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ORIGINAL ARTICLE

Theoretical Study on Physicochemical and Geometrical Properties of Doxorubicin-PEG-FOL Nanoparticles and Daunorubicin-PEG-FOL Nanoparticles

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ABSTRACT
The physicochemical properties of Doxorubicin–PEG–FOL and Daunorubicin-PEG-FOL (Doxorubicin and Daunorubicin conjugated to polyethylene glycol–folate nanoparticles) have been estimated using Density functional Theory (DFT) and Hartree Fock(HF) calculations.In this report some geometrical parameters of Doxorubicin-PEG-FOL complex of the conjugated complex and Daunorubicin–PEG–FOL complex of the conjugated complex were investigated using computational methods and physicochemical properties such as Gibbs free energy of solvation ($\Delta G_{solvation}$),binding energy, partition coefficient, and Dipole Moment (DM) of complexes were investigated.
Our results indicate that water-solubility of Doxorubicin–PEG-FOL and Daunorubicin–PEG–FOL are higher than that of Doxorubicin and Daunorubicin.
***Keywords**: Anti-cancer drugs; Molecular geometry; Doxorubicin-PEG-FOL; nanoparticles; Daunorubicin-PEG-FOL.*

INTRODUCTION

Daunorubicin (or daunomycin) and Doxorubicin (or adriamycin 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].

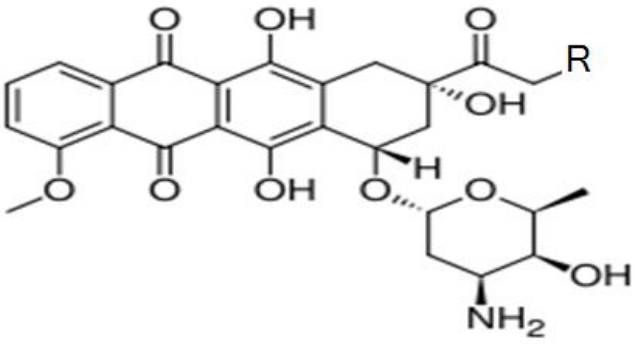

Fig. 1: Structures of Doxorubicin (R = OH) and Daunorubicin (R = H)

Some other researchers have illustrated in experimental studies that nano-particulate drug delivery systems containing anti-cancer agents have received much attention due to their unique behavior of accumulating at the tumor site [5-7]. Enhanced Permeation and Retention (EPR) effect has come in focus these days as a major mechanism for its unique bio-distribution profile in the tumor tissue [8, 9]. For selective delivery in a passive targeting approach of the different anti-cancer agents at the tumor, many nano-particulate carriers, such as, polymer conjugates, polymeric micelles, nanoparticles, and liposomes, are used [10, 11]. However, it has been felt that a more effective and active targeting system is needed to further improve the intracellular uptake of medicine in nano-carriers within cancerous cells at the site of tumor [12]. Various targeting moieties or ligands against tumor-cell-specific receptors have been rendered immobile on the surface of nano-particulate carriers in order to deliver them within cells via receptor-mediated endocytosis. For instance, vitamin folic acid (folate) has been utilized broadly as a targeting moiety for various anti-cancer drugs [13-17]. Folate binding protein, a glycosylphosphatidylinositol (GPI)

anchored cell surface receptor for folate, has been found to be over-expressed in various human tumors including ovarian and breast cancers, while it has been seen to be highly restricted in normal tissues [18]. Therefore, for the purpose of selective targeting against tumors, folic acid has been covalently conjugated to anti-cancer drugs and liposomes [19, 20].

In this research, in order to understand the biological and anti cancer activity of these complexes (Doxorubicin–PEG-FOL nanoparticles and Daunorubicin–PEG–FOL nanoparticles), it is inevitable to study the physicochemical properties of anti cancer drugs-carrier conjugates. Therefore we used B3LYP and HF calculations via Gaussian 03 [21] to study these properties.

In experimental studies, some researchers have chemically conjugated Doxorubicin to PEG-FOL [22].

In this study, we intend to show some of the characteristics of doxorubicin or Doxorubicin- PEG-FOL nanoparticles which have been mentioned above, and have been obtained by other researchers experimentally, through predictable computational calculations including molecular energy, binding energy, dipole moment, ΔG (solvation), distance bound and angle bound [23,24]. Further, our study can predict the physiochemical properties of Daunorubicin-PEG-FOL for the researcher before the process of synthesis.

Doxorubicin –PEG-FOL conjugated complex were synthesized by Hyuk Sang Yoo and colleagues [22].The optimized structures of Doxorubicin-PEG-FO and Daunorubicin-PEG-FOL have been shown in Fig.2. The geometry structure of Doxorubicin-PEG-FOL and Daunorubicin-PEG-FOL were optimized at B3LYP/6-311++g** and HF/6-31g* level of theory and then the Gibbs free energy of solvation ($\Delta G_{solvation}$) was calculated at B3LY/6-31g* level of theory using Gaussian 03. Quantum mechanical molecular simulation was also used to study drug delivery [25].

A.

B.

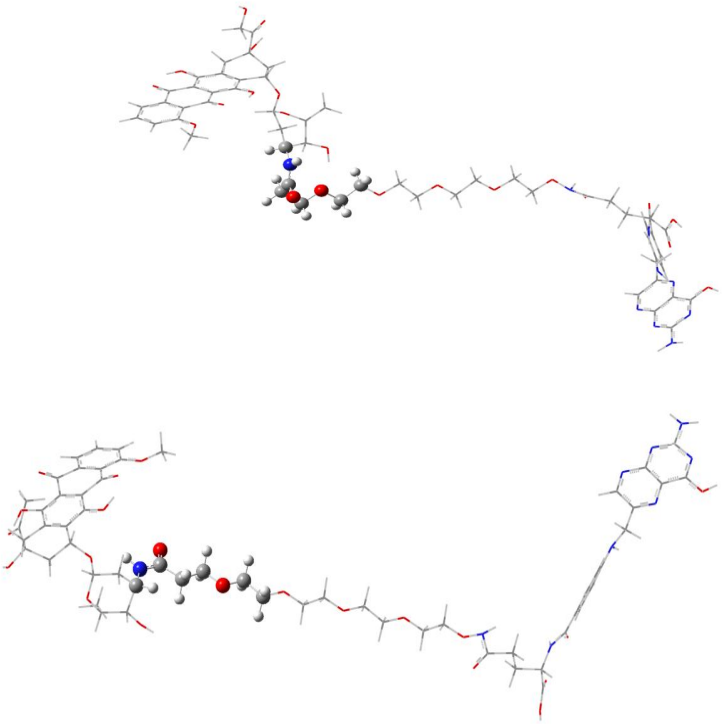

Fig. 2: Structures of Doxorubicin-PEG-FOL (A) Daunorubicin-PEG-FOL (B).

RESULTS AND DISCUSSION

The geometry structure of these two complexes were optimized at B3LYP/6-311++G** and HF/6-31G* level of theory and then the Gibbs free energy of solvation (ΔG solvation) were calculated at B3LYP/6-31G* level of theory [26] using Gaussian 03. Table 1 presents the geometrical parameters of two different complexes mentioned above around linking position (amide group), see also Fig 4.

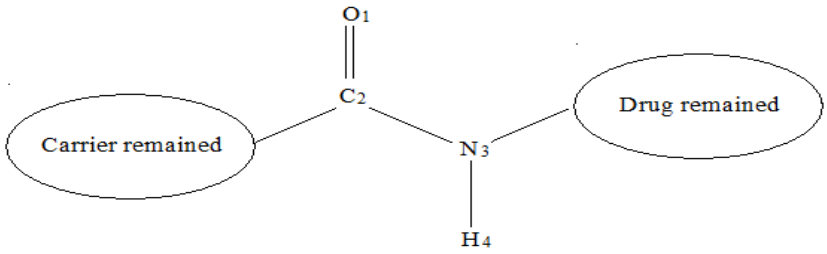

Fig. 3: Structure of linking position in Doxorubicin-PEG-FOL and Daunorubicin-PEG-FOL

Table 1: Geometrical parameter 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-PEG-FOL	1.223	1.363	1.012	121.231	112.435
Daunorubicin-PEG-FOL	1.224	1.367	1.011	120.688	113.717

Some physicochemical properties of Doxorubicin, Daunorubicin, Doxorubicin-PEG-FOL, Daunorubicin-TPEG-FOL 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, as shown in Table 2. The binding energy per molecule was computed using the formula (1):

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

Table 2: Some calculated physicochemical properties of Doxorubicin-PEG-FOL, Daunorubicin-PEG-FOL, Doxorubicin and Daunorubicin

Physicochemical properties	**Doxorubicin-PEG-FOL**	**Daunorubicin-PEG-FOL**	**Daunorubicin**	**Doxorubicin**
Refractivity[a]	296.89	295.26	133.80	135.50
Polarizability	119.03	118.49	51.18	52.00
Hydration energy[a]	-54.75	-49.81	-17.92	-24.03
Surface area[a](Å2)	1493.77	1506.73	541.68	729.45
$\Delta G_{(solvation)}$ (kcal/mol)	-54.25	-54.64	-16.23	-18.08
Dipole moment(Debye)	6.68	9.40	6.123	7.767
BE (ev/mol)	-0.59	-0.02	-	-

[a]Data were calculated using HyperChem 8 software [27]

CONCLUSION

Density functional Theory (DFT) and Hartree Fock (HF) calculation were applied to study some physicochemical properties of Doxorubicin-PEG-FOL, Daunorubicin-PEG-FOL, Daunorubicin and Doxorubicin. Our results indicate that when the carrier PEG-FOL 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.

Considering the Binding Energy (BE) obtained from formula 1, it can be concluded that complex Doxorubicin-PEG-FOL is more stable than Daunorubicin-PEG-FOL. We further conclude in this research that PEG-FOL causes an increase in the hydro affinity properties of Daunorubicin and Doxorubicin.

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