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Review Article

CARBON NANOTUBES AND PHARMACEUTICAL APPLICATIONS

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ABSTRACT
Carbon nanotubes (CNTs) are often described as a graphene sheet rolled up into the shape of a cylinder. These have fascinated scientists with their extraordinary properties. These compounds have become increasingly popular in various fields simply because of their small size and amazing optical, electric and magnetic properties when used alone or with additions of metals. Carbon nanotubes have potential therapeutic applications in the field of drug delivery, diagnostics, and biosensing. Functionalized carbon nanotubes can also act as vaccine delivery systems.
Carbon nanotubes (CNTs) are considered to be one of the innovative resources in nanotechnology with possible use in wide range of biomedical applications *viz*. cancer treatment, bioengineering, cardiac autonomic regulation, platelet activation and tissue regeneration. The effect of CNTs on cells and tissues are extremely important for their use in various complex biological systems. With the increasing interest shown by the nanotechnology research community in this field, it is expected that plenty of applications of CNTs will be explored in future.
KEYWORDS Carbon nano tubes, Applications, Graphene, Functionalization.

INTRODUCTION

The discovery that carbon could form stable, ordered structures other than graphite and diamond stimulated many researchers in the world to search for other allotropes of carbon. Carbon can bond to itself to form extremely strong two-dimensional sheets (graphene) and these sheets can be rolled and folded into a diverse range of three-dimensional structures, of which the most famous are the ball-shaped fullerenes and the cylindrical nanotubes.
Carbon nanotubes, (also known as a buckytube), long, thin, hollow, seamless cylinders of carbon, were discovered in 1991 by S. Lijima. These tubes are normally capped with the half a full fullerene molecules at both the ends[2,3]. These are cylinders of one or several coaxial graphite layer(s) with a diameter in the order of nanometers (1-100).These shows unique chemical, physical and electrical properties[4, 5].
These are large macromolecules that are unique for their size, shape, and remarkable physical properties. Nanotubes are composed of sp^2 bonds, similar to those observed in graphite and they naturally align themselves into ropes held together by vander Waals forces. Physicochemical properties of CNT's include ultra light weight, ordered structure with high aspect ratio, high mechanical strength and metallic or semi-metallic behavior with high surface area. There are some limitations of CNT's also, which includes lack of solubility in most solvents and aggregation. Both these limitations can be overcome by functionalization or modification of their surface[2].
These new nanomaterials belonging to the family of fullerene are the third allotropes of carbon[7]. They are among the stiffest and strongest fibers known, and have remarkable electronic properties and many other unique characteristics[1]. Recently, scientists have also accounted that CNT's hold potential of a drug delivery systems. The studies have shown that CNT's loaded with peptides[8], proteins[9], nucleic acids[10] and drugs[10] comprise effective targeting into the cells.
Graphene is an allotrope of carbon; whose structure is one atom thick planar sheets of sp2 bonded carbon atoms that are densely packed in a honey comb crystal lattice. Curling of this gives the helical carbon nanotube. Tubes of different helicity can be obtained by changing the type of folding/ curling. The electronic structure of the tube varies as the helicity changes.
There are three distinct ways in which graphene rolls in to carbon nanotube. (Fig: 1) The way the graphene sheet wraps can be represented by a pair of indices (n, m) called the chiral vector. The relationship between n and m defines three categories of CNT's viz. (*i*) arm chair ($n = m$ and chiral angle equal to 30°), (*ii*) zigzag ($n = 0$ or $m = 0$ and chiral angle equal to 0°), and (*iii*) chiral (other values of n and m and chiral angles lie between 0 and 30°).

TYPES OF CARBON NANOTUBES

Based on the number of layers CNT'S can be classified as,

Single walled carbon nanotubes (SWCNT)

These are seamless cylinders, were first reported in 1993[3]. Single-walled nanotubes have a diameter of close to 1 nanometer, with a tube length that can be many millions of times longer. SWNT's typically team up to form bundles. These bundles consists hexagonally arranged SWNT's to form a crystal-like structure.

Double walled carbon nanotubes (DWCNT) It consists of two graphene sheets rolled in to concentric circles. The special place of double-walled carbon nanotubes must be emphasized here because their morphology and properties are similar to SWNT but their resistance to chemicals is significantly improved.

Multi walled carbon nanotubes (MWCNT) MWCNT's consist of multiple layers of graphite rolled in, on themselves to form a tube shape with an interlayer spacing of 3.4 Å. The outer diameter of MWCNTs may range from 1 to 50 nm while the inner diameter is usually of several nanometres[12].

The figure2 illustrates the different types of carbon nanotubes.

PREPARATION OF CARBON NANOTUBES

Techniques like carbon arc-discharge, laser ablation, high pressure carbon monoxide (HiPco), and chemical vapour deposition (CVD) are being employed to synthesize CNT's of sizeable quantities. Of these, the CVD method has shown the most promise in terms of its price/unit ratio.

The arc-evaporation method, which produces the best quality nanotubes, involves applying a current of about 50 A between two graphite electrodes in a helium atmosphere. This results in graphite evaporation, part of which condenses on the walls of the reactor vessel and part on the cathode. Deposit on the cathode usually contains the CNT's. SWCNT's are produced when Co and Ni or some other metal is added to the anode. Lijima and Ichihasti[12] have reported the synthesis of SWCNT's with diameters of around 1 nm. Bethune *et al.*[14] have used Co, Ni, and Fe as catalysts to synthesize CNT's. Researchers have also used the mixture of catalysts (Ni-Co, Co-Y, or Ni-Y) in the synthesis of SWCNT's.

In laser-ablation technique, intense laser pulses are used to ablate a carbon target. The pulsed laser-ablation of graphite in the presence of an inert gas and catalyst yields CNT's [15] in the form of ropes or bundles of 5 to 20 nm diameter and tens to hundreds of micrometers long. Fullerenes, graphite Polyhedrons with enclosed metal particles, and amorphous carbon were obtained as the by-products in arc-discharge and laser-ablation technique.

Generally, the CVD technique involves the reaction of a carbon-containing gas (such as methane, acetylene, ethylene, ethanol, etc.) with a metal catalyst particle (usually, cobalt, nickel, iron, or a combination of these such as cobalt/iron or cobalt/ molybdenum) at temperatures above 600°C. Although both arc-discharge and laser-ablation methods produce SWCNT's in high yields (more than 70%), they have disadvantages like (*i*) tangled CNT's that are synthesized to make the purification and applications of CNT's difficult and (*ii*) these processes rely on evaporation of carbon atoms at temperatures more than 3000°C. All the currently known synthesis methods for SWCNT's result in major concentrations of impurities [16].

PURIFICATION OF CARBON NANOTUBES

Nanotubes usually contain a large amount of carbonaceous impurities such as amorphous carbon, fullerenes, nanoparticles, and transition metals introduced as catalysts during the synthesis.There are different methods for 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 CNT's. 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 (H2SO4), but HCl was identified to be the ideal refluxing acid.

Surfactant aided sonication

Filtration and annealing after acid refluxing, the CNT's 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 CNT's to settle down, indicating an even suspension state was achieved.

Although purification based on an initial selective oxidation to remove amorphous carbon followed by a reflux in concentrated nitric acid is effective in removing metal from the reaction products, the

refluxing in nitric acid induces wall damage in the nanotubes[17]. SWCNT's of more than 90% purity were produced using ultrasonically assisted micro filtration from amorphous and crystalline carbon impurities and metal particle [18]. A scalable purification is possible using microwave heating in the presence of air followed by treatment with hydrochloric acid. Microwave assisted purification is also used for purification of MWCNTs[19].

In addition, carboxymethyl cellulose has been employed recently for the purification of SWCNT's. This method involves annealing in air and dispersing the SWCNT's in an aqueous solution of gelatine. The purity of the CNT's can be evaluated by Raman spectroscopy, transmission electron microscopy (TEM), scanning electron microscopy (SEM), atomic force microscopy (AFM), and UV-visible-near-infrared (UV-vis-NIR).

FUNCTIONALIZATION OF CARBON NANOTUBES

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. functionalisation 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. Functionalized carbon Nanotubes (f-CNT's) have been demonstrated to deliver proteins, nucleic acids, drugs, antibodies and other therapeutics. Emerging developments in this area are pointing towards the successful utilization of carbon nanotubes for drug delivery. This is because they can be easily manipulated and modified by encapsulation with biopolymers or by covalent linking of solubilising groups to the external walls and tips. Functionalization of MWCNT's can be achieved by many functional groups followed by acid treatment [20].

APPLICATIONS

CNT's have large inner volumes which can be filled with sundry chemicals and biomolecules, ranging in size from small molecules to proteins [21, 22]. Because the inner and outer surfaces of certain types of nanotubes are distinct, they can be differentially modified to encapsulate specific drugs internally and to evade immunogenic response externally [22]. Finally, the open-mouthed structure of nanotubes renders loading especially simple. Their intrinsic physicochemical features enable covalent and non-covalent binding of several pharmaceutical entities and allow for rational design of novel candidate nanoscale structures for drug development. CNT's can be functionalized with different functional groups to carry simultaneously several moieties for targeting, imaging and therapy[8].

The large inner volume of CNT's allows encapsulation of both low as well as high molecular weight drugs. It also permits encapsulation of both hydrophilic and lipophilic drugs. More than one drug can also be loaded in CNT's in the case of multi-drug therapy. The CNT's can act as controlled release system for drug by releasing the loaded drugs for a long period of time. In this way CNT's can be used multifunctionally for drug delivery and targeting[5].

These nanotubes can act as highly specific electronic sensors for detecting clinically important biomolecules such as antibodies associated with human autoimmune diseases.

CARBON NANOTUBES FOR CANCER THERAPY

For oligonucleotides transported inside the cells by nanotubes, Near Infrared (NIR) laser pulses can trigger the endosomal rupture of the cell thus translocating the oligonucleotides into the cell nucleus. Continuous NIR radiation can cause cell death because of excessive local heating of SWNTs in vitro. This property can be used in photo-thermal therapy for selective cell destruction of tumor cells by functionalization SWNTs with different ligands, which are then taken up by tumor cells without harming the receptor-free normal cells[8].

Among the most interesting examples of such multimodal CNT constructs described is one carrying a fluorescein probe together with the antifungal drug amphotericin B or fluorescein and the antitumor agent methotrexate. The biological action of the drug is retained or enhanced, while CNT's are able to reduce the unwanted toxicity of the drug administered alone.

Liu *et al.* [23] have demonstrated that DOX loaded SWCNTs (PL– SWCNT–DOX) induced significant U87 cancer cell death and cell apoptosis. The main advantage of using SWCNT's as a drug carrier compared to free drug is the potential to target delivery for selective destruction of certain types of cells, reducing the toxicity to non-targeted cells. This novel method provides an easy-to make formulation of the SWCNT–DOX complex with extremely high drug-loading efficiency, which is remarkably higher than that reported for conventional liposome's and dendrimer drug carriers [26].

Dispersion of single walled carbon nanotubes (SWCNT's) by ultrasonication with phospholipid-

polyethylene glycol (PL-PEG) fragments it, thus interfering with its ability to block nonspecific uptake by cells. However, unfragmented PLPEG promoted specific cellular uptake of targeted SWCNT's to two distinct classes of receptors expressed by cancer cells[25]. Conventional adoptive immunotherapy techniques can take weeks, but using carbon nanotubes shortens this time frame by up to two thirds. Using fluorescence resonance energy transfer (FRET) microscopy, the researchers found that the antigens concentrate around defects on the surface of the carbon nanotubes[27]. Nanotube drug delivery is promising for high treatment efficacy and minimum side effects for future cancer therapy with low drug doses [28].

CARBON NANOTUBES FOR DNA DELIVERY

When bound to single-walled carbon nanotubes, DNA probes are protected from enzymatic cleavage and interference from nucleic acid binding proteins which resulted in superior biostability and increased self delivery capability [5].

Ammonium-functionalized CNT's (f-CNT's) are able to condense plasmid DNA (pDNA) and are taken up into the cells. Polyethylenimine-grafted multiwalled carbon nanotubes (PEI-g-MWCNT's) can efficiently immobilize and transport pDNA into cells. It was reported that acid-oxidized CNT's can also be used to afford noncovalent protein or DNA-nanotube conjugates. Ammonium functionalized CNTs can also be considered very promising vectors for gene-encoding nucleic acids. Stable complexes between cationic CNT's and plasmid DNA demonstrated the enhancement of the gene therapeutic capacity in comparison to DNA alone [25].

CARBON NANOTUBES FOR VACCINE DELIVERY

Functionalized carbon nanotubes can also act as vaccine delivery systems. The basic concept is to link the antigen to carbon nanotubes while retaining its conformation, thereby, inducing antibody response with the right specificity.

CARBON NANOTUBES FOR PEPTIDE DELIVERY

Application of CNT as a template for presenting bioactive peptides to the immune system has been studied. For this purpose, by using a bifunctional linker epitope of virus and amine group of CNT can be covalently linked and immunization can be done. Subsequently the immunogenic features of peptide–CNT conjugates can be assessed in vivo. In this way CNT's can achieve high value in peptide delivery [26].

CNT'S FOR BIOENGINEERING

Many potential bioengineering applications have been proposed for carbon nanotubes, including conductive and high strength composite, energy storage and energy conversion devices, sensors, field emission displays and radiation sources, hydrogen storage media and nanometer-sized semiconductor devices[27, 28].

CNT FOR CARDIAC AUTONOMIC REGULATION

Single-walled carbon nanotubes share physicochemical properties with ultrafine component which may impair cardiovascular autonomic control proved after the study conducted in rats, suggest that SWCNT's may alter the baroreflex function, thus affecting the autonomic cardiovascular control regulation [28].

CNT FOR PLATELET ACTIVATION

The study on platelet activation *in vitro*, macro and microcirculatory thrombus formation *in vivo* was studied using platelet P-selectin expression method. It has been reported that SWCNT's when injected into anaesthetized mice, light/dye-induced thrombus formation was noted and the platelet found to be activated [25].

MWCNT's activate blood platelets by inducing extracellular Ca2+ influx that could be inhibited by calcium channel blockers SKF 96365 and 2-APB. CNT-induced platelet activation is associated with a marked release of platelet membrane micro particles positive for the granular secretion markers CD62P and CD63 [25].

CARBON NANOTUBES FOR TISSUE ENGINEERING

The main objective of tissue engineering is to restore unhealthy or damaged tissue with biologic alternative which can reinstate and preserve regular tasks. The carbon nanotubes can be used for tissue engineering by visualizing and enhancing cellular performance and by tracking and labeling of cells. CNTs are combined with polymers, (poly-l-lactide, Polylactide and poly-D, L-lactide-co-glycolide copolymer) which have been used as a scaffolds in tissue regeneration. MacDonald et al., prepared composite materials comprised of a collagen matrix with embedded CNTs by mixing solubilized collagen with solution having carboxylated SWCNTs. Living smooth muscle cell were incorporated at the collagen stage to produce cell-seeded collagen CNT composite matrices. They concluded that such collagen CNT composite mixtures may be useful as scaffolds in tissue regeneration[27].

Armentano et al., processed nanocomposite films based on SWCNTs and poly-D,L-lactide-co-glycolide copolymer, and suggested that the degradation kinetics

of the films could be engineered by varying the MWCNTs content and functionalization[28]

Abarrategi et al., evaluated cell adhesion, viability and proliferation on the external surface of the scaffolds composed of a major fraction of MWCNTs and a minor fraction of chitosan. It has a well defined micro channel porous structure as biocompatible and biodegradable supports for cell growth in vitro[26].

CARBON NANOTUBE MEMBRANES FOR TRANSDERMAL DRUG DELIVERY

Novel skin patch device has been developed for delivering nicotine based on an active layer of aligned carbon nanotubes (CNT) approximately 1.5-7 nm in diameter crossing through a solid polymer film. The ends of the CNTs are modified chemically so that they can be opened or closed at any time by applying or removing a small electric current, respectively.

It is shown that in the open state, small molecules are actively pumped across the membrane five times faster than simple diffusion. In other words, the CNT patch is a programmable system that can be controlled by the physician or the patient to mimic the rapid attainment of high nicotine plasma levels similar to those associated with smoking a cigarette, and then closed to allow a slow return to normal. The usefulness of the CNT patch is not limited to nicotine; many other skin absorbable compounds could be used as well. It has been proposed that opioid withdrawal symptoms could be relieved in a similar manner by the use of the alpha-adrenergic agonist clonidine in the CNT patch.

CARBON NANOTUBES FOR BIOMEDICAL APPLICATIONS

CNT-based nanosensors are highly suitable as implantable sensors. Implanted sensors can be used for monitoring pulse, temperature, blood glucose, and also for diagnosing diseases. One such example is the use of nanotubes to track glucose levels in the blood, which would allow diabetics to check their sugar levels without the need for taking samples by pricking their fingers. Another example is monitoring of the exposure to hazardous radiation like in nuclear plants/reactors or in chemical laboratories or industries. The main purpose in all these cases is to detect the exposure in different stages so that appropriate treatment may be administered.

Filling carbon nanotubes with magnetic materials offers the potential for hyperthermia applications while the insertion of NMR active substances allows the usage as markers and sensors. In addition, a non-invasive temperature control by virtue of a carbon-wrapped nanoscaled thermometer and filling with anti-cancer drugs is possible[34].

CARBON NANOTUBES FOR CELLULAR IMAGING

Nanotubes were employed as carriers for imaging and therapeutic agent delivery and the biodistribution of radio-labeled nanotubes was investigated in mice by in vivo positron emission tomography (PET). It was found that the nanotubes functionalized with phospholipids bearing PEG were surprisingly stable in vivo with long circulation times and low up take by the reticuloendothelial system[4].

CARBON NANOTUBES AS 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.

POSSIBLE TOXICITY OF CARBON NANOTUBES

Nanotechnology is the science involving manipulation of materials at the nanometer scale. Concerns over adverse and unanticipated effects on human health have also been raised. In fact, the same properties that make nanomaterials attractive from a technological and biomedical application could also make these novel materials harmful to human health and the environment. Generally, the harmful effects of nanoparticles arise from the combination of various factors, two of which are particularly important: (a) 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 defenses and can modify the structure of proteins. Therefore, nanoparticles can activate inflammatory and immunological responses and may affect the normal tissue function.

The intrinsic toxicity of CNT depends on the degree of surface functionalization and the different toxicity of functional groups. Batches of pristine CNT (non-purified and/or nonfunctionalised) 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. It has been 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 these nanomaterials 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.[2], and as a result, CNTS are beginning to come under toxicological scrutiny. Relevant workplace regulation regarding exposure is also under consideration. Numerous in vitro and in vivo studies have shown that Carbon Nanotubes and associated contaminants or catalytic materials that arise during the production process may cause oxidative stress and prominent pulmonary inflammation. Recent studies also suggest some similarities between the pathogenic properties of multi-walled Carbon Nanotubes and those of asbestos fibers.

OTHER MODIFICATIONS OF CARBON NANOTUBES

Nanobuds

Carbon Nanobuds form a material (discovered and synthesized in 2006) which combines two previously discovered allotropes. CNTs and spheroidal fullerenes. In this new material, fullerenes are covalently bonded to the outer sidewalls of the underlying nanotube. Consequently, nanobuds exhibit properties of both carbon nanotubes and fullerenes. For instance, the mechanical properties and the electrical conductivity of the nanobuds are similar to those of corresponding carbon nanotubes. However, because of the higher reactivity of the attached fullerene molecules, the hybrid material can be further functionalized through known fullerene chemistry. Additionally, the attached fullerene molecules can be used as molecular anchors to prevent slipping of the nanotubes in various composite materials, thus modifying the composite's mechanical properties.

Nanotorus

Carbon nanotubes bent into rings are the latest nanostructures to display surprising properties, resembling the shape of doughnut. It has favorable structural and chemical properties.

Nanohorns

Carbon Nanohorns, Single-Walled, Double Walled and Multi-Walled are black nano scale cylindrical tubes of graphitic carbon which differ from nanotubes in their "horn-like" shape similar to a sewing thimble giving them numerous applications as both the stiffest and strongest known fibers and because of their unique shape gives them an enormous amount of surface area. The resulting material has found application in proton exchange membrane (PEM) and Polymer Electrolyte (PEFC) fuel cells because they have the duel capability of providing a high surface area conductive layer and open gas paths. They are available in single walled; double walled and multi-walled forms, bundled and unbundled, with tube lengths from 5 to 30 nanometers (nm) and specific surface area (SSA) in the 50 to 500 m 2 /g range.

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. Like detection sensitivity in medical imaging, improved therapeutic effectiveness, and decreased side effects.

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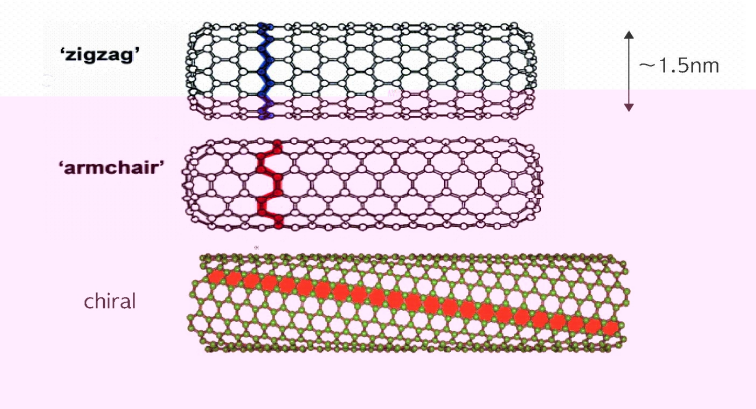

Fig 1: Different ways of rolling of SWNT

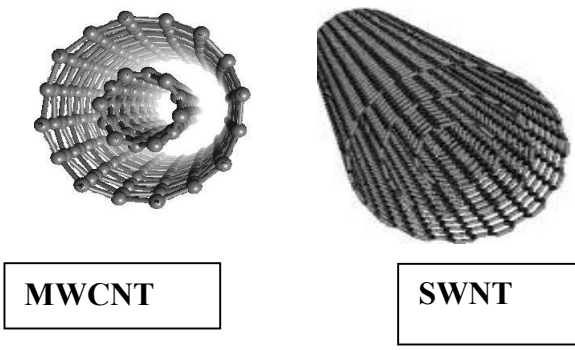

Fig 2: Different types of nanotubes