Studying physicochemical characteristics of Flutamide adsorption on the Zn doped SWCNT (5,5), using DFT and MO calculations

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Abstract
In this study, the adsorption of Flutamide (FLT) anticancer drug on the Zn doped single-walled carbon nanotube (5, 5) (SWCNT-Zn (5, 5)) has been investigated. This study has been examined in the gaseous phase and also in water and ethanol solvents phases, in the basis and excited states, using density functional theory (DFT) and molecular orbitals (MO) calculation methods. DFT calculations were performed at B3LYP quantum chemical level and at 6-311G (d, p) basis orbital set. In the first step, the structure of FLT was optimized at B3LYP/6-311G (d, p) theoretical level. The obtained results clearly demonstrate the energy stability of the optimized geometries and obviously show that the nature of Flutamide adsorption energy on the surface of SWCNT is in the range of the physisorption. Afterwards, the various structures of SWCNT (5, 5) and the adsorption of FLT on the outer surface of SWCNT (5, 5) was investigated using DFT method. The energies of FLT, SWCNT (5, 5), Zn doped SWCNT (5, 5), the energies of HOMO and LUMO orbitals, gap energy and dipole moments have been calculated using DFT and MO methods.

Keywords: Flutamide (FLT); SWCNT; DFT method; MO method; physisorption.

Introduction
Flutamide (FLT) (trade mark Eulexin) (4-nitro-3-fluoromethylisobutryramide) is considered as the earliest attainable non-steroid antiandrogen recognized by the world as the most useful compound to treat prostate cancer. Several studies conducted in this case have been led to the reasonable and interesting results [1-4].

Single-walled carbon nanotubes (SWCNTs) and their prominent features in terms of chemical, electrical and 1D structural properties pioneered in various major fields in science. Proved amazing and unique properties of these structure led to a widespread use of them in various categories of science, including medicine, industry and technology. Due to their inherent features, SWCNTs are able to not only
deliver the bioactive molecules across cell membranes, but also into the cell nuclei because of their very high surface areas [5-8]. Certain theoretical studies on the behaviors of 1, 3-dipolar cycloadditions on the (n,n) SWCNTs have been performed and the results of this investigation have been reported by the authors [9]. The adsorption of several gaseous molecules on the surface of SWCNTs has been investigated using DFT method at B3LYP theoretical level and also the results of NMR data have been indicated [10, 11, and 12]. Some quantum chemistry theoretical investigations on the features of HOMO and LUMO orbitals and their energy gap in the polycyclic aromatic hydrocarbons and metal clusters have been provided the significant results [13,14]. Some physical chemistry characteristics of room temperature ionic liquids have been also studied and the results of its temperature dependence seems to be interesting [15]. In addition, NMR, NQR and the structural studies on nanotubes have been performed using DFT computational method [16-18].

Recently, several physicochemical properties of anticancer drugs adsorption characteristics and also drug delivery features have been studied using DFT and MD theoretical methods [19–21].

In this research, the adsorption of FLT (prostate specific antigen (PSA)) on the surface of carbon nanotubes (5, 5) has been investigated using density functional theory (DFT) and molecular orbitals (MO) methods. All calculations have been performed at B3LYP quantum chemical level and at 6-311G (d, p) basis set. Also, the interaction of FLT with Zn doped SWCNTs (5, 5) has been investigated.

After preparing the models and input files, the structures were optimized properly and the obtained results have been studied. Finally, to realize the drug effectively, the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO), were obtained and studied. All the obtained results of these calculations are presented in the following tables and figures. The optimized structure of FLT is shown in Figure 1.

![Figure 1. The optimized structure of FLT](image-url)
Computational method
In this study, FLT anticancer drug and the interaction between SWNTs (5, 5)-Zn and FLT in the basis and excited states in the gaseous phase, also in the water and ethanol solvents, was investigated. Gaussian 09 program have been used for all computations [22]. All the figures were drawn using Gaussview software, and the calculations were performed using DFT method at B3LYP quantum chemical and at 6-311G (d, p) basis orbital set. Furthermore, molecular orbitals (MO) and magnetic resonance of the nucleus (NMR) calculations have been performed to get more data concerning energy gaps and dipole moments. The assumed carbon nanotube (5, 5) which was used in this study contains 90 carbon atoms where the open ends are saturated by hydrogen atoms. In this investigation, SWCNT (5,5) is considered as the target nanotubes because of its high reactivity, small diameter and also high pyramidalization angle which is an important parameter in the reactivity of nanotubes [6, 9, and 10].

Results and discussion
The comparison of energy and bipolarity of the drug in the both basis and excited states
The energies and dipole moments were computed in basis state (in the both gaseous and solvent phases) and the excited state (in gaseous phase) using DFT method at B3LYP level and at 6-311G (d, p) basis set reported in Table 1. According to Table 1, in the gaseous phase, the energy in the excited state (-28856.576 eV) does not differ significantly the energy of basis state (-28856.007 eV). However, the drug is, more or less, more stable in the gaseous phase and excited state. The dipole moments in the gaseous phase and in the excited state is 4.33540 Debye(D) that is greater than the dipole moment in the same phase and in the basis state (3.4783 D). This fact may be attributed to the different distribution of electronic charges in the two mentioned states.

The energy of basis state in ethanol phase is -28864.07 eV, slightly greater than in the both gaseous and water solvent phases. This suggests that the drug may be more stable in the ethanol solvent phase than others. Moreover, the dipole moment in the basis states and in ethanol solvent phase is 4.7224 D, which is greater than in the water solvent phase (4.61604 D), in the gaseous phase (3.4783 D) and also in the excited state (4.3540 D). This phenomenon can also be attributed to the distribution of electronic charges in the orbitals. According to above results, the polarity of molecule affect its stability. Therefore, the stability of the molecule will be increased significantly by increasing the polarity of molecular structure.

| Table 1. Energy and dipole moment of FLT calculated at B3LYP/6-311G (d, p) theoretical level |
|---------------------------------------------------------------|
| **Phase** | **Basis state** | **Excited state** |
|-----------|----------------|------------------|
|           | **Dipole moment** | **Energy** | **Dipole moment** | **Energy** |
|           | **(D)** | **(eV)** | **(D)** | **(eV)** |
| Gaseous   | 3.4783 | -28856.007 | 4.3540 | -28856.576 |
| Water     | 4.6160 | -28856.957 | - | - |
| Ethanol   | 4.7224 | -28864.075 | - | - |
Analysis of molecular orbitals (MO) at B3LYP theoretical level

In general, studying HOMO and LUMO energies is used to distinguish the charge transfer in the molecule. HOMO and LUMO orbitals are considered as essential parameters that clearly illustrate the ability of electron donating or electron accepting, respectively. Furthermore, the molecules with high HOMO energy are capable to lose easily their electrons, therefore, they can be considered as more reactive. As the same way, LUMO orbitals with a low energy level relative to the energy level of HOMO orbitals are capable to accept easily the electrons which have been transferred from HOMO orbitals. The energy difference between HOMO and LUMO orbitals ($\Delta E_{HOMO-LUMO}$) is called the energy gap ($E_g$) that can be calculated by Equation 1.

$$E_g = \Delta E = E_{HOMO} - E_{LUMO} \quad (1)$$

The energy distance between these orbitals helps us to understand and clarify the kinetic stability and molecular reactivity of molecules, and furthermore, it is possible to study the intermolecular charge transfer. Knowing the energy gap also, can evaluate not only the chemical adsorption but also the electronic characteristics of species, effectively. In fact, the smaller energy distance indicates the more stable LUMO state, which is due to the higher capability of electron acceptance by this orbital. If the energy distance between HOMO and LUMO orbitals is small, therefore, the molecule will be very reactive, and consequently the higher charge transfer will occur and the reactivity increases. The results obtained from calculations at B3LYP/6-311G (d, p) theoretical level are shown in Table 2. This electron acceptance can be due to the electron transfer from HOMO orbital to the LUMO orbital in the basis state and is mainly described by an electron excitation from the HOMO orbital to the LUMO orbital.

Table 2. HOMO energy, LUMO energy and $E_g$ (eV) at B3LYP/6-311G (d, p) theoretical level

| Phase   | $E_{HOMO}$ (eV) | $E_{LUMO}$ (eV) | $E_g$ (eV) | $E_{HOMO}$ (eV) | $E_{LUMO}$ (eV) | $E_g$ (eV) |
|---------|----------------|----------------|----------|----------------|----------------|----------|
| Gaseous | -0.28867       | -0.17516       | 0.11351  | -0.27818       | -0.09994       | 0.17824  |
| Water   | -0.28595       | -0.18202       | 0.10393  | -               | -              | -        |
| Ethanol | -0.25837       | -0.10350       | 0.15487  | -               | -              | -        |

As can be seen in Table 2 and Figure 2 (DOS plots), both $E_{HOMO}$ and $E_{LUMO}$ in the excited state and in gaseous phase are higher than in the basis state. Also, the energy gap in the excited state is greater than the basis state. This may be interpreted by higher reactivity of FLT in basis state. The DOS plots are shown in Figure 2. The shape of the HOMO and LUMO orbitals is also shown in Figures 3 and 4. $E_g$ in the excited state and in gaseous phase (0.17824 eV) is greater than the $E_g$ in the basis state (0.11351 eV) and, as a consequence, the molecule is more stable in excited state and has the lower reactivity comparing to the basis state in gaseous phase. As seen in Figure 2,
and based on the obtained data, $E_{\text{HOMO}}$ and $E_{\text{LUMO}}$ in basis state in both gaseous and water solvent phases is more negative than in ethanol solvent phase. Whereas, $E_g$ in ethanol solvent phase is greater than its value in both gaseous and water solvent phases. These results will lead to the consequence that the drug is more stable in ethanol phase and also less reactive. It seems that, the molecule in the water phase and in the basis state with $E_g=0.10393$ eV has the lowest stability, the highest charge transfers and consequently the most reactivity.

A view of data analysis to obtain $E_g$, HOMO and LUMO

Diagrams 1 and 2 are a part of the Notepad output data and demonstrate that the $E_{\text{HOMO}}$ and $E_{\text{LUMO}}$ are attainable.

**Diagram 1.** An overview of the data analysis to obtain $E_{\text{HOMO}}$, $E_{\text{LUMO}}$ and $E_g$ of FLT

**Diagram 2.** An overview of the data analysis to obtain $E_{\text{HOMO}}$, $E_{\text{LUMO}}$ and $E_g$ of SWCNT (5, 5)-Zn-FLT complex
Figure 2. Orbital densities and Eg of FLT in the basis state (a) in gaseous phase, (b) in ethanol solvent, (c) in water solvent and (d) in the excited state in gaseous phase

Figure 3. HOMO and LUMO orbitals of FLT in the basis state of (a) gaseous phase, (b) water solvent and (c) ethanol solvent phases
Studying the interaction of FLT on the surface of SWCNT and Zn doped SWCNT

The adsorption of FLT on the surface of the pristine single-walled carbon nanotubes (SWCNT) (5, 5) and SWCNT-(5, 5)-Zn complex using DFT method at B3LYP theoretical level and at 6-311G (d, p) basis set was seriously studied. The first attempts were performed to absorb the drug over the surface of nano-tube but with no results. This can be attributed to the repulsive force between the nanotube electron cloud and the non-bonded pair of electrons in oxygen, fluorine and nitrogen atoms in Flutamide. Afterwards, SWCNT was doped with Zn and the interaction of FLT with SWCNT- (5.5) -Zn was occurred and the SWCNT- (5.5)-Zn-FLT complex was formed. Finally, the obtained structure was optimized at B3LYP/6-311 (d, p) theoretical level (Figure 5) and then the results were extracted and studied.

Changes in the bond length of complex

The value of changes in bond lengths in Zn doped carbon nanotubes and the values of dipole moments after drug absorption were calculated at B3LYP/6311(d,p) theoretical level and were reported in Table 3. Generally, if the value of the dipole moment is high,
then the absolute value of the bonding energy will increase consequently. In other words, the greater dipole moment will lead to the noticeable increase of the excitation energy of electron clouds.

Table 3. The values of the bond length (in angstrom) and the dipole moment of drug’s interaction with SWCNT (5, 5)-Zn

| Complex            | Dipole moment (D) | R(C1-C2) (A) | R(C2-C3) (A) | R(C1-Zn) (A) | R(C2-Zn) (A) | R(C3-Zn) (A) |
|--------------------|-------------------|--------------|--------------|--------------|--------------|--------------|
| SWCNT-Zn-FLT       | 4.0753            | 1.41         | 1.42         | 1.94         | 1.97         | 1.94         |

The adsorption energy of drug on the surface of SWCNT (5, 5)-Zn
The interaction of FLT on the outer surface of SWCNT (5, 5)-Zn was studied and the adsorption energy was calculated using Equation 2. The obtained data were reported in Table 4. As seen in Table 4, the adsorption energy is a positive value, therefore, this interaction is endothermic and the amount of energy places it in the physisorption range. The final complex of FLT-SWCNT (5, 5)-Zn was optimized to find a stable structure (Figure 5).

\[
E_{\text{ad}} = E_{\text{tot}}(\text{FLT} + \text{SWCNT}) - E_{\text{tot}}(\text{SWCNT}) - E_{\text{tot}}(\text{FLT})
\]  

(2)

Table 4. Energy values in drug interactions on the surface of Zn doped carbon nanotube (5, 5)

| Element              | Energy (HF)  | Energy (keV) | E_{\text{ad}} (keV) |
|----------------------|--------------|--------------|---------------------|
| SWCNT-Zn             | -7508.79     | -204.33      | -                   |
| FLT                  | -1060/43     | -28.85       | -                   |
| SWCNT-Zn-FLT         | -8531.25     | -232.15      | 1.033               |

*Calculated by equation (2)

Molecular orbital (MO) analysis of FLT-SWCNT (5, 5)-Zn
By the size reducing in semiconductor nanoparticles, the quantum effects will appear. In quantum dots, electrons also have a variety of energies, however, due to the very small size of these nanoparticles, the energy levels are not continuous. The reduction or addition in the numbers of atoms to quantum dots will cause the change in the energy gap, which undoubtedly is due to the very small size of these dots and their quantum effects. Knowing the energy gap not only can provide the useful data about the adsorption of the molecules on the surface of nanotubes, but also make possible to study their electronic characteristics. Hence, the values of EHOMO, ELUMO and energy gap of SWCNT (5, 5), FLT and FLT-SWCNT (5, 5)-Zn in gaseous phase were also calculated using MO method and have been reported in Table 5. Considering the type of adsorption, it seems that the calculations by DFT method leads to more reasonable results.
Table 5. E_{LUMO}, E_{HOMO}, and the energy gap of the FLT on SWCNT (5, 5) -Zn

| Element       | E_{HOMO} (eV) | E_{LUMO} (eV) | E_g (eV) |
|---------------|---------------|---------------|----------|
| SWCNT(5,5)    | -0.15954      | -0.12665      | 0.033    |
| FLT           | -0.27818      | -0.09994      | 0.37812  |
| SWCNT-Zn-FLT  | -0.16652      | -0.12799      | 0.039    |

Studying NMR parameters of FLT

The magnetic resonance of the nucleus (NMR), including isotropic and anisotropic chemical condensation parameters, is one of the best methods that can be used to study the electronic properties of various materials. The chemical tensors created by the positions of semi spin nuclei, C and O, not only are sensitive to the electrons, but also are easily destroyed. Therefore, they provide an important insight into the electrostatic properties of nanostructures in the drug adsorption process.

The main objective purpose in this step is to study the tendency of carbon nucleus on Zn doped SWCNT to form a physical bond with oxygen atoms of FTL (Table 6 and Figure 6). As the charge variations on the atoms increase during the adsorption process, the molecule becomes more symmetrical and the charges of two carbons become similar and take the positive values. The reduction of the anisotropy proves the symmetry of the electron cloud around the carbon atoms (Equations 3, 4 and 5).

\[
\Delta \sigma = \frac{3}{2}(\sigma_{33} - \sigma_{iso}) \quad (3)
\]

\[
\sigma_{iso} = \frac{\sigma_{11} + \sigma_{22} + \sigma_{33}}{3} \quad (4)
\]

\[
\eta_{\sigma} = \frac{3}{2}\left(\frac{\sigma_{22} - \sigma_{11}}{\Delta \sigma}\right) \quad (5)
\]

Table 6. NMR parameters of C-O of SWCNT-Zn (5.5)-FTL

| Element       | Atoms | \(\sigma_{11}^a\) | \(\sigma_{22}^a\) | \(\sigma_{33}^a\) | \(\sigma_{iso}^a\) | \(\Delta \sigma^a\) | \(\eta_{\sigma}^a\) |
|---------------|-------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| FTL           | C_1   | -41.5162          | 63.8179           | 66.6279           | 9.643             | 4.522             | 15.892            |
|               | C_2   | -29.9472          | 19.5015           | 139.0969          | 42.883            | 134.569           | 0.355             |
| FTL-SWCNT-Zn  | C_1   | -207.4312         | 23.2598           | 220.6322          | 12.153            | 312.717           | 24.199            |
|               | C_2   | -41.8461          | 13.7756           | 97.2809           | 97.107            | 111.316           | 14.205            |
|               | C_3   | -211.8356         | 174.9256          | 476.4464          | 580.760           | 494.901           | 175.370           |

*Calculated \(\sigma_{ii}\), \(\sigma_{iso}\) and \(\Delta \sigma\) values are in ppm
Conclusion
In this study, the adsorption of FLT on the outer surface of SWCNT (5,5) and Zn doped SWCNT (5,5) was investigated. The carbon nanotube (5,5) which was chosen in this study have the length of 1.73 nm and the diameter of 7.2 nm. The various structures were obtained using Gaussview software. Then, all structures were optimized properly. The optimization of these structures was carried out using the Gaussian 09 software and at B3LYP / 6-311G (d, p) theoretical level. The drug was made in both basic and excited states using DFT, and DFT-TD methods. To saturate the carbon bonds and create a model close to a real nanotube, the optimum length and diameter were assumed for calculating and finally all structures were optimized effectively. To calculate the adsorption energy, the dipole moment, the energy gap, and the values of HOMO and LUMO energies of drug and the complex, DFT method at B3LYP / 6-311G (d, p) theoretical level and also MO method have been used. All obtained data were reported in the manuscript. The adsorption energy of FLT may be considered in the range of the physisorption. The obtained data clearly prove that the suggested SWCNT (5,5) can be considered as the most reactive nanotube because of its small diameter and high pyramiding angle, which is an important parameter in nanotubes reactivity. Finally, it can be deduced from all the obtained data that the Zn doped nanotube (5,5) to be interesting for drug delivery due to its relatively weak bonding.

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