Chapter 13

Functionalized Carbon Nanomaterials in Drug Delivery: Emergent Perspectives from Application

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.71889

Abstract

Carbon nanotubes (CNTs) have attracted substantial research interest in biomedical sciences and bionanotechnology, rendered from its unique structure, electronic, mechanical, and optical properties. Despite the diverse potential applications, the integration of CNTs in biomedical research is one of the most challenging areas where nanotubes fall under much scrutiny. Pristine nanotubes are highly hydrophobic, and non-dispersible in most of the common aqueous and organic solvents and to render nanotubes biocompatible, functionalization is one of the key prerequisites. In this regard, covalent and noncovalent functionalization are the two widely adopted approaches for co-tethering biologically active molecules on the CNTs. Likewise, the hollow cavity of the nanotube facilitates in the endohedral encapsulation of biomolecules, peptides, DNA oligonucleotides, and proteins, thereby retaining the physiological attributes of the biological molecules. The chapter focuses on the emerging approaches to the functionalization of single-wall CNTs (SWCNTs) and the potential application of functionalized SWCNTs in tuberculosis and cancer chemotherapy using state-of-the-art density functional theory, molecular docking and molecular dynamics simulation methods.

Keywords: carbon nanotubes, drug delivery, molecular dynamics, density functional theory

1. Introduction

1.1. Carbon: The fundamental building block of life

Carbon is the most versatile element in the periodic table that forms the basis of all kinds of life on earth. Elemental carbon displays a complex allotropy depending on the nature of hybridization; diamond (sp^3 hybridized), graphite, graphene, fullerenes, and carbon nanotubes (sp^2 hybridized). Graphite is the most common allotrope of carbon and the word graphite in Greek

means '*to write*'. *Graphene* an acronym for the 2D layered graphite, is the mother of all carbon materials [1], as a graphene sheet can be wrapped to form 0D fullerenes, rolled to form 1D nanotubes, or stacked to form 3D graphite as depicted in **Figure 1**. The unearthing of "*groundbreaking experiments regarding the two-dimensional material graphene*" by Geim and Novoselov in 2010, heralded graphene as the next generation carbon material [2].

CNTs are hexagonally arranged, honey-combed lattice of carbon atoms formed by the rolling of graphene into seamless cylindrical structures (see **Figure 2a**). Nanotubes like graphene have a high diameter to length ratio (aspect ratio) [3] and demonstrate high electrical, mechanical, and thermal conductivity along with structural stability [4–7]. CNTs are broadly classified as single-wall CNTs (SWCNTs) and multi-wall CNTs (MWCNTs). The SWCNT comprise of a single graphene sheet, with diameter ~ 0.5–1.5 nm and length of ~100 μm [8], while MWCNT is formed from the co-axial stacking of SWCNTs, with diameter ~1.4–100 nm, length between 1 nm-μm, and internuclear distance of 0.3–0.4 nm between the co-axial tubes. The representation of a zigzag ($m = 0$), armchair ($n = m$), and chiral ($n \neq m$) nanotube is depicted in **Figure 2b-d**. The (n, m) indices render remarkable electronic properties to the CNTs [9] and the sp^2 hybridization along the tubular axis makes it chemically inert by nature.

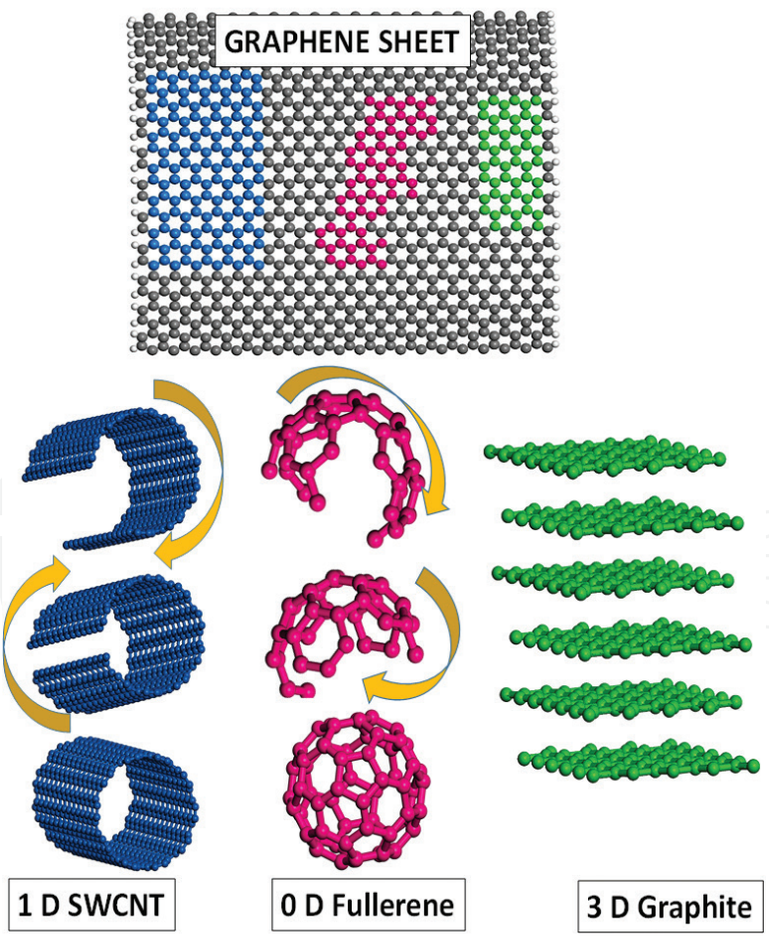

Figure 1. Formation of SWCNT, fullerene and graphite from a single graphene monolayer.

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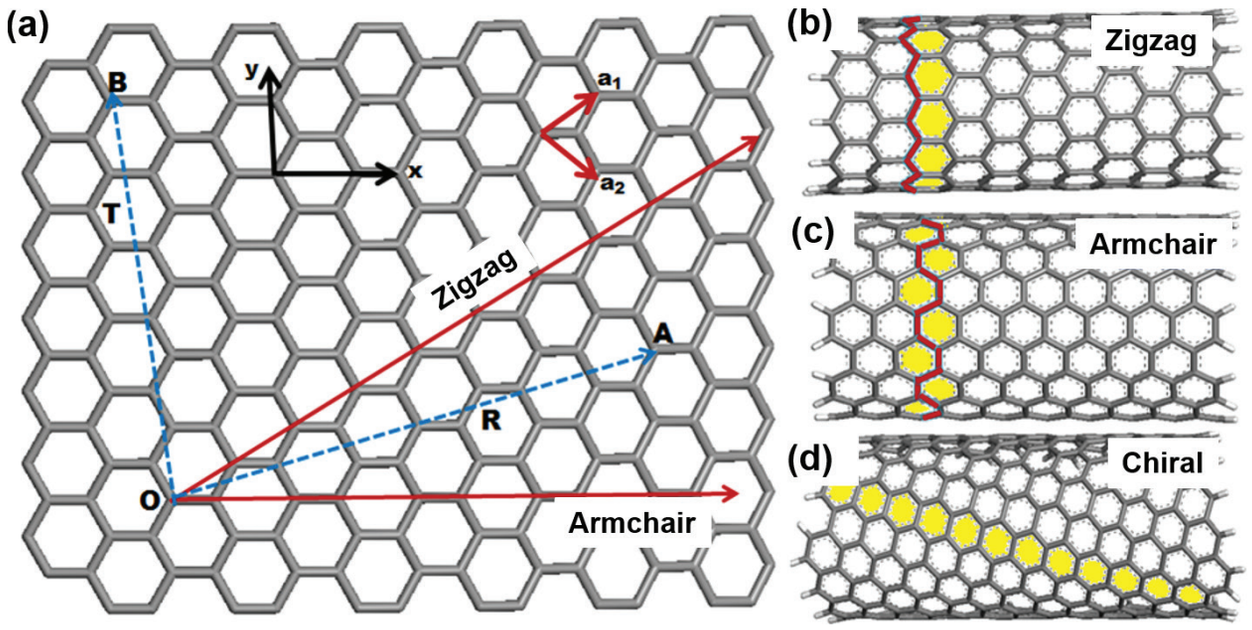

Figure 2. (a) A graphene sheet depicting the (b) zigzag and (c) armchair and (d) chiral CNT based on rolling of carbon atoms along chiral vectors through the circumference (OA) of nanotube.

The unique electronic properties exhibited by CNT are governed by the quantum confinement of electrons where the periodic boundary conditions come into interplay. Because of the quantum confinement, electrons can propagate along the tube axis: forward and backward, along with the conservation of energy and momentum. Unlike metals which have a smooth density of states (DOS), CNTs are characterized by many van Hove singularities [10], and the DOS depends on diameter and chirality of the nanotube [11]. The conducting properties of CNT is an inverse function of its diameter, that is, with increase in diameter, band gap between the valence and conduction bands decreases and at a certain point both the bands overlap to give rise to metallic nanotubes. Semiconducting nanotubes on the other hand (with similar diameter as metallic nanotubes) possess similar van Hove singularities near the Fermi level [12].

These unprecedented properties have largely contributed to the extensive biomedical research, especially as nanocapsules for therapeutic drugs, proteins, and gene delivery [13]. CNTs find application in bionanotechnology and pharmaceutical sciences, and current drug delivery modules have been incorporating CNTs for improved target specific detection and treatment of diseases. Although the potential application of carbon nanomaterials, particularly CNTs are farfetched, the concerns raised over the effect of large-scale synthesis of CNTs to the environment, biocompatibility, toxicity, biodegradation and remediation cannot be undermined and needs to be addressed thoroughly. Hence, a detailed *in vivo* and *in vitro* toxicity analyses is mandatory in understanding CNT-based therapeutic regimes for sustained drug delivery applications.

Some of the questions that underlie the importance of the study are (i) understanding the mechanism of CNT uptake followed by the subsequent release of therapeutic molecules, (ii) *in vivo* biocompatibility, and (iii) long-term practical implication to direct exposure to the

physiological environment. Although theoretical and/or experimental studies have attempted to address the main questions like mechanism of drug-nanotube interaction, the preferable binding sites of drugs onto nanotubes, drug activity under confinement, and change in redox properties of drugs under the physiological conditions, these studies are rather limited in predicting the likelihood of using CNT as carrier vehicles for the long-term storage and release of therapeutic and biologically active molecules *in vivo*.

The chapter in a very comprehensive yet succinct way addresses the potential applications of SWCNTs in drug delivery, managing to draw a fine line between the scopes of application and practical viability of integrating carbon nanomaterials in biomedical research. Herein, we report the theoretical aspects of modeling novel SWCNT-based drug delivery systems using the covalent and noncovalent functionalization schemes. Nanotubes of varying chirality and length are considered for functionalization, drug loading, and targeting onto the active binding sites of receptor proteins. With the successful incorporation of CNTs in cancer therapy, we propose a novel approach toward integrating CNTs in Tuberculosis (TB) therapy. To the best of our knowledge, theoretical studies on the potential application of CNTs in pharmaceutical sciences pertaining to TB and other bacterial diseases have not been discussed extensively. We address the recent theoretical advancements using the state-of-the-art density functional theory (DFT), molecular docking, and molecular dynamics (MD) simulation methods. Molecular docking serves as an instrumental tool in computer-aided drug design for predicting the preferred binding mode of a ligand to a receptor (protein). Docking studies help characterize the protein binding cavity, understand the orientation of ligand with respect to the receptor protein, and the nature of interaction between the protein with functionalized nanomaterial, which can aid in the structure-based design of novel drug delivery systems for future experimental studies.

2. Functionalization of CNTs

Traditional approaches to drug delivery function over a broad spectrum, resulting which, specificity toward drug administration and delivery are rarely accomplished. Development of polymer-based nanocomposite materials has enabled the successful engineering of drug delivery modules via the incorporation of nanomaterials and nanoparticles as nanocapsules for sustained release of therapeutics in a dosage-dependent manner. Nanotechnology, on the other hand, has revolutionized the pharmaceutical sector with the assimilation of functionalized nanomaterials like CNTs in drug, gene delivery, and tissue engineering [14, 15]. CNTs play dual role by rendering directionality in targeting the tumor (malignant) cells and facilitating the controlled mediated release of therapeutic molecules. The application of CNTs as carrier payloads for anticancer drugs cisplatin [16], carboplatin [17], doxorubicin (DOX) [18–20], mechlorethamine [21], paclitaxel [22] and antitubercular drugs like isoniazid (INH) [23], rifampicin, pyrazinamide (PZA) [24] have been reported.

With the inherent limitations in application of pristine, unmodified nanotubes, functionalization is the collective approach toward tailoring nanotubes electronic properties. Pristine

CNTs are generally hydrophobic with low solubility in most of the common aqueous and organic solvents and the hydrophobicity is accounted to the size, structure, and bundling effect which restricts the uptake and assimilation within the biological environment [25]. Functionalization assists in reducing the bundling effect which arises due to the van der Waals (vdW) attractive forces between adjacent nanotube surfaces and is efficient in increasing the biocompatibility thereby facilitating cellular internalization and trafficking. It has been reported that the functionalized nanotubes (*f*CNT) exhibit better biocompatibility with reduced *in vivo* and *in vitro* toxicity [26–28]. The extent of functionalization depends on the nature and reactivity of sidewall (curvature), number of functional groups that can be co-tethered along the sidewall, and steric hindrance between functional groups and nanotube sidewall. The subsequent sections discuss some of the adopted approaches in the functionalization of SWCNTs at the level of experiment and theory.

2.1. Solubilization of CNT through covalent functionalization

Some of the alternative schemes to functionalization of CNT is through covalent method using 1,3-dipolar cycloaddition [29], [2 + 1] cycloaddition of dichlorocarbene, silylene, germylene [30], hydroboration [31], arylation, hydrogenation by Birch reduction [32], carboxylic acid groups [33], Diels-Alder reaction, esterification of carboxylated nanotubes [34] and fluorination reactions [35]. Experimental and theoretical studies have shown that the extent of covalent functionalization depends on the curvature of nanotube as an increase in curvature decreases the reactivity toward sidewall functionalization [36].

2.1.1. 1,3-dipolar Cycloaddition (DC)

The solubility of CNT can be enhanced by the covalent functionalization using 1,3-DC reactions. Azomethine ylide (CH_2NHCH_2), ozone (O_3), nitrone ($CH_2N(H)O$), nitrile ylide ($CHNCH_2$), nitrile imine (CHNNH) are the commonly used functional groups for 1,3-DC reaction. The intrinsic physical properties of CNTs such as photoluminescence and Raman scattering decreases upon covalent functionalization, due to chemical bond formation between the functional group and carbon atoms. Theoretical studies by Lu et al. [30] reported the reaction energies (E_r), barrier heights (E_a) and retro barrier height values of a series of 1,3-dipolar molecules on (5, 5) SWCNT using two-layered ONIOM (B3LYP/6-31G*:AM1) approach. Likewise, experimental studies by Prato and co-workers [37] substantiated the theoretical findings on the 1,3-DC functionalization of CNTs. 1,3-DC functionalization was also achieved through the addition of ozone wherein ozone adds onto the end caps and kink regions rather than nanotube sidewall due to increased strain and loss in conjugation. Lu et al. [38] reported the 1,3-DC reaction of ozone onto nanotube sidewalls using two-layered ONIOM (B3LYP/6-31G*:AM1) method.

Prato and co-workers [39] investigated the 1,3-DC reaction of azomethine ylide on both SWCNT and MWCNT. The water-soluble amine functionalized CNT was highly suitable for immobilization of biomolecules, and purification of pristine nanotubes during syntheses. Attachment of peptide molecules onto covalently functionalized SWCNT was reported by Prato and co-workers [40]. The C-terminal group of peptide chain was attached to N-terminal

side group to form a supramolecular complex of peptide wrapped nanotubes. Gallo et al. [23], incorporated *f*SWCNT and fullerenes as nanovectors for the functionalization of INH drug. Armchair (5, 5) SWCNT was functionalized via 1,3-DC reaction of azomethine ylide with the polyethylene glycol (PEG) oligomer tailored to the INH drug. Increasing the number of functionalized units leads to an increase in HOMO-LUMO energy gap and global hardness, and decrease in binding (−3.52 to −6.65 eV) and solvation energy (−31.60 to −49.99 eV) values. An increase in global hardness with increase in functionalization suggests a net stabilization of the complex. It is noteworthy to mention that the optimum length of PEG oligomer used as a linker for the 1,3-DC functionalization is essential as longer PEG chains can interfere with drug administration, block the interaction between the nanotube and cell lines of the body, cellular uptake of drug, and degrade the therapeutic activity of drug molecules [41]. The PEG units with superior hydrophilicity, biocompatibility, and low immunogenicity can resist the opsonisation and increase the retention time of the nanotube-drug conjugate system *in vivo* [42, 43].

The structure, electronic properties, and reactivity of a series of 1,3-DC functionalized armchair (*n, m*) and zigzag (*n, 0*) SWCNTs with antitubercular drugs 2-methyl heptyl isonicotinate (MHI) and PZA via. PEG linker was investigated using first-principles DFT calculations [44–46]. With increase in sidewall functionalization, the global hardness and HOMO-LUMO energy gap decreases suggesting an overall decrease in stability of the complex, which is indicative of the localized induced deformation in the nanotube at the site of covalent attachment. On the other hand, the solubility of bare INH and PZA drugs was enhanced in presence of nanotube support. We showed that the optimum length and chirality of the nanotube is central to understand the electronic properties of functionalized nanotubes, particularly from a drug delivery perspective.

2.1.2. Functionalization using organic acids

Covalent functionalization of CNTs using carboxylic (−COOH) group was realized through oxidation with strong organic acids like H_2SO_4/HNO_3 [47], phosphates, and sulfur-containing units. Acid functionalized CNTs are highly soluble in water under a wide range of pH and exhibit a significant reduction in the aggregation of nanotube bundles. The dispersibility facilitates in the sidewall, endohedral and end tip functionalization of CNT with organic acids and different functional groups. The sidewall functionalization of CNTs via cycloaddition reaction with azide, ozone, transition metal oxides, and carbenes [48] is illustrated in **Figure 3**.

Lu et al. [31] using two-layered ONIOM (B3LYP/6-31G*:AM1) approach reported the reaction pathway and site selectivity for [2 + 1] cycloaddition of dichlorocarbene, silylene, germylene, and oxycarbonylnitrene onto (5, 5) SWCNT. Dichlorocarbene addition occurs preferentially at the 1,2-pair site. The silylene addition at 1,2-pair site was predicted to be exothermic (−20.7 kcal mol^{-1}) and follows a barrier less reaction pathway. Germylene addition was exothermic by 8.5 kcal mol^{-1}, lower than dichlorocarbene and silylene and proceeds in absence of a transition state pathway. Oxycarbonylnitrene addition onto 1,2-pair site of SWCNT was exothermic by 66.2 kcal mol^{-1}, higher than the other three cycloaddition groups. The transition state had an activation barrier of 7.2 kcal mol^{-1}, which suggested that the cycloaddition reaction was facile in nature.

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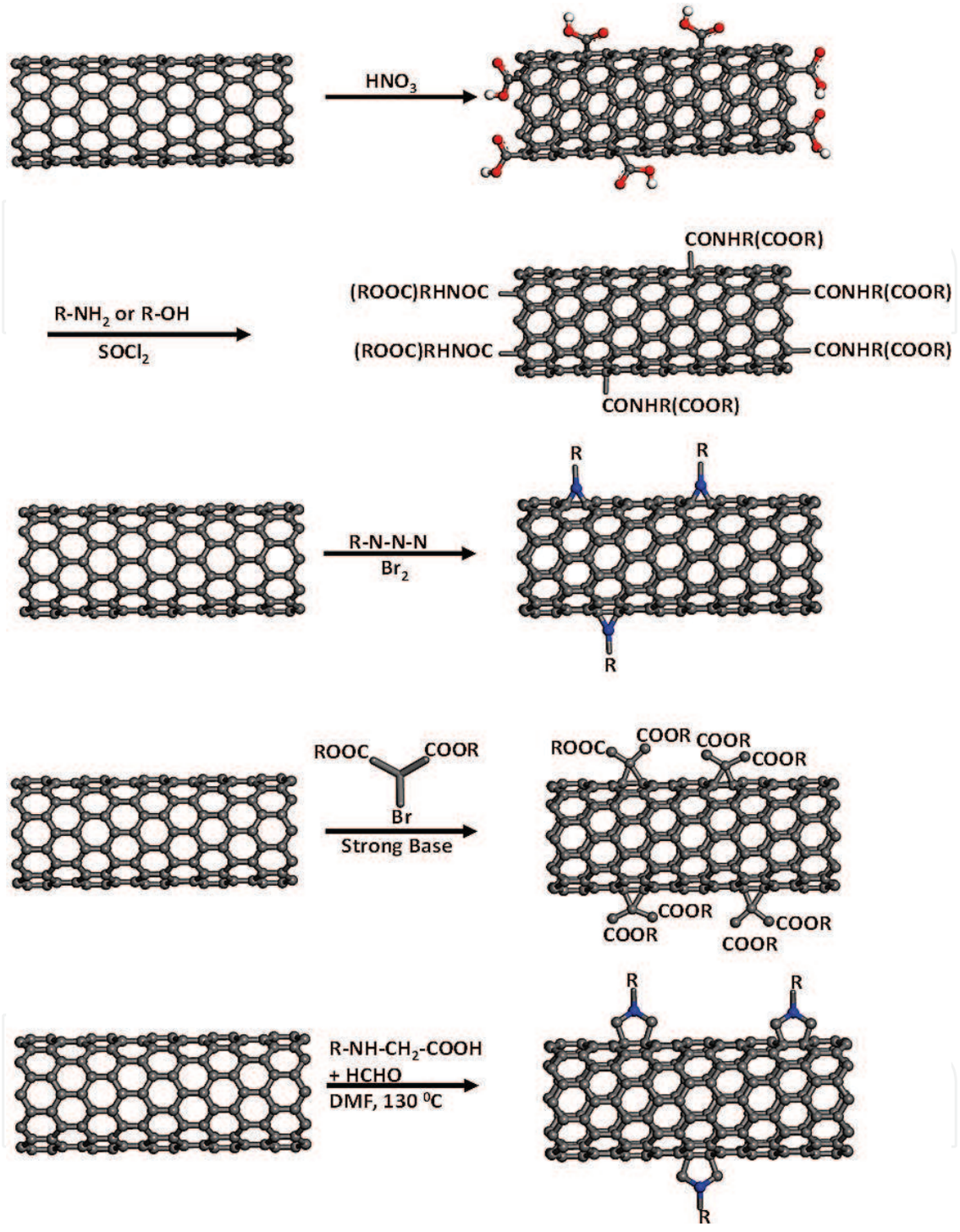

Figure 3. Schemes for sidewall functionalization of SWCNT using covalent bonds. Adopted from Ref. [48].

2.2. Noncovalent functionalization of CNTs

Although covalent functionalization improves the solubility of CNT, it modifies the intrinsic electronic properties by deforming the C-C bond length, perturbing the π-delocalization, and shortening the length of the nanotube. Noncovalent functionalization provides the alternative

approach to improving the solubility of nanotubes without deforming the π-delocalization. For example, exohedral wrapping with polymeric molecules like PEG [49], polymers [50], ss-DNA, and endohedral filling can help in increasing the solubility. Likewise, the polymer molecules can form a surface coating via π-stacking interactions, mediated by weak vdW forces, and hydrophobic interactions. The following subsection discusses some of the widely adopted approaches to the noncovalent functionalization of CNTs.

2.2.1. Functionalization via π-π stacking

The π-π stacking of organic molecules namely pyrene, anthracene, and porphyrin increases the solubility of pristine nanotubes and facilitates in the binding of proteins, polysaccharides, and peptides. Dai and co-workers [51] investigated the noncovalent functionalization of CNT, wherein succinimidyl ester group was co-tethered onto pyrene rings via butanoic acid side chains, facilitating the immobilization of proteins. The amide group of the protein replaces the N-hydroxysuccinimide group that propagates the transportation of biomolecules. Falvo and co-workers [52] reported the functionalization of MWCNT with streptavidin protein, wherein the MWCNT pre-functionalized with 1-pyrene butanoic acid succidymidyl ester (1-pbase) was co-tethered on the nanotube sidewall. The pyrenes formed π-π bonds with the MWCNT sidewall under the influence of which MWCNT undergoes a phase transfer with 1-base acting as a phase transfer catalyst.

The noncovalent functionalization of pyrene on SWCNT was investigated by Cosnier and co-workers [53] for application as modified electrodes in biosensing devices. Calomel electrode was taken as the reference and Pt electrode (5 mm diameter) modified by casting 20 μl THF solution of pristine SWCNT and B-doped SWCNT polished with 20 μm diamond paste as the counter electrode. The SWCNT/pyrene-biotin and B-SWCNT/pyrene-biotin was incubated in 20 μl avidin solutions for 20 min, and the response time for glucose sensing was measured using amperometric response technique. The enzyme-modified SWCNT electrodes were incorporated as electrodes for glucose sensing. In-situ polymerization of MWCNT with polyimide (PI) results in the π-stacking interactions between the imide and aromatic benzene rings of CNT with subsequent wrapping of PI along the nanotube circumferential axis [54]. Polymer wrapping improves the thermal stability and renders the conjugated complex suitable for nanoelectronics devices with improved electronic, thermal and optical properties.

Noncovalent functionalization of porphyrin molecules with SWCNTs have been extensively studied as high yield light-harvesting systems with tunable electronic properties for biological and optoelectronic applications [55, 56]. Roquelet et al. [57], reported an efficient method for the synthesis of porphyrin/SWCNT complex utilizing a micelle-swelling technique in presence of organic solvent. The organic solvent leads to swelling of the micelle facilitating the interaction of porphyrin molecules to the micelle core and SWCNT. Dispersion corrected DFT calculations on the structure, electronic and optical properties of SWCNT functionalized tetraphenylporphyrin (TPP) molecule showed that diameter rather than chirality of the nanotube stabilizes the π-π stacking of TPP molecule [58]. The optical absorption of TPP was not affected by the diameter or chirality of CNT and the optical spectra showed the absorption of π-stacked TPP at almost the same position as the isolated TPP, indicating that the TPP absorption properties were preserved in the complex.

2.2.2. Functionalization using biomolecules and nucleobases

Functionalization of CNTs with biomolecules is useful in the development of nanobio composite devices. Immobilization of DNA in DNA-based biosensors is possible with the incorporation of CNTs in nucleic acid sensing, gene therapy, and biosensor fabrication [59–61]. DNA because of the base pairing sequence facilitates in the alignment of nanotube assembly [62]. Rodger and co-workers [63] investigated the interaction of CNT with DNA using linear dichroism (LD) method. DNA/CNT hybrid exhibited higher LD signals, higher than the sum of the LD spectrum of individual DNA and SWCNT. Jung et al. [64] developed methods for covalent linking of DNA oligonucleotides onto SWCNT films which were later immobilized onto solid surfaces. The carboxylated/aminated DNA oligonucleotides were covalently attached to functionalized SWCNT, the length of which was controlled via oxidation with strong organic acids, leading to the formation of carboxylated SWCNT.

Li et al. [65] investigated the self-assembly of CNT and gold nanoparticles into multicomponent structures using DNA oligonucleotides. The CNT pre-functionalized with -COOH facilitated in the grafting of ssDNA strands and multiple assemblies of nanotubes were thus possible using this technique. In another combined theoretical and experimental study by Sood and co-workers [66], interaction of DNA nucleobases namely adenine (A), guanine (G), cytosine (C), thymine (T) with (5, 5) SWCNT was reported. The *ab initio* studies showed that binding energies of nucleobases onto SWCNT was governed mainly by vdW forces and follow the order: C > G > A > T, respectively. Likewise, the binding energies of A, G, C, T, U nucleobases on (7, 0) SWCNT was predicted to follow the order: G > C > A > T > U, and bears a monotonic dependence on nanotube diameter; that is, nanotubes with small diameter due to low curvature exhibits low interaction energy whereas for nanotubes with high diameter the interaction energy tend to be on the higher side [67].

2.2.3. Noncovalent functionalization using polymers

Polymer wrapping of CNTs mediated via noncovalent functionalization toward the synthesis of highly dispersed, stable and reinforced functional dispersants in aqueous and organic solvents was reviewed by Fujigaya and Nakashima [68]. The polymer wrapping forms a thermodynamically stable coating and any unbound polymer could be removed via dialysis, ultra-centrifugation or chromatographic separation techniques. Similarly, noncovalent functionalization of CNTs using polyethylene glycol (PEG) PEGylated-phospholipid chains forms an effective means of high loading of the drug and biomolecules at the free end of PEG chain and onto nanotube sidewall. PEGylated-phospholipid chain facilitates the high loading (about ~400%) of drug molecules onto CNT and characterizes as a potent carrier vehicle in drug delivery applications. PEG tailored SWCNT exhibit no toxicity for over several months, which was further substantiated from time-dependent assays performed onto mice. Drugs which normally remained insoluble within the biological systems, upon conjugation with PEG modified CNT revealed high solubility as well as retention time within the body. The noncovalent functionalization retained the physical properties of nanotubes without drastically perturbing the overall electronic properties.

First-principles studies on the interaction of conjugated polymers with (8, 0) SWCNT and (10 × 10) graphene sheet was investigated by Jilili et al. [69], to confirm the experimental

observation that polymers are suitable for noncovalent functionalization. The GGA approximation was predicted to be inadequate in describing the physisorbed systems, whereas LDA and vdW corrected GGA yield conclusive results. The electronic structure of SWCNT/graphene was maintained around the Fermi energy with negligible charge transfer between the conjugates. The interaction of polymer-SWCNT/graphene was of weak vdW type with minimal effects on the physical and electronic properties of SWCNT/graphene, important for an effective noncovalent functionalization.

3. Functionalized carbon Nanomaterials in drug delivery

Drug delivery is a process of administering drugs in a controlled, sustained manner to achieve maximal therapeutic efficacy upon transdermal administration. The foremost objectives in developing novel drug delivery systems are to improve the therapeutic competence by [1] increasing bioavailability, [2] preventing toxicity, harmful side-effects by increasing the persistence of a drug, [3] reducing drug exposure toward non-target cells, and [4] minimizing drug degradation and loss [70–73]. Drug delivery systems are designed to improve the pharmacological and therapeutic profile of drug molecules with an ability to cross the cell membrane upon administration [74, 75]. The most important characteristic of SWCNT as a drug delivery system is its ability to penetrate the cell membrane [76], and facilitate the intracellular internalization and trafficking within the cell cytoplasm [77]. A major breakthrough in nanoscience was the advent of CNTs as one of the most sought-after materials for designing novel drug delivery carrier modules to comply with the biotechnological and pharmaceutical objectives. CNT due to its needle-like cylindrical structure can easily penetrate the cell membrane and enter the cell nuclei, while the cell does not recognize it as an intruder.

Functionalized CNTs can act as carriers for antimicrobial agents like amphotericin B [78, 79] and transport it within the mammalian cells. This reduces the antifungal toxicity as compared to the toxicity of free drug (40% of the cells being killed by CNTs-free formulation compared to no cell death by CNTs formulation). The surface-engineered CNTs can capture the pathogenic bacteria in liquid media [80, 81]. In addition, SWCNTs exhibit unique optical properties such as near-infrared region (NIR) fluorescence, and Raman scattering. The fluorescence range spans the entire biological tissue transparent window and is, therefore, promising for drug detection and biological imaging [82–84].

3.1. SWCNTs in tuberculosis therapy

The science of bacteriology is credited to the contributions of Louis Pasteur and Robert Koch. It was the discovery of *Mycobacterium tuberculosis* by Koch that revolutionized medical history [85]. TB is a chronic disease caused by the infection of *Mycobacterium tuberculosis* [86] and is a leading cause of mortality worldwide. The World Health Organization (WHO) 2017 annual report prompted to 10.4 million new TB cases, of which, India and Indonesia alone accounted for a third of the world's TB-burden [87]. In 2016, a total of 9287 new TB cases were reported in the United States [88]. The drastic widespread of TB is mainly accounted to

poverty, homelessness, synergy with HIV/AIDS pandemic, multi-drug resistant (MDR), and extensively drug resistant (XDR) stains of *M. tuberculosis* [89].

Streptomycin was the first antitubercular drug discovered in 1943 [90] and since then several therapeutic drugs like para-amino salicylic acid (1946), isoniazid (INH) (1952), pyrazinamide (PZA) (1952), cycloserine (1952), ethionamide (1956), rifampicin (1957) and ethambutol (1962) have been discovered. The TB therapy involves a combination of four first-line drugs namely; INH, PZA, rifampicin, and ethambutol administered for a period of 2 months followed by minimum 4 months' treatment regimen of INH and rifampicin [91]. PZA (pyrazine-2-carboxamide) is one of the first-line drugs used in TB treatment recommended by the WHO. PZA is metabolized into its active form (pyrazoic acid) by the amidase activity of *M. tuberculosis* nicotinamidase/pyrazinamidase (MtPncA) encoded by the pncA gene [92]. The administration of PZA in high dosage can cause minor to detrimental health problems and the antibiotic resistance of bacteria under prolonged exposure triggers the need for better drug delivery methods to directly bind with the TB bacteria.

We performed DFT, molecular docking and MD studies on the SWCNT-mediated PZA delivery onto the active site of *M. Tuberculosis* pncA enzyme [93]. The DFT calculations predict that the covalent functionalization was thermodynamically favored with negative binding energy values. The decrease in binding energy of PZA/SWCNT with increase in nanotube diameter illustrates that the curvature of nanotube plays an important role in determining the reactivity, and nanotubes with narrow diameter are thermodynamically favorable compared to tubes with larger diameter. The molecular docking studies supported the DFT results thereby establishing that, incorporation of SWCNT facilitates in target specific delivery of PZA within the binding site of pncA as shown in **Figure 4**. The narrow diameter nanotubes were better docked compared to the larger diameter nanotubes and length of PEG chain was predicted to be reasonably adequate for the delivery of PZA within the binding site of pncA. The presence of nanotube did not result in any structural deformation in pncA, rather the incorporation of SWCNT facilitated in the stabilization of PZA conjugated complex.

Noncovalent functionalization of SWCNT and boron nitride nanotubes (BNNTs) with PZA was investigated using DFT and MD simulation (see **Figure 5**) to comprehend the role of nanotube chirality on the electronic properties of the complexes [94]. BNNTs are structural analogs of CNTs with a wide band gap of ~5.5 eV, high chemical, and thermal stability. The potential application of BNNTs is rather limited in terms of its high chemical stability and poor dispersibility. The theoretical results predict the modification in electronic structure of both SWCNTs and BNNTs with the enhancement of electronic states, significant lowering in HOMO-LUMO energy gap and the presence of new dispersionless states within the band gap. Depending on the nanotube chirality, PZA exhibits a preferential selectivity for adsorption, which is further confirmed from the band structure, DOS, total projected DOS, and frontier orbital analysis.

The functionalized nanotube facilitates in the loading and delivery of a PZA onto the active entering pathway of pncA without the nanotube affecting the structural conformation of

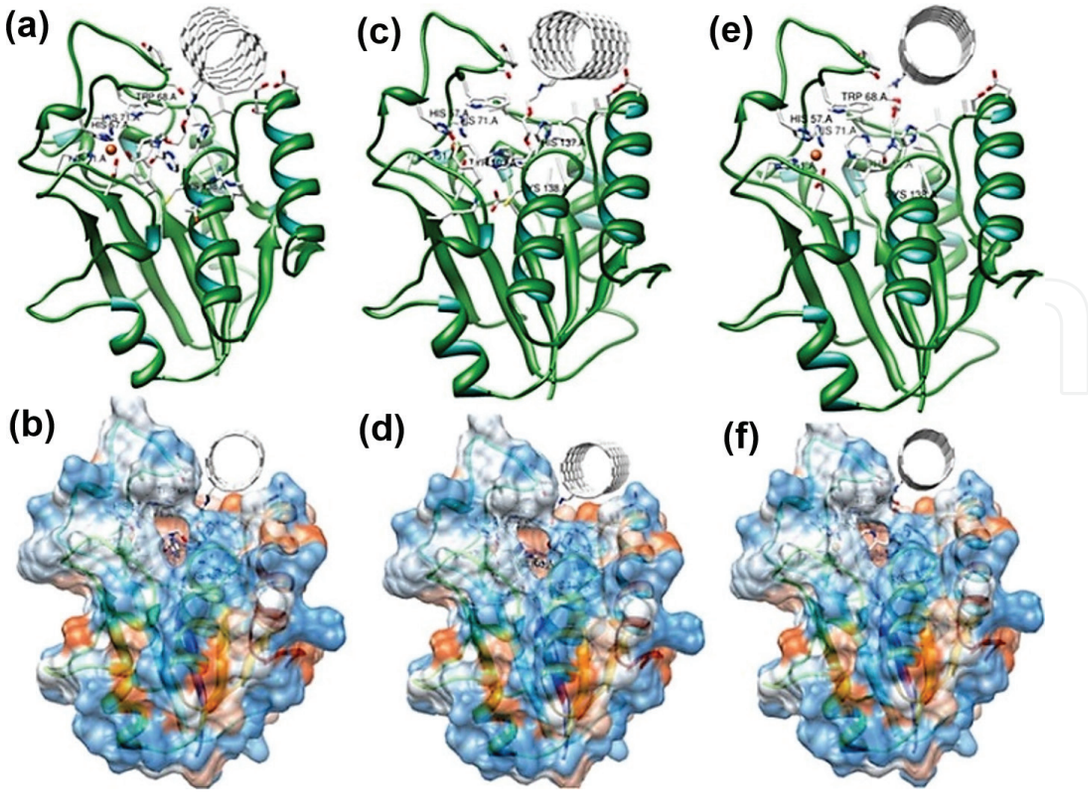

Figure 4. The docked conformation and hydrophobic surface of sidewall functionalized PZA/SWCNT within the active binding site of pncA protein, (a–b) PZA/(9,0) SWCNT (3 unit cells), (c–d) PZA/(9,0) SWCNT (5 unit cells), (e–f) edge functionalized PZA/(9,0) SWCNT (5 unit cells). Reprinted with permission from Ref. [93]. Copyright 2017, Elsevier.

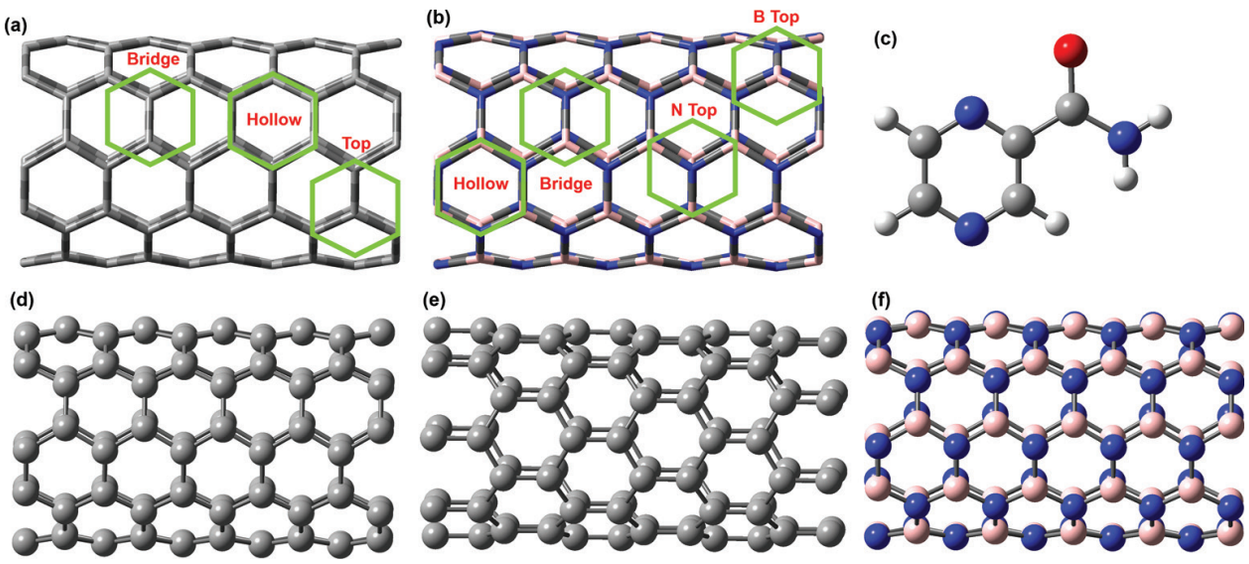

Figure 5. (a) Adsorption sites in the model SWCNT, (b) Adsorption sites in a model (5, 5) BNNT; optimized geometries of (c) PZA, (d) (5, 5) CNT, (e) (8, 0) CNT and (f) (5, 5) BNNT. Adopted from Ref. [94].

pncA as shown in **Figure 6**. The incorporation of nanotube yields better docking scores for PZA then the drug being administered in bare form. Although covalent functionalization aids in achieving target specific delivery of PZA within the active site of pncA, noncovalent functionalization was predicted to be effective for engineering nanotube structure and electronic properties for successful drug delivery applications.

Zanella et al. [95] performed theoretical studies on the interaction of non-steroid anti-inflammatory drug nimesulide with pristine and Si-doped capped SWCNT. The adsorption of nimesulide on Si-doped capped SWCNT exhibit a higher binding energy of 1.8 eV compared to pristine capped SWCNT (0.32 eV) which was due to the high reactive bonding sites on Si atom. The strong interaction of nimesulide with Si-doped SWCNT served as better drug delivery carriers in comparison to pristine capped SWCNT.

Wang and co-workers [96] performed MD studies to investigate the mechanism of encapsulation of nifedipine drug within (10, 10) SWCNT. Their studies showed that the internal

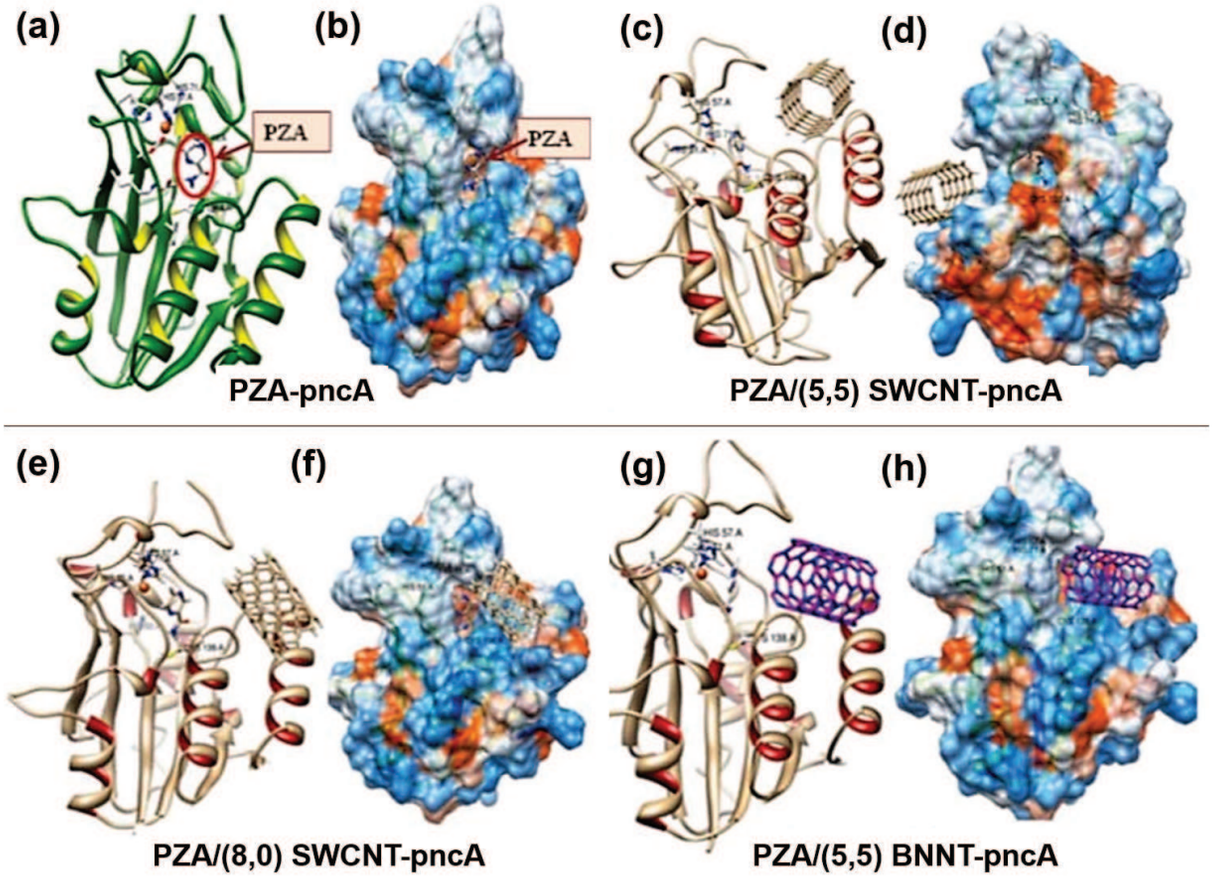

Figure 6. (a) Docked PZA/pncA, (b) electrostatic surface (c) PZA/(5, 5) SWCNT docked onto pncA, (d) electrostatic surface, (e) PZA/(8, 0) SWCNT docked onto pncA, (f) electrostatic surface, (g) docked PZA/(5, 5) BNNT with pncA, (h) electrostatic surface. Adopted from Ref. [94].

adsorption of nifedipine was more stable than external adsorption by 5.3 to 7.8 kcal/mol. In solvent phase, the encapsulation of nifedipine was impeded due to competitive vdW and hydrophobic interactions in SWCNT-nifedipine-water complex. Encapsulation of nifedipine orients the distribution of water molecules inside SWCNT accompanied by the H-bond formation between water molecules and oxygen atom of nifedipine. During the encapsulation process, SWNT undergoes weak fluctuations due to the oscillatory behavior of nifedipine encapsulated within the CNT.

4. SWCNTs in cancer therapy

Platinum-based Phase II and Phase III anticancer drugs hold promise in the treatment of cancer with new drugs being discovered, some of which are still under clinical trials. The two main limitations in use of Pt-based anticancer drugs are [1] the anticancer drugs undergo poor circulation in tissue cells and its activity is reduced with time due to the complex formation with plasma and tissue cells, and [2] tumor cells demonstrate resistance toward Pt-based drugs under prolonged exposure, rendering them ineffective as potent anti-tumor agents. Lippard and co-workers [16, 17] incorporated capped *f*CNT as longboat delivery vehicles for cisplatin anticancer drug through clathrin-dependent endocytosis and measured the changes in redox potential before and after release of the drug. The substituted c,c,t [$Pt(NH_3)_2Cl_2(OEt)(O_2CCH_2CH_2COOH)$] pro-drug was attached to SWCNT functionalized with phospholipid tethered amine with PEG to solubilize the nanotube. Burger et al. [97] investigated the encapsulation of cisplatin in a phospholipid formulation. The lipid-coated cisplatin nanocapsules exhibit drug-lipid ratio and *in vitro* cytotoxicity 1000 times higher than free cisplatin. This method thus formed an effective approach in drug delivery and the means of producing lipid-based nanocapsules for encapsulating different bio- and therapeutic molecules. Hilter and Hill [98] suggested three preferred orientations of cisplatin toward the entry into CNT and probable interactions using mechanical principles and mathematical modeling. The atomic interaction between nanotubes and cisplatin was calculated using hybrid-discrete-continuum approximation. In this approximation, cisplatin was taken as a collection of discrete atoms and the CNT was treated as a continuum body of repeating carbon atoms. Non-bonded interaction, suction, and acceptance energies were calculated using the Lennard-Jones (LJ) potential. For nanotube radius of 5.3 Å, cisplatin exhibited maximum suction energy, depending on the orientation of nanotubes as a function of radii.

We performed density functional studies on the noncovalent functionalization of non-Pt-based anticancer drug camptothecin (CPT) on graphene-based nanomaterials and its prototypes, including graphene oxide (GO) [99]. The noncovalent adsorption of CPT induces a significant strain within the nanosheets and the interaction was thermodynamically favored from energetics perspective. In case of GO, surface incorporation of functional groups resulted in significant crumpling along the basal plane and the interaction was mediated by H-bonding rather than π-π stacking. The molecular docking studies of CPT onto Top1 (**Figure 7a**) showed CPT to be stacked between the Watson Crick AT and GC base pairs and the interaction was mediated via π-π stacking (**Figure 7b**). For the binding of CPT functionalized graphene and GO

with topoisomerase I (top 1) CPT interacts through π stacking with AT and GC base pairs of DNA. The optimum interacting distance of CPT from AT and GC bases was calculated at 3.87 and 3.38 Å, from the central aromatic rings (**Figure 7b**). The re-rank score of bare CPT drug was calculated as −89.01 a.u. with an H-bond score of −2.53 a.u. as shown in **Table 1**.

Likewise, for the docking of CPT/8 × 8 graphene with Top1 (**Figure 8a**) CPT gets docked between the AT and GC base pairs. However, graphene gets docked along the phosphate backbone of the ds-DNA helix as shown from **Figure 8b** indicating a strong interaction between the polar phosphate groups of the DNA helix. Compared to the docking of bare CPT drug, presence of graphene stabilizes the intercalation of CPT between the AT and GC base pairs, as observed from the increase in re-rank score values.

The docking of CPT/GO with Top1 as illustrated in **Figure 9a**, depicts CPT to get docked between AT and GC base pairs of DNA, mediated by π-π stacking interaction similar to that observed for bare CPT and CPT/8 × 8 graphene. However, in the presence of GO, GO undergoes strong interactions with DNA bases and gets docked between the DNA helix and the interaction is stabilized by intermolecular H-bond between polar functional units on the basal plane of GO and DNA nucleobases (**Figure 9b**). The molecular docking studies on bare CPT and CPT functionalized graphene and GO systems showed that the interaction of CPT with Top1 is mediated by π-stacking interaction between the aromatic rings of CPT and the A and C bases of DNA. In presence of graphene and GO, CPT undergoes a similar trend in adsorption while the graphene and GO nanomaterial gets docked along the phosphate backbone indicating a strong preferential interaction with DNA.

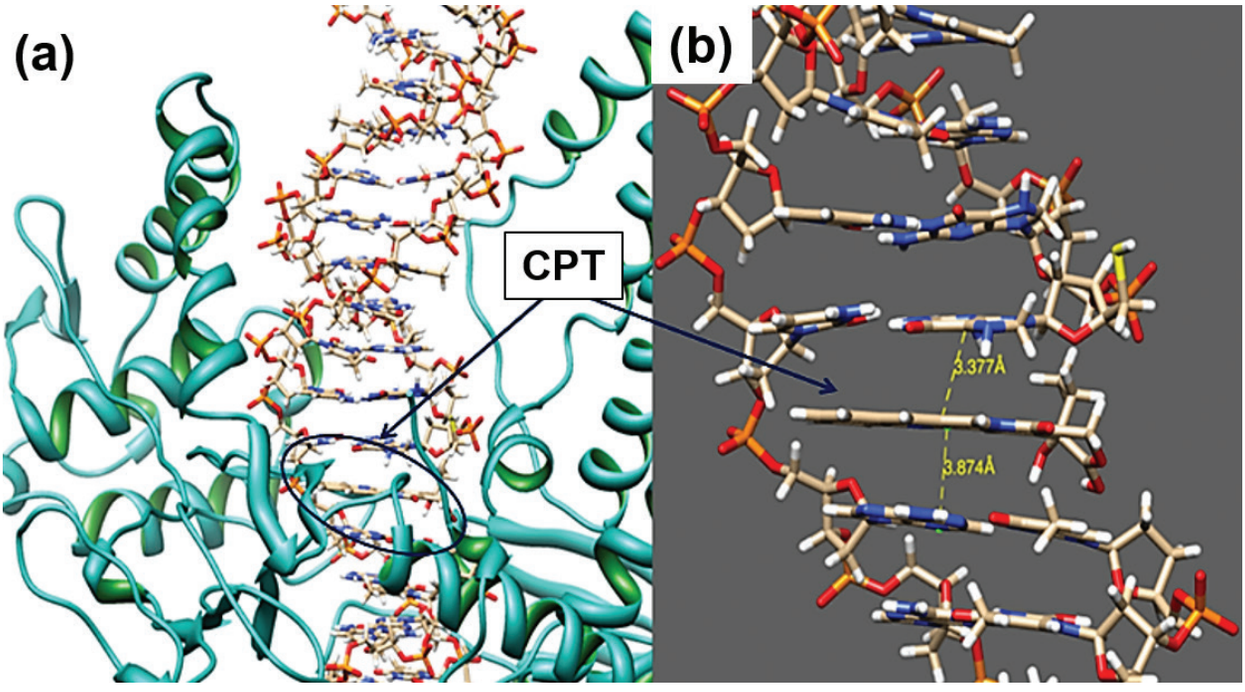

Figure 7. (a) Secondary structure of Top1 protein with the CPT drug docked within the DNA, (b) interacting distance between CPT and the DNA base pairs of top 1. Reprinted with permission from Ref. [99]. Copyright 2017, Elsevier.

System	Re-rank score CPT	Re-rank score nanosheet	H-bond score CPT	H-bond score nanosheet
CPT_Top1	−89.01	—	−2.53	—
8 × 8 graphene/CPT docked onto Top1	−89.10	95.87	−2.57	0.00
8 × 8 GO/CPT docked onto Top1	−90.21	126.21	−2.29	−4.44

Table 1. The re-rank scores and H-bond scores for the best docked conformations of CPT and CPT/8 × 8 graphene, and CPT/8 × 8 GO sheets, respectively.

Boucetta et al. [20] investigated the supramolecular MWCNT-DOX-copolymer complex for anticancer activities. Since DOX, a clinically acclaimed anticancer drug belonging to the family of anthracyclines exhibit fluorescence properties, its uptake and interaction with nanotubes upon administration can be monitored using fluorescent spectrophotometry. The copolymer coated MWCNT formed supramolecular complexes with DOX via π-stacking and revealed enhanced cytotoxicity leading to highly efficient cell killing efficiency. Likewise, Liu et al. reported the use of DOX loaded PEG functionalized CNT for targeted delivery of anticancer drugs in tumor

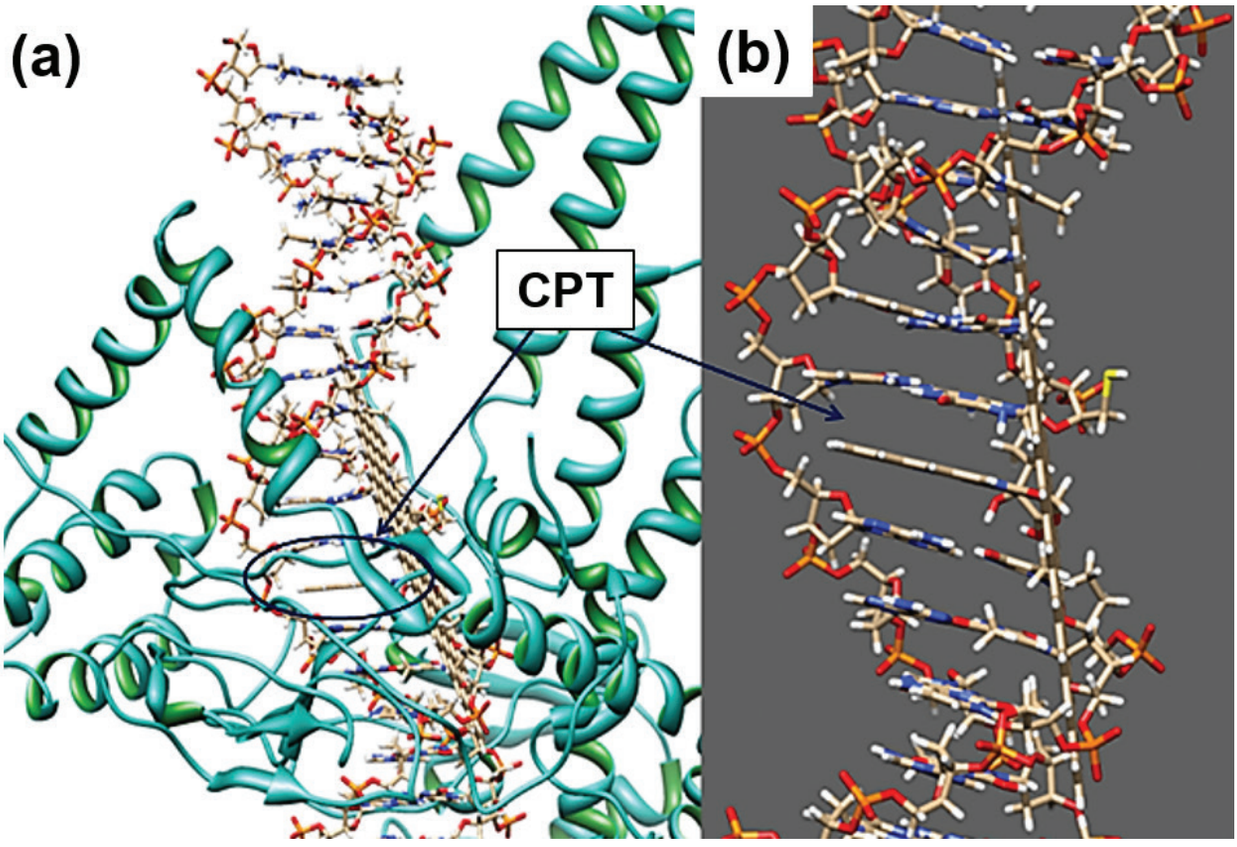

Figure 8. (a) Secondary structure of Top1 with the CPT/8 × 8 graphene sheet docked within the DNA, (b) binding of CPT/8 × 8 graphene sheet with DNA base pairs of top 1. Reprinted with permission from Ref. [99]. Copyright 2017, Elsevier.

http://dx.doi.org/10.5772/intechopen.71889

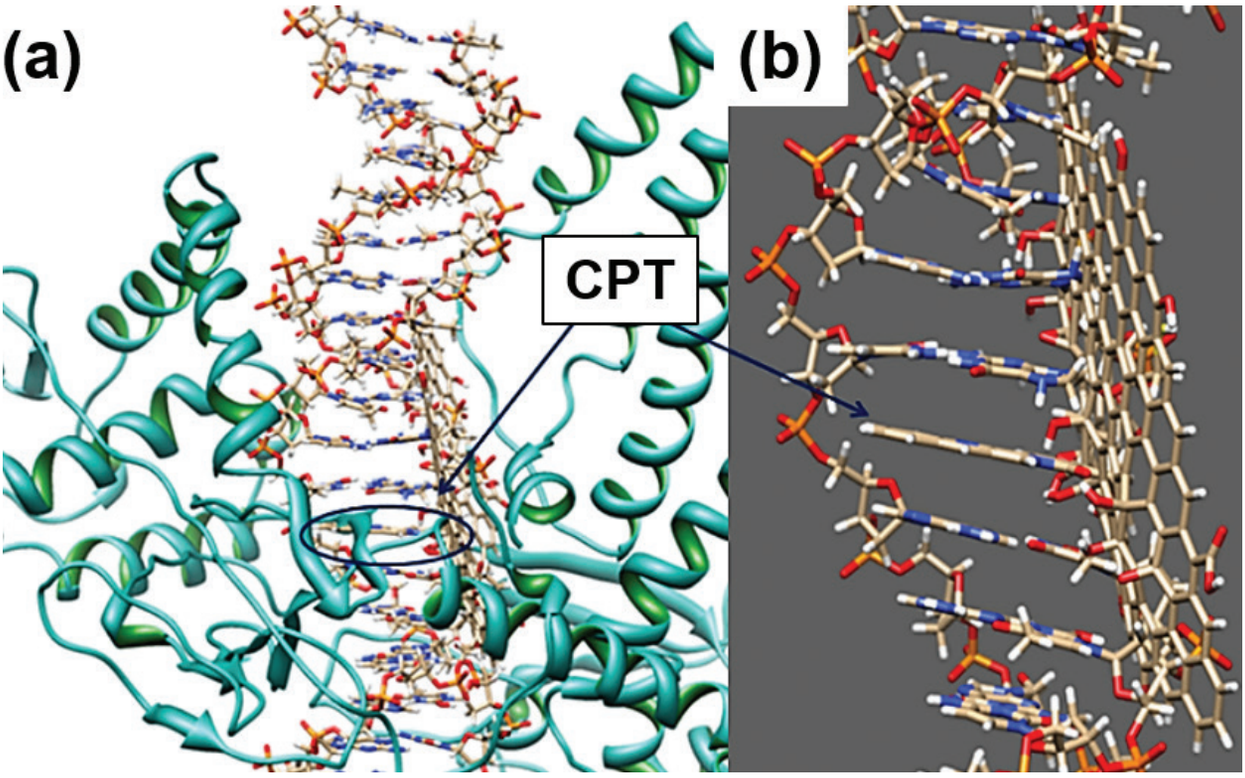

Figure 9. (a) Secondary structure of Top1 protein with the CPT/8 × 8 GO sheet docked within the DNA, (b) the binding of CPT/8 × 8 GO sheet with DNA base pairs of top 1. Reprinted with permission from Ref. [99]. Copyright 2017, Elsevier.

cells [22]. The SWCNT was pre-functionalized with PEG and DOX and a fluorescence probe (fluorescein) was loaded onto the nanotube via π stacking. The loading and subsequent release of DOX were found to be pH dependent; decrease in pH from 9 to 5 showed a decrease in DOX loading. Under acidic conditions (pH 5.5), DOX exhibited increased hydrophilicity and solubility with lysosomes and endosomes, facilitating the release of drug molecules from the nanotube. On decreasing the pH, surface loading of DOX onto nanotube surface lowered and at lower acidic pH, amine group of DOX underwent protonation resulting in increased solubility of DOX molecules.

5. Summary

Carbon nanotubes have proffered as one of the novel functional materials of the 21st century, broadening the theoretical and experimental perspectives in research to explore its novel and intriguing properties. Due to the conjugated π-electron backbone and curvature (properties very similar to fullerene and graphene) they are highly reactive and depending on the size, length and (n, m) indices, the electronic properties can be tuned to fit the desired functionality. Since the synthesis of CNT yields a mixture of both metallic and semiconducting tubes of varying diameter and chirality, separation and purification of nanotubes pose a major problem which restricts the applicability. Secondly, nanotubes are highly

hydrophobic and non-dispersible in most of the common aqueous and organic solvents and tend to aggregate in bundles. To improve nanotube dispersibility, surface modification via functionalization is thus a sought-after approach and covalent and noncovalent functionalization methods can reduce the bundling effect and hydrophobicity. Covalent functionalization although renders high stability to the nanotubes, it tends to distort the structural and inherent electronic properties. Noncovalent functionalization, on the other hand, retains the intrinsic properties of the nanotube, as it forms a surface coating on the nanotube sidewall, and facilitates the uptake of drugs, biomolecules, peptides, proteins, DNA, RNA, and genes within the biological systems.

Although CNTs demonstrate practical applicability in all facets of science, be it biology, physics, medicine, nanotechnology, catalysis, or materials science, its long-term implications need to be assessed from the perspective of human health to environmental risks. The long-term fate of CNTs released into the environment depends on the structural, morphological and synthetic treatments [100]. Methods of reducing toxicity *in vivo* and *in vitro* can be envisaged via functionalization of CNT. Proper assessment and in-depth study are essential to render nanotubes useful for diverse and environmentally benign applications.

We investigated the potential application of SWCNTs, graphene-based nanomaterials and its prototypes in TB and cancer chemotherapy using conventional DFT methods supported by molecular docking and MD simulation on the nature of interaction of therapeutic drug functionalized SWCNTs/graphene with the binding site of the protein. The functionalization of SWCNTs with therapeutic drugs using covalent and noncovalent schemes were adopted to investigate the drug binding with the nanotube and the stability of the conjugated complexes. DFT results supported by molecular docking and MD simulation helps in contemplating the feasibility of SWCNT-based novel drug delivery in cancer and TB therapy.

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