Theoretical study of encapsulation of diethylstilbestrol drug into the inner surface of BNNT toward designing a new nanocarrier for drug delivery systems

Maryamossadat Hosseinzadeh¹, Shiva Masoudi¹∗, Nasrin Masnabadi²∗ and Fatemeh Azarakhsht³

¹ Department of Chemistry, Central Tehran Branch, Islamic Azad University, Tehran, Iran
² Department of Chemistry, Roudehen Branch, Islamic Azad University, Roudehen, Iran
³ Department of Chemistry, Varamin-Pishva Branch, Islamic Azad University, Varamin, Iran

Authors to whom any correspondence should be addressed.
E-mail: shmasoudi@yahoo.com, Masnabadi@riau.ac.ir and masnabadi2009@gmail.com

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Abstract

In this research, the encapsulation and intermolecular non-bonded interactions of an anticancer drug, Diethylstilbestrol (DES), into the inner surfaces of BNNT (8,8–12) were investigated. All Density Functional Theory (DFT) calculations were performed in a gas phase. So, this research focuses on intermolecular hydrogen bonding, van der Waals and steric interactions between active sites of the BNNT and DES by quantum theory of atom in molecule (QTAIM) theory. QTAIM and non-covalent interaction index (NCI) analyses showed the interactions between the DES drug and the BNNT nanotube. The HOMO-LUMO orbitals, Density of States (DOS) plots, and reduced density gradient (RDG) analyses were carried out to determine the effect of DES adsorption into the nanotube. Furthermore, the effect of the abovementioned interactions between the DES and BNNT (8,8–12) on the electronic characteristics, and natural charges have also been estimated. Based on the results, the thermodynamic parameters of BNNT (8,8-12)/DES are in very close agreement with the NCI analysis and showed that the BNNT (8,8–12) adsorb DES via a physisorption process rather than chemical one and the sorption procedure was exothermic in benign and thermodynamically favorable. Therefore, the use of BNNT (8,8–12) as a carrier for DES drug has been confirmed theoretically.

Abbreviations

DFT Density Functional Theory
QTAIM Quantum theory of atom in molecule
HOMO Highest Occupied Molecular Orbital
LUMO Lowest Unoccupied Molecular Orbital
FMO Frontier Molecular Orbital
DOS Density of States
RDG Reduced density gradient
NCI Noncovalent Interaction
MEP Molecular Electrostatic Potential
LOL Localized Orbital Locator
ELF Electron Localization Function
1. Introduction

Diethylstilbestrol (DES) is known as a synthetic ethinyl estrogen, which its antitumor activity is proved against prostate cancer [1]. It has recently been shown that androgen receptors have vital roles in castration-refractory prostate cancer (CPRC). However, DES has a high affinity to androgen receptors and in this way, controls the CPRC disease [2]. Moreover, DES increases the pituitary prolactin secretion and sex hormone-binding globulin levels [3, 4]. Geisler et al have shown that DES can also inhibit the function of leydig cells and the discharge of androgenic steroids, which finally results in decreasing the testosterone secretion [5]. Furthermore, DES act as an inhibitor of telomerase activity [6]. Another application of DES is the usage of this drug to prevent miscarriage or premature birth in pregnant women who are prone to infertility. The mechanism of action of DES is as follows: like estrogens it could be placed in its target cells and interact with special protein receptors for creation of estrogen receptors. The female reproductive system, mammary gland, hypothalamus, and pituitary gland are the target cells. The estrogen binding to its receptors increases hepatic synthesis of sex hormone-binding globulin, thyroid-binding globulin, and other serum proteins and suppresses follicle-stimulating hormone from the anterior pituitary [7]. However, like other drugs, this synthetic estrogen has its side effects that restricts its widespread application. These side effects are consisting of breast cancer, clear cell adenocarcinoma of the vagina and cervix, irregularities in the female genital area and irregularities of the male reproductive system [8].

Improving the effectiveness of drugs and decreasing their adverse effects can be targeted through drug delivery carriers, which can modify and control the secretory characteristics of medicines [9, 10]. Using these carriers, the uptake, distribution, transport, accumulation, and elimination of drugs are modified in such a way that better health conditions and considerable effectiveness were attained. In the cancer therapy process, the targeted drug delivery is utilized to release the drug wherever it needs (cancerous tissue), which can reduce the side effects of the drug [11, 12]. Among various carriers applied for this purpose, thanks to the unique properties like chemical stability, oxidation resistivity, high specific surface area, large pore volume, independent electronic characteristics from the diameter of the tube, along with inherent biocompatibility, boron nitride nanotubes (BNNTs) are recognized as potential candidates to be used in various medical fields and especially targeted drug delivery [13–16]. BNNTs are a class of inorganic semiconductors with large bandgap that vary in tube diameter and hence manipulation properties [16, 17]. The synthesis of BNNTs was first reported in 1995 [18] by Chopra, based on an arc discharge method. Following the first report, several methods including arc discharge [19, 20], chemical vapor deposition (CVD) [21–23], substitution reactions [24–26], ball milling [27, 28], laser ablation [29–31], and low temperature methods [32–34] were reported. The CVD and ball milling methods are currently the two most widely used methods for the synthesis of BNNTs. Considering the high potential applications of BNNTs, many theoretical studies have been reported on the structure, characteristics, and the chemical functionalization of BNNTs [35–37]. However, only few papers were published on the reactivity of BN nanostructures. In this regard, Nirmala and Kolandaivel have studied the structure and electronic properties of armchair BNNTs as a function of tube diameter using DFT methods [38].

Recently, BNNTs are utilized for encapsulation of several compounds like metal nanoparticles, DNA and RNA oligonucleotides, peptides, and anticancer drugs [16]. The reasons for this application of BNNTs, are the capability of BNNTs to interact with chemical functionalities and to attach to proteins and cells, which makes them promising candidates for encapsulation purposes [39–41]. Dehaghani and co-workers reported the encapsulation of the anti-cancer drug (5-FU) inside both BNNT (8,8) and CNT, followed by calculation of the numbers of drugs that can be encapsulated in the BNNT cavity through molecular dynamics (MD) simulation. They were observed that the drug was rapidly adsorbed inside the nanotubes and remained encapsulated up to the end of the simulation. However, the adsorption procedure was accelerated for the drug–BNNT complex because of the stronger van der Waals (vdW) interaction energy between the drug and BNNT. The values of vdw interaction energy in systems consisting of CNT and BNNT decreased to the values of the −15 and −45 kcal·mol⁻¹, respectively, at the end of the simulation (15 ns), which was in favor of the adsorption process. However, the lower value of the free energy in the system containing the BNNT revealed more stability of the encapsulated drug inside the cavity of the BNNT as compared to the system having CNT. It was observed that the average six numbers of the drugs would be stably encapsulated inside the BNNT cavity [42]. However, it seems that this strategy including loading of drug compound within the carrier could increase the performance of the encapsulated component and reduce its adverse effects.

Regardless of the high potential of BNNTs as drug delivery transporters, there are rare data on the interaction mechanisms between BNNT-drug as well as energy studies that provide us invaluable information for the optimization of the performance of whole drug delivery configuration [39]. However, an investigation of the detailed interaction between the two components consisting of the BNNT-drug via molecular-scale methods could be very helpful for future design of drug delivery systems based on BNNT carriers. The usage of these theoretical strategies prior to experimental runs for the design of drug delivery systems prevents monotonous
3.1. Optimized structures

In the current research, all computations are conducted using Gaussian 09 program package [43]. All geometry optimizations have been carried out at the M06-2X/6-31G(d) level of theory [44]. The drug was located in different directions inside of boron nitride nanotube, and resulting geometry was optimized. Also, the frequencies were calculated in the same level of theory. We did not observe any imaginary frequencies and all the frequencies taken positive quantities indicating the global minima in the structural configuration (data not shown). After finding optimum conditions for geometry, density of states (DOS) analysis on a BNNT (8,8), DES drug, and DES/BNNT complexes were done at the same level of theory. The M06-2X has also been established as a widely employed functional density for studying the influence of level variation on the molecular geometry and its corresponding characteristics [45]. The adsorption energy ($E_{ads}$) of the DES drug on the BNNT is calculated as follows:

$$E_{ads} = E_{BNNT}/DES - (E_{DES} + E_{BNNT})$$  (1)

Where $E_{BNNT}/DES$ is the adsorption energy of the DES drug into the BNNT, $E_{BNNT}$ is the energy of the isolated BNNT (8,8–12) with a length of 12 Å, and $E_{DES}$ is the energy of the free DES molecule (table 1). The optimized structures of the compounds are illustrated in figures 1 and 2.

The calculation of NCIs (Noncovalent Interactions) provides the identification of noncovalent interactions such as hydrogen bonds, π–π stacking, steric repulsion, and van der Waals interactions. The NCI calculations were done by the NCIPLOT code [46, 47]. However, the topological analysis is carried out by examining the gradient of the electron density according to the Quantum Theory of Atoms in Molecules, QTAIM, using the AIMAll [48, 49] based on the wave functions obtained from the M06-2X/6-31G* level of theory.

3. Results and discussion

3.1. Optimized structures

The structures of the DES, BNNT (8, 8–12) were primarily optimized by the computational M06-2X/6-31G(d) method (figure 1). The $E_g$ value of the complex by the presence of both DES drug and BNNT components is increased compared to pure DES (figures 1 and 2). This enhancement of energy gap of the DES by inclusion within the structure of BNNT (complex) is related to the decreasing of the reactivity of complex as compared to pristine DES. Furthermore, it could be concluded that the conductivity and optical properties of the complex was improved as compared to pristine BNNT since the gap energy were increased following introducing of DES drug into the nanotube [50].

Thermodynamic factors that could influence the interaction among the components within the drug delivery system have been investigated via M06-2X/6-31G*. Thus, the summation of electronic (E) and thermal enthalpies (H), the summation of electronic (E) and thermal energies (T), the summation of electronic (E) and

| Parameter | DES | BNNT | DES/BNNT |
|-----------|-----|------|---------|
| $E + G$ (Hartree) | −847.729 | −6394.014 | −7241.782 |
| $E + H$ (Hartree) | −847.661 | −6393.810 | −7241.535 |
| $E + T$ (Hartree) | −847.662 | −6393.811 | −7241.536 |
| $E_d$ | −848.022 | −6395.158 | −7243.245 |
| $S$ (cal/mol.K) | 143.066 | 428.011 | 518.537 |
| $\Delta G_{adsorption}$ | — | — | −0.039 |
| $\Delta H_{adsorption}$ | — | — | −0.064 |
| $\Delta S_{adsorption}$ | — | — | 52.54 |

Table 1. Thermochemical parameters for the interaction of the DES drug loaded into the BNNT (8,8–12) calculated at M06-2X/6-31G* level of theory.
Figure 1. The optimized geometry and DOS plots using M06-2X/6-31G* method of (a) BNNT (8,8–12), and (b) DES.

Figure 2. The optimized geometry and DOS plots of the DES/BNNT complex using M06-2X/6-31G* method.
The reactivity of the complex decreased following the loading of DES in the BNNT. Moreover, the stability of the complex is increased when compared to pristine DES. Another issue which could be pointed out from Table 1, is that the interaction among the DES molecule and BNNT is exothermic in nature. More interestingly, the entropy of the complex state is higher than those of pure BNNT and DES molecule components which is favorable from the thermochemical point of view. Thermochemical studies demonstrate that the sorption of DES molecule into the inner parts of the BNNT is favorable from both enthalpy and entropy points of view [51].

Figure 3 demonstrates the distances among H(39), O(20), and O(19) atoms in the DES molecule with selected atoms (N(162), N(71), and B(148)) in the BNNT. According to this figure, the distances among O(20)···N(71), H(39)···N(162), and O(19)···B(148) are 3.115, 2.401, and 2.885 Å, respectively. Taking into account the oxygen atoms in the hydroxyl groups of the DES drug, it was found that the oxygen atoms of 20 and 19 are closer to the nitrogen (71) and boron (148) atoms of the nanotube, respectively. Therefore, this proximity between the atoms could increase the possible interactions among the guest drug and host nanotube.

The strength of the hydrogen bonds is depending on the distances between corresponding atoms responsible for hydrogen bonding formation. Thus, very powerful, strong, standard, and fragile hydrogen bonds have distances of (under 2.5 Å), (2.5 ~ 2.7 Å), (2.7 ~ 2.9 Å), and (upper than 2.9 Å) between the hydrogen atom and heteroatoms, respectively [52]. Thus, the intramolecular bond between H39 atom of DES drug and N162 of the BNNT (8,8–12) (H(39)···N(162)) can be considered as a strong hydrogen bond. Therefore, the adsorption of DES in the inner surfaces of BNNT (8,8–12) may be related to the existence of this intramolecular hydrogen bonding.

For further evaluation the nature of interactions between the DES drug and BNNT, the non-covalent interaction index (NCI) has been chosen for identifying the benign of intermolecular interactions and measuring the properties of weak interactions between the components within the nanocarrier drug system, which it can be calculated by the following equation [53]:

$$RDG(r) = \frac{1}{2(3\pi^2)^{1/3}} \frac{\left| \nabla \rho(r) \right|}{\rho(r)^{4/3}}$$  \hspace{1cm} (2)

The scatter graphs of reduced electron density gradient (RDG) versus the electron density ($\rho$) multiplied by the sign ($\lambda_2$) are shown in Figure 4, whereas the X-axis and Y-axis are sign ($\lambda_2$)$\rho(r)$ and RDG function, respectively. The sign ($\lambda_2$)$\rho(r)$ and NCI–RDG plots are obtained using the Multiwfn program [54]. The sign ($\lambda_2$)$\rho(r)$ is utilized to differentiate the bonded ($\lambda_2 < 0$) interactions from nonbonding ($\lambda_2 > 0$) interactions. It is also must be denoted that small quantities of RDG indicates Non–covalent interactions [53]. RDG was obtained from electron density and its first derivative and was used as a criterion for identification of the deviation from the homogenous distribution of electron [53]. In the RDG scatter graph, the red color was utilized to show the repulsive/steric interactions and green color one was utilized to show the low electron density areas, corresponding to weak van der Waals interactions. At the critical points, whereas weak interactions exist, the gradient of the density vanishes and peaks appear in the NCI plot. Thus, RDG scattered points in blue color was used to show H-bonding interactions in the negative domain [55]. The NCI plot of the DES/BNNT complex (figure 4) shows that the interactions between DES drug and BNNT are weak. However, there are some areas of the green isosurface in the NCI plot. These areas occur between the BNNT inner surface and the terminative side chain of the DES, corresponding to the weak hydrogen bonding interactions among the hydrogen atoms of the DES.
hydroxyl groups of DES drug and nitrogen atoms of the BNNT in good agreement with the results of figure 3. Similarly, another area with red color is corresponding to the steric effect interactions between aromatic rings on DES and BNNT, in addition to the hydrogen atoms at the edge of the BNNT. Moreover, there are some parts within the RDG plot with a mix of green and red colors. All results suggest that intramolecular interactions between the DES guest and BNNT host atoms are van der Waals interactions and also electrostatic interactions among the positively charged hydrogen atoms and the negatively charged nitrogen and oxygen atoms. In the case of DES drug, high green areas inside the BN nanotube dedicate that more interactions occur due to the inclusion of DES molecule inside the nanotube. However, small \( \rho \) values imply the presence of weak interactions between the components within the composition of the complex material. It is also must be denoted that both DES guest and BNNT host compound include aromatic functionalities that undoubtedly could contribute in the van der Waals interactions as observed from strong RDG spikes in figure 4.

To analyze the points introduced by the interactions between the DES drug and BNNT, the reduced density gradient map of the drug/BNNT interacting complex is analyzed (figure 5). Some bond lengths of the optimized DES, BNNT (8,8–12) and DES/BNNT (8,8–12) complex structures are shown in figure 5. When the DES molecule is trapped within the nanotube, some of its bond lengths increase and some of them decrease. However, all the bond lengths of the BN nanotube remained nearly constant, except those of B84-N83, and B84-N86 bonds. These results reveal that the adsorption of the DES within the inner surface of BNNT does not change the bond lengths of pristine BNNT. More interestingly, it is also must be denoted that as it is seen from figure 5, the diameter of the BNNT is quite well fitted with the size of the DES guest molecule and BNNT could be used to accommodate the DES adsorbate through inner surface of nanotube [47].

3.2. NBO analysis
The NBO method has been employed to study intramolecular and intermolecular bonding and bonding interactions in titled molecular systems [56]. The electron delocalization from donor orbitals (full NBOs) to acceptor orbitals (empty NBOs) describes a conjugative electron transfer process between them [57]. The stabilization energy, \( E_2 \), which is related to the donor-acceptor electronic delocalization, is explicitly estimated by the following equation (equation (3)):

\[
E_2 = q_{i,j} \frac{F^2(i, j)}{\epsilon_j - \epsilon_i}
\]

In the NBO method, the electronic wave functions are expressed as a set of occupied Lewis and a set of unoccupied non-Lewis-localized orbitals. Delocalization effects are related to off-diagonal elements of the Fock matrix [58]. The NBO method for DES/nanotube complex was employed using DFT (M06-2X/6-31G* level of theory) computation, and the results are presented in tables 2 and 3.

The results of NBO method prove that the maximum stability energy due to the absence of electronic delocalization from BNN nanotube to DES is related to the transfer of \( \pi^* \) (B160–N162) to \( \sigma^* \) (O19–H39) with \( E_2 = 2.26 \) kcal mol\(^{-1}\). Furthermore, according to the mentioned results, the \( \sigma \rightarrow \pi^* \) transitions from DES to BNN (8,8–12) occurs as \( \sigma(C1–H21) \rightarrow \pi^* \) (B85–N98), \( \sigma(C3–H22) \rightarrow \pi^* \) (B46–N200), \( \sigma(C4–H23) \rightarrow \pi^* \)
$\pi^* (B_{141} - N_{142}) \rightarrow \pi^* (B_{141} - N_{142})$, and $\sigma^*(C11 - H30) \rightarrow \pi^* (N63 - B64)$ with stabilization energy $E_2$ of about 1 kcal mol$^{-1}$ (table 3). The NBO analysis results illustrate that the maximum stability energy from DES to BNN nanotube is related to the electronic delocalization from LP$_2$ O$_{19}$ to $\sigma^* (C9 - H25)$ with $E_2 = 2.89$ kcal mol$^{-1}$. Similarly, for LP$_2$ O$_{20}$ to $\pi^* (N147 - B148)$, electronic delocalization is equivalent to

![Table 2](image-url)
addition to the two lone pairs at the oxygen atoms being better donor orbitals in the DES drug within DES related to electronic delocalization from DES into BNNT and contrariwise. Interestingly, the results show that in nanotube complex, they also cause the drug to have a non-bonding interaction with drug.

Second order perturbation theory analysis of Fock matrix in NBO basis from DES to BNNT nanotube

| Donor   | Acceptor | E2/kcal mol⁻¹ | E(i)−E(j)/a.u.¹ | F(i, j)/a.u.² |
|---------|----------|---------------|-----------------|--------------|
| σ(C1−H21) | π⁺(B85–N98) | 1.01 | 0.70 | 0.025 |
| σ(C3−H22) | π⁺(B46–N200) | 1.01 | 0.70 | 0.025 |
| σ(C4−H23) | π⁺(B48–N193) | 0.96 | 0.69 | 0.024 |
| σ(C10−H27) | π⁺(B141–N142) | 1.12 | 0.67 | 0.026 |
| σ(C11−H30) | π⁺(N63–B64) | 1.12 | 0.66 | 0.026 |
| σ(C12−H34) | LP*(1)B77 | 1.50 | 0.61 | 0.03 |
| σ(C15−H36) | π⁺(B133–N134) | 1.17 | 0.70 | 0.027 |
| σ(C17−H37) | π⁺(B173–N175) | 1.16 | 0.70 | 0.027 |
| LP(1)O19 | π⁺(N147–B148) | 1.76 | 0.78 | 0.035 |
| LP(2)O19 | π⁺(N147–B148) | 2.89 | 0.49 | 0.034 |
| LP(1)O20 | π⁺(N71–B84) | 1.47 | 0.8 | 0.032 |
| LP(2)O20 | π⁺(N71–B84) | 2.72 | 0.51 | 0.034 |
| Sum of E2 | | 17.89 | |

² E2 Energy of hyperconjugative interactions.
³ Energy difference between donor and acceptor i and j NBO orbitals.
⁴ F(i, j) is the Fock matrix element between i and j NBO orbitals.

2.72 kcal mol⁻¹, checked with the other transitions (table 3). Tables 2 and 3 show other resonance energies related to electronic delocalization from DES into BNNT and contrariwise. Interestingly, the results show that in addition to the two lone pairs at the oxygen atoms being better donor orbitals in the drug within DES/nanotube complex, they also cause the drug to have a non-bonding interaction with drug/nanotube complex. Therefore, it can be concluded that the most important interaction between the DES drug and the BNN (8,8–12) is due to the effects of stereo electronics. In this study, we investigated this interaction between DES drug and nanotube and compared it with another analysis. According to NBO analysis, the significant interactions from BNN (8,8–12) to DES drug are such as π*(B160–N162) → σ⁺(O19–H39), π⁺*(N63–B64) → σ⁺(C11–H30), π⁺(B48–N195) → σ⁺*(C4–H23), π⁺*(B46–N200) → σ⁺*(C3–H22), and π⁺*(B173–N175) → σ⁺*(C17–H37) transitions with resonance energy values (E2) of 2.26, 0.95, 0.76, 0.80, and 0.72 kcal mol⁻¹, respectively. The summation of resonance energies from drug to BNNT nanotube and vice versa were found to be E2 = 17.89 E2 = 10.22 kcal mol⁻¹, respectively. However, the summation of the electronic delocalization from drug to BNNT nanotube is significantly greater than that of BNNT to drug nanotube. The higher E2 value shows that BN nanotube acts as an acceptor alongside DES. Results of NBO show that when the DES and nanotube are under the impact of each other magnetic field, some of electronic transitions energies in molecular orbitals in pristine DES, compared with the complex, changes significantly, which offer these molecular orbitals to be more active in the complex when compared with a pristine model of DES.

Moreover, for investigation the electron charge transportation among DES guest molecule and BNNT host, natural bond orbital (NBO) analysis is carried out. However, we have calculated the charge distributions for equilibrium geometry of the BNNT (8,8–12), DES, DES/BNNT (8,8–12) complex using the NBO charges [59] at M06-2X/6-31G* level of theory. The computed natural charges for the designated atoms in compounds are collected in table 4.

According to the natural charge’s distribution for the selected atoms which are listed in table 4, the natural charges for the B60, B63, B71, B77, B84, B85, B88, B96, B141, B145, B148, B157, B172, and H222 atoms of the BNNT (8,8–12) after the capsulation of the drug have increased about 0.01 e. The charge of another nanotube-related atoms mentioned in this table also increased about 0.5 e after the adsorption of the DES over the nanotube. Interestingly, the natural charges for C1, C3, C5, C8, C9, C10, C11, C12, C13, C15, C17, H28, H33, H37, H39, and H40 atoms of the drug after adsorption over nanotube have increased about 0.01 e. These atomic charges variation have induced changes in the dipole moments of the nanotube and DES drug following the adsorption of this drug into the DES/BNNT (8,8–12) and showed that the charge transportation within the complex material has happened from the DES drug toward the inner surface of the BNNT.

3.3. Electronic properties

The frontier molecular orbitals (FMO), HOMO, and LUMO are important due to their role in calculating essential parameters for the prediction the reactivity of the chemicals [60, 61].
Taking into account the chemical hardness, wide and thin frontier orbital gaps demonstrate the presence of hard and soft molecules, respectively. Based on the Pearson’s theory, soft molecules have lower HOMO-LUMO gaps in comparison to hard molecules \[62\]. Thus, the effect of interaction between DES molecule and BNNT (8,8–12) on the electronic properties of pristine materials and complex have been evaluated. The molecular descriptive parameters, including ionization potential \(I\), electronegativity \(\chi\), global hardness \(\eta\), electronic chemical potential \(\mu\), global electrophilicity \(\omega\), electron affinity \(A\), and chemical softness \(S\) for the investigated molecular systems were calculated in terms of the following equations \[63\]:

\[
\begin{align*}
[I &= -E_{HOMO}], \quad [A = -E_{LUMO}], \\
[\eta &= I - A/2], \quad [\chi = (I + A)/2], \\
[\mu &= -(I + A)/2], \quad [\omega = \mu^2/2\eta], \quad [S = 1/2\eta]
\end{align*}
\] (4)

### Table 4. NBO charges (e) for the selected atoms in the BNNT (8,8–12), DES, and the DES/BNT (8,8–12) complex calculated by the M06-2X/6-31G* method.

| Atoms | DES | BNN | DES/BNN |
|-------|-----|-----|---------|
| C 1   | −0.28774 | —   | −0.2821 |
| C 3   | −0.31845 | —   | −0.30824|
| C 5   | −0.09348 | —   | −0.0844 |
| C 8   | −0.01821 | —   | −0.01263|
| C 9   | −0.47851 | —   | −0.47213|
| C 10  | −0.6814 | —   | −0.67378|
| C 11  | −0.47851 | —   | −0.47168|
| C 12  | −0.6814 | —   | −0.67196|
| C 13  | −0.09348 | —   | −0.08457|
| C 15  | −0.28774 | —   | −0.28206|
| C 17  | −0.31845 | —   | −0.30651|
| H 28  | 0.22551 | —   | 0.23677 |
| H 33  | 0.22551 | —   | 0.23831 |
| H 37  | 0.23523 | —   | 0.24024 |
| H 39  | 0.4926 | —   | 0.50495 |
| H 40  | 0.4926 | —   | 0.50159 |
| B 60  | — | 1.20294 | 1.21299 |
| B 61  | — | 1.20368 | 1.20931 |
| B 73  | — | 1.20293 | 1.21094 |
| B 77  | — | 1.20295 | 1.21025 |
| B 84  | — | 1.18742 | 1.20019 |
| B 85  | — | 1.20326 | 1.20874 |
| B 88  | — | 1.20366 | 1.20899 |
| B 96  | — | 0.81704 | 0.82545 |
| B 141 | — | 1.20368 | 1.21206 |
| B 145 | — | 1.20325 | 1.21175 |
| B 148 | — | 0.817   | 0.8249 |
| B 157 | — | 1.20295 | 1.20863 |
| B 172 | — | 1.20329 | 1.21377 |
| H 203 | — | 0.43957 | −0.08164|
| H 204 | — | −0.08758 | 0.44134 |
| H 206 | — | −0.0876 | 0.44075 |
| H 207 | — | 0.43956 | −0.08811|
| H 208 | — | −0.08757 | 0.43989 |
| H 209 | — | 0.43957 | −0.08772|
| H 211 | — | 0.43957 | −0.08734|
| H 212 | — | −0.08758 | 0.43964 |
| H 214 | — | −0.0876 | 0.43962 |
| H 215 | — | 0.43956 | −0.08818|
| H 216 | — | −0.08757 | 0.44005 |
| H 218 | — | 0.43956 | −0.08449|
| H 221 | — | −0.08759 | 0.44262 |
| H 222 | — | −0.0876 | −0.08142|
| H 226 | — | 0.43956 | −0.0874 |
| H 229 | — | −0.08759 | 0.4396 |
| H 232 | — | 0.43956 | −0.08771|
The effect of various parameters on the electronic properties of the nano-drug delivery system has been investigated and the results are presented in table 5. With the capsulation of DES within the BNNT (8,8–12), the HOMO and LUMO energies of the DES drug decreased from $-6.758$ and $0.758$ eV to $-7.321$ and $0.402$ eV, respectively. The HOMO and LUMO energies of the nanotube has increased in the BNNT/DES complex from $-7.961$ eV to $-7.321$ eV, and from $-0.893$ eV to $0.402$ eV, respectively. The HOMO and LUMO orbital shapes of DES, BNNT (8,8–12), and BNN/DES compounds are shown in figure 6. According to figure 6, the HOMO orbital of the DES drug concentrates on double bonds (C=C) of aromatic rings, C7=C8 bond, and the oxygen atom in the terminal hydroxyl group. However, in the case of BNNT, the HOMO is placed at the edge of tube, and created majorly by N atoms that are linked to terminated H atoms. In other words, the LUMO is found at the N–B pair through the main axis [39]. The charge transmission from the HOMO to LUMO in the compounds is remarkably due to the relationship of pi-bonds of aromatic rings, lone pairs of the oxygen atoms, and C7=C8 bond between two aromatic rings. As mentioned, in the BNNT (8,8–12), the HOMO and LUMO orbitals mainly rely on nitrogen and boron atoms, respectively. Moreover, the charge transportation between FMO orbitals is due to the contribution of nitrogen and boron atoms. Moreover, due to the results of FMO analysis, the energy gap between LUMO and HOMO orbitals of the DES is $7.516$ eV, while after capsulation with BNNT (8,8–12), it increased up to about $7.724$ eV. In contrast, the energy gap between LUMO and HOMO orbitals of the nanotube decreased about $1.13$ eV (from $8.854$ eV to $7.724$ eV) owing to the capsulation DES in the nanotube.

The chemical potential quantities of BNNT prior and after adsorption of DES molecule are negative, which obviously specifies that the complex material is chemically stable. Moreover, from the $\mu$ variations, it can be concluded that the spontaneous electron movement pathway will be from the DES drug to the BNNT. The other electronic property of the titled compounds that has also changed with the adsorption of the DES on the BNNT (8,8–12), is the global electrophilicity ($\omega$). This parameter measures the tendency of compounds to embrace electrons. However, $\omega$ values were found to be $1.198$ eV and $1.550$ eV for the DES molecule and DES/BNNT (8,8–12) complex, respectively. Thus, it could be concluded that BNNT (8,8–12)/DES complex is more electrophilic than pristine DES molecule. More interestingly, the results of electrophilicity index are in good compromise with chemical potential investigation and demonstrate that BNNT could act as an electrophile material and accept electrons from the DES molecule within the adsorption procedure.

The global hardness ($\eta$) of the DES, BNNT (8,8–12), and DES/BNNT (8,8–12) complex are $3.758$ eV, $4.427$ eV, and $3.862$ eV, respectively. However, the global hardness of the DES drug increases by about $0.104$ eV following the adsorption on the BNNT inner surface and it seems that DES become harder molecule than pristine DES maybe owing to confinement through the tubular structure of BNNT. Also, the global hardness ($\eta$) of the BNNT (8,8–12) after the interaction has decreased from $4.427$ eV to $3.862$ eV means that BNNT (8,8–12) is a softer molecule after inclusion of DES molecule within its structure. Increasing the softness of the BNNT within the composition of the complex could increase the tendency of the nanocarrier drug delivery system into the target cells i.e. cancer cells. It is previously reported that the dipole moment is an important parameter to designate the polarity of a molecule [64]. Moreover, the values of the dipole moments of the DES, BNNT (8,8–12), DES/BNNT (8,8–12) complex were found to be $2.527$, $0.0002$, and $2.362$ Debye, respectively. Correspondingly, with the adsorption of the drug on the BNNT (8,8–12), the value of dipole moment for the drug decreased about $0.2$ Debye (table 5). The dipole moment values, polarizability, and electronic structure are correlated with atomic charges [65].

### Table 5. The calculated electronic properties of the BNNT (8,8–12), DES, and the DES/BNNT (8,8–12) complex using the M06-2X/6-31G* method.

| Property               | DES       | BNNT     | DES/BNNT |
|------------------------|-----------|----------|----------|
| Dipole moment          | 2.527     | 0.002    | 2.362    |
| $E$ (Hartree)          | $-848.022$| $-639.158$| $-7243.245$|
| $E_{\text{HOMO}}$ (eV) | $-6.758$  | $-7.961$ | $-7.321$ |
| $E_{\text{LUMO}}$ (eV) | 0.758     | 0.893    | 0.402    |
| $E_p$ (eV)             | 7.516     | 8.854    | 7.724    |
| $E_{\text{ad}}$ (eV)   | —         | —        | $-1.768$ |
| $I$ (eV)               | 6.758     | 7.961    | 7.321    |
| $A$ (eV)               | $-0.758$  | $-0.893$ | $-0.402$ |
| $\chi$ (eV)           | 3.000     | 3.534    | 3.460    |
| $\gamma$ (eV)         | 3.758     | 4.427    | 3.862    |
| $\mu$ (eV)            | $-3.000$  | $-3.534$ | $-3.460$ |
| $\omega$ (eV)         | 1.198     | 1.410    | 1.550    |
| $S$ (eV$^{-1}$)        | 0.133     | 0.113    | 0.129    |
3.4. Atom in molecule method

The AIM calculation has been performed by exploiting the wave function which obtained from the DFT: M06-2X/6-31G* level of theory by utilizing the AIMAll package [66]. To better understand the electrical attributes of DES loaded over BNNT, electron densities (ρ) and Laplacian of the electron densities (∇²ρ) at the bond critical points (BCP) were calculated using AIMALL program [66–68]. It was investigated that the values of ∇²ρ, ρBCP, the potential energy (VBCP), and the kinetic energy (GBCP), and the total electronic energy (HBCP) of the bonds in the critical points are pertinent to the strength and type of the interactions between the attractive atom pairs.

The ρBCP, ∇²ρ, HBCP, VBCP, and GBCP properties were calculated for the all adsorption models and the results are presented in table 6. Interaction sites as well as molecular geometry of the complex are also provided in figure 7. According to figure 7, the attendance of the bond critical point (BCP) between DES drug and nanotube is a key parameter for approval the interaction between DES and nanotube.

Positive quantities of ∇²ρ shown the existence of ionic interaction, while negative ones dedicated the presence of covalent interaction among the components within the complex material. simultaneous inspection of ∇²ρ and HBCP could be used to identify the types of interactions. Negative ∇²ρ and HBCP values refer to the strong covalent bond interaction, whereas positive ∇²ρ and HBCP values denote the weak covalent interactions, and positive ∇²ρ >0 and negative H < 0) demonstrate the presence of partially covalent bond [39, 69]. In other words, the |V/G| relation is a trusty parameter to categorize the molecular interactions. Based on this parameter, weak interactions are related with |V/G| < 1, normal interactions 1 < |V/G|<2, and strong interactions |V/G|> 2. In the case of DES/BNNT complex, both ∇²ρ and H values are positive, which dedicate the presence of weak covalent bond interactions between DES and BN nanotube. The ratio of |V/G| for the interactions between the O20 atom of DES drug and the N71 atom of nanotube [(C2−O20 (DES). . .N71

Figure 6. Calculated HOMO and LUMO orbitals of the compounds DES (a), BNNT (8,8–12) (b), and DES/BNNT complex (c) by M06–2X/6–31G* method.
(nanotube)), and between the H39 atom of DES molecule and the N162 atom of nanotube \([O19\text{-}H39\text{(DES)}\ldots N162\text{(nanotube)}]\) were less than 1.0, which indicate weak interactions at these sites. Amongst the interactions of the DES with the nanotube, it can be seen that there are eleven hydrogen bonds. Moreover, the local energy density method (LED), which was proposed by Espinosa et al.\(^{49,70}\), was applied to estimate the intermolecular interactions such as hydrogen bonds. Accordingly, values of Espinosa energy, as shown in Table 6, were within the range of 0.628 to 2.510 kcal \(\text{mol}^{-1}\), and the largest Esp value \((2.51 \text{ kJ} \cdot \text{mol}^{-1})\) was related to the hydrogen bond among the O20 and N71 atoms, and H39 and N162 atoms. Besides, the largest \(\nabla^2 \rho\) and the largest \(\rho\) values are associated with the hydrogen bonds between H39 and N162 atoms \((\nabla^2 \rho = 0.0399; \rho = 0.0097)\) and O20 and N21 atoms \((\nabla^2 \rho = 0.0329; \rho = 0.0097)\). Thus, these interactions are more potent in this complex than others. The minor values of the electron density \((\rho \sim 0.01)\) and the positive values of the laplacian of electron density at BCPs \((\nabla^2 \rho > 0)\) indicate van der Waals interactions between the DES and the nanotube. The ellipticity \((\varepsilon)\) at BCP is a sensitive index for monitoring the pi-character of a bond. The analysis of bond ellipticity of the DES/BNNT complex was performed to investigate the effect of pi-electron delocalization on the bonds associated with H23 from the drug and N47 from the BNNT, O20 from DES and N71 from BNNT, C3 from DES and N58 from BNNT, and H27 from DES and N154 from BNNT. Also, the values of \(\varepsilon\) for bonds of H22-N59, H21-N87, N142-H29, H32-N79, C3-H23, N58-H39, and N154-H39, and C3-H38-N186 in the ring of the nanotube were calculated to be in the range of 0.1362 to 0.9564 (Table 6). The maximum values of \(\varepsilon\) were agreed well with those recommended for the aromatic bonds as mentioned above. This observation approves that these intramolecular hydrogen bonds are associated with electronic delocalization. We expect that the obtained results of the encapsulation of DES over BNNT (8,8–12) could be applied for the propagation of

**Table 6.** QTAIM topological parameters at the BCPs of the studied DES/BNNT (8,8–12) complex.

| Bond       | \(\rho\) | \(\nabla^2 \rho\) | \(G\)   | \(H\)   | \(|V/G|\) | \(\varepsilon\) | \(\text{Esp}\) |
|------------|---------|-----------------|--------|--------|--------|-------------|-----------|
| C3-H22-N59 | 0.0087  | 0.028           | 0.0059 | 0.0012 | 0.796  | 0.96        | 1.255     |
| C1-H21-N87 | 0.0076  | 0.027           | 0.0054 | 0.0013 | 0.753  | 0.78        | 1.255     |
| C3-H22-N58 | 0.0072  | 0.025           | 0.0051 | 0.0012 | 0.770  | 2.24        | 1.255     |
| C10-H29-N142| 0.0072 | 0.026           | 0.0053 | 0.0012 | 0.767  | 0.56        | 1.255     |
| C12-H32-N79 | 0.0073  | 0.024           | 0.0051 | 0.0010 | 0.792  | 0.91        | 1.255     |
| C14-H35-N131| 0.0025 | 0.009           | 0.0016 | 0.0005 | 0.667  | 0.47        | 0.628     |
| C17-CH37-N174| 0.0099 | 0.034           | 0.0071 | 0.0014 | 0.806  | 0.41        | 1.883     |
| C4-H23-N47 | 0.0062  | 0.022           | 0.0043 | 0.0011 | 0.735  | 5.70        | 1.255     |
| C11-H30-N64 | 0.0067 | 0.023           | 0.0047 | 0.0012 | 0.749  | 2.43        | 1.255     |
| C2-O20-N71 | 0.0097  | 0.033           | 0.0077 | 0.0006 | 0.924  | 5.22        | 2.510     |
| C16-O19-B148| 0.0102 | 0.031           | 0.0076 | 0.0002 | 0.978  | 0.36        | 2.510     |
| C10-H27-N154| 0.0080 | 0.027           | 0.0055 | 0.0011 | 0.798  | 1.52        | 1.255     |
| C19-H39-N162| 0.0127 | 0.040           | 0.0094 | 0.0006 | 0.939  | 0.14        | 2.510     |
| C18-H38-N186| 0.0064 | 0.021           | 0.0043 | 0.0010 | 0.772  | 0.40        | 1.255     |

Figure 7. Molecular graph of DES/BNNT complex.
nonodrug delivery-based systems to tumor cells and could reduce drug interaction and in fact side effects of the drug in communication with healthful texture.

3.5. Molecular electrostatic potential (MEP) analysis

Molecular electrostatic potential (MEP) maps were utilized to show the sites of electrophilic and nucleophilic reactions by scanning the electronic density through molecules. The drift in the electrostatic potential at different molecular areas are signified by several colors. The negative areas (red) of the MEP are related to areas with large electron densities, and demonstrate the electrophilic reactivity at these areas. In contrast, positive areas (blue) have little electron density and are related to nucleophilic reactivity, whereas the green color areas are corresponded to neutral areas of reactivity [71]. We have studied the charge partitioning using MEP calculations. The MEPs of the DES/BNNT (8,8–12) complex were gained by theoretical computations using the DFT: M06–2X/6-311 + G(d) level of theory. Figure 8 portrays MEP maps of the DES and DES/BNNT (8,8–12) complex. As it is seen from figure 8, oxygen atoms and two benzene rings, which were shown in yellow color, are related to areas with maximum electron densities. Nitrogen atoms in BN nanotube have blue color; consequently, they can be identified as electropositive atoms. Moreover, the green color areas confirm the neutral (zero potential) portions of the DES/BNNT (8,8–12) complex.

The two-dimensional topography analysis of electron localization function (ELF) and localized orbital locator (LOL) were done via Multiwfn program and related figs have been shown in figure 9. Both ELF and LOL could be used to show the electron localization in a molecular structure. The electron localization could be measured by considering the Pauli repulsion that is also related to the kinetic energy of electrons [72, 73]. Large and small quantities of ELF demonstrate that electrons are localized and delocalized, respectively [74]. In good harmony with ELF, high LOL values were attained at areas with covalent bonds, which at these areas electrons highly localized. For instance, a full binding between the H39 atom of the DES and the N162 atom of the BNNT (8,8–12) is offered. However, these parameters changed within the range of 0 and 1 that designate the greatest delocalized and localized areas, respectively. The blue color areas show the delocalized electron cloud, whereas
the red color show the areas of localized electrons. The electron localization function (ELF) and LOL plots confirm the electron-rich DES/nanotube connections. Remarkably, the blue circles around the nuclei are related to the electron discharge region between the valence and internal shell.

4. Conclusion

In the current study, non-bonding interactions of the DES drug and BNNT (8,8–12) have been distinguished at the DFT: M06-2X/6-31G* level of theory. The calculated results have displayed an interaction between anticancer DES drug and BNNT (8,8–12). The calculated adsorption energy designates that the formation of complex is preferred. The formation of the complex between BNNT (8,8–12) and the DES anticancer drug caused a structural modification in the BNNT (8,8–12) with no critical change in the DES geometries. The atomic charges have similarly redistributed due to the non-bonding interactions between the DES drug and BNNT (8,8–12). The electronic properties of DES are sensitive to adsorption on BN tubular structure (8,8–12). The global hardness of the drug with adsorption on the BNNT has incremented by about 0.104 eV. Consequently, it has changed to a rigid and hard compound as compared to pristine DES single component. According to the values of ω, it can be concluded that the DES/BNNT (8,8–12) complex is more electrophilic compared to DES. Additionally, by the adsorption of the drug into the BNNT (8,8–12), the value of dipole moment for the drug reduced by about 0.2 Debye. This reduction in the quantity of dipolar moment designates that electrostatic interaction was produced between the nanotube/drug mixes. This study indicated that the properties of the nanotube are modified by DES adsorption. The density of states (DOS) of the DES drug, BNNT (8,8–12), and the complex was calculated using the M06-2X/6-31G* method. Furthermore, DOS designs have exhibited a variation in the energy gaps. QTAIM and NCI analyses presented interactions between the DES and the nanotube, so that eleven hydrogen bonds have been discovered. Also, the maximum ∇₂ρ and the main ρ values were related to the hydrogen bond between H39 and N162 atoms and between O20 and N21 atoms. Therefore, these interactions are stronger in DES/nanotube complex than single components including DES and BNNT. Interestingly, the results of QTAIM calculations are entirely consistent with the results of NCI analysis, as both methods showed that the interaction between the nanotube and drug is based on van der Waals, hydrogen bonding, and steric interactions. Interestingly, this study could open new way for future experimental evaluations of this drug delivery system especially for the treatment of cancer cells.

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Data availability statement

The data generated and/or analysed during the current study are not publicly available for legal/ethical reasons but are available from the corresponding author on reasonable request.

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Conflicts of interest/competing interests

The authors declare that they have no conflict of interest.

Authors’ contributions

Maryamossadat Hosseinzadeh: Conceptualization; Data analysis; Writing-Original draft; Shiva Masoudi: Conceptualization; Data analysis; Supervision; Methodology; Resources; Writing- Editing and review; Nasrin Masnabadi: Conceptualization; Data analysis; Supervision; Methodology; Resources; Writing- Editing and review; Fatemeh Azarakhshi: Data analysis; Writing-Original draft.
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