INTERNATIONAL RESEARCH JOURNAL OF PHARMACY
www.irjponline.com
ISSN 2230 – 8407

Review Article

PRODUCTION, PURIFICATION AND FUNCTIONALIZATION OF CARBON NANOTUBES FOR MEDICAL APPLICATIONS

Yonas Brhane * and Tesfaye Gabriel
Department of Pharmaceutics and Social Pharmacy, School of Pharmacy, College of Health Sciences,
Addis Ababa University, P. O. Box 1176, Addis Ababa, Ethiopia
*Corresponding Author Email: Yonipharm2001@yahoo.com

Article Received on: 01/05/16 Revised on: 10/06/16 Approved for publication: 11/07/16

DOI: 10.7897/2230-8407.07780

ABSTRACT

Carbon nanotubes (CNTs) are needle-like potential carriers of bioactive including drug, genes and proteins. This review considers several techniques that have been developed for fabricating, purifying and functionalizing CNT structures. Commonly, three techniques are being used for producing CNTs: the carbon arc-discharge technique; the laser-ablation and chemical vapor deposition (CVD) technique. Carbon nanotube usually contains a large amount of impurities such as metal particles, amorphous carbon, and multishells. So purification is needed before attachment of drugs onto CNTs. Depending on technique of their synthesis and types of nano tubes, there are many different methods and procedure for purification. Almost all purification procedures have the following main steps: deletion of large graphite particles and aggregations with filtration, dissolution in appropriate solvents to eliminate catalyst particles (concentrated acids as solvent) and fullerenes (use of organic solvents), and microfiltration and chromatography to size separation and remove the amorphous carbon clusters. Generally there are two methods of carbon nanotube purifications these are chemical method and physical methods. Raw carbon nanotubes have highly hydrophobic surfaces, and are not soluble in aqueous solutions. For medical applications, surface chemistry modifications or functionalization is required to solubilize CNTs in aqueous solvent, improve biocompatibility and to decrease the toxicity of CNTs to the normal cells.

Keywords: carbon nanotubes, arc-discharge, the laser-ablation, chemical vapor deposition, purifications, functionalization.

INTRODUCTION

Delivering of drugs to the target site is a major problem in treatment of many diseases by using conventional methods. This approach is also characterized by limited effectiveness, poor bio-distribution, and lack of selectivity. These limitations and drawbacks can be overcome by using control and targeted drug delivery systems. In controlled and targeted drug delivery systems, the drug is transported to the site of action thus; its influence on vital tissues and undesirable side effects can be minimized. In addition, advanced and targeted drug delivery systems can protect the drug from rapid degradation or clearance and enhance drug concentration in target tissues enabling economical utilization of important drugs.[1]

Such controlled and targeted therapy can be achieved through nanosized structures; such as Liposomes, solid lipids nanoparticles, dendrimers, polymers, nanoemulsions, nanocapsules, nano fibers, ceramic nanoparticles, metalic nanoparticles and carbon nanotubes (CNT)that deliver drugs to specific sites.[2]

These nanosized structures have unique physical and chemical properties such as large specific surface area, excellent electrical and thermal conductivity and high mechanical strength. Their size also allowing them to penetrate through network of vessels to a target site and their non-immunogenicity and biocompatibility such and other characteristics make them preferable drug delivery systems.[3,4]
Carbon nanotubes (CNTs) are needle-like potential carriers of bioactive including drug, genes and proteins.[5] This paper examines several techniques that have been developed for fabricating CNT structures which mainly involve gas phase processes. Commonly, three techniques are being used for producing CNTs: the carbon arc-discharge technique; the laser-ablation and chemical vapor deposition (CVD) technique.[6,7]In addition, this review focuses on the different methods of purification of CNTs before attachment of drugs onto CNTs.

PRODUCTION OF CARBON NANOTUBES

Commonly, three techniques are being used for producing CNTs: the carbon arc-discharge technique; the laser-ablation and chemical vapor deposition (CVD) technique.[6,7]

Arc Discharge Method

The arc discharge methods for carbon nanotubes productions was firstly used by SumioIijima in 1991, and he used, two graphite rods that are placed in an enclosure that is filled with some inert gas (like helium or argon) at low pressure (between 50 and 700 mbar). The carbon rods act as electrodes which are kept at different potentials. The anode is moved close to the cathode until an arc appears and the electrodes are kept at the distance of 1 mm for the whole duration of the process that takes about one minute. After cooling of the chamber the nanotubes together with the by-products, can be collected.[8]

By this method, best quality nanotubes were produced by passing a current of about 50-100 amps between two graphite electrodes in an atmosphere of helium. This causes the graphite to vaporize where some of it is condensing on the walls of the reaction vessel and some other portion on the cathode. It is the deposit on the cathode which contains the carbon nanotubes.[9]

Single-Walled Carbon Nanotubes (SWCNTs) are produced using catalysts such as: Co and Ni or some other metal which are added to the anode as shown in Figure 1. Carbon nanotubes can also be made by passing a carbon-containing gas, such as a hydrocarbon, over a catalyst. These particles catalyze the breakdown of the gaseous molecules into carbon, and a tube then begins to grow with a metal particle at the tip.[10,11] The advantage of catalytic synthesis over arc-evaporation is that it can be scaled up for volume production.

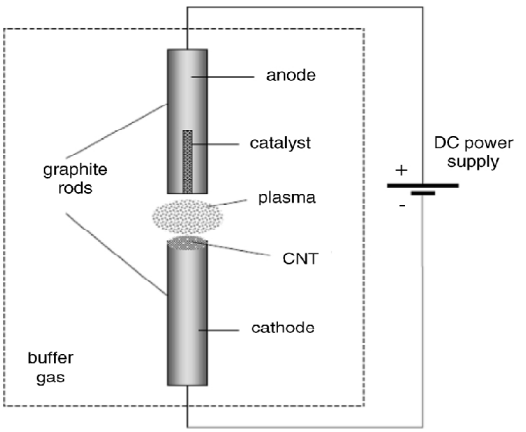

Figure 1: Schematic diagram of an arc-discharge system.[12]

Laser Ablation Method

In 1995 Richard E. Smalley and his group used for the first time laser ablation to grow high quality nanotubes. In this method as depicted in Figure 2 intense laser pulses ablate a carbon target which is placed in a tube-furnace heated to 1200°C. During the process some inert gas like helium or argon flows through the chamber to carry the grown carbon nanotubes to the cooler collector. After the cooling of the chamber the nanotubes and the by-products, like fullerenes and amorphous carbon over-coating on the sidewalls of nanotubes can be collected.[13] The laser is then focused onto a carbon targets containing 1.2 % of cobalt/nickel with 98.8 % of graphite composite that is placed in a 1200°C quartz tube furnace under the argon atmosphere (~500 Torr) as shown in Figure 2.[14]

Nanometer-size metal catalyst particles are formed in the plume of vaporized graphite. They catalyze the growth of SWCNTs in the plasma plume, but many by-products are formed at the same time. As the vaporized species cool, small carbon molecules and atoms quickly condense to form larger clusters. The catalysts also begin to condense, but more slowly at first, and attach to carbon clusters and prevent their closing into cage structures. From these initial clusters, tubular molecules grow into single-wall carbon nanotubes until the catalyst particles become too large, or until conditions have cooled sufficiently that carbon no longer can diffuse through or over the surface of the catalyst particles.[15]

The SWCNTs formed in this case are bundled together by van der waals forces. The nanotubes and by-products are collected via condensation on a cold finger downstream from the target. In principle, arc discharge and laser ablation are similar methods, because both used a metal-impregnated graphite target (anode) to produce SWCNTs, and both produce multiple wall carbon nano tube (MWCNTs) and fullerenes when pure graphite is used. But the length of MWCNTs produced through laser ablation is much shorter than that produced by arc discharge method. The quantity and quality of produced carbon nanotubes depend on several factors such as the amount and type of catalysts, laser power and wavelength, temperature, pressure, type of inert gas, and the fluid dynamics near the carbon.[16]

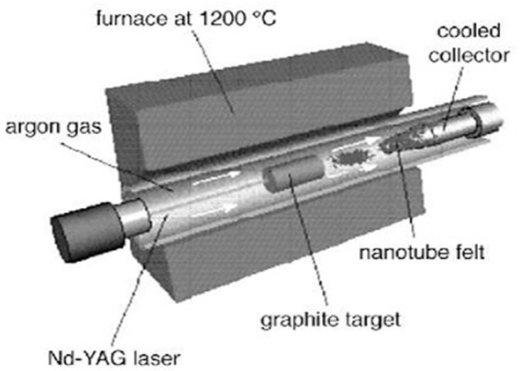

Figure 2: Schematic diagram of the laser ablation apparatus.[14]

Chemical vapor deposition

The other method for production of CNTs is chemical vapor deposition (CVD). CVD method has been used first for the production of carbon filaments however, it was utilized to grow MWCNTs since 1993.[6] There are different techniques of CVD for carbon nanotube growth such as plasma enhanced CVD, thermal CVD, alcohol catalytic CVD, laser assisted CVD and aero-gel supported CVD. Thermal CVD method will be explained below in details.[17]

Carbon nanotube growth includes two main steps; the first one is the catalyst preparation and the other one is the nano tube growth on this catalyst. In order to synthesis nano catalyst particles, a thin film layer can be used by annealing or a catalyst can be synthesized by some chemical methods. At the first step, prepared catalyst sample is placed in a quartz tube which is in a furnace and the temperature is set to a desired point. During the increase of the temperature to the set point, an inert gas flow takes place through the tube to prevent the oxidation of samples. When the furnace reaches to the desired temperature a preannealing can be done with H_2 to reduce catalyst nano particles from oxide form to metal form. The other step is sending hydrocarbon gas to the system as a carbon precursor. Generally used hydrocarbon gases are CH_4, C_2H_4, C_2H_2, and C_6H_6 for carbon nanotube growth. During growth process, hydrocarbon gas decomposes and carbon deposits onto the catalyst. Carbon has a low solubility in these metals at high temperature and therefore the carbon precipitates to form carbon nanotubes.[18]

In this method the main parameters for CNTs growth are the catalyst system, temperature, composition and the flow rate of the carrier and hydrocarbon gases.[19] In CVD method transition metals such as Fe, Co, and Ni are used as catalyst to synthesize CNTs. As support, inorganic porous materials such as silica (SiO_2), alumina (Al_2O_3) and magnesium oxide (MgO) are generally used.[20]

CVD is the most preferred method to produce carbon nanotubes, because this method is performed at low temperature compared with the other methods. The other reason is this method allows controlling the diameter of CNTs by controlling catalyst nanoparticles size. It is also easy to perform CVD process and

suitable method for large scale production.[21,22] The schematic illustration of CVD system is depicted in Figure 3.

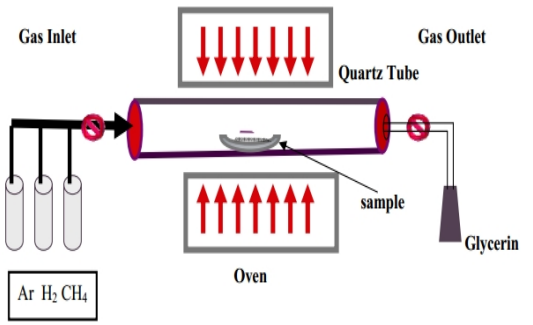

Figure 3: A schematic illustration of a Chemical vapor deposition System.[23]

CHARACTERISTICS OF CARBON NANOTUBE FABRICATIONS

Arc-discharge and laser ablation employs solid-state carbon precursors to provide carbon sources needed for nanotube growth and involve carbon vaporization at high temperatures. These methods are well established in producing high-quality and nearly perfect nanotube structures, despite large amounts of byproducts associated with them. Chemical vapor deposition (CVD) utilizes hydrocarbon gases as sources for carbon atoms and metal catalyst particles as "seeds" for nanotube growth that takes place at relatively lower temperatures. Nonetheless, arc-discharge and laser ablation techniques haveproduced SWCNTs with impressively narrow diameter distributions. CVD methods have come a long way from producingcarbonfibers, filaments, and multiwall carbon nanotube to the synthesis of SWCNTs with high crystalline and perfection comparable to those of arc and laser materials, as revealed by electrical transport and microscopy and spectroscopy measurements.[23]

As compared with laser ablation, CVD is an economically practical method for large-scale and quite pure CNT production and so the important advantage of CVD are high purity obtained material and easy control of the reaction. The relative ease with which one can set up a CVD system also makes of it the most promising route for the mass production of CNTs.[5]

Table 1: Summary and comparison of the three most common carbon nanotube synthesis methods[5]

Method	Arc discharge	Laser ablation	CVD
Yield rate	>75%	>75%	>75%
SWCNT or MWCNT	Both	Both	Both
Advantage	Simple, inexpensive	Relatively high purity	Simple, low temperature, high purity, large-scale production, aligned growth possible
Disadvantage	High temperature, purification required, tangled nanotubes	Method limited to the lab scale, Crude product purification required	Synthesized CNTs are usually MWCNTs, defects

CARBON NANOTUBE PURIFICATION

Carbon nanotube usually contains a large amount of impurities such as metal particles, amorphous carbon, and multishells. So purification is needed before attachment of drugs onto CNTs. Depending on technique of their synthesis and types of nano tubes, there are many different methods and procedure for purification. Almost all purification procedures have the following main steps: deletion of large graphite particles and aggregations with filtration, dissolution in appropriate solvents to eliminate catalyst particles (concentrated acids as solvent) and fullerenes (use of organic solvents), and microfiltration and chromatography to size separation and remove the amorphous carbon clusters. Generally there are two methods of carbon nanotube purifications these are chemical method and physical methods.[24]

Chemical Purification

The most commonly used chemical purification involves the oxidation of synthesized CNTs in both wet and dry conditions. The wet condition generally refers to the oxidation using a solution of concentrated acids or strong oxidants; while the dry condition mainly refers to the oxidation by air, oxygen, or other gases at a controlled temperature. Oxidation may lead to tips' opening of the carbon nanotube.[25]

Liquid (wet) phase oxidation reagents

The most homogeneous oxidation takes place in solutions where the CNTs can be well dispersed. The most commonly used oxidation reagents for this method of oxidation is acid refluxing. And the processes are as follow:Boil the CNTs in strong acid is effective in reducing the amount of metal particles and amorphous carbon. Acids that commonly used were hydrochloric acid (HCl), nitric acid (HNO_3) and sulphuric acid (H_2SO_4).[26,27]

It is the most commonly applied methods for purification and it involves treatment of the CNTs with oxidizing acids such as HNO_3 and/or H_2SO_4. CNTs are subjected to acid refluxing in concentrated acid to dissolve metal particles and carbon impurities, together with some chemical surface modification. The duration of oxidation as well as the reflux temperature is the crucial factors that determine the effectiveness of the removal of catalyst particles. Prolonged refluxing at high temperatures and acid concentrations will normally attack the defective sites of the CNT surfaces; this will result in the shortening and destruction of the structure, whereas the exposure of CNTs to a short period of acid refluxing, low acid concentration, and low temperature results in the incomplete removal of the metal particles. Most studies showed that employed acid refluxing treatment for shorter duration (~30min) in concentrated nitric acid effectively dissolve the metal particles and open the tube tips without causing significant structural damages to the CNTs.[25,28]

Oxidants that are commonly used in the purification of carbon nano tubes include potassium permanganate ($KMnO_4$), hydrogen peroxide (H_2O_2) etc.[29] Carbon surfaces have been oxidized using metal cations of sufficiently high oxidation potential. The extent of oxidation depends on the redox potential

of the system and also on the structural features of the nanotubes.[27]

The purification with liquid phase oxidation always leads to surface chemical modification on CNTs. Many studies have shown that CNTs can be cut into short fragments by acid modification in which length distributions become narrow.[25]

For many industrial applications, particularly in the production of electronic devices, require short undamaged CNTs in order to place nanotubes with a specific band gap and precise length in a well-defined location on the substrate. In addition to this modification of the nano tube by functional groups like carboxylic acids, aldehyde, alcohol, and other oxygenated functional groups would be a useful modification for drug delivery since, this type of functional group were water soluble.[4]

Gas phase oxidation reagents

Among the gas phase oxidation, air oxidation is the most commonly applied procedure in CNTs purification. Thermal air oxidation is useful in reducing the amount of amorphous carbon and metal catalyst particles. Optimal oxidation condition is found to be at 673 k for 40 min. Dynamic oxidation allows for an efficient removal of carbonaceous impurities without significant loss of nanotube.[30,31]
The oxidation of amorphous carbon in gas phase is advantageous against wet oxidation, because it is more controllable. Unlike liquid phase oxidation, gas phase oxidation preferentially oxidizes CNTs without introducing sidewall defects. Gas phase purified nanotubes to align in tight bundles that are well separated from each other and do not form clusters as observed in acid-oxidized SWCNTs. Moreover, the procedure does not require complex apparatus, and no filtration or other separation is needed after purification.[32]

Physical Purification

To reduce the damage caused by direct oxidation, nonconventional methods such as ultrasoniction, filtration, and chromatography have been used to purify CNTs.[33,34]

Filtration

Filtration with membranes of narrow pore size distribution has been developed to separate the CNTs from impurities and also to fractionate the nanotubes by length.[35]Filtration using membranes with different pore diameters in sequence from the largest to smallest in the cross-flow system is useful. In such a way, no oxidative treatment was required. Since all large aggregates were retained by the larger pore size membranes, whereas CNTs were retained on the smaller pore size membranes. In this manner, the CNTs, polyhedral nanoparticles, and large aggregates were separated from each other during the filtration. However, this filtration has some disadvantages as it leaves some amorphous particles stuck to the nanopores. It was also found that this method is less effective for low quality CNTs, such as those generated by arc-discharge.[36]

Sonication

Sonication has been identified as one of the effective processes to purify the amorphous impurities when the CNTs were treated with high-energy ultrasound in the presence of the suitable solvents such as dichloromethane and O-dichlorobenzene. During Sonication, the solvent molecules are able to interact with CNTs and hence lead to solubilization. It was observed that the sonicated carbon nanotubes demonstrated a very high concentration of defects such as bending and bucking while the outer graphite layers were gradually striped off, giving rise to the thinning of the nanotubes. CNTs produced by these methods appeared shorter due to the Sonication-induced nanotube cutting, and the tips opening of the CNTs are also observed.[37]

Chromatography exclusions

Purification and length separation of CNTs can be achieved through chromatography. High performance liquid chromatography (HPLC) and size exclusion chromatography (SEC) are the most commonly used techniques which are successful in length separation. SEC separation can be carried out without or with the assistance of reagents to improve the CNT dispersion in common solvent.[25]

FUNCTIONALIZATION OF CARBON NANOTUBES

Raw carbon nanotubes have highly hydrophobic surfaces, and are not soluble in aqueous solutions. For medical applications, surface chemistry modifications or functionalization is required to solubilize CNTs in aqueous solvent, improve biocompatibility and to decrease the toxicity of CNTs to the normal cells.[38]There are a number of approaches for functionalization of CNTs but the common used approaches are covalent and non-covalent functionalizations.[39]

Covalent functionalization of carbon nanotubes

Functionalized carbon nanotubes have been developed by various covalent reactions and oxidation methods. CNT oxidation is carried out with oxidizing agents such as nitric acid, oxygen, air, concentrated sulfuric acid, aqueous hydrogen peroxide.[40]

During the process, carboxyl groups are formed at the ends of tubes as well as at the defects on the sidewalls. The extent of the induced carboxyl group functionality depends on the oxidation procedures and oxidizing agents.[41,42]CNT permitted the incorporation of different functional groups on the nanotube which could be further derivatized.[43]

Surface modification of CNTs with functional moieties is a key step to extend their biological and industrial applications. Surface functional groups can alter the surface charge, functionality, and reactivity of the surface and enhance the stability and dispensability of CNTs. For example, functionalization of MWCNTs with the –COOH moiety can change the wettability of MWCNTs from hydrophobicity to hydrophilicity and provide active sites for further conjugation.[44]

Studies shows that surface modifications, in particular, the addition of carboxyl groups to MWCNTs will reduce or eliminate the bioactivity of the CNTs in macrophages exposed *in vitro*.[45]The removal of surface amorphous carbon and residual metals in MWCNTs was approached through hydrochloride (HCl) refluxing treatment and MWCNTs were functionalized with the −COOH moiety via nitric acid oxidation. Studies of the bioactivity of the MWCNTs were conducted using primary alveolar macrophages (AM) isolated from mice and compared to differentiated cells with respect to toxicity and activation of the NLRP3 inflammasome. HCl refluxing was used to remove amorphous carbon and the residual Ni catalyst as shown in Figure 4. It is known that a large number of defects exist on the surface of amorphous carbon, which facilitates relatively easy adsorption of hydroxyl groups onto it during HCl reflux treatment.[42]

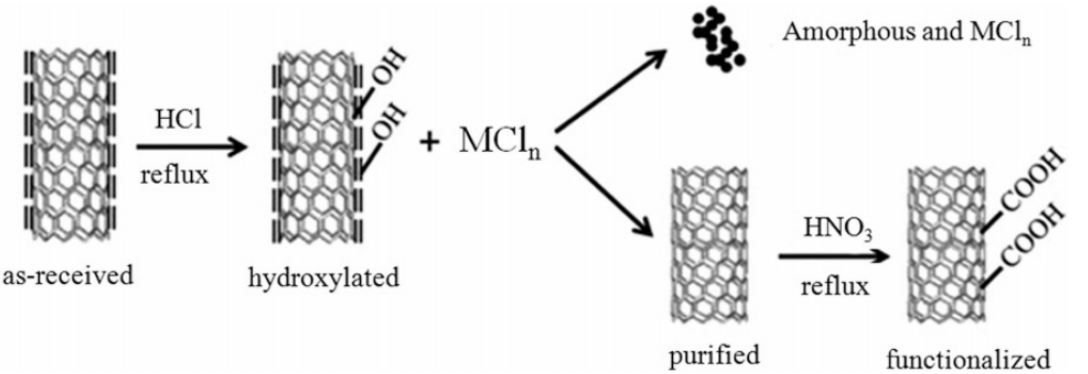

Figure 4: Schematic illustration of multiple wall carbon nano tube purification and sidewall functionalization.[46]
Note: "M" refers to any metals and "n" refers integer numbers.

On the other hand, residual metal catalysts can react with HCl to form metal chloride. HCl is a non- oxidative acid and cannot introduce oxygen-containing groups, but it can enhance the exposure of amorphous carbon grafted onto the disordered carbon, leading to increased water dispersibility. Hydroxylated amorphous carbon and nickel chloride will remain in the liquid phase, while the MWCNTs deposit. Hydroxylated amorphous carbon and metal chloride are separated from MWCNTs by centrifugation and decantation procedures.[46]

HNO_3 oxidation is a common approach that imparts the −COOH functional group onto MWCNTs because of its simplicity and efficiency.[47]"Raw" (unfunctionalized MWCNTs) and HCl-purified MWCNTs have poor water solubility. In contrast, after HNO_3 oxidation, of MWCNTs show good water solubility.[45]

Functionalized MWCNTs were relatively nontoxic compared to the raw or purified MWCNTs at high concentrations (50 µg/ml or greater). Purification had no apparent effect on toxicity. Studies show that concentration-dependent NLRP3 inflammasome activation demonstrated by particle-exposed mice, raw MWCNTs produced the largest response followed by the purified MWCNTs, which was significantly lower than the raw MWCNTs at 25 and 50µg/ml. Both forms of functionalized MWCNTs ("Raw" and purified functionalized MWCNTs) are less toxic compared to either the raw or purified MWCNTs. Phagolysosomal rupture, disruption, or possible malformation is an initial step in the NLRP3 inflammasome activation process and it happen if there is accumulation of raw CNTs and other factors also.[48,49]Studies conducted on mice show that the macrophage response to the raw MWCNTs and functionalized raw MWCNTs particles was exactly the same as the corresponding purified MWCNT and functionalized purified MWCNTs.[50]

In vitro toxicity and NLRP3 inflammasome activity results indicated the same relational pattern among the four MWCNTs. The raw MWCNTs were the most bioactive followed by the purified, that were much more active than the "raw" functionalized, followed by the purified and functionalized being the least active.[51]

Functionalization of the MWCNTs with −COOH had dramatic effects on both the properties and bioactivity of the MWCNTs. Raw or purified MWCNTs resuspend very poorly and form large agglomerates even when using protein/lipid dispersants. Therefore, the bioactivity is most likely due to these agglomerates being taken up by macrophages rather than any single MWCNTs. In contrast, the functionalized MWCNTs were well dispersed in water and formed stable suspensions. Furthermore, functionalization of the MWCNTs dramatically decreased bioactivity (toxicity and activation of the NLRP3 inflammasome). The mechanism for the decrease in bioactivity could be due to the changes in surface properties, better dispersion, and/or differences in the extent of phagocytosis or mechanism of phagocytosis. Clearly, the changes in surface properties (hydrophobic to hydrophilic) had a significant impact on dispersion status.[52]

Non covalent functionalization of carbon nanotubes

In contrast to covalent functionalization, noncovalent functionalization of CNTs can be carried out by coating CNTs with amphiphilic surfactant molecules or polymers. Since the chemical structure of the π- π network of carbon nanotubes is not disrupted, except for shortening of length due to the Sonication employed in the functionalization process, the physical properties of CNTs are essentially preserved by the non covalent approach.[53]

It mainly involves surfactants, bio macromolecules or wrapping with polymers. The nanotubes are enclosed by the hydrophobic components of the related micelles and polymers can wrap around CNTs, forming supra molecular complexes. The noncovalent dispersion of CNT in solution allows preservation of their aromatic structure and thus their electronic characteristics.[54]

Polyaniline, polypyrrole, polythiophene and their derivatives have been considered as promising materials for modifying the surfaces of CNTs and due to the existence of various oxidation structures, electrically conducting polymers.[55]

Poly ethylene glycol (PEG) has been one of the most preferred synthetic molecular species for various purposes in bio-related applications owing to its non-toxicity as well as its good solubility under various physiological conditions. Using amphiphilic molecules to functionalize CNT surfaces has been recognized as one of the most useful approaches to improve the dispersion of CNTs in aqueous media. Park and his co-workers described a noncovalent process for surface functionalization of SWCNTs using amphiphilicdiblock copolymer, consisting of hydrophilic and hydrophobic surfaces, with remarkably enhanced solubility particularly in aqueous media.[56]

Using polymer chains to 'wrap' CNTs is a versatile and effective way for CNT functionalization. In particular, block copolymers (BCPs) may provide a series of attractive noncovalent wrapping for the functionalization of CNTs. These approaches can be driven by distinct interactions between CNTs and polymers.[57]

Zhang and his co-workers have investigated the effect of melt mixing on the interaction between MWCNTs and polystyrene (PS) matrix. They found that the interaction between pristine MWCNTs and PS in solution did exist but not strong enough to allow MWCNTs to be soluble in solvent.[58]

Among the noncovalent functionalization, due to absence of reactive groups in the functionalized CNTs, the interfacial interaction between CNTs and epoxy is weak. Li and his groups described that the non-covalent functionalization of MWCNTs by using 2- amino ethanol ($H_2NCH_2CH_2OH$) in the presence of sodium hydroxide and the application for conductive composites with higher conductivity. The introduced amine group is expected to react with epoxide group from epoxy prepolymer to improve the interfacial interaction between MWCNTs and epoxy matrix leading to efficient MWCNTs dispersion. Good solubility of inherently insoluble CNTs in organic solvents has been achieved through surface modification with various homopolymers and/or block copolymers, either covalently such as surface-targeted grafting or in situ polymerization, or noncovalent.[53]

Non-covalent functionalization to the CNT not only is a much simpler method compared with covalent functionalization but also has the advantage of preserving nanotube's sp2 structure, thus the electronic properties.[59]

The potential use of CNTs in bio related areas has prompted many researchers to investigate the functionalization of CNTs with biological macromolecules such as proteins and oligosaccharide. Noncovalent functionalization of CNTs with bio-macromolecules, such as DNA and proteins is an additional potential strategy to prepare new bio electronic nano materials, which could take advantage of the molecular recognition properties of the bound bio molecules.[60]Wei and his co-workers found that a hydrophobic protein called polycyclic aromatic nitrogen heterocycle molecules (PANHS) can be utilized for controlled noncovalent functionalization of MWCNTs and at the same time can be used to control the assembly of Gold nanoparticle (AuNPs) after binding AuNPs onto the proteins.[61]

They also investigated the formation of MWCNT–AuNP hybrids by incubating protein-protected AuNPs with PANHS functionalized MWCNTs, as indicated in Figure 5. They found that proteins, as an intermediate that can react with both MWCNTs and AuNPs, play a significant role for mediating the assembly of AuNPs and formation of different hybrids based on MWCNTs.[61]

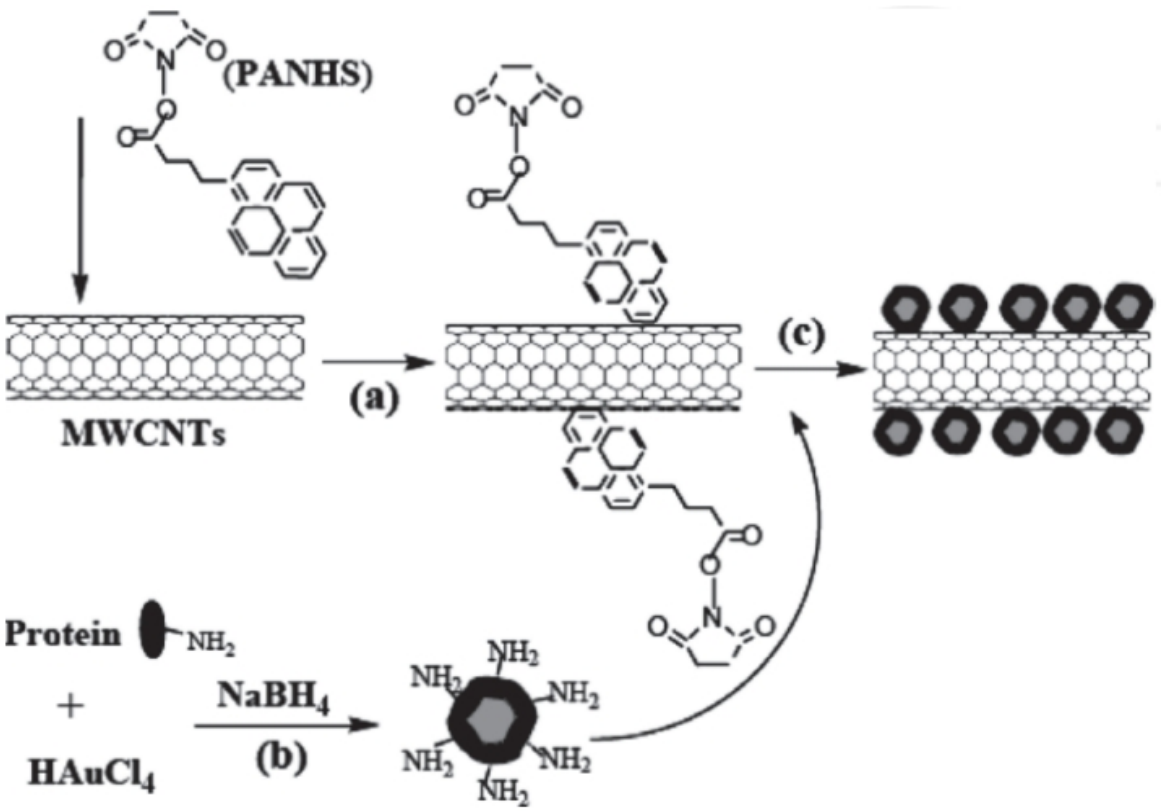

Figure 5: Model representation for the protein-mediated formation of multiple wall carbon nano tube – Gold nanoparticle hybrids. Functionalization of Multiple wall carbon nano tube with polycyclic aromatic nitrogen heterocyclic molecules (a), Preparation of protein-protected Gold nanoparticles (b), Self-assembly of protein-protected Gold nanoparticle on multiple wall carbon nano tube by the nucleophilic substitution of nitrogen heterocycle molecules group with primary and secondary amines on the surface of protein (c).[62]

MEDICAL APPLICATIONS

Tremendous effort has been devoted to the development of nanocarriers for the efficient delivery of therapeutic agents to the targeted site.[63]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. In vitro studies showed selective cancer cell killing obtained by hyperthermia due to the thermal conductivity of CNT internalized into those cells. 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. Detection of cancer at early stages is a critical step in improving cancer treatment. Currently, detection and diagnosis of cancer usually depend on changes in cells and tissues that are detected by a doctor's physical touch or imaging expertise. The potential for nanostructures to enter and analyze single cells suggests they could meet this need.[64]Carbon nanotubes can also be used as molecular probes, with potential applications in scanning probe instruments, chemistry and biology.[65]

CONCLUSION

Currently, three techniques are being used for producing CNTs: the carbon arc-discharge technique; the laser-ablation and chemical vapor deposition (CVD) technique. Carbon nanotube usually contains a large amount of impurities such as metal particles, amorphous carbon, and multi-shells. So purification is needed before attachment of drugs onto CNTs. For medical applications, functionalization is required to solubilize CNTs in aqueous solvent, improve biocompatibility and to decrease the toxicity of CNTs to the normal cells.Due to rapid evolution of complicated disease the existing methods of drug delivery and treatment are becoming less effective. Therefore, modern health care requires more sophisticated and effective carriers for such problems. The present paper provides information regarding thefabrication, purification,functionalization and medical application ofCNT structures.

REFERENCES

1. Shao W, Arghya P, Yiyong M, Rodes L, SatyaPrakash. Carbon Nanotubes for Use in Medicine: Potentials and Limitations, Syntheses and Applications of Carbon Nanotubes and Their Composites, Dr. Satoru Suzuki (Ed.), InTech, DOI: 10.5772/51785. 2013 [Accessed 2016 July 15]. Available from: http://www.intechopen.com /books/syntheses-and-applications-of-carbon-nanotubes-and-their-composites/carbon-nanotubes-for-use-in-medicine-potentials-and-limitations
2. Sagadevan S, Periasamy MN. A review on role of nanostructures in drug delivery system. Rev.Adv.Mater. Sci.2014;36:112-117.
3. Beg S, Rizwan M, Sheikh AM, Hasnain MS, Anwer K, Kohli K. Advancement in carbon nanotubes: basics, biomedical applications and toxicity. J. Pharm. Pharmacol. 2011; 63:141- 163.
4. Eatemadi A, Daraee H, Karimkhanloo H, Kouhi M, Zarghami N, Akbarzadeh A, et al. Carbon nanotubes: properties, synthesis,purification, and medical applications. Nanoscale Res. Lett. 2014; 9:393.
5. Mody N, Tekade RK, Mehra NK, Chopdey P, Jain NK. Dendrimer, Liposomes, Carbon Nanotubes and PLGA Nanoparticles: One Platform Assessment of Drug Delivery Potential. AAPS PharmSciTech. 2014; 15:388-399.
6. Yaceman MJ, Yoshida MM, Rendon L, Santiestaban JG. Catalytic growth of carbon microtubules with fullerenes structure. Appl. Phys. Lett. 1993; 62: 202-204.
7. Journet C, Master WK, Berneir P, Loisequ A. "Large scale production of single wall carbon nano tubes by electric arc technique". Nature 1997; 388: 756 -758.
8. Ijma S, Ajayan PM.Growth model for carbon nano tubes. Phys.Rev. lett. 1992; 69:3100 -3103.
9. Vanderwal RL, Berger GM, Ticich TM. Carbon nanotube synthesis in a flame using laser ablation for insitu catalyst generation. Appl. Phys. A. 2003; 77:885- 889.
10. Thess A, Lee R, Nikolaev P, Dai H, Petit P, Robert J, et al. Crystalline ropes of metallic carbon nanotubes. Science 1996; 273:483–487.
11. Hirlekar R, Yamagar M, Garse H, Vij M, Kadam V.Carbon nanotubes and its applications: A review. Asian Journal of Pharmaceutical and Clinical Research 2009; 2:17-27.
12. Rümmeli MH, Ayala P, Pichler T. Carbon Nanotubes and Related Structures: Production and Formation, in Carbon Nanotubes and Related Structures: Synthesis, Characterization, Functionalization, and Applications. (eds D. M. Guldi and N. Martín), Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany. 2010. doi: 10.1002/9783527629930.ch1.
13. Guo T, Nikolaev P, Thess A, Colbert DT, Smalley RE.Catalytic growth ofsingle-walled nanotubes by laser vaporization. Chemical Physics Letters 1995; 243:49-54.
14. Kumar R, Dhanawat M, Kumar S, Singh BN, Pandit JK , Sinha VR.Carbon Nanotubes: A Potential Concept for Drug Delivery Applications. Recent Patents on Drug Delivery & Formulation 2014; 8:12-26.
15. Sinnott SB, Andrews R.Carbon Nanotubes: Synthesis, properties and applications. Critical Reviews in Solid State and Materials Sciences2001; 26:145–249.
16. Chico L, Crespi VH, Benedict LX, Louie SG, Cohen ML.Pure carbon nanoscale devices: nanotube heterojunctions. PhysicalReview Letters 1996; 76:971-974.
17. Singh C, Shaffer MS, Windle H. Production of controlled architectures of aligned carbon nanotubes by an injection chemical vapours deposition method. Carbon 2003; 41: 359-368.
18. Cui H, Eres G, Hawe JY.Growth behavior of carbon nanotubes on multilayered metal catalyst film in chemical vapor deposition. Chemical Physics Letters2003; 374: 222-228.
19. Biris AR, Li Z, Dervishi E, Lupu D, Xu Y, Saini V, et al. Effect of hydrogen on the growth and morphology of single wall carbon nanotubes synthesized on a Fe-Mo/MgO catalytic system. Physics Letters A. 2008;372:3051-3057.
20. Liu BC, Lyu SC, Jung SI, Kang HK, Yang CW, Park JW, et al. Single-Walled Carbon Nanotubes Produced by Catalytic Chemical Vapor Deposition of Acetylene over Fe-Mo/MgO Catalyst. Chemical Physics Letters 2004; 383: 104-108.
21. Kong J, Cassell AM, Dai H.Chemical vapor deposition of methane for single-walled carbon nanotubes. Chemical Physics Letters 1998; 292:567–574.
22. Weifeng L, Cai W, Yao L, Li X, Yao Z. Effects of methane partial pressure on synthesis of single walled carbon nanotubes by chemical vapor deposition. Journal of Materials Science 2003; 38: 3051- 3054.
23. Dai H. Carbon Nanotubes: Synthesis, Integration, and Properties. Acc. Chem. Res. 2002; 35:1035-1044.
24. Patole SP, Alegaonkar PS, Lee HC, Yoo JB. Optimization of water assisted chemical vapor deposition parameters for super growth of carbon nanotubes. Carbon 2008; 46:1987–1993.

25. Ismail AF, Goh PS, Tee JC, Sanip SM, Aziz M. A review of purification techniques for carbon nanotubes. Nano2008; 3:127-143.
26. Martinez MT, Callejas MA, Benito AM, Cochet M, Seeger T, Anson A et al.Modifications of single-wall carbon nanotubes upon oxidative purification treatments. Nanotechnology2003;14:691.
27. Strong KL, Anderson DP, Lafdi K, Kuhn JN.Purification process for single-wall carbon nanotubes. Carbon 2003; 41: 1477-1488.
28. Pinilla JL, Moliner R, Suelves I, Lízaro MJ, Echegoyen Y, Palacios JM.Production of hydrogen and carbon nanofibers by thermal decomposition of methane using metal catalysts in a fluidized bed reactor. International Journal of Hydrogen Energy 2007; 32:4821–4829.
29. Piedigrosso P, Konya Z, Colomer JF, Fonseca A, Tendeloo GV, Nagy JB.Production of differently shaped multi-wall carbon nanotubes using various cobalt supported catalysts. Phys. Chem. Chem. Phys.2000;2: 163-170.
30. Eklund PC, Pradhan BK, Kim UJ, Xiong Q, Fischer JE, Friedman AD, et al. Large-scale production of single-walled carbon nanotubes using ultrafast pulses from a free electron laser. Nano Letters 2002; 2:561–566.
31. Landi BJ, Raffaelle RP, Castro SL, Bailey SG.Single-wall carbon nanotube polymer solar cells. Progress in Photovoltaics2005; 13:165–172.
32. Wiltshire JG, Khlobystov AN, Li LJ, Lyapin SG, Briggs GAD, Nicholas RJ.Comparative studies on acid and thermal based selective purification of HiPCO produced single-walled carbon nanotubes. Chemical Physics Letters 2004; 386: 239–243.
33. Holling TM, Schooten E, van Den Elsen PJ.Function and regulation of MHC class II molecules in T-lymphocytes: of mice and men.Human Immunology 2004;65: 282-90.
34. Wu CH.Studies of the equilibrium and thermodynamics of the adsorption of Cu^{2+}onto as-produced and modified carbon nanotubes. Journal of Colloid and Interface Science 2007;311:338- 346.
35. Nunez JD, Maser WK, Mayoral MC, Andres JM, Benito AM.Platelet-like catalyst design for high yield production of multi-walled carbon nanotubes by catalytic chemical vapour deposition. Carbon2011;49: 2483-2491.
36. Shelimov KB, Esenaliev RO, Rinzler AG, Huffman CB, Smalley RE.Purification of Single wall carbon nano tube by ultrasonically assisted filtration. Chemical Physics Letters1998; 282:429-434.
37. Li LY, Li CY, Ni C.Polymer crystallization-driven, periodic patterning on carbon nanotubes. J. Am. Chem. Soc.2006;128:1692-1699.
38. Niemirowicz K, Car H.Nanocarriers in modern drug delivery systems. Chemik2012; 66:875-881.
39. Ferro-Flores G, Ocampo-García BE, Santos-Cuevas LC, Morales-Avila E; Azorín-Vega E. Multifunctional Radiolabeled Nanoparticles for Targeted Therapy. Current Medicinal Chemistry2014; 21: 124-138.
40. El-Say KM.Nano diamond as a drug delivery system: Applications and prospective. Journal of Applied Pharmaceutical Science2011;01: 29-39.
41. Jin Z, Sun X, Xu G, Goh SH, Ji W.Nonlinear optical properties of some polymer/multi-walled carbon nanotube composites. Chemical Physics Letters 2000; 318:505-510.
42. Datsyuk V, Kalyva M, Papagelis K, Parthenios J, Tasis D, Siokou A, et al.Chemical oxidation of multi-walled carbon nanotubes. Carbon2008; 46:833-840.
43. Gao C, Yan D.Hyperbranched polymers: from synthesis to applications. Progress in Polymer Science 2004; 29:183–275.
44. Jain S, Thakare VS, Das M, Godugu C, Jain AK, Mathur R, et al.Toxicity of multi walled carbon nanotubes with end defects critically depends on their functionalization density. Chemical Research in Toxicology2011; 24:2028-2039.
45. Brozena AH, Moskowitz J, Shao B, Deng S, Liao H, Gaskell KJ et al.Outer wall selectively oxidized, water-soluble double-walled carbon nanotubes. J. Am. Chem. Soc.2010; 132:3932-3938.
46. Hamilton RF, Xiang C, Li M, Ka I, Yan F, Ma D, et al.Purification and sidewall functionalization of multiwalled carbon nanotubes and resulting bioactivity in two macrophage models. Inhal. Toxicol.2013; 25: 199-210.
47. Worsley KA, Kalinina I, Bekyarova E, Haddon RC.Functionalization and dissolution of nitric acid treated single-walled carbon nanotubes. J. Am. Chem. Soc.2009; 131:18153–18158.
48. Martinon F, Mayor A, Tschopp J.The inflammasomes: guardians of the body. Annual Review of Immunology2009; 27:229–265.
49. Tschopp J, Schroder K.NLRP3 inflammasome activation: the convergence of multiple signaling pathways on ROS production. Nature Reviews Immunology 2010; 10:210–215.
50. Sager TM, Wolfarth MW, Andrew M, Hubbs A, Friend S, Chen T et al. Effect of multiwalled carbon nanotube surface modification on bioactivity in the C57Bl/6 mouse model. Nanotoxicology2014; 8:317-327.
51. Hamilton RF, Girtsman TA, Xiang C,Wu N, Holian A.Nickel contamination on MWCNT is related to particle bioactivity but not toxicity in the THP-1 transformed macrophage model. International Journal of Biomedical Nanoscience and Nanotechnology2013;3:107-126.
52. Pietruska JR, Liu X, Smith A,McNeil K, Weston P, Zhitkovich A, et al.Bioavailability, intracellular mobilization of nickel, and HIF-1α activation in human lung epithelial cells exposed to metallic nickel and nickel oxide nanoparticles. Toxicological Sciences 2011; 124:138–148.
53. Zhang W, Zhang Z, Zhang Y.The application of carbon nanotubes in target drug delivery systems for cancer therapies. Nanoscale Research Letters2011; 6:555-560.
54. Sarojini S, Rajasekar S and Koumaravelou k.Carbon nanotubes: a new weapon in health care treatment. International Journal of Pharma and Bio Sciences 2010; 1:644-649.
55. Reddy ALM, Rajalakshmi N, Ramaprabhu S.Cobalt-polypyrrole-multiwalled carbon nanotube catalysts for hydrogen and alcohol fuel cells. Carbon2008; 46:2-11.
56. Park C, Lee S, Lee JH, Lim J, Lee SC, Park M, et al.Controlled assembly of carbon nanotubes encapsulatedwith amphiphilic block copolymer. Carbon2007; 45:2072-2078.
57. Zou J, Liu L, Chen H, Khondaker SI, McCullough RD, Huo Q, et al.Dispersion of pristine carbon nanotubes using conjugated block copolymers. Advanced MaterialsWeinheim2008; 20:2055-2060.
58. Zhang Z, Zhang J, Chen P, Zhang B, He J, Hu GH.Enhanced interactions between multi-walled carbonnanotubes and polystyrene induced by melt mixing. Carbon 2006;44:692-698.
59. Tournus F, Latil S, Heggie MI, Charlier JC.π-stacking interaction between carbon nanotubes and organic molecules. Physical review B. Condensed matter and materials physics 2005; 72:75-83.
60. Bale SS, Asuri P, Karajanagi SS, Dordick JS, Kane RS.Protein directed formation of silver nanoparticles on carbon nanotubes. Advanced Materials2007; 19:3167-3170.

61. Wei G, Pan CJ, Reichert J, JandtKD.Controlled assembly of protein-protected gold nanoparticles on noncovalent functionalized carbon nanotubes.Carbon2010;48:645-653.
62. Chen L, Xie H and Yu W.Functionalization Methods of Carbon Nanotubes and Its Applications, Carbon Nanotubes Applications on Electron Devices, Prof. Jose Mauricio Marulanda (Ed.), InTech, DOI: 10.5772/18547. 2011[Accessed 2016 July 16]. Available from: http://www.intechopen.com/books/carbon-nanotubes-applications-on-electron-devices/functionalization-methods-of-carbon-nanotubes-and-its applications.
63. Bose S. Nano Drug Delivery System in Pharmacy and Chemistry Review Article. IOSR Journal of Pharmacy and Biological Sciences 2015; 10:1-6.
64. Varshney K. Carbon Nanotubes: A Review on Synthesis, Properties and Applications. International Journal of Engineering Research and General Science 2014; 2: 660-677.
65. Rajkumar K, Palla S, Paladugu A, Reddy ERK, Reddy KR. Carbon nanotubes: a review on preparation techniques and applications in various fields. Int. Res. J. Pharm. 2013;4(2): 36-44.

Cite this article as:

Yonas Brhane and Tesfaye Gabriel. Production, purification and functionalization of carbon nanotubes for medical applications. Int. Res. J. Pharm. 2016;7(7):19-27 http://dx.doi.org/10.7897/2230-8407.07780

Source of support: Nil, Conflict of interest: None Declared