ISSN: 1999-1630

SEU Journal of Science and Engineering, Vol. 13, No. 2, December 2019

Study of Correlation Between Chemical Functionalization and Surface Area of Armchair and Zigzag Single-Walled Carbon Nanotubes for Targeted Drug Delivery

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Abstract

In conventional drug delivery systems (e.g., oral, sublingual, rectal, etc.) more than 90% of the administered drug remains unused and becomes toxic when it crosses the permissible limit. For targeted drug delivery systems, recently, Single-Walled Carbon Nanotube (SWCNT) has gained much attention due to several unique properties of SWCNTs. However, these non-functionalized pure SWCNTs are not compatible with living cells. On that account, the functionalization of SWCNTs should be an imperative consideration in developing the SWCNT-based drug delivery system. In this work, we have investigated the surface area of two different types of SWCNTs and it is theoretically found that armchair conformation gives more sites for functionalization than zigzag conformation. More sites for functionalization impart less usage of SWCNTs but carrying equal or even more drugs to the respective cells. Therefore, less toxicity will be realized due to SWCNT as well as maximum consumption of the drug can be achieved with minimum side effects owing to the unused remnant drug in the living organ.

Keywords*:* SWCNTs, Functionalization, Drug Delivery, Toxicity.

I. Introduction

The ability to deliver therapeutic drugs to ailing cells is a pressing issue for effectively treating human illnesses without any side effects. Conventional chemotherapy or radiotherapy requires highly meticulous and systemic supervision due to non-specific bio-distribution and rapid metabolism of free drug molecules in the human body before reaching their targeted cells that cause damage to many nearby cells and significant side effects due to detrimental toxicity. Moreover, in various cases, tumor cells resist the chemotherapeutic drugs to penetrate the cells (M. M. Gottesman *et al.*, 2002). To decrease the toxic effects, non-penetration of drugs and killing of non-dividing healthy cells owing to conventional nonspecific drug delivery, targeted drug delivery systems have been researched and developed as an intelligent substitution of existing treatments (N. Nasongkla *et al.*, 2006, D. Peer *et al*., 2007, H. Li *et al*., 2019, H. Y. Kim *et al*., 2020). These encompass the microscopic atomic-arrangements which choose particular intracellular routes in cells of carcinoma as well as the other new technique named methylation on beads (mob) capable of targeting molecules on their surface. However, they also can generate side effects by carrying toxic payloads. While designing an effective drug delivery system, firstly, it should be considered that the higher the ratio of drug to the carrier, the lower the probability of generation of toxicity due to the carrier. Secondly, the drug must penetrate and enter into the cell. It is worth referring that the search & survey with the experiments of new types of carriers/transporters becomes imperative for efficient utilization of mobs in the therapy of commonly occurring neoplasm, such as carbon nanotubes (CNTs). It is also worth mentioning that, the consequence of heat/temperature-effect ensued from targeted CNTs can give rise to significant benefits. It is observed by several groups that the use of Near-Infrared (NIR) resonant nanostructures, that comprises gold-nano-shells and CNTs, are very effective to thermally ablated cancer cells (A. M. Gobin *et al*., 2007, C. Loo *et al*., 2005, X. Huang *et al*., 2006, L. Hirsch *et al*., 2003, N. W. S. Kam *et al*., 2005, S. Yu *et al*., 2018).

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Among them, single-wall carbon nanotubes (SWNTs) have enhanced specific surface areas. It can be smoothly mingled with various bio-molecules suggestively through chemical attachment, adsorption, or encapsulation (A. Hirsch, 2002). Sophistic analysis of nanoparticle bio-conjugates is necessary for the forthwith success in this field (L. Zhang *et al*., 2008, A. Z. Wang *et al.*, 2008, G. C. Jensen *et al*., 2009). In particular, some other factors are very important especially for drug delivery, such as scale/size dispersal of nano-particles (nanotubes) and the count of living-molecules per unit length of the nano-particles.

The SWCNTs were employed into testicular cells of carcinoma by endocytosis. In the cell, the decline in p^H was observed and that facilitates the reductive release of the platinum (II) core complex. The diffusion of the platinum (II) core complex was investigated by platinum atomic absorption spectroscopy. The capture of the SWCNTs within the endosomes was confirmed by fluorescence microscopy of SWCNTs accommodating the tethered fluorescein as well as platinum units. In a different method attempted by another group of Z. Yinghuai *et al*., 2005, SWCNT has been functionalized with alternated carborane cages to create a new conveyance system for an efficient boron neutron entrap. This category of water-soluble CNTs was intended for the recuperation of cancer cells. To produce a stable dispersion in water, T. Ohta *et al*., 2016, wrapped SWCNTs with H-(-Lys-Trp-Lys-Gly-)$_7$-OH [$(KWKG)_7$]. To enhance the aqueous diffusion and dispersion, the SWCNTs-$(KWKG)_7$ composite was further reformed with polyethylene glycol (PEG) at the lysine remnant through the formation of an amide bond. Concomitantly, a new type of drug delivery system (DDS) involving chitosan (CHI) amended single-walled carbon nanotubes (SWCNTs) for regulatory loading of anti-cancer doxorubicin (DOX) has been narrated by S. Tavakolifard *et al*., 2016. CHI propagates water-solubility and biocompatibility properties to the SWCNTs and thereby CHI became non-covalently covered around SWCNTs. In another study, P. Jeyamohan *et al*., 2013 recounted the photo-thermal effect of SWCNTs in conjunction with the anticancer antidote doxorubicin (DOX) for selectively directional and rapid ruination of cancer cells in the breast. A selective drug-transportation strategy was constructed for the targeted ruination of carcinoma in breast cells with polyethylene glycol biofunctionalized and DOX-filled SWCNTs combined with folic acid. Before these reports, J. Chen *et al*., 2008, demonstrated a distinctive approach for the chemical functionalization of SWCNTs (f-SWCNTs) in breast cancer treatment. SWCNT is selected because it acts as a good carrier of biologically active molecules as well as it can cross the cell membranes (H. Chen *et al*., 2012). From these explorations, it can be noted that biotin-functionalized SWCNT composites have been efficaciously developed and synthesized as a distinctive and thriving candidate for effective utilization in tumor-selective treatment (J. Chen *et al*., 2008).

In this study, it is aimed to analytically assess the surface area of SWCNTs in its different conformations during the defect-group functionalization and also to establish a relationship with its toxicity.

II. Materials and Methodology

Among the allotropes of carbon, carbon nanotube (CNT) is regarded as one of the prominently pertinent nano-substance in low-dimensional technology (O. T. Wang *et al*., 1998).

The origin of CNT is mainly based on graphene. The graphene sheet is formed by the sp^2 hybridization of valence electrons that assures an impeccably straight 2D construction of condensed benzenoid items. Several methods are popular for the fabrication of SWCNTs. The first technical route is arc eject of graphite in the presence of metal catalysts such as Iron, Cobalt, or Nickel. Alternative methods are dependent on the radiative evaporation of graphite-Ni-Co concoctions and chemical vapor deposition (CVD), where bases of carbon such as acetylene, metallocenes, $Fe(CO)_5/C_2H_2$, and CO can be applied. In the CVD technique where CO renders as the carbon originator, quite thin nanotubes can be produced.

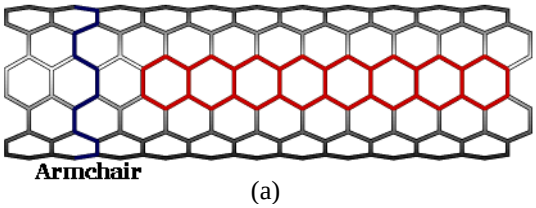
SWCNTs can be composed into 3 individual conformations: Armchair, Chiral, and Zigzag. The confirmation is contingent on the way the graphene is intertwined into a cylinder. An SWCNT's construction is depicted by a couple of indices (n, m) known as the chiral index (n and m are integer constants). For Armchair, it becomes (n, n), for Zigzag (n, 0) (Fig.1), and for Chiral it is (n, m). The constructional conformation has a direct consequence on the nanotube's

electrochemical characteristics. The diameter (D) of these configurations (Armchair, Zigzag, and Chiral) (Figure 1) can be calculated using the indices (n, m) from the following equation:

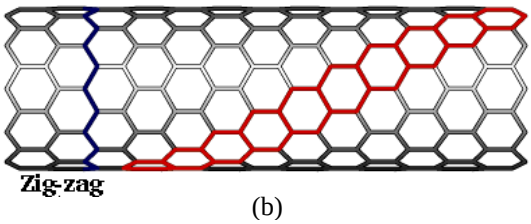
$$D = \frac{a\sqrt{3(n^2 + m^2 + mn)}}{\pi} \quad (1)$$

,where, a = 0.142 nm is the spacing between adjacent atoms in graphene.

The pure forms of these nanotubes are hardly soluble in water and other possible fluids. Although solubility under the physiological condition is a major precondition of making CNT biocompatible with cell fluid in drug delivery systems. Functionalization is one of the several methods used to enhance the solubility of CNTs.



(a)



(b)

Figure 1: Two different conformations of SWCNT; (a) Armchair, (b) Zigzag

CNT undergo oxidization through robust acids, causing the decline of their dimension while producing carboxylic groups, which escalates their diffusibility in aqueous solutions (G. S. Duesberg *et al*., 1998). Moreover, further reaction to the CNT exterior walls and tips create them solvable in water (G. Herlem *et al*., 2019).

Several attempts of functionalization include impurity functionalization, functionalization (covalency) of the lateral walls, hexahedral functionalization (non-covalency), and endohedral functionalization (A. Hirsch, 2002).

This kind of functionalization in SWCNT mainly starts at the defective sites which were produced during its manufacturing process. Certain imperfections of the six-membered-ring carbon structure of the nanotubes, such as the insertion of five- or seven-membered rings in the carbon complex, originate from the preliminary foundation of the tubes (A. Hirsch, 2002).

CNT's venomousness is contingent on several additional issues than concentration, comprising their somatic form, their width, their length, and the characteristics of involved molecules or nano-particles. D. B. Warheit *et al*., 2004, conducted a study in rats, relating the granuloma formation probably due to aggregation of CNT. Research also discovered that utilizing antibody coupled radio-characterized CNTs functionalized by 1,3-dipolar cycloaddition display gentle urinal flow and elevated CNT uptake in the organs (liver, spleen) (S. Park *et al*., 2019). Therefore, based on these probe/exploration, in this report, we intend to methodically evaluate and weigh the consequences or out-turns of the surface area of SWCNT in terms of its variegated structures/conformations while assessing its functionalization with the defect-group and together to find an association with its noxiousness with the help of existing empirical equations.

III. Results and Discussion

A. Soluble Mechanism of functionalized SWCNT

Carbon nanotubes (CNTs) are extensively adapted for biomedical utilization as intracellular carriers of biomolecules mostly due to their aptitude to penetrate cell membranes. Essentially three uptake mechanisms have been reported and they are phagocytosis, diffusion, and endocytosis. Phagocytosis seems regarded as the internalization conduit for CNT combinations, packets, clusters or single dispersed nanotubes whose length is 1000 nm or furture. For nanotubes, endocytosis is considered as the internalization process of the formation of supra-molecular constructions, and dispersion is the internalization process in the case of submicron CNTs that do not produce supra-molecular constructions (V. Rafia *et al*., 2010). The spatial arrangements and conversion of CNT normal to the plasma membrane during application ensued an action alike to nanoneedles, that pierce and dispersed through the lipid bilayer of the plasma membrane without incurring cell demise. Dynamics simulation investigations have revealed that amphiphilic nanotubes can supposedly travel

through imitated lipid bilayers via an analogous action (C. F. Lopez *et al*., 2004, C. W. Bauschlicher *et al*., 2000). It has been understood that macrophage cells could devour cabalistic quantities of nanotubes without traceable poisonous possessions. The internalized tubes stayed fluorescent and could be recognized at wavelengths past 1100 nm. Hence, it implies fulcrum evidence that f-CNTs are proficient ineffectual cellular uptake by a mechanism that has not so far been recognized (Fig. 2 and Fig. 3).

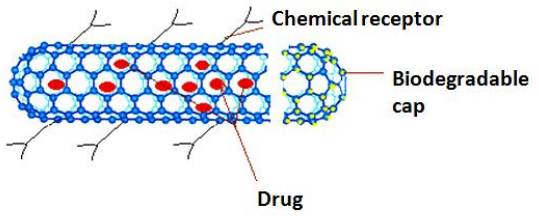


Figure 2: Drug loaded SWCNT with biodegradable cap

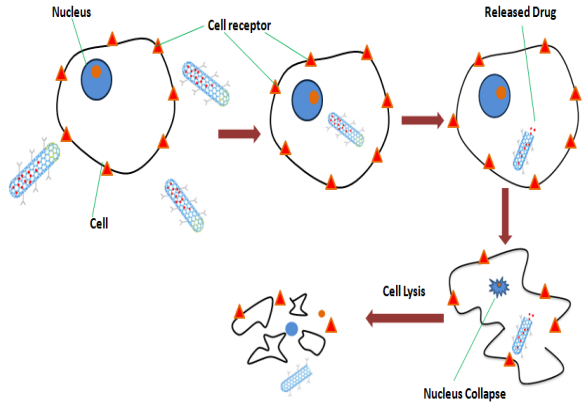


Figure 3: Solubilisation and drug carrier mechanism of functionalized SWCNT

B. Surface Area and Number of sites for functionalization

Functionalized SWCNTs possess notable inherent features that distinguish themselves for directional drug carriage and imaging, comprising: (i) Worthy bio-feasibility, water solubility and declined-toxicity ensuing suitable functionalization; (ii) Exceptional aptitude to penetrate cell membranes by clathrin-mediated endocytosis; (iii) Biodistribution and pharmacokinetic possessions that can be adjusted by governing the size, the chemistry of surface, and the pointing assemblies; (iv) An increased drug filling capacity and meticulous drug discharge via pH, NIR light (Near Infrared light), temperature, etc.

For Armchair SWCNT the chiral indices are (n, n). Therefore, using equation (1), the diameter of the armchair SWCNT is found to be 0.1368*n* nm. And the surface area is realized to be 429.77*n* nm^2 (for 1 μm long SWCNT). Similarly, for zigzag SWCNT the chiral indices are (*n*,0), so, using equation (1), the diameter of zigzag SWCNT is found to be 0.079*n* nm and the surface area is 248.18*n* nm^2 (for 1 μm long SWCNT). For 1.4 nm diameter and length of 300 nm, the surface area is observed to be 1319.472 nm^2. For 1319.472 nm^2 area, the number of C atoms is 50,000 (V. Rafia *et al*., 2010, C. F. Lopez *et al*., 2004). Therefore, for armchair SWCNT the number of C atoms in 429.77n nm^2 is approximately 16286n. Similarly, for zigzag SWCNT the number of C atoms in 248.1864n nm^2 is approximately 9405n.

It is revealed that the imperfections or dislocations are observed both in the open ends and the sidewalls of these nanotubes (V. Rafia *et al*., 2010). It is confirmed, upon the experiments that about 5% of the C atoms in an SWCNT are confined at the dislocation site. Reactive groups, appropriate for extended functionalization of the tubes, rest at these sites of dislocation (V. Rafia *et al*., 2010). Therefore, from our analysis, the number of sites for functionalization in the case of armchair SWCNT is approximately revealed as 814n (16286*n* × 5%). And while for zigzag SWCNT the number is found to be approximately 470*n* (9405n×5%). Therefore, the number of functionalizable sites in armchair SWCNT is found to be 1.73 times higher than zigzag SWCNT. The calculated diameter, surface area, and the number of C atoms are presented in Table 1.

The structure of SWCNT (except for both ends cap) may be described by a vector called the chiral vector, C_h.

$$\boldsymbol{C_h} = n\mathbf{a_1} + m\mathbf{a_2}. \quad (2)$$

,where, *n*, *m* are integers ($0 \leq m \leq n$) and a_1, a_2 are the unit vectors of the graphene, a_1 specifies the zigzag direction whereas a_2 specifies the armchair direction. The restraining circumstances of (*n*, 0) zigzag and (*n*, *n*) armchair nanotubes (Figure 4) are designated by tore strokes. It can be

seen that the angular distance between the zigzag configuration and C_h is negative. Here, *n* is the number of indices. Since the number of '*n*' is higher in the armchair, so the number of carbon atoms will be higher in armchair configuration compared to zigzag. As a result, it is easier to functionalize armchair SWCNT than zigzag SWCNT. Due to more available active sites in armchair SWCNT, it is possible to get the desired result by using less amount of SWCNT. It can be presumed that the use of a lesser amount of SWCNT as a drug carrier can result in less toxic effects on the cell in the living organ. The recent work of Z. Li *et al.* 2019 and A.V.V.V.R Kiran *et al.* 2020 revealed that the proper functionalization of SWNT nanocarriers might still be a promising alternative to deliver drugs and the functionalization is governed by the surface area of the SWCNT. Therefore, this work is in line with the latest literature on SWCNT-based drug delivery systems.

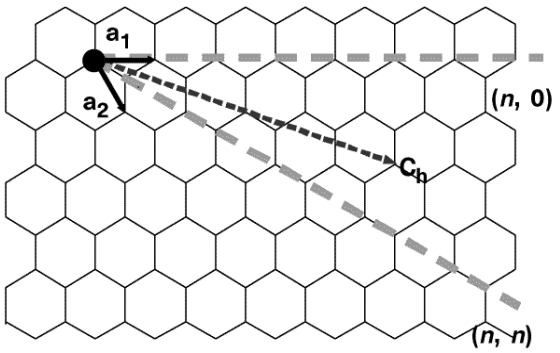


Figure 4: Single sheet of Graphene (O. T. Wang *et al*., 1998)

Table 1: The diameter, surface area (considering 1 nm long CNT), C atoms, and functionalized sites of the armchair and zigzag SWCNTs

Type of CNT	Dia-meter (nm)	Surface area (nm^2)	Number of C atoms	Function alized sites
Arm-chair	0.1368n	429.77n	16286n	814n
Zigzag	0.079n	248.18n	9405n	470*n*

IV. Conclusions

In this paper, we reviewed the recent works on SWCNT-based drug delivery systems. Most of the works found that SWCNT-based drug delivery systems become toxic to living cells due to the lack of functionalization. Thereafter based on the previous study, we calculated the surface area of two different types of SWCNTs and it is noticed that armchair SWCNT has a larger surface area than that of zigzag SWCNT. From our analytical analysis, it is found that the number of functionalizable sites in armchair SWCNT is 1.73 times higher than that of zigzag SWCNT. Therefore, armchair SWCNTs can be used in drug delivery due to its higher surface area that attributes more available sites for functionalization. Moreover, the amount of SWCNT provides a sufficient amount of drug and thus produces fewer toxic effects on the living organs.

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