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ORIGINAL ARTICLE

An Iron-enhanced nanocone assisted drug delivery of Aspirin: DFT assessments

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Abstract

By the importance of customizing appropriate carriers for the specific drugs to approach a successful drug delivery process, the drug delivery of aspirin (ASP) was assessed by the assistance of an iron-enhanced nanocone (FCONE), using density functional theory (DFT) calculations. ASP, CONE, and FCONE models were optimized to be prepared for involving in bimolecular interactions to form ASP@CONE and ASP@FCONE complexes along with re-optimization calculations and vibrational frequency confirmations. Benefits of the enhanced FCONE model were seen for better interacting with the ASP counterpart comparing with the CONE and ASP interactions within the evaluated values of -26.35 and -10.07 kcal/mol for the corrected binding energies to yield a meaningful "recovery time" term. Additionally, the electronic molecular orbital features showed a priority for a better detection of ASP counterpart by the FCONE, in which the variations of energy gap values yielded a meaningful "conductance rate" especially for the ASP@FCONE complex. As a consequence, the recognized models of ASP@CONE and ASP@FCONE complexes were learned by a better advantage of enhanced FCONE model to be worked a s better proposed carrier for the ASP drug delivery process.

Keywords: *Adsorption; DFT; Drug Delivery; Molecular Interaction; Nanocone.*

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INTRODUCTION

The term of "drug delivery" has been become very alive after the innovation of nanotechnology, in which the newly invented nanostructures have been found very suitable for dealing with the biological systems and working as adsorbents of other substances such as drugs [1-3]. In this case, the nanostructures have been investigated up to now to be customized for working as carriers of adsorbed drugs to deliver them as a specific target in the living systems [4-6]. Indeed, variations of diseases and uncontrollability of their successful treatments forced the researchers to investigate many ways of medications to approach a more efficient protocol [7-9]. Additionally, separating and removing the wastes of pharmaceutical industries have been also found as an important role of nanostructures to adsorb different substances for desired purposes [10-12]. At the first step of approaching such purposes and processes, the available interactions between the adsorbent and adsorbate counterparts should be examined due to customizing the function of nanostructure towards the drug adsorption [13-15]. In this regard, assessing the features of nanostructures is needed to learn the capability of explored systems for employing them in a specific target and procedure [16-18]. Not only the pioneering carbon nanotubes, but also the advantages of several other types of nanostructures have been found useful for this purpose [19-21]. The models of nanostructures were significantly varied by the composition and geometrical architectures

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especially regarding their featured applications [22, 23]. Among them, the conical forms; so called nanocone, were found as possible nanostructures in both of carbon and non-carbon compositions with a main advantage of providing a tip for specifically involving in interactions with other chemical substances [24, 25]. In addition to the pure carbon composition, implanting some atoms such as metals could even enhance the capability of nanostructures for working in a more efficient level to approach the desired purposes [26]. Performing such atomic decorations or doping could lead to the generation of new types of nanostructures with the specific electronic features related to the semiconducting issues [27]. In this regard, the models could be followed by a new sensing function for pushing forward a successful detection and adsorption process of the external chemical substance [28]. Accordingly, this work was done to assess the aspirin drug delivery be the assistance of an iron-enhanced nanocone using density functional theory (DFT) calculations. Since the interacting systems are complex to be studied, employing DFT computations could reveal helpful insights for exploring the nanostructures functions for adsorbing the drug substances to approaching the drug delivery terms [29-32].

Acetylsalicylic acid or aspirin (ASP) is among the nonsteroidal anti-inflammatory drugs (NSAIDs) to control or reduce the impacts of inflammation, fever and pain in the human body system [33]. Besides the short term consumption, ASP has been also prescribed for the long-term treatments to help the high-risk patients not exposing to heart attacks or blood clots [34]. Besides such useful and important pharmaceutical functions, arising the adverse effects such as stomach related issues makes the ASP to be carefully used for avoiding the appearance of serious issues such as stomach ulcers and bleeding in the patients [35]. In this regard, the efforts of improving the drug efficacy of ASP have been significantly done to overcome the adverse effects, in which the conjugation of ASP with other complementary counterparts has been learned as a possible method of drug modification for approaching a better level of treatment [36-38]. The earlier works indicated the advantages of nano-conjugations to improve

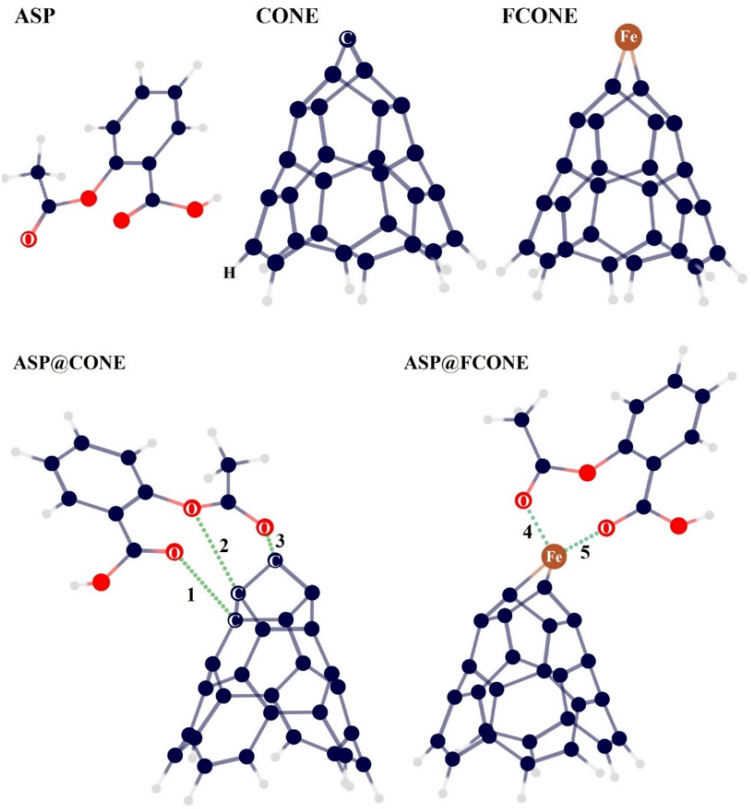

Fig. 1. Structures of ASP, CONE, and FCONE singular models and ASP@CONE and ASP@FCONE complexes.

the features of drugs and also ASP for providing a better treatment protocol [39-42].

Hence, this work was carried out to assess the features of ASP in the conjugation with an iron-enhanced nanocone (FCONE) to approach the term of drug delivery by proposing an enhanced carrier. As shown in Fig. 1, ASP, CONE, and FCONE, were considered as the original parental models of this work, in which their combinations yielded new interacting ASP@CONE and ASP@FCONE complexes. Subsequently, additional structural and electronic features were computed for the models to examine details of such complex formation processes, in which the evaluated graphical and tabulated results for the investigated models of this work were summarized in Figs. 1-3 and Tables 1-3. Accordingly, the models were discussed in details by the achieved data of DFT calculations.

COMPUTATIONAL METHOD

Gaussian program was used for running the computations of this work at the wB97XD/6-31G* DFT level under the charge = 0 and multiplicity = 1 conditions [43-45]. Aspirin (ASP) with the formula

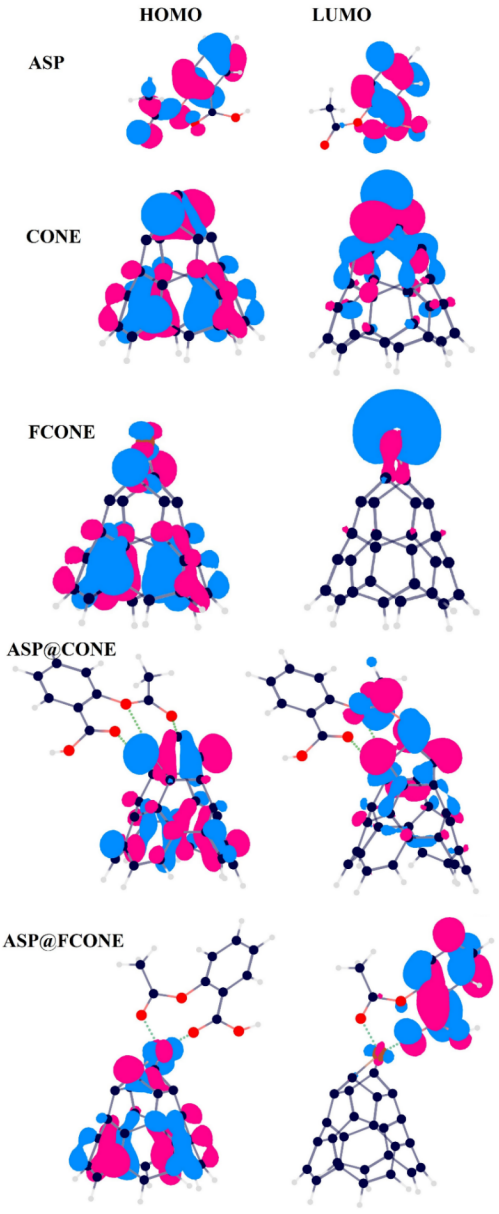

Fig. 2. Distribution patterns HOMO and LUMO levels.

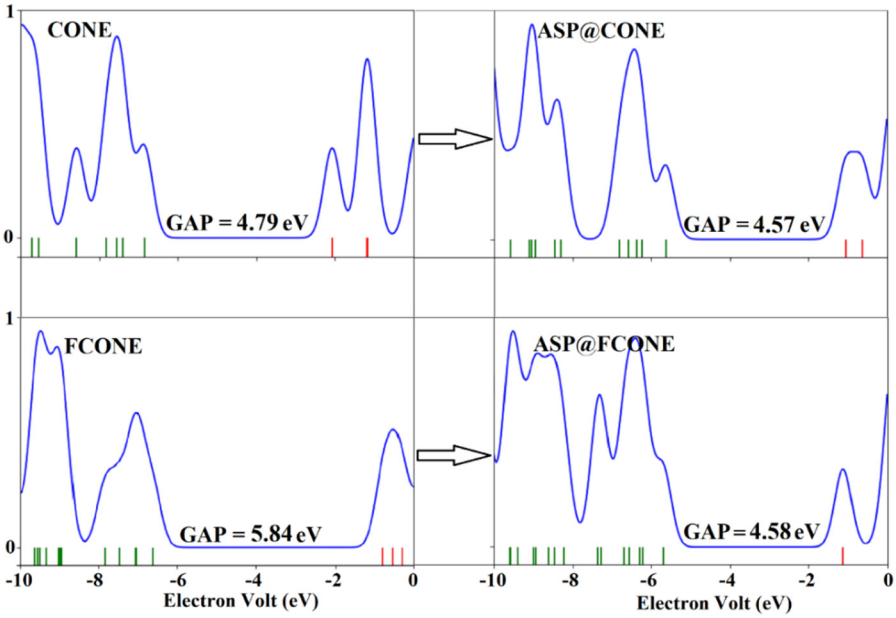

Fig. 3. DOS diagrams.

Table 1: The interaction and QTAIM features of optimized complexes. *

Complex	BE (kcal/mol)	BSSE (kcal/mol)	Corrected BE (kcal/mol)	Interaction	Distance (Å)	ρ (au)	$\nabla^2\rho$ (au)	H (au)
ASP@CONE	-15.02	4.95	-10.07	1: O…C	3.28	0.0242	0.1665	0.0017
				2: O…C	2.86	0.0264	0.2567	0.0018
				3: O…C	1.48	0.0521	0.5969	0.0023
ASP@FCONE	-30.84	4.49	-26.35	4: O…Fe	1.88	0.0904	0.7581	0.0054
				5: O…Fe	1.97	0.0738	0.4733	-0.0011

*The values of HOMO and LUMO were calculated as following and, and the other features were calculated directly:
$BE = E_{Complex} - E_{ASP} - E_{CONE\ (or\ FCONE)}$
Corrected BE = BE + BSSE

$C_9H_8O_4$, pure carbon nanocone (CONE) with the formula $C_{27}H_8$, and an iron-enhanced nanocone (FCONE) with the formula $C_{26}H_8Fe$ were the main parental materials of this work (Fig. 1). As could be seen, the tip of CONE was implanted by an iron atom to create the FCONE material for providing a metal-based region of interaction with the ASP counterpart. Geometries of the singular parental models were optimized and their minimized-energy structures were found and confirmed by calculating the vibrational frequencies to affirm the avoidance of any imaginary frequency within the optimized structures. Next, possible conjugations of ASP and each of CONE and FCONE were examined along with performing re-optimization calculations and vibrational frequency confirmations leading to the formation of interacting ASP@CONE and ASP@FCONE complexes (Fig. 1). By obtaining such complex systems, the interaction details were analyzed using the quantum theory of atoms in molecule (QTAIM) and Multiwfn program [46, 47]. Additionally, the frontier molecular orbitals distribution patterns of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) were evaluated using ChemCraft program (Fig. 2) besides showing the illustrated diagrams of density of states (DOS) using GaussSum program (Fig. 3) [48, 49]. To this point, the required data were evaluated for the models in terms of structural and electronic features as shown in Figs. 1-3 and Tables 1-3 for assessing the adsorption process and examining the sensing function of FCONE adsorbent towards the ASP drug substance along with employing beneficial DFT calculations [50-53].

Table 2: Thermochemistry features of optimized complexes. *

Complex	ΔG (kcal/mol)	ΔH (kcal/mol)	ΔS (kcal/mol)
ASP@CONE	-3.92	-17.83	-46.70
ASP@FCONE	-30.31	-44.79	-48.62

*The values were calculated as following for a symbolic X feature:
$\Delta X = X_{Complex} - X_{ASP} - X_{CONE\ (or\ FCONE)}$

Table 3: The molecular orbital features of optimized complexes and singular models. *

Model	HOMO (eV)	LUMO (eV)	GAP (eV)	μ (eV)	η (eV)
ASP	-9.19	0.08	9.28	-4.55	4.64
CONE	-6.85	-2.06	4.79	-4.46	2.39
FCONE	-6.62	-0.78	5.84	-3.70	2.92
ASP@CONE	-5.62	-1.05	4.57	-3.34	2.29
ASP@FCONE	-5.71	-1.12	4.58	-3.42	2.29

*The values of HOMO and LUMO were calculated directly, and the other features were calculated as following:
GAP = LUMO – HOMO
μ = ½ (LUMO + HOMO)
η = ½ (LUMO – HOMO)

RESULTS AND DISCUSSION

Binding energy

To deeply go inside the complexes to learn their features, the models were assessed by their binding energy indicated by BE value in Table 1. To find this value, energies of models in the parental and bimolecular states were differentiated to extract a quantity in correspondence with the bimolecular formation strength. Additionally, the effects of basis set superposition error (BSSE) were also implemented in the energy calculations to yield the corrected BE for avoiding any overestimation of energy values [54]. The corrected BE values showed a total strength for the formation of each of ASP@CONE and ASP@FCONE complexes with a higher strength of ASP@FCONE complex formation (corrected BE = -26.35 kcal/mol) rather than that of ASP@CONE complex formation (corrected BE = -10.07 kcal/mol). Using these values, it could be emphasized on the benefits of iron-enhancement for the formation of a stronger complex between ASP and FCONE counterparts in comparison with ASP and CONE counterparts. The optimized geometries of singular models including aspirin (ASP), nanocone (CONE) and iron-enhanced nanocone (FCONE), and those of bimolecular models including ASP@CONE and ASP@FCONE complexes were exhibited in Fig. 1.

QTAIM analyses

The interacting ASP@CONE and ASP@FCONE complexes (Fig. 1) were found as the result of optimizing the singular counterparts through the existence of recognized interactions by the assistance of further QTAIM analyses. In this case, the involving interactions were recognized to be existed for stabilizing the configuration of bimolecular complex models showing the possibility of involving non-covalent interactions. Based on the QTAIM analyses, three O…C interactions with the distances 3.28, 2.86, and 1.48 Å were found for the ASP@CONE complex and two O…Fe interactions with the distances 1.88 and 1.97 Å were found for the ASP@FCONE complex. In this case, the models were analyzed by the contribution of each interaction to the ASP@CONE and ASP@FCONE complex formations. Based on the total electron density (r), Laplacian of electron density ($\tilde{N}^2r$), and energy density (H) values of QTAIM features, the O…C interactions were found weaker than the O…Fe interactions; however, their strengths were still meaningful for providing the complex configuration. The positive sign of H values indicated the existence of non-covalent interactions in which a stronger interaction was found for one O…Fe interactions by a negative sign of H value (-0.0011 au), but still in the non-covalent state by the positive values of r and $\tilde{N}^2r$. To this point, the recognized interactions between the involving counterparts were used for assessing the formation of complex models in details.

Thermochemistry features

The results of thermochemistry features including Δ values of Gibbs free energy (ΔG),

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enthalpy (ΔH) and entropy (ΔS) were evaluated for the models (Table 2) through the comparison of each value of the complex and its counterparts. The results indicated a higher suitability of formation for the ASP@FCONE complex in comparison with the ASP@CONE complex in all thermochemistry features of ΔG, ΔH and ΔS with the higher significance for the ASP@FCONE complex formation. Especially in the terms of ΔG, the obtained values of -3.92 and -30.31 kcal/mol for ASP@CONE and ASP@FCONE complexes indicated a higher tendency of formation for the ASP@FCONE complex in comparison with the ASP@CONE complex.

Molecular orbital analysis

By the analyses of HOMO-LUMO patterns of parental models (Fig. 2), it was supposed that a more significant interaction level could be expected for the complex formation of ASP with the FCONE in comparison with the CONE counterpart by a remarkable LUMO localization at the iron-enhanced region of FCONE. Accordingly, the results of corrected BE values indicated the availability of such a strong situation for the formation of ASP@FCONE complex in comparison with the formation of ASP@CONE complex. A significant role of iron-enhanced region was to manage the interactions of ASP and FCONE counterparts in a more appropriate route regarding the variated interactions of ASP@CONE complex. Examining the variations of HOMO-LUMO patterns in Fig. 2 could also show the role of FCONE for attracting the whole electronic portion to its side as the HOMO was located at the FCONE part and the LUMO was located at the ASP part. On the other hand, a similar localization of HOMO and LUMO patterns was found between both of ASP and CONE counterparts. To this aim, the models were found to be mainly managed by the assistance of FCONE to form the interacting complexes; however, it was a weaker role for CONE to do such function. As a result, the models were found suitable and their features indicated a benefit of iron-enhancement for approaching a more appropriate result of ASP@FCONE complex formation in comparison with the ASP@CONE complex formation to manage a better interacting route and situation.

Further investigations of models were based on the evaluated electronic molecular orbital quantities using the energy values of HOMO and LUMO and their related features; energy gap (GAP), chemical potential (m) and chemical hardness (h), as listed in Table 3. The obtained results indicated the effects of variations between the singular and bimolecular models in accordance with the molecular orbital features, in which the magnitudes of such changes could relate to the impact of changes for the molecular systems and models. It was interesting that the iron-enhancement induced a higher semi-conductivity for the FCONE in comparison with the CONE structure by examining the GAP values of 5.84 eV and 4.79 eV for them, respectively. Accordingly, the other related m and h values detected such effects by the movement of models from CONE to FCONE. In the case of bimolecular models, the gap values of 4.57 eV and 4.58 eV were found for ASP@CONE and ASP@FCONE complexes, respectively, as a result of HOMO and LUMO variations through the complex formation. Additionally, the gap change of ASP@FCONE complex was more significant than the change of gap for the ASP@CONE complex leading to a more suitable detection process of the adsorbed substance. This achievement was visually show in Fig. 3 by the illustrated diagrams of DOS for the singular and bimolecular models. In this regard, an advantage of iron-enhancement was found for a better detection of the adsorbed ASP drug not only by the observed GAP value, but also by the other orbitals features variations before/after the HOMO/LUMO levels. Indeed, in the case of separation processes, this in an important issue of careful detection of the exact substance in the presence of other mixed substances. To clarify this issue in a brighter term, it should be mentioned that two terms of “recovery time” and “conductance rate” could be followed by the changes of binding energy and energy gap in accordance with eqs. (1) and (2), respectively, have been show the detection of bimolecular complex formation [55]. Based on the relationship between the recovery time and binding energy and the conductance rate and energy gap, increasing the binding energy strength could lead to longer recovery time detection and increasing the band gap change could lead to more specific conductance rate detection for the investigated models.

$$\text{Recovery Time } \alpha \exp(-BE/KT) \quad (1)$$

$$\text{Conductance Rate } \alpha \exp(-GAP/2KT) \quad (2)$$

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Accordingly, the current models indicated a significance of iron-enhancement for making a more suitable FCONE adsorbent towards the ASP drug for working as a better surface than the original CONE structure to approach a better insight of interactions of a drug by a proposed carrier substance. In such an adsorption process, the models were analyzable and discussable for approaching the required terms of providing a detection function of drug by the assistance of a proper adsorbent for customizing a specific drug carrier substance. As a consequence, the idea of iron-enhancement was suitable enough to approach appropriate results of managing the ASP drug delivery process.

CONCLUSION

Exploring the impacts of iron-enhancement on the features of FCONE for the ASP drug delivery was approached as a main goal of this work using the results of DFT calculations. At the first step, the stabilized structures of CONE and FCONE were found and their electronic molecular levels indicated significant changes between the properties of CONE and FCONE substances towards the interacting ASP drug substance. In the next step, the models were examined for the formation of ASP@CONE and ASP@FCONE complexes, in which the models were obtained by better values of binding energy for the iron-enhanced involving complexes formations. Moreover, variations of electronic molecular orbital levels indicated a better advantage of FCONE function for detecting the ASP drug in comparison with the other system. The meaningful values of binding energy and energy gap changes yielded the meaningful terms of "recovery time" and "conductance rate", in which both terms were found with a higher significance for the interacting ASP@FCONE complex formation in comparison with the interacting ASP@CONE complex formation. The models were analyzed in details by their recognized interactions, in which the iron-enhanced region played a significant role of managing interactions between ASP and FCONE counterparts. Accordingly, the main idea of this work was approached by assigning the FCONE enhanced model to be considered as a possible carrier of ASP for the drug delivery related purposes. Indeed, the structural and electronic features indicated a managing role of FCONE for the ASP@FCONE complex formation revealing the importance of such activity for approaching a more controllable ASP in the state of ASP@FCONE complex rather than the free ASP. As a result, the investigated model of this work could be proposed for further assessments in the related fields of drug delivery processes.

CONFLICT OF INTERESTS

There is no conflict of interests for the authors.

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