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Keywords: Plasmodium falciparum, drug-delivery system, binding energy, computational modeling, hydrogel, hydrogen bond

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Theoretical Study of the Adsorption Process of Antimalarial Drugs into Acrylamide-Base Hydrogel Model Using DFT Methods: The First Approach to the Rational Design of a Controlled Drug Delivery System

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Abstract: The interaction between three widely used antimalarial drugs chloroquine, primaquine and amodiaquine with acrylamide dimer and trimer as a hydrogel model, were studied by means of density functional theory calculation in both vacuum and water environments, using the functional wb97xd with 6-31++G(d,p) basis set and polarizable continuum model (C-PCM) of solvent. According to binding energy, around −3.15 to −11.91 kJ/mol, the interaction between antimalarial compounds and hydrogel model are exothermic in nature. The extent of interaction found is primaquine > amodiaquine > chloroquine. The natural bond orbital (NBO) calculation and application of second-order perturbation theory show strong charge transfer between the antimalarial and hydrogel model. In addition, the results suggest these interactions are polar in nature, where hydrogen bonds play a principal role in stabilization of the complex. Comparing with the gas-phase, the complexes in the water environment are also stable, with suitable values of Log P (Partition coefficient), and dipolar momentum. Consequently, these results encourage to test acrylamide hydrogels as antimalarial delivery systems.

Keywords: *Plasmodium falciparum*; hydrogen bond; hydrogel; computational modeling; binding energy; drug-delivery system

1. Introduction

Malaria is a chronic infection caused by protozoans of the genus Plasmodium and it is considered as one of the deadliest diseases of the planet. Dramatically, 60% of the world's population lives under

risk of contracting this illness; in addition, according to the world Malaria report, nearly 800,000 people died in 2011 because of malaria, and most of them were children [1].

The Increasing antimalarial resistant plasmodium strains has gained the attention of the World Health Organization (WHO) and its effort for eradication or elimination of this illness [2]. This fact, and the toxicity degree of antimalarials, represent a challenge for the scientific community; consequently, overcoming these two facts is a WHO goal of the millennium; however, it is obvious this goal demands multidisciplinary fronts, mainly related to efficient and rational strategies for new delivery systems as well as the development of new antimalarial drugs [2,3].

Drug delivery systems that can control the release behaviors of multiple drugs have recently become an attractive route for enhanced therapeutic effects [4]. Hydrogels, lipids, and polymer-drug conjugate composites, have been studied as drug delivery systems on several illnesses [5,6].

Regarding malaria, several studies about antimalarial-drug delivery have been reported, however, the liposome was one of the most effective systems [7]. Combining primaquine (PQ), chloroquine (CQ) with liposomes and the polymeric matrix, have shown better behavior attaining a decreasing in drugs toxicity [7]. These results represent strong piece of evidence that these types of systems constitute a potential alternative to the conventional administration of drugs [7–9].

A hydrogel is a three-dimensional network polymer, with a size-porous structure depends on the degree of crosslinking [8]. The degree of crosslinking, in turn, determines the degree of swelling of the matrix. They are hydrophilic and biocompatible; thus, these properties allow its uses for biomedical applications mainly as drug-delivery carriers [8]. Nevertheless, the ability of a hydrogel to release a specific drug will depend almost exclusively on the compatibility between both, drug and hydrogel or polymeric matrix [7–12].

Compatibility between drugs and polymers concerns not only the miscibility but also the extent of interaction with no alteration in the chemical structure neither the polymer or the drug [13]. A good interaction (physisorption) between drug and delivery hydrogel/polymers is the first step in the design of drug delivery systems; however, no delivery carrier prepared from a particular polymer will serve as a universal carrier for all drugs. Hence, the assessment of the compatibility plays a pivotal role in successful design [13–17].

Several techniques are used to estimate the compatibility between the polymer and a specific drug. The interaction drug-polymer can be monitored by the construction of delivery profiles from the adsorbed drug into the polymer in order to obtain the kinetic parameters for the process and gain information about the interaction stability. Among the analytical techniques used for this aim, are differential scanning calorimetry (DSC), X-ray powder diffraction (XRD), nuclear magnetic resonance and Fourier transformed infrared spectroscopy (FTIR) [5,6]. However, these methods require a long analysis- time and cannot be used to predict compatibility.

Several kinds of molecular interactions could take place between drugs and polymer matrixes; however, the most important are dipole-dipole interactions and dispersion forces, where the first one is the strongest [18,19]. Generally, the presence of dipole-dipole forces into polymer-drugs systems guarantees the formation of a stable complex [19]. In addition, the dipole-dipole interaction between polymer and water makes the hydrogel swelling easier, then, the release of the drugs through the diffusion process takes place. In this sense, the study of intermolecular interactions between drugs and hydrogels allows adequate selection, but also suitable modification under a polymeric matrix to a specific drug delivery [20–24].

Energetic magnitudes of molecular interactions that come from drug-delivery systems could be estimated through thermodynamic parameters derived from Gibbs function, i.e., enthalpy (ΔH), entropy (ΔS), and free energy changes (ΔG) [19]. The associative interaction between drug-delivery systems could include hydrogen bonding, ionic aggregation, electrostatic interaction, and solvent complex formation. In this sense, the calculation of ΔH, ΔS, and ΔG, describe the entire interaction into the system [16,24–26].

Since the binding energy is of the order of thermal energy, bond formation (or interaction) is reversible; bonds are created and destroyed by the change in temperature or reactant concentration. Thus, thermodynamic function estimations not only represent the extent of interaction but also allows to estimate the dissociation-temperature of the complex as well [26–29].

Computational chemistry represents an excellent tool for estimating molecular interactions, as well as thermodynamic parameters and elucidating reaction mechanisms [30–32]. Nowadays, computational chemistry is the starting point in the design and rational synthesis of drug discovery, herbicides, and insecticides [33,34]. Therefore, using computational chemistry represents a useful tool to estimate the molecular interaction taking place in the drug delivery system, obtaining a predictive model for behavior of these systems. On the other hand, this will allow rational selection of the drug and the suitable system delivery. Moreover, computational simulation of drug delivery systems has emerged for use recently, mainly in controlled anticancer and antituberculosis drug delivery [32,35–39].

Despite the importance of eradicating or mitigating the malarial disease and the potential use of antimalarial delivery system drugs to reach this goal, there is no work reported where computational simulation is used with the purpose of gaining insight the molecular association in the antimalarial-delivery system. For this reason, the main objective of this work is to obtain the electronic and structural properties to determine if the non-covalent addition of drugs to a polymer administration system is favorable, in addition to determining the chemical reactivity using molecular descriptors.

This is the first theoretical study that evaluates the possibility of using polyacrylamide as a matrix for the antimalarial delivery system. Dimer (DAA) and trimer of acrylamide (TAA) were used as the models of polyacrylamide hydrogels; the molecular interactions with chloroquine (CQ), primaquine (PQ) and amodiaquine (AMQ) antimalarials were studied using Density Functional Theory (DFT) as the level of theory and the wb97xd/631++G(d,p) basis set. Electronic transferences energies and charge distribution were calculated by the means of the conceptual DFT jointly with Natural bond orbital, respectively [29,40].

2. Materials and Methods

Computational Methods

The minimum potential energy surface of three antimalarial drugs and their complexes with polyacrylamide models (DAA, TAA, DAA-CQ, DAA-PQ, DAA-AQ, TAA-CQ, TAA-PQ and TAA-AQ) were performed at Density Functional Theory (DFT) level, using functional exchange-correlation of wb97xd, taking into account both short-range and long-range interactions, combined with the basic set 6-31++G(d,p), from Gaussian 16 software [41]. This methodology has demonstrated to be accurate enough to evaluate the interaction between organic molecules [42–44].

The algorithm of Berny analytical gradient was used throughout as the optimization criterion. The requested convergence was density matrix 10^{-9} atomic units, maximum displacement threshold 0.0018 Å, and maximum force threshold 0.00045 Hartree Bohr-1. The nature of stationary points was recognized by calculating and diagonalizing the Hessian matrix (force constant matrix). Minimum energy geometry was characterized by means of normal-mode analysis, by having all positive frequencies.

Frequency calculations were used with the purpose to obtain some important parameters as zero-point vibrational energy (ZPVE), temperature corrections (E(T)) and absolute entropies (S(T)). When the calculation was carried out in the vacuum, the entire species i.e., reactant, complexes and products, were considered an ideal gas, with harmonic frequencies and inertia momentum estimated from the statistic mechanical standard method at 298.15 K and 1 atm [45].

Dimer and trimer of acrylamide (AA) were used as a model of polyacrylamide-based hydrogels. Some reports have proved the trimer of acrylamide (AA) represents a good model for simulation of polyacrylamide properties [30,46].

In order to achieve a better estimation of the binding energy [47,48], the basis-set superposition error (BSSE) correction was applied in the optimized structure of the various clusters by the standard counterpoise method in which the binding energy (BE) of a complex is defined as:

$$\Delta E_b = E_{Complex} - \left[E_{\frac{Model}{DAA} or TAA} + E_{drugs} \right] + BSSE, \quad (1)$$

where $E_{complex}$, E_{Model}, and E_{drugs} are energies of DAA or TAA with drugs, energies of DAA or TAA and Free drugs molecules energies. BSSE is the basis set superposition error [49,50]. The negative value of ΔEb indicates a minimization of energy; on the other hand, the interaction is exothermic [47].

Natural bond orbital (NBO) analysis [29] was used to understand the orbital interactions and changes in charge distribution as well as the bond order into the complex and free models and drugs. From the DFT point of view, the global interaction between drugs and polymers model is described by ΔN, which determines the number of electrons transferred from a molecule A to molecule B, and computed as:

$$\Delta N = \frac{(\mu_B - \mu_A)}{(n_B + n_A)}, \quad (2)$$

where μ is electronic potential, n is global hardness; A and B are acceptor and donor molecules, respectively. A negative value on ΔN indicates the electron flow will be spontaneous from A to B; the reverse direction will have positives values [40].

Solvation energy (ΔGs) and LogP (QSAR properties) were computed. ΔGs were calculated using the C-PCM method, with the wb97xd/6-31++G(d,p) theory level using Gaussian 16 [41]. The Log P was calculated using the Spartan software by selecting the Ghose–Crippen method. This method is independent of the wave energy function, that is, the calculation does not influence whether it obtained using a quantum mechanics, molecular mechanics, or a semi-empirical method. The Ghose–Crippen method was parameterized [51] taking in account 110 atoms/bonds, including the most common atoms such as C, H, O, N, S, and the halogens. Log P is a measure of solubility of the substance in water and into lipid phase (octanol). In this sense, it is necessary that the polymer chains interact with water, in order to swell and release the drugs through a diffusion process. Hence, the hydrophilicity and solvation energy are an important parameter in drug delivery system simulation.

3. Results

3.1. Geometrical Structures and Binding Energy

The study of polymer-antimalarial drugs was carried out using the wb97xd/6-31++G(d,p) level of theory. The minimum energy geometries of antimalarial drugs and complexes DAA-CQ, DAA-PQ, DAA-AQ, TAA-CQ, TAA-PQ and TAA-AQ were confirmed through frequency calculation.

The minimum energy structures are shown in Figures 1 and 2. Application of second derives criterion using frequency calculation proved that all of them were minimum energy geometries.

Table 1 illustrates the geometric parameters for the structure studied in the vacuum. Nevertheless, when several possible interaction geometries of the model and drugs were studied, the structure of minimum energies was always the one in which the dipole-dipole interactions between the drug and polymer model takes place. Besides, Table 1 reveals that the interatomic bonds lengths are in the range ($1.02 \leq A \leq 3.54$) Å. The small interatomic length found for PQ and AQ suggest dipole-dipole interaction. Likewise, this result indicates a better interaction between hydrogel-PQ and AQ than hydrogel-CQ.

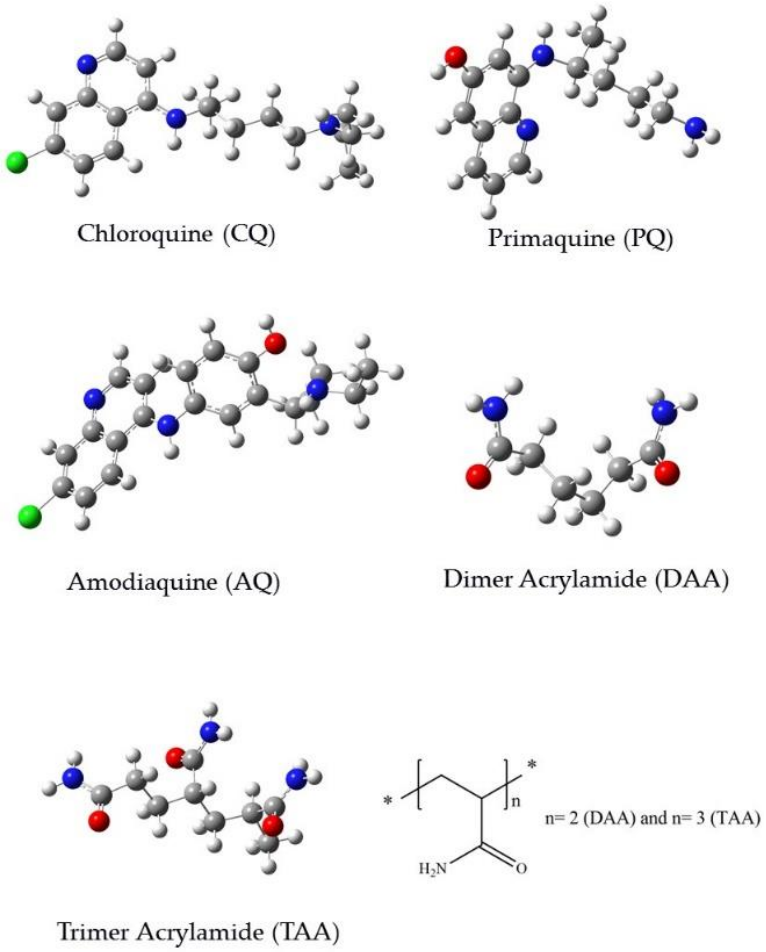

Figure 1. Geometrical structure for the minimum found at the wb97xd/6-31++G(d,p) level of theory for antimalarial compounds as well as the acrylamide dimer and trimer used as model of the polymer.

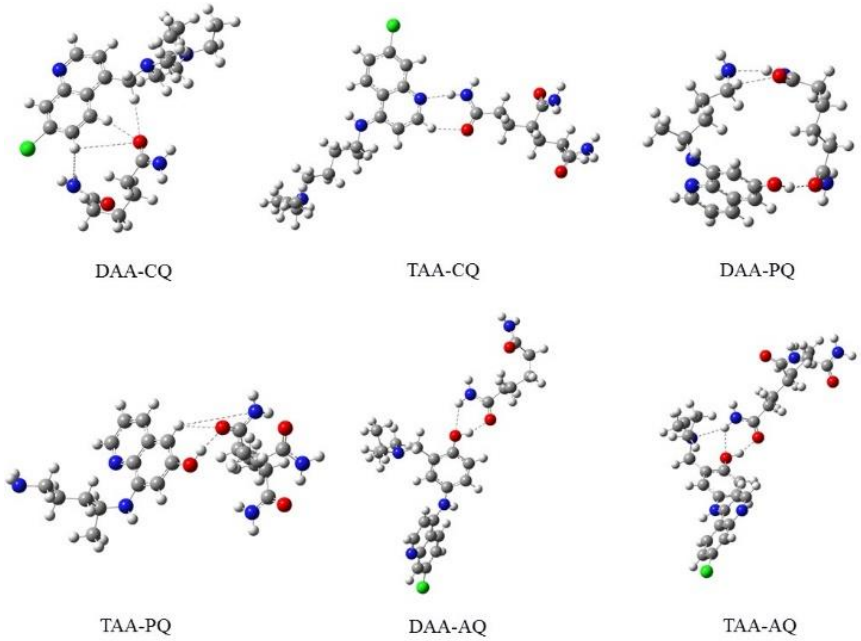

Figure 2. Minimum energy geometry for complexes antimalarial-hydrogel model at the wb97xd/6-31++G(d,p) theory level. Dashed line shows the short-range interactions.

Table 1. Geometry parameters for complexes DAA-CQ, DAA-PQ and DAA-AQ at wb97xd/6-31++G(d,p).

Complex	Bond Length Å					
DAA-CQ	53O-20H 2.450	53O-29H 3.181	53O-14H 3.364	53O-2C 1.230	49N-14H 3.542	49N-50H 1.89
DAA-PQ	5O-59H 2.877	5O-31H 2.853	5O=4C 2.233	58O-59H 0.977	19N-20H 1.025	55N-20H 2.104
DAA-AQ	5O-50H 2.738	5O-48H 2.996	49O-50H 0.990	49O-2H 2.292	1N-2H 1.014	1N-50H 2.679
TAA-CQ	76O-13H 2.339	76O-75C 2.233	17N-78H 2.004	77N-78H 1.027	77N-13H 3.149	77N-75C 1.356
TAA-PQ	65O-37H 2.738	65O-9H 2.752	650-64C 1.242	36O-62H 2.682	36O-37H 0.989	36O-6C 1.354
TAA-AQ	75O-29H 2.692	75O-27H 3.177	28O-29H 0.994	28O-77H 2.297	76N-29H 2.687	76N-77H 1.021

Table 2 shows the binding energy, corrected using BSEE described previously. It could be noted that the higher the acrylamide monomers number, the slower the binding energy. In general, the values of binding energy obtained vary from 62 to −55 kJ/mol and are in the non-covalent range of energy. These results and the equilibrium distances between drugs–polymer (2.00–4.3 Å) indicate these kinds of antimalarial drugs could physically adsorb into the hydrogel matrix; thus, they represent strong evidence to test the possibility of its use as a drug release system.

Table 2. Geometry energy values from drugs (EF), hydrogel model (EH), complex (EC) and binding energy (ΔE) corrected with basis-set superposition error (BSSE) at the wb97xd/6-31++G(d,p) level of theory.

Complex	10^{-5} EF (kcal/mol)	10^{-5} EH (kJ/mol)	10^{-5} EC (kJ/mol)	ΔE_b (kJ/mol)
DAA-CQ	−5.21	−3.11	−11.43	−03.15
DAA-PQ	−4.92	−3.11	−8.030	−06.51
DAA-AQ	−9.25	−3.11	−1.230	−09.78
TAA-CQ	−8.31	−4.66	−12.98	−05.96
TAA-PQ	−4.92	−4.66	−22.78	−13.20
TAA-AQ	−9.25	−4.66	−13.91	−11.51

It could be noted that the binding energy follows the order: ΔE_b (TAA-PQ) < ΔE_b (TAA-AQ) < ΔE_b (TAA-CQ) < 0, suggesting the polymeric matrix interacts better with primaquine and amodiaquine than chloroquine.

In order to understand the interactions between antimalarials and the model of hydrogels, the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbitals (LUMO) were studied. Figure 3 shows the frontier molecular orbital of antimalarial compounds and hydrogel model studies herein.

It could be noted for completely antimalarial drugs, i.e., chloroquine, primaquine and amodiaquine, HOMO orbitals are located into a specific molecular region. Presence of dipolar momentum in these molecules could be used in order to find the best polymeric matrix; consequently, permanent dipolar region or donor-acceptor region into molecules, could warrant the suitable interaction within the dipolar region of the hydrogel model. It can note that TAA has a similar characteristic of the HOMO-LUMO orbital, i.e., acceptor-donor regions, to the drugs frontiers orbitals. Therefore, there is a high probability of a better interaction between antimalarial and hydrogel as the monomer chain increases.

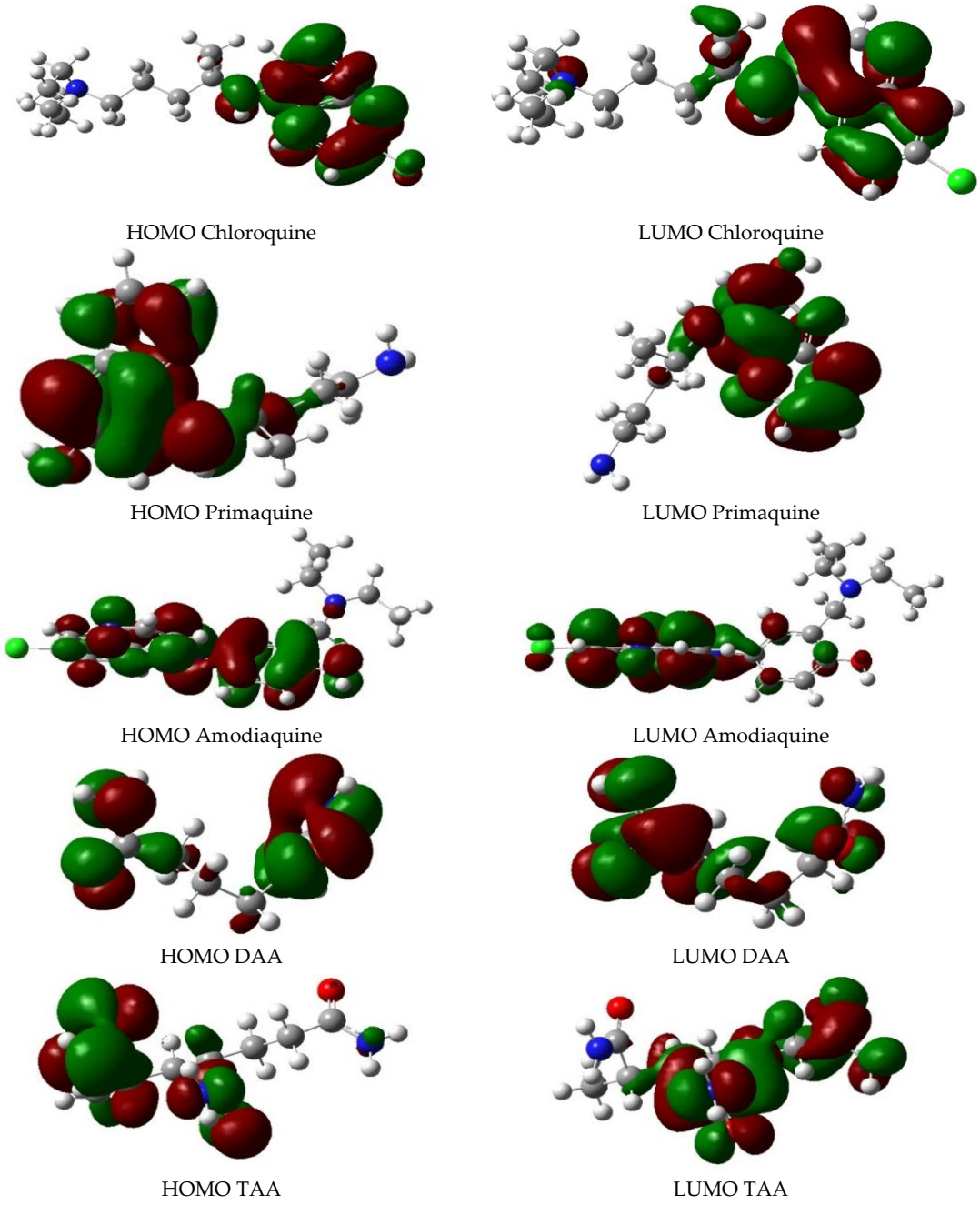

Figure 3. Frontier orbital for the all molecule studies herein. HOMO: High-occupied molecular orbital; LUMO: low unoccupied molecular orbital.

The dual DFT descriptor ΔN was calculated in order to understand the dipole interaction in nature. For this goal, polymeric models were considered as species B and antimalarial compounds as species A. Negatives values in all cases suggest the electrons flux goes from antimalarial to hydrogel model. Likewise, the hydrogel is acting as an acceptor species and drugs are the electronic donors (see Table 3). It can be seen that the electronic potential is negative, confirming the stability of all complexes between the hydrogel model and drugs. These results are strong evidence for the potential use of these complexes as an antimalarial drug delivery system.

Table 3. Molecular descriptors from frontier orbitals, for the complex drugs-hydrogel model at wb97xd/6-31++G(d,p).

Descriptors	DAA-CQ	TAA-CQ	DAA-PQ	TAA-PQ	DAA-AQ	TAA-AQ
HOMO (kJ/mol)	−125.330	−135.991	−120.711	−116.332	−124.690	−129.202
LUMO (kJ/mol)	−40.420	−36.712	−29.243	−26.882	−33.200	−35.202
-(HOMO-LUMO) (kJ/mol)	84.901	99.281	91.472	89.453	91.491	94.002
Global Hardness(n) (kJ/mol)	42.451	49.645	45.731	44.721	45.750	47.001
Electronic potential (μ)	−82.881	−86.353	−74.971	−71.612	−78.941	−82.201
ΔN (Hydrogel-Drugs) (kJ/mol)	−0.0403	−0.036	−0.111	−0.099	−0.040	−0.032

3.2. Natural Bond Orbital (NBO) Analysis

The nature of the intermolecular bond for DAA-CQ, DAA-PQ, DAA-AQ, TAA-CQ, TAA-PQ and TAA-AQ complexes, were studied by means of NBO analysis. In this way, second-order perturbation theory was used in order to gain insights about the donor (*i*) acceptor (*j*) orbital binding. Associated stabilization energy was calculated using Equation (3), from Fock matrix analysis on NBO calculation [29,52–54].

$$E_{ij}^{(2)} = -q_i \frac{\left(F_{ij}\right)^2}{E_j - E_i}, \quad (3)$$

where *qi* is the donor electronic occupied orbital; *Ej* and *Ei* are orbital energies, and *Fij* is out-diagonal Fock matrix element. Table 3 shows the most important interactions between donor and acceptor elements in complexes DAA-CQ, DAA-PQ, DAA-AQ, TAA-CQ, TAA-PQ, and TAA-AQ. In all cases, the donor element is the lone pair from N, Cl, or O atoms, while the acceptor one is the antibonding, σ*, C-H, O-H, and N-H orbitals, confirming the molecular interactions are mainly dipolar in nature.

A close inspection of Table 4 reveals the most important interaction between PQ and AQ with TAA, occurs through a hydrogen bond with high stabilization energies in both PQ and AQ. Moreover, these results imply a greater extent for the interaction of the hydrogel model with primaquine and amodiaquine, but a little interaction with chloroquine. Likewise, these results are in agreement with the large bond energies obtained for TAA-PQ and TAA-AQ in comparison with the TAA-CQ complex.

Table 4. The second order perturbation theory for the drugs-Acrylamide trimer by using Fock matrix from Natural Bond Orbital (NBO) calculation at the wb97xd /6-31G++(d,p) theory level.

Complex	Donor (i)	Acceptor (j)	E^2_{ij} (kJ/mol)
TAA-CQ	LP(1) 76N	BD* 77N-H78	14.39
	LP(1) Cl	BD* 11C-H13	4.140
	LP(2) Cl	BD* 11C-H13	8.870
TAA-PQ	LP(1) 65O	BD* 36O-H37	29.12
	LP(2) 65O	BD* 36O-H37	80.50
	LP(2) 36O	BD* 61C-H62	2.170
TAA-AQ	LP(1) 65O	BD* 36O-H37	29.46
	LP(2) 65O	BD* 36O-H37	97.74
	LP(2) 36O	BD* 61C-H62	2.180

3.3. Water Environment Behavior

Quantitative structure–activity relationship (QSAR) approaches, as progressive tools in modeling and prediction of many physiochemical properties, offers a fast measure of predictability in the absence of extensive experimental or computed data on compound properties. In this respect, the QSAR properties derived from Hyperchem software were calculated, with the purpose to estimate the performance of complexes in the water environment. Table 5 shows three fundamental properties that have a great influence on a drug-delivery system: hydrophilicity (Log P), solvation free energy

(Gibbs free energy), and dipole momentum. These descriptors allow estimating the behavior of the drugs, once they are delivered into the receptor.

Table 5. Quantitative structure–activity relationship (QSAR) properties of complex TAA-antimalarial, in water environment.

Descriptor	TAA-AQ	TAA-CQ	TAA-PQ
LogP	−7.550	−10.00	−13.48
Gibbs free energy in water (kJ/mol)	−146.54	−135.75	−125.23
Dipole momentum, μ, (Debye)	6.9400	6.5190	7.4930
Stabilization energy (E_{H2O}-Egas) kJ/mol	−24.96	−31.32	−22.27

According to Table 5, all of the complexes have solvation energy <0, thus, all of them are stable in water. In addition, the values of Log P indicate all complexes are hydrophilic (Log P < 0) and polar in nature ($\mu > 0$). These results are strong evidence about the possibility to test these models as a drug-delivery system; polarity and hydrophilicity are a warranty of the interaction of water and polymeric chain; in this sense, hydrogels would start to swell and then, release the antimalarial drugs.

4. Conclusions

Minimum energy structure of Chloroquine, (CQ), Primaquine (PQ) and Amodiaquine (AQ) and their Van der Waals complexes with dimer and trimer of acrylamide, were calculated using density functional theory (B3LYP/6-31++G(d,p) in both gas phase and water solution (C-PCM). The binding energy suggests all compounds could form a stable complex with acrylamide hydrogel in both vacuum and water. The second order perturbation theory suggests the complexes formed mainly through dipole-dipole interaction and hydrogen bonds play a pivotal role in the stability of these complexes. Additionally, QSAR properties as Log P, solvation free energy, and dipolar momentum, μ, show the complexes could be soluble, stable and could interact with water molecules, allowing the swelling of the hydrogel and release of the antimalarial drugs. The results show herein suggest amodiaquine (AQ) and primaquine (PQ) are suitable antimalarial drugs for delivery from an acrylamide-based hydrogel.

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