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Full Length Article

Comprehensive theoretical prediction of the dynamics and stability properties of Tegafur pharmaceutical agent on the Graphene based nanostructures in aqueous environment

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ABSTRACT

In this study, the molecular dynamics (MD) simulations are applied to elucidate the mechanisms governing the dynamics and binding strength of Tegafur (TG) anticancer drug interacting with two-dimensional carbon-based nanomaterials including hydroxyl (G-OH) and carbonyl (G-CO) functionalized Graphene nanosheets as well as Graphene oxide (GO). It is found that Tegafur drug exhibits the strongest affinity for the adsorption on Graphene oxide in terms of van der walls (vdW) amount energy. Furthermore, the total number of hydrogen bonding (HB) for the interaction of TG drug with GO is more than those with G-OH and G-CO models which be associated with maximum number of contacts between Tegafur molecules and Graphene oxide and higher stability. Based on these results, selection of Graphene oxide nanosheet as the suitable nano-carrier plays an important role in the greater effectiveness of TG drug with further experimental and theoretical investigations of nanoscale drug delivery systems.

1. Introduction

Recently, attributing to the rapid development of nanotechnology, various nanomaterials with different compositions and biological properties have been extensively studied for drug and gene delivery systems and demonstrated to be promising in cancer therapy. Traditional cancer chemotherapy is severely hampered by poor water solubility, nonspecific delivery and sever side effect [1]. Among nanomaterials that can be readily synthesized, materials in the graphite carbon family i.e. carbon nanotubes and Graphene have garnered particular interest due to their remarkable physical, morphological, and thermal and electrical conductivity properties [2]. Graphene and its derivatives have opened up a class of new biomaterials which provide exciting opportunities for the development of drug delivery and biological applications due to their unique properties including surface area, layer number, lateral dimension, surface chemistry and purity [3].

In order to develop safe nanomaterial-based drug delivery systems, several types of Graphene monolayers such as the oxidized Graphene and Graphene oxide are considered in this study and the extent and strength to which Tegafur anticancer drug (TG) is bound to the monolayers are explored by molecular dynamics (MD) simulations.

TG as a prodrug of 5-fluorouracil is a very effective drug in the treatment of a wide variety of solid malignancies, including head, neck, breast, and colon cancers [4].

Graphene nanosheet (GNS) as a monomolecular layer of carbon atoms which are densely packed in a hexagonal honeycomb arrangement [5,6] is highly hydrophobic and poorly dispersible in water, and require surfactants or surface modification to be used for any biological applications. Thus, the surface functionalization of Graphene nanosheet offers a promising way to increase the solubility and reactivity of GNS.

It is accepted that GO can be described as a random distribution of oxidized areas with the oxygenated functional groups, combined with nonoxidized regions where in most of the carbon atoms preserve sp^2 hybridization [7]. The presence of oxygenated functional groups creates the remarkable hydrophilic character in Graphene oxide and it can be dispersed in water to form stable colloids. However, the oxidized Graphene is moderately hydrophobic but can be dispersed in water to some extent. The oxidized Graphene is a two dimensional single-atom-thick planer sheet decorated with oxygen-containing functional groups.

2. Computational details

2.1. Molecular dynamics simulation

In order to investigate TG drug adsorption on the derivatized forms of Graphene nanosheet, i.e., hydroxyl (G-OH) and carbonyl (G-CO)

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functionalized Graphenes as well as Graphene oxide nanosheet (GONS), molecular dynamics simulation are applied at 310 K temperature in the NPT ensemble. It is noticeable that these types of Graphene monolayers with similar dimensions have different surface chemistries. GONS is constructed based on a molecular formula of $C_{10}O_1(OH)_1(CO)_{0.5}(COOH)_{0.5}$ which reflects a typical outcome of a standard oxidation process (i.e., two epoxy and two hydroxyl on both sides of basal plane of Graphene nanosheet, and one carbonyl group and one carboxyl group on the edges of Graphene, per twenty carbon atoms) [8,9]. Each designed simulation systems consists of ten drug molecules and a monolayer of each studied oxidized GNS which solvated in the simulation periodically box $5 \times 5 \times 6$ Å^3 with TIP3P water model for the arrangement of water molecule [10]. The parameters of carbon atoms as well as the hydroxyl, carboxyl, carbonyl and epoxy groups are taken from the CHARMM27 force field. The topology and parameters of the anticancer drug molecules for the CHARMM27 force field are obtained from the Swiss Institute of Bioinformatics [11]. We equilibrated the simulation systems in the water environment and conducted full simulation using the GROMACS 4.5.4 software package [12] for 30 ns with a time step of 2 fs.

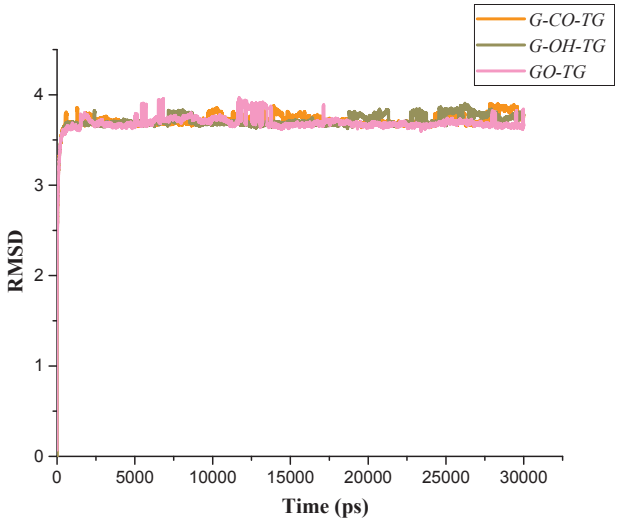

Fig. 2. RMSD curves for the simulated systems as a function of time.

3. Computational molecular dynamics simulation results and discussion

In this work, molecular dynamics simulation method is used to investigate dynamic interactions between nanostructured functionalized Graphene nanosheets and Tegafur drug molecules in the water environment. The snapshots of the final state of the considered nanostructured-Tegafur systems are presented in Fig. 1.

3.1. Description of equilibrium systems

The thermodynamic parameters such as total and potential energies of the system, temperature and pressure are monitored during each simulation case to observe the simulation accuracy. For all simulation systems, equilibrium as determined by stable curves of the potential energy is achieved after 30 ns of MD simulations as shown in Fig. SF1, Supporting information. Also, the structural stability of the studied systems is compared by analyzing the root mean square deviation (RMSD) as shown in Fig. 2. The evolution of RMSD between TG molecules and the nanosheet surfaces confirms the simulation systems have reached energy equilibration state. Close inspection of Fig. 2 and SF1, Supporting information, also reveals that the RMSD and the energy curves of the equilibrated systems do not fluctuated much during 30,000 ps trajectories which demonstrate that this simulation time is sufficient for achieving equilibrium in all the investigated systems [13–17].

3.2. The nature of the interaction of TG drug with the nanostructured functionalized Graphene nanosheets

Because all the partial charges of the atoms in Tegafur molecule and the considered functionalized nanosheets have been assigned to zero, the electrostatic interactions do not contribute to the nonbonded interaction energies. Therefore, the molecular dynamic descriptions of the interactions between nanostructures and drug molecules are governed exclusively by van der Waals (vdW) energy. The vdW interaction energy as a function of time for the simulation systems is depicted in Fig. 3. Also, Table 1 tabulated the average calculated vdW energy values for all the simulation systems. As shown in Fig. 3 the van der Waals energy declined rapidly due to the approach of the drug molecules to the nanosheet surfaces, suggesting the high strength of the drug adsorption process. Furthermore, it is observed that the vdW energy values are fluctuated around similar values which suggests that the nanostructure-Tegafur simulation systems are equally stable during this time frame.

With functionalization Graphene nanosheet, the LJ interactions of

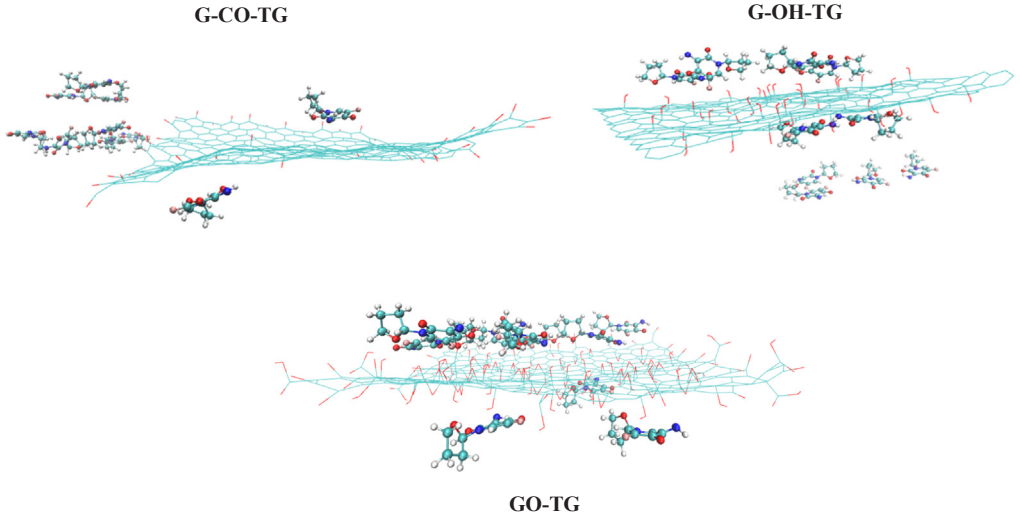

Fig. 1. The snapshots of the final state of the considered nanostructured-Tegafur systems. Water molecules are not displayed for clarity.