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Fullerene Derivatives (C$_N$-[OH]$_\beta$) and Carbon Nanotubes Modelled as Transporters for Doxorubicin Drug in Cancer Therapy

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Abstract

Carbon nanomaterials have received increasing attention in drug delivery applications because of their distinct properties and structures, including large surface areas, high conductivity, low solubility in aqueous media, unique chemical functionalities and stability at the nano-scale size. Particularly, they have been used as nano-carriers and mediators for anticancer drugs such as, combination with Cisplatin, Camptothecin and Doxorubicin. Cancer has become the most challenging disease because its sophisticated therapy and classified as one of the top killers according to the World health organization records. The aim of the current work is to study and investigate the mechanism of combination between single-walled carbon nanotubes (SWCNTs) and the fullerene derivatives (C$_N$-[OH]$_\beta$) as mediators, and anticancer drugs for photodynamic therapy directly to destroy the infected cells without damaging the normal ones. Here, we obtain a bio-medical model to determine the efficiency of usefulness of Doxorubicin (DOX) as an antitumor agent conjugated with SWCNTs with variant radii $r$ and fullerene derivative (C$_N$-[OH]$_\beta$). The two sub-models are obtained mathematically to evaluate the potential energy arising from the DOX-SWCNT and DOX-(C$_N$-[OH]$_\beta$) interactions. DOX modelled as two-connected spheres, small and large, each interacting with different SWCNTs (variant radii $r$) and fullerene derivatives C$_N$-[OH]$_\beta$, forming based on the number of carbon atoms (N) and the number of Hydroxide molecules (OH) ($\beta$), respectively.

Keywords: Fullerene derivatives, Single-walled carbon nanotube (SWCNT), Doxorubicin (DOX), Conjugation, Cancer Therapy, van der Waals interaction and Lennard-Jones potential.

1 Introduction

Cancer is defined as the uncontrolled growth of cells that destroys normal organs and tissues. According to the World Health and Cancer Research Organizations in the UK in 2012, the most sophisticated and frequent types of cancers including stomach, colon, lung and breast cancers causing death$^{[1,2]}$. Nanotechnology manipulation focuses on enhancing the intrinsic properties of matter, including the assembly, control, synthesis, and measurement, on the atomic and molecular levels. Since the discovery of carbon nanotubes by Iijima in 1991$^{[3]}$ and fullerene was reported by Kroto in 1985$^{[4]}$, this technology has widely been applied in a huge number of applications in different fields such as mechanics, electronics, biology and chemistry. Furthermore, manipulated nanotechnology has also been used in biomedical fields for diagnosis, imaging and detection. Drug delivery system, particularly with respect to cancer therapy,
advanced carbon nanodevices have a huge potential to achieve the objective of early diagnosis and cancer treatment\cite{5}. Carbon nanoparticles (CNPs) used in biomedical applications including fullerenes and CNTs which can be classified as organic and inorganic, and are considered to be promising vectors for diagnosis and treatment of cancer.

CNPs have generated a great interest of attention in bio-medical fields because of their unique properties and structures. Particularly, functionalized CNPs are attractive as transporters for the delivery of drugs, genes, proteins and chemotherapy\cite{6}. Traditional chemotherapy can be used for cancer detection in the early stages by attacking and killing the infected and normal tissues. Therefore, new treatment techniques for delivering anticancer drugs specifically into tumors to improve therapeutic efficacy and reduce side effects are greatly needed\cite{7}. In the past few decades, the possibility of combination between fullerene derivatives and chemotherapy agents for the delivery of anticancer drugs, including platinum (Pt)-based drugs and topoisomerase inhibitors, are examined\cite{7}. Here, we will focus on studying and investigating the bio-medical model which describes the chemotherapeutic agent conjugated with SWCNTs and fullerene derivatives \(C_{N-}[\text{OH}]_\beta\) (Figure 1). Particularly, fullerene \(C_{60}\) considered as one of the common CNPs because of its unique structure and properties, which can be used as transporter in many medical fields such as for measuring sensitivities\cite{8}, a photosensitizer for transferring electrons\cite{9}, antioxidant agents\cite{10}, gene and drug delivery\cite{11-15}, antitumor agents\cite{16} and work of Prylutska et al.\cite{17} who addressed that the fullerene \(C_{60}\) possibly combined with Cisplating drug can inhibit the growth of cancer cells and reduce the neoplasm formation. In addition, fullerene derivatives, \(C_{60}\)\cite{18,19} and \(C_{60}-[\text{OH}]_\beta\)\cite{20-22}, modelled as antitumor agents by conjugating with different drugs to inhibit the growth of tumor, increase the water solubility ([OH]_\beta binding with fullerene derivatives) and deliver the maximum drug loading to the targeted cells.

In our model, we discuss the medicinal application which addresses the efficacy of SWCNTs and fullerene derivatives \(C_{N-}[\text{OH}]_\beta\) that can be used as antiviral compounds conjugated with DOX chemotherapy agent for cancer therapy (Figure 2(i) and (ii)), respectively. This model obtained mathemat-
Figure 2: Schematic geometry for DOX an atniviral compound as two-connected spheres interacting: i) with an interior atom inside a SWCNT of radius \( r \) at point \( P \) off-setting from the central-axis by a distance \( \alpha \) ii) with an interior atom inside a fullerene derivative (\( C_N-(\text{OH})_\beta \)) of radius \( r_s \) at point \( P \) off-setting from the central-axis by a distance \( \alpha \).

Figure 3: Schematic geometry for: i) DOX an atniviral compound as an arbitrary atom interacting with SWCNT of radius \( r \) ii) DOX an atniviral compound as an arbitrary atom interacting with fullerene derivatives (\( C_N-(\text{OH})_\beta \)) of radius \( r_s \).

chemically to evaluate the interaction energy arising from DOX-SWCNT and DOX-(\( C_N-(\text{OH})_\beta \)) interactions. DOX is a chemotherapy medication, with chemical formula C\(_{27}\)H\(_{29}\)NO\(_{11}\), isolated from cultures of streptomyces peucetius var caesius, used for treating the ovarian tumors such as stomach, breast, leukemias and bladders cancers. It is directly injected into a vein and interfering with DNA’s function\(^{[23]}\). Based on the work of Li et al.\(^{[24]}\) who showed that the therapeutic efficacy of DOX can be improved by conjugation with CNPs and folic acid. Using similar technique, Zhang et al.\(^{[25]}\) who developed a targeted drug delivery system by using the single and multi-walled carbon nanotubes (MWCNTs) as nano-carriers to deliver a maximum loading of DOX into the infected areas. The results for the latter two studies shows that the developed system (DOX-CNTs) have a good stability under physiological conditions by releasing DOX drug at low pH such as intracellular lysosome. Results of the long-term studies show that fullerene derivative C\(_{60}\)-(OH)\(_{20}\) plays a significant role in cancer therapy process by activating the immune system and reduce the vessels density of tumor tissues\(^{[22]}\), for the C\(_{60}\)-(OH)\(_{22}\) can modulate the activity on DOX-induced toxicity in the lines of breast cancer cells\(^{[20]}\), while C\(_{60}\)-(OH)\(_{24}\) derivative protects the tissues of liver and heart against the toxicity and prevents oxidation for cell death with no toxicity\(^{[26,27]}\).

This paper is structured as follows: In section 1, we discuss the significance of CNPs used as nano-carriers in drug delivery applications and also outline the possibility of combination of CNPs, SWCNT and C\(_N\)-(OH)\(_\beta\), with chemotherapeutic agents. Next, we apply the discrete-continuum approach, the van der Waals and Lennard-Jones potential obtained to calculate the magnitude of interaction energy by performing the volume or surface integrals for each interaction. Following this we discuss the numerical results for the proposed model. Finally, conclusions are stated.
Table 1: The Lennard-Jones constants ($\epsilon$:Bond length; $\sigma$:Non-Bond distance; single bond: sb and double bond: db)\textsuperscript{[28]}.

| Interaction | $\epsilon$ (Å) | $\sigma$ (Å) | Interaction | $\epsilon$ (Å) | $\sigma$ (Å) |
|-------------|----------------|--------------|-------------|----------------|--------------|
| H-H         | 0.74           | 2.886        | O-H         | 0.96           | 3.193        |
| O-O (sb)    | 1.48           | 3.500        | O-O (db)    | 1.21           | 3.500        |
| N-N         | 1.45           | 3.660        | N-H         | 1.00           | 3.273        |
| C-C (sb)    | 1.54           | 3.851        | C-H         | 1.09           | 3.368        |
| C-C (db)    | 1.34           | 3.851        | C-O (sb)    | 1.43           | 3.675        |
| C-O (db)    | 1.20           | 3.675        | C-N         | 1.47           | 3.755        |
| N-O         | 1.09           | 3.368        | S-S         | 2.05           | 4.035        |
| S-H         | 1.34           | 3.461        | S-C         | 1.77           | 3.943        |

2 Mathematical Model

In this section, we obtain two medicinal applications (cancer treatment) which describe the encapsulation of DOX as an antitumor agent inside SWCNTs with variant radii $r$ and fullerene derivatives $C_N$-(OH)$_\beta$ of radius $r_s$, respectively. These models are obtained mathematically by using van der Waals forces and the classical Lennard-Jones potential. The Cartesian coordinate $(x, y, z)$ used as a reference system to model each of the two interacting molecules. The non-bond interaction energy obtained by summing the interaction energy for each interacting atom,

$$E = \eta_c \eta_l \sum_i \sum_j \Phi(\rho),$$

where $\Phi(\rho)$ is a potential function for atoms $i$ and $j$ at distance $\rho$. Here, we apply discrete approach and atoms are assumed to be uniformly distributed over the surfaces of the two interacting molecules. The double summation in Equation (1) can be replaced by a double integral, which average over the surface of each atom

$$E = \eta_c \eta_l \int_{S_c} \int_{S_l} \Phi(\rho) dS_c dS_l,$$

where $\eta_c$ and $\eta_l$ are the atomic surface densities for the two molecular structures and $\rho$ is the distance between the two interacting molecules. The classical Lennard-Jones potential for two molecules at a distance $\rho$ apart can be given as

$$\Phi(\rho) = -\frac{A}{\rho^6} + \frac{B}{\rho^{12}},$$

where $A$ and $B$ are the attractive and repulsive constants, respectively. The Lennard-Jones potential and Morse potential used as empirical combining laws, which are given by $\epsilon_{ij} = \sqrt{\epsilon_i \epsilon_j}$ and $\sigma_{ij} = (\sigma_i + \sigma_j)/2$, where $\epsilon$ is the well depth and $\sigma$ is the van der Waals diameter\textsuperscript{[29,30]}, to calculate the physical parameters involved in this model; $A = 4\epsilon \sigma^6$ and $B = 4\epsilon \sigma^{12}$. For more details about the Morse potential law and its application see the references\textsuperscript{[31,32]}.

2.1 Adsorption of DOX into SWCNT

In this section, we obtain the adsorption medical application as a mathematical model to evaluate the interaction energy arising from the DOX-SWCNT interaction. DOX molecule is split into two connected spheres; a small sphere of radius $b_1$ and a large sphere of radius $b_2$ as shown in Figure 3(i). Discretely, the small spherical molecule of radius $b_1 = (\sigma_{NH} + \sigma_{CH} + 2\sigma_{CC})/2 = 7.71$ Å consists of six carbon, nine hydrogen, three oxygen and one nitrogen atoms and we consider twenty one carbon,
where eight oxygen and twenty hydrogen atoms containing a large spherical shell of radius \( \rho \) distance shell of radius \( b \) approximation and Lennard-Jones potential to calculate the interaction energy arising from the spherical shell of radius \( b \) located at \((0,0,0)\).

### Table 2: Physical parameters (\( A \) and \( B \)) involved in this model.

| Interaction | Attractive Value (Å\(^6\) kcal/mol) | Repulsive Value (Å\(^{12}\) kcal/mol) |
|-------------|-------------------------------------|--------------------------------------|
| \( C_{60} \) | \( A_{C_{60}} \) 17.40 | \( B_{C_{60}} \) 29000 |
| \( C_{70} \) | \( A_{C_{70}} \) 17.40 | \( B_{C_{70}} \) 29000 |
| \( C_{80} \) | \( A_{C_{80}} \) 17.40 | \( B_{C_{80}} \) 29000 |
| SWCNT | \( A_{SWCNT} \) 17.40 | \( B_{SWCNT} \) 29000 |
| Fullerene derivative \( [C_{60} - (OH)_{22}] \) | \( A_{60-22} \) 19.08 | \( B_{60-22} \) 50626 |
| Fullerene derivative \( [C_{70} - (OH)_{22}] \) | \( A_{70-22} \) 19.46 | \( B_{70-22} \) 52246 |
| Fullerene derivative \( [C_{80} - (OH)_{22}] \) | \( A_{80-22} \) 19.77 | \( B_{80-22} \) 53549 |
| Fullerene derivative \( [C_{70} - (OH)_{24}] \) | \( A_{70-24} \) 18.85 | \( B_{70-24} \) 49658 |
| Fullerene derivative \( [C_{80} - (OH)_{24}] \) | \( A_{80-24} \) 19.58 | \( B_{80-24} \) 51347 |
| DOX | \( A_{DOX} \) 19.29 | \( B_{DOX} \) 54617 |
| Small Spherical shell (\( b_1 = 7.73\)Å)(DOX) | \( A_{b_1} \) 29.18 | \( B_{b_1} \) 88331 |
| Medium Spherical shell (\( b_2 = 11.21\)Å)(DOX) | \( A_{b_2} \) 35.29 | \( B_{b_2} \) 108923 |

### Table 3: Parameters for fullerene derivatives, SWCNTs and DOX molecules.

| Parameter | Value |
|-----------|-------|
| Radius of CNT(22,19) | 14.03 Å |
| Radius of CNT(22,21) | 14.49 Å |
| Radius of CNT(23,21) | 15.07 Å |
| Radius of fullerene derivative \( [C_60(OH)]_{20} \) | 19.871 Å |
| Radius of fullerene derivative \( [C_70(OH)]_{22} \) | 23.138 Å |
| Radius of fullerene derivative \( [C_80(OH)]_{22} \) | 23.233 Å |
| Radius of fullerene derivative \( [C_80(OH)]_{24} \) | 21.869 Å |
| Radius of fullerene derivative \( [C_80(OH)]_{24} \) | 25.137 Å |
| Radius of the large sphere (DOX) | \( b_1 = 7.73 \) Å |
| Surface density for the large sphere (DOX) | \( \eta_{b_1} = 0.016 \) Å\(^{-2}\) |
| Surface density for the fullerene \( C_{60} \) | \( \eta_{C_{60}} = 0.015 \) Å\(^{-2}\) |
| Surface density for the small sphere (DOX) | \( \eta_{b_2} = 11.21 \) Å |

Eight oxygen and twenty hydrogen atoms containing a large spherical shell of radius \( b_2 = (\sigma_{NH} + \sigma_{CH} + 4\sigma_{CC})/2 = 14.87\) Å. A SWCNT is assumed to be a cylindrical tube which can be parameterized at \((r \cos \theta, r \sin \theta, z)\), where \( r \in [0,1], \theta \in [0,2\pi] \) and \( z \in (-\infty, \infty) \) and each sphere is assumed to be located at \((b \cos \theta \sin \phi, b \sin \theta \sin \phi, b \cos \phi)\), where \( b \in [0,1], \theta \in [0,2\pi] \) and \( \phi \in [-\pi, \pi] \), and the distance \( p \) between the spherical molecule and a typical point on the cylindrical tube is \( p^2 = (r \cos \theta - b \cos \theta \sin \phi)^2 + (r \sin \theta - b \sin \theta \sin \phi)^2 + (z - b \cos \phi)^2 \). From Cox’s Work et al.[33] who adopt the continuum approximation and Lennard-Jones potential to calculate the interaction energy arising from the spherical shell of radius \( b \) interacting with a typical point \((p)\) on cylindrical tube of radius \( r \) is given as

\[
E = \eta_b \pi b \int \int \int \left[ \frac{A}{2} \left( \frac{1}{\rho_1(p_1 + b)^4} - \frac{1}{\rho_1(p_1 - b)^4} \right) - B \frac{1}{5} \left( \frac{1}{\rho_1(p_1 + b)^{10}} - \frac{1}{\rho_1(p_1 - b)^{10}} \right) \right] dV
\]

\[
= \eta_b \pi b \int \int \int \left[ \frac{A}{2} \left( \frac{1}{\rho_1(p_1 + b)^4} - \frac{1}{\rho_1(p_1 - b)^4} \right) - B \frac{1}{5} \left( \frac{1}{\rho_1(p_1 + b)^{10}} - \frac{1}{\rho_1(p_1 - b)^{10}} \right) \right] dr d\theta dz,
\]

where \( \eta_b \) is the atomic surface density of the spherical shell and \( dV = r^2 dr d\theta dz \) is the element volume.
2.2 Adsorption of DOX into fullerene derivatives (C$_N$-[OH]$_\beta$)

Here, DOX’s structure is accounted as two-connected spheres; small and large spheres with radii $b_1$ and $b_2$ (Fig. 3(ii)), respectively. Firstly, we consider six carbon, nine hydrogen, and three oxygen atoms forming a spherical molecule with radius $b_1 = (\sigma_{NH} + \sigma_{CH} + 2\sigma_{CC})/2 = 7.71\text{Å}$. Secondly, the large sphere consists of twenty one carbon, eight oxygen and twenty hydrogen atoms of radius $b_2 = (\sigma_{NH} + \sigma_{CH} + 4\sigma_{CC})/2 = 14.87\text{Å}$ as shown in Figure 3(ii). Each sphere considered as an arbitrary point parameterized by $(0, 0, \alpha)$, while the fullerene derivative defined as a spherical cage can be parameterized by $(r_s, \cos \theta, r_s \sin \theta, r_s \cos \phi)$. The distance $\rho$ between the spherical molecule and a typical point on the spherical cage of fullerene derivative is $\rho^2 = (r_s \cos \theta \sin \phi)^2 + (r_s \sin \theta \sin \phi)^2 + (r_s \cos \phi - \alpha)^2 = r_s^2 + \alpha^2 - 2r_s \alpha \cos \phi$. The interaction energy arising from the spherical shell and a typical point inside the fullerene derivative (C$_N$-[OH]$_\beta$) can be given as

$$E = \eta_b \sum \Phi(\rho) dV,$$

the summation given in Equation (5) can be replaced by the volume integral which is given by

$$E = \eta_b \int V \Phi(\rho) dV = \eta_b [-A I_3 + B I_6],$$

where $\eta_b$ is the atomic volume density of the spherical shell of radius $b_1$ and $dV = r_s \sin \theta dr_s d\theta d\phi$ is the element volume.

$$I_n = \int_{-\pi/2}^{\pi/2} \int_{-\pi}^{\pi} \int_0^1 \left[ \frac{r_s \sin \theta}{(r_s^2 + \alpha^2 - 2\alpha r_s \cos \phi)^n} \right] dr_s d\theta d\phi$$

$$= 2 \int_{-\pi/2}^{\pi/2} \int_0^\pi \int_0^1 \left[ \frac{r_s \sin \theta}{(r_s^2 + \alpha^2 - 2\alpha r_s \cos \phi)^n} \right] dr_s d\theta d\phi. \quad (7)$$

We do integration to equation(7). So, $I_n$ can be given as

$$I_n = 2 \int_{-\pi/2}^{\pi/2} \int_0^\pi \int_0^1 \left[ \frac{r_s}{(r_s^2 + \alpha^2 - 2\alpha r_s \cos \phi)^n} \left( \int_0^\pi \sin \theta d\theta \right) \right] dr_s d\phi$$

$$= 4 \int_{-\pi/2}^{\pi/2} \int_0^\pi \int_0^1 \left[ \frac{r_s}{(r_s^2 + \alpha^2 - 2\alpha r_s \cos \phi)^n} \right] dr_s d\phi. \quad (8)$$

we then take $(r_s^2 + \alpha^2)$ as common factor to re-write $I_n$ in simpler form

$$I_n = 4 \int_{-\pi/2}^{\pi/2} \int_0^\pi \left[ \frac{r_s}{(r_s^2 + \alpha^2)^n} \left( 1 - \frac{2\alpha r_s}{r_s^2 + \alpha^2} \cos \phi \right)^n \right] \left( \int_0^\pi \cos \phi d\phi \right) dr_s$$

$$= 4 \int_{-\pi/2}^{\pi/2} \int_0^\pi \left[ \frac{r_s}{(r_s^2 + \alpha^2)^n} \left( 1 + \left( \frac{2\alpha r_s}{r_s^2 + \alpha^2} \cos \phi \right)^n \right) \right] dr_s d\phi. \quad (9)$$

By using the binomial series,$^{34}$

$$(1 + X)^{-n} = \sum_{k=0}^{\infty} \left( \begin{array}{c} -n \\ k \end{array} \right) X^k,$$  

we can re-write the equation (9) to be given by

$$I_n = 4 \int_0^1 \left[ \frac{r_s}{(r_s^2 + \alpha^2)^n} \left( \sum_{k=0}^{\infty} (-1)^k \left( \begin{array}{c} -n \\ k \end{array} \right) \left( \frac{2\alpha r_s}{r_s^2 + \alpha^2} \right)^k \right) \cos^k \phi d\phi \right] dr_s$$

$$= 4 \int_0^1 \left[ \frac{r_s}{(r_s^2 + \alpha^2)^n} \left( \sum_{k=0}^{\infty} (-1)^k \left( \begin{array}{c} -n \\ k \end{array} \right) \left( \frac{2\alpha r_s}{r_s^2 + \alpha^2} \right)^k \right) \int_{-\pi/2}^{\pi/2} \cos^k \phi d\phi \right] dr_s. \quad (11)$$
Here, we have two cases for the value of \( k \); odd and even. When \( k \) is an even, the integral \( I_n \) becomes zero. By using the trigonometric formula as mentioned below

\[
\int \cos^{2k+1} \phi \, d\phi = \frac{1}{2^{2k}} \sum_{i=0}^{k} \left[ \binom{2k+1}{i} \frac{\sin(2k-2i+1)\phi}{2k-2i+1} \right].
\] (12)

So, \( I_n \) can be written on the following form:

\[
I_n = 4 \int_0^1 \left\{ \frac{r_s}{(r_s^2 + \alpha^2)^n} \sum_{k=0}^{\infty} (-1)^k \binom{-n}{k} \left( \frac{2\alpha r_s}{(r_s^2 + \alpha^2)^{n+k}} \right)^k \right\} \times \left( \frac{2k+1}{i} \right) \left( \frac{2 \sin(2k-2i+1)(\pi/2)}{2k-2i+1} \right) \right\} \, dr_s
\]

\[
= 8 \int_0^1 \left\{ \sum_{k=0}^{\infty} (-1)^k \binom{-n}{k} \left( \frac{2k+1}{i} \right) \left( \frac{2 \alpha r_s^{k+1}}{(r_s^2 + \alpha^2)^{n+k}} \right) \times \left( \sin(2k-2i+1)(\pi/2) \right) \right\} \, dr_s.
\] (13)

We may re-write the integral \( I_n \) which can be given as

\[
I_n = 8 \int_0^1 \left[ \sum_{k=0}^{\infty} \sum_{i=0}^{k} (-1)^k \binom{-n}{k} \binom{2k+1}{i} \left( \frac{2k+1}{i} \right) \left( \frac{2 \alpha r_s^{k+1}}{(r_s^2 + \alpha^2)^{n+k}} \right) \left( \frac{1}{2^{2k}} \sin(2k-2i+1)(\pi/2) \right) \right] \, dr_s
\]

\[
= 8 \int_0^1 \left[ \sum_{k=0}^{\infty} \sum_{i=0}^{k} (-1)^k \binom{-n}{k} \binom{2k+1}{i} \left( \frac{2k+1}{i} \right) \left( \frac{2k+1}{i} \right) \left( \frac{\alpha r_s^{k+1} \sin(2k-2i+1)(\pi/2)}{2k+1(2k-2i+1)(r_s^2 + \alpha^2)^{n+k}} \right) \right] \, dr_s.
\] (14)

We may re-arrange \( I_n \) to be on nicer and easier form

\[
I_n = \sum_{k=0}^{\infty} \sum_{i=0}^{k} \left\{ \left( -1 \right)^k \binom{-n}{k} \binom{2k+1}{i} \left( \frac{2k+1}{i} \right) \left( \frac{\alpha^{k+1} \sin(2k-2i+1)(\pi/2)}{2k+1(2k-2i+1)(r_s^2 + \alpha^2)^{n+k}} \right) \right\} \times \left( \int_0^1 r_s^{k+1}(r_s^2 + \alpha^2)^{-(n+k)} \, dr_s \right).
\] (15)

By using the Beta function and special hypergeometric function

\[
\int_0^{u} t^{\lambda-1} (u-t)^{\mu-1} (t^2 + \gamma^2)^{v} \, dt = \gamma^{2v} \beta(\lambda, \mu) \, _3F_2[-v, \lambda + 1, 2; \lambda + \mu + 1, \lambda + \mu + 1, \frac{-u^2}{\gamma^2}],
\] (16)
We may re-write equation (15) by substituting \( \lambda = k + 2, u = 1, \mu = 1, \gamma = \alpha \) and \( v = n + k \). So, \( I_n \) can be re-written as

\[
I_n = \sum_{k=0}^{\infty} \sum_{i=0}^{k} \left\{ (-1)^k \binom{n}{k} \left( \frac{2k+1}{i} \right) \left( \frac{\alpha^k \sin(2k - 2i + 1)(\pi/2)}{2^{k-3}(2k-2i+1)} \right) \times \left[ \frac{1}{\alpha^2} \right] \right\}
\]

\[
= \sum_{k=0}^{\infty} \sum_{i=0}^{k} \left\{ (-1)^k \binom{n}{k} \left( \frac{2k+1}{i} \right) \left( \frac{\sin(2k - 2i + 1)(\pi/2)}{2^{k-3}\alpha^{2n+k}(2k-2i+1)} \right) \times \left[ \frac{1}{\alpha^2} \right] \right\}.
\]

3 Results and discussion

In this paper, we present a mathematical model which describes the mechanism of conjugation between the DOX drug with SWCNTs and fullerene derivatives. The numerical value for the magnitude of interaction energy arising from DOX molecule encapsulated inside SWCNTs and fullerene derivatives \( (C_N\mbox{-}[OH]_{\beta}) \) are obtained by using the Lennard-Jones potential and the continuum approach. Firstly, we need to calculate the physical parameters involved in the proposed model to be able to evaluate the magnitude of interaction energy arising from DOX-SWCNT and DOX-(C\_N\mbox{-}[OH]_{\beta}) interaction. The physical variables, well-depth \( \epsilon \) (non-bond energy) and van der Waals diameter \( \sigma \), are shown in Table 1. \( \epsilon \) and \( \sigma \) are used to calculate the significant physical parameters, attractive \( A = 4e\sigma^6 \) and repulsive \( B = 4e\sigma^{12} \) constants, involved in this model shown in Table 2. Radii \( r \) of SWCNTs, the radius of each sub-configuration (DOX) and the atomic surface density for each sub-configuration are given in Table 3. The surface or volume atomic density for each configuration calculated as the total number of atoms which are containing the interacting molecule divided by the surface area or the volume of the molecule structure, spherical shape \( (\eta_b) \) and cylindrical tube \( (\eta_c) \) which are \( \eta_b = \text{number of atoms}/(4\pi b^2) \) and \( \eta_c = \text{number of atoms}/(2\pi r L) \), respectively.

MAPLE package used to evaluate and plot the interaction energy for each configuration which represented by using two techniques; the relationship between the magnitude of total energy along the range on the z-axis (Fig. 4) and based on determining the critical radius that would accept the DOX molecule inside a SWCNT (Fig. 5). From Figure 4(i-vi) shows that the orientation for each configuration evaluated along the range \(-25 \leq z_0 \leq 25 \text{ Å} \) (negative and positive sides of the origin). We investigate the DOX-SWCNT interaction by considering the nanotubes (22,19),(23,19),(22,21),(22,22),(23,21) and (23,22) which have radii 14.03, 14.26, 14.49, 14.72, 15.07 and 15.27 Å, respectively. We also observe that the encapsulation of DOX molecule inside the SWCNT occurs when \( r \) is greater than 14.32 Å and the minimum energy is obtained when \( r = 15.27 \text{ (SWCNT(23,22)) Å} \). To confirm our results above as shown in Fig. 4, we use another technique by calculating and plotting the relationship between interaction energy and the radius of SWCNT \( r \) (Fig. 5).

By comparing our result with the recent findings addressed in long-term studies, we notice that the work of Elhissi et al.\(^6\) show that CNPs are excellent tools for drug delivery and cancer therapy applications. Son’s work et al.\(^7\) also support our numerical results which indicate that CNTs can be used as carriers and mediators (antiviral compounds). Ghasemvand et al.\(^35\) who addressed that SWCNT have been successfully loaded with different biomolecules and drugs, such as paclitaxel (PTX) and doxorubicin (DOX) via \( \pi-\pi \) interaction.

As shown in Figure 6 to 8, we investigate the encapsulation of DOX drug inside the fullerene derivative; \( C_{N\mbox{-}[OH]_{20}}, C_{N\mbox{-}[OH]_{22}} \) and \( C_{N\mbox{-}[OH]_{24}} \) where \( N \) is variant. The interaction energy evaluated and plotted for each configuration along the range of z-axis (both sides of origin). Significantly, we can see there is
Figure 4: Interaction energy ($E$) arising from DOX molecule interacting with SWCNTs of various radii $r$: i) $r = 14.03$ Å ii) $r = 14.26$ Å iii) $r = 14.49$ Å iv) $r = 14.72$ Å v) $r = 15.07$ Å vi) $r = 15.27$ Å.

a minimal difference in the level of energy for the three sub-models (DOX-(C$_N$-[OH]$_\beta$)). Obviously, we note that the fullerene derivative C$_{60}$-[OH]$_{22}$ has practically been loaded with DOX molecule and has the lowest energy obtained, then followed by C$_{80}$-[OH]$_{22}$ and C$_{70}$-[OH]$_{22}$ which are of approximately -0.384, -0.339 and -0.308 kcal/mol, respectively, as shown in Table 4. We also observe that the DOX-C$_{70}$-(OH)$_{20}$ interaction has a magnitude of energy is greater that of DOX-(C$_{70}$-[OH]$_{24}$), but for DOX-(C$_{80}$-[OH]$_{20}$) and DOX-C$_{80}$-(OH)$_{24}$ are roughly equal which about -0.178 to -0.197 kcal/mol. Throughout investigation, we can see that the fullerene C$_{60}$, binding with OH molecules (Hydroxide) as antiviral compound against the growth of cancer pathogens, is the most favorable fullerene derivative adopting the DOX molecule in compared to the fullerenes C$_{70}$ and C$_{80}$. This is because the fullerene C$_{60}$ having distinct properties and ideal structure, such as its symmetry around the axis, high conductivity and low stability in aqueous media.

Interestingly, our results are in very good agreement with the recent findings which verified by using experiments and simulation techniques. We show that the three fullerene derivatives are practically functionalized to the DOX drug and there are no energetic barriers which is consistently agree with work of Ghasemvand et al.$^{[35]}$ who confirmed that the DOX molecule was bonded covalently to SWCNTs and MWCNTs with variant radii. In addition, Liu’s work et al.$^{[22]}$ concluded that C$_{60}$-[OH]$_{20}$ derivative plays a vital role in cancer treatment by reducing the vessels density of cancer cells and activating the immune system. Moreover, Bogdanovic’s et al.$^{[20]}$, in their long-term study who confirmed that the DOX-induced can be modulated with C$_{60}$-[OH]$_{22}$ to reduce the toxicity of breast tumor tissues. Another significant results indicate that the fullerene derivative C$_{60}$-[OH]$_{24}$ can prevent the oxidation arising from the death cells$^{[27]}$ and protect the tissues of liver and heart against the toxicity$^{[26]}$. 
Figure 5: Interaction energy ($E$) arising from DOX molecule as tow-connected spheres, each interacting with SWCNT (relationship between the interaction energy and radius of SWCNT $r$).

Figure 6: Interaction energy ($E$) arising from DOX molecule as tow-connected spheres, each as an arbitrary point interacting with fullerene derivatives ($C_N$-[$\text{OH}_{20}$]).
Figure 7: Interaction energy ($E$) arising from DOX molecule as tow-connected spheres, each as an arbitrary point interacting with fullerene derivatives ($C_N$-[OH]$_{22}$).

Figure 8: Interaction energy ($E$) arising from DOX molecule as tow-connected spheres, each as an arbitrary point interacting with fullerene derivatives ($C_N$-[OH]$_{24}$).
Table 4: The interaction energy \( (E) \) arising from each configuration interacting with SWCNT and fullerene derivatives.

| Interaction          | Minimum energy \( (E) \) kcal/mol | Statistical errors |
|----------------------|-----------------------------------|--------------------|
| DOX-SWCNT            | -0.368 ± 0.01                     |                    |
| DOX-[C\(_{60}\)-(OH)\(_{20}\)] | -0.288 ± 0.005                   |                    |
| DOX-[C\(_{60}\)-(OH)\(_{22}\)] | -0.384 ± 0.007                   |                    |
| DOX-[C\(_{70}\)-(OH)\(_{20}\)] | -0.211 ± 0.007                   |                    |
| DOX-[C\(_{70}\)-(OH)\(_{22}\)] | -0.247 ± 0.005                   |                    |
| DOX-[C\(_{70}\)-(OH)\(_{24}\)] | -0.308 ± 0.007                   |                    |
| DOX-[C\(_{70}\)-(OH)\(_{24}\)] | -0.185 ± 0.005                   |                    |
| DOX-[C\(_{80}\)-(OH)\(_{20}\)] | -0.191 ± 0.005                   |                    |
| DOX-[C\(_{80}\)-(OH)\(_{22}\)] | -0.339 ± 0.007                   |                    |
| DOX-[C\(_{80}\)-(OH)\(_{24}\)] | -0.178 ± 0.005                   |                    |

4 Conclusions

In this paper, we use the discrete-continuum approach together with the van der Waals force and the Lennard-Jones potential function to evaluate the interaction energy arising from the DOX molecule interacting with fullerene derivatives and SWCNTs with variant radii \( r \). The analytical expressions and special hypergeometric functions are obtained and used to evaluate the minimum energy arising from DOX molecule encapsulated inside the \((C\(_N\)-[OH]\(_\beta\))\) derivatives and SWCNTs varying in radii \( r \), and to determine the critical radius that would accept DOX molecule. In the proposed model, we model the DOX molecule as two-connected spheres; small and large. Next, we evaluate the sub-interaction for each configuration interacting with fullerene derivatives and SWCNTs \( (r: \text{variant}) \) then gather all interaction pairs to determine the total energy. As shown in Fig. 4, we calculate the interaction energy in two techniques; along the range of \( z \)-axis and based on the radius of SWCNT \( (13.8 \leq r \leq 15.1 \text{ Å}) \). We find that the DOX molecule would be more stable and acceptable when \( r \) is greater than 14.32 Å and also the minimum energy arising from DOX-SWCNT interaction occurs when \( r = 15.49 \text{ Å} \) (the most favorable nanotube \((23,21)\)). For the DOX-\((C\(_N\)-[OH]\(_\beta\))\) interactions, we find that DOX-\((C\(_{60}\)-[OH]\(_{22}\))\) interaction has the minimum energy which means that DOX molecule would be acceptable and more stable inside \((C\(_{60}\)-[OH]\(_{22}\))\) and \((C\(_{70}\)-[OH]\(_{\beta}\))\) derivatives bonded to DOX drug are more effective as inhibitors against the growth of tumor than \((C\(_{80}\)-[OH]\(_{\beta}\))\) derivatives as shown in Figures 6 to 8. The numerical results obtained in our proposed model have a good approximation and more accurate which are consistently agree with the most recent studies, for example, Liu’s work et al.\(^{[22]}\) shown that \((C\(_{60}\)-[OH]\(_{20}\))\) derivative helps in activating the immune system, while Bogdanovic’s et al.\(^{[20]}\) who used DOX-\((C\(_{60}\)-[OH]\(_{22}\))\) as antioxidant agent. Another significant results indicate that the fullerene derivative \((C\(_{60}\)-[OH]_{24})\) can prevent the oxidation and protect the heart and liver tissues.\(^{[26,27]}\). Their experimental results show that \((C\(_N\)-[OH]_{\beta})\) derivatives were practically bonded and loaded with DOX drug and could offer an opportunity to enhance the nano-devices properties which can be used as antiviral compounds in drug delivery applications, such as against the tumor growth and attacking the pathogens.

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Conflict of Interest
Has no conflict of interest.

Ethical approval
This article does not contain any studies with animals performed by any of authors.

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Dr. Hakim Al Garalleh has written the proposed model, introduction, the numerical results, the conclusions besides reviewed the data analysis including the statistical errors.
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