Investigation of interaction between graphene and its compounds as carriers on anti-cancer drug of 5-fluorouracil

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5-fluorouracil molecule (5-FU) is a fluorinated pyrimidine analogue chemotherapeutic agent using as solid cancer treatment like esophagus, stomach, intestines, and carcinoma. The adsorption process as the first factor in drug conductivity systems is very important, and also in this study, importance of adsorption, for measuring the efficiency of graphene as drug carriers was studied. In this study, the electronic and adsorption properties of the graphene interacted with 5-fluorouracil molecule (5-FU) were theoretically investigated in the gas phase using the B3LYP density functional theory (DFT) calculations and 6-311G* basis set. Graphene due to its unique properties is very important compound. It was found that the adsorption behavior of 5FU molecule on the Graphene are electrostatic in nature.
**Keywords**: Graphene, 5-fluorouracil drug, density functional theory.

INTRODUCTION
Drug delivery

Nowadays, the concept of drug transmission is an important topic in the field of drug delivery research. Generally, the use of a method for delivering a pharmaceutical active ingredient (by minimizing toxicity) to its place of action in vivo is called drug transmission, and to achieve this goal, we must overcome to some problems such as unwanted characteristics of certain drugs such as low solubility and high hydrophobicity. The set of strategies that are used to drug delivery is called Formulation Technology [1]. Today, with the arrival of nanotechnology in the medical field, the limitations of traditional drug delivery are being overcome Nanomedicine has been focused on bioimaging, drug delivery systems and new drug herapies using nanoparcticles (NP), which are ultrafine particles in the range of 1-100 nanometers in size [2-8].

For quantum computing in the study of interaction between 5-fluorouracil drugs with graphene, commonly used software of quantum mechanical calculations was used (Fig. 1). Then the data that obtained from quantum computing were analyzed

Anti-cancer drug of 5-fluorouracil

In this study, 5-FU is applied for regional drug delivery by analytical methods (Fig. 2).
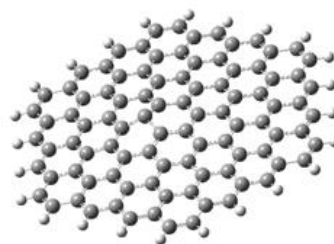
Fig. 1. Graphene
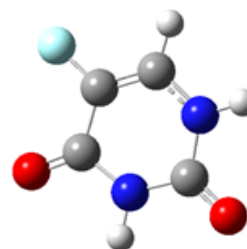
Fig. 2. 5-Fluorouracil drug
Drug interaction with graphene
First, the drug and graphene without agent that already have been optimized put into the software to do the calculations.

COMPUTATIONAL METHODS

In this study, the interaction between graphene with 5-fluorouracil drug has been studied theoretically. Electronic and structural properties of graphene e and 5-fluorouracil drugs were evaluated by using quantum computing at the level of density functional theory of B3LYP in the basis set of 6-311G*. In this work we studied the geometry of graphene and 5-fluorouracil drug. Then we put the

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5-fluorouracil drug at a suitable distance from graphene for optimization were repeated in the target structures. According to quantum computing, to study structural and electronic properties of macromolecules, a lot of computational cost and time is required, therefore, in this study, to investigate the above-mentioned properties with lower costs, we were studied a part of graphene instead of taking into account the total combination. In this study, the effect of factors that listed below have been studied on the structural and electronic properties such as dipole moment, atomic charge of Mulliken, molecular orbitals, and the adsorption energy.

RESULTS AND DISCUSSION
Optimization of geometric structure

At first, optimized structure of 5-fluorouracil drug complex with different models of Graphene is shown in Figure 3.
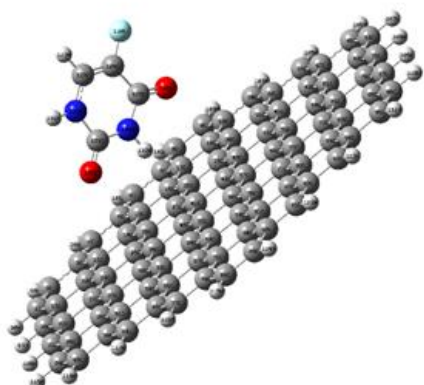
Fig.3. The optimized structure of Graphene with 5-fluorouracil drug in theory level of B3LYP / 6-311G *

According to (Fig.3) the drug becomes close to graphene surface through hydrogen area, in this case, distance of graphene carbon with hydrogen of drug is 2.62 Å. And distance of hydrogen with nitrogen in the drug increased from 1.03 Å to 1.05 Å. Also distance of nitrogen with carbon in the drug reaches

from 1.4 Å to 1.5 Å. And distance of carbon with oxygen reduced from 1.4 Å to 1.22 Å. The bond length between carbon atoms in Graphene increased from 1.35 Å to 1.46 Å. And the rest of these bonds remain fix. This decrease and increase in bond lengths is indicated that Graphene and drug have been interacted.

Study of the bond angle

When the drug is optimized with Graphene, bond angle of graphene and drug do not change.

The interaction energy of the Graphene and 5-fluorouracil molecules

Considering the advantages of density functional theory (DFT) in calculating of the amount of molecules' energy with molecular correlation, energy of 5-fluorouracil drug and functionalized Graphene and Graphene molecules is given in Table (1).

Table 1. Energy of Primary molecules by Harter (H)

Combined	5-fluorouracil	Graphene
The combined energy H	514.17763006	3673.3925367-7

After optimization of all configurations in different states of 5-fluorouracil drug along with graphene, adsorption energy for all configurations of graphene and drug molecules can be calculated using the following equation:

$$E_{gd} = E_{(g-drug)} - \{E_g + E_{drug}\}$$

In this equation, E_{gd} refers to the absorbing energy of drug and graphene graphene molecules in the desired configuration, E_g refers to the energy of a graphene molecule, E_{drug} refers to the energy of drug and E (g - drug) is the energy of drug and Graphene complex. In Table 2, the calculated energy values in this way have been listed..

Table 2. E_{com} and E_{gd} values in ev for complex compounds of 5-fluorouracil drug and Graphene (G-F), in theory level of B3LYP / 6-311G *

Complex	Ecom(H)	Ecom (ev)	Egd(ev)
G-F	-4187.57373222	-113952.256401171	-0.09702

Also in this table the amount of energy adsorption is -1.4523561ev. Since the amount of physical adsorption energy at room temperature is in this range, therefore, adsorption in this complex occurs physically.

Density of states (DOS)

So, to review and approve the obtained results in this section, diagram of density of states (DOS) will be examined.
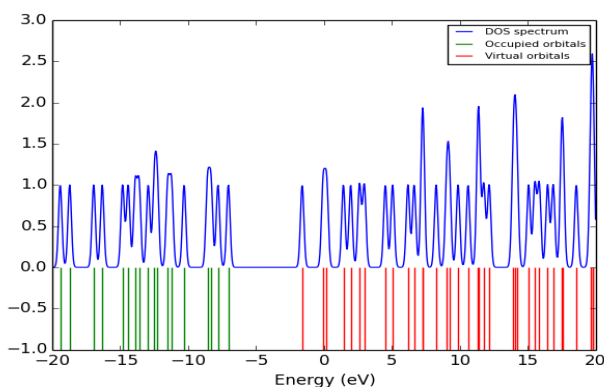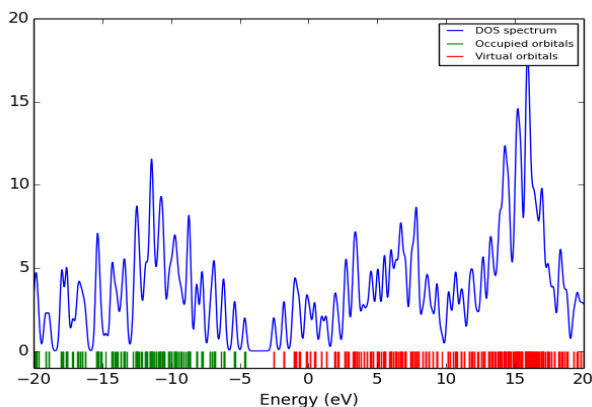
Fig. 4. Dos graph for 5-fluorouracil drug.
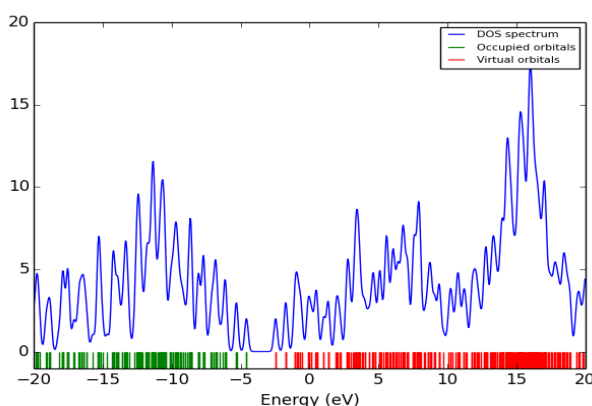

Fig. 5. Dos graph for Graphene

Fig. 6. Dos graph for 5-fluorouracil drug- Graphene complex.

Electrical dipole moment

Polarity is one of the important properties of chemical bonds. If the electronegativity of two atoms that have covalently bond with together, not being equal, according to the principle of electronegativity equality, bonding electrons are transported, so the centers of positive and negative charges in primary bonds are separated from each other, and bond becomes as an electrical dipole. Such a bond is called polar bond.

If the molecule is a poly-atomic molecule, it can be identified that molecule is polar or non-polar by the use of the resultant dipole moment. Since the most of bonds interface between pure ionic and pure covalent bonds, as a result, to determine the nature of bonds in a molecule, a molecular dipole moment was used. If the difference in electronegativity between atoms being larger, so covalent bond will become most polar, and will have more interactions with environment. Amount of dipole bonding, is expressed by dipole moment; the dipole moment is degree of separation of positive and negative electrical charges in the system. In fact, it is the size and amount of the total polarity of system and its unit is charge* distance .

$$\mu = Q * r$$

In this equation, μ refers to the dipole moment, Q is the size of two equal charges with different symbols, and r refers to the distance between two charges. Based on the contract, unit of dipole moment is Debye (D), that is equal to $1D = 3.36*10^{-30}$ cm. Electric dipole moment is one of the most important properties of molecules, that gives very important information about the geometry and electronic structure of molecules [9].

Values of electrical dipole moment μ based on Debye were measured for Graphene - drug complex and Graphene, and these values have been reported in the following tables, respectively.

Table 3. The amount of dipole moment in Debye

Compound	Dipole moment in Debye
Flu	3.9704
Gr	0.0012
Gr-Flu	3.4431

Study of Mulliken atomic charges

Electrostatic properties of a molecule can refer to the distribution of electrons and nuclei, thus, partial atomic charge can be calculated by using quantum mechanics. One way for calculation of partial atomic charge by the use of quantum mechanics, is Population Analysis method. The set of charges that obtained by this method, has called Mulliken charges. After the drug connected to the dendrimers, the atomic change distribution on the atoms will be charge. For this purpose, Mulliken atomic charge were calculated before and after binding of drugs to the dendrimer, and it was reported in the following tables.

Table 4. Distribution of Mulliken atomic charge in e for Graphene complexes.

Compound	Partial charge of Graphene	Partial charge with drug
Gr-Flu	-0.763	0.763

Since the direction of charge transfer is from positive to negative, so it was observed that the direction of charge transfer in all combinations will be from Graphene to drug. Also, transfer of partial load, confirms little shifts in the spectrum of density graph mode.

Molecular orbitals and the energy gap

Molecular orbital perturbation theory includes the concept of border orbitals control. According to this concept, the most important interactions are between a pair of special orbitals (Highest Occupied Molecular Orbital, HOMO, and Lowest Unoccupied Molecular Orbital, LUMO). Because these orbitals, have the closest energy with each other among reactant orbitals. According to a postulate of the molecular orbital perturbation theory, interaction between orbitals depends on the relative energy, this means that whatever they become closer together in terms of energy, the interaction between orbitals will be stronger. Furthermore, when the spacing of energy in border orbitals decrease, their overlap of wave functions because of external field will increases, and their role in the molecular processes as electron transfer and interaction with the external field will increase, too. As a result, their mutual interaction will increase [10].

The distance of molecular orbital of (HOMO) from molecular orbital of (LUMO) is called HLG briefly, (HLG = ELUMO - EHOMO), HLG is an excellent way to determine the properties and characteristic as a results of electron transfers. Also the energy of outermost molecular orbitals include HOMO, LUMO and amounts HLG, which are the basic parameters for determining the molecular conductivity. Value of electronic energy of molecular orbitals such as HOMO, LUMO, slot energy of (HLG) for the Graphene, was recorded in the following tables.

Table 5. The values of HOMO, LUMO energy and slot energy of HLG (eV) in theory level of B3LYP / 6-311G *

Compound	EHOMO	ELUMO	HLG(ev)
Gr-Flu	-0.05251	0.146672	0.19919184

CONCLUSIONS

In summary, we investigated the structural and electronic properties of 5-fluorouracil drug molecule through interaction with the graphene based on the first principle density functional theory calculations.in this study, We used B3LYP method and 6-311G* basis set. It was found that the 5FU can be physically adsorbed upon graphene with the energy value of -0.097.

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