IIETA International Information and Engineering Technology Association
Advancing the World of Information and Engineering

Journal of New Materials for Electrochemical Systems
Vol. 25, No. 4, October 2022, pp. 234-239
Journal homepage: http://iieta.org/journals/jnmes

A DFT study of Graphene as a drug carrier for gemcitabine anticancer drug

Abdulaziz A. M. Abahussain[1], S.Z.J. Zaidi[2,*],M.H.Nazir [3], M.Raza[3], M.H. Nazir[4] S. Hassan[5]

[1]Department of Chemical Engineering, King Saud University, Riyadh, Saudi Arabia
[2,3]Laboratory for Energy Water and Healthcare Technologies, Institute of Chemical Engineering and Technology, University of the Punjab, 54000, Lahore, Punjab, Pakistan
[4]Faculty of Computing Engineering and Sciences, University of South Wales, United Kingdom
[5] Department of Mechanical Engineering, University of Hong Kong, Hong Kong

Corresponding Author Email: zohaib.icet@pu.edu.pk

https://doi.org/10.14447/jnmes.v25i4.a02

Received: March 20-2022
Accepted: September 15-2022

Keywords:
gemcitabine, graphene, density functional theory,drug delivery

ABSTRACT

Research is being carried out worldwide for possible treatment of cancer. Graphene has been studied as a drug carrier for various cancer-related drugs [1-2]. In the present work, we apply theoretical models to study the electrons interactions, thermodynamic properties, and solvent interaction of the drug-carrier configuration. The stability of graphene means that it can be a nanocarrier in the biological system. The simulations result shows that graphene provides a stable base, where gemcitabine is a highly dissolvable and reactive drug. The adsorption of gemcitabine on the graphene was physical. The drug carrier configuration formed a highly impactful drug-carrier design.

1. INTRODUCTION

Cancer is a group of diseases that involve abnormal cell growth in the body of a host with the potential to invade or spread to other parts of the body [3-4]. Cancer is the cause of a huge number of deaths annually all over the world. Recently, advances have been made in using graphene and graphene-based compounds for the treatment, detection, and chemotherapy drug delivery system designs for cancer [5-7]. In various treatment methods, from regenerative medicine to therapeutical medicine, graphene has been studied widely due to its wide set of properties like excellent physicochemical, electrical, large surface area, and biocompatibility [8-10]. Gemcitabine, the anticancer drug, is used in chemotherapy for the chemotherapy of various cancers such as breast cancer, pancreatic bladder, tumor, and lung cancer [11].

Gemcitabine works by incorporating itself in the DNA of the cancer cell and inhibiting its growth, When DNA is rewritten, gemcitabine is mistakenly incorporated into the DNA of the structure instead of the cytosine nucleoside as it does not mate with other nucleosides [12-14]. The use of a prodrug strategy improves selectivity while also improving bioavailability for the intended target and in chemotherapy, this strategy may also decrease cytotoxicity [15-16]. Gemcitabine is a hydrophilic drug, which means it dissolves easily in water, this leads towards a high degree of dissolvability and disassociation in the biological setting of the human body [17-18].

As gemcitabine is highly hydrophile and reactive, it means for the drug to have a high impact on the targeted area, it needs a stable delivery system that will protect the drug from degradation before it reaches its target area. For the drug delivery system graphene has been widely reported to be used as a safe and stable method, as it is biocompatible which means it does not have an effect on the biological features of the human body [19-23].

The density function theory (DFT) is a quantum mechanical computing method that is mainly used to study electronic structures in the fields of chemistry, physics, and material sciences [23-25]. The DFT has also been used to study various cancer-related drugs their treatment, delivery systems, and increase efficiency [26-27]. These DFT studies also include graphene and graphene-related compounds specific to cancer drugs [28-29].

We used the DFT computational method X to evaluate the performance of graphene as a drug delivery method for gemcitabine anti-cancer. The simulation was carried out using Gaussian 09 software, with 6-31g(d) B3LYP was used as basis sets for the electronic evaluation and AM1 semi-empirical basis sets for the thermodynamic evaluation of the configured graphene-gemcitabine structure. The stability and biocompatibility of graphene protect gemcitabine, which is hydrophilic, from dissolving in the water solvent to deliver the anticancer drug at the targeted area.

2. SIMULATION DESIGN

Multiple simulations were run to study graphene as a carrier for gemcitabine. First, the structures of graphene and gemcitabine under study as shown in Figure 1(a) and 1(b) were geometrically optimized to a minimum. The basis set model used was 6-31g(d) with B3LYP. The non-polar basis was selected for the optimization of graphene. Vibrational Frequencies were calculated at the same level that the optimized geometries are at true local minima

The Hartree-Fock theory was used to evaluate the optimization of both graphene and gemcitabine. The functionals normally used in density functional theory are

integrals of some function of the density and possibly the density gradient:

$$EX[P] = \int f(\rho\alpha(r),\rho\beta(r),\nabla\rho\alpha(r),\nabla\rho\beta(r))dr \qquad [30\text{-}31]$$

where the methods differ in which function f is used for EX and which (if any) f is used for EC. This model with the specific basis set shows the most accurate result.

Then, the graphene-gemcitabine as shown in Figure 1(c) is optimized using the same model and basis set. Water is introduced in the model as a solvent to simulate real-life biological conditions of the human body. This model also helps in evaluating the structural density of electron in the whole molecule.

2.1 Different Values Calculations

The $E_{homo\text{-}lumo}$ gap is calculated by subtracting E_{homo} and E_{lumo}. The adsorption energy E_{ad} is calculated as:

$E_{ad} = E_{nanostructure} - E_{nanostructure\ complex}$

Where $E_{nanostructure}$ is the energy of the studied nanostructure and $E_{nanostructure\ complex}$ is the energy of the studied complexes.

Furthermore, different thermodynamic values given in table 2 are evaluated by using the Semi-Empirical model with AM 1 as a basis set. Moreover, the Frequency with the same model and basis set is used to get multiple thermodynamic values.

3. RESULTS AND DISCUSSION

The DFT calculations performed will be extremely relevant to diagnose the potential applications of graphene as efficient Carrier for targeted drug delivery including Gemcitabine anticancer drug. Figure 1 shows graphene and gemcitabine's initial and optimized structure. There were a total of 9 intermediate geometries observed for graphene and a total of 34 intermediate geometries observed for gemcitabine. The final optimized structures were used to study the effectiveness of graphene as a delivery method for gemcitabine.

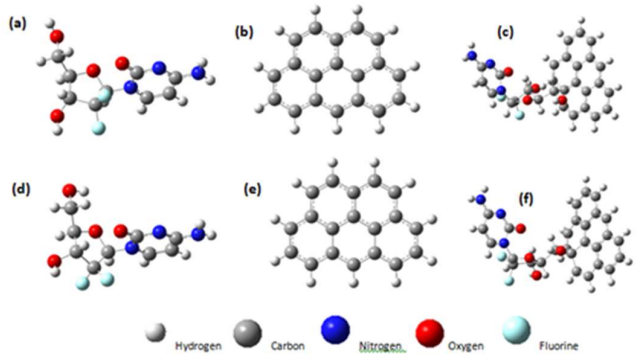

Figure 1. Initial structures and final optimized geometries a, gemcitabine initial geometry b, Graphene Initial Geometry c, Optimized structures of graphene and gemcitabine forming the delivery system d, optimized geometry of gemcitabine e, optimized structure of graphene f, the optimized structure of drug delivery system with graphene as delivery base

3.1 Study of the initial geometries

The initial structures and final optimized structures of all the studied complexes are shown in Figure 1. We can see from the Figure 1b and e that graphene during its optimization remains fairly stable throughout the whole simulation. This stability retained throughout the whole process means that graphene is non-volatile, which makes it extremely useful as a delivery base. Because it means that it will not interact with the cells in the human body or change their chemistry or have any negative effect. It will also protect gemcitabine from degradation before it reaches its destination. The graphene and gemcitabine form a bond through the attraction of highly negative oxygen atom with a carbon of graphene.

When gemcitabine is optimized, it shows significant changes with some bond changes, as can be seen in fig 1 a and c. This shows the volatile nature of the compound. From Figure 1 c and f, we can see that the designed delivery system goes through some very significant changes in the form of bonds breakage and also bond length changes. The complex shown in Figure 1 c was optimized in the presence of water as a solvent. The graphene remains stable as a drug carrier, but the volatility of gemcitabine means it is highly soluble in water. It also tells us about gemcitabine's reactivity. The simulated results show that in the presence of water as a solvent, the reactivity of gemcitabine increases, where graphene provides a stable delivery method while reducing its degradation during the delivery, gemcitabine in a biological setting in presence of water increases its reactivity which is also noted in table 1. Table 1 shows first the adsorption energy of gemcitabine when it does not have a delivery method and then it shows adsorption energy when water is used as a solvent and graphene is used as a drug delivery method. The whole provides an excellent working condition for gemcitabine to show its whole potential as a cancer drug.

Table 1. Energy Table

Name	E_{homo}	E_{lumo}	$E_{homo\text{-}lumo}$	E_{ad}
Unit	hartree	hartree	hartree	kJ/mol
graphene	-0.14742	-0.04713	0.10029	-47.657
gemcitabine	-0.20742	-0.03524	0.17218	-41.262
Graphene-gemcitabine	-0.14453	-0.04090	0.10363	-145.48

Figure 2 shows various electronic properties of graphene and gemcitabine from HOMO and LUMO orbitals to charge distribution.

These various properties showed in Figure 2 will help us evaluate the configuration of our graphene-gemcitabine. The charge distribution and charge on each atom of graphene and gemcitabine are shown in Figure 2a and e. Gemcitabine has highly negative oxygen, whereas the charge distribution of graphene is fairly evenly distributed. Highly negative from the inside and highly positive as we move away from the center. This means a fairly stable configuration will be the introduction of gemcitabine on graphene from its highly negatively charged oxygen. Even though gemcitabine overall shows almost no polarity, but we can use the highly negative oxygen to configure our design.

The HOMO of gemcitabine is shown in Figure 2b, the electron distribution is high on the lower side of the molecule, the red area shows where electrons concentration is very high and green which represents extremely low electronic concentration.

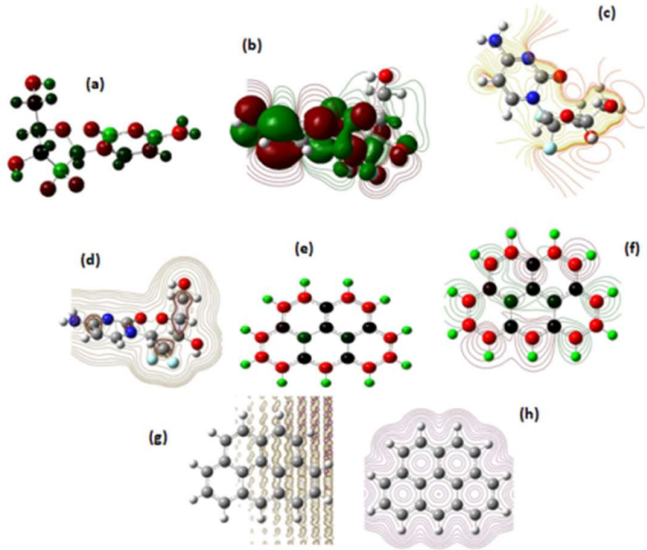

Figure 2. Evaluated electronic properties of graphene and gemcitabine a, Charge distribution on gemcitabine b, HOMO of gemcitabine c, LUMO orbital of gemcitabine d, Laplacian occupied orbital of gemcitabine e, Charge distribution on graphene f, HOMO of graphene g, Laplacian occupied orbital of graphene h, LUMO of graphene

Where from Figure 2f, we see again a highly stable distribution of electrons, this means that graphene will be a highly excellent base for highly reactive gemcitabine.

Figure 2d and g show us the Laplacian occupied orbitals for gemcitabine respectively. The Laplacian contour for the occupied orbitals was carried out for both. The l

Laplacian contour here tells us the divergence of gradient on Euclidean space. It means that it will tell us where the electrons will be during the whole process. Here, graphene shows perfect symmetry which further supports our conclusion that graphene is highly stable, whereas gemcitabine shows a highly divergent result, which shows the volatility and reactivity of graphene. It all shows that the stability of graphene combined with gemcitabine has the potential to be a highly effective drug delivery system for various treatments.

3.2 Graphene-gemcitabine configuration electronic and orbitals

The various properties related to electronic interactions are shown in Figure 3 and the bond length of optimized gemcitabine is shown in Figure 4. The charge distribution changes when graphene and gemcitabine configure is optimized with water as the solvent. This change in the overall charge distribution may be due to graphene stabilizing gemcitabine in a water environment. As we have noted before, in the presence of water, the dissolvability, and reactivity of gemcitabine increases. This charge distribution shows that the whole configuration is trying to stabilize itself. The same can be seen in Figure 3 b wherein HOMO the electron density is highly configured towards graphene in the whole configuration. Figure 3 c shows the Laplacian contour of LUMO of the configuration. The weird static-like gold color shows that the LUMO is not static, but very mobile. Figure 4 shows the bond length at various points in the configuration.

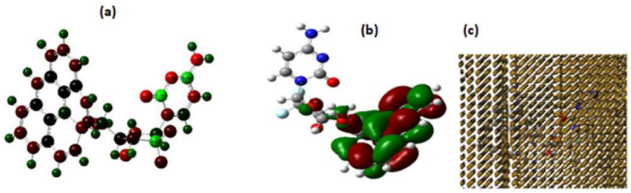

Figure 3. Graphene-gemcitabine configuration charges and orbitals a, Charge distribution on the graphene-gmcitabine b, HOMO of the configuration c, LUMO Laplace contour of the configuration

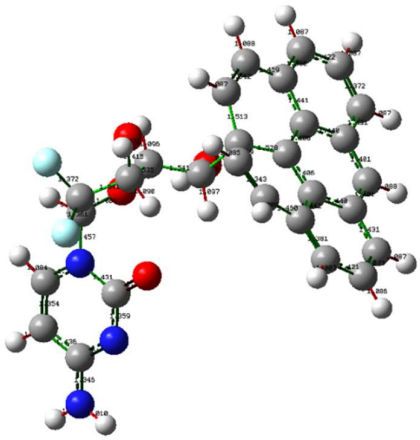

Figure 4. Atomic bond lengths in the configuration

3.3 Energy, forces and displacements

Figure 5 shows the total energy, various forces, and displacement at each intermediate geometry or optimization step of graphene, gemcitabine, and graphene-gemcitabine configuration all plotted together. One thing that can be noted is graphene has way less intermediate geometries as compared to gemcitabine and the configuration which have 34 and 31 configurations respectively. The less intermediate geometries that are seen in graphene-gemcitabine configurations are due to introduction of graphene in the configured design of our delivery method which results in increased stability of the whole configuration. The total energy for all three is on a decreasing trend as shown in Figure 5a

All Figures show a stable and decreasing trend except for Figure 5c and 5e, where gemcitabine and graphene-gemcitabine show a volatile trend, an up and downtrend, whereas graphene is still on a steady decreasing trend with each stable. This further enforces our conclusion that graphene is a point of stability for the whole configuration. The max and RMs internal displacement shown in Figure 5c and 5e respectively show how many electrons change their positions relative to the center of atom or molecule.

This means that graphene-gemcitabine configured structure is highly volatile and has high reactivity in a water environment, while all the other Figures show a stable decreasing trend, the drug delivery system lower total energy at each step, while a volatile internal displacement means that it can be fairly concluded that it will deliver a stable highly effective dose at the targeted area. The various thermodynamics properties are noted in Table 2.

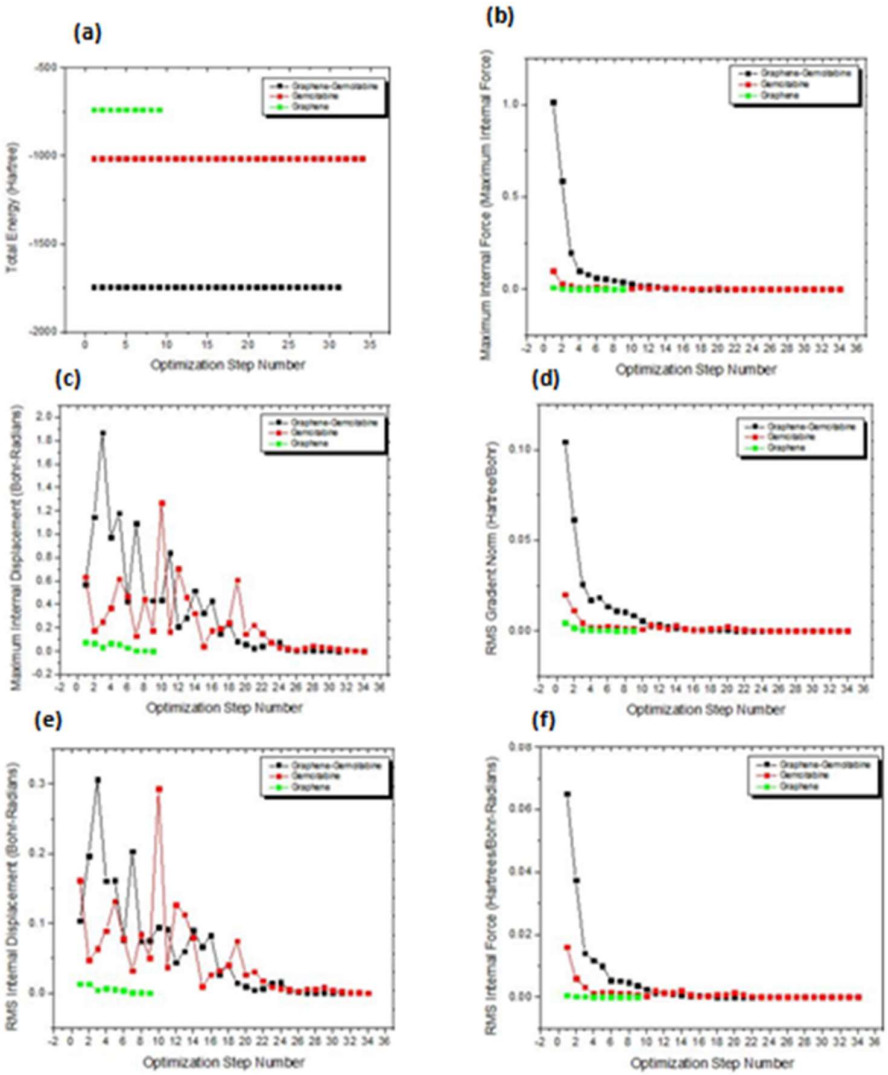

Figure 5a. Total energy graph at each optimization step for graphene, gemcitabine, and graphene-gemcitabine configuration b, Max internal force of all three c, Max internal displacement d, RMS gradient e, RMS internal displacement f, RMS internal force

Table 2. Theoretical thermodynamics properties at standard temperature and pressure

Compound		Quantity	Value in kcal/mol
Graphene	G		-2.09
	H		-2.64
	E		2.63
Gemcitabine	G		-1.938
	H		-2.466
	E		2.4566
Graphene-gemcitabine	G		-4.256
	H		-5.026
	E		5.036

Here G is gibbs free energy, H is Enthalpy and E is the thermal energy all expressed in kcal/mol.

4. CONCLUSION

In this paper, graphene was studied as a possible drug delivery method for the gemcitabine drug, where graphene becomes a base for the drug. The Gibbs free energy and Enthalpy are both decreasing from their stand-alone compound in the graphene-gemcitabine configuration as shown in Table 2. This means that the process is reversible which can lead to the conclusion that when gemcitabine reaches the targeted area, the configuration splits up and gemcitabine is delivered. The graphene here has a dual usage. It not only protects gemcitabine from degradation in the water solvent, which was used to simulate real biological conditions of the human body, but it also reduces gemcitabine's reactivity before it reaches the target area. While graphene highly stable structure has also been evaluated in the paper, this stability means that graphene does not interact with the cells in our body or disturbs the biological function in any way. In our current studied configuration, graphene acts as a carrier for our drug delivery system, without disturbing or affecting any of the surroundings. Thus it can be reasonably concluded that the drug delivery design in the paper which is studied can be a highly effective and efficient form. The paper will hopefully

lead to experimental studies of the result that is concluded in the paper.

REFERENCES

[1] Cheung, F., 2020. Engineering of new graphene-based materials as potential materials to assist near-infrared photothermal therapy cancer treatment, Heliyon, 6(6), 04131.

[2] Majidi, R, and Nadafan, M., 2020. Detection of exhaled gas by γ-graphyne and twin-graphene for early diagnosis of lung cancer: A density functional theory study, Physics Letters A, 384(1), 126036.

[3] The National Cancer Institute.2015. What is Cancer?

[4] Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C et al., 2013., Cancer Incidence and Mortality Worldwide, International Agency for Research on Cancer, GLOBOCAN,1.

[5] Deepa, Nohwal, P and Pundir, CS., 2020. An electrochemical CD59 targeted noninvasive immunosensor based on graphene oxide nanoparticles embodied pencil graphite for detection of lung cancer, Microchemical Journal, 156, 104957.

[6] Molaei, M., 2020. Two-dimensional (2D) materials beyond graphene in cancer drug delivery, diagnosis, photothermal and photodynamic therapy, recent advances and challenges ahead: a review, Journal of Drug Delivery Science and Technology, 1010838.

[7] Ruiyi, L, Tinling, P, Hongxia, C, Jinsong, S and Zaijun, L., 2020. Electrochemical detection of cancer cells in human blood using folic acid and glutamic acid-functionalized graphene quantum dot-palladium@gold as redox probe with excellent electrocatalytic activity and target recognition, Sensors and Actuators B: Chemical, 309, 127709.

[8] Kenry, Lee, W, Loh, K and Lim, C,. 2018. When stem cells meet graphene: Opportunities and challenges in regenerative medicine, Biomaterials, 155, pp. 236-250.

[9] Orsu, Prabahakar, Koyyada and Arun., 2020. Recent progresses and challenges in graphene based nano materials for advanced therapeutical applications: a comprehensive review, materialstodaycommunications, 22, 100823.

[10] Raslan, A, Saenz del Burgo, L, Ciriza, J and Pedraz, J., 2020. Graphene oxide and reduced graphene oxide-based scaffolds in regenerative medicine, International Journal of Pharmaceutics, 580, 11926.

[11] Tsume, Y, J. Drelich, A, E. Smith, D and L. Amidon, G., 2017. Potential Development of Tumor-Targeted Oral Anti-Cancer Prodrugs: Amino Acid and Dipeptide Monoester Prodrugs of Gemcitabine, Molecules, 22, 1322.

[12] Saliev, T., The Advances in Biomedical Applications of Carbon Nanotubes., 2019. The Advances in Biomedical Applications of Carbon Nanotubes, Journal of Carbon Research, 5(29).

[13] Cerquira, N.M, Fernandes, P.A, and Ramos, M.J., 2007. Understanding Ribonucleotide Reductase Inactivation by Gemcitabine, Chemistry Europe, 13(30), pp. 8507-8515.

[14] Federico, C, Morittu, V.M, Britti, D, Trapasso, E and Cosco, D., 2012. Gemcitabine-loaded liposomes: rationale, potentialities and future perspectives, International Journal of Nanomedicine, 7, pp. 5423-5436.

[15] Kakwere, H, Ingham, E.S, Tumbale, S.K, and Ferrara, K.W., 2020. Gemcitabine-retinoid prodrug loaded nanoparticles display in vitro antitumor efficacy towards drug-resilient human PANC-1 pancreatic cancer cells, Materials Science and Engineering: C, 117, 111251.

[16] Zhang, H.T, Sun, J, Yan, Y, Cui, S.H, Wang, H, Wang, C.H, Qui, C, Chen, X, Ding, J.S, Qian, H.G, Wang, J.C and Zhang, Q., 2019. Encapsulated microRNA by gemcitabine prodrug for cancer treatment, 316, pp. 317-330.

[17] Mini, E, Nobili, S, Caciagli, B, Landini, I and Mazzei, T., 2006. Cellular pharmacology of gemcitabine, Annals of Oncology, 7(12).

[18] Alvarellos M.L, Lamba J, Sangkuhl K, Thorn C.F, Wang L, Klein D.J, Altman R.Band Klein T.E., 2014. PharmGKB summary: gemcitabine pathway, Pharmacogenetics and Genomics, 24(11), pp.564-574.

[19] Deb, A and Vimala, R., 2018. Camptothecin loaded graphene oxide nanoparticle functionalized with polyethylene glycol and folic acid for anticancer drug delivery, Journal of Drug Delivery Science and Technology, 43, pp.333-342.

[20] Shahabi, M and Raissi, H., 2020. Payload delivery of anticancer drug Tegafur with the assistance of graphene oxide nanosheet during biomembrane penetration: Molecular dynamics simulation survey, Applied Surface Science, 517, 146186.

[21] Rahimi, R and Solimannejad, M., 2020. BC3 graphene-like monolayer as a drug delivery system for nitrosourea anticancer drug: A first-principles perception, Applied Surface Science, 525, 146577.

[22] Wang, Y and Wang, C., 2020. Self-assembly of graphene sheets actuated by surface topological defects: Toward the fabrication of novel nanostructures and drug delivery devices, Applied Surface Science, 505, 144008.

[23] Shariatinia, Z and Jalali, A.M., 2020. Molecular dynamics simulations on chitosan/graphene nanocomposites as anticancer drug delivery using systems, Chinese Journal of Physics, 66, pp. 362-382.

[24] Garip A.K, Arslan, H, Rapetti, D and Ferrando, R., 2020. A DFT study of chemical ordering and oxygen adsorption in AuPtPd ternary nanoalloys, materialstodaycommunications, 25, 101545.

[25] Liu, J, Ling, M and Xie, H., 2020. Mechanisms of chemoselectivity for acyl and decarbonylative Suzuki–Miyaura coupling of N-acetyl amide with arylboronic acid catalyzed by Pd and Ni catalysts: Insights from DFT calculations, Computational and Theoretical Chemistry, 1185, 112889.

[26] Mahmoud, W.H, Deghadi, R.G and Mohamed, G.G., 2020. Cyclometalated complexes containing ferrocenyl Schiff base: Preparation, characterization, DFT calculations, application in cancer and biological researches and MOE studies, Arabian Journal of Chemistry, 13(5), pp. 5390-5405.

[27] Hesabi, M, and Ardakani, R.B., 2017. Interaction between anti-cancer drug hydroxycarbamide and

boron nitride nanotube: A long-range corrected DFT study, Computational and Theoretical Chemistry, 1117, pp. 61-80.

[28] Begum, S.S, Gour, N.K, Sonavane, U, Ray, S.K and Deka, R.C., 2019. Computational studies of anti-cancer drug mediated by graphene and reaction mechanism of drug generated alkyl radical with guanine, Journal of Molecular Structure, 1196, pp. 527-535.

[29] Anota, E.C, Morales, A.E, Villanueva, M.S, Cuchillo, O.V and Rosas, E.R., 2012, On the influence of point defects on the structural and electronic properties of graphene-like sheets: a molecular simulation study, Journal of Molecular Modeling, 19, pp. 839-846.

[30] Hohenberg, P and Kohn, W., 1964. Inhomogeneous Electron Gas, Physical Review Journals, 136, B864.

[31] Becke, A.D,. 1992. Density ‐ functional thermochemistry. I. The effect of the exchange ‐ only gradient correction, The Journal of Chemical Physics, 96, 2155.