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CARBON NANOTUBES: A REVIEW ON PROPERTIES, PREPARATION, CHARACTERIZATION AND APPLICATIONS

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ABSTRACT

Carbon nanotubes one of the unique one-dimensional nanomaterials offer an alternative and promising platform of drug delivery system due to their distinct physicochemical properties. Because of their specific characters, versatile functionalization chemistry, and biological compatibility Carbon nanotubes (CNTs) have gained great attention in past few decades. There are excellent properties such as optical, electrical, magnetic, thermal, chemical, and mechanical in Carbon nanotubes. A lot of attention has been drawn by Carbon nanotubes (CNTs) due to their physical properties and tuneable morphologies. Carbon nanotubes are useful for cancer therapy due to their unique properties such as drug loading, thermal ablation, and cellular uptake. An ideal carrier for targeted drug delivery systems should have capability for targeting the drug at the specific site. The transporting capabilities of carbon nanotubes with appropriate surface modifications and physicochemical properties show great effect as the targeted drug delivery. Carbon nanotubes (CNTs) have been introduced as a novel carrier system for both small and large therapeutic molecules. This review will discuss its synthesis, drug loading, the therapeutic applications of CNTs and many other aspects.

KEYWORDS: carbon nanotubes, buckytubes, fullerenes, functionalization.

INTRODUCTION

After more than 25 years of fundamental and applied research, nanotechnologies are nowadays commonly used to manufacture a plethora of commercial products.[1] The major aim of developing nanocarrier drug delivery systems is to enhance the therapeutic effect or reduce toxicity of therapeutically active materials.[2,3] The use of nanotechnology in drug delivery has spread rapidly, with nanoparticles(NPs) emerging as highly efficient delivery systems for targeted drug release.[4] In addition to these NPs, the discovery of Carbon nanotubes (CNTs) which are one of the nanomaterials that are widely used in such area in recent years has opened novel therapeutic opportunities. They have got more and more attention because of their unique properties.[5] Nanotubes have diameter ranging from 1 to 100nm and lengths of up to millimeters.[6] CNTs gain the popularity over other nano-carriers due to nano-size diameter and length, ultralightweight, high aspect ratio, rich surface chemistry, photoluminescence, non-immunogenicity, biocompatibility, biliary excretion pathway, high drug cargo ability, etc.[7] The cylindrical carbon molecules with unique properties that make them potentially useful in a wide variety of applications are called as buckytubes.[8] These nanomaterials are constructed in cylindrical tubes with nanometer scale in diameter and several millimeters in length and are allotropes of carbon, made of graphite.[9.10] CNTs are found to be unsuitable for interaction with biomolecules because they agglomerate or have lack of solubility in an aqueous milieu. Through chemical modifications on CNTs, such as adsorption, interactions (covalent and non-covalent interactions), carboxylation, amidation, acylation, esterification, PEGylation and polymer coatings these can be improved upon by functionalization.[11-13] In targeting specific cancer cells with a dosage lower than conventional drugs used CNTs as drug delivery vehicles have shown potential[14] that is just as effective in killing the cells, however does not harm healthy cells and significantly reduces side effect.[15] Recently, CNT have generated great interest in biology,[16] where suitably modified CNT can serve as vaccine delivery systems[17] or protein transporters.[18] These features make them a useful tool for all kinds of diagnosis and therapeutic as well as drug delivery application.[19]

STRUCTURE OF CNTs

CNTs, also known as tubular fullerenes, are cylindrical graphene sheets of sp2-bonded carbon atoms. In CNTs the graphene sheet is rolled upon itself to form different allotropes of carbon, graphite, fullerenes and CNTs.[20] From a chemical reactivity point of view, CNT can be differentiated into two zones such as the tips and the sidewalls as shown in Fig. 1.[21-25]

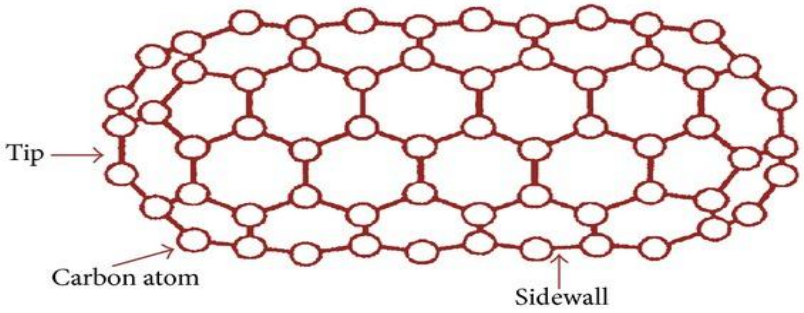

Fig. 1: Representation of structure of carbon nanotube.

An important factor that controls these properties comes from a variation of tubule structures that are caused by the rolling up of the graphene sheet into a tube which is done in three distinct ways to do rolling are armchair, zigzag, and chiral as shown in Fig. 2.[26-29] When *m*= 0, the nanotubes are named zigzag nanotubes; when *n* = m, the nanotubes are named armchair nanotubes, and other state are called chiral. The chiral vector C = na_1 + ma_2 (a_1 and a_2 are the base cell vectors of graphite) also determines the tube diameter *d* Fig. 2 A carbon nanotube with closed ends.

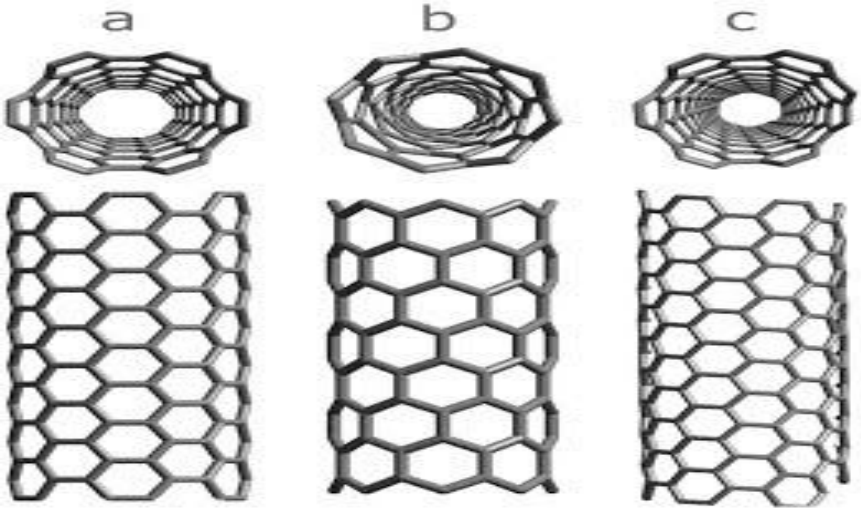

Fig. 2: Representation of armchair, zigzag, chiral nanotubes.

TYPES OF CNTs

CNTs have been classified into the main four classes based on the presence of walls: (i) Single-walled CNTs (SWCNTs) consists of only single graphitic sheet wrapped into cylindrical tube structure with diameter ranges between 0.4 and 2.5 cm and length vary from 20 to 1000 nm. (ii) Double-walled CNTs (DWCNTs) are coaxial nanostructures, with two concentric graphene cylinders. It is a synthetic blend of SWCNTs and MWCNTs(iii) Triple-walled CNTs (TWCNTs) are made up of three concentric graphene layers(iv) Multi-walled CNTs (MWCNTs) are made up of several concentric layers of graphene and tend to form the unordered clumps as shown in Fig. 3. Their diameter varies from 1.4 to 100 nm and lengths vary from 1 to several micrometers.[30,31] The interlayer separation of the graphene layers of MWCNTs is approximately 0.34 nm in average, each one forming an individual tube, with all the tubes having a larger outer diameter (2.5 to 100 nm) than SWCNTs (0.6 to 2.4 nm).[32,33] Synthesis of SWCNTs requires the use of different precursors, which are either a pure metal or a metal mixture while MWCNTs can be obtained without the use of a catalyst.[20,34,35]

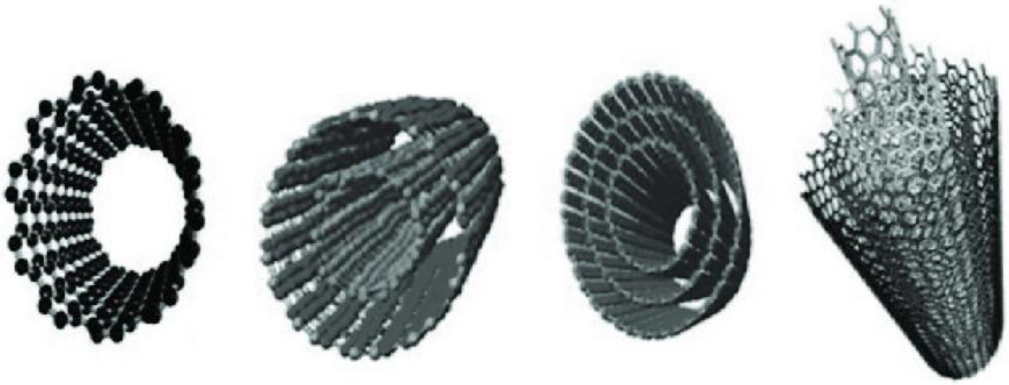

Fig. 3: Various types of carbon nanotubes: (A) Single-walled, (B) Double-walled, (C) Triple-walled, and (D) Multi-walled carbon nanotubes.

PROPERTIES

CNTs reportedly have extremely high surface areas, large aspect ratios, and remarkably high mechanical strength. The tensile strength of CNTs is 100 times greater than that of steel, and the electrical and thermal conductivities approach those of copper.[36,37]

- **MECHANICAL PROPERTIES**

CNTs are characterized both by the high tensile strength known in the materials, making them very stable, and by a surprising elasticity under axial compressive forces. These properties have direct applications for drug delivery because they can penetrate and/or perforate cells as needles.[38,39]

- **THERMAL PROPERTIES**

The incorporation of pristine and functionalized nanotubes to different materials can double the thermal conductivity for a loading of only 1%, showing that nanotube composite materials may be useful for thermal management applications in industries.[40]

- **SOLUBILITY**

Pristine CNTs are not soluble. To functionalize these molecules with organic groups and render them soluble that opened the way to bio applications of CNTs was only after the development. In order to enhance their dispersibility in the aqueous phase or to provide the appropriate functional groups CNTs can be surface engineered (i.e., functionalized) that can bind to the desired therapeutic material or the target tissue to elicit a therapeutic effect.[41-44] Aggregation and formation of bundles are observed in aqueous media, and a separation of the CNTs is a prerequisite for medical applications. Dispersibility can be achieved by incorporating surfactants, polymers, or other colloidal particles.[45]

- **ELECTRICAL PROPERTIES**

CNTs, due to their electronic nature, can be used in transistors and other switching applications in advanced electronics.[46] CNTs also allow fluorescence emission in the NIR region, which, by using video rate imaging, can reveal the tumor location through the enhanced permeability and retention of the tissues.[47,48]

CELLULAR UPTAKE

The cellular uptake pathway of SWNTs is controlled by their surface chemistry and dimension. Cellular uptake of short SWNTs less than 50 nm was through the energy independent insertion and diffusion, whereas SWNTs of 50–100 and 100–200 nm in length entered cells through the endocytic pathway. SWNTs of 100–200 nm mainly distributed in cytoplasm, but SWNTs of 50–100 nm could even enter the cell nucleus. They suggested the appropriate length of SWNTs used for targeted drug delivery was around 200 nm.[49] Using an atomic force microscope (AFM) tip and functionalized MWNTs attached to a model cargo compound via a disulfide linker the nanoinjector was developed. Into the cell where the disulfide bond was broken, the MWCNTs nanoinjector were successfully transported resulting in the release of the cargo compound within the cytosol. Uptake of CNTs was similar to that of nanoneedles which diffuse through cell membrane without causing cell death was suggested by the perpendicular positioning of the nanotubes to the cell membranes.[43]

FUNCTIONALIZATION

The biomedical developments were limited even though CNTs have many advantages. There is still no development of purification. In biomedical application CNTs use is limited because they are difficult to dissolve in aqueous media, although this disadvantage can be overcome through functionalization.[50] The functionalization of CNTs thus clearly appears as a method to modify in a suitable way their efficacy in biological media, i.e., to improve the vectorization in the targeting processes, to increase the drug-delivery dose, and to reduce, simultaneously, the damage that will be caused by the CNTs themselves.[51] The functionalization procedure of CNTs can be divided into two main approaches, depending on the nature of the biomolecule linked to carbon nanotube, that is, covalent attachment (chemical bond formation) and noncovalent attachment (physio adsorption) as illustrated in Fig. 4.[22,29]

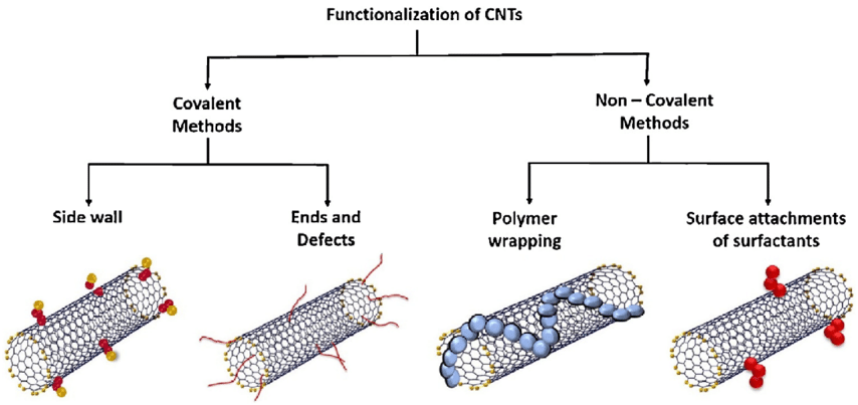

Fig. 4: Representation of functionalization of carbon nanotubes.

- **Non-covalent**

Many small, as well as large, polymeric anticancer agents can be adsorbed non-covalently onto the surface. Many small, as well as large, polymeric anticancer agents can be adsorbed non-covalently onto the surface of pristine CNTs. Forces that govern such adsorption are the hydrophobic and π-π stacking interactions between the chains of the adsorbed molecules and the surface of CNTs.[52,53] When working with hydrophobic interactions, it is quite usual to use long chains of aliphatic compounds that interact directly with the hydrophobic surface of CNTs. These molecular chains can be absorbed on the CNT surface, which is then covered with active sulfate groups.[54] Some common examples of this type of functionalization include use of surfactant, especially with SWNTs, CNT wrapping, and non-covalent protein interactions.[55]

- **Covalent**

CNTs covalent functionalization can be achieved via the functionalization of "ends and defects" and "side walls." The ends and defects technology has high specificity and reaction compared with the function of side walls.[56] To the surface or at the ends of the CNTs various chemical groups such as carboxylic, p-aminobenzoic acid, fluorine, added dichloro-carbon groups are attached.[57-60] For drug delivery the stable functionalized CNTs can be obtained via covalent coupling, which makes it become a more suitable tool. But during this process, the side wall of the CNTs has been damaged, which leads to the change of other properties of the CNTs.[25,61] So the functionalization of CNTs should not be used in some applications, for example, imaging.[62] A number of covalent functionalisation reactions have been used to modify carbon nanotubes to suit various applications.[63]

SYNTHESIS

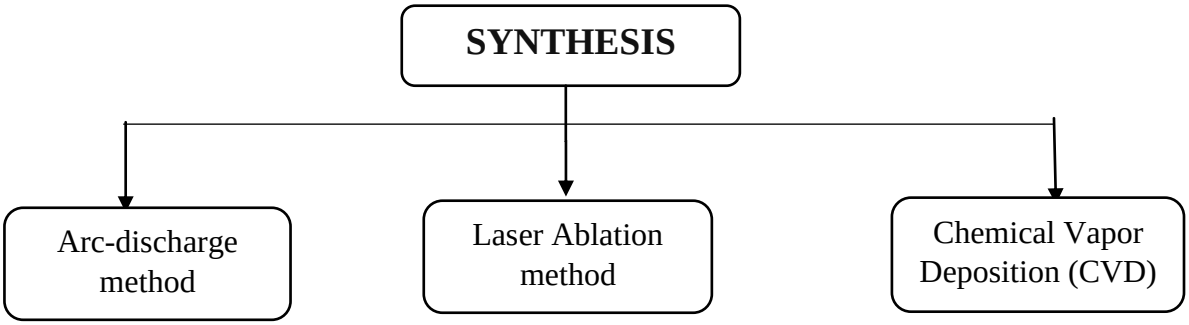

Fig. 5: Flowchart of types of synthesis.

Three main techniques generally used for SWCNTs and MWCNTs production as shown in Fig. 5. are: Arc-Discharge method (using arc vaporization of two carbon rods), Laser Ablation method (using graphite), and Chemical Vapor Deposition (using hydrocarbon sources: CO, methane, ethylene, acetylene).[10,22,64]

- **Electric Discharge Method**

Iijima in 1991 introduced the electric discharge approach which is based on high-purity graphite sublimation at temperature close to 4000K on an anode, followed by its condensation at the cathode in an inert atmosphere and under low pressure to produce MWCNTs.[65,66] Anode will get evaporated due to this and rod-shaped tubes will be deposited on cathode. Bulk production of CNTs depends on uniformity of plasma arc and temperature of deposition.[67-69] Arc-discharge technique uses higher temperatures (above 1,700°C) for CNT synthesis which typically causes the expansion of CNTs with fewer structural defects in comparison with other methods.[70] For the growth of single-wall tubes, a metal catalyst is needed in the arc-discharge system.[34] The main advantage of arc-discharge technique is ability and

potential for production of a large quantity of nanotubes.[71]

- **Laser Abalation**

This synthesis was first reported in 1995, by Smalley's group at Rice University. A pulsed or continuous laser is used to vaporize a graphite target in an oven at 1200oC.[72] The aim of using laser is vaporizing the graphite within the quartz. As described about the synthesis of SWNT by using arc-discharge method, for generating of SWNTs, using the laser technique adding of metal particles as catalysts to the graphite targets is necessary. When the laser pulse power is increased, the diameter of the tubes became thinner.[73] The growth of high-quality SWCNTs at the 1–10 g scale was also produced using a laser-ablation (laser oven) method.[74]

- **Chemical vapour deposition**

The standard technique for CNT synthesis is Catalytic chemical vapor deposition (CCVD). Mentioned for the first time in 1993 as a means to synthesize MWCNTs using acetylene vapor deposition at 1000K[73] or benzene deposition at 1400K[75] on iron particles. A layer of metal catalyst particles are prepared and process a substrate at approximately 700°C in CVD processing. Most commonly, metal catalyst particles are nickel, cobalt, iron, or a combination.[76] The carbon compounds which are volatile or gaseous are decomposed, catalyzed by metallic nanoparticles, which also serve as nucleation sites for the initiation of carbon-nanotube growth in CVD. In contrast the previous two methods, CVD has been proven to be a preferred route for large-scale production of carbon nanotubes.[77,78]

CHARACTERIZATION

- **Electron microscopy (SEM, TEM)**

To examine objects on a very fine scale Electron Microscopy is a scientific technique used There are two types of electron microscopy, namely the transmission electron microscopy and the scanning electron microscopy. The results that can be examined are as follows:

• The topographical information indicates the surface features of an object or "how it looks", its texture.

• The morphological information indicates the shape and size of the particles making up the object.

• The composition information indicates the elements and compounds that the object is composed of and the relative amounts of them.[79] In cases where the required measurements exceed the resolution of SEM (1–20 nm), transmission electron microscopy (TEM) is used.[80,81]

- **X-ray diffraction**

The diffraction of a beam of incident X-rays to different specific directions are caused to the samples in XRD. Consequently, analysis of CNTs by XRD yields information about the average structure and the spatial correlations between atoms within a single layer. XRD also supplies information about the nature of inter-layer correlations and about the number, diameter, length and chirality of layers.[82]

- **Raman spectroscopy**

RS is one of the most powerful characterization techniques for CNTs. It is commonly employed for the characterization and purity analysis of CNTs due to the simple sample preparation and the non-destructive and non-invasive nature of this technique.[83] From highly ordered CNT sidewalls, Raman spectra of CNTs typically consist of a graphitic or G-band, while disorder in the sidewall structure results in a D-band. By determining the ratio between these two bands (ID:IG), a quantitative measure of defect density in the CNT sidewall can be determined. In the case of SWCNTs, a vibrational mode known as the radial breathing mode (RBM) can also be used to determine the SWCNT's diameter based on its peak position.[84] Thus, other RS-based approaches such as tip-enhanced Raman spectroscopy (TERS) have been applied to the study of carbon nanotubes, with high spatial resolution obtained by local enhancement of the incident and scattered fields.[85]

APPLICATIONS

Nanotechnology can be used in different applications in various fields, including nano-medicine, energy, the environment, and in sensors as shown in Fig. 6.[86]

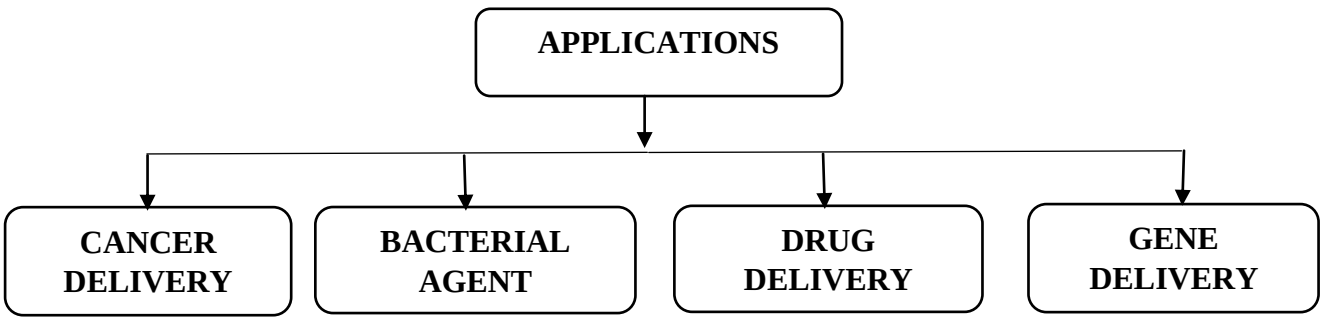

Fig. 6. Flowchart of applications of CNTs.

- **Cancer delivery**

Cancer therapy based on CNTs is a novel interesting approach with high potential to treat patients suffering from this disease. CNTs functionalized with antitumor molecules or active drugs (e.g., paclitaxel or doxorubicin) have been found to display effective

anticancer activity in preclinical models.[87,88] Liu et al.[89], made DOX loaded onto branched PEG-functionalized SWNTs designed in order to prolong blood circulation time, they have injected the SWNT-DOX complex to tumor mice. DOX can be delivered in tumor and SWNT can be cleared from systemic blood circulation via renal excretion. For avoiding the harmful effect of anticancer drug on healthy organs and cells, our group[90] has linked epirubicin with a magnetic CNTs complex obtained by fixing a layer of magnetite (Fe3O4) nanoparticles on the surface of the nanotubes with necklace-like type and on the tips of shortened MWCNTs.[90]

- **Bacterial agent**

Antimicrobial activity may be present in CNTs, since bacteria may be adsorbed onto the surfaces of CNTs, such as the case of E. coli. The antibacterial effect was attributed to carbon nanotube-induced oxidation of the intracellular antioxidant glutathione, resulting in increased oxidative stress on the bacterial cells and eventual cell death.[28] In another study,[91] the authors examined the length dependent antibacterial effects of SWCNTs on gram-negative food-borne pathogens (Salmonella). To determine cell survival before and after treatment with SWCNTs conventional plating method was used. The results showed that the longer SWCNTs presented a higher antimicrobial activity than the shorter ones.[91]

- **Drug delivery**

To improve the efficacy of therapeutic molecules drug delivery has been a major area of focus for researchers to aim at. Researchers are trying to overcome some obstacles these include poor drug distribution among cells, unwanted damage to healthy tissue, toxicity, and lack of the ability to select a particular cell type for treatment.[92] Because of their unique ultrahigh surface area many drugs, polypeptides and nucleonic acid, can be integrated into CNTs. Due to the existence of endocytosis and other mechanisms, the functional CNTs can pass through the membrane of mammalian cells.[93-95] For instance, trans-activator of transcriptione-chitosan-functionalized MWCNTs loaded with DOX were a more promising candidate for drug delivery compared with pristine MWCNTs as evaluated by non-invasive fluorescence and bioluminescence imaging in vivo.[96]

- **Gene delivery**

In gene delivery the application of CNTs as gene carriers has been considered quite promising. Gene therapy involves not only the gene-based treatment for cancers but also that for the infectious diseases by introducing genetic materials.[97] Because the CNT-gene complex has conserved the ability to express proteins the use of CNTs as gene therapy vectors has shown that these engineered structures can effectively transport the genes inside mammalian cells and keep them intact.[98] Ammonium-functionalized single-walled CNTs has the capability to penetrate human and murine cells and facilitate the delivery of plasmid DNA leading to expression of marker genes was studied by Singh R et al.[99] The results indicate that all three types of cationic carbon nanotubes are able to condense DNA to varying degrees, indicating that both nanotube surface area and charge density are critical parameters that determine the interaction and electrostatic complex formation between f-CNTs with DNA.[99]

CONCLUSION

This minireview reveals many spectacular benefits of carbon nanotubes during their recent applications in different areas of pharmacy and medicine this review reveals many spectacular benefits of carbon nanotubes. Functionalization of CNTs, and particularly CNTs of defined length, diameter, and chirality, will lead to the better control of CNT-based materials and devices at the molecular level. Using it in cancer treatment can guarantee 85% of the cure which other treatments cannot afford and having 100% site target with its body friendly nature adds to its advantage. This novel CNT based platform can provide us with a safer and more effective way for the various therapy in the future.

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