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ORIGINAL ARTICLE

Adsorption of ibuprofen by an iron-doped silicon carbide graphene monolayer: DFT exploration of drug delivery insights

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Abstract

Drug delivery insights were provided by performing density functional theory (DFT) calculations to investigate the adsorption of a non-steroidal anti-inflammatory drugs; ibuprofen (IBU), by an iron-doped silicon carbide (FSiC) graphene monolayer. In this regard, the single models of IBU, SiC, and FSiC were optimized to obtain their stabilized geometries and features, in which a remarkable achievement was found for the enhanced FSiC graphene monolayer towards the original SiC graphene monolayer for interacting with the IBU substance. Subsequently, the formation of interacting complex of IBU and each of SiC and FSiC graphene monolayers was investigated by re-optimizing the bimolecular models to obtain IBU@SiC and IBU@FSiC complexes with interaction energies of -1.44 kcal/mol and -43.14 kcal/mol, respectively. Additionally, a remarkable role of iron-doped region for managing the interactions between FSiC and IBU counterparts was found. The existence of O...Fe interaction in the formation IBU@FSiC complex was affirmed by the results of quantum theory of atoms in molecules (QTAIM) analyses. The electronic molecular orbitals results indicated a softer FSiC graphene monolayer than SiC graphene monolayer for a better participation in interactions with the IBU substance. Comparing the changes of density of states (DOS) diagrams and energy gap (GAP) distances of frontier molecular orbital levels from the single graphene monolayer to the complex state have been revealed an easier IBU detection by the FSiC than the SiC. As a final note, a suitability of IBU@FSiC complex formations was found for working as a proposed drug delivery platform upon further investigation in this field.

Keywords: *DFT; Drug delivery; Graphene Monolayer; Ibuprofen; Molecular Interaction.*

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INTRODUCTION

The appearance of new and wild diseases needs a non-stop investigation on the medical design and developmental efforts [1-3]. Although several medicinal treatments have been proposed and employed up to now, but the medications have not been certain yet [4-6]. In this case, the roles of non-steroidal anti-inflammatory drugs; or NSAIDs, are vital in treatments of different patients by reducing the levels of inflammation, pain, and fever [7]. Although so many efforts have been done to customize NSAIDs with the minimum side effects, but there are still serious signs of side effects for the patients regarding their consumption dosage and duration requiring further investigations [8-10]. Inhibiting the activity of overexpressed cyclooxygenase (COX) enzymes is the main therapeutic role of NSAIDs, in which the identification of this target could help to provide a better environment of ligand-target interaction occurrence [11-13]. To this aim, setting up an appropriate drug delivery platform could carry the uploaded drug up to a correct target to improve the drug efficacy besides reducing the adverse side effects because of drug interaction by other unspecified targets [14-16]. In this case, learning details of interactions between a drug and an adsorbent could help to investigate benefits of adsorbents for working as possible drug carriers

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of complicated drug delivery platforms [17-19]. Earlier works indicated benefits of employing computational chemistry tools for assessing the variations of structural and electronic features of chemical substances especially for the drugs through the adsorption process by the adsorbent to see the possibility of proposing a customized platform [20-22]. Accordingly, density functional theory calculations (DFT) calculations were performed in this work for exploring insights into the drug delivery of ibuprofen (IBU) by an iron-doped silicon carbide graphene monolayer (FSiC). Indeed, the availability of a suitable surface area made the nanostructures very useful adsorbents for interacting with other substances and counterparts even with the drug substances [23-25]. By the identification of various types of nanostructures after the innovation of pioneering carbon nanotubes, graphene monolayers have been found as an independent category of single-standing nanostructures with suitable surface areas [26-29]. Although graphene has been found as the leading monolayer, but the combination of other atoms has been also found as the other graphene-like monolayers [30]. Since both of carbon and silicon atoms are located in the same group of elements, their combination has been already investigated for introducing new hetero-atomic nanostructures [31]. Additionally, inserting the iron atom in the composition of nanostructures has been found very important for improving the semi-conductivity of graphene monolayer [32-34]. As a consequence, the adsorption of IBU drug by such an enhanced FSiC graphene monolayer was investigated in the current work for customizing a new drug delivery platform.

After the innovation of nanostructures, and due to the complexity of these novel structures, several efforts have been dedicated to learn various aspects of nanostructures especially regarding their applications in the biological related systems and environments [35-38]. In both cases of single-standing and combinations with other substances, nanostructures have been seen as very important materials for providing specific and targeted applications [39-42]. Accordingly, several modes of biological and biomedical applications have been developed for the nanostructures up to now [43-46]. In the case of drug issues, investigating interactions of drug-nanostructure complexes was found very important for providing insights into the drug delivery platforms, in which the existence of covalent and non-covalent interactions should be known to see the availability of irreversible and reversible drug delivery processes [47-49]. To obtain such an important issue, a careful investigation of drug-nanostructure interaction should be done to find the information of existing interactions for proposing the applicability of investigated platforms [50-52]. Accordingly, the current work was done by optimizing the single and double molecules to find their features for approaching a reliable state of generating the required information for the purpose. After optimizing the structures, the evaluated structural and electronic features were used to analyze the models to show the impacts of adsorption process on both of IBU and FSiC counterparts. The “recovery time” and “conductance rate” terms; as important parameters to be learned for recognizing the sensing function of an adsorbent, were assessed for the models accordingly [53]. Hereby, the drug delivery insights were explored in this work using the DFT-evaluated features of adsorption of IBU drug by an enhanced FSiC graphene monolayer.

MATERIALS AND METHODS

The wB97XD/6-31G* DFT calculations were performed for the investigated models of this work using the Gaussian program [54]. To this point, the single models were prepared as the molecular models of IBU and the FSiC, in which the original SiC model was also investigated for making a comparison of SiC and FSiC graphene monolayers for adsorbing the IBU drug substance. The optimized geometries of single models were shown in Fig. 1. The interactions of IBU and each of SiC and FSiC graphene monolayers were investigated by performing optimization calculations of double molecular models of IBU@SiC and IBU@FSiC complexes to approach their minimized energy states. The double or bimolecular models were obtained based on their suitable interacting configurations as shown in Fig. 2. In addition to obtaining the structural geometries and configurations, the quantum theory of atoms in molecules (QTAIM) analyses were performed to learn interactions details of IBU@SiC and IBU@FSiC complexes [55]. Afterwards, the electronic features of frontier molecular orbitals (FMO) were evaluated based on the energy levels of HOMO and LUMO standing for the highest occupied molecular orbital and the lowest unoccupied

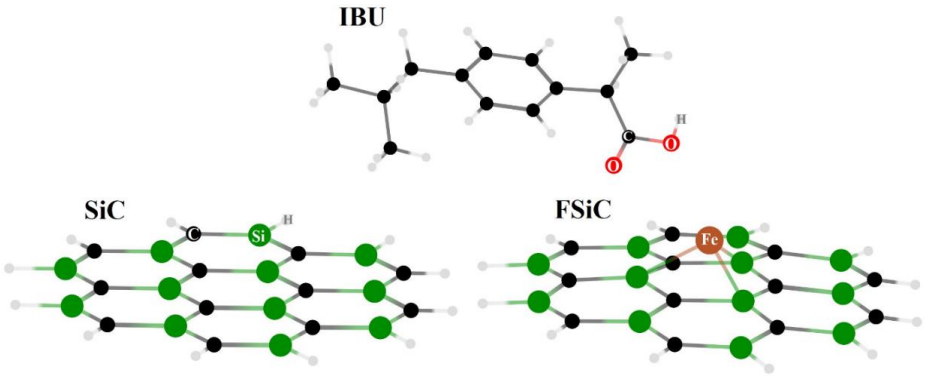

Fig. 1. Optimized forms for single models.

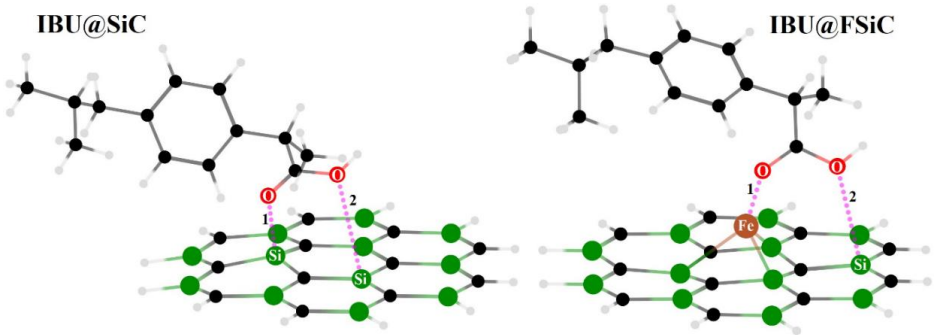

Fig. 2. Optimized forms for complexes.

Table 1. Interactions details of IBU@SiC and IBU@FSiC complexes.

Complex	Interaction	Distance (Å)	Rho (au)	Del²-Rho (au)	H (au)	E (kcal/mol)
IBU@SiC	1: O…Si	2.04	0.0521	0.1318	0.0098	-1.44
	2: O…Si	3.35	0.0075	0.0218	0.0001	
IBU@FSiC	1: O…Fe	1.81	0.1193	0.8411	-0.0168	-43.14
	2: O…Si	3.17	0.0088	0.0229	0.0004	

Distance, Rho, Del²-Rho, and H were calculated directly.

$E = E_{Complex} - E_{Monolayer} - E_{IBU} + BSSE$

molecular orbital. The interaction details of IBU@SiC and IBU@FSiC complexes were tabulated in Table 1 and the electronic molecular orbital parameters were tabulated in Table 2. Diagrams of density of states (DOS) and distribution patterns of HOMO and LUMO were graphically represented in Figs. 3 and 4. The main goal of this work was followed by the evaluated information for exploring the drug delivery insights through the interactions of IBU and each of SiC and FSiC graphene monolayers for proposing a customized platform along with DFT calculations. For better clarification of the calculations steps, it should be noted that the minimized energy states of geometries of single models were obtained by optimizations at the first step of calculations. Next, the double models were obtained by optimizing the combinations of IBU@SiC and IBU@FSiC complexes. Subsequently, performing additional analyses and data extractions yielded the structural and electronic features. Some of the obtained features were obtained directly whereas some of them were obtained using some formulas as presented in the footnote of each table. For

Table 2. Electronic molecular orbital parameters of single models and complexes.

Model	HOMO	LUMO	GAP	ΔGAP	CP	CH
	eV	eV	eV	eV	eV	eV
SiC	-5.40	-1.69	3.71	n/a	-3.54	1.85
IBU@SiC	-4.93	-1.74	3.19	-0.52	-3.33	1.59
FSiC	-4.46	-2.57	1.90	n/a	-3.52	0.95
IBU@FSiC	-4.22	-1.64	2.57	0.67	-2.93	1.29
IBU	-6.35	-0.12	6.23	n/a	-3.23	3.11

HOMO and LUMO were calculated directly.
GAP = LUMO – HOMO
ΔGAP = $GAP_{Complex}$ – $GAP_{Monolayer}$
CP = ½ (LUMO + HOMO)
CH = ½ (LUMO – HOMO)

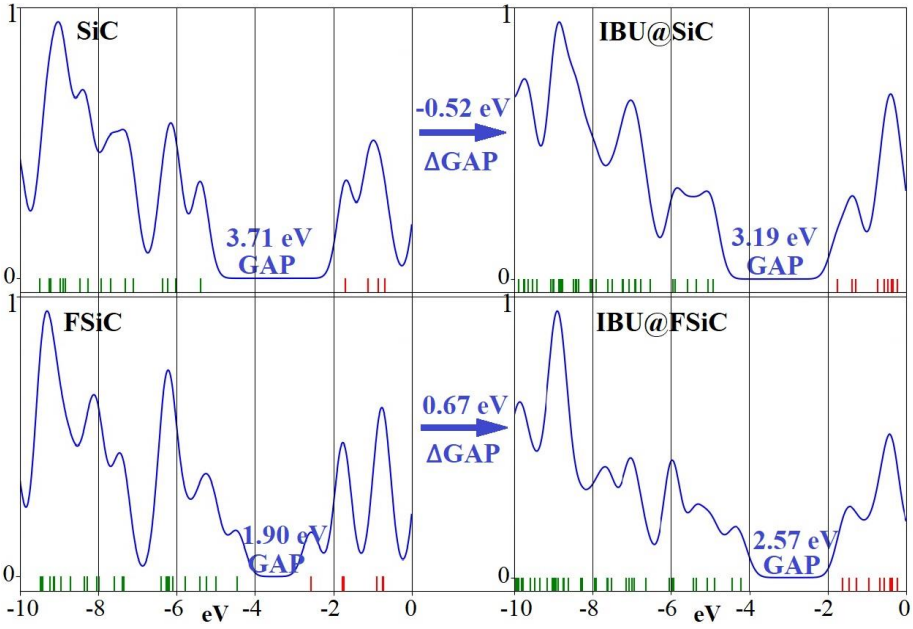

Fig. 3. Diagrams of DOS for graphene monolayers and complexes.

evaluating more reliable results of interaction energies, the basis set superposition error (BSSE) was also investigated within this work [56]. Indeed, the current work is a representative of those works employing the computational tools to solve the research problems in detailed clarifications [57-60].

RESULTS AND DISCUSSION

The results of performed DFT calculations were summarized in Tables 1 and 2 and Figs. 1-4 to approach the main goal of this work for exploring the adsorption of ibuprofen (IBU) by an iron-doped silicon carbide (FSiC) graphene monolayer regarding the drug delivery insights based on the evaluated structural and electronic parameters. The minimized energy structures of single models of IBU and SiC and FSiC graphene monolayers were obtained through the optimization calculations (Fig. 1). The IBU molecule ($C_{13}H_{18}O_2$) was containing the carbonyl and hydroxyl groups as the most probable sites of interactions with the other substances for this molecule. On the other hand, the graphene monolayers were including a combination of silicon and carbon atoms for the pure SiC graphene monolayer ($Si_{12}C_{12}H_{12}$) with an additional iron atom for the doped FSiC graphene monolayer ($FeSi_{12}C_{12}H_{12}$), in which the hydrogen atoms were included in the molecular structure for terminating the valance shells of edging

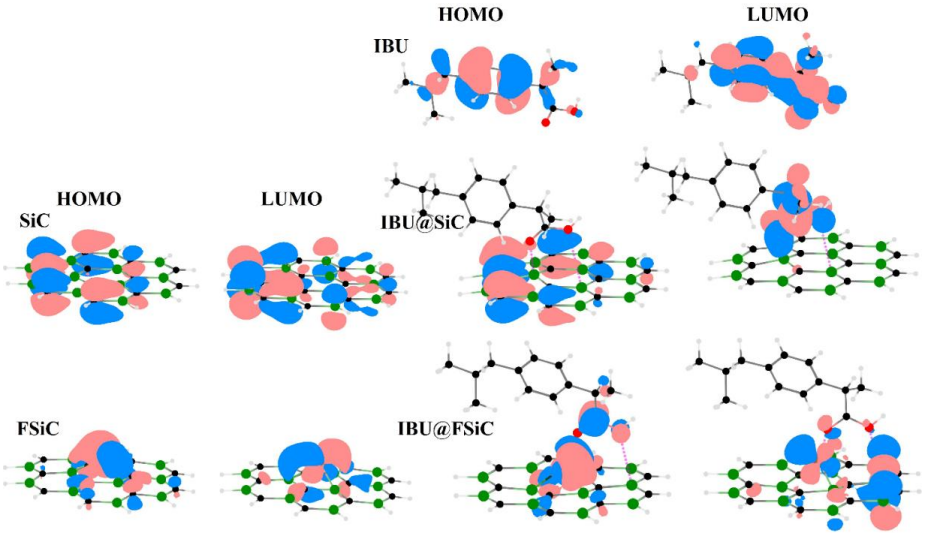

Fig. 4. Distribution patterns of HOMO and LUMO for single and complex models.

atoms. As could be found by the models of Fig. 1, the doped iron atom was working as a linker for connecting the FSiC and IBU counterparts and as a result of optimizing the bimolecular counterparts, the complexes of Fig. 2 were obtained. Examining the interactions between IBU and SiC yielded the IBU@SiC complex and the interactions between IBU and FSiC yielded the IBU@SFiC complex. Accordingly, the models were stabilized in a bimolecular configuration along with the existence of non-covalent interactions. In this case, both of carbonyl and hydroxyl groups were involving in interactions with both of SiC and FSiC graphene monolayers through two main types of O…Si and O…Fe interactions. To recognize such types of interactions, the QTAIM analyses were done to learn the existing interactions and their features as indicated by Rho standing for the total electron density, Del^2-Rho standing for Laplacian of electron density, and H standing for energy density for each of the involving interactions (Table 1). Additionally, the total energy term (E) of IBU and graphene monolayer interactions was also evaluated to indicate the total strength of complex binding and formation. Afterwards, HOMO and LUMO energy levels, GAP standing for the energy gap of HOMO and LUMO levels, ΔGAP standing for the difference of GAP values of complex and graphene monolayer, CP standing for the chemical potential, and CH standing for the chemical hardness were tabulated in Table 2 as the results of electronic molecular orbitals evaluations. In addition to the evaluation of quantities, the qualitative representations of DOS diagrams and distribution patterns HOMO and LUMO were shown in Figs. 3 and 4 to show the electronic features in a graphical way. Comparing the variations of models before the complex formation and after it could lead to the knowledge of molecular interactions impacts on the original features, in which learning such detailed information could be achievable by performing such atomic and molecular scales calculations. Indeed, both of structural and electronic features are very important as descriptors for determining the function of a molecular system and the variations of such features should be learned to propose a suitable platform for the investigated systems especially in the case of employing in the biological related systems.

The existence of two main interactions for the formation of each complex model was identified by the QTAIM results, in which two O…Si interactions were involving in the IBU@SiC complex and one O…Fe interaction and one O…Si interaction were involving in the IBU@FSiC complex. In this case, the models were in the interacting state to be stabilized towards each other in a non-covalent mode of interacting counterparts. Although possibilities of interactions between IBU and graphene monolayers were examined, but the results of Fig. 2 were the main suitable configurations of formations of IBU@SiC and IBU@FSiC complexes. Accordingly, details of interactions were analyzed along with the models stabilizations

for examining the variations of structural and electronic features of complex systems. A significant role for contributing to interactions was found for the carbonyl oxygen atom of IBU in both complexes, in which it was involved in the O…Si and O…Fe interactions in the IBU@SiC and IBU@FSiC complexes. Next, the oxygen atom of hydroxyl group of IBU was involving in the O…Si interaction in both complexes with a higher significance in the IBU@FSiC complex in comparison with the IBU@SiC complex. To this aim, the models were found within their interactions with priority of formation of the IBU@FSiC complex in comparison with the IBU@SiC complex. For confirming this claim, the values of E were comparable with a significant difference between the IBU@SiC and IBU@FSiC complexes with the values of -1.44 kcal/mol for IBU@SiC and -43.14 kcal/mol for IBU@FSiC. These values showed the strength of formation for the complexes, in which the formation of IBU@FSiC complex was more significant than that of IBU@SiC complex. As a consequence, the QTAIM analyses and E values helped to recognize the structural features of models. It should be also mentioned that a shorter distance between IBU and graphene monolayer was found for the IBU@FSiC complex in comparison with the IBU@SiC complex meaning that the relaxation of IBU counterpart at the surface of graphene monolayer was dependent on the structural and energetic features.

Further discussion of the results was focused on the obtained HOMO and LUMO electronic features. Both of HOMO and LUMO levels play significant roles for managing the electron transferring systems inside or outside a molecule, these parameters could be very useful to show the advantage of a model and its features for working in a specific purpose. A first analysis of this results could be done by comparing the HOMO and LUMO levels of single states of SiC and FSiC, in which the levels came to a very shorter distance towards each other in the FSiC graphene monolayer showing a higher sensitivity of this adsorbent for communicating with the IBU substance. As could be found by the values of GAP parameters, 3.71 eV and 1.90 eV were found for the SiC and FSiC graphene monolayers. Accordingly, a better suitability of FSiC than SiC for involving in interactions and reactions was found based on the values of CP and CH. Especially in the case of CH, the FSiC graphene monolayer was found as a softer adsorbent (CH = 0.95 eV) in comparison with the SiC graphene monolayer (CH = 1.85 eV). As a consequence, the models of graphene monolayers could be learned by the advantage of iron-doping to obtain better features for working as an adsorbent graphene monolayer. It could be remembered from the results of E and QTAIM features that a better suitability was found for the formation of IBU@FSiC complex than the formation of IBU@SiC complex, which were described here by a softer behavior of the FSiC graphene monolayer for interacting with the IBU counterpart in comparison with the SiC graphene monolayer. The values of ΔGAP also indicated a remarkable change for the GAP of IBU@FSiC complex formation from the FSiC graphene monolayer in comparison with that of IBU@SiC complex formation from the SiC graphene monolayer. During the complex formation, the GAP value of SiC was changed from 3.71 eV to 3.19 eV in the complex state and that of FSiC was changed from 1.90 eV to 2.57 eV in the complex state. Not only the magnitude, but also the direction of change was also different as seen by a decrease of GAP in the formation of IBU@SiC complex and an increase of GAP in the formation of IBU@FSiC complex. For better clarifying these results, the illustrated DOS diagrams of Fig. 3 could lead to a better clearance state for showing the changes of molecular orbital energies not only for the HOMO and LUMO levels but also for other levels before and after such frontier levels. As could be known by the colors, the green color was for the localizing the molecular orbitals before the HOMO level and the red color was for the localizing the molecular orbitals after the LUMO level. Changes of the features inside the HOMO-LUMO region or outside this region will all show the electronic variation of molecular systems for working in the diagnostic functions. In the case of such adsorption processes, the recovery time could be learned by the magnitude of E and the conductance rate could be learned by the magnitude of ΔGAP, in which a highlighted situation was found for FSiC for working as an adsorbent of IBU drug substance for two purposes of carrying and detecting. A significant role of iron-doped region for managing the further reactions and interactions of FSiC with the IBU substance was also emphasized by the evaluated HOMO-LUMO distribution patterns (Fig. 4) whereas the situation of SiC was not found as a managed system. Localizing the HOMO-LUMO patterns around the iron-doped region was an

evidence of such claim to recognize a suitable FSiC graphene monolayer.

CONCLUSION

In this work, the main models were single structures of the IBU drug substance and SiC and FSiC graphene monolayers as obtained by the optimization calculations. Afterwards, additional optimization calculations were performed to combine the IBU and each of the SiC and FSiC graphene monolayers to obtain the stabilized geometries of interacting IBU@SiC and IBU@FSiC complexes. To assess the goal of this work regarding the complex formations, DFT calculations were performed to explore the adsorption of IBU by the FSiC graphene monolayer for providing the drug delivery insights. The results of QTAIM analyses revealed the existence of interactions with a significance of O…Fe interaction in the formation of IBU@FSiC complex in addition to the available O…Si interaction in both complexes. The values of E also indicated the suitability of formation of the IBU@FSiC complex in comparison with the IBU@SiC complex. As a result, the complex models were recognized with a priority of formation of IBU@FSiC complex by a highlighted role of the iron-doped region for managing the interactions between the IBU and graphene monolayer counterparts. Additionally, the electronic molecular orbital features indicated a more sensitivity of FSiC than SiC to contribute to further interactions and reactions, in which the results were emphasizing on the benefits of FSiC for a better detection of IBU substance in addition to its strong adsorption feature. In the case of employing a graphene monolayer for the IBU drug delivery, the enhanced FSiC graphene monolayer could be proposed for approaching such an important purpose of treating the biological media upon performing further investigations.

CONFLICT OF INTERESTS

There is no conflict of interests for the authors.

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