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Review Article

CARBON NANOTUBE: A FLEXIBLE APPROACH FOR NANOMEDICINE AND DRUG DELIVERY

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ABSTRACT

Nanostructures of carbon were first observed in 1952, which gained worldwide interest due to their various physicochemical properties. Carbon nanotubes (CNTs) have found wide applications in the delivery of therapeutic agents such as peptides, proteins, siRNA, nucleic acids, genes, vaccines and also in bone and neural tissue regeneration. Functionalized CNTs have found to be biocompatible. The eye-catching features of these structures are their electronic, mechanical, optical and chemical characteristics, which open a way to future applications and make them good candidates for a wide variety of applications, including drug transporters, new therapeutics, delivery systems and diagnostics. Their unique surface area, stiffness, strength, and resilience have led to much excitement in the field of pharmacy. They can pass through membranes, carrying therapeutic drugs, vaccines, and nucleic acids deep into the cell to targets that are previously unreachable. The applications of carbon nanotubes are in tissue engineering, drug carrier release system, wound healing, in cancer treatment and as biosensor. The successful realization of CNT-based biosensors requires proper control of their chemical and physical properties, as well as their functionalization and surface immobilization. Real applications are still under development. The modifications are done to improve efficiency of carbon nanotubes by formulating luminescent carbon nanotubes, ultrathin carbon nano-needles, magnetically guided nanotubes. Researchers have recently developed a new approach to boron neutron capture therapy in the treatment of cancer using substituted carborane-appended water-Soluble single-wall carbon nanotubes. This article provides an overview of current nanotube technology, with a special focus on synthesis and purification, properties, benefits, and applications.

Keywords: Carbon nanotubes, Biosensors, Tissue engineering, Biocompatible.

INTRODUCTION

These are allotropes of carbon with cylindrical carbon molecules having novel properties thus making them potentially useful in many fields like electronics, nanotechnology, optics and other fields including architecture. They have a wide variety of applications and also used in the construction of body armor. They are efficient thermal conductors due to their extraordinary strengths and unique electrical properties. In order to promote the use of carbon nanotube (CNT) in research and in development, more reliable methods of production have been developed out of which chemical vapor deposition (CVD), arc discharge and laser ablation are the most common methods [1]. They can be divided into single wall CNTs (SWCNT) and multi wall CNTs (MWCNT). In the former process, a cylindrical nanostructure formed by rolling up a single graphite sheet into a tube whereas the latter comprises of multi layered grapheme cylinders that are concentrically nested like rings on a tree trunk. Both have high tensile strength, ultralight weight and high chemical and thermal stability. It is also proved that CNT can enhance the chemical reactivity of important biomolecules and promote electron transfer reaction of proteins. These CNTs have the ability to buckle and collapse reversibly due to high stiffness and resilience. The hexagonal network having high C-C bond stiffness produces an axial young's modulus of approximately 1 TPa and a tensile strength of 150 GPa, which makes these particles one of the most stiffest materials known yet have the capacity to deform electrically under compression.

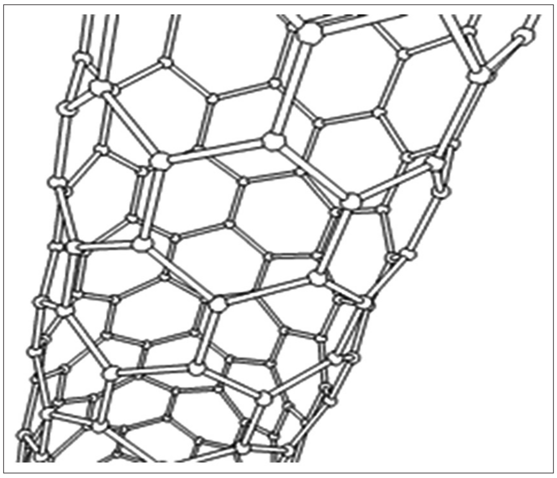

Fig. 1: Structure of a carbon nanotube

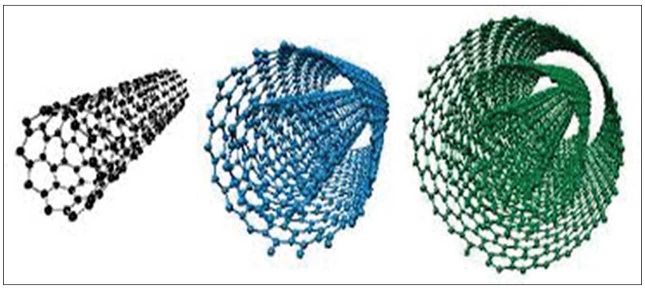

Fig. 2: Single-walled carbon nanotube (CNT), double-walled CNT, and triple-walled CNT

STRUCTURE [2]

Nanotubes are considered as the members of fullerene structural family including the spherical buckyballs. The name nanotube is derived from their size where the diameter of a nanotube is of a few nanometers of approximately 1/50,000th the width of a human hair. There exist many exotic fullerene structures like cones, tubes, regular spheres and also more strange and complicated shapes. Some of the most important and best known structures are as in Figs.1-4:

- Cylinder: It is one of the structures of which a SWCNT is composed. These cylinders are generated when a grapheme sheet of a particular size is wrapped in a particular direction. We can roll the sheet only in a discreet set of directions to form a closed cylinder. For this, two

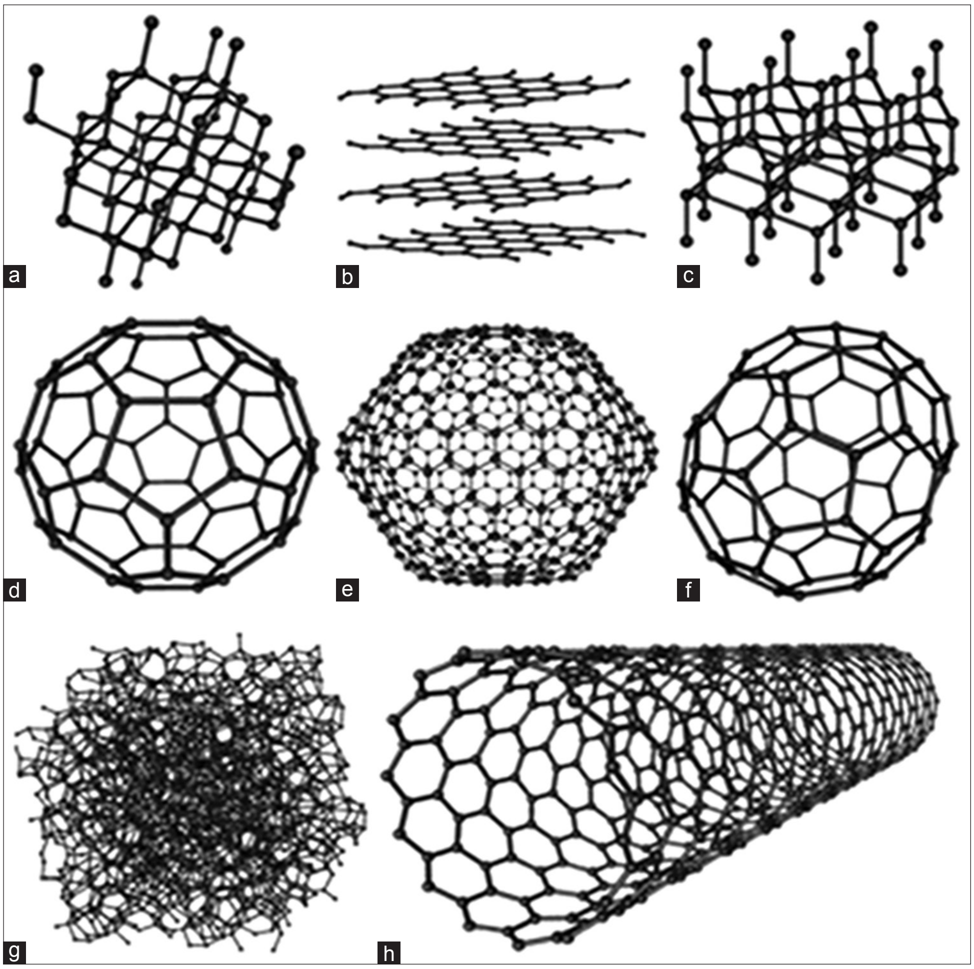

Fig. 3: (a) Diamond, (b) graphite, (c) lonsdaleite, (d-f) fullerenes (C60, C540, C70), (g) amorphous carbon and (h) carbon nanotube

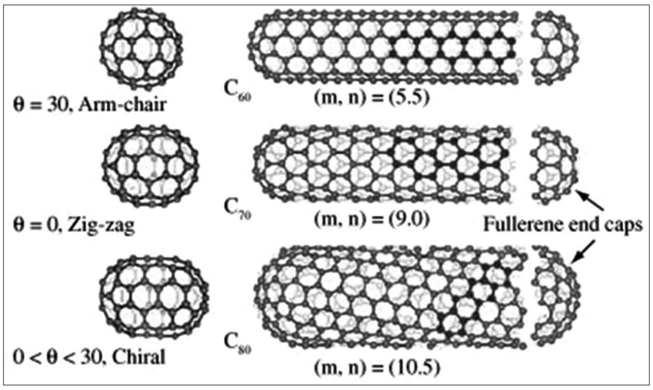

Fig. 4: Arm-chair, Zig-zag, and chiral fullerenes

grapheme sheets are chosen where one of them acts as the origin and the sheet is rolled till the two atoms coincide. Chiral vector is a vector pointing from the first atom to the other and here the length equals with the circumference of the nanotube. Chiral vector and the axis of the nanotube are perpendicular to each other.

- Tubes: These can be considered as long wrapped grapheme sheets. They are considered to be one-dimensional (1D) structure as they generally have a length to diameter ratio of about 1000. The SWCNTs consist of two separate regions having different physical and chemical properties where one comprises of the side wall, and the other is the end cap of the tube. Hexagons and pentagons are comprised of carbon atoms form the end cap structure. Euler's theorem states that 12 pentagons are needed to obtain a closed cage structure that contains only pentagons and hexagons. A pentagon and surrounding five hexagons combine together resulting in desired curvature of the surface to enclose a volume. The other rule, the isolated pentagon rule states that in order to attain a more stable structure, a minimal local curvature and surface stress is obtained is obtained by maximizing the distance between pentagons on the fullerene structure. SWCNTs having different chiral vectors have dissimilar properties like optical activity, mechanical strength, and electrical conductivity.

PROPERTIES

CNTs can be made stronger and lighter than steel because they have an extremely high strength to weight ratio. They can also be made for good conduction of heat and electricity which are the desirable properties found separately in graphite and diamond. CNTs are adaptable and are designed to alter their properties based on their environment that was as listed in Fig. 5.

- Strength [3-5]: The strength resulting from sp^2 bonds between individual carbon atoms makes the CNTs the strongest and stiffest materials yet discovered in terms of tensile strength and elastic modulus respectively. A MWCNT was tested to have a tensile strength of 63 Gpa. It has specific strength of up to 48,000 KN/m/kg, which is the best of known materials.
- Hardness [6]: without any deformation, a standard SWCNT can withstand a pressure up to 24 GPa and then transforms to super hard phase nanotubes. Current experimental techniques show that the maximum pressures these CNTs can withstand are found to be 55 GPa but these new super hard phase nanotubes at even higher albeit and unknown pressure.

- Thermal properties: Diamond was believed to be the best thermal conductor until CNTs have been invented which are shown to have a thermal conductivity twice as that of diamond [7]. These CNTs have the uniqueness of feeling cold to the touch. Like in metal, the sides with the tube ends are exposed but are similar to wood on the other sides. Phonons are used to determine the specific heat and thermal conductivity of CNT system. When measured, they showed linear specific heat and thermal conductivity above 1 K [8-13]. Thermoelectric power measurement of nanotube system gives direct information for the type of carriers and conductivity mechanisms.
- Dispersion and solubility: The pre-requisite for the biocompatibility of CNTs is their solubility in aqueous solvents and therefore CNT composites in therapeutic delivery should meet their basic requirement. Hence, it should be assured that those CNT dispersions are uniform and stable to obtain an accurate concentration data. In their deference, the solubilization of pristine CNTs in aqueous solvents hinders in realizing their potential as pharmaceutical excipients. Due to the hydrophobic characters of graphene sidewalls coupled with strong P-P interactions between individual tubes that help CNTs to congregate as bundles. In order to disperse the CNTs successfully, the dispersing medium should be capable of wetting the hydrophobic tube surfaces and modifying the tube surfaces to decrease the aggregation. Dispersion can be obtained using four different basic approaches like:
  i. Surfactant aided dispersion
  ii. Solvent dispersion
  iii. Functionalization of CNT sidewalls
  iv. Biomolecular dispersion.
- Electrical properties: The peculiar electronic structure of graphite and the 1D character of carbon nanotubes reveal their unique electrical properties to a large extent. These carbon nanotubes have an extremely low electrical resistance. Resistance can be seen when an electron collides with some defect in the crystal structure of the material through which it is passing. These defects can be an impure atom or a defect in the crystal structure or an atom vibrating about its position in the crystal. Collisions between electrons and the defective materials deflect the electron path and the electrons in the CNTs are not scattered so easily. Electrons can scatter at any angle in a three-dimensional conductor where any scattering results in electrical resistance. In the case of 1D conductor, electrons can move only front and back under which only back scattering leads to electrical resistance. Back scattering is less likely to happen since they require strong collisions that leave with a fewer opportunities to scatter. Thus, CNTs attain their low resistive property from their reduced scattterity. Also, in addition, they carry highest density current of any known material as high as 10^9 A/cm^2. Nanotubes are shown to super conduct at low temperature.

SYNTHESIS OF CARBON NANOTUBES

Though, scientists are researching more economic ways to produce CNTs, techniques have been developed to produce nanotubes in sizeable quantities including arc discharge, laser ablation, and CVD. In the method of arc discharge, a vapor is created by an arc discharge between two carbon electrodes with or without catalyst. The resulting carbon vapor helps the nanotubes to self assemble. Laser ablation technique involves the principle that a high power laser beam impinges on a volume of carbon containing feed stock gas such as methane or carbon monoxide. At this point, the laser ablation produces a small amount of clean nanotubes. In CVD, growth of CNTs can occur in a vacuum or at atmospheric pressure.

Growth mechanism [14]

The growth mechanism in which the nanotubes are formed is not exactly known which is still a subject of controversy, and more than one mechanism might be operative during the formation of CNTs. One of those mechanisms consists of the following steps as in Fig. 6:

a. In first step, a precursor to the formation of nanotubes and fullerenes, C_2 is formed on the surface of the particle of the metal catalyst. A rod like carbon is formed rapidly from this metastable carbon particle.
b. Slow graphitization of its wall is seen in the second step that is based on in-situ transition electronic microscopy (TEM) observations. The technique used for this determines the exact atmospheric conditions.

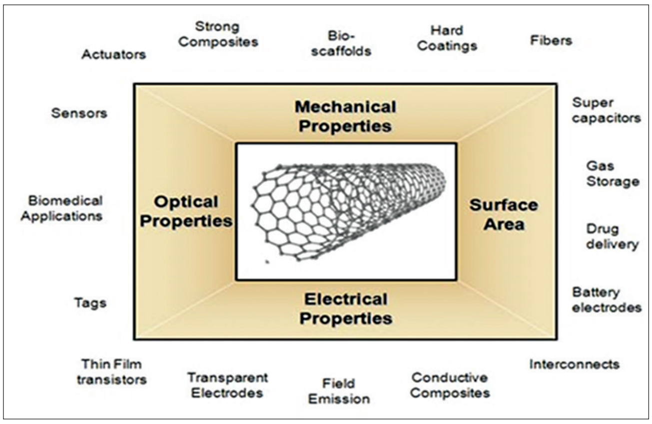

Fig. 5: Various properties of carbon nanotube in various field

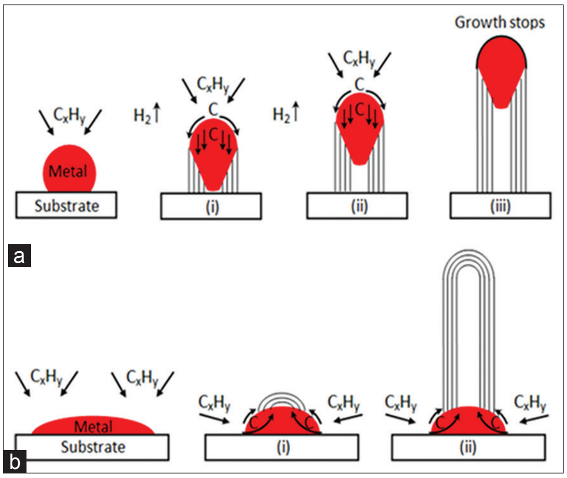

Fig. 6: Growth mechanism of carbon nanotube

Numerous theories have been stated on the exact growth mechanisms of nanotubes. One among those postulates states that metal catalyst particles are floating or are supported on graphite or other substrate. It is, therefore, presumed that the catalyst particles are spherical or pear shaped where the deposition takes place only on one-half of the surface. Diffusion of carbon is based on concentration gradient and precipitates on the opposite half of below and around the bisecting diameter. However, precipitation does not take place from the apex of the hemisphere that accounts for hollow core that is the characteristic property of these filaments. In supported metals, filaments can be formed either by "extrusion" where the growth of nanotube is upward from the metal particles that remain attached to the substrate or particles detach and move at the head of growing nanotube called "tip growth." SWCNT or MWCNT are grown depending on the size of the catalyst particles. If no catalyst is present in the arc discharge method, MWCNT will be grown on carbon particles that are formed in the plasma. These methods are briefly discussed below.

Arc discharge method [15]

This is the most common and easiest way which is initially used for producing C_{60} fullerenes. This technique (Fig. 7) produces a mixture of components and requires separating nanotubes from the soot and the catalytic metals present in the crude products. Nanotubes are thus created through arc vaporization of two carbon rods placed end to end separated by approximately 1mm in an enclosure that is usually filled with inert gas at low pressure. A high temperature discharge is created between the two electrodes by passing a direct current of 50-100 A driven by 20 V where one of the carbon rod is vaporized and forms a small rod shaped deposit on the other rod. High yield of nanotubes depends on the uniformity of plasma arc and temperature of the deposit formed on the carbon electrode.

The different diffusion coefficients and thermal conductivities of the mixture of Helium and Argon affect the speed with which carbon and catalyst molecules diffuse and cool affecting nanotube diameter in arc process. Depending on the quenching rates in the plasma it can be implied that single layer tubules nucleates and grow on metal particles in different sizes. It suggests that the temperature, carbon and metal catalyst densities affect the diameter distribution of nanotubes. It is possible to selectively grow SWCNT or MWCNT.

Laser ablation [16]

During 1995, carbon nanotubes synthesized by laser vaporization were developed by Smalley's group at Rice University, who at the discovery of carbon nanotubes were blasting metals with laser to produce various metal molecules. Continuous or pulsed laser is used to vaporize a graphite target in a high temperature reactor while an inert gas is bled into the chamber to keep the pressure at 500 torr. Major difference between continuous and pulsed laser is that pulsed laser demands a much higher light intensity. Much hot vapor plume is formed which expands and cools rapidly. When the vaporized species start to cool, small carbon atoms and molecules quickly condenses to form larger clusters including fullerenes. Along with these the catalyst also begins to condense more slowly at first thereby attaching to carbon clusters and prevent their closing into cage structure. Tubular molecules grow from these initial clusters until the catalyst particles become too large or till that conditions have cooled sufficiently that carbon no longer diffuses over or through the catalyst. There is also a chance that particles become over coated with carbon layer, and they cannot absorb more and nanotube stops growing. The formed SWCNTs are bounded together by Vander Waals forces. Arc discharge and laser ablation are almost similar since the background gas and catalyst mixture in laser ablation is same as in arc discharge process. This may be due to similar reaction conditions needed and reactions probably occur with same mechanisms (Fig. 8).

CVD [17]

Researchers at the University of Cincinnati developed a method in 2007 to grow aligned carbon nanotube arrays having length of 15 mm on First Nano ET 3000 carbon nanotube growth system. Hey are synthesized by putting a carbon source in gas phase and energy source such as plasma or resistively heated coil to transfer energy to a gaseous carbon molecule. These carbon sources include acetylene, methane, and carbon monoxide. The molecule is cracked into reactive atomic carbon using this energy source. Then the carbon diffuses toward the substrate that is heated and coated with a catalyst where it binds. Positional control over nanometer scale as well as excellent alignment can be achieved using CVD. Diameter as well as growth rate of nanotubes can also be maintained. Use of the appropriate catalyst preferably grows single rather than multi walled nanotubes. Synthesis of nanotubes through this method is necessarily a two-step process consisting of catalyst preparation followed by actual nanotube synthesis. Catalyst is prepared by sputtering a transition metal onto a substrate and then inducing catalyst particle nucleation using either chemical etching or thermal annealing. The latter results in cluster formation on the substrate from which the nanotubes grow. Ammonia can be used as an etchant. Temperatures should be maintained within 650-900°C. Different techniques for carbon nanotube synthesis using this method have been developed in the last decennial such as Thermal CVD (Fig. 9), plasma enhanced CVD, alcohol catalytic CVD, aero gel supported CVD and laser assisted CVD.

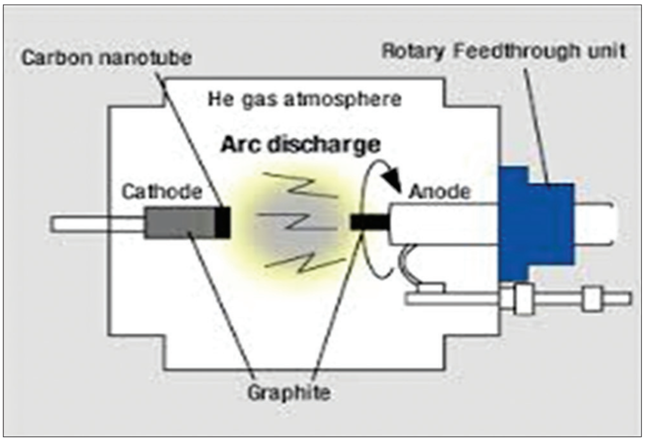

Fig. 7: Arc discharge method

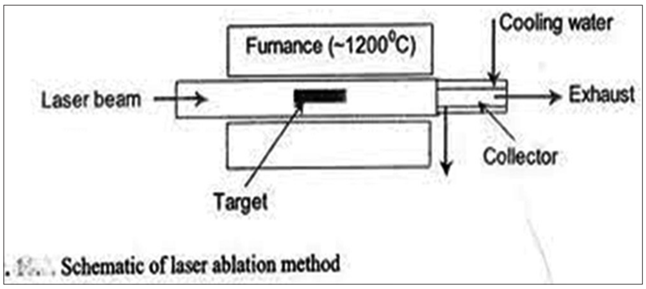

Fig. 8: Laser ablation method

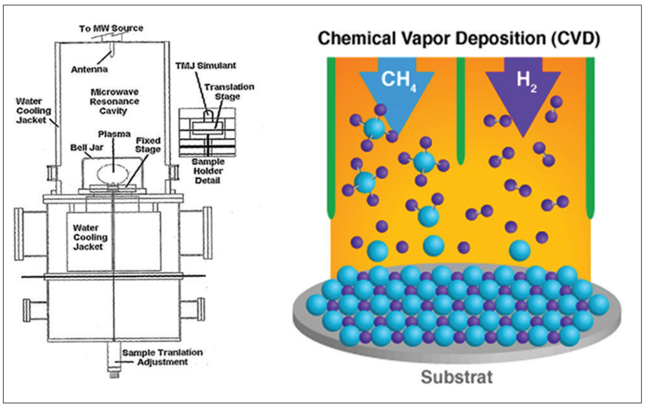

Fig. 9: Chemical vapor deposition method

PURIFICATION

Major problem regarding the nanotube application next to large scale synthesis is purification. The as-produced single walled nanotubes soot contains lot of impurities in which amorphous carbon, graphite sheets, metal catalyst and small fullerenes form main impurities that interferes with most of the desired properties of SWCNT. In the fundamental research, it is preferred to obtain SWCNTs or impurities as pure as possible in order to understand the measurements better. Common industrial practices use strong oxidation and acid refluxing techniques which have an effect on the structure of the tubes. These techniques can be divided into two main streams - structure selective and size selective separations where the former one separates SWNTs from the impurities and the latter ones will give a more homogenous diameter or size distribution. Commonly employed industrial techniques are usage of strong oxidation and acid refluxing techniques, which have an effect on the structure of the tubes. Given below are some of the purification techniques of nanotubes [18]:

- Oxidation
- Acid treatment
- Annealing
- Ultrasonication
- Magnetic purification
- Functionalization
- Cutting
- Micro filtration.

Oxidation [18]
A good way to remove carbonaceous impurities or to clear the metal surface is oxidative treatment of SWNTs, but the main disadvantages of oxidation are that along with impurities, the SWNTs are also oxidized. But the damage to SWNTs is less than the damage to impurities. Impurity oxidation is preferred majorly because these impurities are most commonly attached to a metal catalyst which also acts as oxidizing catalyst. The efficiency and the yield of the procedure are highly dependable on a lot of factors such as metal content, oxidation time, environment, oxidizing agent and temperature.

Acid treatment [19]
Acid treatment is used to remove the metal catalyst. In the first step, the surface of the metal must be exposed by oxidation or sonication. Then the metal catalyst is exposed to acid and solvated, and the SWNTs remain in suspended form. Using the treatment in HNO_3, the acid only has an effect only on the metal catalyst but not on the SWNTs and other carbon particles. If HCl is used instead of HNO_3, the acid also has a little effect on the SWNTs and other carbon particles. Treatment with a mild acid (4 M HCl reflux) is basically the same as the HNO_3 reflux, but here the metal has to be totally exposed to the acid to solvate it.

Annealing [19]
This technique employs high temperatures (873-1873 K) where the nanotubes will be rearranged, and defects will be consumed. Graphitic carbon and the short fullerenes get pyrolyse as result of high temperatures. While high temperature vacuum treatment (1873 K) are used, the metal will be melted and can also be removed.

Ultrasonication [19]
Here, particles are separated due to ultrasonic vibrations. Aggregates of different nanoparticles will be forced to vibrate and will become more dispersed. Particle separation is highly dependable on the surfactant, solvent and reagent used. Stability of the dispersed tubes in the system is influenced by the solvent. SWNTs are more stable if they are still attached to the metal in poor solvents. But, mono dispersed particles are relatively stable in some solvents, such as alcohols. The purity of the SWNTs depends on the exposure time when an acid is used. Only the metal is solvated when the tubes are exposed to the acid for a short time, but for a longer exposure time, the tubes will also be chemically cut.

Magnetic purification [19]
This method is used to remove ferromagnetic (catalytic) particles mechanically from their graphitic shells. To remove the ferromagnetic particles, the SWNTs suspension is mixed with inorganic nanoparticles (mainly ZrO_2 or $CaCO_3$) in an ultrasonic bath and then the particles are trapped with permanent magnetic poles, a high purity SWNT material will be obtained after a subsequent chemical treatment.

Micro filtration [19]
This method is based on size or particle separation. A small amount of carbon nanoparticles and SWNTs are trapped in a filter whereas the other nanoparticles (catalyst metal, fullerenes, and carbon nanoparticles) are passing through the filter. Soaking the as-produced SWNTs first in a CS_2 solution is one way of separating fullerenes from the SWNTs by micro filtration. The CS_2 insolubles are then trapped in the filter and the fullerenes that are solvated in the CS_2, pass through the filter.

Cutting [19]
This method can either be induced by chemical, mechanical or as a combination of these. Chemically, SWNTs can be cut by partially functionalizing the tubes, for example with flour and then the fluorated carbon will be driven off the sidewall with pyrolization in the form of CF_4 or COF_2 leaving behind the chemically cut nanotubes. Mechanical cutting of the nanotubes can be induced by ball-milling resulting in the breaking of bonds due to the high friction between the nanoparticles, and the nanotubes will be disordered. Combination of mechanical and chemical cutting of the nanotubes is ultrasonically induced cutting in an acid solution where the ultrasonic vibration will give the nanotubes sufficient energy to leave the catalyst surface. The nanotubes will rupture at the defect sites in combination with the acid.

ANALYTICAL TECHNIQUES FOR CNTS

In order to evaluate the purity, dispersion, physical and functional properties of CNTs for pharmaceutical applications, a consistent protocol must be developed. Properties such as size, type, surface defects, electronic characteristics, mechanical strength and thermal conductivity can be analyzed. Various techniques have been developed to characterize their strength and morphology of CNTs, to establish the presence or absence of exogenously found moieties on these CNT walls. Techniques such as thermo gravimetric analysis, scanning electronic microscopy (SEM), TEM, atomic force microscopy (AFM), Raman spectroscopy, IR spectroscopy and nuclear magnetic resonance (NMR) are extensively used. TEM, SEM, and AFM have been used for the quantitative establishment of general morphology of CNTs. The presence of functional groups on CNTs can be confirmed using IR, NMR and Raman spectroscopy [20].

The amount of carbon and non-carbon materials in bulk CNT samples as well as CNT homogeneity and thermal stability can be determined quantitatively by thermo gravimetric analysis. It is a non-selective method for the assessment of CNT qualitatively because this does not differentiate CNTs from metallic impurities in the sample. Hence it is used conjunctively with other techniques.

TEM [21]
The morphology and qualitative insight into the purity of produced CNTs can be determined by TEM. It provides information on size, shape; structure and non-CNT structured impurities in the sample. Identification of metallic impurities and differentiation from MWNT can be achieved. It has also been used to image cellular uptake of CNT drug composites and to determine the fate of CNT components after cellular uptake.

SEM [22]
SEM is used for the preliminary evaluation of CNT morphology. This technique is limited by its identity to differentiate catalyst and carbonaceous impurities from CNTs. SEM coupled with an energy dispersive X-ray analysis detector is used in the estimation of metallic content of CNT samples. However, SEM is probably the only technique, which can provide information on both CNT morphology and metallic impurity content.

Raman spectroscopy [23]
Synthesis and purification process of SWNTs can be evaluated by Raman spectroscopy. Major obstacle in interpreting the Raman spectra of SWNTs are carbonaceous impurities as they possess characteristic Raman features identical to that of SWNTs.

Proton NMR [24]
The progress of CNT functionalization can be monitored by NMR. Functional groups can be predicted by characteristic peaks arising from the difference in the magnetic environment.

IR spectra [24]
It is the primary tool to identify functional groups and nature of their attachment to CNT sidewalls. The different functional groups absorb

characteristic frequencies of IR radiation giving rise to fingerprint identification of bonds.

APPLICATIONS OF CNTS [25]

Biomedical applications

Protein/enzyme filled or protein-encapsulated nanotubes, due to their fluorescence ability in the presence of specific biomolecules have been tried as implantable biosensors. Nanocapsules filled with magnetic materials, radioisotope enzymes, can be used as biosensors. Nanosize robots and motors with nanotubes can be used in studying cells and biological systems. Biomedical Applications suggests that the carbon nanotubes are suitable scaffold materials for osteoblast proliferation and bone formation.

Gene therapy

This method uses a gene to promote cells to produce their own therapeutic proteins. CNTs and CNHs are used to manipulate genomes and atoms to develop bioimaging genomes, proteomics, and tissue engineering. They are used as vectors in gene therapy due to their tubular nature. The SWNTs are swirled by unbound DNA by connecting its specific nucleotides causing change in its electrostatic properties thus creating a way for potential applications in diagnostics and therapeutics.

Implants

Graft rejection reaction is normally seen for implants with post administration pain. Miniature sized nanotubes, and nanohorns get attached with other proteins and amino acids to prevent the rejection. They can also be used as implants in the form of artificial joints without host rejection reaction. CNTs filled with calcium and arranged in the structure of bone can act as bone substrate due to their high tensile strength.

Preservatives or anti oxidizing agents

Carbon nanohorns and nanotubes are antioxidant in nature and hence used to preserve the formulations prone to oxidation. Oxidation of impurities skin components can be prevented using their antioxidant property in antiaging cosmetics with Zinc oxide as sun screen dermatologic.

Carrier for drug delivery

Carbon nanohorns are the spherical aggregates of CNTs with irregular horn like shape. Research studies suggest that CNTs and CNHs as potential carriers for drug delivery systems.

- Functionalized CNTs are reported for targeting amphotericin B to cells (Fig. 10).
- Intracellular penetration is enhanced in case of Doxorubicin- an antibiotic is given with nanotubes.
- Enhanced permeability, distribution and retention of anticancer drug polyphosphazene platinum are seen in brain when given with nanotubes to their controlled lipophilicity.
- Slow release of Cisplatin in an aqueous environment is achieved when incorporated with oxidized SWNTs that had been effective in terminating the growth of human lung cancer.
- A successful oral alternative administration of Erythropoietin is achieved with CNT based carrier system which has not been possible so far because of denaturation of erythropoietin by gastric enzymes.

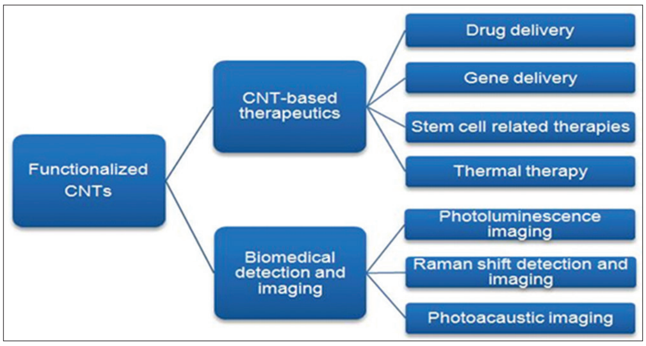

Fig. 10: Functionalized carbon nanotubes for various drug delivery systems

CONCLUSION

This review has addressed recent advances in the application of CNT for electrochemical biosensing. The attractive properties of CNT have paved the way for the construction of a wide range of electrochemical biosensors exhibiting an attractive analytical behavior. The marked electrocatalytic activity toward hydrogen peroxide and NADH permits effective low-potential amperometric biosensing of numerous important substrates. The enhanced electrochemical reactivity is coupled to the resistance to surface fouling and hence to high stability. The use of CNT molecular wires offers great promise for achieving efficient electron transfer from electrode surfaces to the redox sites of enzymes. Better control of the chemical and physical properties of CNT and understanding of their use as molecular wires should lead to more efficient electrical sensing devices. Electrochemical DNA biosensors can greatly benefit from the use of CNT support platforms and from the enhanced detection of the product of the enzyme label or the target guanine. Such developments suggest that future interdisciplinary efforts could yield new generations of CNT-based biosensors for a wide range of applications. It is thus fair to say that the real biosensing opportunities of CNT still lie in the future.

REFERENCES

1. Wang X, Li Q, Xie J, Jin Z, Wang J, Li Y, *et al*. Fabrication of ultralong and electrically uniform single-walled carbon nanotubes on clean substrates. Nano Lett 2009;9(9):3137-41.
2. Wang H, Chhowalla M, Sano N, Jia S, Amaratungal GA. Large scale synthesis of single walled carbon nanohorn by submerged arc. Nanotechnology 2004;15(5):546-50.
3. Yu MF, Lourie O, Dyer MJ, Moloni K, Kelly TF, Ruoff RS. Strength and breaking mechanism of multiwalled carbon nanotubes under tensile load Science 2000;287:637-40.
4. Collins PG. Nanotubes for Electronics. Scientific American; 2000. p. 67-9.
5. Jensen K, Mickelson W, Kis A, Zettl A. Buckling and kinking force measurements on individual multiwalled carbon nanotubes. Phys Rev 2007;B76:195436.
6. Popov M, Kyotani M, Nemanich RJ, Koga Y. Superhard phase composed of single wall carbon nanotube. Phys Rev 2000;B65:033408.
7. Hone J. Phonons and thermal properties of carbon nanotubes. Appl Phys 2001;273-286.
8. Yi W, Lu L, Zhang DL, Pan ZW, Xie SS. Linear specific heat of carbon nanotubes. Phys Rev B 1999;59:9015.
9. Mizel A, Benedict LX, Cohen ML, Louie SG, Zettl A, Budraa NK, *et al*. Analysis of the low-temperature specific heat of multiwalled carbon nanotubes and carbon nanotube ropes. Phys Rev B 1999;60:3264.
10. Hone J, Batlogg B, Benes Z, Johnson AT, Fischer JE. Quantized phonon spectrum of single- wall carbon nanotubes. Science 2000;289:1730.
11. Lasjaunias JC, Biljakoviæ K, Benes Z, Fischer JE, Monceau P. Low-temperature specific heat of single-wall carbon nanotubes. Phys Rev B 2002;65:113409.
12. Hone J, Whitney M, Piskoti C, Zettl A. Thermal conductivity of single-walled carbon nanotubes. Phys Rev B 1999;59:2514.
13. Kim P, Shi L, Majumdar A, McEuen PL. Thermal transport measurements of individual multiwalled nanotubes. Phys Rev Lett 2001;87(21):215502.
14. Anazawa K, Shimotani K, Manabe C, Watanabe H, Shimizu M. High purity carbon nano tube synthesis method. Appl Phys Lett 2002;81:739-41.
15. Bianco A, Kostarelos K, Partidos CD, Prato M. Biomedical applications of functionalised carbon nanotubes. Chem Commun (Camb) 2005;(5):571-7.
16. Bianco A, Hoebeke J, Kostarelos K, Prato M, Partidos CD. Carbon nanotubes: On the road to deliver. Curr Drug Deliv 2005;2(3):253-9.
17. Moore V, Strano M, Haroz E, Hauge R, Smalley R. Individually suspended single-walled carbon nanotubes in various surfactants. Nano Lett 2003;3:1379-82.

18. Vaisman L, Wagner HD, Marom G. The role of surfactants in dispersion of carbon nanotubes. Adv Colloid Interface Sci 2006;128-130:37-46.
19. Fernando KA, Lin Y, Sun YP. High aqueous solubility of functionalized single-walled carbon nanotubes. Langmuir 2004;20(11):4777-8.
20. Saini RK, Chiang IW, Peng H, Smalley RE, Billups WE, Hauge RH, *et al*. Covalent sidewall functionalization of single wall carbon nanotubes. J Am Chem Soc 2003;125(12):3617-21.
21. Kim BM, Qian S, Bau HH. Filling carbon nanotubes with particles. Nano Lett 2005;5(5):873-8.
22. Abdulkareem AS, Afolabi AS, Iyuke SE, Vz Pienaar HC. Synthesis of carbon nanotubes by swirled floating catalyst chemical vapour deposition method. J Nanosci Nanotechnol 2007;7(9):3233-8.
23. Eklund P, Holden J, Jishi R. Vibrational modes of carbon nanotubes; spectroscopy and theory. Carbon 1995;33:959-72.
24. Yinghuai Z, Peng AT, Carpenter K, Maguire JA, Hosmane NS, Takagaki M. Substituted carborane-appended water-soluble single-wall carbon nanotubes: New approach to boron neutron capture therapy drug delivery. J Am Chem Soc 2005;127(2):9875-80.
25. Hirlekar R, Yamagar M, Garse H, Vij M, KadamV. Carbon nanotubes and its applications. Asian J Pharm Clin Res 2009;2(4):24-6.