REVIEW ARTICLE

Therapeutic approach of carbon nanotube: Revolutionize nanomaterial in biomedical and pharmaceutical sector

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Abstract

Carbon nanotubes (CNTs) has emerged as a promising nanomaterial with a wide range of potential applications due to their unique structural, mechanical, electrical, and thermal properties. However, numerous obstacles must be overcome for CNTs to be used successfully, including low solubility, aggregation, and a lack of specialized functions. Diverse techniques have been developed for the manufacture, purification, and functionalization of CNTs in order to overcome these issues. The main aim of this review article is to provide brief knowledge about CNTs and strategies to use this revolutionized nanomaterial in drug delivery. Prepare CNTs cannot be directly used as drug carrier molecules due to the presence of impurities, so purification is an essential aspect of their use. In addition, various functionalization procedures are used frequently for drug conjugation with other benefits, such as reduced toxicity and targeted delivery. Their nano needle structure can penetrate any cell without damaging it with improved efficiency in targeted drug delivery, cancer cell identification, anticancer molecule delivery, antifungal treatment, and transdermal approaches. This nanostructure also has some antimicrobial activity, and conjugation with some antimicrobial agents shows a synergistic response.

Keywords: Carbon nanotube, Functionalization, Graphene, Pharmaceutical application

1. Introduction

Carbon nanotubes (CNTs) are graphene sheets rolled up into a structure that shows various interesting properties attracting them towards more pharmaceutical applications than other carbon allotropes and nanostructures like fullerene, diamond, carbon nano horns, and carbon nanofibers. Carbon molecules can be hybridized as sp, sp2, or sp3, but in CNTs, they are arranged as nanometres-range sp2 hybridized hexagonal rollup structures, though structural properties came from graphene, from which CNTs are prepared [1,2]. They are generally prepared by fabricating the graphene sheet as a cylinder through various physical and chemical methods. This hexagonal structure is perfectly described by a chiral vector (c), which is the connection between the center of two hexagons, where C = na1 + ma2. Where n and m are known as chiral indices and a1 and a2 are the basic vectors of graphene. The chiral index classifies the different forms of hexagon armchairs where n = m, zigzag where m = 0, and chiral (all others) [3,4]. Those carbon atoms composed of special structures can classified into two categories depending on the presence of sidewall single-walled carbon nanotubes (SWCNTs). SWCNTs are single-layer cylindrical graphene rollup structures where carbon is present as an armchair, zigzag, chiral, or helix. In SWCNTs, the carbon atoms are attached through a c−c covalent bond. SWCNT has different diameters, ranging from 0.4 nm to 2 nm, and this diameter depends mainly upon the synthesis temperature (high temperatures produce a larger diameter) [5]. Multi-walled carbon nanotubes (MWCNTs) are several-layer roll-up structures held up by

Received 27 February 2024; accepted 24 September 2024.
Available online 15 December 2024

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https://doi.org/10.38212/2224-6614.3531

Vanderwall interaction between sheets where the distance with the next sheet is near about 0.340 nm in the case of MWCNTs, which is shown in Fig. 1. In MWCNT, the inner sheet diameter is about 0.2–2 nm, and the outer sheet diameter can be 2 nm up to 100 nm [6]. MWCNTs are used in various drug delivery methods by plugging one end of the tube or by plugging both ends after loading the drug in the tube. According to their structure, MWCNTs are further divided into two types: the parchment model where the multi-walled structures are made from one large graphene sheet by rolling upon itself too many times like a parchment paper. Another is the Russian doll model, where the multi-walled structure is made by the presence of many tubes of

Abbreviations

BBB	Blood–brain barrier
COOH	Carboxylic acid
CVD	Chemical vapor disposition
DNA	Deoxyribonucleic acid
ETS	Electron transmission chain
MWCNTs	Multi-walled carbon nanotubes
PDT	Photodynamic therapy
PEG	Polyethylene glycol
PTT	Photothermal therapy
SEM	Scanning electron microscopy
SWCNTs	Single-walled carbon nanotubes
TEM	Transmission electron microscopy
TGA	Thermogravimetric analysis

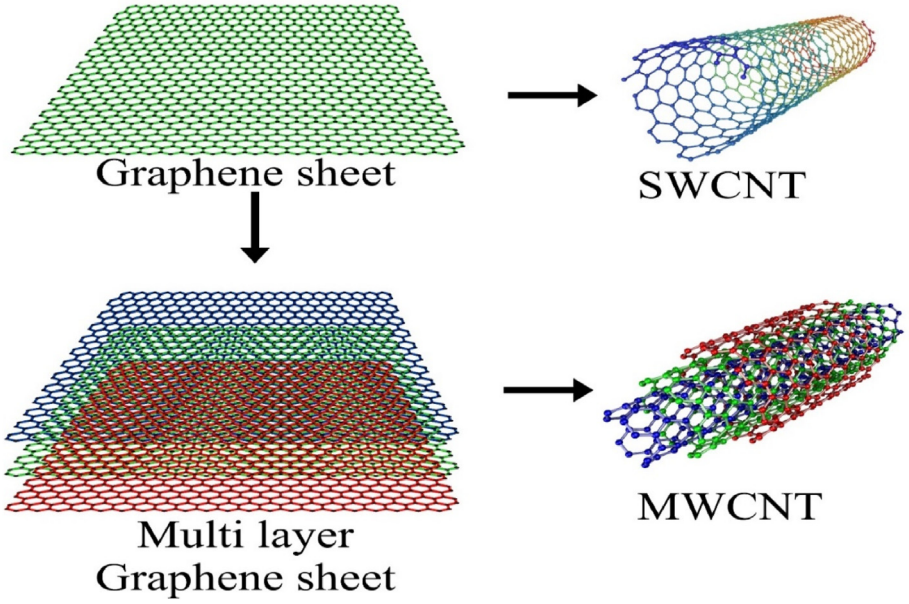

Fig. 1. Preparation of carbon nanotube from graphene sheet.

Table 1. Basic difference between multiwall carbon nanotube and single-wall carbon nanotube.

Characteristic	MWCNT	SWCNT
Structure	Multi-layer rollup structure of graphene with different diameters is observed.	Single layer rollup of graphene having smaller diameter is observed.
Synthesis process	Bulk synthesis is possible without the presence of a catalyst.	Bulk synthesis is difficult due to improper control over growth and the presence of a catalyst was necessary.
Pharmaceutical application	Because of its small inside space, a low amount of drugs could be delivered. So, for them, drugs are attached inside or outside.	Its hollow cylindrical structure provides more inside space, which is why drug loading efficiency is high.
Drug accumulation	Its complex structure causes more accumulation in the body of nanotubes.	Because of its simple structure accumulation is low in the body.
Toxicity	They cause toxicity because of abnormal phagocytosis and, plasma membrane damage, higher aggregation, but they don't form bundles because of their low surface area.	Generally, they caused oxidative damage, but due to their less aggregation, they could be phagocytosed easily. Though they can form bundles.

different diameters, where the tubes with a large diameter stay on the outside, and the smaller ones stay inside; the basic difference between the two has been tabulated in Table .1 [7,8].

After the discovery of CNTs by Japanese scientist Sumoi Iijima in 1991, CNTs became an exciting subject in the pharmaceutical field due to their many qualities [9]. They have an ultralightweight and 100% elimination rate (96% by urine and 4% by feces). They have high elastic power, so they can easily enter into the cells without damaging their structure by bending or twisting. They can also act as a thermal conductor and have good thermal stability (at normal 750 °C and in vacuum pressure up to 2800 °C). They are non-biodegradable, non-immunogenic, and biocompatible with living systems. They have a high electrical current carrying capacity, which is thousand times higher than copper wire. Recently, they have been applied to prepare nanomedicine, nanoelectronics devices, actuators, etc.

As versatile nanocarriers for targeted drug administration, carbon nanotubes have enormous potential to enhance the therapeutic effectiveness and safety of various pharmacological drugs. Personalized medicine and precision treatments have the potential to significantly improve as long as CNT-based drug delivery devices are developed and optimized. This review article discusses simple strategic ways to utilize CNTs, a revolutionized nanomaterial in the biomedical and pharmaceutical sectors. We address that area we must take care of before using them in drug delivery.

2. Preparation of CNTs

CNTs are expensive and tedious to produce on a large scale, but their industrial application is growing daily due to their exceptional quality. Various researchers are working on developing the preparation process to minimize the difficulties; in this review article, we discuss a few synthesizing processes.

2.1. Arc discharge

This CNTs synthesis method is done in an airtight chamber at a high temperature (1700–6000 °C). The chambers contain a graphite electrode where the cathode and anode are placed at a certain distance (1–2 m) with facial direction, and the chamber is fitted with inert gases like helium and argon [10]. Sometimes, evaporated carbon molecules are added for quick action. Arching is done by passing a direct current that causes a high temperature that produces sublimelt graphite and carbon vapor, and during this conversion of graphite, carbon atoms are ejected too, which are deposited in the negative charge electrode (cathode), which has a slightly lower temperature than the positively charged electrode (anode), which decayed during the arc discharge process and formed the cylindrical structure of CNT in the cathode which starts with nucleation then the growth of nanotubes [3]. The inert gas plays an important role in the formation of CNTs. At higher temperatures, the inert gas ionizes and migrates with high velocity, hitting the anode and increasing the rate of carbon vapor formation. It also helps in the formation of carbon ions from carbon vapor. The application of catalyst precursors depends upon the type of CNTs required [11]. Catalysts like cobalt, nickel, iron, yttrium, and many other catalyst mixtures are used in the formation of SWCNTs as a complex anode (graphite + catalyst) that, given the high production rate, the preparation of MWCNTs doesn't require a complex anode. The main advantage of this method is that high-quality CNTs can be prepared at a high production rate. CNTs prepare by introducing the catalyst needed for purification, and this process has little control over chirality, which was the main disadvantage of this process [12].

2.2. Laser ablation method

This process is done in quartz chambers that contain pure graphite, which is heated at 1200 °C by a furnace, a laser beam for vaporizing the graphite, laser powder to control the diameter of the tube (the diameter of the tube decreases when the laser powder increases), catalysts like Ni, Co, and inert gases like argon, He and N_2 flow during the synthesis. This process is quite similar to arc discharge. Here, the chamber is heated at 1200 °C by furness, which ionizes the inert gas. The laser beam is directly applied over the graphite to vaporize them, and the vapor condenses as CNT in the collector, which has a lower temperature as compared to other parts of the chamber. The type of CNTs prepared depends upon the selection of graphite material, if pure graphite material is used as a source of carbon, then MWCNT is produced, and for the production of SWCNTs graphites are combined with catalysts. The preparation of CNT by laser ablation can be affected by parameters like the properties of the laser, flow, and pressure of the gas, and temperature (defects at lower temperatures. In this technique, impurities are lower than the arc discharge, but nanotubes prepared by this technique sometimes contain branching; they are not uniform and straight. This technique is also

expensive due to the requirement of highly pure graphite, laser powder, and a laser beam [13].

2.3. Chemical vapor disposition (CVD)

As the name suggests, hydrocarbon vapor carbon molecules are deposited and formed as CNTs. This process involves the interaction between a metal catalyst and carbon in high temperatures (600°C-1200 °C). As a carbon source, hydrocarbons are used; they can be solid (camphor), liquid (benzene), or vapor (acetylene, carbon monoxide), and they are injected into the chamber with the help of carrier gas like H_2, N_2 [14]. High heat converts them into hydrocarbon vapor, and through reactions with metal crystals, they separate into hydrogen and carbon [15]. Carbon molecules attract catalysts, and they react with substrates. As substrate materials, zeolite, graphite, silicon, and alumina can be used. The selection of substrate becomes important to maintain the quality and rate of production. The substrate catalyst reaction initiates the growth of CNTs, which is generally of two types: base growth and tip growth. In base growth, hydrocarbons decompose at the top, but due to strong interactions between substrate, catalyst, and metal particles, the growth of CNTs occurs near the substrate (base). In tip growth, the decomposition of hydrocarbons is very similar, but due to the weak substrate–catalyst interaction, the CNTs grow at the top, away from the substrate. The formation of CNTs depends upon the use of hydrocarbons; if cyclic hydrocarbons (benzene) are used, then curve nanotubes are formed, and if linear hydrocarbons (acetylene, methane) are used, then straight CNTs are formed. Metal catalysts play an important role in CNTs formation [16]. Catalysts like cobalt, nickel, iron, magnanimous, and aluminum are used, they can be used in combination (MgO, Al_2O_3) to develop the surface area and yield [17]. The growth of CNT depends upon the property and size of the catalyst, the ideal catalyst should show control over the growth with good stability, temperature control, and good dispersing stability. The size of the catalyst has a significant role in the production of SWCNTs and MWCNTs, larger particles (10 mm) lead to the formation of MWCNTs, while smaller catalysts produce SWCNTs, and the length of CNTs depends upon reaction time. By applying this technique, CNTs can be prepared with high purity by controlling the growth and reaction times at a comparatively low temperature and a low cost. According to the use of different catalytic agents, this process can be further referred to as radio frequency CVD, microwave plasma CVD, oxygen-assisted CVD, hot filament CVD, water-assisted CVD, etc [16,18].

2.4. Chemical method

The conventional method of carbon nanotube preparation involves high temperature and pressure and a few other ingredients which make them expensive but preparation through the chemical method CNTs can be prepared very easily. Lee et al. was reported about CNTs preparation through some modification of the Staudenmaier process at room temperature by using graphite powder as a source of carbon. According to them, a mixture of sulfuric acid and nitric acid (2:1) was prepared and pure graphite powder was added to the mixture slowly with stirring, which increased the temperature. Then, the mixture was transferred to an ice bath to reduce its temperature to lower than 5 °C. After that, potassium chlorate was cautiously added to the preparation and heated for a day at 70 °C. The mixture was then kept in air for three days for reaction. The reacted carbon moved upwards and was then transferred into water and after 1 h of stirring, the solution was filtered and further dried to obtain CNTs, which was confirmed by SEM and TEM.

3. Purification

CNT prepared using those techniques contains various unwanted materials in the final product separation of those materials from CNT, known as purification. Purification became an important aspect because the presence of metal crystals and other carbonaceous impurities raises various problems when they are used to deliver drugs in the body, like blood clotting, Saviour heart conditions, and cellular toxicity [19].

Generally, impurities in CNT are two types: carbonaceous impurities and metal particles. Carbon nanoparticles, polyhedral carbon, graphite particles, and fullerenes can be present in CNT as carbonaceous impurities; among them, polyhedral carbon and graphite particle separation is more difficult because of their similar Oxidation rate with CNT. Metal impurities are the part of metal catalysts encapsulated by carbon layers during synthesis. Purification of CNT can be divided into three types: chemical, physical, and combined Purification [20].

3.1. Physical purification

Filtration, centrifugation, Chromatography, electrophoresis, and high-temperature annealing can be done as Physical methods. Filtration purification is

done based on the solubility and size of the carbon nanotube. Metal and polychromate carbon are separated by dipping the nanotube in an organic solvent combination (like water + sodium dodecyl sulfate). Then, impurities are separated by passing the solvent through the filter repeatedly until pure CNTs are observed. Sometimes, sonication and filtration are also used to conduct the process smoothly. The filtration process doesn't damage the structure of CNTs so that process can be beneficial [21]. Another technique used for purification is centrifugation, where different ranges of speed (2000 g–200,000 g) were applied over the CNT, and impurities were separated due to the gravitational force. Low-weighted particles (impurities) are settled down in the chamber according to their difference in weight. High-temperature annealing is another technique used to remove the impurities in which high temperature is applied. CNTs can withstand high temperatures (3000 °C), but carbonaceous impurities and metal particles cannot withstand that much heat; they evaporate at low temperatures (near about 1400 °C). CNTs were separated. Purification is also done by solubilization, where a functional group is attached to the surface of the CNT to solubilize them, then by applying chromatography or filtration. The impurity is separated, and the functional group's letter is removed using thermal treatment. This process is also capable of maintaining the original structure of the nanotube. Except for mechanical and magnetophoretic purification, other physical purification methods were also employed [22].

3.2. Chemical purification

The basic principle of chemical purification is the selective oxidation of carbonaceous impurities, and purification is done by chemical oxidation by using their oxidation state difference. Impurities with more oxidative activity due to their structural defects and immobilized free radicals oxidize more quickly than CNT. Chemical purification is further classified into different categories- Furthermore, gas-phase oxidation is a simple method for purification in which an oxidizing environment is created by introducing mixtures of gas like H_2O, Cl_2, HCL, O_2, SF_6, H_2S, $C_2H_2F_4$. in the presence of air at high temperatures (225–760 °C). Different combinations of gas provided different yield percentages. Increasing the oxidation resistance difference is an essential parameter for this type of purification.

- The advantage of this process is that it is very effective in removing carbonaceous impurities without damaging the structure of CNTs. This technique easily purified arc-discharged process-made CNTs.
- The disadvantage of this process is that it cannot purify metal crystals, for which further acid treatment was recommended [23].

Liquid phase oxidation can remove carbonaceous impurities as well as metal particles continuously by using liquid phase oxidants like $KMNO_4$, H_2O_2 or oxidants mixture like (NaOH + $KMNO_4$), (H_2O_2 + HCL), (HNO_3 + $KMNO_4$ + H_2SO_4). The efficiency and purity of this process are very high, but it increases the solubility and chemical activity through the modification of nanotube sidewalls.

- Advantage: This process can be used for the industry's continuous large-scale production.
- Disadvantage: This process cannot remove large graphite particles and also damage the nanotube structure [21].

3.3. Combined purification

Physical and chemical purification have their limitation. They are effective in purifying single types of impurities, and yield is low in most cases, as a solution of that combined purification is done, which provides higher yield with better purification. This type of purification uses both physical and chemical purification in various stages. That's why this purification is also called multi-step purification [24]. According to the use of different methods, there can be different types-

* Kim et al. used magnetic filtration with oxidation and obtained effective filtration with high yield [25]. More than 90% purification was obtained for SWCNTs by Bandow et al. by using this technique where fast carbon nanospheres were removed by using microfiltration after those carbonaceous impurities were removed by oxidizing them in air. Metal particles were separated by treating them in HCl [26].
* **Ultra-sonication in combination with oxidation**: The oxidation process is highly effective in removing carbonaceous impurities, and ultra-sonication in an appropriate solvent (liquid nitrogen, HCL, HNO_3, H_2SO_4, etc.) effectively removes metal particles. Combining those processes provides 95%–96% purity for SWCNT. This process also minimizes the risk of modification and damage of CNTs [27].
* **Extraction with high-temperature annealing**: Combining those processes shows a high yield

for MWCNTs purification. Where high-temperature annealing is effective in removing metal particles and extraction by using polymer to remove carbon impurities [28].

3.4. Purity assessment

After the purification process, it became necessary to determine the purity efficiency and defects due to the purification process. For this purpose, thermogravimetric analysis (TGA), Raman spectroscopy, UV–visible–near infrared spectroscopy, electron microscopy, and energy dispersive spectroscopy are commonly used. Those processes quantitatively and qualitatively determined impurities in CNTs [29–31].

4. Functionalization

Functionalizing those aromatic cylindrical structures became an important part of pharmaceutical applications because of the high toxicity and bio incompatibility of raw CNTs. Functionalization is necessary to make them biocompatible, increase their dispersibility in biological fluids, and reduce enzymatic degradation, reducing toxicity. Generally, the process of functionalization can be divided into two types: one is noncovalent, and another is covalent, as presented in Fig. 2. In noncovalent functionalization, specific molecules are attached through physical interactions where π-π interactions, van der Waals forces, hydrogen bonds, and electrostatic forces play an important part. CNT biomolecule complexes are formed by absorbing molecules onto the CNT surface. This attachment can be done by using biomolecules like carbohydrates, DNA, peptides, surfactants, polymers, antibodies, etc [32,33].

Moreover, carbohydrate molecules, amylose, and iodine mixture can be used for functionalizing CNTs, where the Vander wall's force plays a vital role in the attachment. Other molecules like B − cyclodextrin, gum Arabica, and various polysaccharide molecules can be used as carbohydrate sources for carbon nanotube Functionalization. CNT can Functionalize by DNA molecules through π- π interaction, π-stacking or charge transfers, or anionic-cationic bonds and can be used for targeted drug delivery, gene transport, or in various nanosystems [34]. Peptides containing amino acids like tryptophan, tyrosine, and phenylalanine are highly capable of binding with CNT and delivering the drug to the desired site. Amphiphilic and high-specific peptides are also capable of the functionalization of CNTs.

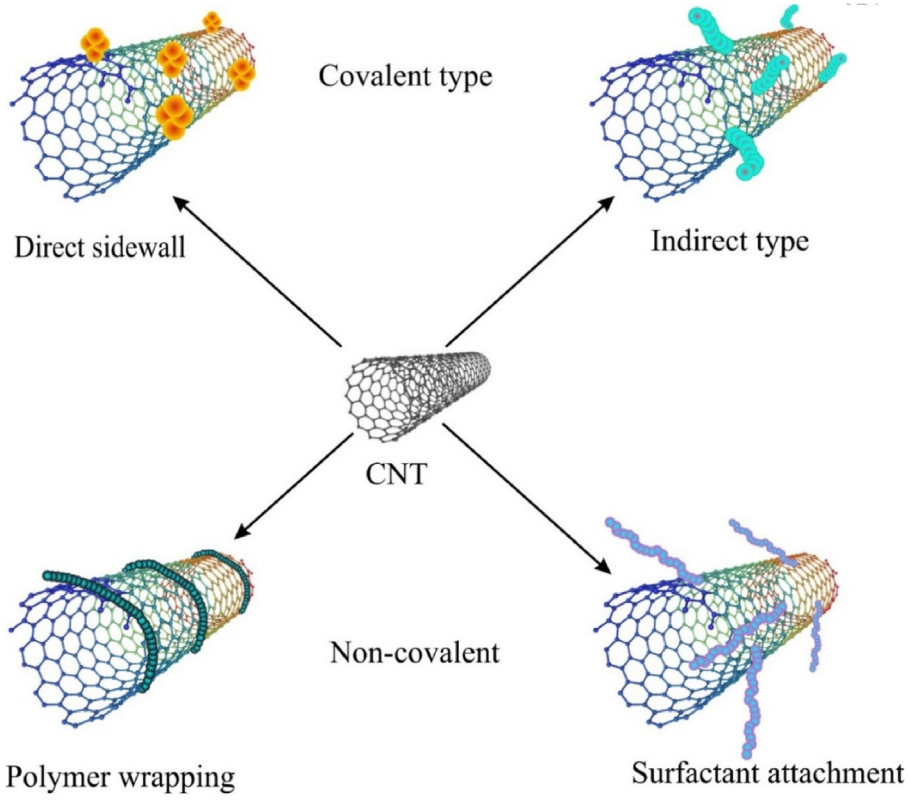

Fig. 2. Functionalization process of carbon nanotube.

RGD (arginine-glycine-aspartic acid) and NGR (asn-gly-arg) tripeptides are capable of binding with αvβ3 & CD13, respectively, and overexpress cancer cells [35].

Covalent functionalization can be done more efficiently in various ways like carboxylation, addition reaction, or by introducing an amino group, the result being due to the covalent linkage between the introducing group and CNTs by sharing at least one electron pair, which can be used for delivering a drug in the human body. This process also increases reactivity along with dispersibility and processability [36,37]. This introduction can be further divided into direct and indirect covalent functionalization. For single-walled carbon nanotubes (SWCNTs), carboxylation can make covalent functionalization, which is a very simple and quick process. The attachment of the carboxylic acid group increased the hydrophilicity and dispersibility of SWCNTs [37]. Thiol and amine groups are easily bound after carboxylation, another advantage of this process. For multi-walled carbon nanotubes (MWCNTs), Sahoo et al. developed this process by using PNA where MWCNTs were first oxidized by using H_2SO_4 and HNO_3 in a 1:3 ratio, then attached COOH by carbodiimide-activated esterification [38].

Therefore, the attachment of amines is preferable because of the presence of lone pair electrons in nitrogen, which could quickly bond with other molecules. For multi-walled carbon nanotubes (MWCNTs), this process is used by Zardini et al. where microwave radiation was used to attach amino acid arginine and lysine [39]. Rahimpour et al. used phase inversion for attaching polyethersulfone in MWCNTs [40]. The addition reaction was also capable of both types of covalent functionalization, direct as well as indirect.

The main disadvantage of covalent functionalization is that it destroys double bonds and alters the electronic and optical properties of CNTs. Covalent functionalization is further divided into direct sidewall functionalization and defect group functionalization. In the case of direct type functionalization fluorination, alkali metal-based reduction, radical addition, electrochemical addition, cycloaddition, and nucleophilic addition are used. However, electro, nucleophilic, and cycloaddition caused rehybridizing into sp3 in the case of sp2, CNTs original structure. Defect group functionalization increases the reactivity of neighboring C atom and local strain due to rehybridization in sp3 or the presence of default ring structure (presence of five or seven members in place of six members ring) or defects created in the time of Purification [36,37,41].

5. Drug loading in CNTs

Those carbon-made cylindrical nanostructures contain large inside apace with both side openings. Drugs can be loaded into the insider space at the time of CNTs synthesis or after synthesis and capping those openings for delivery of the drug into the desired site. Drug loading can be of two types; capillarity is the most common method in which the introduction of drugs depends upon surface tension mainly, and CNTs diameter, hydrophobic force, and Vander wall force also take a part [42]. Another method is known as decoration, where drug substances are attached inside or outside the tube with the help of the functional group. After drug loading, the current is used for capping the enclosed drug materials. Buffer washing is also done to remove excess residue [43]. For example, Hammadi et al. loaded doxorubicin after OH−COOH functionalization to treat human cancer by dispersing CNTs in prepared aqueous doxorubicin solutions by stirring for 24 h under dark conditions. They then vacuumed the mixture for 3 h at room temperature and centrifuged the solution at 10,000 rpm to get doxorubicin-loaded CNT. Finally, they performed phosphate buffer washing to remove unentrapped drugs and vacuum-dried them at room temperature [44].

Another method used for CNT loading is the steered molecular dynamic technique, where an external force is applied in a particular direction to change the particle coordination and load CNTs by using harmonic restraint. Arsawang et al. used this method in the past for loading SWCNTs with the anticancer drug gemcitabine and observed π-π stacking between the CNTs' inner surface and the cytosine ring present in gemcitabine [45]. Drug loading in CNTs depended upon other factors as well. One research group showed the inhibitory effect of doxorubicin encapsulation in the presence of extracellular ethanol molecules. This study also confirmed that the presence of other molecules minimized the cell membrane penetration capacity of the drug-CNTs complex. Extracellular ethanol molecules reduced the bonding strength between the inner nanotube surface and the drug molecule, which resulted in the release of the drug moiety before the penetration of the cell membrane, as shown in Fig. 3 [46].

6. *In vitro* behavior of CNTs

Pharmacokinetic parameters (Absorption, distribution, metabolism, elimination) along with other pharmacological parameters like half-life, blood circulation time, and accumulation must be considered for treatment through CNTs. Generally,

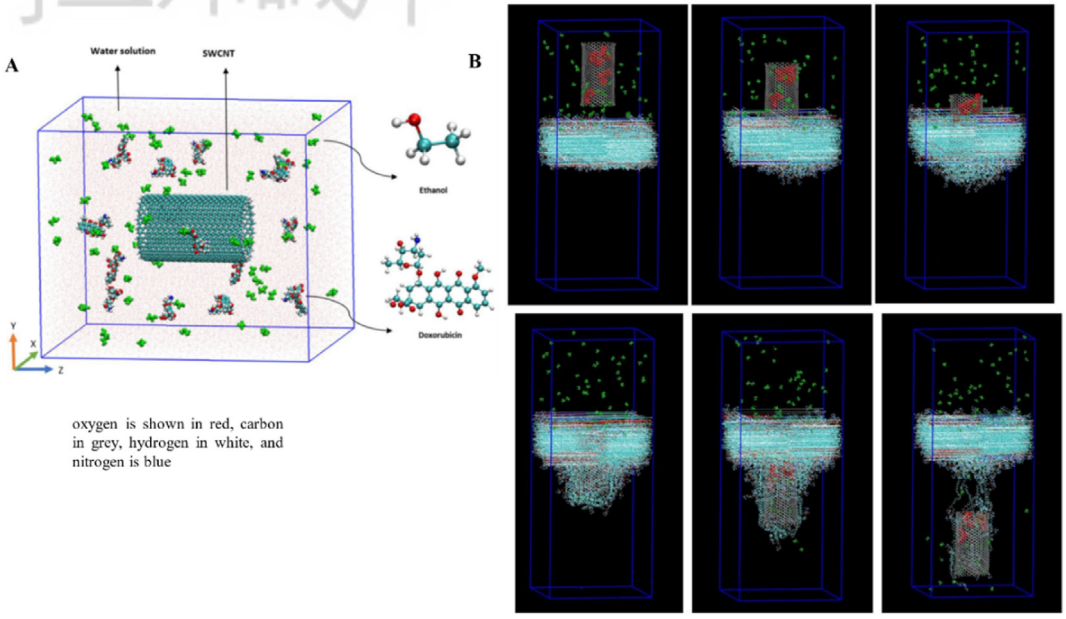

Fig. 3. (A) The initial structure of the ethanol-doxorubicin-CNTs system (B) MD snapshots of penetration mechanism of SWCNT containing 4 DOX molecules and 40 ethanol molecules randomly distributed in extracellular environment at 310 K. Reprinted with permission [46].

for drug delivery with CNTs oral, intramuscular injection, abdominal injection, intravenous injection, and local injection, subcutaneous injection is preferable [32]. For any drug, absorption is the most fundamental parameter and due to the administration through different routes, the absorption and transport of CNT are also different. Oral absorption of erythropoietin-loaded CNTs with different lengths was studied by Yokako et al. on rat intestines, which showed that absorption depended upon the length of CNTs; the absorption of short-length CNTs was much higher than that of long-length tubes. The use of amphoteric surfactant with long CNTs reduced the bioavailability. For example, erythropoietin delivery through CNTs was investigated, revealing that the short fiber length CNTs delivered more both erythropoietin and absorption enhancer to the absorptive cells of the rat small intestine, and the aggregation of CNTs was not the critical factor for the oral delivery of erythropoietin [47]. Due to their nano needle-like structure, they could penetrate any structure (blood–brain barrier) without causing any cell damage and release the drug diagrammatized in Fig. 4. Their uptake occurred by endothelial cells. Orally delivered CNTs are easily absorbed through the intestine, and subcutaneous and abdominal administration occurs through the lymphatic canal and local tissue. Absorbed CNTs were transported through systemic circulation and were easily targeted.

In another innovative work, gemcitabine-loaded magnetic MWCNTs were used for targeted

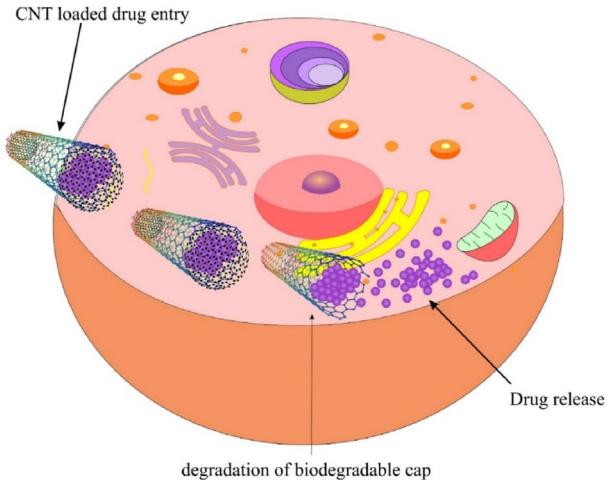

Fig. 4. Drug release process from carbon nanotube inside the cell.

lymphatic cancer treatment. They showed a higher accumulation of MWCNTs in lymph nodes with no significant presence in other major organs. Intravenous administration showed effective organ distribution, and clearance through this route could be increased by surface modification. The duration of action of CNTs could be increased by surface coating, such as PEGylation, where polyethylene glycol covering reduces immunogenic destruction [48].

CNTs arrive after absorption for further action in the desired site, known as distribution. The biodistribution of CNTs can be determined using Raman or position emission spectroscopy. *In vivo*

biodistribution of Na–I125 glycol-SWCNTs through the intravenous route shows high-affinity organ accumulation in single photon emission computed tomography. Metabolism and excretion are another important parameter for clinical use. Functionalization processes sometimes increase the metabolism of CNTs as carboxylated SWCNTs show phagolysosomal degradation. They can further increase excretion by enhancing dispersion. Recent research indicates that the biodegradation of SWCNTs can be catalyzed in neutrophils by hypochlorite and radical-reactive intermediates of human neutrophil myeloperoxidase. Macrophage also shows some degradative effects on CNTs [32].

7. Biosafety

Various exciting properties attract CNTs towards pharmaceutical applications, but its biosafety has always been a concern, and it is necessary to understand their effect on biological systems. Research reports make this tropic more controversial because some conclude CNTs are safe, and few are the opposite. The toxicity of CNT can be reduced to a certain level by functionalizing or modifying it, and their distribution can be controlled by specific targeting, which also minimizes unwanted organ toxicity. Metabolism of CNTs occurs by the liver's enzymatic system and is further excreted through the kidney. Therapeutic and toxicological doses are different for CNT; that's why toxicity can be controlled. Their cytotoxicity can be reduced by functionalization and surface modification [49–51]. Several factors, such as length, diameter, type of carbon nanotube, functionalization, and metal impurities, are involved in the toxicity of CNTs. Toxicity of CNT is mainly caused by accumulation, concentration of CNTs, presence of catalytic residue, length of CNT, dispersion state, and electronic structure that's shown in Fig. 5 [50]. Long CNTs cause bio persistence and are retained, whereas small can easily pernitrate cell membranes, and the clearance is also high. Different types of CNTs behave differently in the study. SWCNTs showed less aggregation so they can be phagocytosed easily, but they tend to form bundles because of their high surface area. MWCNTs showed higher aggregation and caused abnormal phagocytosis and plasma membrane damage that produced toxicity.

In addition, on inhalation, they can cause malignant mesothelioma, fibrosis, and inflammation. Nano-dispersed SWCNTs are quickly eliminated from the body through macrophage and glandular clearance. For example, intratracheal administration of nano-dispersed SWCNTs for 30 days in rat

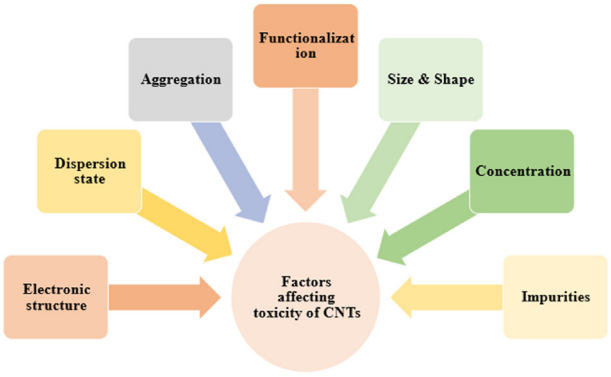

Fig. 5. Factor affecting toxicity of CNTs.

models shows no aggregation. In higher doses (400 mg/kg), SWCNTs enter and cause mitochondrial damage through dilation, vacuole formation, and cristae dispersion. After the mitochondrial damage, the lysosome is also destroyed. However, they do not cause mitochondrial or lysosomal damage in small doses. So, it can be concluded that mitochondria are the primary site and lysosome is the secondary site for high dosage SWCNT destruction. They destroy mitochondria by altering mitochondrial membrane potential by interfering with the electron transmission chain (ETS), which increases the free electron density inside mitochondria and decreases ATP formation, resulting in reactive oxygen species and free radical development, further promoting lysosomal damage. This mechanism leads to cell death by releasing lysosomal enzymes [52–54].

8. Pharmaceutical application of CNTs

The application of CNTs in drug delivery became an essential aspect in the twenty-first century due to their ability to deliver drugs into selected organs without destroying their original structure, along with various advantages, as described earlier. They can be used to treat multiple cancers and biomolecules like DNA, hormones, antibodies, and vaccine drug delivery. They show synergistic activity when they are used for antimicrobial and antifungal treatment [55–57].

Numerous studies have been demonstrating the use of CNTs as nanocarriers for a variety of drugs, including a range of anticancer medications, such as gemcitabine, doxorubicin, methotrexate, paclitaxel, and docetaxel. Additionally, the transport of hormones, anti-inflammatory medications, and genetic elements such as plasmid DNA, microRNA, and small interfering RNA has been investigated using CNTs.

However, their non-biodegradability questions about their possible toxicity and environmental

effects still need to be answered. The goal of ongoing research is to resolve these problems and learn more about the behavior of CNTs-based drug delivery and *in vivo* behavior.

8.1. Application of CNT in cancer

Application of different nanocarriers in anticancer drug delivery became more helpful, due to disadvantages like less selectivity and specificity, less solubility, poor distribution, and cytotoxicity in conventional chemotherapeutic agent administration [58]. Among various nanocarriers like quantum dots, graphene, dendrimers, liposomes, and niosomes, CNTs get special attention due to their effective and safe drug delivery along with various unique properties. CNT-based cancer therapy can consider the following:

- **Application of CNTs as a nanocarrier** - where they are used as carriers of anticancer molecules, genes, and proteins.
- **CNTs as mediators** - in thermal and photodynamic therapy for direct destruction of cancer cells.
- **Cancer cell detection** – using CNTs with different detection procedures has shown better results [59,60].

Their needle-like structure can penetrate cell structure more easily, and they show great response in the delivery of various anticancer molecules like topoisomerase inhibitors, platinum, and anti-microtubules. Topoisomerase inhibitors reduce cancer cell growth by blocking topoisomerase activity like DNA stand braking and cellular reproduction, as shown in Fig. 6. As Topoisomerase I inhibitors, campotothecin, irinotecan, topotecan, and etoposide, teniposide as topoisomerase II inhibitor are used. A few anticancer drugs (doxorubicin, anthracycline, daunorubicin. etc) have also shown topoisomerase inhibition. Platinum-conjugated CNTs are used with a drug like 5-fluorouracil, cisplatin for cancer treatment shows great response [60]. Microtubules play an important role in cell division, their growth can terminate by using anti-microtubule agents like docetaxel, and paclitaxel. CNTs are widely used for various gene carriers like siRNA, aptamer, plasmid DNA, and protein carriers as an example, ammonium-functionalized MWCNTs and

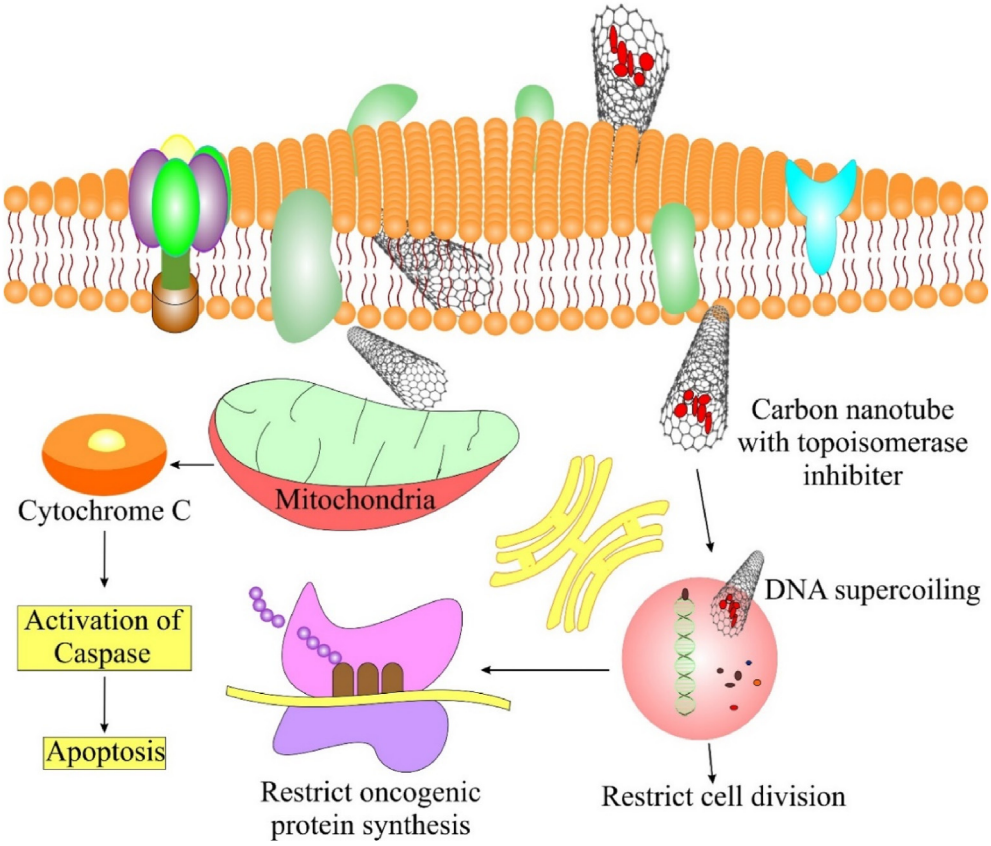

Fig. 6. Mechanism of cancer therapy through CNT.

lysine-functionalized SWCNTs with pDNA investigated by a group of scientists [61]. Mitochondria play an essential part in apoptosis by the activation of caspase through cytochrome C. So, in the case of cancer, mitochondrial targeting can be done effectively by using CNTs to control the apoptosis process and destroy cancer cells like MWCNTs with fluorescent rhodamine-110, pegylated CNTs [32,62].

Non-invasive techniques like Photothermal and photodynamic therapy by CNTs are one of the most highly efficient novel approaches to cancer treatment, which is diagrammatized in Fig. 7. The use of CNTs in photothermal became more helpful due to their ability to heat production by absorbing near-infrared radiation so, by introducing optical coupling phenomena external heat can be transmitted inside the body and destroy the cancer cell [63]. Gannon et al. show *in vivo* and *in vitro* thermal destruction of cancer cells by SWCNTs in the presence of radiofrequency [64]. Surface defective CNT can produce more heat so intentional use of defective nanotubes in this area with p-type dopants (boron, nitrogen) to improve the thermal destruction of cancer cells. In photodynamic therapy, photosensitizer absorbs visible light and transfers the energy into oxygen molecules. Energy-absorbing oxygen molecules convert into excited singlet oxygen and destroy cancer cells [65]. The combination of photothermal and photodynamic methods shows high efficacy. Shi et al. showed that combination efficacy was much higher than single use of those methods [60]. Their nanostructure is also helpful for the detection of cancer cells. In the early stage, once cells are asymptomatic, they don't show any neoplastic disorder, so identification through the traditional process becomes complicated. Applying CNTs combined with MRI increases tissue permeation and resolution, and their

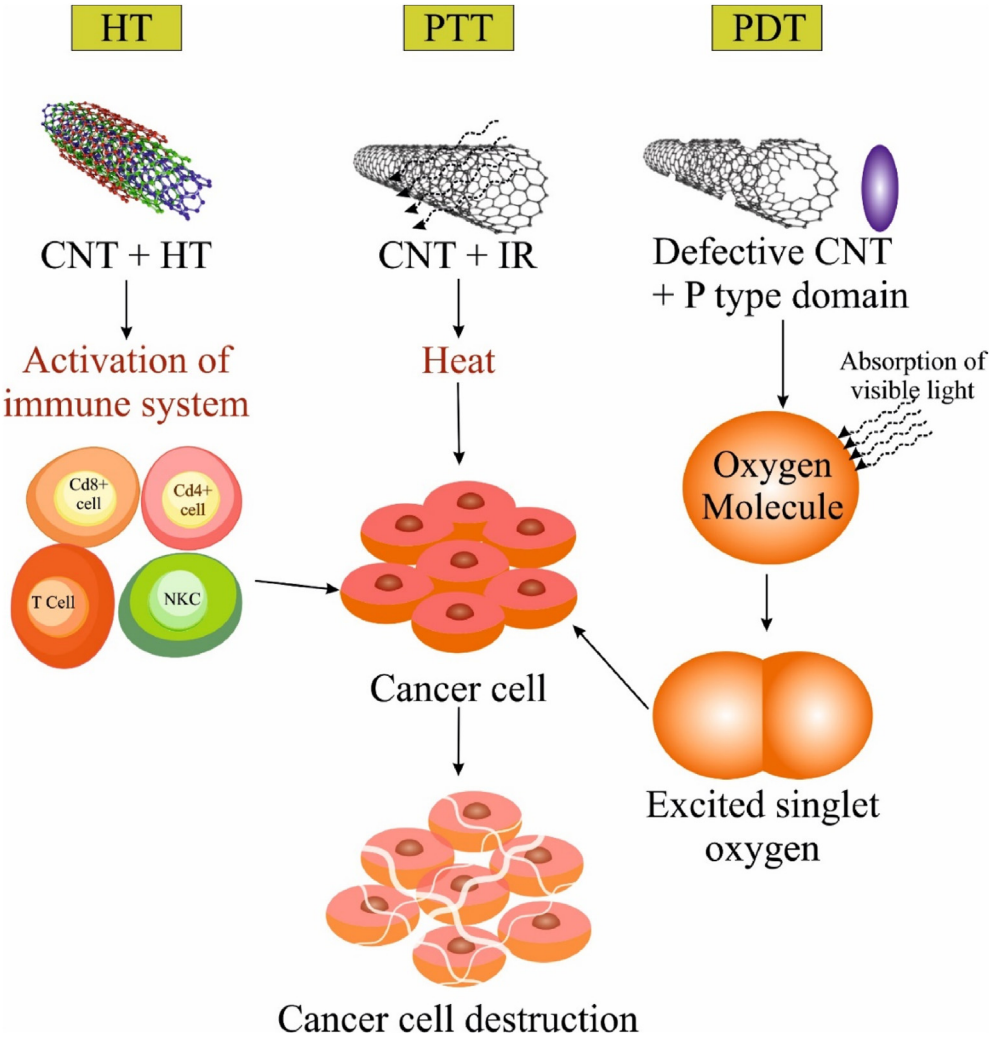

Fig. 7. Non-invasive cancer therapy by CNTs (Photothermal and photodynamic).

combination with radiolabelled substances also increases tissue penetration and sensitivity. They are further used as biomarkers for detecting cancer cells, using p-type CNTs, and MWCNTs-glass carbon electrodes as prostate-specific antigen biomarkers. Microelectrode arrays modified with SWCNT as total prostate-specific antigen biomarker [66,67].

Hyperthermia is another approach used for cancer cell destruction by using carbon nanotubes that involve raised body temperature (39–50 °C) that causes tumor cell destruction by activating the immune system. Muhammad et al. study the hyperthermia effect by oxidized MWCNTs and observed stimulation of natural killer cells, T cells, $CD4^+$, and $CD8^+$ cells which suppress (Hsp70) Heat shock protein (Hsp70) expression to treat breast cancer [68].

8.2. CNTs in antimicrobial treatment

Applying novel carriers in antimicrobial drug delivery is necessary because inappropriate and excessive use of antimicrobial compounds develops antibiotic resistance. Among all those available nanocomposites, CNTs got special attention after Kang et al. first reported the antimicrobial activity of SWCNTs against *E. coli* [69]. The mechanism of action of CNTs as antimicrobials involves microbial cell membrane interference, electronic structure-based microbial cell oxidation, physical interaction, etc. Some studies also show that the functionalization process increases the antimicrobial activity and reduces cytotoxicity [69,70]. Few research also shows the difference in antimicrobial action. Some of them are listed in Table 2. Between SWCNTs and MWCNTs, they concluded that SWCNTs have more antibacterial activity than MWCNTs [69,71]. However, surface coating can increase their activity (e.g.-Silver coating). Besides its activity, applying CNTs as a drug molecule carrier provides higher bioavailability and targeted action. Drug molecules immobilized through a covalent bond improve efficacy and provide sustained release action. The antimicrobial activity also depends upon size, and the diameter of CNTs lower diameter nanotube shows more activity [72,73].

As carrier molecule CNTs can attached to metal particles, polymers, or antimicrobial drugs, they show different mechanisms of action. CNTs with antimicrobial drugs can inhibit cell wall and protein synthesis or increase cell membrane permeabilization. Metal particles with CNTs cause protein dysfunction, loss of membrane potential, or increased oxidative stress. CNTs with polymer promote contact between the bacterial cell wall and

Table 2. Use of carbon nanotube in microbial treatment.

Materials type	Material name	Effectiveness	Reference
CNTs with antimicrobial agent	SWCNTs + Azithromycin	Shows effective *in vitro* activity ($p < 0.05$) against *M. luteus*	[79]
	MWCNTs + Cefalexin	They reduce 50%–80% viability of bacteria like *E. coli*, *S. aureus*, *B. subtilis*, etc.	[73]
	MWCNTs + Rifampicin	Causes biofilm formation inhibition (50%) up to 5 days in *S. epidermidis* species.	[80]
CNTs with polymer	MWCNTs + Chitosan	Shows strong antimicrobial activity in gram negative bacteria like *E. coli*, *Candida tropicalis*, *S. aureus*, etc.	[81]
	MWCNTs + Chitosan	They also show decrease in adhered cell number in *S. aureus* by hydrogel application	[82]
	MWCNTs + Polypyrrole	Application in wound healing shows field dependent anti-biofilm activity on *S. aureus* (90%) and *E. coli* (40%)	[83]
	MWCNTs + PEG	Reduce bacterial adhesion by 85.3% in electrospun/polyurethane coated with MWCNTs + PEG	[84]
	MWCNTs + polyester amide	Application in Wound healing shows higher efficacy against *S. aureus* and *B. subtilis* (2–3 log reduction), lower efficacy against *E. coli* and *K. pneumoniae* (1 log reduction)	[85]
CNTS with metal nanoparticles	SWCNTs + Ag NPs (nanoparticles)	The presence of Ag-SWCNTs hybrid films reduces bacterial colony 4 log times.	[86]
	MWCNTs + Zinc hydroxyapatite	This composite shows bacterial growth zone inhibition.	[87]

CNTs and they also alter surface morphology like increased roughness, and hydrophobicity [69,73].

8.2.1. Transdermal use of CNTs

Transdermal drug delivery is capable of effectively delivering the drugs in systemic circulation with reduced toxicity, without 1st pass metabolism, and capable of maintaining blood drug concentration for a long time by sustained release action and also a very choicable option due to its easy and comfortable uses. However, drug application by this route is very selective due to the low permeability of the majority of drugs through the stratum corneum. Through internal or external stimulation, this problem can resolved. Due to the low diameter and nanoneedle structure, they can penetrate the skin by passive diffusion.

Degim et al. had shown enhanced penetration when indomethacin (IND) was combined with CNTs, where double-walled CNTs (DWCNTs) had shown more penetration power than multi-walled CNTs (MWCNTs) [72,74,75]. The transdermal efficiency could have been increased by using the electrical conductivity of CNTs to increase skin permeation. Lee et al. used MWCNTs along with polyethylene oxide and pentaerythritol triacrylate polymer to prepare an electrosensitive transdermal delivery system, and they observed that the drug release was increased with the acceleration of electrical voltage, which was controlled and biocompatible [76].

8.3. Others applications

They also show the ability to cross the blood–brain barrier so that CNTs can be used as carriers for drug delivery in the brain. For example, acetylcholine deficiency causes Alzheimer's disease, but due to the hydrophilic nature of acetylcholine given, Ach does not reach the brain by crossing the blood–brain barrier. The use of SWCNTs with non-covalently attached Ach can resolve the problem [56,77]. With Levodopa carboxylated - SWCNTs show higher BBR penetration and sustained release action as anti-parkinson agents [78]. They can be helpful as artificial implants like MWCNTs with polyacrylic acid on human embryonic stem cells increase cellular differentiation towards neurons. Flahaut et al. used porous SWCNTs with polycarbonate membranes on osteoblast-like cells and observed cytoskeletal and lamellipodial extension [18]. CNTs could be a potential antifungal carrier, Benincasa et al. used functionalized CNTs- Amphotericin B conjugate and showed better action than a single application of Amphotericin B or Amphotericin B-deoxychol as an antifungal agent.

9. Conclusion

The future prospects of using CNTs in drug delivery are promising, as these graphene rollup nanostructures prepared using various processes show interesting properties that attract their utilization in different fields like biosensor-based applications, tissue engineering, artificial implants, and various drug delivery applications. CNTs undergo a few processes for pharmaceutical applications, such as purification to remove carbonaceous and metal impurities used during nanotube preparation. Functionalization is one of the most important aspects that helps in drug molecule attachment, increases cellular uptake, and reduces toxicity. These nanostructures show great potential as anticancer carriers and biomarkers, antimicrobial agents, and transdermal delivery. However, it is essential to thoroughly investigate the safety and potential environmental and human health effects of CNTs before they are widely adopted for drug delivery. Past research focuses on accurately characterizing the tested materials and developing methods to mimic how CNTs interact with cells and tissues.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publish

Not applicable.

Author's contributions

Shovan Ghosh did the review of literature and wrote the whole manuscript. Vivek Dave and Pranay Wal planned the work and revised the manuscript.

Funding

We did not receive any funding for completing this work.

Data availability statement

This submitted article contains all of the data generated or analysed during this investigation.

Conflict of interest

The authors declare that they don't have any conflict of interest in the publication.

Acknowledgements

Authors are highly obliged to Department of Pharmacy, Central University of South Bihar.

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