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Carbon Nanotubes in Drug and Gene Delivery

Mahdi Karimi
Amir Ghasemi
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Seyed Masoud Moosavi Basri
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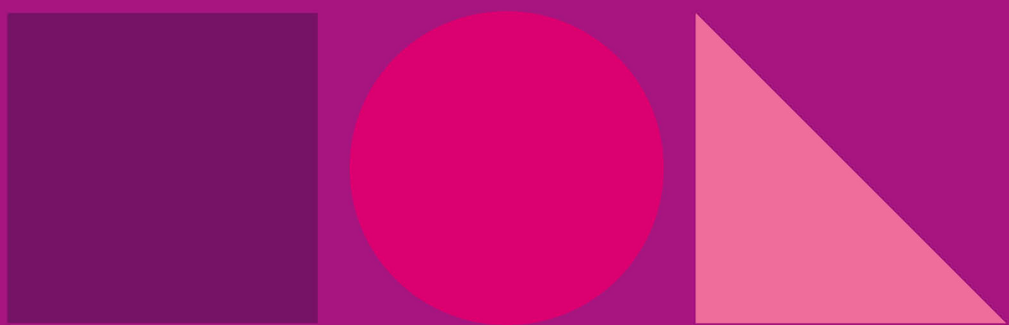

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Carbon Nanotubes in Drug and Gene Delivery

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Dedicated to our beloved parents, and wives
for their sacrifice through the years.

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Preface

Nanotechnology is fast becoming one of the signature scientific fields of the 21st Century. Ever since Richard Feynman's famous lecture 'There's Plenty of Room at the Bottom' delivered in 1959, nanotechnology has steadily and progressively seized the imagination of the scientific community, and indeed the general public at large. Feynman proposed that the ability to manipulate matter on an atomic scale could lead to the construction of 'nanoscale machines that arrange the atoms the way we want'. He also presented the possibility of 'swallowing the doctor', and perhaps tiny surgical robots could be constructed that could travel throughout the body detecting the early signs of disease and fixing them before the patient even noticed any symptoms.

Almost sixty years later it is interesting to see how much nanotechnology has really changed our lives. There have been large changes in materials science, in nano-electronics, and even consumer products (cosmetics, packaging etc). But how close are we to realizing the long-held dreams of nanomedicine? Among the many achievements of nanotechnology (gold nanostructures, quantum dots, fullerenes, mesoporous silica nanoparticles, smart liposomes, etc) carbon nanotubes (CNTs) occupy an almost starring role. Their astonishing properties in terms of mechanical strength, ability to conduct both heat and electricity, stability against chemical and physical degradation, large surface area, tunable aspect ratio, have led to scientists devising ever more ingenious applications. But will they have a role in nanomedicine?

The present ebook seeks to provide some answers to this intriguing question. Many medical applications in nanomedcine have centered around the use of nanovehicles for drug and gene delivery. Smart and targeted drug delivery continues to fascinate multi-disciplinary nanomedicine laboratories. CNTs are no exception to this rule of thumb. However, there are concerns about whether CNTs can ever be used in clinical applications, considering widespread fears about possible toxicity and side-effects, even going as far as possible carcinogenicity. In the following chapters we summarize the properties and synthesis methods of CNTs. We discuss their interactions with cells, and applications to drug and gene delivery including smart stimulus-responsive and targeted approaches. Finally, issues of toxicity and environmental damage are addressed.

Acknowledgments

We would like to express our special thanks of gratitude to all those who provided support during the process of writing and preparing of this book, in particular, to Mr Hamed Mirshekari for the process of selection and editing. The authors deeply extend their appreciation to the guidance and contribution of the Production team at Morgan & Claypool and IOP Publishing, for their expert help.

Author biographies

Mahdi Karimi

Mahdi Karimi received his BSc degree in medical laboratory science from the Iran University of Medical Science (IUMS), in 2005. In 2008, he achieved an MSc degree in medical biotechnology from Tabriz University of Medical Science and joined Tarbiat Modares University as a PhD student in the nanobiotechnology field, and completed his research in 2013.

During his research, in 2012, he became affiliated with the laboratory of Professor Michael Hamblin in the Wellman Center for Photomedicine at Massachusetts General Hospital and Harvard Medical School as a researcher visitor. There, he contributed to the design and construction of new smart nanoparticles for drug/gene delivery. On finishing his studies, he joined the Department of Medical Nanotechnology at IUMS as an assistant professor. His current research interests include smart nanoparticle design in drug/gene delivery and microfluidic systems. He has established a scientific collaboration between his lab and Professor Michael Hamblin's lab to design new classes of smart nanovehicles in drug/gene delivery systems.

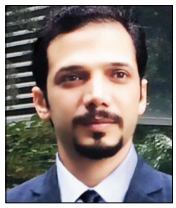
Amir Ghasemi

Amir gained his BSc at Sharif University of Technology (SUT), the most prestigious technical university in Iran. He has been a member of a polymeric materials research group since 2012, and received his MSc in materials engineering from SUT. For his MSc project, he worked on thermoplastic starch (TPS)/cellulose nanofibers (CNF) biocomposites, under the supervision of Professor Bagheri. He synthesized a fully biodegradable nanocomposite, and evaluated the effects of CNF on the mechanical- and bio-degradation of TPS. The advent of innovative nanomaterials and nanotechnology interested him in interfacial sciences/technologies and also nanomedicine, including nanoparticlebased drug delivery systems and nanobiosensors. He has now joined Professor Karimi's Nanobiotechnology Research lab in the Iran University of Medical Science, Tehran, Iran, in association with Professor Hamblin from Harvard Medical School, Boston, USA; working on smart micro/nanocarriers applied in therapeutic agent delivery systems employed for diagnosis and therapy of various diseases and disorders such as cancers and malignancies, inflammations, infections, etc.

Soroush Mirkiani

Soroush Mirkiani received his BSc from Sharif University of Technology at Materials Science and Engineering. He continued his studies in the field of Biomaterials at Faculty of New Sciences and Technology at University of Tehran. During his MSc he developed a degradable Brushite Bone Cement reinforced by calcium phosphate whiskers. In 2015, he contributed to the Advanced Nanobiotechnology & Nanomedicine Research Group (ANNRG) at Iran University of Medical Science, starting his researches about smart drug delivery systems.

Seyed Masoud Moosavi Basri



S M Moosavi-Basri is a young multidisciplinary researcher. He succeeds to obtain the Top Student Award in Civil Engineering department in his BSc. As an engineer with enthusiasm for applying fundamental science in biology, he conducted his Master thesis In Biomimetics and Bioinspiration at Shahid Beheshti University in collaboration with Bioenvironmental Research Center at Sharif University of Technology. He is developing a novel approach leading to obtaining promising results in Biomimetics. Also, he is pursuing his interests in Biology disciplines by holding remote collaborations with some labs and journals around the globe (e.g. Harvard Medical School, Wyss Institute for Biologically Inspired Engineering, USERN, Iran Pasteur Institute, etc) as a Researcher and Scientific Illustrator as well.

Michael R Hamblin

Michael R Hamblin PhD is a principal investigator at the Wellman Center for Photomedicine, Massachusetts General Hospital, an associate professor of dermatology, Harvard Medical School and the affiliated faculty of Harvard–MIT Division of Health Science and Technology. He received his PhD in organic chemistry from Trent University in the UK. He directs a laboratory of around a dozen scientists who work in photodynamic therapy (PDT) and photobiomodulation. He has published 376 peer-reviewed articles, is Editor or Associate Editor for ten journals, and serves on NIH study sections. He has an h-factor of 82 and >25 000 citations. He has authored/edited 11 proceedings volumes together with ten other major textbooks on PDT and photomedicine. Dr Hamblin was honored by election as a Fellow of SPIE in 2011, and received the 1st Endre Mester Lifetime Achievement Award in Photomedicine from NAALT in 2017.

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Mahdi Karimi, Amir Ghasemi, Soroush Mirkiani, Seyed Masoud Moosavi Basri and Michael R Hamblin

Chapter 1

Introduction

1.1 Introduction

Recent important discoveries and developments in nanotechnology have had a remarkable and ever-increasing impact on many industries, in particular materials science, pharmaceuticals, and biotechnology. Nanocarriers have been investigated for a wide variety of different medical applications. Some examples of these nanocarriers include polymersomes, liposomes, micelles, and carbon-based nanomaterials [1–5].

Until the 1980s, only two allotropic forms of elemental carbon were known, i.e. diamond and graphite [6] (figure 1.1(a) and (b)). An important discovery in 1985 uncovered a new form of elemental carbon in the form of a closed-cage structure resembling a soccer ball. This new molecule was composed of 60 carbon atoms and was obtained by applying laser light to carbon in the presence of helium gas. It was named 'Buckminster fullerene' due to its similarity to a geodesic dome, and was rapidly nicknamed the 'buckyball' [7] (figure 1.1(c)). Subsequently, other forms of closed-cage carbon nanostructures were recognized, such as C_{70}, C_{76}, and C_{84}. This new class of carbon molecules is called 'fullerenes', in which carbon atoms are arranged in six-member hexagons and five-member pentagons, all linked by covalent sp^2-hybridized bonds [8].

Later it was shown that sp^2-hybridized carbon atoms were also able to form long cylindrical shapes called 'carbon nanotubes' (CNTs), also known as 'buckytubes' [9] (figure 1.1(d)).

Although the basic properties of CNTs had previously been briefly discussed [10], in 1991 Japanese scientist Sumio Iijima explained for the first time the shape, structure, and production method of these needle-like carbon tubular structures [11]. To date, many other production methods have been discovered, such as arc-discharge methods [12], hyper-catalysis [13], and capping with fullerene hemispheres [14]. There is now a

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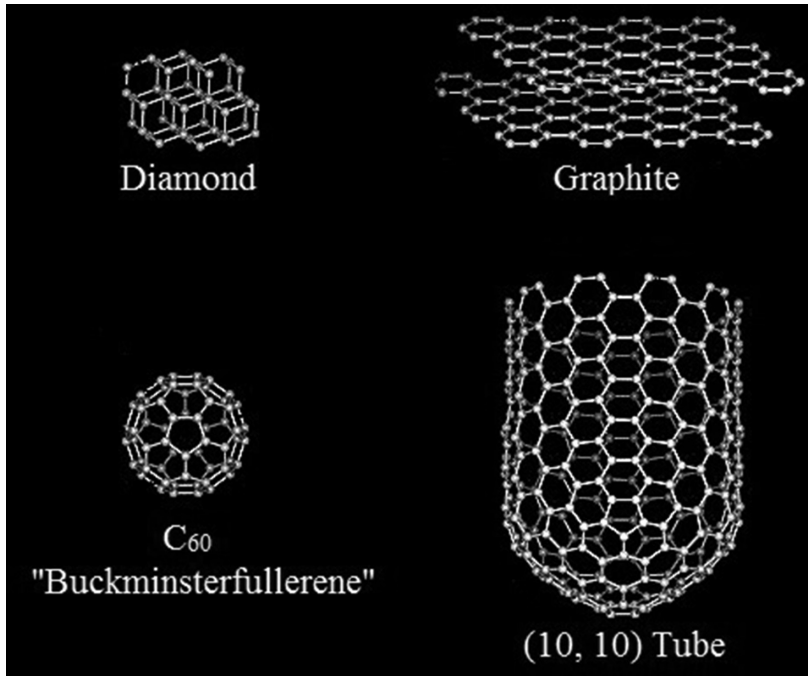

Figure 1.1. General structures of carbon-based allotropes. (a) Diamond, a cubic structure of sp^3-hybridized carbon atoms forming a very hard structure. (b) Graphite, a soft structure made from sheets of sp^2-hybridized carbon atoms. (c) Fullerene, a ball of sp^2-hybridized carbon atoms with pentagonal and hexagonal rings. (d) CNTs, single- and multi-walled cylindrical structures of sp^2-hybridized carbon atoms.

thriving research community working on applications of CNTs in materials science, nano-electronics, and of course medicine [15–17].

CNTs are becoming increasingly important because of their excellent structural, electronic, and mechanical properties [18]. Furthermore, they possess good thermal stability, an excellent surface-area-to-mass ratio, and the ability to conduct electricity, either as metallic conductors or as semiconductors [19]. CNTs produced by different synthetic techniques can consist of different numbers of concentric rolled graphene layers that can be thought of as 'tubes within tubes' [20]. CNTs are therefore categorized as single-walled CNTs (SWCNTs), or as multi-walled CNTs (MWCNTs). Given their extensive surface area, CNTs can easily be conjugated with a large range of different biological molecules (e.g. enzymes, proteins, nucleic acids, etc) [17, 19, 21, 22]. van der Waals interactions hold together the individual rolled-graphene sheets, creating large aggregates that resemble bunches of asparagus. The poor solubility and high hydrophobicity of these strongly attached bundles of CNTs (in water and also in most other organic solvents), has severely limited their use in biomedical, chemical, and biochemical applications [23–26].

In this book we describe different features of CNTs, surveying the properties of both the multi-walled and single-walled varieties, and cover their applications in drug and gene delivery. First, we explain the structure and properties of CNTs

prepared by different methods (chapter 2), and cover their isolation and purification (chapter 3). The main production methods—laser ablation, arc discharge, and chemical vapor deposition (CVD) (e.g. hot filament and plasma-enhanced CVD (PECVD), water-assisted CVD (WA-CVD) and so on)—are explained. Next the importance of functionalization of CNTs by both covalent and non-covalent methods is discussed, including the role of surfactants, biomolecules, polymers, and peptides in non-covalent methods, and direct and indirect functionalization in covalent methods (chapter 4). In the functionalization reaction, an active molecule is attached to the structure of CNTs to generate a base for the attachment of cargo groups. This reaction also increases the solubility of the CNTs and reduces the aggregation of CNTs in aqueous conditions, such as those found in living systems. In chapter 5 we explain the molecular mechanism of CNT uptake by different kinds of cells. CNTs, owing to their nanostructured needle shape, can cross the cell membrane without causing cell death or excessive damage. Cell uptake can occur by both the mechanisms of energy-independent translocation, and energy-dependent phagocytosis. Chapters 6 and 7 discuss the main topic of this book, the use of CNTs in the delivery of drugs (small molecules as well as proteins) and genes (plasmid DNA (pDNA), small-interfering ribonucleic acid (siRNA), and micro-RNA (miRNA)). The special electrical, thermal, mechanical and optical properties of CNTs make them excellent candidates for the diagnosis of cancer cells and delivery of active molecules into targeted tissues. In chapter 8 we discuss the possible toxicity of CNTs for living cells and organisms and possible deleterious effects on eco-systems and the environment. CNTs have been considered to have a similar structure to asbestos fibers, which cause mesothelioma (a form of lung cancer), and must therefore be carefully tested for toxicity. Chapter 9 addresses the future of CNTs in the field of biomedical science, which will depend on minimizing their adverse effects by careful study of their structure and properties.

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Chapter 2

Carbon nanotubes: properties and classification

2.1 Introduction

The advent of graphene sheets and CNTs has ignited much interest in these novel allotropic forms of carbon among physicists and chemists in the last two decades [1, 2]. The special properties of CNTs, such as their high surface-area-to-volume ratio, high elastic modulus, and good tensile strength, have led to them being investigated as promising, versatile, and practically efficient delivery vehicles in biomedical applications [3, 4]. CNTs can behave as very good conductors for transferring both heat and electrical current. Moreover, they have interesting optical properties, with high optical absorption at many different wavelengths [5–7]. Moreover, the excellent capacity of CNTs to retain energy and resist thermal ablation, their high surface area which allows good cargo loading, as well as their suitability for versatile functionalization and modification make CNTs a potential carrier for targeted molecular delivery systems, and a candidate for scaffold construction in tissue engineering [8–10]. Furthermore, CNTs possess the capability to transform electromagnetic energy into thermal and sonic energy, thereby facilitating the application of photothermal and photoacoustic therapies in oncology [11–13]. The surface functionality of CNTs can create a potential platform for transferring different types of bioactive molecules—such as chemotherapeutic drugs [14, 15], antibiotics [16], various types of nucleic acids [17], antibodies [18], and protein-based vaccines [19]—to enhance cell-specific delivery and reduce the potential unwanted side-effects and toxicity of these cargoes. The general properties of CNTs are illustrated in figure 2.1.

CNTs are very prone to aggregate into bundles (and this applies to both semiconducting and metallic SWCNTs, which are often present in a mixture of 1/3 to 2/3, respectively). The properties of these bundles are mostly worse than those of the isolated SWCNTs, and successful separation of these aggregates into individual CNTs must be performed prior to functionalization and subsequent construction of nano-devices. CNTs show excellent mechanical properties due to their high tensile strength;

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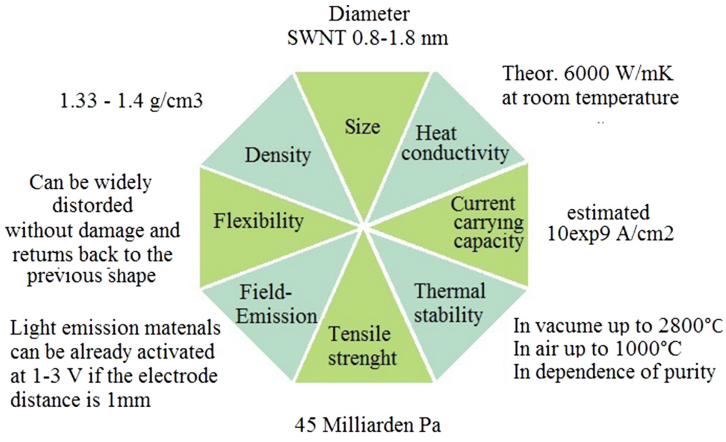

Figure 2.1. General properties of CNTs.

they also have excellent conductivity of both heat and electricity, are ultra-lightweight, and possess excellent chemical and thermal stability [20, 21]. In addition to their high elasticity, their tensile strength and density-normalized Young's modulus are, respectively, 19 and 56 times greater than those of a comparable steel wire and also 2.4 and 1.7 times greater than those of silicon carbide nanorods. CNTs are chemically unreactive, and are comparably lightweight due to the empty space inside them, while also having high mechanical strength. These properties together with their electrical conductivity have made them a great candidate for use in structural applications, nano-optoelectronics, and nanomedicine devices [22, 23].

The fact that CNTs are taken up into targeted cells leads to enhanced accumulation of CNT–drug complexes inside cells. This may even occur independent of functionalization of the CNT or recognition by targeted cell types [24]. Further, CNTs will accumulate in tumor sites owing to the hyper-permeable blood vessels and lack of drainage due to fewer lymphatic vessels typical of tumors (enhanced permeability and retention (EPR) effect) [25, 26]. CNTs can also carry a very high amount of cargo due to their ability to load cargo into both their inner and outer loading spaces. Cargo can be attached to these surfaces of the CNTs either covalently or non-covalently [27]. This flexible property of CNTs provides the ability of CNTs to act as 'smart drug delivery vehicles' with the potential for single-, dual-, or even multi-responsiveness to a variety of stimuli. Employing a smart delivery vehicles increases the precision and decreases the side-effects, even in cases of multi-drug resistant cancer or infections [28].

2.2 Classification of CNTs

In 1960 Roger Bacon reported the formation of concentric helical graphitic microtubes, and in 1991 Iijima, during experimentation with fullerene synthesis, discovered carbon cylinders formed of graphitic sheets [29]. Iijima first described these needle-like carbon filaments—which accumulated on the negative tip of a graphite electrode

(carbon electrode) during arc-discharge evaporation in an atmosphere filled with argon gas at 100 Torr pressure—as 'rolled graphite sheets inserted into each other with a range of 2–50 concentric sheets' [30]. The following year, Ebbesen and Ajayan were successful in achieving larger quantities of these hollow tubes (~1 g of graphitic tubes) using the arc-discharge evaporation method and optimizing the conditions [31]. They found that the tubes have diameters in the range of 2–20 nm.

The chosen method of CNT preparation may also change the characteristics of the CNTs and influence their interactions with the loaded drug(s) [32, 33]. CNTs interact with therapeutic compounds through three main mechanisms: first, the drug is adsorbed onto the exterior of the CNT molecular mesh; second, the drugs may be absorbed into the inner channel of the CNT; and third, the CNT surface may be modified to bind the loading cargo via covalent and non-covalent linkages [34]. Generally, there are two main types of CNTs: SWCNTs, which are formed of one monolayer graphene sheet, and MWCNTs, which consist of several concentric graphene layers (like rolling up a newspaper). MWCNTs can be further sub-divided into three types: double-walled CNTs (DWCNTs), three-walled CNTs (TWCNTs), and MWCNTs [35–37] (figure 2.2).

2.2.1 Single-walled carbon nanotubes (SWCNTs)

SWCNTs are made of a graphite monolayer that is rolled into a cylindrical shape (figure 2.3). They have the most straightforward structure of the CNTs and their

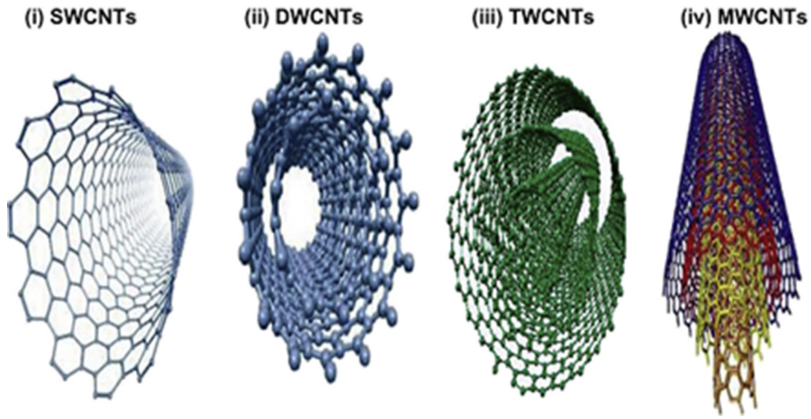

Figure 2.2. The four main types of CNTs. Reprinted with permission from [38].

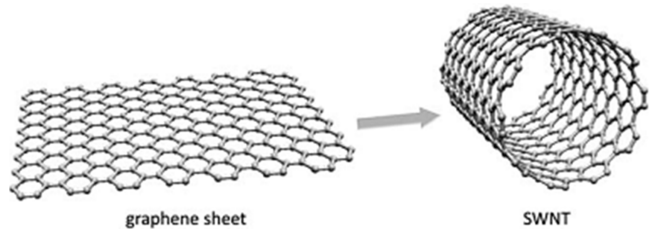

Figure 2.3. Basic SWCNT formation from a single-layer graphene sheet [39].

diameters range from 0.4–2.5 nm, although their average diameter is around 1 nm. However, their length can be considerably longer than their diameter (up to several million times) [41, 42].

The rolling of a graphene sheet can produce different configurations of CNT. The structure of a nanotube is generally defined by its chiral vector, which is related to the tube axis and the hexagonal lattice orientation (figure 2.4), and is represented by the chiral indices (n, m). Based on the geometric arrangement of the carbon atoms in the cylinder's seam, SWCNTs can be divided into three categories. Both the armchair form ($n = m$) and the zigzag form ($m = 0$) have mirror symmetry, while the

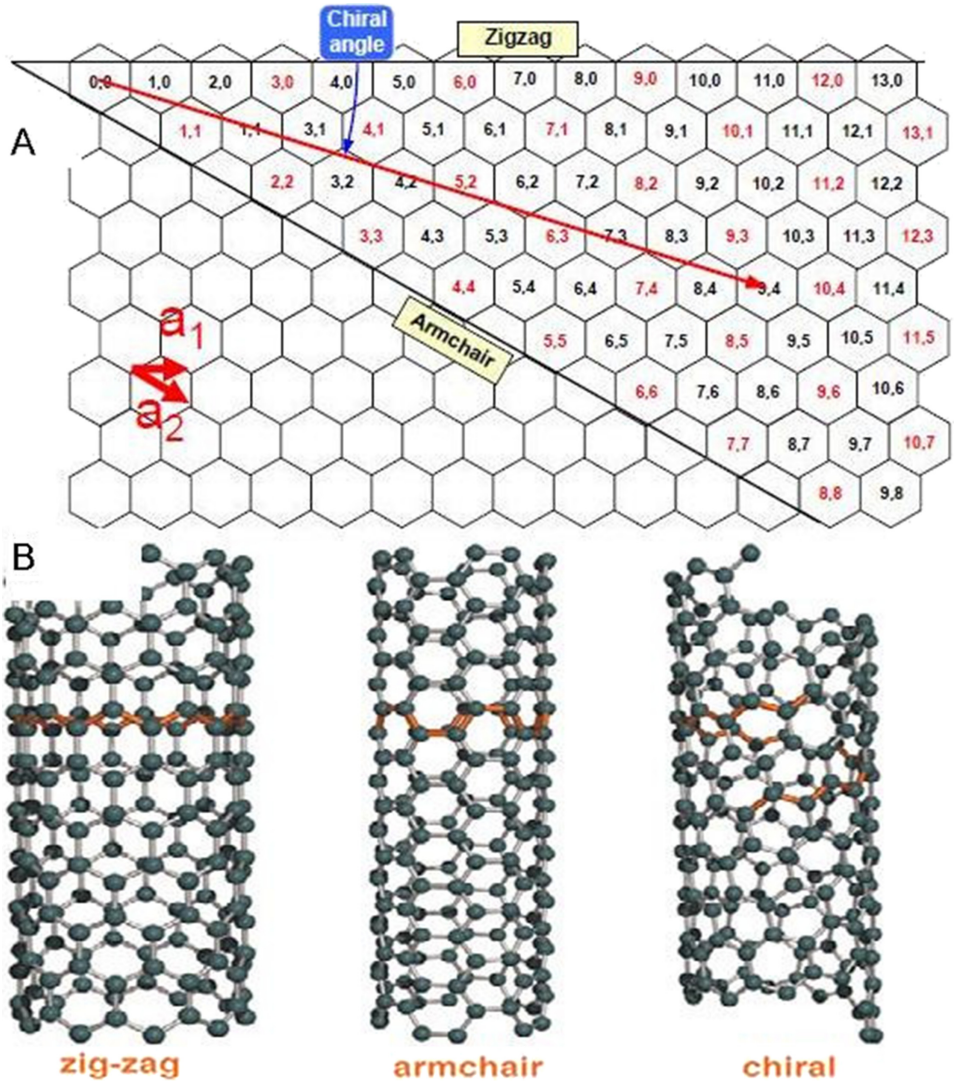

Figure 2.4. Schematic representation of three types of SWCNTs: (a) armchair (10, 10), (b) chiral (13, 6), and (c) zigzag (14, 0) [40].