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Research article

Computational study on encapsulation of 5-fluorouracil drug in nanotubes

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Abstract: Cancer remains a major health concern worldwide, causing high rates of morbidity and mortality. Although chemotherapy with antitumor drugs is the most common treatment for cancer, certain disadvantages limit its usage, such as the damage caused to healthy cells, side effects, and toxicity. Owing to their geometric and mechanical properties, nanotubes are promising nanocarriers of anticancer drugs. Here, the interaction energies of the encapsulation of an anticancer drug by single-walled nanotubes were calculated through the application of the 6–12 Lennard-Jones function with a continuous approach. In particular, the interaction energies of the 5-fluorouracil drug entering three different nanotubes (carbon, silicon and boron nitride) and the offset equilibria inside the nanotubes were obtained. This study aimed at determining the appropriate type and favorable size of nanotubes that can be used to encapsulate the 5-fluorouracil drug. The results showed that the optimal radii of nanotubes for encapsulating the 5-fluorouracil drug were approximately 6.08, 6.05 and 5.98 Å for carbon, boron nitride and silicon nanotubes, corresponding to −16.55, −18.20 and −17.81 kcal/mol, respectively.

Keywords: nanotubes; anticancer; drug delivery; 5-fluorouracil; continuous approach; encapsulation; mathematical modeling
Mathematics Subject Classification: 92-XX, 92-10

1. Introduction

Cancer is a disease caused by irregular cell growth. It remains a global health problem and is considered as the second leading cause of human death [1], despite the development of many successful drugs in clinical use, such as chlorambucil, carboplatin, doxorubicin, cyclophosphamide, cisplatin and 5-fluorouracil. 5-fluorouracil (5-FU) ($C_4H_3FN_2O_2$) is utilized to treat solid tumors, and it has shown unique biological properties against tumors [2]. It can be used for the treatment of colon, pancreatic, esophageal, stomach, breast and cervical cancers, as well as precancerous dermatoses. However, 5-FU

drugs, similar to other anticancer drugs, often cause side effects, such as deoxyribonucleic acid (DNA) toxins, hair loss, birth defects, fatigue, mouth sores and liver disease. In addition, it can cause oxidative DNA damage and cell death [3–5]. The encapsulation of a 5-FU drug into nanoparticle molecules, such as nanotubes, can aid in preventing such side effects and may result in the formation of a nontoxic complex to deliver the drug to the target cells safely.

Currently, nanotubes (NTs) such as boron nitride nanotubes (BNNTs), carbon nanotubes (CNTs) and silicon nanotubes (SiNTs) have attracted significant attention, particularly in the medical field, because of their interesting properties. Depending on size, shape, surface functionality and chemical stability of nanotubes, they may be designed to carry multiple drugs to the target cells to avoid the known toxicity caused by anticancer drugs to healthy cells. The geometric configuration of NTs is described using a chiral vector (i, j), where i and j are two positive integer numbers, which are known as the chiral vector numbers; for example, when $i = j$ the nanotube is referred to as an armchair nanotube [6–8]. There are several advantages in the use of nanotubes as anticancer drug carriers: for example, reaching the cancer cells directly, further enhanced therapeutic efficacy, preventing interaction with the biological environment and the ability to be readily taken up by cells.

The encapsulation and interaction of the 5-FU drug with nanotubes and the possibility of using them as nanocarriers for the 5-FU drug have been studied experimentally and through density functional theory (DFT) and molecular dynamics (MD) simulation. Shayan and Nowroozi studied the interaction of the (5,5)–(8,8) armchair BNNTs with the 5-FU drug using DFT. They observed that the encapsulation of the 5-FU drug inside (8,8) BNNT was the most stable compared with the other BNNTs. In addition, they showed that the encapsulation inside BNNTs with a small radius, such as 5-FU@(5,5) BNNT and 5-FU@(6,6) BNNT, was unstable [9]. Dehaghani et al. conducted an MD simulation to compare the performance of the (8,8) armchair BNNT and CNT as nanocarriers for the 5-FU drug. Their results indicated that the adsorption of the 5-FU molecule within the BNNT was more rapid than that within the CNT [1]. Moreover, their results showed that the encapsulation of the 5-FU inside the BNNT and CNT happened spontaneously, with interaction energies of -25 and -14 kcal/mol, respectively. Soltani et al. used DFT to investigate the adsorption of the 5-FU molecule on the BNNTs [10] and found that the 5-FU drug might be adsorbed physically onto the walls of (8,0) and (5,5) BNNTs with energy values of -3 and -2.54 kcal/mol, respectively. In addition, they indicated that the low values of the binding energies implied relatively weak binding of the 5-FU molecule to the exterior walls of the tubes. Moreover, the 5-FU molecule underwent weak physical adsorption owing to van der Waals forces. Al-anber and Al-Masoudi performed modified neglect of diatomic overlap (MNDO)/d calculations to study the adsorption of the fluorouracil on the surface of a CNT and showed that with increase in the CNT diameter, the binding energies decreased [11].

The use of the nanoparticles, specifically nanotubes, may provide a protected environment for the drug molecule prior to ingestion into the cell, for example, from chemical reactivity, such that it may assist in avoiding the need for a solvent medium or liquid carrier. Therefore, specific investigation of the utilization of a solvent medium in this study was not required [22]. Moreover, several studies have investigated the interaction and the possibility of encapsulation of different types of antitumor drugs in nanotubes [12–19]. Hilder and Hill used traditional applied mathematical modelling to adapt the Lennard-Jones potential and the continuum approximation to examine the encapsulation behaviors of various drugs, including doxorubicin, cisplatin and paclitaxel molecules, inside different types of nanotubes [20–24]. Their results indicated an appropriate size of the tube that results in the optimum

encapsulation mechanics for the drug molecules.

Mathematical modeling is a feasible way to understand and solve various problems in biotechnology and the medical industry. It is faster than certain methods such as molecular dynamics simulations, and the results can be used for comparison with the values of the software that is used to construct representations of molecules and pores, such as molecular mechanics software. Moreover, Ferrari stated that, to secure the full import of nanotechnology into oncology, new mathematical models are required [25]. This study aimed to computationally investigate the encapsulation of the 5-FU drug inside three different types of armchair (i, i) SWNT through the calculation of van der Waals (vdW) forces between the 5-FU drug and SWNTs.

2. Modeling approach

The physical mechanisms of 5-FU molecule encapsulation in SWNTs were determined, which can be explained as a mathematical model using vdW forces between non-bonded atoms. The Lennard-Jones (LJ) potential coupled with the continuous approach was adopted to investigate the encapsulation behavior of the 5-FU molecule in the three different types of single-walled nanotubes. For examining the interactions between the nanotubes with drug with respect to the radius of the tube, the nanotubes with different chiralities (chiral and zigzag) can be examined using the same method, as shown in the work done by Hilder and Hill [20]. The atoms on the nanotubes and 5-FU molecule were assumed to be uniformly distributed over the surfaces of the two molecules, such that the continuum approach can be employed. Thus, the total interactions were obtained by performing two surface integrals, expressed as

$$E^{tot} = \ell_1 \ell_2 \int_{S_1} \int_{S_2} U(d)\, dS_1\, dS_2, \tag{2.1}$$

where $U(d)$ is the potential function between two surface elements at a distance d, and it is expressed as

$$U(d) = -\frac{A}{d^6} + \frac{B}{d^{12}}. \tag{2.2}$$

Further, ℓ_1 and ℓ_2 are the mean atomic surface densities of the two molecules (nanotube and 5-FU), where the mean surface densities of the nanotubes are expressed as $\ell_{CNT} = 0.3812$, $\ell_{BNNT} = 0.122$ and $\ell_{SiNT} = 0.1527$ Å^{-2} [21], respectively, and the mean surface density of the 5-FU molecule can be obtained from

$$\ell_d = \frac{\text{number of the atoms of the molecule} = 12}{\text{surface area of the sphere} \approx 88.247} \approx 0.136\text{Å}^{-2}. \tag{2.3}$$

Additionally, the LJ parameters are expressed as $A = 4DR^6$ and $B = 4DR^{12}$, where D and R are the energy well-depth and the van der Waals diameter, respectively, and their values were obtained from [26]; they are listed in Table 1. The mixing rules were used to compute the two different types [27], and they are expressed as

$$R_{12} = \frac{(R_1 + R_2)}{2} \tag{2.4}$$

and

$$D_{12} = \sqrt{D_1 D_2}. \tag{2.5}$$

Table 1. Values of the LJ parameters [26].

Interaction	A (Å^6 kcal/mol)	B (Å^{12} kcal/mol)
CNT–5-FU	442.189	1030668.406
BNNT–5-FU	493.351	1098124.574
SiNT–5-FU	1236.572	2429791.665

In this model, the interactions between cylindrical (nanotube) and a spherical (5-FU) surfaces were considered, as shown in Figure 1. The cylindrical coordinate system of the nanotube with a radius τ is expressed by $(\tau\cos\theta, \tau\sin\theta, z)$, where $z \in (-\infty, \infty)$ and $\theta \in (-\pi, \pi]$.

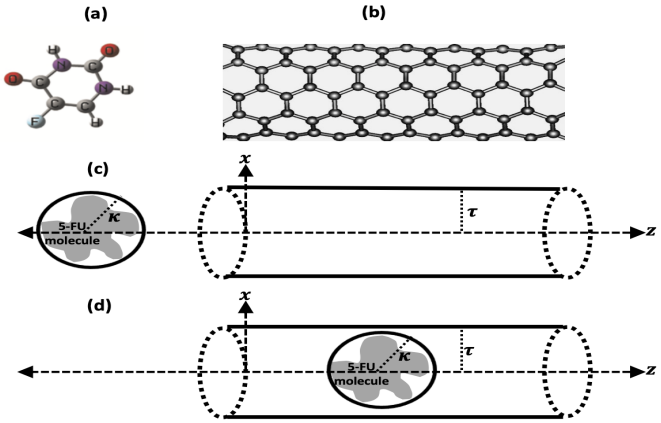


Figure 1. Geometry of (**a**) 5-Fluorouracil ($C_4H_3FN_2O_2$) (C grey, F light blue, N purple, H white and O red), (**b**) single-walled nanotube, (**c**) 5-FU entering SWNT and (**d**) 5-FU inside SWNT.

In the subsequent subsections, the underlying mathematics used to describe (i) the interactions of the 5-FU molecule entering the NTs and (ii) the equilibrium offset positions of the 5-FU drug inside the NTs are outlined.

2.1. 5-FU molecule entering nanotube

The interaction energy of a drug molecule entering nanotubes is defined here as the total energy (E_S) by the interaction of vdW acquired by the 5-FU drug from being inserted inside the nanotube. It may be written as

$$E_S = \int_0^{\infty} \frac{dE^{tot}}{d\delta}\, d\delta, \tag{2.6}$$

where δ is the distance from the center of the 5-FU to the end of the nanotube, with the center of mass of the 5-FU molecule assumed to be located on the z-axis of the nanotube. Using the Cartesian

coordinate system (x, y, z), the coordinates of the center of the 5-FU molecule are $(0, 0, \delta)$, and the cylinder is expressed parametrically by $(\tau\cos\theta, \tau\sin\theta, z)$, where $z \in [0, \infty)$ and $\theta \in (-\pi, \pi]$, as shown in Figure 2.

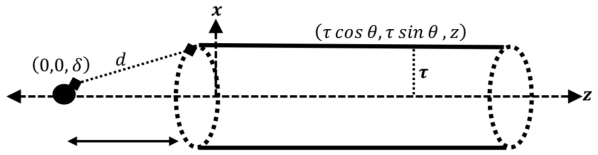


Figure 2. Geometric parameterization of a point entering nanotube.

Thus, the distance d between a point on the surface of tube and the center of the 5-FU is expressed as $d^2 = \tau^2 + (z - \delta)^2$. Now, the interaction of a point entering an open nanotube is determined as

$$E^{tot} = \tau\ell_T \int_{-\pi}^{\pi}\int_0^{\infty}\left(-\frac{A}{d^6} + \frac{B}{d^{12}}\right) dzd\theta = \ell_T\left(-AQ_3 + BQ_6\right), \tag{2.7}$$

where $T \in \{CNT, BNNT, SiNT\}$. The integral Q_n is evaluated as follows, where $(n = 3, 6)$:

$$Q_n = \tau\int_{-\pi}^{\pi}\int_0^{\infty}\frac{1}{\left[\tau^2 + (z-\delta)^2\right]^n} dzd\theta. \tag{2.8}$$

The integration of θ is trivial; therefore,

$$Q_n = 2\pi\tau\int_0^{\infty}\frac{1}{\left[\tau^2 + (z-\delta)^2\right]^n} dz. \tag{2.9}$$

Moreover, by using integration techniques such as substitution and integration using trigonometric identities, combined certain particular formulae from [28], the integral Q_n is expressed as

$$Q_3 = \pi\tau^{-5}\left[\frac{3\pi}{8} + \frac{3}{4}\tan^{-1}\left(\frac{\delta}{\tau}\right) + \frac{3\delta\tau}{4(\tau^2+\delta^2)} + \frac{\delta\tau^3}{2(\tau^2+\delta^2)^2}\right], \tag{2.10}$$

and

$$\begin{aligned} Q_6 = \pi\tau^{-11}\Bigg[&\frac{9\pi}{3840} + \frac{3}{640}\tan^{-1}\left(\frac{\delta}{\tau}\right) + \frac{\delta\tau^9}{5(\tau^2+\delta^2)^5} + \frac{9\delta\tau^7}{40(\tau^2+\delta^2)^4} \\ &+ \frac{7\delta\tau^5}{60(\tau^2+\delta^2)^3} + \frac{\delta\tau^3}{16(\tau^2+\delta^2)^2} + \frac{3\delta\tau}{80(\tau^2+\delta^2)}\Bigg], \end{aligned} \tag{2.11}$$

and these expressions are completed (2.7).

2.2. An offset 5-FU molecule inside nanotube

In this section, the equilibrium position for a 5-FU molecule inside an SWCNT was studied to determine the optimal radius of tube that may be used to accommodate the drug molecule. In axially symmetric cylindrical polar coordinates, the 5-FU molecule is assumed to be located inside the NTs

at $(\eta, 0, 0)$, as shown in Figure 3, where η is the equilibrium distance from the central axis of the tube to the center of the offset drug molecule.

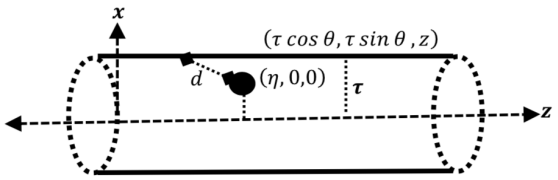


Figure 3. Geometric parameterization of a point in nanotube.

Thus, the distance d between the 5-FU and the CNT molecules is expressed as $d^2 = (\tau - \eta)^2 + z^2 + 4\tau\eta \sin^2(\theta/2)$. Subsequently, the interaction of a point with an infinite NT is calculated as

$$E_{OP} = \ell_T \int_S \left(-\frac{A}{d^6} + \frac{B}{d^{12}}\right) dS = \eta_{NT} \left(-AJ_3 + BJ_6\right), \tag{2.12}$$

where J_n $(n = 3, 6)$ is the integral to be evaluated:

$$J_n = \int_{-\infty}^{\infty} \int_{-\pi}^{\pi} \frac{1}{\left[(\tau - \eta)^2 + z^2 + 4\tau\eta \sin^2(\theta/2)\right]^n} \, d\theta \, dz. \tag{2.13}$$

Considering $y^2 = (\tau - \eta)^2 + 4\tau\eta \sin^2(\theta/2)$ and using the change of variables and special functions such as, the hypergeometric function $F(b^*, c^*; d^*; \delta^*)$, the beta function $\mathrm{B}(\Xi, \xi)$ and the gamma function $\Gamma(a^*)$, the integral J_n becomes

$$\begin{aligned} J_n &= \frac{2\tau}{(\tau - \eta)^{2n-1}} \mathrm{B}(n - 1/2, 1/2) \frac{\Gamma(1/2)\Gamma(1/2)}{\Gamma(1)} F(n - 1/2, 1/2; 1; \Delta) \\ &= \frac{2\pi}{\tau^{2n-2}} \mathrm{B}(n - 1/2, 1/2) \sum_{m=0}^{\infty} \left(\frac{(n - 1/2)_m \eta^m}{m!\, \tau^m}\right)^2, \end{aligned} \tag{2.14}$$

where $\Delta = -4\tau\eta/(\tau - \eta)^2$ and $(k^*)_m$ is the Pochhammer symbol. Thus, the energy E_{OP} may be deduced as

$$E_{OP} = \frac{\pi^2 \ell_T}{192} \left[-\frac{A}{\tau^4} \sum_{m=0}^{\infty} \left(\frac{(2m + 4)!\, \delta^m}{(m + 2)!\, m!\, (4\tau)^m}\right)^2 + \frac{B}{9676800\, \tau^{10}} \sum_{m=0}^{\infty} \left(\frac{(2m + 10)!\, \delta^m}{(m + 5)!\, m!\, (4\tau)^m}\right)^2\right]. \tag{2.15}$$

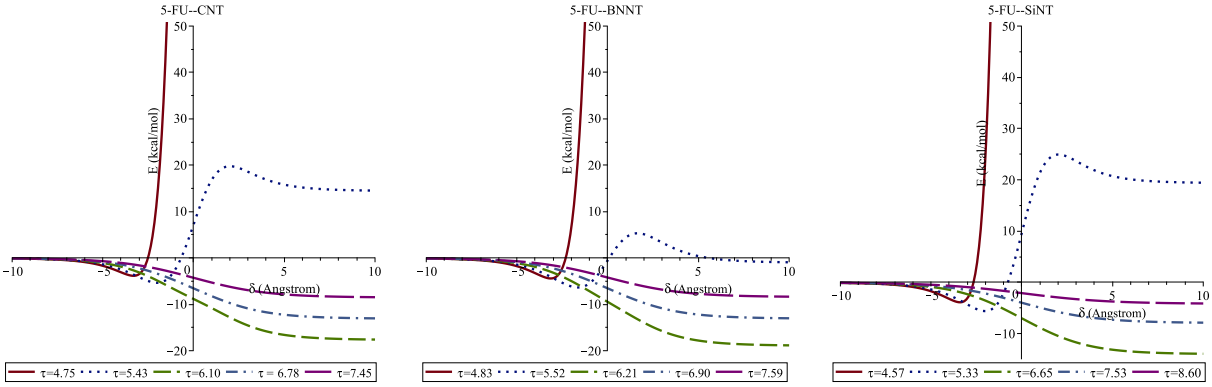
However, the interaction between a sphere (5-FU) and a cylinder (tube) must be determined, which is expressed as

$$E^{tot} = 8\pi^3 \kappa^2 \tau \ell_T \ell_d \left[-\frac{A}{2}\left(2J_3 + 4\kappa^2 J_4\right) + \frac{B}{5}\left(5J_6 + 80\kappa^2 J_7 + 336\kappa^4 J_8 + 512\kappa^6 J_9 + 256\kappa^8 J_{10}\right)\right], \tag{2.16}$$

where J_n is presented in (2.14).

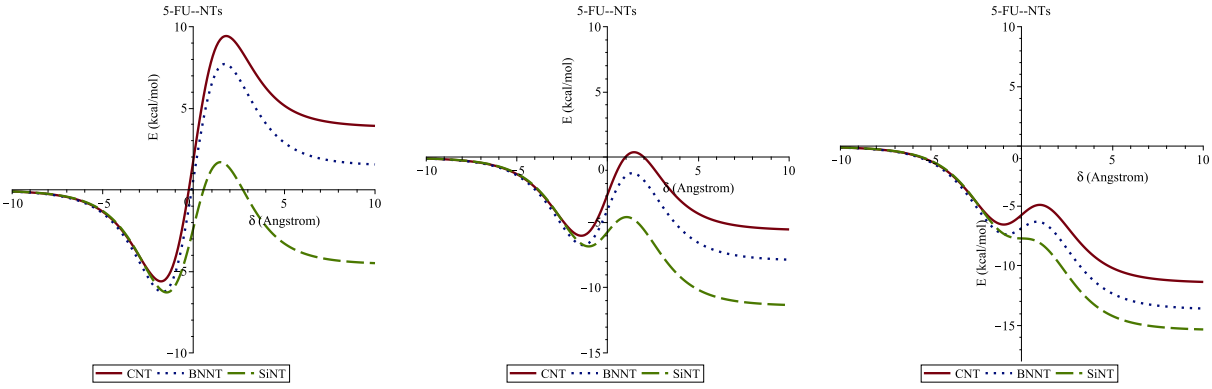
3. Numerical results

The numerical solutions of the interaction energies between the 5-FU molecule and SWNTs can be found from Eqs (2.7) and (2.16), respectively, using the algebraic computer package MAPLE coupled with the aforementioned constant values and the LJ parameters presented in Table 1. Figure 4 shows the relations between the interaction energy and the distance δ, which were determined for each specific armchair (i, i) CNT, BNNT and SiNT. The results obtained indicate the non-existent possibility of insertion of the 5-FU molecule inside the $(7, 7)$ and $(8, 8)$ CNTs and BNNTs and $(4, 4)$ and $(5, 5)$ SiNTs. Moreover, the results show that the lowest energies occurred for the cases of $(9, 9)$ CNT, $(9, 9)$ BNNT and $(6, 6)$ SiNT, corresponding to the radii $\tau = 6.10$ Å, $\tau = 6.21$ Å and $\tau = 6.65$ Å, respectively. In addition, Figure 5 shows that the drug may enter the nanotubes when the radius is bigger than ≈ 5.6 Å.



(a) Armchair CNT (7,7)–(11,11) (b) Armchair BNNT (7,7)–(11,11) (c) Armchair SiNT (4,4)–(8,8)

Figure 4. Interaction energies of 5-FU entering NTs for different radii τ with respect to the distance δ.

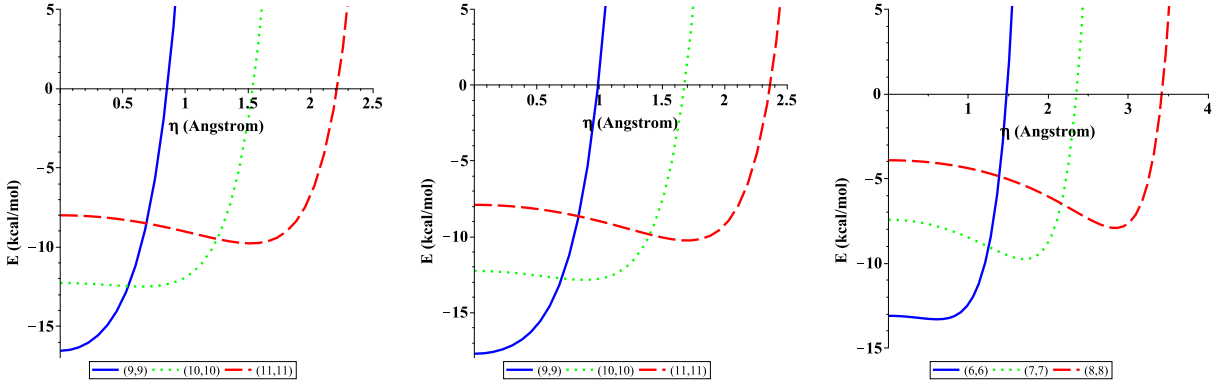


(a) $\tau = 5.5$ Å (b) $\tau = 5.6$ Å (c) $\tau = 5.7$ Å

Figure 5. Interaction energies of 5-FU entering NTs for $\tau = 5.5 - 5.7$ Å with respect to the distance δ.

The energy as given by Eq (2.16) was plotted with respect to η for the drug molecule in the (i, i)

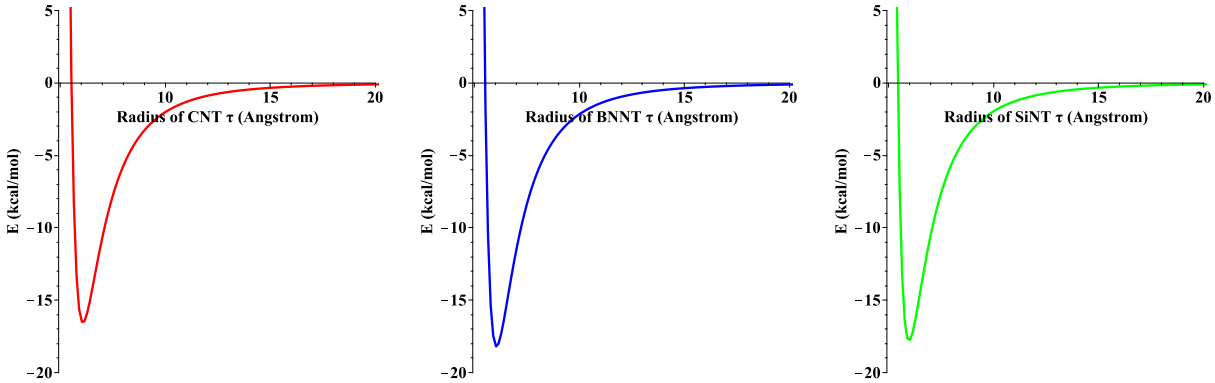
nanotubes. As shown in Figure 6, the preferred position of the 5-FU molecule inside the (9, 9) CNT and BNNT was with the axis of the drug molecule lying on the tube axis (i.e., $\eta \approx 0$). In the cases of (10, 10) and (11, 11) CNTs and BNNTs, $\eta = 0.66, 0.88$ Å, $\eta = 1.52, 1.70$ Å, respectively, were obtained. Furthermore, for the cases of (6, 6), (7, 7) and (8, 8) SiNTs, the values of η were approximately 0.61 Å, 1.70 Å and 2.83 Å, respectively. These results showed that, with the increase in the radius of the tube, the position of the drug molecule within the NTs tended to be closer to the nanotube wall, where the minimum energy occurred.



(a) CNT (9,9)–(11,11) (b) BNNT (9,9)–(11,11) (c) SiNT (6,6)–(8,8)

Figure 6. Interaction energies of an offset 5–FU molecule inside (i, i) SWNTs with respect to the radial distance η.

Finally, Figure 7 shows the relation between the interaction energy and the radius of the nanotubes to determine the preferred radius of NTs to encapsulate the 5-FU molecule by minimizing the interaction energy. Thus, the optimal radii were found to be approximately 6.08 Å, 6.05 Å and 5.98 Å for the CNT, BNNT and SiNT, corresponding to -16.55, -18.20 and -17.81 kcal/mol, respectively. These results suggest that the radii at which the minimum energies occur are not significantly different for the three types of nanotubes.



(a) CNT (b) BNNT (c) SiNT

Figure 7. Interaction energies between 5-FU molecule and NTs as function of tube radius τ.

The results for the energies of the 5-FU molecule inside the CNT and BNNT were consistent with those provided in [1] with minor differences, where they reported the encapsulation of the 5-FU the drug inside the CNT and BNNT with energies of -14 and -25 kcal/mol, respectively.

Thus, the results suggested that the interaction between the 5-FU drug and BNNT was slightly stronger than with the CNT and SiNT. The lower value of the interaction energy for BNNT is a signature of a relatively more stable encapsulation of the drug inside the BNNT compared to the CNT and SiNT. This observation is consistent with results obtained from the MD simulation conducted by Dehaghani et al. [1]. They indicated that the adsorption of the 5-FU molecule inside the BNNT was more stable than in the CNT.

In addition, once the radius of the NTs increased, the interaction energy between the drug and the nanotubes tended toward zero. Although the minimum values of the interaction energies between the 5-FU molecule and the three nanotubes were not significantly different, silicon nanotubes may be the most ideal drug delivery capsule when compared to boron nitride and carbon nanotubes owing to certain significant implications, such as the reduced quantity of material required for the encapsulation. However, a smaller radius was required to fill an SiNT with the 5-fluorouracil molecule, where the use of the material was less for delivery of the drug, thereby reducing toxicity in the system. It was concluded that when the drugs are delivered to the cancer cell and ejected into it, the remaining drug nanocarrier may either slowly clear from the body or may remain; thus, it is necessary to use the smallest amount of the materials, required for efficient encapsulation.

4. Conclusions

This study investigated the utilization of nanotubes in the medical field, specifically in drug delivery, using classical applied mathematical modelling. Analytical expressions were derived to better understand the encapsulation behavior. Further, the minimum interaction energies between a 5-FU molecule and three types of nanotube were obtained to determine the appropriate type and favorable size of a nanotube for encapsulating the 5-fluorouracil drug. Here, the silicon nanotube was shown to be the most ideal drug carrier capsule for the 5-fluorouracil drug when compared to boron nitride and carbon nanotubes. This study is expected to assist in improving the delivery of anticancer drugs with a high selectivity to target cells in cancer using nanocarriers. Consequently, this can help to decrease the systemic toxicity of these drugs and achieve quick progress in the treatment of cancers.

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Conflict of interest

The author declares that there is no conflict of interest.

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