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NANOTUBE: A VERSATILE DRUG DELIVARY SYSTEAM: A REVIEW

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ABSTRACT

In nano-science and nanotechnology basically more no of nano material has been synthesized and discovered rapidly. Nanotube are most disparate origin. Nanotube are other forms of carbon nano-materials with new properties and application these nano-tube are found in crude oil at very low concentration like 1000 ppm. Meteorites, interstellar dust and proto planetary nebulae as well as in certain sediment layers on Earth. It can also be produced in the laboratory by using various method chemical vapor deposition or by laser ablation process. Nanotube have excellent mechanical and optical properties, also high surface areas and tunable surface structures. Nanotube are prepared by various methods like plasma based synthesis,thermal synthesis process,plasma enhanced CVD . Here we review the synthesis, structure, properties, and applications of individual Nano tubes and clusters of Nanotubes and their useful applications in medical and biological applications.

KEYWORDS: Nanotechnology, Nanoparticle, Nanotube,CVD Method.

INTRODUCTION

Carbon nanotubes (CNTs) are nanostructures basically derived from rolled graphene planes and possess various chemical and physical properties, that have been largely used in biomedicine. The discovery of CNTs using High Resolution Electron Microscopy (HREM) has increase intense experimental and theoretical studies on carbon nano-tubes.[1] carbon nanotube are allotropes of carbon that have a nanostructure, which can have a length of diameter ratio more than 1,000,000 reseracher studies have predicted interesting electronic properties for the nanotubes. The intense application of carbon nanotubes to the synthesis of nano wires has been demonstrated.[2] HREM is an pathway for the characterization of microstructure and it is most adapted to the study of nanotubes, it should be pointed out that the image obtained is a two-dimensional projection of a three-dimensional object.[3] CNT's can be linked with various biological molecules including drugs and nucleic acid to ensure biofunctionalities.[4,5] Moreover, the aromatic network existing on the Carbon nanotube surface let the efficient load of aromatic molecules such as chemotherapeutic API via stacking. The versatile and novel chemistry of carbon nanotubes ensures a wide range of their applications in biomedicine.[6] They show several interesting properties, such as high aspect-ratio, ultra-light weight, tremendous strength.[7] high thermal conductivity and remarkable electronic properties ranging from metallic to semiconducting.[8] It is unclear yet which of the two systems are more beneficial: SWCNTs offer the supplementry photoluminescence property that could be expertly applied in diagnostics, while MWCNTs present a broader surface that allows a more active internal encapsulation and external functionalization with active molecules. They have both been used for various different roles including biosensors, field-effect transistors (FET), and scanning probe elements.[9]

HISTORY

The carbon nanotube is discovered by lijima and coworker in 1991,carbon nanotube have been investigated by many scientist all over the world .length of nanotube upto several microns and diameter up to few nanometer ,nanotube can be as the nearly one dimensional form of fullerenes .so that these material are expected to posses additional interesting electronic ,mechanic and molecular properties.Especially in beginning ,all studies on carbon nanotubes focused on the influence of the nearly one dimensional structure on electric and molecular properties.[10]

STRUCTURE OF NANOTUBES

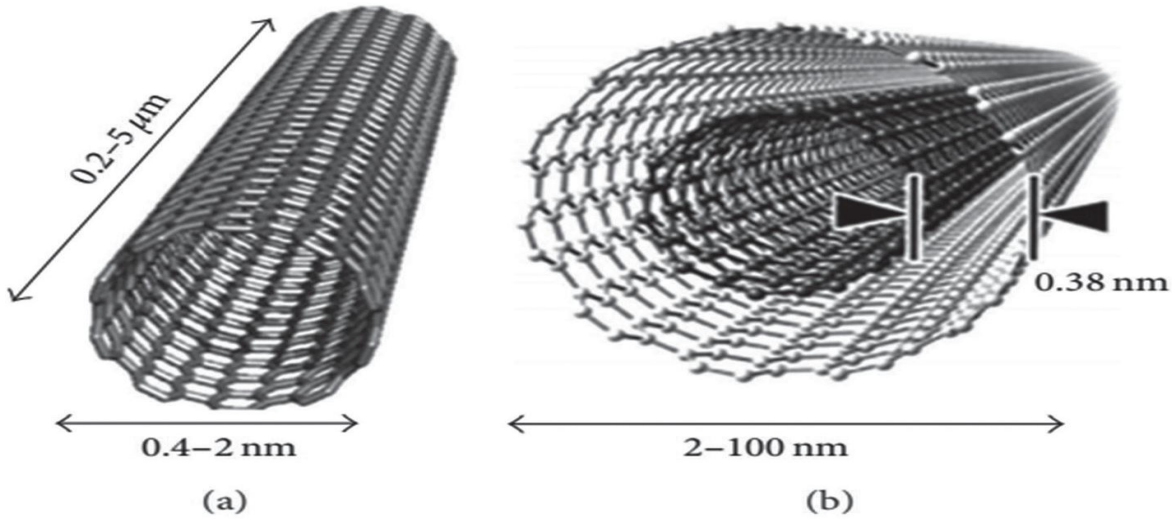

Fig1: schematic representation of possible hybridization in nanotube.

Carbon with sp2-like hybridization is exclusive. This is because its valence permitted scientific community to researcher a large collection of molecular architectures over the years. For instance, fullerenes structurally similar a soccer ball, whereas CNTs and grapheme are planner and cylindrical arrangement of carbon atoms, respectively , No matter how unrelated their carbon nanotube structures appear to be, these allotropes of carbon ultimately converge on numerous aspects, including thermal and electrical conductivity, respectable mechanical strength, and chemical inert properties . Hence, these nanostructures are in demand by today's pharmaceutical science, and vital for nanoscience, electronics, and biomedical applications. The morphology carbon nanotube are cylinders formed by rolling one or multiple graphene layers. This description hints on how carbon nanotubes are structurally classified: single-walled carbon nanotubes and multiple-walled carbon tube. Single wall carbon nanotube harbor one single cylinder of graphite sheet, with a diameter ranging from 0.4 to 3.0 nm (Iijima, 1991). By contrast, multiple wall carbon nanotube are conventionally depicted as an array of tubes, which are coaxially aligned around a central hollow. The distance between two layers seems invariable, and opposite roughly to the distance of graphite-layer spacing. The diameters of multiple wall carbon nanotube are dictated by the numbers of layers: the inner diameter can change from 0.4 nm to some nm, while the outer diameter ranges from 2 to 100 nm. The first one is the length of the tube: the relevant MWCNs have generally a length in the range of micrometer, as that of SWCNTs varies from 1 μm to a few centimeters . And the second one is the precision in diameter, such that single wall carbon nanotube have well-defined diameters, whereas multiple wall carbon nanotubes are known to suffer from some structural defects, rendering them relatively less stable materials[11,12]

TYPES OF NANOTUBES

The carbon nanotubes are of two types namely
1) Single walled carbon nanotubes (SWCNTs)
2)Multiple walled carbon nanotubes (MWCNTs)

Single wall carbon nanotube

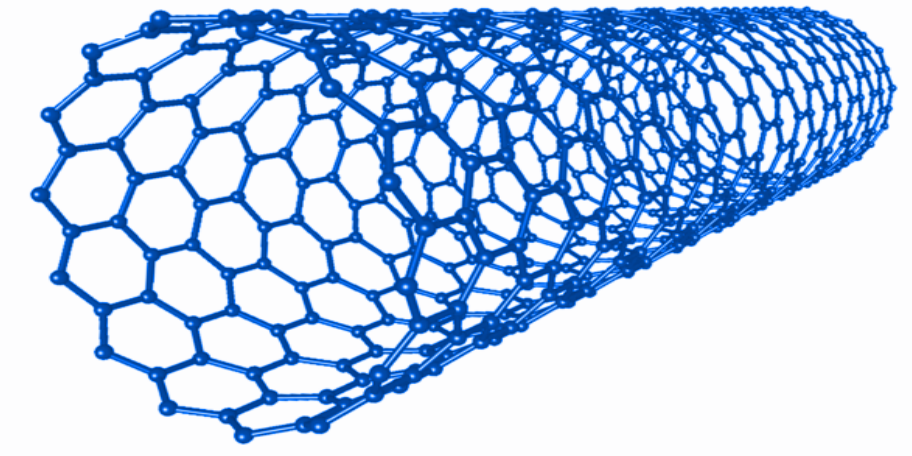

Fig 2: single wall carbon nanotube.

SWCNTs contain of a single cylindrical form carbon layer with a diameter in the range of 0.4-2 nm, depending on the temperature factor at which they have been synthesized. Reseacher was found that the higher the growth temperature larger is the diameter of CNTs.[13] The cylindrical structure of SWCNTs may be arm chair, zigzag, chiral, or helical arrangements.[14] The SWCNTs have an upperhigh surface area as large as 1300 m2/g, which renders enough space for drug loading and bio conjugation[15] . In drug delivery, SWCNTs are known to be more preferable than MWCNTs. This is due to the reason that SWCNTs have ultrahigh surface area and sufficient drug-loading capacity. It has been found that a SWCNTs anticancer drug complex has a ultrahigh longer blood circulation time than the anticancer drug on its own. This leads to high prolonged and sustained uptake of the drug by tumor cells via the enhanced permeability and retention effect. Once the functionalized of SWCNTs releases the drug into a target site , it is gradually excreted from the body via the biliary site pathway and finally in the feces. This suggested that SWCNTs are more suitable candidates for drug delivery and a promising nanoplatform for cancer therapeutics.[16]

Multiple walled carbon nanotubes

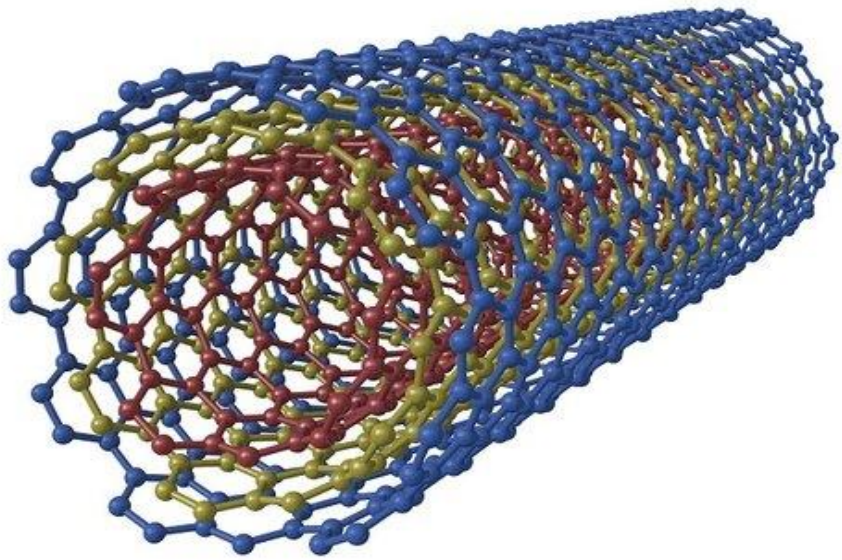

Fig 3: multiple wall carbon nanotube.

MWCNTs contain coaxial like cylindrical structure, each one made of a single grapheme sheet surrounding a hollow core. The external diameter of MWCNTs ranges from 0.002-0.1 mm, while the internal diameter is in the range of 0.001-0.003 mm, and their length is one to several micrometers .[17] The sp2 like hybridizationis present in MWCNTs, a delocalized electron cloud along with wall is produced which is responsible for the interactions between two side cylindrical layers in MWCNTs resulting in a less flexible and more number of structural like defects .[18] MWCNTs structure can be divide into two categories based on their arrangements of graphite layers: in that one has a parchment-like structure which consists of a graphene sheet rolled up around it and the other one is known as the Russian doll model where layers of graphene sheets are arranged within a concentric circular structure.[19] Decoration of multiwall carbon nanotubes (MWCNTs) consists of accumulating nanoparticles on the MWCNT walls or ends, attached by physical interaction with potential applications in catalysis, biosensors, biomedical, magnetic and electric data storage, and electronic devices biomedical science therpy. The various methods used for this purpose include oxidation, precipitation, hydrolysis at high temperature, or chemical decomposition of a metal precursor . efficient and simple purification methods. Most common purification methods are generally based on acid treatment of synthesized CNTs.[20]

METHOD OF PREPARATION OF NANOTUBE

1) Plasma based synthesis method or Arc discharge evaporation method
2) Laser Ablation Method .
3) Thermal Synthesis Process .
4) Chemical vapor deposition (CVD)
5) Plasma Enhanced CVD (PECVD

A) plasma based synthesis method or arc discharge evaporation method

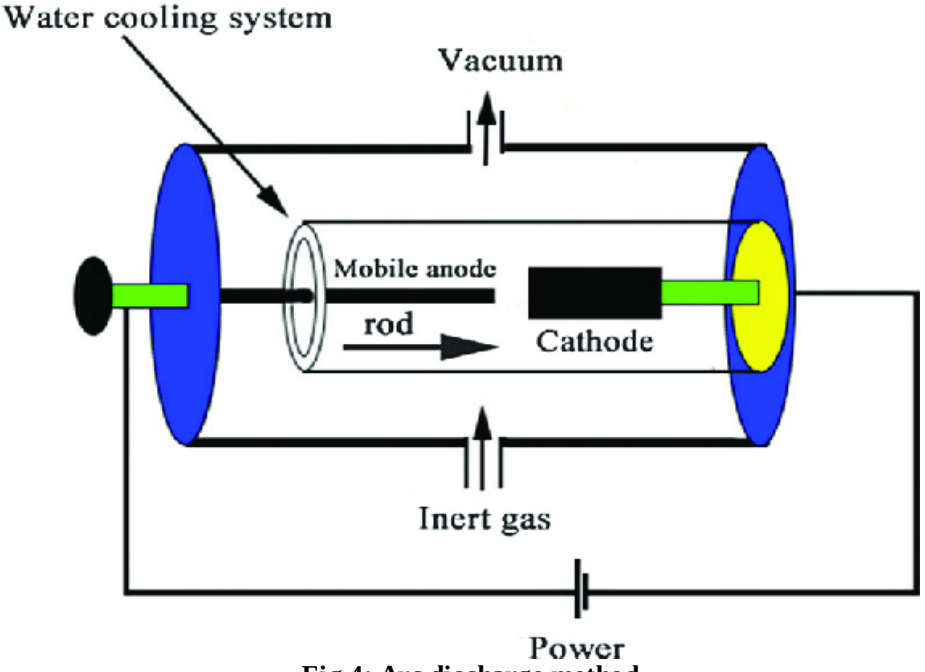

Fig 4: Arc discharge method.

In Arc discharge methods, use of upper temperatures (above 1700 ^{0}C) for CNT synthesis, which usually causes the expansion of CNTs with fewer structural defects compared with other techniques. the electrical arc mode used for producing C60 fullerenes, is that the foremost usual and perhaps the only due to produce CNTs. Multi-wall carbon nanotubes were determined in 1991 by Iijima by the arc-discharge evaporation technique. SWCNTs were produced subsequently in 1993 by the same.[21] during this method, electrical conduction created between two graphite electrodes winds up in an especially warmth which is sufficient to sublimate carbon. Either MWCNTs or SWCNTs can he formed when the carbon vapours cools and condenses Generally, MWCNT are formed when there is not any catalyst particles between two graphite electrodes; and also the SWCNT are often generated by adding Fe, Ni, or Co as catalysts. The catalysts are often introduced by packing metal powder into a hole within the anode. The metal was consumed alongwith the graphite and created catalyst particles favouring small-diameter SWCNTs.[22]

In case of MWCNTs, the purity and yield depended sensitively on the force per unit area within the reaction vessel. Different atmospheres markedly influence the last word morphology of CNTs. They used DC arc discharge of graphite electrodes in helium and methane. By evaporation under high pressured methane gas and high arc current, thick nanotubes embellished with many carbon nanoparticles were obtained. However, thin and long MWNTs were obtained under a methane force per unit area of fifty Torr and an arc current of 20 A for the anode with a diameter of 6 mm.[23] Moreover, it had been found that the variation of nanotube morphology was more marked within the case of evaporation in methane gas than that in helium gas.[24] The SWNTs are often produced when the transition metal catalyst is used. the tactic of SWNTs growth in arc discharge utilizes a composite anode, usually in hydrogen or argon atmosphere. The anode is made as a composition of graphite and a metal, such as Ni, Fe, Co, Pd, Ag, Pt. etc. or mixtures of Co, Fe, Ni with other elements like Co-Ni, Fe-Ni, Fe-No, Co-Cu, Ni-Cu, Ni-Ti etc. The metal catalyst plays **a** giant role within the method yield. to substantiate high efficiency, the tactic also should be held at a seamless gap distance between the electrodes which ensures stable current density and anode consumption rate. during this process, unwanted products like MWNTs or fullerenes are usually produced too.[25]

B) Laser ablation method

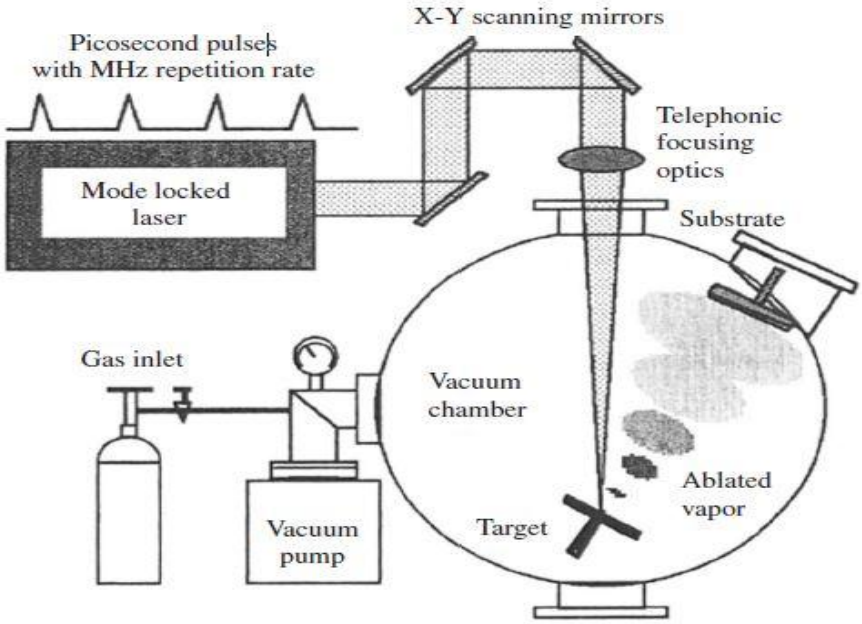

Fig 5: Laser ablation method.

The laser ablation method uses a pulsed and continuous laser to vaporize a graphite target in an oven, which is full of helium or argon gas to stay pressure. The laser ablation is comparable to the arc discharge, both taking advantage of the very heat generated, with the similar optimum background gas and catalyst mix observed. The very similar reaction conditions needed to point that the reactions probably occur with the identical mechanism for both the laser ablation and electric arc methods.[26] SWNTs were prepared by continuous wave green house emission without International Journal of Pharmaceutical Science and Research .applying additional heat to the target. They found that the common diameter of SWNTs produced by carbon dioxide laser increased with increasing laser power[27] . have successfully applied commercial MWNTs and MWNTs-polystyrene targets (PSNTs) for accumulation of composite thin films onto silicon substrates using PLD with a pulsed, diode pumped, Tm: Ho: LuLF laser (a laser host material LuLF (LuLiF4) is doped with holmium and thulium so as to achieve laser light production with in vicinity of two mm. They found that usage of pure MWNTs targets gives rise to a skinny film containing much higher quality MWNTs compared to PSNTs targets.[28] Similarly, prepared MWNTs thin films were deposited by PLD techniques (with Nd: YAG laser ablating commercially polystyrene-nanotubes pellets on alumina substrates.[30]

Thermal synthesis process

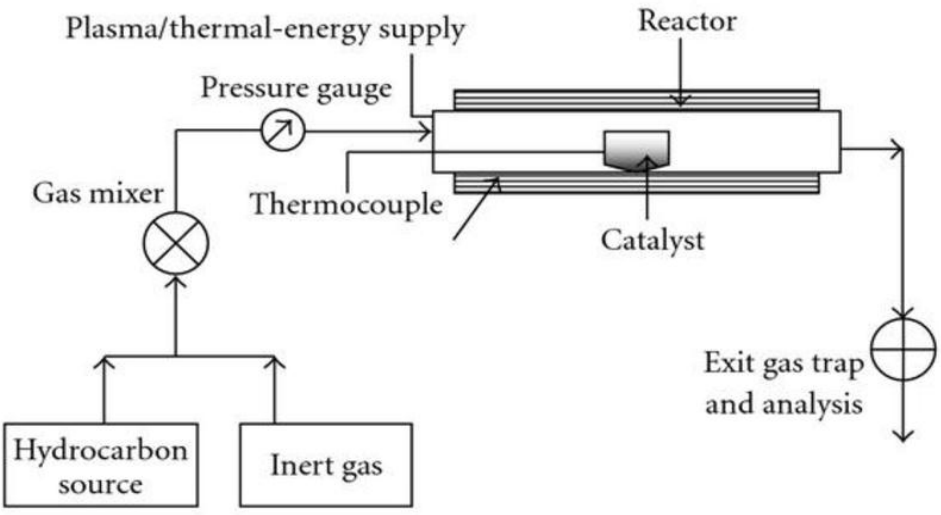

Fig 6: thermal synthesis process.

Arc discharge and laser ablation these two methods are fundamentally plasma based synthesis. However, in thermal synthesis process, only thermal energy is required and the hot zone of reaction never goes beyond 1200 ^{0}C, including the case of plasma enhanced CVD. In almost all cases, in the presence of active catalyst such as Fe, Ni, and Co, carbon feedstock produce CNTs depending on the carbon feedstock; Mo and Ru are sometimes added as stimulators to render the feedstock more active for the formation of CNTs. In fact, thermal synthesis is a more prone generic term to represent various chemical vapor deposition methods. It includes Chemical Vapor Deposition processes, Carbon monoxide synthesis techinque and flame synthesis technique.[30]

Chemical vapor deposition (CVD)

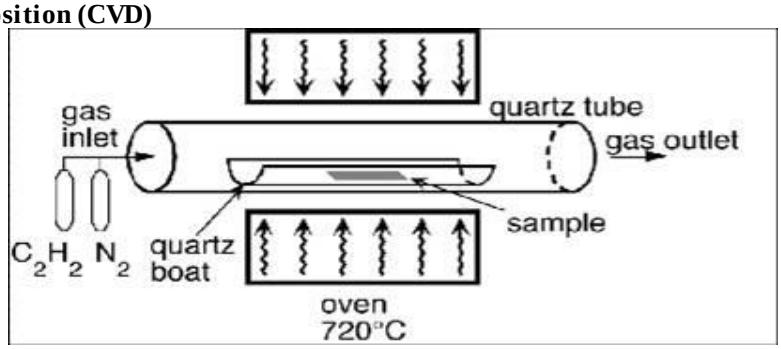

Fig7: chemical vapour deposition.

Catalytic CVD synthesis can be done by putting carbonin gas phase and using plasma or a resistively heated coil to heat the gaseous carbon containing molecules. The essential heat is used to "crack" the molecule into reactive atomic carbon. The most widely used catalysts are transition metals, primarily Fe, Co, or Ni. Sometimes, the traditionally used catalysts are further doped with other metals, e.g. with Au. Concerning the carbon source, the most preferred in Chemical vapour deposition are hydrocarbons such as methane, ethane, ethylene, acetylene, xylene, eventually their mixture, isobutane or ethanol. In the case of gaseous carbon source, the Carbon nanotube growth efficiency strongly depends on the reactivity and concentration of gas phase intermediates produced together with reactive species and free radicals as a result of hydrocarbon accumulation. These studies showed that growth efficiency strongly depends on the reactivity and concentration of gas phase intermediates produced as a result of complex gas phase reactions. On this basis, it can be expected that the most efficient intermediates, that have the potential of chemisorption or physisorption on the catalyst surface to initiate carbon nanotube growth should be produced in the gas phase. The overall kinetics of the growth process depend on the interaction, competition of gas phase and surface reaction.[31] Hydrocarbon molecules are often used as carbon sources, and ferrocene (FeCp2) as a catalyst. the SWCNTs with a mean diameter of 3.23 nm through the catalytic decomposition of a hydrocarbon with hydrogen, helium as the carrier gases[32] .in year 2010 prepared MAVNTs with diameters of 40-60 nm by the catalytic decomposition of methane at 680 ^{0}C for 120 min using nickel oxide-silica binary aerogels as the catalyst[33] .

Plasma enhanced CVD (PECVD):

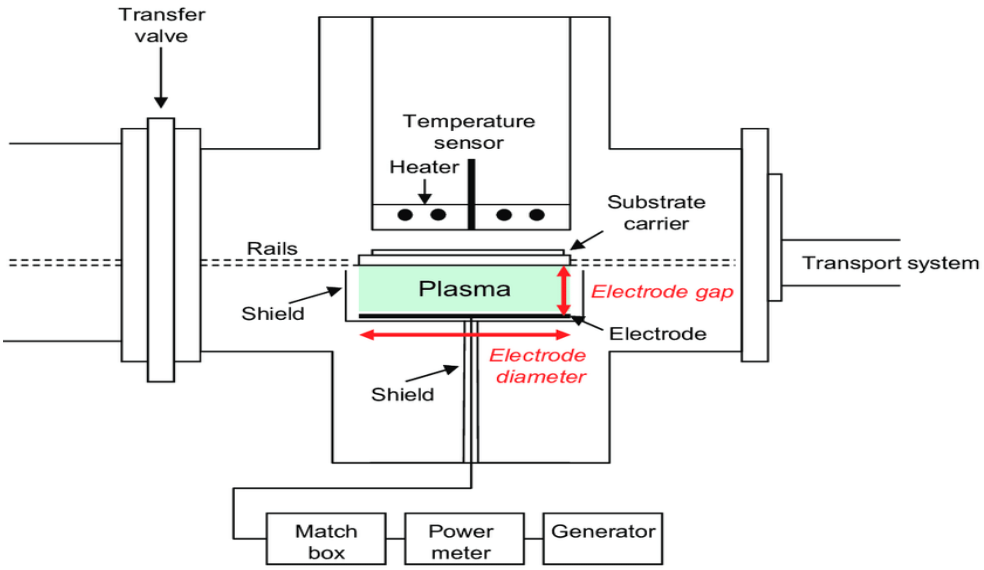

Fig8: plasma enhanced CVD.

Plasma-enhanced chemical vapour deposition (PECVD) systems are accustomed quality production of both SWNTs and MWNTs. PECVD may be simple term, encompassing several differing synthesis technique. generally PECVD may be direct or remote. Direct PECVD systems may be used for the assembly of MWNT field emitter towers and few SWNTs. A far off PECVD may also be used to produce both MWNTs and SWNTs. For SWNT synthesis in the direct PECVD system, the scientist heated the substrate up to 550-850 ^{0}C utilized a CH4-H2 gas mixture at 500 mT, and applied 900 W of plasma power as well as externally applied magnetic field. The plasma enhanced CVD method to generates glow discharge in a chamber or a reaction furnace by a high frequency voltage applied to both electrodes. A substrate is placed in the grounded electrode. In order to form a constant film, the reaction gas is supplied from the opposite plate. Catalytic metal, such as Fe, Ni and Co are used on a Si, SiO2 or glass substrate using thermal CVD or sputtering. As such, PECVD and HWCVD as essentially a crossover between plasma-based growth and CVD synthesis technique. In contrast, to arc discharge method, laser ablation, and solar furnace, the carbon for PECVD synthesis technique comes from feedstock gases such as CH4 and CO, so there is no need for a solid graphite source. The argon-assisted plasma is used to cut down the feedstock gases into C2, CH, and other reactive carbon species (CxHy) to facilitate growth at low pressure and tempreture[33]

ANALYTICAL TECHNIQUE FOR CARBON NANOTUBE

TEM

TEM technique is used to determine the external structure and to give qualitative insight into the ultrahigh purity of produced CNTs. TEM uniquely provides qualitative information on the size, shape, and structure of carbon nanotube materials, as well as non-CNT structured impurities in a sample. However, it is not able to identify metallic impurities, and do not differentiate from MWNTs. TEM has also been application to image cellular uptake of CNT-drug composites and to determine the mechanism of the CNT component after cellular uptake.[34]

SEM

Scanning electron microscopy method used in the preliminary evaluation of CNT morphology. In CNTs conventional setting method is limited by its inability to differentiate catalyst and carbonaceous more impurities from CNTs. However, the metallic content of carbon nanotubes samples are consistently estimated by SEM coupled with an energy dispersive x-ray analysis detector (SEM-EDX). Reckless, scanning electron microscope is probably the only method that can provide information on both CNT morphology and the metallic impurity content.[35]

RAMAN SPECTROSCOPY

Raman spectroscopy method used to evaluate the synthesis and purification processes of SWNTs. Carbonaceous impurities (graphite, fullerenes, amorphous carbon, etc.) present a major obstacle in interpreting Raman spectra of Single wall carbon nanotube, because these impurities have characteristic Raman features (D- and G-bands) identical to that of SWNTs.[36]

Proton NMR

Proton NMR used to monitor the progress of CNT functionalisation. The presence of functional groups can be detected by characteristic peaks arising from the difference in the magnetic environment. H-NMR of functionalized CNTs is characterized by broad bands for protons close to the Carbon nanotube, becoming sharper with distance. H-NMR techinque has been used to monitor the synthesis and attachment of functional groups to CNTs.[37]

IR Spectroscopy

IR Spectroscopy is primarily a qualitative tool used to identify functional groups and the nature of their attachment to Carbon nanotube sidewalls. Diverse functional groups absorb characteristic frequencies of infrared radiation, giving rise to a fingerprint identification of bonds. It is a equivalent technique to NMR, to confirm the presence of bonds between carbon nanotubes and of attached moieties.[37]

APPLICATION OF NANOTUBES

By drug delivery

CNTs can be used as drug carriers to treat cancer . The efficacy of antitumors drugs used alone is restrained not only by their systemic toxicity and narrow therapeutic window but also by drug inhibition and limited cellular penetration. Because CNTs can conveniently across the cytoplasmic membrane and nuclear membrane, anticancer drug transported by this agency will be emancipated in situ with complete concentration and consequently, its action. In the cancer cell will be higher than that administered alone by traditional therapy. Thus, the development of novel delivery systems with the ability to enhance cellular uptake of existing potent drugs is needed. The increase aspect ratio of CNTs offers great advantages over the existing delivery vectors, because the high surface area provides multiple attachment sites for drugs .Most anticancer drugs have been conjugated with functionalized CNTs and successfully tested in vitro and in vivo such as epirubicin, doxorubicin, cisplatin, methotrexate, quercetin, and paclitaxel.For avoiding the toxic effect of anticancer drug on healthy organs and cells, epirubicin linked with a magnetic CNTs complex obtained by fixing a layer of magnetite (Fe3O4) nanoparticles on the surface of the NTs and on the tips of short- ened MWCNT. epirubicin magnetic CNTs complex is also used for lymphatic tumor targeting.

Carrier for drug delivery

Research studies have proved carbon nanotubes and CNHs as a potential carrier for drug delivery system.

1) Functionalised carbon nanotubes are predicted for targeting of Amphotericin B to Cells.

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

3) Anticancer drug Polyphosphazene platinum given with CNTs had intensified permeability, distribution and retention in the brain due to controlled lipophilicity NTs.

4) Antibiotic, Doxorubicin given with NTs is recited for intensified intracellular penetration.

5) The gelatin Carbon nanotube mixture (hydro-gel) has been used as potential carrier system for biomedicals.

6) Carbon nanotube-based carrier system can accord a successful oral substitute administration of Erythropoietin, which has not been possible as far due of the denaturation of EPO by the gastric environment conditions and enzymes.

7)They can be adapted as lubricants in medicine tablet manufacturing because of its nanosize and sliding nature of graphite layers attached with vander waals forces.[38]

Genetic Engineering

In genetic engineering, CNTs and CNHs are used to manipulate genomes and atoms in the growth of bioimaging genomes, proteomics and tissue engineering. Their tubule like nature has proved them as a vector in gene therapy. The unwound DNA winds around Single wall nanotube by connecting its specific nucleosides and causes change in its electrostatic properties. This creates its potential application in diagnostics (polymerase chain reactions) and therapeutics[38]

Artificial Implants

Most of time body shows rejection reaction for implants with the post administration pain. But, miniature sized nanotubes and nanohorns get attached with other proteins and amino acids for avoiding rejection. Also, they can be used as implants in the form of artificial joints without host rejection reaction. Moreover, due to their increase tensile strength, carbon nano tubes filled with calcium and arranged/grouped in the structure of bone can act as bone substitute.[38]

Preservative

Carbon nanotubes and nanohorns are rich antioxidant in nature. Hence, they are used to preserve drugs formulations prone to oxidation. Their efficient antioxidant property isused in antiaging cosmetics and with zincoxide as sunscreen dermatological to prevent oxidation of important skin components.[38]

Diagnostic Tool

Protein-encapsulated or protein/enzyme filled nanotubes, due to their fluorescence ability in presence of essential biomolecules have been tried as implantable biosensors. Even, nanocapsules is completely filled with magnetic materials, radioisotope enzymes can be used as biosensors. Nanosize robots and nanomotors with nanotubes can be used in studying cells and biological systems.[38]

As Catalyst

Nanohorns offer large surface area and hence, the catalyst at molecular level can be developed into nanotubes in large amount and simultaneously can be released in required to produced rate at particular time. Hence, reduction in the frequency and amount of catalyst addition can be achieved by using Carbon nano tubes and CNHs.[38]

CONCLUSION[37].[37].[37]

Nanotube drug delivery system is one of the best examples of great evolution in drug delivery technologies and nanotechnology. It is obvious that Nanotube appears to be a well preferred drug delivery system over other dosage form as nanotube mostly stable in nature and economic. Nanotubes provide great opportunity for the different innovative applications, especially due to their biocompatibility and minimal cytotoxicity in biological condition. Nanotube is the state-of-the-art material widely used in polishing materials, polymers, lubricants and electrolytes .There is lot of scope to encapsulate toxic anti-cancer drugs, anti-infective drugs, anti-AIDS drugs, anti-inflammatory drugs anti-viral drugs, etc.

Thus these areas require further systemic consideration and research so as to bring out commercially and valuable available Nanotube preparation. The concept of incorporating the drug into or Nanotubes for a better targeting of the drug at appropriate tissue destination is widely accepted by researchers and academician .

Nanotubes are very useful in bright future for pharma industries. So far only animal experimentation of this targeted drug delivery system is reported but further clinical investigations in human volunteers, pharmacological and toxicological investigations in animals and human volunteers may help to exploit nanotubes as prosperous drug carriers for targeting drugs more efficiently, for treating cancer, infection and AIDS etc. Thus Nanotubes present itself as a versatile tool in therapeutics.

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