Functionalized Carbon Nanotube for Various Disease Treatment

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Abstract

The delivery of therapeutic medications employing nanoparticles has been used in pharmacy and the medical field because of their vast electrical, superior chemical, and enormous surface area. It has been shown that carbon nanotubes (CNTs) are an excellent drug delivery system because they efficiently enter cells as well as because of their polyaromatic nature, and they keep the medication intact during transit in the body without metabolizing it. Drug-CNT conjugates for drug delivery are safer and more effective than the drug used alone in conventional manufacturing as functionalized CNTs can safely carry significant molecules across nuclear and cytoplasmic membranes as well as reduce the toxicity associated with CNT as such. They are chosen as a basis for attaching antibiotics and anticancer medications to carbon nanotubes for the treatment of infections and cancer. Subsequently, other biomolecules were joined to CNTs and investigated for a variety of uses, including gene therapy, immunotherapy, tissue repair, and disease diagnostics and treatment.

Keywords

Functionalized carbon nanotubes · Toxicity · Cancer therapy · Drug delivery

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6.1 Introduction

Nanomaterials, which exist as a form of carbon allotrope graphite and exhibit a nanometer-scale diameter and a few millimeters in length (Hirlekar et al. 2009; Singh et al. 2012), have been built in cylindrical tubes. Their outstanding structural, mechanical, and electronic properties are the result of their small size and mass, incredible mechanical strength, and exceptional electrical and thermal conductivity (Usui et al. 2012; Zhang et al. 2010). Ever since the beginning of the twenty-first century, nanoparticles have been utilized in pharmacy and medicine as a therapeutic medication delivery system owing to their large surface area, superior chemical stability, and extensive electrical. It has been demonstrated that carbon nanotubes (CNTs) are an ideal vehicle for drug administration since they immediately penetrate cells and maintain the medication intact without metabolism during transit in the body (Hirlekar et al. 2009; Singh et al. 2012; Usui et al. 2012; Zhang et al. 2010) due to their polyaromatic nature. Numerous studies have shown that these compounds may be transported into cells more efficiently and securely when attached to CNTs (Singh et al. 2012; Usui et al. 2012; Zhang et al. 2010). To cure cancer and infections, it was first used to bind anticancer medicines and antibiotics to carbon nanotubes. Then additional biomolecules have been linked to CNTs and tested for various applications, such as gene therapy, immunotherapy, tissue repair, and disease diagnosis (Kateb et al. 2010; Liu et al. 2007a; Zhang et al. 2011; Rosen and Elman 2009; Bekyarova et al. 2005).

6.1.1 Carbon Nanotubes: Configurational Structures, Types, and Preparation

All of the carbon atoms that make up carbon nanotubes (CNTs) are organized in a sequence of condensed benzene rings and wrapped up into a tube-like form. This novel artificial nanomaterial is found in the native sp2 (planar) and sp3 (cubic) forms in the class of fullerenes, the third allotropic carbon structure after diamond and graphite (Hirlekar et al. 2009; Singh et al. 2012; Liu et al. 2007a). The architectures of CNTs are divided into two groups depending on the number of layers: single-walled carbon nanotubes (SWCNTs) and multiwalled carbon nanotubes (MWCNTs). SWCNTs often appear as tightly packed hexagonal bundles and are made up of an individual graphene cylinder with a diameter that ranges from 0.4 to 2 nm. Each of the coaxial cylinders present in the MWCNTs are constructed of a single layer of graphene encircling a narrow center. MWCNTs' outer diameter is between 2 and 100 nm, while the inner diameter is between 1 and 3 nm, and their length is from 0.2 to several millimeters (Singh et al. 2012; Bekyarova et al. 2005). The tips and the side walls of CNTs are two distinct zones. Rolling the graphene sheet into a tube results in a variety of tubule shapes, which play a significant role in regulating these peculiar features. Depending on its direction, the molecule can roll in one of three different ways: chiral, zigzag, and armchair (Singh et al. 2012; Usui et al. 2012; Zhang et al. 2010; Kateb et al. 2010; Liu et al. 2007a).

6.1.2 Applications of Carbon Nanotubes in the Pharmaceutical and Medical Fields

The functionalized CNTs are coated on the surface or loaded inside with the drug. Functionalized CNTs can transport desired molecules beyond the cytoplasmic and nuclear membranes without creating a harmful outcome. The conjugates of carbon nanotubes reveal to be both safer and much more potent than the medications used alone via conventional preparation (Zhang et al. 2010; Kateb et al. 2010; Liu et al. 2007a).

6.2 Properties of Carbon Nanotubes

6.2.1 Physical Property

6.2.1.1 Young's Modulus and Tensile Strength

Tensile strength and Young's modulus are measured using a stress-strain puller to drag long ropes holding plenty of aligned nanotubes. The rope's Young's modulus, its tensile strength, and the associated rope elongation can all be determined at once by exerting an axial force on the rope to confirm the number of broken tubes a load was applied along with continuous monitoring of electric conductivity. The sample's cross-section and the tubes' filling factor were determined from scanning (SEM) and transmission electron microscopy (TEM) observations to produce the stress-strain curve. While the tensile strength of the tube cannot be determined by merely averaging the values of all the tubes mostly from the data, the Young's modulus can. According to the parallel structure model of the samples, the first tube to break in a rope made up of numerous parallel and isolated tubes of varying strengths is always the weakest one. As a result, as the load is redistributed, the remaining, undamaged tubes are put under more stress, which eventually leads to the breakage of the second weak tube. This technique will reduce the apparent value of the rope's tensile strength and will undoubtedly reduce the tube's derived value (Daniels 1945).

6.2.2 Mechanical Property

6.2.2.1 CNT Deformation Under Stress

The deformation of carbon nanotubes using various methods is being studied, and in recent attempts, carbon nanotubes distributed in a polymeric film were subjected to significant compressive strains (Lourie et al. 1998). The results for the buckling of thick tubes show that the axial compression deformation of CNT when compared to single-layer CNT was less due to the hollow shape and high aspect ratio. Buongiorno Nardelli et al. (1998); however, there are differences in the plastic collapse or breakage of thin tubes. For thin tubes, the critical stress for inward collapse or fracture is anticipated to be between 100 and 150 GPa, with the compressive strain assessed to be greater than 5%. The fundamental finding of those investigations is

that the compression strength of both thin-walled and thick-walled carbon nanotubes is orders of magnitude greater than those of any other known fiber. The toughest tubes are zigzag and armchair forms, with the 0 K stress being very sensitive to helicity, as shown by the molecular dynamics calculations of SWNTs in a TB-large-scale model under significant applied strains (both elongation and compression) (Ozaki et al. 2000).

In all methods, carbon nanotubes transform into new shapes with a sudden release of stress energy when subjected to substantial deformations (Buongiorno Nardelli et al. 1998). The bending is reversible up to very large bending degrees, despite imperfections and highly strained tubule regions. This flexibility property comes from the ability of the C-C bonds in the sp2 network to reversibly change the hybridization when deformed out of the plane. With increased curvature, the sp3 nature of C-C bonds in the deformed region becomes stronger. The mechanisms of strain produced in carbon nanotubes under uniaxial tension have also been investigated in order to address the question of the ultimate tensile strength of these nanoparticles (Buongiorno Nardelli et al. 1998; Lourie et al. 1998; Ozaki et al. 2000; Yakobson 1998; Srivastava et al. 1999).

6.2.3 Thermal Property

6.2.3.1 Specific Heat

In a carbon nanotube, a single graphene sheet has been wound into a cylinder as a carbon nanotube. Covering the sheet twice has a considerable impact on the phonon band structure. The two-dimensional (2D) photon band structure of the sheet first "folds" into the 1D band structure of the tube. Additionally, the distribution of the lowest-lying modes changes because the tube is firmer than the sheet due to its cylindrical shape (Saito et al. 1998; Benedict et al. 1996). As a result, changing the dimensionality of a system can significantly affect the low-energy projected density of states (PDOS) and, consequently, the low-temperature-specific heat. The magnitude of this effect in graphite is related to the up to 10 meV Debye energy of the interlayer modes. It is expected that forming 3D crystalline arrays of tubes will reduce low-energy PDOS in nanotubes (Mizel et al. 1999).

6.2.3.2 Thermal Conductivity

The materials with the highest-documented thermal conductivity at ambient temperature are diamond and graphite; consequently, nanotubes do need to function appropriately here as well. A recent theoretical study (Berber et al. 2000; Hone et al. 2000a) indicated that the thermal conductivity of nanotubes at ambient temperature might reach as high as 6600 W/m K. The consequences of 1D quantization should also be seen in the thermal conductivity at low temperatures, just like they are in the specific heat. The thermal conductivity of a highly anisotropic material is particularly susceptible to phonons with high velocities and extended scattering wavelengths. It follows that thermal conductivity should directly probe on tube phonons and be robust to intertube coupling even in nanotube bundles. Thermal

conductivity in all samples has a completely linear temperature dependence below 40 K. Given that only the tube's acoustic modes transport any heat flow during 1D quantization, this temperature dependence is most likely caused by this phenomenon. The impact of intertube connections on $K(T)$ (temperature)'s dependency is unknown, though. To more precisely assess whether the linear $K(T)$ is due to 1D quantization, we evaluated $K(T)$ in samples with different nanotube diameters. Since the phonon subband separation rises with a decreasing tube diameter (Llaguno et al. 2002; Hone et al. 1999), we predict that the linear $K(T)$ could reach a wider temperature range in samples with a smaller average tube diameter. Composite materials with high thermal conductivity have a variety of possible applications, particularly in heat lowering for electronics and motors.

Carbon nanotubes' distinctive structure as well as small size are closely related to their thermal characteristics. These characteristics make nanotubes potentially the best material for the study of low-dimensional phonon physics and controlling the temperature on both a macro- and microscale the specific heat and thermal conductivity of bulk SWNT samples were examined to investigate the thermal characteristics of nanotubes. Single-walled nanotubes have a different specific heat than both 2D and 3D graphenes, particularly at low temperatures, where the 1D quantization of the phonon band structure is seen. Nanotubes have high thermal conductivity even in bulk materials; aligned bundles of SWNTs display thermal conductivity of $>$200 W/m K at room temperature. According to the measurements of $K(T)$ of samples with various average nanotube diameters, a linear $K(T)$ up to about 40 K may be the result of 1D quantization (Maarouf et al. 2000; Biercuk et al. 2002; Hone et al. 2000b; Kahn and Lu 1999; Teizer et al. 1999).

6.2.4 Optical Property

CNT has shown scope in several applications. Aligned carbon nanotube arrays in particular have displayed a variety of intriguing optical characteristics, including photonic crystal phenomena (Zhao et al. 2006; Kempa et al. 2003; Lidorikis and Ferrari 2009), directed wavelength-selective emission, polarization-dependent (Wang et al. 2004a; Shoji et al. 2008) reflection, emission (Slepyan et al. 2006; Kempa et al. 2007; Wang et al. 2009), and increased absorptivity (Yang et al. 2008; Mizuno et al. 2008).

The atomic structure of each CNT determines the optical characteristics of CNT arrays before their collective configuration. The optical characteristics of MWCNTs and SWCNTs should be taken into account separately for each CNT. The detailed atomic structure (chirality) of SWCNTs, particularly those with diameters smaller than 1 nm, exhibits a very high dependence on optical properties (Lin 1994; Bachilo et al. 2002; Guo et al. 2004a). In experiments, it is still challenging to achieve chirality-controlled CNT growth or chirality separation. As a result, SWCNT arrays often have a wide range of chirality with random distribution, which makes it more difficult to create optical characteristics and functionalities (Liu et al. 2002).

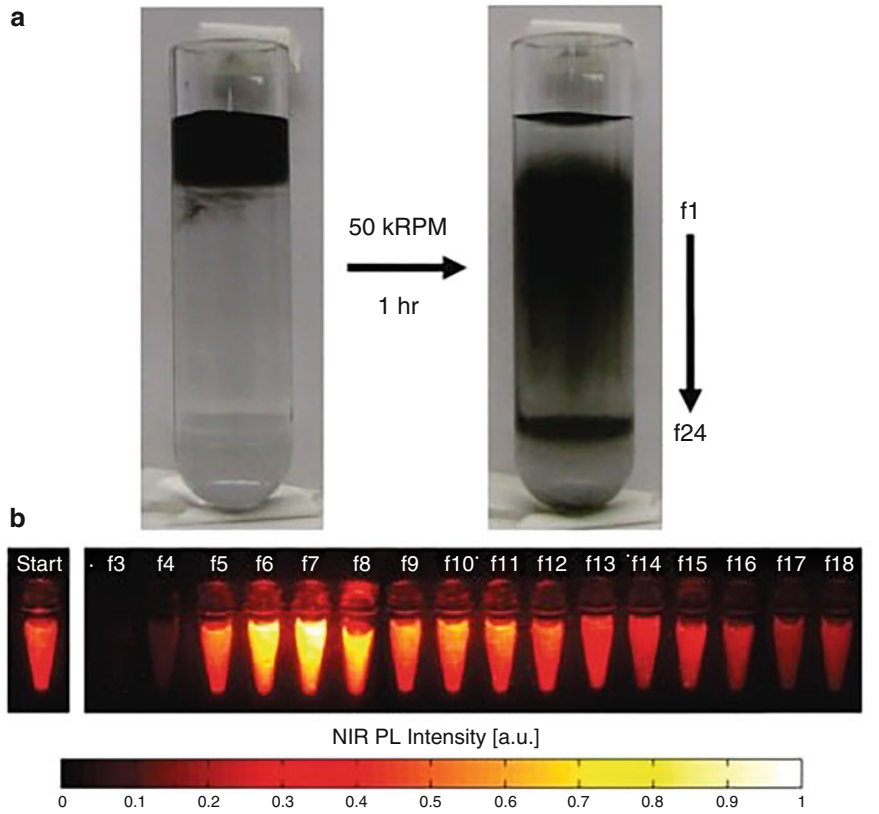

Fig. 6.1 The centrifugation of sodium-cholate-suspended single-walled carbon nanotubes (SWNTs) through a density gradient containing 1% sodium cholate, with discontinuous steps of 5%/10%/15%/20%/60% iodixanol at 50,000 rpm for 1 h, yielded a continuous distribution of SWNTs as well as a band formed at the 60% iodixanol boundary, as is clear from (**a**) photographs taken before and after DGC. Following the aliquoting of 100 μL fractions (f #), as shown in (**a**), and normalization to the same optical density, photoluminescence under 808 nm excitation (**b**) showed varying quantum yields relative to the starting material ("start"), increasing from f3 to f6–7 and decreasing monotonically thereafter (Lin 2000)

MWCNTs, in contrast, exhibit more consistent and uniform optical characteristics because of their bigger size (Lin 2000) (Fig. 6.1).

6.2.5 Electrical

Improved electrochemical properties can be obtained from CNTs loaded with metals like Si (Ganesh 2013), Sn, and Pd, along with transition metal oxides (Li et al. 2017) and sulfides (Poudel and Li 2018). It was demonstrated that irregularities, such as structural flaws produced during synthesis procedures, or physical flaws, such as

Table 6.1 Difference between SWCNT and MWCNT (Singh et al. 2012; Saifuddin et al. 2013; He et al. 2013)

SWCNT	MWCNT
• Single layer of graphene. • Not as much accumulation in the body. • Catalyst is essential for the synthesis. • Characterization and evaluation are easy. • It is more flexible and can be twisted more effortlessly. • Form bundled aggregates that are not completely distributed. • Chance of defect is higher during functionalization. • Resistivity usually in the range of 10^{-4} to 10^{-3} Ω m. • Bulk synthesis is challenging because it needs the careful management of growth and ambient conditions. • Purity is low; samples created using the chemical vapor deposition (CVD) process typically contain between 30 and 50 wt.% of SWCNTs. However, employing the arc discharge synthesis process has been shown to produce high purity of up to 80%.	• Multiple layers of graphene. • Progressively accumulates in the body. • Synthesis without a catalyst is possible. • Difficult due to its complex structure. • It cannot be easily twisted. • Homogeneously dispersed with no apparent bundled formation. • A chance of defect is less, especially when synthesized by the arc-discharged method. • Resistivity usually in the range of 1.8×10^{-5} to 6.1×10^{-5} Ω m. • Bulk synthesis is easy. • Purity is high. Typical MWCNT content in as-prepared samples by the CVD method is about 35–90 wt%.

those brought on by extremely high mechanical pressures, could change the way electrons move through CNTs. On the other hand, it has been found that semiconductor nanotubes are the most sensitive. The electrical properties of CNTs are significantly impacted by the presence of doping substances. Dopants can interact physically with the CNT electrical structure or chemically with the CNT framework (Janas et al. 2017). Many inexpensive synthetic approaches, such as laser ablation, arc discharge, solvothermal processing, etc., for CNT lately have made bulk production easy and cost-effective. CNTs have exceptional electrical properties, with a carrying capacity 1000 times greater than that of copper cables, as shown by theoretical and experimental data. CNTs are therefore probably going to have a big impact as additives in enhancing the electrical properties of composite materials (Nakano et al. 2003; Liu and Gao 2005). The difference between SWCNT and MWCNT is given in Table 6.1.

6.3 Characterization

6.3.1 Carbon Nanotubes: Structures, Types, and Preparation

Carbon nanotubes (CNTs) are tubular structures made of all the carbon atoms organized in a series of condensed benzene rings. This novel synthetic nanomaterial belongs to the family of fullerenes, which also includes graphite and diamond, which

are respectively sp2 (planar) and sp3 (cubic) forms of naturally occurring carbon (Hirlekar et al. 2009; Liu et al. 2007a; Pang et al. 1993). The third allotropic type of carbon is fullerene. Based on the number of layers, the models of CNTs are separated into two categories: single-walled carbon nanotubes (SWCNTs) and multiwalled carbon nanotubes (MWCNTs).

SWCNTs typically appear as hexagonal, close-packed bundles and are made up of a single graphene cylinder with a diameter anywhere from 0.4 to 2 nm (Fig. 6.2). MWCNTs are built up of two to three coaxial cylinders that each have a hollow core and are covered with a single graphene sheet. MWCNTs have an outside diameter that ranges from 2 to 100 nm, an inner diameter that is between 1 and 3 nm, and a length that spans from 0.2 to several meters (Singh et al. 2012; Bekyarova et al. 2005). The tips and the sidewalls of CNTs are two distinct zones. Rolling the graphene sheet into a tube results in a variety of tubule shapes, which play a significant role in regulating these peculiar features. Depending on its direction, the molecule can roll in one of three different ways: chiral, zigzag, and armchair.

The arc-discharge approach, which involves the arc vaporization of two carbon rods; the laser ablation method, which uses graphite; and chemical vapor deposition are indeed the three primary methods that are frequently used to produce SWCNTs and MWCNTs (using hydrocarbon sources: carbon monoxide (CO), methane,

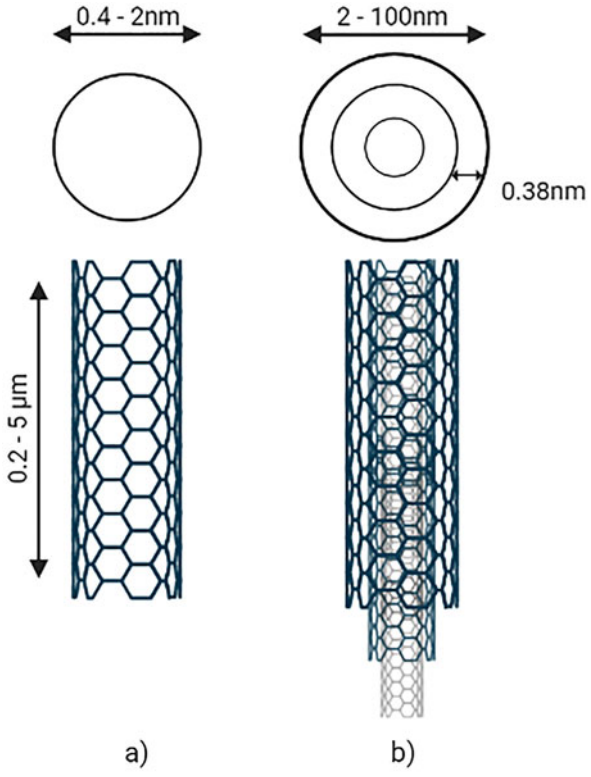

Fig. 6.2 (**a**) Conceptual diagram of single-walled carbon nanotubes (SWCNTs) and (**b**) multiwalled carbon nanotubes (MWCNTs) (He et al. 2013)

ethylene, acetylene). Amorphous carbon, fullerenes, and transition metals supplied as catalysts during the synthesis are examples of defects or impurities that are removed from CNTs after manufacture using acid refluxing, surfactant-aided sonication or the air oxidation technique (Singh et al. 2012; Usui et al. 2012; Digge et al. 2012).

6.3.2 Carbon Nanotube Structure

Graphite sheets are curled into tubes to form carbon nanotubes (Thostenson et al. 2001). Due to their large length-to-diameter ratio, nanotubes are regarded as having almost one-dimensional structures. Single-walled nanotubes (SWNTs) and multiwalled nanotubes are the most significant structures (MWNTs). An SWNT is seen as a cylinder with a single graphene sheet wrapped around it. Concentric SWNT clusters resemble multiwalled nanotubes (MWNTs). These structures are considerably different from SWNTs in terms of their length and diameter, and they also have quite different characteristics. A single vector C describes all properties of single-walled nanotubes except for their length (called a chiral vector). One of the two selected atoms in a planar graphene sheet serves as the origin. Different models that describe multiwalled carbon nanotubes are in good accord with experiments, particularly with the images from electron microscopy. Coaxially curved, coaxially polygonal, or scrolled graphene sheets can be used to make CNTs (Amelinckx et al. 1999). Although the coaxial cylindrical model for CNTs is largely accepted, polygonized tubes have also been found. These are often limited to large tube sizes, allowing three-dimensionally correlated regions; this allows for the observation of a low-angle tilt and well-aligned borders (Ajayan and Ebbesen 1997).

6.3.3 Morphological and Structural Characterizations

Similarly to CNTs, fullerenes are closed spheres made of pentagons and hexagons that are carbon-based compounds. The arrangement of these pentagons and hexagons determines their curvatures. A reversible diatomic exchange results in Stone-Wales transformation in carbon nanotubes. Two pentagons and two heptagons in pairs make up the final construction. The heptagon, a novel CNT defect that enables concave regions within the nanotube, is brought about by this change. Thus, different equilibrium shapes can be created and not just straight tubes with hemispherical crowns (Chen et al. 1999). CNTs have special mechanical and electrical features. Nevertheless, CNTs need to undergo chemical processing to be purified and to be given the required functionalization to acquire these qualities. Common treatments include oxidative techniques with nitric acids. These purification methods involve removing the caps from the ends of the CNTs, which reveal flaws such as carboxylic acid groups on the surface (Hu et al. 2001). The locations of these flaws on the walls and at the ends affect the nanotubes' characteristics (Mawhinney et al. 2000). For the study of the characteristics of nanotubes, a determination of the

concentration of these flaws would be beneficial. There are several ways to measure the concentration of carboxylic acid groups produced by purifying processes.

6.3.4 Photoluminescence Spectroscopy

Both metallic and semiconducting types of SWNTs are possible. The semiconducting tubes' gap energy is inversely proportional to the tube's diameter and is correlated with chirality (Ouyang et al. 2001; Lauret et al. 2004). It is to be assumed that the recombination of electron-hole pairs near the bandgap will result in photoluminescence. The SWNTs are typically bundled together, as was observed. Nanotubes in a bundle engage in Van der Waals force interactions with one another. These bundles of nanotubes contain a few metallic nanotubes that resemble nonradiative channels. Inside these channels, the semiconducting tubes in these bundles relax their luminosity. Frequently, no photoluminescence signal is recorded because of this interaction between semiconducting and metallic nanotubes. The bundles must be divided into individual tubes to view the photoluminescence phenomenon. This separation might be accomplished using some procedures. The ultrasonication of nanotubes with surfactants in aqueous suspensions, such as SDS (sodium dodecyl sulfate), seems to be one of the most well-liked methods (Lauret et al. 2004; Lefebvre et al. 2004; Weisman et al. 2004; O'Connell et al. 2003; Lebedkin et al. 2003). Different CNT samples could be used for this procedure. Utilizing individual nanotubes grown in zeolite channels, photoluminescence has also been demonstrated (Guo et al. 2004b). The photoluminescence method could provide access to nature (whether semiconducting or not), geometries, and diameters. Additionally, it appears that the luminescence spectra are particularly sensitive to both the purity of the materials and the existence of chemical flaws (Lauret et al. 2004).

6.3.5 X-Ray Photoelectron Spectroscopy (XPS)

The XPS method can provide details about the chemical composition of carbon nanotubes. However, the most frequently cited information focuses on how the structure of CNT walls has changed as a result of chemical interactions with organic molecules or gas adsorption. XPS research on nitrogen incorporated into carbon nanotubes was carried out to understand the chemical changes formed due to the incorporation of nitrogen. There has been significant research on N1s and C1s peaks. C1s peak shows both a shift and an asymmetric widening at higher binding energies when compared to nonnitrogenated samples. Because of the polar nature of the carbon-nitrogen bond (Hammer et al. 2000), this peak's tip shift serves as proof that nitrogen was incorporated into the nanotube structure. On carbon nanofibers, XPS research was also carried out (Pham-Huu et al. 2002), and the C1s peak was compared to one discovered on a spotless highly ordered pyrolytic graphite (HOPG) (0 0 0 1) surface. The relative concordance between the highest binding

energy and the surface plasmon peak at 291 eV indicates that the carbon nanofibers are graphitic. However, flaws and C H terminating surfaces are blamed for a broadening of the peak. There is a little widening at about 286.5 eV that can be attributed to surface oxygen groups with single bonds. The description of surface oxygen groups with many carbon-oxygen bonds was provided by a contribution at about 289.5 eV, though. As a result, it can be said that the nanofiber material is more similar to carbon oxide than a specific type of graphite (Pham-Huu et al. 2002).

6.3.6 X-Ray Diffraction

Using this nondestructive characterization method, some information on impurities, structural strain, and interlayer spacing is obtained. However, carbon nanotubes can be orientated in a wide variety of ways in contrast to the X-ray incident beam. Along with varying diameters, MWNTs also exhibit a range in layer counts and chirality distribution. This leads to the statistical characterization of carbon nanotubes. Due to CNTs inherent properties, the principal X-ray diffraction patterns are almost similar with those of graphite. (Figure 6.3): As CNT and graphite show similar results i.e., (1) The Bragg rule can be used to calculate the interlayer spacing from the location of a peak that resembles graphite (0 0 2 l).; (2) The individual graphene sheet's honeycomb lattice results in a family of (h k 0) peaks. As a result, the X-ray diffraction profile (Zhu et al. 2003) can be utilized to assess sample purity but is unsuitable for differentiating microstructural characteristics between CNTs and the graphite structure (catalyst, functional groups). As calculated in turbostratic graphite using the (0 0 2 l) peak location, the interlayer spacing is typically seen to be larger than in HOPG and near that value (Lambin et al. 2002; Saito et al. 1993). When compared to graphite, the peak position for SWNTs moved from 26.5° to 26° in 2θ. Additionally, the (0 0 2 l) peaks' line form is weaker and slightly widened in the low diffraction angle area as compared to graphite. The asymmetry is brought on by the presence of distinct crystalline species. At least two of the common and difficult-to-distinguish forms are the coiled graphitic plane, which is made up of a carbon nanotube, and pure graphite particles, comprised of a stack of graphene sheets. On the contrary side, the shape of the (0 0 2 l) peaks is influenced by both inner diameter distribution (Lambin et al. 2002) and the reduction in interlayer spacing with increasing shell diameter (Kiang et al. 1998). The amplitude and width of the (0 0 2 l) peaks are related to the number of layers, variations in interlayer spacing, lattice distortions, and the alignment of the carbon nanotube with regard to the incoming X-ray beam (Reznik et al. 1995; Burian et al. 1999). This is primarily because of the nanotube's curvature: the (h k 0) peaks are asymmetric (Lambin et al. 2002), and the (h k l) reflections only appear in X-ray diffraction (Liu and Cowley 1994; Bernaerts et al. 1998a). These examples include leftover carbon particles and flat graphitic layers in polygonal tubes. It has been shown that no (0 0 2) peak may be recorded by X-ray diffraction with well-aligned straight nanotubes on the substrate surface when X-ray diffraction is utilized in particular investigations on the alignment of CNTs

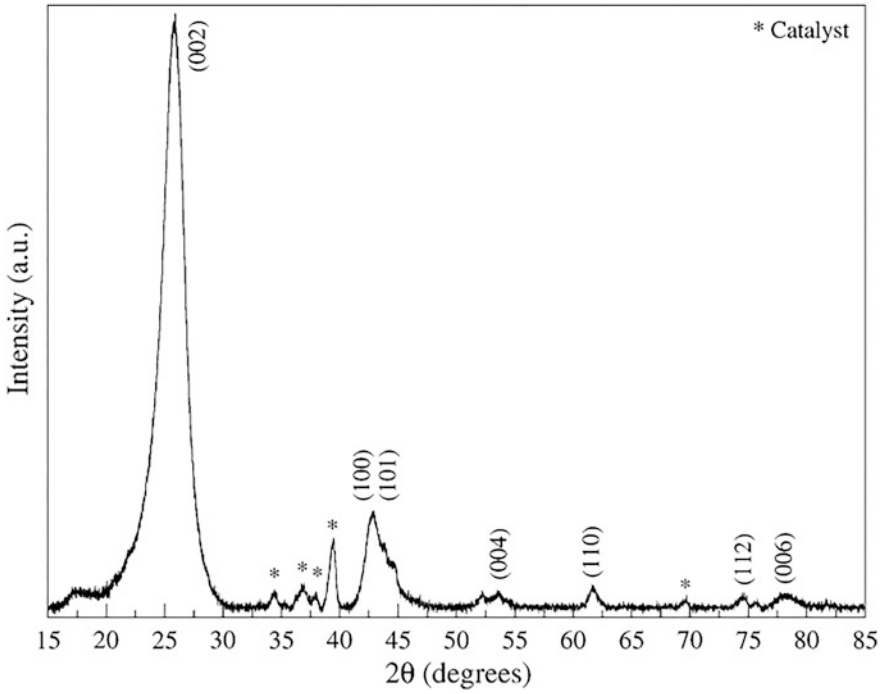

Fig. 6.3 XRD pattern of MWNTs synthesized by CVD at the CSIC laboratory (diameter of about 60 nm). The incident X-ray wavelength is $\lambda = 0.154056$ nm. The most significant Bragg peaks are noticed with Miller indices. The presence of catalysts (Co and Mo) in the CNT sample is shown by stars (Zhu et al. 2003)

(Cao et al. 2001). In the case of carbon nanotubes with a tube axis perpendicular to the substrate surface, the arriving X-ray beam is scattered within the sample and is not captured. As a result, the intensity of the (0 0 2) peak decreases monotonically as CNT alignment improves. The mean diameter of CNTs can be calculated using the Debye-Scherrer relation on the (0 0 2) peak. As this (0 0 2) peak incorporates contributions from residual graphite and nanotubes, the values are calculated through peak decomposition employing pseudo-Voigt profiles.

The consecutive SWNT diffraction amplitudes must be added in order to determine the MWNTs' diffraction patterns. The powder diffraction spectra of SWCNT bundles were computed using general X-ray diffraction formulas (Rols et al. 1999; Kuzmany et al. 2001). Numerous characteristics have been explored, including the impact of the mean tube diameter, the finite size of the bundles, and the diameter dispersivity of the tubes. Each of these factors has a big impact on the locations and sizes of the (1 0) peak. It was concluded, as a result, that these traits lead to a consistent underestimation of the tube diameter.

6.3.7 Transmission Electronic Microscopy

Transmission electronic microscopy (TEM) is an image analysis technique created to analyze multiwalled nanotubes (Gommes et al. 2003). Following numerical treatments, a model based on Lambert's law is used to fit the intensity throughout a nanotube section. Therefore, it is acceptable to calculate the outer and inner radii, as well as the linear electron absorption coefficient. When MWNTs were previously studied both before and after annealing, the electron absorption coefficient increased noticeably. It was concluded that this rise might be explained by a better-organized arrangement of the wall material. High-resolution TEM images were used in the study (Kiang et al. 1998) of the intershell spacing of MWNTs. The intershell gap is found to fluctuate with nanotube diameter and ranges from 0.34 to 0.39 nm (Fig. 6.4a–c). The graphite interplanar distance, which is 0.336 nm, is a little bit bigger than these values, however (Charlier et al. 1999). The curvature of the graphene sheets, which is altered by the tube radius, is likely to blame for this rise in intershell space. The size effect is stronger in the tiny diameter due to this curvature's increase in repelling force (below 10 nm). These authors also noted that altering the intershell gap will alter the physical and chemical properties. Increasing reactivities or creating practical features for storage media can both benefit from this. Interlayer interactions in double-wall nanotubes have been studied theoretically (Tanaka et al. 1997). The results show that a larger tube's diameter results in a weaker interlayer connection. It is anticipated that the energy gap between the two adjacent occupied and/or vacant orbitals would narrow. The nature of interlayer interaction does not change, though. A modest Van der Waals force holds the graphene layer planes together in the graphite. The arrangement of the tubes in MWNTs was Similar to the graphene layers seen in turbostratic graphite. Furthermore, there is no correlation between the many honeycomb sheets of varying widths that make up the MWNTs. As has already been seen with intercalation chemicals in graphites, dopant atoms or molecules could be inserted between neighboring nanotubes in MWNTs (Dresselhaus and Endo 2001). The intershell gap also increases as a result of this. Whenever the nanotube is parallel to this one, two or more graphitic layers are bridged by the incident electron beam (Qin 1998; Qin et al. 1997a, b) (Fig. 6.5b). When the tube is helical, these layers are out of alignment. The angle of this misalignment is therefore twice as large as a helical angle. The two sets of the resulting electron diffraction pattern are then separated. It has been shown that the true helicity of CNTs can be inferred from electron diffraction patterns by neglecting the nanotube's curvature and using half of the misalignment angle as the actual helical angle as a first approximation.

As is commonly seen, nanotubes occasionally appear independent but are typically bundled together by van der Waals forces. A bundle of nanotubes is arranged in a close-packed hexagonal pattern (Kuhlmann et al. 1998). It can be said that this structure is a two-dimensional hexagonal lattice (Fig. 6.5a). TEM in conjunction with electron diffraction can be used to determine the architectures of CNTs within the bundles. To measure the helicity of SWNTs within the bundles, many works

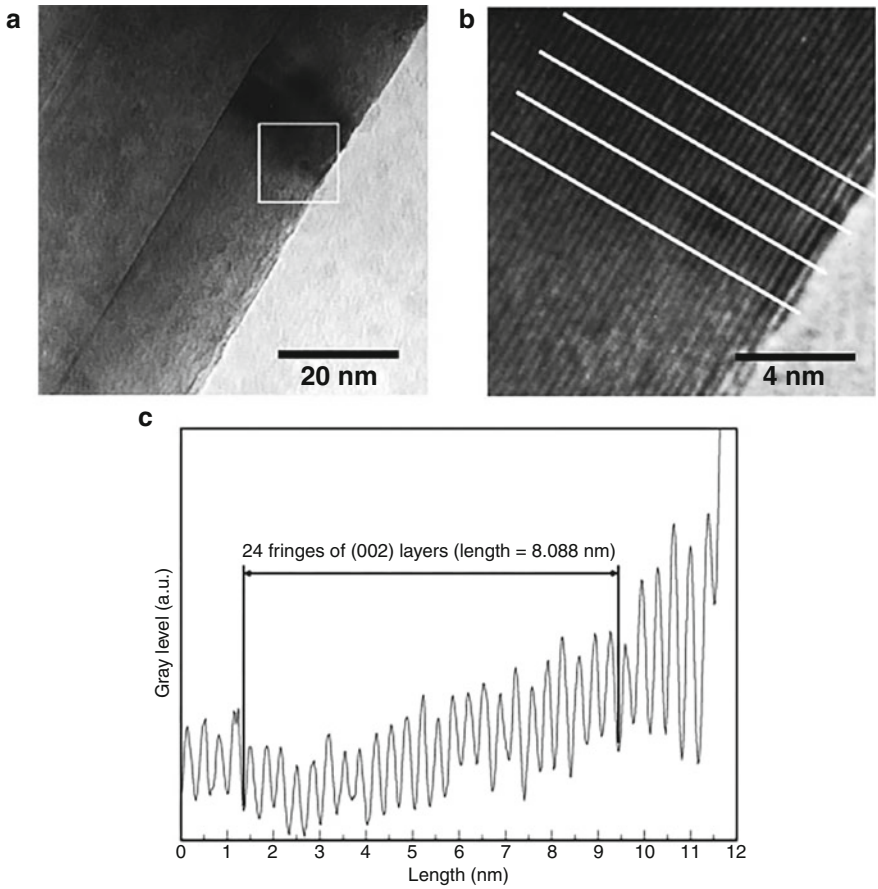

Fig. 6.4 (**a**) TEM image of a multiwalled nanotube synthesized by the CSIC laboratory. These MWNTs were produced by CVD, followed by several oxidation processes. The contrast of the walls is visible. (**b**) Enlargement of the walls of the nanotube. White lines are used in the determination of the intershell spacing. (**c**) Mean profile of the intensity levels of the walls showing the fringes of the (0 0 2) layers used in the determination of the intershell spacing. Here, the value of the intershell spacing is 0.337 ± 0.023 nm and is really close to the graphite one (Kiang et al. 1998)

have been done (Qin et al. 1997b; He et al. 1998; Cowley et al. 1997; Bernaerts et al. 1998b; Cowley and Sundell 1997).

6.3.8 Infrared Spectroscopy (FTIR)

FTIR is widely used to evaluate functionalization, which could also be categorized as a fault. The level of functionalization will modify the wettability of the nanotubes in various surfactants, which might also modify their toxicity. A trustworthy model for the dielectric function of nanotubes was developed by using the intrinsic

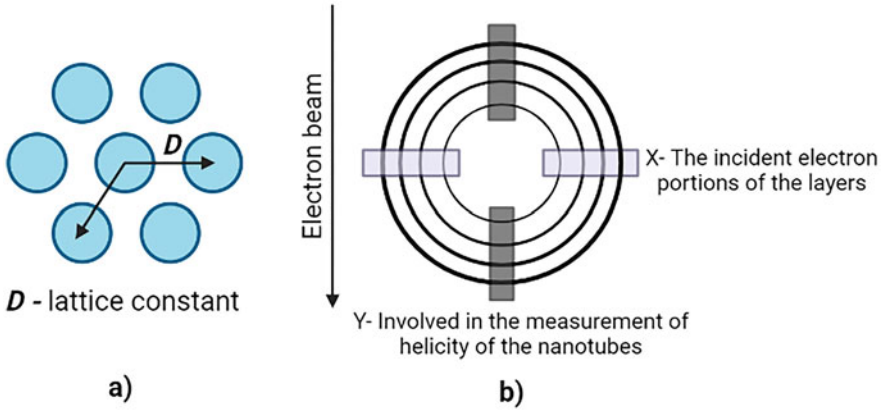

Fig. 6.5 (**a**) Two-dimensional hexagonal lattice of SWNTs within a bundle. *D* is given by the diameter of the nanotube and the intertube spacing. (**b**) Cross-section of a multiwalled nanotube. Scheme of the conditions of observation: the nanotube axis is perpendicular with respect to *X*. The portions of the layers in *Y* are involved in the measurement of the helicity of the nanotubes. The misalignment of these layers leads to the existence of a helical angle (Kuhlmann et al. 1998)

polarization-dependent properties of graphite and considering the tube in two separate situations: a cylinder and a hollow cylinder (Garcia-Vidal et al. 1997). The optical properties of graphite have been well documented and are classified as birefringent. The macroscopic optical properties of MWCNTs will therefore be constrained by tube orientation with regard to the direction of beam propagation, namely, tubes aligned with the tube axis perpendicular to or parallel to the electric field of incoming radiation. SWNTs that depend on symmetry are chiral, zigzag, and armchair and have seven to nine infrared active modes (Kuhlmann et al. 1998). The A2u and E1u modes are the major active modes for carbon nanotubes in infrared spectroscopy (Kuzmany et al. 1998). These phonon modes are seen in MWNTs at around 868 and 1575 cm^{-1}, respectively (Kastner et al. 1994; Eklund et al. 1995); nevertheless, it was discovered that these modes (at approximately 850 and 1590 cm^{-1}) appear in all CNTs symmetrically regardless of the diameters. These findings explain two structures with dimensions between 874 ± 2 and 1598 ± 3 in samples that primarily included SWNTs. The frequencies, however, depart by 5 and 8 cm^{-1} regions, respectively, from the graphite frequencies to higher values. To identify contaminants left over from production or compounds capped on the nanotube surface, infrared spectroscopy is frequently utilized in the characterization of CNTs. Numerous studies have been conducted on CNTs and organic molecules. Infrared spectroscopy shows all the structural changes made to CNTs as well as the types of compounds that have been added. Chemical modifications utilizing amino compounds are used to describe the reaction products of MWNTs (Saito et al. 2002). The characterization of molecules connected to CNTs (He et al. 2004; Aizawa and Shaffer 2003) and the catalytic characteristics of CNTs (Singh et al. 2012; Mbuyise et al. 2017) can be divided into two groups. Multiwalled carbon nanotubes were

found to have catalytic properties in the oxidative dehydrogenation of ethylbenzene (ODE), according to a study published by Pereira et al. (2004). They observed that CNTs performed better than samples of activated carbon and graphite because of their inherent structure, which makes them more resistant to oxidation. The MWNTs that have been oxidized before the catalytic studies have maximum catalytic activity. The results of the investigations indicated that the crucial factor is the number of oxygenated surface groups. Alternatively, (Wang et al. 2004b) the potential applications of CNTs in the catalytic oxidation of NOx. FT-IR was used to track the changes in the nitric oxide (NO), nitrite (NO_2), nitrate (NO_3), and carbon-containing CNT signals. These tests were run using CNTs that contained 1 weight percent Pd for each CNT. In this system, the hydrogenation of CNTs is accelerated by the palladium particles. The hydrogenated CNTs act as a reducing agent to supply carbon and hydrogen again for the reduction of NO.

6.3.9 Raman Spectroscopy

Raman spectroscopy is among the best techniques for identifying carbon nanotubes. Without actually prepping the sample, a rapid, nondestructive analysis is still possible. Raman spectroscopy is active in all allotropic forms of carbon, including fullerenes, carbon nanotubes, amorphous carbon, polycrystalline carbon, etc. (Arepalli et al. 2004). The locations, widths, and relative intensities of the bands vary with the carbon forms (Ferrari and Robertson 2000) (Fig. 6.6). The characteristics that stand out the most are (1) a low-frequency peak of the SWNT with a wavelength of 200 cm^{-1} (or many peaks for polydisperse samples when resonant conditions are satisfied), attributed to the A1g "breathing" mode of the tubes, whose frequency is mostly dependent on tube diameter (RBM: radial breathing mode); (2) a significant structure (1340 cm^{-1}) attributed to remaining disordered graphite, the so-called D line; (3) a high-frequency bunch (between 1500 and 1600 cm^{-1}) known as the G band, which is likewise distinctive of nanotubes and corresponds to a splitting of the E2g stretching mode of graphite (Mamedov et al. 2002). This technique produces bands by changing the polarizability of the molecules in the presence of light. Therefore, when these molecules get into touch with light, they could be screened by specific vibrations that they emit. Due to a distinctive pattern, single-walled and multiwalled CNT quality and distribution may be determined by Raman spectroscopy (Saito et al. 2002).

6.3.10 Thermogravimetric Analysis (TGA) and Purity

A variety of techniques, including Raman spectroscopy, imaging, thermogravimetric analysis (TGA), and X-ray microanalysis, can be used to assess the sample's general quality. Impurities include metal impurities, additional chemical species connected to the nanotube, and other forms of carbon (such as amorphous or graphitic carbons or other structured carbons like SWCNTs or fullerenes). TGA has been used for bulk

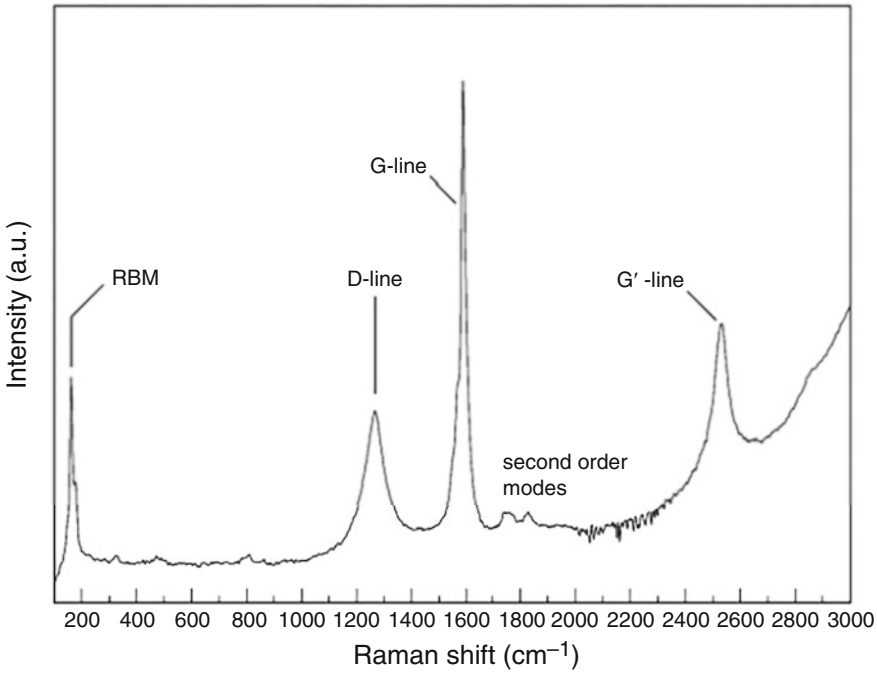

Fig. 6.6 Raman spectrum showing the most characteristic features of CNTs: radial breathing mode (RBM), D band, G band, and G′ band. Second-order modes are also observed. Spectrum obtained from an SWCNT sample (diameter of about 1.07 nm) mixed with KBr using $E_{max} = 1.16$ eV ($\lambda = 1064.5$ nm) excitation. This sample is produced by an electric arc-discharge method, followed by air oxidation at the CSIC laboratory (Ferrari and Robertson 2000)

samples to confirm batch-to-batch uniformity and the quality control of carbon nanotube populations if we are convinced that MWCNTs are presently based on sampling. TGA can be used to examine the thermal stability and purity of a material. The weight-loss curve measures important variables, such as start temperature, oxidation temperature, and residual mass. Commencement temperature is the temperature at which a substance begins to disintegrate. Oxidation temperature, which is referred to as the peak in the derivative of the weight loss as a function of temperature, is where the greatest weight loss takes place. Oxidation temperature is widely used to characterize a material's thermal stability. The mass that has remained after heating is the residual mass. The metal catalyst employed to create carbon nanotubes and its oxidation by-products is typically blamed for the residual bulk of carbon nanotubes in TGA. Based on the consistency and quality of the material, residual masses can range from almost 0% to 50%. According to studies, highly crystalline MWCNTs are more oxidation resistant than other types of carbon, such as diamond, soot, graphite, and C60 (Pang et al. 1993). The aromatic bonding of the MWCNT structure is directly responsible for its thermal stability, but other factors, such as the

number of walls of the sample, catalyst presence and composition, tube flaws, and the presence of other materials, can also have an impact (i.e., amorphous carbon, graphitic particles).

6.4 CNT Functionalization

The medicine is immobilized on the surface or within the functionalized carbon nanotubes in a functionalized carbon nanotube delivery system. Functionalization is done for a variety of reasons, including targeted delivery, increased stability, diagnosis of diseases, or other reasons. The resulting conjugate is then administered to the animal via traditional routes (oral, injectable), directly to the target region using a magnetic conjugate, to the target organ, and so on. After the cell absorbs the drug's CNT capsule, the drug is delivered when the contents of the nanotube leak into the cell (Singh et al. 2012; Usui et al. 2012; Zhang et al. 2010, 2011; Kateb et al. 2010; Liu et al. 2007a, b). Functionalized CNTs can transport important molecules across nuclear and cytoplasmic membranes without causing toxicity; as a result, drug CNT conjugates are both safer and more potent than the drug employed alone in conventional synthesis. Once the drug has reached the target cell, it can be distributed in one of two ways: either the drug internally absorbs the CNT carrier, or both the drug and the CNT carrier internalize the cell. The second internalization step is more efficient than the first because the intracellular environment breaks down the drug carrier conjugate after it enters the cells, releasing drug molecules in situ, or inside the cells. There is a potential that the drug may break down during this penetration on its own even though, in the noninternalization procedure, the extracellular environment aids in the degradation of drug carrier conjugates before the drug crosses the lipid membrane to enter the cells (Fig. 6.7).

6.4.1 Functionalized Carbon Nanotubes Used for Cancer Therapy

The functionalized carbon nanomaterials have proven to be very effectively taken up by cancer cells and tissues to enable cancer treatments (Yang et al. 2010a; Liu et al. 2007b).

Methotrexate and a fluorescein probe are both present in f-CNT (Pastorin et al. 2006). A popular and effective anticancer drug, methotrexate, is also used to treat autoimmune illnesses (Wong and Esdaile 2005). However, methotrexate has severe side effects and limited bioavailability (Pignatello et al. 2004). Therefore, a tailored administration and enhanced bioavailability are both highly preferred. If there is a targeting unit present, f-CNT may be able to increase bioavailability and target only cancer cells. According to the results of a cell culture study, methotrexate conjugated with nanotubes is just as effective as methotrexate alone. The absence of increased efficacy between the f-CNT and nonconjugated medicine may be attributed to the stable amide bond between methotrexate and the nanotubes. In fact, it is possible that the drug is released from the tubes into the cytoplasm too slowly for it to effectively

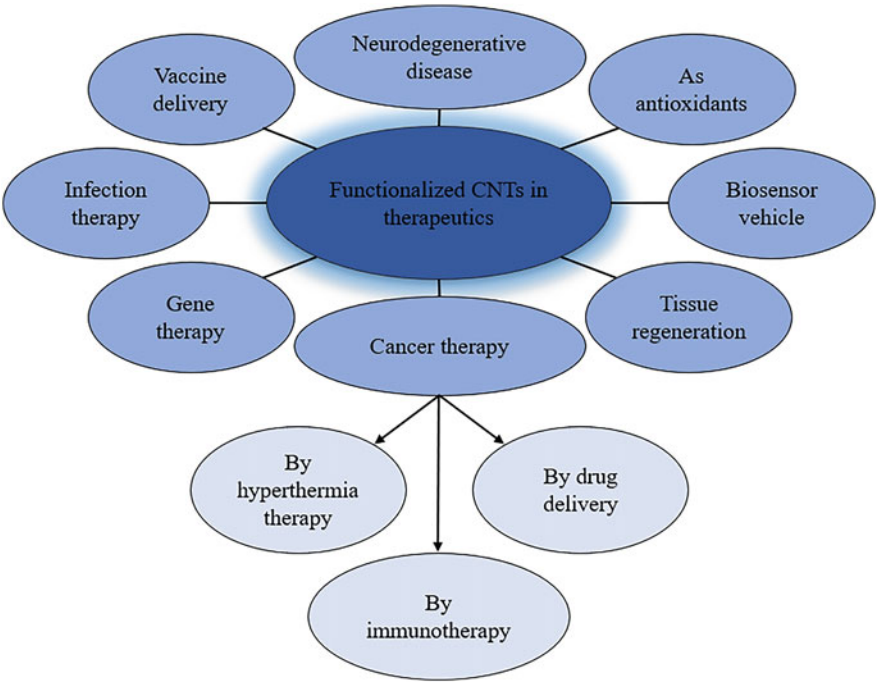

Fig. 6.7 Schematic representation of carbon nanotube application in therapeutics and biomedical diagnosis and analysis

reach its receptor. Single-walled CNT was functionalized with a substituted carborane cage for boron neutron capture treatment. The biodistribution study on different tissues revealed that intravenously injected water-soluble carborane nanotubes were more abundant in tumor cells than in other organs.

6.4.1.1 By Drug Delivery

To treat tumors, CNTs can act as medication transporters (Zhang et al. 2011; Liao et al. 2011; Liu et al. 2009a; Digge et al. 2012; Yang et al. 2007; Al-Jamal et al. 2011; Madani et al. 2011; Lay et al. 2011; Elhissi et al. 2012). Drug resistance and poor cellular penetration are additional factors that restrict the effectiveness of anticancer medications when taken alone, in addition to their systemic toxicity and small therapeutic window. Since CNTs may readily pass through the cytoplasmic and nuclear membranes, the anticancer medication delivered by this vehicle will be released in situ with intact concentration. As a result, it will have a greater impact on the tumor cell than standard therapy alone. To improve the cellular uptake of already strong medications, effective delivery mechanisms have to be developed. Because CNTs have a large surface area and numerous attachment sites for medicines, they have a high aspect ratio compared to other delivery vectors (Chen et al. 2011). A combination made of CNT and antibodies against antigens overexpressed on the

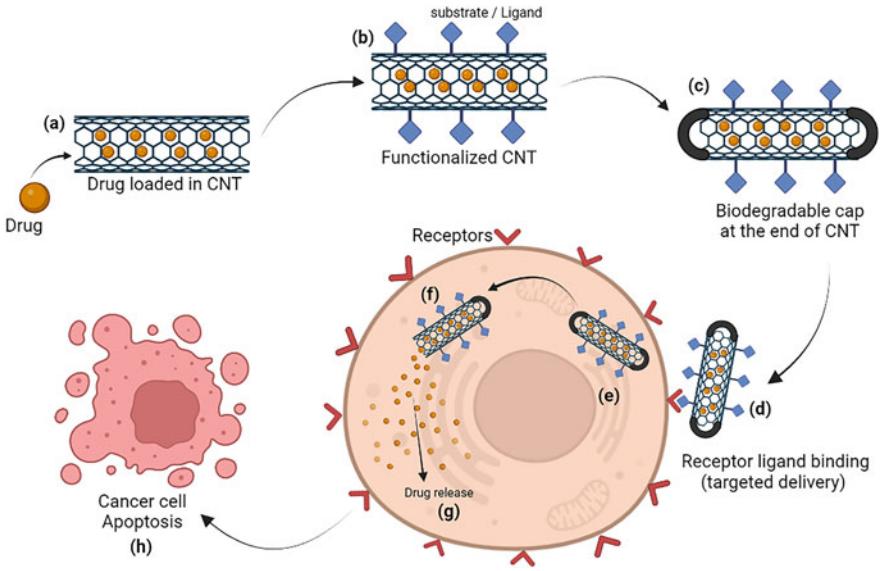

Fig. 6.8 Schematic illustration of the drug delivery process. (**a**) CNT loaded with the drug to be delivered. (**b**) substrate/ligand attached to the CNT surface as functionalization along with drug-loaded inside (**c**) the open end of the CNT is capped with a biodegradable polymer, (**d**) drug-CNT carrier is introduced in the body and reaches the target cells due to receptor on cells and ligands on CNT surface, (**e**) cell internalizes CNT by cell receptors (V) via endocytosis pathway for example, (**f**) cap is removed or biodegrades inside the cell, then drugs are released, (**g**) drug release from CNT in the cell. (**h**) Cancer cell death

surface of malignant cells can bind chemotherapy drugs (Abu Lila et al. 2021). Targeting delivery is made possible by the attraction of antigen-antibody, which allows the tumor cell to receive the CNTs only before the anticancer medicine is released from the CNTs (Madani et al. 2011; Lay et al. 2011; Elhissi et al. 2012). The multidrug resistance brought on by the increased efflux of anticancer medications by the overexpressed p-glycoprotein, which results in poor anticancer efficacy, is a significant barrier to successful anticancer therapy (Elhissi et al. 2012). SWCNT paclitaxel conjugate has been administered in vivo in a mouse breast cancer model, and it is more effective at reducing tumor development and is less harmful to healthy organs (Zhang et al. 2011; Madani et al. 2011). Longer blood circulation, greater tumor absorption, and a slower rate of drug release from SWCNTs could be the causes of increased therapeutic efficacy and fewer negative effects (Digge et al. 2012) (Fig. 6.8).

6.4.1.2 By Antitumor Immunotherapy

CNTs can be successfully used as carriers in antitumor immunotherapy (Singh et al. 2012; Digge et al. 2012; Yang et al. 2007; Al-Jamal et al. 2011; Madani et al. 2011; Lay et al. 2011; Elhissi et al. 2012; Chen et al. 2011; Li et al. 2010; Pantarotto et al.

2004a). In order to combat the cancerous tumor cells, this treatment entails activating the patient's immune system. This reaction can be triggered by the administration of a therapeutic antibody or a cancer vaccine as medicine. The use of CNTs in vaccine delivery devices has been authorized (Pantarotto et al. 2004a). The combination of CNTs and tumor immunogens can act in vitro as naturally occurring antigen-presenting cells (such as mature dendritic cells) by delivering tumor antigens to immune effector T cells because of the high avidity of the antigen on the surface and the negative charge. CNTs' effects on the complement system and their adjuvant properties may help advance anticancer immunotherapy; however, the exact mechanism is uncertain (Yang et al. 2007; Pantarotto et al. 2004a).

6.4.1.3 By Local Antitumor Hyperthermia Therapy

Exceptional near-infrared absorption is exhibited by SWCNTs (NIR; 700–1100 nm). These nanomaterials are thought to be excellent candidates for hyperthermia therapy because they generate a significant amount of heat when activated by NIR light (Madani et al. 2011; Lay et al. 2011; Elhissi et al. 2012). The photothermal effect can lead to the local thermal destruction of tumor cells by scorching SWCNTs trapped in tumor cells, such as in pancreatic cancer.

6.4.2 Carbon Nanotubes for Infection Therapy

CNTs have been tested to find solutions to issues like infectious agent resistance to various antiviral and antibacterial medications or due to a particular vaccine's ineffectiveness in the body. It has been shown that functionalized CNTs can serve as carriers for antibacterial substances such as antifungal amphotericin B (Rosen and Elman 2009; Rosen et al. 2011). Amphotericin B can bind covalently to CNTs, which can then carry it into mammalian cells. Compared to free medication, this combination displays a 40% reduction in antifungal toxicity (Rosen et al. 2011). Functionalized CNTs can also be used as delivery systems for vaccines (Liao et al. 2011; Rosen et al. 2011). A bacterial or viral antigen can be linked to CNTs to maintain antigen conformation, which leads to the proper kind of particular antibody response (Digge et al. 2012). Fixing B- and T-cell peptide epitopes to functionalized CNTs can create a multivalent system that can elicit a potent immunological response, making it a promising option for vaccine administration (Usui et al. 2012; Yang et al. 2007). Since microorganisms, like *E. coli*, may be adsorbed onto the surfaces of CNTs, CNTs themselves may have antibacterial properties. The antibacterial action was thought to be caused by the intracellular antioxidant glutathione being oxidized by carbon nanotubes, which raised oxidative stress on the bacterial cells and ultimately led to cell death (Digge et al. 2012). Antibiotics may be used to functionalize carbon nanotubes. An antimycotic drug called amphotericin B is used to treat exceptionally hardy fungi strains (Zotchev 2003). Due to its severe toxicity to mammalian cells and low solubility in water, as well as its propensity to clump and to create gaps in cell membranes, it is only marginally useful. It is believed that the toxicity and antimycotic effectiveness of amphotericin B may be

modified by conjugating it into carbon nanotubes (Wu et al. 2005). Based on the cytotoxicity of f-CNT against mammalian cells, it is discovered that CNT-conjugated amphotericin B, employed at varying concentrations (up to 40 g/mL, equal to a concentration of amphotericin B attached to the tubes of 10 g/mL), was not hazardous, although amphotericin B is very toxic at 10 g/mL concentration, reaching 40% cell mortality. The ability of f-CNT containing both amphotericin B and fluorescein to penetrate cells was then examined. The identification of f-CNT in the cells is made possible by the latter component. It was easy to see the fluorescence inside the cell compartments. The toxicity mostly against yeasts as well as fungi was also increased at the same time.

6.4.3 Carbon Nanotubes for Gene Therapy by DNA Delivery

A new sector is developing around the use of carbon nanotubes for biomedical purposes (Erol et al. 2016). The primary factors attracting interest in the creation of photonic and electronic devices are CNTs' excellent electrical conductivity and mechanical stability (Mbuyise et al. 2017; Oseni et al. 2018). CNTs have indeed been designed through numerous groups as effective gene-delivery vehicles (Kiran and Gangadharappa 2019). The deoxyribonucleic acid (DNA)-SWCNT complex demonstrates improved biostability and enhances the self-delivery capability of DNA when compared to DNA employed alone because DNA probes are shielded from enzymatic cleavage and interference from nucleic acid binding proteins when linked to SWCNTs (Usui et al. 2012; Bekyarova et al. 2005; Li et al. 2008). Stable interactions between plasmid DNA and cationic CNTs have shown improved gene therapy potential in comparison to bare DNA. DNA-conjugated CNTs were discovered to release DNA before it was destroyed by the cell's defense mechanism, dramatically increasing transfection (Liu et al. 2007a; Liao et al. 2011; Li et al. 2013). Because the CNT-gene complex has preserved the ability to express proteins, it has been demonstrated that these designed structures can successfully transport the genes inside mammalian cells and retain them intact (Li et al. 2008). New SWCNT-DNA complexes that have been functionalized have been created (Pantarotto et al. 2004a) and have shown to have higher DNA expression than bare DNA. In the initial investigations examining the capacity of f-CNT to deliver genes, it was discovered that they also effectively complex (Lacerda et al. 2006) and translocate DNA inside cells (Pantarotto et al. 2004b; Singh et al. 2005) because they are cationic under physiological conditions. We have created supramolecular complexes, including the beta-galactosidase marker gene on plasmid DNA and f-CNT. This unique method of gene delivery can be viewed as promising because the expression of the marker gene utilizing f-CNT was five to ten times higher than that of the plasmid DNA given alone. For applications involving gene silencing, the potential of gene therapies based on carbon nanotubes has been further investigated (Kam et al. 2005; Zhang et al. 2006). To specifically target and eliminate cancer cells, complexes of single-walled carbon nanotubes with small interfering ribonucleic acid (siRNA) strands modified with a hydrocarbon tail were employed.

6.4.4 Carbon Nanotubes for Tissue Regeneration and Artificial Implants

Considering they are biocompatible, are resistant to biodegradation, and could be functionalized with proteins to enhance organ regeneration, carbon nanotubes may be the best tissue engineering candidate among a variety of substitute materials, including natural and synthetic polymers for tissue scaffolds. CNTs can be used as additions in this field to increase the mechanical strength of tissue scaffolding and conductivity by integrating them with the host's body (Usui et al. 2012; Zhang et al. 2010; Kateb et al. 2010; Bekyarova et al. 2005; Liao et al. 2011; MacDonald et al. 2005). A composite nanomaterial that acts as a scaffold for tissue regeneration has been successfully created by combining polymer or collagen (poly-L-lactide or poly-D,L-lactide-co-glycolide) with carboxylated SWCNTs (MacDonald et al. 2005). Other CNT tissue engineering applications, such as cell tracking and labeling, sensing cellular behavior, and enhancing tissue matrices, have also been the subject of a recent study (Singh et al. 2012; Usui et al. 2012; Zhang et al. 2010; Kateb et al. 2010; MacDonald et al. 2005). For instance, it has been observed that CNTs effectively enhance in vitro mouse bone tissue regeneration and neurogenic cell differentiation caused by embryonic stem cells (Singh et al. 2012; Zhang et al. 2010).

6.4.5 Carbon Nanotubes for Neurodegenerative Diseases and Alzheimer's Syndrome

CNTs have been applied in neurosciences as a promising biological material (Singh et al. 2012; Zhang et al. 2010; Liao et al. 2011; Yang et al. 2010b). Due to their small size and openness to external alterations, CNTs can penetrate the blood-brain barrier via a variety of targeting methods and serve as efficient delivery vehicles for the target brain. Many more functionalized SWCNTs or MWSCNTs have been employed as effective delivery vehicles for the treatment of brain tumors or neurodegenerative illnesses (Bekyarova et al. 2005; Liao et al. 2011; Digge et al. 2012). Overall, these research findings showed that CNT-therapeutic molecule conjugates had superior impacts on neuronal development to medicines taken on their own as an individual drug compared to treating with a combination of medicine.

6.4.6 Carbon Nanotubes as Antioxidants

CNTs, specifically carboxylated SWCNTs, are antioxidants by nature and may be used medicinally to prevent chronic diseases, slow the aging process, and preserve food (Daniels 1945; Galano 2008). SWCNTs' ability to scavenge free radicals was proven to be increased by the presence of carboxylic acid (-COOH) groups, and it was found that carboxylated SWCNTs are at least as good as, if not superior to, their

nonfunctionalized counterparts (Francisco-Marquez et al. 2010). To protect the skin from free radicals produced by the body or by ultraviolet (UV) light, their antioxidant activities have been used in sunscreen lotions and antiaging cosmetics (Singh et al. 2012; Digge et al. 2012). More research will be needed in the future to improve the useful effect of different CNT forms as free radical scavengers because free radicals are well known to be a very damaging species for biomedical and environmental applications (Galano 2008; Pham-Huy et al. 2008).

6.4.7 Carbon Nanotubes as Biosensor Vehicles for Diagnostic and Detection

A very intriguing application area for therapeutic monitoring and in vitro and in vivo diagnostics is the use of CNTs in biosensing nanotechnology. For better accuracy and easier manipulation than using biosensors alone, CNTs and glucose-oxidase biosensors were coupled for blood sugar control in diabetic patients (Usui et al. 2012; Digge et al. 2012; Wang 2005). For various treatment monitoring and diagnostics, further CNT-based dehydrogenase biosensors, peroxidase biosensors, and catalase biosensors have also been produced (Wang 2005; Zhu et al. 2011). Alkaline phosphatase (ALP) enzyme linked to CNTs had a greater test sensitivity for electrical DNA detection than ALP alone. In comparison to conventional fluorescence and hybridization experiments, the sensitivity of the SWCNT-DNA sensor assay was significantly higher, thanks to the integration of SWCNTs with single-strand DNAs (ssDNA). By utilizing particular antibody-antigen recognition, this CNT-biosensor-linked assay can be customized for antigen detection. As a result, it might offer a quick and easy method for molecular diagnostics in illnesses that have molecular markers, like DNA or protein (Liao et al. 2011; Wang 2005). It is strongly advised to use CNTs as biosensor vehicles to build sensitive approaches for diagnostics and analysis from the laboratory to the clinic due to their length scale and distinctive structure.

6.4.8 Carbon Nanotubes for Therapeutic and Diagnostic Applications

To produce CNT conjugates with pharmacological action, therapeutic agents can further modify any new functional group, including amines and carboxylates. Nanotubes with the capacity to carry one or more therapeutic moieties with optical or other (e.g., magnetic) probes for imaging and/or specific recognition signals for targeting may offer multimodal options in the treatment of cancer and other multifaceted diseases in which activity is only required at specific sites in the body. Normally, even after these synthetic goals are accomplished, there will still be a

number of technical issues to be resolved, mostly in the area of pharmaceutical development. The stability of the complexes under physiological conditions, the degree of in vivo aggregation, the right timing, and the place of drug release are a few of these concerns. Despite this, CNT is a valuable technological foundation for the development of candidates for simultaneous diagnostics, transportation, and medication delivery due to the large range of conceivable combinations (Bianco et al. 2005a, b). The possibility of developing CNT for biomedical applications emerged as a reality after several effective ways for their functionalization were made public (Tasis et al. 2006). The nanotubes have been rendered soluble and suitable for physiological conditions utilizing a variety of techniques. This is a major issue for its integration into environments with biological systems. The level of toxicity of all CNT materials must be taken into consideration while establishing their biocompatibility. The research so far suggests that the cytotoxic effects of CNTs are greatly reduced by functionalization, while their biocompatibility is increased (Sayes et al. 2006; Singh et al. 2006). The possibility of utilizing nanotubes for medication administration is increased by evidence to date that CNTs are safer the more functionalized they are, especially when compared to pristine, purified CNT.

6.4.9 Functionalized Carbon Nanotubes for Vaccine Delivery

Their immunostimulatory peptide-based constructions fall under a different category of carbon-nanotube-based therapeutic prospects. By combining functionalized nanotubes with B- and T-cell peptide epitopes, it is possible to create a multivalent system that can vigorously elicit an immune response (Pantarotto et al. 2003a, b). Peptides can be attached to tubes using chemo-selective techniques (Goodman et al. 2002; Muller et al. 1999). Using peptides having a cysteine residue at one end, functionalized carbon nanotubes with a maleimide group that easily combines with it are created. The thiol group of the cysteine with the maleimide forms a long-lasting covalent bond. This approach has the advantage of having the peptide, produced through solid phase synthesis, completely deprotected and defined before being joined to the nanotubes. By adding a lysine branch to the f-CNT, The antigenic and immunogenic qualities of these conjugates were evaluated. In contrast to the nonconjugated peptide, the antibody responses to f-CNT were particularly high. The ability of the produced antibodies to neutralize the virus was also demonstrated, highlighting the potential of carbon nanotubes as ingredients in the production of synthetic vaccines.

6.5 Toxicity

See Fig. 6.9.

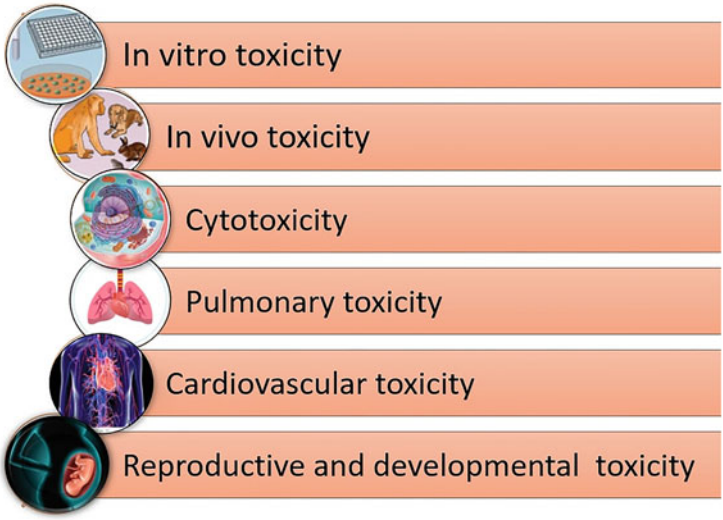

Fig. 6.9 Toxicity associated with carbon nanotube as a drug delivery system

6.5.1 In Vivo Toxicity of CNTs

The level of toxicity of a substance determines how much harm it can do to something with a metabolic function. The term "toxicity" can refer to the impact on an entire organism, such as an animal, bacterium, or plant, as well as the impact on an organism's cells or organs, such as the liver (hepatotoxicity). As a result, not all changes in organisms may be categorized as harmful reactions. When triggered by alien items, organisms will naturally react (Francis and Devasena 2018). When ingested, even flour powder can cause pulmonary alterations (Ren et al. 2010). Additionally, a variety of parameters, such as dosage, contaminants, pretreatment procedures, physical shape, surface chemistry, degree of aggregation, etc., appear to affect how hazardous CNTs are. Recent years have seen extensive investigation into CNT in vivo toxicology. In humans, cutaneous toxicity may result in an inflammatory response through skin contact. Mice exposed to unpurified CNTs typically develop localized alopecia, oxidative stress, glutathione depletion, an increase in dermal cell number, and thickened skin (Koyama et al. 2009; Murray et al. 2009). The number of metals, particularly iron, may have an impact on CNT toxicity. By interacting mostly with the skin, producing oxidative stress, and activating redox-sensitive transcription factors, metals can affect or trigger inflammation. However, the absence of skin hair loss in mice implanted with incredibly pure and uncontaminated tubes suggests that purification is an effective strategy for improving the biocompatibility of CNTs. The most likely site of CNT exposure is the lung. Inhalation is the most appropriate method for determining the toxicity of CNTs for a wide range of reasons. First, airborne CNTs are subjected to the physics of impaction, sedimentation, and diffusion, whereas implanted CNTs are not. Second,

inhaled CNTs pass the lung's distal regions. Third, compared to an instilled bolus dose in an aqueous medium, inhaled CNTs are much more diffused and less aggregated. Because CNTs and asbestos fibers both have large aspect ratios (length to width), there is fear that inhaling CNTs could result in similar lung diseases (Crouzier et al. 2010; Elgrabli et al. 2008; Tantra and Cumpson 2007). The pleural pathology brought on by asbestos fibers is distinct from the pathology caused by MWCNTs. MWCNTs generated mononuclear cell agglomeration and focal subpleural fibrosis (Ryman-Rasmussen et al. 2009), while asbestos induces diffuse pleural fibrosis and pleural inflammation (granulomas) (Choe et al. 1997; Kane 2006).

Occupational situations, which require special consideration from an exposure standpoint, may include high concentrations of CNTs. For handling CNTs in professional environments and research labs, there are not many resources available. Therefore, the study (Pauluhn 2010) is very valuable for establishing standards for occupational exposure in the workplace environment and determining a fair occupational exposure limit (OEL), which will aid the government in developing relevant regulations.

6.5.2 In Vitro Toxicity of CNTs

The impact of the potentially toxic effects of CNTs on cells is a crucial factor in determining and understanding CNT compatibility vs. toxicity (Cheng et al. 2009; Davoren et al. 2007; Gellein et al. 2009; Thurnherr et al. 2009; Tutak et al. 2009). Cellular uptake and the processing of CNTs via various pathways; effects on cell signaling; lipid bilayer disruptions; production of cytokines, chemokines, and reactive oxygen species (ROS); overt toxic reactivity; cell apoptosis; and no obvious toxicity are among the interactions with both cells and CNTs that are being studied (Hillegass et al. 2010). The most common approaches typically involve the in vitro culturing of primary cells or cell lines (tissue harvested) on plastic plates, with or without serum, with bolus dosing of CNTs and, subsequently, monitoring of cell activity. Various cellular types, including cancer cell lines and neuronal, phagocytic, and other cell types, have also been chosen for study. It was found that the toxicity of human lung cancer cell lines increased from evenly distributed CNTs to asbestos and then to agglomerated CNTs (Wick et al. 2007a). CNTs are more hazardous than metal oxide nanoparticles and do not demonstrate length-dependent cytotoxicity, even in the presence of metal catalyst impurities (Simon-Deckers et al. 2008a). The proportion of CNTs that are too long for cells to absorb in long and short samples is likely approximately the same, and CNTs that cannot be taken by cells have effects that are equivalent regardless of length, so the length made little to no difference.

Studies with functionalized CNTs demonstrated that purification could improve their biocompatibility and reduce their cellular toxicity (Liu et al. 2007c). Even though it is generally agreed that well-dispersed CNTs are less dangerous than agglomerated ones (especially when using a bio-dispersant), various in vitro studies have found different levels of apparent toxicity for CNTs. Due to the special

characteristics of CNTs, evaluations of their toxicity may also depend on the circumstances surrounding their modification and surface chemistry.

6.5.3 Cytotoxicity

An investigation of the cytotoxic potential of MWCNTs and titanium oxide nanoparticles was conducted (Simon-Deckers et al. 2008b). Investigations were also conducted into intracellular nanomaterial accumulation and cell survival. The findings of this study demonstrated that nanoparticles and nanotubes may both enter cells and disperse within the cytoplasm. Metal oxide nanoparticles exhibit reduced toxicity as compared to CNTs. The cytotoxicity of CNTs is unaffected by CNT length or the presence of metallic contaminants (Simon-Deckers et al. 2008b). The cellular membrane of rat macrophages (NR8383) was discovered to be penetrated by CNTs in a recent study, which altered the macrophages' physiology and cellular function (Pulskamp et al. 2007). Commercial CNTs were found to lower the potential of the mitochondrial membrane and increase intracellular reactive oxygen species in human A549 lung cells and rat macrophages (NR8383). In pure CNTs, which have a reduced metal content, these effects were either negligible or nonexistent (Pulskamp et al. 2007). Researchers hypothesized that the biological impacts could be caused by the metals linked with commercial CNTs based on the outcomes of a recent experiment. It was discovered that CNTs dispersed in surfactant were less hazardous than CNTs aggregated. It is interesting to note that string-like agglomerated CNTs were more solid, rigid, and voluminous than asbestos (Wick et al. 2007b). Even at small concentrations (0.001–0.1 mg/mL), CNT toxicity has been shown to trigger immune-mediated cytotoxicity against a variety of human cells. Lower concentrations of CNTs have been hypothesized to boost the release of cytokines that signal lymphocyte activation and increase the expression of NF-kB in immune cells, which results in indirect cytotoxicity (Sun et al. 2011).

6.5.4 Pulmonary Toxicity

Investigating the potentially harmful effects of these materials is strongly encouraged by the possible applications of CNTs. Due to their use in innovative products, nanotubes can now enter the body through a variety of exposure methods, including cutaneous and gastrointestinal contact. During manufacturing, CNTs may get into the workers' respiratory systems and build up in their lungs. Nanotubes could enter customers' stomachs and intestines if they are utilized as fillers in food-packaging items. SWCNTs and MWCNTs were harmful when ingested by rodents, according to several reports. These investigations implied that CNTs might pose a risk to people. Animals developed lung granulomas as a result of exposure to pure and metal-doped SWCNT preparations in a dose-dependent manner. Inducing an inflammatory response, oxidative stress, collagen deposition, and fibrosis in mice were found to be more successful with inhaled SWCNTs than pharyngeal aspiration.

In a study on the respiratory toxicity of MWCNTs, MWCNTs or ground MWCNTs suspended in sterile saline (0.9% NaCl) (Muller et al. 2005) were used. After 2 months of exposure, granulomas rich in collagen began to form in the lung lesions as a result of inhalation. MWCNTs and ground MWCNTs both encouraged tumor necrosis factor (TNF) production. Moreover, by evaluating the amount of hydroxyproline in the lung tissue, dose-related pulmonary fibrosis was identified. The outcomes supported MWCNTs' toxicity. When compared to asbestos and carbon black, the inflammatory effect of MWCNTs had a middle level of severity (Muller et al. 2005). After 14 days of whole-body inhalation exposure to MWCNTs at high dosages, immune suppression was observed in mice, but MWCNTs did not exhibit inflammation or granuloma formation, as previously reported (Mitchell et al. 2009). Depending on the dosage and delivery method, highly distributed MWCNTs may result in pulmonary lesions (Morimoto et al. 2012). Pneumonia in guinea pigs has reportedly been caused by CNTs of several sorts (Grubek-Jaworska et al. 2006).

6.5.5 Cardiovascular Effects

Initial animal investigations (Muller et al. 2005; Lam et al. 2004; Shvedova et al. 2005; Warheit et al. 2004) provided evidence that exposure to CNTs causes both immediate and long-lasting pulmonary inflammation. The results of the research suggested that CNT exposure should be assessed as a potential cardiovascular risk factor based on the oxidative and inflammatory hypothesis of atherosclerosis and air pollution (Simeonova and Erdely 2009) used acid-purified SWCNTs to examine potential cardiovascular harm. According to the study, CNT-induced lung inflammation generated inflammatory mediators and activated blood cells that had harmful consequences on the cardiovascular system. Stress and dosage both affected the damage to the mitochondrial DNA of the aorta that was seen after CNT mice were exposed through pharyngeal aspiration. In comparison to controls, mice treated with SWCNTs exhibited considerably more atherosclerotic plaque on the surface of the aorta. Additionally, brachiocephalic arteries were shown to have an increase in atherosclerotic lesions. The outcomes demonstrated that mouse atherosclerosis progresses more quickly after exposure to SWCNTs (Li et al. 2007).

6.5.6 Reproductive and Developmental Toxicity

Studies examining the impact of functionalized CNTs revealed that after exposure to very low concentrations (10 ng/mouse), resorptions and fetal abnormalities started and increased. Also noted was an increase in ROS production in the placentas of exposed dams (Pietroiusti et al. 2011). The effects of functionalized CNTs on reproduction and development were investigated in *Drosophila melanogaster* as well as in CD-1 mice. The results showed that severe morphological deformities, skeletal abnormalities, and resorption rates were all significantly higher in fetuses exposed to 10 mg/kg fCNTs. The external faults included open eyelids, abnormal leg

structures, and abnormal tail structures. The percentage of fetuses with aberrant cervical vertebrae reduced phalange ossification of the pectoral and pelvic limbs, and variable sternal ossification was higher in these cases than in controls.

6.5.7 Toward the Reduction of Its Toxicity Issues

Toxicity issues with SWCNTs and MWCNTs are mostly caused by their physico-chemical characteristics, which would include their aspect ratio, size, chemical composition, form, crystal structure, stability, surface area, surface roughness, surface energy, and surface charge (Gatoo et al. 2014; Kostal et al. 2015). Modulating and/or changing these properties would therefore be the most effective strategy for lowering the allied toxicities of the CNT. There is a critical necessity guideline for building safer CNTs, given the broad range of applications for CNT-based systems in the biomedical and healthcare sectors (Rahamathulla et al. 2021). Surface modification is the widely used method; due to their hydrophobic surfaces, CNTs are insoluble in water, and direct contact of pure nanotubes with biological systems may result in interactions with different biomolecules, leading to toxicity (Fig. 6.10).

6.5.7.1 Covalent Modification

CNT sidewalls are frequently chemically altered in order to solubilize nanotubes in aqueous solutions. Typically, it is achieved by grafting functional moieties onto oxidized CNT sidewalls (Karousis et al. 2010; Banerjee et al. 2005). H_2SO_4 and/or HNO_3 are used to oxidize nanotubes in order to produce carboxylic groups. Furthermore, it was found that cells were exposed to several harmful effects when oxidized

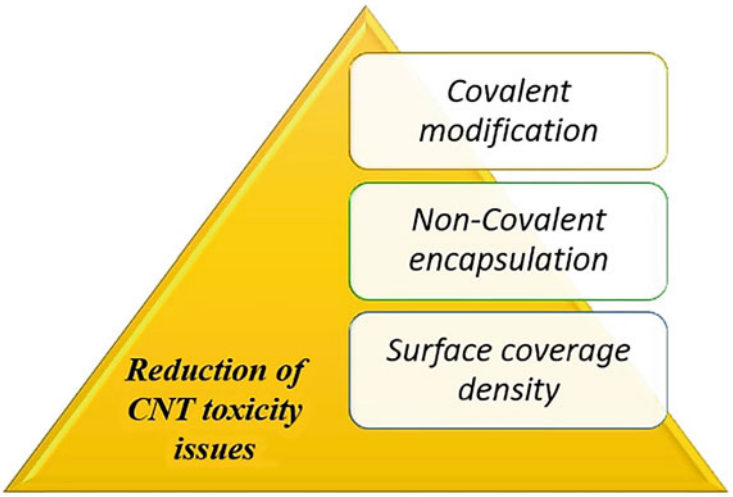

Fig. 6.10 Various methods involved in the reduction of toxicity issues associated with CNT

CNTs were employed without additional coating. The direct, extended exposure of oxidized CNTs to lung epithelial cells would stimulate the development of cancer stem cells with malignant characteristics (Luanpitpong et al. 2014), and these cells would become aggressive and form tumors. Due to surface flaws and the chemical groups that oxidation introduces, these nanotubes may be more hazardous than pure, unprocessed nanotubes (Kumarathasan et al. 2014). Therefore, oxidized CNTs without additional surface modifications should be employed with caution in both in vitro and in vivo applications. It was shown in this context that grafting antifouling polymers onto the nanotube backbone network is a successful technique for decreasing direct interactions of CNTs with biological components. Consider the often-used polyethylene glycol (PEG)-modified CNTs, which are typically created by amidating the -COOH groups of oxidized nanotubes with the -NH_2 groups of PEG. This procedure produces PEG-modified CNTs that maintain nanotubes as single and/or tiny bundles in colloidal suspensions and are stable in conditions with high salt and serum concentrations. The cellular toxicity of oxidized SWCNTs is dramatically decreased by PEG covalent grafting techniques. The branching PEG-modified CNTs appear to be more biocompatible than their linear PEG-modified counterparts due to tight binding and wide nanotube coverage. This is because fewer cellular components are in contact with the nanotube framework.

6.5.7.2 Noncovalent Encapsulation

The covalent modification of nanotube surfaces described above results in sp3 hybridization bonds by the addition of chemical groups. These changes may dramatically degrade the mechanical, physical, or chemical properties of nanotubes. While these characteristics are the basis for many bio-applications of CNTs, extensive covalent functionalization often reduces the intrinsic near-infrared (NIR) photoluminescence capabilities of nanotubes (Cognet et al. 2007; Hong et al. 2015). Using biologically acceptable amphiphilic materials, noncovalent-based nanotube solubilization is a typical approach for these purposes. In general, CNTs can be enclosed, and surface coatings with cationic, anionic, or nonionic charges can be used to control the outer charge of coated nanotubes. Because the plasma membrane is negatively charged, interactions between nanotubes and cell membranes, nanotube internalization pathways, and intracellular fate are greatly influenced by the surface charge of encapsulated CNTs. Compared to neutral and anionic nanoparticles, cationic nanoparticles frequently connect more strongly with the cell membrane and have higher absorption efficiency (Tonga et al. 2014). It is also known that negatively charged nanoparticles can be efficiently ingested through membrane diffusion or pinocytosis (Frohlich 2012; He et al. 2010; Xiao et al. 2011). Thus, maintaining neutrally charged nanotube surfaces seems to be the key to decreasing nanotubes' nonspecific binding to serum proteins and cell membranes. Additionally, nanoparticle hydrophobicity needs to be managed because it affects cellular absorption and subcellular destiny (Gupta et al. 2011; Moyano et al. 2012). In the area of possible biological applications, DNA molecules constitute a different class of biomolecules that are frequently utilized to solubilize CNTs (Zheng et al. 2003). DNA is a malleable biopolymer that can change the shape of its molecules to

wrap around the exterior walls of CNTs by creating a helical configuration (Zheng et al. 2003; Battigelli et al. 2013). The aromatic nucleotides along the DNA perpendicular axis engage in noncovalent interactions, notably stacking interactions, with the CNT backbone network. This small DNA wrapping may be CNT chirality selective based on the DNA sequences (Shankar et al. 2014). Furthermore, DNA-coated CNTs are anticipated to show reduced cytotoxicity since DNA is intrinsically biocompatible. Numerous studies have suggested that the DNA sequence, chirality, and length of the nanotubes may all have an impact on how biological serum macromolecules attach to DNA-coated CNTs and how successfully they are absorbed by cells (Salem et al. 2016; Becker et al. 2007).

6.5.7.3 Surface Coverage Density

The density of chemical functionalities on the sidewall of CNTs has a big impact on how the nanotubes behave on their surface and how they interact with biological systems. Noncovalently suspended carbon nanotubes demonstrated increased solubility (Liu et al. 2009b) and decreased toxicity with increasing coverage of coating molecules, corresponding to covalently modified CNTs. In addition to improving CNT solubility in biological fluids for both covalent and noncovalent surface coverage, increasing PEG density and branching degree also made nanotubes less hazardous by lowering unintended interactions with biological elements, particularly proteins (Heister et al. 2012).

6.6 Future Prospective

Carbon nanotubes have the chance to be a more affordable alternative to metal wires because of their great electrical conductivity. They are candidates to replace current computer chips due to their semiconducting qualities. In the future, CNTs are likely to compete with carbon fiber for high-end applications, especially in applications where weight is an issue, like Kevlar. CNTs have also been discovered to be a more eco-friendly, flame-retardant component to plastics. A safer alternative to dangerous, biocide-containing paints, MWNT-containing paints have also been found to lessen the biofouling of ship hulls by preventing the attachment of algae and barnacles.

6.6.1 In 3DPC Efficiency Enhancement

CNT is anticipated to be a viable material for 3DPC. The configuration time of 3DPC can be significantly decreased and production efficiency increased by using CNT. It can increase the printing quality, the early strength of 3DPC, and the drying shrinkage of 3DPC. Last but not the least, it can fill the pores in 3DPC, increase its hardness, and then increase the shape stability following extrusion. On CNT-reinforced 3DPC, however, no related research has been done as of yet. The primary problem is that domestic 3DP technology is still in its early stages and that the 3DP method is not precisely specified. Carbon materials have a high cost of

manufacturing and a difficult production procedure. These are the constraints of using CNT to improve concrete in 3DPC. But when constructing small models, CNT strengthening of the 3DPC becomes practical since 3DP can provide some intricate designs in accordance with the model.

6.6.2 In Electrochemical Sensing

Carbon nanotubes should be able to facilitate electron transfer processes with electroactive species in solutions, when utilized as electrode materials, according to delicate electronic characteristics. Electrodes made of carbon nanotubes could therefore be employed for electrochemical sensing. Carbon nanotubes demonstrated better behavior as electrode materials than conventional carbon electrodes, which would include good conducting ability and great chemical stability.

References

Abu Lila AS, Soliman MS, Kiran HC, Gangadharappa HV, Younes KM, Khafagy E-S, Shehata TM, Ibrahim MM, Abdallah MH (2021) Tamoxifen-loaded functionalized graphene nanoribbons for breast cancer therapy. J Drug Deliv Sci Technol 63:102499., ISSN 1773-2247. https://doi.org/10.1016/j.jddst.2021.102499

Aizawa M, Shaffer M (2003) Chem Phys Lett 368:121

Ajayan P, Ebbesen T (1997) Rep Prog Phys 60:1025

Al-Jamal KT, Nerl H, Muller KH et al (2011) Cellular uptake mechanisms of functionalised multi-walled carbon nanotubes by 3D electron tomography imaging. Nanoscale 3(6):2627–2635

Amelinckx S, Lucas A, Lambin P (1999) Rep Prog Phys 62:1471

Arepalli S, Nikolaev P, Gorelik O, Hadjiev V, Holmes W, Files B, Yowell L (2004) Carbon 42: 1783

Bachilo SM, Strano MS, Kittrell C, Hauge RH, Smalley RE, Weisman RB (2002) Structure-assigned optical spectra of single-walled carbon nanotubes. Science 298:2361–2366

Banerjee S, Hemraj-Benny T, Wong SS (2005) Adv Mater 17:17–29

Battigelli A, Menard-Moyon C, Da Ros T, Prato M, Bianco A (2013) Adv Drug Deliv Rev 65: 1899–1920

Becker ML, Fagan JA, Gallant ND, Bauer BJ, Bajpai V, Hobbie EK, Lacerda SH, Migler KB, Jakupciak JP (2007) Adv Mater 19:939–945

Bekyarova E, Ni Y, Malarkey EB et al (2005) Applications of carbon nanotubes in biotechnology and biomedicine. J Biomed Nanotechnol 1(1):3–17

Benedict LX, Louie SG, Cohen ML (1996) Heat capacity of carbon nanotubes. Solid State Commun 100:177

Berber S, Kwon YK, Tomanek D (2000) Phys Rev Lett 84:4613

Bernaerts D, Amelinckx S, Lambin P, Lucas A (1998a) Appl Phys A Mater Sci Process 67:53

Bernaerts D, Zettl A, Chopra N, Thess A, Smalley R (1998b) Solid State Commun 105:145

Bianco A, Kostarelos K, Partidos CD, Prato M (2005a) Biomedical applications of functionalised carbon nanotubes. Chem Commun:571–577

Bianco A, Kostarelos K, Prato M (2005b) Applications of carbon nanotubes in drug delivery. Curr Opin Chem Biol 9:674–679

Biercuk MJ, Llaguno MC, Radosavljevic M, Hyun JK, Johnson AT, Fischer JE (2002) Carbon nanotubes for thermal management. Appl Phys Lett 80(15):2767–2769

Buongiorno Nardelli M, Yakobson BI, Bernholc J (1998) Mechanism of strain release in carbon nanotubes. Phys Rev B 57(8):R4277–R4280
Burian A, Dore J, Fischer H, Sloan J (1999) Phys Rev B 59:1665
Cao A, Xu C, Liang J, Wu D, Wei B (2001) Chem Phys Lett 344:13
Charlier A, McRae E, Heyd R, Charlier M, Moretti D (1999) Carbon 37:177–179
Chen P, Wu X, Sun X, Lin J, Ji W, Tan K (1999) Phys Rev Lett 82:2548
Chen Z, Pierre D, He H et al (2011) Adsorption behavior of epirubicin hydrochloride on carboxylated carbon nanotubes. Int J Pharm 405(1–2):153–161
Cheng C, Muller KH, Koziol KKK, Skepper JN, Midgley PA, Welland ME et al (2009) Toxicity and imaging of multi-walled carbon nanotubes in human macrophage cells. Biomaterials 30: 4152–4160
Choe N, Tanaka S, Xia W, Hemenway DR, Roggli VL, Kagan E (1997) Pleural macrophage recruitment and activation in asbestos-induced pleural injury. Environ Health Perspect 105: 1257–1260
Cognet L, Tsyboulski DA, Rocha J-DR, Doyle CD, Tour JM, Weisman RB (2007) Science 316: 1465–1468
Cowley J, Sundell F (1997) Ultramicroscopy 68:1
Cowley J, Nikolaev P, Thess A, Smalley R (1997) Chem Phys Lett 265:379
Crouzier D, Follot S, Gentilhomme E, Flahaut E, Arnaud R, Dabouis V et al (2010) Carbon nanotubes induce inflammation but decrease the production of reactive oxygen species in lung. Toxicology 272:39–45
Daniels HE (1945) Proc R Soc Lond A 183:405
Davoren M, Herzog E, Casey A, Cottineau B, Chambers G, Byrne HJ et al (2007) In vitro toxicity evaluation of single walled carbon nanotubes on human A549 lung cells. Toxicol In Vitro 21: 438–448
Digge MS, Moon RS, Gattani SG (2012) Applications of carbon nanotubes in drug delivery: a review. Int J PharmTech Res 4(2):839–847
Dresselhaus MS, Endo M (2001) Top Appl Phys 80:11
Eklund P, Holden J, Jishi R (1995) Carbon 33:959
Elgrabli D, Floriani M, Abella-Gallart S, Meunier L, Gamez C, Delalain P et al (2008) Biodistribution and clearance of instilled carbon nanotubes in rat lung. Part Fibre Toxicol 5:20
Elhissi AMA, Ahmed W, Hassan IU, Dhanak VR, D'Emanuele A (2012) Carbon nanotubes in cancer therapy and drug delivery. J Drug Deliv 2012:837327., 10 pages
Erol O, Uyan I, Hatip M, Yilmaz C, Tekinay AB, Guler MO (2016) Recent advances in bioactive 1D and 2D carbon nanomaterials for biomedical applications. Nanomed Nanotechnol Biol Med 14:2433–2454. https://doi.org/10.1016/j.nano.2017.03.021
Ferrari A, Robertson J (2000) Phys Rev B 61:14095
Francis AP, Devasena T (2018) Toxicity of carbon nanotubes: a review. Toxicol Ind Health 34(3): 200–210. https://doi.org/10.1177/0748233717747472
Francisco-Marquez M, Galano A, Martínez A (2010) On the free radical scavenging capability of carboxylated single-walled carbon nanotubes. J Phys Chem C 114(14):6363–6370
Frohlich E (2012) Int J Nanomedicine 7:5577–5591
Galano A (2008) Carbon nanotubes as free-radical scavengers. J Phys Chem C 112(24):8922–8927
Ganesh EN (2013) Single walled and multi-walled carbon nanotube structure, synthesis and applications. Int J Innov Technol Explor Eng 2(4):311
Garcia-Vidal FJ, Pitarke JM, Pendry JB (1997) Effective medium theory of the optical properties of aligned carbon nanotubes. Phys Rev Lett 78(22):4289–4292
Gatoo MA, Naseem S, Arfat MY, Dar AM, Qasim K, Zubair S (2014) Physicochemical properties of nanomaterials: Implication in associated toxic manifestations. Biomed Res Int 2014:498420
Gellein K, Hoel S, Evje L, Syversen T (2009) The colony formation assay as an indicator of carbon nanotube toxicity examined in three cell lines. Nanotoxicology 3:215–221
Gommes C, Blacher S, Masenelli-Varlot K, Bossuot C, McRae E, Fonseca A, Nagy JB, Pirard JP (2003) Carbon 41:2561

Goodman M, Felix A, Moroder L, Toniolo C (2002) Methods of organic chemistry, vol E22b. Houben-Weyl, Thieme, Stuttgart
Grubek-Jaworska H, Nejman P, Czumińska K et al (2006) Preliminary results on the pathogenic effects of intratracheal exposure to one-dimensional nanocarbons. Carbon 44(6):1057–1063
Guo GY, Chu KC, Wang DS, Duan CG (2004a) Linear and nonlinear optical properties of carbon nanotubes from first-principles calculations. Phys Rev B 69:205416
Guo J, Yang C, Li ZM, Bai M, Liu HJ, Li GD, Wang EG, Chan CT, Tang ZK, Ge WK, Xiao X (2004b) Phys Rev Lett 93:017402–017401
Gupta A, Mandal D, Ahmadibeni Y, Parang K, Bothun G (2011) Eur Biophys J 40:727–736
Hammer P, Victoria N, Alvarez F (2000) J Vac Sci Technol 18:2277
He R, Jin H, Zhu J, Yan Y, Chen X (1998) Chem Phys Lett 298:170
He B, Sun W, Wang M, Liu S, Shen Z (2004) Mater Chem Phys 84:140
He C, Hu Y, Yin L, Tang C, Yin C (2010) Biomaterials 31:3657–3666
He H, Pham-Huy LA, Dramou P, Xiao D, Zuo P, Pham-Huy C (2013) Carbon nanotubes: applications in pharmacy and medicine. BioMed Res Int 2013:578290., 12 pages
Heister E, Neves V, Lamprecht C, Silva SRP, Coley HM, McFadden J (2012) Carbon 50:622–632
Hillegass JM, Shukla A, Lathrop SA, MacPherson MB, Fukagawa NK, Mossman BT (2010) Assessing nanotoxicity in cells in vitro. Wiley Interdiscip Rev Nanomed Nanobiotechnol 2: 219–231
Hirlekar R, Yamagar M, Garse H, Vij M, Kadam V (2009) Carbon nanotubes and its applications: a review. Asian J Pharm Clin Res 2(4):17–27
Hone J, Whitney M, Piskoti C, Zettl A (1999) Phys Rev B 59:R2514
Hone J, Llaguno MC, Nemes NM, Johnson AT, Fischer JE, Walters DA, Casavant MJ, Schmidt J, Smalley RE (2000a) Appl Phys Lett 77:666
Hone J, Batlogg B, Benes Z, Johnson AT, Fischer JE (2000b) Science 289:1730
Hong G, Diao S, Antaris AL, Dai H (2015) Chem Rev 115:10816–10906
Hu H, Bhowmik P, Zhao B, Hamon MA, Itkis ME, Haddon RC (2001) Chem Phys Lett 345:25
Janas D, Milowska KZ, Bristowe PD, Koziol KKK (2017) Improving the electrical properties of carbon nanotubes with interhalogen compounds. Nanoscale 9(9):3212–3221
Kahn D, Lu JP (1999) Phys Rev B 60:6535
Kam NWS, Liu Z, Dai H (2005) Functionalization of carbon nanotubes via cleavable disulfide bonds for efficient intracellular delivery of siRNA and potent gene silencing. J Am Chem Soc 127:12492–12493
Kane AB (2006) Animal models of malignant mesothelioma. Inhal Toxicol 18:1001–1004
Karousis N, Tagmatarchis N, Tasis D (2010) Chem Rev 110:5366–5397
Kastner J, Pichler T, Kuzmany H, Curran S, Blau W, Weldon DN, Delamesiere M, Draper S, Zandbergen H (1994) Chem Phys Lett 221:53
Kateb B, Yamamoto V, Alizadeh D et al (2010) Multi-walled carbon nanotube (MWCNT) synthesis, preparation, labeling, and functionalization. Methods Mol Biol 651:307–317
Kempa K, Kimball B, Ryhczynski J, Huang ZP, Wu PF, Steeves D, Sennett M, Giersig M, Rao DVGLN, Carnahan D, Wang DZ, Lao JY, Li WZ, Ren ZF (2003) Photonic crystals based on periodic arrays of aligned carbon nanotubes. Nano Lett 3:13–18
Kempa K, Ryhczynski J, Huang ZP, Gregorczyk K, Vidan A, Kimball B, Carlson J, Benham G, Wang Y, Herczynski A, Ren ZF (2007) Carbon nanotubes as optical antennae. Adv Mater 19: 421–426
Kiang C, Endo M, Ajayan P, Dresselhaus G, Dresselhaus M (1998) Phys Rev Lett 81:1869
Kiran HC, Gangadharappa HV (2019) Reinforcing nanomedicine using graphene nanoribbons. J Drug Deliv Sci Technol 49:334–344.,ISSN 1773-2247. https://doi.org/10.1016/j.jddst.2018.12.004
Kostal J, Voutchkova-Kostal A, Anastas PT, Zimmerman JB (2015) Identifying and designing chemicals with minimal acute aquatic toxicity. Proc Natl Acad Sci U S A 112:6289–6294
Koyama S, Kim YA, Hayashi T, Takeuchi K, Fujii C, Kuroiwa N et al (2009) In vivo immunological toxicity in mice of carbon nanotubes with impurities. Carbon 47:1365–1372

Kuhlmann U, Jantoljak H, Pfander M, Bernier P, Journet C, Thomsen C (1998) Chem Phys Lett 294:237
Kumarathasan P, Breznan D, Das D, Salam MA, Siddiqui Y, Mackinnon-Roy C, Guan J, de Silva N, Simard B, Vincent R (2014) Nanotoxicology 0:1–14
Kuzmany H, Burger B, Thess A, Smalley R (1998) Carbon 36:709
Kuzmany H, Plank W, Hulman M, Kramberger C, Gruneis A, Pichler T, Peterlik H, Kataura H, Achiba Y (2001) Eur Phys J B 22:307
Lacerda L, Pastorin G, Wu W, Prato M, Bianco A, Kostarelos K (2006) Functionalised carbon nanotube autofluorescence as a tool to monitor bundle formation and dissociation in aqueous phases by fluorescence spectrophotometry: the effect of plasmid DNA complexation. Adv Funct Mater 16:1839–1846
Lam CW, James JT, McCluskey R et al (2004) Pulmonary toxicity of single-wall carbon nanotubes in mice 7 and 90 days after intratracheal instillation. Toxicol Sci 77(1):126–134
Lambin P, Loiseau A, Culot C, Biro L (2002) Carbon 40:1635
Lauret JS, Voisin C, Cassabois G, Roussignol P, Delalande C, Filoramo A, Capes L, Valentin E, Jost O (2004) Phys E 21:1057
Lay CL, Liu J, Liu Y (2011) Functionalized carbon nanotubes for anticancer drug delivery. Expert Rev Med Devices 8(5):561–566
Lebedkin S, Hennrich F, Skipa T, Kappes MM (2003) J Phys Chem B 107:1949
Lefebvre J, Fraser JM, Homma Y, Finnie P (2004) Appl Phys A Mater Sci Process 78:1107
Li Z, Hulderman T, Salmen R et al (2007) Cardiovascular effects of pulmonary exposure to single-wall carbon nanotubes. Environ Health Perspect 115(3):377
Li S, He H, Jiao Q, Pham-Huy C (2008) Applications of carbon nanotubes in drug and gene delivery. Prog Chem 20(11):1798–1803
Li R, Wu R, Zhao L, Wu M, Yang L, Zou H (2010) Pglycoprotein antibody functionalized carbon nanotube overcomes the multidrug resistance of human leukemia cells. ACS Nano 4(3): 1399–1408
Li L, Lin R, He H, Jiang L, Gao MM (2013) Interaction of carboxylated single-walled carbon nanotubes with bovine serum albumin. Spectrochim Acta A 105:45–51
Li T, Tang Z, Huang Z, Yu J (2017) A comparison between the mechanical and thermal properties of single-walled carbon nanotubes and boron nitride nanotubes. Physica E 85:137–142
Liao H, Paratala B, Sitharaman B, Wang Y (2011) Applications of carbon nanotubes in biomedical studies. Methods Mol Biol 726:223–241
Lidorikis E, Ferrari AC (2009) Photonics with multiwall carbon nanotube arrays. ACS Nano 3: 1238–1248
Lin MF (1994) Plasmons and optical properties of carbon nanotubes. Phys Rev B 50:17744
Lin MF (2000) Optical spectra of single-wall carbon nanotube bundles. Phys Rev B 62:13153
Liu M, Cowley J (1994) Carbon 32:393
Liu Y, Gao L (2005) A study of the electrical properties of carbon nanotube-$NiFe_2O_4$ composites: effect of the surface treatment of the carbon nanotubes. Carbon N Y 43(1):47–52
Liu X, Pichler T, Knupfer M, Golden MS, Fink J, Kataura H, Achiba Y (2002) Phys Rev B 66: 045411
Liu Z, Sun X, Nakayama-Ratchford N, Dai H (2007a) Supramolecular chemistry on water-soluble carbon nanotubes for drug loading and delivery. ACS Nano 1(1):50–56
Liu Z, Cai W, He L, Nakayama N, Chen K, Sun X, Chen X, Dai H (2007b) In vivo biodistribution and highly efficient tumour targeting of carbon nanotubes in mice. Nat Nanotechnol 2:47–52
Liu XY, Gurel V, Morris D, Murray DW, Zhitkovich A, Kane AB et al (2007c) Bioavailability of nickel in single-wall carbon nanotubes. Adv Mater 19:2790
Liu Z, Tabakman S, Welsher K, Dai H (2009a) Carbon nanotubes in biology and medicine: in vitro and in vivo detection, imaging and drug delivery. Nano Res 2(2):85–120
Liu Z, Tabakman SM, Chen Z, Dai H (2009b) Nat Protoc 4:1372–1381
Llaguno MC, Hone J, Fischer JE, Johnson AT (2002) Thermal properties of carbon nanotubes and nanotube-based materials. Appl Phys A 74(3):339–343

Lourie E, Cox DM, Wagner HD (1998) Buckling and collapse of embedded carbon nanotubes. Phys Rev Lett 81(8):1638–1641
Luanpitpong S, Wang L, Castranova V, Rojanasakul Y (2014) Part Fibre Toxicol 11:22–22
Maarouf AA, Kane CL, Mele EJ (2000) Phys Rev B 61:11156
MacDonald RA, Laurenzi BF, Viswanathan G, Ajayan PM, Stegemann JP (2005) Collagen-carbon nanotube composite materials as scaffolds in tissue engineering. J Biomed Mater Res A 74(3): 489–496
Madani SY, Naderi N, Dissanayake O, Tan A, Seifalian AM (2011) A new era of cancer treatment: carbon nanotubes as drug delivery tools. Int J Nanomedicine 6:2963–2979
Mamedov AA, Kotov NA, Prato M, Guldi DM, Wicksted JP, Hirsch A (2002) Nat Mater 1:190
Mawhinney DB, Naumenko V, Kuznetsova A, Yates JT Jr, Liu J, Smalley RE (2000) Chem Phys Lett 324:213
Mbuyise XG, Arbab EAA, Kaviyarasu K, Pellicane G, Maaza M, Mola GT (2017) Zinc oxide doped single wall carbon nanotubes in hole transport buffer layer. J Alloy Comp 706:344–350. https://doi.org/10.1016/j.jallcom.2017.02.249
Mitchell LA, Lauer FT, Burchiel SW et al (2009) Mechanisms for how inhaled multiwalled carbon nanotubes suppress systemic immune function in mice. Nat Nanotechnol 4(7):451–456
Mizel A, Benedict LX, Cohen ML, Louie SG, Zettl A, Budraa NK, Beyermann WP (1999) Analysis of the low-temperature specific heat of multiwalled carbon nanotubes and carbon nanotube ropes. Phys Rev B 60:3264
Mizuno K, Ishii J, Kishida H, Hayamizu Y, Yasuda S, Futaba DN, Yumura M, Hata K (2008) A black body absorber from vertically aligned single-walled carbon nanotubes. Proc Natl Acad Sci U S A 106:6044–6047
Morimoto Y, Hirohashi M, Ogami A et al (2012) Pulmonary toxicity of well-dispersed multi-wall carbon nanotubes following inhalation and intratracheal instillation. Nanotoxicology 6(6): 587–599
Moyano DF, Goldsmith M, Solfiell DJ, Landesman Milo D, Miranda OR, Peer D, Rotello VM (2012) J Am Chem Soc 134:3965–3967
Muller S (1999) Synthetic peptides as antigens. In: Pillai S, van der Vliet PC (eds) Laboratory techniques in biochemistry and molecular biology, vol 28. Elsevier, Amsterdam, pp 79–131
Muller J, Huaux F, Moreau N et al (2005) Respiratory toxicity of multi-wall carbon nanotubes. Toxicol Appl Pharmacol 207(3):221–231
Murray AR, Kisin E, Leonard SS, Young SH, Kommineni C, Kagan VE et al (2009) Oxidative stress and inflammatory response in dermal toxicity of single-walled carbon nanotubes. Toxicology 257:161–171
Nakano S-i, Uotani Y, Nakashima S, Anno Y, Fujii M, Sugimoto N (2003) Large stabilization of a DNA duplex by the deoxyadenosine derivatives tethering an aromatic hydrocarbon group. J Am Chem Soc 125(27):8086–8087
O'Connell MJ, Bachilo SM, Huffman CB, Moore VC, Strano MS, Haroz EH, Rialon KL, Boul PJ, Noon WH, Kittrell C, Ma J, Hauge RH, Weisman RB, Smalley RE (2003) Science 297:503
Oseni SO, Kaviyarasu K, Maaza M, Sharma G, Pellicane G, Mola GT (2018) ZnO:CNT assisted charge transport in PTB7:PCBM blend organic solar cell. J Alloy Comp 748:216–222. https://doi.org/10.1016/j.jallcom.2018.03.141
Ouyang M, Huang JL, Cheung CL, Lieber CM (2001) Science 292:702
Ozaki T, Iwasa Y, Mitani T (2000) Stiffness of single-walled carbon nanotubes under large strain. Phys Rev Lett 84(8):1712–1715
Pang LSK, Saxby JD, Chatfield SP (1993) Thermogravimetric analysis of carbon nanotubes and nanoparticles. J Phys Chem 97(27):6941–6942
Pantarotto D, Hoebeke J, Graff R, Partidos CD, Briand J-P, Prato M, Bianco A (2003a) Synthesis, structural characterization and immunological properties of carbon nanotubes functionalized with peptides. J Am Chem Soc 125:6160–6164

Pantarotto D, Partidos CD, Hoebeke J, Brown F, Kramer E, Briand J-P, Muller S, Prato M, Bianco A (2003b) Immunization with peptide-functionalized carbon nanotubes enhances virus-specific neutralizing antibody responses. Chem Biol 10:961–966

Pantarotto D, Singh R, McCarthy D et al (2004a) Functionalized carbon nanotubes for plasmid DNA gene delivery. Angew Chem 43(39):5242–5246

Pantarotto D, Singh R, McCarthy D, Erhardt M, Briand J-P, Prato M, Kostarelos K, Bianco A (2004b) Functionalised carbon nanotubes for plasmid DNA gene delivery. Angew Chem Int Ed 43:5242–5246

Pastorin G, Wu W, Wieckowski S, Briand J-P, Kostarelos K, Prato M, Bianco A (2006) Double functionalisation of carbon nanotubes for multimodal drug delivery. Chem Commun:1182–1184

Pauluhn J (2010) Multi-walled carbon nanotubes (baytubes (R)): approach for derivation of occupational exposure limit. Regul Toxicol Pharmacol 57:78–89

Pereira M, Figueiredo J, Orfao J, Serp P, Kalck P, Kihn Y (2004) Carbon 42:2807

Pham-Huu C, Keller N, Roddatis V, Mestl G, Schlogl R, Ledoux MJ (2002) Phys Chem Chem Phys 4:514

Pham-Huy LA, He H, Pham-Huy C (2008) Free radicals, antioxidants in disease and health. Int J Biomed Sci 4(2):89–96

Pietroiusti A, Massimiani M, Fenoglio I et al (2011) Low doses of pristine and oxidized single-wall carbon nanotubes affect mammalian embryonic development. ACS Nano 5(6):4624–4633

Pignatello R, Guccione S, Forte S, Di Giacomo C, Sorrenti V, Vicari L, Uccello Barretta G, Balzano F, Puglisi G (2004) Lipophilic conjugates of methotrexate with short-chain alkylamino acids as DHFR inhibitors. Synthesis, biological evaluation, and molecular modeling. Bioorg Med Chem 12:2951–2964

Poudel YR, Li W (2018) Synthesis, properties, and applications of carbon nanotubes filled with foreign materials: a review. Mater Today Phys 7:7–34

Pulskamp K, Diabaté S, Krug HF (2007) Carbon nanotubes show no sign of acute toxicity but induce intracellular reactive oxygen species in dependence on contaminants. Toxicol Lett 168(1):58–74

Qin L (1998) Chem Phys Lett 297:23

Qin L, Ichihashi T, Iijima S (1997a) Ultramicroscopy 67:181

Qin L, Iijima S, Kataura H, Maniwa Y, Suzuki S, Achiba Y (1997b) Chem Phys Lett 268:10

Rahamathulla M, Bhosale RR, Osmani RAM, Mahima KC, Johnson AP, Hani U, Ghazwani M, Begum MY, Alshehri S, Ghoneim MM et al (2021) Carbon nanotubes: current perspectives on diverse applications in targeted drug delivery and therapies. Materials 14:6707. https://doi.org/10.3390/ma14216707

Ren HX, Chen X, Liu JH, Gu N, Huang XJ (2010) Toxicity of single-walled carbon nanotube: how we were wrong? Mater Today 13:6–8

Reznik D, Olk C, Neumann A, Copley J (1995) Phys Rev B 52:116

Rols S, Almairac R, Henrard L, Anglaret E, Sauvajol J (1999) Eur Phys J B 10:263

Rosen Y, Elman NM (2009) Carbon nanotubes in drug delivery: focus on infectious diseases. Expert Opin Drug Deliv 6(5):517–530

Rosen Y, Mattix B, Rao A, Alexis F (2011) Carbon nanotubes and infectious diseases. In: Hunter RJ (ed) Nanomedicine in health and disease. Science Publishers, London, UK, pp 249–267

Ryman-Rasmussen JP, Cesta MF, Brody AR, Shipley-Phillips JK, Everitt JI, Tewksbury EW et al (2009) Inhaled carbon nanotubes reach the subpleural tissue in mice. Nat Nanotechnol 4:747–745

Saifuddin N, Raziah AZ, Junizah AR (2013) Carbon nanotubes: a review on structure and their interaction with proteins. J Chem 2013:676815, 18 pages

Saito Y, Yoshikawa T, Bandow S, Tomita M, Hayashi T (1993) Phys Rev B 48:1907

Saito R, Dresselhaus G, Dresselhaus MS (1998) Physical properties of carbon nanotubes. Imperial College Press, London
Saito R, Matsushige K, Tanaka K (2002) Phys B Condens Matter 323:280
Salem DP, Landry MP, Bisker G, Ahn J, Kruss S, Strano MS (2016) Carbon 97:147–153
Sayes CM, Liang F, Hudson JL, Mendez J, Guo W, Beach JM, Moore VC, Doyle CD, West JL, Billups WE, Ausman KD, Colvin VL (2006) Functionalization density dependence of single-walled carbon nanotubes cytotoxicity in vitro. Toxicol Lett 16:135–142
Shankar A, Mittal J, Jagota A (2014) Langmuir 30:3176–3183
Shoji S, Suzuki H, Zaccaria RP, Sekkat Z, Kawata S (2008) Optical polarizer made of uniaxially aligned short single-wall carbon nanotubes embedded in a polymer film. Phys Rev B 77:153407
Shvedova AA, Kisin ER, Mercer R et al (2005) Unusual inflammatory and fibrogenic pulmonary responses to single-walled carbon nanotubes in mice. Am J Phys Lung Cell Mol Phys 289(5): L698–L708
Simeonova PP, Erdely A (2009) Engineered nanoparticle respiratory exposure and potential risks for cardiovascular toxicity: predictive tests and biomarkers. Inhal Toxicol 21(Suppl 1):68–73
Simon-Deckers A, Gouget B, Mayne-L'Hermite M, Herlin-Boime N, Reynaud C, Carriere M (2008a) In vitro investigation of oxide nanoparticle and carbon nanotube toxicity and intracellular accumulation in A549 human pneumocytes. Toxicology 253:137–146
Simon-Deckers A, Gouget B, Mayne-L'Hermite M et al (2008b) In vitro investigation of oxide nanoparticle and carbon nanotube toxicity and intracellular accumulation in A549 human pneumocytes. Toxicology 253(1):137–146
Singh R, Pantarotto D, McCarthy D, Chaloin O, Hoebeke J, Partidos CD, Briand J-P, Prato M, Bianco A, Kostarelos K (2005) Binding and condensation of plasmid DNA onto functionalized carbon nanotubes: towards the construction of nanotube-based gene delivery vectors. J Am Chem Soc 127:4388–4396
Singh R, Pantarotto D, Lacerda L, Pastorin G, Klumpp C, Prato M, Bianco A, Kostarelos K (2006) Tissue biodistribution and blood clearance rates of intravenously administered carbon nanotube radiotracers. Proc Natl Acad Sci U S A 103:3357–3362
Singh BGP, Baburao C, Pispati V et al (2012) Carbon nanotubes. A novel drug delivery system. Int J Res Pharm Chem 2(2):523–532
Slepyan GY, Shuba MV, Maksimenko SA (2006) Theory of optical scattering by achiral carbon nanotubes and their potential as optical nanoantennas. Phys Rev B 73:195416
Srivastava D, Menon M, Kyeongjae C (1999) Nanoplasticity of single-wall carbon nanotubes under uniaxial compression. Phys Rev Lett 83(15):2973–2976
Sun Z, Liu Z, Meng J et al (2011) Carbon nanotubes enhance cytotoxicity mediated by human lymphocytes in vitro. PLoS One 6(6):e21073
Tanaka K, Aoki H, Ago H, Yamabe T, Okahara K (1997) Carbon 35:125
Tantra R, Cumpson P (2007) The detection of airborne carbon nanotubes in relation to toxicology and workplace safety. Nanotoxicology 1:251–265
Tasis D, Tagmatarchis N, Bianco A, Prato M (2006) Chemistry of carbon nanotubes. Chem Rev 106:1105–1136
Teizer W, Hallock RB, Dujardin E, Ebbesen TW (1999) Phys Rev Lett 82:5305
Thostenson E, Ren Z, Chou T (2001) Comp Sci Technol 61:1899
Thurnherr T, Su DS, Diener L, Weinberg G, Manser P, Pfander N et al (2009) Comprehensive evaluation of in vitro toxicity of three large-scale produced carbon nanotubes on human Jurkat T cells and a comparison to crocidolite asbestos. Nanotoxicology 3:319–338
Tonga GY, Saha K, Rotello VM (2014) Adv Mater 26:359–370
Tutak W, Park KH, Vasilov A, Starovoytov V, Fanchini G, Cai SQ et al (2009) Toxicity induced enhanced extracellular matrix production in osteoblastic cells cultured on single-walled carbon nanotube networks. Nanotechnology 20:255101
Usui Y, Haniu H, Tsuruoka S, Saito N (2012) Carbon nanotubes innovate on medical technology. Med Chem 2(1):1–6

Wang J (2005) Carbon-nanotube based electrochemical biosensors: a review. Electroanalysis 17(1): 7–14
Wang Y, Kempa K, Kimball B, Carlson JB, Benham G, Li WZ, Kempa T, Rybczynski J, Herczynski A, Ren ZF (2004a) Receiving and transmitting light-like radio waves: antenna effect in arrays of aligned carbon nanotubes. Appl Phys Lett 85:2607
Wang S, Zhu W, Liao D, Ng C, Au C (2004b) Catal Today 93–95:711
Wang XJ, Flicker JD, Lee BJ, Ready WJ, Zhang ZM (2009) Visible and near-infrared radiative properties of vertically aligned multi-walled carbon nanotubes. Nanotechnology 20:215704
Warheit DB, Laurence BR, Reed KL et al (2004) Comparative pulmonary toxicity assessment of single-wall carbon nanotubes in rats. Toxicol Sci 77(1):117–125
Weisman RB, Bachilo SM, Tsyboulski D (2004) Appl Phys A Mater Sci Process 78:1111
Wick P, Manser P, Limbach LK, Dettlaff-Weglikowska U, Krumeich F, Roth S et al (2007a) The degree and kind of agglomeration affect carbon nanotube cytotoxicity. Toxicol Lett 168:121–131
Wick P, Manser P, Limbach LK et al (2007b) The degree and kind of agglomeration affect carbon nanotube cytotoxicity. Toxicol Lett 168(2):121–131
Wong JM, Esdaile JM (2005) Methotrexate in systemic lupus erythematosus. Lupus 14:101–105
Wu W, Wieckowski S, Pastorin G, Benincasa M, Klumpp C, Briand J, Gennaro R, Prato M, Bianco A (2005) Targeted delivery of Amphotericin B to cells using functionalized carbon nanotubes. Angew Chem Int Ed 44:6358–6362
Xiao K, Li Y, Luo J, Lee JS, Xiao W, Gonik AM, Agarwal RG, Lam KS (2011) Biomaterials 32: 3435–3446
Yakobson BI (1998) Mechanical relaxation and 'intramolecular plasticity' in carbon nanotubes. Appl Phys Lett 72(8):918–920
Yang W, Thordarson P, Gooding JJ, Ringer SP, Braet F (2007) Carbon nanotubes for biological and biomedical applications. Nanotechnology 18:412001., 12 pages
Yang Z-P, Ci L, Bur JA, Lin S-Y, Ajayan PM (2008) Experimental observation of extremely dark material made by a low-density nanotube array. Nano Lett 8:446
Yang K, Zhang S, Zhang G, Sun X, Lee ST, Liu Z (2010a) Graphene in mice: ultrahigh in vivo tumor uptake and efficient photothermal therapy. Nano Lett 10:3318–3323. https://doi.org/10.1021/nl100996u
Yang Z, Zhang Y, Yang Y et al (2010b) Pharmacological and toxicological target organelles and safe use of single-walled carbon nanotubes as drug carriers in treating Alzheimer disease. Nanomedicine 6(3):427–441
Zhang Z, Yang X, Zhang Y, Zeng B, Wang S, Zhu T, Roden RB, Chen Y, Yang R (2006) Delivery of telomerase reverse transcriptase small interfering RNA in complex with positively charged single-walled carbon nanotubes suppresses tumor growth. Clin Cancer Res 12:4933–4939
Zhang Y, Bai Y, Yan B (2010) Functionalized carbon nanotubes for potential medicinal applications. Drug Discov Today 15(11–12):428–435
Zhang W, Zhang Z, Zhang Y (2011) The application of carbon nanotubes in target drug delivery systems for cancer therapies. Nanoscale Res Lett 6:555–577
Zhao GL, Bagayoko D, Yang L (2006) Optical properties of aligned carbon nanotube mats for photonic applications. J Appl Phys 99:114311
Zheng M, Jagota A, Semke ED, Diner BA, McLean RS, Lustig SR, Richardson RE, Tassi NG (2003) Nat Mater 2:338–342
Zhu W, Miser D, Chan W, Hajaligol M (2003) Mater Chem Phys 82:638
Zhu Y, Wang L, Xu C (2011) Carbon nanotubes in biomedicine and biosensing. In: Naraghi M (ed) Carbon nanotubes—growth and applications. Shanghai, InTech, pp 135–162
Zotchev SB (2003) Polyene macrolide antibiotics and their applications in human therapy. Curr Med Chem 10:211–223

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