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DFT study on interaction between naproxen and lactic-glycolic acid oligomers

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ABSTRACT

In this study, the interaction of naproxen molecule with poly lactic-co-glycolic acid (PLGA) has been investigated using density functional theory (DFT) calculations. In the first step, we studied the interaction energies and geometries of all interacting sites of a naproxen molecule with a monomer of lactic-co-glycolic acid (LGA) i.e. anhydride of lactic (LA) and glycolic acid (GA) and dimmer LGA. We found that the most stable interacting site appears when both naproxen and LGA interacts from the acidic side. This experience was used to find the interaction of naproxen and LGA oligomers up to hexamer. From the interaction energies and the vibrational spectra of naproxen-PLGA we found that this complex is highly stable and this is a reason for the stabilization of naproxen in the PLGA host. Using atom in molecule (AIM) critical points and bonding pathway calculations we concluded that the hydrogen bonds are very strong between naproxen molecule and polymer.

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1. Introduction

Naproxen, (+)-6-methoxy-α-methyl-2-naphthalene acetic acid, is a non-steroidal anti-inflammatory drug normally used for the reducing of moderate to severe pains, fever and inflammation along with stiffness caused by osteoarthritis, rheumatoid arthritis, psoriatic arthritis. It has been reported that using this drug causes side effects as gastrointestinal problems such as heartburn, constipation, diarrhea, ulcers, and stomach bleeding. [1- 3]

In the field of pharmaceutics, drug additives are used to decrease the side effect and stabilize drug. For naproxen, poly lactic-co-glycolic acid (PLGA) is a very widely used additive, which also help in decreasing these side effects and delivering naproxen on target with the lowest risk [4].

PLGA is a copolymer, which is used in a host of Food, and Drug Administration approved therapeutic devices, owing to its biodegradability and biocompatibility. PLGA has been successful as a biodegradable polymer because it undergoes hydrolysis in the body to produce the original monomers, LA and GA. These two monomers under normal physiological conditions are by-products of various metabolic pathways in the body [5-6].

Applying these structures, drugs can be delivered in a sustained manner and encapsulated drugs are protected in the polymer network from gastric and enzymatic degradation as well [7,8].

The physicochemical characterization of naproxen–PLGA have already been studied using different techniques like X-ray powder diffraction (XRPD), Fourier transform infrared spectroscopy (FT-IR) and Differential scanning calorimetry. (DSC) [9] However to understand the detailed information of naproxen-PLGA interaction, theoretical investigations are essential.

In this work we use DFT calculations to study the physicochemical characterization of the naproxen-PLGA interaction. We first studied the structure of a single naproxen and monomer of lactic-co-glycolic acid (LGA). Then the interaction of a naproxen molecule with a monomer LGA has been studied, including all the possible interaction sites. The same work has been done for the interaction of naproxen molecule with dimer LGA to find the best possible structure. This procedure is done for the interaction of naproxen and di, tri, tetra, penta and hexamer of LGA to find the Gibbs free energy of the interaction of naproxen with PLGA.

The stability of naproxen-PLGA are reported based on the Gibbs free energy.

2. Computational details

In this study, we apply Density functional theory calculations to the interaction of naproxen and PLGA. We used B3LYP hybrid density functional which implemented in the Gaussian 09 software package [10]. The B3LYP hybrid functional has shown to successfully predict a wide range of molecular properties. We also used cam-B3LYP functional for calculation in order to include dispersion interaction between drug and polymer.

Using this method of theory, we optimized all the geometries. Subsequently, vibrational frequency analysis has also been performed using 3-21G basis sets in order to identify whether the optimized structures correspond to a true local minimum or not. All the structures all relaxed again using a moderate basis set i. e. 6-31G(d, p).

The interaction energies and the stabilities of the structures are calculated using the same method of theory. The interaction Gibbs Free energies are calculated as follows:

$$G_{binding} = G_{nap\text{-}LGA} - (G_{nap} + G_{LGA}) \quad (1)$$

Where $G_{binding}$ is the interaction Gibbs free energy, $G_{nap\text{-}LGA}$ is the Gibbs energy of the optimized structure of the naproxen-LGA complex, G_{nap} and G_{LGA} are the energies for an isolated naproxen and LGA in the same scheme. Similarly the interaction energies $E_{binding}$ were calculated.

3. Results and discussion

3.1. Naproxen molecules

The structure of the naproxen molecule is optimized within the theory level discussed previously. The optimized structure is shown in the Figure 1. The calculated IR frequencies are shown in the Figure2.

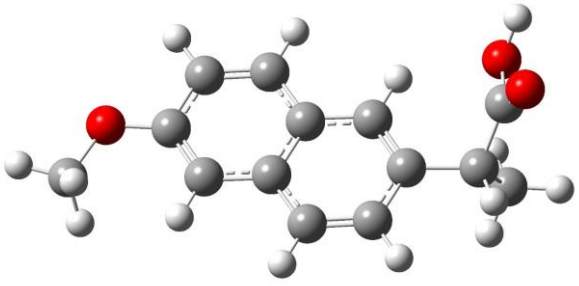

Figure 1. Optimized structure of naproxen molecule using B3LYP/3-21G method of theory.

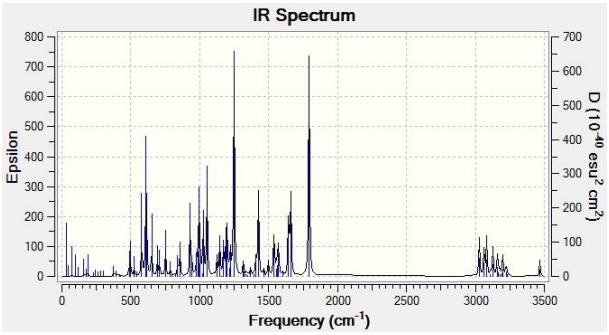

Figure 2. Calculated IR spectra of the naproxen obtained at the theory level discussed in the text.

3.2. PLGA Polymer

PLGA is a linear copolymer that can be prepared at different ratios between its constituent monomers, LA and GA (Figure 3)

Depend on the ratio of LA to GA used for the polymerization, different forms of PLGA are produced. These types are usually identified with regard to the monomer ratio used, for example PLGA 75:25 identifies a copolymer consisted of 75% LA and 25% GA [11].

In this work, we applied PLGA 50:50 where LA and GA monomers are in the same ratio and line alternately in the structure of copolymer.

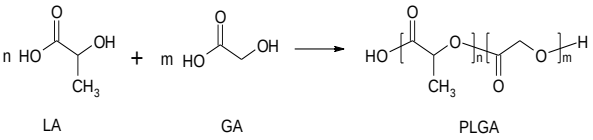

Figure 3. Chemical structure of PLGA and its monomers.

The smallest size of PLGA 50:50 is produced from the interaction of one LA and one GA molecules i.e. n = m =1 in Figure 3. If this molecule is used as a constituent monomer of larger, size PLGA then a PLGA 50:50, which PA and LA line alternately in the polymer chain, will be produced.

A real PLGA may consist of too many of this monomer. However, due to the computational limit and the complexity of calculations, we only limited this study for PLGA up to 6 monomers (n = m = 6)

3.3. Interaction of naproxen and PLGA

Hydrogen bonding is the strongest possible force between a naproxen molecule and a unit of LGA. Due to the existence of O-H and O- units in both LGA and naproxen, varieties of these bonding are possible. For instance, in the interaction between monomer LGA and naproxen seven situations are possible. We optimized all these complexes with the theory level discussed before. The final optimized structures are shown in Figure3. The O-H bond lengths in hydrogen bridges are also shown in Figure 3. Using Eq. 1 we calculated $G_{binding}$ of reactions for all reacting complexes where are also represented in Figure 3. The values of O-H bond lengths in hydrogen bridges as well as the interaction Gibbs free energies, reveal large hydrogen bonding between LGA and naproxen molecule.

The most stable reacting case appears when carboxylic groups of both LGA and naproxen contribute to the interaction and produce two hydrogen bonding as represented in Fig. 4 a.

The same procedure has been applied to find the interaction energies and geometries of a dimmer LGA-naproxen complex. Due to the higher numbers of oxygen atoms in dimmer than monomer the possible interacting situations increase to 11.

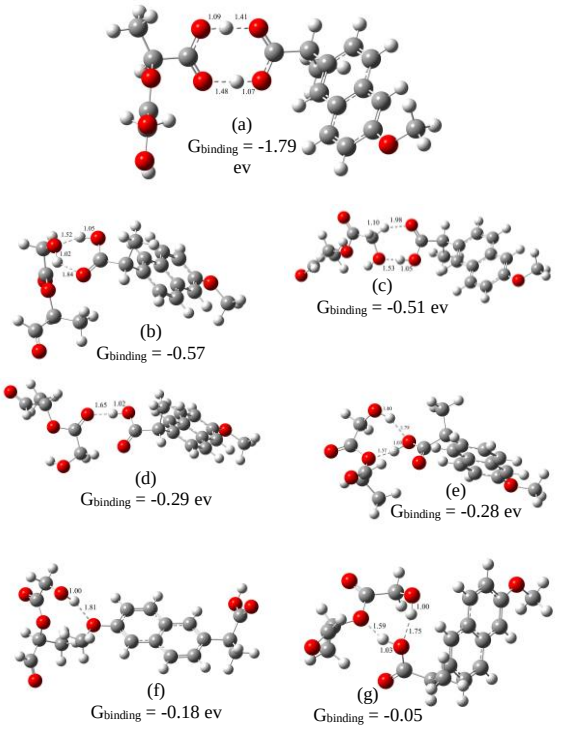

Figure 4. All possible structures for monomer LGA-naproxen interaction. Dash lines represent the hydrogen bonds. The bond lengths (Å) of contributed O-H bonds in hydrogen bridges are also shown in figure. ΔG^0 is the interaction Gibbs free energy obtained using Eq. 1.

We optimized all these structures to obtain which situation has the higher interacting energy. Again, we concluded that the structure which two carboxylic groups of both particles contribute to hydrogen bonding (Fig 5) is the most stable structure with $G_{binding}$ = -1.73 ev. Due to the high numbers of interacting situations (11 possibilities), we only reported the most stable structure in Figure 5.

As the most stable complex obtained for the case that LGA and naproxen interact from the acidic side for both monomer and dimmer LGA, we applied this type of interaction to find the optimized geometries and interaction energies for tri, tetra, penta and hexamer LGA-naproxen complexes. In all these optimized structures two hydrogen bridges such as the one, which is shown in Figure 5, are formed. The distances

between the two oxygens in these hydrogen bridges are about 2.5 Å, which are even, less than the length between the two oxygens in water Hydrogen Bridge (1.8Å). Therefore, a strong hydrogen bonding between PLGA and naproxen is evaluated.

Using Eq. 1 we then obtained reaction Gibbs free energies of PLGA-naproxen complexes. The results for the most stable structures are summarized in table1. The large absolute values for $G_{binding}$ is another argument that the hydrogen bonds here are strong

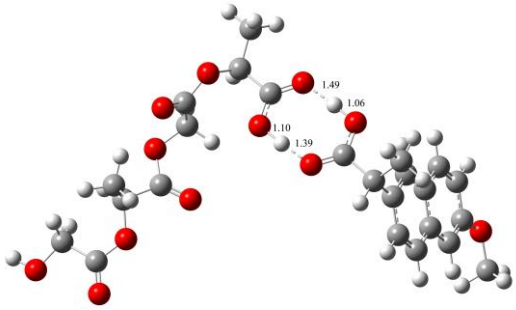

Figure 5 the most stable structure of dimmer LGA-naproxen complex. The numbers represent the O-H bond lengths in Å

Table 1 Calculated reaction Energies in two level of theory and the reaction Gibbs free energies (eV) for the most stable structure of PLGA-naproxen as discussed in the text.

Monomer No.	1	2	3	4	5	6
$G_{binding}$ (B3LYP/3-21G)	-1.69	-1.73	-3.06	-2.07	-1.52	-1.72

Figure 6 represents the PLGA-naproxen interaction Gibbs free energies ($G_{binding}$) as a function of LGA monomers. The results of table 1 and Figure 6 reveal that there is no simple trend for the interaction energies and the size of PLGA. The reason refers to the optimized geometries and the numbers of possible hydrogen bonding.

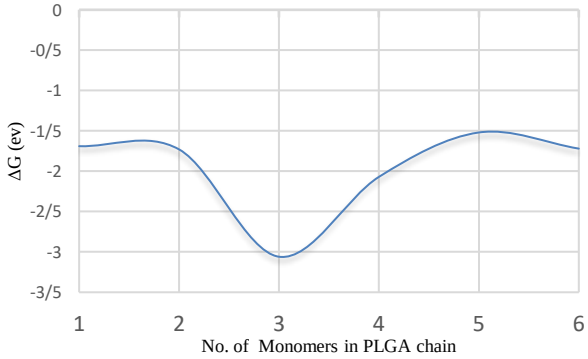

Figure 6 PLGA-naproxen interaction Gibbs free energies ($G_{binding}$) as function of PLGA monomers obtained using B3LYP/3-21G level of theory

The comparative size of naproxen and trimmer LGA simplify hydrogen bonding between O atoms at the terminals of both molecules (Figure 7) i.e. in addition of two hydrogen bridges which appear in the interaction of carboxylic groups of naproxen and PLGA, another hydrogen bonding establishes between etheric O of naproxen and alcoholic O-H group of trimmer LGA. Therefore, this structure has the higher interaction energy among the considered structures.

The numbers in Figure 7 represent the O-H bond lengths of the ones, which contribute in the hydrogen bridges. The bond lengths are in the range of 1.5-1.9 Å which are in the range of bond lengths of water hydrogen bonding (1.8Å) or even smaller. The value of Gibbs free energies and O-H bond lengths show that hydrogen bonding is the main interacting phenomena in the PLGA-Nap interactions. These results show that naproxen strongly interact with PLGA to produce a stable complex. This could be the reason that PLGA stabilize naproxen from the degradation. The real interaction energy in the mixture of PLGA and naproxen can be obtained by averaging all data in table 1 including the populations of each size of PLGA that can be obtained from experiment.

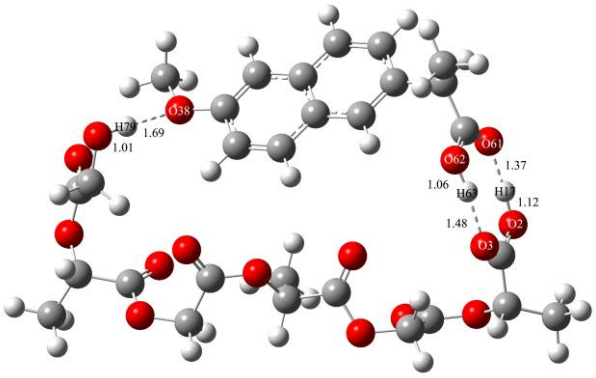

Figure 7. The optimized geometry of the trimmer LGA-naproxen complex.. Three hydrogen bridge make this structure the most stable one among the all studied complex. Dash lines represent the hydrogen bonds and the numbers show the bond lengths (Å) of contributed O-H bonds in hydrogen bridges

Table 2 Results of atoms in molecule (AIM) calculated about the critical points of the hydrogen bridges using trimmer LGA-naproxen complex relaxed geometry that obtained with Cam-B3LYP/6-31G(d, p) level of theory. Atom numbers in two left columns are shown in Fig. 7

AIM		ρ	$\nabla^2\rho$	H
Polymer	Naproxen			
H17	O61	0.296805	-0.269804	-0.07251
O3	H63	0.235449	-0.219147	-0.014454
H79	O38	0.187793	-0.186588	-0.019405

3.4. QTAIM analysis

In order to assess the strength of the hydrogen bonds between PLGA-Naproxen AIM critical points and bonding pathway calculations for the trimmer LGA-naproxen complex relaxed geometry that obtained with Cam-B3LYP/6-31G(d, p) level of theory were performed using AIM2000 software package [12]. The electron density (ρ), Laplacian (∇^2) and electron Hamilton (H) for the Hydrogen bonds are summarized in table 2. The negative values for Laplacians reveal strong hydrogen bond between Naproxen molecule and

polymer. Moreover, the large values for ρ and H predict that these type of hydrogen bonds are very strong.

4. Conclusion

We studied the interaction of naproxen with PLGA 50:50. The hydrogen bonding is the major intermolecular force between these two molecules. Due to the several O-H and O- units in both PLGA and naproxen, varieties of interacting structures are possible. For LGA monomer and dimmer, we studied all the possible structures based on the hydrogen bonding between PLGA and naproxen. For these two groups the structure that two carboxylic groups of both PLGA and naproxen contribute to the interaction is the most stable complex. For the larger size of PLGA with more than two monomers, we only study the interaction between PLGA and naproxen from the head of carboxylic groups up to the PLGA with six monomers. We concluded that there is no meaningful trend for the dependence of PLGA sizes and the interaction energies. The PLGA with three monomer produce the highest interacting energy while it represents the highest numbers of hydrogen bridges.

Conflict of interest

The authors declare no competing interests.

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References

[1] T. Hautaniemi, N. Petrenko, A. Skorinkinad, R. Giniatullin, Neuroscience, 2012, 209, 32–38. https://doi.org/10.1016/j.neuroscience.2012.02.023

[2] R. Sammour, G. Ohel, M. Cohen, R. Gonen, Int J Gynecol Obstet, 2011, 113, 144–147. https://doi.org/10.1016/j.ijgo.2010.11.024

[3] P. Mura, N. Zerrouk, N. Mennini, F. Maestrelli, C. Chemtob, Eur. J. Pharm. Sci., 2003, 19, 67–75. https://doi.org/10.1016/S0928-0987(03)00068-X

[4] K. Dillen, W. Weyenberg, J. Vandervoort, A. Ludwig, Eur. J. Pharm. Biopharm., 2004, 58, 539–549. https://doi.org/10.1016/j.ejpb.2004.03.035

[5] R. Manchanda, A. Fernandez-Fernandez, A. Nagesetti, A. J. McGoron, Colloids Surf., B, 2010, 75, 260–267. https://doi.org/10.1016/j.colsurfb.2009.08.043

[6] H. Gupta, B.Pharm, M.Pharma, M. Aqil, M. Pharm, K. Khar, M.Pharm, A. Ali, M. Pharm, A. Bhatnagar, G. Mittal, Nanomedicine, 2010, 6, 324–333. https://doi.org/10.1016/j.nano.2009.10.004

[7] N. D. Stebbins, J. J. Faig, W. Yu, R. Guliyev, K. E. Uhrich, Biomater. Sci., 2015, 3, 1171-1187

[8] Y. Ji, A. K. Lesniak, A. Prudic, R. Paus, G. Sadowski, AIChE J. 2016, aic.15282. https://doi.org/10.1002/aic.15282

[9] Y. Javadzadeha, F. Ahadi, S. Davarana, G. Mohammadi, A. Sabzevari, Kh. Adibkia, Colloids Surf., B, 2011, 81, 498–502. https://doi.org/10.1016/j.colsurfb.2010.11.014

[10] M. J., Frisch, et al. "Gaussian 03, revision A. 1; Gaussian." Inc., Pittsburgh, PA (2003).

[11] P. Gentile, V. Chiono, I. Carmagnola, P. V. Hatton, Int. J. Mol. Sci., 2014, 15, 3640-3659. https://doi.org/10.3390/ijms15033640

[12] F. Biegler-Konig, J. Schonbohm, AIM2000 Ver. 2, 2002