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Targeted Drug Delivery-Carbon Nanotubes; A Review

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ABSTRACT: Targeted drug delivery utilizing carbon nanotubes has emerged as a promising approach in the field of nanomedicine. Various carbon nanotube (CNT) generation methods include vapour deposition, discharge using an electric arc, and laser ablation mechanisms driven by functionalization, allowing for in-depth characterization and manipulation of CNTs. CNTs' inherent elasticity, electromechanical, chemical, and optical properties have a significant impact on their stability and reactivity. This review provides a comprehensive overview of the applications, strategies, and advancements in the use of carbon nanotubes for precise drug delivery. We discuss the properties of carbon nanotubes that make them suitable for this purpose, drug delivery to diseased tissues. Additionally, This review consolidates recent research, offering insights into the current. state of the field and its potential for revolutionizing the treatment of various medical through targeted drug delivery.

KEYWORDS: Carbon Nanotube, Drug delivery, Nanomedicine, Nanoparticles, Controlled delivery.

I. INTRODUCTION

[1]Targeted drug delivery, also known as smart drug delivery, is a method of delivering drugs to patients in a way that increases drug concentrations in some parts of the body compared to other parts. This delivery vehicle is mainly based on Nanomedicine and aims to overcome the drawbacks of traditional drug delivery by nanoparticle-mediated drug delivery. These nanoparticles are loaded with drugs to target specific parts of the body, including only the affected tissue. Avoid interaction with healthy tissue.

[2]The purpose of targeted drug delivery systems is to prolong, localize, target, and achieve protected drug interaction with diseased tissue. In traditional drug delivery systems, drugs are absorbed through biological membranes, whereas targeted delivery systems release drugs in dosage form.

[3]Targeted drug delivery systems have been developed to optimize regenerative techniques. The system is based on the administration of specific amounts of therapeutically active ingredients to the injured area of the body over a long period of time. This helps maintain necessary drug levels in the plasma and tissues and prevents drug damage to healthy tissues. Drug delivery systems are highly integrated and require the integration of different disciplines such as chemists, biologists, and engineers to optimize the system.

[4] Research related to the development of targeted drug delivery system is now a day is highly preferred and facilitating field of pharmaceutical world. It has crossed the infancy period and now touching height of growths from the pharmacy point of view. Targeted delivery of drugs, as the name suggests, is to assist the drug molecule to reach preferably to the desired site. Targeted drug delivery is a method of delivering medication to a patient in a manner that increases the concentration of the medication in some parts of the body relative to others.

[5]Targeted drug delivery seeks to concentrate the medication in the tissues of interest while reducing the relative concentration of the medication in the remaining tissues. This improves efficacy of the while reducing side effects. This improves efficacy of the while reducing side effects. Drug targeting is the delivery of drugs to receptors or organs or any other specific part of the body to which one wishes to deliver the drugs exclusively.

[7] In June 1991, Japanese scientist, SUMIO LIJIMA NEC Laboratory in Tsukuba found an extremely thin needle-like material when examining carbon materials under an electron microscope. He named these materials "carbon

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nanotubes" since then name has been widely accepted.

[8]Carbon nanotubes are allotropes of carbon, made of graphite, and have been constructed in cylindrical tubes with nanometer scale in diameter and several millimeters in length. Carbon nanotubes (CNTs) consist exclusively of carbon atoms arranged in a series of condensed benzene rings rolled up into a tubular structure. This nanomaterial belongs to the family of fullerenes, the third allotropic form of carbon along with graphite and diamond. These are often described as a graphene sheet rolled up into the shape of a cylinder. Carbon nanotubes have potential therapeutic applications in the field of drug delivery, diagnostics, and bio sensing. Functionalized carbon nanotubes can also act as vaccine delivery systems.

[9] They have a very broad range of electronic, Thermal, and structural properties Besides these main applications of CNTs, they have been shown as a powerful tool for enantiomer separation of chiral drugs and chemicals in pharmaceutical industry as well as in laboratory Carbon nanotubes have the potential to carry drugs in the organism as they are hollow and much smaller than the blood cells.

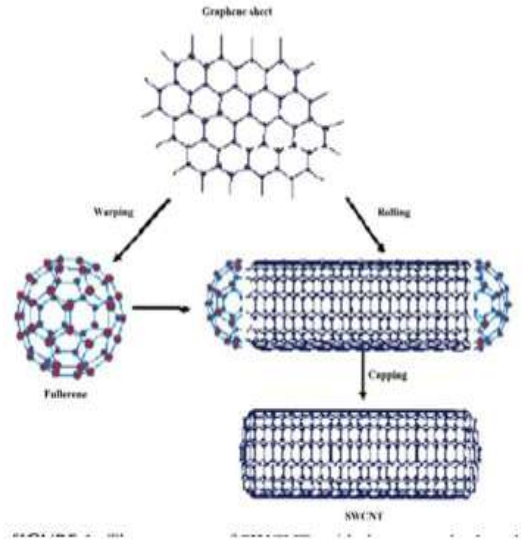

Fig No. 1. Structure of Carbon Nanotube

II. RATIONALS FOR CARBON NANOTUBES CARRIER SYSTEM

1. High Surface Area: CNTs have an exceptionally high surface area, which allows for the efficient loading and delivery of a wide range of therapeutic agents, such as drugs, genes, and imaging agents.
2. Controlled Release: CNTs can be engineered to release cargo in a controlled and sustained manner. This controlled release profile can enhance the therapeutic effect of drugs and reduce side effects.
3. Targeted Delivery: Functionalized CNTs can be designed to target specific cells, tissues, or organs. This targeting capability ensures that the therapeutic
agent reaches the intended site, increasing treatment precision.
4. Improved Solubility: CNTs can improve the solubility of poorly water-soluble drugs, making it easier to formulate and administer medications.
5.Biocompatibility: With appropriate functionalization, CNTs can be made biocompatible and reduce the chances of adverse reactions when used in the body.
6. Enhanced Therapeutic Efficacy: By improving drug stability, protecting drugs from degradation, and facilitating their uptake by cells, CNTs can enhance the therapeutic efficacy of drugs.
7. Versatility: CNTs can serve as carriers for wide range of payloads, including small molecules, proteins, nucleic acids, and imaging agents, making them versatile for different medical applications.
8. Reduced Toxicity: Controlled drug release and targeted delivery can reducethe overall exposure of healthy tissues to the drug, potentially reducing toxicity.

III. MECHANISM OF CARBON NANOTUBES CARRIE SYSTEM

There are several mechanism for carbon nanotubes are occur through:-

- Direct penetration through cell membrane.
- Passive uptake.
- Endocytosis:there are included some types

1. Phagocytosis
2. Pinocytosis
3. Receptors mediate endocytosis: there are included some subtypes

1) Caveolin mediated endocytosis
2) Clathrin mediated endocytosis
3) Clathrin independent endocytosis

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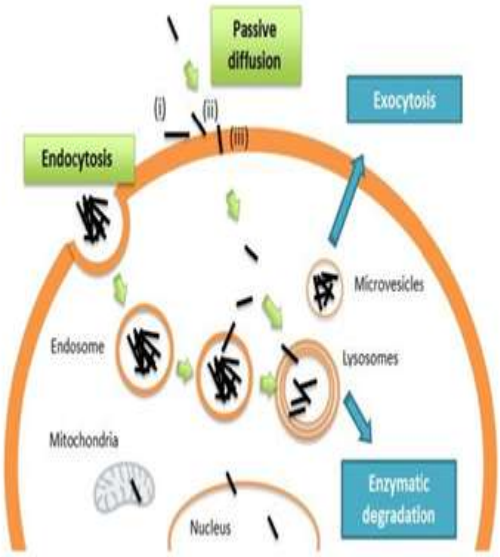

Fig No. 2 mechanism of carbon nanotubes as carrier

PASSIVE UPTAKE MECHANISM

[10]The cellular internationalization of CNTs can occur via a passive pathway or a needle diffusion mechanism across the lipid bilayer of the cell membrane. The high adherence rate and needle-like structure help CNTs overcome these obstacles.

ENDOCYTOSIS

[10]Another pathway of CNT internalization includes endocytosis which can be divided into five categories: phagocytosis, pinocytosis (mainly micropinocytosis), clathrin-mediated endocytosis or receptor-mediated endocytosis, Caveolin-mediated and clathrin/caveolaeindependent endocytosis. Phagocytosis is an intracellular pathway in which large particles (~1 μm) are taken up by cells. For example, phagocytosis predominates in macrophages, neutrophils, and monocytes.Receptor-mediated phagocytosis is the major cellular uptake pathway involved in formation of clathrin-coated endocytic vesicles. Caveolae invaginations consist of nanomaterials approximately 60 nm in size. They are rich in proteins such as cholesterol and sphingolipids. Caveolin-mediated endocytosis is used for vesicular transport as well as the uptake of bacteria and viruses.Results from various researchers have shown that cells can internalize CNTs grow up to 100 nm in size by endocytosis mediated by Caveolin and clathrin; however, larger CNTs, larger than 300 nm, are absorbed by macropinocytosis mechanisms. In addition to the advantages of CNTs and their cell-penetrating drug cargo, each mechanism has disadvantages should be examined carefully teria, dead cells, or other foreign materials. The cell extends pseudopods (projections of its membrane) to surround the particle and create a large vesicle called a phagosome.Specialized cells, like macrophages and neutrophils, are primarily responsible for

IV. TYPES OF CARBON NANOTUBES

There are two types of carbon nanotube :

1. Single -walled Carbon Nanotube.
2. Multi -walled Carbon Nanotube.

SINGLE-WALLED CARBON NANOTUBES :

[11] SWNTs have been found to have strong antimicrobial activity when incorporated into electrospun polysulfone (PSf) nanofibers. This increases the conductivity of electrospinning solutions, resulting in more uniform nanofibers with fewer beads. However, the use of SWNTs as an antibacterial material may be limited by practicality and cost. Single-walled Carbon Nanotubes is represented as SWCNT. They exist in a one dimensional structure. Some of the examples for a Single-walled CNT are zig-zag and armchair.

The properties of Single-walled Carbon Nanotubes are:

1. A Single-walled Carbon nanotube's diameter isAround 2nm.
2. They are also known as a nanowire as they exist in just one dimension.
3. A single-walled Carbon nanotube can be used to miniaturize Electronics.
4. They have a bandgap that varies from 0 to 2 electron volts (eV).
5. They have conductive properties like that of a semiconductor. Therefore, they show both semiconductive and metallic behaviour.

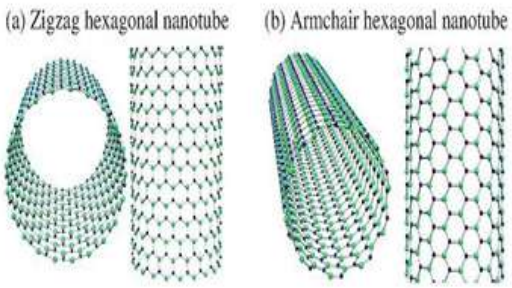

Fig No. 3 single Walled Carbon Nanotubes

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MULTI WALLED CARBON NANOTUBES :

[12] They are represented as MWCNT. They are made up of various nested carbon Nanotubes. This kind of nanotubes has two Different diameters, one is called the outer Diameter while the other is called the inner Diameter. Chiral multi-walled carbon nanotubes is A fine example of multi-walled carbon nanotubes. MWCNTs are preferred by suppliers due to their Bulk production and lower cost. Produced using "Catalytic Chemical Vapour Deposition" these nanotubes have a diameter of 5-20 nm and length of 10 microns. They have a purity of over 99.99% and minimal impurities.

The properties of multi-walled carbon nanotubes are as follows:

1. The outer diameter of multi-walled carbon nanotubes is around 2 to 20 nanometers.
2. The inner diameter of multi-walled carbon nanotubes is around 1 to 3 nm.
3. The length of multi-walled carbon nanotubes is around 5 to 6 micrometres.

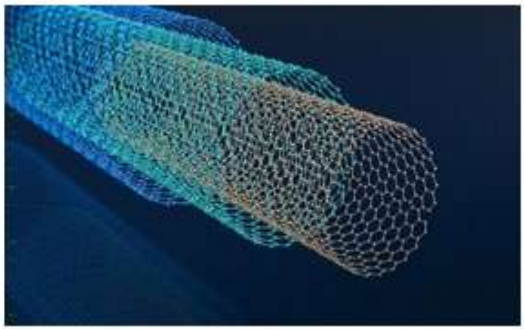

Fig No. 4 Multi Walled Carbon nanotubes

V. METHOD OF SYNTHESISE

1) CHEMICAL VAPOR DEPOSITION METHOD

[13] Requirements:

Sources for carbon: The precursor for carbon nanotubes are hydrocarbon gases such as acetylene, ethylene, methane, etc.

Substrate used: Substrates are materials on which the CNTS are grown. The commonly used substrates in CVD method are zeolite, silica, silicon plate coated with iron particles,etc..

Catalyst used: To produce single-walled carbon nanotubes metal catalyst nanoparticles such as iron, cobalt, nickel, molybdenum, iron-molybdenum alloys, etc. are used.

Conditions maintained:

Temperature: 500-900°C

Inert gas atmosphere: Argon gas.

[14] Procedure:

1. A quartz tube is placed inside a furnace that is kept at a high temperature (500-900°C) and heated by an RF heater in this method.
2. A crucible containing the catalyst nanoparticle-coated substrate is put inside a quartz tube filled with an inert atmosphere such as argon gas
3. The hydrocarbon gas (carbon source) is injected into the quartz tube, where it undergoes pyrolysis and produces vapour
carbon atoms.
4. These carbon atoms attach to the substrate and come together via the
5. Vanderwaal force of attraction, resulting in the formation of multi-walled carbon nanotubes (MWCNTs) on the substrate.
6. Catalyst nanoparticles of Fe, Co, and Ni are utilised to synthesise single-walled carbon nanotubes. The resulting CNTs are refined further to achieve the pure form of CNTs.

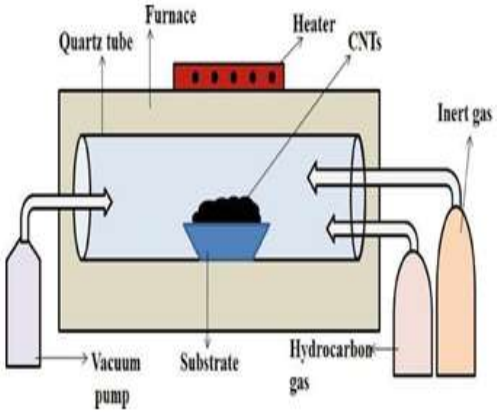

Fig. No. 5- Chemical Vapour Deposition Method

2) ELECTRIC ARC DISCHARGE METHOD

[13] Requirements:

Pure graphite rods (both positive and negative electrodes) are used as electrodes. The spacing between the two electrodes can be maintained by adjusting the positive electrode from the outside.

Electrode diameter: 5-20 micrometres. 1 mm gap between electrodes.

Current range: 50-120 amps.

Voltage range: 20-25 V.

Inter gas pressure:100-500 torr inert gas pressure (no CNT produced below 100 torr). To produce CNTs, an inert gas is required to chill the condensation of atoms. The structure of carbons in CNTS is determined by inert gas. Helium gas is a common inert gas.

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Temperature range: 3000-3500° C.
Reactor: It has a quartz chamber that is linked to a vacuum pump p and a diffusion pump for inter gas supply. The vacuum pump creates the initial chamber, which is filled with helium gas by the diffusion pump.

[14] Procedure:
1. In this process, Two graphite electrodes are used. One of them is typically filled with a carbon source material, like graphite or a metal- carbon mixture (often a transition metal, e.g., iron, cobalt, or nickel).
2. These electrodes are placed in a chamber that can be evacuated or filled with an inert gas (usually helium) to create an environment free of oxygen.
3. An electric arc is generated between the two graphite electrodes. This is typically achieved by applying a high voltage between them. The arc discharge produces very high temperatures (above 3,000°C) in the region between the electrodes.
4. The intense heat causes the carbon source electrode to vaporize. Carbon vapor is created in this process.
5. If a metal-carbon mixture is used in one of the electrodes, metal nanoparticles (catalyst particles) are also formed in the vapor phase.
6. In the hot environment of the arc, carbon atoms or clusters are formed. These carbon species are carried away from the vaporized electrode towards the cooler regions of the reactor.
7. As the carbon species move away from the arc, they self-assemble into carbon nanotubes. The metal catalyst particles can act as nucleation sites for the growth of CNTs. This process is akin to a "bottom-up" growth approach.
8. The synthesized CNTs are collected on a surface or substrate located downstream from the arc.

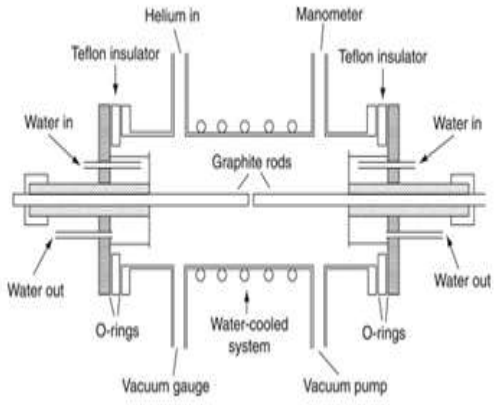

Fig No. 6 Electric Arc Discharge method.

3) LASER ABLATION METHOD
[13] Requirements:
Targeted source: The most commonly used carbon source target is solid graphite, which is irradiated by a laser source and vaporized into vapor carbon atoms.
Laser source: Continuous laser sources such as CO2 lasers or pulsed laser sources such as Nd:YAG lasers (Neodymium doped Yttrium Aluminum Garnet, Nd:Y,Al,012) can be used to vaporize target material into target vapor atoms.
Substrate:The water-cooled copper collector on which the vaporized carbon atoms deposit and grow into CNTs is employed as the substrate in this process.
Inert gas atmosphere: Argon gas is typically utilized as an inert gas that flows at a consistent pace towards the water-cooled copper collector.

[14] Procedure:
1. A high-power laser, typically an excimer or Nd:YAG laser, is used to generate a focused laser beam.
2. A target material, often a graphite rod or metal-carbon mixture, is placed in a reaction chamber filled with an inert gas (typically helium or argon). The target material serves as the source of carbon atoms
3. The high-intensity laser beam is directed onto the target material. The laser beam vaporizes and ablates the target material.
4. The laser pulse creates extremely high temperatures in a localized region, causing the target material to undergo sublimation.
5. The ablation process generates a vapor plume containing carbon atoms and clusters, as well as metal catalyst particles if a metal-carbon mixture is used.
6. If a metal-carbon mixture is used, metal nanoparticles (catalyst particles) can be formed in the vapor plume
7. As the carbon vapor plume expands and cools, carbon atoms or clusters self-assemble into carbon nanotubes. The metal catalyst particles can act as nucleation sites for CNT growth. This is a "bottom-up" approach.
8. The synthesized CNTs are collected on a substrate placed in the path of the vapor plume.

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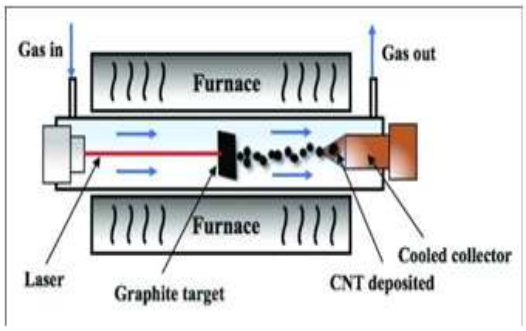

Fig. No.7 Laser Ablation Method

4) PULSE LASER METHOD

[14] Procedure:

1. In PLD, a high-energy pulsed laser, often an excimer or Nd:YAG laser, is used to create a laser pulse with high intensity.
2. A target material, in this case, a carbon-containing target, is placed in a vacuum chamber.
3. When the high-intensity laser pulse is directed at the target material, it causes the surface of the target to be ablated.
4. The laser ablation process creates a plume of material from the target, which includes carbon atoms, clusters, and other species.
5. A substrate, typically made of silicon or another material, is placed in the path of the vapor plume generated during laser ablation.
6. The material ablated from the target is deposited onto the substrate
7. As the ablated material condenses on the substrate, it forms a thin film or coating. The properties of the film depend on factors such as the laser energy, the target material, and the substrate temperature.

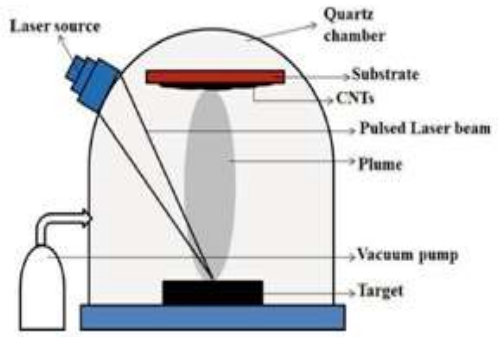

Fig No. 8 pulse laser method.

VI. PURIFICATION

SWNT contains impurities like graphite sheets, amorphous carbon, metal catalyst, and smaller fullerenes, which can interfere with desired properties. Fundamental research prefers pure SWNTs without altering them. Homogeneous samples are essential for better measurements. Industrial techniques like oxidation, acid treatment, Annealing, ultrasonication, Functionalization are used

OXIDATION

[15] Oxidative treatment of SWNTS removes carbonaceous impurities and clears the metal surface. However, it damages SWNTs less than impurities due to defects and open structures. Impurity oxidation is preferred due to their attachment to the metal catalyst. Efficiency and yield depend on factors like metal content, Oxidation time, environment, quiding agent, and temperature.

ACID TREATMENT

[15]Acid treatment removes metal catalysts by oxidation or sonication, solvating them and leaving suspended SWNTs. HNO treatment only affects the metal catalyst, while HCI treatment has little effect on SWNTs and other carbon particles. Mild acid treatment (4 M HCI reflux) exposes metal tabs to acid for solvation.

ANNEALING

[15] Due to high temperatures (873-1873 K) the nanotubes will be rearranged and defects will be consumed. The high temperature also causes the graphitic carbon and the short fullerenes to palys When using high temperature vacuum treatment (1873 K) the metal will be melted and can also be removed.

FUNCTIONALIZATION

[15] Functionalization makes SWNTs more soluble, allowing easy separation from impurities like metal. It also preserves SWNT structure for chromatographic size separation, and can be easily
recovered through thermal treatment.

VII. PROPERTIES

CHEMICAL REACTIVITY

[14] The chemical reactivity of a CNT is increasedwhen compared to a graphene sheet due to thecurvature of the CNT surface. The reactivity of carbon nanotubes is directly proportional tothe orbital mismatch generated by increasedcurvature. As a result, a distinction must be made between a nanotube's sidewall and end caps. A smaller nanotube diameter results in higher reactivity for

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the same reason. Covalent chemical alteration of either sidewalls or end caps has been demonstrated.

ELECTRICAL CONDUCTIVITY

[14] Depending on their chiral vector, carbon nanotubes with modest diameters can be semi-conductive or metallic. Differences in conductivity are caused by molecular structure and the characteristics of graphene sheets. Nanotubes (nm) are metallic, and their resistance to conduction is regulated by quantum mechanical factors.

OPTIC ACTIVITY

[15] Nanotubes grow in size. As a result, it is hypothesised that these characteristics would also influence other physical properties. The use of optical activity may result in optical devices in which CNTS play a significant role.

MECHANICAL STRENGTH

[14] Carbon nanotubes have an extremely high Young modulus in the axial direction. Because of its length, the nanotube as a whole is exceedingly flexible. As a result, these compounds may have applications in composite materials that require anisotropic characteristics.

AREA OF HIGH SURFACE

[14] CNTs have an extremely high surface area, making them ideal for adsorbing and transporting numerous compounds, including medicines.

VIII. APPLICATION

DRUGS DELIVERED

Specific medication delivery is crucial in medicine, particularly in cancer therapy, as chemotherapy can cause severe side effects by destroying both cancer and healthy cells, making it a significant challenge in cancer treatment.

BREAST CANCER

[16] HER2 Overexpresionis responsible for 20-25% of invasive breast cancer. SWNT administration of paclitaxel was found to be more effective at tumour suppression than taxol by Liu et al. SWNT-PTX Has a high water solubility and is equally dangerous to cancer cells. Even at modest doses, it inhibits tumour growth.

LIVERCANCER

[18] When compared to CNT-NH-asODN and dendrimer alone, polyamidoamine dendrimer modified CNTs (dMWCNTs) efficiently delivered antisense c-myc oligonucleotide (asODN) into liver cancer cell lines HepG2 and HepG2, inhibiting cell growth and down regulating c-myc gene and protein expression.

BRAIN CANCER

[18] PL-PEG functionalized SWCNTs coupled with protein A and fluorescein-labeled integrin monoclonal antibody (SWCNT-PEGmAb) were created by Xing et al. Confocal microscopy revealed that U87MG cells had good targeting effectiveness with low cellular toxicity, whereas MCF-7 cells had low targeting efficiency.

GEN THERAPY

[19] CNTs have the ability to transport therapeutic molecules such as DNA and RNA to disease sites, which holds promise for anticancer treatment. Their wire-like structure and flexibility boost therapeutic advantages. In vivo siRNA sequence therapy of human lung carcinoma resulted in cytotoxicity and cell death, triggering an apoptotic cascade.

TRANSDERMAL DRUG DELIVERY

[19] Transdermal systems are appealing medication administration technologies, particularly for treating patients for drug addiction, such as nicotine for smoking cessation. Drug administration to the skin can be modulated using functionalized carbon nanotube (CNT) membranes and a modest electrical bias to develop a programmable drug delivery device. A transdermal patch system that may be adjusted to a patient's specific demands would improve patient compliance while also providing far more efficient therapy.

CARDIAC AUTONOMIC REGULATION

[19] Single-walled carbon nanotubes are employed in cardiac autonomic control. Single-walled carbon nanotubes have physicochemical features with fine components that may harm cardiovascular autonomic function, according to a study in rats. SWCNTs may disrupt the autonomic cardiovascular control regulation via altering baroreflex function.

PLATELET ACTIVATION

[19] When SWCNTs were injected into anaesthetized mice coupled with platelet P-selectin, light dye promoted thrombus formation and the platelet was discovered to be activated.

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Activate blood platelets via increasing extracellular Ca2+ influx, which calcium channel blockers can prevent.

IX. CURRENT DEVELOPMENT

[20] The discovery of CNTs has opened novel therapeutic opportunities leading to the development of innovative drug-delivery or biosensor devices. CNTs have, since then, proved to be very efficient drug vectors, and when conjugated to different therapeutic and diagnostic agents. CNT's often show improved efficacy.

[21] Their specific properties make them ideal systems to combine with optical probes for imaging and for specific recognition and targeting abilities of active drug molecules. New applications for carbon nanotubes are expected to arise due to recent developments in Nanotechnology, particularly in manufacturing processes and reinforcement with other materials.

[22]Research institutes and carbon nanotube manufacturers are also aggressively probing this market to find new uses for carbon nanotubes These factors will encourage the expansion of the market over the expected period. Rising environmental concerns, health and safety issues, and high-purity carbon nanotubes that may increase the cost of production may act as serious restraints for the growth of the global carbon nanotube market. The high cost of single-walled CNTs limits access to its application domains. The Asia Pacific region dominates the global carbon nanotube market. On the other hand, North America is the second largest market for global carbon nanotube.

X. CONCLUSION

The above discussion Carbon Nanotubes have shown significant benefits in pharmacy and medicine, as they can pass through cell membranes to deliver drugs, genes, and vaccines. They resist biodegradation and are effective in repairing organs. CNTs, when combined with biosensors, are used for therapeutic monitoring, disease diagnosis, and drug analysis. Further research is needed to understand their environmental and health impacts. This article provides an overview of the synthesis and purification of carbon nanotubes, highlighting various techniques such as arc discharge synthesis, laser ablation, chemical vapour deposition. The arc discharge synthesis method is widely used but lacks control over chirality. Laser ablation produces CNTs with small impurities but is expensive. Chemical vapour deposition is suitable for large-scale manufacturing at an economical cost. Chemical-based purification methods, such as gas phase, liquid phase, and intercalation, can efficiently eliminate impurities while preserving the structure of CNTs. And also provide an

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