, intense electrical properties, extreme-light weight, strong thermal conduction, and huge surface area, reflected CNTs as an ideal tool utilized in the field of materials science. CNTs have also emerged as optical biosensors and novel electronic device to recognize the biomolecules, such as peptide, nucleic acid, cells, proteins, and microorganisms. The credit for successful applications of CNTs goes to desired conductivity, specificity, selectivity, high aspect ratio, high porosity and loading, ease in surface modification, and non-toxicity.[2] Even, most frequently used cytotoxic agents are often required to improve their solubility, rapid clearance, ability to cross cell membranes, limited biodistribution, and receptor-type conjugates that lead to a targeted organ.[3]

STRUCTURE AND TYPES OF CARBON NANOTUBES (CNTs)

The CNTs are a subset of the fullerene family, and the chemical bonding of each carbon atom to each other is via sp^2 orbital hybridization. Orbital hybridization is the arrangement of the orbitals of atoms during chemical bond-formation. In contrast to sp^2 hybridization, an example of sp^3 hybridization is the arrangement of carbon atoms in diamond, while sp hybridization is observed in carbyne. CNTs can be visually conceptualized by 'rolling-up' a sheet of graphene (a planar sheet of sp^2 orbital hybridized carbon atoms) in 3D space.[4] However, once CNTs are functionalized at their surface/tips, the sp^2 hybridization switches to sp^3. The CNTs, also known as tubular fullerenes, are cylindrical graphene sheets of sp^2-bonded carbon atoms. In CNTs, the graphene sheet is rolled upon itself to form different allotropes of carbon, including graphite, fullerenes, and CNTs.[5]

Depending on the number of sheets rolled into concentric cylinders, there are 4 broad categories of CNTs, namely, single-walled (SWCNTs), double-walled (DWCNTs), triple-walled (TWCNTs), and multi-walled (MWCNTs) (Figure 1).[6]

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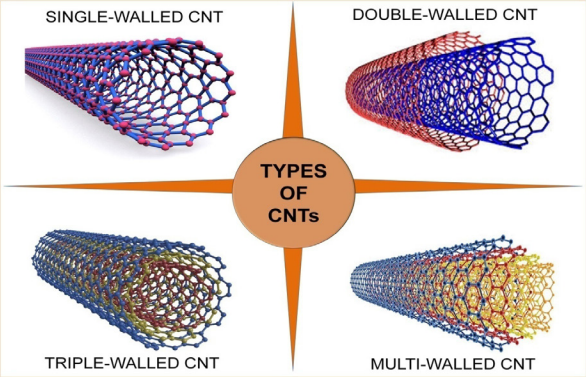

Figure 1: Types of CNTs

SWCNTs are made of a single graphene sheet rolled upon itself with a diameter of 1-2 nm. The length can vary depending on the preparation methods. SWCNTs are made up of a single graphene layer wrapped into a hexagonal close-packed cylindrical structure whose diameter varies from 0.4 to 3 nm, and length ranges from 20 to 1,000 nm, and are held together by van der Waals forces, which makes them easily twistable and more pliable. SWCNTs are produced by the electric are[7] laser ablation,[8] chemical vapor deposition (CVD),[9] and gas-phase catalytic processes (HiPco or high-pressure CO conversion).[10] DWCNTs are made of two concentric CNTs in which the outer tube encloses the inner tube. The presence of three graphene sheet layers indicates TWCNTs. The MWCNTs consist of multiple layers of graphene rolled upon itself with diameters ranging from 2 to 50 nm, depending on the number of graphene tubes. These tubes have an approximate inter-layer distance of 0.34 nm.[6] MWCNTs consist of several coaxial cylinders, each made of a single graphene sheet surrounding a hollow core. The outer diameter of MWCNTs ranges from 2 to 100 nm, while the inner diameter is in the range of 1-3 nm, and their length is one to several micrometers.[11] Electric arc and CVD are the main techniques for their production. Owing to the sp^2 hybridization in MWCNTs, a delocalized electron cloud along the wall is generated, which is responsible for the π-π interactions between adjacent cylindrical layers in MWCNTs resulting in a less flexible and more structural defects.[12]

SYNTHESIS METHODS OF CARBON NANOTUBES (CNTs)

In the quest to synthesize high-quality CNTs at scale, different techniques have been proposed and established over the past two decades. Carbon nanotubes can be synthesized in two forms: on substrate and as powder (substrate free). The former includes vertically aligned CNTs, which are generally used in sensors and electronic devices. The most popular and widely used nanotube synthesis techniques are arc discharge, laser ablation, and chemical vapor deposition. Apart from these methods, electrolysis, flame synthesis, pyrolysis, hydro-thermal synthesis, ball milling, and HiPCO methods have also been used.[13] Various methods used for the synthesis of CNTs on a large scale are described in the following section[14]:

Flame Synthesis Method

The flame synthesis method employs hydrocarbon (e.g., CH_4, C_2H_2, C_2H_4, C_2H_6, etc.) flame, which helps the initiation and growth of CNTs. The flame supports endothermic carbon deposition reactions and solid black carbon deposits on the catalysts. However, the synthesis of CNTs in larger amounts depends on the appropriate catalyst, flame, and reaction conditions.[15] Although any of the aforementioned methods can synthesize CNTs, currently, the electric arc and laser ablation processes are the best methods available to synthesize the ideal nanotubes. They can be purified by chemical as well as physical methods. The drawback associated with these techniques is that it is not scalable, which has created a bottleneck in the research and development of CNTs.

Pyrolysis

A nebulized spray pyrolysis technique has also been utilized for the synthesis of MWCNTs with quite consistent diameters in aligned bundles. At 800°C, ferrocene (catalyst), and ethanol (solvent and carbon source) are sprayed by an ultrasonic nebulizer into a tubular furnace. The advantage of this technique is the easy scaling for production due to the constant feed of the reactants into the furnace.[16]

Electrolysis

The electrolysis method is used less commonly for the synthesis of CNTs. Here, MWCNTs are synthesized by passing current through two electrodes immersed in molten ionic salts, such as LiCl, at 600ºC followed by extraction of carbon matter by dissolving the ionic salt in distilled water. The synthesized MWCNTs have 10-15 walls with 10-20 nm diameter and length > 500 nm.[17]

Laser Ablation Method

In the laser ablation method, a constant high-power laser is used to vaporize graphite targets inside a furnace at 1,200°C temperature with argon or helium gas at 500 torr pressure. The CNTs synthesized using this method have fewer structural defects, high purity, controlled size, as well as chirality, with approximately 70% yield. This method is used for the synthesis of both SWCNTs and MWCNTs. CNTs with high crystallinity can be produced with this method. However, amorphous carbon, catalysts, and fullerenes are present in the final product.[18]

Electric Arc Discharge (EAD) Method

This method is based on the vaporization of carbon in an inert atmosphere (helium or argon) from a graphite cathode heated by an applied current. In this method, the application of high-voltage current (50-100 amps) and high pressure (50-700 mbar) generates high-temperature discharge between two electrodes placed 1 mm apart, and carbon rods evaporate and are deposited on the cathode as rod-shaped tubes. Various metal catalysts like Fe, Ni, Rh, Pt, or Co are used for the synthesis of SWCNTs. The properties of CNTs may be modulated by varying the current intensity and by introducing catalysts in the cathode.[19]

BIOMEDICAL APPLICATIONS OF CARBON NANOTUBES (CNTs)

Transdermal Drug Delivery (TDD)

A TDD system is defined as a self-contained, discrete dosage form, also known as a "patch."[20] The main objective of a TDD system is to deliver drugs into systemic circulation through the skin at a predetermined rate with minimal inter- and intra-patient variation.[21] CNTs are not directly incorporated inside the organism, but in these systems, those are applied outside the stratum corneum of the skin, and only the active pharmaceutical ingredient is intended to cross the body barriers.[22] Kang *et al.* prepared and characterized CNT-framed membranes that were prepared by self-assembly of highly thermoconductive CNT molecules hybridized with chitosan, and they concluded that membranes indicating highly effective drug-loading/ -releasing characteristics could have a potential use as a skin heat signal responsive patch-type TDD system in the medicinal field.[23] Similarly, drug-loaded bucky papers were prepared based on different types of CNTs and were characterized; they present a potential for their use in the development of novel transdermal delivery systems. Also, a major step in the development of a programmable TDD system was the CNT patch. A novel skin patch device for delivering nicotine based on an active layer of aligned CNTs approximately 1.5-7 nm in diameter crossing through a solid polymer film was developed and proved effective.[24]

Cancer Therapy

Cancer is the second leading cause of human death worldwide, with an expected 7.6 million people die every year, which represents 13% of total deaths. The current situation of cancer prevalence will be worse in the near future, and cancer-related mortality is expected to increase by 13.1 million till 2030.[25] Many patients who succumb to death due to cancer do not die as a result of the primary tumor, but because of the systematic effects of metastases on the other regions away from the original site. One of the aims of cancer therapy is to prevent the metastatic process as early as possible. Therefore, significant amounts of research have been carried out to overcome these problems. The main problem incurred with various chemotherapies for treating cancer is the lack of selectivity of the anticancer drug towards cancer cells.[26]

CNTs provide larger internal as well as external surface areas for the greater attachment of drugs. Furthermore, functionalization boosts the attachment of drugs and targeting moieties on the outer surface of CNTs. The biocompatible coating of CNTs with polyethylene glycol (PEG), poly-(glycolide) (PGA), and poly-(lactide) (PLA) in single or multiple layers enhances the loading of the drug along with improving biocompatibility.[27]

The physical and chemical properties of CNTs are associated with the structure, surface area, mechanical strength, metallic behavior, electrical and thermal conductivity, and ultra-lightweight. CNTs are a suitable candidate for enormous biomedical applications due to a vast number of characteristic physical and chemical properties. CNTs absorb light of near-infrared (NIR) region that results in heating of the nanotubes, this property is known as a thermal effect which has been used to target the cancer cells.[28] In cancer cells, overexpression of folic acid (FA) receptors takes place and various research groups have prepared engineered nanocarriers having FA derivative conjugated biomaterials. Moreover, it has been demonstrated that CNTs are retained in the lymph nodes for longer periods of time as compared to spherical nanocarriers. In another study, researchers loaded the gemcitabine (anticancer molecule) into magnetic MWNTs and injected subcutaneously in mice and reported the high activity against lymph node.[29] CNTs can identify the surface receptors that result in receptor-mediated endocytosis of CNTs upon interaction of drug delivery systems with cancer cells. CNTs-based drug delivery enhances the bio-distribution and blood circulation of therapeutics, so it causes decreased usage dose and increased pharmaceutical efficacy.

Taking consideration of prolonged blood circulation due to CNTs, Liu and colleagues made DOX-loaded branched PEG functionalized SWNTs and injected the SWNT-DOX complex to the tumor site in mice. They found that DOX can be delivered into tumors, and SWNTs can be cleared from systemic blood circulation via renal excretion. Paclitaxel (PTX) is a chemotherapy drug used to treat various cancers, but the poor solubility of PTX in aqueous solution makes the physical loading of PTX difficult at targeted tumor site.[30] To overcome this problem, Lay and co-worker made PEG-graft SWCNTs and PEG-graft MWCNTs enhance the loading ability, and they found that the delivery of PTX can be persistent over 40 days *in vitro*.[31] In addition, researchers have modified SWCNTs as the Epidermal Growth Factor (EGF) mediated SWCNT carrier to improve the drug delivery efficiency of anticancer agents. MWNTs can be used for thermal ablation as a carbon based nanomaterial which results in hyperthermia for destroying cancer cells. The cancer cells absorb the CNTs complex and release the chemotherapeutic agents into intracellular space so that the drugs can more effectively control the spreading of cancer cells. So the CNTs based drug delivery approach has various advantages such as minimal side-effects, and decreased cytotoxicity decreased as well.[32] SWCNTs showed a higher ability of drug loading as compared to the traditional liposomes and dendrimer drug carriers because of the high specific surface area.[26]

As Catalyst

A catalyst at the molecular level can be incorporated into nanotubes in large amounts and can be released at a required rate at a particular time, as nanohorns offer a large surface area. Many researchers have proved this application. Shi *et al.* synthesized graphene-encapsulated Fe_3C embedded in CNTs with direct pyrolysis of renewable biomass, and this catalyst proved very active for selective hydrogenation of C-C bond in several compounds.[33] In similar research, nitrogen-doped CNT platinum-based catalyst supports were prepared, which were synthesized using a self-degraded template method. It

was concluded that using the graphene-encapsulated Fe_3C CNTs as support greatly reduces the loading of noble metal platinum, further promoting the commercialization process of proton exchange membrane fuel cells.[34] So, CNTs have an application as a catalyst.

Infection Therapy

The CNTs have found application in this case because of the resistance of infectious agents against numerous antiviral and antibacterial drugs or due to certain vaccine inefficacy in the body. Functionalized CNTs have been demonstrated to be able to act as carriers for antimicrobial agents such as the antifungal amphotericin B. The CNTs can attach covalently to amphotericin B and transport it into mammalian cells, and this conjugate has reduced the antifungal toxicity about 40%, as compared to the free drug.[35] Jiang *et al.* have successfully combined an antimicrobial agent, pazufloxacin mesilate, with amino-MWCNT with high adsorption, which will be applied to experimental assays for infection treatment. Functionalized CNTs also have a role in antigen delivery and in the field of vaccination. There is an induced antibody response with a right specificity, as the linkage of a bacterial or viral antigen with CNTs permits keeping an intact antigen conformation. The MWCNTs functionalized with recombinant Dengue Virus 3 envelop proteins induced specific as well as significant immune responses in mice. The fixation of functionalized CNTs with B and T cell peptide epitopes can generate a multivalent system that is able to induce a strong immune response; thereby, CNTs turn out to be a good candidate for vaccine delivery. Besides, CNTs themselves might have antimicrobial activity since bacteria may be adsorbed onto the surfaces of CNTs.[36]

In a research, SWCNTs were used for antimicrobial activity, and it was demonstrated that bacterial death was the result of the direct contact with CNT aggregates. The antibacterial effect was attributed to CNT-induced oxidation of the intracellular antioxidant glutathione, resulting in increased oxidative stress on the bacterial cells and eventual cell death. So, CNTs are also potential candidates as building blocks of antimicrobial agents. The antimicrobial activity of carbon-based nanostructures may be investigated in the near future owing to their large inner volume, high surface/ volume ratio, and other unique properties. In addition, application of functionalized carbon nanomaterials as carriers for the ordinary antibiotics will possibly enhance their bioavailability, decrease the associated resistance, and provide their targeted delivery.[37]

Genetic Engineering

The CNTs are used to manipulate genes and atoms in the development of bioimaging genomes, proteomics, and tissue engineering. Gene therapy is an approach to correct a defective gene that causes some chronic or hereditary diseases by introducing a DNA molecule into the cell nucleus.[38] The unwound DNA winds around the SWCNT by connecting its specific nucleotides and causes change in its electrostatic property. Wrapping of CNTs by single-stranded DNA was found to be sequence-dependent so that it can be used in DNA analysis. Nanotubes, due to their unique cylindrical structure and properties, are used as carriers for genes to treat cancer and genetic disorders.[39] Their tubular nature has proved them as a vector in gene therapy. Nanotubes complexed with DNA were found to release DNA before it was destroyed by a cell's defense system, boosting transfection significantly. Nanostructures have shown an antiviral effect in respiratory syncytial virus, a virus with severe bronchitis and asthma. The treatment is generally done by combining nanoparticles and gene-slicing technologies. RNA fragments capable of inhibiting a protein are encapsulated within nanotubes and administered in the form of nasal sprays or drops. Nanotubes are reported for helical crystallization of proteins and growth of embryonic rat brain neurons. Recent research has reported a novel CNT-based device that supports cell growth and enables high-efficiency gene transfection through the lumens of CNTs into cells within a short period of time. This device provides the ability to accommodate a wide range of sizes of biomolecules, from 0.66 kDa (propidium iodide) and 3 kDa (tetramethyl rhodamine dextran) to 3900 kDa (6000 bp plasmid DNA).[39] The possibility of using nanocarriers based on MWCNTs and SWCNTs to deliver genetic material into mesophyll protoplasts, callus cells, and leaf explants was also reported. Hence, CNTs have found applications in plant genetics transformation for use in agriculture.[24]

TOXICITY ASPECTS OF CARBON NANOTUBES (CNTs)

The CNTs required very pure and well-characterized materials for biological application. Whether that may be length-diameter, the number of walls, metal contaminants, chirality, level of modification, or accuracy. Purification is important challenge since its discovery.[40] However, post-manufacturing processes like (partial) removal of metallic contaminants can control further changed in physicochemical properties of the original CNTs.[41] To developed hydrophilicity, functional side groups (such as carboxyl and hydroxyl groups) are predictably applied to the CNT surface.[42]

Functional groups and the surface area are strongly associated with the pharmacokinetics, fate, and toxicity of CNTs. Singh and his collogue reported with high-level radioactivity detection in the skin, kidney, muscle, and blood, observed after 30 mins of water-soluble functionalized SWCNT administration with the chelating molecule diethylentriaminepenta acetic (DTPA). However, rapid elimination from systemic blood circulation through the renal excretion route occurred within 3 hours.[43] In addition, surface modifications of CNTs are able to alter the interaction process with the cellular lipid bilayer, which significantly changed in the cell uptake and viability. Despite that, another group of researchers obtained conflict in results where the acid-treated SWCNTs and unpurified SWCNTs were found aggregated within lysosomes but more significantly in the cytoplasm of human cells, causing cell mortality in a dose-dependent manner. *In vitro* studies of all pristine and modified SWCNTs had partial toxicity on endothelial cells measured by morphology and metric-related characteristics

like surface area, particle size, chemical composition, growth, and survival assays. Mayer *et al.* suggested that negatively charged nanoparticles (NP) with the hydrodynamic diameter ≤ 60 nm are low hematotoxic than lesser ones. Binding of NP with plasma protein can be affected by surface charge. The cationic surface is moderately toxic, whereas anionic surface is non-toxic. The cationic surface also cause platelet aggregation and hemolysis.[44,45]

CONCLUSION AND FUTURE PROSPECTIVES

The CNTs are providing a number of opportunities in different fields of applications such as genetic engineering, artificial implants, sensors, therapeutics, and drug delivery. There are a number of factors such as size, structure, and shape that affect the properties of nanotubes and, ultimately, their application. The functionalization of CNTs has made it possible to utilize them in many more applications. Drug delivery systems are one such application where the treatment of diseases like cancer has been made more accurate. The success of these applications largely depends on the toxicity of CNTs to human beings as well as the environment. With the increasing utilization of CNTs, research is needed to know their toxicity**.**

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