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Research Paper

Comparative Analysis of Mitoxantrone and Doxorubicin Interactions with Single-Walled Carbon Nanotubes Using Molecular Dynamics Simulations

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Abstract: The field of nanotechnology has made remarkable advancements in drug delivery systems, enabling improved drug penetration and direct delivery to specific areas. These systems, known as drug delivery systems (DDSs), aim to enhance drug efficacy and safety by controlling release rate, timing, and targeted location within the body. Carbon nanotubes (CNTs) have emerged as promising materials due to their ability to target specific sites and regulate molecule release. In this study, molecular dynamics simulation was used to compare the interactions between commonly used drugs such as mitoxantrone (MTX) and doxorubicin (DOX) and single-walled carbon nanotubes (SWCNTs). The adsorption process of these drugs was observed in a non-aqueous simulation box to evaluate their compatibility with nanocarriers for biomedical applications. The results demonstrated positive energetic interactions between anti-cancer drugs and SWCNTs, driven by π-π interactions and significant interaction energies. According to the RDF results, it was observed that mitoxantrone and doxorubicin drugs had π-π interactions with the carbon nanotube with approximately 3.5 Å - 4.0 Å. Additionally, interaction energy values were calculated as -92.43 kJ/mol and -105.42 kJ/mol for SWCNT-MTX and SWCNT-DOX systems, respectively. While MTX and DOX interacted effectively with the carbon nanotube, doxorubicin showed a more efficient interaction.

Keywords: Single-walled carbon nanotubes, drug interactions, molecular dynamics, mitoxantrone, doxorubicin

1. Introduction

In recent years, the rapid pace of industrialization has led to an alarming increase in various diseases, particularly cancer [1]. Cancer is characterized by the abnormal growth and proliferation of cells, which can potentially spread to other parts of the body. It encompasses a broad spectrum of diseases, with more than 100 different types, all stemming from uncontrolled cell division in different regions of the human body [2]. If left unchecked, cancer can be fatal, requiring a prolonged and arduous battle. This battle not only encompasses physical health challenges but also imposes substantial financial and emotional burdens on individuals and their families. The prevalence of cancer remains a global concern, affecting millions of individuals worldwide. Each year, approximately 19.3 million new cases are diagnosed, leading to 10 million deaths [3]. Cancer is a disease that does not discriminate, impacting people of all ages, genders, languages, religions, and races. It accounts for around 25% of all reported deaths globally in 2015 [4]. The types of cancer most observed differ between men and women. Prostate cancer, lung and bronchus cancer, colon and rectum cancer, and urinary bladder cancer are prevalent in men, while breast cancer, lung and bronchial cancer, colon and rectum cancer, and thyroid cancer are frequently encountered in women [5].

Nanotechnology, which focuses on studying materials and phenomena at the nanoscale (approximately 1 to 100 nanometers), offers new avenues for scientific exploration and potential

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advancements in various fields. Studies on nanotechnology are quite important to improve product features because of the ability to display, measure, and process at the atomic scale [6]. Nanotechnologies find applications in various areas, including biomedical and environmental fields [7]. Among these, carbon nanotubes (CNTs) stand out as one of the most intensively researched nanoscale materials today [8]. CNTs are cylindrical structures composed of carbon atoms and serve as promising nanocarriers [9]. These nanotubes are formed by rolling graphene sheets into cylinders with a high aspect ratio, ranging from diameters as small as 1 nm to several micrometers. CNTs can have open ends or can be capped. When a single graphene sheet is rolled into a cylinder, it forms a single-walled carbon nanotube. Moreover, CNTs consisting of multiple graphene sheets are referred to as multi-walled carbon nanotubes (MWCNTs) [10]. Both are used in many application areas because of their chemical and physical properties such as large surface areas, high aspect ratios, high surface chemical functionalities potential, and size stability at the nanoscale as the ease of processing like biotechnology, electronics, and materials science [11,12,13]. Nanocarriers, such as SWCNTs, offer a promising approach to enhance stability, absorption, and drug carrier capacity in various fields, including cancer prevention and anti-inflammation applications. These nanocarriers can potentially improve the targeted delivery of drugs while minimizing off-target effects [14,15]. In recent years, research in various disciplines has focused on maximizing the potential benefits of drug-carrying capacity through the carbon nanotube interaction of anti-cancer ("antineoplastic" or "cytotoxic") chemotherapy drugs such as mitoxantrone (MTX) and doxorubicin (DOX). MTX, which is also known as Mitozantrone in Australia and marketed under the trade name Novantrone, is classified as an anthracenedione antineoplastic agent. It is primarily utilized for the treatment of specific cancer types, particularly acute myeloid leukemia. Significantly, it has demonstrated effectiveness in enhancing the survival rate of children who face a relapse in acute lymphoblastic leukemia [16]. For example, in the context of prostate cancer, the combination of mitoxantrone and prednisone was previously approved as a first-line treatment for metastatic hormone-refractory prostate cancer [17]. Like mitoxantrone, doxorubicin is an anti-cancer drug used to treat various types of cancers, including breast, ovarian, bladder, and lung cancers. It exhibits a significant inhibitory effect on the growth of cancer cells. In recent years, researchers have actively focused on increasing the selectivity of doxorubicin and improving its therapeutic index. By developing targeted delivery systems or combining them with other agents, efforts are being made to enhance its specificity towards cancer cells and reduce its toxicity to normal cells. Doxorubicin is hydrophobic this is why it is hardly soluble in water. This situation limits the effectiveness of the drug in the treatment. Therefore, it is important to find an efficient method for carriers of the drug [18,19]. One of the main advantages of mitoxantrone over doxorubicin lies in its tendency to cause lower levels of cardiotoxicity in both humans and animals [20,21]. Its clinical applications encompass the treatment of various malignancies, including lymphoma [22]. Remarkably, mitoxantrone has emerged as a promising option for cancer patients who experience difficulties in tolerating the adverse consequences associated with doxorubicin treatment. Of notable importance, mitoxantrone has demonstrated notably reduced occurrences of nausea, vomiting, stomatitis, and alopecia even when administered at doses that induced equivalent or more pronounced myelosuppression compared to doxorubicin. Furthermore, there was a decreased incidence of cardiac toxicity observed in patients treated with mitoxantrone, as indicated by a lower occurrence of congestive heart failure and/or reduced left ventricular ejection fraction [23].

Molecular simulations hold great promise in the in-silico design of drug delivery formulations. They provide valuable insights into the properties and behavior of formulations, enabling predictions to be made before the actual synthesis takes place. By utilizing computational techniques, molecular simulations can reduce the need for extensive in vitro and in vivo experimentation [24]. Molecular dynamics (MD) simulations are an indispensable computational tool in the realm of computer-aided drug discovery and design. With their capability to delve into atomistic-level interactions, MD simulations provide invaluable insights into diverse systems, including drug delivery systems (DDSs). These simulations are widely employed to predict properties and unravel intricate

interactions among drugs, biomolecules, nanoparticles, and other entities. However, the study of single-walled carbon nanotubes poses specific challenges, encompassing intricate interactions, computational resource limitations, selection of simulation parameters, and the inherently multiscale nature of the problem. Despite these challenges, MD simulations hold tremendous potential for advancing drug delivery technology by augmenting our comprehension of SWCNT-drug interactions and propelling the optimization of DDS design, thereby paving the way for innovative therapeutic strategies [25].

In recent years, there has been a significant surge in research focusing on the development of drug delivery systems [26]. Studies involving carbon nanotubes as drug delivery systems have gained prominence. For instance, Arsawang et al. conducted a study utilizing molecular dynamics (MD) simulations to investigate the structural properties necessary for encapsulating the anti-cancer drug gemcitabine within single-walled carbon nanotubes [27]. The findings of their study revealed that the drug molecule exhibited a preference for residing inside the SWCNTs, with π-π stacking interactions forming between the CNTs and the cytosine ring of the drug. This insight contributes to our understanding of the potential use of SWCNTs as effective carriers for delivering anti-cancer drugs. Drug delivery systems have started to be used quite frequently in the diagnosis of cancer disease. In this way, these systems, which can be used as drug delivery systems, will play an important role in the treatment of cancer disease by minimizing side effects, keeping harmful effects at a minimum, and performing full targeting.

Due to their chemical, physical, and biological characteristics, SWCNTs are well-suited for various biomedical applications, including cellular imaging, MRI contrast agents, tumor treatment, and drug carriers. Their high surface area and excellent chemical stability make them the preferred choice for this study. Mitoxantrone and Doxorubicin are potent chemotherapy drugs commonly used in treating various cancers, including breast cancer. However, their systemic administration can result in side effects and harm healthy tissues. Investigating their interactions with Carbon Nanotubes is crucial for developing a more specific and targeted drug delivery system. Therefore, the primary objective of this study is to investigate and understand the adsorption mechanism of Mitoxantrone and Doxorubicin on single-walled carbon nanotubes through the application of molecular dynamics simulations and to obtain an anti-cancer drug carrier system.

2. Experimental Methods

2.1. Computational methods and details

In this study, Materials Studio 8.0 software has been used to study the interaction of each drug with each nanotube type and to simulate the whole system. First, the basic system of the structures was prepared. Firstly, a single-walled armchair CNT (SWCNT) having (6,6) chirality, with a diameter of 8.14 Å, and length of 24.60 Å was generated by using the "Build Nanostructure" module as the Table 1.

Table 1. Single-walled carbon nanotube properties

Nanotube	Chirality	Diameter (Å)	Length (Å)
single-walled CNT	(6,6)	8,14	24,6

SWCNT is given in Figure 1. This diameter was small enough to prevent the diffusion of drug chains inside the nanotube. Secondly, the first drug molecule mitoxantrone, which we observed to analyze between SWCNT, was generated from taking the Zinc database. For the system equilibrium, all

generated structures were geometrically minimized using Materials Studio's Smart algorithm using the forcite module with the COMPASS force field [28]. This is the first force field parameterized and validated for molecules in isolation utilizing condensed phase characteristics as well as diverse and empirical data [29].

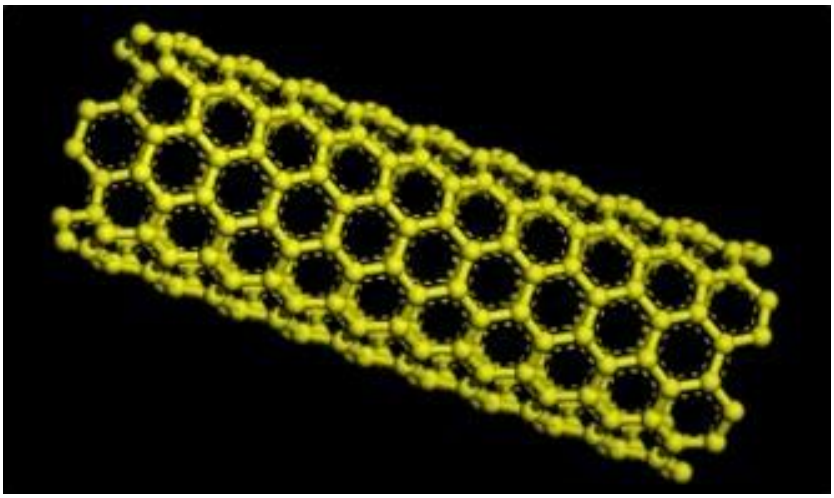


Figure 1. Schematic representation of single-walled carbon nanotube

Generally, simulation boxes should be packed with a suitable solution to take results. However, in this study, this step was performed using a vacuum medium. The simulation box was constructed with a volume of 40*40*40 sizes using the "Build Crystals" module to carry out all MD and quench simulations. Then, in the center of the box, CNT was fixed, and its charge was set to zero. The "Adsorption Locator" module was used to adsorb mitoxantrone drug molecules on the surface of CNTs using the Ewald summation approach for electrostatic interactions and a fixed energy of 100 kcal/mol [30]. Single-walled carbon nanotube with doxorubicin is given in Figure 2.

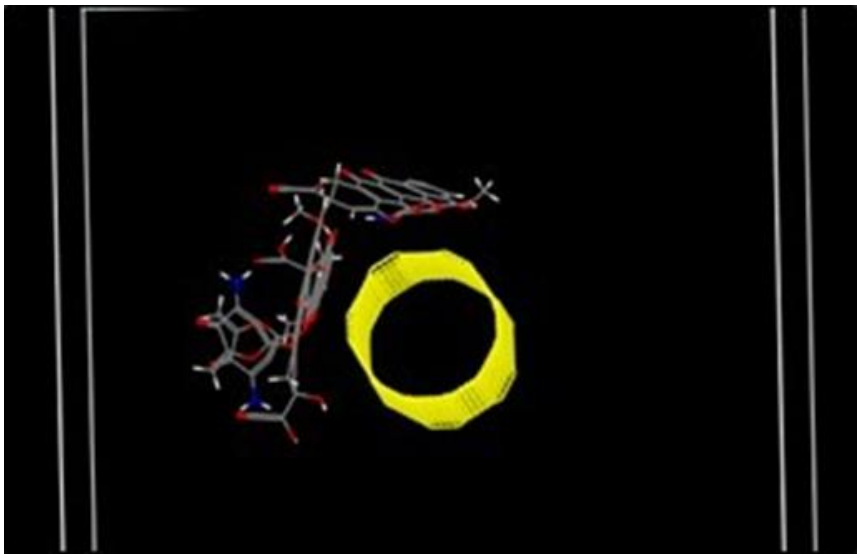


Figure 2. Schematic representation of single-walled carbon nanotube with doxorubicin.

The same force field was consistently applied in all MD simulations. The canonical ensemble was used in the simulations, which had a constant number of atoms, volume, and temperature (NVT) at temperature 298 K. The structure has been thermally stabilized using this method. It was regulated by a Berendsen thermostat, which is a method for controlling the temperature of MD simulations by

rescaling particle velocity. Because the thermostat suppresses variations in the system's kinetic energy, it is unable to create trajectories that are compatible with the canonical ensemble [31].
In the simulation, the temperature of the system was adjusted using the Berendsen thermostat, which applies corrections to the temperature by exponentially decreasing the deviation with a time constant τ. For the calculation of electrostatic interactions, the Ewald summation method was employed, and a cut-off distance of 12.5 Å was set to account for long-range interactions.

The simulation of the systems was conducted for a duration of 1 nanosecond (1 ns), which was deemed sufficient to observe the adsorption process of the drug molecules on the single-walled carbon nanotube. The molecular dynamics parameters used in the simulations are shown in Table 2.

Table 2. Molecular Dynamics Parameters of SWCNT

Ensemble	NVT
Initial Velocity	Random
Temperature	298 K
Time step	2 fs
Total simulation time	1 ns
No. of steps	50000
Frame output every	1000
Thermostat	Berendsen
Force field	COMPASS
Cut-off distance	12.5 Å

3. Result and Discussion

3.1. Interaction Between Drug Molecules (Mitoxantrone, Doxorubicin) and Single-Walled Carbon Nanotubes

In this study, the interaction between drug molecules (mitoxantrone and doxorubicin) and single-walled carbon nanotubes (SWCNTs) was investigated. The primary focus was to compare the individual interactions of mitoxantrone and doxorubicin with SWCNTs. Interaction energies were calculated and analyzed to gain insights into the binding affinities.

A pivotal aspect of this investigation was the analysis of potential π-π interactions between the single-walled carbon nanotubes and the drug molecules. The presence of such interactions could indicate the potential for drug transportation by SWCNTs. This analysis was crucial in understanding the feasibility of utilizing SWCNTs as carriers for these drug molecules. In this investigation, three molecules of the drug molecules were used. To explore the loading of drug molecules into SWCNTs, The loading process was simulated, and the resulting complexes were examined for stability and suitability. First of all, two molecules, three molecules, and four molecules of drugs were loaded into the single-walled carbon nanotubes of the sizes chosen respectively. After that, observed that two molecules of the drug were insufficient, and four molecules of the drug were too much to make any

adsorption locator from Materials Studio. Since three molecules of drugs loading to nanotubes were most convenient. The interactions between SWCNTs and three drug molecules were extensively studied using Quench Dynamics and Molecular Dynamics simulations. These simulations provided dynamic insights into the behavior of the drug molecules within the SWCNT environment. Snapshots of SWCNT-MTX and SWCNT-DOX complexes from Materials Studio after Quench Dynamics are given in Figure 3.

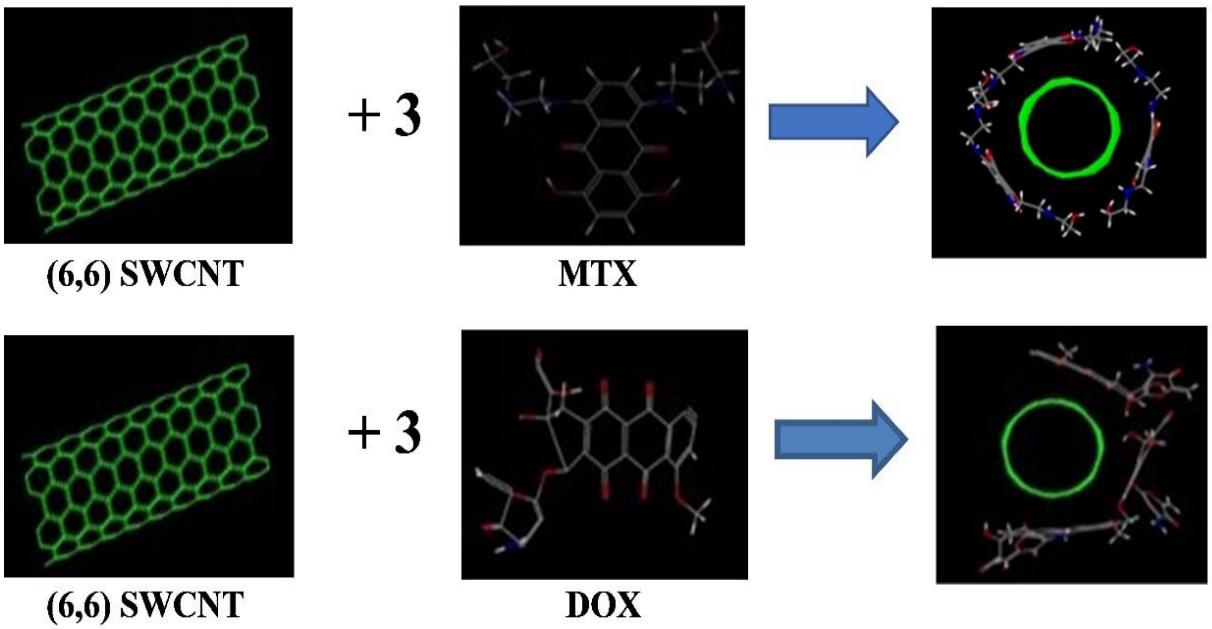


Figure 3. Snapshots of SWCNT-MTX and SWCNT-DOX from Materials Studio (Quench Dynamics).

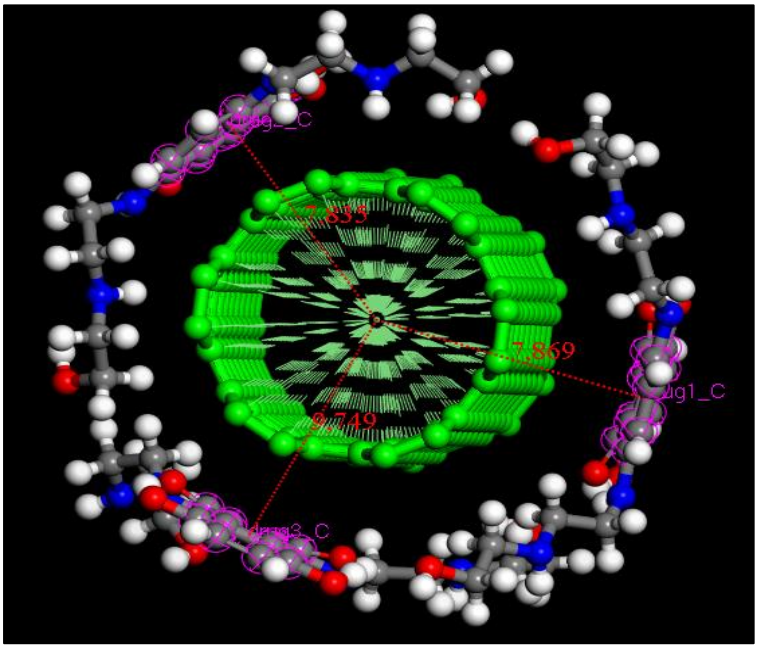
3.2 π-π Interactions and Radial Distribution Function Analysis

The Molecular Dynamics simulations revealed significant π-π interactions between the drug molecules (mitoxantrone and doxorubicin) and the single-walled carbon nanotubes (SWCNTs). In particular, mitoxantrone drug molecules exhibited π-π interactions with the SWCNT, with a mean distance of approximately 4.2 Å, as illustrated in Figure 4. Similarly, doxorubicin drug molecules also engaged in π-π interactions with both SWCNTs, with an average distance of 3.58 Å.

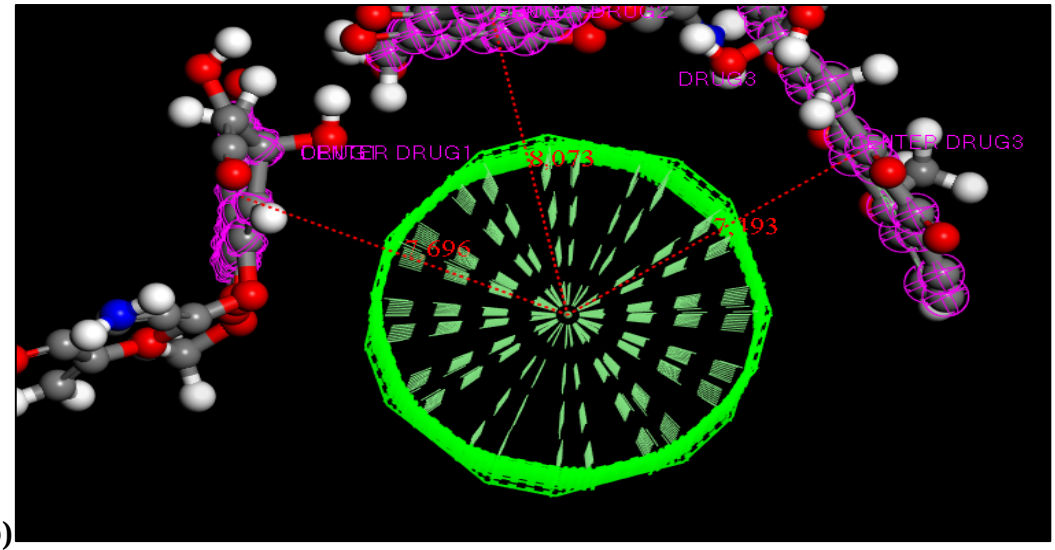
In addition, the presence of π-π interactions was further supported by Radial Distribution Function (RDF) analysis. For the RDF analysis, the center of aromatic groups for each drug molecule in the system and the center of the SWNTs have been chosen, and radial distribution graphs for the total MD period of 1 ns have been plotted using the "Forcite Analysis" module. These graphs demonstrate the presence probability of MTX and DOX at a particular range to the center of SWNTs. In the given Figure 5, for the SWCNT it is seen that the probability of mitoxantrone to be adsorbed at a distance of about intervals of 7.0 Å and 8.0 Å from the center of SWCNT. Similarly, in Figure 6, it is observed that the likelihood of doxorubicin to be adsorbed at about the interval of 7.0 Å and 8.0 Å from the center of SWCNT. When the nanotube radius is subtracted from these values, it was seen that π-π interactions are made with a distance of approximately 3.5 Å- 4.0 Å. These results mean that drug molecules display a strong tendency to be adsorbed to the SWNTs.

Figure 5 demonstrates the RDF analysis results for mitoxantrone. The probability of mitoxantrone adsorption is observed at intervals of approximately 7.0 Å and 8.0 Å from the center of the SWCNT. When the nanotube radius is subtracted from these values, a π-π interaction distance of approximately

3.5 Å to 4.0 Å is obtained. This analysis reinforces the propensity of mitoxantrone molecules to form π-π interactions with SWCNTs.



a)



b)

Figure 4. Snapshots and mean distance of (a) SWCNT-MTX system and (b) SWCNT-DOX system.

In Figure 6, the RDF analysis outcomes for doxorubicin are depicted. Similar to mitoxantrone, the probability of doxorubicin adsorption is observed within intervals of around 7.0 Å and 8.0 Å from the center of the SWCNT. Upon accounting for the nanotube radius, π-π interactions are inferred to occur at a distance of approximately 3.5 Å to 4.0 Å. These results further emphasize the strong affinity of doxorubicin molecules for SWCNTs.

In Figure 6, the RDF analysis outcomes for doxorubicin are depicted. Similar to mitoxantrone, the probability of doxorubicin adsorption is observed within intervals of around 7.0 Å and 8.0 Å from the center of the SWCNT. Upon accounting for the nanotube radius, π-π interactions are inferred to occur at a distance of approximately 3.5 Å to 4.0 Å. These results further emphasize the strong affinity of doxorubicin molecules for SWCNTs.

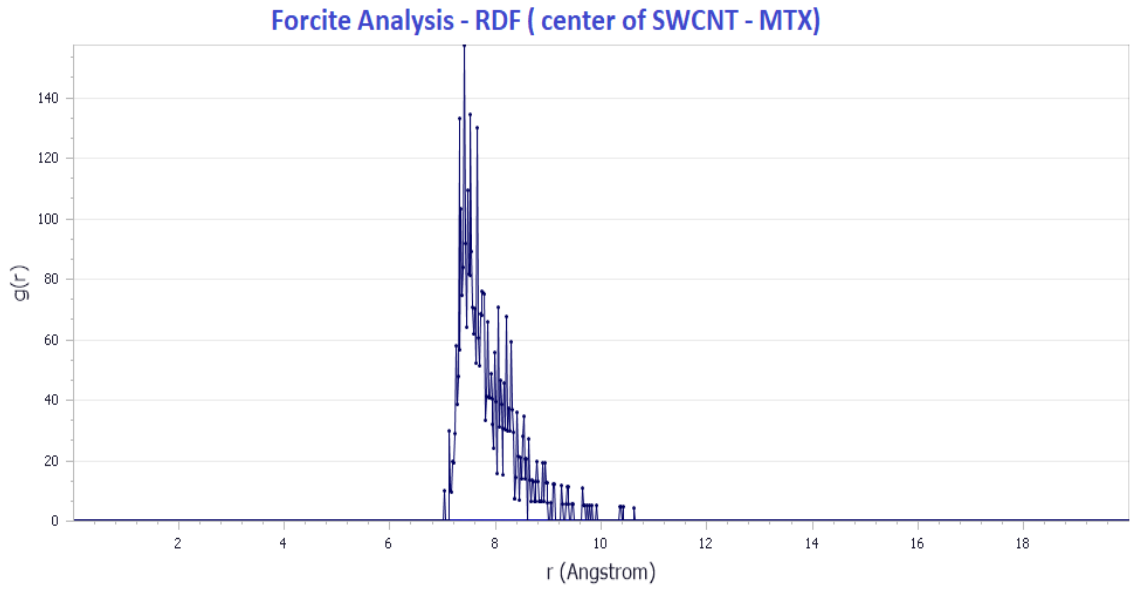


Figure 5. RDF graph of drugs (mitoxantrone)-the center of SWCNT

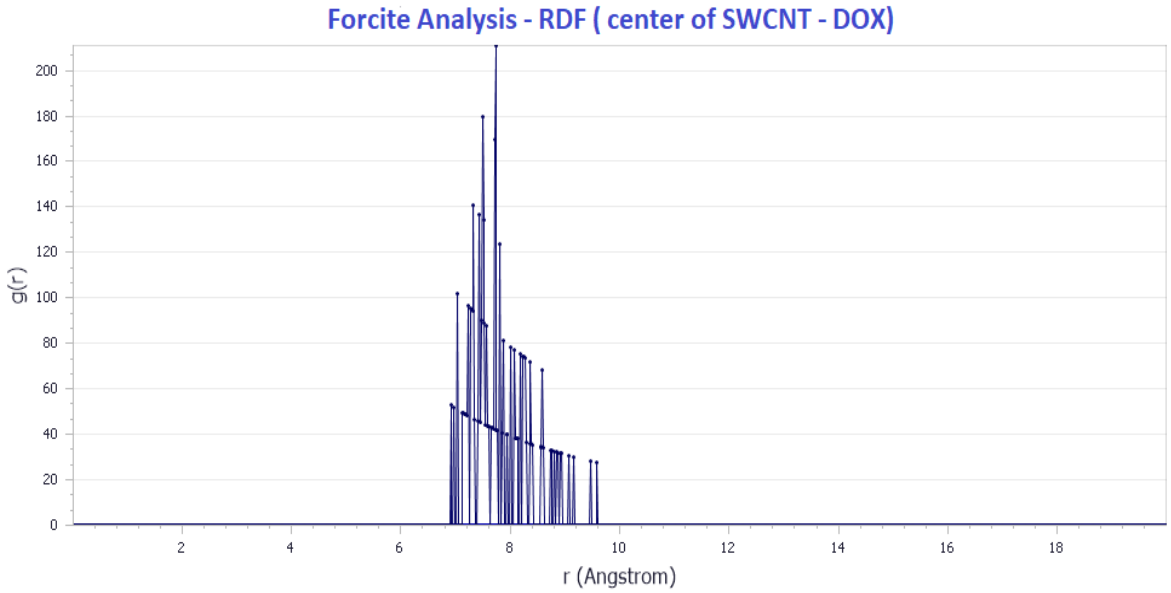


Figure 6. RDF graph of drugs (doxorubicin)-the center of SWCNT

3.3 Interaction Energy Values

Interaction energy values were calculated from Quench Dynamics results with the following equation

$$E_{interaction} = E_{system} - (E_{CNT} + E_{drug}) \quad (1)$$

where $E_{interaction}$ is the interaction energy, E_{system} is the total energy of the system (SWNT and three molecule drugs), respectively. According to this equation, a negative interaction energy indicates that the SWCNT/drug combination is thermodynamically stable, whereas positive adsorption energy indicates that drug molecules cannot connect with the nanotube due to a barrier [31].

Interaction energy values were calculated for SWCNT-MTX, and SWCNT-DOX systems as -92.43 kJ/mol and -105.42, kJ/mol respectively as seen in Figure 7. Based on the obtained results, it can be concluded that both mitoxantrone and doxorubicin drug molecules exhibit favorable energetic interactions when paired with single-walled carbon nanotube (SWCNT) systems. However, upon

closer examination and comparison of these two drugs, doxorubicin emerges as the more favorable candidate for interaction with SWCNTs due to its notably lower interaction energy. This observation emphasizes the significance of doxorubicin in the context of SWCNT-based systems, suggesting its potential for enhanced compatibility and binding affinity. The specific interaction energies of SWCNT-drug systems are comprehensively illustrated in Figure 8, providing a visual representation of the differences in binding strengths between mitoxantrone and doxorubicin with SWCNTs.

(a)

	A	B
		L : Interaction Energy
1	Number of sample points	11
2	Range	8,39321000
3	Maximum	-87,67250719
4	Minimum	-96,06571561
5	Mean	-92,42507761
6	Median	-92,97958778
7	Variance	6,27511000
8	Standard deviation	2,62728000
9	Mean absolute deviation	2,03199000
10	Skewness	0,41950800
11	Kurtosis	-1,18506000

(b)

	A	B
		L : Interaction Energy
1	Number of sample points	8
2	Range	27,36930000
3	Maximum	-95,81601061
4	Minimum	-123,18528779
5	Mean	-105,41988260
6	Median	-103,72514230
7	Variance	81,87400000
8	Standard deviation	9,67318000
9	Mean absolute deviation	7,15623000
10	Skewness	-0,69467400
11	Kurtosis	-1,15047000

Figure 7. Interaction energy values for SWCNT-MTX (a), and SWCNT-DOX (b) systems

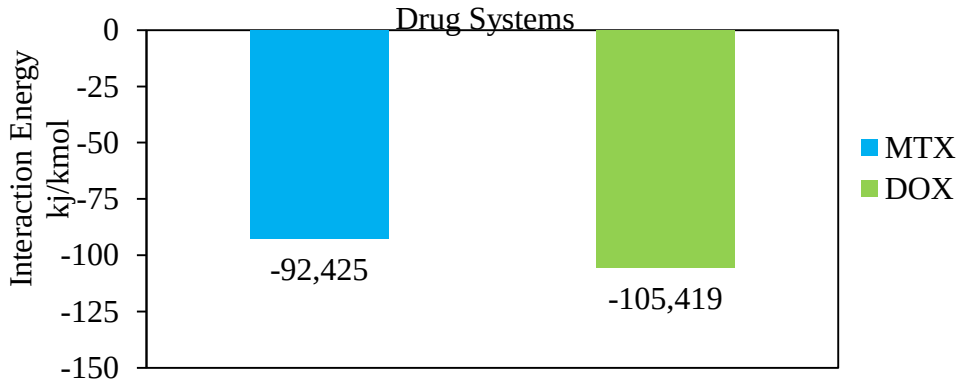


Figure 8. Interaction energies of drug carrier systems

4. Conclusions

In this study, MD simulations were performed to compare the interactions between anti-cancer drugs and nanotube surfaces. According to the simulation results, interaction energies and π-π interaction energies for each drug-SWCNT complex were analyzed to understand the nature of the main interactions between drug molecules and nanotubes. When we compared the interactions of the two drugs with SWCNTs, we observed that doxorubicin was more suitable in terms of energy. The obtained results showed that both mitoxantrone and doxorubicin can be adsorbed to SWCNT by π-π stacking formed between drug molecules and surfaces of these nanotubes.

The findings of this study show that the interactions of chemotherapy drugs such as Mitoxantrone and doxorubicin with carbon nanotubes may present significant advantages in cancer treatment. Drugs can be delivered to cancer cells more precisely and successfully using nanotube-based drug

delivery systems, improving the efficacy of treatments. These systems can reduce side effects by decreasing the likelihood of drugs reaching non-target tissues. Carbon nanotubes can protect drugs and help them transport them stably. Nanotube-based systems allow drugs to be utilized to the patient's specific needs and tumor characteristics. These advantages can contribute to making cancer treatment more effective and personalized and help achieve better results than traditional treatment methods. Although nanotubes contain many secrets and questions that have not yet been answered in terms of usage areas, it is possible to see that these SWCNT-based drug delivery systems will come to very important places in our daily lives and the future. Overcoming these challenges through innovative engineering holds the promise of propelling these systems to remarkable heights.

Authors' Contributions

The author contributed to the final version of the manuscript.

Competing Interests

The author declares that there is no conflict of interest.

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