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Theoretical study on the conjugation of PLGA and PLGA-PEG Carriers to Doxorubicin and Daunorubicin

F. Rahimi[1*], A.Bahlake[2], Z. Chamani[3], S. Bagheri[4]

[1]*Department of Chemistry, Quchan Branch, Islamic Azad University, Quchan, Iran*
[2]*Department of Petrochemical Engineering, Amirkabir University of Technology (Tehran Polytechnic), Mahshahr Campus, Mahshahr, Iran*
[3]*Department of Chemistry, Quchan Branch, Islamic Azad University, Quchan, Iran*
[4]*Department of Chemistry, North Tehran Branch, Islamic Azad University, Tehran, Iran*

ABSTRACT

Daunomycin (or daunorubicin) and adriamycin (or doxorubicin or 14-hydroxydaunomycin) are well-known anti-cancer agents used in cancer chemotherapy. They are anthracycline antibiotics and are commonly used in the treatment of a wide range of cancers. Doxorubicin and Daunorubicin were chemically conjugated to a terminal end group of poly (D,L-Lactic-co-glycolic acid)[PLGA] and Doxorubicin–PLGA-PEG((doxorubicin-conjugated poly (DL-lactic-co-glycolic acid) (PLGA) and polyethyleneglycol (PEG)). In this research, the molecular structure, Binding Energy(BE), Dipole Moment (DM), Gibbs free energy of solvation ($\Delta G_{(solvation)}$) and some physicochemical properties of the Doxorubicin- PLGA carriers, Daunorubicin-PLGA carriers, Doxorubicin- PLGA-PEG carriers and Daunorubicin-PLGA-PEG carriers were investigated using Density Functional Theory (DFT) and Hartree Fock (HF) calculations. Our results show an increase in solubility of polyethyleneglycol-polylactic conjugation acid rather than that of polylactic acid. The binding of PEG to PLGA causes a higher solubility of Doxorubicin-PLGA-PEG and Daunorubicin-PLGA-PEG in comparison with that of Doxorubicin-PLGA and Daunorubicin-PLGA.

Keywords: PLGA, PLGA-PEG, Carriers, Doxorubicin, Daunorubicin, DFT.

INTRODUCTION

Daunomycin (or daunorubicin) and adriamycin (or doxorubicin or 14-hydroxydaunomycin) are well-known drugs used in cancer chemotherapy. Biochemical data confirms that these drugs make complexes with DNA thereby blocking the any replication or transcription [1-4]. Adriamycin has a wide range of anti-cancer activity and has been used to treat severe lymphoblastic and myeloblastic leukaemias, malignant lymphomas of both Hodgkins and non-Hodgkins types, carcinoma of different parts of the human body, e.g. breast, lung, bladder, thyroid and ovary cancer, etc. [5-13]. Daunomycin is specifically useful in the cure of leukemia in man. Although the structures of adriamycin and daunomycin are only slightly different, their activities differ significantly. PLGA (copoly lactic acid/glycolic acid) is superior in biocompatibility and biodegradability, and is useful material as base material for sustained-release formulation.

PLGA has been successful as a biodegradable polymer because it undergoes hydrolysis in the body to produce the original monomers, lactic acid and glycolic acid. These two monomers under normal physiological conditions are by-products of various metabolic pathways in the body. Since the body effectively deals with the two monomers, there is minimal systemic toxicity associated with using PLGA for drug delivery or biomaterial applications.

Poly (lactic-co-glycolic acid) (PLGA), have been extensively studied for a wide variety of pharmaceutical and biomedical applications. The biodegradable polyester family has been regarded as one of the few synthetic biodegradable polymers with controllable biodegradability, excellent biocompatibility, and high safety. The need for a variety of drug formulations for different drugs and delivery pathways resulted in development of various types of block copolymers (eg, diblock, triblock, multiblock, and star-shaped block) consisting of the biodegradable polyesters and poly (ethylene glycol) (PEG). Extensive studies throughout the world have produced encouraging results demonstrating many desirable, unique properties of PLGA-PEG block copolymers.

In this research it is investigated some physicochemical properties of two carriers PLGA and PLGA-PEG. Binding effects of these carriers to Doxourubicin and Daunorubicin are investigated by computational simulations too.

In experimental studies, some researchers have chemically conjugated Doxorubicin to a terminal end group of poly (D,L-Lactic-co-glycolic acid)[PLGA] and conjugated doxorubicin-PLGA formulating this into carriers to sustain the release of doxorubicin. Doxorubicin-PLGA conjugated complex was synthesized by Tae Gwan Park and colleagues [14]. Further, our study can predict the physiochemical properties of Daunorubicin-PLGA for the researchers before the process of synthesis.

In experimental studies carried out by some other researchers, it has been illustrated that Amphiphatic block copolymers self-assemble into polymeric micelles in aqueous solution, and potentially can be used as parenteral drug delivery systems [15-19] Various polymeric micelles have been used for the solubilization of water insoluble drugs within the interior region of micelles. Biodegradable polymeric micelles containing doxorubicin in the core region were prepared from a di-block copolymer composed of doxorubicin-conjugated poly(DL-lactic-coglycolic acid) (PLGA) and polyethyleneglycol (PEG). This complex was synthesized by Hyuk Sang Yoo,Tae Gwan Park and colleagues[14]. Further, our study can predict the physiochemical properties of Daunorubicin-PLGA-PEG for the researchers before the process of synthesis.

2. COMPUTATIONAL DETAILS

Computational chemistry uses tools to understand chemical reactions and processes. Scientists use computer software to gain insight into chemical processes. To calculate the properties of the molecules, we need to generate a well-defined structure. A calculation often requires a structure that represents a minimum on a potential energy surface [20, 21]. Then we optimized the complexes by Gaussian 03[22]. We used "ONIOM'' approach because the size of complexes was large. The methods and basis sets for high and low level were B3LYP/6-311++G** and HF/6-31G* respectively. The optimized structure is used as a starting point for subsequent calculations, such as binding energy (BE), dipole moment, ΔG (solvation), distance bound and angle bound which have been listed in Table 1 and table 2.

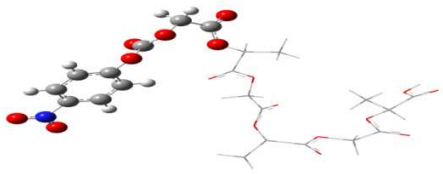
RESULTS AND DISCUSSION

3.1. Structural optimization of PLGA, PLGA-PEG, Doxorubicin, Daunorubicin, Doxorubicin-PLGA, Daunorubicin-PLGA, Doxorubicin-PLGA-PEG and Daunorubicin-PLGA-PEG

In this study, Density functional Theory (DFT) and Hartree Fock (HF) calculations were used to optimize the molecular geometries of PLGA, PLGA-PEG, Doxorubicin, Daunorubicin, Doxorubicin-PLGA, Daunorubicin-PLGA, Doxorubicin-PLGA-PEG and Daunorubicin-PLGA-PEG.

3.1.1. PLGA, PLGA-PEG

The optimized PLGA and PLGA-PEG structures obtained from Density Functional Theory B3LYP/6-311++G** method and from the ab initio HF/6-31G* method were identical (Figure 1) and some physicochemical properties of two carrier have obtained by Gaussian 03 and listed in table 1.



A.

B.

Figure1: Optimized structure of PLGA (A) and PLGA-PEG (B)

Table1: Some calculated physicochemical properties of PLGA and PLGA-PEG

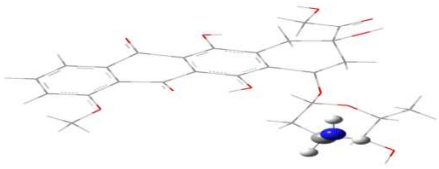
Physicochemical properties	PLGA	PLGA-PEG
Refractivity[a]	113.74	107.40
Polarizability	42.87	40.86
Hydration energy[a]	-19.51	-16.78
Surface area[a](Å2)	780.17	846.09
$\Delta G_{(solvation)}$ (kcal/mol)	-11.02	-12.92
Dipole moment(Debye)	3.20	9.80

[a]*Data were calculated using HyperChem 8 software[23]*

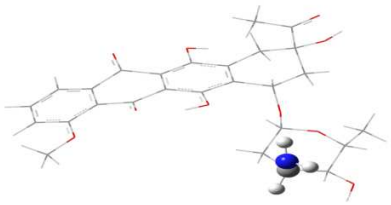
3.1.2. Doxorubicin and Daunorubicin

The structure of Doxorubicin and Daunorubicin were optimized at B3LYP/6-311++g** and HF/6-31g* level of theory and then the Gibbs free energy of solvation (ΔG (solvation)) was calculated at B3LY/6-31g* level of theory using Gaussian 03. The optimized structures of Doxorubicin and Daunorubicin have been shown in Fig.2.

Some physicochemical properties of Doxorubicin and Daunorubicin such as, Refractivity, polarizability, Hydration energy, Gibbs free energy of solvation (ΔG solvation) and Dipole moment (DM) were obtained from optimal structure [24], as shown in Table 2.



A.



B.

Figure2: Optimized structure of Doxorubicin (A) and Daunorubicin (B)

Table 2: Some calculated physicochemical properties of Doxorubicin and Daunorubicin

Physicochemical properties	Daunorubicin	Doxorubicin
Refractivity[a]	133.80	135.50
Polarizability	51.18	52.00
Hydration energy[a]	-17.92	-24.03
Surface area[a](Å2)	541.68	729.45
$\Delta G_{(solvation)}$ (kcal/mol)	-16.23	-18.08
Dipole moment(Debye)	6.123	7.767

[a]*Data were calculated using HyperChem 8 software[23]*

3.1.3. Doxorubicin-PLGA, Daunorubicin-PLGA, Doxorubicin-PLGA-PEG and Daunorubicin-PLGA-PEG

The geometrical structure of Doxorubicin-PLGA, Daunorubicin-PLGA, Doxorubicin-PLGA-PEG and Daunorubicin-PLGA-PEG were optimized at B3LYP/6-311++g** and HF/6-31g* level of theory and then the Gibbs free energy of solvation ($\Delta G_{(solvation)}$) were calculated at B3LY/6-31g* level of theory using Gaussian 03. Table 3 presents the geometrical parameters of four different complexes, mentioned above, around linking position (amide group – see also Fig 3).

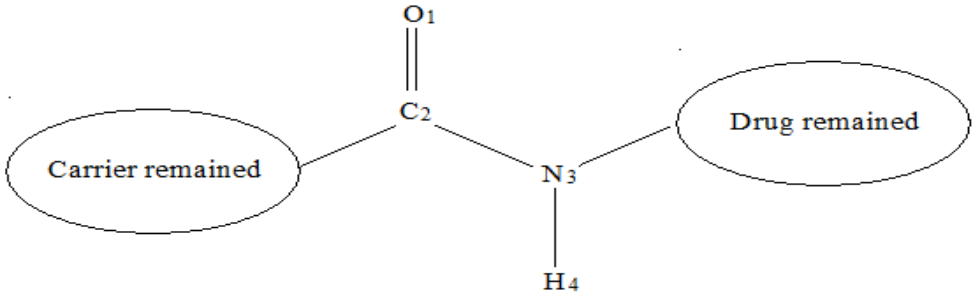


Fig. 3: Structure of linking position in Doxorubicin-PLGA, Daunorubicin-PLGA, Doxorubicin-PLGA-PEG, Daunorubicin-PLGA-PEG

Table 3: Geometrical parameters of complexes around linking position

Complex	C_2=O_1 (Å)	C_2-N_3 (Å)	N_3-H_4 (Å)	O_1-C_2-N_3 (°)	C_2-N_3-H_4 (°)
Doxorubicin-PLGA	1.224	1.343	1.010	125.652	118.985
Daunorubicin-PLGA	1.224	1.342	1.010	125.655	118.974
Doxorubicin-PLGA-PEG	1.212	1.301	1.009	126.238	115.352
Daunorubicin-PLGA-PEG	1.213	1.351	1.009	126.246	115.380

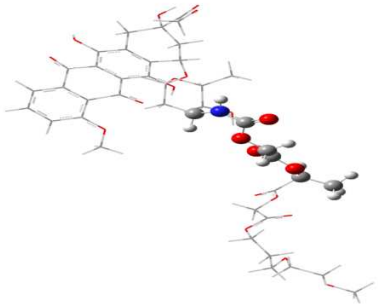
Some physicochemical properties of Doxorubicin-PLGA, Daunorubicin-PLGA, Doxorubicin-PLGA-PEG and Daunorubicin-PLGA-PEG conjugates, such as, Refractivity, polarizability, Hydration energy, binding energies (BE), Gibbs free energy of solvation (ΔG solvation) and Dipole moment (DM) were obtained from optimal structure [22], as shown in Table 4. The binding energy per molecule was computed using the formula (1):

$$\Delta E = E_{complex} - E_{drug} - E_{carrier} \quad (1)$$

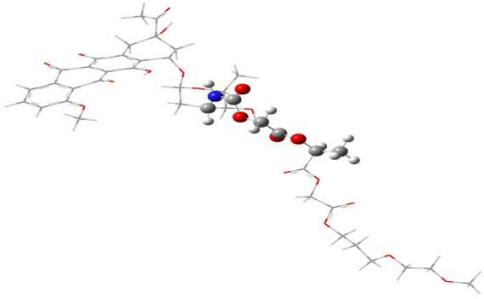
Table 4: Some calculated physicochemical properties of Doxorubicin-PLGA, Daunorubicin-PLGA, Doxorubicin-PLGA-PEG and Daunorubicin-PLGA-PEG

Physicochemical properties	Doxorubicin-PLGA	Daunorubicin-PLGA	Doxorubicin-PLGA-PEG	Daunorubicin-PLGA-PEG
Refractivity[a]	214.17	212.47	207.83	206.13
Polarizability	82.54	84.64	80.52	79.89
Hydration energy[a]	-39.18	-26.73	-27.05	-21.86
Surface area[a](Å2)	987.26	970.39	1126.80	1110.27
$\Delta G_{(solvation)}$ (kcal/mol)	-13.56	-6.96	-28.20	-21.56
Dipole moment(Debye)	7.736	6.187	11.775	10.246
BE (ev/mol)	-0.872	-0.872	-0.790	0.0272

[a]*Data were calculated using HyperChem 8 software[24]*



A.



B.

Fig. 4: Structures of Doxorubicin-PLGA-PEG (A) Daunorubicin-PLGA-PEG (B)

CONCLUSION

Density functional Theory (DFT) and Hartree Fock (HF) calculations were applied to study some physicochemical properties of Doxorubicin-PLGA, Daunorubicin-PLGA, Doxorubicin-PLGA-PEG and Daunorubicin-PLGA-PEG. Our results indicate that when the carrier PLGA-PEG is conjugated with doxorubicin and Daunorubicin, it improves the biological anti cancer activity of the latter. Thus it can be utilized in the treatment of cancer. We further conclude in this research that PLGA-PEG causes an increase in the hydro affinity properties of Daunorubicin and Doxorubicin Adding PLGA to these two anti-cancers causes an increase in their lipophlicity properties. The presence of PEG in Doxorubicin-PLGA-PEG and Daunorubicin-PLGA-PEG causes their lipophlicity properties to be more than that of Doxorubicin-PLGA and Daunorubicin-PLGA.

Taking into account the calculations carried out, we draw this significant conclusion that computational chemistry is closely consistent with experimental results. Regarding the experimental results, lipophilicity of daunorubicin is

higher than that of Doxorubicin; this fact can be verified through the $\Delta G_{(solvation)}$ obtained for Daunorubicin and Doxorubicin using Gaussian 03.

REFERENCES

[1].A. Di Macro, F. Arcamone, F. Zunino, Daunomycin (daunorubicin) and adriamycin and structural analogues, Biological activity and mechanism of action antimicrobial and antitumor agents, (Springer Verlag, Berlin, **1975**).
[2].S. Neidle, *Prog. Med. Chem*., **1979**, 16, 151.
[3].S.T Crooke, S.D Reich, Anthracylines current status and new developments , Academic Press, New York,**1980**.
[4].M.A. Viswamitra, O. Kennard, P.G. Jones, et al., *Nature*, **1978**, 273(5664), 687.
[5].M. Manfait, A.J. Alix, P. Jeannesson, et al., *Nucleic Acids Res*., **1982**, 10(12), 3803.
[6].K.R. Hande, *Biochim. Biophy. Acta*., **1998**, 1400(1), 173.
[7].J. Dancey, E.A. Eisenhauer, *Br. J. Cancer*, **1996**, 74(3), 327.
[8].M. Harrison, D. Tomlinson, S. Stewart, *J. clin. Oncol*., **1995**, 13(4), 914.
[9].F. Porzolt, E.D. Kreuser, G. Meuret, et al., *Cancer Treat. Rev*., **1990**, 17(2), 287.
[10].P.S. Kushwaha, P.C. Mishra, *J. Mol. Struct*., **2003**. 636(1), 149.
[11].E. Berman, G. Heller, J. Santorsa, et al., *Blood*, **1991**, 77(8), 1666.
[12].M.D. Sidney Farber, *JAMA*, **1966**, 198, 826.
[13].F. Arcamone, Doxorubicin anticancer antibiotics Medicinal Chemistry a series of medicinal chemistry, Academic Press, New york, **1981**.
[14].H.S. Yoo, T.G. Park, *Journal of Controlled Release*., **2001**, 70(1), 63.
[15].K. Kataoka, G. Kwon, M.Y.okoyama, et al., *J. Controlled Release*., **1992**, 24, 119.
[16].G.S. Kwon, T. Okano, *Adv. Drug Del. Rev*., **1996**, 16,107.
[17].G. Kwon, M. Naito, M.Y. okoyama, et al., *J. Controlled Release*., **1997**, 48, 195.
[18].G.S. Kwon, S. Suwa, M.Y. okoyama, et al., *Pharm. Res*., **1995**, 12, 192.
[19].M. Yokoyama, G.S. Kwon, M. Naito, et al., *Bioconjug. Chem*., **1992**, 3(4), 295.
[20].H. Chahremani, S.M. Hassani, *Int. J. PharmTech Res*., **2012**, 4(1), 148.
[21].T. Srinophakun, J. Boonmee, *Int. J. Mol. Sci*., **2011**, 12(3), 1672.
[22].M.J. Frisch, G.W. Trucks, H.B. Schlegel, et al., Gaussian 03, Revision B.03, Gaussian, Inc., Wallingford CT, **2004**.
[23]. www.Hyperchem.com
[24].S.M. Hassani, H. Ghahremani, S. Bagheri, *Archives of Applied Science Research*, **2011**.3(6), 296.
[25].S. Bagheri, Z. Chamani, S.M. Hassani, *Int. J. ChemTech Res*., **2012**, 4(1), 144.