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Review Article

A COMPUTATIONAL METHOD FOR PREDICTING THE SOLUBILITY OF DOXORUBICIN-PLLA-PEG

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ABSTRACT

Doxorubicin is a chemotherapeutic drug used as a cure for cancer. Being an anthracycline antibiotic, it is commonly used in treating a wide varieties of cancers. In this report, the molecular structure, Binding Energy(BE), Dipole Moment (DM), Gibbs free energy of solvation (ΔG(solvation)) and some physicochemical properties of Doxorubicin were conjugated chemically to the terminal end of a di-block copolymer which was composed of poly(L-lactic acid)(PLLA) and methoxy-poly(ethylene glycol) (mPEG) and were investigated using computational methods. In this report, computational calculation carried out on the acid-cleavable linkages, a hydrazone bond(complex A) and a cis-aconityl bond(complex B) were used for the conjugation of doxorubicin to the terminal end of poly(L-lactic acid) in a di-block copolymer of PLLA–PEG. Wherein Complex A and B being large molecules.

For large reactive systems, the calculation of energies can be simplified by treating the active part with a high-level quantum mechanical (QM) ab initio or density functional. One such method is the original ''Our-own-N-layer Integrated molecular Orbital, Molecular Mechanics ONIOM'' approach. We used this approach for optimization of DOX-PLLA-PEG complexes. Our results indicate that these complexes mentioned above can be used to improve anti cancer activity and water-solubility of Doxorubicin.

Keywords: Anti-cancer drugs**,** Doxorubicin, Ab initio calculation, di-block copolymer, acid-cleavable linkages.

INTRODUCTION

Doxorubicin, an anthracycline ring antibiotic, is a widely used therapeutic drug in cancer cure[1]. The Doxorubicin scheme is seen as follows in Fig1:

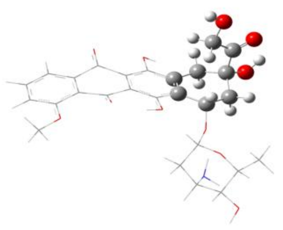

Fig 1: Doxorubicin

Further, although doxorubicin is used widely as an anticancer agent, the cytotoxicity that it shows to normal tissue and its inherent effect of multidrug resistance are major problems that have yet remained unsolved[2,3]. In order to increase the efficacy of this therapeutic nature of doxorubicin, several systems of drug delivery, based on liposomes, nanoparticles, polymer conjugates, and polymeric micelles, have been comprehensively researched. There have also been extensive studies on Polymer–drug conjugates using poly (*N*-(2-hydroxypropyl)methacrylamide) and are in the clinical trial stage[4]. Experimental work performed by other researchers has illustrated that the potential of biodegradable polymeric nanoparticles and solid lipid nanoparticles has also been identified and utilized as doxorubicin carriers[5]. The characteristics and uniqueness of structure of polymeric micelles have recently been the focus of much attention[6-9]. Composed of hydrophilic and hydrophobic polymer blocks, a di-block copolymer in aqueous solution can self-associate to form a micellar structure with a diameter of less than 100 nm. In our previous study[10], however, an amide or ester linkage that was not readily cleaved under physiological conditions was used for conjugating doxorubicin to the terminal end of a PLGA chain. The conclusion showed that the released doxorubicin was composed of a mixture of doxorubicin species conjugated with water-soluble PLGA oligomers. In the present study, acid-cleavable linkages, a hydrazone bond and a *cis*-aconityl bond, were used for the conjugation of doxorubicin to the terminal end of poly (L-lactic acid) in a di-block copolymer of PLLA–PEG. Their acid cleavability makes the hydrazone linkage and the cis-aconityl bond instrumental in the conjugation of anticancer agents to monoclonal antibodies requiring a rapid cleavage of the drug under acidic conditions, as in the vicinity of tumor tissues or within endosomes[11-14].

Tools are required for computational chemistry to study chemical reactions and processes. Computer software gives scientists insight into chemical processes. A well-defined structure needs to be generated before molecular properties can be calculated. A calculation often requires a structure that represents a minimum on a potential energy surface[15,16]. In view of the above, we optimized the complexes using Gaussian 03. The ONIOM'' approach was also carried out as the size of complexes was large.

The methods and basis sets for high and low level were set at B3LYP/6-311++G** and HF/6-31G*, respectively. The structure optimized was used as a starting point for subsequent calculations, such as, molecular energy, binding energy, dipole moment, ΔG (solvation), partition coefficient (logP), distance bound and angle bound[17,18].

RESULTS AND DISCUSSION

The ketone group of doxorubicin was conjugated to the terminal hydroxyl moiety of PLLA segment in a PLLA-PEG di-block copolymer via a hydrazone linkage (complex A), as shown in fig. 2. This complex was synthesized by Eun Ah Lee and colleagues[10]. Similarly, the conjugation of doxorubicin to PLLA-PEG via a cis-aconityl bond is shown in fig .3. This complex was also originally synthesized by Eun Ah Lee and colleagues[10].

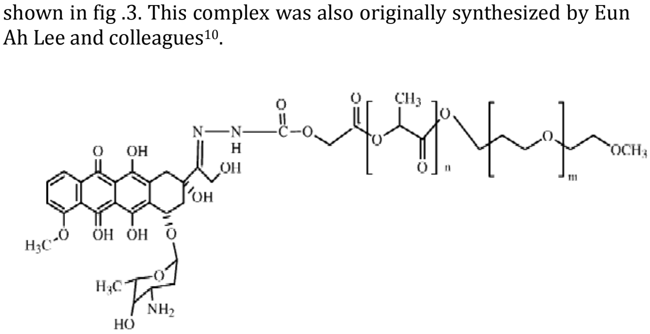

Fig 2: Dox–plla–peg conjugate via a hydrazone linkage (complex a)[10]n=1 m=2

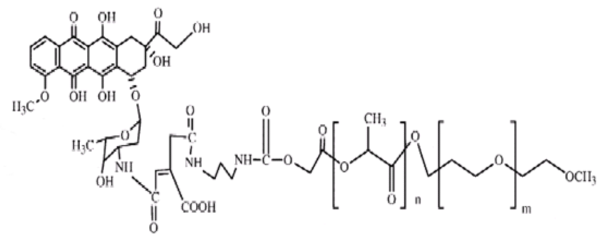

Fig 3:Dox-plla-peg conjugate via a cis-aconityl linkage (complex b)[10] n=1 m=2

The geometry structure of DOX- PLLA-PEG di-block copolymer was optimized at B3LYP/6-311++g** and HF/6-31g* level of theory via a hydrazone linkage(complex A) and then the Gibbs free energy of solvation (ΔG $_{(solvation)}$) was calculated at B3LY/6-31g* level of theory using Gaussian 03[19]. Table 1 presents the geometrical parameters of this above mentioned complex around linking position (hydrazone group), see also Fig4. Some physicochemical properties of complex A, complex B and doxorubicin, such as, Refrectivity, Polarizability, Log p, Hydration Energy, Binding Energies (BE), Gibbs Free Energy of Solvation (ΔG solvation) and Dipole Moment (DM) were obtained from optimal structure[20] as shown in Table 2.

The binding energy per molecule was computed using the formula (1):

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

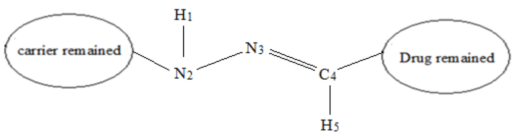

Fig 4:Structure of linking position in dox-plla-peg (complex a)

Table 1: Geometrical Parameter Of Complex A Around Linking Position

Geometrical Parameters Of Complex A	
H1-N2 (Å)	1.016
N2-N3 (Å)	1.358
N3-C4 (Å)	1.278
C4-C5 (Å)	1.513
H1-N2-N3(°)	119.573
N3-C4-C5(°)	122.750
N2-N3-C4(°)	119.973

Table 2: Some Physicochemical Properties Of Complex A, Complex B And Doxorubicin

Physicochemical properties	Complex a	Complex b	Doxorubicin
Refrectivity[a]	202.46	242.73	135.50
Polarizability	78.33	95.01	52.00
Log p[a]	-0.82	-2.91	0.110
Hydration energy[a]	-29.710	-35.74	-24.03
Surface area[a](Å2)	1068.840	1335.23	729.45
ΔG $_{(solvation)}$ (kcal/mol)	-26.990	-33.47	-18.08
Dipole moment(Debye)	8.648	5.749	6.848
BE (ev/mol)	-1071.359	-0.218	

[a] Data were calculated using Hyper Chem 8 software[21]

The geometrical structure of DOX- PLLA-PEG di-block copolymer was optimized at B3LYP/6-311++g** and HF/6-31g* level of theory via a cis-aconityl bond linkage(complex B)and then the Gibbs free energy of solvation (ΔG $_{(solvation)}$) was calculated at B3LY/6-31g* level of theory using Gaussian 03[19]. Table 3 presents the geometrical parameters of this complex mentioned above around linking position (amide group), see also Fig 5.

Some physicochemical properties of complex B conjugate such as Refrectivity, Polarizability, Log p, Hydration Energy, Binding Energies (BE), Gibbs Free Energy of Solvation (ΔG solvation) and Dipole moment (DM) are obtained from optimal structure[20] and are present in Table 2.

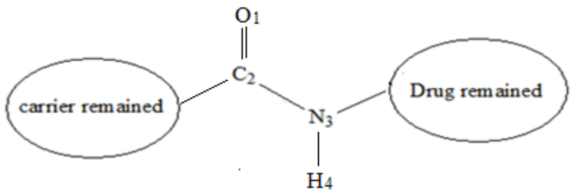

Fig. 5: structure of linking position in dox-plla-peg complex b

Table 3: Geometrical Parameter Of Complex B Around Linking Position

Geometrical Parameter Of Complex B	
C2-O1(Å)	1.221
C2-N3(Å)	1.357
N3-H4(Å)	1.009
C2-N3-H4 (°)	118.235
O1-C2-N3 (°)	124.270

CONCLUSION

The Density Functional Theory (DFT) and Hartree Fock (HF) calculation were applied to study some physicochemical properties of DOX–PLLA–PEG conjugate – via a hydrazone linkage (complex A), DOX-PLLA-PEG conjugate – via a cis-aconityl linkage (complex B) and Doxorubicin .

With regard to the calculations carried out, this significant conclusion was drawn that computational chemistry is closely consistent with experimental results. The experimental results show doxorubicin conjugated micelles with a *cis*-aconityl bond, doxorubicin was released much faster than doxorubicin conjugated micelles with a hydrazone linkage at pH 3. This fact can be verified through the Binding Energy (BE) obtained for complex A and complex B using formula (1). The value of the BE of these complexes mentioned in table 2, confirm that complex A is more stable than complex B. Thus, doxorubicin conjugated micelles with a *cis*-aconityl bond, doxorubicin was released much faster than doxorubicin conjugated micelles with a hydrazone linkage.

With regards to the calculation results, hydrophilicity of complex B is higher than that of complex A and Doxorubicin; this fact can be verified through the Gibbs free energy of solvation (ΔGsolvation) obtained for these complexes using Gaussian 03. Therefore, complex B is more soluble than that complex A. Our results are clear proof that the complexes mentioned above can be used to improve the anti- cancer activity and the water-solubility of Doxorubicin.

REFERENCES

1. Kushwaha PS, Mishra PC. Molecular electrostatic potential maps of the anti-cancer drugs daunomycin and adriamycin an ab initio theoretical study. J Mol Struct 2003; 639:149-156.
2. Minko T, Kopeckova P, Pozharov V, Kopecek J. HPMA copolymer bound adriamycin overcomes MDR1 gene encoded resistance in a human ovarian carcinoma cell line. J Control Release 1998; 54:223-233.
3. Verdiere CA, Dubernet C, Nemati F, Poupon MF, Puisieux F, Couvreur P. Uptake of doxorubicin from loaded nanoparticles in multidrug resistant leukemic murine cells. Cancer Chemother Pharmcol 1994; 33:504-508.
4. Duncan R, Seymour LC, Scarlett L, Lioyd JB, Reimanova P, Kopecek J. Fate of N-(2-hydroxypropyl)methacrylamide copolymers with pendent galactosamine residues after intravenous administration to rats. Biochem Biophy Acta 1986; 880:62-71.

5. Yoo HS, Oh JE, Lee KH, Park GP. Biodegradable nanoparticles containing doxorubicin-PLGA conjugate for sustained release. Pharm Res 1999; 16:1114-1118.
6. Kataoka K, Kwon G, Yokoyama M, Okano T, Sakurai Y. Block copolymer micelles as vehicles for drug delivery. J Control Release 1992; 24:119-132.
7. Kwon G, Okano T. Polymeric micelles as new drug carriers. Adv Drug Del Rev 1996; 21:107-116.
8. Yokoyama M, Kwon GS, Naito T, Okano T, Sakurai Y, Seto T et al. Preparation of micelle forming polymer drug conjugates. Bioconjugate chem 1992; 3:295-301.
9. Yoo HS, Park TG. Biodegradable polymeric micelles composed of doxorubicin conjugated PLGA-PEG block copolymer. J Control Release 2001; 70:63-70.
10. Yoo HS, Lee EA, Park TG. Doxorubicin conjugated biodegradable polymeric micelles having acid cleavable linkages. J Control Release 2002; 82:17-27.
11. Mueller BM, Wrasidlo WA, Reisfeld RA. Antibody conjugates with morpholinodoxorubicin and acid cleavable linkers. Bioconjug Chem 1990; 1:325-330.
12. Kaneko T, Willner D, Monkovic I, Knipe JO, Braslawsky GR, Greenfield RS et al. New hydrazone derivatives of adriamycin and their immunoconjugates a correlation between acid stability and cytotoxicity. Bioconjug Chem 1991; 2:133-141.
13. Greenfield RS, Kaneko T, Daues A, Edson MA, Fitzgerald KA, Olech LJ et al. Evaluation in vitro of adriamycin immunoconjugates synthesized using an acid sensitive hydrazone linker. Cancer Res 1990; 50:6600-7.
14. Shen WC, Ryser HJ. Cis aconityl spacer between daunomycin and macromolecular carriers of a model of pH sensitive linkage releasing drug from a lysosomotropic conjugate. Biochem Biophys Res Commun 1981; 102:1048-54.
15. Bayat Z, Nejatpour M, Mahdizadeh SJ. Theoretical study on physicochemical properties of paclitaxel and their complexes in order to understand their biological and anti cancer activities, J Chem Pharm Res 2011; 3:940-946.
16. Bayat Z, Nejatpour M, Mahdizadeh SJ. Theoretical study on physicochemical properties of 7-Glycolypaclitaxel 2-O- α-glucooligosaccharides novel taxol (paclitaxel) prodrugs of ester linked oligosaccharide series compounds. J Chem Pharm Res 2011; 3:928-931.
17. Bagheri S, Hassani SM, Mahdizadeh SJ. Theoretical study on the physicochemical and geometrical properties of DOX-GA3 and DOX-mGA3, J Chem Pharm Res 2011; 3:524-527.
18. Bagheri S, Taghizadeh E, Hassani SM. Theoretical study on physicochemical and geometrical properties of Doxorubicin and its different carriers such as PEG-FOL and PEO-b-PCL. J Chem Pharm Res 2011; 3:755-759.
19. Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR et al. Gaussian 03, Revision B.03, Gaussian, Inc., Wallingford CT, 2004.
20. Bagheri S, Hassani SM. The estimation of the solubility of the DOX-PLGA-PEG & DOX-PLGA and Doxorubicin based on theoretical study, J Chem. Pharm. Res 2011; 3:680-683.
21. www.Hyperchem.com