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Theoretical study on physicochemical and geometrical properties of Doxorubicin and Daunorubicin conjugated to PEO-b-PCL nanoparticles

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ABSTRACT

Daunorubicin (or daunomycin) and Doxorubicin (or adriamycin 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 PEO-b-PCL (poly(ethylene oxide)-block-poly(□-caprolactone)) nanoparticles. 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- PEO-b-PCL and Daunorubicin- PEO-b-PCL were investigated. Our results indicate that these complexes mentioned above can be used to improve the anti-cancer activity.

Keywords: Anti-cancer drugs, Molecular geometry, Doxorubicin, Daunorubicin, PEO-b-PCL nanoparticles.

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]. Doxorubicin 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]. Daunorubicin is specifically useful in the cure of leukemia in man. Although the structures of Doxorubicin and Daunorubicin are only slightly different, their activities differ significantly (Fig. 1).

During the past few decades, a lot of research in the field of pharmaceuticals has been focused upon the development of new dosage vehicles that can change the normal outcome of drugs in a biological system and direct them toward their cellular or sub-cellular targets. Nano-delivery systems having suitable stability, size, and surface properties have been designed in such a way that they are able to avoid permeation through continuous capillary in normal tissue, evade glomerular filtration in kidneys and avert reception by the reticuloendothelial system (RES), thereby, circulating for longer periods in the blood and finally accumulating in solid tumors through the enhanced permeability and retention (EPR) phenomenon. However, the accumulation in the tumor by the carrier does not guarantee a preferential access of the incorporated drug to its targets. Further to the aforementioned qualities for

efficient drug targeting, the carrier should be able to restrain the incorporated drug during blood circulation and preferentially release it in the extracellular space or appropriate intracellular organelle of the targeted tumor. Polymeric micelles have recently obtained a lot of interest as promising delivery systems for drug targeting as they have shown to be having the potential for conforming to most of these criteria [14-16]. As a result of the EPR effect, Polymeric micelles have the right dimension and the required surface properties for accumulating in the tumor. And last but not the least, the structure of the core and the shell of polymeric micelles can be manipulated chemically so as to achieve the required micellar stability, drug release and cellular interaction profile befitting the incorporated drug.

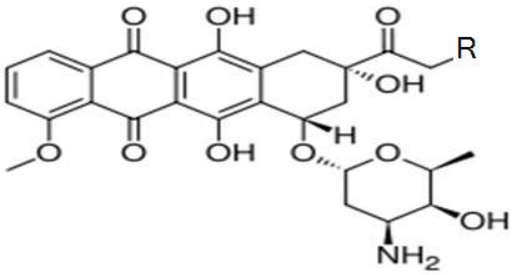
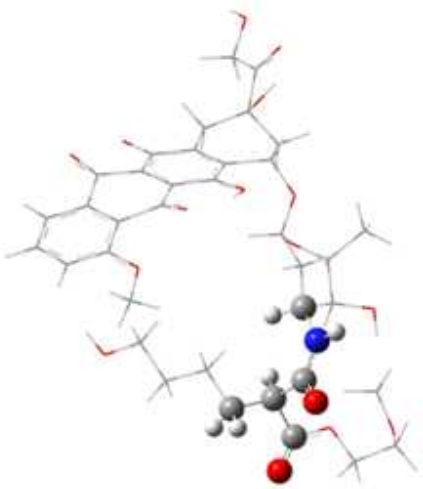


Fig. 1: Structures of Doxorubicin (R = OH) and Daunorubicin (R = H)

In experimental studies carried out by some other researchers, it has been illustrated that chemical conjugation of DOX to the polymeric micellar core in PEO-b-P(CL-DOX) is expected to reduce the chance of premature drug release outside tumor tissue. On the other hand, since PCL backbone is prone to hydrolysis especially in acidic environment, core degradation followed by micellar dissociation and release of DOX-caprolactone (DOX-CL) derivatives may be facilitated in the acidic environment of the edosome/lysosomes after endocytosis of PEO-b-P(CL-DOX) micelles by tumor cells[17-19]. DOX-PEO-b-PCL complex was synthesized by Abdullah Mahmud and colleagues[20]. In order to understand the biological and anti cancer activity of these complexes, it is inevitable to study the physicochemical properties of doxorubicin-carrier conjugates. Therefore we used B3LYP and HF calculations via Gaussian 03[21] to study these properties. In this study, we intend to show some of the characteristics of doxorubicin or Doxorubicin- PEO- b-PCL 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 [22-23]. Further, our study can predict the physiochemical properties of Daunorubicin-PEO-b-PCL for the researcher before the process of synthesis. The optimized structures of Doxorubicin- PEO-b-PCL and Daunorubicin-PEO-b-PCL have been shown in Fig.2. The geometry structure of Doxorubicin-PEO-b-PCL and Daunorubicin-PEO-b-PCL 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. Quantum mechanical molecular simulation was also used to study drug delivery [24].



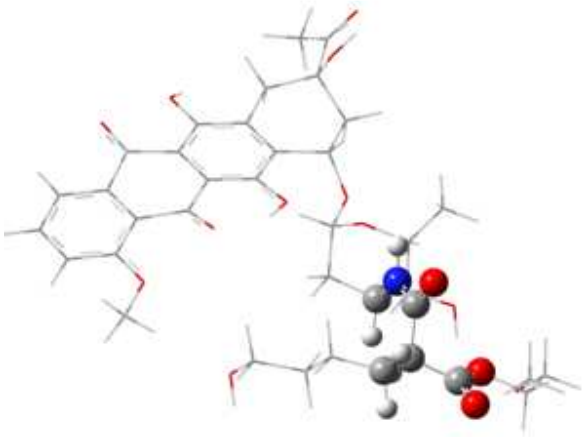


Fig. 2: Structures of Doxorubicin-PEO-b-PCL (a) Daunorubicin-PEO-b-PCL (b)

RESULTS AND DISCUSSION

The geometrical structure of Doxorubicin-PEO-b-PCL, Daunorubicin-PEO- b-PCL, 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 ($\Delta G_{(solvation)}$) were calculated at B3LY/6-31g* level of theory using Gaussian 03. Table 1 presents the geometrical parameters of two different complexes, mentioned above, around linking position (amide group–see also Fig 3).

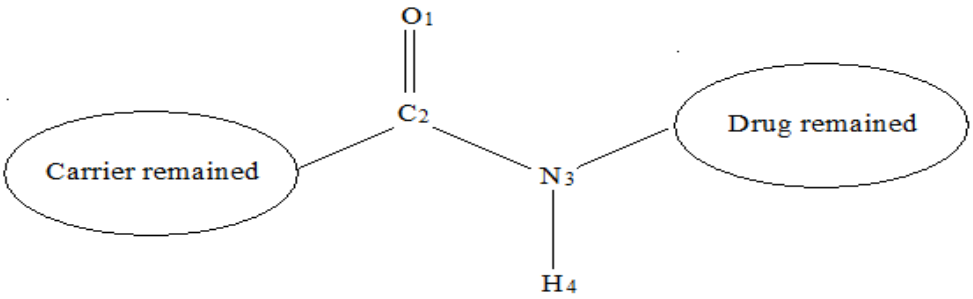


Fig. 3: Structure of linking position in Doxorubicin-PEO-b-PCL and Daunorubicin-PEO-b-PCL

Table 1: 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-PEO-b-PCL	1.220	1.369	1.013	120.324	111.964
Daunorubicin-PEO-b-PCL	1.222	1.362	1.011	121.016	112.7375

Table 2: Some calculated physicochemical properties of Doxorubicin-PEO-b-PCL, Daunorubicin-PEO-b-PCL, Doxorubicin and Daunorubicin

Physicochemical properties	Doxorubicin- PEO-b-PCL	Daunorubicin- PEO-b-PCL	Daunorubicin	Doxorubicin
Refractivity[a]	185.66	163.89	133.80	135.50
Polarizability	71.74	53.43	51.18	52.00
Hydration energy[a]	-27.39	-17.83	-17.92	-24.03
Surface area[a](Å2)	834.12	828.39	541.68	729.45
$\Delta G_{(solvation)}$ (kcal/mol)	-18.60	-12.72	-16.23	-18.08
Dipole moment(Debye)	4.44	7.289	6.123	7.767
BE (ev/mol)	0.054	-10.57	-	-

[a]*Data were calculated using HyperChem 8 software[26]*

Some physicochemical properties of Doxorubicin, Daunorubicin, Doxorubicin- PEO- b-PCL, Daunorubicin-PEO-b-PCL 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 [25], as shown in Table 2. The binding energy per molecule was computed using the formula (1):

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

CONCLUSION

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

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.

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