A cyclodextrin-bioconjugate as carrier for anticancer drugs: from synthesis to molecular modeling

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In recent years, many efforts have been devoted to the development of new, specific drug delivery systems, conceived to enhance the therapeutic performance of pharmacologically active molecules by promoting the specific accumulation at target sites. With the aim of designing a new targeting system for cancer treatment, some of us have recently synthesized a ?-cyclodextrin derivative (CD-PEG-FA), in which folic acid was conjugate to the carbohydrate macrocycle via a 700 Da PEG spacer.

In this paper, we present the results of a combined experimental/molecular modeling study of this CD-bioconjugate and its inclusion complexes with some anticancer active compounds such as estradiol, chlorambucil and taxol.

Taxol exhibits a dimensionally relevant central part surrounded by some smaller and rather rigid "tails" formed by the hydrophobic phenyl rings. Accordingly, only these parts can actually be included into the CD cavity, and more than one CD-bioconjugate molecule is necessary to wrap up and complex the active principle. The analysis of the frames extracted from the molecular dynamics (MD) simulation of taxol with two CD-PEG-FA revealed that, during the simulation, the bioconjugate molecules approach one another while the taxol molecule lies on top, in a kind of "chaise longue" model fashion. Accordingly, more bioconjugate CD molecules will ultimately surround the drug, giving rise to a complex with higher than 2:1 stoichiometry.

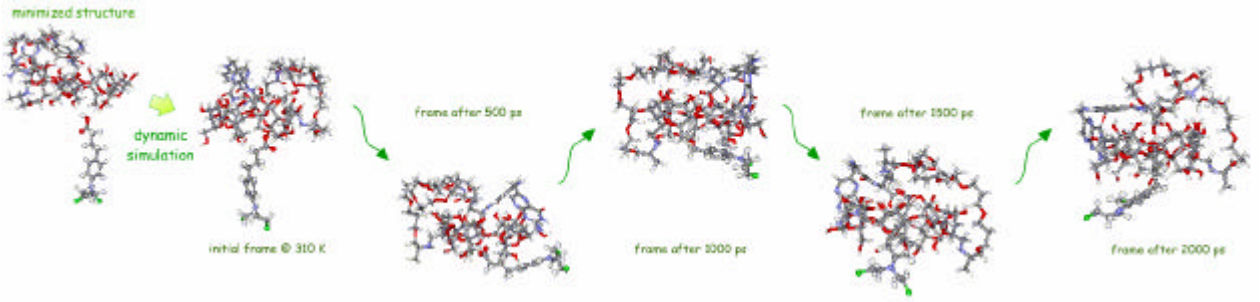
In the case of estradiol, for which a 2:1 stoichiometry was assumed, again the drug is not fully included in the cyclodextrin cavities, but gives rise to a sandwich like molecular assembly, leading to drug dissolution.

Finally, in the case of chlorambucil, the possibility of formation of stable inclusion complexes with CD-PEG-FA is suggested by several factors:

1) the limited drug molecular dimensions;
2) the presence of a central, disubstituted phenyl ring;
3) the literature evidence of 1:1 inclusion complexes between chlorambucil and native ?-CD.

In this case, the aim of our MD simulation was to follow the dynamics of the inclusion complex formation and the behavior of the resulting assembly during a 2 ns time period (see Figure 1). During the equilibration phase, the drug moves towards the cavity: the first frame (second from left, Figure 1) shows the drug closer to the cavity with respect to the energy minimized, initial situation (first from left, Figure 1).

During the first half of dynamic simulation, the drug tends to dispose parallel to the cavity, with the acetyl group within the cavity (0.5-1ns). Around 1.5 ns of simulation, the drug is aligned with the cavity axis and with the phenyl ring well inserted in the host (see Figure 1). The last part of the simulated period shows the slow drug release from the cavity, mainly due to the partial insertion of the folic acid into the cavity itself.



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