A REVIEW ON BIOMEDICAL APPLICATIONS OF CNTS

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ABSTRACT

In this review we explore an important nanomaterial, the Carbon NanoTubes (CNTs), which are allotropes of carbon organized as graphite tubes one nanometer in diameter and many millimeters in length. Their compact size and mass, great mechanical potency, and high electrical and thermal conductivity account for their remarkable structural, mechanical, and electronic qualities. The large surface area of CNTs allows them to adsorb or conjugate with a broad range of medicinal and diagnostic substances, which has led to their effective use in pharmacy and medicine (drugs, genes, vaccines, antibodies, biosensors, etc.). They have already been shown to be a reliable method of transporting drugs into cells without being broken down first. In addition to their use in drug and gene treatments, CNTs have been put to wide use in other fields, including tissue regeneration, biosensor detection, enantiomer separation of chiral medicines, drug extraction, and pollution monitoring. Perspectives, benefits, and challenges of this intriguing bio nanotechnology are discussed, and the pharmacokinetics, metabolism, and toxicity of several types of CNTs are analyzed.

KEYWORDS: *CNTs, Applications in medicine and pharmacy, Toxicity of CNTs.*

I. INTRODUCTION

Nanotechnology is the study of materials with a size between 0.1 and 100 nm. The National Academies divided nanoscale materials into four groups, such as metal oxides, nanoclays, nanotubes, and quantum dots [1]; the US Environmental Protection Agency (EPA) categorised them as carbon-based materials, metal-based materials, dendrimers, and composites, including nanoclays.
Sumio Iijima, a Japanese scientist, studied the carbon soot produced by a direct current arc-discharge between carbon electrodes in 1991 and identified several molecules that have since been the focus of intense scientific investigation. Using a High-Resolution Transmission Electron Microscope (HRTEM), it was discovered that these long molecules were made up of multiple coaxial cylinders of carbon [2]. Although the creation of carbon filaments had previously begun in the 1980s and 1970s through the synthesis of vapour-grown carbon fibers, it is this discovery that has propelled the area of carbon nanotube research.
In this review we analyze the numerous exciting new uses for carbon nanotubes in healthcare and pharmaceuticals. Because CNTs are small enough to cross the membrane of cells, they can transport drugs, genes, biomolecules, vaccines, and so on to parts of the body that were previously inaccessible. This breakthrough in bio nanotechnology has made it possible to develop novel medication delivery strategies that are more efficient than the conventional approaches.

II. Structure of Carbon Nanotubes

Since their discovery, Carbon Nanotubes (CNTs) have attracted a lot of attention from researchers who want to showcase their potential and define new uses for them in a variety of industries. Carbon atoms are organized in condensed benzene rings and then wrapped up into tubular structures to form CNTs.

Graphite and diamond, two naturally occurring examples of the sp2 (planar) and sp3 (cubic) forms of carbon, are also members of the fullerene family, which includes this novel synthetic nanomaterial [3-4]. The third allotropic type of carbon is fullerene.

There are two categories of CNTs that may be distinguished based on the number of layers: Multi-walled Carbon Nanotubes (MWCNTs) and Single- Walled Carbon Nanotubes (SWCNTs).

a) A Single-Walled Carbon Nanotube is a cylindrically shaped roll of graphene with a diameter between 0.4 and 2 nm and a length of up to 100 m. SWCNTs may be categorized into three groups: chiral, zigzag, and armchair.
b) A Multi-Walled Carbon Nanotube is characterized by two to many coaxial cylinders, each having an inner diameter (1 to 3 nm) and outer diameter (2 to 100 nm) and a length that ranges from 0.2 to several μm.

III. IMPURITIES COEXISTING WITH CNTS

To discover the wide range of potential applications and to investigate the fundamental physical and chemical properties of CNTs, highly effective purification of the as-prepared CNTs is crucial. CNTs synthesized using the methods invariably contain several impurities [5-6] that frequently increase with the decrease of their diameter. Among these impurities, it is important to remember:

- Pollutants: Carbonaceous Substances (including amorphous carbon, fullerenes, and carbon nanoparticles).

Since the vaporization of graphite rods provides the supply of carbon for arc discharge and laser ablation, the finished product often contains unvaporized graphitic particles that have detached from the graphite rods during the vaporization process. Moreover, graphitic polyhedrons containing metal particles within also coexist with CNTs obtained by arc discharge, laser ablation, high temperature chemical vapor deposition (>1000 °C), and other methods. Amorphous carbon is rather simple to eradicate due to its high density of flaws, which allow it to be oxidized under mild circumstances, but also fullerenes may be quickly removed thanks to their solubility in certain organic solvents.

The major problem is how to eliminate polyhedral carbons and graphitic particles, which have a comparable oxidation rate as CNTs, particularly in SWCNTs.

- metal catalyst particles.

Remains from the transition metal catalysts are typically found as metal impurities. These metal particles are occasionally covered with carbon layers, which renders them impermeable and prevents them from dissolving in acids.

Another issue that needs to be solved is that, depending on the synthesis conditions, both carbonaceous and metal impurities have very wide particle size distributions and varying degrees of defects or curvature, which makes it challenging to develop a unified purification method to produce reproducibly high-purity CNT materials.

IV. PURIFICATION METHODS

CNT purification techniques may essentially be divided into three groups: chemical, physical, and a mix of the two [7].

The basic concept on which the chemical method is based is the idea of purifying CNTs by selective oxidation, where carbonaceous impurities are oxidized at a quicker rate than the same CNT, dissolving metallic impurities by acids. In general, there are three types of chemical oxidation: electrochemical oxidation, liquid phase oxidation, and gas phase oxidation (using things like air, oxygen, chlorine, and hydrogen).

Amorphous carbon and metal particles may be efficiently removed with this technique, apart from those contained within polyhedral graphitic particles. Nevertheless, it has drawbacks since it frequently opens the end of CNTs, slices them, destroys the surface structure, and adds oxygenated functional groups (-OH, -C = O, and -COOH) to CNTs. Because of this, the purified CNTs can later be used as chemical reactors or as a starting point for further nanotube surface chemistry.

A technique that isolates CNTs from contaminants based on variations in their physical size, aspect ratio, gravity, magnetic characteristics, etc. is needed to get around issues caused by chemical purification methods, thus avoiding oxidative treatment. Filtration, chromatography, centrifugation,

electrophoresis, and high temperature (1400-2800 °C) annealing are examples of physical-based techniques that have undergone substantial research.

In addition to being non-destructive and non-oxidizing, the most notable aspect of these procedures is that most of the purifications are carried out in solutions, necessitating that the as-prepared samples have high dispersibility in the solutions. Typically, the physical approach is employed to separate CNTs with different diameter/length ratios or to remove graphitic sheets and carbon nanospheres (CNSs).

The third type of purification produces high yield and high-quality CNT products by combining the advantages of physical and chemical purification. Due to the variety of the CNT samples as prepared, including the CNT type, CNT morphology and structure, as well as the type and morphology of impurities, this last method takes a skilful fusion of several purification procedures to produce CNTs with the appropriate purity.

V. FUNCTIONALIZATION FOR BIOMEDICAL APPLICATIONS

Numerous researchers have proposed the notion of adding new functions to CNT surfaces to enhance their existing chemical properties. CNTs' surfaces may be modified in several ways, including by covalent and noncovalent (van der Waals) bonding, defect generation, sidewall functionalization, and exo- and endohedral functionalization [8]. The sp2 carbon framework often receives chemical functionality including OH, COOH, and NH2 groups during CNT modification. This type of functionalization encourages the CNTs' dispersion in a variety of solvents and polymers, enabling the usage of nanotubes in several applications. Non-covalent modifications rely on the van der Waals force and π-π interactions, whereas covalent modifications employ chemical bonds to attach the desired functional group to the ends or sidewalls of the carbon nanotubes.

VI. APPLICATIONS OF CNTs IN PHARMACY AND MEDICINE

The use of CNTs has been extended to many pharmacy and medicine applications.

6.a CNTs USED FOR CANCER THERAPY

- *By drug delivery*

Many drug delivery methods have been developed with CNTs in mind, with the potential to cure a broad range of diseases. Many of the CNT-based anticancer medications depend on two strategies: the first is the use of specific tumor receptors to facilitate targeted delivery, and the second is the slow, steady release of chemicals known to be present in tumors, such as those responsible for the abnormally low pH. Both strategies are essential to the success of CNT-based anticancer drugs. [9-13]. This makes possible for CNTs to carry tiny quantities of medication directly to the location of the tumor, minimizing systemic toxicity, but also the unfavorable side effects of conventional anticancer medications.

In combination with CNTs, a selection of anticancer medicines [14-19], have been put through in vivo and in vitro experiments. Numerous research has been conducted to avoid the negative impact of anticancer medications on healthy cells and organs.

A magnetic CNTs complex made of epirubicin and magnetite (Fe3O4) nanoparticles was initially proposed. Later, the epirubicin magnetic CNTs complex was utilized to create a device that could be steered by an external magnet to target local lymph nodes and treat lymphatic tumors [20].

In a similar manner, it is conceivable to connect chemotherapeutic drugs to a complex CNT-antibody that is directed against an antigen overexpressed on the surface of malignant cells. It is only possible for the tumor cell to take up the CNTs through the attraction of antigen-antibody if the anticancer medicine has not yet been cleaved off the CNTs. Additionally, the combination of SWCNT and paclitaxel has been used in a breast cancer model, with results showing greater effectiveness in reducing tumor growth and fewer toxic effects on healthy organs. This may be because SWCNTs have longer blood circulation, a higher tumor uptake rate, and a slower rate of drug release.

- *By antitumor immunotherapy*

CNTs utilized as carriers have been shown to be useful in anticancer immunotherapy in several studies [21-23], because they encourage body's natural defenses to wage war against the cancerous cells. It is possible to reach this goal by administering a anti-cancer vaccine or a antibody’s therapy to the patient as a kind of treatment. For instance, research has shown that administering MWCNTs together with

tumor lysate protein selectively increases the effectiveness of anticancer immunotherapy in mice with H22 liver tumors [23].

By exposing immunological effector T cells to tumor antigens in vitro, CNT-tumor immunogen conjugates can serve as natural antigen-presenting cells (like mature dendritic cells); the combination of the negative charge and the highly avid antigen on the surface causes this reaction. Although the mechanism is currently unclear, CNTs' impacts on the complement system and their adjuvant effects may contribute to the promotion of anticancer immunotherapy [23–24].

- *By local antitumor hyperthermia therapy*

Recently, the use of CNTs in hyperthermia therapy has been proposed as an effective method for the treatment of cancer. These nanomaterials have a high absorption capacity and may produce a sizable quantity of heat when excited by near-infrared light. When SWCNTs encased in tumor cells, such as those of pancreatic cancer, are warmed, the photothermal activity can result in local thermal ablation of the tumor cells.

6.b CNTS USED FOR INFECTION THERAPY

Functionalized Carbon Nanotubes have also been used to address issues brought on by infectious agents' resistance to antiviral and antibacterial medications or by the ineffectiveness of vaccines in the body. They have been demonstrated to be effective vaccine and antimicrobial agent delivery vehicles; antimicrobial agents include the fungicide amphotericin B [25-26]. A bacterial or viral antigen can be linked to CNTs to maintain the antigen's shape while still triggering the proper specificity in the antibody response.

6.c DNA DELIVERY WITH CNTS IN GENE THERAPY

In gene therapy, DNA molecules are surgically introduced into a patient's cells to correct a faulty gene that is thought to be at the root of several debilitating and inherited diseases. This is done to correct a gene that is thought to be at the root of several diseases. DNA may be transferred via a variety of delivery techniques [27-28], including liposomes, cationic lipids, and nanoparticles like the recently discovered CNTs. In contrast to DNA employed alone, DNA probes attached to SWCNTs, for instance, are shielded from cleavage and interference by nucleic acid binding proteins, improving DNA's capacity to self-deliver, and exhibiting improved biostability [29].

6.d CNTS IN TISSUE ENGINEERING AND ARTIFICIAL IMPLANTS

Stem cells make it possible to regenerate tissues in the body in a way that is anatomically and functionally comparable to how they were originally found in the body. This necessitates the use of biodegradable scaffolds to provide seed cells something to attach to. CNT-based tissue engineering (i.e., bone, neural, and cardiac tissues) and regenerative medicine are now possible thanks to recent advances in cell/organ transplantation of CNTs chemistry and their biocompatibility, resistance to biodegradation, and ability to be functionalized with biomolecules to enhance organ regeneration [30–33]. While CNTs have numerous potential uses in tissue engineering, one study stands out for its innovative usage of carboxylated SWCNTs in a composite nanomaterial utilized as a scaffold. CNTs have also been investigated for their potential in cell labeling and tracking, cellular activity detection, and the enhancement of tissue matrices [34]. CNTs, for instance, have been demonstrated to enhance bone tissue regeneration in mice and embryonic stem cell-induced neurogenic cell differentiation in vitro [35].

6.e CNTs'APPLICATION TO NEUROGENERATIVE AND ALZHEIMER'S DISEASES

CNTs' tiny size and adaptability make them a promising candidate for use as delivery vehicles that can cross the blood-brain barrier to reach the intended brain region [35]; functionalized SWCNTs or MWCNTs have been used to treat brain tumors or neurodegenerative diseases successfully, for example., SWCNTs' capacity to transport acetylcholine in Alzheimer-affected mouse brains has been shown [36]. Overall, these research' findings demonstrate that CNT-therapeutic chemical conjugates are more effective in promoting neuronal development than pharmaceuticals alone.

6.f CNTs USED AS ANTIOXIDANTS

According to some recent studies, CNTs and carboxylated SWCNTs are natural antioxidants with potential biomedical applications in the treatment of aging, chronic illnesses, and food preservation [37-38]. Their antioxidant qualities have also been utilized in the creation of sunscreen lotions and anti-aging cosmetics to shield skin from free radicals produced by the body and UV rays.

6.g CNTs AS BIOSENSING TOOLS FOR DIAGNOSIS AND DETECTION

The novel idea of using CNTs as part of a biosensor might potentially be of tremendous help to therapeutic monitoring as well as in vivo and in vitro diagnostics. An electrolyte solution and the analytes that are contained within it may be analyzed using analytical instruments known as biosensors. Biosensors are analytical instruments that combine a biological constituent with a detector of physicochemical nature. When compared to employing either component alone, combining sensors based on glucose oxidase for monitoring and regulating glucose levels in conjunction with CNTs results in greater accuracy and makes the biosensors more amenable to manipulation [39].

There is evidence that carbon nanotubes are suggested for use as a biosensor vehicle, due to their length scale as well as the one-of-a-kind structure they possess. An improved and less complicated technique for molecular diagnostics is provided by combining single-strand DNAa (ssDNA) with single-walled carbon nanotubes (SWCNTs) or by electrically detecting DNA produced using the alkaline phosphatase enzyme connected to carbon nanotubes. One example of this is the electrical DNA's detection obtained using the alkaline phosphatase enzyme linked to carbon nanotubes. Compared to commercially available silicon- or other material-based sensors, CNT-based biosensors have several benefits.

These benefits consist of:

A) hollow-tube shape and high surface-to-volume ratio provide great sensitivity and substantial biological activity by trapping enzymes [40];
B) fast response time, CNTs can facilitate electron-transfer processes because of their superior capacity to mediate rapid electron-transfer kinetics, such as the interaction between NADH and hydrogen peroxide;
C) less impacts of surface fouling and a low potential for redox reaction;
D) extensive longevity and great stability [41].

6.h ENANTIOSEPARATION OF CHIRAL DRUGS AND BIOCHEMICAL COMPOUNDS USING CNTs

The US Food and Drug Administration (FDA) recently released a policy statement [38] in which it called for the development of novel chiral medications as single enantiomers and suggested that the body's activity of racemic pharmaceuticals be assessed separately for each enantiomer. Because of this, numerous new chiral separation technologies have been developed. One example of this is the chiral stationary phase of multi-walled carbon nanotubes (MWCNTs) cross-linked with hydroxypropyl—cyclodextrin [42], which is used for the enantioseparation of racemic clenbuterol, which is a bronchodilator.

It is well established that carbon nanotubes (CNTs) exhibit chiral properties due to the helical wrapping of the graphitic rings around the tube axis. As enantio-specific adsorbents, they may not be effective. Alternatively, chiral selector modified carbon nanotubes (CNTs) have been used to effectively identify enantiomers from a range of racemic medicines [42].

6.i CNTs USED IN THE PROCESS OF SOLID-PHASE EXTRACTION OF PHARMACEUTICALS AND BIOCHEMICALS

Strong interactions between CNT surfaces and, for example, those with benzene rings, make CNT surfaces excellent adsorbents. Analytical extraction of pharmaceuticals, pesticides, or natural chemicals from a wide range of media (i.e., as bodily fluids, plants, animal organs, etc.), has been examined using CNTs as Solid Phase Extraction (SPE) adsorbents [43-44]. According to the findings of a few research, carbon nanotubes (CNTs) have a higher capacity for adsorption than either silica-based sorbents or macroporous resins. Benzodiazepines, sulfonamides, non-steroidal anti-inflammatory (NSAI), barbiturates, antidepressants, propranolol, cinchonine, and quinine are some examples of drugs that

have been pulled out by SPE using SWCNTs/MWCNTs as adsorbents in the matrices that have been mentioned above, and then examined by various physicochemical techniques [43].

VII MECHANISMS OF CNTs TOXICITY

The kind and level of toxicity are greatly influenced by the type and physical characteristics of CNTs discussed in the section above. In the literature describing the mechanisms of toxicity, three potential mechanisms of CNT cytotoxicity—oxidative stress, cell membrane damage, and genotoxicity—are presented. These processes are explored below.

7.a OXIDATIVE STRESS

Reactive oxygen species (ROS) or oxygen free radicals cause oxidative stress when their production exceeds the body's antioxidant defenses. Reduced levels of GSH and other antioxidants, as well as an increase in oxygen species production, might be indicative of this imbalance [44]. Proteins, nucleic acids, and lipids are quickly oxidized by the ensuing ROS, losing their functionality, and ultimately disrupting homeostasis [45]. Studies conducted in vitro indicate a correlation between rising SWCNT concentration and an increase in ROS production as well as a decrease in GSH levels [46]. A similar correlation between GSH levels and SWCNT-induced E. coli viability loss was also suggested [47]. Human embryonic kidney cells (HEKs) showed a similar pattern of cytotoxicity for MWCNT in a dose-dependent manner [48]; in addition, it has been demonstrated that the surface functionalization of MWCNTs affects ROS cytotoxicity within the cell [49]. In mice, SWCNT injections demonstrated negligible toxicity in vivo [77]. It has been demonstrated that neuronal PC12 cells may be protected against SWCNTs-induced toxicity by pretreatment with vitamin E (VE), which increases cell survival, decreases cell apoptosis, and reduces ROS formation in a dose-dependent way [50].

It has been shown that the physical and chemical properties of CNTs, in addition to the presence of reactive species and transition metals, have a substantial influence in the production of oxidative stress by CNTs. Accumulation of nanomaterials inside cells or at greater concentrations may lead to the development of oxidative stress or cell death [51]. Additionally, oxidative stress has been demonstrated to disrupt cellular signaling, which may result in apoptosis. Furthermore, oxidative DNA damage, cytotoxicity, and necrosis are all outcomes of CNT-induced oxidative stress.

7.b CELL MEMBRANE INJURY

In several studies, membrane damage has been mentioned as a potential additional mechanism by which CNTs might cause cytotoxicity. Among these results, one shows that when highly pure MWCNTs (67 nm) are presented to mice macrophages (J774.1), membrane damage—rather than oxidative stress—plays a role in cytotoxicity [52]. Buthionine sulfoximine BSO, an inhibitor of glutathione formation, and N-(NAC) acetylcysteine, an antioxidant, both had no impact on cytotoxicity, lending credence to these results. Furthermore, the treatment had little effect on the MAP kinase or apoptotic pathways. The findings suggests that membrane damage is caused by membrane expansion during MWCNT engulfment.

Dendritic cells (DCs) were shown in another investigation to be capable of phagocytosing MWCNTs while exhibiting no cytotoxicity or immunological activity [53]. In fact, macrophages may damage lysosomes and trigger necrotic cell death when they extend down the CNT fiber to swallow particles. Another study demonstrates that double wall CNTs (DWCNTs) impact membrane integrity without the use of ROS by inducing potassium efflux, which activates the Nlrp3 inflammasome [54].

7.c GENOTOXICITY

Genotoxicity, which encompasses gene mutations, chromosome breakage, and rearrangements, is a term used to describe any DNA or chromosomal damage [55]. The capacity of CNTs to permeate nuclear membranes [55], their size resemblance to microtubules [56], and their strong affinity for G-C rich regions of DNA sequences [57] are only a few of the variables that may facilitate their interaction with genetic material and the development of genotoxicity. SWCNTs and MWCNTs, according to in vitro study [58], may damage DNA in mesothelial cells. The genotoxicity of MWCNTs has been demonstrated not only in human and animal cells, but also at cellular level in plants (Allium cepa) and

DNA strands that are included in a plasmid (pBR322) [59- 60]. Carbon nanoparticles may induce genotoxicity in two different ways: directly (primary genotoxicity) and indirectly (secondary genotoxicity); the first one occurs when the nanomaterials interact with DNA or the mitotic apparatus, while the second one is brought on by oxidative stress and inflammatory reactions.

- Primary Genotoxicity of CNTs

The principal genotoxicity of CNTs occurred from the particles' proximity to DNA. MWCNTs directly induce genotoxicity via aneugenic and clastogenic activity [61]. Possible mechanisms for the aneugenic impact or chromosome loss include CNTs coming into touch with mitotic spindle components or interacting with proteins like tubulin and actin that are directly or indirectly involved in chromosome segregation. Possible outcomes of these interactions include micronuclei and chromosomal abnormalities (also known as aneuploidy) in daughter cells, both indicators of genetic instability. On the other side, a clastogenic action causes adducts or chromosomal aberrations to form. Physical association of SWCNTs with DNA, microtubule, and centrosome fragments has also been associated with multipolar mitotic spindles and aneuploidy.

- Secondary Genotoxicity of CNTs

When inflammatory cells interact with different cell parts, they release ROS, which might have a clastogenic effect on CNTs. This is the mechanism through which CNTs indirectly cause genotoxicity by oxidizing DNA, breaking DNA, etc. [62] because of the interaction between the generated ROS and the DNA. Numerous studies have discussed the connection between genotoxicity and oxidative stress [63]. It is interesting to note that the purity and dispersion qualities of SWCNTs have a nongenotoxic impact, indicating that the risk of genotoxicity can be decreased by decreasing parameters linked to ROS formation, such as CNT purity [64].

VIII. CONCLUSIONS

In this review we have analyzed the numerous exciting new uses for carbon nanotubes in healthcare and pharmaceuticals. Because CNTs are small enough to cross the membrane of cells, they can transport drugs, genes, biomolecules, vaccines, and so on to parts of the body that were previously inaccessible. This breakthrough in bio nanotechnology has made it possible to develop novel medication delivery strategies that are more efficient than the conventional approaches. Collagen carbon nanotube (CNT) materials are a breakthrough approach to the fabrication of artificial implants and artificial tissue since CNTs are resistant to biodegradation and are a potent engineering choice when compared to other materials that are currently utilized to repair damaged organs. In addition, carbon nanotubes, when combined with biosensors or other types of materials, have shown to be effective instruments for therapeutic monitoring, the detection of illnesses, and the study of medications in a range of different environments. While the early stages of CNT research have yielded some unexpected findings, there is still a wealth of untapped potential and serious threats that must be addressed. Although the processes through which CNTs produce toxicity have been identified, further research is needed to fully understand them; it is for this reason that many steps have been taken to better understand possible in vivo/in vitro toxic effects of CNTs and many strategies for overcoming these problems have been investigated.

With increasing production of CNTs, there is an urgent need to refine strategies to assess their possible effects on employees, who represent the main exposed population so that appropriate safety regulation can be formulated. Standardized protocols to evaluate the toxicity of CNTs and categorize their associated risks would help to accelerate their routine application. Current toxicity reports on biological risk may have to be evaluated in the context of exposure due to ambient environment. Additionally, the hazards of treatment with CNTs need to be compared with other treatments to arrive at safe doses and relative benefits of CNTs over current regimens. If the risk/benefit aspects are satisfactorily answered, then the use of CNTs in biological systems might be feasible.

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