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

S. BAGHERI1*, S.M. HASSANI2 AND S.J. MAHDIZADEH3

1Department of Chemistry, Islamic Azad University, Quchan Branch, Iran, 2Department of Chemical engineering, Shahrood Branch, Islamic Azad University Shahrood, Iran, 3Department of Chemistry, Ferdowsi University of Mashhad, Mashhad, Iran.

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 (\(\Delta G_{\text{solvation}}\)) 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. 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 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. 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. Doxorubicin is a traditional anticancer and antimitabolization drug, which is widely applied to cancer treatment, 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. Doxorubicin Dialdehyde starch (DOX-DAS) and Doxorubicin-Dialdehyde starch nanoparticles (DOX-DASNP) conjugated complexes were synthesized by LIU XuanMing and colleagues. The conjugation scheme is illustrated in Fig. 1. 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 (\(\Delta G_{\text{solvation}}\)) were calculated using Gaussian 03. 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.

Fig. 1: Synthesis of DASNP and DOX-DASNP. (a) Synthesis of DASNP; (b) synthesis of DOX-DASNP.
In this study, we intend to show some of 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, $\Delta G_{(\text{solvation})}$, distance bound and angle bound.

**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 ($\Delta G_{(\text{solvation})}$) were calculated at B3LYP/6-31g* level of theory using Gaussian 03. 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 Refractivity, polarizability, Hydration energy, binding energies (BE), Gibbs free energy of solvation ($\Delta G_{(\text{solvation})}$) and Dipole moment (DM) are obtained from optimal structure which have been shown in Table 2. The binding energy per molecule was computed using the formula (1):

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

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

<table>
<thead>
<tr>
<th>physicochemical properties</th>
<th>DOX-DAS</th>
<th>DOX-DASNP</th>
<th>Doxorubicin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractivity°</td>
<td>265.15</td>
<td>261.64</td>
<td>135.50</td>
</tr>
<tr>
<td>Polarizability</td>
<td>103.78</td>
<td>102.37</td>
<td>52.00</td>
</tr>
<tr>
<td>Hydration energy°</td>
<td>8.17</td>
<td>3.73</td>
<td>-24.03</td>
</tr>
<tr>
<td>Surface area(Å²)</td>
<td>1218.90</td>
<td>1113.46</td>
<td>729.45</td>
</tr>
<tr>
<td>ΔG (solvation) (kcal/mol)</td>
<td>-51.43</td>
<td>-49.4</td>
<td>-23.21</td>
</tr>
<tr>
<td>Dipole moment(Debye)</td>
<td>21.019</td>
<td>9.643</td>
<td>6.848</td>
</tr>
<tr>
<td>BE (ev/mol)</td>
<td>-1071.845</td>
<td>-1071.845</td>
<td></td>
</tr>
</tbody>
</table>

<sup>°</sup>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

17. www.hyperchem.com