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REVIEW ARTICLE

Polymer-wrapped single-walled carbon nanotubes: a transformation toward better applications in healthcare

Mazzura Wan Chik[1] · Zahid Hussain[1] · Mohd Zulkefeli[2] · Minaketan Tripathy[1,3] · Sunil Kumar[4] · Abu Bakar Abdul Majeed[3] · K. Byrappa[5]

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Abstract
Carbon nanotubes (CNTs) possess outstanding properties that could be useful in several technological, drug delivery, and diagnostic applications. However, their unique physical and chemical properties are hindered due to their poor solubility. This article review's the different ways and means of solubility enhancement of single-wall carbon nanotubes (SWNTs). The advantages of SWNTs over the multi-walled carbon nanotubes (MWNTs) and the method of non-covalent modification for solubility enhancement has been the key interest in this review. The review also highlights a few examples of dispersant design. The review includes some interesting utility of SWNTs being wrapped with polymer especially in biological media that could mediate proper drug delivery to target cells. Further, the use of wrapped SWNTs with phospholipids, nucleic acid, and amphiphillic polymers as biosensors is of research interest. The review aims at summarizing the developments relating to wrapped SWNTs to generate further research prospects in healthcare.

Keywords Carbon nanotubes · Single-wall carbon nanotubes · Superhydrophobicity · Polymer wrapping · Solubility enhancers · Targeted drug delivery

Introduction

Carbon nanotubes (CNTs) are the novel nanostructures derived by bottom up chemical synthesis approaches [1]. They represent simplest chemical composition, atomic bonding configuration, yet exhibit the most diversity and richness among the nanomaterial in regard to structure-property relations. Solubilization and stable dispersion of these materials in aqueous solvents at high concentration is critically important to their processing and applications, as they possess outstanding properties in various emerging fields [1–3]. Moreover, the aqueous dispersion of these nanomaterials plays a pivotal role, regarding their use especially in biomedical research. Even after a decade of research, the full potential of employing CNTs as reinforcements has been severely limited because of the difficulties associated with dispersion of entangled CNTs during processing and poor interfacial interaction between CNTs and polymer matrix [3]. The nature of dispersion problem for CNTs is rather different from other conventional fillers, such as spherical particles and carbon fibers, because CNTs are characteristic of small diameter in nanometer scale with high aspect ratio (> 1000) and thus extremely large surface area. In addition, the commercialized CNTs are supplied in the form of heavily entangled bundles, resulting in inherent difficulties in dispersion [3].

Currently, CNTs are playing an important role in drug delivery as a carrier system because of their several unique physical and chemical properties [4, 5]. Studies show that CNTs are toxic and that the extent of that toxicity depends on their properties such as structure (single wall or multiple wall), length and aspects ratios, surface area, degree of aggregation,

✉ Minaketan Tripathy
minaketantripathy@gmail.com

[1] Laboratory Fundamental of Pharmaceutics, Faculty of Pharmacy, University Teknologi MARA (UiTM), Bandar Puncak Alam, Selangor 42300, Malaysia

[2] Department of Pharmaceutical chemistry, School of Pharmacy, International Medical University, Bukit Jalil, Kuala Lumpur 57000, Malaysia

[3] Pharmaceutical Life Sciences Department, Faculty of Pharmacy, University Teknologi MARA (UiTM), Bandar Puncak Alam, Selangor 42300, Malaysia

[4] ICAR-NBAIM, Kushmaur 275103, India

[5] Mangalore University, Mangalgangothri, Mangalore, Karnataka 574199, India

extent of oxidation, bound functional group(s), method of manufacturing, concentration, and dose [6]. People could be exposed to CNTs either accidentally (by coming in contact with the aerosol form of CNTs during production) or by exposure as a result of biomedical use. Numerous in vitro and in vivo studies have shown that CNTs and/or associated contaminants or catalytic materials that arise during the production process may induce oxidative stress, prominent pulmonary inflammation, apoptosis in different cell types, and induction of cytotoxic effects on lungs [5]. Targeted drug delivery is one of the key areas of research in diagnosis and rational treatment of various types of diseases. Their pharmaceutical significance and therapeutic feasibility is due to their inherent physicochemical and exceptional pharmacological activities including anticancer and antimicrobial actions [7].

In this review, the authors intend to summarize the aspects of CNTs, their types, super hydrophobicity related issues, means of improvement in solubility or dispersion, and their applications in particular to health care. Emphasis has been given to single-wall carbon nanotubes because of their superiority over multi-wall CNTs.

Carbon nanotubes

History of CNTs

CNTs are a type of carbon family materials accidentally found by Oberlyn et al. (1976) using a vapor-growth technique. These authors discovered hollow carbon tubes of nanometer-sized diameters. Later, CNTs became popular when lijima successfully clarified the structure of the nanotube and was able to grow bulk of single-wall carbon nanotubes (SWNTs) [1]. In general, carbon allotropes (pure carbon) can be categorized as graphite, diamond, fullerene (C_{60}), and more complex structures such as carbon nanotube [2, 3] (Fig. 1).

CNTs are several micrometers long, with diameter of up to 100 nm [4]. It consists of a layer of graphitic sheet rolled up to form SWNTs with diameter ranging from 0.4 to 5 nm. A stack of single-wall nanotubes rolled to form multi-wall carbon nanotubes (MWNTs) [5] with bigger diameter from a few to tens of nanometers. Figure 2 shows the structure of SWNTs and MWNTs [9]. CNTs are able to form fullerene [6], a carbon sheet with the two end caps of SWNTs joined together. CNT has remarkable physical, thermal, electrical, mechanical, and optical properties [7] due to its strong sp^2 hexagonal pattern which is a basic structure for other sp^2 carbon allotropes. The carbon sp^2 atoms are pyramidalized and the π-orbitals seem misaligned [8] that gives rise to the unexceptional strong properties of CNTs.

Regardless of their beneficial properties, CNTs are known to show signs of toxicity when inhaled and used as carrier for the administration of drugs for different case of human

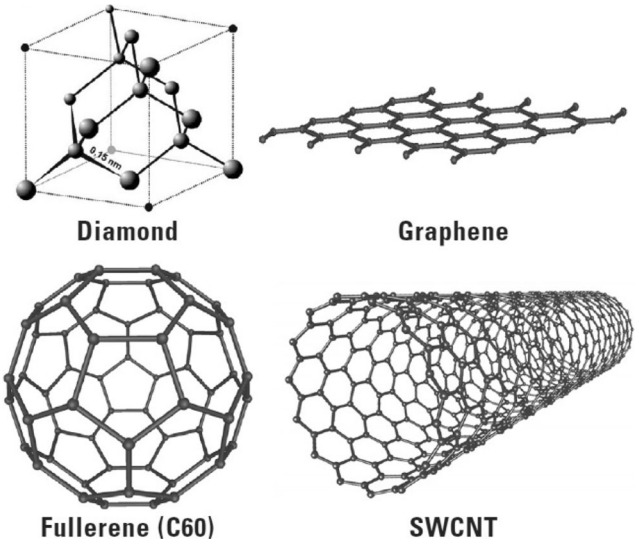


Fig. 1 The structure of some carbon allotropes [2]. Permission for the reprint has been granted from copyright source

diseases. The nanotubes could affect, distribute, and deposited within the lung compartments. This could cause an inflammatory to the lung and the respiratory tract [5]. The toxicity effect was subjected to the structure (SWNTs, MWNTs, functionalized SWNTs, or functionalized MWNTs), length and surface area, extent of oxidation, and bound of functional groups. Both SWNTs and MWNTs might induce apoptosis in different type of cells [10, 11]. However, a few studies showed a

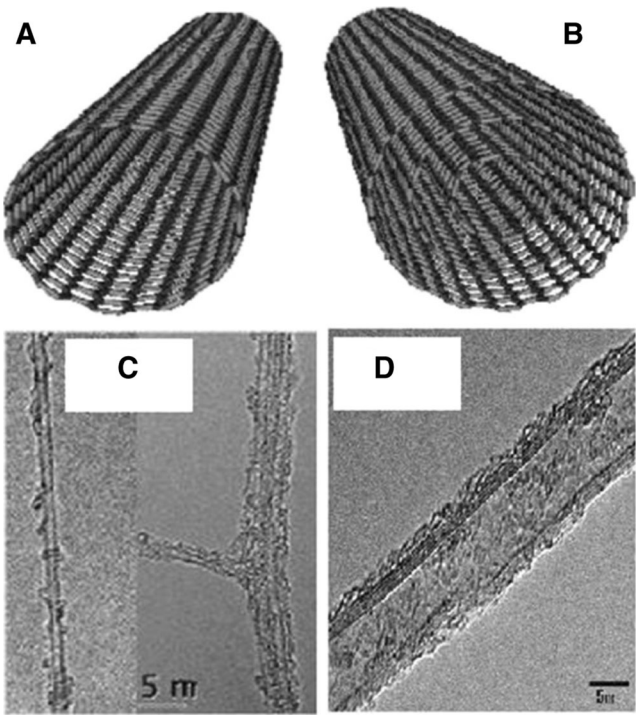


Fig. 2 Schematic structure of **a** SWNT and **b** MWNT. The transmission electron microscope (TEM) of **c** SWNT and **d** MWNT [9]. Permission for the reprint is not required as the source is an open access article distributed under the terms of the Creative Commons Attribution License

low toxicity of MWNTs compared to SWNTs, whereas functionalized SWNTs (f-SWNTs) proposed low toxicity toward living cells [12]. The toxicological assessments need to be carried out and fully explored to develop understanding on their effects in biological environment.

CNTs are known to have poor solubility in organic and polar solvents. They possess a π-system with highly hydrophobic surface and tend to entangle due to strong van der Waals interactions. Two mechanisms have been proposed to increase the solubility of CNTs which are covalent modification by attaching molecules to the CNT sp^2 backbone and non-covalent modification of CNTs by adsorption of molecules onto the nanotube surface [13, 14]. The non-covalent modification method is more preferable prior to its ability to preserve the intrinsic properties of nanotubes, whereas the other method caused alteration of the tube sidewall which damaged the nanotubes properties [15, 16].

In the present review, the authors focus on SWNTs owing to several advantages over MWNTs characteristic. Table 1 shows the differences in characteristics of SWNTs and MWNTs [9]. An attempt has been made to review the properties of SWNTs and its solubility enhancement with non-covalent mechanism using polymer.

Single-walled carbon nanotubes

SWNT is a rolling sheet of graphene (Fig. 2) along an (*n*, *m*) lattice vector in the graphene plane and formed a cylindrical tube with diameter of about 1–2 nm. The (*n*, *m*) lattice vector determines the diameter and chirality [9]. SWNTs can be either metals or semiconductors depending on the chirality (Fig. 3) [6, 17]. Following the general opinion, SWNTs are named as zigzag when $m = 0$, armchair when $n = m$, and other state are called chiral [9]. The armchair form is usually having metallic behavior, whereas the other form commonly acts as a semiconductor. The small diameter semiconducting SWNT (s-SWNT) and large diameter metallic SWNT (m-SWNT) are approximately two-third and one-third of SWNTs production, respectively.

SWNTs can be synthesized and purified altogether through method of dual pulsed laser vaporization [18] that purified SWNTs in a large scale and arc discharge [19] method involving combination of acid washing followed by a high temperature hydrogen treatment. These treatments successfully remove amorphous carbon, clean the SWNT, and yield purified SWNTs. In advanced method, s-SWNT and m-SWNT can be separated using chemical vapor deposition (CVD) growth of SWNTs [20] with 90% purity and a defined chirality along with controlled structures. The separation was done by using special scotch tape composed of polydimethylsiloxane (PDMS) as supporting material and 3-aminopropyl-triethoxysilane ($C_3H_{23}NO_3Si$, APTES) and triethoxyphenylsilane ($C_{12}H_{20}O_3Si$, PTEOS) as functional glues for s-SWNT and m-SWNT respectively.

Recently, Hou et al. (2014) have reported that modified floating catalyst chemical vapor deposition method (FCCVD) using hydrogen gas as the selective etchant has positively removed s-SWNTs and yielded about 88% of m-SWNTs. The exact yield of m-SWNTs without s-SWNTs offered great potential applications in high-performance transparent conductive devise [21]. The ability to control the diameter and chirality of nanotubes has been in demand for structural control and specific application in certain devices, which can be achieved by adjusting the furnace temperature or selecting a suitable catalyst [22, 23]. Soumyendu et al. [24] proposed an ordinary process of CVD with a lower concentration of catalyst used and has reduced the diameter spread of the SWNTs synthesized from 1.65 to 1.13 nm. The main advantage of this method is because of its simplicity.

The diameter of SWNT can be enlarged on purpose by heat-treatment. The tubes were heat-treated in vacuum of 10^{-6} Torr for 5 h in the temperature range of 1000–2000 °C [25]. Later, at 1800 and 2000 °C, a few SWNTs with diameters of about 1.53 and 1.75 nm have appeared. Two years later, Yudasaka et al. further investigated the effect of heat treatment using HiPco SWNT and single-wall carbon nanohorn (SWNH) heated at 1000–2400 °C that resulted in the formation of multi-wall carbon nanotubes at higher temperature specifically at temperature more than 2000 °C [26]. Similarly, Yudasaka et al. (2003) have attempted to incorporate a guest molecule namely C_{60} inside the enlarged tube of SWNT via methods of nano-extraction and nano-condensation. The method involved heat-treated HiPco SWNT at 1780 °C in vacuum producing SWNT with diameter from 1 to 2 nm. The sample then treated with C_{60} crystallite into 10 ml of ethanol and ultrasonicated for 3 min [27]. The so-called nano-extraction method is easy to apply while the nano-condensation method is very convenient as the process is faster.

Medicinal properties of SWNTs

Utility in medicine and health

The use of carbon nanotubes in medicine and health has gained greater attention from researchers. CNTs play important roles in drug delivery system (DDS) as successful nanocarrier since their hollow tube provide spaces for small molecules to be incorporated inside it [27–29]. This will open novel path in DDS as drug moieties can be loaded inside the hollow tube and delivered to target cells [30]. Arsawang et al. (2010) have investigated the molecular properties of the encapsulated anticancer drug gemcitabine inside SWNTs via molecular dynamics (MD) simulation [31], which showed that the drug molecule always exists in the tube through the π-π

Table 1 Comparison between SWNT and MWNT

SWNT	MWNT
1. Single layer of graphene	1. Multiple layers of graphene
2. Synthesis requires the use of catalyst	2. Can be produced without a catalyst
3. Poor purity	3. High purity
4. More chances of defect during functionalization	4. Less chances of defect during functionalization
5. Less accumulation in the body	5. More accumulation in the body
6. Simple structure that allow easy characterization and evaluation	6. Very complex structure
7. Pliable and can be twisted	7. Cannot be twisted easily

stacking conformation formed between its cytosine ring and the tube surface. SWNTs are found to be well conjugated with many therapeutics [32], able to release the drug moieties inside cells [33], and more versatile because of their superior property in penetrating cells including hard and transfect types of cells [34]. They work fine for bioimaging [35], biosensing [36], and biomedical applications [37].

As reported, SWNTs can be internalized into cells via phagocytosis and endocytosis [38, 39] supporting delivery of medicine into a targeted cell. A stable PEGylated-nanotube with doxorubicin incubated with Hela cells showing localization within endosomes that suggests engulfment of drug-SWNTs complexes in endosomes [40]. Besides, SWNTs were also able to cause cell apoptosis which is a favorable characteristic to kill cancer cells [10]. SWNTs upon exposure to laser light can cause SWNTs sheets to adsorbed water molecules and heated to more than 100 °C that caused nanobomb. The nanobombs in the study showed specific explosion to the human BT474 breast cancer cells treated with SWNTs while the untreated surrounding cells were viable [41].

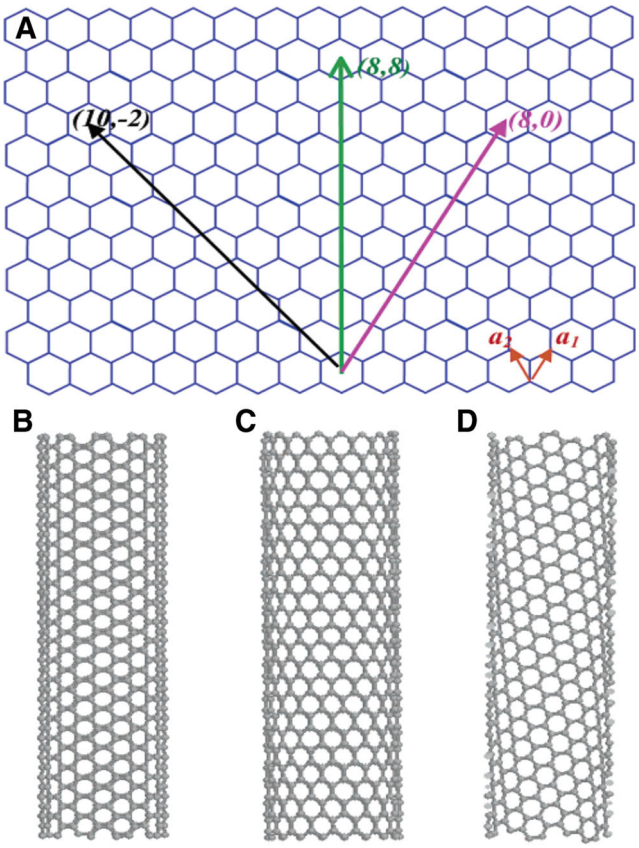


Fig. 3 **a** Schematic honeycomb structure of a graphene sheet. Shown in the picture are the two basis vectors a_1 and a_2. Folding of (8,8), (8,0), and (10–2) vectors lead to **b** armchair, **c** zigzag, and **d** chiral tubes, respectively [17]. Permission to reprint has been granted from American Chemical Society (Copyright © 2002)

Lee and co-workers (2013) have developed a conjugated cetuximab-SWNTs (SWNTs-c225) linked to poor solubility chemotherapeutic drug [42, 43] SN38 (7-ethyl-10-hydroxycamptothecin), a topoisomerase I inhibitor that has strong toxicity against various types of cancer cell such as lung, colorectal, and ovarian. The conjugated drug had successfully overcome the poor solubility disadvantage of SN38 by using SWNTs as the delivery vehicle. Three different overexpressed colorectal cancer cell lines (HCT116, HT29, and SW620) were used to study the anticancer agent SN38 using the SWNTs carrier. The result showed that the intracellular SN38 was first dissociated from the SWNT carrier before entering the nucleus while SWNT-carrier remained in the cytoplasm. The active drug was released enzymatically and caused cell apoptosis of HCT116, HT29, and SW620 cells after 72 h of incubation [44].

Another study on cancer treatment had been reported by Liu et al. (2008) when their water-soluble conjugated SWNTs with paclitaxel (SWNTs-PTX), a cancer therapeutic drug, showed higher efficiency in suppressing tumor growth in murine 4T1 breast cancer model compared to clinical Taxol [45]. The in vivo study can be classified as successful due to prolonged blood circulation and ten-fold higher uptake of PTX by the tumor cells that result in cell apoptotic. Besides, SWNTs were found excreted through biliary pathway which is promising for cancer treatment as it possessed minimum side effects with low drug doses for cancer therapy.

As the safety of CNTs is a growing concern, many researchers have investigated the toxicity of CNTs [46, 47]. Treatment of two types of SWNTs (single and double walled)

and MWNTs-50 on 24 male Wistar rats showed over 500 μm fibrotic lesions in MWNTs-50 treatment. This massive fibrosis was not observed in both types of SWNTs but observed in MWNTs-50 (Fig. 4a) which suggest that SWNTs had lower carcinogenicity to mesothelial cells [48]. Recent study showed that MWNTs possess huge behavioral toxicity such as anxiety and depression compared to SWNTs [46]. Meanwhile, SWNTs at lower concentration showed significant Chinese Hamster Ovarian (CHO) cell survivor with minimal changes in the cell morphology and cell numbers (Fig. 4b) [49].

The study of SWNTs in DDS has not stopped and it is ongoing. Donkor and Tang (2013) reported that SWNTs that underwent extended period of acid treatment for 32 and 44 h lead to ultra-short SWNTs (US-SWNTs) [50] with an approximate yield of 77% of SWNTs above 35 nm and over 80% within 10–35 nm length. Two systems of US-SWNTs (SWNTs-30 and SWNTs-50) with lengths of 30 and 50 nm respectively and linked covalently with 6-arm polyethylene glycol (PEG) showed better cellular uptake for active targeting. Depending on the cell type, SWNT-30 showed spontaneous cellular uptake for active targeting and rapid excretion out of Hela and hepatoma but not Huvec cells (Fig. 4c). Hence, this results in the prevention of intracellular accumulation of SWNTs that could lead to toxicity.

Single-walled carbon nanohorns (SWNHs) have been investigated as drug carrier due to their horn-shaped single-walled graphene sheets [51]. SWNHs incorporating with cisplatin forming CDDP@SWNHox is an anti-cancer drug that had the potential to kill human lung-cancer cells, NCI-H460 [30]. The cisplatin released from CDDP@SWNHox was able to reduce the proliferation of NCI-H460 cells, whereas the carrier SWNHox showed non-toxic behavior against non-cancer cells. Iijima et al. (2014) reported that SWNHs with gadolinium oxide (GD) when orally administered to normal and colitics-induced mice showed that black SWNHs particles were only found in the gastrointestinal tract and feces (Fig. 4d) but not in the spleen, blood, or liver thus preventing the accumulation of SWNHs in the body that would have caused toxicity [52]. However, this result is contradicted with the article reported by Han et al. (Fig. 4e) [53]. The summary of medicinal utility of CNTs has been presented in Table 2.

Antimicrobial properties of SWNTs

SWNTs have also been investigated to treat microbes and surprisingly SWNTs showed strong antimicrobial activity (Fig. 5a, b) [54] and antiseptic properties [55]. SWNTs have become potent candidates to treat multidrug-resistant microorganisms such as viruses, bacteria, fungi, and protozoa that caused microbial infection and mortality globally [56]. The discovery of antimicrobial properties of SWNTs gives hope for application of functionalized carbon nanotubes (*f*-CNTs) as carrier for antibiotics to overcome resistant developed by microorganisms toward antibiotics and enhance their bioavailability and provide their targeted delivery [57].

Functionalized SWNTs (*f*-SWNTs) with –OH and –COOH groups appear to show a strong antimicrobial activity toward both gram-negative and gram-positive bacterial cells [58] by disrupting the microorganism cellular membrane integrity, metabolic processes, and morphology. Later, Pasquini et al. (2012) reported that surface functionalization of SWNTs with nine different functional groups had showed different aggregation state and dispersity that indirectly affect the bacterial cytotoxicity [59]. Conjugation of SWNTs with a widely known metal that possess antimicrobial properties like silver has been attributed to strong bactericidal against both mucoid and nonmucoid strains of *Pseudomonas aeruginosa* [60]. It is the first report of antimicrobial activity of AgCNTs against a mucoid variant of *P. aeruginosa* a more virulent phenotype that normally causes human infections.

Effects of SWNTs length and concentration on the antimicrobial properties of SWNTs were studied by Yang et al. [61] and Le et al. [62] respectively. SWNTs owing metallic properties showed better antimicrobial activity against *Escherichia coli* cells compared to semiconducting SWNTs [63]. The unique properties of SWNTs were not only studied by microbiologist but also by ecotoxicologist [64]. Besides, single- and double-wall carbon nanotubes were also used as the removal of antibiotics from aqueous solution with highest removal capacity was achieved by using SWNTs compared to MWNTs [65]. This result is crucial in controlling and treating aquatic pollution caused by pharmaceutical drugs and surfactant.

Super hydrophobicity of SWNTs and related issues

SWNTs like other nanotubes are naturally highly hydrophobic and cannot dissolve in the aqueous environment [66]. The strong hydrophobicity, π-π stacking, and the van der Waals attraction within the nanotubes system support cluster of SWNTs formation. These bundled SWNTs have hindered them from solubilizing in organic solvents and water-based systems [67]. The incapability to solubilize might restrict or prevent their use in most promising applications especially in biological systems including drug delivery, biosensors, biomedical devices, and cell biology [68].

Strategies to enhance solubility

Dispersing individual SWNTs in water or other solvents is critical for biological applications and certain composite material applications. Dispersing SWNTs without the aid of a solubilizing agent seems to be impossible due to a strong van der Waals interaction of the nanotube particles. Initially,

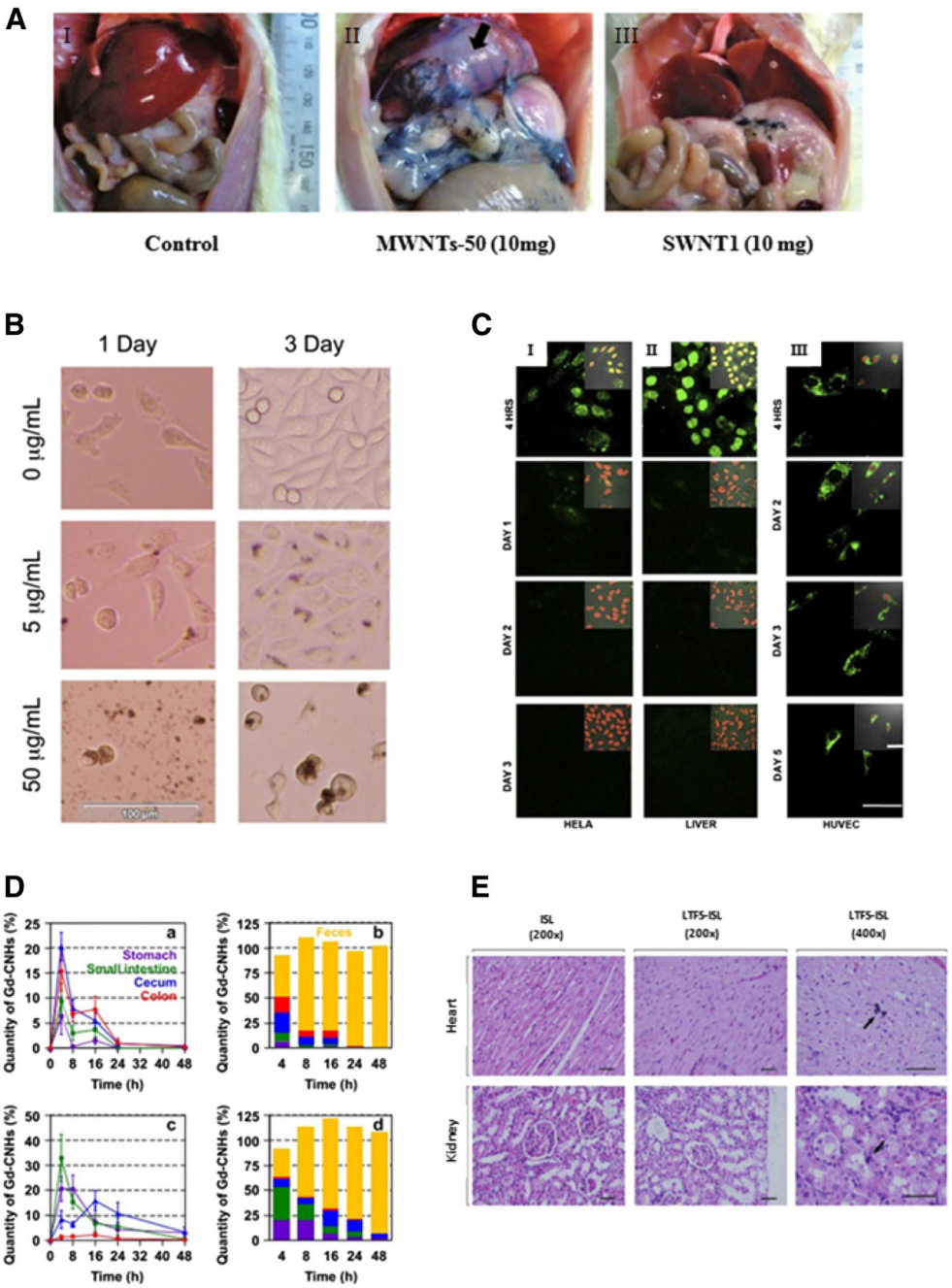


Fig. 4 The in vivo and in vitro results of SWNTs treated with various cells. **a** The massive fibrosis present in the rat peritoneal cavity 4 weeks after a single injection of each type of CNTs with MWNTs-50 showed massive fibrosis with chronic inflammation. **b** The CHO cell numbers and morphology does not significantly reduce at lower SWNTs' concentration. **c** The time courses confocal images of spontaneous nuclear uptake of SWNTs_30 is cell type dependent with (I) HeLa cells and (II) hepatoma show spontaneous nuclear uptake of SWNTs_30 (green) at 4 h and efficient excretion over day 1–3 and (III) SWNTs_30 present in HUVEC cells over 5 days. **d** Gastrointestinal actions of Gd-CNHs in normal (a and b) and DSS-treated (c and d) mice. Quantities of Gd-CNHs in the stomach (purple), small intestine (green), cecum (blue), colon (red), and feces (yellow) are shown as percentages. **e** The effect of isoliquiritigenin (ISL) and long-term fate single-walled carbon nanotubes-isoliquiritigenin (LTFS-ISL) on the heart and kidneys where arrows indicate that the carbon nanotubes remained in heart and kidney [48–50, 52, 53]. Reprint permissions have been granted from copyright sources

SWNTs are insoluble in any type of solvent until recently, where organic functionalization by modifying the sidewalls and linking them with chemical substances has increased the solubility of SWNTs [34]. SWNTs have various utility in the physical and biological environment. However, the low aqueous solubility of SWNTs poses a major hindrance for its usage in those environments. Solubility of SWNTs can be enhanced by covalent functionalization (Fig. 6) [34] and non-covalent wrapping with surfactants, peptides, and polymers [69–71]. The method of non-covalent wrapping is found to be a simple way of SWNTs solubilization.

Covalent functionalization involves methods of acid oxidation of SWNTs. This method is designed specially to remove carbonaceous and metal particulate impurities but somehow it introduces functional groups such as carboxylic groups and other oxygen-bearing groups to the side wall or end of nanotubes [72] which contribute to SWNTs solubility. The method often caused shortening

Table 2 The summary of SWNTs' utility in medicine and health

Material	Utility	Experiment	Result	Ref.
SWNTs	Carrier for drug molecules	Gemcitabine encapsulated inside SWNTs was studied via molecular dynamics simulation	Drug molecule existed in the tube	[31]
Doc-oxSWNTs-$_{PEG}$	Carrier for anti-cancer drug doxorubicin	Binding conditions were studied (pH, temperature, and light) to achieve maximal dispersion stability and studied on drug loading and effect to Hela cells	Optimal binding conditions for doxorubicin were at pH 8 or lower, low temperature and no light	[40]
SWNTs exposed to laser light	Convert optical energy into thermal energy	SWNTs suspension was adsorbed onto center of larger breast cancer cell treated with Tryptan blue dye and exposed to light	Hydrating SWNTs upon exposure to light caused thermal energy to heat water molecules and created pressure inside SWNTs that caused explosion	[41]
SWNT25/Py38	Carrier for chemotherapeutic drug SN38	Drug SN38 were attached to PEGylated pyrene butanol before being released	SN38 dissociated from SWNT-carrier caused cell death after 72 h of incubation while the carrier stays in cytoplasm	[44]
SWNT-PTX	Vehicle for drug paclitaxel in mice	Paclitaxel loaded in SWNTs were treated to 4T1 murine breast cancer cell line and injected into 4T1 tumor model mice. This study was compared to common clinical drug formulation, Taxol	SWNT-PTX showed prolonged blood circulation, little toxicity, excreted via biliary pathway and 10-fold higher tumor PTX drug uptake	[45]

SWNTs; *Doc-oxSWNTs$_{PEG}$*; *SWNT25/Py38*; *SWNT-PTX*

of the tube [73], alteration of the intrinsic property, and modification of the nanotubes sidewall. In contrast to covalent functionalization, the non-covalent method of SWNTs is safer and more preferable because it preserves the nanotube aromatic surface and its intrinsic properties [74]. Most of the solubilizing agents are not directly attached to the damaged nanotube sidewall but only adsorbed to it. This is often a better way for one to tailor properties with intrinsic traits remaining unchanged.

Functionalization versus wrapping of SWNTs

The concepts about

Both methods of functionalized and wrapping of SWNTs are powerful to increase solubility of SWNTs in many solvents. Researchers have reported that SWNTs possess a high turnover in functionalization [38] that increases their dispersion in the aqueous solution. Buffa et al. (2005) performed the

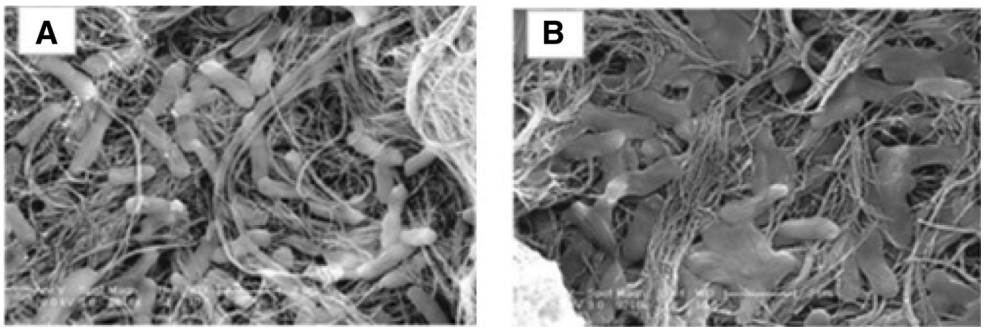


Fig. 5 The micrograph images of *E. coli* cells exposed to CNTs. **a** Incubation of cells with MWNTs for 60 min. **b** Cells incubated with SWNTs for 60 min [54]. Permission to reprint has been granted from American Chemical Society (Copyright © 2007)

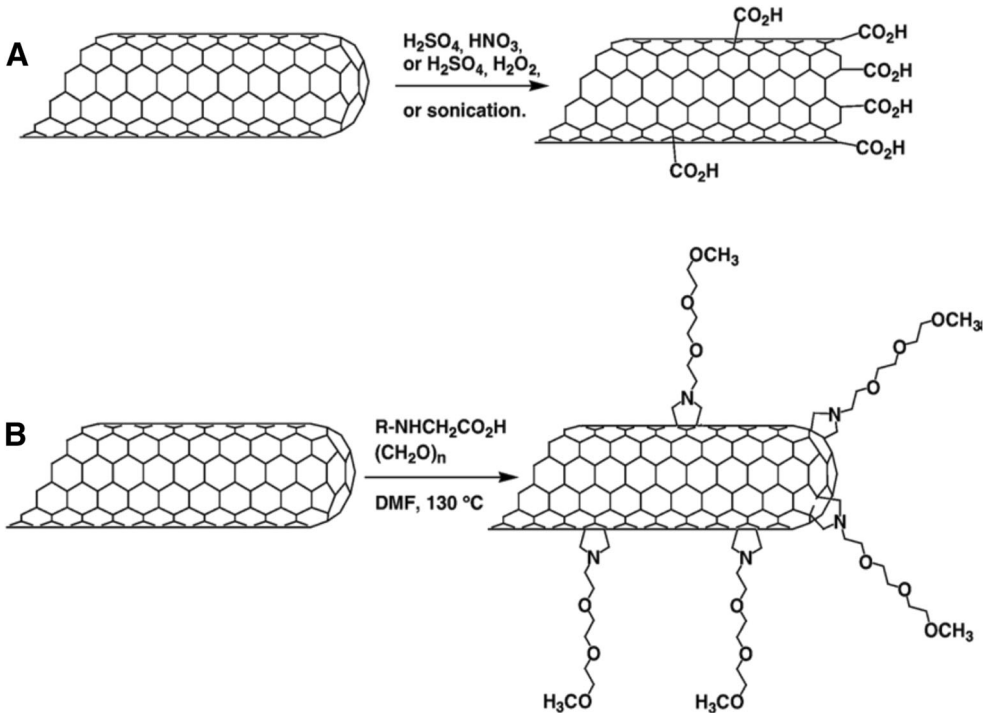


Fig. 6 **a** Pristine carbon nanotubes treated with acid being cut and forming carboxylic groups at the tip and sidewall. **b** 1,3-Dipolar cycloaddition of carbon nanotubes [34]. Permission to reprint has been granted from Elsevier B.V. (Copyright © 2005)

sidewall functionalization of SWNTs with hydroxymethylaniline (HMA) followed by the polymerization with poly-ϵ-caprolactone (PCL) and achieved better solubilization of SWNTs in chloroform [75]. The polystyrene (PSt) functionalized SWNTs lead to their increased solubilization in organic solvents. This phenomenon has been further supported by the atomic force microscopy (AFM) microphotograph of the former in the form of broken individual ropes (Fig. 7) [76]. Polyimide (PI-NH_2) functionalized SWNTs have been synthesized to achieve their greater dispersion, hence being utilized for the preparation of composite films [77]. However, covalent modification of SWNTs causes permanent change in structure, from sp^2 to sp^3 orbital hybridization that may result in optical, electrical, and mechanical deterioration [78].

A non-covalent approach comprises of micellar formation and wrapping technique of SWNTs with hydrophilic substances such as surfactants, deoxyribonucleic acid (DNA), peptide, and polymer [79, 80]. This technique is preferred because it preserves the electronic conjugation of the rolled graphene sheet [81] as well as dispersing and preventing them from forming bundles and ropes. Surfactants' structures are very diverse with different modes of action. For example, charged surfactants such as sodium dodecylsulphate (SDS) and tetraalkylammonium bromide stabilize nanotubes by electrostatic repulsion between micelles [81, 82] and charged-neutral surfactants or non-ionic surfactants such as poly(vinyl-pyrrolidone) (PVP) acts by assembling around the nanotube due to the large solvation shell created by the hydrophilic part (as shown in Fig. 8) [80].

Advantages of wrapping over functionalization

The main advantage of wrapping over functionalization is that it can minimize strain in the conformation of polymer-SWNTs by wrapping it in a helical fashion [83, 84]. It is known that wrapping nanotubes with polymer reduces the entropic penalty of

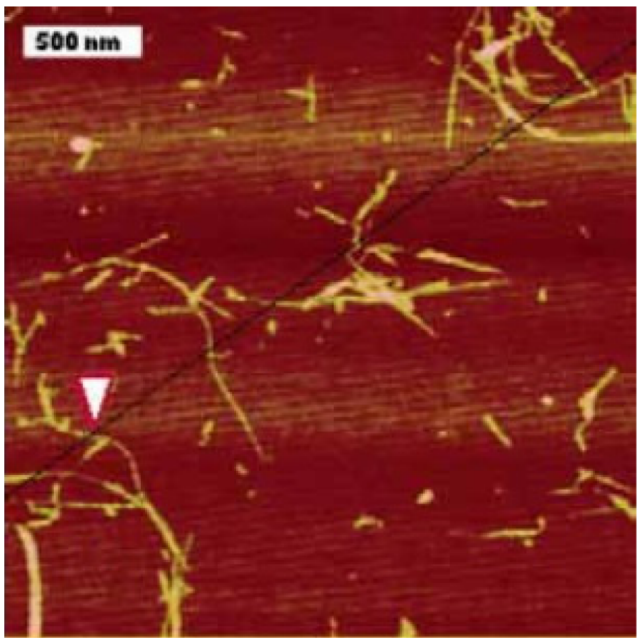


Fig. 7 AFM microphotograph of PSt grafted SWNTs as broken individual small ropes [76]. Permission to reprint has been granted from American Chemical Society (Copyright © 2004)

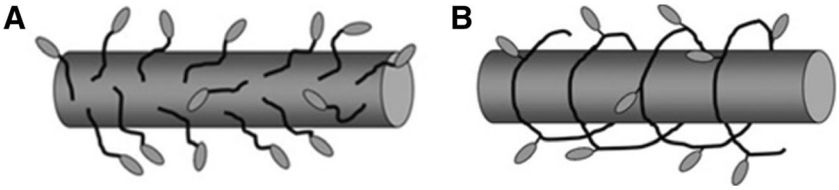


Fig. 8 Noncovalent mechanism of ambiphilic molecules on SWNTs surface. **a** Micelle formation of surfactant and **b** polymer wrapping of surfactant (the ellipsoids structure are the hydrophilic group and the black line is the hydrophobic groups) [80]. Permission to reprint has been granted from American Chemical Society (Copyright © 2008)

micellar formation. Some conjugated polymers showed significantly higher energy of interaction with nanotubes compared to small molecules with nanotubes which result in better solubilization of SWNTs in solvents. Advantages and disadvantages of the wrapping and functionalization method are summarized in Table 3.

Polymer-wrapped SWNTs

Wrapping with chronological view point

The work of wrapping of SWNTs with polymers was started more than a decade ago. The work was first established to study the interaction of π-π backbone and van der Waals forces of the polymer and SWNTs side wall that presumably enhance solubility of SWNTs without disrupting the π-system of the tube. It started with SWNTs' wrapping with poly{(m-phenylenevinylene)-co-[(2,5-dioctoxy-p-phenylene)vinylene]} (PmPV) a type of polymer that can wrap itself around the nanotube. However, this polymer is inflexible and less efficient in segregating bundles of SWNTs that requires more polymers for more nanotube solubilization [85]. An improvised polymer with hyper-branched molecule was prepared by self-polymerization of AB_X monomers. The synthetic hyperbranched polymer using dendrimer proposed more dispersion of single-strands SWNTs as observed on a mica wafer [83].

The wrapping of water-soluble polymers, poly(ethylene glycol) (PEG), and poly(vinyl alcohol) (PVA) onto SWNTs has been tried, but it was not successful [86]. Using a nontoxic and simple technique [87] called supercritical carbon dioxide (SC CO_2) antisolvent-induced polymer epitaxy (SAIPE) method, Zhang et al. (2008) proposed PEG and PVA being effectively wrapped onto SWNTs (Fig. 9a–c) [88] forming nanohybrid shish-kebab (NHSK) structure by using lower concentration of SWNTs approximately about 0.002 wt%. Using the same method (SAIPE) but different experimental conditions, Zhang et al. (2008) have managed to obtain structure of SWNTs being wrapped with PEG_{10000} in helical style which had been proved by Smalley et al. (2001) in his previous study [86]. He reported that the water-soluble polymer poly(vinylpyrrolidone) (PVP) was wrapping SWNTs helically and later Kang et al. [89] proved the helical wrapping of poly(p-phenyleneethynylene) (PPES) with SWNTs (Fig. 10).

Caddeo et al. (2010) have studied the molecular dynamics of simulation helical wrapping of poly(3-hexylthiophene) (P3HT) interact with SWNTs [90]. From the simulation, it is proven that neighboring polymer chains stabilize the helical wrapping and the nanotube chirality does affect the coiling angle and the helix morphology. A schematic summary of three-steps' structural changes of non-aromatic poly(dialkylsilane) (Psi1a) wrapping on SWNTs have been reported by Chung et al. (2013) and isolated SWNTs were rapidly mixed in *N*,*N*-dimethylformamide (DMF) to initiate spontaneous wrapping. Psi showed selectivity to SWNTs with diameter of 0.9 nm resulting in specific wrapping toward (7, 6) and (9, 4) SWNTs (Fig. 11) [91]. The result was first monitored with the stopped-flow technique. Deria et al. (2013) have proposed that helical wrapping of SWNTs by chiral and highly charged binaphthelene (BN)-based semiconducting polymers resulted in both left-handed (expected) and right-handed (unexpected) helical structure wrapping on SWNTs [92].

Researchers continuously prompted studies regarding methods to solubilize nanotubes in polar and non-polar solvents without altering the nanotube system. A well-known redox mediator often used for biosensing, ferrocene, or its conjugate polymer known as polyvinylferrocene (PVF) was used to control both SWNTs and MWNTs dispersion and reprecipitation in organic liquid as it demonstrates redox-switchable affinity for chloroform with the use of ferum (III) chloride ($FeCl_3$) and potassium iodide (KI) [93] to oxidize and reduce respectively of the ferrocene. The complete coprecipitation of CNTs and PVF upon oxidation was confirmed with electrochemical process when CNTs and PVF codeposited on the electrode surface during switchable redox transformation.

Using conjugated polymers to study the solubility of SWNTs with different mechanisms has become popular. Liu et al. [87] have investigated the formation of conjugated polymer nanowires (CPNWs) on SWNTs which was similar to that of hybrid shish-kebab [87] and theoretical formulation of

Table 3 The advantages and disadvantages of wrapping (non-covalent) over covalent functionalization

Method		Principle	Advantage	Disadvantage	Interaction with dispersant material
Chemical	Sidewall	Hybridization of C atoms	1. Effective reinforcement of the functionalized material 2. Higher dispersion stability	1. Change in intrinsic property 2. Shortening of the CNT	S
	Defect	Defect transformation			S
Physical	Polymer wrapping	Van der Waals force (π-π stacking)	1. Simple procedure 2. Minimum damage 3. Improve performance	1. Weak coating stability 2. Reversible solubilization 3. Dispersant material easily removed by filtration and dialysis	V
	Surfactant absorption	Physical adsorption			W
	Endohedral method	capillary effect			W

S strong, *W* weak, *V* variable

centipede-like supramolecular CPNWs-CNTs structure [94]. Unlike Liu et al. [87], Liang et al. [95] have prepared a stable dark polymer-SWNT solution with no flocculation observed over several months by adding 3 mg of raw SWNTs powder into 50 mg of tetrathiafulvalene copolymerized with fluorene (TTFV-fluorene) solution in toluene (sonicated). TTFV-fluorene copolymer exhibits switchable conformational changes upon protonation with trifluoroacetic acid (TFA) and results in the formation of SWNTs precipitates after being successfully dispersed in toluene. The release of SWNTs from its copolymer enables the recovered polymer to be used again to redisperse the precipitated SWNTs [95]. This demonstrates that the dissolution-precipitation process is reversible.

Solubilizing SWNTs in different types of solvents is very important for different practices. Aggregation of SWNTs in many solvents, mainly in more polar solvents such as water, has hindered their applicability in biological applications. The solute solvent interactions study of polyvinyl pyrrolidone-wrapped SWNTs (PVP-SWNTs) carried out by Mohamed et al. (2013) proves that the polymer-SWNTs are soluble in water [71]. The interaction of the solute (PVP-SWNTs) and solvent (water) was studied using viscometric studies [96] and acoustic methods [97]. These studies mainly emphasized on the viscosity, and ultrasonic velocity and density respectively. Summary of the polymer-wrapped SWNTs were summarized in Table 4.

Mechanisms of polymer wrapping

Polymer wrapping of SWNTs can be achieved via introducing the nanotubes to aromatic polymers or non-aromatic polymers. The aromatic polymers such as DNA and PSi's have the π-π interactions between the polymers and the curve surface of SWNTs that played a crucial role for the chiral separation. The aromatic polymers formed a self-assembled single layer adopted the trans-zigzag conformation in which they can spontaneously bind on the cylindrical graphene sheet of SWNTs with specific chiral indices even without π-π

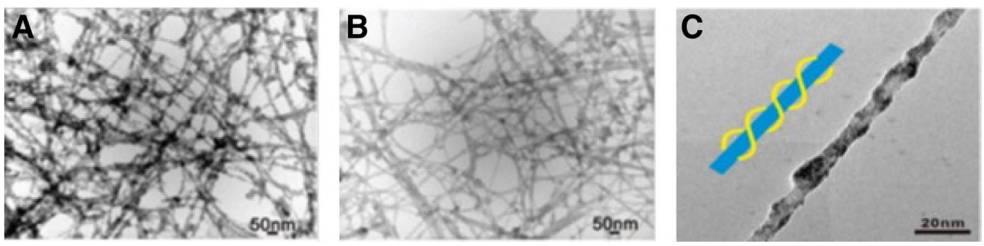


Fig. 9 TEM images of PEG_{10000} helical wrapping decorated SWNTs produced in the same SC CO_2 conditions with different CNTs concentrations. **a** 0.004 wt% CNTs, **b** 0.008 wt% CNTs. **c** TEM image of enlarged PEG10000/SWNTs wrapping structure in the same experimental conditions as (**a**) [88]. Permission to reprint has been granted from American Chemical Society (Copyright © 2008)

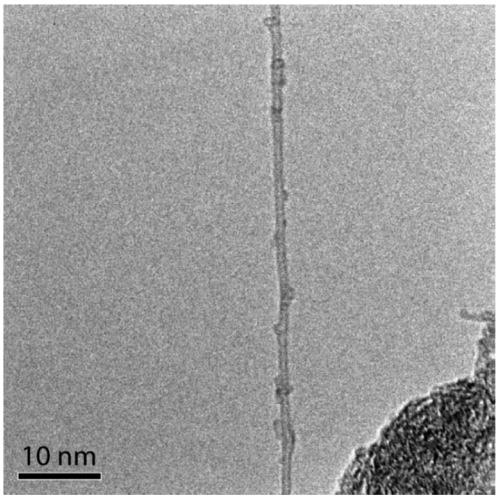


Fig. 10 TEM image of PPES-SWNTs [89]. Permission to reprint has been granted from American Chemical Society (Copyright © 2006)

interactions [91]. While polymers without the aromatic moieties such as PVP have the weak noncovalent interaction (CH-π and Van der Waals forces) to serve as the driving force to stimulate the spontaneous wrapping [98]. Meanwhile, the stability of the helical wrapping and the nanotube chirality were supported by the neighboring polymer chains [90].

The disruption of the hydrophobic interface between the aggregated nanotubes and the aqueous medium by wrapping of SWNTs with water-soluble polymer is found to be driven largely by a thermodynamic factor. The favorable enthalpy interaction gives a maximum free energy penalty for SWNT-wrapped polymer conformational restriction at 25 °C of 17 kJ/mol nm. The loss of the hydrophobic surface was achieved by shielding the nanotube from the water in which it is immersed, and was estimated from the surface tension of the corresponding hydrophobic cavity. In other mean, the regular wrapping arrangement was smaller than the gain achieved by overcoming the hydrophobic penalty between the SWNTs and their surrounding water [82].

Utility of polymer-wrapped SWNTs

Polymer-wrapped SWNTs have been used in biomedical applications as they are biocompatible with the aqueous environment. Generally, the polymer-wrapped carbon nanotubes in drug delivery reveal low toxicity, sustained drug release, and persist in circulation without aggregation [99]. Earlier, researchers tried using SWNTs-fluorophore/dye molecules to penetrate the cell membrane for biomedical imaging. Fluorophore and dye molecules have both hydrophobic and hydrophilic moieties. They are able to interact with SWNTs and increase the tubes solubility with different efficiency. Koh et al. (2012) have reported that SWNTs with different types of fluorophores showed different levels of cell transfection

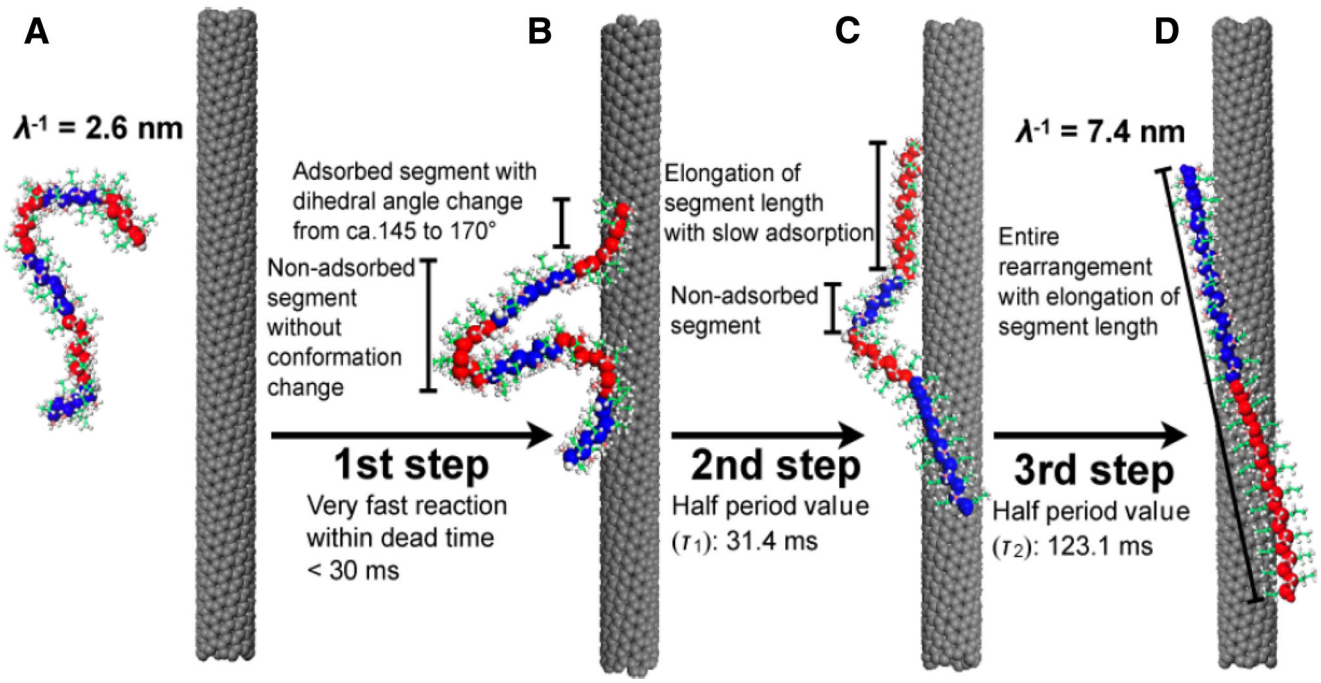


Fig. 11 Schematic summary of the three-step wrapping model of Psi1a on SWNTs. **a** Psi1a before interaction. **b** Fast adsorption of several segments within the dead time (0–30 ms). **c** Conformation change from helical to nearly planar with half period value (τ_1) of 31.4 ms. **d** Slow rearrangement of Psi with elongation at τ_2 of 123.1 ms [91]. Permission to reprint has been granted from American Chemical Society (Copyright © 2013)

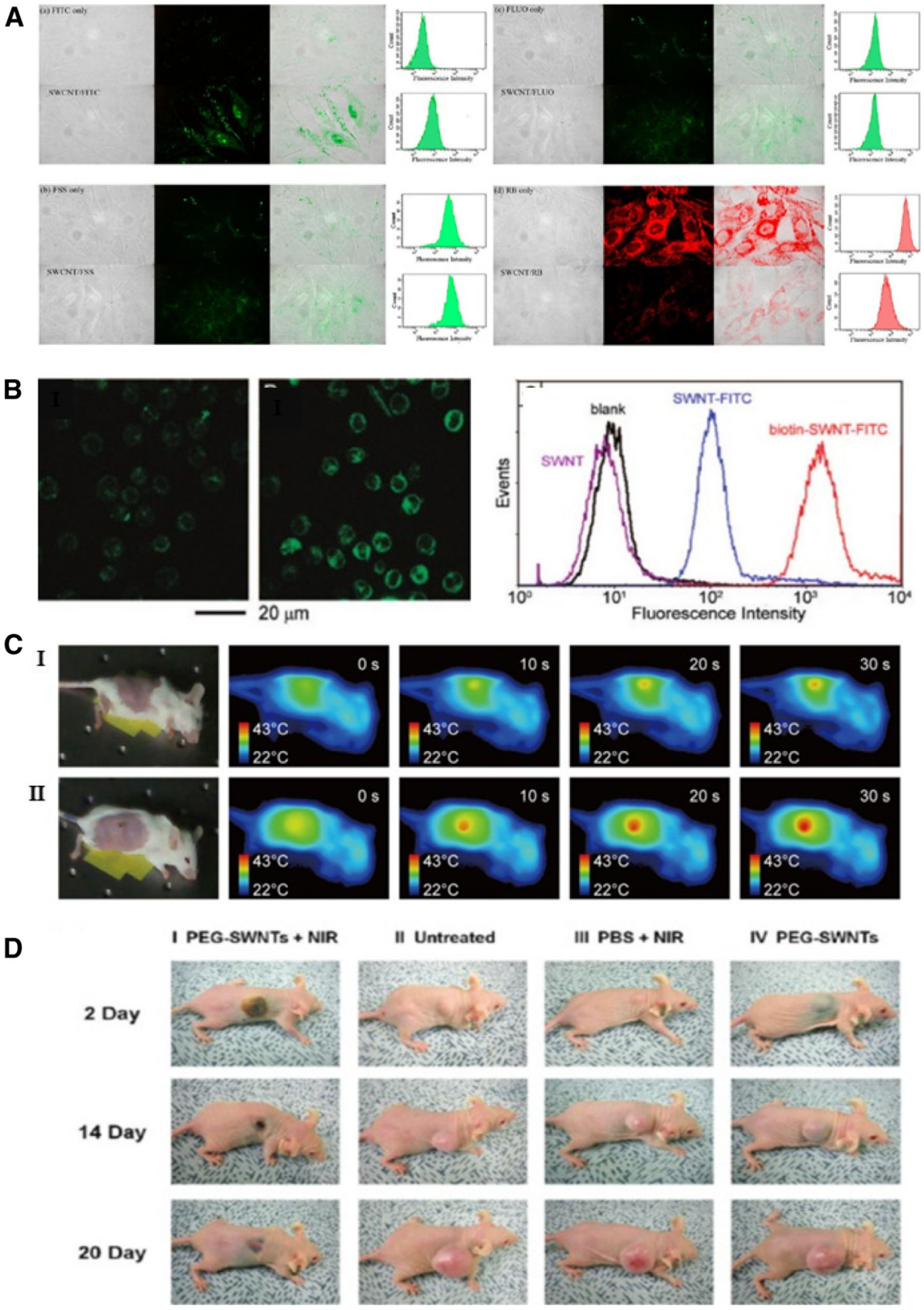
Table 4 Summary of different polymer wrapped onto SWNTs

Polymers	Findings	Ref
Poly{(*m*-phenylenevinylene)-*co*-[(2,5-dioctoxy-*p*-phenylene)vinylene]} (PmPV)	SWNT/PmPV molecule was evidenced isolated from the SWNT bundles. However, synthesis of PmPV in the bis(triphenylphosphonium) salt was difficult due to solubility issue.	[85]
Polyvinyl pyrrolidone (PVP)	PVP-wrapped SWNTs disrupted the hydrophobic interface between water and nanotubes producing single SWNT with at most a monolayer of polymer. By changing the solvent system, the SWNT will be unwrapped.	[86]
Hyperbranch PmPV polymer	The branching of the PmPV polymer offers pockets for better fit for the SWNTs resulted in more observable single strands of SWNTs on mica wafer.	[83]
Poly(ethylene glycol) (PEG) and poly(vinyl alcohol) (PVA)	Using a method called supercritical carbon dioxide (SC CO_2) antisolvent-induced polymer epitaxy method (SAIPE), periodic patterning of PVA (nanohybrid shish-kebab structure) and PEG (helical or flowerlike structure) of nanocrystal wrapping on SWNTs were observed.	[88]
Poly(3-hexylthiophene) (P3HT)	A molecular dynamics simulation of helical wrapping of long polymer chain P3HT on SWNTs was found to be metastable due to interactions among neighboring polymer chains. Besides that, the simulation showed that in the absence of solvent, the polymer tends to unwrap and align to the nanotube.	[90]
Poly(dialkylsilane)s (PSi's)	This study emphasized on specific wrapping of non-aromatic polymer (Psi's) toward (7,6) and (9,4) SWNTs. It provides knowledge on molecular design of polymers in SWNTs wrapping with desired chiral selectivity.	[91]
Polyvinylferrocene (PVF)	The CNTs were individualized at high concentrations in organic solvents when non-covalently interact with PVF. This ferrocene-based dispersants do not use any ionic moiety to disperse the nanotubes. It is a novel redox-tunable affinity for organic solvents potentially used for biosensor and pseudocapacitors.	[93]
Vinylogous tetrathiafulvalene (TTFV)-fluorene	The copolymer TTFV and fluorene synthesized showed strong interaction with SWNTs surface allowing dispersion in many organic solvents. The copolymer-SWNTs interaction is size selective and desorbed polymer upon protonation. The polymer was easily recovered and reused.	[95]
Polyvinyl pyrrolidone (PVP)	PVP-wrapped SWNTs synthesized was studied its solute-solvent interactions during solubilization in water by viscometric methods. It was found that both PVP and PVP-SWNTs solution showed reduced viscosity with increasing of temperature due to interaction weakening.	[96]

efficiency with fluorescein isothiocyanate (SWNTs-FITC), which showed the highest penetration into cells (Fig. 12a) compared to other fluorophores [100]. Chen et al. (2008) have reported that biotin-SWNTs-FITC conjugates showed specificity to cancer cells, overexpressing biotin receptors on the cells surface and are able to release taxoid molecules inside the cancer cells [101]. The synthesized biotin-SWNTs-FITC was incubated with leukemia cell lines (L1210FR) for 3 h to induce endocytosis (Fig. 12b) which showed better fluorescent. The cellular uptake of bio-conjugate SWNTs may be beneficial to deliver molecules that have difficulty in penetrating cell membrane.

Malignant cells could have a better procurement with early detection by using methods of imaging and sensoring [102]. SWNTs with cellular imaging properties have clearly diagnosed and differentiated malignant from non-malignant cells [103]. SWNTs wrapping with different polymers such as phospholipids, nucleic acids, and amphiphilic polymers perform as biosensors for detection of neurotransmitter. Neurotransmitters play a major role of neurotransmission in chemical synapses [104] and a central part of data processing in the brain. Kruss et al. (2014) have studied a new technique named corona phase molecular recognition (CoPhMoRe) which is used to identify adsorbed polymer on fluorescence SWNTs that allows selective detection of neurotransmitters including dopamine [105]. These authors report that DNA- and RNA-wrapped SWNTs showed better fluorescent-turn on sensors with an increase in fluorescence from 11 to 80% upon the addition of dopamine.

CNTs with thermal property afford a new insight in photothermal therapy of tumors when conventional surgery



is not possible. The nanoparticles are used to convert near-infrared (NIR) radiation to vibrational energy and produce sufficient heat to kill cancer cells [106]. Single-walled carbon nanotubes with the help of a designated peptide, H(-Lys-Phe-Lys-Ala-)$_7$-OH (KFKA)$_7$ forming SWNT-(KFKA)$_7$ peptide composite. It was used to reduce the proliferation of tumor

◀ **Fig. 12** The effects of polymer-wrapped SWNTs on cells fluorescent intensity. **a** 9 L gliosarcoma cells treated with (a) FITC only (top), SWCNT/FITC (bottom); (b) FSS only (top), SWCNT/FSS (bottom); (c) FLUO only (top), SWCNT/FLUO (bottom); (d) RB only (top), and SWCNT/RB (bottom). **b** L1210FR cells incubated with SWNT-FITC 1 (A) and biotin-SWNT-FITC 2 (B) at the final concentration of 10 μg/mL at 37 °C for 2 h. **c** Comparison of fluorescence intensities of L1210FR cells by flow cytometry upon treatment with pristine SWNTs 0 (purple), conjugate 1 (blue), and conjugate 2 (red). Effects of NIR laser irradiation with the present of SWNTs on nude mice. **d** Mice bearing tumor tissue given NIR laser irradiation (I) without SWNT-(KFKA)7 and (II) with SWNT-(KFKA)7. **e** The In vivo photothermal effects of PEG-SWNTs for tumor obliteration. Representative photographs of the mice treated in different groups at various time points after each treatment (I, PEG-SWNTs + NIR; II, untreated; III, PBS + NIR; IV, PEG-SWNTs). Noted that the black mark is a skin burn scar resulted from the excessive heating of PEG-SWNTs by NIR [100, 101, 107, 108]. Permission to reprint has been granted from copyright sources

cells [107]. The study was carried out in vitro and in vivo using the cell culture of murine rectum (colon 26) and human hepatocellular carcinoma cell lines (HepG2). In vitro and in vivo intratumoral injection of colon 26 tumor into healthy murine was made. The in vitro experiment showed a large number of tumor cells death in both cell lines when SWNTs-$(KFKA)_7$ and NIR irradiation were delivered to the cell culture. The in vivo experiment showed effective therapeutic effect of SWNTs-$(KFKA)_7$ plus NIR irradiation against colon 26 tumor. The NIR irradiation increased rapidly the temperature of the tumor tissues treated causing reduction of tumor growth (Fig. 12c).

NIR irradiation has been suggested as a non-invasive and harmless skin-penetrated radiation which provides safe thermal ablation therapy for cancer cells [103]. SWNTs have become potent candidates for photothermal therapy due to their photon-to-thermal conversion property that generates a significant amounts of heat when employed with NIR light (NIR, λ = 700–1100 nm). Moon et al. (2009) have covalently functionalized Hipco SWNTs with PEG_{2000} preparing a PEG-SWNTs solution. The solution was then injected intratumorally into the nude mice bearing human epidermoid mouth carcinoma tumor cells and irradiated with NIR light for 3 min. After 20 days, the result showed complete destruction of tumors with one observable black round marks on the mice skin (heating effects from PEG-SWNTs with NIR radiation) (Fig. 12d) while the control showed proliferation of tumor cells that led to mice death. The treated mice showed no recurrence of tumor over 6 months with positive result of PEG-SWNT excretion from the body [108].

Future prospects

Wrapping of SWNTs with polymers adopting non-covalent approach using suitable polymers should be of interest due to their hydrophobic alkyl backbone and hydrophilic pendant groups that can coil around the nanotube where the backbone keeps contact with the nanotube and hydrophillic group exposed to water. The polymer-wrapped SWNTs with enhanced solubility in water will have great utility in biological environments. They can be further investigated as a drug carrier to the targeted site. Further toxicological studies relating wrapped SWNTs are of particular importance.

Summary

In the present review, we provide the details of the non-covalent wrapping of SWNTs with polymer including the advantages over the method of functionalization. The method consistently shows improvement of aqueous dispersion of SWNTs in aqueous media, hence the resultant improvement in the different field of applications. The antimicrobial and applications in the areas of health care are highlighted. Yet this review of the previously carried out research clearly suggests the future endeavor needed in the directions of the development of better therapeutic modalities using the several nano-technological means giving due importance to the absorption, distribution, metabolism, and excretion of the wrapped SWNTs.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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