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Molecular dynamics study on the configuration and arrangement of doxorubicin in carbon nanotubes

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ABSTRACT

Carbon nanotubes are potential candidates for drug delivery system (DDS) design due to their capacity to internalize and control the release of molecules. In this work, single-walled carbon nanotubes (SWCNTs) are the high-capacity drug carrier under study, and doxorubicin (DOX) is the model drug. Molecular dynamics simulations were performed to investigate the configuration and arrangement of different loading amounts of DOX in SWCNTs. The results show that the orientation and arrangement of DOX molecules can be influenced by drug concentration and by the diameter of the SWCNT. If the diameter of SWCNT is relatively small and there is strong confinement (e.g., in SWCNT (10,10)), DOX molecules prefer to form a single-file helix inside the SWCNT, which suggests that the controlled loading and release of a single drug molecule can be achieved by precise manufacture of SWCNTs with specific diameters, thus overcoming the disadvantage of aggregated DOX structure in solution and reducing chemotherapy dosage.

1. Introduction

Doxorubicin (DOX), as a broad-spectrum anti-tumor anthracycline antibiotic, has shown an obvious inhibitory effect on a wide range of cancers through intercalating DNA or inhibiting macromolecular biosynthesis, thereby disrupting or blocking the process of cancer cell replication. However, DOX cannot distinguish tumor cells from normal cells, which results in great toxicity to both normal and tumor cells. Moreover, DOX is hydrophobic and hardly soluble in water, which reduces its cycle time in the body and limits its effectiveness in the clinical treatment of cancer. Therefore, it is important to explore different methods and carriers that could serve as the basis for controllable and effective DOX drug delivery systems (DDSs).

In the past few years, DDSs have been developed to control drug distribution in the body, improve therapeutic effects, and reduce adverse effects [1–3]. Until now, one of the major challenges in DDS is designing an appropriate delivery carrier. Numerous efforts have been undertaken to provide new approaches for targeted drug delivery by different carriers, such as dendrimers [4,5], polymeric particles [6], liposomes [7,8], and microspheres and nanoparticles (NPs) [9,10].

Nanoparticles have advantages that could prevent premature drug release in the convection of vascular circulation before they reach tumor sites including sufficient stability, proper size, and outstanding surface properties. For example, Cheng et al. [11] developed a highly efficient drug vector by synthesizing PEGylated gold nanoparticle (NP) conjugates. Mejri et al. [12] investigated the conditions affecting encapsulated cisplatin inside a carbon nanotube (CNT) through molecular dynamics (MD) simulation; the result indicates that these molecules can stay inside the CNT for a long time if the simulation water boxes increase around the carriers (typically, during its transportation).

In biomedical applications, there are many types of NPs including graphene oxide (GO), CNT, and calcium phosphate [13–19]. Among them, CNTs have been considered as one of the most advanced nanovehicles for efficient delivery of drugs and biomolecules due to their large specific surface area, high chemical stability, and high capacity for drug loading [20–22]. Anticancer drugs can be loaded onto or into carbon nanotubes to improve the efficiency of the drugs' selectively via their enhanced permeability and retention (EPR) effect or by localizing in cancer tissues. For example, Panczyk et al. demonstrated the potential applicability of doxorubicin co-adsorbed with various dye molecules on/in carbon nanotubes as a drug delivery system [23].

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Recently, it has been demonstrated that CNTs can be loaded with drugs [21,22], nucleic acids [24], and peptides [25] by forming stable covalent bonds or supramolecular assemblies through noncovalent interactions. For example, Liu et al. [26] suggested that the noncovalent binding of DOX on single-walled nanotubes (SWNTs) most likely occurs via supramolecular π-π stacking and hydrophobic interactions due to the aromatic nature of both DOX and the SWNT surface. SWNTs are also considered as ideal candidates for releasing drugs inside the cell directly through internalization inside the cell membrane [27,28]. Therefore, CNTs offer new opportunities for application in nanobiotechnology and nanomedicine.

In the past few years, tumor-targeted drug delivery systems based on CNTs have received much attention from experimentalists and theoreticians. For example, Xu et al. [29] introduced PEGylation to carbon nanotubes via a bio-inspired strategy, and this system can be used for highly efficient delivery of DOX into cells for cancer treatment. Fan et al. [30] fabricated a multi-functional anti-cancer prodrug system and found that DOX could be released under lower pH and preferably internalized by FR-positive cells through CNT-based prodrug systems. Ji et al. [31] reported that the DOX-FA-CHI-SWNT complex is significantly more effective than free DOX, both in vitro and in vivo. This complex exhibited superior pharmaceutical efficiency and lower systemic toxicity on HCC SMMC-7721 cells. In addition, MD simulations have been confirmed as a powerful tool for investigating the delivery mechanism in DDSs, which would provide useful information at molecular level [32–37]. For example, Ortega-Guerrero et al. [36] studied the interaction between a single-walled carbon nanotube (SWCNT) and human transient receptor potential capsaicin receptor channel (hTRPV1), and found that there is an attractive potential between the SWCNT surface and hTRPV1, which affects adsorption of hTRPV on the SWCNT. Tomasz et al. [37] investigated the mechanism of cisplatin release from carbon nanotubes via MD simulations, and found that the release proceeds basically in two steps due to the different diffusivities in water and in the inner space of carbon nanotubes.

Although many studies focus on the feasibility of CNTs and their modification for delivery of DOX, it is still challenging to understand the loading and releasing mechanism and the configuration of DOX in SWCNTs. Because the molecular configuration and arrangement of DOX inside SWCNTs are highly correlated to DOX delivery properties, and thus influence the therapeutic effect, in this work, MD simulations were employed to investigate the configuration and arrangement of DOX with different loading amounts in SWCNTs. The effect of SWCNT diameters on these properties was also studied and is discussed.

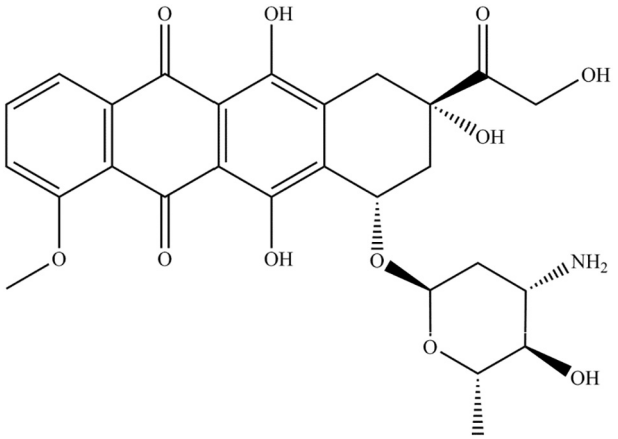

Fig. 1. Chemical structure of doxorubicin.

2. Simulation details

The structure of DOX is shown in Fig. 1. The force field parameters of DOX were derived from the general AMBER force field (GAFF) and the standard AMBER 2003 force field, respectively, using AmberTools [38]. The partial charge of all atoms in DOX molecules were calculated by the HF/6-31G+ method in Gaussian03 software [39]. The total charge of the DOX molecule is zero. The details of the non-bonded parameter and the partial charges of each atom in the DOX molecule are summarized in Fig. S1, Table S1, and Table S2 in the Supporting Information. Three rigid carbon nanotubes with different diameters were constructed, and the diameters of SWCNT (10,10), SWCNT (12,12), SWCNT (14,14) are 13.57 Å, 16.25 Å, 18.96 Å, respectively. The periodic boundary conditions were applied in all directions in these simulations. All CNT models in the axial direction are continuous and thus the length of these CNTs is infinite. The non-bonded interaction parameter for carbon atoms in SWCNTs was taken from Walther's work [40]. All carbon atoms in the SWCNTs were set to be neutral with the Lennard-Jones parameters $\sigma = 3.85$ Å and $\varepsilon/k_B = -0.439$ kcal/mol. The LJ cross-interaction parameters between different atoms were obtained from the Lorentz-Berthelot rules [41]. To investigate the drug release and the configuration of the drug inside the SWCNT, four systems with different DOX uptakes in the SWCNT cavity were created by increasing the number of DOX molecules from one to four. Before the simulation, DOX molecules were placed in the middle of the CNT with equivalent inter-molecular distances between each neighboring drug molecule when more than one DOX molecule was present. The TIP3P [42] mode was employed to describe water molecules, and water molecules were employed to fill the box. The number of water molecules in each system is slightly different; this information is listed in Table S3 in the Supporting Information. Our simulations were performed under neutral conditions without consideration of the ionic strength of the solution. As an example, Fig. S2 in the Support Information shows the initial configuration of SWCNT (10,10) filled with 4 DOX molecules and TIP3P water molecules.

In this work, all MD simulations were performed by Gromacs 4.5.2. The Particle Mesh Ewald (PME) summation was used to calculate the long-range electrostatic interactions, and the cutoff distance for van der Waals interaction is set to be 12 Å. The time step of the simulation is set to be 2 fs. V-rescale method was used to control the constant temperature at 310 K. The total simulation time of each system was 40 ns. All MD simulations were carried out in the NVT ensemble with the velocity Verlet numerical integrator.

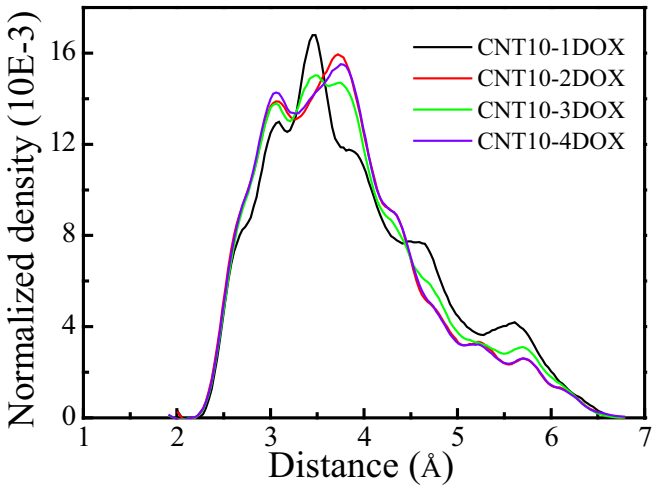

Fig. 2. Normalized radial density profiles of DOX inside SWCNT (10,10). The horizontal coordinates are the distance between the center of mass (COM) of the DOX molecule and the SWCNT sidewall.