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# Computational Procedure for determining Physicochemical Properties of Doxorubicin- PLGA Nanoparticles and Daunorubicin-PLGA Nanoparticles

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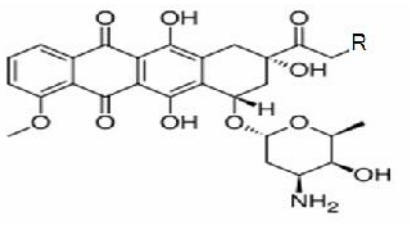
**Abstract:** Daunomycin (or daunorubicin) and adriamycin (or doxorubicin or 14-hydroxydaunomycin) are well-known anti-cancer agents used in cancer chemotherapy. They are anthracycline antibiotics and are commonly used in the treatment of a wide range of cancers. Doxorubicin and Daunorubicin were chemically conjugated to a terminal end group of poly (D,L-Lactic-co-glycolic acid)[PLGA] .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 nanoparticles and Daunorubicin-PLGA nanoparticles were investigated using Density Functional Theory (DFT) and Hartree Fock (HF) calculations. Our results indicate that this conjugation results in an enhanced lipophilicity of both agents.
**Keywords**: Anti-cancer drugs, Molecular geometry, Doxorubicin, Daunorubicin, PLGA nanoparticles.

## 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 (Fig. 1).

**Fig. 1: Structures of adriamycin (R = OH) and daunomycin (R = H)**



Drug delivery technology (DDT) has become an increasingly essential component of drug development. The range and sophistication of DDTs available has expanded with the aim of increasing the success rate of new chemical complexes with an increasing diversity of compounds addressing more drug targets. There are many procedures for drug delivery via drug/drug carrier combinations, such as encapsulation, hydrogel formation, nanoaggregation, and micellar delivery. Among these, doxorubicin, encapsulation and micellar delivery have been the focus of much attention because they can protect and carry the drug directed to its chosen target.

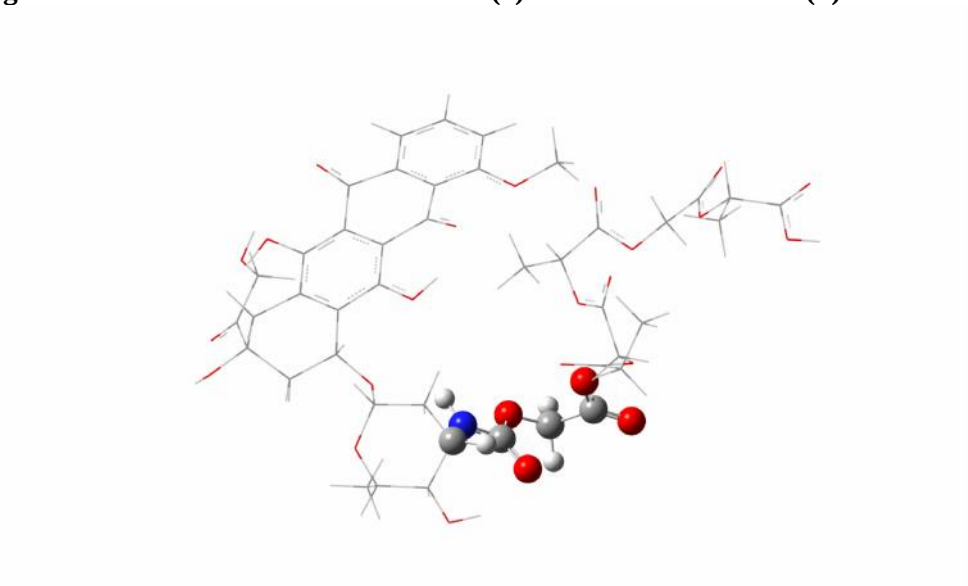
One of the main strategies for drug modifications is polymer–drug conjugation as it influences and controls the curative agents at the molecular level to increase their solubility, permeability and stability, and therefore, biological activity. Such a strategy is based on a basic hypothesis that in order to make analogous agents chemically distinct from the original compound, the molecular structure of drugs can be modified and yet produce a similar or even enhanced biological effect (14). The bio-distribution of the therapeutic agent can be significantly changed by Polymer–drug conjugation and thereby improve its pharmacokinetics (PK) and pharmacodynamics (PD), increase its therapeutic effects and reduce its side effects, as well as supply a means for evading the problem of multidrug resistance (MDR). Polymer–anticancer drug conjugation has been studied comprehensively and some prodrugs have shown much promise (15,16).

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 nanoparticles to sustain the release of doxorubin.

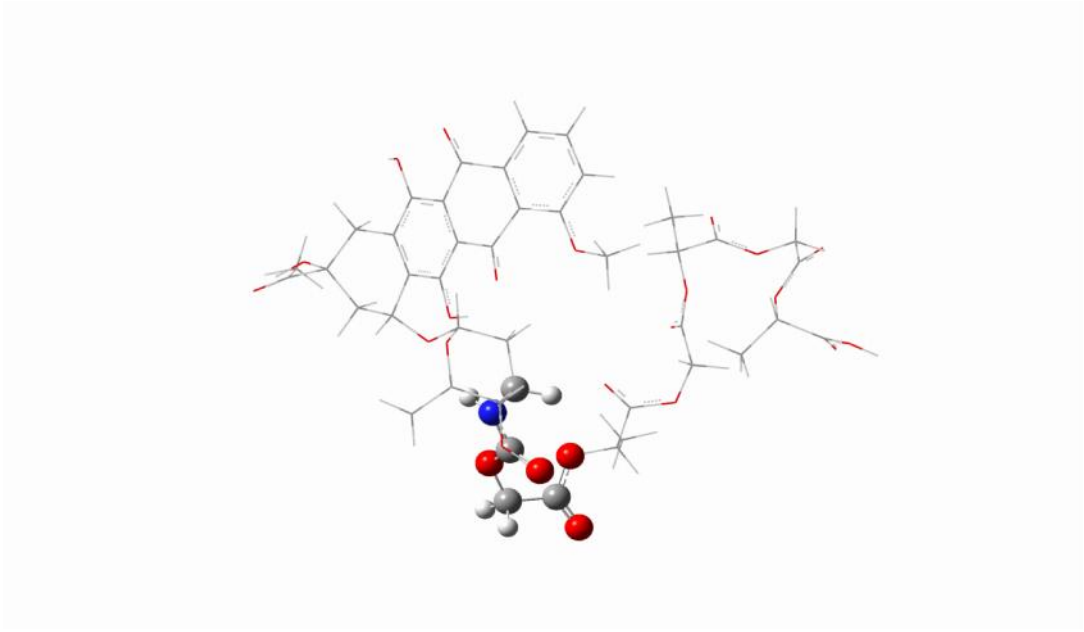
In this study, we intend to show some of the characteristics of doxorubicin or Doxorubicin-PLGA nanoparticles which have been mentioned above, and have been obtained by other researchers experimentally, through predictable computational calculations including molecular energy, binding energy, dipole moment, ΔG (solvation), distance bound and angle bound (17,18). Further, our study can predict the physiochemical properties of Daunorubicin-PLGA for the researcher before the process of synthesis.

Doxorubicin PLGA conjugated complex were synthesized by Tae Gwan Park and colleagues (19). The optimized structures of Doxorubicin-PLGA and Daunorubicin-PLGA have been shown in Fig.2. The geometry structure of Doxorubicin-PLGA and Daunorubicin-PLGA 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 (20). Quantum mechanical molecular simulation was also used to study drug delivery (21).

**Fig. 2: Structures of Doxorubicin-PLGA (a) Daunorubicin-PLGA (b)**



**a.**



**b.**

## RESULTS AND DISCUSSION

The geometrical structure of Doxorubicin-PLGA, Daunorubicin-PLGA, 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-PLGA and Daunorubicin-PLGA**

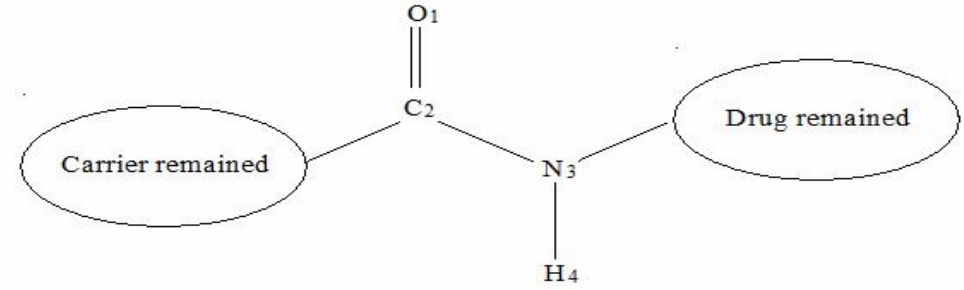



**Table 1: Geometrical parameter of complexes around linking position**

| 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-PLGA | 1.224 | 1.343 | 1.010 | 125.652 | 118.985 |
| Daunorubicin-PLGA | 1.224 | 1.342 | 1.010 | 125.655 | 118.974 |

**Table 2: Some calculated physicochemical properties of Doxorubicin-PLGA, Daunorubicin-PLGA, Doxorubicin and Daunorubicin**

| Physicochemical properties | Doxorubicin-PLGA | Daunorubicin-PLGA | Daunorubicin | Doxorubicin |
|---|---|---|---|---|
| Refractivity[a] | 214.17 | 212.47 | 133.80 | 135.50 |
| Polarizability | 82.54 | 84.64 | 51.18 | 52.00 |
| Hydration energy[a] | -39.18 | -26.73 | -17.92 | -24.03 |
| Surface area[a](Å2) | 987.26 | 970.39 | 541.68 | 729.45 |
| $\Delta G_{(solvation)}$ (kcal/mol) | -13.56 | -6.96 | -16.23 | -18.08 |
| Dipole moment(Debye) | 7.736 | 6.187 | 6.123 | 7.767 |
| BE (ev/mol) | -4.034 | -4.034 | - | - |

[a]Data were calculated using HyperChem 8 software(23)

Some physicochemical properties of Doxorubicin, Daunorubicin, Doxorubicin-PLGA, Daunorubicin-PLGA conjugates, such as, Refractivity, polarizability, Log p, 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 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-PLGA, Daunorubicin-PLGA, Daunorubicin and Doxorubicin. Our results indicate that when the carrier PLGA 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. We further conclude in this research that PLGA causes an increase in the lipo affinity properties of Daunorubicin and Doxorubicin.

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