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Original Research Paper

Quantum Chemical Study of Interaction of PLGA Polymeric Nanoparticles as Drug Delivery with Anti-Cancer Agents of Thiazoline

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ABSTRACT

Thiazoles derivatives are consisted in chemical compounds such as antimicrobial and anticancer medicine. Since polylactic-co-glycolic acid (PLGA) polymeric nanoparticles has been conversed about nanomedicine applications and particularly as drug delivery systems. Because of molecular self-assemblies and biodegradability of PLGA polymer, it can be used to carry anti-cancer and antimicrobial drugs. The capability of PLGA polymer-based drug delivery system in the treatment of cancer has been studied by quantum MM/QM approach. Theoretical study of the interaction between polylactic-co-glycolic acid polymeric nanoparticles and thiazoline derivatives has been performed by combination of DFT and molecular mechanics approach. The results obtained from this study, displayed that PLGA polymeric nanoparticles has feasible interaction that include hydrogen bond and Vander Waals interaction and showed clearly that these systems have comparatively low permanence and so PLGA polymer is suitable drug delivery that have been studied for anti-cancer drug. Investigation of QM/MM calculations and the interaction energies of the thiazoline derivatives and PLGA polymeric nanoparticles with

counterpoise method represent that this carrier can be utilized to modify the biological and anti-cancer activity of thiazoline derivatives.

Keywords: Polylactic-co-Glycolic Acid (PLGA), Polymeric Nanoparticles, Anti-Cancer Agents, Thiazoline Derivatives, Quantum Mechanics/Molecular Mechanics.

Introduction

Thiazole derivatives have amassed profit during the years because of their diverse biological and medicinal activities [1]. The thiazolo[5,4-d]pyrimidinone derivative, which has been synthesized by Bondock, has been evaluated as an anti-microbial and anti-cancer agent [2] . Medicinal chemists have also carried out considerable research for novel anti-microbial and anti-cancer agents bearing a pyrimidine moiety. Trimethoprim and sulfadiazine are chemotherapeutic drugs containing a pyrimidine segment currently used in the therapy of epidemic malady [3]. A series of thiazoline derivatives bearing a hydrazone moiety have been synthesized by Altintop et al. that have potential anti-microbial effects and cytotoxicity[4]. Thio linked thiadiazole, tetrazole, triazole and pyrimidine as the side chain have been used in designing the molecules. The most effective anti-cancer compounds have been evaluated for their DNA synthesis inhibitory activity. The quantitative structure–activity relationship of these novel thiazoline derivatives with anti-cancer activity has been investigated with the density functional theory by Madadi et al. [5].

Most anti-cancer agents do not recognize between cancer cells and the normal ones, resulting in adverse reactions in tissues and organs. The drug delivery systems can reduce these inadequacies by encapsulation methods, which control the detrimental effects of the toxic drug, and preserve the drug before it reaches the target cells [6]. In the past years, many synthethic polymers have been investigated for application of nanomedicine and exclusively, as drug delivery systems. For objective, the polymers must be biodegradable, nonpoisonous, and biocompatible. Polylactic-co-glycolic acid (PLGA) is one of the most useful polymers, because of its biodegradability, the capability to self-assemble into nanometric micelles that are capable to trap same molecules as well as drugs, and the ability to reach them into the body in a time- controlled release. The use of PLGA polymeric nanoparticles as a new drug delivery system for nanomedicine uses [7] emerged as the most promising material for the fabrication of the drug carriers of nanocarriers.

Hence, PLGA polymeric nanoparticles are one of the most utilized polymers for application of biomedicine, it possesses not only extreme biocompatibility, but also mechanical stability that makes it appropriate for a large variety of medical artifices such as sutures or fibres [8] However, the real strength of PLGA polymeric nanoparticles is the ability to self-assemble into polymeric devices like microcapsules, microspheres, and nanoparticles, which are optimal for delivery-systems construction. These are water-soluble and can be introduced to the body locally or orally. Moreover, these PLGA-derived systems can be loaded with a variety of drugs, peptides, and proteins which are released into the body slowly [9].

The theoretical investigation of the interaction between the components of the systems of biological for designing the new medicines is very important [10]. The molecular dynamics simulations have been done in investigations on the propagation of drug via the carriers. Wang et al. performed this approach of diffusion of the aspirin molecules via poly (vinyl alcohol) and evaluated the data obtained from the experiments [11]. To predict the interactions between the the drugs and tyrosine-derived copolymer, MD simulations and docking calculations have been studied by Costache et al. [12]. Also, the interactions between the drugs diltiazem, cyanocobalamin, benzoates and dextrans on the one hand, and poly (*N*-isopropyl acrylamide) (PNIPA) polymer on the other hand, have been investigated [13]. The theoretical investigation of the interaction between thiadiazolyl thio acetamide derivatives as anti-HIV agents and PCA-PEG-PCA copolymer have been studied with ONIOM2 (B3LYP/6-31G: UFF) method [14-16].

Experimental

The hybrid of the QM and MM method has seen excellent success in biological science [17]. The success of the QM/MM methods is due to multistage modality, in which the system is divided into different regions computed at suitable levels of theory. The full geometry optimization and frequency calculations were performed using a combined QM and MM method, according to the ONIOM approach [18] with the Gaussian 03 programme [19]. The set of atoms computed with QM and MM parts are depicted in Figure 1. In the vibrational frequency analysis on the Hessian matrix, the local minimum was afirmed by the without of negative eigenvalues (NIMAG = 0). The ONIOM approach is explained in detail in the review articles by Morokuma [20].

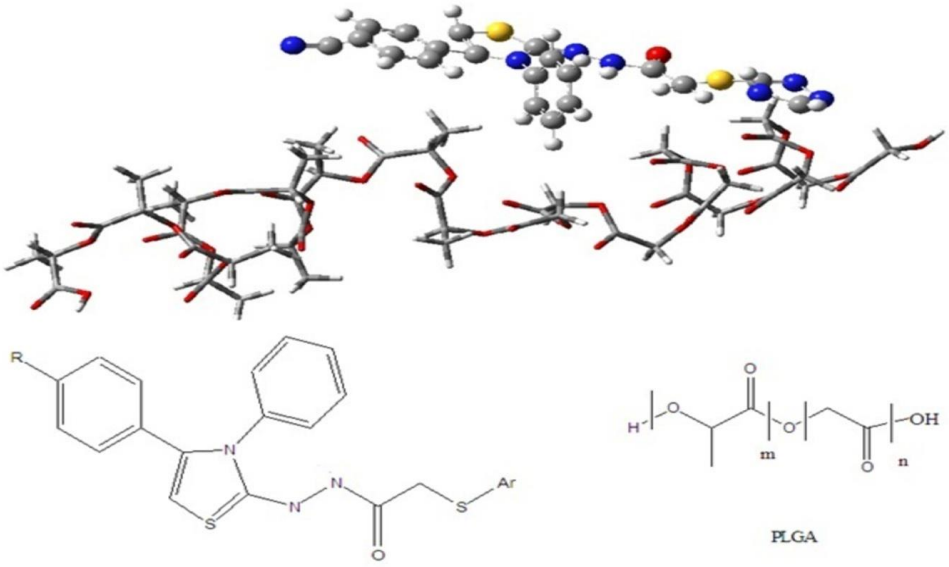

Figure 1. Thiazoline derivatives and PLGA polymer ONIOM2 (B3LYP/6-31G: UFF).

The fulfilment used in this research considers that all energies are gained by summed up the contributions of the QM region (E_{QM}) and the external region ($E_{ext.}$), which account for the physical and the chemical environment around the QM region (see Figure 1). The E_{ext} is gained by an MM calculation on the total real system ($E_{MM(real)}$), and reducing the energy received by the MM calculation of the model system ($E_{MM(model)}$). Therefore, the energies are calculated conforming in equation 1:

$$E_{(ONIOM2)} = E_{(High,\ Model)} + E_{(Low,\ Real)} - E_{(Low,\ Model)}$$
$$= E_{(High,\ Model)} + \Delta E_{(Low,\ Real \leftarrow Model)} \quad (1)$$

where 'Real' means the total system, which is computed at the 'Low' level, while 'Model' expounds the part of the system for which the energy is computed at both 'High' and 'Low' levels. Clearly that this method can be looked at as an extrapolation method. Starting at E_{Low} model, the extrapolation to the high-level computation ($E_{High,\ Model} - E_{Low,\ Model}$) and the extrapolation to the real set ($E_{Low,\ Real} - E_{Low,\ model}$) are assumed to give an approximation for $E_{High,\ Real}$. The ONIOM approach put out an extrapolated energy (E_{ONIOM2}) for a system subdivided in this manner.

With this ONIOM approach, we can also calculate the gradient of the energies and the Hessian of the energy that give the allowable frequency and optimization calculations on the optimized structures. The QM region was behaviour at the gradient-corrected DFT [21] level using B3LYP [22-23]. The MM region was calculated using the universal force field (UFF). This level of calculation will henceforth be

named ONIOM2 (B3LYP: UFF). The stationary points put on potential energy surface were controlled by calculating the Hessian matrices at the (B3LYP: UFF) level, where the minimum energy of compounds have no imaginary frequency. Interaction energy (E_{int}^{AB}) is interpreted as the difference between the energy of the sum of the energies of its segments and the complex. It can be defined in equation 2:

$$E_{int}^{AB} = E_{AB}^{opt} - E_{A}^{opt} - E_{B}^{opt} + \delta_{AB}^{BSSE} \quad (2)$$

Where δ_{AB}^{BSSE} is the basis set superposition error (BSSE) correction. Boys and Bernardi have been calculated BSSE with the counterpoise procedure method advanced [24]. BSSE is discussed to be one of the main origins of error in calculating the interaction energy of weakly-bound Vander Waals interactions and the likes, and the tightly-bound covalent complexes. The counterpoise correction (CP) method of Boys and Bernardi is the most extensively applied technique for avoiding the problems associated with BSSE [25-26].

Results and discussion

One of the purposes of design of drug regards the ability to compute drug-receptor and drug-carriers interactions. Fixed-charge calculation of electrostatic interactions is one of the most important topics of molecular mechanics (MM) force fields. As a immediate stage in computational elaboration, it appears natural to combine QM within a hybrid QM/MM approach, which has seemed to be a helpful tool to depict mechanistic and structural states of interactions of drugs with carriers and receptors. The possibility of reaction can be approximated from the difference in energies between the products and the reactants. These modelings consisted two steps. First, molecular structures were optimized, second the molecular energies were calculated via by ONIOM2 (DFT: UFF). The calculation of energies can be made simple by acting the active section with a high-level quantum mechanical (QM) ab initio or density functional for large reactive systems. One of these methods is the principal ONIOM approach. We used this approach for the optimization of the thiazoline derivatives and PLGA polymer. Our results display that the studied complexes can be used to modify anti-cancer activity of the thiazoline derivatives. However the application of the QM/MM energy as a recording function in docking algorithms shows impractical at this point as section of the high-throughput virtual screening, it is important to point out that its use does lead to modified results when checked with classical scoring methods. The binding energy (BE) analysis of the appointed complexes permitted the basic specifications of the PLGA polymer interactions to be recognized, based on the ONIOM approuch. The structures of the thiazoline derivatives and PLGA polymer ONIOM2 (B3LYP/6-31G: UFF) have been shown in figure 1. According to our

results, the binding energies of the optimized configuration between the thiazoles derivatives as an anti-cancer drug and the PLGA polymer as a drug-delivery system, have been summarized in Table 1 at the B3LYP/6–31G (d): UFF level of calculation.

Table 1. Binding energies calculated of thiazoline derivatives (E_A) and PLGA polymer by ONIOM2 (B3LYP/6-31G (d): UFF) method.

Compound	R	Ar	Binding Energy (kcal/mol) (gas phase)	Binding Energy (kcal/mol) (water phase)
1	CN	4-Methyl-4H-1,2,4-triazol-3-yl	2.4030	-1.7470
2	H	4-Methyl-4H-1,2,4-triazol-3-yl	2.5843	-1.5657
3	CH_3	1-Methyl-1H-tetrazol-5-yl	-5.1635	-7.3135
4	NO_2	1-Methyl-1H-tetrazol-5-yl	1.0287	-3.1213
5	Br	1-Methyl-1H-tetrazol-5-yl	4.2818	-0.1318
6	F	1-Methyl-1H-tetrazol-5-yl	4.4854	-0.3354
7	CH_3	1-Phenyl-1H-tetrazol-5-yl	-5.5909	-7.7409
8	CN	1-Phenyl-1H-tetrazol-5-yl	4.0137	-0.1363
9	F	Pyrimidin-2-yl	2.1299	-2.0202

The ONIOM2 calculations of the complexes display they have weak interaction, which includes the hydrogen bond and the Vander Waals interactions. The results showed plainly that these complexes have comparatively low stability and so, the PLGA polymer can be used as a drug-delivery system. Through the thiazoles derivatives, the compounds 3 and 7 with R=CH_3 and Ar =1-Methyl-1H-tetrazol-5-yl and 1-Phenyl-1H-tetrazol-5-yl, lead to the highest binding energies, and almost other compounds have small binding energies. The interaction energies of the anti-cancer compounds (thiazoline derivatives)-polymer with BSSE were obtained at the B3LYP/6-31G(d) level of theory with the functional counterpoise (CP) scheme and have been reported in table 2. The values of the obtained interaction energies of the anti-cancer drugs (thiazoles derivatives)-polymer systems display relative stability. The molecules 3 and 7 had

higher interaction energies than the others, which demonstrate that the substitutions of 1-Methyl-1H-tetrazol-5-yl and 1-Phenyl-1H-tetrazol-5-yl reason higher binding interactions between the drug and polymer. Results displayed that this PLGA polymer can be employed to modify the anti-cancer and biological activity of the thiazoles derivatives. Also, to confirm the results, natural bond orbital (NBO) was performed on both the thiazoles derivatives and the thiazoles derivatives-polymer. The NBO analysis [27] stresses the role of the intermolecular and the intramolecular interactions. Based on the data, the anti-bonding orbitals of the acceptor can interact with the lone pair of N and S (the thiazole ring), S and N of the thiazoline derivatives being the donor orbital in all compounds.

The NBO analysis of the interaction between the thiazoline derivatives and the PLGA polymer shows that the charge transfers of the thiazoline derivatives change very little. Results displayed that the interactions of drug and polymer are weak and thus the PLGA polymer is suitable for drug delivery of the thiazoline derivatives.

Table 2. Total electronic energies for constituents, thiazoline derivatives (E_A) , PLGA polymer (E_B), and combined systems, E_{AB}, including BSSE and $E_{interaction}$, calculated by ONIOM2 (B3LYP/6-31G(d):UFF) method.

Compound	E_A (Hartree)	E_B (Hartree)	E_{AB} (Hartree)	BSSE (Hartree)	$E_{interaction}$ (kcal/mol)
1	-2025.9419	-5027.0055	-7052.9649	0.0045	-8.1582
2	-1933.6980	-5027.0055	-6960.7214	0.0042	-8.5694
3	-1988.5799	-5027.0055	-7015.6030	0.0031	-9.0987
4	-2137.7151	-5027.0055	-7164.7386	0.0041	-8.7034
5	-2279.4975	-5027.0055	-7306.5200	0.0043	-8.02158
6	-2032.5028	-5027.0055	-7059.5225	0.0034	-8.4022
7	-2219.5925	-5027.0055	-7246.6155	0.0024	-9.47525
8	-2272.4881	-5027.0055	-7299.5115	0.0042	-8.5970
9	-2055.0082	-5027.0055	-7082.0299	0.0031	-8.2077

Conclusion

This study was carried out in order to consider the geometry and binding energy of the complex between PLGA copolymers and the thiazoline derivatives. The investigation of the ONIOM binding energies displayed clearly that these complexes have compratively low stability and so, the PLGA polymer can be used for drug delivery. The substitutions of 1-Methyl-1H-tetrazol-5-yl and 1-Phenyl-1H-tetrazol-5-yl cause more potent binding interactions between the drug and the polymer. Also, the analysis of interaction energy shows that almost all compounds have energy interaction negative and low, again corroborating that the PLGA polymer can be a good carrier for anti-cancer drugs, especially of thiazoline derivatives.

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