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Carbon nanotubes part I: preparation of a novel and versatile drug-delivery vehicle

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Abstract

Introduction—It is 23 years since carbon allotrope known as carbon nanotubes (CNT) was discovered by Iijima, who described them as “rolled graphite sheets inserted into each other”. Since then, CNTs have been studied in nanoelectronic devices. However, CNTs also possess the versatility to act as drug- and gene-delivery vehicles.

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Areas covered—This review covers the synthesis, purification and functionalization of CNTs. Arc discharge, laser ablation and chemical vapor deposition are the principle synthesis methods. Non-covalent functionalization relies on attachment of biomolecules by coating the CNT with surfactants, synthetic polymers and biopolymers. Covalent functionalization often involves the initial introduction of carboxylic acids or amine groups, diazonium addition, 1,3-dipolar cycloaddition or reductive alkylation. The aim is to produce functional groups to attach the active cargo.

Expert opinion—In this review, the feasibility of CNT being used as a drug-delivery vehicle is explored. The molecular composition of CNT is extremely hydrophobic and highly aggregation-prone. Therefore, most of the efforts towards drug delivery has centered on chemical functionalization, which is usually divided in two categories; non-covalent and covalent. The biomedical applications of CNT are growing apace, and new drug-delivery technologies play a major role in these efforts.

Keywords

addition reaction; carbon nanotubes; functional group; functionalization; purification; synthesis

1. Introduction

New breakthroughs in nanotechnology have had critical effect on many different industrial fields especially those of the materials science, biotechnology and pharmaceutical industries. Different nanocarriers such as liposomes, polymersomes, micelles and carbon-based nanomaterials have been tested for different purposes [1–4]. Carbon nanotubes (CNTs) have attracted much attention since their discovery in 1991 on account of their outstanding structural, electronic and mechanical properties, high surface area, thermal stability and metallic-to-semiconducting current carrying capacity. CNTs can be obtained by various synthetic techniques, and are classified either as single-walled CNTs (SWCNTs), or as multi-walled CNTs (MWCNTs) depending on the number of concentric rolled graphene layers. Owing to their large surface area, CNTs may be readily conjugated with various biological molecules, such as proteins, enzymes, nucleic acids and drugs. These rolled graphene sheets are held together by van der Waals interactions. These strong interactions direct CNT to bundle together and lead to the formation of large aggregates resembling bunches of asparagus. The limited solubility of CNTs (not only in water but also in most organic solvents), which is the result of these bundles, has severely impacted their use in chemical, biochemical and biomedical applications [5–7].

Two main approaches have currently been proposed for the modification of the CNT surface to achieve the dissolution and the complete exfoliation of the pristine CNTs. One is the covalent attachment of functional groups to the sidewalls or to the defect sites. The other is the non-covalent functionalization of the sidewall. In contrast to the covalent method, the non-covalent approach can attach different functional molecules on the surface of CNTs while maintaining their pristine structure and graphene-type surface. Thus, functionalization of CNTs improves their ability to be processed and modifies their physical and chemical properties [5–7].

2. Carbon nanotubes

The discovery of microtubules and graphitic sheets eventually led to the appreciation of a new allotropic form of carbon that has become a fascinating subject for physicists and chemists in the last two decades. Roger Bacon in 1960 reported concentric helical graphitic microtubes and Iijima in 1991 discovered carbon cylinders consist of graphitic sheets while experimenting with fullerene synthesis [8]. These first needle-like carbon filaments were grown during the arc-discharge evaporation of carbon in argon gas at 100 Torr pressure. Iijima described these filaments, which were grown on the negative end of the graphite electrode, as 'rolled graphite sheets inserted into each other'. The number of these concentric sheets varied from 2 to 50 [8,9].

In 1992, Ebbesen and Ajayan optimized the conditions for the growth of hollow graphitic tubes to obtain a larger quantity (~ 1 g of graphitic tubes) by the arc-discharge evaporation method [10]. An inert gas atmosphere (flow of Ar or He) of ~ 100 Torr pressure was created in the reaction vessel. Two graphite rods bearing DC current (~ 100 A) with applied potential of ~ 18 V were brought together at ~ 1 mm distance. As a result, a discharge occurred and plasma formed. CNTs along with some carbon nanoparticles were deposited on the larger rod. The reported yield of CNT was 75%. These nanotubes had the same structure as those described by Iijima and consisted of 2–50 concentric graphitic sheets. The minimum diameter of the tubes was 2 nm and maximum was 20 nm [8,9].

2.1 Structure and properties

As mentioned above, CNT can be classified into two main types: SWCNTs, which consist of one single layer of graphene sheet seamlessly rolled into a cylindrical tube, and MWCNTs, which are made up of several concentric graphene layers (Figure 1). The distance between two graphite sheets in MWCNT is typically 0.340 nm, slightly greater than the distance between two consecutive sheets in single crystal graphite, 0.335 nm, which may be explained by specific cylindrical geometry. In single graphite sheets, the carbon atoms are bonded with together by covalent C–C bonds, while for MWCNT structures, due to the weak van der Waals interaction between sheets, the distance between cylindrical layers is increased. They have nanoscale dimensions, with single-walled nanotubes (SWNTs) having diameters in the range of 0.4–3 nm and lengths between 20 and 1000 nm, whereas MWCNT have diameters between 2 and 100 nm and lengths of 1–50 μm . CNTs generally have an aspect ratio (L/D) of around 1:1000 [11].

The walls of these CNTs are made up of a hexagonal lattice of carbon atoms analogous to the atomic planes of graphite. The ends of their atomic structures are covered with one half of a fullerene-like molecule [12]. In the most general case, a CNT is composed of a concentric arrangement of many cylinders (Figure 1B). Such MWCNTs can reach diameters of up to 100 nm. A special case of these multi-walled tubes is the double-walled CNT composed of just two concentric cylinders. SWCNTs possess the simplest geometry and have been observed with diameters ranging from 0.4 to 3 nm [11,13].

In reality, however, CNT are not ideal or perfect structures, but rather contain defects formed during synthesis. Typically around 1–3% of the carbon atoms of a nanotube are

located at a defect site [14]. A frequently encountered type of defect is the so-called Stone–Wales defect, which can be seen in Figure 2. This type of defect is known as a 7-5-5-7 defect because of two pairs of five- and seven-membered rings. A Stone–Wales defect leads to a local deformation of this curvature, addition reactions are most favored at the carbon–carbon double bonds in these defects [15].

The formation of a CNT can be visualized through the rolling of a graphene sheet. Based on the orientation of the tube axis with respect to the hexagonal lattice, the structure of a nanotube can be completely specified through its chiral vector (Figure 3), which is denoted by the chiral indices (n, m) . CNTs are classified into two categories based on the geometric structure of carbon in cylinder's seam. Both of armchair ($n = m$) or zigzag ($m = 0$) possess mirror symmetry, nanotubes with $m \neq n$ are chiral [16].

According to the zone-folding approach, which derives the electronic structure of nanotubes directly from graphite, a nanotube behaves either as a metal or as a semiconductor, depending on its chiral vector [17].

CNTs have the tendency to aggregate into bundles with large numbers of both metallic and semiconducting SWCNTs in a mixture of one third and two thirds, respectively, because of a high surface energy and excellent flexibility. Bundle properties are generally inferior to those of isolated SWCNTs and effective separation of aggregates must be achieved prior to functionalization and construction of nanodevices.

CNTs possess high tensile strength, are ultra-light weight and have excellent transport conductivity, as well as thermal and chemical stability. The mechanical properties of CNTs are also outstanding. The density-normalized Young's modulus and ultimate tensile strength of typical SWCNT are 19 and 56 times that of a steel wire and 2.4 and 1.7 times that of silicon carbide nanorods, respectively, in addition to their high elasticity. Nanotubes are chemically inert by nature and the presence of empty space inside them in addition to their high mechanical strength, described earlier and electrical conductivity make them attractive for use in structural applications, nanomedicine and nano-optoelectronics devices [18,19].

2.2 Synthesis and purification techniques

The high prices of CNTs (e.g., around 50–100 Euros/g of SWCNTs) is a main concern for those contemplating large-scale production. In this part, arc-discharge, laser ablation and chemical vapor deposition (CVD) as main methods for the production of both types of CNTs and the modulation of their dimensions are reviewed.

2.2.1 Arc discharge—As mentioned above S. Iijima [9] used a DC arc discharge in argon consisting of a set of carbon electrodes. The discharge temperature was in the range of 2000–3000°C at nominal conditions of 100 A and 20 V. This apparatus produced multi-walled nanotubes in the soot. Later, SWCNTs were grown with the same set-up by adding to the electrodes suitable catalyst particles, for example, of Fe, Co, Ni or rare-earth metals [20].

This method is a slightly modified version of the method used for fullerene production. An arc discharge is generated between two graphite electrodes placed face to face in the

machine's principal airtight chamber (Figure 4A) under a partial pressure of helium or argon (typically 600 mbar). The electrical discharge that results brings the temperature up to 6000°C. This is hot enough for the carbon contained in the graphite to sublime—that is, transform from a solid state to gaseous one without turning into a liquid first. During sublimation, the high energies involved can eject single carbon atoms from the solid forming plasma. These atoms move towards colder zones within the chamber, allowing a nanotube deposit to accumulate on the cathode. In fact, in the chamber, the gas ionizes to electrons and positively charged ions and produces a very hot plasma. The electrons impact the anode with high velocity, and the carbon material is raised to such a high temperature that carbon vapor is produced, and then the carbon is ionized to give carbon ions. Next, the carbon ions and vapor migrate to the cathode, which is cooler than the anode electrode, where they form clusters, due to the decreased temperature, by a phase transition to liquid carbon and then to solid carbon where it has been found that CNTs are synthesized [21]. It has been reported that different kind of substances such as large quantities of rubbery soot, web-like structures between the cathode and the chamber walls, grey hard deposits, and a spongy soft coating like a belt called 'collaret' can be formed in different parts of reactor besides CNT [22]. The type of nanotube that is formed depends crucially upon the presence of metal catalysts. If small amounts of transition metals such as Fe, Co, Ni or Y are introduced in the target graphite, then SWCNTs are the dominant product [23,24].

There are many physical and chemical parameters such as the dispersion and concentration of the carbon vapor in the inert gas, the temperature inside the reactor, the addition of promoters, the exact composition of the catalyst, and the presence of hydrogen which affect the arc-discharge process. The nucleation and the growth of the nanotubes, their inner and outer diameters and the type of nanotubes (SWCNTs, MWCNTs) are the main characteristics that can be influenced by the above-mentioned variables [25].

Liquid N₂, deionized water and aqueous solutions of NiSO₄, CoSO₄, FeSO₄ and NaCl have been added to the reaction environment in the arc-discharge method. The precise composition of the reaction environment has a huge impact on the characteristics of the products [26,27]. For instance, in liquid nitrogen in the range of 22 – 27 V, a high density of MWCNTs with distorted morphology, degraded structure and irregularly shaped multishelled carbon 'onions' were obtained [24,28,29]. This method has recently been modified to improve the efficiency and properties of CNTs. The use of an electric field-assisted arc-discharge technique resulted in direct synthesis of de-bundled SWCNTs. In this report, > 50% of SWCNTs obtained were < 3 nm in diameter. Since diameter of individual SWCNT is 1.3 – 2.7 nm, this meant that > 50% of them were isolated or at most bundles of two SWCNTs [24]. Table 1 shows some of the parameters in the arc-discharge method.

2.2.2 Laser ablation—The secondarily method of SWCNT synthesis was laser ablation – laser vaporization of a graphite rod in an oven with Co and Ni as catalysts [30]. This mechanism of the CNT production is similar to the arc-discharge method. As shown in Figure 4, in this method, a carbon-metal composition is placed in a heated chamber with a flow of argon at 500 Torr with a flow rate of 50 sccm (standard cubic centimeters per minute). The laser beam is focused on the target, and the soot produced by the laser was deposited onto a cooled copper collector (Figure 4B) [31].

SWCNTs with about 90% purity and with a better-graphitized structure than those produced in the arc process can be achieved by the laser ablation method. Laser ablation can produce a low amount of CNTs but with high purity, and vice versa, the arc-discharge method can produce a large amount of CNTs but with significant impurities. Parameters such as: gas flow rate, carrier gas type, catalyst, substrate for nucleation and time are the most important parameters that affect the CNTs structure and growth [32]. One of the crucial factors in CNT synthesis is the composition of the target material, and in fact using pure graphite targets in laser ablation yields fullerenes and nano-onions rather than nanotubes [8,33,34]. Isolated SWCNTs have been reported when a graphite target containing monometallic Co or Ni dopants has been used. On the other hand, it is found that applying bimetallic graphite containing a Ni/Y catalyst (with the concentration of Ni always higher than that of Y, or Ni/Co in equal concentration) resulted in a high yield of SWCNT bundles [35]. Additionally, the CNT yield and quality depended on the reaction temperature with the best result at 1200°C. The quality of the CNTs diminished and lots of defects appeared at lower temperatures [31,32].

Although laser ablation and arc discharge yield nanotubes with high quality, these techniques suffer from the following shortcomings:

1. Obtaining large quantities of graphite is problematic, which limits large-scale production.
2. The purification process of the tangled form of nanotubes mixed with unwanted materials is problematic and expensive.
3. Energy consumption can be very high in these methods.

In comparison with other methods, these two methods have a higher reaction temperature, which causes difficulties in designing an industrial process [32,36].

2.2.3 Chemical vapor deposition—The third popular synthesis method is the catalytic growth of carbon tubules by decomposition of hydrocarbons, which was introduced in 1992 [35]. By this method, later named as catalytic CVD, MWCNTs and SWCNTs were produced. As a carbon source one can use acetylene, propylene, ethylene or methane [36,37]. Decomposition temperature was between 650 and 900°C. The diameter of the multi-walled nanotubes depends on the diameter of catalyst particles, and the length on the reaction time. The yield of nanotubes was generally higher than that observed in the arc-discharge method [38]. More CVD methods are presented in the following.

2.2.3.1 Hot filament: The hot filament CVD (HFCVD) is an economical technique for the synthesis of CNTs and other carbon nanostructures such as carbon nanoflakes [39] and carbon nanowalls [40]. In HFCVD, a relatively inexpensive substrate can be used to produce CNT. Bouanis *et al.* [41] fabricated SWCNTs by the HFCVD method. They used Ru nanoparticle as a catalyst and methane gas as a carbon source heated by a 2 W filament. A substrate consisting of clay minerals containing kaolinite, sepiolite and nontronite was used to prepare MWCNTs by Pastorková *et al.* [42] CH₄ was the carbon source and H₂ was the carrier gas fed at a pressure ~ 3 KPa into the reactor, containing the clay mineral substrate coated with iron to act as a catalyst and heated to 600°C. They concluded three-dimensional

grids, nonaligned CNT and aligned MWCNTs were formed by kaolinite, nontronite and sepiolite substrates, respectively. Sanchez-Valencia *et al.* [43] synthesized chiral CNTs using a bottom-up technique using cyclodehydrogenation on a platinum catalyst. $C_{96}H_{54}$ was the precursor that was decomposed at 497°C under vacuum condition in order to produce (6,6) ‘armchair’ nanotube seeds. Finally, by epitaxial elongation chiral CNTs grew free of defects. In 2009, Swierczewska *et al.* [44] first used gadolinium and europium as inner transition metal catalysts to grow SWCNTs by the CVD method, yielding nanotubes with 1.9 nm diameter and a narrow distribution of lengths.

2.2.3.2 Plasma enhanced CVD: Plasma enhanced CVD (PECVD) is another promising method to fabricate vertically aligned CNT (VACNTs) [45]. In this method, a gas containing a carbon source mixed with a carrier gas was injected into a vacuum chamber containing a heated substrate, which was coated with catalyst. The main role of plasma is the dissociation of hydrocarbon molecules in order to produce C atoms and reactive radicals such as CH, CH_2 , CH_3 and H^+ ions at a lower temperature compared to arc discharge or laser ablation. VACNTs were produced from acetylene gas with a silicon substrate and nickel catalyst as reported by Saghafi *et al.* [46]. The vacuum chamber was maintained 10^{-2} Torr, 65°C and 1.5 – 2 W/cm²DC power to heat the plasma in order to fabricate the VACNTs that had 78 nm diameter and 1 – 8 μ m length.

The variation in plasma power, pressure at which the precursors are injected, temperature of the substrate, and the chamber growth time, catalyst content and catalyst thickness are the most important parameters in the PECVD technique as has been comprehensively investigated by Löffler *et al.* [47] and Jeong *et al.* [48]. Some researchers have applied plasma-enhanced HFCVD (PEHFCVD) as a complementary technique [49]. Wang *et al.* [50] fabricated CNTs from an amorphous carbon film without a metallic catalyst on a Si substrate using PEHFCVD. They generated CNTs with about 5 nm diameter and 300 – 800 nm length.

2.2.3.3 Radio frequency plasma-enhanced CVD: Radio frequency plasma-enhanced CVD (RF-PECVD) can produce a higher concentration of reactive radicals from the carbon source at a lower temperature in comparison to PECVD [51]. Wang *et al.* [51] synthesized MWCNTs with a Ni catalyst on Si, TiN/Si and a glass substrate by a RF-PECVD with RF power 600 W and 13.56 MHz at relatively low temperatures (140°C and 180°C) and injected CH_4 , H_2 and Ar into the chamber. They evaluated parameters such as substrate temperature and type, plasma intensity, gas flow rate and gas compositions. Dervishi *et al.* [52] devised an inexpensive method for the preparation of CNTs using a radio frequency generator and an electrical furnace in a hydrogen/ argon atmosphere. They used an iron oxide-graphene substrate without using any hydrocarbon gas at a relatively low temperature between 150 and 500°C. They reported that if they used iron oxide nanoparticles with a diameter of 5 nm then CNT were formed at 150°C, whereas if 15 nm nanoparticles were used, the temperature needed to be 400°C or higher.

2.2.3.4 Microwave plasma-enhanced CVD: The microwave plasma-enhanced CVD (MPECVD) method is often used for the synthesis of CNTs at low temperature and high yield. For example, flat panel displays were fabricated by growing CNT on the surface of a

soda-lime glass substrate using acetylene at 550°C without deformation [53]. Park *et al.* [54] fabricated MWCNTs by the MPECVD method from methane and hydrogen gases at a pressure of 2.13 KPa and microwave generator power of 800 W. Corning 1737 glass containing precipitated TiN and Ni was the substrate with a bias voltage about – 200 V. They could isolate MWCNTs with 20 nm diameter and 5 µm length at temperatures below 500°C and reported that increasing substrate temperature, improved the crystallinity of the MWCNTs. Another study [55] with the same conditions, focused on changes of the DC bias voltage between –250 and –50 V and its effect on the length, structure, crystallinity and electrical properties of the MWCNTs.

2.2.3.5 Water-assisted CVD: In 2004, water-assisted CVD (WA-CVD) was presented by Hata *et al.* [56]. By adding an amount of water into the CVD reactor, the catalyst activity, rate of formation and length increased, and the CNT diameter changed [57]. WA-CVD was called ‘super-growth CVD’ due to the improved CNTs synthesis [58,59]. Ren *et al.* [60] synthesized SWCNTs by using Co-MCM-41 as a catalyst in water/ethanol-assisted CVD. They found that by increasing the H₂O/C₂H₅OH ratio, the SWCNTs’ diameter increased. A study that examined the effect of water in the CVD process was published by Cui *et al.* [61].

2.2.3.6 Oxygen-/carbon dioxide-assisted CVD: Oxygen or carbon dioxide can also enhance CVD technique for CNTs synthesis. Kim *et al.* [62] reported that oxygen-assisted MPECVD using a mixture of CH₄/H₂ gases with a Fe/Al₂O₃/Si substrate and a temperature of 700°C could give MWCNTs with 4.08 µm length and 5 – 10 nm diameter. They found that upon adding O₂ to the chamber, the CNTs growth rate increased three-fold in comparison with MECVD and two-fold in comparison with WA-MECVD. Recently, Qi *et al.* [63] investigated the effect of oxygen on the length and purity of CNTs using the PECVD technique with a Co catalyst on a Si substrate and a methane/hydrogen mixture at a flow rate of 0 – 6 sccm. They showed that by increasing the O₂ flow rate, the nanoparticle adhesion on the CNTs surface decreased, and with a 3 sccm flow rate the CNTs length increased to 7 µm and at a 6 sccm flow rate the CNTs growth decreased. They concluded that by adding O₂ to system, OH radicals were formed.

Wen *et al.* [64] showed by using 0.1 – 1.5% CO₂ in the feed gas (methane) on a Fe/Mo/MgO catalyst, the amorphous carbon could be removed, the holes in the MgO support decreased, its specific surface area increased and the CNTs purity was improved. Techniques such as alcohol-assisted CVD [65], camphor-assisted CVD [66], thermal pyrolysis and flame synthesis [67] and low-pressure CVD [68] are some other methods, which have been used by researchers in order to improve CNTs synthesis. A schematic diagram of the reactor is shown in Figure 4C.

2.2.3.7 CVD with organometallic precursors: An interesting idea was to combine a carbon source and the catalyst in a single compound by using organometallic precursors like ferrocene or nickelocene for CNT synthesis [69]. The pyrolysis of these compounds was carried out using a mixture of methane or acetylene at 1100°C and produced SWCNTs or MWCNTs depending on the process conditions [69]. A few rather unusual sources of carbon for CNT synthesis have also been tried with some success. For example, a ferrocene/benzene mixture enriched with thiophene as a growth promoter was injected into a hydrogen

flow. If about 0.5 – 5 wt% of thiophene was added into the stream, SWCNT could be produced. If the thiophene was increased to > 5% then MWCNT could be formed [70]. The use of a ferrocenexylene mixture can also produce MWCNT. The reported yield was ~ 25% of the total carbon stock [71,72].

3. Preparing CNTs for drug delivery

CNTs are materials that are practically insoluble and hardly able to be dispersed, in any kind of solvent. To integrate the nanotube technology into the biological environment, the solubility of the nanotubes, especially in aqueous solutions must be drastically improved. Functionalization is a technique used to overcome this issue. The most popular route to administer CNTs is intravenous (i.v.) injection. However, when given by i.v. route, the, CNTs are found to accumulate in the reticuloendothelial system especially in the liver and lungs. CNTs are also excreted in urine; therefore, the i.v. route is suitable for delivery of the drug to the kidney and urethra. Moreover, subcutaneous administration of CNTs has been proposed by researchers, but due to possible stimulation of dendritic cells in the skin it may lead to immune response [73–75].

Generally, the functionalization process involves the attachment of materials to the sides or end of the CNTs, hence improving their biocompatibility. Functionalized CNTs have been intensively studied in the last few years. The attachment may be achieved via covalent or non-covalent bonding. There are advantages and disadvantages related to the two strategies of functionalization, which will be tackled in the following paragraphs [76,77].

3.1 Non-covalent

Attaching different molecules to the basic structure of CNTs via physical interaction is the fundamental mechanism of non-covalent functionalization. Adsorption mediated by different forces, such as van der Waals force, electrostatic force, π -stacking interactions and hydrogen bonds are the basic foundation of non-covalent functionalization which is mainly based on formation of supramolecular complexes [78]. Owing to the drawbacks of covalent modification such as distortion of pristine CNT, the difficulty and expense, and drawbacks of γ -conjugation, many studies have emphasized the advantages of easy, nondestructive, cheap and 'one-step' non-covalent methods for surface functionalization of CNTs. The dispersion procedures usually involve ultrasonication, centrifugation and filtration and are quick and easy to perform. Hydrophobic or π - π interactions are often evoked as likely being responsible for non-covalent stabilization. Three main classes of important molecules that can be used for dispersion of CNTs are classified as, surfactants, polymers and biopolymers (nucleic acids and peptides). These materials have been selected because of their low cost and easy availability [79].

3.1.1 Surfactants—A variety of anionic, cationic and nonionic surfactants have been applied to disperse nanotubes. In order to obtain CNTs suspensions up to 0.1 and 0.5 mg/ml, SDS and Triton X-100 were used, respectively [80]. However, the stability of this suspension was no longer than 1 week. Using sodium dodecyl benzene sulfonate resulted in over 1 month stable 10 mg/ml concentration of the suspension. Studying of SDS/CNTs dispersions via atomic force microscopy and electronic transmission microscopy (TEM)

revealed that CNTs are mainly present as individual tubes uniformly covered by the surfactant [81]. Triton-X mainly interacts by π -stacking. Another approach for the adsorption/dispersion of CNTs via π -interaction achieved by use of 1-pyrenebutanoic acid activated as succinimidyl ester, which promptly reacts with the amino groups present in the proteins like ferritin or streptavidin [82]. The solubility of CNTs was in the range of 0.1 and 0.7 mg/ml, which is rather low but acceptable for biological use. Surfactants are efficient in the solubilization of CNTs. However, they are known to permeabilize plasma membranes and have a toxicity profile of their own.

Recent developments in surfactant synthesis have extended the variety of biocompatible surfactants available. The surfactants known as Pluronics, are a group of nonionic triblock copolymers. Among the various types of Pluronic available, PF127 and PF108 have shown excellent CNT dispersion properties because of their amphiphilic nature and steric hindrance effect [83]. The ability of these surfactants to entirely disperse CNTs depends on length of the polymer chain [84]. Bovine serum albumin (BSA) was compared to PF108 as dispersants for MWCNTs in terms of tube stability as well as profibrogenic effects *in vitro* and *in vivo*. While BSA-dispersed tubes were a potent inducer of pulmonary fibrosis, the PF108 coating protected the CNT from damaging the lysosomal membrane and causing pulmonary fibrosis [85]. The surfactant 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-*N*-[amino(polyethylene glycol)-2000] (DSPE-PEG2000) was used as a bridge to join CNTs to peptides like NGR (Asn-Gly-Arg) in order to enhance tumor targeting efficacy of the system [86]. DSPE-PEG2000 increased the blood circulation time of the system [87]. Investigation of the zeta potential of CNT conjugated to DSPE-mPEG showed that the best ratio of CNT:mPEG was 1:8 [88].

3.1.2 Biomolecules—Because of large surface area of CNTs, they can easily interact with different biomolecules including biopolymers via van der Waals interactions, with nucleic acids although π - π stacking interactions, and with proteins by hydrophobic interaction [89].

3.1.2.1 DNA: Owing to properties such as simple chemical structure, ease of synthesis, variable size with small pieces possible, reversible denaturation, a high sequence specificity, and its flexibility, nucleic acids (and DNA in particular) are excellent building blocks to construct macromolecular networks. Functionalization of CNTs with DNA molecules can be used in applications such as nanodevices or nanosystems, electronic sequencing and gene transporters [90]. The π - π interactions typical of double-stranded DNA are used for CNT dispersion [91]. In order to form supramolecular complexes based on π -stacking between the aromatic bases and the CNTs surface, nucleic acids are ideal candidates [73]. The interaction between DNA and CNT is between anionic groups of DNA, with cationic groups on CNTs, resulting in superior biostability. The combination of CNT with DNA can enhance the expression of modified DNA and provide a mechanism for cellular uptake.

Enyashin *et al.* [92] reported systematic quantum mechanical modeling of the stability and the electronic properties of complexes based on SWCNT, which were helically wrapped by DNA molecules. They studied the effect of the CNT diameter and the kind of nucleotides in the homopolymeric DNAs. CNT wrapped by homopolymeric single-stranded DNA molecules showed a density-functional tight-binding conformation. A phenomenological

model of the CNT-DNA formation energy as a function of the nanotube radii led to the decoration of a CNT by only a few DNA chains, but which resulted in a high water solubility of CNT-DNA. In order to wrap the CNTs, pyrimidine-based DNAs were more effective. In a few specific cases, charge transfer from the DNA to the CNT occurred and an additional gain in the CNT-DNA formation energy was observed. Das *et al.* [93] constructed SWNT-based chemiresistor aptasensors for highly sensitive and selective detection of weakly or uncharged molecules using the displacement format. ATP, a small weakly charged molecule, was detected by displacement of the ssDNA anti-ATP aptamer hybridized to a small capture oligonucleotide covalently attached on SWNTs, with picomolar sensitivity and selectivity over GTP. Taghdisi *et al.* used π - π interaction for functionalization of CNTs with the sgc8 aptamer that targets leukemia biomarker, protein tyrosine kinase-7 to form a complex between daunorubicin and SWNT to enhance targeted delivery of Dau to acute lymphoblastic leukemia T-cells (Molt-4) [73].

3.1.2.2 Carbohydrates: In 2002, Stoddart *et al.* [94] first reported the preparation of a 'starched SWCNT'. Preformed amylose/iodine complexes could disperse CNT, but the aqueous solution of amylose alone could not dissolve SWCNTs. According to these observations, they suggested a 'pea-shooting' mechanism where the CNTs can enter the helical amylose/iodine complex by sequentially displacing the iodine inside the complex. They also proposed that pure SWCNTs could be precipitated and obtained after adding amyloglucosidase into the aqueous solution of the starch-wrapped SWNTs. Thus, starch complexes could be a practical method to purify SWCNTs. Kim's group [95], studied the interaction between amylose and SWCNTs in aqueous Dimethyl sulfoxide solution in the absence of iodine. In this reaction medium, amylose is only loosely coiled, compared to the case when iodine is present. Results showed that weakly twisted A/S-C structures with a diameter of about 30 nm were formed by amylose acting as a host-guest molecule allowing occupation by a guest CNT with a diameter of > 1 nm.

A theoretical basis for the preparation of carbohydrate/ CNT complexes has been proposed. Soh *et al.* [96] studied the mode of interaction between the initially separated amylose and SWCNT fragments by molecular dynamics simulations. It was found that the van der Waals force was dominant, which promotes non-covalent association. As a result, amylose molecules could be used to bind with nanotubes, and the size of nanotubes affected the non-covalent functionalization of CNTs.

Single-chain schizophyllan and curdlan (s-SPG and s-curdlan, respectively) were also used by Numata *et al.* [97] to dissolve SWCNTs in aqueous solution. Interestingly, s-SPG or s-curdlan could wrap around SWCNTs resulting in a twined helical structure. It was observed from the high-resolution TEM images that the two s-SPG chains twined around one SWCNT and the helical motif was right-handed.

The hydroxyl groups present on polysaccharides make it possible to further functionalize CNTs by attaching yet more groups. Moreover, because of the recurring periodic structure of linked carbohydrate monomers on the composite surface, it can be inferred that one could design carbohydrate-CNTs using the concept of supramolecular or self-assembly chemistry.

Gum Arabic and cyclodextrins have also been used to functionalize CNTs [98–100]. There are three main types of cyclodextrins; however, only β -cyclodextrin has an inner cavity diameter of 0.75 – 0.83 nm and therefore has the ability to accommodate a guest molecule as large as a nanotube, into its inner cavity and form an inclusion complex [101].

3.1.3 Polymers—It has been shown that the structure, chemical properties and electrical charge of polymers can influence the dispersion and properties of CNTs. Properties such as facile electrochemical polymerization, ion exchange with the medium, good capacity to enhance adhesive coatings, make polypyrrole (PPy) a good candidate polymer to be used for improving the electronic conductivity of CNTs [102]. Polyvinylpyrrolidone is an amphiphilic stable polymer that is nontoxic and biocompatible and has been used for modification of SWCNTs under physiological conditions in aqueous media [103].

Kayatin *et al.* discovered during a study of polymer functionalization of CNTs, that having excess styrene in the reaction compared to Li/NH₃ led to facile polymerization and conjugation to the side walls of SWCNTs. They applied polystyrene (PS) to stabilize CNTs and found that small PS bound to SWNT outer walls to increase its dispersibility. They then used reductive alkylation of SWNT with dodecyl surface groups to calculate the PS MW [104]. In another study, Soylak *et al.* used PPy to increase the solubility and time-life of the MWCNTs [105]. Separately, Karadas *et al.* found that oxidation of PPy could produce a negative charge density on the surface of MWCNTs, and increase the porosity and drug loading efficiency via an ion exchange process [102]. Wu *et al.* synthesized a pentablock-polymer-SWCNT conjugate to increase thermoresponsiveness, stability and dispersibility of the CNTs. This design stabilized the drug-CNT hybrid without any sedimentation over 2 months of storage as well as reversible switching between the aggregated state and exfoliation according to the temperature cycling [106].

Moradian *et al.* investigated polyethyleneimine (PEI) polymer to functionalize CNT. The presence of PEI on the surface of CNTs increased the hydrophobic chain size from 70.89 to 110.1 nm and the surface potential of acid treated MWCNTs was raised from 40.7 to 39.3. PEI could enhance the binding efficiency of pDNA and DNA condensation, and produce a homogeneous dispersion in aqueous solution [107]. In a separate study, PEI was conjugated with DSPE-PEG then bound to the CNTs to reduce the toxicity and increase the efficiency of siRNA loading [74]. Bagheri *et al.* applied polyphenylamine to disperse CNTs [108]. Polyaminothiophenol also was used as a conductive polymer to functionalize the CNTs to increase thermal stability, porosity and nanotube diameter [109]. Yan *et al.* decorated CNTs with poly(3-hexylthiophene) by addition of phenylbutyrate-methyl ester to obtain polyethylenedioxythiophenopolystyrenesulfonate-SWNTs [110]. MWCNT-polyvinyl alcohol was found to have good adsorption of polycyclic aromatic hydrocarbons in aqueous solutions [111].

3.1.4 Peptides—Proteins and polypeptides are often used to functionalize CNTs. Protein is an outstanding natural nanomaterial for construction of molecular machines. Amphiphilic peptides are an efficient dispersion agent for CNTs. The presence of amino acids (e.g., tyrosine, phenylalanine and tryptophan) is mainly responsible for this interaction. These peptides could either be selected from phage-display peptide libraries or synthesized by

design. The sequence of highly specific peptides able to wrap around the CNT make it possible to assure solubility and may even provide a useful tool for size separation [112].

Poly-L-lysine (PLL) is one of the natural peptides that have been used for modification of CNTs. Properties such as multiple amino groups, good water solubility and flexible backbone make it a suitable candidate for this purpose. After cross-linking of the amino group of the PLL with CNT, the modified CNT is able to better bind biological compounds and drugs [113]. Ling *et al.* used *N*-carboxyanhydride polymerization to synthesize PLL-modified MWCNTs. The non-covalent MWCNTs-PLL composite increased the dispersion of CNT compared to MWCNTs-SDS and provided a pH-responsive element [114]. Hashida *et al.* designed seven different peptides to form a β -sheet structure to wrap the SWCNTs to enhance dispersibility and stability. Among the peptides H-(Lys-Phe-Lys-Ala)₇-OH showed satisfactory properties of stability and could be applied in photothermal cancer therapy [115].

RGD is a tripeptide (arginine-glycine-aspartic acid) that binds to $\alpha v\beta 3$ integrins that are overexpressed on cancer cells. RGD peptide was conjugated to SWCNTs bound to phospholipid and PEG and was specifically targeted to its receptor on cancer cells. The NGR peptide has the ability to bind to CD13 which is also over-expressed on cancer cells. NGR was conjugated to SWCNTs and bound docetaxel to target tumor cells. The NGR-SWCNTs were also bound to 2-methoxyestradiol for neovascular targeting of the drug [89].

Iancu *et al.* [116] proposed a method for non-covalent functionalization of MWCNTs with human serum albumin (HSA) protein for targeting laser-induced necrosis to liver cancer cells. Briefly, oxidized MWCNTs and human serum albumin-fluorescein isothiocyanate (HSA-FITC) were mixed in water at concentrations of 0.25 and 1.25 mg/ml, respectively. Then, the mixture was sonicated for 1 h with a tip sonicator in an ice bath and centrifuged for 5 min at 12,000 r.p.m. The HSA-MWCNT conjugate was purified using gel chromatography.

3.2 Covalent functionalization

Covalent functionalization is based on the covalent linkage of functional moieties onto the CNT carbon scaffold. The covalent bonding of a functional group to the SWCNTs will produce stable functionalized SWCNTs making the material suitable for a variety of applications such as drug delivery. However, using covalent functionalization, the electronic properties of SWCNTs are disturbed, and double bonds are irreversibly lost. There are two categories of covalent functionalization, direct covalent functionalization and indirect covalent functionalization with carboxylic groups on the surface of CNTs [75].

A common type covalent functionalization is achieved through addition reactions to CNTs. The chemistry of fullerenes plays the main role in this method. Association of changes in hybridization from sp² to sp³ with a loss of conjugation after direct covalent functionalization have been widely studied [117]. Favvas *et al.* conjugated a phenol group on the outer surface of MWCNTs and found excellent dispersion behavior of phenol-functionalized MWCNTs in *N*-Methylpyrrolidone solvent [118].

Carboxylation of SWCNTs is another common method for the covalent functionalization of SWCNTs since the preparation is relatively simple and quick. The oxidation process does not require complex apparatus and can be achieved in a short period of time. Madani *et al.* [5] investigated the treatment of SWCNTs with a combination of acids. The system, which was used to coat the surface of the SWCNT, resulted in the attachment of carboxylic acid groups (COOH), producing dispersible, hydrophilic SWCNTs. They also pointed out that the ability of COOH groups to bind to other functional groups such as amines or thiols is another benefit of carboxylation. Finally, they suggested that treating pure SWCNTs with HNO₃/H₂SO₄ (1:3) at 120°C for 120 min was an effective method. Mubarak *et al.* used acid oxidative methods; first they mixed MWCNT with a concentrated mixture of HNO₃ and H₂SO₄ (ratio of 1:3 (v/v)) heated at 40°C for 4.5 h, followed by filtration via hydrophilized PTFE membrane and alcohol treatment [119]. Functionalization of CNTs was found to occur during the purification process in nitric acid solution and in the presence of HNO₃ and H₂SO₄ [120]. Sahoo *et al.* used PNA for functionalization of MWCNTs after oxidation with HNO₃ and H₂SO₄ (ratio of 3:1). Then carbodiimide-activated esterification reaction is applied for conjugation of PVA to the COOH [121].

Amines can be added in a relatively simple procedure compared to other functional groups attached to CNTs. The nitrogen atom of the amino group (–NH₂) has a lone pair of electron, which makes it bond to other molecules easily. The amine-functionalized CNTs are frequently used in fabrication of electrodes [122] due to the mentioned reactivity. Among amine molecules, diamines can function as a cross-linker to attach other compounds to CNTs [123]. Some conventional methods such as sonication and mixing have already employed to introduce adiamine functionality. However, these methods are often time-consuming, involving multiple steps [124].

Rahimpour *et al.* [125] prepared amine-functioned MWCNTs attached to polyethersulfone (PES) membranes using phase inversion induced by immersion precipitation. Crude MWCNTs were chemically treated using strong acids (H₂SO₄/HNO₃) and 1,3-phenylenediamine (mPDA) to produce the functional amine groups on their surfaces (Table 2). In this study, they fabricated novel NH₂-functionalized MWCNTs and blended them with PES casting solution in order to improve the surface properties and performance of ultrafiltration membranes. Maghrebi *et al.* [126] attached three different diamines (Ethylenediamine, Hexamethylenediamine and 3,3'-Diaminobenzidine) to the surface of MWCNTs in a microwave-assisted method. The procedure was fast, one-pot, simple and resulted in a high degree of functionalization as well as solubility in ethanol.

Vázquez *et al.* [127] developed a strategy for the functionalization and solubilization of CNTs based on the 1,3-dipolar cycloaddition of azomethineylides. The main advantage of this reaction was the attachment to the sidewalls of CNTs of pyrrolidine rings substituted with different functionalities. Azomethineylides were prepared by the decarboxylation of immonium salts derived from condensation of α -amino acids with aldehydes. Functioned aldehydes led to 2-substituted pyrrolidine moieties located on the sidewalls of CNTs, while N-modified α -amino acids led to N-substituted pyrrolidines. Mulvay *et al.* synthesized covalent amine-functionalized SWCNTs 1,3-cycloaddition using tert-butyloxycarbonyl (H-

Lys-(Boc)-OH). Then, this conjugated CNT was bound to radiometalated chelator and exhibited good wrapping of siRNA [128].

Zardini *et al.* [129] functionalized MWCNTs with two amino acids (lysine and arginine) using microwave radiation. The NH groups indicated the occurrence of amidation reactions between the amino groups of arginine/lysine and the carboxyl groups on the surfaces of the MWCNTs. Polo-Luque *et al.* [130] suggested that ionic liquids could be used for functionalization reactions avoiding the use of strong acids or organic solvents. The resulting compounds obtained with the latter strategy retained the original properties of each component. The most important strategies for non-covalent and covalent functionalization are illustrated in (Figure 5).

4. Conclusion

There are three major methods to synthesize CNT, which differ in yield, type of CNT produced and the type and amount of impurities. New techniques have been developed in order to increase the yield of the synthetic procedure and lessen the amount of contaminants. It is almost impossible to use CNT in drug delivery without employing one of several different kinds of functionalization procedures. The functionalization strategies can be divided into two major groups: covalent and noncovalent functionalization. The first one is based on formation of chemical bonds between functional groups and CNTs, whereas in the latter case, π - π interactions are considered to be the fundamental mechanism. The negative aspect of covalent functionalization is that damage is introduced to the pristine surface which can adversely affect the electrical and optical properties of CNT. On the other hand, covalent functionalization does provide a strong linkage between the cargo and the CNT, which can be designed to be released according to the properties of the biological media in which CNT is going to be used. Research is expected to continue into different chemical strategies to functionalize CNT (both covalently and non-covalently) as interest in their use as drug-delivery vehicles continues to grow.

5. Expert opinion

In the past two decades, CNTs have attracted a tremendous amount of attention both amongst scientists and even amongst the general public. The idea of a spontaneously formed pure carbon molecule with an inherently attractive and recognizable shape has certainly struck a chord. The unique mechanical strength of CNT combined with excellent thermal and electrical conductivity properties have led to a host of applications in nanoelectronics, materials science, nano-optics, energy generation and storage technologies and so on. The question addressed in the present reviews is: do CNT have promise as a drug-delivery vehicle? Here it is fair to conclude that the jury is still out. As we have shown in Part 1, chemists have developed methods of preparing, purifying and characterizing CNT, both the multi-walled and single-walled varieties. The molecular composition of entirely sp^2 hybridized carbon atoms means that CNT are extremely hydrophobic and highly prone to aggregation. These tendencies taken together mean that pristine CNT are highly incompatible with biological systems. Therefore most of the efforts to use CNT in drug delivery has centered on chemical functionalization. The functionalization strategy chosen

has two side-by-side objectives: i) to provide solubility in water and reduce aggregation and ii) to provide functional groups to allow the biological cargo to be attached.

Non-covalent functionalization relies on the tendency of a wide variety of different molecules to attach themselves to, or to wrap themselves around CNT. These molecules include surfactants or detergents, synthetic polymers, nucleic acids, peptides and proteins, and carbohydrates. These molecules may be the active cargo themselves or may act as an intermediate linker to allow another active cargo to be attached. Since biological macromolecules by definition have high compatibility with water, the covering or wrapping of biomolecules around the hydrophobic CNT structure, both increases solubility and at the same time reduces aggregation. In the case of covalent functionalization, two types of functional groups commonly satisfy the requirements, namely amines and carboxylic acids. Both these groups can be ionized in water, and this dramatically increases hydrophilicity. Furthermore, established conjugation chemistry routes are available to attach biomolecules to these groups, frequently by formation of an amide bond. The fact that CNT are entirely composed of carbon atoms means that carboxylic groups can be relatively easily introduced into the molecules by treatment with strong oxidizing acids, and this has become a commonly used strategy.

One of the most discussed possible disadvantages of the use of CNT as drug-delivery vehicles is the widespread concern over nanotoxicology. This aspect has been intensively investigated in recent years, with somewhat divergent findings. A summary of these reports is given in Part 2. It is also necessary to critically analyze what are the unique properties of CNT that make them particularly suitable for use as drug-delivery vehicles, that cannot be provided by any of a large and growing range of nanoscale constructs that are also being applied in drug delivery. To our knowledge, this comparison has not yet been attempted in a convincing manner.

Nevertheless, interest in the use of CNT in biomedical applications is expected to grow strongly in the coming years, and new drug-delivery technologies are expected to play a major role in these efforts.

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Article highlights

- Carbon nanotubes (CNTs) are receiving growing attention as drug- and gene-delivery vehicles.
- Synthesis methods include arc discharge, laser ablation and chemical vapor deposition (CVD).
- Several new methods for enhancing CVD using plasma, water or oxygen/carbon dioxide have been developed.
- Non-covalent functionalization relies on attachment of biomolecules by coating the CNT with surfactants, synthetic polymers and biopolymers.
- Covalent functionalization involves the introduction of carboxylic acids or amine groups, diazonium addition, 1,3-dipolar cycloaddition or reductive alkylation.

This box summarizes key points contained in the article.

Figure 1.
Schematic of (A) single-walled carbon nanotube (B) multi-walled carbon nanotube.

Figure 2.
Stone-Wales (or 7-5-5-7) defect on sidewall of nanotube.

Figure 3.

(A – C) classification of SWCNTs, armchair, zigzag and chiral respectively. Armchair and zigzag refer to the shape of cross sectional ring. (D) Unrolled honeycomb lattice of a SWCNT.

SWCNT: Single-walled carbon nanotube.

Figure 4. Schematic of (A) arc discharge (B) laser ablation and (C) chemical vapor deposition methods.

Figure 5. Different methods for functionalization of CNTs
CNT: Carbon nanotube.

Table 1

Arc-discharge parameters in recent publications.

Type of CNTs	Diameter (nm)	Arc Current (A)	Synthesis time (min)	Catalyst type	Environment	Year	Ref.
SWCNTs	> 10	120	–	Fe, Co, Ni, FeS	Hydrogen, 240 Torr	2014	[24]
MWCNTs	10–20	90	–	–	Methane, 100, 300 and 500 Torr	2014	[131]
SWCNTs	1.3–1.6	90	–	Ni-Y	Helium, 375 Torr	2014	[132]
DWCNTs	–	80	20	–	Air, 50 Torr	2013	[133]
CNTs	–	75–95	5	Ni–Y ₂ O ₃	Hydrogen–argon, 150 Torr	2013	[134]
SWCNTs	10–30	80	10	Fe–W	Hydrogen–argon, 200 Torr	2013	[135]
Few-walled CNTs	1.6–6	90	–	Fe–S	Air, 0.75–135 Torr	2013	[136]
MWCNTs	–	75	–	–	Deionised water	2013	[137]
MWCNTs	50–100	50	5–10	–	Argon, 525 Torr	2013	[26]
CNTs	–	105	5–8	–	–	2012	[138]
MWCNTs	10.4	100	–	–	Argon	2012	[139]
MWCNTs	15	80	–	–	Air, 60 Torr	2012	[139,140]
SWCNTs	–	120	–	Ni-Y ₂ O ₃	Hydrogen–helium, 530 Torr	2012	[141]
SWCNTs	–	90	–	Ni-Y	Helium, 375 Torr	2012	[142]
MWCNTs	–	80, 100, 150	8	–	Helium, 760 Torr	2012	[143]
Few-walled CNTs	1–10	150	–	Fe-Rh	Hydrogen–argon, 200 Torr	2012	[144]
MWCNTs	–	80	20	–	Air, 40–300 Torr	2012	[145]
CNTs	40–60	210	4	–	Hydrogen, 50 Torr	2012	[146]
CNTs	–	2.5	–	–	Air	2012	[147]
MWCNTs	–	10	15	–	Argon, 525 Torr	2012	[148]
CNTs	5	20	60	Metal catalysts	De-ionized water	2012	[149]

CNT: Carbon nanotube; MWCNT: Multi-walled carbon nanotube; SWCNT: Single-walled carbon nanotube.

Table 2

Examples of CNT functionalization.

Investigation	Method	Result	Ref.
Treatment of SWCNT with a combination of acids	Coating the surface of SWCNTs with $\text{HNO}_3/\text{H}_2\text{SO}_4$ (1:3) at 120°C for 120 min	Produces dispersible, hydrophilic SWCNTs	[5]
Attaching carbonyl (C=O) groups on the SWCNT surface	Oxidation reaction of HiPCO SWCNTs at a 3:1 $\text{H}_2\text{SO}_4/\text{HNO}_3$	Produces an amine/amide link between the SWCNTs and biological systems	[150]
Different solubility properties of modified SWCNTs depending on the amines and solvents used	Reacting the amines octadecylamine, 2-aminoanthracene, 1-H pentadecafluorooctylamine, 4-perfluorooctylamine and 2,4-bis aniline with CNTs	Intermediate behavior of SWCNTs modified with amines	[151]
Attaching biomolecules onto CNTs with covalent bonding	Acid-oxidizing the CNx MWCNTs to form carboxylic acid groups and activating by EDAC (forming reactive O-acylisourea)	Forming amide bonds between the CNTx MWCNTs and proteins	[152]
Preparing amine F-WCNTs/PES	Using strong acids ($\text{H}_2\text{SO}_4/\text{HNO}_3$) and 1,3-phenylenediamines	Removing toxic coupling reagent (SOCl_2), improving the hydrophilicity of PES membranes	[125]
Using microwaves radiation for conjugation	Adding 3 diamines (EDA, HMDA and DBA) to the surface of MWCNT in a microwave-assisted method	Less defects in CNTs sidewalls, Fast, one-pot and simple functionalizing	[126]
Functionalization of CNTs with Ionic liquids	Replacing volatile organic solvents by Ionic liquids	Environment-friendly method, achieving multifunctionalized compound	[130]
Functionalization and dispersion of MXCNTs modified with Poly-Lysine	Non-covalent Functionalization of MWCNT using Poly-Lysine	Can be used in bio-nano material because of pH responsivity	[114]
Functionalization of CNT by nitric acid vapors	Functionalization at zeotropic concentration by adding $\text{Mg}(\text{NO}_3)_2$ salt to the $\text{HNO}_3 + \text{H}_2\text{O}$ solution	Increasing the nanotube functionalization with HNO_3 vapor	[153]
Functionalization of MWCNTs with natural amino acids under microwave irradiation	Mixing amino acid with DMAC and then sonicating MWCNT-COOH, adding NaNO_2 and finally heating	Dispersing MWCNTs in polar organic solvents	[154]

CNT: Carbon nanotube; DBA: Dibutylamine; DMAC: Dimethylacetamide; EDA: Ethylenediamine; HMDA: Hexamethylenediamine; MWCNT: Multi-walled carbon nanotube; PES: Polyethersulfone; SWCNT: Single-walled carbon nanotube.