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Application of Carbon Nanotubes in Drug Delivery: A Review

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Abstract: Nanotechnology is a most promising field for generating new applications in medicine. Carbon nanotubes (CNT) exhibit many unique intrinsic physical and chemical properties and have been intensively explored for biological and biomedical applications in the past few years. Their unique surface area, stiffness, strength and resilience have led to much excitement in the field of pharmacy. Nanotubes are classified as single-walled nanotubes and multiple walled nanotubes. Methods of Productions of CNTs such as Arc discharge, Laser ablation, Chemical vapor deposition, Silane solution method and Flame synthesis method. The properties and characteristics of CNTs are still being researched heavily and scientists have barely begun to tap the potential of these structures. Carbon Nanotubes holds good for desired drug delivery systems for the treatment of cancer, gene transfer and DNA applications. Functionalized carbon Nanotubes (f-CNTs) are emerging as new tools in the field of nanobiotechnology and nanomedicine. Carbon NanoTube-based drug delivery has shown promising target drug delivery of small interfering RNA (siRNA). They can pass through membranes, carrying therapeutic drugs, vaccines and nucleic acids deep into the cell to targets previously unreachable.
Keyword: Carbon nanotubes (CNT), Cancer, Gene Transfer, Nanobiotechnology, Nanomedicine.

INTRODUCTION

Scientists use nanotechnology to approach classical and novel drug delivery applications. Controlled and targeted deliveries are the most enviable requirements expected from a carrier, which involves multi-disciplinary site specific or targeted approach. Pharmaceutical nanoparticles are subnanosize based structure, contain drug or bioactive substances with in them and constituted of several tens or hundreds of atoms or molecules with a variety of sizes [1,2].

Carbon Nanotubes (CNTs) have become strongest candidates mainly in the field of biomedical engineering; biotechnology and pharmaceutical nanotechnology after their discovery in 1991.These are an important new class of technological materials that have numerous novel and useful properties. They have received very much attention as new classes of nanomaterials .These are the long hollow seamless cylinders of graphene. The diameter of these tubes is in the range of 1-100 nm. These tubes are normally capped with the half a full fullerence molecules at both the ends. Carbon Nanotubes are cylinders of one or several coaxial graphite layers with a diameter in the order of nanometers these shows unique chemical, physical and electrical properties. CNTs with $3A^0$ diameter have been recently reported. Nanomaterials have sizes ranging from about one nanometer up to several hundred nanometers, comparable to many biological macromolecules such as enzymes, antibodies, and DNA plasmids [3, 4, 5].

HISTORY

In 1952 Radushkevich and Lukyanovich published clear images of 50 nanometer diameter tubes made of carbon in the Soviet Journal of Physical Chemistry [6]. A paper by Oberlin, Endo, and Koyama published in 1976 clearly showed hollow carbon fibres with nanometer-scale diameters using a vapor-growth technique[7]. John Abrahamson presented evidence of carbon nanotubes at the 14th Biennial Conference of Carbon at Penn State University in 1979. The conference paper described carbon nanotubes as carbon fibers which were produced on carbon anodes during arc discharge[8]. Using TEM images and XRD patterns, the authors suggested that their "Carbon multi-layer tubular crystals" were formed by rolling graphene layers into cylinders[9].

In 1987 Howard G. Tennent of Hyperion Catalysis was issued a U.S. patent for the production of "cylindrical discrete carbon fibrils" with a "constant diameter between about 3.5 and about 70 nanometers, length 10 times the diameter, and an outer region of multiple essentially continuous layers of ordered carbon atoms[10]. A Large percentage of academic and popular literature attributes the discovery of hollow, nanometer sized tubes composed of graphitic carbon to Sumio Iijima of Nippon Electric Company in 1991[1].

STRUCTURE AND MORPHOLOGY[1, 11, 12]

Each atom joined to three neighbours, as in graphite so that bonding in carbon nanotubes is sp^2. The tubes can therefore be considered as rolled-up graphene sheets. This bonding structure, which is stronger than the sp^3 bonds found in diamond, provides the molecules with their unique strength. Under high pressure, nanotubes can merge together, trading some sp^2 bonds for sp^3 bonds, giving the possibility of producing strong, unlimited length wires through high-pressure nanotube linking. Structure of nanotubes is as shown in fig.1.

Carbon occurs in many forms, and the properties depend of each form on its special structure makes carbon a truly unique building block for nanomaterials. Carbon nanotubes discovered in 1991 by Iijima and coworkers. Each of which is pair of fullerene caps connected by a tube that is a rolled up seamless graphene sheet. [Fig. 2.]

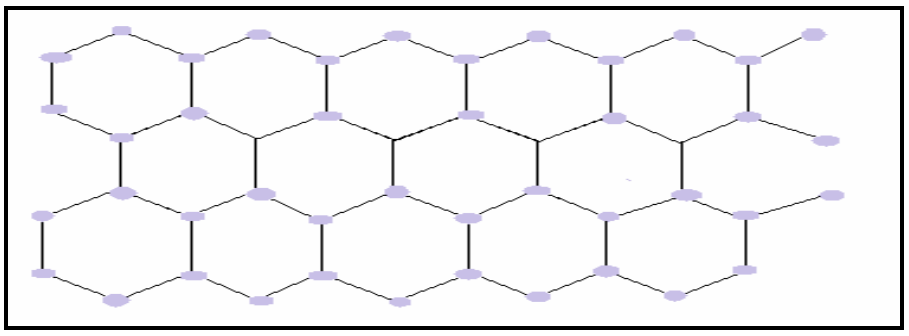

Fig. 1. Single sheet of Graphene

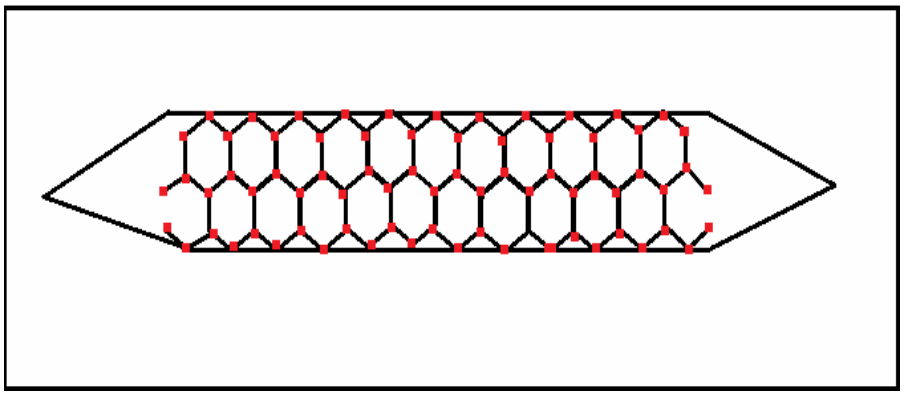

Fig. 2. General representation of carbon nanotubes having ends close with some functional groups of hemi fullerenes.

CLASSIFICATION OF CARBON NANOTUBES

Carbon nanotubes are classified in following two types

1) Single walled carbon nanotubes (SWNTs) [1, 13, 14].

These can be imagined perfect graphene sheets in which grapheme being the same poly -aromatic mono- atomic layer made of hexagonal display of sp^2 hybridized carbon atoms, rolled up into a cylinder, with the hexagonal rings put in contact to join seamlessly[1, 13, 14].

2) Multiple walled carbon nanotubes (MWNTs)

The MWCNTs consists of multi walled grapheme sheets rolled up in concentric CNTs, filling each other's inner cavities to end up with Nanotubes[15,16] .The intertube distance is in a MWCNTs is approximately that of inter-graphene distance in turbostratics poly aromatic solids & hence these MWCNTs are more stronger in their strength in comparisons to SWCNTs. SWCNTs are grapheme sheet rolled up into a tube form with nanodimensions[17,18].

METHODS OF PRODUCTIONS OF CNTs

1) Arc Discharge[19]

Arc discharge initially used to producing C_{60} fullerenes, is the most common and easiest way to produce CNTs. This method creates CNTs 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 direct current of 50 to 100 A^0, driven by a potential difference of approximately 20 V creates a high temperature discharge between the two electrodes. The discharge vaporizes the surface of one of the carbon electrodes and forms a small rod-shaped deposit on other electrode. By changing metal catalyst, nanotubes with a diameter of 0.6 to 1.2 nm are produced. Catalysts used are Cobalt and Molybdeum.Fig.3.

2) Laser ablation[20]

In Laser ablation laser vaporization pulses were followed by a second pulse, to vaporize the target more uniformly. The use of two successive laser pulses minimizes the amount of carbon deposited as soot. The second laser pulse breaks up the larger particles ablated by the first one, and feeds them into the growing nanotubes structure. The material produced by this method appears as a mat of ropes, 10-20 nm in diameter and upto 100µm or more in length.Fig.4.

3) Chemical Vapor Deposition[21]

Chemical Vapor Deposition of hydrocarbons over a metal catalyst is that has been used to produce various carbon materials like carbon fibers and filaments. Large amount of CNTs can be formed by catalytic CVD of acetylene over cobalt and iron catalysts supported on silica or zeolite. High yields of single walled nanotubes have been obtained by catalytic decomposition of H_2-CH_4 mixture all over well dispersed metal particles such as cobalt, nickel and iron on magnesium oxide 10000C.The decomposition of CH4 over the freshly formed nanoparticles prevents their further growth and thus results in a very high proportion of SWNTs and few MWNTs.Fig.5**.**

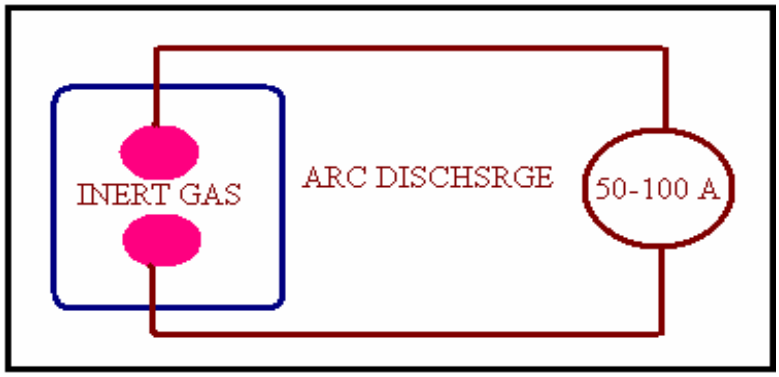

Fig.3. Diagrammatical representation of Arc Discharge setup for Synthesis and growth of nanotube

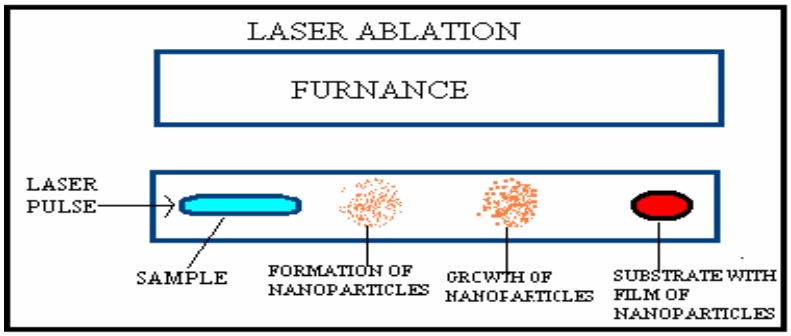

Fig. 4. Diagrammatical representation of Laser Ablation setup for nanotube synthesis and growth.

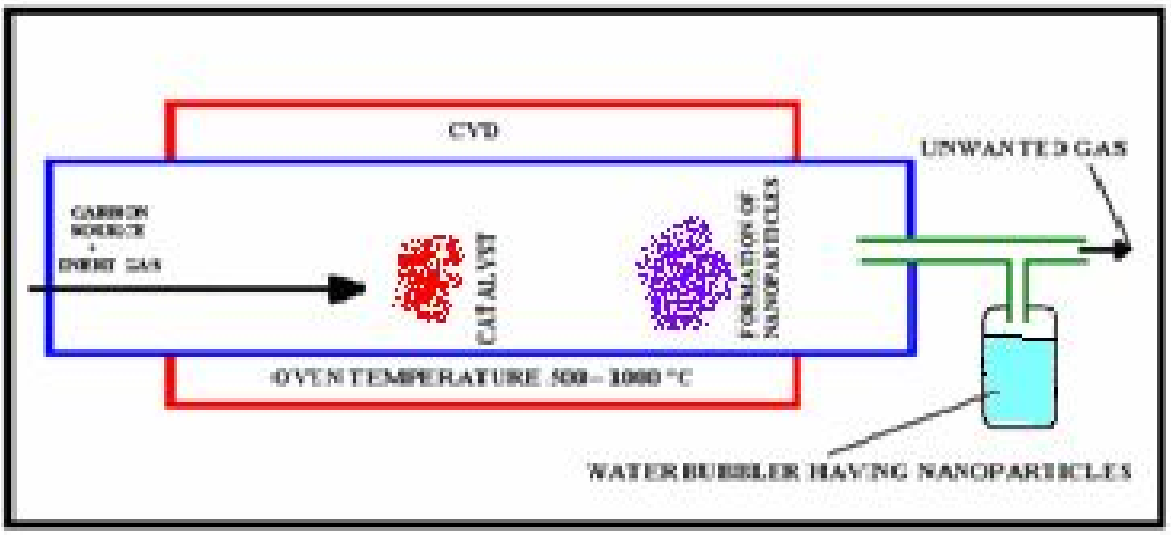

Fig.5. Diagrammatical representation of Chemical vapor deposition (CVD) setup for nanotube synthesis and growth.

4) Flame Synthesis Method[22]

SWNTs are formed in controlled flame environment from hydrocarbon fuels and small aerosol metal catalyst. Single-walled nanotubes have been observed in the post-flame region of a premixed acetylene/oxygen/argon flame operated at 50 Torr with iron pentacarbonyl vapor used as a source of metallic catalyst. Between 40 and 70 mm heights above burner nanotubes are observed to form and coalesce into clusters.

5) Silane Solution Method[23]

Carbon nanotubes were produced using a silane solution method, in which a substrate such as carbon paper or stainless steel mesh was immersed in a silane solution of a metal catalyst, preferably Co: Ni in a 1:1 ratio and a feedstock gas containing a carbon source such as ethylene inserted through the substrate and the catalyst deposited thereon while the substrate was heated by applying an electrical current.

PURIFICATION OF CNTs[24]

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

1) Air Oxidation

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

2) 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 (HNO_3) and

sulphuric acid (H_2SO_4), but HCl was identified to be the ideal refluxing acid.

3) Surfactant aided sonication, filtration and annealing

After acid refluxing, the CNTs were purer but, tubes were entangled together, trapping most of the impurities, such as carbon particles and catalyst particles, which were difficult to remove with filtration. So surfactant-aided sonication was carried out. Sodium dodecyl benzenesulphonate (SDBS) aided sonication with ethanol (or methanol) as organic solvent were preferred because it took the longest time for CNTs to settle down. The sample was then filtered with an ultra filtration unit and annealed at 1273 k in N_2 for 4 h. Annealing is effective in optimizing the CNT structures. It was proved the surfactant-aided sonication is effective to untangle CNTs, thus to free the particulate impurities embedded in the entanglement.

FUNCTIONALIZATION OF CARBON NANOTUBES FOR BIOLOGICAL APPLICATIONS:

Raw carbon nanotubes have highly hydrophobic surfaces, and are not soluble in aqueous solutions. For biomedical applications, surface chemistry or functionalization is required to solubilize CNTs improve biocompatibility and low toxicity. covalent and noncovalent two type of Surface fuctionalization of carbon nanotubes[25]. Chemical reactions forming bonds with nanotube sidewalls are carried out in the covalent fictionalization.

1. Covalent functionalization of carbon nanotubes

functionalize carbon nanotubes have been developed by Various covalent reactions and oxidation being one of the most common. CNT oxidation is carried out with oxidizing agents such as nitric acid[26, 27]. During the process, carboxyl groups are formed at the ends of tubes as well as at the defects on the sidewalls. Zeng et al. observed sp3 carbon atoms on SWNTs after oxidation and further covalent conjugation with amino acids[28]. Modification can be achieved by attaching hydrophilic polymers such as poly ethylene glycol (PEG) to oxidized CNTs, yielding CNT-polymer conjugates stable in biological environments. Now used covalently PEGylated SWNTs synthesized by this strategy for both In vitro and in vivo applications. [2+1] Cycloadditions can be conducted by photochemical reaction of CNTs with azides or carbene generating compounds via the Bingel reaction. A 1, 3-dipolar cycloaddition reaction on CNTs developed by Prato et al. is now a commonly used reaction . An azomethine-ylide generated by condensation of an α-amino acid and an α-aldehyde is added to the graphitic surface, forming a pyrrolidine ring coupled to the CNT sidewall. Functional groups e.g., amino terminated PEG introduced via a modified α-amino acid can be used for further conjugation of biological molecules[29, 30].

2. Noncovalent fuctionalization of carbon nanotubes

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

The polyaromatic graphitic surface of a carbon nanotube is accessible to the binding of aromatic molecules via π -π stacking. Taking advantage of the π- π interaction between pyrene and the nanotube surface. Chen et al. showed that proteins can be immobilized on SWNTs functionalized by an amine-reactive pyrene derivative. A recent study conducted by Wu et al.Beside pyrene derivatives, single-stranded DNA molecules have been widely used to solubilize SWNTs by virtue of the π-π stacking between aromatic DNA base units and the nanotube surface . A recent report by Moon et al. showed that DNA molecules coated on SWNTs could be cleaved by nucleases in the serum, suggesting that DNA functionalization of SWNTs might not be stable in biological environments containing nucleases[30. 31, 32].

Cherukuri et al used Tween-20 and a Pluronic triblock copolymer to noncovalently functionalize nanotube surfaces to reduce the nonspecific binding of proteins in the case of SWNT-based biosensors Pluronic tri-block polymer. An ideal noncovalent functionlization coating on CNTs for biological applications should have the following characteristics. First, the coating molecules should be biocompatible and nontoxic. Second, the coating should be sufficiently stable to resist detachment from the nanotube surface in biological solutions, especially in serum having high salt and protein contents[31. 32, 33].

Noncovalent functionalization of SWNTs by PEGylated phospholipids (PL-PEG) was developed by our group to meet the above requirements, including high water solubility of nanotubes and versatile functionalities Phospholipids are the major component of cell membranes, and are safe to use in biological systems. The two hydrocarbon chains of the lipid strongly anchor onto the nanotube surface with the hydrophilic PEG chain extending into the

aqueous phase, imparting water solubility and biocompatibility[33].

APPLICATIONS OF CNTs

1) GENETIC ENGINEERING

CNTs are used to manipulate genes and atoms in the development of bioimaging genomes, proteomics and tissue engineering. The unwound DNA winds around SWNT by connecting its specific nucleotides and causes change in its electrostatic property. Wrapping of carbon nanotubes by single-stranded DNA was found to be sequence-dependent, and hence can be used in DNA analysis. Nanotubes due to their unique cylindrical structure and properties are used as carrier for genes to treat cancer and genetic disorders[34]. Their tubular nature has proved them as a vector in gene therapy. Nanotubes complexed with DNA were found to release DNA before it was destroyed by cells defense system, boosting transfection significantly. Nanostructures have showed antiviral effect in respiratory syncytical virus (RSV), a virus with severe bronchitis and asthma. The treatment is generally done by combining nanoparticles and gene slicing technologies. RNA fragments capable of inhibiting a protein is encapsulated within nanotubes and administered in the form of nasal sprays or drops. Nanotubes are reported for helical crystallisation of proteins and growth of embryonic rat brain neurons[35, 36].

2) BIOMEDICAL APPLICATIONS[36, 37]

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

3) CARBON NANOTUBES IN DETECTION[38]

For detection of chemical and biological agents CNTs are used by forming its casting on suitable sensitized electrodes and can be exposed to enzymes solution for immobilization procedure

A) Detection of Toxic Organophosphoric Compounds[39]

These Organophosphoric compounds are generally used in insecticides, pesticides. These chemicals are CNS affecting by inhibiting acetylcholine esterase which functions on acetylcholine neurotransmitters. Carbon Nanotubes are the electrode materials has the possibility of promoting electron transfer reaction at enzymes immobilization. Acetylcholine esterase is immobilized on Nanotubes surface and catalyses hydrolysis if thiocholine ester, forms thiocholine and oxidation of thiocholine can be detected by electrochemical techniques. On Organophosphoric compounds action acetylcholine esterase catalytic property become reduced and simultaneously the oxidation of thiocholine inhibited and this can be detected by amperometric analysis using CNTs electrodes.

B) Detection of Alkylating Agents Containing Sulphur and Nitrogen[40, 41].

Alkylating agents such as Nitrogenmustards, Ethylenimes, Alkylsulphonates, Triazenes, Piprazenes, and Nitrosureas can be detected by DNA sensing as the biological recognition element which could have numerous applications. To improve the sensitivity aligned CNTs should be used as nanoelectrodes array for DNA recognition

C)Detection of Toxic Proteins and Micro Organisms

By change in electrical signals, the CNTs can be used as a measuring platform for various toxic proteins which will immobilized on the CNTs by both covalent and noncovalent means. This immobilization properties of antibodies by means of sensing improves their activity in antigen antibodies biosensors[42, 43, 44]. Scanning electron microscope (SEM) and electrochemical chemiluminescence (ECL) can be used to test the bonds of proteins with antibodies on CNTs platform. Finally the detection can be done by integrating these sensor tips to a single conditioning and processing circuits and measurements analysis of conductance and electrical signals obtained in presence of toxic proteins[45-48].

D) Detection of Chemical Substances

Colinet al. found that CNTs exhibit very good adsorption properties because of there high specific surface area and nanoscale structures which provide large number of sites where the chemical in gaseous form can react. Young et al. achieved ultrahigh sensitivity detection of NO_2 gas using composite film of SWCNTs mash doped with alkanethiol monolayer protected gold cluster (MPC). Penza,et al. fabricated micro acoustic sensor, for organic vapour detection at room temperature, in which SWCNTs were imbedded in Cadmium arachidate(CdA) ampiphillic matrix[25, 49]

4) AS CATALYST:

Nanohorns offer large surface area and hence, the catalyst at molecular level can be incorporated into nanotubes in large amount and simultaneously can be released in required rate at particular time. Hence, reduction in the frequency and amount of catalyst addition can be achieved by using CNTs[25, 50].

5) 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 prevents oxidation of important skin components[51].

6) CARBON NANOTUBES IN DRUG DELIVERY

A) Carbon Nanotube Membranes for Transdermal Drug Delivery

The CNT patch represents a major step forward in developing a programmable, transdermal drug delivery system that can usefully treat a variety of syndromes and be tailored to an individual patient's needs in a manner that will both improve therapeutic administration and efficacy.

Dr. Hinds and his colleagues have developed a novel skin patch device 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 [52].

B) CNT'S for cancer treatment

Though the current treatments of cancer by surgery, radiation and chemotherapy are successful in several cases, these curative methods also kill healthy cells and cause toxicity to the patient. The spread of cancer cells between organs, a process known as metastasis, is the cause of most cancer death. CNT's can be considered as antitumor agents and when in combination with onventional drugs, can significantly enhance their chemotherapeutic effect with the help of the advanced drug delivery system. It has been reported that Paclitaxel loaded PEG--CNT's are promising for cancer therapeutics. Aqueous solution of functionalized SWCNTs on exposure to radiofrequency (RF) field experiences efficient heating and this property has been exploited by Gannon et al for a noninvasive and selective thermal destruction of human cancer cells with minimal or no toxic effects to normal cells. This demonstrates that carbon nanotubes are capable of leading to new exciting directions and approaches in therapeutic oncology. A photo-thermal effect can be employed to induce thermal cell death in a noninvasive manner, provides important information on potential therapeutic targets for pancreatic cancer treatment. There are three key features of this nanoscale drug delivery system (DDS):

i) Use of functionalized SWCNTs as a biocompatible platform for the delivery of therapeutic drugs or diagnostics,

ii) Conjugation of prodrug modules of an anticancer agent that is activated to its cytotoxic form inside the tumor cells upon internalization and in situ drug release,

iii) Attachment of tumor-recognition modules to the nanotube surface [53, 54].

C) CNTs 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 SWCNTs may alter the baroreflex function, thus affecting the autonomic cardiovascular control regulation[55].

D) CNTs for platelet activation

SWCNTs using alongwith platelet P-selectin when injected into anaesthetized mice, light dye-induced thrombus formation was found and the platelet found to be activated. MWCNTs 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 microparticles positive for the granular secretion markers CD62P and CD63[56].

E) CNT for tissue regeneration

CNTs are combined with polymers such as poly-l-lactide, Polylactide and poly-D,Llactide- 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[20].

C) Carbon Nanotubes in Drug Delivery: Recent Trends

f-CNTs 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. Ammonium functionalized CNTs can also be considered very promising vectors for gene-encoding nucleic acids. Stable complexes between cationic CNTs and plasmid

DNA and demonstrated the enhancement of the gene therapeutic capacity in comparison to DNA alone[57].

CONCLUSION

CNTs and their composite materials are likely to become important biomaterials in the near future due to their superior and unique characteristics over conventional biomaterials. CNTs will find numerous applications as biomaterials and have important roles in the development of emerging technologies. CNTs are also promising new materials for molecular delivery in biological systems. Functionalized carbon Nanotubes (f-CNTs) are emerging as new tools in the field of Nanobiotechnology and Nanomedicine. A number of significant challenges remain to be overcome with superior CNTs for application as biomaterials, which will be of great benefit to large numbers of patients in the near future.

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