J. Nanoanalysis., 5(3): 202-209 Summer 2018

ORIGINAL RESEARCH PAPER

Fluorouracil functionalized Pt-doped carbon nanotube as drug delivery nanocarrier for anticarcinogenic drug: A B3LYP-D3 study

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Received: 2018-07-06 Accepted: 2018-08-05 Published: 2018-08-10

ABSTRACT

The interaction between drugs and nanostructured materials such as nanotubes is proving to be of fundamental interest for drug delivery and nanobiosensing. In the present work, the interaction of Fluorouracil, as an anticarcinogenic drug, with pristine CNT and Pt-doped CNT was investigated at the B3LYP-D3/TZVP level. Full optimization procedure has been carried out for all interacting systems to better understand the trends in binding nature of drug molecule interacting with the selected nanocarrier. We have evaluated the various stable configurations at both gas phase and aqueous solution for the considered complexes based on their interaction nature. Calculated adsorption energies indicated that Fluorouracil can form stable binding with Pt-CNT in aqueous media with adsorption energy of −1.12 eV which was found to be a chemisorption process. Charge analysis revealed that, upon binding of Fluorouracil to the nanocarrier, the overall charge on the host and guest systems changes and significant charges have been transferred from Fluorouracil to the substrates. Quantum molecular descriptors calculations also demonstrate the significant changes in the electronic properties of the nanostructures due to the Fluorouracil attachment. Interaction between Fluorouracil and pristine CNT however has been found to be typical for the physisorption with adsorption energy of about −0.405 eV. Our findings offer fundamental insights into the functionalization of the Pt-doped CNT and envisage the applicability of these nanostructured materials as a novel drug delivery vehicle for the transportation of anticarcinogenic drug within the target cells.

Keywords: *DFT Calculations, Drug Delivery, Fluorouracil, Pt-doped CNT*

How to cite this article
Khalili Z, Darvish Ganji M, Mehdizadeh M. Fluorouracil functionalized Pt-doped carbon nanotube as drug delivery nanocarrier for anticarcinogenic drug: A B3LYP-D3 study. J. Nanoanalysis., 2018; 5(3): 202-209.
DOI: 10.22034/jna.2018.542770

INTRODUCTION

Besides its proven advantages, fluorouracil is known to develop significant side effects, similar to other anti-carcinogenic medicines [1]. As a chemotherapeutic agent with analogy to fluorinated pyrimidine, the fluorouracil has its mechanism of action based on thymidylate synthase inhibition irreversibly [2-3]. Fluorouracil has been commonly used to treat gastrointestinal cancer including esophagus, stomach, and carcinoma, among other applications [4-5]. As mentioned above, this medicine suffers from cardiac side effects, including coronary vasospasm and coronary thrombosis [6-7]. Reports have further indicated cases where the patient has encountered acute coronary syndrome with thrombotic subtotal coronary artery occlusion in the setting of home fluorouracil infusion, placing an emphasis on the necessity of performing cardiac assessments prior to administering the medicine and careful monitoring of the patient in the course of the administration period [6-10]. Accordingly, there is a need for new approaches to the attenuation

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of the side effects by formulating either new drugs of smaller side effects or organ-targeted drug delivery systems. Given the significant costs of developing brand new formulations, the focus has been on the invention of organ-targeted drug delivery systems when it comes to side effect attenuation [12-14].

The more accurate a drug delivery system targets the specific organ or tissue to be treated, the lower and the higher will be side effects and effectiveness of the drug, respectively [11]. Another advantage of a well-targeted drug delivery system is optimality of the release rate depending on the natures of the drug and the specific organ(s) engaged. The release rate imposes large contributions to the drug performance; accordingly, drug excretion and inefficiency are common consequences of too high and too low release rates, respectively. Different drug delivery systems have been proposed to cope with the mentioned difficulties.

A review on the bulk and nanomaterials proposed for drug delivery applications so far shows superiority of the nanomaterials thanks to their large surface area and optimal binding energy [15]. Among others, TiO_2 nanoparticles, Fe_3O4 magnetic nanoparticles, gold nanoparticles, and silver nanoparticles as well as several carbon-based compounds such as graphite, carbon nanotube, nanoporous carbon, mesoporous silica nanoparticles, and nano-scaled alumina particles have been already proposed as drug carriers for targeted drug delivery. Lots of attention has been paid to structure and electronic configuration of titanium oxide nanotubes (TiO_2) in relation to the development of special therapeutic devices and imaging probes for nanodrugs. Moreover, large potentials of TiO_2/ZnS nanotubes for bio-imaging applications have been confirmed on cultured cells of sycamore [16]. As another example, attempts have been made to deliver non-aqueous-soluble tin complex (a biological diagnostic marker) via mesoporous silica nanoparticles [17-18]. Recent research works on drug delivery systems have been focused on carbon-based nanostructures, among other nanomaterials, especially carbon nanotubes (CNTs) [19-27]. Shortly following their emergence in the last decade, CNTs and their potential applications in medicine attracted a great deal of interest. Helicity and central layers of CNTs determine their electronic properties. On the other hand, chemical inertness and structural stability of CNTs keep them from becoming toxic to health and environment; the non-toxicity coupled with large surface area and unique physical and morphological characteristics have provided a basis for a wide range of applications, especially in drug delivery systems [28]. Nevertheless, fluorouracil molecules are known not to interact with pure CNTs appropriately, so that a functionalization process is required to boost the interaction. Among other approaches to the functionalization, doping with metallic atoms (e.g., Pt) represents the most promising approach. Being a non-reactive metal, platinum has been long used in orthopedic implants and dentals [29-35]. Accordingly, Pt was selected as the point of focus of the present research due to its prevalence in many organometallic complexes with extensively studied, both theoretically and experimentally, anti-cancer properties. In the present work, Pt-doped CNTs were simulated by substituting a Pt atom for a C atom on the CNT. Furthermore, ab-initio density functional theory (DFT) was adopted to optimize structure and molecular properties of the fluorouracil drug for interaction with the Pt-doped CNT.

THEORETICAL METHODS

The structure optimizations and corresponding total energy calculations of the structural geometries were carried out within the framework of the all-electron density functional theory (DFT) method. We used the B3LYP method as described by Becke′s three parameter for exchange functional while the correlation energy was parametrized by Lee, Yang and Parr scheme [36, 37] as implemented in ORCA quantum chemistry code (version 3.0.3) [38]. The proposed triple-ζ valence plus polarized basis set (def2-TZVP) by Ahlrichs and co-workers [39] was utilized for both structural optimizations and total energy calculations. We also employed the Resolution of Identity (RI) approximation (new efficient RIJCosX algorithm) to integrate the coulomb part [40] and the Grid5 for the DFT integration grid for the SCF iterations and final energy estimations. All molecular structures have been fully optimized (without frozen core approximation) to satisfy the NormalOpt convergence criteria and the SCF iterations was adopted to SCFCONV10 to decrease the numerical noise in gradient estimations. The long-range dispersion interactions was accounted by the third version of Grimme's atom pair-wise dispersion corrections within the Becke-Johnson damping scheme (D3-BJ) [41-43], hereafter, denoted as B3LYP-D3 method. For the Pt atom the [SD (28,

MDF)] effective core potential (ECP) [44] with def2-TZVPP basis set was utilized. For accurate adsorption energy calculation the counterpoise correction formalism [45] was applied to eliminate the basis set superposition error (BSSE). The adsorption energy values were calculated by the following equation:

$$E_{ads} = E_{complex} - (E_{substrate} + E_{adsorbate}) \quad (1)$$

Where the expression indicate the total energy of the complex, substrates (individual nanotube/nanosheet) and adsorbate (individual fluorouracil molecule), respectively.

RESULTS AND DISCUSSION

The Stable Geometry of the Fluorouracil and CNT/Pt-CNT

We first explored for the structural geometries and charge population of Fluorouracil and Pt-doped CNT (Pt-CNT) systems with the DFT/B3LYP-D3 model of theory. The equilibrium bond lengths were calculated after the geometries were fully optimized. The calculated structural parameters for Fluorouracil molecule (see Fig. 1a) were found to be in good agreement with the experiment [46]. The calculated bond distances of O-C, C-C and C-N in isolated drug molecule are respectively 1.209, 1.468 and 1.404 Å. Optimized geometry of the Pt-CNT system show that doping of Pt atom causes the deformation of the hexagonal rings in the doping region and the shape of the nanotubes deform from cylindrical form (see Fig. 1b). The closest Pt–C distance between Pt and adjacent C atoms in the CNT is determined to be about 1.907 Å and the C-C-Pt angle is 160.89°, as shown in the figure. These structures were used in the rest of our calculations to study the interaction between the Fluorouracil and Pt-CNT adsorbent.

Charge population analysis by Mulliken approach shows that F and O atoms around the aromatic ring were negatively charged. The charges were mostly extracted from C atoms in the ring and also from H atoms around the ring. This charge transfer between heteroatoms leads to the creation of negatively/positively charged center in

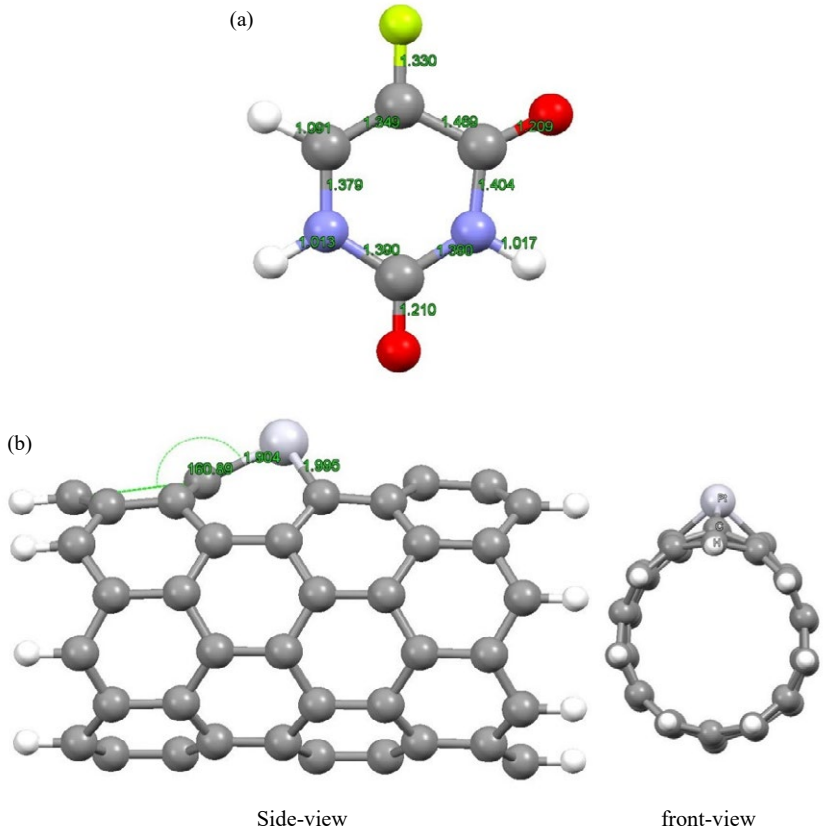


Fig. 1. Optimized structures of (a) Fluorouracil and (b) Pt-CNT (7, 0) in gas phase at B3LYP-D3/def2-SVP level. Atom color code: yellow: flour; blue: nitrogen; grey: carbon; red: oxygen and white: hydrogen.

the molecule. The Mulliken analysis indicates that Pt atom was positively charged while C atoms were negatively charged. Calculated charge population for the considered molecular system is shown in Table 1.

As the ambient condition is a staple factor for such systems thus for making approximation in as much as reality we have considered solvent effect in current study. The bond distances of O-C, C-C and C-N in drug in the aqueous solution are calculated 1.220, 1.458 and 1.395 Å, respectively. In general the bond distances of drug in gas phase and solvent media are slightly different. In the equilibrium geometries of Pt-CNT, the computed closest bond lengths of Pt-C is 2.267 Å and the C-C-Pt angles is 162.32°. The results of the Mulliken analysis in the solvent are similar to the gas ones as shown in Table 1 (Pt and C atoms were positively and negatively charged, respectively) while the amount of accommodated charges on each atoms are different in various media.

Interaction between the Fluorouracil and CNT/Pt-CNT

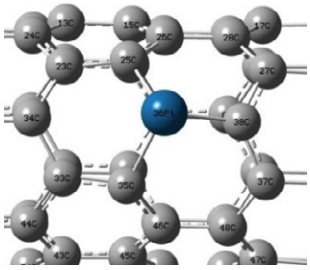
We now describe the interaction between Fluorouracil molecule and Pt-CNT (7, 0) substrate in the gas phase. Various interaction orientations have been considered for the interacting drug molecule (negative active cites as nucleophile centers-denoted as O-ortho (O atom adjacent to the F atom), O-para (O atom far from the F atom), F (F atom) and Ring (hexagonal ring)) with Pt atom of substrate (positive active cite as electrophile center). After full structural optimization of all considered systems it was found that the O-ortho configuration gives stronger adsorption energy than the other configurations. The calculated adsorption energy and equilibrium binding distance for the energetically favorable state are determined to be respectively −1.120 eV and 2.257 Å (see Fig. 2a). Table 1 presents the adsorption energies of all considered configurations.

Comprehensive calculations procedures have been performed for the interacting drug with Pt-CNT substrate in aqueous solution. The energetically favorable states in the solvent condition were found to be the same as in the gas phase but the adsorption energies follow the reverse trend for the considered adsorbent. The calculated adsorption energies and equilibrium distances were found to be namely −1.743 eV and 2.287 Å for the Flu/Pt-CNT (see Fig. 2b). The obtained adsorption energy for all optimized complexes and their charge transfers in solvent condition are given also in Table 2. In contrast with the gas phase, the stronger interaction was seen between the drug and Pt-CNT in solvent media. The adsorption nature of these complexes is found to be typical for the chemisorption [47-49].

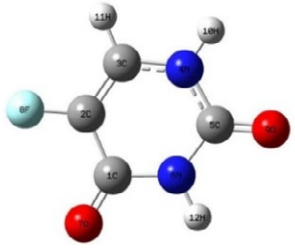
In order to clarifying the binding nature in

Table 1. Calculated charges with Mulliken population method for atoms in Pt-CNT (7, 0) and Fluorouracil systems.

Systems		Gas	Water
Pt-CNT	25:C	-0.226	-0.213
	36:Pt	0.385	0.573
	35:C	-0.232	-0.234
	38:C	-0.028	0.009
	1:C	0.184	0.221
	2:C	0.170	0.180
	3:C	-0.025	-0.026
	4:N	-0.238	-0.206
	5:C	0.298	0.326
	6:N	-0.233	-0.207
Fluorouracil	7:O	-0.292	-0.417
	8:F	-0.183	-0.213
	9:O	-0.327	-0.434
	10:H	0.243	0.292
	11:H	0.159	0.207
	12:H	0.244	0.276



Pt-CNT (7, 0)



Fluorouracil

these complexes, we evaluated the total electron density maps of Fluorouracil adsorbed onto the considered substrate. Fig. 2c represents the calculated isosurface plots of the optimized structures for the energetically favorable states of Flu/Pt-CNT complex. These plots were obtained with the B3LYP-D3/TZVP theoretical model. For both complexes, it was found that the chemically adsorbed Fluorouracil which is close to the substrate almost affects the electronic charge distribution of surface atoms of the CNT and thus charge transfer between the adsorbent and adsorbate orbitals occurs. It is clearly revealed that strong hybridization between the O and Pt atoms states occurs, resulting in a significant charge transfer in the system.

As a comparison the adsorption of Fluorouracil onto the pure CNT has also been investigated. Two possible configurations were considered for the approaching molecule to the CNT side wall (stacking and perpendicular configurations as shown respectively in Fig. 2d, e). After full structural optimization of the whole system we found that Fluorouracil prefers to be attached to the pure CNT side wall by stacking orientation in which the aromatic ring of the molecule was positioned parallel to the surface of the tube. The calculated adsorption energy was estimated to be about −0.405 eV with equilibrium distance of 3.167 Å which both indicate the existence of physisorption in the interaction process. The adsorption energy for the perpendicular orientation was about −0.305

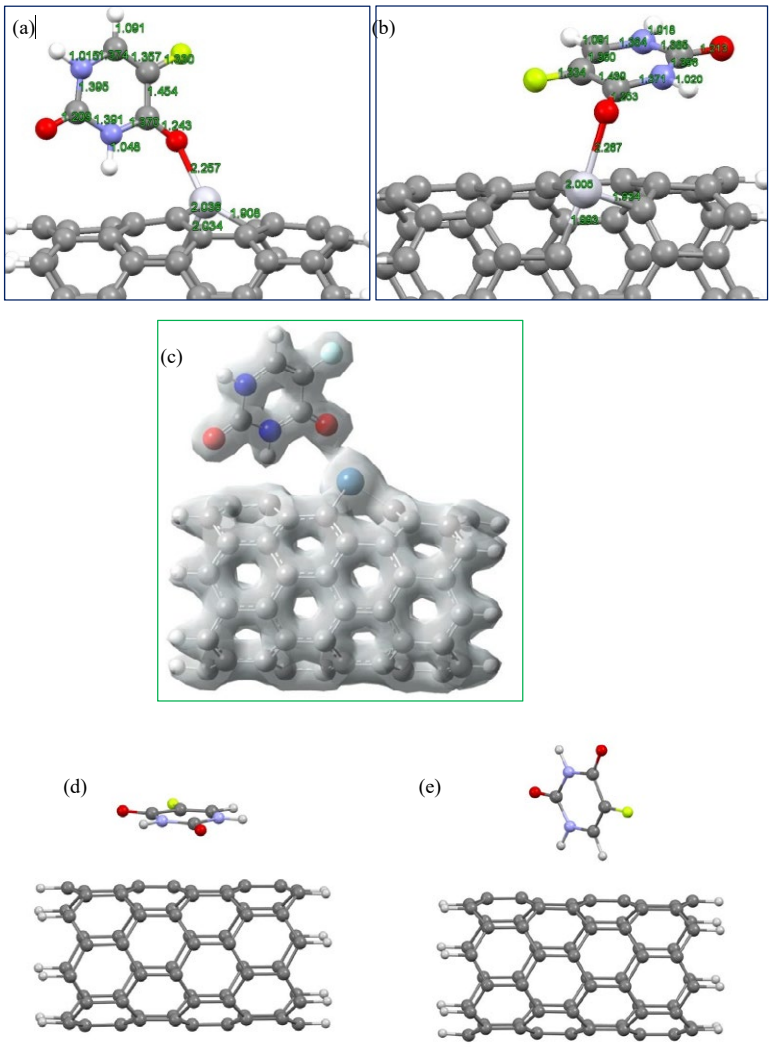


Fig. 2. Fully optimized structures of Flu/Pt-CNT (7, 0) in (a) gas phase, (b) aqueous solution with B3LYP-D3/def2-SVP theoretical model. (c) Calculated total charge density plot for the Flu/Pt-CNT (7, 0) complex (isovalue set to 0.05 au). Models considered for attached Fluorouracil molecule to the pristine CNT with (d) stack and (e) perpendicular orientations.

eV. From the results, one can find that Pt-CNT bound stronger to the Fluorouracil molecule than the pristine CNT and hence more suitable for functionalization and drug delivery application.

Molecular Properties

We now explore the global molecular quantities [50] such as chemical potential (μ), global hardness (η), global softness (S), electrophilicity index (ω), and electronegativity (χ) with the B3LYP-D3/TZVP model to realize the molecular reactivity of systems under study. The following equations were used to determine the above mentioned properties:

$$I = -E_{HOMO} \text{ and } A = -E_{LUMO} \quad (1)$$

$$\eta = \frac{1}{2}(I - A) \quad (2)$$

$$S = \frac{1}{2\eta} \quad (3)$$

$$\mu = -x = -\frac{1}{2}(I + A) \quad (4)$$

$$\omega = \frac{\mu^2}{2\eta} \quad (5)$$

All calculated molecular properties are given in Table 3. The calculated values of stability and reactivity exhibit contradictory trends. The hardness, chemical potential and gap energy have a similar trend with stability and are in contrast with the reactivity. The changes of electrophilicity and softness are compatible with the reactivity. According to Table 3, we can conclude that after interaction, the stability of complexes decreases and hence the reactivity increases. Our studies also point out the interaction of Fluorouracil molecule with Pt-CNT for loading and delivery process. By comparison of molecular properties of bare Fluorouracil and Fluorouracil with Pt-CNT system indicates that presence of nanostructures increases softness and electrophilicity of drug molecule. As mentioned above, along the increment of softness and electrophilicity after interaction, the reactivity rises and the loading and delivery might be carried out better accordingly.

Furthermore, the dipole moments for the Fluorouracil, pristine Pt-CNT and corresponding complex were calculated. We found that dipole moments increase for the substrate after complexation while the value for the Flu/Pt-CNT is higher than the Fluorouracil drug one. The solubility and dispersion power could be enhanced with increasing polarity of Pt-CNT in the presence of Fluorouracil molecule compared

Table 2. Adsorption energies and the amount of transferred charges between the Fluorouracil and Pt-CNT (7, 0) in gas phase and aqueous solution (negative sign denotes charge transfer from Fluorouracil to substrates).

Systems	Gas		Water	
	E_{ads} (eV)	Q_t (e)	E_{ads} (eV)	Q_t (e)
Flu/Pt-CNT-O-o	-1.120	-0.089	-1.743	-0.117
Flur/Pt-CNT-O-p	-1.034	-0.112	-0.961	-0.201
Flur/Pt-CNT-Ring	-0.539	-0.090	-0.931	-0.209
Flur/Pt-CNT-F	-1.014		-0.838	-0.183

Table 3. Calculated values of molecular properties (ionization potential (I), electron affinity (A), softness (S), hardness (η), chemical potential (μ), electronegativity (x), electrophilicity index (ω) and dipole moment) for Fluorouracil, Pt-CNT and Flu/Pt-CNT in (a) gas phase and (b) aqueous solution at B3LYP-D3/def2-TZVP level.

(a) Gas phase

Systems	I (eV)	A (eV)	η (eV)	S (eV)	μ (eV)	x (eV)	ω (eV)	*Dipole moment* (Debye)
Fluorouracil	1.721	7.062	-2.670	-0.187	-4.392	4.392	-3.611	4.068
Pt-CNT (7, 0)	3.409	4.014	-0.303	-1.652	-3.711	3.711	-22.750	3.550
Flur/Pt-CNT (7, 0)	3.197	3.836	-0.319	-1.565	-3.517	3.517	-19.361	10.605

(b) Aqueous solution

Systems	I (eV)	A (eV)	η (eV)	S (eV)	μ (eV)	x (eV)	ω (eV)	*Dipole moment* (Debye)
Fluorouracil	1.452	6.801	-2.674	-0.187	-4.127	4.127	-3.184	6.005
Pt-CNT (7, 0)	3.261	3.992	-0.366	-1.368	-3.627	3.627	-17.990	13.424
Flur/Pt-CNT (7, 0)	3.212	3.898	-0.343	-1.458	-3.555	3.555	-18.423	20.616

Table 4. The calculated LUMO energy, HOMO energy and, HOMO-LUMO gap (E_g) with B3LYP-D3/def2-TZVP model.

(a) Gas phase

$Systems$	$E_{HOMO}\ (eV)$	$E_{LUMO}\ (eV)$	$Gap\ energy\ (eV)$
Fluorouracil	-7.062	-1.721	5.340
Pt-CNT (7, 0)	-3.992	-3.261	0.731
Flur/Pt-CNT (7, 0)	-3.836	-3.197	0.639

(b) Aqueous solution

$Systems$	$E_{HOMO}(eV)$	$E_{LUMO}(eV)$	$Gap\ energy\ (eV)$
Fluorouracil	-1.452	-6.801	5.349
Pt-CNT (7, 0)	-3.261	-3.992	0.731
Flur/Pt-CNT (7, 0)	-3.197	-3.836	0.639

to the pristine ones. The dipole moment of pristine Fluorouracil is more than complex however due to enhancement in reactivity, this interaction is favorable. In addition, the dipole moment analysis show the charge redistribution caused by drug adsorption. The calculated dipole moments for the Pt-CNT system are smaller than the values of the corresponding complex, indicating that introducing drug molecule significantly affects the electronic properties of considered nanostructure.

Investigation and comparison between systems in two different conditions (gas phase and solvent) shows that molecular properties are in the same range. However, the amount of dipole moment change in different media, increase in the solvent media, which reveals that the solubility of drug increase in aqueous solution.

CONCLUSION

We have investigated the functionalization of Pt-CNT with an anticancer drug, Fluorouracil molecule, by means of DFT-D3 calculations at the B3LYP/TZVP level of theory. Various possible configurations were considered for a Fluorouracil molecule approaching the Pt atom of the substrate. Our *first-principles* calculations revealed that the O side of the Fluorouracil binds strongly with doped Pt atom of both considered nanostructures. The calculated adsorption energies for Flu/Pt-CNT (7, 0) complex were estimated to be −1.120 eV. This clearly indicates that Fluorouracil drug could be chemisorbed onto the Pt-CNT surface with high adsorption energy. The effect of solvent on the stability of functionalized Pt-CNT system was evaluated at the same theoretical level. The Flu/Pt-CNT complex has higher adsorption energy in aqueous solution than in gaseous phase. The electronic structures (total charge density) as well as dipole moment analyses emphasized the strong interaction between interacting entities. Also the results revealed that the electronic properties of nanostructured substrates change significantly after functionalization. Meanwhile, our DFT calculations revealed that Fluorouracil interact with pristine CNT weaker than the Pt-CNT system with adsorption energy of about −0.405 eV. It was found that Pt-CNT may serve as superior nanocarriers of the Fluorouracil drug within solution environments.

The structural parameters and chemical reactivity of the functionalized Pt-CNT significantly change, as dictated by the calculated global chemical reactivity descriptors. The chemical binding features of the drug molecule remain intact in the Flu/Pt-CNT complex. These findings suggest that Pt-CNT may be promising nanocarriers for the delivery of the Fluorouracil drug to the target cells.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge support of this work by the Pharmaceutical Sciences Branch, Islamic Azad University, Tehran, Iran.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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