Encapsulation of Paclitaxel in Single-Walled Carbon Nanotubes (CNT) for Targeted Drug Delivery of Cancer: A Simulation Study

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Abstract. The application of nanotechnology is significant in that it is exploited substantially, such as employing CNTs for targeted delivery of anti-cancer drugs. Through molecular dynamics (MD) simulations with Materials Studio Software, the anti-cancerous carbon nanotube drug delivery system for supporting SWCNTs has been studied. Secondly, Paclitaxel is an anticancer drug that inhibits the DNA synthesis of active cells – cancer cells; subsequently, the drug can reduce the tumour size. One promising strategy for achieving controlled drug release involves placing paclitaxel drugs inside SWCNT. This has been studied in the current article. The drug moved down the end to about the tube's midline within just 50 ps. Essential properties, such as energy, temperature, etc., have also been identified. The study thus reports a quick encapsulation behaviour of this drug within the SWCNT.

Keywords: Biomaterials, Carbon nanotube, Drug delivery system, Encapsulation, Molecular Simulation, Paclitaxel

1 Introduction

Presently, approximately 19.3 million different types of cancers have been reported. [1] Despite the improvements in the efficiency of treatments over the last few decades, most conventional chemotherapeutic formulations (tablet, capsule, injection) pose multiple problems. [2] Some of the associated issues include drug toxicity and efficiency loss during circulation. Drug management systems can endorse molecular systems to inhibit the processes of tubing and particles.

Nanomaterials are used as drug-delivery molecules for anticancer compounds to address these concerns. Some of these nanomaterials, including carbon nanotubes, metallic nanoparticles, and liposomes, among others, possess specific characteristics that may be harnessed for use in cancer detection, thermotherapy, and drug delivery systems.

Carbon nanotubes (CNTs) have become a cancer diagnosis and therapy tool due to their distinctive physical and chemical properties. [2, 3, 4,] Carbon nanotube mediators have also been used in Photothermal treatment (PTT) and photodynamic therapy (PDT) for the direct and indirect devastation of cells of cancer. [5]

CNT is significant as a cancer diagnostic and therapeutic tool due to its surface charge, surface chemistry, surface morphology and ability to overcome biological barriers inside the body. [3] Due to its small size, CNT may easily penetrate living tissues. Because of their portability and great penetration, CNTs are also suited for carrying drugs, proteins, and vaccinations. The surface or inside of this device may be filled with pharmacological compounds. [6] Nanometer-sized tubular carbon nanotubes (CNTs) can also target specific organ or tissue drug molecules. [7]

Molecular dynamics (MD) is an efficient method for studying atomic and molecular systems. In MD research, the system's behaviour is simulated using traditional MD techniques, with atomic and molecular forces considered. By simulating the interactions between CNTs and drug molecules, molecular dynamics (MD) analyses reveal their potential effectiveness as drug delivery devices. [8]

Paclitaxel (C47H51NO14), an anticancer drug, decreases tumours by causing DNA damage to rapidly proliferating cancer cells. [9] Systemic administration may cause adverse side effects at non-specific sites. Encapsulation of the drug into the CNTs may increase its efficacy and facilitate the site-specific targeted

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delivery, which will broaden a biomolecule's therapeutic profile. [10] Therefore, encapsulating Paclitaxel into CNT would be pretty favourable for cancer treatment.

Previously, in 2018, Karnati et al. [11] reported the loading of the Paclitaxel drug, along with Doxorubicin, on the CNT. Tohidifar and Strodel [12], in 2021, studied the loading of this drug with different CNTs. Hashemzadeh and Raissi [13], 2017 studied the surface adsorption of this drug onto the CNTs. However, a detailed study has yet to report this drug's encapsulation behaviour within the CNT. Therefore, in this study, we have attempted to document the encapsulation behaviour of this drug within a Single- Walled CNT (SWCNT) using MD simulation.

To examine the interaction between CNTs and drug molecules in a virtual setting, a molecular dynamics (MD) study of CNT as a drug delivery system was conducted in Biovia Material Studio X, a computational tool.

2 Materials

Paclitaxel, whose chemical structure is shown in Figures 1(A) and 1(B), was employed throughout the investigation. Secondly, (16,16) sized armchair SWCNT with 21.70 Å diameter was used for the experiment design shown in Figure 1(C). For computational purposes, the SWCNT length was kept to a few nanometers, i.e., 49.19 Å, corresponding to 10 repeating units (RU).

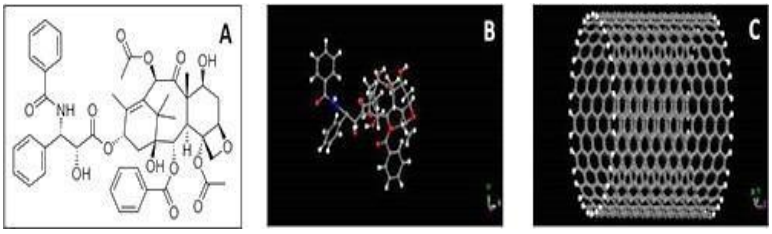

Fig. 1. (A) Chemical Structure of Paclitaxel drug; (B) Paclitaxel Drug Chemical Structure in Ball and Stick; (C) (16,16) sized Single-Walled Carbon Nanotube

2.1 MD Simulation Characteristics

All MD simulations involved using the FORCITE module and the COMPASS forcefield. The condensed-phase-optimised molecular potentials for atomistic simulation studies were employed in the FORCITE module of the Materials Studio software for including potentials and charges to the individual atom, which is found to predict the condensed properties and structural units of CNT with high accuracy.

Characteristics of MD simulation were similar to the ones reported in a study by Sarwar et al. [14]. Specifically, we spaced the drug molecule 1–2 angstroms from the SWCNT's aperture in this study. The investigation opted for the NVT Ensemble with Nose Thermostat at a temperature of 298K [15]. Each simulation took 50 ps and used a fixed time step of 1fs. All these studies yielded data points with the same consistent interval of 1ps. In these MD simulations, velocities and forces were incorporated into the trajectories. The atomic structure inspires the Electrical and Van der Waal summation techniques.

2.2 Parameters Setting for Simulation

At 298K, the velocities in a system were the random starting velocities according to the Maxwell-Boltzmann distribution and velocity Verlet Integration steps were taken to keep the system under the canonical condition. This system trend operates in the potential energy region and indicates the balance.

For each thousand steps, the frame is generated, and the atomic trajectories are saved to show the evolution of the partnership's behaviour—an atom-based summing behaviour for Van der Waals forces with the cut-off distance 15. For Van der Waals interactions, 5 nm was also used. At the same time, another method I . e. Ewald was also employed to treat long-range electrostatic interactions.s

2.3 Interaction Energies

The interaction energy (E(int)) was computed at each MD simulation's output frame to illuminate the drug-SWCNT interaction during the MD trajectory. For this computation, we utilised equation (1).

$$E(int) = E(system) - (E(drug) + E(SWCNT)) \quad (1)$$

3 Software

Materials Studio is a versatile molecular simulation software suite widely used in materials science, chemistry, and drug discovery. It provides a full range of functions for analysing the behaviour of materials at the nano and micro levels. Material Studio is a computational molecule-level physics software that incorporates quantum mechanics and molecular dynamics. In molecular dynamics simulations of CNTs as drug delivery systems, Material Studio is applied to model potential interactions between CNTs and drug molecules in terms of CNTs and drugs' size and shape, as well as chemical properties. In addition, the simulation may predict how rapidly the drug will be released from the CNTs and at which points the individual drug molecules are located within the CNTs. Its utilisation has been seen in developing and enhancing drug molecules, testing chemical compound libraries, and predicting molecule behaviour in different environments. Materials Studio also aids in studying material properties under various conditions and designing materials with specific characteristics. Thus, Materials Studio provides valuable insights and predictions regarding material and molecular properties based on their structure.

4 Results and Discussion

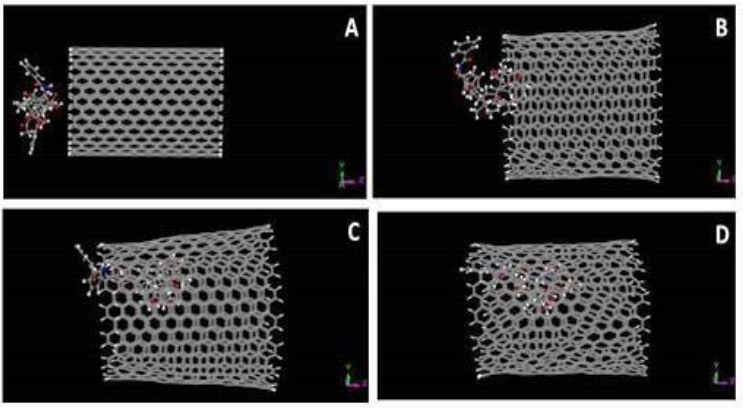

Fig. 2. (A) Paclitaxel Drug SWCNT before encapsulation; (B) Drug during encapsulation at six ps; (C) Drug during encapsulation at 21 ps; (D) Drug encapsulated in SWCNT (50 ps).

At the start, the drug was placed outside the SWCNT (figure 2 (A)). As the simulation progressed, the drug progressively entered the nanotube (figure 2 (B and C)), and finally, at 50 ps, it was successfully encapsulated inside the nanotube (figure 2 (D)). Most simulations have been performed using the standard SWCNT model (16,16) and have shown promising results.

Several energies between the drug and the nanotube were calculated to examine interactions between the drug and the SWCNT. Figure 3 shows the computed van der Waals, Electrostatic and Non-Bond energies between the drug and CNT. As can be observed, the van der Waals interaction between drug molecules and CNTs is weak at the beginning of the simulation when the Paclitaxel molecule is approaching the CNT surface, as shown by the higher energy values. However, as the simulation progresses, the energies show a steep decrease at the start, depicting the development of a strong interaction between the drug and the nanotube. After the first few picoseconds of the simulation, the energy values stabilise, denoting equilibrium while the drug is inside the simulation. This result corroborates the modelling of drug molecule dynamics and quantum

mechanics. The large non-polar portion of the drug molecule is amenable to interacting with the nanotube's non-polar surface through Van der Waals interactions.

Van der Waals and electrostatic forces will likely predominate in the paclitaxel-carbon nanotube interactions simulated in Materials Studio, which have implications for the drug's and the nanotube's characteristics and behaviour. Due to this interaction, a medicinal molecule may be adsorbed onto the nanotube surface. When pharmaceuticals are adsorbed onto nanotubes, they gain solubility, stability, and bioavailability. [17,18]

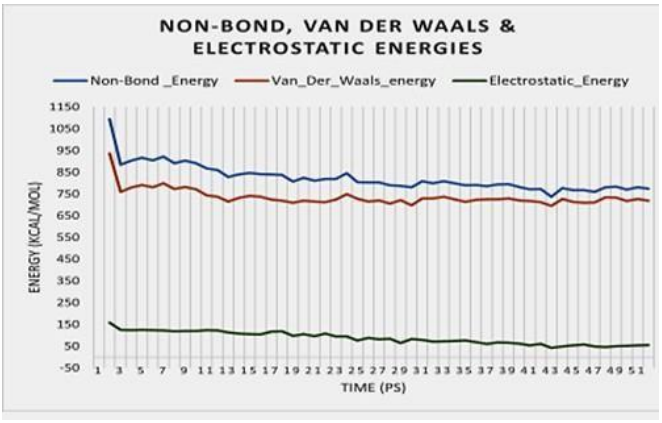

Fig. 3. Non-Bond, Van der Waals and Electrostatic energies of Drug and SWCNT system after Encapsulation

The interaction energy between the drug and the SWCNT was also calculated throughout the MD simulation. The sign of the interaction energy tells whether there is an attraction or repulsion between the drug molecules. Initially, the drug was outside the CNT, and the interaction was fragile, but as the drug was encapsulated, the interaction energy got highly damaging. This highly negative value shows powerful attraction between the drug and SCWNT, as shown in Fig 4. Furthermore, it can be observed that as the drug molecule starts entering the SWCNT, the interaction energy starts to stabilise. It has been reported that the attainment of system stability during an MD simulation is attributed to achieving equilibrium. [14] This stability can be mechanical or stabilising energy, temperature, or other properties. In the case of encapsulation, this achievement of stability and equilibrium is called successful encapsulation. [14,19,20] This study reports successfully encapsulating a Paclitaxel drug molecule within an Armchair SWCNT in just 50 ps.

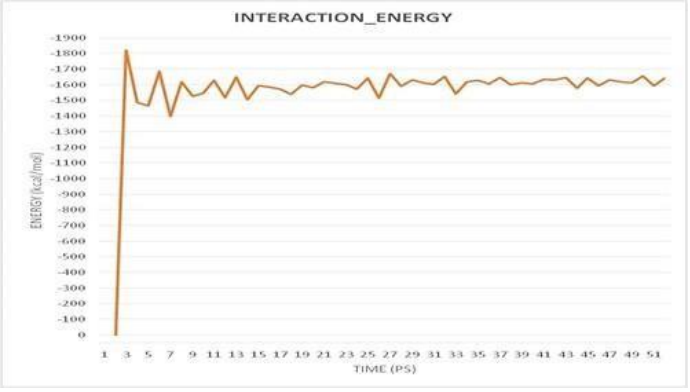

Fig. 4. Interaction Energy of the Drug and SWCNT throughout the simulation.

To further strengthen our results, we have obtained the temperature graph using the FORCITE module (Fig 5). It also shows the stabilisation of the system dynamics

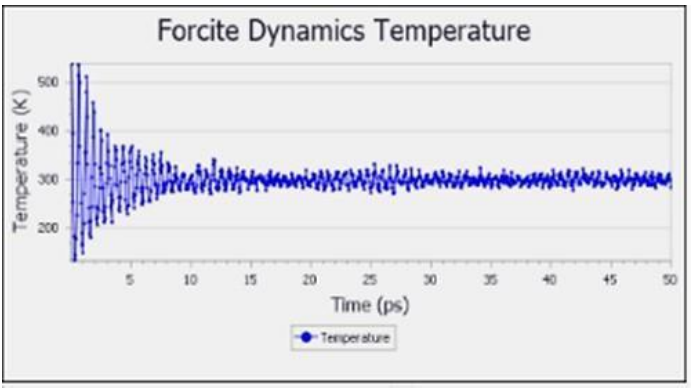

Fig. 5. FORCITE Dynamic Temperature of Drug 10 Repeat Unit SWCNT system

The Velocity Autocorrelation function has also been calculated through equation 2 using the FORCITE Analysis module.

$$\Psi(t) = \langle v_i(t_0) \cdot \ v_i(t_0 + t) \rangle \tag{2}$$

Where v_i is the velocity of the atom i. Fig 6 is shown below.

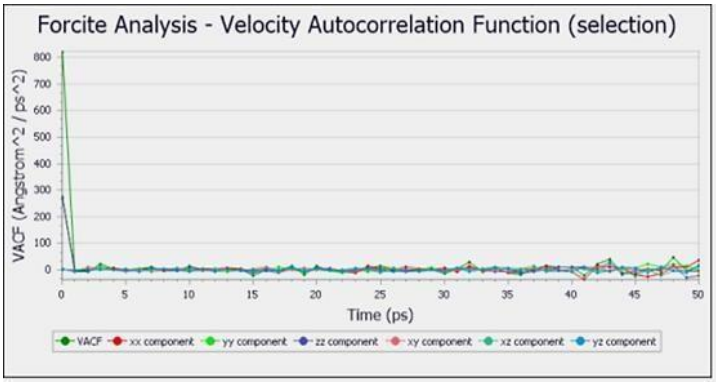

Fig. 6. Velocity Autocorrelation Function of drug and SWCNT with 10 RU after encapsulation.

The velocity-correlation function (VACF) characterises the temporal dependence of velocity correlations among particles or molecules in a system. [21] After 10 RU of Carbon nanotube encapsulation, we found that the drug molecule adsorbs onto the nanotube surface and gets immobilised, corresponding to a VACF amplitude drop.

5 Conclusion

This MD study exposed the significant relationship between the SWCNT and the Paclitaxel drug molecule, thus advocating for CNT as a drug carrier. This has been observed through the encapsulation of this drug within just 50 picoseconds. As the energies, temperature and VACF analyses have confirmed, this encapsulation behaviour's success can be boasted of. Functionalising CNT to improve their interactivity and biocompatibility

is possible, considering them as potential materials for cancer treatment. Molecular dynamic simulations for validation, verification, and optimise drug release to enhance efficiency—assessment of toxicity and biocompatibility of functionalised CNTs Identification of possible synergistic effects of multiple drugs.

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