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Molecular simulation of curcumin loading on graphene and graphene oxide for drug delivery applications

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A B S T R A C T

Curcumin loading capacity of polyethylene glycol (PEG) functionalized graphene and graphene oxides are investigated using molecular dynamics and Monte Carlo (MC) adsorption locator simulations. These simulation methods were performed as a function of oxidation extent to study the effect of functional groups on curcumin loading and release properties. Adsorption locator energy calculations suggest that the curcumin drug molecule prefers to adsorb at the less oxidized sites of graphene oxide. One of the phenolic rings of curcumin drug prefers to have a planar interaction with graphene and graphene oxide framework due to the pi-pi interaction. Molecular dynamic studies are conducted in aqueous medium under neutral pH. Mean square displacement and radial distribution functions are obtained to determine the nature of the curcumin attachment and release in aqueous medium. The molecular simulations show that separation distance of the curcumin molecule from GO sheet is 4.4 Å. The molecular simulations presented in this work will help to design new synthetic methods of nanocarriers for curcumin delivery applications.

1. Introduction

Curcumin is a polyphenol derived from the curcuma longa plant, commonly known as turmeric. Curcumin has been extensively used in ayurveda medicine for centuries, as it is nontoxic and has a variety of therapeutic properties.[1,2] More recently curcumin has been found to possess anti-cancer activities through its effect on biological pathways involved in mutagenesis, oncogene expression, cell cycle regulation, apoptosis, tumor genesis and metastasis.[1,3] The multi-targeted property of curcumin is used to perform a wide spectrum of functions which are better than the other therapeutic drugs.[4] The reported in vitro studies establish that the 50% of cancer cell growth was inhibited with concentration of 5–30 μM.[5] Designing the curcumin loading and releasing nanocarriers for in vivo drug delivery applications has been intensely investigated.[6] Recently, graphene oxide (GO) based nanocarriers for drug delivery have attracted attention in the field of biomedical applications like biosensors, tissue engineering, gene and drug delivery, cancer therapy and bio imaging.[7,8] GO sheets have desired advantages over inorganic quantum dots as they have low toxicity and low cost of synthesis. The

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organic framework of GO sheets renders water insoluble drugs can be easily attached to them and delivered at the site of interest by changing the temperature and pH.[9] This study involves molecular simulations and estimation of curcumin loading capacity of GO with different oxidation extent. Curcumin loading capacity of GO sheets depends on the hydroxyl and carbonyl groups of GO sheets. Curcumin loading capacity was obtained using Monte Carlo adsorption locator simulations.[10] The adsorption locator helps to determine the basic interactions responsible for the adsorption of curcumin molecule on to the GO sheet. An integrated representation of the mean binding energy for the degree of binding between curcumin molecules and GO sheets were obtained using adsorption locator calculations. To understand the binding forces instantaneous interaction energy, deformation energy and instantaneous binding energy were obtained using MC simulations. The drug loading ability of the sheets has shown dependency on oxidation extent. Molecular dynamic simulations were conducted under neutral pH with NPT ensemble. The bare graphene sheets are hydrophobic in nature which prevents their use as drug delivery agent in aqueous media.[11] The water compatibility of graphene is further studied by PEGylation of graphene framework. The dynamic behavior of adsorption of curcumin on to the GO sheet was studied for GO with two different oxidation extents (GO1 and GO2) using molecular dynamic simulations. MD simulations studies reveal the dynamic equilibrium states between curcumin and GO sheets. The formulation methods for drug loading on to the graphene also involves the attachment of polyethylene glycol (PEG) molecules to the graphene sheets.[12] In this study, curcumin loading on the PEG coated graphene, GO1, and GO2 were studied using MC simulations. Radial distribution function calculations were obtained from MD trajectories and the equilibrium distance of separation of curcumin molecules from the GO sheets was determined. These molecular simulations will help in the optimization of the chemical nature of the nanocarriers for drug delivery, which can be manipulated during the synthesis process.

2. Computational details

The molecular structures of the graphene and GO were built using Accelrys Materials Studio (v7.0) software. GO1 and GO2 were built with size of the GO sheet of 20×20 $Å^2$. Highly oxidized GO was denoted as GO1 and the least oxidized sheet as GO2. GO1 and GO2 were created by randomly adding hydroxyl and epoxied groups on to the graphene sheet. GO1 and GO2 have oxygen to carbon (O/C) ratios of 3.0 and 8.1, respectively. The PDB of the curcumin molecule was downloaded from PubChem (Compound CID: 969516, MF: $C_{21}H_{20}O_6$, MW: 368.4 g/mol). The geometry and energy of the molecules were optimized using forcite module by smart algorithm and COMPASSII force field.[13] The optimized structures of the graphene, GO1 and GO2 sheets, and curcumin are shown in Fig. 1.

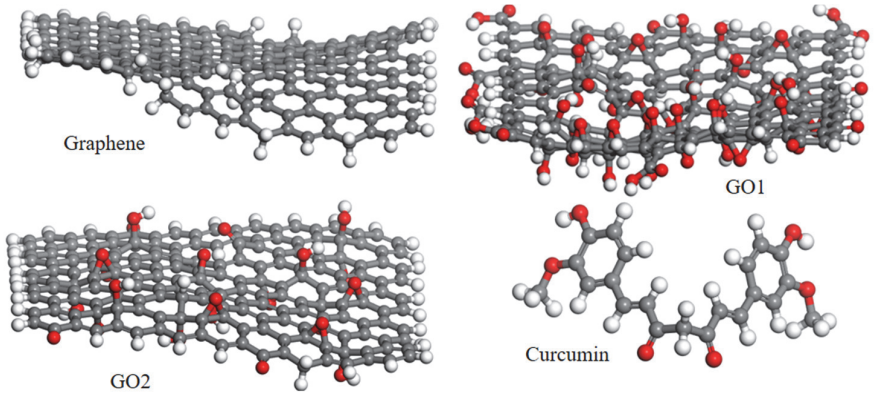

Fig. 1. Geometry and energy optimized structures (COMPASSII force field) of graphene, GO1 and GO2 sheets, and curcumin (Gray-C atoms, White-H atoms, Red-O atoms).

2. 1 Monte Carlo adsorption locator simulations

Adsorption locator studies were performed to determine the quantitative loading of curcumin on the graphene and GO sheets. Energy and geometry optimized curcumin were adsorbed on GO sheets using adsorption locator in material studio using COMPASSII force field. The electrostatic and Vander Waals forces of interactions were treated with Ewald and group of the atoms, respectively.[14]

2.2 Molecular dynamics

MD simulation studies were performed using forcite module in Materials studio (V7.0). MD simulations for the loading of curcumin on to the GO sheets with different oxidation extents were carried out using COMPASSII force field. The cubic simulation box with cell parameter of 33.8 Å was built using amorphous cell generator by adding 5 curcumin molecules, 1 GO sheet and 1000 water molecules. The generated simulation box was energy and geometry optimized using COMPASSII force field. The simulation box temperature was maintained at 300 K using Nose-Hoover thermostat and pressure by Berendsen-Barostat. The short-range electrostatic interaction cut-off is set at 12.5 Å using Particle–particle/particle–mesh (PPPM).[15] The MD simulations for loading curcumin on to the GO sheet were studied under neutral pH with NPT ensemble, and the trajectory information is saved every 5 ps interval of time.

3. Results and discussions

3.1 Adsorption locator studies

The adsorption locator for curcumin molecule helps in determining the quantitative amount of curcumin drug loading on to the graphene and GO sheets. MC simulation is a configurational method, which helps in exploring the adsorption sites for the substrate molecule. Configuration search algorithm is used in N dimensional phase space to determine the low energy configuration. Curcumin loading capacity on to graphene, GO1, and GO2 sheets is determined and one of the configurations obtained for each substrate are shown in Fig. 2.

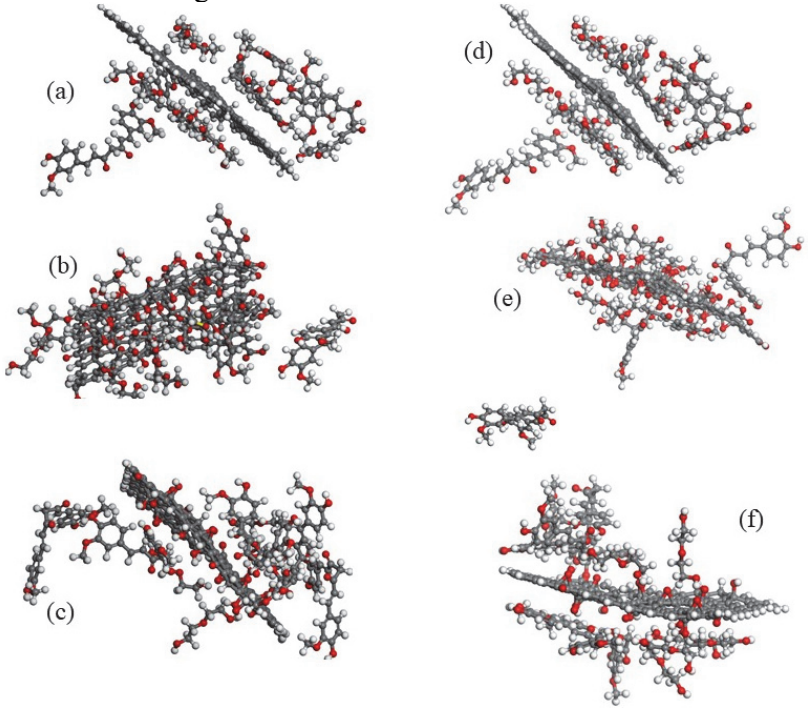

Fig. 2. One of the configurations of (a) G/curcumin, (b) GO1/curcumin, (c) GO2/curcumin, (d) G-PEG/curcumin, (e) GO1-PEG/curcumin, and (f) GO2-PEG/curcumin systems obtained by adsorption locator using Monte Carlo Method

The curcumin molecule has a bent geometry with two phenolic groups and the phenolic ring interacts with the graphene aromatic ring. In all the configurations, the phenolic ring was parallel attached to the GO sheet. From Fig. 2 it is clear that the amount of curcumin loading decreases with increasing oxidation groups. The energy distribution of adsorption loading on the graphene and GO sheets is shown in Fig. 3. The adsorption and configurational energies are listed in Table 1. From the energy calculations it is evident that hydrogen-terminated graphene has highest curcumin loading capacity. The substrate energy during calculations was set to zero and the adsorption energy was calculated using the equation 1. Total energy of the configurations obtained includes energies of adsorbate components, deformation energy upon adsorption, and rigid adsorption energy. Table 1 shows dEad/dNi, which is the energy of GO/Curcumin configurations when the adsorbed molecule was released. From Fig. 2, it is evident that the curcumin molecule prefers aromatic framework of the graphene over the oxidation groups of GO. This is because of the pi-pi interaction, which stabilizes the adsorption of curcumin on GO sheet under neutral pH. To understand the effect of functionalization of G, GO1, and GO2 with PEG on curcumin loading on graphene framework MC simulations were employed. The MC confiscations obtained for PEG functionalized graphene frameworks are shown in Fig. 2(d, e, and f). The energy profiles are shown in Fig. 3(d, e, and f). The adsorption data shows that PEGylation of graphene framework does not improve the curcumin loading.

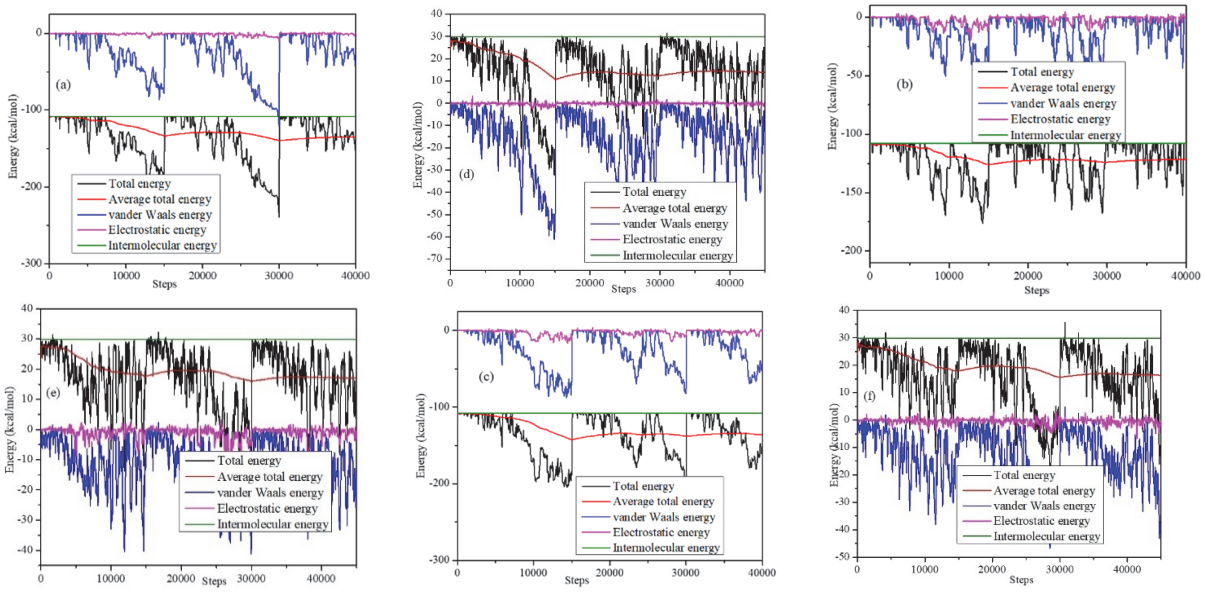

Fig. 3. Energy distribution of adsorption locator for (a) G/curcumin, (b) GO1/curcumin, (c) GO2/curcumin, (d) G-PEG/curcumin, (e) GO1-PEG/curcumin, and (f) GO2-PEG/curcumin systems.

Table 1. Energies calculated using adsorption locator simulations. Energy of the most stable graphene/GO1,2-Curcumin configurations. (GO1 has more hydroxyl and epoxide functional groups compared to GO2).

Structures	Total energy	Adsorption energy	Rigid adsorption energy	Deformation energy	cur : dEad/dNi
Substrate	0				
Curcumin	-21.6323				
G	-271.8556	-163.6936	-169.2822	5.5886	-33.4617
GO1	-204.3149	-96.1529	-100.2700	4.1171	-23.1342
GO2	-255.7880	-147.6260	-153.6490	6.0233	-22.0816
G-PEG	-44.6186	-74.5680	-75.8554	1.2873	-10.2506
GO1-PEG	-35.9312	-65.8806	-67.1913	1.3107	-3.0020
GO2-PEG	-42.8358	-72.7852	-74.0453	1.2601	-8.3355

3.2 Molecular dynamics simulations

MD simulations of GO1, GO2/Curcumin were conducted in aqueous solution under neutral pH using molecular dynamics using forcite module. The simulation box obtained from amorphous cell was

energy and geometry optimized. The total energy fluctuation during the MD simulations are provided in Fig. 4 (a, b). To evaluate the equilibrium adsorption distance between curcumin molecules and GO1 and GO2 sheets, radial distribution function (RDF) calculations were analyzed. The RDF of the curcumin molecule adsorption on GO sheets is shown in Fig. 4(c).

RDF is an important estimation of probable distance of separation of dyes from the GO surface. RDF is calculated using Eq. (1).[16]

$$g_{XY}(r) = \frac{\rho_Y(r)}{\rho_Y} \quad (1)$$

$\rho_Y(r)$: Average density of molecule Y at a distance r, around the molecule X.

ρ_Y: Density of the molecule *B* averaged over all spheres around the molecule X until r_{max}.

The distances of separation curcumin molecules which are attached on GO1 and GO2 sheets are 4.38 and 4.4 Å which were obtained from the radial distribution curves shown in Fig. 4(c).

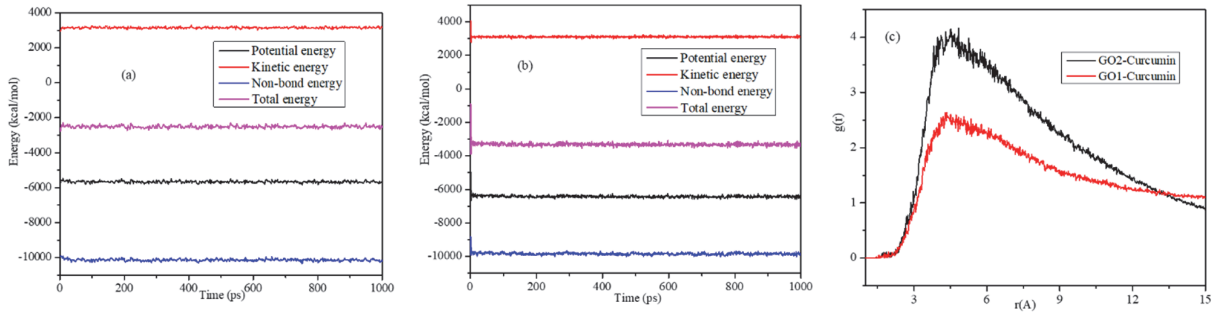

Fig. 4. Total energy fluctuations during Molecular dynamics simulations for 1000 ps of the (a) Curcumin/GO1, (b) Curcumin /GO2, and (c) Radial Distribution Functions between curcumin and GO

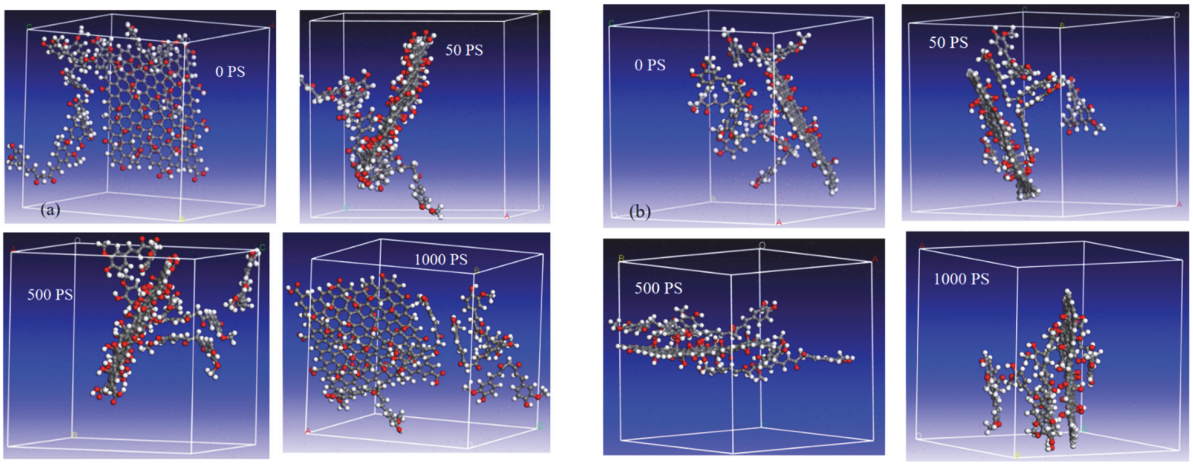

Fig. 5. Snapshots of MD simulations for the (a) Curcumin/GO1 and (b) Curcumin/GO2 systems.

The snapshots at 0, 50, 500, and 1000 ps simulation times are shown in Fig. 5. At 0 ps the molecules were randomly arranged for better visibility of the curcumin and GO sheet. The water molecules font size was set to zero. From the Fig. 5 it is clear that the solubility of curcumin molecules in water is limited and less number of molecules were attached to GO1 framework compared to GO2 at 1000 ps. The orientation of attachment of curcumin molecules on GO sheets shows that the preferred interaction is π-π between aromatic rings of graphene and phenolic ring of curcumin. The equilibrium distance of separation of curcumin molecule from GO sheet obtained from MC and MD simulations are

comparable. To load the maximum amount of curcumin to form the nano-formulations, optimum oxidation of GO sheet with water compatibility is required.

4. Conclusions

Curcumin drug loading capacity on the graphene oxide sheets with different oxidation extents were determined using Monte Carlo adsorption locator and MD simulations. MC simulations and the adsorption energy calculations obtained for graphene, GO/Curcumin configurations shows that the drug loading capacity is high for the pristine graphene whereas it is the least for the highly oxidized graphene oxide sheet GO1. Molecular dynamic simulations conducted under NPT ensemble under neutral pH also shows that the loading of curcumin is least for the highly oxidized sheet GO1. Although, the loading capacity is different for GO1 and GO2, the equilibrium distance of curcumin from both sheets is 4.4 Å. The equilibrium configurations obtained after 1000 ps simulation time shows that only two molecules were adsorbed on the GO1 sheet, whereas four curcumin molecules are adsorbed on GO2 sheet. The simulation studies presented here give insight for the nano formulation of curcumin loading and releasing agents, which can be used to synthetically design the properties of GO sheets.

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