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The estimation of the solubility of the DOX-PLGA-PEG, DOX-PLGA and Doxorubicin based on theoretical study

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ABSTRACT

Doxorubicin is a drug used in cancer chemotherapy. It is an anthracycline antibiotic and it is commonly used in the treatment of a wide range of cancers.The physicochemical properties of Doxorubicin–PLGA-PEG(doxorubicin-conjugated poly (DL-lactic-co-glycolic acid) (PLGA) and polyethyleneglycol (PEG)) and Doxorubicin–PLGA (poly(DL-lactic-co-glycolic acid)) have been estimated using Density functional Theory (DFT) and Hartree Fock(HF) calculations.In this report some geometrical parameters of DOX-PLGA-PEG complex of the conjugated complex and Doxorubicin–PLGA 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 DOX-PLGA-PEG and DOX-PLGA is higher than that of Doxorubicin.

Keywords: Anti-cancer drugs; Doxorubicin; PLGA; PLGA-PEG; solubility.

INTRODUCTION

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 [1–5] 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-co-glycolic acid) (PLGA) and polyethyleneglycol (PEG)[6]. This complex was synthesized by Hyuk Sang Yoo,Tae Gwan Park and colleagues[6] .The conjugation scheme is in Fig. 1.

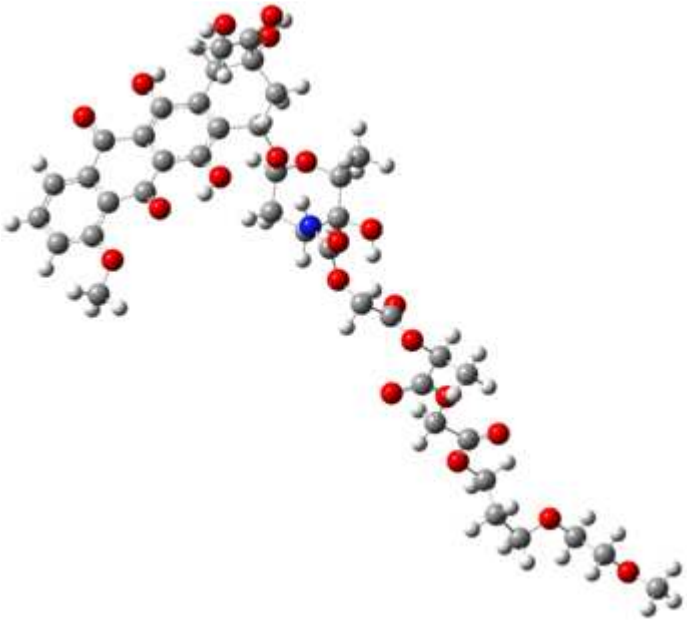

Fig.1. DOX-PLGA-PEG

Also polymer–drug conjugation is one of the other major strategies for drug modifications, which manipulates therapeutic agents at molecular level to increase their solubility, permeability and stability, and thus biological activity.Doxorubicin was chemically conjucated to aterminal group of poly (DL-lactic-co-glycolic acid)PLGA polmer chain. This complex was synthesized by Hyuk Sang Yoo,Tae Gwan Park and colleagues[6].The conjugation scheme is in Fig. 2.

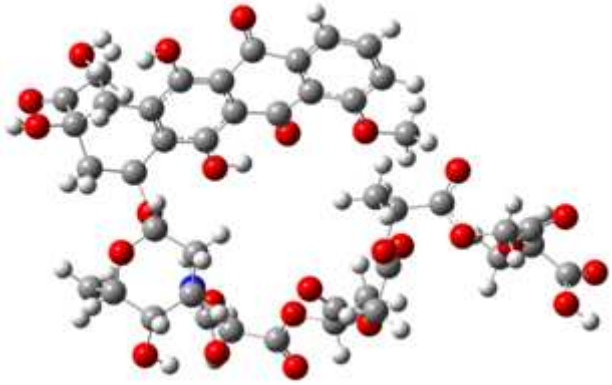

Fig.2.DOX-PLGA

In this study, some physicochemical properties[7-8] such as Gibbs free energy of solvation ($\Delta G_{solvation}$),binding energy, partition coefficient, and Dipole Moment (DM) of DOX-PLGA and DOX-PLGA were investigated.

RESULTS AND DISCUSSION

The geometry structure of DOX-PLGA-PEG and DOX-PLGA 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[9]. Table 1 presents the geometrical parameters[8] of two different complexes mentioned above around linking position (amide group), see also Fig 2.

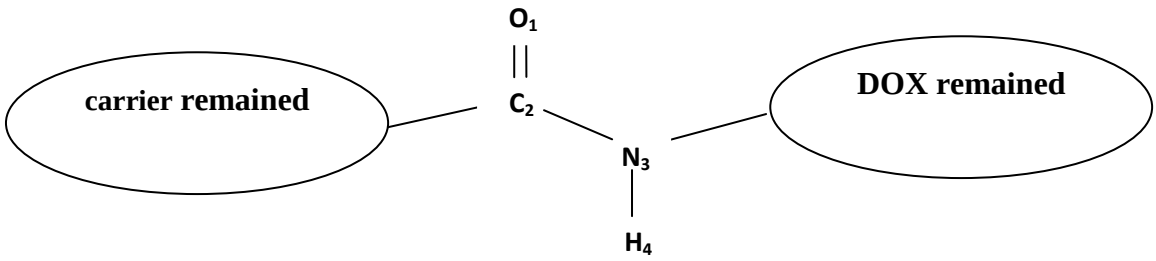

Fig 2. Structure of linking position in DOX-PLGA-PEG and DOX-PLGA complexes

Table 1. Geometrical parameter of complexes around linking position

complex	C2=O1 (Å)	C2-N3 (Å)	N3-H4 (Å)	C2-N3-H4 (°)
DOX-PLGA-PEG	1.212	1.351	1.009	115.352
DOX-PLGA	1.224	1.343	1.010	118.985

some physicochemical properties of DOX-PLGA-PEG and DOX-PLGA conjugates 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 which have been shown in Table 2.

The 1-octanol/water partition coefficient is an important thermodynamic variable usually employed to understand and quantify the partitioning of solutes between aqueous and organic phases.

The logP is found according to equation (1). These values and the logP obtained from Hyperchem software[10] .in this report we calculeted logP by using Hyperchem software and equation (1) . These values presents in table 2.

From Gibbs free energies of solvation in two different phases at temperature *T*, one can calculate the corresponding partition coefficient, according to the following eqation:

$$\log P = -\left(\frac{\Delta G_{sol,oct} - \Delta G_{sol,w}}{2.30RT} \right) \quad (1)$$

Here R is gas constant and T is the temperature. The solvation free energy is used to compute the logP based on equation (1) and only solvation free energies in water and 1-octanol are needed to calculate log P.

Table 2. Some calculated physicochemical properties of DOX-PLGA-PEG, DOX-PLGA and Doxorubicin

physicochemical properties	DOX-PLGA-PEG	DOX-PLGA	Doxorubicin
Refrectivity[a]	207.83	214.17	135.50
polarizability	80.52	82.54	52.00
Log p[a]	-1.21	-1.25	-0.33
Log p[b]	0.007	0.117	0.101
Hydration energy[a]	-27.05	-31.91	-24.03
Surface area[a](Å2)	1126.80	987.26	729.45
$\Delta G_{(solvation)}$ (kcal/mol)	-28.20	-13.51	-18.08
Dipole moment(Debye)	11.775	7.736	6.848
BE (ev/mol)	-3.679	-3.333	

[a]Data were calculated by using HyperChem 8 software[10], [b]data were obtained by using eqation(1)

CONCLUSION

Density functional Theory (DFT) and Hartree Fock (HF) calculation were applied to study some physicochemical properties of DOX-PGA-PEG , DOX-PLGA and Doxorubicin .Regarding the calculation results, hydrophilicity of DOX-PLGA and DOX-PLGA-PEG are higher than that of Doxorubicin ; this fact can be verified through the Gibbs free energy of solvation ($\Delta G_{solvation}$)obtained for DOX-PLGA and DOX-PLGA-PEG using Gaussian 03. It is also predictable that, based on dipole moment rates, there is higher solubility of DOX-PLGA-PEG and DOX-PLGA than Doxorubicin, which is higher lipophilicity of Doxorubicin than DOX-PLGA and DOX-PLGA-PEG. Our results indicate that these complexs mentioned above can be used to improve anti cancer activity and water-solubility of Doxorubicin.

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