Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

Vol 4, Suppl 1, 2012 ISSN- 0975-1491

Research Article

# COMPUTATIONAL PROCEDURE FOR DETERMINING PHYSICOCHEMICAL PROPERTIES OF DOXORUBICIN DIALDEHYDE STARCH (DOX-DAS) AND DOXORUBICIN-DIALDEHYDE STARCH NANOPARTICLES (DOX-DASNP)

**S. BAGHERI[1*], S.M. HASSANI[2] AND S.J. MAHDIZADEH[3]**

[1]Department of Chemistry, Islamic Azad University, Quchan Branch, Iran, [2]Department of Chemical engineering, Shahrood Branch, Islamic Azad University Shahrood, Iran, [3]Department of Chemistry, Ferdowsi University of Mashhad, Mashhad, Iran.
Email: s_bagheri1316@yahoo.com

*Received: 25 Nov 2011, Revised and Accepted: 2 Feb 2012*

**ABSTRACT**

Doxorubicin (or Adriamycin) is well known anti-cancer agent. It is an anthracycline antibiotic**.** The use of doxorubicin against neoplasms is limited due to its severe cardiotoxicity. The cytotoxicity of doxorubicin can be minimized by linking it to an affinity tag. In this report, the molecular structure, Binding Energy(BE), Dipole Moment (DM), Gibbs free energy of solvation ($\Delta G_{(solvation)}$) and some physicochemical properties of Doxorubicin Dialdehyde starch (DOX-DAS) and Doxorubicin-Dialdehyde starch nanoparticles (DOX-DASNP) conjugated complexes were investigated using Density functional Theory (DFT) calculations. Our results indicate that this complex mentioned above can be used to improve anti cancer activity and water-solubility of doxorubicin.

**Keywords:** Anti-cancer drug, DFT calculations, DOX-DASNP, DOX-DAS, Doxorubicin.

## INTRODUCTION

Doxorubicin is an anthracycline ring antibiotic that is widely used as a cancer therapeutic. Common treatment side effects include nausea and vomiting, loss of appetite, diarrhea and swelling, but development of a system capable of selectively delivering the drug to the intended target cells may be able to reduce these complications. There are many approaches to drug delivery via drug/drug carrier combinations, such as encapsulation, hydrogel formation, nanoaggregation, and micellar delivery. For doxorubicin delivery, encapsulation and micellar delivery have received increased attention because this system can protect and carry the drug directed to its intended target[1]. In experimental studies carried out by some other researchers, it has been illustrated that As a natural biomaterial, starch is a traditional filling agent which has been used in curatorial field for a long time[2-4], and in recent years it is found to have more properties through physical and chemical denaturalization, thus it could be used diffusely in medicine field as drug carrier material[5,6]. As one kind of starch ramification, dialdehyde starch is prepared by oxidation of starch with periodic acid or periodate, which is a selective oxidizing agent, and can cleave the C2, C3 linkage of anhydroglucose units with the formation of dialdehyde. Dialdehyde starch not only is biocompatible and biodegradable as starch, but also has more chemical activities. For example, it can react with hydrazine, acid, amine, imine and so on, so it is much more widely used in medicine field[7,10]. Doxorubicin is a traditional anticancer and antimetabolization drug, which is widely applied to cancer treatment[11], but it also has its limitation because of its heavy poisonous side-effect. So it is considered to be combined with natural or synthetical macromolecule polymer and prepared to polymer drug-loaded particles, which resulted in target delivery and sustaining release[12,13]. Doxorubicin Dialdehyde starch (DOX-DAS) and Doxorubicin-Dialdehyde starch nanoparticles (DOX-DASNP) conjugated complexes were synthesized by LIU XuanMing and colleagues[14]. The conjugation scheme is illustrated in Fig. also optimized structures of DOX-DAS and DOX-DASNP have been showed in Fig.2. The geometry structure of DOX-DAS and DOX-DASNP were optimized at B3LYP/6-31g* level of theory and then the Gibbs free energy of solvation (ΔG (solvation)) were calculated at B3LY/6-31g* level of theory using Gaussian 03[15].in this study unit number of DAS is 4. Based on these previous experiments, we concluded that doxorubicin can be conjugated to a biopolymer that selectively targets cancer cells. Quantum mechanical molecular simulation can be used to study drug delivery[1].

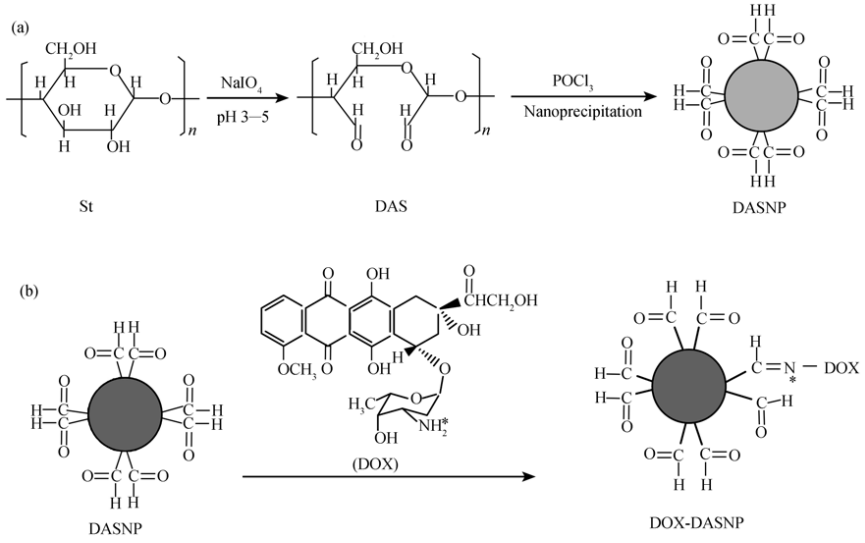
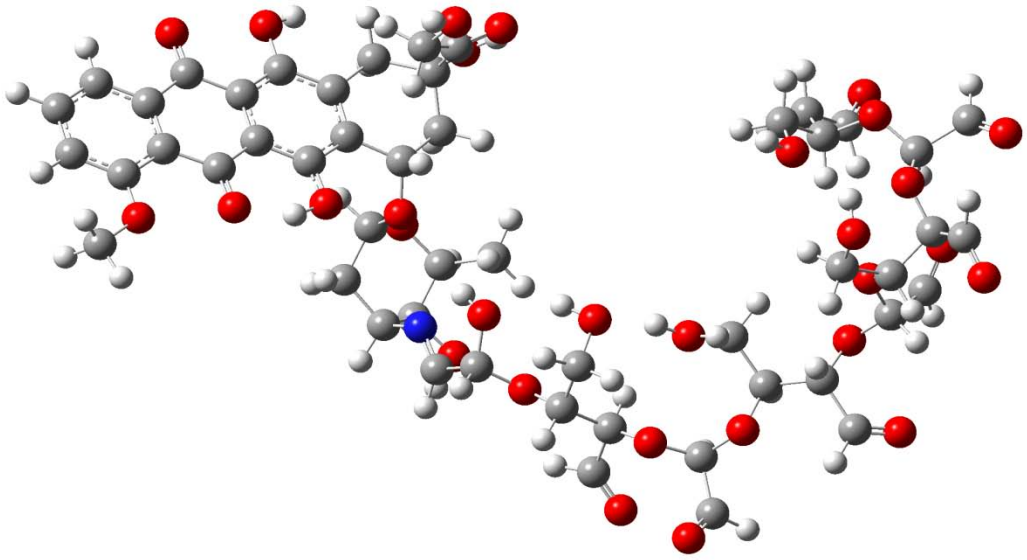



**Fig. 1: Synthesis of DASNP and DOX-DASNP. (a) Synthesis of DASNP; (b) synthesis of DOX-DASNP [14]**

**(a)**



**(b)**

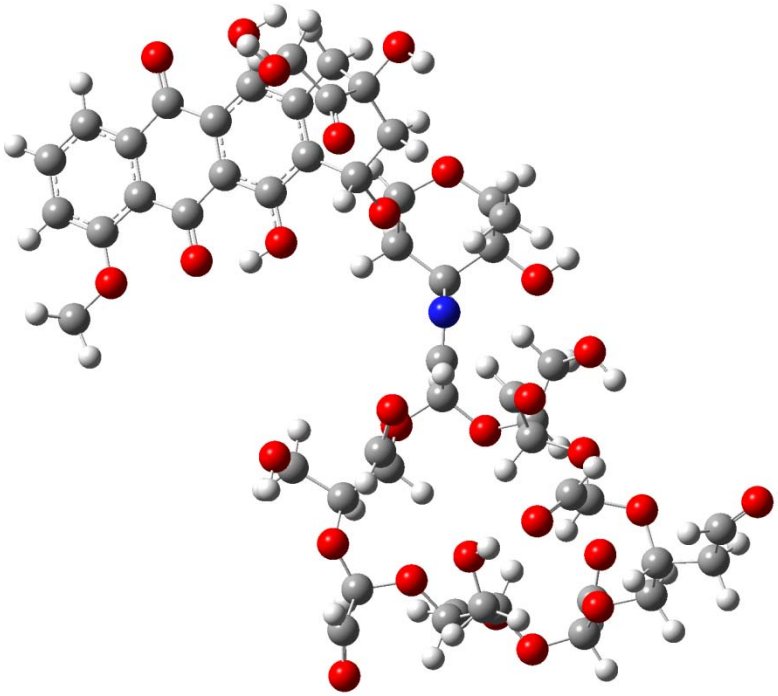


**Fig. 2: Structures of DOX-DAS (a) and DOX-DASNP (b) n=4**

In this study, we intend to show some the characteristics of doxorubicin, DOX-DAS and DOX-DASNP which have been mentioned above and have been obtained by other researchers experimentally through predictable computational calculations including molecular energy, binding energy, dipole moment, $\Delta G_{(solvation)}$, distance bound and angle bound[16].

## RESULTS AND DISCUSSION

The geometry structure of DOX-DAS and DOX-DASNP were optimized at B3LYP/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[15]. Table 1 presents the geometrical parameters of two different complexes mentioned above around linking position (imine group), see also Fig 3.

Some physicochemical properties of DOX-DAS , DOX-DASNP and Doxorubicin conjugates such as Refrectivity, polarizability, Hydration energy, binding energies (BE), Gibbs free energy of solvation (ΔG solvation) and Dipole moment (DM) are obtained from optimal structure[17] which have been shown in Table 2. The binding energy per molecule was computed using the formula (1):

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

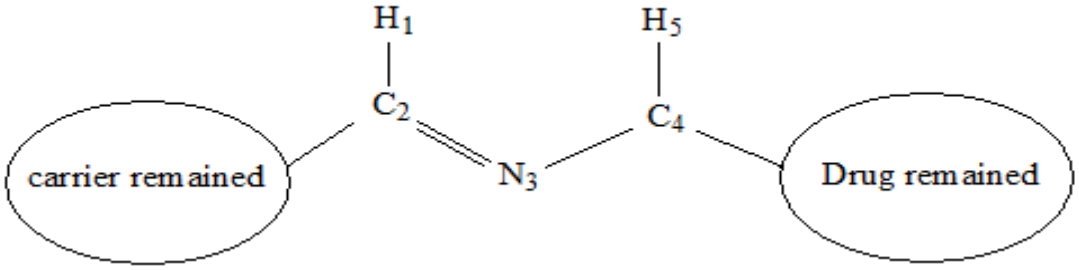



**Fig. 3: Structure of linking position in DOX-DAS and DOX-DASNP complexes.**

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

| Complex | R($H_1$-$C_2$) (Å) | R($C_2$=$N_3$) (Å) | R($N_3$-$C_4$) (Å) | $C_2$-$N_3$-$C_4$ (°) | $N_3$-$C_4$-$H_5$ (°) |
|---|---|---|---|---|---|
| DOX-DAS | 1.097 | 1.262 | 1.449 | 121.889 | 110.155 |
| DOX-DASNP | 1.101 | 1.265 | 1.455 | 117.753 | 110.315 |

**Table 2: Some calculated physicochemical properties of DOX-DAS, DOX-DASNP and Doxorubicin**

| physicochemical properties | DOX-DAS | DOX-DASNP | Doxorubicin |
|---|---|---|---|
| Refrectivity[a] | 265.15 | 261.64 | 135.50 |
| Polarizability | 103.78 | 102.37 | 52.00 |
| Hydration energy[a] | 8.17 | 3.73 | -24.03 |
| Surface area[a](Å2) | 1218.90 | 1113.46 | 729.45 |
| $\Delta G_{(solvation)}$ (kcal/mol) | -51.43 | -49.4 | -23.21 |
| Dipole moment(Debye) | 21.019 | 9.643 | 6.848 |
| BE (ev/mol) | -1071.845 | -1071.845 | |

[a]Data were calculated using HyperChem 8 software

## CONCLUSION

Density functional Theory (DFT) calculations were applied to study some physicochemical properties of DOX-DAS, DOX-DASNP and Doxorubicin. Regarding the calculation results, hydrophilicity of DOX-DAS and DOX-DASNP are higher than that of Doxorubicin; this fact can be verified through the Gibbs free energy of salvation (ΔG solvation) obtained for these complexes using Gaussian 03. Therefore, DOX-DAS and DOX-DASNP are more soluble than of Doxorubicin. These calculations also show that doxorubicin release from DOX-DAS and DOX-DASNP complexes takes place in a long period of time. On the other hand it means that we have a gradual release which is predictable according to Binding Energy. Our results indicate that these complexes mentioned above can be used to improve anti cancer activity and water-solubility of Doxorubicin.

## REFERENCES

1. Pirawattana T, Srinophakun T. Simulation of doxorubicin delivery via glucosamine (ethylene glycol) carrier. Int J Mol Sci 2008; 9:2290-2305.
2. Wikingsson LD, Sjöholm I. Polyacryl starch microparticles as adjuvant in oral immunisation including mucosal and systemic immune responses in mice. Vaccine 2002; 20:3355-63.
3. Pohja S, Suihko E, Vidgren M, Paronen P, Ketolainen J. Starch acetate as a tablet matrix for sustained drug release. J Control Release 2004; 94:293-302.
4. Tuovinen L, Ruhanen E, Kinnarinen T, Rönkkö S, Pelkonen J, Urtti A et al. Starch acetate microparticles for drug delivery into retinal pigment epithelium in vitro study. J Control Release 2004; 98:407-413.
5. Jun HX, Bin S, Ning LX. Production and application on dialdehyde starch. Chin J Bioproc Engin 2004; 2:1-4.
6. Wongsagon R, Shobsngob S, Varavinit S. Preparation and physicochemical properties of dialdehyde tapioca starch. Starch- Stärke 2005; 57:166-172.
7. Para A, Kostuch SK. Metal complexes of starch diadehyde dithiosemicarbazone. Carbohyd Polym 2002; 50:151-158.
8. Tang R, Du Y, Fan L. Dialdehyde starch crosslinked chitosan films and their antimicrobial effects. J Polym Sci B Pol Phys 2003; 41:993-7.
9. Ping WH, Qin WR, Bin S, Ning LX, Ping W, Hua Z et al. Study on flexible immobilized papain with dialdehyde starch. Chin J Bioproc Engin 2004; 2:25-29.
10. Onishi H, Nagai T. Characterization and evaluation of dialdehyde starch as an erodible medical polymer and a drug carrier. Int J Pharm 1986; 30:133-141.
11. Wolf MB, Baynes JW. The anti cancer drug doxorubicin causes oxidant stress induced endothelial dysfunction. BBA-Gen Sub 2006; 1760:267-271.
12. Han HD, Shin BC, Choi HS. Doxorubicin-encapsulated thermosensitive liposomes modified with poly (N-isopropylacrylamide-co-acrylamide) drug release behavior and stability in the presence of serum. Eur J Pharm Biopharm 2006; 62:110-6.
13. Azarmi S, Tao X, Chen H, Wang Z, Finlay WH, Löbenberg R et al. Formulation and cytotoxicity of doxorubicin nanoparticles carried by dry powder aerosol particles. Int J Pharm 2006; 319:155-61.
14. Danumi YU, Suyao X, Chunyi T, Lin C, Xuanming L. D. Dialdehyde starch nanoparticles Preparation and application in drug carrier. Chin Sci Bull 2007; 52:2913-18.
15. Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Chessman JR et al. Gaussian 03, Revision B.03, Gaussian Inc., Wallingford CT, 2004.
16. Bagheri S, Hassani SM, Mahdizadeh SJ. Theoretical study on physichochemical and geometrical properties of DOX-GA3 and DOX-mGA3. J Chem Pharm Res 2011; 3:524-527.
17. Bagheri S, Taghizadeh E, Hassani SM. Theoretical study on physichochemical and geometrical properties of doxorubicin and its different carriers such as PEG-FOL and PEG-b-PCL. J Chem Pharm Res 2011; 3:755-759.
18. www.hyperchem.com