

Insertion of Thiazolidinediones into Carbon Nanotube

Behnoush Zare, Mojdeh Akhavan, Ahmad Reza Dehpour

II. METHOD

Abstract—In this study we investigate the insertion of pioglitazone, a Thiazolidinedione, into the two different sizes of Carbon nanotub. It was shown that the insertion of pioglitazone into the carbon nanotube in a water solute environment could be related to the diameter of the nanotube and in the flow of the waters via hydrophilic interactions. This encapsulated drug-carbon nanotube molecule can be further applicable in other investigations in target therapy with these agents regarding to reduce their potential toxic effects.

Keywords—Carbon Nanotube, MD Simulation, Thiazolidinedions

I. INTRODUCTION

THE peroxisome proliferator-activated receptors (PPARs) belong to the family of nuclear hormone receptors whose involved in adipocyte differentiation, glucose homeostasis [1] and also in neuro-immunological diseases like multiple sclerosis [2, 3]. More studies showed that these nuclear receptors have an important role in neurodegenerative disorders like Alzheimer's and Parkinson's disease [3-5]. Synthetic thiazolidinediones (TZD), including troglitazone and pioglitazone which are commonly prescribed for the treatment of type II diabetes, are selective PPAR γ agonists. These agents have so many benefits on lowering plasma glucose, improvement of insulin resistance and reducing blood pressure [6-8]. Besides of the benefits of the synthetic peroxisome proliferators some studies showed that they have carcinogenic consequences in the liver of rodents.[6, 9]. Because of sever toxic effects on liver, troglitazone was withdrawn from the worldwide market. Also pioglitazone has subsequently been found to be associated with bladder tumors and has been withdrawn in some western countries. Thus by emphesizing in the strongly great effectiveness of thiazolidinediones as the known ligands of PPARs and aiming to decrease the toxicity of them we thought about target therapy in which nanoparticles are applicable as the carrier for these drugs. Carbon nanotubes with their excellent chemical properties and large surface area strongly attracts biomolecules and are candidate for drug delivery. In this study we investigate the insertion of pioglitazone into the carbon nanotubes using molecular dynamics simulation.

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Carbon nanotubes were generated using the nanotube coordinate generator from Maruyama's Molecular Dynamics Site. [10]

The designed drug-CNT system consists of one molecule of pioglitazone and a series of uncapped armchair (8,8) and (10,10) carbon nanotubes (1.1 and 1.37 nm in diameter respectively and 3.5 nm long). As initial configurations, CNT and drug were aligned along the nanotube axis and separated by 0.5 nm. Molecular dynamics simulation was performed using GROMACS software version 4.0.[11] The drug-CNT complex was solvated in a periodic box with SPC216 water as solvent, the charge of the system was zero and its dynamics was simulated for 200 ps at temperature 400 K and pressure 2 bar.[12] The particle-mesh-ewald method was applied to evaluate electrostatic interaction. We used CHARM27 All-Atoms force field based to model atomic interactions. No external forces were applied to the pioglitazone for entering into the nanotubes.

III. RESULTS AND DISCUSSION

The primary results showed that the drug did not insert into the (8,8) carbon nanotube after 200 ps (Figure1). Firstly pioglitazone moved far from the nanotube, then the drug turned and went just above it and finally was positioned beside the tube.

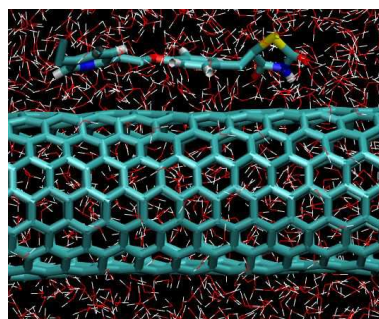


Fig. 1 Molecular Dynamics Simulation of pioglitazone interacting with a (8,8) carbon nanotube at 200 ps. Water molecules are displayed around and inside the carbon nanotube

The van der Waals energy calculation between pioglitazone and the nanotube (8,8) (Figure 2) showed there is not any interaction between the drug and the tube until 80 ps and then a few interaction could be detected as pioglitazone came near to the nanotube.

However the water molecules showed different behavior and they went inside the tube as shown in Figure 1 and the interaction between the solute molecules and the tube decreased during the simulation and the system equilibrate.

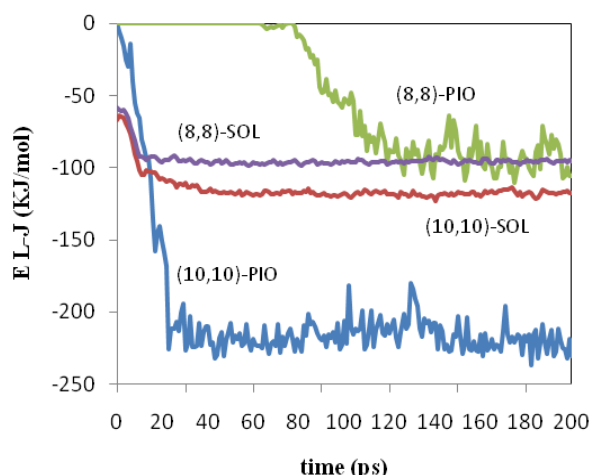


Fig. 2 Van der Waals energy between nanotubes (8,8), (10,10) and pioglitazone (PIO) and between nanotubes (8,8), (10,10) and water molecules (SOL) as a function of simulation time

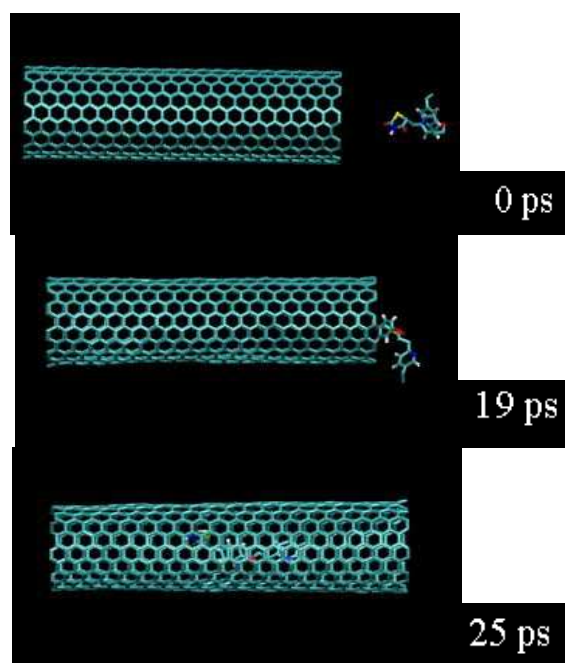


Fig. 3 Molecular Dynamics Simulation of pioglitazone interacting with a (10,10) carbon nanotube at 0, 19 and 25 ps. Water molecules are not shown

Also during the simulation there was a flow of water into the nanotube. The flow of water through synthetic nanotubes has been extensively investigated using computer simulations and it had been showed that they can mimic the function of biological ion channels.[13]

The snapshots of the pioglitazone-CNT system shown in Figure 3 indicated a very fast insertion process of pioglitazone into the carbon nanotube (10,10). At the time of 19 ps the first atom of the pioglitazone has begun to enter the nanotube. After 25 ps, the molecule totally inserted into the nanotube. Correspondingly, the center of mass (COM) distance, d (Figure 4) between pioglitazone and CNT rapidly decreases

with time up to nearly 25 ps. The decreased and nearly constant d , shown in Figure 4 afterward indicated that the system has reached equilibrium.

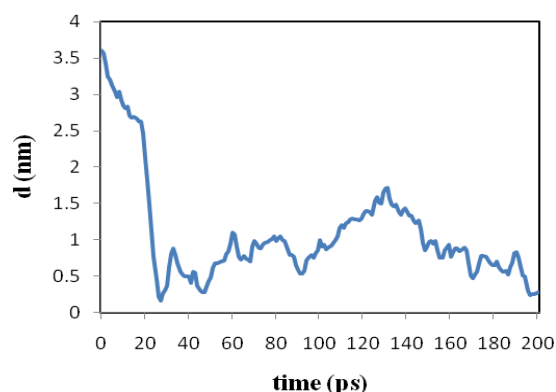


Fig. 4 Alteration of the center-of-mass distance (COM) of pioglitazone-carbon nanotube (10,10) complex (PIO-CNT) during the simulation

The van der Waals interactions between pioglitazone and carbon nanotube (CNT-PIO) (10,10) and between water molecules and carbon nanotube (CNT-SOL) (10,10) (Figure 2) decreased as the drug inserted into the nanotube and then the system reached to the constant and minimum energy.

As mentioned earlier the water molecules can insert inside the carbon nanotubes. Here these molecules in Figure 4 are displayed around and inside the carbon nanotube (10,10) and it seems the solutes had some interactions with the drug molecule. All of the synthetic TZDs have polar properties because there are some polar groups such as aromatic nitrogen, oxygen and sulfur in their chemical structures so the water molecules interact with pioglitazone via hydrophilic interactions. Thus the drug might be attracted with hydrophilic forces and the current of waters into the nanotube might bring the drug inside the tube (10,10) (Figure 5).

Also Figure 2 shows that the solute molecules entered the nanotube (8,8) easier than (10,10) and the van der Waals energy between these particles with nanotube was greater than with nanotube (10,10) even when it had been reached to the constant value. So it seems the current of water and interaction of waters with nanotube (8,8) was better than (10,10) in the absence of pioglitazone molecule.

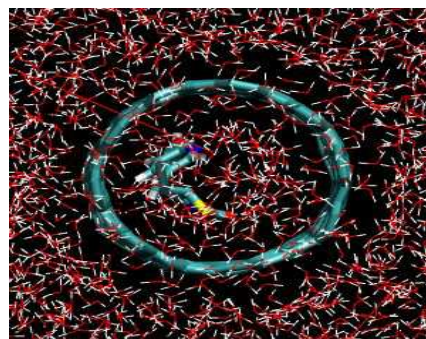


Fig. 5 Snapshot of drug-CNT system simulated after 200 ps. Water molecules are displayed around and inside the carbon nanotube

There are some investigations show the suitable diameter of the nanotube is another important factor for the drug insertion [12, 14] so according to our results pioglitazone could not be entered into the nanotube (8,8) with lower diameter. Even the flow of water molecules, went to the inside the tube (8,8) could not guide the drug molecule toward it until 200 ps. But may be longer simulation time give the chance to pioglitazone to insert into the nanotube (8,8).

In conclusion molecular dynamics simulation have indicated that pioglitazone could insert into the carbon nanotubes, with specific diameter in a water solute environment. The entering of the drug accompanied by the water molecules followed by decreasing the COM and the van der waals interaction energy, observed to be a minimum, might reveal the mechanism of the insertion process of pioglitazone into the carbon nanotube.

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