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Research Article

Computational Study of Carbon, Silicon and Boron Nitride Nanotubes as Drug Delivery Vehicles for Anti-Cancer Drug Temozolomide

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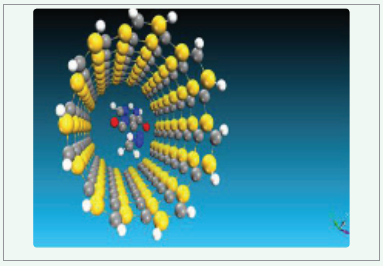
ABSTRACT

Using various nanotubes for targeted drug delivery systems as well as interactions between drug and nanotubes with diverse properties such as gender, structure, and diameter are investigated based on Density Functional Theory (DFT) for the first time. A wide assortment of weak absorption on SWCNTs and SWBNNTs, it is demonstrated that Temozolomide (TMZ) molecule tend to be physical absorption into SWSiCNTs. The geometrical structures, energetics, and electronics properties of TMZ molecule and nanotubes obtained. There is a tolerable competing amount between decreasing of diameter and curvature effect that results indicate curvature has a much more salient effect. The results obtained by the Density of State (DOS) and Molecular Orbitals (MO) indicates adsorption of the drug into nanotubes is physical.

Graphical Abstract: Drug located into nanotube, and drug distance of the nanotube interior surface is equivalent



Keywords: Nanotube; Drug delivery; Temozolomide; Encapsulation; Drug carrier

INTRODUCTION

Cancer is one of the great reasons for mortality overall in the whole world [1]. Generally, unshielded and direct using chemotherapy drugs for cancer treatment is one of the approaches collation with this disease that has pretty dangers for healthy cells [2]. In recent studies, many researchers have employed targeted Drug Delivery Systems (DDS) for obliterating cancer's tissues, by taking nanostructures have been provided [3-6]. Nanotubes are the great materials that possess potential applications in the DDS domain [4,7-13]. Currently, the huge interior region, needles shape and the viable surface functionalization of the nanotubes, those have been converted to perfect Nano carriers for DDS [14-23]. Besides, most of the small drug molecules confined in CNTs have been investigated theoretically, including Doxorubicin (DOX), cisplatin, gemcitabine, ciprofloxacin, indomethacin, lamivudine, amantadine, and TMZ. Furthermore, for decreasing of the toxicity effect of the anti-cancer drugs developing DDS is necessary [24]. TMZ drug molecule has been continuously attracted attention some of the researchers because of its extended use as an oral alkylating agent in treatment dangerous brain tumors such as glioblastoma, astrocytoma, and melanoma which are serious types and offensive of the brain cancer. It is frequently used in the treatment of a type of tumor namely known glioma. Thus, this pharmaceutical molecule is in current first-line of chemotherapy for behaving against brain cancer. Despite this positive effect of the TMZ on cancer's tissues, practically procedure of patient's treatment is quite poor. On the other hand, this process totally rejects many factors such as to cross over the Blood-Brain Barrier (BBB), short half-life in circulation, low drug arrival and extreme drug permeating in the tumor cells [24-27]. TMZ has pretty inclined to join other combinations, especially, with the pharmaceutical feature materials. With this in mind, that has capable of constituting non-covalent bonds and building supra-molecular structures. Nevertheless, for the purposeful drug delivery, encapsulation drug into nanotubes are one of the most efficacious methods. Additionally, nanotubes have got analogous structures although they possess various properties including biocompatibility, solubility, functionalization, and cellular uptake. So, this diversity of the properties has been attributed to symmetry and type cross-link bonds on the nanotube walls, that on the base it, nanotubes had to divide into three diverse types consisting of an armchair, zigzag and chiral. Symmetry is one of the key factors in an interaction between drug and nanotubes. Moreover, a considerable number of studies have been done on the both of the experimental and theoretical about to use nanotubes as Nano-carriers of anti-cancer drugs [8,28-40].

Yixuan et al. [41] looked into theoretically to adsorbing process of DOX as an anti-cancer drug on the surface, and into single-walled carbon nanotubes. Progressively, they were comprehension that drug encapsulated was better and stronger than the adsorption on a sidewall of the nanotubes, owing to the fact that there was in the process of drug encapsulation, hydrogen bonding, and π-π stacking were together, despite the adsorption on a surface of the nanotubes there was only have a little π-π stacking interaction. Thereby the process of drug encapsulation and drug release of nanotubes would occur slowly, and also little drug amounts would be missed before arriving at tumor' tissues, that's quite vital in DDS. Generally, the Interaction between TMZ and SWCNT open-ended have been investigated in various environments and temperatures by molecular mechanics and quantum mechanics methods. As a result, have been indicated that the most stable environment for the interaction between TMZ and SWCNT open-ended was water solvent in 310 K [42]. In fact, there were some made natural capsules bio-molecules for example proteins, peptides, and an anti-cancer drug molecule has been successfully done [43,44]. For this purpose, roosta et al had investigated the encapsulation process of the anti-cancer drug Gemcitabine (GMC) in Single-Walled Boron Nitride Nanotubes (SWBNNTs) open-ended, and Single-Walled Carbon Nanotubes (SWCNTs) open-ended by Molecular Dynamics (MD) simulations. Indeed, the study results of the encapsulation have shown that GMC inclined to come through in BNNT and located in its center [31,43]. Therefore, a suitable understanding of the behavior of drug molecules inside nanotubes in the encapsulation process is vital for the extension of drug delivery carriers [18].

In this study, the process of encapsulation of TMZ as an anti-cancer drug was investigated by quantum mechanics methods. As the first step in this direction, a wide variety of nanotubes was used, to predict the most favorable structure toward carrier of the drug to tumor cells including SWCNTs, SWBNNTs, and Single-Walled Silicon Carbide (SWSiCNTs) open-ended for the first. Equally important, effects of type (gender), structure and diameter of nanotubes in this research has been investigated. In conclusion, the totally optimized geometry of structures, including drug, nanotubes, and complexes (like as drug@nanotubes) have been done, and binding energies of complexes have been calculated as well as electronic properties of structures such as Density of States (DOS) have been determined.

COMPUTATIONAL METHOD

Preparation of initial models

In this research, the zigzag and armchair open-ended single-walled nanotubes with a diameter ranging from 12 to 16 angstrom and length ranging from 17 to 24 angstrom have been considered, wherein, the fully optimized geometry structure of drug and nanotubes and information details them presented in figure 1 and table 1 [45]. For instance, nanotubes structure have been designed by NANOTUBE MODELER package [32,46]. The structure of drug has been constructed by GAUSS VIEW 5.0 package. The diameter of the drug is 9.171 angstrom. Optimization of drug and nanotubes geometry structure has been done by GAMESS-US/UK package [47]. All nanotubes are open-ended and for unfeeling dangling bond effect, and a decrease of time calculation, a mouth of nanotubes were enriched with H atoms [46,48].

Quantum mechanics

All calculations optimized geometry structures, and also complexes, binding energies have been done by density functional theory (DFT-Semi-core Pseudopods) method. Owing to the fact that the core electrons are dropped, the calculation is less computationally expensive, but because of these core potentials including some degree of relativistic effects, they can be very useful approximations for heavier elements. In the present work, Ab initio calculations have been performed on the Generalized-Gradient Approximation (GGA) with the Perdew-Wang 91 (PW91) functional, as well as all of the calculations performed on Double Numerical Polarization (DNP) as a basis set [41].

RESULTS AND DISCUSSION

Under those circumstances, results being demonstrated a process of encapsulation of drug inside nanotubes, in the first stage, in order to understand the nanotube/drug interactions, the Binding Energy (Eb) of the drug onto nanotube is defined as shown in a table 2. All nanotubes are proportionate to the drug diameter. The diameter of the drug is 9.171 angstrom. In this regard, the negative Eb values indicate that the stability of complex nanotubes/drug is energetically favorable. Computation of binding energies described by the ensuing equation:

$$E_b = E_{NT\text{-}Drug} - (E_{NT} + E_{Drug})$$

Where, ENT-Drug, ENT, Drug are respectively total energies of Drug@nanotube complex, the isolated nanotubes, and isolated TMZ. According to the definition, the polarity of the drug molecule indicates that the process of drug encapsulation into polarity

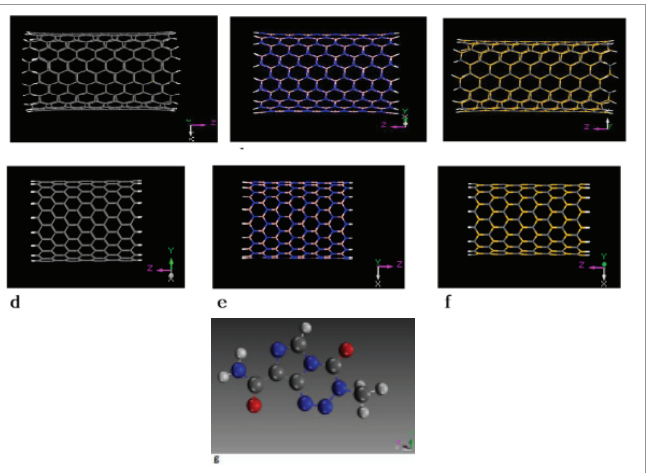


Figure 1: Fully optimized structures of a) CNT (10, 10) b) BNNT (10, 10) C) SiCNT (8, 8) d) CNT (10, 0) e) BNNT (10, 10) f) SiCNT (14, 0) g) Drug.

Table 1: Pristine nanotubes considered.

Species	Diameter (A°)	Length (A°)a
Pristine CC (10, 10)	14.2	19.07
Pristine CC (17, 0)	13.8	17.8
Pristine BN (10, 10)	14.3	19.7
Pristine BN (17, 0)	13.6	18.1
Pristine SiC (8, 8)	14.3	22.6
Pristine SiC (14, 0)	14.07	22.2

[a]A*: Angstrom.

Table 2: Binding energy (E_b) of TMZ into SWNTs considered.

Species	Eads (kcal/mol)
CC (10, 10)@Drug	-5.3
CC (17, 0)@Drug	-5.9
BN (10, 10)@Drug	-7.7
BN (17, 0)@Drug	-7.5
SiC (8, 8)@Drug	-9.1
SiC (14, 0)@Drug	-11.1

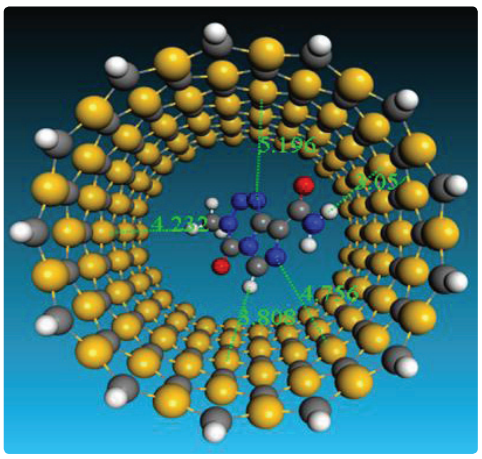


Figure 2: A final optimized geometries, drug located into the tube, and the equilibrium distances drug of interior' surface of the tube.

nanotubes are energetically favorable in figure 2. These results have been indicated structure and type (gender) of nanotubes play a vital role in the stability of drug into tubes (Figure 3).

In order to understand the effect of diameter in the process of drug encapsulation into nanotubes, different diameters shown in the table 3 was considered.

The results indicate that a decrease in the diameter is responsible for the strongest of interactions. Also, effects Basis Set Superposition Error (BSSE) on the interaction energy between drug and nanotube can be obtained by the following equation:

$$E_{ads} = E_{NT\text{-}Drug} - (E_{NT} + E_{Drug}) + E_{bsse}$$

Primary calculation results show that among all selected nanotubes, an interaction between TMZ and SiCNT (7, 7), SiCNT (13, 0) is more favorable and reliable and promising than other tubes (Figure 4). In addition, investigation of the nanotubes diameters, before and after the encapsulation process, indicate that diameter of CNT (n, m) increasing after to encapsulate whereas for the CNT (n, 0) diameter decreased. Furthermore, the diameters of both of type (armchair, zigzag) BNNTs, SiCNTs are increased after the encapsulation process [8,35]. In the other words, whether the decrease in diameter is responsible for more interaction between the drug and the interior surface of the nanotube or effect of curvature. Obtained results have indicated according to the calculations performed in the DFT environment, the effect of curvature is more [48].

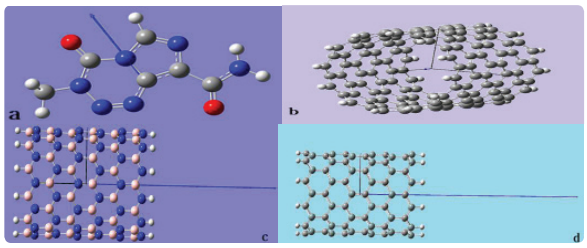


Figure 3: Determination of dipole moment of a) drug b) CNT c) BNNT d) SiCNT.

To the deepen understanding of values of the adsorption energy between TMZ and SWNTs and nature of bonds, we evaluated electronic properties based on the Density of States (DOSs) for the all of the complexes, isolated nanotubes, and isolated drug. As shown in figure 5. An insignificant change in the DOS spectra indicates that there isn't a noticeable difference between the pristine nanotube and nanotube@drug complexes. Correspondingly, this data shows the presence of physical interaction between them. The above results were confirmed with more analyses. First, based on the change in the electronic structure of all complexes, could have been received that insignificant values of electrons are transferred in the process of encapsulation drug molecule between the drug molecule and nanotubes. Second, with respect to, results of Mulliken Population Analysis (MPA) exhibit that complexes charge transfer is negligible. Comparatively, in the CNTs, a charge transferred from the interior surface of the nanotube to drug molecule, but in the BNNTs, SiCNTs, the charge transferred from drug molecule to interior surface of the nanotube. As noted, the best interaction among complexes was related to SiCNT (7, 7)@Drug and SiCNT (13, 0)@Drug. A negligible change in the DOS spectra could be found for both desirable complexes, before and after the encapsulation process. In the other words, the low difference in the DOS plot before and after encapsulation process could be shown nature of bonds and also illustrated that adsorption was physical.

The final point which deserves some words here is that molecular orbital results analysis provides an impressive method for studying intra-and intermolecular bonding and interaction among bonds and provides a suitable basis for investigating charge transfer. Therefore, the electronic properties of pristine components and nanotube/drug systems are considered. The electron population analysis reveals that considerable charge transfer occurs during the adsorption and

Table 3: Types of nanotubes considered.

Species	Diameter (A°)	Length (A°)	Species@Drug	binding energy (kcal/mol)	Adsorption energy (kcal/mol)
Pristine CC (9, 9)	12.923	19.074	CC (9, 9)@Drug	-6.82	-4.41
Pristine CC (10, 10)	14.227	19.076	CC (10, 10)@Drug	-5.32	-3.35
Pristine CC (11, 11)	15.528	19.074	CC (11, 11)@Drug	-4.76	-2.18
Pristine CC (16, 0)	12.599	17.821	CC (16, 0)@Drug	-6.56	-4.31
Pristine CC (17, 0)	13.818	17.818	CC (17, 0)@Drug	-5.99	-4.05
Pristine CC (18, 0)	14.184	17.819	CC (18, 0)@Drug	-3.95	-2.01
Pristine BN (9, 9)	13.207	19.686	BN (9, 9)@Drug	-9.27	-7.47
Pristine BN (10, 10)	14.363	19.389	BN (10, 10)@Drug	-7.76	-6.41
Pristine BN (11, 11)	15.518	19.268	BN (11, 11)@Drug	-7.47	-6.00
Pristine BN (16, 0)	12.941	18.150	BN (16, 0)@Drug	-9.00	-7.17
Pristine BN (17, 0)	13.652	18.150	BN (17, 0)@Drug	-7.54	-5.74
Pristine BN (18, 0)	14.556	18.151	BN (18, 0)@Drug	-7.65	-5.94
Pristine SiC (7, 7)	12.662	24.185	SiC (7, 7)@Drug	-10.91	-9.39
Pristine SiC (8, 8)	14.349	22.635	SiC (8, 8)@Drug	-9.12	-7.91
Pristine SiC (9, 9)	16.109	24.184	SiC (9, 9)@Drug	-8.64	-7.60
Pristine SiC (13, 0)	12.916	21.094	SiC (13, 0)@Drug	-11.54	-10.27
Pristine SiC (14, 0)	14.072	22.191	SiC (14, 0)@Drug	-11.18	-9.98
Pristine SiC (15, 0)	14.098	21.098	SiC (15, 0)@Drug	-9.56	-8.40

encapsulation processes. The Energy of the Highest Orbital Molecular Occupied (HOMO) and Lowest Orbital Molecular Unoccupied (LUMO) was calculated (Table 4). Fermi energy calculation for this systems indicates charge transfer happening between drug and tubes is negligible. As have been shown, the increase in diameter in the pristine armchair nanotubes, the gap energy amount is increased. In the light of, gap energy of armchair nanotubes complexes is increased while the number of gap energies for the zigzag pristine nanotubes and complexes at first increased and afterward decreased which displayed that chirality plays a salient role in the nanotube reactivity [35].

CONCLUSION

In summary, according to the materials we have investigated the geometrical structures, energetics, and electronic properties as well as interactions between the drug molecule and nanotubes. In this work, we have reported a theoretical study of encapsulation of TMZ drug molecule into both armchair and zigzag different nanotubes. A wide variety of nanotubes with various properties like gender, structure, and diameter considered. The results obtained show that the drug molecule inclined to locate into SWSiCNT by physical adsorption. In case, the polarity of the drug molecule indicates that the process of drug encapsulation into polarity nanotubes are energetically favorable. Curvature effect plays a vital role in the encapsulated

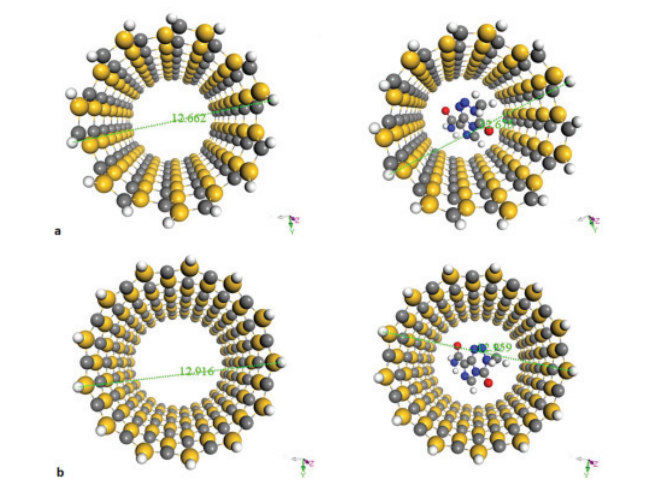


Figure 4: Calculated diameter of a) pristine SiC (7, 7) and complexes with drug b) pristine SiC (13, 0) and complexes with drug.

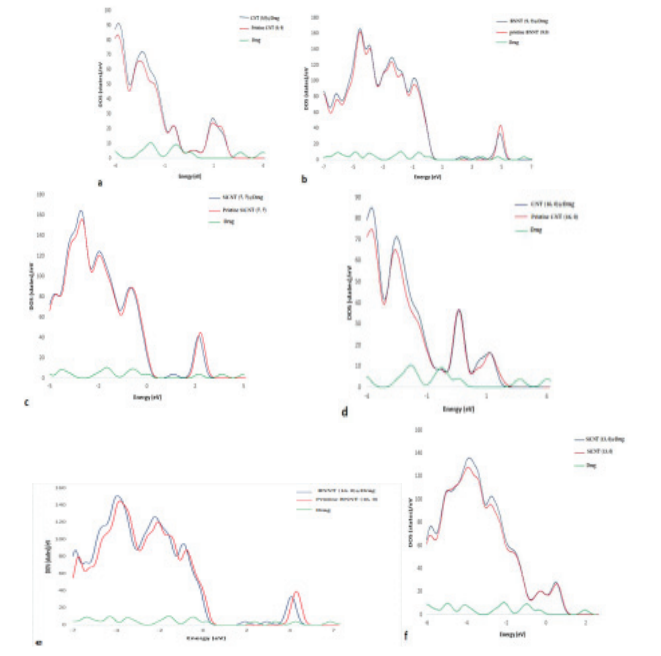


Figure 5: Calculated density of state for the complexes, pristine nanotubes and pure drug a) CNT (9, 9) b) BNNT (9, 9) c) SiCNT (7, 7) d) CNT (16, 0) e) BNNT (16, 0) f) SiCNT (13, 0).

Table 4: The calculated energies of HOMO (eV), LUMO (eV) and gap energy of Complexes, pristine nanotubes and drug.

Species	Fermi energy (eV)	E_{HOMO} (eV)	E_{LUMO} (eV)	Gap energy (eV)
Pristine CC (9, 9)	-0.148255	-3.955	-3.737	0.218
Pristine CC (10, 10)	-0.14866	-3.987	-3.731	0.256
Pristine CC (11, 11)	-0.148823	-3.971	-3.713	0.258
Pristine CC (16, 0)	-0.145842	-3.896	-3.744	0.152
Pristine CC (17, 0)	-0.14598	-3.914	-3.892	0.022
Pristine CC (18, 0)	-0.146021	-3.979	-3.9	0.079
Pristine BN (9, 9)	-0.212046	-5.527	-0.941	4.586
Pristine BN (10, 10)	-0.211638	-5.588	-1	4.588
Pristine BN (11, 11)	-0.211	-5.531	-1.037	4.494
Pristine BN (16, 0)	-0.210681	-5.438	-1.267	4.171
Pristine BN (17, 0)	-0.21048	-5.446	-1.26	4.186
Pristine BN (18, 0)	-0.210603	-5.741	-1.355	4.386
Pristine SiC (7, 7	-0.183764	-4.816	-2.495	2.321
Pristine SiC (8, 8)	-0.183316	-4.824	-2.5	2.324
Pristine SiC (9, 9)	-0.182771	-4.984	-2.652	2.332
Pristine SiC (13, 0)	-0.146874	-3.814	-3.572	0.242
Pristine SiC (14, 0)	-0.146439	-3.797	-3.62	0.177
Pristine SiC (15, 0)	-0.146003	-3.811	-3.623	0.188
CC (9, 9)@Drug	-0.147789	-4.028	-3.673	0.355
CC (10, 10)@Drug	-0.148219	-4.036	-3.655	0.381
CC (11, 11)@Drug	-0.148782	-4.047	-3.648	0.399
CC (16, 0)@Drug	-0.145505	-3.9	-3.848	0.052
CC (17, 0)@Drug	-0.145729	-4.005	-3.952	0.053
CC (18, 0)@Drug	-0.145715	-3.972	-3.893	0.079
BN (9, 9)@Drug	-0.210703	-5.72	-3.527	2.193
BN (10, 10)@Drug	-0.210583	-5.719	-3.371	2.348
BN (11, 11)@Drug	-0.210252	-5.72	-3.373	2.347
BN (16, 0)@Drug	-0.2091	-5.676	-3.562	2.116
BN (17, 0)@Drug	-0.20954	-5.698	-3.476	2.222
BN (18, 0)@Drug	-0.209094	-5.695	-3.366	2.329
SiC (7, 7)@Drug	-0.183405	-4.992	-3.376	1.231
SiC (8, 8)@Drug	-0.183035	-4.979	-3.586	1.393
SiC (9, 9)@Drug	-0.182582	-4.968	-3.496	1.472
SiC (13, 0)@Drug	-0.147434	-4.127	-3.917	0.21
SiC (14, 0)@Drug	-0.146863	-4.105	-3.949	0.156
SiC (15, 0)@Drug	-0.146241	-4.1	-3.917	0.183
Drug	-0.215385	-5.861	-3.441	2.42

process. Especially, when the nanotube diameter goes decrease. It should be noted results obtained from DOS plot indicate the drug adsorption into nanotube was physical. It also negligible changes in amounts of energy between HOMO and LUMO indicates the drug molecule bonds with nanotubes are quite weak which it is a critical issue in releasing the drug molecule in vitro process. In case, some theoretical findings such as binding energies, charge transfer, a density of states plots, and total density introduced the nanotubes, typically SiCNT an efficacious nano-carrier for delivery of TMZ drug at nano-medical predominant. In that case, it's hoped that the research will broaden our understanding of encapsulation behavior of drug molecules into nanotubes that have a vital role in developing drug delivery vehicles at the nano domain.

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