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REVIEW PAPER

Computational study of the fullerene effects on the properties of 16 different drugs: A review

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Abstract

In this study, the influence of fullerene junction on the chemical features of 16 different drugs including Captopril, Clonidine, Methyldopa, Naphazoline, Oxymetazoline, Tetrahydrozoline, Xylometazoline, Tolazoline, Clemastine, Procyclidine, Tyramine, Nicotine, Dextroamphetamine, Fluoxetine, Metoprolol and Enalapril was investigated computationally. For this purpose, the mentioned drugs were placed on the fullerene firstly. Then single molecules of drugs and their fullerene derivatives were optimized geometrically. Afterwards, adsorption energies and also some chemical properties such as HOMO and LOMO energy levels, energy gap, chemical hardness, electrophilicity, maximum transmitted electron and dipole moment in the reactions were determined for each drug and their fullerene derivatives. In the next step, the results were presented as tables and charts, and the effect of fullerene on the chemical traits of the drugs was evaluated. The obtained results indicate that fullerene has a strong interaction with methyldopa, Dextroamphetamine, Tyramine, Tolazoline, Enalapril and Metoprolol drugs. And this nanostructure can be an electroactive sensing material or a prominent carrier for these drugs. All of the calculations were implemented by Density functional theory (DFT) in the level of B3LYP/6-31G (d).

Keywords: *Adsorption energy; Density functional theory (DFT); Drug delivery; Electrochemical sensor; Fullerene.*

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INTRODUCTION

Nowadays bombarding cancer cells with Nanoscale weapons or recognition the ambush of viruses in the body by Nanoparticles are not a dream or a science fiction story anymore and these subjects have become true examples of Nanotechnology applications in this golden era which have influenced health and medicine science dramatically [1-5]. Controlled release of drugs, reducing side effects and drug toxicity, improved absorption, increasing drug efficiency in the treatment process and targeting specific tissues or malignant tumors are the unique goals which pharmaceutical industries are eager to achieve, through Nanotechnology [6-8]. To ensure that a drug has a therapeutic effect, it should be protected until it reaches to the target tissue and it's physical, chemical and biological properties must be preserved and unfortunately, many drugs can be damaged or decomposed by getting exposure to the stomach acid or by other phenomena. In addition, some drugs such as anticancer ones or tricyclic antidepressants may lead to negative and intolerable side effects that can affect all organs of the body and drug delivery by Nanocarriers can solve this issue via conveying the drug to the target organ. All of the mentioned matters demonstrate the importance of drug

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delivery [9-13].

Nano drug carriers including fullerenes usually keep drug molecules like a reservoir in themselves. These systems release the drug at a specific dosage and in a particular place which might eventuate to improving the function of the drug and reducing its side effects [14-16]. Two categories of compounds that have recently been highlighted in drug delivery are carbon nanotubes and fullerenes. Their size, shape and surface properties have made them available for utilization in drug delivery [17]. In order to increment the solubility, biocompatibility and also delivering different materials the surface of these particles would be functionalized with various compounds and groups. Nanostructures have the potential to be used as a carrier for biologic molecules such as proteins, DNA and pharmaceutical compounds, because these materials can be loaded on the nanostructures, easily [18].

In addition, the matters of counterfeit pharmaceutical products and quality control of medicines have become a cosmopolitan concern and dilemma. And one of the best ways for evaluating the quality of a medicine is determination of its active ingredient content [19]. Despite the fact that many analytical methods including high-performance liquid chromatography (HPLC), capillary electrophoresis, gas chromatography, Uv-Visible spectrophotometry and radioimmunoassay (RIA) have been designed for determination of drugs, but most of them have considerable drawbacks such as needing to intricate and expensive instrumentations, being time consuming, requiring sample treatment steps which leads to the destruction of the sample matrices and needing sophisticated operators for implementing the experiments [20-23]. Fortunately, electrochemical sensors can be a good alternative for the aforementioned techniques because they have outstanding upsides such as being economical, portability, simplicity, being time saving and having ideal sensitivity and wide linearity domain [24]. However, the first and main step of developing an electrochemical sensor is finding an appropriate electroactive sensing material. On the other hand, C_{60} fullerene (Fig. 1) is a nanostructure which has a great surface/volume ratio and this feature provides a large adsorption area that is available for adsorption procedure. And its performance for detection of gases was also evaluated in prior reports. Moreover, its interaction with various drugs was also inspected due to its potential capability in drug delivery. Indeed, Fullerenes have the privilege to enter and exist in the inner hydrophobic fluids of cells and tissues because of their spherical shape. Moreover, its nanoscale structure gives these substances prominent nano traits and these superiorities could eventuate to outstanding pharmaceutical properties [25-29].

Therefore, the interaction of C_{60} fullerene with 16 different drugs was investigated, in this research. One of the studied groups is imidazolium derivatives that have sympathomimetic activities including Naphazoline, Oxymetazoline, Tetrahydrozoline, and Xylometazoline. These drugs are selective alpha agonists and have strong alpha-adrenergic effects· This group of drugs is usually used for alleviating congestion of nose, irritation, and itching of eyes and they induce their decongestant effect by tightening the swollen and inflamed veins [30]. The second evaluated drug is Procyclidine that is used for treating Parkinson, akathisia and acute dystonia by blocking central cholinergic receptors and balancing cholinergic and dopaminergic activity. Clemastine was the third investigated drug; this chemical is categorized in antihistamines group and is widely prescribed for allergy, sneezing, and rhinorrhea. Six antihypertensive medications including Captopril, Clonidine, Enalapril, Tolazoline, Metoprolol and Methyldopa were also inspected. This type of drugs usually lowers the blood pressure by stimulating alpha-adrenergic central receptors and reducing total peripheral resistance [31-34]. Nicotine and Dextroamphetamine are two drugs that are used for treating smoking addiction and ADHD respectively. They influence Central Nervous

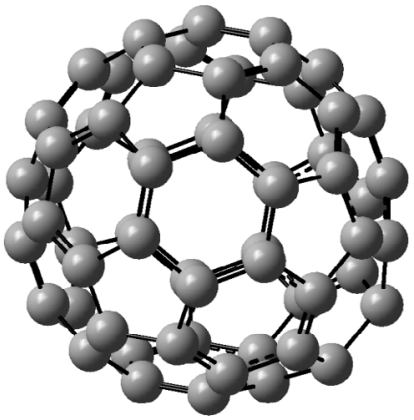

Fig. 1. C_{60} fullerene nanostructure.

System (CNS) and may create some negative side effects and disorders [35-40]. The next studied drug is Tyramine; it acts as a neuromodulator which provokes the growth of neurons and binds as an agonist to $TAAR_1$ and $TAAR_2$ receptors in the brain and peripheral tissues [39]. Fluoxetine is the last investigated drug; this compound is a selective serotonin reuptake inhibitor which is widely prescribed for treating depression and bipolar disorder. Fluoxetine has negative effects on digestive and sexual systems. So, drug delivery can play a decisive role in promoting the safety of these drugs and in order to estimate the capability of fullerene as a nano drug carrier for the mentioned drugs, and also evaluating its performance as an electroactive sensing material in constructing electrochemical sensors, it is very important to evaluate the influence of this nanostructure on the chemical properties of the drugs in advance.

In this regard, it was decided in this paper to review the impact of the fullerene on the chemical traits of 16 various drugs that had been inspected by the author in the past [40-51].

EXPERIMENTAL

Owing to the fact that this paper is a review of the author's previous works. Explaining the utilized computational methods in details seems necessary for better clarifying of the subject. In our former works, the structures of Captopril, Clonidine, Methyldopa, Tolazoline, Clemastine, Naphazoline, Oxymetazoline, Tetrahydrozoline, Xylometazoline, Procyclidine, Tyramine, Nicotine, Dextro-amphetamine, Metoprolol, Enalapril and Fluoxetine (Fig. 2) drugs and their simulated fullerene derivatives (Fig. 3) were designed primarily by using Gauss View 3.1 and nanotube modeler 1.3.0.3 softwares. Afterwards, geometrical

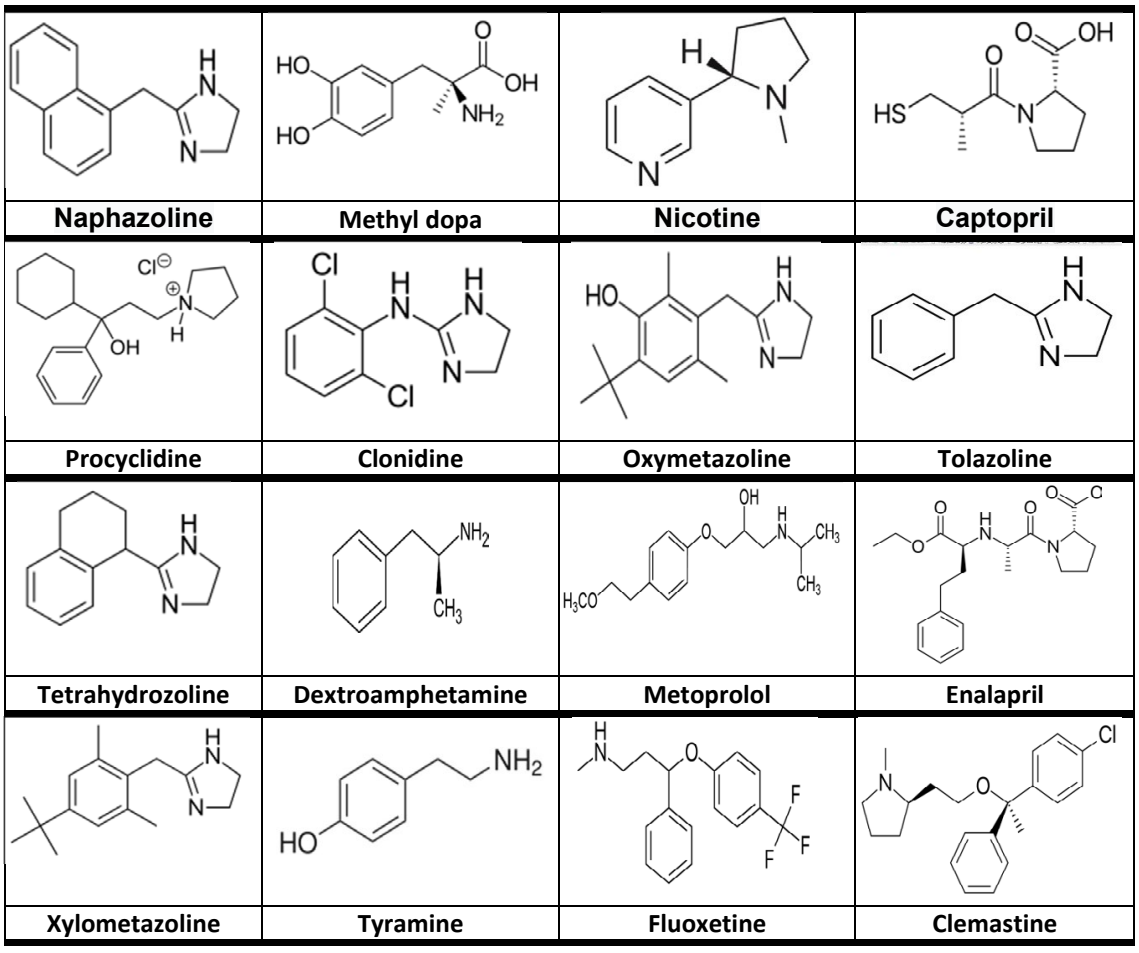

Fig. 2. Chemical structures of Captopril, Clonidine, Methyldopa, Naphazoline, Oxymetazoline, Tetrahydrozoline, Xylometazoline, Tolazoline, Clemastine, Procyclidine, Tyramine, Nicotine, Dextroamphetamine, Fluoxetine, Metoprolol and Enalapril.

optimization and HOMO-LUMO orbitals related calculations were performed on them with Spartan software. It should be noted that each drug was placed near the surface of fullerene in various positions and the geometrical optimization step was performed on all of them and their SCF total energy were also calculated. And the structures of drug-fullerene derivatives that had the lowest SCF total energy were selected for the rest of the calculations.

Initial optimizations and HOMO-LUMO orbitals related calculations were carried out on structures by using the Density functional theory in the level of B3LYP/6-31G(d). This basis set was chosen in all works because in former studies that carried out by others, it produced results that were in a great accordance with experimental findings. All of the computations took place in Windows XP operating system by considering water as the solvent, the pressure of 1 atmosphere and temperature of 298 K. After quantum computing, all the results were first extracted and final conclusions were concluded on their base.

Some structural properties in the drugs' structures and their fullerene derivatives including HOMO and LUMO Gap (HLG), chemical hardness (η), Chemical potential (μ), electrophilicity (ω) and ΔN_{max} were also investigated. In chemistry, HOMO and LUMO are types of molecular orbitals and the energy difference between them is termed the HOMO–LUMO gap (HLG). The HOMO is highest occupied molecular orbital and LUMO is lowest unoccupied molecular orbital. (HLG) can be acquired by Equation (1), in Equation (2); η is the chemical hardness which can be calculated by the mentioned formula. The electrophilicity Index (ω) in atomic units is a measure of the electrophilic power of a molecule that is given by Equation (3). The maximum amount of electronic charge index (ΔN_{max}) describes the charge capacity of

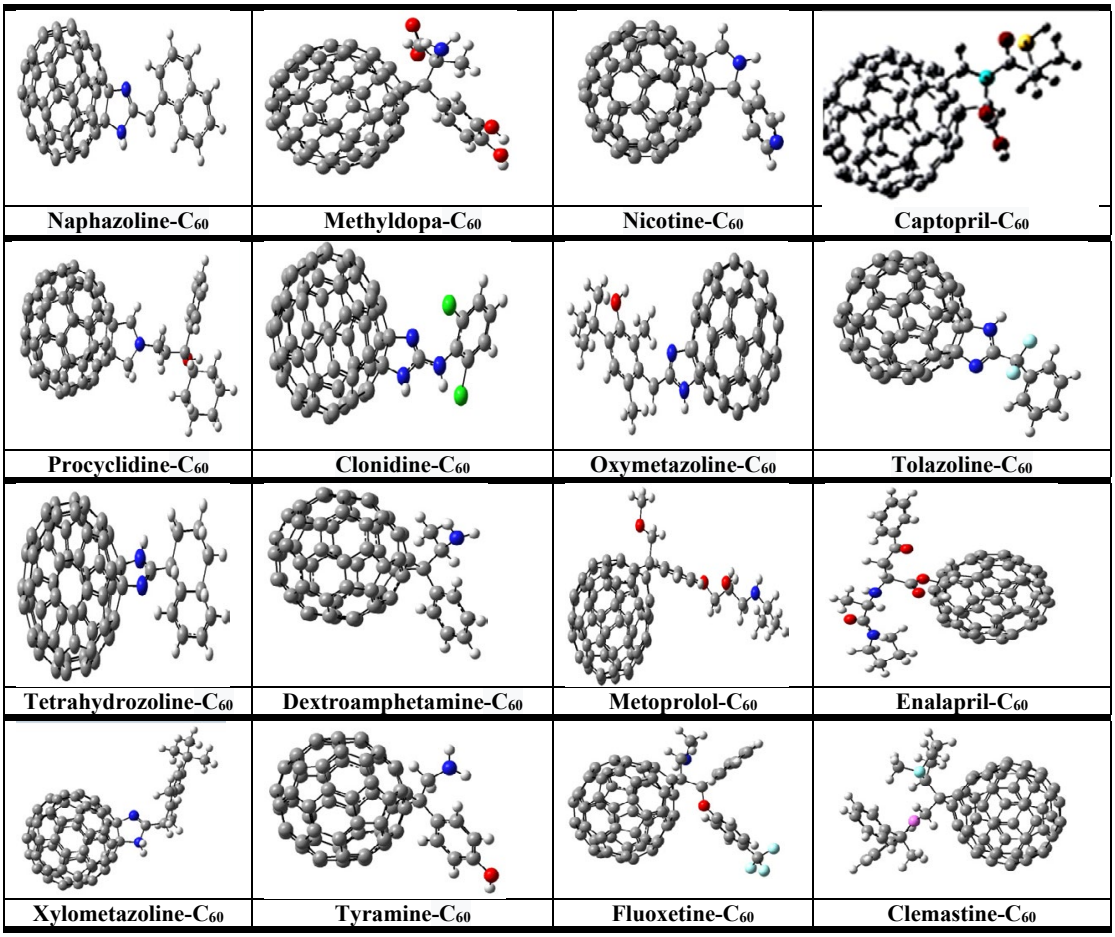

Fig. 3. Chemical structures and names of fullerene derivatives of investigated drugs.
Atom colors: grey—carbon, white—hydrogen, blue—nitrogen, red—oxygen, green— Chlorine and yellow—Sulfur.

the molecule that the electrophone system may accept; it can be calculated by Equation (4).

$$HLG=E_{LUMO} - E_{HOMO} \quad (1)$$

$$\eta = (E_{LUMO} - E_{HOMO})/2 \quad (2)$$

$$\omega = \mu^2/2\eta \quad (3)$$

$$\Delta N_{max}=- \mu/ \eta \quad (4)$$

RESULTS AND DISCUSSIONS

Calculation and verifying the Adsorption energy value (E_{ads})

Adsorption energy is an appropriate parameter for evaluating the stability and mechanism of the adsorption process. In this regard, after optimization step was performed on the fullerene, drugs' molecules and the derived products from the interaction between fullerene and drugs' molecules, the adsorption energy values were calculated from Equation (5):

$$E_{ads} = [E_{C60-R}]-[E_{C60} + E_R] \quad (5)$$

In this formula, E_{C60}, E_R, E_{C60-R}, represents the total electronic energy of the optimized structures of fullerene, drug molecule and fullerene-drug derivative, respectively. Then, the obtained total electronic and adsorption energy values were presented in (Table 1). As it can be witnessed from the table, methyldopa, Dextroamphetamine, Tyramine, Tolazoline, Enalapril and Metoprolol have a strong interaction with the fullerene because their adsorption energies are so negative. It seems the adsorption of the cited drugs on the fullerene surface is exothermic and experimentally feasible from the energetic point of view. Moreover, owing to their great negative obtained adsorption energy values, it can be deduced that methyldopa, Dextroamphetamine, Tyramine, Tolazoline, Enalapril and Metoprolol could make a covalent bond with the fullerene. And this strong interaction is an outstanding privilege for developing a sensor or a drug delivery system for these drugs. But on the other hand, the adsorption energy values of other drugs including Captopril, Naphazoline, Procyclidine, Tetrahydrozoline, Xylometazoline, nicotine, clonidine, Oxymetazoline, Fluoxetine and Clemastine are extremely positive. This means that these drugs do not have any interaction with the fullerene and their adsorption process on the surface of fullerene is endothermic and probably impossible experimentally.

Polarity of molecules

The dipole moment is a key factor that has a direct relationship with solubility. Compounds with higher dipole moments have better solubility

Table 1. Calculated total electronic energy (eV) and Adsorption energy (eV) of the derived products from the interaction between drugs' molecules and fullerene in the temperature of 298 K.

	Total electronic energy (eV)		Adsorption energy (eV)
	R	C_{60}-R	C_{60}-R
Captopril	-16349.43	-75603.26	1782.33
Naphazoline	-17614.00	-77287.31	1362.86
Procyclidine	-23420.67	-83214.28	1242.56
Tetrahydrozoline	-16614.56	-76287.91	1362.82
Xylometazoline	-19832.30	-79505.61	1362.85
Methyldopa	-20253.97	-82414.25	-1124.11
Dextroamphetamine	-11032.54	-73192.97	-1124.27
Tyramine	-11931.70	-73696.06	-728.20
Nicotine	-12504.86	-72095.23	1445.80
Clonidine	-38860.28	-98533.79	1362.66
Oxymetazoline	-21868.11	-81531.87	1372.40
Tolazoline	-11393.93	-78504.04	-6073.94
Fluoxetine	-29428.60	-87438.64	3026.12
Enalapril	-31089.76	-92853.71	-727.78
Metoprolol	-23435.06	-85198.58	-727.35
Clemastine	-25575.46	-86310.76	300.86

in polar solvents like water. In addition, the results of calculations are given in (Table 2). Exhibit that all of the evaluated drugs have lower dipole moment values than their fullerene derivatives except Xylometazoline. Indeed, the solubility of the drugs in polar solvents has been improved after binding with fullerene because of the significant rise in the dipole moment value after linking to the surface of fullerene. The conductivity and reactivity of the drugs can also enhance by incrementing the amount of dipole moment. But in the case of Xylometazoline, attachment to fullerene has lead to decreasing of solubility due to the fall of the dipole moment from 18.5382 to 10.4801. Another valuable matter that can be realized from the table is that the dipole moment of fullerene is zero. This fact implies that this nanostructure has an extremely poor solubility in water. Therefore, the sensor that is developed on the basis of this nanostructure as an electroactive sensing material could have a long lifetime. Because most of the electrochemical sensors such as ion selective electrodes lose their sensitivity after a while due to the leakage of the sensing material to the solutions' matrices. And utilizing more lipophilic compounds that are not soluble in water usually increases the lifespan of this type of sensors [17].

HOMO and LUMO energies and band gap

The HOMO and LUMO related parameters were computed by Spartan software. The band gap (HLG) was calculated by Equation 1 and the

Table 2. The obtained dipole moment values for drugs, fullerene and drug-fullerene derivatives.

Drugs		Dipole moment (deby)
Fullerene	C_{60}	0.0000
Captopril	C_{60}-R	6.7763
	R	6.0588
Naphazoline	C_{60}-R	15.7764
	R	10.8746
Procyclidine	C_{60}-R	14.9788
	R	11.5260
Tetrahydrozoline	C_{60}-R	32.5633
	R	6.9693
Xylometazoline	C_{60}-R	10.4801
	R	18.5382
Methyldopa	C_{60}-R	5.6772
	R	4.3522
Levodopa	C_{60}-R	5.5242
	R	4.2838
Dextroamphetamine	C_{60}-R	4.2521
	R	1.7192
Tyramine	C_{60}-R	4.3391
	R	2.6705
Nicotine	C_{60}-R	4.1479
	R	4.0017
Clonidine	C_{60}-R	5.2380
	R	1.8434
Oxymetazoline	C_{60}-R	5.0970
	R	3.9901
Tolazoline	C_{60}-R	3.6500
	R	3.1525
Fluoxetine	C_{60}-R	5.8517
	R	5.5197
Enalapril	C_{60}-R	7.0587
	R	2.6400
Metoprolol	C_{60}-R	9.1473
	R	4.8413
Clemastine	C_{60}-R	5.2053
	R	2.2173

acquired results are tabulated in (Table 3). The band gap is a good parameter for investigating the conductivity and reactivity of a compound. The materials with lower energy gaps are more conductive and reactive than the substances with higher energy gaps. In other words, by increasing the HLG, the conductivity gets lower and lower. As it can be observed from the table the energy gap values of all of the inspected drugs after adsorption process on the fullerene surface have reduced significantly. In fact, a drastic surge has happened in the conductivity and reactivity of the system after the linkage of drugs on the surface of fullerene. Due to the fact that the adsorption energies for methyldopa, Dextroamphetamine, Tyramine, Tolazoline, Enalapril and Metoprolol were greatly negative among all of the investigated drugs and the band gap of these drugs has also decreased after linking to the fullerene. It seems fullerene can be used for determination of these drugs especially by conductometric titration method because this technique is based on the alterations that occur in the conductivity of the system [52].

Electrophilicity and the maximum amount of electronic charge index

The electrophilicity concept was described for the first time in 1999 by Parrand colleagues. The electrophilicity and the maximum amount of electronic charge indices are pertinent to electronic charge. The maximum amount of electronic charge index (ΔN_{max}), describes the charge capacity of the molecule that the electrophone system can

Table 3. The obtained HOMO and LUMO energy and band gap values for the investigated substances.

Drugs		E_H (eV)	E_L (eV)	HLG(eV)
Fullerene	C_{60}	-8.0273	-0.4898	7.5376
Captopril	C_{60}-R	-6.0744	-3.2599	2.8145
	R	-6.2945	-0.8006	5.4940
Naphazoline	C_{60}-R	-10.1610	-2.9818	7.1792
	R	-10.3686	-0.4503	9.9183
Procyclidine	C_{60}-R	-10.2244	-2.7361	7.4883
	R	-11.7961	1.1312	12.9273
Tetrahydrozoline	C_{60}-R	-9.3972	-4.1650	5.2322
	R	-12.0193	-4.0921	7.9272
Xylometazoline	C_{60}-R	-10.3090	-2.9345	7.3746
	R	-11.1319	-0.2068	10.9251
Methyl dopa	C_{60}-R	-7.5800	-0.3693	7.2107
	R	-8.2997	3.8529	12.1526
Levodopa	C_{60}-R	-7.6037	-0.3796	7.2241
	R	-8.3057	3.9130	12.2187
Dextroamphetamine	C_{60}-R	-7.5340	-0.3382	7.1958
	R	-8.5180	4.2798	12.7978
Tyramine	C_{60}-R	-7.5637	-0.3464	7.2173
	R	-8.3359	3.7900	12.1259
Nicotine	C_{60}-R	-7.6309	-0.4223	7.2086
	R	-9.3253	3.5598	12.8851
Clonidine	C_{60}-R	-7.5903	-0.3491	7.2412
	R	-8.7147	3.1486	11.8634
Oxymetazoline	C_{60}-R	-7.9299	-0.5197	7.4102
	R	-8.2178	4.0999	12.3178
Tolazoline	C_{60}-R	-7.6301	-0.3864	7.2437
	R	-8.7642	3.7190	12.4832
Fluoxetine	C_{60}-R	-7.8211	-0.4112	7.4099
	R	-9.2282	3.1818	12.4100
Enalapril	C_{60}-R	2.1633	9.5240	7.3607
	R	-7.8573	-0.4275	7.4298
Metoprolol	C_{60}-R	-7.6382	-0.2395	7.3988
	R	-8.1008	4.1729	12.2737
Clemastine	C_{60}-R	-5.3802	3.1203	8.5006
	R	-8.4693	3.8267	12.2960

accept, this parameter is calculated by Equation 4. If a compound has a positive value of ΔN_{max}, it will act as an electron donor. But on the other hand, the electrophilicity index (ω) is a variable that shows the electrophilic power of a material and it could be calculated from the Equation 4. When two molecules react with each other, one of them behaves as a nucleophile. But, the other one acts as an electrophile. A molecule that has a great electrophilicity index demonstrates higher electrophilic power. Hence, the amount of ω describes the propensity of the system to obtain an additional electronic charge from the environment. The calculated ω and ΔN_{max} values are presented in (Table 4). As it is obvious from the provided data in the following table, the electrophilicity and maximum amount of electronic charge indices for fullerene are 2.4060 (eV) and -30.7479 (eV) respectively. By a closer look in the table, it can be concluded that fullerene shows different behaviors towards the various evaluated drugs, because the electrophilicity value of fullerene is greater than the electrophilicity values of methyldopa, Levodopa, Dextroamphetamine, Tyramine, nicotine, clonidine, Oxymetazoline, Tolazoline, Enalapril and Metoprolol drugs with a tangible discrepancy. This matter reveals that in the interaction of the mentioned drugs and the fullerene, this nanomaterial acts as a Lewis acid due to its high affinity for accepting the electron. Whilst, methyldopa, Levodopa, Dextroamphetamine, Tyramine, nicotine, clonidine, Oxymetazoline, Tolazoline, Enalapril and Metoprolol

Table 4. The electrophilicity and maximum amount of electronic charge indices for fullerene, drugs, and fullerene- drug derivatives.

Drugs		ω (eV)	ΔN_{max}(eV)
Fullerene	C_{60}	2.4060	-30.7479
Captopril	C_{60}-R	7.7394	-90.2478
	R	2.2907	-35.1417
Naphazoline	C_{60}-R	6.0151	-49.8155
	R	2.9504	-29.6825
Procyclidine	C_{60}-R	5.6079	-47.0966
	R	2.1996	-22.4492
Tetrahydrozoline	C_{60}-R	8.7885	-70.5334
	R	8.1862	-55.3046
Xylometazoline	C_{60}-R	5.9458	-48.8673
	R	2.9420	-28.2416
Methyldopa	C_{60}-R	2.1909	-29.9984
	R	0.4068	-9.9572
Levodopa	C_{60}-R	2.2056	-30.0711
	R	0.3948	-9.7827
Dextroamphetamine	C_{60}-R	2.1531	-29.7695
	R	0.3509	-9.0115
Tyramine	C_{60}-R	2.1673	-29.8235
	R	0.4261	-10.2014
Nicotine	C_{60}-R	2.2492	-30.3998
	R	0.6450	-12.1759
Clonidine	C_{60}-R	2.1763	-29.8353
	R	0.6529	-12.7671
Oxymetazoline	C_{60}-R	2.4087	-31.0285
	R	0.3442	-9.0969
Tolazoline	C_{60}-R	2.2179	-30.1145
	R	0.5098	-10.9979
Fluoxetine	C_{60}-R	2.2865	-30.2312
	R	0.7365	-13.2578
Enalapril	C_{60}-R	2.3312	-30.6277
	R	0.7365	-13.2578
Metoprolol	C_{60}-R	2.0969	-28.9728
	R	0.3143	-8.7085
Clemastine	C_{60}-R	4.0872	-7.2343
	R	11.9248	-10.2742

drugs act as an electron donor or a Lewis base because their tendency to the electron is lower than fullerene. In other words, a complex can be formed between the fullerene and methyldopa, Levodopa, Dextroamphetamine, Tyramine, nicotine, clonidine, Oxymetazoline, Tolazoline, Enalapril and Metoprolol drugs due to the difference in electrophilicity. And obtained ΔN_{max} values have also confirmed this result since the maximum amount of electronic charge index of fullerene is lower than all of the cited drugs' ones. But on the other hand, there is not any meaningful discrepancy between the electrophilicity value of fullerene and Captopril, Naphazoline, Procyclidine, Tetrahydrozoline and Xylometazoline drugs because their electrophilicity values are near to each other. The closeness between the ΔN_{max} index of the fullerene and the referred drugs is another proof that supports this idea. Thus, the interaction of fullerene and Captopril, Naphazoline, Procyclidine, Tetrahydrozoline and Xylometazoline might be very poor and weak [50-52]. The Clemastine was the only medicine that its electrophilicity was greater than fullerene. It means in the case of the Clemastine, fullerene plays the role of a Lewis base and it donates the electron to this drug and Clemastine acts as a Lewis acid due to its high eager for accepting the electron. Therefore, the complexation between fullerene and Clemastine can be feasible.

The next valuable point that can be understood from the table is that after the binding of drugs to the fullerene, the electrophilicity index has experienced a noticeable increase in all cases except Clemastine and Enalapril drugs. Indeed, C_{60}-R structures are more electrophile and stronger Lewis acids than single molecules of drugs. The maximum amount of electronic charge index (ΔN_{max}) values have also confirmed this result because after adsorption of drugs on the fullerene surface a substantial fall has occurred in ΔN_{max} values for all drugs except Clemastine and Enalapril. The obtained results from ΔN_{max} and ω are in a great accordance with each other [12,17].

Chemical Hardness

Chemical hardness has experienced a noticeable decline with the connection of drugs to the fullerene in all cases. By abating chemical hardness value, the structure becomes smoother chemically and transmission of electrons which is necessary for the implementation of chemical reactions can be done more easily. Therefore, it can be inferred that the reactivity of drugs has improved after binding to the fullerene (Table 5).

Table 5. The chemical potential and chemical hardness values for fullerene, drugs, and fullerene- drug derivatives.

Drugs		η(eV)
Fullerene	C_{60}	3.7688
Captopril	C_{60}-R	1.4072
	R	2.7470
Naphazoline	C_{60}-R	3.5896
	R	4.9591
Procyclidine	C_{60}-R	3.7442
	R	6.4637
Tetrahydrozoline	C_{60}-R	2.6161
	R	3.9636
Xylometazoline	C_{60}-R	3.6873
	R	5.4626
Methyldopa	C_{60}-R	3.6054
	R	6.0763
Levodopa	C_{60}-R	3.6120
	R	6.1094
Dextroamphetamine	C_{60}-R	3.5979
	R	6.3989
Tyramine	C_{60}-R	3.6086
	R	6.0630
Nicotine	C_{60}-R	3.6043
	R	6.4426
Clonidine	C_{60}-R	3.6206
	R	5.9317
Oxymetazoline	C_{60}-R	3.7051
	R	6.1589
Tolazoline	C_{60}-R	3.6218
	R	6.2416
Fluoxetine	C_{60}-R	3.7050
	R	6.2050
Enalapril	C_{60}-R	3.6803
	R	3.7149
Metoprolol	C_{60}-R	3.6994
	R	6.1369
Clemastine	C_{60}-R	4.2503
	R	6.1480

CONCLUSIONS

Investigating the interaction of drugs with nanomaterials is of a great importance for developing drug delivery systems and also designing electrochemical sensors for accurate determination and quality control of drugs. Hence, the influence of C_{60}-fullerene on the chemical properties of 16 various drugs has been evaluated, in this study. According to the Carried out studies, among all of the inspected drugs only methyldopa, Dextroamphetamine, Tyramine, Tolazoline, Enalapril and Metoprolol can be adsorbed on the surface of fullerene exothermically and make a strong interaction with this nanostructure due

to their great negative adsorption energies. The calculated band gap energies demonstrate that conductivity and reactivity of drugs have been ameliorated after binding with fullerene because the fullerene-drug derivatives have lower band gap than the single drugs. And owing to the remarkable variations that carried out in the energy gap and consequently in the conductivity of the system. Fullerene can be helpful for determination of drugs by conductometric methods. The achieved electrophilicity and maximum amount of electronic charge indices show that the fullerene and some of the drugs have the potential to form a complex with each other. The findings reveal that after the linkage of drugs to the fullerene, they become more electrophile and stronger Lewis acids in most cases. The dipole moment values have increased in all cases except Xylometazoline by the junction of drugs to the fullerene and their solubility in water has ameliorated. In terms of chemical hardness, all of the studied drugs have become smoother after adsorption on the surface of fullerene. To conclude, the results indicate that fullerene can be an appropriate nano-carrier and a sensing material for methyldopa, Dextroamphetamine, Tyramine, Tolazoline, Enalapril and Metoprolol drugs owing to its strong interaction with these drugs.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

REFERENCES

[1] Ahmadi R., Madahzadeh Darini N., (2016), Study of 5-Picrylamino-1, 2, 3, 4-tetrazole (PAT) with nanostructures of fullerene and boron nitride nano-cages in different conditions of temperature, using density functional theory. *Int. J. Bio-Inorg. Hybrid Nanomater.* 5: 273-278.

[2] Ahmadi R., Boroushaki T., Ezzati M., (2014), Computational study of chemical properties of xylometazoline and the connected form to fullerene (C_{60}) as a medicine nano carrier. *Int. J. Bio-Inorg. Hybrid Nanomater.* 3: 23-27.

[3] Parlak C., Alver Ö., (2017), A density functional theory investigation on amantadine drug interaction with pristine and B, Al, Si, Ga, Ge doped C60 fullerenes. *Chem. Phys. Lett*. 678: 85-90.

[4] Samanta P. N., Das K. K., (2017), Noncovalent interaction assisted fullerene for the transportation of some brain anticancer drugs: A theoretical study. *J. Mol. Graph. Model*. 72: 187-200.

[5] Shariatinia Z., Shahidi S., (2014), A DFT study on the physical adsorption of cyclophosphamide derivatives on the surface of fullerene C_{60} nanocage. *J. Mol. Graph. Model*. 52: 71-81.

[6] Ganji M. D., Yazdani H., Mirnejad A., (2010), $B_{36}N_{36}$ fullerene-like nanocages: A novel material for drug delivery. *J. Mol. Graph. Model*. 42: 2184-2189.

[7] Kia M., Golzar M., Mahjoub K., Soltani A., (2013), A first-principles study of functionalized clusters and carbon nanotubes or fullerenes with 5-Aminolevulinic acid as vehicles for drug delivery. *Superlatt. Microstruct*. 62: 251-259.

[8] Ahmadi R., Shemshaki L., (2017), The synthesis of α, 2, 4, 6-tetranitrotoluene from the reaction of 2, 4, 6-trinitrotoluene (TNT) with Fluorotrinitromethane in different temperature conditions, the DFT method. *AM. J. Chem. Tech.* 5: 6-11.

[9] Tian J., Zhang D., Liu G., Zhao L., (2013), Utilizing fullerene-induced polymer spherulites as controlled drug delivery systems. *J. Control. Release*. 172: 45-50.

[10] Simon F., Peterlik H., Pfeiffer R., Bernardi J., Kuzmany H., (2007), Fullerene release from the inside of carbon nanotubes: A possible route toward drug delivery. *Chem. Phys. Lett.* 445: 288-292.

[11] Gallo M., Favila A., Mitnik D. G., (2007), DFT studies of functionalized carbon nanotubes and fullerenes as nanovectors for drug delivery of antitubercular compounds. *Chem. Phys. Lett.* 447: 105-109.

[12] Ahmadi R., Pirahan-Foroush M., (2014), Ab initio studies of fullerene effect on chemical properties of naphazoline drop. *Ann. Mil. Health. Sci. Res*. 12: 86-90.

[13] Shi J., Liu Y., Wang L., Gao J., Zhang J., Yu X., Ma R., Liu R. , Zhang Z., (2014), A tumoral acidic pH-responsive drug delivery system based on a novel photosensitizer (fullerene) for in vitro and in vivo chemo-photodynamic therapy. *Acta Biomater.* 10: 1280-1291.

[14] Hazrati M. K., Hadipour N. L., (2016), Adsorption behavior of 5-fluorouracil on pristine, B-, Si-, and Al-doped C60 fullerenes: A first-principles study. *Phys. Lett*. 380: 937-941.

[15] Naderi E., Mirzaei M., Saghaie L., Khodarahmi G., Gülseren O., (2017), Relaxations of methylpyridinone tautomers at the C60 surfaces: DFT studies. *Int. J. Nano Dimens.* 8: 124-131.

[16] Alver Ö., Bilge M., Atar N., Parlak C., Şenyel M., (2017), Interaction mechanisms and structural properties of MC19 (M=Si and Al) fullerenes with chlorophenylpiperazine isomers. *J. Mol. Liq.* 231: 202-205.

[17] Ahmadi R., Boroushaki T., Ezzati M., (2012), Study on effect of addition of nicotine on nanofullerene structure C60 as a medicine nanocarrier. *Orient. J. Chem.* 28: 773-779.

[18] Chigo-Anota E., Escobedo-Morales A., Hernández-Cocoletzi H., Lópezy-López J. G., (2015), Nitric oxide adsorption on non-stoichiometric boron nitride fullerene: Structural stability, physicochemistry and drug delivery perspectives. *Physica E Low Dimens. Sys. Nanostruct*. 74: 538-543.

[19] Lenik J., Wardak C., (2012), Characteristic of a new sensor for indomethacin determination. *Procedia. Eng.* 47: 144-147.

[20] Baciu T., Botello I., Borrull F., Calull M., Aguilar C., (2015), Capillary electrophoresis and related techniques in the determinationof drugs of abuse and their metabolites. *Trends Anal. Chem*. 74: 89-108.

[21] Moeller M. R., Steinmeyer S., Kraemer T., (1998), Determination of drugs of abuse in blood. *J. Chromatogr. B*. 713: 91-109.
[22] Mullett W. M., (2007), Determination of drugs in biological fluids by direct injection of samples for liquid-chromatographic analysis. *J. Biochem. Biophys. Methods*. 70: 263-273.
[23] Chollet D. F., (2002), Determination of antiepileptic drugs in biological material. *J. Chromatogr. B*. 767: 191-233.
[24] Vytras K., (2002), The use of ion-selective electrodes in the determination of drug substances. *J. Pharm. Biomed. Anal*. 7: 789-812.
[25] Moradi M., Nouraliei M., Moradi R., (2017), Theoretical study on the phenylpropanolamine drug interaction with the pristine, Si and Al doped [60] fullerenes. *Physica. E. Low Dimens. Syst. Nanostruct.* 87: 186-191.
[26] Bashiri S., Vessally E., Bekhradnia A., Hosseinian A., Edjlali L., (2016), Utility of extrinsic [60] fullerenes as work function type sensors for amphetamine drug detection: DFT studies. *Vacuum*. 136: 156-162.
[27] Farmanzadeh D., Ghazanfary S., (2014), Interaction of vitamins A, B1, C, B3 and D with zigzag and armchair boron nitride nanotubes: A DFT study. *C. R. Chim.* 17: 985-993.
[28] Saikia N., Deka R. C., (2011), Density functional calculations on adsorption of 2-methylheptylisonicotinate antitubercular drug onto functionalized carbon nanotube. *Comput. Theor. Chem.* 964: 257-261.
[29] Li W., Li G., Lu X., Ma J., Zeng P., He Q., Wang Y., (2016), Strong adsorption of Al-doped carbon nanotubes toward cisplatin. *Chem. Phys. Lett.* 658: 162-167.
[30] Ahmadi R., Mirkamali E. S., (2016), Determination of thermodynamic parameters of produced materials from (ATTz) with boron nitride nano-cages in different conditions of temperature, with DFT method. *J. Phys. Theor. Chem.* 13: 297-302.
[31] Sadeghi B., Vahdati R. A. R., (2012), Comparison and SEM-characterization of novel solvents of DNA/carbon nanotube. *Appl. Surf. Sci*. 258: 3086-3088.
[32] Verster J. C., Volkerts E. R., (2004), Antihistamines and driving ability: evidence from on-the-road driving studies during normal traffic. *Ann. Allergy. Asthma. Immunol*. 92: 294-304.
[33] Ahmadi R., (2017), Study of thermodynamic parameters of (TATB) and its fullerene derivatives with different number of Carbon (C_{20}, C_{24}, C_{60}), in different conditions of temperature, using density functional theory. *Int. J. Nano Dimens*. 8: 250-256.
[34] Vahdati A. R., Sadeghi B., (2013), A study on the assessment of DNA strand-breaking activity by silver and silica nanoparticles. *J. Nanostruct. Chem.* 3: 7-12.
[35] Ahmadi R., Boroushaki T., Ezzati M., (2015), The usage comparison of occupancy parameters, gap band energy, ΔN_{max} at xylometazoline medicine ratio its medical conveyer nano. *Int. J. Nano Dimens.* 6: 19-22.
[36] Ahmadi R., Pirahan-Foroush M., (2014), Fullerene effect on chemical properties of antihypertensive clonidine in water phase. *Ann. Mil. Health. Sci. Res,* 12: 39-43.
[37] Gökpek Y., Bilge M., Bilge D., Alver Ö., Parlak C., (2017), Adsorption mechanism, structural and electronic properties: 4-Phenylpyridine & undoped or doped (B or Si) C60. *J. Mol. Liq*. 238: 225-228.
[38] Lin M. S., Chen R. T., Yu N. Y., Sun L. C., Liu Y., Cui C. H., Xie S. Y., Huang R .B., Zheng L. S., (2017), Fullerene-based amino acid ester chlorides self-assembled as spherical nano-vesicles for drug delayed release. *Colloids Surf. B: Biointerf.* 159: 613-619.
[39] Hansten, P. D., Horn, J., (2003), Drug Interactions Analysis and Management. St. Louis, MO: Wolters Kluwer Health Inc. 123-185.
[40] Stern G., (1974), Focus on Levodopa. *J. Neurol. Sci.* 22: 521-527.
[41] Houston M. C., (1981), Clonidine hydrochloride: Review of pharmacologic and clinical aspects. *Prog. Cardiovasc. Dis.* 23: 337-350.
[42] Rodman J. S., Deutsch D. J., Gutman S. I., (1976), Methyldopa hepatitis: A report of six cases and review of the literature. *Am. J. Medi.* 60: 941-948.
[43] Nally J. V., Black H. R., (1992), State-of-the-art review: Captopril renography—pathophysiological considerations and clinical observations. *Semin. Nucl. Med*. 22: 85-97.
[44] Glasser A. M., Collins L., Pearson J. L., Abudayyeh H., Niaura R. S., Abrams D. B., Villanti A. C., (2017),
Overview of electronic nicotine delivery systems: A systematic review. *Am. J. Prev. Med*. 52: e33-e66.
[45] Golinko B. E., (1984), Side effects of dextroamphetamine and methylphenidate in hyperactive children— A brief review. Prog. Neuropsychopharmacol. *Biol. Psychiatry*. 8: 1-8.
[46] Ahmadi R., Pourkarim, S., (2015), Investigation of fullerene (C_{60}) effects on chemical properties of metoprolol: A DFT study. *Int. J. Bio-Inorg. Hybd. Nanomat.* 4: 249-254.
[47] Ahmadi R., (2012), Computational study of chemical properties of Captopril drug and the connected form to Fullerene (C_{60}) as a medicine nano carrier. *J. Phys. Theor. Chem. IAU. Iran*. 9: 185-190.
[48] Ahmadi R., Rezaei Asl A., (2015), Computational study of chemical properties in fullerene derivatives of enalapril drug. *Int. J. New Chem*. 4: 189-198.
[49] Ahmadi R., Salmaniha M., (2015), Investigation of chemical properties in fullerene derivatives of fluoxetine drug: A DFT study. *Int. J. New Chem.* 4: 152-160.
[50] Baei M. T., Peyghan A. A., Moghimi M., Hashemian S., (2012), First-principles calculations of structural stability, electronic, and electrical responses of GeC nanotube under electric field effect for use in nanoelectronic devices. *Superlatt. Microstruct.* 52: 1119-1130.
[51] Dai X., Meng Y., Xin M., Wang F., Fei D., Jin M., Wang Z., Zhang R., (2012), Energetics and electronic properties of a neutral diuranium molecule encapsulated in C90 fullerene. *Procedia. Chem.* 7: 528-533.
[52] Arriagada D. C., Escobar N. V., Ortega, D. E., (2018), Fe-doped Graphene nanosheet as an adsorption platform of harmful gas molecules (CO, CO_2, SO_2 and H_2S), and the co-adsorption in O_2 environments. *Appl. Surf. Sci.* 427: 227-236.