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Review

Carbon Nanotubes and Its Applications in Medical Science: A Review

Author: Mr.Debesh Nandan Rath, Lecturer in Physics,
Affiliation: G.Sc College, Athgarh
Corresponding E-mail: debeshnandan@gmail.com

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Abstract: With the prospect of gene therapy, cancer treatments, and innovative new answers for life-threatening diseases on the horizon, the science of nanomedicine has become an ever-growing field that has an incredible ability to bypass barriers. The properties and characteristics of CNTs are still being researched heavily and scientists have barely begun to tap the potential of these structures. Single and multiple walled carbon nanotubes have already proven to serve as safer and more effective alternatives to previous drug delivery methods. They can pass through membranes, carrying therapeutic drugs, vaccines, and nucleic acids deep into the cell to targets previously unreachable. They also serve as ideal non-toxic vehicles which, in some cases, increase the solubility of the drug attached, resulting in greater efficacy and safety. Overall, recent studies regarding CNTs have shown a very promising glimpse of what lies ahead in the future of medicine.

Keywords: MWNTs, Plasma Temperature, Pharmacokinetics, Nanoscale Dimensions, Biosensors, Membranes, Nanomedicine

Production of MWNTs

MWNTs are produced with the use of pure graphite arc with an inner diameter 1-3nm and outer diameter10nm (approx.). Since catalyst is not used in this process there is no need for a heavy acidic purification. So, MWNTs can be formed with a less number of defects. Different methods used to synthesize are

Plasma Rotating Arc Discharge

The centrifugal force caused by the rotation generates turbulence and accelerates the carbon vapor perpendicular to the anode and the rotation distributes the micro discharges uniformly and generates stable plasma. Consequently, it increases the plasma volume and raises the plasma temperature. At the rotation speed of 5000 rpm, a yield of 60 % was found at a temperature 1025 °c without the use of a catalyst. The yield can be increased up to 90% after purification if the rotation speed is increased and the temperature is enlarged.

Magnetic Field Synthesis

MWNTs formed by this method are defect free and having high purity. In this arc- discharge is controlled by a magnetic field around the arc plasma. Extremely pure graphite rods (purity > 99.999 %) are used as electrodes. Highly pure MWNTs (purity > 95 %) are obtained without further purification, which disorders walls of MWNTs.

Synthesis in Liquid Nitrogen

MWNTs are formed by generating arc-discharge in liquid nitrogen. For which low pressure and expensive inert gas are not needed. Yield is about 70% of reaction product.

PURIFICATION OF CNTs

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

Air Oxidation:

The carbon nanotubes are having less purity; the average purity is about 5- 10%. So purification is needed before attachment of drugs onto CNTs. Air oxidation is useful in reducing the amount of amorphous carbon and metal catalyst particles (Ni, Y). Optimal oxidation condition is found to be at 673 k for 40 min.

Acid Refluxing

Refluxing the sample in strong acid is effective in reducing the amount of metal particles and amorphous carbon. Different acids used were hydrochloric acid (HCl), nitric acid (HNO3) and sulphuric acid (H_2SO4), but HCl was identified to be the ideal refluxing acid.

Surfactant Aided Sonication, Filtration and Annealing

After acid refluxing, the CNTs were purer but, tubes were entangled together, trapping most of the impurities, such as carbon particles and catalyst particles, which were difficult to remove with filtration. So surfactant-aided sonication was carried out. Sodium dodecyl benzene sulphonate (SDBS) aided sonication with ethanol (or methanol) as organic solvent were preferred because it took the longest time for CNTs to settle down, indicating an even suspension state was achieved. The sample was then filtered with an ultra filtration unit and annealed at 1273 k in N2 for 4 h. Annealing is
effective in optimizing the CNT structures. It was proved the surfactant-aided sonication is effective to

untangle CNTs, thus to free the particulate impurities embedded in the entanglement. Nanotube can also be purified by multi-step purification method.

Functionalisation of CNTs

For biological and biomedical applications, the lack of solubility of carbon nanotubes in aqueous media has been a major technical barrier. To overcome this problem the modification of the surface of CNT i.e. fictionalization is done. With different molecules it is achieved by adsorption, electrostatic interaction or covalent bonding of different molecules and chemistries that render them more hydrophilic. Through such modifications, the water solubility of CNT is improved and their biocompatibility profile is completely transformed. Moreover, the bundling/aggregation of individual tubes through vander Waals forces are also reduced by the fictionalization of their surface. The recent expansion in methods to chemically modify and functionalize carbon nanotubes has made it possible to solubilize and disperse carbon nanotubes in water, thus opening the path for their facile manipulation and processing in physiological environments. Equally important is the recent demonstration that biological and bioactive species such as proteins, carbohydrates, and nucleic acids can be conjugated with carbon nanotubes. These nanotube bioconjugates will play a significant role in the research effort toward bioapplications of carbon nanotubes. One focal point has been the development of nanoscale bioelectronics systems based on carbon nanotubes, which has been driven by the experimental evidence that biological species such as proteins and DNA can be immobilized either with the hollow cavity of or on the surface of carbon nanotubes. Concerning the intrinsic toxicity of CNT, in vitro studies had indicated that SWNT functionalized by a covalent method with phenyl-SO3H or phenyl- (COOH)2 groups produced less cytotoxic effects than aqueous dispersions of pristine SWNT stabilised with a surfactant— 1% of Pluronic F108 . Moreover, in the same study, the cytotoxicity of covalently modified SWNT has been reported to be further decreased with the increase in the degree of sidewall fictionalization.

PHARMACOLOGY OF CNTs

The biodistribution and pharmacokinetics of nanoparticles rely to a large extent on their physicochemical characteristics such as size, shape, aggregation, chemical composition, surface fictionalization and solubility 24-25. Two studies have been reported so far concerning the bio distribution of CNT. Both studies were performed with water-soluble CNT, which are biocompatible with the body fluids. None of the studies report toxic side effects or mortality. Wang et al.26 have used 125Iodinelabeled multiple hydroxylated SWNT (125I-SWNT-OH), functionalized by oxidation of the nanotubes, and radio traced their distribution in mice after administration by, primarily, intraperitoneal (i.p.) administration. Other routes of administration were compared to i.p. such as subcutaneous, oral (by stomach intubation) and intravenous. This study reported that the CNT bio distribution was not significantly influenced by the administration route and that the 125ISWNT-OH distribute quickly throughout the whole body. The preferred organs for accumulation were the stomach, kidneys and bone. Most importantly from the safety point of view, 94% of the nanotubes were excreted into the urine and 6% in the feces as observed in this study. No tissue damage or distress was reported. Second study, focusing on the intravenous route of administration and using functionalized SWNT and MWNT following a different surface chemistry (i.e. via the 1, 3-dipolar cycloaddition reaction) compared to the SWNT used in the study by Wang et al., was performed27. The CNT were functionalized with the chelating molecule diethylene triaminepentaacetate (DTPA) and radio labeled with 111Indium ([111In] DTPA-CNT). In this study, the effect on biodistribution and blood circulation half lives of different degrees of surface fictionalization with DTPA was also studied, using 100% and 60% surface fictionalization with DTPA (the remaining 40% functional group were amino functions). The biodistribution profiles obtained were found very similar for both types of functionalized DTPA-SWNT which showed an affinity for kidneys, muscle, skin, bone and blood 30 min after administration. However, all types of nanotubes were found to be rapidly cleared from all tissues and a maximum blood circulation half-life of 3.5 h was determined. The excretion of DTPACNT, both SWNT and MWNT functionalized with 100% DTPA were found to be excreted through the renal route into the bladder and urine following intravenous administration. Moreover, both types of DTPA-CNT were observed intact in the excreted urine by transmission electron microscopy.

TOXICITY OF CNTs

Generally, the harmful effects of nanoparticles arise from the combination of various factors, two of which are particularly important:

The high surface area and (b) the intrinsic toxicity of the surface. In contrast with conventional particles of larger mean diameter, nanoparticles under 100 nm can potentially be more toxic to the lung (portal of entry), can redistribute from their site of deposition, can escape from the normal phagocytic defences and can modify the structure of proteins. Therefore, nanoparticles can activate inflammatory and immunological responses and may affect the normal tissue function. CNT, in the context of toxicology, can be classified as 'nanoparticles' due to their nanoscale dimensions, therefore unexpected toxicological effects upon contact with biological systems may be induced. The nanometer-scale dimensions of CNT make quantities of milligrams possess a large number of cylindrical, fibre-like particles, with a concurrent very high total surface area. This total surface area will also depend on their degree of bundling and aggregation of nanotubes in solution. The intrinsic toxicity of CNT depends on the degree of surface fictionalization and the different toxicity of functional groups. Batches of pristine CNT (non-purified and/or non functionalised) readily after synthesis contain impurities such as amorphous carbon and metallic nanoparticles (catalysts: Co, Fe, Ni and Mo), which can also

be the source of severe toxic effects. Donaldson et al. have shown that the structural characteristics of nanomaterials, such as the fibre shape, the length and the aggregation status of the CNT, can also influence their local deposition in the lungs and the immunological response following exposure to CNT. Another important factor is the bioavailability of CNT in the body.

The mechanism of CNT metabolism, degradation or dissolution, clearance and bioaccumulation requires attention and study in order to obtain a clearer idea of the limitations of such nanomaterials as components of pharmaceuticals. So far the vast majority of reports published on the administration of CNT are primarily concerned with the toxicology of CNT, addressing the possible negative side effects of this nanomaterial on human health and environment, and particularly from the point of view of public health and safety for CNT production plant workers. As large-scale manufacturing gradually becomes routine for the production of CNT, handling and exposure (dermal and pulmonary) of workers to CNT brings exposure-risk issues to the surface. Maynard et al.30 have studied the release of particles from unrefined SWNT material into the air and the potential routes of exposure of the workers in a small-scale production facility. They have found that handling of unrefined material produces airborne particle concentrations of 53 μg/m3 and glove deposits of 0.2–6 mg per hand.

APPLICATIONS OF CNTs

Various applications of CNTs are as follows:

1. Carrier for Drug delivery: Carbon nanohorns (CNHs) are the spherical aggregates of CNTs with irregular horn like shape. Research studies have proved CNTs and CNHs as a potential carrier for drug delivery system.

2. Functionalized carbon nanotubes are reported for targeting of Amphotericin B to Cells.

3. Cisplatin incorporated oxidized SWNHs have showed slow release of Cisplatin in aqueous environment. The released Cisplatin had been effective in terminating the growth of human lung cancer cells, while the SWNHs alone did not show anticancer activity

4. Anticancer drug Polyphosphazene platinum given with nanotubes had enhanced permeability, distribution and retention in the brain due to controlled lipophilicity of nanotubes.
5. Antibiotic, Doxorubicin given with nanotubes is reported for enhanced intracellular penetration.

6. The gelatin CNT mixture (hydro-gel) has been used as potential carrier system for biomedical.

7. CNT-based carrier system can offer a successful oral alternative administration of Erythropoietin (EPO), which has not been possible so far because of the denaturation of EPO by the gastric environment conditions and enzymes.

8. They can be used as lubricants or glidants in tablet manufacturing due to nanosize and sliding nature of graphite layers bound with van der waals forces.

Genetic Engineering

In genetic engineering, CNTs and CNHs are used to manipulate genes and atoms in the development of bioimaging genomes, proteomics and tissue engineering. The unwound DNA (single stranded) winds around SWNT by connecting its specific neucleotides and causes change in its electrostatic property. This creates its potential application in diagnostics (polymerase chain reaction) and in therapeutics. Wrapping of carbon nanotubes by single-stranded DNA was found to be sequence-dependent, and hence can be used in DNA analysis. Nanotubes due to their unique cylindrical structure and properties are used as carrier for genes (gene therapy) to treat cancer and genetic disorders.

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 cells defense system, boosting transfection significantly. Nanostructures have showed antiviral effect in respiratory syncytical virus (RSV), a virus with severe bronchitis and asthma34. The treatment is generally done by combining nanoparticles and gene slicing technologies. Here RNA fragments capable of inhibiting a protein (which is needed for virus multiplication) is encapsulated within nanotubes and administered in the form of nasal sprays or drops. The promising results have been noted inhibiting further growth of virus34. Nanotubes are reported for helical crystallization of proteins and growth of embryonic rat brain neurons. Streptavidin protein is successfully immobilized on CNT via 1-pyrene butanoic acid and succinimidyl ester. Nanotubes and nanohorns can adhere various antigens on their surface, hence act as source of antigen in vaccines. Hence, by use of nanotubes, use of dead bacteria as source for antigen which is sometimes dangerous can be avoided.

Biomedical Applications

Bianco et al. have prepared soluble CNTs and have covalently linked biologically active peptides with them. This was demonstrated for viral protein VP1 of foot mouth disease virus (FMDV) showing immunogenicity and eliciting antibody response. In chemotherapy, drug embedded nanotubes attack directly on viral ulcers and kills viruses. No antibodies were produced against the CNT backbone alone, suggesting that the nanotubes do not possess intrinsic immunogenicity. Combination of all the described features of the vaccine system with the fact that the capacities of the anti-peptide antibodies to neutralize FMDV have been enhanced has indicated that CNT can have a valuable role in the construction of novel and

effective vaccines. In vitro studies by Kam et al. showed selective cancer cell killing obtained by hyperthermia due to the thermal conductivity of CNT internalized into those cells. The work developed regarding the use of CNT as gene therapy vectors have shown that these engineered structures can effectively transport the genes and drugs inside mammalian cells. The CNT-transported genetic material has conserved the ability to express proteins.

Artificial Implants

Normally body shows rejection reaction for implants with the post administration pain. But, miniature sized nanotubes and nanohorns get attached with other proteins and amino acids avoiding rejection. Also, they can be used as implants in the form of artificial joints without host rejection reaction. Moreover, due to their high tensile strength, carbon nanotubes filled with calcium and arranged/grouped in the structure of bone can act as bone substitute.

Preservative

Carbon nanotubes and nanohorns are antioxidant in nature. Hence, they are used to preserve drugs formulations prone to oxidation. Their antioxidant property is used in antiaging cosmetics and with zinc oxide as sunscreen dermatological to prevent oxidation of important skin components.

Diagnostic tool

Protein-encapsulated or protein/enzyme filled nanotubes, due to their fluorescence ability in presence of specific bimolecules have been tried as implantable biosensors. Even, nanocapsules filled with magnetic materials, radioisotope enzymes can be used as biosensors38. Nanosize robots and motors with nanotubes can be used in studying cells and biological systems.

As Catalyst

Nanohorns offer large surface area and hence, the catalyst at molecular level can be incorporated into nanotubes in large amount and simultaneously can be released in required rate at particular time. Hence, reduction in the frequency and amount of catalyst addition can be achieved by using CNTs and CNHs.

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.

Conclusion:

With the prospect of gene therapy, cancer treatments, and innovative new answers for life-threatening diseases on the horizon, the science of nanomedicine has become an ever-growing field that has an incredible ability to bypass barriers. The properties and characteristics of CNTs are still being researched heavily and scientists have barely begun to tap the potential of these structures. Single and multiple walled carbon nanotubes have already proven to serve as safer and more effective alternatives to previous drug delivery methods. They can pass through membranes, carrying therapeutic drugs, vaccines, and nucleic acids deep into the cell to targets previously unreachable. They also serve as ideal non-toxic vehicles which, in some cases, increase the solubility of the drug attached, resulting in greater efficacy and safety. Overall, recent studies regarding CNTs have shown a very promising glimpse of what lies ahead in the future of medicine.

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